CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207946Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	207946
Generic Name:	Paliperidone Palmitate 3 month Injection (PP3M)
Strength:	(b) (4) mg-eq./mL
Trade Name:	Invega Trinza®
Dosage Strengths and Form:	273 mg, 401 mg, 546 mg and 819 mg ER IM injection
Sponsor:	Janssen
Indication:	Treatment of Schizophrenia
Submission Type:	Original NDA
Classification:	Priority
Submission Date:	11/18/2014
OCP Division:	DCP1
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1 EXECUTIVE SUMMARY

The sponsor submitted an application requesting approval for Paliperidone Palmitate injection administered intramuscularly (IM) every 3 months (PP3M) to be used for the [redacted] (b) (4) treatment of schizophrenia after patients are stabilized on Paliperidone Palmitate injected IM monthly (Invega Sustenna®, PP1M)) for 4 months. Invega Sustenna® is approved for acute and maintenance treatment of schizophrenia. Once a day oral formulation, Paliperidone extended release tablets (Invega®), is also approved for acute and maintenance treatment of schizophrenia and schizoaffective disorder as monotherapy and an adjunct to mood stabilizers and/or antidepressants. The following is cross-referenced from the oral Paliperidone extended release (ER) submission: ADME (absorption, metabolism, and excretion), specific populations' data (elderly, patients with impaired renal or hepatic function), drug-drug interaction studies as well as QT and D2 receptor occupancy studies.

After IM injection of PP3M, the undissolved Paliperidone Palmitate particles are localized at the site of injection as agglomerate and they are slowly dissolved because of very low water solubility before being hydrolyzed to paliperidone, which is absorbed into the systemic circulation. By slowly releasing paliperidone from the injection site, the Paliperidone Palmitate formulation enables a dosing interval that achieves therapeutic plasma concentrations of paliperidone for duration of 1 month (PP1M) or 3 months (PP3M), depending on the [redacted] (b) (4) dose. The drug substance and the mechanism of release are reported to be identical for the approved PP1M and the proposed PP3M.

The clinical program for PP3M consisted of a phase 1 study and a placebo-controlled phase 3 relapse prevention trial involving patients who were currently clinically stable on PP1M. The phase 1 study was a single-dose study in subjects with schizophrenia or schizoaffective disorder. A population pharmacokinetic analysis based on the phase 1 and the phase 3 studies was used to support labeling claims in regards to dosage administration, recommendations regarding missed doses and transition to and from the other paliperidone products, and in specific populations.

Office of Clinical Pharmacology (OCP) key findings are summarized as follows:

- The sponsor's proposal to [redacted] (b) (4) does not appear to be necessary, therefore not recommended.

- Paliperidone Palmitate 3-month formulation (PP3M) when administered at doses that are 3.5-fold higher than the corresponding dose of Paliperidone Palmitate 1-month formulation (PP1M), results in paliperidone exposures similar to those obtained with corresponding monthly doses of PP1M.

- The following dosing regimen proposed by the sponsor is acceptable

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Table 1: The Proposed Dose of PP3M Based on Doses of INVEGA SUSTENNA ® (PP1M)

If the last INVEGA® SUSTENNA® (PP1M)dose is:	Initiate INVEGA® TRINZA® (PP3M) at the following dose:
78 mg	253 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

- Patients that have missed a regular dose for up to 4 months should be reinitiated on the regular dosing regimen as soon as possible. Patients that have missed a regular dose for up to 9 months need to be reinitiated based on a predefined scheme where two doses (1 week apart) of PP1M are used to bring the patient to therapeutic concentrations before PP3M administration is resumed. Patients that have missed a regular dose for more than 9 months need to be reinitiated based on a predefined schedule where two doses (1 week apart) of PP1M are administered, followed by 3 additional PP1M injections (1 month apart).

- The proposed schedule of switching from PP3M injection to Paliperidone Oral Extended Release tablet is appropriate.

Table 2: PP3M Doses and Once-Daily Paliperidone Extended-Release Conversion Regimens Needed to Attain Similar Paliperidone Exposures

	Weeks since last PP3M dose		
Last PP3M Dose	**≥ 3 months to ≤ 18 weeks**	**> 18 weeks to ≤ 24 weeks**	**> 24 weeks**
	Doses of oral paliperidone extended-release tablets		
273 mg [175 mg eq.]	3 mg	3 mg	3 mg
410 mg [263 mg eq.]	3 mg	3 mg	6 mg
546 mg [350 mg eq.]	3 mg	6 mg	9 mg
819 mg [525 mg eq.]	6 mg	9 mg	12 mg

- No change in dosing regimen is needed due to injection site (deltoid versus gluteus), sex, BMI, race and age.

- Paliperidone exhibits flip-flop kinetics when administered as PP3M, i.e., the apparent half-life is driven by the absorption process. Paliperidone Tmax is approximately 23 to 34 days and an apparent T ½ of approximately 2 to 4 months after single dose administration of PP3M.

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- After single dose administration of PP3M, paliperidone can be detected in low levels (0.2 – 0.3 ng/mL following 819 mg dosing) after 544 (~ 18 months) days post injection.

- The PK of paliperidone from the PP3M formulation was dose-proportional over a dose range of 75 to 525 mg eq. after single dose administration.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information submitted in NDA 207946 and supports a recommendation of approval for Paliperidone Palmitate 3 Month (PP3M) injection for the treatment of schizophrenia after patients have been stabilized for 4 months on Paliperidone Palmitate 1 Month (PP1M) injection provided an agreement on the label can be reached with the sponsor. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Recommendations and Comments
• Overall	☒ Yes ☐ No ☐ NA	• Pending labeling agreements with the sponsor.
• Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	• Pivotal safety and efficacy trials and supportive trial
• Proposed dose for general population	☒ Yes ☐ No ☐ NA	• See Table 1 above
• Proposed dosing (b) (4)	☐ Yes ☒ No ☐ NA	• Recommendations: It does not appear to be necessary to (b) (4) PP3M should not be administered to patients with moderate to severe renal impairment
• Pivotal bioequivalence studies	☐ Yes ☐ No ☒ NA	• The To Be Marketed and Clinical Trial formulations are the same.
• Labeling	☐ Yes ☒ No ☐ NA	• Pending satisfactory agreement with the sponsor.

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1.2 Post Marketing Studies

No post-marketing studies are recommended by OCP

1.3 Labeling Recommendations

It does not appear to be necessary to [redacted] (b) (4)

1.4 Summary of Clinical Pharmacology Findings

1.4.1 Population Pharmacokinetics (PopPK)

The dosing regimen proposed by the sponsor is acceptable. The paliperidone exposure following PP3M administration is similar to exposure following oral paliperidone treatment. It should be noted that PP3M administration results in higher Cmax/Cmin ratio compared to PP1M administration but lower compared to the oral ER formulation.

The proposed dosing regimen outside of schedule time points is adequate. Briefly, the sponsor proposes that the product can be administered ± 2 weeks every 3 months while maintaining therapeutic concentrations. Patients that have missed a regular dose for up to 4 months should be reinitiated on the regular dosing regimen as soon as possible. Patients that have missed a regular dose for up to 9 months need to be reinitiated based on a predefined scheme where two doses (1 week apart) of PP1M are used to bring the patient to therapeutic concentrations before PP3M administration is resumed. Patients that have missed a regular dose for more than 9 months need to be reinitiated based on a predefined schedule where two doses (1 week apart) of PP1M are administered, followed by 3 additional PP1M injections (1 month apart).

The proposed schedule of switching from PP3M injection to Paliperidone oral extended release tablet is appropriate. The change in plasma concentration when converting from PP3M formulation to oral extended release tablets was evaluated using simulations. Paliperidone extended-release tablets should be started 3 months after the last PP3M dose and transitioned over the next several months following the last PP3M dose.

The sponsor's proposal to [redacted] (b) (4) does not appear to be necessary by the 16% expected increase in Cmax and approximately 14% increase in AUC at steady state. As CrCL goes from 90 to 60 mL/min, CL decreases by about 14% which translates to a difference in AUC of approximately 14%. [redacted] (b) (4) PP3M is not recommended to be used in moderate to severe renal impaired patients.

No change in dosing regimen is needed due to injection site (deltoid versus gluteus), sex, BMI, race, age, and liver function test. Negligible differences were predicted between injections sites, BMI category, and sex. Therefore, no changes in dosing are recommended. Differences in exposure where observed due to age, however, when adjusting for the declining renal function in subjects >60 years, these differences where no longer observed.

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A catastrophic failure to administer the PP3M dose to a patient results in a 2.54 higher probability of treatment failure within the first 90 days after the failed administration, (HR: 2.54, 95%CI: [1.2-5.4]). Catastrophic failure assumes that no drug is administered and that the patient was stable on the PP1M formulation before the failed PP3M administration. The hazard ratio is estimated by the cox proportional hazard model using the applicant's data where all individuals with events after 90 days are right censored. Patients receiving the PP3M paliperidone product prior to the catastrophic failure are expected to have a HR lower than 2.54 due to the longer half-life of PP3M compared to PP1M product.

1.4.2 Pharmacokinetics

Paliperidone exhibits flip-flop kinetics when administered as PP3M, i.e., the apparent half-life is driven by the absorption process. After i.m. injection of PP3M, Paliperidone Palmitate is slowly absorbed, reflected by a Paliperidone Tmax of approximately 23 to 34 days and an apparent T ½ of approximately 2 to 4 months after single dose administration of PP3M. Based on a PopPK analysis, the median apparent T ½ of paliperidone from PP3M ranged from 84-95 days following deltoid injections and 118-139 days following gluteal injections.

The PK of paliperidone from the PP3M formulation was dose-proportional for AUC and Cmax over a dose range of 75 to 525 mg eq.

After both single and multiple injections of PP3M, overall paliperidone exposure (AUC) was similar between the gluteal and deltoid injection sites. Mean paliperidone Cmax and AUC were approximately 11.6% and 14.2%, respectively higher after injection into the deltoid compared with gluteal muscle. Injection sites can be used interchangeably from a PK perspective.

The pre-dose concentrations after PP1M were similar to that observed after PP3M injection upon multiple dose administration.

Inter-subject Variability

The variability for single dose AUC $_{0-\infty}$ (%CV) range from 22.0% to 34.8%. The variability in paliperidone (%CV) for Cmax ranged from 49.1% to 99.2%. The intersubject variability was similar to that observed with PP1M, with %CV for single-dose AUC $_{0-\infty}$ and Cmax ranging from 19.3% to 43.1% and 39.3% to 59.7%, respectively. Based on PopPK analysis, intersubject variability in clearance (CL) and apparent central volume of distribution (V) were estimated to be 35.7% and 62.8%, respectively.

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2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Paliperidone, the active metabolite of risperidone, is available for therapeutic use in 2 formulations: an oral extended-release (ER) osmotic pump technology (OROS®) tablet formulation (paliperidone ER tablets, INVEGA®) and a long-acting injectable (LAI) formulation: Paliperidone Palmitate 1-month injection (PP1M; INVEGA® SUSTENNA®). Paliperiodone Palmitate 3- month injection (PP3M) is a second LAI formulation intended to be injected once every 3 months. PP3M for intramuscular injection is in dose strengths of 273 mg, 410 mg, 546 mg, or 819 mg paliperidone palmitate. Paliperidone Palmitate hydrolyzes to the active moiety, paliperidone, resulting in equivalent dose strengths of 175 mg, 263 mg, 350 mg and 525 mg paliperidone, respectively. For commercial use, the Paliperidone Palmitate eq. (b) (4) mg eq./mL extended release suspension for injection (F015) will be provided in a prefilled syringe. The intended doses are achieved by including various volumes of the suspension in pre-filled syringes.

The clinical development of the PP3M program for this compound includes one Phase 3 (R092670-PSY 3012) study in adult subjects with schizophrenia and one Phase 1 (R092670-PSY-1005) study in adult subjects with schizophrenia or schizoaffective disorder.
Support for the efficacy of PP3M for treatment of schizophrenia in adults who have been adequately treated with PP1M for at least 4 months comes from Study PSY-3012. Evidence for the PK profile following PP3M administration is based on data from Studies PSY-1005 and PSY-3012. The submitted population PK analysis is used to support labeling claims in regards to dosage administration and in specific populations. Support for the safety of PP3M in the target indication is derived from data collected from the 2 completed clinical studies in adults with schizophrenia – Phase 3 Study PSY-3012 and Phase 1 Study PSY-1005 – along with select blinded safety data from the ongoing Phase 3 Study PSY-3011.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

The PP3M formulation (F015) uses the same technology as the 1-month formulation (F013) and contains the same drug substance and the same excipients. The major differences between the PP3M and PP1M formulations are (b) (4) and injection volume (administered dose).

Paliperidone Palmitate is an aqueous suspension for intramuscular (IM) injection. Based on its extremely low water solubility, Paliperidone Palmitate dissolves slowly after injection before being hydrolyzed to paliperidone, which then enters the systemic circulation. By slowly releasing

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paliperidone from the injection site, the Paliperidone Palmitate formulation enables a dosing interval that achieves therapeutic plasma concentrations of paliperidone for 1 month (PP1M) or 3 months (PP3M), depending on [redacted] (b) (4) and dose. Due to the slow release of paliperidone from injection site, PP3M is intended to be used in patients who have already demonstrated a therapeutic effect and ability to tolerate PP1M over a treatment period of at least 4 months at the time of initiation of PP3M. Paliperidone Palmitate 3 month (PP3M) injection formulation differs from the PP1M formulation in its [redacted] (b) (4) and higher fill volume in order to ensure a physically and chemically stable 3-month formulation that is easily resuspendable and minimizes injection force. The following table compares the approved PP1M and PP3M formulations

Table 3: Comparison of Characteristics of PP1M and PP3M Formulations of Paliperidone Palmitate

	PP1M Formulation (F013)	PP3M Formulation (F015)
[redacted] (b) (4)		
Dose[b]	25, 50, 75, 100, 150 mg eq.	175, 263, 350, 525 mg eq.[c]
Fill volume	0.25 – 1.5 mL	0.875 – 2.625 mL
[redacted] (b) (4)		

[b] Palmitate ester of paliperidone has a conversion factor of 1.56.
[c] There is no PP3M dose corresponding to a 25 mg eq. dose of PP1M.

Source: Sponsor's Clinical Overview

Table 4: Composition of Paliperidone Palmitate [redacted] (b) (4) mg eq./mL Extended Release Suspension for Injection (F015)

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
Paliperidone palmitate (R092670) [redacted] (b) (4)	Company Specifications[b]	Active drug substance	[redacted] (b) (4)
Polysorbate 20	NF	[redacted] (b) (4)	10
Polyethylene glycol 4000	NF		75
Citric acid monohydrate	USP		7.5
Sodium dihydrogen phosphate monohydrate	USP		[redacted] (b) (4)
Sodium hydroxide	NF		
Water for Injection	USP		
[redacted] (b) (4)			

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2.1.3 What are the proposed mechanism (s) of action and therapeutic indication(s)?

The mechanism of action of paliperidone is unknown. However, it has been proposed that the paliperidone therapeutic activity in schizophrenia is mediated through a combination of central D2 and 5HT2A receptor antagonism. PP3M is indicated for the treatment of schizophrenia in adult patients who have been treated with PP1M for at least 4 months.

2.1.4 What are the proposed dosage and route of administration?

With a 3.5-fold higher clinical doses as compared to the doses of PP1M, the PP3M formulation deliver similar paliperidone exposure over a period of 3 months, as compared to 3 consecutive injections of the PP1M. At the time when the next PP1M injection dose is to be scheduled, switching to PP3M should be initiated with an equivalent dose as shown in the following table:

Table 5: Conversion Between PP1M and PP3M Doses Using 3.5 as a Multiplier

PP1M Dose		PP3M Dose	
mg paliperidone palmitate	mg eq. paliperidone	mg paliperidone palmitate	mg eq. paliperidone
78	50	273	175
117	75	410	263
156	100	546	350
234	150	819	525

mg eq. = milligram equivalent; PP1M = paliperidone palmitate 1-month formulation; PP3M = paliperidone palmitate 3-month formulation

Source: Sponsor's Summary of Clinical Pharmacology

2.2 General Clinical Pharmacology

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

The PP3M program includes one Phase 3 study (R092670-PSY-3012) in adult subjects with schizophrenia and one Phase 1 study (R092670-PSY-1005) in adult subjects with schizophrenia or schizoaffective disorder. The Phase 3 study was a multinational, randomized, double-blind, placebo-controlled, relapse prevention study to establish the efficacy and safety of PP3M after initiation of treatment with PP1M/PP3M over a period of 29 weeks in subjects with schizophrenia. The phase 3 study, if deemed adequate, provides substantial evidence to support the claims of safety and efficacy. The submitted population PK analysis, based on the Phase 3 and Phase 1 studies, is used to support labeling claims with regard to dosage administration and dosing in specific populations and situations such as when doses are missed.

The Phase 1 study (1005) was a multinational, randomized, open-label, parallel-group Phase 1 study designed to evaluate the PK, safety, and tolerability of a single dose of PP3M and to document its relative bioavailability in comparison with a 1 mg immediate release (IR) formulation of paliperidone

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2.2.2 *What was the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers and how are they measured in clinical pharmacology and clinical studies?*

Because of the extensive clinical efficacy and safety data available with the approved PP1M formulation, the Agency decided that a single placebo-controlled relapse prevention study involving patients who had been treated with and stabilized on PP1M was acceptable. Accordingly, demonstration of efficacy for Paliperidone Palmitate, injected IM every 3 months across the dose range of 175 to 525 mg eq., in delaying the time to relapse of symptoms of schizophrenia among adult subjects who had achieved satisfactory symptom control with PP1M compared to those receiving placebo was the response end point. PP3M is not intended to be used for the initiation of treatment without prior exposure to PP1M. For the clinical pharmacology endpoints, plasma paliperidone exposures from PP3M were targeted to be similar to the paliperidone exposures for corresponding PP1M doses.
Protocol-specified relapse criteria involved 1 or more of the following: sustained worsening in the PANSS total score (an increase from randomization of 25% if the score at randomization was >40 or by 10 points if the score was ≤40 on 2 consecutive visits separated by 3 to 7 days); clinically significant, overt symptomatology manifested by psychiatric hospitalization, suicidal/homicidal ideation or aggressive behavior, or deliberate self-injury and/or violent behavior resulting in injury; or sustained worsening of individual PANSS items of delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, or uncooperativeness (score of ≥5 if maximum score at randomization was ≤3, or score of ≥6 if maximum score at randomization was 4, on 2 consecutive visits separated by 3 to 7 days). The date of relapse for an individual subject was defined as the date of the first positive findings from a PANSS assessment for symptoms of relapse, rather than the date of confirmation.

2.2.3 *What were the design features of the pivotal efficacy and safety trials?*

The design features of the pivotal efficacy and safety trial are summarized in the following Table

Table 6: Clinical Study Supporting the Efficacy and/or Safety of PP3M for Treatment of Schizophrenia

Study Type/Protocol	Study Description	Study Treatments	No. of Subjects
R092670-PSY-3012	Randomized, double-blind, placebo-controlled, multicenter, relapse prevention study of variable duration preceded by a 17-week , open-label transition phase[a] with PP1M and a 12-week open-label maintenance phase with PP3M	PP3M (fixed dose[b]: 175, 263, 350, or 525 mg eq./3 mos based on 3.5 times PP1M dose at end of OL transition phase) Placebo (Double-blind phase only)	OL transition phase: n = 506 OL maintenance phase, n=379 DB phase: PP3M: 160 Placebo:145

[a]All subjects in Study PSY-3012 (except those continuing PP1M or switching from another LAI antipsychotic) were scheduled to receive the first PP1M injection of 150 mg eq on Day 1 and the second injection of 100 mg eq on Day 8, both in the deltoid muscle Injections of PP1M on Days 36 and 64 could have been given in the deltoid or gluteus muscle and were flexibly dosed (50 to 150 mg eq) At Day 92, subjects received the same dose of PP1M as on Day 64
[b]Treatment in the double-blind phase started on Day 204; those assigned to PP3M received the same dose as on Day 120 of open-label maintenance phase
Key: DB = double-blind; mg eq = milligram equivalent; mos = months; OL = open-label; PP1M = paliperidone palmitate 1-month injection; PP3M = paliperidone palmitate 3-month injection; wks = weeks

Source: Sponsor's Clinical Overview

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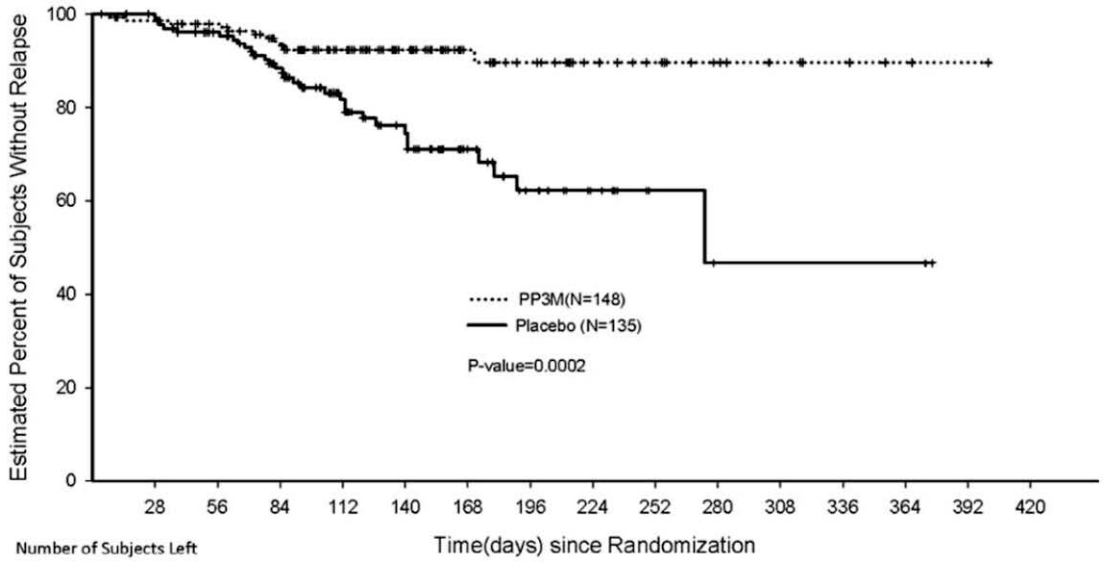
2.2.4 What are the evidences of efficacy provided by the sponsor in support of the application?

The sponsor reported that based on the preplanned interim analysis conducted by the independent data monitoring committee (IDMC) after 42 relapse events had occurred, 31 (23.0%) of 135 subjects randomly switched from open-label PP3M to double-blind placebo experienced a relapse event compared with 11 (7.4%) of 148 subjects randomized to remain on PP3M. Subjects who continued treatment on PP3M during the double-blind phase experienced relapse significantly later than those who were switched to placebo ($p<0.001$, based on log rank test).

Figure 1: Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase – Interim Analysis (Study R092670-PSY-3012: ITT (DB) Analysis Set)



Number of Subjects Left

Time	0	28	56	84	112	140	168	196	224	252	280	308	336	364	392	420
PP3M	148	143	133	104	81	59	35	28	19	15	9	6	4	2	1	0
Placebo	135	131	116	91	61	44	27	18	12	4	2	2	2	0	0	0

DB = double-blind; ITT = intent-to-treat; PP3M = paliperidone palmitate 3-month formulation
Source: Sponsor's clinical overview

Refer to medical review for Agency's conclusions of the efficacy of PP3M.

2.3 Population Pharmacokinetics/Exposure Response

2.3.1 Is the proposed dosing regimen acceptable?

Yes. The paliperidone exposure following PP3M administration is similar to exposure following PP1M and oral paliperidone, as shown in figure 2.

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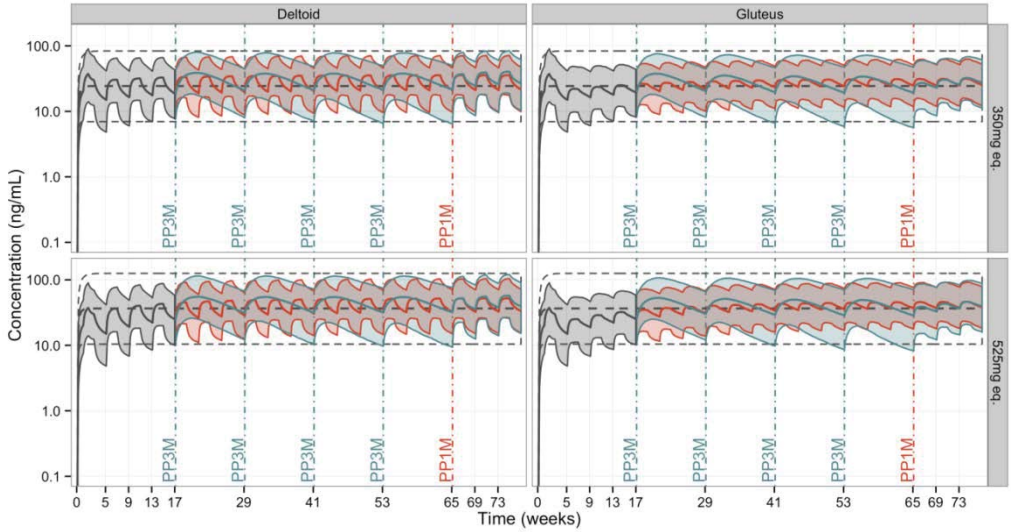
Figure 2: Paliperidone Exposure Following PP3M Administration (Teal Areas), Compared to Paliperidone Exposure following PP1M Administration (Red Areas) and Per Oral Treatment (Dashed Lines)



The solid lines and shaded areas represent the median paliperidone concentrations and 90% prediction intervals. Black and grey colors represent the PP1M initiation phase, red and blue colors represent the PP1M and PP3M maintenance regimens, respectively, and the thick and thin dashed lines represent the median paliperidone concentrations and 90% prediction interval following treatment with ER.
Source:Figure 12, report REP-1-JAN-PAL-PMX-1

2.3.2 Is the applicant's proposal for dosing regimens outside of scheduled time point appropriate?

Yes. The sponsor evaluated the influence of missed PP3M doses on paliperidone plasma concentration using simulations. The sponsor's recommendations on how to reinitiate therapy were evaluated using the same approach. Briefly, sponsor proposes that the product can be administered ± 2 weeks every 3 months while maintaining therapeutic concentrations. Patients that have missed a regular dose for up to 4 months should be reinitiated on the regular dosing regimen as soon as possible. Patients that have missed a regular dose for up to 9 months need to be reinitiated based on a predefined scheme where two doses (1 week apart) of PP1M are used to bring the patient to therapeutic concentrations before PP3M administration is resumed. Patients that have missed a regular dose for more than 9 months need to be reinitiated based on a predefined schedule where two doses (1 week apart) of PP1M are administered, followed by 3 additional PP1M injections (1 month apart).

The sponsor's performed simulations to evaluate the management of missed doses. Results of the sponsor's simulation of delayed doses (up to three weeks) show marginal decrease in exposure (Table 7). Similarly, administering doses up to three weeks before schedule resulted in marginally increase Cmax values. The reviewers agree with the applicant's proposals.

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Table 7: Median C_{min} and C_{max} when Switching from PP1M to PP3M at Week 17, ±1 Week, and Dosing Windows around the Regularly Scheduled 12-Week Dosing Interval, ±1, ±2 and ±3 Weeks, after Subjects Reached Apparent Steady-State on Treatment with PP3M Deltoid Injections

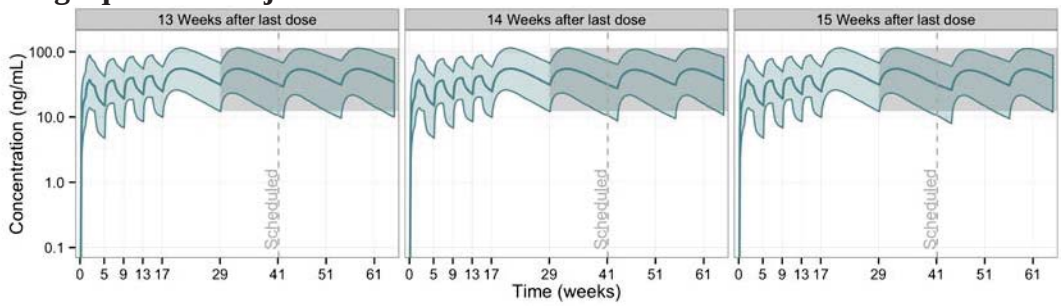
Type	Parameter	Dose	Default	±1 week	±2 weeks	±3 weeks
Switching to PP3M	C_{min} (ng/mL)	175 mg eq.[a]	11.6	10.2		
	C_{max} (ng/mL)	525 mg eq.[b]	58.2	60.2		
Maintenance PP3M	C_{min} (ng/mL)	175 mg eq.[a]	11.0	10.3	9.7	9.0
	C_{max} (ng/mL)	525 mg eq.[b]	56.4	57.1	58.0	58.8

[a] +X week simulations were performed with the lowest PP3M dose strength of 175 mg eq. to simulate a worst-case scenario (ie, largest % drop in C_{min}) since the lowest dose has the shortest apparent $t_{1/2}$.
[b] -X week simulations were performed with the highest PP3M dose strength of 525 mg eq. to simulate a worst-case scenario (ie, largest % increase in C_{max}).
C_{max}: maximum concentration; C_{min}: minimum concentration; PP1M: paliperidone palmitate 1-month formulation; PP3M: paliperidone palmitate 3-month formulation

Source: Table 8 report: REP-1-JAN-PAL-PMX-1

The sponsor's simulations show that paliperidone PP3M formulation can be reinitiated at the regular dosing interval and dose strength if a scheduled dose was missed by less than 4 months (Figure 3)

Figure 3: Missed Dose Simulations When Less Than 4 months Had Elapsed Since the Last 525 mg eq. Deltoid Injections of PP3M.

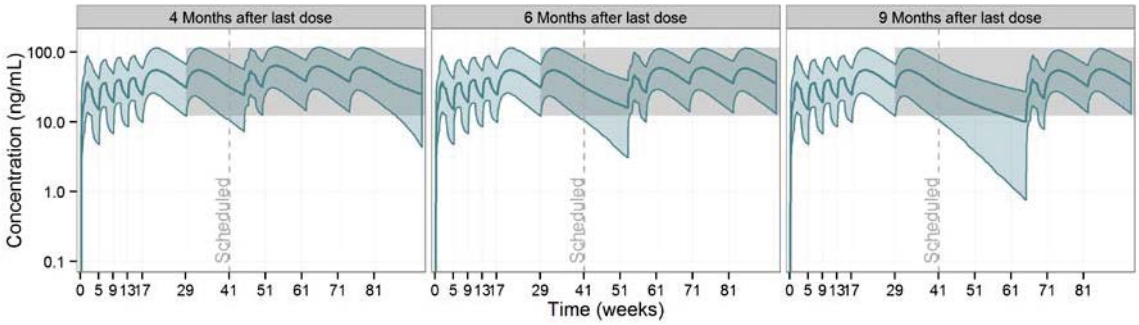


Source: Figure 14 report: REP-1-JAN-PAL-PMX-1

Missed dose simulations when 4 to 9 months had elapsed since the last 525 mg eq. deltoid injections of PP3M (Figure 4).

Reference ID: 3748068

Figure 4: Missed Dose Simulations When 4 to 9 months Had Elapsed Since the Last 525 mg eq. Deltoid Injections of PP3M.



Source: Figure 15 report: REP-1-JAN-PAL-PMX-1

Table 8: Re-initiation regimen after missing between 4 and 9 months of PP3M

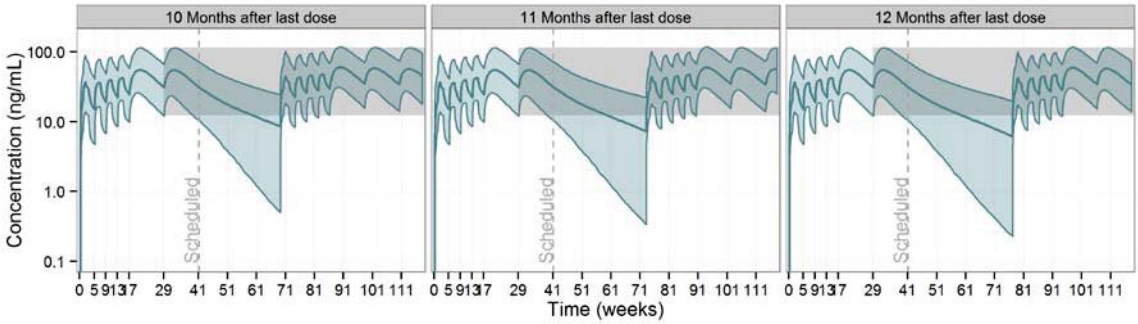
Last PP3M Dose	Administer PP1M two doses one week apart		Then administer PP3M
	Day 1 →	**Day 8 →**	**1 month after Day 8**
273 mg [175 mg eq.]	78 mg →	78 mg →	273 mg
410 mg [263 mg eq.]	117 mg →	117 mg →	410 mg
546 mg [350 mg eq.]	156 mg →	156 mg →	546 mg
819 mg [525 mg eq.]	156 mg →	156 mg →	819 mg

Source: Adapted from sponsor's proposed labeling

For doses missing more than 9 months, simulations show that paliperidone PP3M formulation can be reinitiated with a PP1M deltoid injection of 150 mg eq. on Day 1 and a second PP1M deltoid injection of 100 mg eq. on Day 8, followed by 3 additional 150 mg eq. PP1M injections, followed by 525 mg eq. PP3M dosing every 12 weeks if a scheduled dose was missed by more than 9 months (Figure 5).

Reference ID: 3748068

Figure 5: Missed Dose Simulations When More Than 9 Months Had Elapsed Since the Last 525 mg eq. Deltoid Injections of PP3M



Source: Figure 15 report: REP-1-JAN-PAL-PMX-1

2.3.3 Is the sponsor's proposal for switching from the PP3M formulation to oral extended release tablets appropriate?

Yes. The change in plasma concentration when converting from PP3M formulation to oral extended release tablets was evaluated using simulations. Briefly, paliperidone extended-release tablets should be started 3 months after the last PP3M dose and transitioned over the next several months following the last PP3M dose. Different oral doses should be given based on the PP3M dose (Table 9). Simulated paliperidone concentration time profile following 525 mg PP3M and converted to oral paliperidone as shown in Figure 6 as an example.

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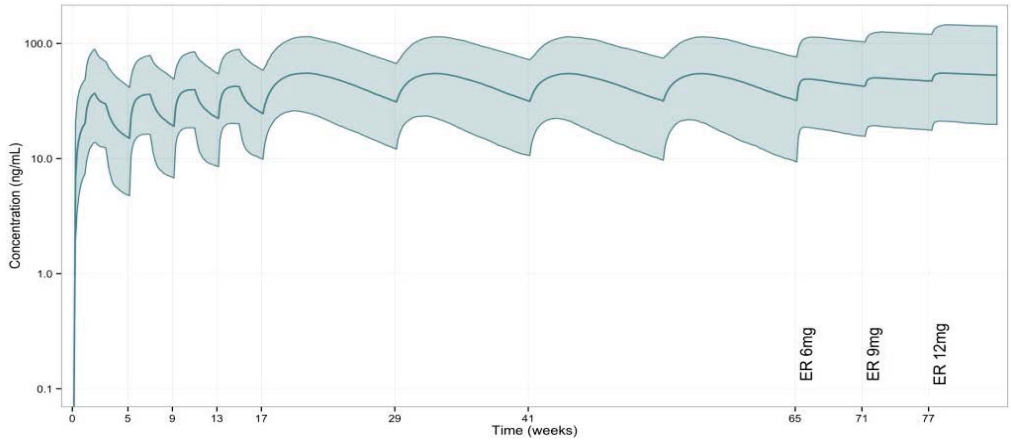
Figure 6: Transition From PP3M (525 mg eq.) to Oral Paliperidone ER



Source: Figure 16 report: REP-1-JAN-PAL-PMX-1

Table 9: PP3M Doses and Once-Daily Paliperidone Extended Release Conversion Regimens Needed to Attain Similar Paliperidone Exposures

	Weeks since last PP3M dose		
Last PP3M Dose	**≥ 3 months to ≤ 18 weeks**	**> 18 weeks to ≤ 24 weeks**	**> 24 weeks**
	Doses of oral paliperidone extended-release tablets		
273 mg [175 mg eq.]	3 mg	3 mg	3 mg
410 mg [263 mg eq.]	3 mg	3 mg	6 mg
546 mg [350 mg eq.]	3 mg	6 mg	9 mg
819 mg [525 mg eq.]	6 mg	9 mg	12 mg

Source: Adapted from sponsor's proposed labeling

2.3.4 Is the sponsor's proposal (b) (4) *necessary?*

No. The applicant's proposal (b) (4) does not appear to be necessary by the 16% expected increase in Cmax (Table 10) and 14% increase in AUC at steady state in patients with mild renal impairment as compared to patients with normal renal function.

The impact of mild renal impairment on paliperidone exposure following ER tablets, PP1M, and PP3M is shown in the following Table. Due to the profound absorption rate limiting kinetics of intramuscular paliperidone administration (PP1M and PP3M), the influence of mild renal impairment on Cmax decreases with decreasing absorption rate.

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Table 10: Impact of Mild Renal Impairment on Paliperidone Exposure

Formulation, Study, number of subjects	Cmax ratio Mild/Normal	Dosing recommendation Initiation, maintenance	
		Normal renal function	Mild renal impairment
ER Tablets (PO), REI-1001, n=11	1.63[a]	6 mg QD, (3-12 mg QD)	3 mg QD, (3-6 mg QD)
PP1M, (IM), R092670-PSY-3007, n=188	1.22[b]	175 mg on day 1 and 100 mg on day 8. Thereafter 25–150 mg	100 mg on day 1 and 75 mg on day 8. Thereafter 50 mg
PP3M (IM), R092670-PSY-3012, n=52	1.16[c]	3.5 fold of PP1M 175 mg - 525 mg	3.5 fold PP1M, 175 mg -350 mg

a) Table 100 from Clinical pharmacology review NDA21999, dated: November 30, 2005
b) Derived from Figure 25 population-PK-report, NDA22264
c) Figure A17-7, report: REP-1-JAN-PAL-PMX-1
Note: See PM review for more details

2.3.5 Should the dose be adjusted due to patient's age, race, gender, or BWI?

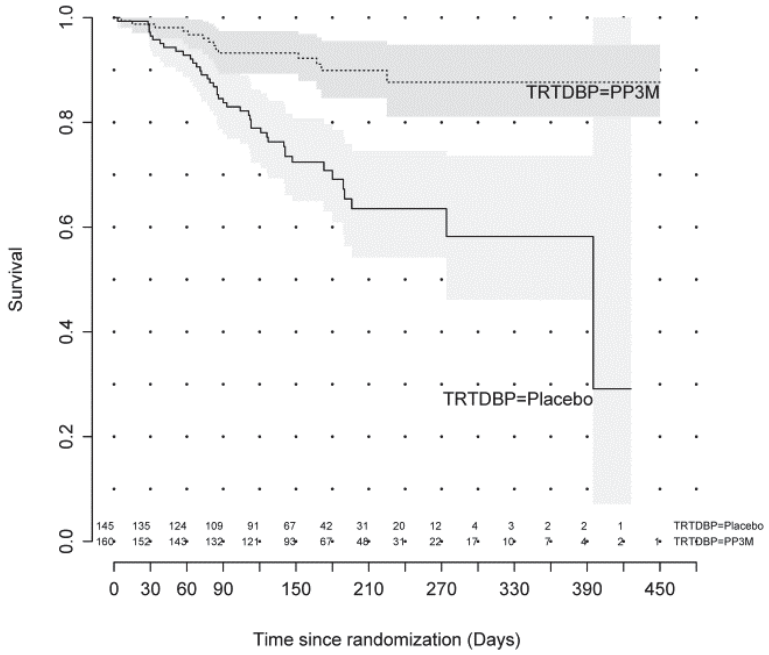
No change in dosing regimen is needed due to injection site (deltoid versus gluteus), sex, BMI, race, age, and liver function test. Negligible differences were predicted between injections sites, BMI category, and sex, they do not warrant any action. Differences in exposure were observed due to age, however, when adjusting for the declining renal function in subjects >60 years, these differences where no longer observed.

2.3.6 What is the impact of incomplete or failed PP3M administration on probability of treatment failure?

A catastrophic failure to administer the PP3M dose to a patient results in a 2.54 higher probability of treatment failure within the first 90 days after the failed administration, (HR: 2.54 , 95%CI: [1.2-5.4]). Catastrophic failure assumes that no drug is administered and that the patient was stable on the PP1M formulation before the failed PP3M administration. The hazard ratio is estimated by the cox proportional hazard model using the applicant's data where all individuals with events after 90 days are right censored. Patients receiving the PP3M product prior to the catastrophic failure are expected to have a HR lower than 2.54 due to the longer half-life of PP3M compared to PP1M product.

Reference ID: 3748068

Figure 7: Survival Curve Illustrating Probability of Treatment Failure For The Placebo and The PP3M Group In The Phase 3 Trial



Source: TTE.csv

2.3.7 Are there any unexplained high concentrations observed in patients?

Yes. Patient number 9185 in the phase 1 trial was observed to have a maximum plasma concentration of 416 ng/mL approximately 24 hours after dose. This is 5.53-fold higher than the arithmetic mean of 75.19 ng/mL observed in the same dose group with the median time to Cmax of 576 hr (3.4 weeks). The applicant does not provide any explanation for this observation other than measurable paliperidone palmitate (the ester prodrug) in this individual. Subsequent 3 observations in the same individual at 71, 119, and 215 hr after dose are also unusually high (243, 194, and 125 ng/mL). Due to several high observations within the same individual, the reviewers do not believe that an analytical error is responsible for the high concentrations. Individual 9198 in the Phase 1 trial was observed to have a maximum plasma observation of 223 ng/mL. This observation occurred at 81 weeks after the single dose administration. The observation immediate before this was below limit of quantification. At median Tmax for the 525 mg eq. dose group, this individual had a moderate Cmax of 28 ng/mL which is within above the 5th percentile in that dose group. Because of these reasons, the reviewers think that an analytical error can be responsible for this high observation.

Besides these two individuals, concentrations above 125 ng/mL in the other 15 individuals are believed to be due to natural between subject variability in pharmacokinetics. Figure 8 shows the concentration time profile for all the 15 individuals. Time is represented as time after last dose and not absolute time since first dose.

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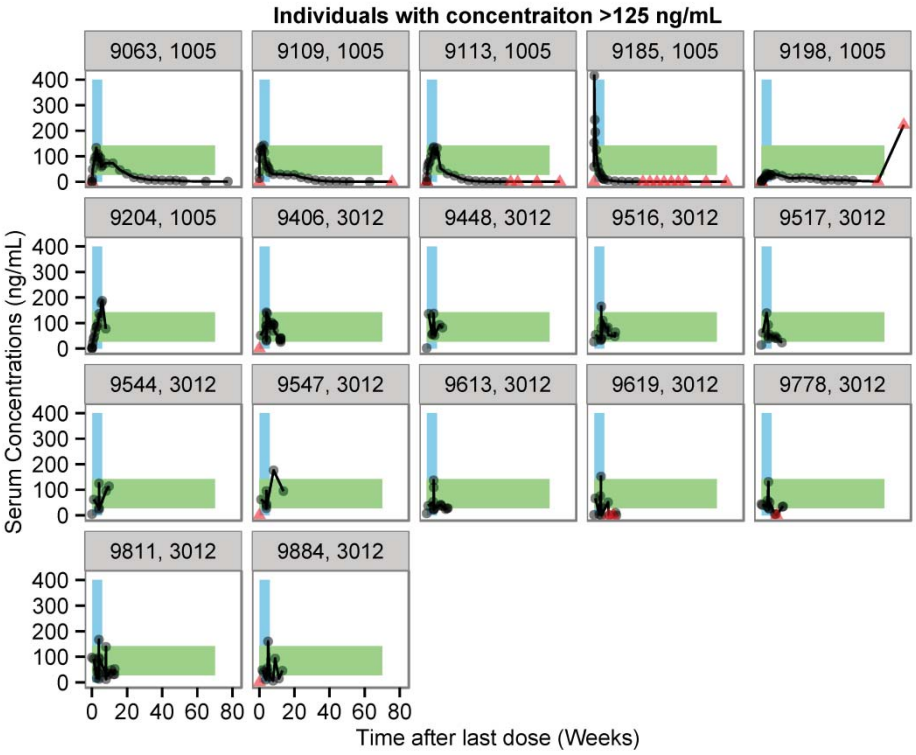
In communication with the medical reviewer, she indicated that the sponsor's clinical review of the identified cases of concentration greater than 125 ng/mL revealed no clinically relevant safety findings associated with the high plasma concentrations of paliperidone. Refer to medical review for details.

Figure 8: Subjects with Plasma Concentrations ≥ 125 ng/mL



Note: Green areas represent the 95 and 5 percentile of Cmax in 525 mg dose group in the Phase 3 study (27.35-142 ng/mL). Blue areas represent the range of T_{max} in the 525 mg dose group of Phase 1 trial (2-41 days). Red triangles are observations below limit of quantification or observations that were identified as outliers and excluded from the analysis. Please see discussion on data exclusion in the main body of the review.

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2.4 General Pharmacokinetics

2.4.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Yes. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays for the quantification of paliperidone in human heparin plasma were developed and validated. The assay methods are acceptable.

2.4.2 What are the PK characteristics of paliperidone after PP3M administration?

2.4.2.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in patients

After a single dose i.m. injection of 75-525 mg-eq. Paliperidone Palmitate (PP3M) in the gluteal or deltoid muscle, paliperidone median Tmax was approximately 23 to 34 days and mean apparent half-life of approximately 2-4 months. Paliperidone AUC $_{0-\infty}$ and Cmax increased dose-proportionally in the 75-525 mg eq. range. Paliperidone AUC $_{0-\infty}$ was comparable between injection sites, whereas mean C_{max} was higher (approximately 11 – 25%) after equal doses in deltoid compared with gluteal injection. This increase in Cmax after deltoid injection should not be clinically relevant. Therefore, PP3M can be injected in both the deltoid and gluteal sites.

Table 11: Summary of Key Pharmacokinetic Parameters of Paliperidone after Single Dose IM injection of PP3M (Study R092670-PSY-1005)

Dose	75 mg eq. Gluteal			150 mg eq. Gluteal			350 mg eq. Gluteal			450 mg eq. Gluteal			525 mg eq. Gluteal		
Parameter (t_{max}: median [range])	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median
C_{max}, ng/mL	20	10.8 (59.4)	10.1	18	12.2 (99.2)	8.33	24	44.0 (87.5)	36.7	21	40.3 (63.8)	35.0	24	63.8 (59.7)	56.3
t_{max}, days	20	29.00 (16.98-113.99)		18	27.51 (8.09-41.00)		24	31.03 (5.00-84.08)		21	28.00 (13.00-54.98)		24	23.01 (2.00-41.00)	
AUC_{∞}, ng.h/mL	16	22,007 (31.7)	22,214	10	39,323 (22.0)	42,963	16	101,244 (32.3)	102,894	13	115,241 (28.8)	123,273	18	145,611 (34.8)	142,201
$t_{1/2}$, days	18	83.0 (100.1)	44.9	10	96.6 (69.3)	79.6	19	94.7 (77.3)	77.4	15	120.5 (77.3)	81.5	20	91.8 (72.6)	68.5
$F_{rel, AUC\infty}$, %	13	113.92 (16.4)	117.65	10	104.37 (27.6)	103.33	16	118.93 (21.4)	115.91	11	109.36 (17.2)	111.61	18	107.80 (23.6)	107.41
Dose	-			**175 mg eq. Deltoid**			**300 mg eq. Deltoid**			**450 mg eq. Deltoid**			**525 mg eq. Deltoid**		
Parameter (t_{max}: median [range])	**n**	**Mean (%CV)**	**Median**	**n**	**Mean (%CV)**	**Median**	**n**	**Mean (%CV)**	**Median**	**n**	**Mean (%CV)**	**Median**	**n**	**Mean (%CV)**	**Median**
C_{max}, ng/mL	-	-	-	25	25.8 (50.5)	21.2	20	32.4 (49.1)	28.0	24	45.0 (54.4)	40.1	24	80.0 (94.7)	57.9
t_{max}, days	-	-		25	23.99 (5.00-56.10)		20	34.00 (13.00-83.12)		22	23.98 (12.99-51.07)		24	24.51 (0.99-54.99)	
AUC_{∞}, ng.h/mL	-	-	-	22	50,407 (32.5)	46480	17	78,166 (22.3)	77925	17	132,645 (28.0)	131651	22	144,173 (26.4)	128,969
$t_{1/2}$, days	-	-	-	22	56.6 (57.7)	51.7	17	77.7 (50.1)	73.5	18	85.9 (65.8)	71.8	22	60.7 (47.7)	56.9
$F_{rel, AUC\infty}$, %	-	-	-	22	108.77 (17.0)	107.94	15	106.61 (17.8)	102.60	14	108.43 (20.4)	101.78	20	112.72 (16.2)	109.98

Source: Sponsor's summary of clinical pharmacology

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Paliperidone Cmax and AUC during a dosing interval (AUC0-τ) increased with PP3M dose after multiple im injections. Multiple dose pharmacokinetic were evaluated both by non-compartment methods and PopPK methods. Table 12 contains summary of PK parameters after multiple dose determined via non-compartmental methods.

Table 12: Summary of Key Pharmacokinetic Parameters of Paliperiodone after multiple dose administration of PP3M (noncompartmental analysis:Study R092670-PSY-3012)

Parameter (mean ± SD, t_{max}: median [range])	PP3M, 175 mg eq.				PP3M, 263 mg eq.				PP3M, 350 mg eq.				PP3M, 525 mg eq.			
	n	mean		SD	n	mean		SD	n	mean		SD	n	mean		SD
$C_{predose}$, ng/mL	3	8.23	±	4.82	6	25.8	±	11.0	40	25.9	±	14.7	29	29.5	±	14.1
C_{max}, ng/mL	3	15.7	±	4.28	6	38.5	±	8.04	34	41.5	±	21.7	24	45.9	±	16.4
t_{max}, days	3	8.94 (6.93-19.86)			6	28.36 (0.00-54.96)			34	27.86 (0.00-54.99)			24	25.92 (0.00-54.90)		
AUC_{τ}, ng.h/mL	3	22,635	±	5,511	6	60,660	±	14,062	34	62,893	±	30,514	24	70,793	±	25,850
C_{avg}, ng/mL	3	11.2	±	2.73	6	30.7	±	6.43	34	32.0	±	15.6	24	35.1	±	13.1
Peak–to-trough-ratio	3	2.52	±	1.94	6	1.63	±	0.54	34	1.91	±	0.96	21	2.59	±	3.89
DN- C_{max}, ng/mL	3	31.3	±	8.56	6	51.2	±	10.7	34	41.5	±	21.7	24	30.6	±	10.9
DN- AUC_{τ}, ng.h/mL	3	45,270	±	11,022	6	80,726	±	18,714	34	62,893	±	30,514	24	47,195	±	17,233

DN: dose normalized to 350 mg eq.

Source: Summary of clinical pharmacology

Using a 3.5-fold multiple of the final PP1M dose, paliperidone trough concentrations were maintained after switching from PP1M to PP3M. The use of 3.5-fold multiple factor of the final PP1M dose to determine the equivalent PP3M dose is acceptable. Paliperidone predose plasma concentrations after administration of PP1M during the transition Phase at 75, 100 and 150 mg eq. were comparable to paliperidone predose plasma concentrations after administration of the corresponding PP3M doses of 263, 350 and 525 mg eq. at the maintenance phase.

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Table 13: Predose plasma concentrations of paliperidone after administration of PP1M and PP3M

Predose Plasma Concentrations Paliperidone	PP1M, 50mg eq. / PP3M, 175 mg eq.			PP1M, 75 mg eq. / PP3M, 263 mg eq.			PP1M, 100 mg eq. / PP3M, 350 mg eq.			PP1M, 150 mg eq. / PP3M, 525 mg eq.		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
PP1M (Transition Phase)												
$C_{Day\ 64,\ Week\ 9}$, ng/mL	9	17.4	10.5	27	21.5	9.06	155	21.6	11.9	145	23.0	14.0
$C_{Day\ 92,\ Week\ 13}$, ng/mL	6	13.9	5.61	28	20.7	8.24	148	21.7	11.0	135	24.6	13.0
$C_{Day\ 120,\ Week\ 17}$, ng/mL	6	15.1	5.75	22	21.0	6.94	142	24.1	12.5	119	31.7	18.1
PP3M (Maintenance and Double Blind Phase)												
$C_{Day\ 204,\ Week\ 29}$, ng/mL	5	10.3	4.29	14	18.8	9.65	62	22.4	11.4	49	27.4	14.0
$C_{Day\ 288,\ Week\ 41}$, ng/mL	4	9.44	2.12	9	20.2	9.33	56	21.5	10.4	39	30.1	15.0
$C_{Day372\ ,\ Week\ 53}$, ng/mL	3	8.23	4.82	6	25.8	11.0	34	24.5	12.8	27	29.7	14.6
$C_{Day456\ ,\ Week\ 65}$, ng/mL	-	-	-	1	-	-	8	26.7	18.4	16	30.7	14.7
$C_{Day540\ ,\ Week\ 77}$, ng/mL	-	-	-	1	-	-	1	-	-	6	36.7	8.74

17-week transition phase: 150 mg eq. PP1M on Day 1, 100 mg eq. PP1M on Day 8, flexible dose on Day 36 and Day 64 (50, 75, 100, or 150 mg eq.), dose of Day 92 is the same as Day 64
12-week maintenance phase: single injection of a fixed dose of PP3M (175, 263, 350 or 525 mg eq.)
Double blind phase: injection of a fixed dose of PP3M (175, 263, 350 or 525 mg eq.) or placebo every 3 months
Source: Summary of clinical pharmacology

2.4.2.2 What is the inter- and intra-subject variability of the PK parameters in patients with the target disease

The estimated inter-subject variability (% CV) for $AUC_{0-\infty}$ and Cmax varied between 22.0% and 34.8%, and 49.1% and 99.2% respectively, for the different treatment groups after single dose im injection.

2.4.2.3 What are the characteristics of drug absorption?

Paliperidone exhibits flip-flop kinetics when administered as PP3M, i.e., the apparent half-life is driven by the absorption process. The median apparent half-life of PP3M after single doses of PP3M (75 to 525 mg eq.) in the single dose study ranged from 45 to 82 days. Simulations with the final population PK model estimated median paliperidone T ½ from the PP3M formulation to be in the range of 84 to 95 days following deltoid injections and 118 to 139 days following gluteal injections of 175 to 525 mg eq. PP3M.

2.4.2.4 What are the characteristics of drug distribution?

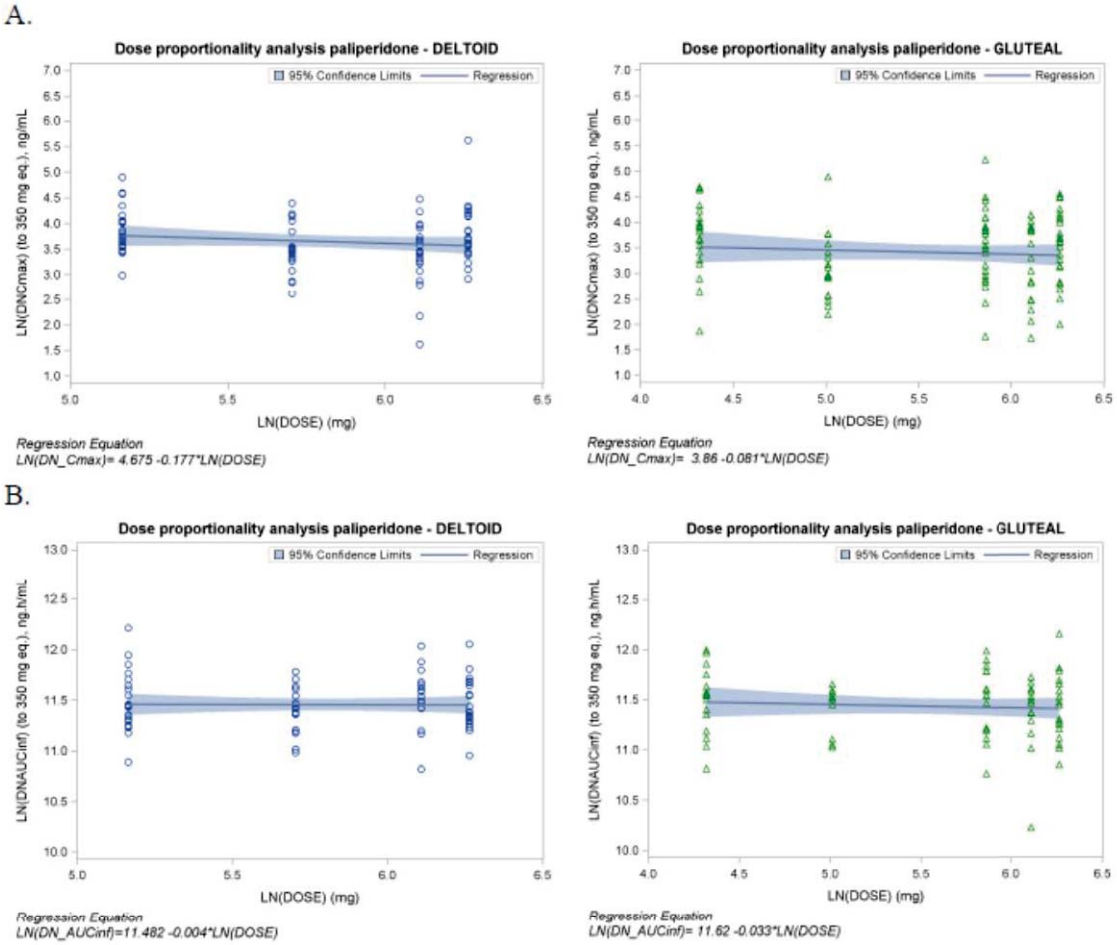
Population PK modeling analysis estimated an apparent volume of distribution of 1960L for paliperidone after administration of PP3M. No additional plasma protein binding studies. Based on the data obtained with the oral paliperidone ER formulation, the plasma protein binding of racemic paliperidone is 74%.

Reference ID: 3748068

2.4.2.5 Based on the PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Across the dose range of 75 to 525 mg eq. PP3M after single dose administration, paliperidone Cmax and AUC $_{0-\infty}$ increased proportionally with dose for both the deltoid and gluteal injections sites (Figure 6 and Table 14)

Figure 9: Linear Regression Model of Paliperidone Individual Dose Normalized Bioavailability Parameters Cmax (A) and AUC $_{0-\infty}$ (B) after Single Dose Administration of Paliperidone Palmitate in the Deltoid or the Gluteal Muscle.



DN: dose-normalized to 350 mg eq.
Source: Sponsor's summary of clinical pharmacology

Reference ID: 3748068

Table 14: Dose-Proportionality Analysis of Pharmacokinetic Parameters of Paliperidone After Single Dose IM Injection – Across Panel

Injection Site	Parameter	Slope	95% CI	p-value
Deltoid	C_{max} (ng/mL)	-0.177	(-0.437; 0.084)	0.1806
	AUC_{∞} (ng.h/mL)	-0.004	(-0.139; 0.130)	0.9481
Gluteal	C_{max} (ng/mL)	-0.081	(-0.291; 0.129)	0.4469
	AUC_{∞} (ng.h/mL)	-0.033	(-0.136; 0.069)	0.5171
Overall	C_{max} (ng/mL)	-0.064	(-0.222; 0.094)	0.4250
	AUC_{∞} (ng.h/mL)	-0.021	(-0.097; 0.055)	0.5839

Panel B and D, Period 2: i.m. injection with 175 mg eq., 300 mg eq., 450 mg eq. or 525 mg eq. paliperidone palmitate F015 injected in the deltoid or 75 mg eq., 150 mg eq., 350 mg eq., 450 mg eq. or 525 mg eq. in the gluteal muscle.

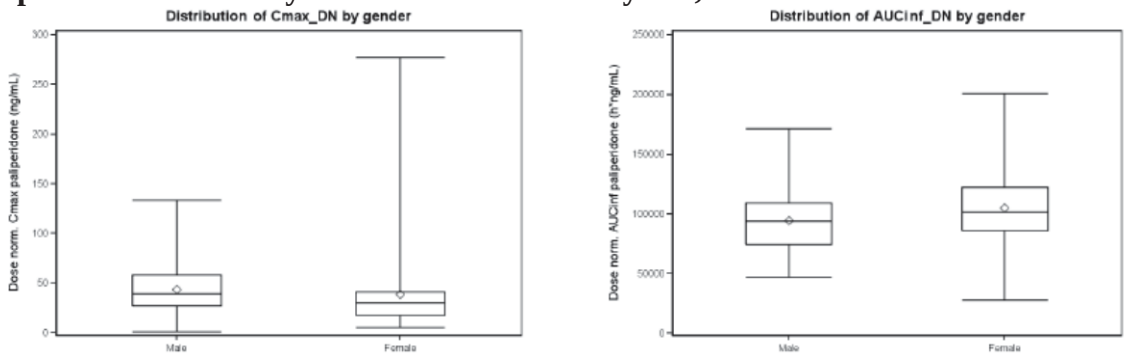
Source: Sponsor's clinical pharmacology

2.4.3 Intrinsic Factors

2.4.3.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in subjects and how much of the variability is explained by the identified covariates?

Based on simulations, sex, BMI, race, age, and liver function did not affect paliperidone exposure after administration of PP3M. Although small differences were predicted between injections sites, BMI category, and sex, they do not warrant any action. Differences in exposure were observed due to age, however, when adjusting for the declining renal function in subjects <60 years, these differences where no longer observed. After single dose administration of PP3M, no clinically relevant differences in exposure were observed based on sex, BMI and race.

Figure 10: Box-plots of Dose Normalized (to 350 mg eq.) Pharmacokinetic Parameters of Paliperidone from Study R092670-PSY-1005 - By Sex, BMI and Race - Across Panel



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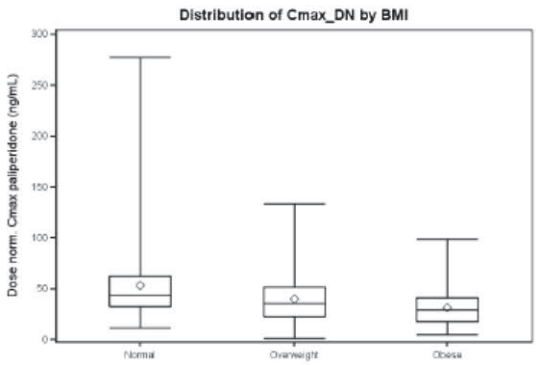
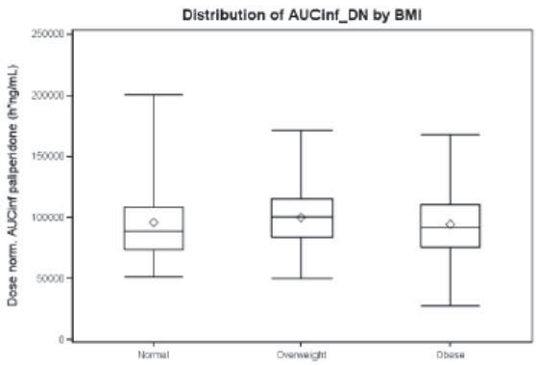
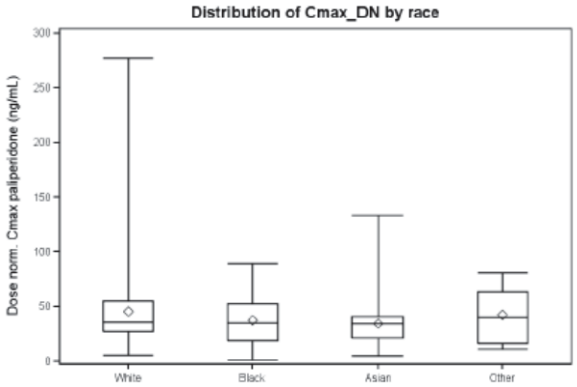
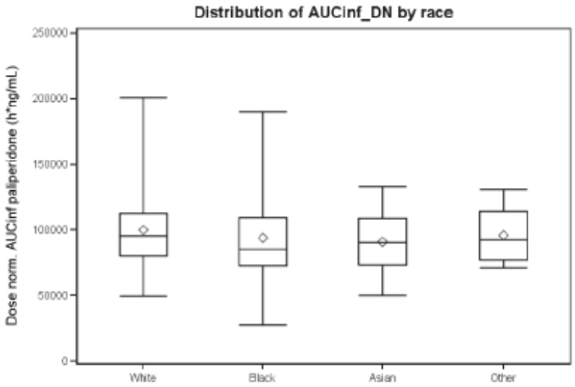




Normal < 25 kg/m^2, overweight 25 0 30 kg/m^2, obese > 30 kg/m^2





Boxes: 25th percent quartile, median, 75th percent quartile; Whiskers: min and max within 1.5xIQR; Diamond: arithmetic mean;

2.4.3.2 Renal Impairment

Patients with mild renal impairment are recommended a lower dose of paliperidone PP1M formulation. The PP3M dose should be based on the conversion factor of 3.5 (same as for subjects with normal renal function). (b) (4) Based on the pharmacometric review, the mean expected difference in Cmax at steady state between patients with mild renal impairment and patients with normal function is 16% and AUC is expected to be increased by 14% . The reviewers do not recommend any dose adjustments of PP3M in patients with mild renal impairment.

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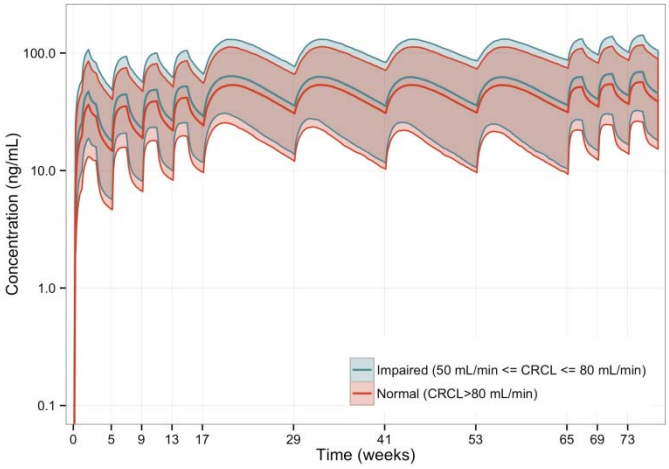
Figure 11: Influence of Renal Function on Paliperidone Exposure. The Full Line and the Shaded Areas Represent the Median, and the 90% Prediction Intervals



The Cmax after the fourth deltoid injection with 525 mg eq. of PP3M was 55.1 ng/mL in subjects with normal renal function and 64.1 ng/mL in subjects with mild renal impairment. Source: Figure A17-7, report: REP-1-JAN-PAL-PMX-1

The influence of age on paliperidone exposure is shown in Figures 12 and 13. The full line and the shaded areas represent the median, and the 90% prediction intervals. Patients greater than 60 years of age are presented by red color and patients less than 60 years of age are presented by blue color. The difference in pharmacokinetic profiles is small between the two age groups. Age is shown to have impact over exposure (top graph), however, this largely due to the correlation of age and creatinine clearance. Adjusting for creatinine clearance, age by itself has negligible effect on exposure (bottom).

Figure 12: Influence of Age on Exposure

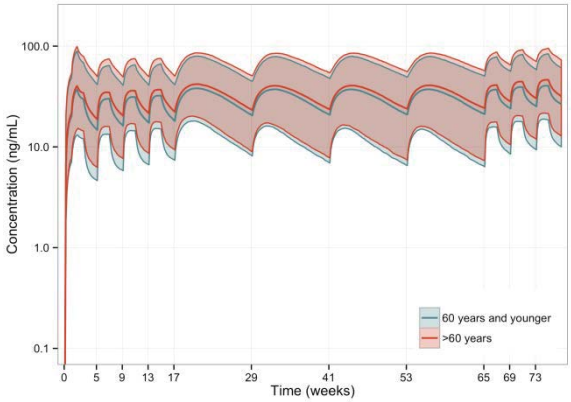


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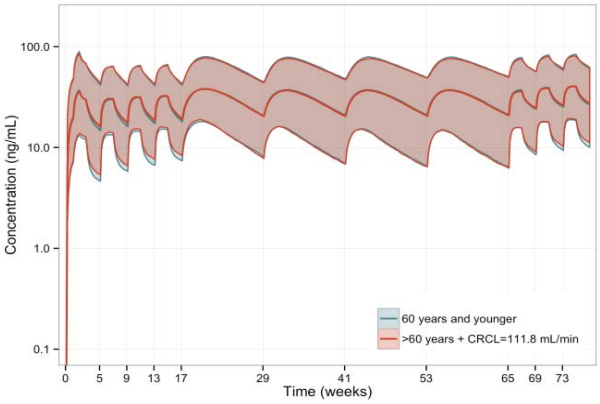
Figure 13: Influence of Age adjusted for CRCL



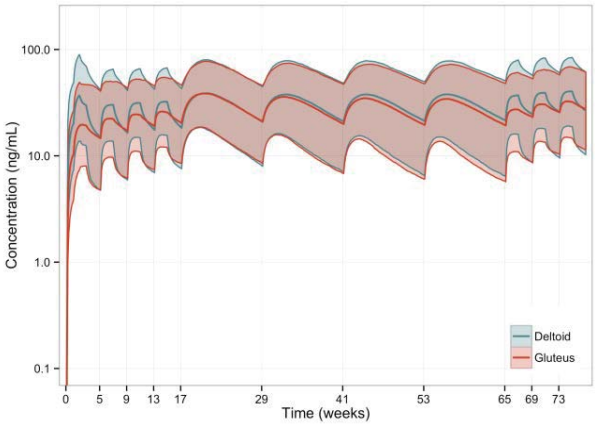
Note:
Source: Figure A17-10, and figureA17-11, report: REP-1-JAN-PAL-PMX-1

2.4.4 Extrinsic Factors

2.4.4.1 Is the exposure different after injection into the gluteal vs deltoid muscle?

Based on simulations, the PK of paliperidone when administrated as PP3M were not significantly different between injection sites. At steady-state, median paliperidone Cmax and Cmin were 11% to 12% higher after injection in the deltoid muscle compared with injection in the gluteal muscle.

Figure 14: Influence of Injection Site



Note: After the fourth 350 mg eq. PP3M dose, the expected median Cmin was 2.2 ng/mL lower after gluteal injections than after deltoid injections. Source:Figure A17-4, report: REP-1-JAN-PAL-PMX-1

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Evaluation of the single dose study also indicated that Cmax was higher after deltoid vs gluteal single dose injection but it is not expected to be clinically relevant.

Table 15: Effect of Injection Site on Dose-Normalized Pharmacokinetic Parameters of Paliperidone from Study R092670-PSY-1005- Across Panel

Parameter	LSmeans[a]		LSmeans ratio, %	90% CI, %[d]
	deltoid muscle (test)	gluteal muscle (reference)		
$C_{max, DN}$, ng/mL[a]	38.5	30.3	127.05	107.89 - 149.62
$AUC_{\infty, DN}$, ng.h/mL[b]	94,504	92,465	102.21	94.31 - 110.76
$F_{rel\ AUC\infty}$, %[c]	107.88	108.62	99.32	93.73 - 105.24

Panel B and D, Period 2: i.m. injection with 175 mg eq., 300 mg eq., 450 mg eq. or 525 mg eq. paliperidone palmitate F015 injected in the deltoid (test) or 75 mg eq., 150 mg eq., 350 mg eq., 450 mg eq. or 525 mg eq. in the gluteal muscle (reference).
DN: dose-normalized to 350 mg eq.
[a] n=107 for reference and N=91 for test
[b] n=73 for reference and N=78 for test
[c] n=68 for reference and N=71 for test
[d] 90% confidence intervals
Source: Sponsor's summary of clinical pharmacology

2.4.4.2 What are the drug-drug interactions?

No new drug-drug interactions were conducted for this application. Drug interaction studies that were conducted as part of the clinical pharmacology programs for oral paliperidone ER and PP1M are included in the proposed label. These studies investigated the effects of paroxetine (potent CYD2D6 inhibitor), carbamazepine (potent inducer of CYP-enzymes and Pgp), and trimethoprim (organic cation inhibitor) on the PK of oral paliperidone. Furthermore, the interactions between valproic acid and paliperidone ER were evaluated.

2.5 2.5 General Biopharmaceutics

2.5.1 How is the proposed to be marketed formulation linked to the clinical trial material?

The PP3M clinical trial material is the same as the proposed to be marketed formulation

2.5.2 How is PP3M related to the approved PP1M formulation?

The PP3M formulation uses the same mechanism for prolonged release as PP1M and contains the same drug substance and excipients. PP3M mainly differs in [redacted] (b) (4) as compared to the PP1M formulation. Based upon the relationships shown for PP1M, [redacted] (b) (4) The release characteristics and pharmacokinetics of PP3M are determined by [redacted] (b) (4) and the administered dose (injection volume).

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Table 15: The composition comparison of PP3M and PP1M are provided in the table below

Component	Function	Concentration (mg/ml)	
		F013	F015
[redacted]			
Paliperidone palmitate	Active drug substance	[redacted]	[redacted]
Polysorbate 20	[redacted]	[redacted]	10
Polyethylene glycol 4000			75
Citric acid monohydrate			7.5
Disodium hydrogen phosphate, anhydrous			[redacted]
Sodium dihydrogen phosphate Monohydrate			
Sodium Hydroxide			
Water for Injection			
[redacted]			

Source: Sponsor's Summary of Biopharmaceutics

2.5.3 What is the Relative Bioavailability of PP3M with an Immediate Release Paliperidone Suspension injection as Reference?

Comparison of paliperidone exposure after single IM injection of PP3M versus an IR paliperidone formulation showed relative bioavailability of PP3M, irrespective of dose and injection site, with mean estimates of Frel (based on dose normalized AUC∞) ranging from 99.6% to 112.3%

2.5.4 What is the evidence that the PP3M formulation in vivo consistently shows claimed extended release characteristics?

The PP3M formulation displays characteristics of sustained release by showing lower Cmax, longer Tmax, and longer T½ relative to the PP1M or IR injection following either single- or multiple-dose administration.

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2.6 Analytical Methods

2.6.1 What bioanalytical methods are used to assess concentrations of paliperidone and its enantiomers and is the validation complete and acceptable?

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays for the quantification of paliperidone and its enantiomers. The methods are validated and acceptable.

Table 17: Bioanalytical Methods

Method name	Paliperidone (Janssen R&D) BA192 (Mod5.3.1.4/BA192)	Paliperidone [redacted] (b) (4) BA10294 (PBRL-RD-1361/JJP549EL-115493-D) (Mod5.3.1.4/BA10294)	Paliperidone [redacted] (b) (4) JNJ-R857 (Mod5.3.1.4/JNJ-R857)
Matrix	Heparin plasma	Heparin plasma	Heparin plasma
Validated concentration range	0.1-250 ng/ml	0.1-100 ng/ml	0.1-250 ng/ml
Inter-run accuracy (%)	101.0-102.6	93.6-109.8	92.0-104.0
Inter-run precision (%CV)	3.4-4.4	2.1-4.9	3.8-6.7
Intra-run accuracy (%)	97.4-105.3	88.3-114.6	93.0-103.0
Intra-run precision (%CV)	≤ 7.1	≤ 5.3	≤ 3.6
Dilution integrity	100 x dilution (FK3447)	10 x dilution	100 x dilution
Incurred sample reproducibility	within criteria	Study (PSY3012): within criteria	Study (PSY1005): within criteria
Matrix effect in 2% hemolysed plasma (accuracy %)	not determined	91.9-102.5	not determined
Selectivity	within criteria	within criteria	within criteria
Stability in heparin blood	72 hours at 4°C 24 hours at room temperature 2 hours at 37°C (FK3447)	2 hours on melting ice 2 hours at room temperature	not determined
Stability in heparin plasma	4 freeze-thaw cycles 2 weeks at room temperature 4 weeks at 4°C 96 hours at 37°C 1816 days at -20°C (FK3447)	5 freeze-thaw cycles at -20°C and -70°C 96 hours at room temperature 96 hours at 4°C 96 hours at 37°C 482 days at -20°C * 661 days at -70°C	not determined
Processed sample stability	5 days at 4°C	121 hours at 10°C	96 hours at 4°C
Stability in methanol stock solution	6 months at -20°C 1 month at 4°C 3 days at room temperature	135 days at -20°C 24 hours at room temperature	not determined

CV=coefficient of variation

* The long term stability data for paliperidone in human heparin plasma at [redacted] (b) (4) met the acceptance criteria after storage at -20°C for 482 days. After 609 and 661 days however, the Long term stability failed to meet the criteria at -20°C but did meet the criteria at -70°C. Long term stability data from the laboratories of Janssen R&D are within criteria after storage for 1816 days at -20°C. The reason why the acceptance criteria were not met after more than 600 days at -20°C at [redacted] (b) (4) is currently under investigation. All study samples were analyzed within 482 days after receipt at [redacted] (b) (4) The entire storage period of the samples from sampling to analysis is covered by the long term stability data obtained at the laboratories of Janssen R&D.

Method name	Paliperidone palmitate (Janssen R&D) BA192 (Mod5.3.1.4/BA192)
Matrix	Heparin plasma
Validated concentration range	0.2-100 ng/ml
Inter-run accuracy (%)	94.1-100.0
Inter-run precision (%CV)	2.7-5.7
Intra-run accuracy (%)	91.2-106.5
Intra-run precision (%CV)	≤ 4.2
Incurred sample reproducibility	not determined **
Selectivity	within criteria
Stability in blood (FK3449)	4 hours at 4°C
Stability in plasma (FK3449)	4 freeze-thaw cycles 72 hours at room temperature 96 hours at room temperature followed by 3 freeze/thaw cycles at 37°C 96 hours at 37°C 777 days at -20°C 1477 days at -70°C
Processed sample stability	5 days at 4°C
Stability in methanol stock solution	6 months at -20°C 1 month at 4°C 3 days at room temperature

CV=coefficient of variation

** insufficient number of samples with concentrations above the LLOQ available

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Method name	S-paliperidone (b) (4) BA10290 (PBRL-RD-1365/JJP549EL-115493-F) (Mod5.3.1.4/BA10290)	R-paliperidone (b) (4) BA10290 (PBRL-RD-1365/JJP549EL-115493-F) (Mod5.3.1.4/BA10290)
Matrix	Heparin plasma	Heparin plasma
Validated concentration range	0.2-100 ng/ml	0.2-100 ng/ml
Inter-run accuracy (%)	98.2-101.5	98.3-105.4
Inter-run precision (%CV)	0.0-6.4	0.8-4.9
Intra-run accuracy (%)	94.0-106.9	96.9-110.3
Intra-run precision (%CV)	≤ 6.0	≤ 4.5
Dilution integrity	10 x dilution	10 x dilution
Incurred sample reproducibility	Study (PSY1005): within criteria	Study (PSY1005): within criteria
Selectivity	within criteria	within criteria
Matrix effect in 2% hemolysed plasma (accuracy %)	88.5-105.4	98.9-108.2
Stability in blood	1.5 hours on melting ice 2 hours at room temperature	1.5 hours on melting ice 2 hours at room temperature
Stability in plasma	5 freeze-thaw cycles at -20°C and -70°C 24 hours at room temperature 497 days at -20°C	5 freeze-thaw cycles at -20°C and -70°C 24 hours at room temperature 497 days at -20°C
Processed sample stability	69 hours at 10°C	69 hours at 10°C
Stability in methanol stock solution	135 days at -20°C 24 hours at room temperature	135 days at -20°C 24 hours at room temperature

CV=coefficient of variation

Source: Sponsor's Summary of Biopharmaceutics

2.7 Appendix

2.7.1 Pharmacometric Review

2.7.2 Individual Studies Review

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OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 207946
Submission Date	11/18/2014
Compound	paliperidone
Dosing regimen (route of administration)	175, 263, 350, or 525 mg eq. every 3 months, intra muscular injection
Indication	Schizophrenia
Clinical Division	Division of Psychiatry Products
Primary PM Reviewer	Dinko Rekić, MSc, Ph.D.
Secondary PM Reviewer	Kevin Krudys, Ph.D.

1 SUMMARY OF FINDINGS

The applicant has submitted results from a Phase 3 randomized double-blind placebo-controlled trial where patients who were stable on the approved paliperidone 1 month formulation (PP1M) where randomized to placebo or the novel paliperidone 3 month formulation (PP3M). The phase 3 trial, if deemed adequate, provides substantial evidence to support the claims of effectiveness. The submitted population PK analysis is used to support labeling claims in regards to dosage administration and in specific populations.

1.1 Key Review Questions

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

1.1.1 Is the proposed dosing regimen acceptable?

Yes. The paliperidone exposure following PP3M administration is similar to exposure following oral paliperidone treatment. It should be noted that paliperidone PP3M administration results in higher Cmax/Cmin ration compared to PP1M administration. The Cmax/Cmin ration can be reduced if PP3M is administered in the deltoid and not in the gluteal muscle. Paliperidone plasma concentration following PP3M or PP1M administration is shown in **Figure 1.**

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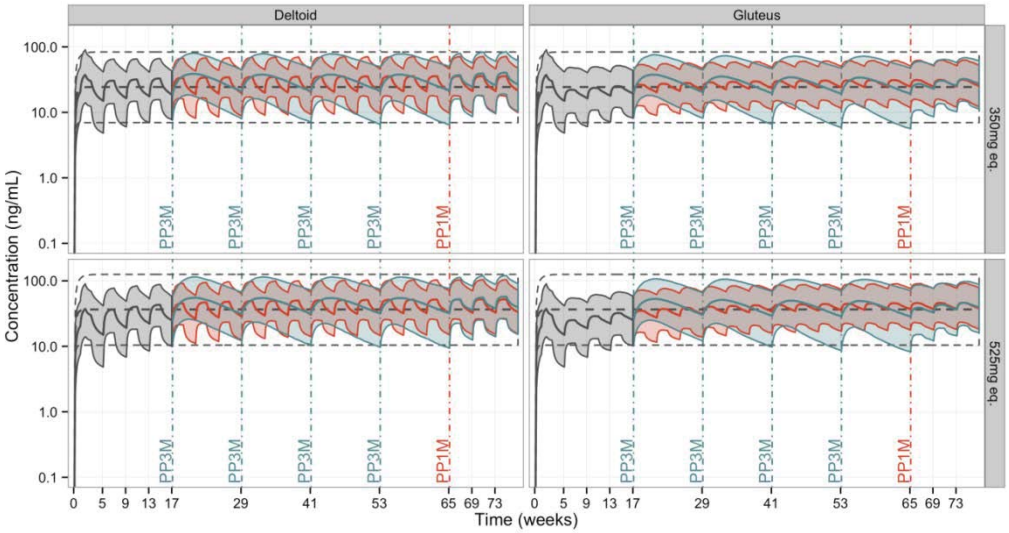
Figure 1 Paliperidone exposure following PP3M administration (teal areas), compared to paliperidone exposure following PP1M administration (red areas) and per oral treatment (dashed lines)



Note: The solid lines and shaded areas represent the median paliperidone concentrations and 90% prediction intervals. Black and grey colors represent the PP1M initiation phase, red and blue colors represent the PP1M and PP3M maintenance regimens, respectively, and the thick and thin dashed lines represent the median paliperidone concentrations and 90% prediction interval following treatment with ER.

Source: Figure 12, report REP-1-JAN-PAL-PMX-1

1.1.2 Is the applicant's proposal for dosing regimens outside of scheduled time point appropriate?

Yes. The applicant evaluated the influence of missed PP3M doses on paliperidone plasma concentration using simulations. The applicant's recommendations on how to reinitiate therapy were evaluated using the same approach. Briefly, applicant proposes that the product can be administered ± 2 weeks every 3 months while maintaining therapeutic concentrations. Patients that have missed a regular dose for up to 4 months should be reinitiated on the regular dosing regimen as soon as possible. Patients that have missed a regular dose for up to 9 months need to be reinitiated based on a predefined scheme where two doses (1 week apart) of PP1M are used to bring the patient to therapeutic concentrations before PP3M administration is resumed. Patients that have missed a regular dose for more than 9 months need to be reinitiated based on a predefined schedule where two doses (1 week apart) of PP1M are administered, followed by 3 additional PP1M injections (1 month apart). Results of applicant's simulations and a summary of their recommendations are discussed in detail in section **3.2.7**.

1.1.3 Is the applicant's proposal for switching from the PP3M formulation to oral extended release tablets appropriate?

Yes. The change in plasma concentration when converting from PP3M formulation to oral extended release tablets was evaluated using simulations. Briefly, paliperidone extended-release tablets should be started 3 months after the last PP3M dose and

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transitioned over the next several months following the last PP3M dose. Results of applicant's simulations and a summary of their recommendations are discussed in detail in section **3.2.8**.

1.1.3.1 Is applicants risk mitigation strategy [redacted] (b) (4) [redacted] appropriate?

[redacted] (b) (4) is not justified by the 16% expected increase in maximum concentrations at steady state.

Reference is made to **Figure 9,** where the impact of mild renal impairment on paliperidone exposure is illustrated. The impact of mild renal impairment on paliperidone exposure following ER tablets, PP1M, and PP3M is shown in **Table 1**. Due to the profound absorption rate limiting kinetics of intramuscular paliperidone administration (PP1M and PP3M), the influence of mild renal impairment decreases with decreasing absorption rate, (PP3M<PP1M<ER tablet).

Table 2 shows the highest administered dose to patients with mild renal impairment in the phase 3 trial. The most frequently administered dose in patients with mild renal impairment in the double blind phase was 350 mg eq PP3M (n=14). Six patients received the 525 mg eq. PP3M dose. The most frequently administered PP1M dose in the transition phase was 150 mg eq.

Based on the relative small difference in exposure between patients with mild renal impairment and normal renal function, as well as the experience of administration of doses higher than 350 mg eq., this reviewer does not recommend any adjustment to the dosing regimen of PP3M in patients with mild renal impairment.

Table 1. Impact of Mild Renal Impairment on Paliperidone Exposure

Formulation, Study, number of subjects	Cmax ratio Mild/Normal	Dosing recommendation Initiation, maintenance	
		Normal renal function	Mild renal impairment
ER Tablets (PO), REI-1001, n=11	1.63[a]	6 mg QD, (3-12 mg QD)	3 mg QD, (3-6 mg QD)
PP1M, (IM), R092670-PSY-3007, n=188	1.22[b]	175 mg on day 1 and 100 mg on day 8. Thereafter 25–150 mg	100 mg on day 1 and 75 mg on day 8. Thereafter 50 mg
PP3M (IM), R092670-PSY-3012, n=52	1.16[c]	3.5 fold of PP1M 175 mg - 525 mg	3.5 fold PP1M, 175 mg -350 mg

a) Table 100 from Clinical pharmacology review NDA21999, dated: November 30, 2005
b) Derived from Figure 25 population-PK-report, NDA22264
c) Figure A17-7, report: REP-1-JAN-PAL-PMX-1

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Table 2. Highest Dose Administered to Patients With Mild Renal Impairment in The Phase 3 Trial (R092670-PSY-3012)

Study part	Formulation	Highest Dose administered [mg eq]	Creatinine Clearance			n
			Median	Min	Max	
Transition phase	PP1M	75	69.5	na	na	1
Transition phase	PP1M	100	67.29	51.48	68.6	3
Transition phase	PP1M	**150**	72.50	41.35	79.3	36
Double blind phase	PP3M	175	66.66	41.35	75.6	3
Double blind phase	PP3M	263	69.51	67.33	79.3	3
Double blind phase	PP3M	**350**	67.52	51.48	79.3	14
Double blind phase	PP3M	525	75.31	69.2	77.4	6

1.1.3.2 Should the dose be adjusted due to patient´s CYP2D6 status?

No. The current label states that no discernible difference in paliperidone exposure exists between poor and extensive CYP2D6 metabolizers. The submitted population PK analysis did not investigate CYP2D6 as a covariate. Given the larger influence of slow absorption on paliperidone exposure (flip-flop PK) for the PP3M formulation compared to the PP1M formulation, there is no reason to believe that the influence of CYP2D6 status on paliperidone exposure will increase.

1.1.3.3 Should the dose be adjusted due to patient´s age, race, gender, or BMI?

No change in dosing regimen is needed due to injection site (deltoid versus gluteus), sex, BMI, race, age, and liver function test. Although small differences were predicted between injections sites, BMI category, and sex, they do not warrant any action. Differences in exposure where observed due to age, however, when adjusting for the declining renal function in subjects <60 years, these differences where no longer observed.

1.1.4 What is the impact of incomplete or failed PP3M administration on probability of treatment failure?

A catastrophic failure to administer the PP3M dose to a patient results in a 2.54 higher probability of treatment failure within the first 90 days after the failed administration, (HR: 2.54 , 95%CI: [1.2-5.4]). Catastrophic failure assumes that no drug is administered and that the patient was stable on the PP1M formulation before the failed PP3M administration. The hazard ratio is estimated by the cox proportional hazard model using the applicant’s data where all individuals with events after 90 days are right censored.

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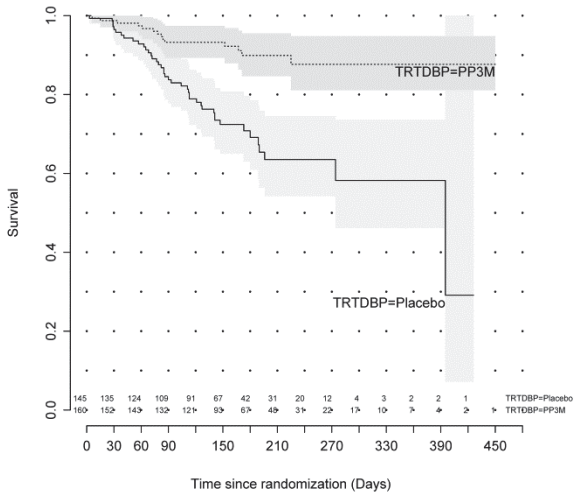
Patients receiving the PP3M paliperidone product prior to the catastrophic failure are expected to have a HR lower than 2.54 due to the longer half-life of PP3M compared to PP1M product. A Kaplan–Meier curve for the phase 3 trial is shown in **Figure 2.**

Figure 2. Survival Curve Illustrating Probability of Treatment Failure For The Placebo and The PP3M Group In The Phase 3 Trial



Source: *TTE.csv*

1.1.5 Are there any unexplained high concentrations observed in patients?

Yes. Patient number 9185 in the phase 1 trial was observed to have a maximum plasma concentration of 416 ng/mL approximately 24 hours after dose. This is 5.53-fold higher than the arithmetic mean of 75.19 ng/mL observed in the same dose group. Median time to Cmax was 576 hr (3.4 weeks). The applicant does not provide any explanation for this observation other than measurable paliperidone palmate (the ester prodrug) in this individual. Subsequent 3 observations in the same individual at 71, 119, and 215 hr after dose are also unusually high (243, 194, and 125 ng/mL). Due to several high observations within the same individual, this reviewer does not believe that an analytical error is responsible for the high concentrations. **Figure 3** shows the concentration time profile for all individuals in the two studies that were observed to have plasma concentrations above 125 mg/mL. Time is represented as time after last dose and not absolute time since first dose. The implications of this finding are not known. Please refer to the medical review for evaluation of safety in this patient and other patients with high plasma concentrations.

Individual 9198 in the Phase 1 trial was observed to have a maximum plasma observation of 223 ng/mL. This observation occurred at 81 weeks after the single dose administration. The observation immediate before this was below limit of quantification. At median Tmax for the 525 mg eq. dose group, this individual had a moderate Cmax of 28 ng/mL which is within above the 5th percentile in that dose group. Because of these reasons, this reviewer believes that an analytical error is responsible for this high observation.

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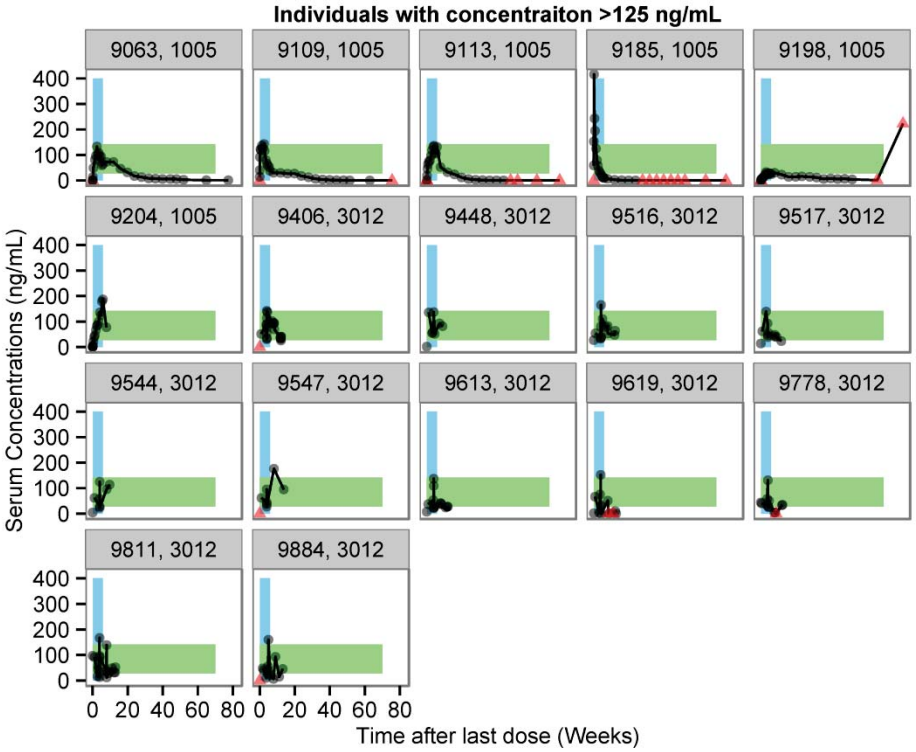
Besides these two individuals, concentrations above 125 ng/mL in the other 15 individuals are believed to be due to natural between subject variability in pharmacokinetics.

Figure 3. 17 Subjects with plasma concentrations > 125 ng/mL



Source: *dat-analysisdatafinal-csv.xpt*

Note: *Green areas represent the 95 and 5 percentile of Cmax in 525 mg dose group in the Phase 3 study (27.35-142 ng/mL).*
Blue areas represent the range of T_{max} in the 525 mg dose group of Phase 1 trial (2-41 days).
Red triangles are observations below limit of quantification or observations that were identified as outliers and excluded from the analysis. Please see discussion on data exclusion in the main body of the review.

1.2 Recommendations

Division of Pharmacometrics finds NDA 207946 acceptable from a Pharmacometrics perspective. (b) (4)

1.3 Label Statements

Section 2.5 Dosage adjustments

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TRADENAME has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min [Cockcroft-Gault Formula]), [redacted] (b) (4) *[See Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*

2 PERTINENT REGULATORY BACKGROUND

Paliperidone received U.S. FDA marketing approval in December 2006 (NDA 21999) for acute treatment of schizophrenia and in April 2007 for maintenance treatment of schizophrenia. Currently there are two approved paliperidone and paliperidone palmitate formulations, paliperidone extended release (ER) tablets (INVEGA®) and paliperidone 1 month long acting injection formulation (LAI).The 1 month LAI is referred to as the PP1M formulation or product in the review.

This submission is intended to support approval of a 3 months LAI formulation (PP3M) for treatment of schizophrenia in adults who have been adequately treated with PP1M for at least 4 months. The 3 month injection regimen is not currently available for any other antipsychotic agent. The increased dosing interval is expected to result in favorable treatment outcomes in patients that are likely to be non-adherent. The applicant has been granted priority review on that basis.

Dosing regimens paliperidone ER, PP1M and the proposed PP3M formulation are shown in **Table 3.** Milligram equivalent (mg eg.) refers to the paliperidone palmitate prodrug dose that is equivalent to the paliperidone dose when administered as an extended release (ER) tablet in its active form.

Table 3. Conversion of doses for ER, PP1M, PP3M formulations of paliperidone and paliperidone palmitate

Invega ER	Invega Sustenna PP1M	Invega Trinza PP3M
3 mg →	39 mg (25 mg eq) to 78 mg (50 mg eq)	78 mg PP1M→273 mg (175 mg eq)
6 mg →	117 mg (75 mg eq) →	410 mg (263 mg eq)
9 mg	156 mg (100 mg eq) →	546 mg (350 mg eq)
12 mg →	234 mg (150 mg eq) →	819 mg (525 mg eq)

3 RESULTS OF SPONSOR'S ANALYSIS

The applicant has submitted a population PK report (REP-1-JAN-PAL-PMX-1), prepared by the applicant's consultant [redacted] (b) (4) The report describes a population PK analysis of data obtained from a Phase 1 study (Study R092670-PSY-1005) and a Phase 3 study (Study R092670-PSY-3012). The two studies will be referred to as the Phase 1 and

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the Phase 3 study, while the 1 and the 3 month formulation will be referred to as the PP1M and PP3M formulation from this point forward.

The main objective of the population PK analysis was to characterize the pharmacokinetics of PP3M and to propose dosing strategies for missed doses, transitions from PP1M to PP3M, transition from PP3M to PP1M and transition from PP3M to extended release oral tablets.

Data supporting the model, the model itself, the results, and conclusions from the applicants simulation's based on the model are reviewed in sections **3.1** and **3.2.**

3.1 Summary of the Population PK Analysis (Study Report: REP-1-JAN-PAL-PMX-1)

The applicant's model is based on data from a Phase 1 study and a Phase 3 study. The studies are briefly summarized below:

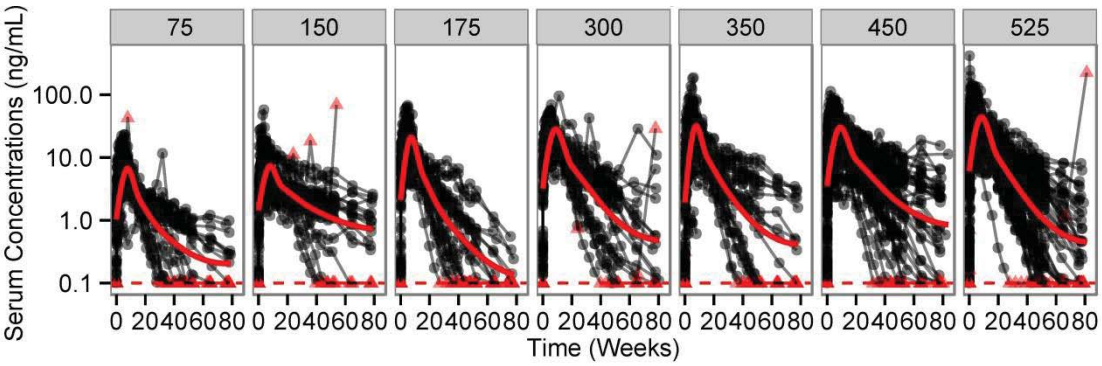
3.1.1 Phase 1 study (R092670PSY1005)

R092670PSY1005 was a two-period, single-dose, parallel-group study in patients with schizophrenia. All subject received an intra-muscular (IM) injection of an immediate release (IR) paliperidone formulation in the first period. In period 2, patients received IM of PP3M formulations with two different suspension strengths (200 mg eq/mL or 100 mg eq/mL) manufactured by wet or dry milling techniques. Panels and period are shown in **Table 4.** The average patient was a 42 year old white male, with normal renal function with a body weight of 78 kg and a BMI of 27 (kg/m^2). Baseline categorical and continuous covariates are tabulated in **Table 9** and **Table 10.**

Inadequate shaking of the syringe prior to administration resulted in incomplete injection in some subjects in panels A and C. These panels were not included in the population PK analysis. In total, 5290 pharmacokinetic samples from 217 subjects contributed to the final model. Twenty-nine plasma samples per patients were planned. The last sample was planned to be collected 18 months after administration. Concentration-time profiles stratified by dose are shown in **Figure 4**.The applicant identified 13 samples as outliers based on estimated conditional weighted residual (CWRES) value of >5. One sample was identified as an outlier by graphical inspection. Samples that were below lower limit of quantification (LOQ: 0.1 ng/mL) were excluded from the analysis (n=547). The samples excluded from the analysis are shown as orange triangles in **Figure 4**. A complete list of exclusion reasons is shown in **Table 5** and **Table 6.**

Reference ID: 3748068

Figure 4. Paliperidone plasma concentrations versus time. Phase 1 study (R092670-PSY-1005)



Note: Solid red line is a non-parametric smoother (loess), Dashed red line is the LOQ (0.1 ng/mL). Orange triangles are observations excluded from the analysis.

Source: dat-analysisdatafinal-csv.xpt

Table 4. Treatment panels and periods of the Phase 1 study (R092670PSY1005)

	Panel			
	A	**B[a]**	**C**	**D[a]**
Period 1	1 mg paliperidone IR solution in the gluteal muscle n=72	1 mg paliperidone IR solution in the deltoid or gluteal muscle. n=128	1 mg paliperidone IR solution in the gluteal muscle n=25	1 mg paliperidone IR solution in the deltoid or gluteal muscle. n=100
Period 2	PP3M, 200 mg (gluteal), n=66, 200 mg eq./mL, wet /dry milling technique	PP3M, 75 mg (gluteal), n=23 150 mg (gluteal), n=25 450 mg (gluteal), n=22 300 mg (deltoid), n=25 450 mg (deltoid), n=25 200 mg eq./mL, wet milling technique	PP3M, 150 mg (gluteal), n=24 100 mg eq./mL, wet milling technique	PP3M, 175 mg (deltoid), n=25 525 mg (deltoid), n=24 350 mg (gluteal), n=24 525 mg (gluteal), n=25 200 mg eq./mL, wet milling technique

Note: [a] Pharmacokinetic data from panels B and D (period 2) were used to support the population PK model. Panels A and C were compromised due to incomplete injection in some subjects as a result of insufficient shaking of the syringe prior to the injection.

Source: R092670PSY1005 Study synopsis page 7.

Reference ID: 3748068

Table 5. Excluded PK samples and dosing records

Study/Type	OCC	Exclusion reason 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	# Excl[a]
Study R092670-PSY-1005																		
PK sample	1	547	0	0	0	218	49	0	3	0	1	0	0	0	0	0	0	642
Dose record	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
All	All	547	0	0	0	218	49	0	3	0	1	0	0	0	0	0	0	642
Study R092670-PSY-3012																		
Transition phase (PP1M)																		
PK sample	0	154	5	0	0	504	281	13	14	1	0	126	0	0	0	0	76	510
PK sample	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	2	2
PK sample	2	1	1	0	0	0	0	0	1	1	0	16	0	0	4	0	16	23
PK sample	3	6	3	0	0	0	0	0	5	0	0	95	0	0	1	0	31	103
PK sample	4	5	2	0	0	0	0	0	6	3	0	124	0	0	2	1	36	136
PK sample	5	14	8	0	0	0	0	0	3	2	0	164	0	1	0	1	25	181
Dose record	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	41	41
Dose record	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	39	39
Dose record	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	32	32
Dose record	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	24	24
Dose record	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14	14
All	All	181	20	0	0	504	281	13	29	7	0	526	0	1	7	2	336	1105
Maintenance and double-blind phase (PP3M)																		
PK sample	5	0	0	0	0	0	0	0	1	3	0	53	0	0	1	0	17	58
PK sample	6	23	14	0	0	0	0	0	2	3	0	273	0	3	4	1	36	298
PK sample	7	25	8	0	0	0	0	0	1	3	0	137	0	1	5	2	26	168
PK sample	8	25	10	0	0	0	0	0	1	0	0	58	0	1	4	0	12	87
PK sample	9	29	16	0	0	0	0	0	0	0	0	20	0	0	0	0	3	49
PK sample	10	5	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	7
PK sample	11	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6
PK sample	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dose record	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	6
Dose record	6	0	0	0	0	0	0	0	0	0	0	0	20	0	0	0	14	34
Dose record	7	0	0	0	0	0	0	0	0	0	0	0	138	0	0	0	9	146
Dose record	8	0	0	0	0	0	0	0	0	0	0	0	101	0	0	0	4	104
Dose record	9	0	0	0	0	0	0	0	0	0	0	0	39	0	0	0	1	40
Dose record	10	0	0	0	0	0	0	0	0	0	0	0	12	0	0	0	0	12
Dose record	11	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	2
Dose record	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
All	All	113	48	0	0	0	0	0	5	9	0	543	312	5	14	3	128	1017
All studies																		
All types	All	841	68	0	0	722	330	13	37	16	1	1069	312	6	21	5	464	2764
PK sample	All	841	68	0	0	722	330	13	37	16	1	1069	0	6	21	5	280	2270
Dose record	All	0	0	0	0	0	0	0	0	0	0	0	312	0	0	0	184	494

Note: The absorption sub-model required the data files to have 2 dose records at the time of each actual dose, and therefore the source data files contained 2 dose records per administration of PP1M and PP3M. The actual number of doses (and not dose records) meeting the exclusion criteria are presented in this table.

[a] Total number of excluded records. More than one exclusion reason possible for each record

OCC: occasion number; PK: pharmacokinetic; PP1M: paliperidone palmitate 1-month formulation; PP3M: paliperidone palmitate 3-month formulation

Source: Population PK report (REP-1-JAN-PAL-PMX-1), Appendix 2, Table A2-2

Table 6. Reasons for exclusions from the population PK analysis

Reason #	Reason for data exclusion
1	BLQ or not done
2	Date/time missing
3	Previous dose time imputed
4	AMT=0 (Study R092670-PSY-1005) or if the dose was missed (Study R092670-PSY-3012)
5	Pre-treatment
6	Pre-dose concentration >3 ng/mL
7	PK sample in the first 7 weeks after CO3 injection
8	Sample taken during intake of CO1 or CO2
9	Sample taken after intake of CO4
10	No available dosing
11	Risperidone detected in PK sample
12	AMT=0
13	EOS sample after intake CO2
14	EOS sample after intake CO1
15	EOS sample after injection CO4
16	No valid PK samples

AMT: dose amount (NONMEM data item); BLQ: below limit of quantification; CO1: oral risperidone; CO2: oral paliperidone; CO3: intramuscular risperidone; CO4: intramuscular paliperidone palmitate; EOS: end of study; PK: pharmacokinetic

Source: Population PK report (REP-1-JAN-PAL-PMX-1), Table 1.

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3.1.2 Phase 3 study (R092670-PSY-3012)

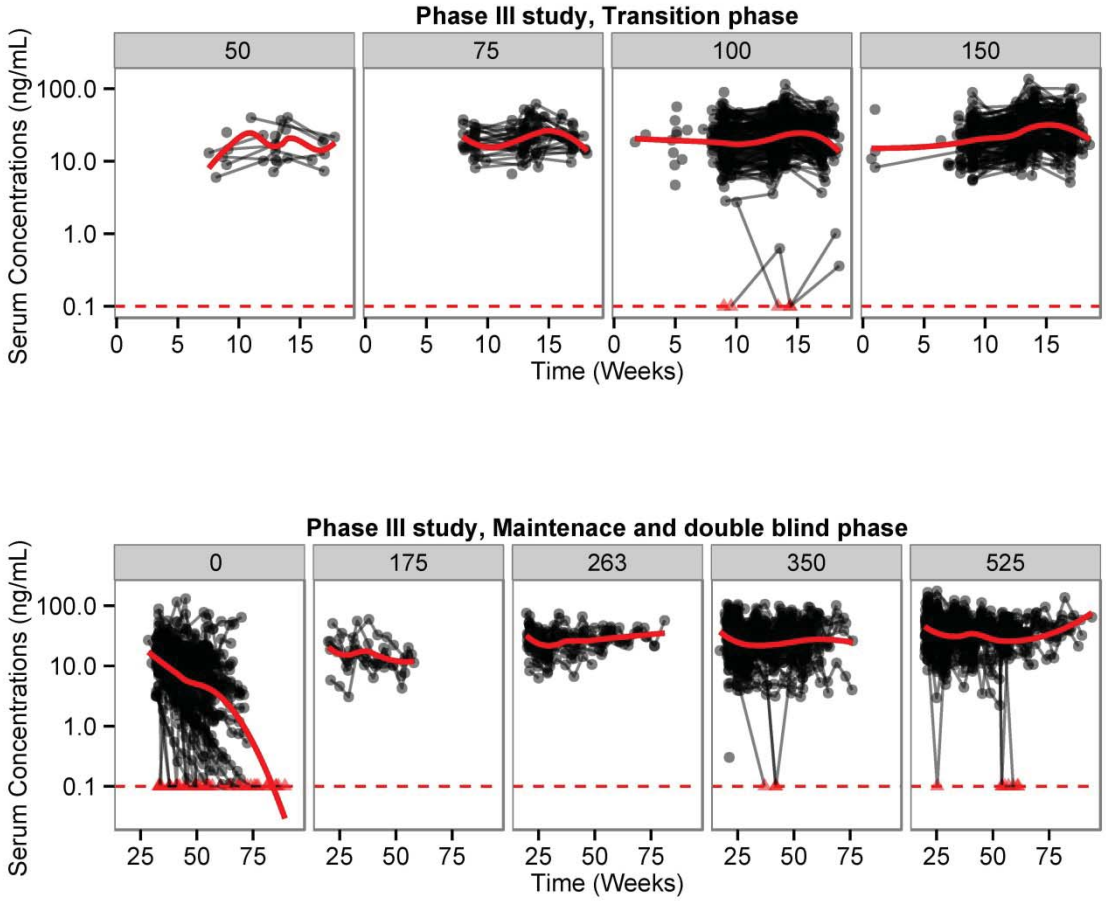
R092670-PSY-3012 was a randomized, double-blind, parallel group, placebo-controlled, multicenter study designed to determine the efficacy and safety of PP3M in adults 18 to 70 years of age with schizophrenia. Patients meeting entry criteria, who were stable (with safety or tolerability problems) with their current medications or were in a state of acute exacerbation were enrolled in a 3 week screening phase. Following washout of non-permitted medications or tolerability test of oral paliperidone patients were rolled over to the transition phase where they received PP1M injections according to the label (n=506). Flexible PP1M dosing (50, 75, 100, 150 mg) was allowed on days 36 and 64 of the transition phase. Patients were switched to a PP3M dose equivalent to 3.5-fold the PP1M dose at the start of the maintenance phase (n=379). At the start of the double-blind phase, patients were randomly (1:1) assigned a fixed dose of PP3M (n=160) or placebo (n=145). The fixed dose was the same as the dose on day 120 of the maintenance phase. The length of the double-blind phase varied for each patient. The dosing administration and PK sampling schedule are shown in **Table 7** and **Table 8**.

In total, 3700 pharmacokinetic samples from 434 subjects contributed to the final model. Concentration-time profiles stratified by dose are shown in **Figure 5**. Samples that were below lower limit of quantification (LOQ: 0.1 ng/mL) were excluded from the analysis (n=294). Samples where risperidone was detected were also excluded (n=1069). A complete list of exclusion reasons is shown in **Table 5** and **Table 6**.

The average patient was a 37 year-old white male, with normal renal function with a body weight of 77 kg and a BMI of 25.5 (kg/m^2). Baseline categorical and continuous covariates are tabulated in **Table 9** and **Table 10**.

Reference ID: 3748068

Figure 5. Paliperidone plasma concentrations versus time. Phase 3 study (R092670-PSY-3012)



Note: Solid red line is a non-parametric smoother (loess), Dashed red line is the LOQ (0.1 ng/mL).
Orange triangles are observations excluded from the analysis.
All patients received PP1M during the transitions phase
All patients received PP3M during the maintenance and

Source: dat-analysisdatafinal-csv.xpt

Reference ID: 3748068

Table 7. Dosing administrations for the phase 3 study

	Transition Phase					Maintenance Phase			Double-blind Phase			
Visit	2	3	4	5	6	8	9	10	11	12	13	Every 12 weeks
Day	1[a]	8[a]	36	64	92	120	148	176	204	232	260	
PP1M Dose	150 mg eq.	100 mg eq.	50-150 mg eq.	50-150 mg eq.	50-150 mg eq.	--	--	--	--	--	--	--
Muscle	D	D	D or G	D or G	D or G	D or G			D or G			D or G
Flexible or Fixed	Fixed	Fixed	Flexible	Flexible	Fixed [b]	Fixed [c]	--	--	Fixed [c]	--	--	Fixed [c]
PP3M/ Placebo Dose	--	--	--	--	--	X	--	--	X	--	--	X

D=deltoid muscle; G=gluteal muscle; PP1M=paliperidone palmitate 1 month formulation; PP3M=paliperidone palmitate 3 month formulation

[a] For subjects who are stable on PP1M, will have their last dose on Day -21and their first study dose on Day 8, which is the same dose as their last PP1M injection (50, 75, 100, or 150 mg eq. D/G). For subjects who are stable on other LAIs will have their last dose on Day -21, Day -14, Day -7 or Day 1 for 4-weekly, 3-weekly, 2-weekly or once a week regimens respectively and their first dose of 150 mg eq. PP1M on Day 8. For subjects who are stable on Risperdal Consta (2-weekly regimen) will have their last dose on Day -7 and their first dose of 50, 75, 100 mg eq. PP1M corresponding to 25, 37.5 and 50 mg of Risperdal Consta respectively on Day 8.

[b] Dose on this visit should be the same as given on Visit 5 (Day 64)

[c] The dose of PP3M given will be a 3.5-fold multiple of the PP1M dose given on Visit 6 (Day 92)

Source: Clinical Pharmacokinetic Report R092670PSY3012 version 2, page 9.

Table 8. PK sampling schedule for the phase 3 study

Period	**Screening**	**Transition**						**Maintenance**			**Double-Blind**									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	Visits every 4 weeks[a]	Visits every 8 weeks[a]	Visits every 12 weeks[a]	Week 54 PK	Week 55 PK	EOS/ Early WD Visit
Week	-3 to -1		1	5	9	13	14	17	21	25	29	33	37	41						
Day	-21 to -1	1	8	36	64	92	99	120	148	176	204	232	260	288						
Window (days)		NA	± 3	± 7	± 7	± 7	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	NA
Study drug administration																				
Administer study medication		X[b]	X	X	X	X		X			X			X			X			
Pharmacokinetic Procedures																				
PK Sample collection [c]		X			X	X	X	X	X	X	X	X	X	X	X			X[d]	X[d]	X

[a] After Visit 14 (Week 41), visits will take place every 4 weeks. Assessments listed for every 12 weeks will be performed at Week 41, Week 53, Week 65, etc. Assessments listed for every 8 weeks will be performed at Week 37, Week 45, Week 53, Week 61, etc. The assessments in these columns will be performed mutually inclusive of each other.

[b] Day 1 injection of PP1M does not apply to subjects who are being switched from another depot antipsychotic (including Risperdal CONSTA), or stable subjects who are continuing on current treatment with PP1M at enrollment.

[c] Venous samples of 4 mL should be obtained prior to dose administration on each PK day. Unscheduled PK samples may be obtained at the Investigator's discretion for cases of severe or serious adverse events that may be potentially related to unexpected increases in plasma concentrations of study drug.

[d] PK samples should be obtained 10 days (Week 54) and 20 days (Week 55) after study drug injection at Week 53.

Source: Clinical Pharmacokinetic Report R092670PSY3012 version 2, page 10.

Reference ID: 3748068

Table 9. Baseline categorical covariate statistics in the analysis data set

	Study R092670-PSY-1005 N = 217	Study R092670-PSY-3012 N = 434	Combined N = 651
Sex			
Men	63% (137)	75% (326)	71% (463)
Women	37% (80)	25% (108)	29% (188)
Renal function			
Severe renal impairment	0% (0)	0% (0)	0% (0)
Moderate renal impairment	0% (0)	0% (1)	0% (1)
Mild renal impairment	10% (22)	7% (32)	8% (54)
Normal renal function	90% (195)	92% (401)	92% (596)
Race			
White, not Hispanic or Latino	59% (127)	56% (241)	57% (368)
Black	12% (27)	20% (87)	18% (114)
White, Hispanic or Latino	5% (10)	6% (26)	6% (36)
Asian	20% (43)	7% (31)	11% (74)
Native Hawaiian or Pacific	0% (0)	0% (1)	0% (1)
American Indian	0% (0)	0% (0)	0% (0)
Other	5% (10)	11% (48)	9% (58)
Region			
Europe	53% (115)	49% (211)	50% (326)
America	15% (33)	41% (177)	32% (210)
Asia	26% (57)	11% (46)	16% (103)
Africa	6% (12)	0% (0)	2% (12)
Other	0% (0)	0% (0)	0% (0)
Country			
Colombia	0% (0)	7% (31)	5% (31)
Korea	6% (12)	2% (9)	3% (21)
Malaysia	8% (17)	5% (22)	6% (39)
Mexico	0% (0)	6% (26)	4% (26)
Romania	0% (0)	9% (39)	6% (39)
Turkey	0% (0)	3% (15)	2% (15)
Ukraine	0% (0)	40% (172)	26% (172)
USA	15% (33)	28% (120)	24% (153)
Belgium	4% (9)	0% (0)	1% (9)
Bulgaria	12% (27)	0% (0)	4% (27)
Croatia	9% (19)	0% (0)	3% (19)
Israel	7% (16)	0% (0)	2% (16)
Slovakia	17% (36)	0% (0)	6% (36)
South Africa	6% (12)	0% (0)	2% (12)
Spain	11% (24)	0% (0)	4% (24)
Taiwan	6% (12)	0% (0)	2% (12)

Note: Numbers are presented as percentages (number of subjects with that observation)

Source: Population PK report (REP-1-JAN-PAL-PMX-1), Appendix 7, table A7-1

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Table 10. Baseline continuous covariate statistics in the analysis data set

	Study R092670-PSY-1005 N = 217	Study R092670-PSY-3012 N = 434	Combined N = 651
Age (years)	21.0 **42.0** 63.0 (41.8± 9.8)	18.0 **37.0** 67.0 (38.1±11.1)	18.0 **38.0** 67.0 (39.3±10.8)
Body weight (kg)	50 **78** 122 (78± 15)	44 **77** 140 (79± 17)	44 **78** 140 (79± 16)
Height (cm)	145.0 **170.0** 191.5 (169.3± 8.9)	145.0 **173.0** 205.0 (172.6± 9.3)	145.0 **172.0** 205.0 (171.5± 9.3)
Serum creatinine (umol/L)	43 **78** 127 (79± 16)	49 **80** 203 (82± 17)	43 **80** 203 (81± 17)
Creatinine clearance (mL/min)	51 **115** 215 (117± 30)	41 **115** 226 (119± 30)	41 **115** 226 (118± 30)
Lean body mass (kg)	36.1 **55.9** 80.0 (55.8± 9.0)	33.6 **57.6** 85.9 (57.7± 9.6)	33.6 **57.2** 85.9 (57.1± 9.4)
Body mass index (kg/m^2)	18.3 **27.0** 37.0 (27.2± 4.2)	17.1 **25.5** 39.8 (26.4± 4.8)	17.1 **26.1** 39.8 (26.7± 4.6)
Body surface area (m^2)	1.44 **1.93** 2.56 (1.93±0.22)	1.33 **1.94** 2.78 (1.95±0.24)	1.33 **1.94** 2.78 (1.94±0.23)
Albumin (U/L)	34.0 **41.0** 51.0 (41.6± 3.4)	31.0 **42.0** 56.0 (42.4± 3.7)	31.0 **42.0** 56.0 (42.1± 3.6)
Alanine aminotransferase (U/L)	5 **20** 134 (25± 16)	6 **21** 145 (27± 18)	5 **21** 145 (26± 17)
Asparate aminotransferase (U/L)	8.0 **20.0** 57.0 (21.3± 7.2)	9.0 **21.0** 243.0 (23.9± 15.3)	8.0 **20.0** 243.0 (23.0± 13.2)
Alkaline phosphatase (U/L)	37 **71** 184 (75± 22)	31 **72** 225 (77± 25)	31 **71** 225 (76± 24)
Total bilirubin[a](umol/L)	1.5 **5.0** 28.0 (6.3± 3.8)	1.5 **7.0** 51.0 (8.5± 5.4)	1.5 **6.8** 51.0 (7.8± 5.0)
Total protein (g/L)	58.0 **71.0** 84.0 (71.4± 4.7)	57.0 **74.0** 89.0 (73.6± 5.0)	57.0 **73.0** 89.0 (72.9± 5.0)
Gamma glutamyl transferase (U/L)	7 **22** 214 (29± 28)	6 **20** 153 (27± 22)	6 **20** 214 (28± 24)
Lactate dehydrogenase (U/L)	67 **156** 291 (158± 29)	66 **156** 933 (160± 50)	66 **156** 933 (160± 44)

Numbers represent minimum, **median**, maximum, (mean±SD)
The median age for subjects with mild or moderate renal impairment was 52 years.
[a] TB observations below LOQ were assigned a value of the LOQ/2=1.5 µmol/L.
LOQ: limit of quantification; SD: standard deviation; TB: total bilirubin

Source: Population PK report (REP-1-JAN-PAL-PMX-1), Appendix 7, table A7-2

3.2 Summary of the applicant's population PK model

3.2.1 PP1M model

The applicant has previously developed a population PK model for the PP1M formulation. The PP1M model was able to describe concentration following PP1M administration in the transition phase of the phase 3 study when model parameters were assigned priors based on 10% uncertainty. The prediction corrected visual predictive checks (PcVPC) indicated adequate model performance when fitted to the Phase 3 transition phase data [1].

The structural components of the model included one central compartment with linear elimination. Absorption is modeled as two parallel processes; one zero order process and one first order with lag-time. The PP1M model was previously submitted, and previous review of the model is available in the pharmacometric review by Drs. Hao Zhu and Yaning Wang(Feb 9, 2009).

3.2.2 PP3M model (base model)

The PP3M formulation has a considerably slower absorption profile than the PP1M formulation. Attempts to fit the PP1M model to PP3M data resulted in inadequate model performance as indicated by the PcVPCs in the applicant's report. The applicant derived several absorption sub models that would account for the slower absorption profile of PP3M. The final absorption sub model described the absorption as two parallel saturable processes; one fast and one slow. The processes were parameterized using the hill function, the slow absorption process included a hill coefficient that was greater than 1 (1.44). The PP3M model retained the 1 compartment structure with linear elimination that was used for the PP1M model. However, because of the more profound absorption

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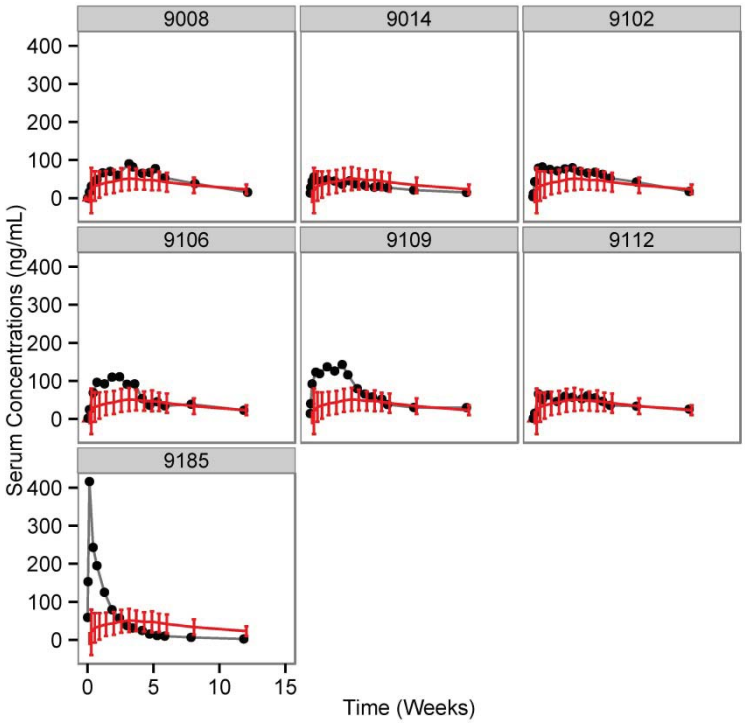
rate-limiting pharmacokinetics of PP3M formulation, CL and V were estimated at somewhat different values.

The PP3M model was developed based on the rich data from the phase I study. Modeling the phase I data and relative sparse data from the phase 3 study simultaneously resulted in an increase in V and F3 leading to under prediction of C_{max}. The applicant chose to fix some parameters (V, F3, BMI-V covariate relationship) to estimates obtained from the fit of the phase I data.

Seven subjects had measurable paliperidone palmitate (the ester prodrug) in plasma. A high Cmax was observed for these 7 subjects and a separate V parameter ($V_{Palmitate}$=156 L vs V=1969 L) was fixed after attempts to estimate this parameter resulted in rounding errors but a significant drop in OFV. Concentration time profiles for the seven subjects are shown in **Figure 6**.

Figure 6. Individual Paliperidone plasma concentrations versus time in the 7 subjects with detectible Paliperidone Palmitate concentrations. Phase 1 study, dose 525 mg.



Note: The black lines are the individual paliperidone concentrations in the seven subjects with detectible paliperidone Palmitate concentrations. The red line and error bars are the mean ± SD concentration for all patients in the Phase 1 study that received the 525 mg dose. The x-axis has been truncated to 15 weeks.

Source: dat-analysisdatafinal-csv.xpt

Reviewer's comment: It appears that the concentration time profile is higher in those individuals compared to the average profile in that dose group. One individual (ID=9185) has especially high concentrations reaching 400 ng/mL, more than 4-fold the average Cmax in that dose group.

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Applicant's base model included the following covariate relationships: creatinine clearance (CRCL) and clearance (CL), body mass index (BMI) and volume of distribution (V), injection volume (IVOL) and absorption rate parameters.

3.2.3 PP3M model (final covariate model)

The applicant initiated a stepwise covariate analysis with these pre-specified covariates and parameters relationships:

- CL and age, alanine aminotransferase(ALT), BMI, sex, race, total bilirubin (TB)
- V and age, sex, race
- Absorption parameters and age, BMI, injection site (INJS), needle length, race, sex

Relationships between continuous covariates and parameters were parameterized as centered power models. Relationships between categorical covariates and parameters were parameterized as fractional difference to the most common category. The total effect of multiple covariates on a parameter was parameterized as the product of the covariate terms. The applicant utilized the stepwise covariate model building procedure (SCM)[2]in Perl-speaks-NONMEM (PsN) . The relatively long runtimes required use of the linearized FOCE based approximation of the covariate parameter relationships[3]. Criteria for forward inclusion and backward deletion were set at p-values 0.01 and 0.001, respectively. Two covariate relationships were excluded from the final model despite passing the predefined statistical criteria. These were: sex-CL (excluded due to failed covariance step), and age-F_3 (excluded due to failed minimization). A summary of the stepwise covariate procedure is shown in **Table 11**. Final parameter estimates and their associated precision are shown in **Table 12**.

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Table 11. Covariate model building

Model Step	Pharmacokinetic parameter	Patient specific variable (Covariate)
Base model	*Disposition Parameters:*	
	CL	CRCL
	V	BMI
	Absorption parameters:	
	F3	
	$k_{a1\ max}$	IVOL[1]
	$k_{a3\ max}$	IVOL[1]
	$k_{amt1\ 50}$	IVOL[1]
	$k_{amt3\ 50}$	IVOL[1]
Full covariate model	*Disposition Parameters:*	
	CL	Sex, CRCL
	V	BMI
	Absorption parameters:	
	F3	Age
	$k_{a1\ max}$	IVOL[1], INJS, Sex, BMI
	$k_{a3\ max}$	IVOL[1]
	$k_{amt1\ 50}$	IVOL[1]
	$k_{amt3\ 50}$	IVOL[1], BMI
Final covariate model	*Disposition Parameters:*	
	CL	CRCL, (Sex)[2]
	V	BMI
	Absorption parameters:	
	F3	(age)[3]
	$k_{a1\ max}$	IVOL[1]
	$k_{a3\ max}$	IVOL[1], Sex, INJS
	$k_{amt1\ 50}$	IVOL[1]
	$k_{amt3\ 50}$	IVOL[1]

[1] *IVOL influence on absorption rate parameters was estimated with one parameter.*
[2] *Sex influence on CL was excluded from the final model due failed covariance step.*
[3] *Age influence on absorption allocation was excluded from the final model due to failed minimization.*

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Table 12. Parameter estimates of the final paliperidone population PK model

	Final model
OFV	−6766

	Unit	Final model Value	RSE (%)	SHR (%)
CL	L/h	3.84	2.16	
V	L	1960	(FIX)	
$k_{a1\ max}$	ug/h	90.4	6.96	
$k_{amt1\ 50}$	mg	120	3.83	
γ		1.44	1.65	
$V^a_{Palmitate}$	L	156	(FIX)	
F_3		0.209	(FIX)	
$k_{a3\ max}$	ug/h	164	4.65	
$k_{amt3\ 50}$	mg	21.4	9.52	
CRCL on CL		0.316	21.5	
BMI on V		1.18	(FIX)	
IVOL on absorption[b]		0.808	7.41	
INJS on $k_{a1\ max}$[c]		-0.254	14.8	
Sex on $k_{a1\ max}$[d]		-0.206	16.8	
IIV CL	(CV)	0.357	3.17	31.6
IIV V	(CV)	0.628	(FIX)	35.6
IIV $k_{a1\ max}$	(CV)	0.827	5.01	31.3
IIV $k_{amt1\ 50}$	(CV)	0.500	10.1	51.9
IIV F_3	(CV)	1.08	(FIX)	29.5
IIV $k_{amt3\ 50}$	(CV)	0.867	14.2	63.7
Residual error	(CV)	0.306	0.321	12.2

[a] V for subjects with paliperidone palmitate in plasma

[b] All 4 absorption rate parameters used the same IVOL covariate effect (run 50 compared to runs 52 and 53 in Appendix 10, Table A10-1)

[c] Lower $k_{a1\ max}$ after gluteal injections

[d] Lower $k_{a1\ max}$ for women

The RSE for IIV parameters and the residual error are reported on the approximate. SD scale (SE/variance estimate)/2

BMI: body mass index; CL: apparent clearance; CRCL: creatinine clearance; CV: coefficient of variation; F_3: fraction of the dose entering the systemic circulation via a rapid and saturable absorption process after administration of PP3M; FIX: value fixed; γ: hill factor; IIV: inter-individual variability; INJS: injection site; IVOL: injection volume; $k_{amt1\ 50}$: amount of paliperidone at the absorption site when half of the maximum absorption rate is achieved for the slow absorption process; $k_{amt3\ 50}$: amount of paliperidone at the absorption site when half of the maximum absorption rate is achieved for the rapid absorption process; $k_{a1\ max}$: maximum absorption rate for the slow absorption process; $k_{a3\ max}$: maximum absorption rate for the rapid absorption process; OFV: objective function value; PK: pharmacokinetic; RSE: relative standard error; SD: standard deviation; SE: standard error; SHR: shrinkage; V: apparent volume of distribution; $V_{Palmitate}$: V for subjects with paliperidone palmitate in plasma

Source: Population PK report (REP-1-JAN-PAL-PMX-1) Table 6.

Reviewer's comments: Some parameters were fixed based on estimates from model run66.mod (V, F3, [BMI on V]). Based on results from run66, these parameters where estimated with high precision (RSE%≤25.2). Interindividual variability of F3 was also fixed based on run66.mod and was estimated with high precision (RSE%=8.2).

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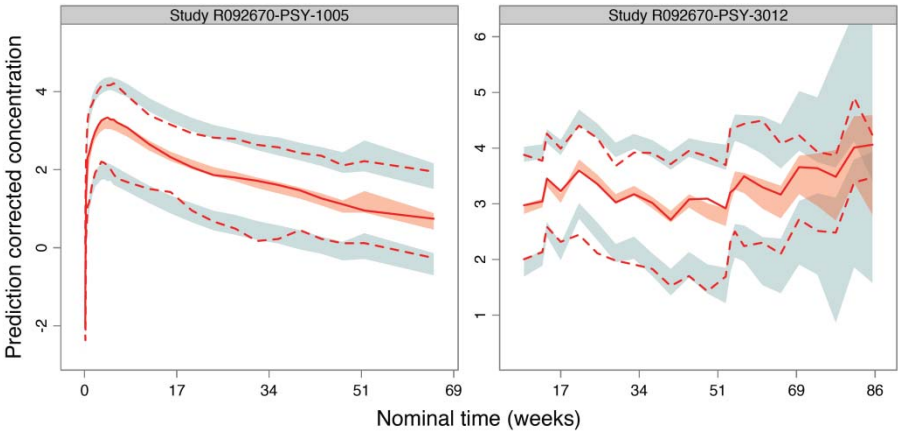
3.2.4 Applicant's evaluation of model performance

Applicant evaluated model performance based on simulation-based diagnostics (numerical and visual prediction checks), standard residual plots, parameter precision, condition number, and shrinkage. Criteria for accepting the final model was specified in the data analysis plan.

Reviewer's comments: All of applicant's evaluations have been reviewed. A selection of informative diagnostic plots is shown below in **Figure 7** ***a*** *through* ***e****. Overall, the model appears to perform adequately.*

Figure 7. Selected diagnostic plots

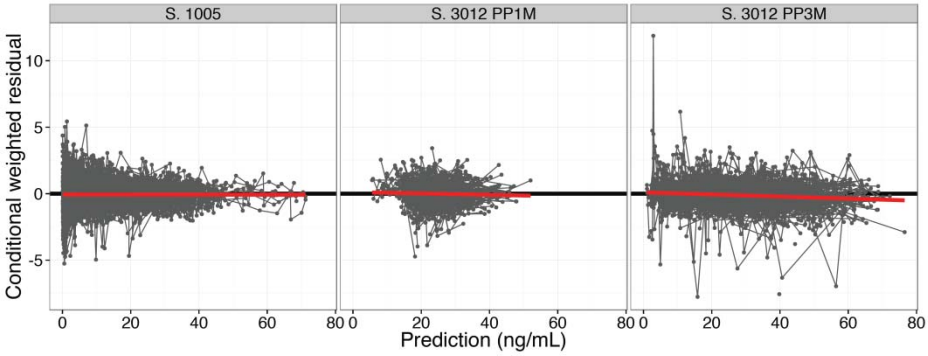
a



Source: Population PK report (REP-1-JAN-PAL-PMX-1) Figure 96.

Reviewer's comment: Prediction corrected visual predictive checks (PrVPC) indicate that the final model is able to describe the data from both the Phase 1 and the Phase 3 study adequately.

b



Source: Population PK report (REP-1-JAN-PAL-PMX-1), Appendix 16.3 Figure A16-7.

Reviewer's comment: There are no apparent trends as indicated by the red smoother line. However, population predictions of low concentrations show high conditional weighted residuals, especially for the Phase 1 study.

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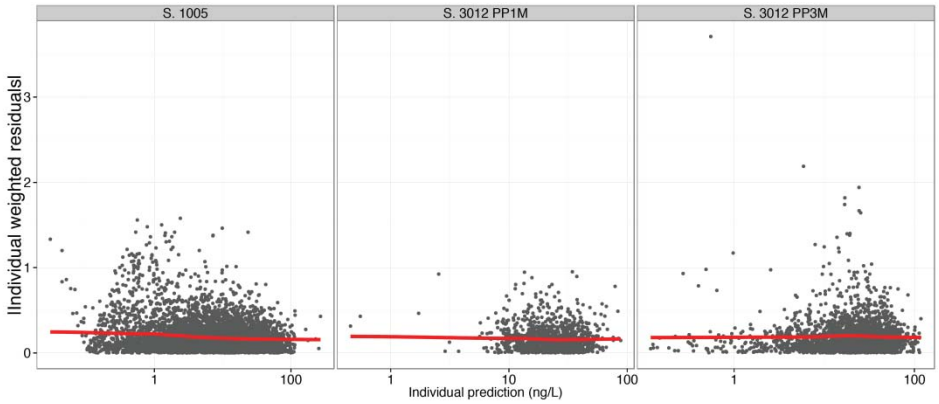
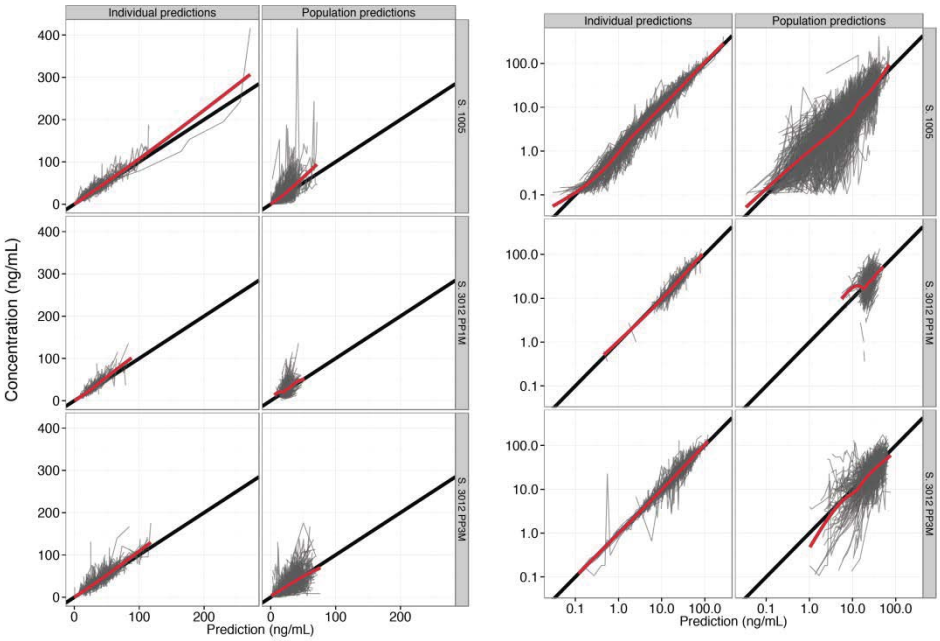
c



Source: Population PK report (REP-1-JAN-PAL-PMX-1), Appendix 16.3 Figure A16-8.

Reviewer's comment: There are no apparent trends as indicated by the red smoother line.

d



Note: Individual and population predictions versus individual observations for the Phase 1 study (upper panel), transition phase of the Phase 3 study (middle panel), and maintenance phase of the Phase 3 trial (lower panel). Figure on the left shows log transformed concentrations.

Source: Population PK report (REP-1-JAN-PAL-PMX-1), Appendix 16.3 Figure A16-6.

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Reviewer's comment: There are no apparent trends as indicated by the red smoother line. However, some individual observations are not captured by the model.

3.2.5 Influence of covariates on paliperidone exposure

The applicant used simulations to assess the influence of covariates on paliperidone exposure shown in **Figure 8-10**. A simulation protocol was prespecified in the applicant's data analysis plan. All simulations were to be performed with the final model for the different formulations, based on 5000 resampled (with replacement) individuals from the available PK dataset. Results of simulations were evaluated by graphical display of predictions (median and 90% prediction interval).

Based on simulations, the applicant concludes that no change in dosing regimen is needed due to injection site (deltoid versus gluteus), sex, BMI, race, age, and liver function test. Although small differences were predicted between injections sites, BMI category, and sex, they do not warrant any action. Differences in exposure where observed due to age, however, when adjusting for the declining renal function in subjects >60 years, these differences where no longer observed.

[redacted] (b) (4)

Reviewer's comment: The reviewer agrees with applicant's recommendations except for the recommendation for [redacted] (b) (4) *The mean expected difference in Cmax at steady state* [redacted] (b) (4) *is 16%. There is no indication that increase in Cmax by 16% is expected to affect the risk/benefit profile for paliperidone. This reviewer does not recommend* [redacted] (b) (4)

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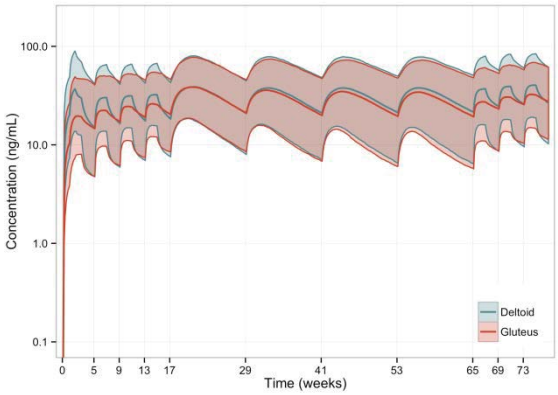
Figure 8. Influence of Injection site, sex and BMI on paliperidone exposure. The full line and the shaded areas represent the median, and the 90% prediction intervals.

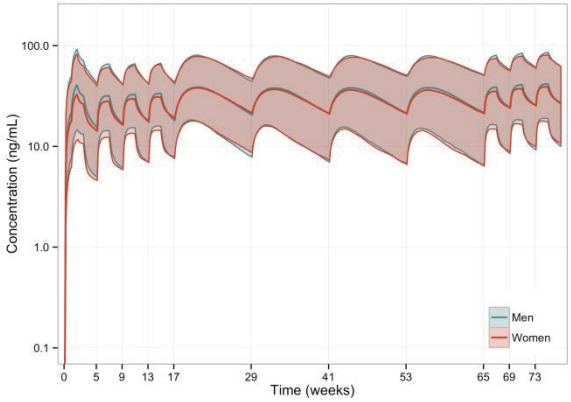
a) Influence of injection site



Note: *After the fourth 350 mg eq. PP3M dose, the expected median Cmin was 2.2 ng/mL lower after gluteal injections than after deltoid injections.*

Source: *Figure A17-4, report: REP-1-JAN-PAL-PMX-1*

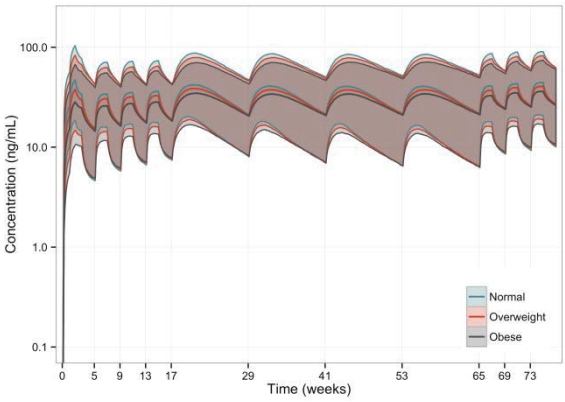
b) Influence of sex



Note: *The expected median Cmin after 350 mg eq. deltoid injections were similar in men and women.*

Source: *Figure A17-5, report: REP-1-JAN-PAL-PMX-1*

c) Influence of BMI



Note: *Subjects with a high BMI are expected to have a lower Cmax, but Cmin was similar for PP3M between normal, overweight and obese subjects.*

Source: *Figure A17-6, report: REP-1-JAN-PAL-PMX-1*

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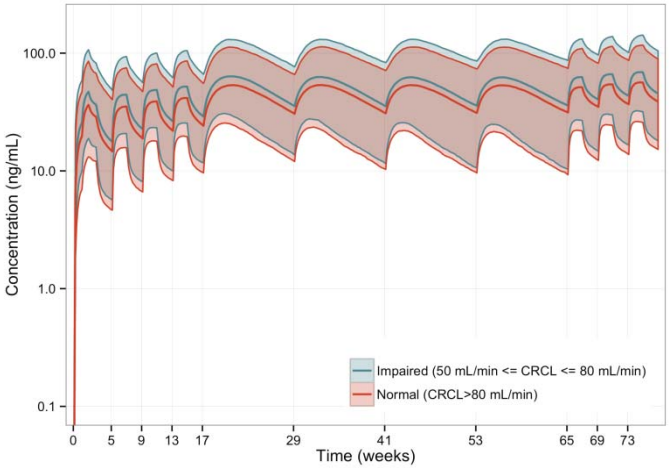
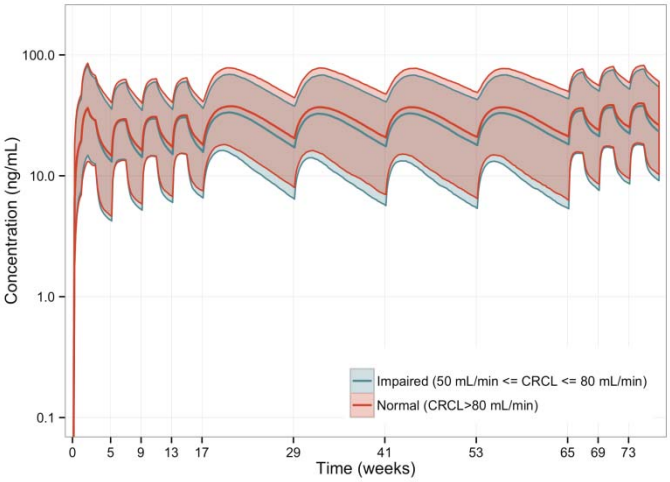
Figure 9. Influence of renal function on paliperidone exposure. The full line and the shaded areas represent the median, and the 90% prediction intervals.



a)

The Cmax after the fourth deltoid injection with 525 mg eq. of PP3M was 55.1 ng/mL in subjects with normal renal function and 64.1 ng/mL in subjects with mild renal impairment.
Source: Figure A17-7, report: REP-1-JAN-PAL-PMX-1



b)

After deltoid injections of 350 mg eq. in subjects with normal renal function and 263 mg eq. in subjects with mild renal impairment (25% dose reduction), the Cmin was 21.1 and 18.2 ng/mL, respectively.
Source: Figure A17-8, report: REP-1-JAN-PAL-PMX-1

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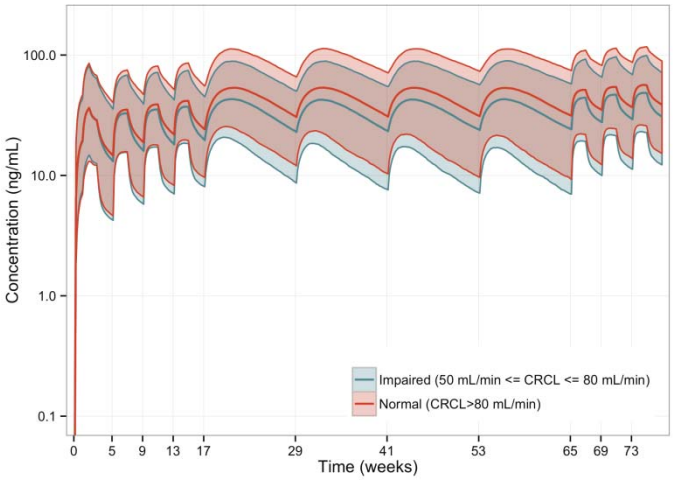


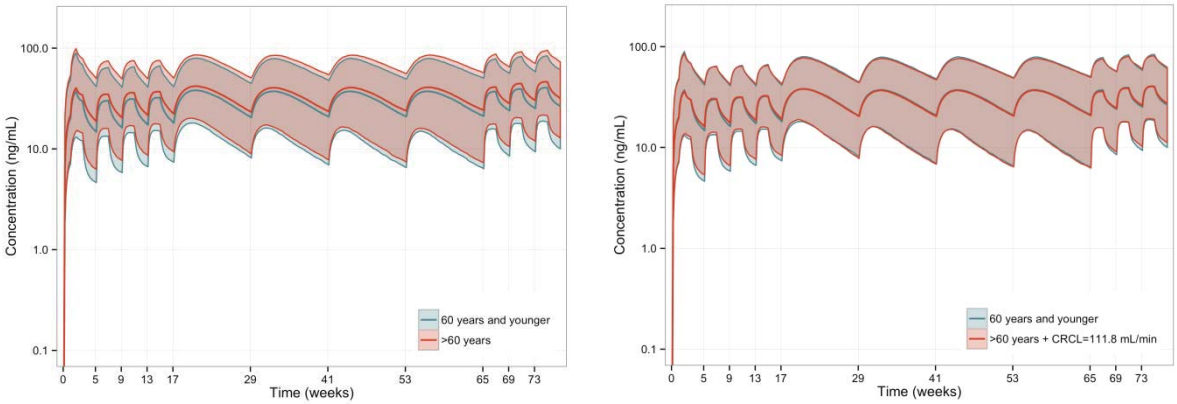
After deltoid injections of 525 mg eq. in subjects with normal renal function and 350 mg eq. in subjects with mild renal impairment, the Cmin was 31.3 and 24.1 ng/mL, respectively.

Source: Figure A17-9, report: REP-1-JAN-PAL-PMX-1

c)

Figure 10. The influence of age on paliperidone exposure. The full line and the shaded areas represent the median, and the 90% prediction intervals.

Influne of age **Influence of age asjusted for CRCL**



Note: Age is shown to have impact over exposure (left), however, this largely due to the correlation of age and creatinine clearance. Adjusting for creatinine clearance, shown that age by itself has little effect on exposure (left).

Source: Figure A17-10, and figureA17-11, report: REP-1-JAN-PAL-PMX-1

3.2.6 Simulation of maintenance and initiation regimens

Figure 11 shows simulated paliperidone concentrations after 4 months of treatment with PP1M, followed by a transition to PP3M. Expected concentrations following continued PP1M or ER (no transition to PP3M) are overlaid to facilitate comparison (red lines and areas or dashed lines). Based on the simulations the applicant concludes that administration of PP3M doses that are 3.5 fold the corresponding PP1M dose; result in

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paliperidone exposure similar to exposures obtained following ER tablet administration. Furthermore, the peak to trough variability after multiple injections of PP3M was higher over a 3-month time period than the variability observed for PP1M over a 1-month time period and similar to the variability observed with QD paliperidone ER.

Predicted mean maximum observations as well as the mean peak-trough ratio following maintenance PP1M and PP3M treatment is shown in **Table 13**. The following is inferred from **Table 13**:

- Maximum concentrations following maintenance PP3M treatment are higher than the corresponding PP1M doses. This holds true for all dose strengths and both sites of administration.
- *Deltoid administration:* Trough concentrations following maintenance PP3M treatment are *higher* than those following corresponding dose of PP1M treatment.
- *Deltoid administration:* Peak to trough ratio is similar or lower for doses lower than 525 mg. The 525 mg PP3M dose results in higher peak to trough ratio than the corresponding PP1M dose.
- *Gluteal administration:* Trough concentrations following maintenance PP3M treatment are *lower* than those following corresponding dose of PP1M treatment.
- *Gluteal administration:* Peak to trough ratio is *higher* for all doses following PP3M treatment compared to PP1M treatment.

Table 13. Median values for secondary PK parameters when on maintenance treatment with PP3M or PP1M

	PP3M				PP1M		
Injection site	**Dose (mg eq.)**	**C_{max} (ng/mL)**	**C_{max}/ dose**	**Peak/ Trough[a]**	**Dose (mg eq.)**	**C_{max} (ng/mL)**	**Peak/ Trough[a]**
Deltoid	175	20.8	0.12	1.71	50	19.4	1.88
	263	30.2	0.11	1.69	75	28.0	1.74
	350	39.1	0.11	1.67	100	36.4	1.66
	525	56.4	0.11	1.64	150	52.9	1.57
Gluteal	175	18.8	0.11	1.74	50	16.7	1.33
	263	27.2	0.10	1.72	75	24.4	1.29
	350	35.2	0.10	1.70	100	31.8	1.26
	525	50.9	0.10	1.68	150	46.4	1.23

[a] Peak/Trough is computed as a ratio of C_{max} to C_{min} (minimum concentration at the end of a dosing interval) for each subject.
All values are medians of simulations based on 5,000 subjects.
C_{max}: maximum concentration; PK: pharmacokinetic; PP1M: paliperidone palmitate 1-month formulation; PP3M: paliperidone palmitate 3-month formulation

Source: Table 11, report: REP-1-JAN-PAL-PMX-1

Reviewer's comments: The applicant has demonstrated safety and efficacy in a phase 3 trial. The larger peak to trough variability in PK following PP3M administration compared to PP1M administration is therefore not clinically significant. Furthermore, the peak to trough ratio appears similar for PP3M and ER tablet treatment.

It should be noted that if it is desirable to decrease the plasma fluctuations then Deltoid administration is recommended for the PP3M formulation while Gluteal administration is recommended for the PP1M formulation.

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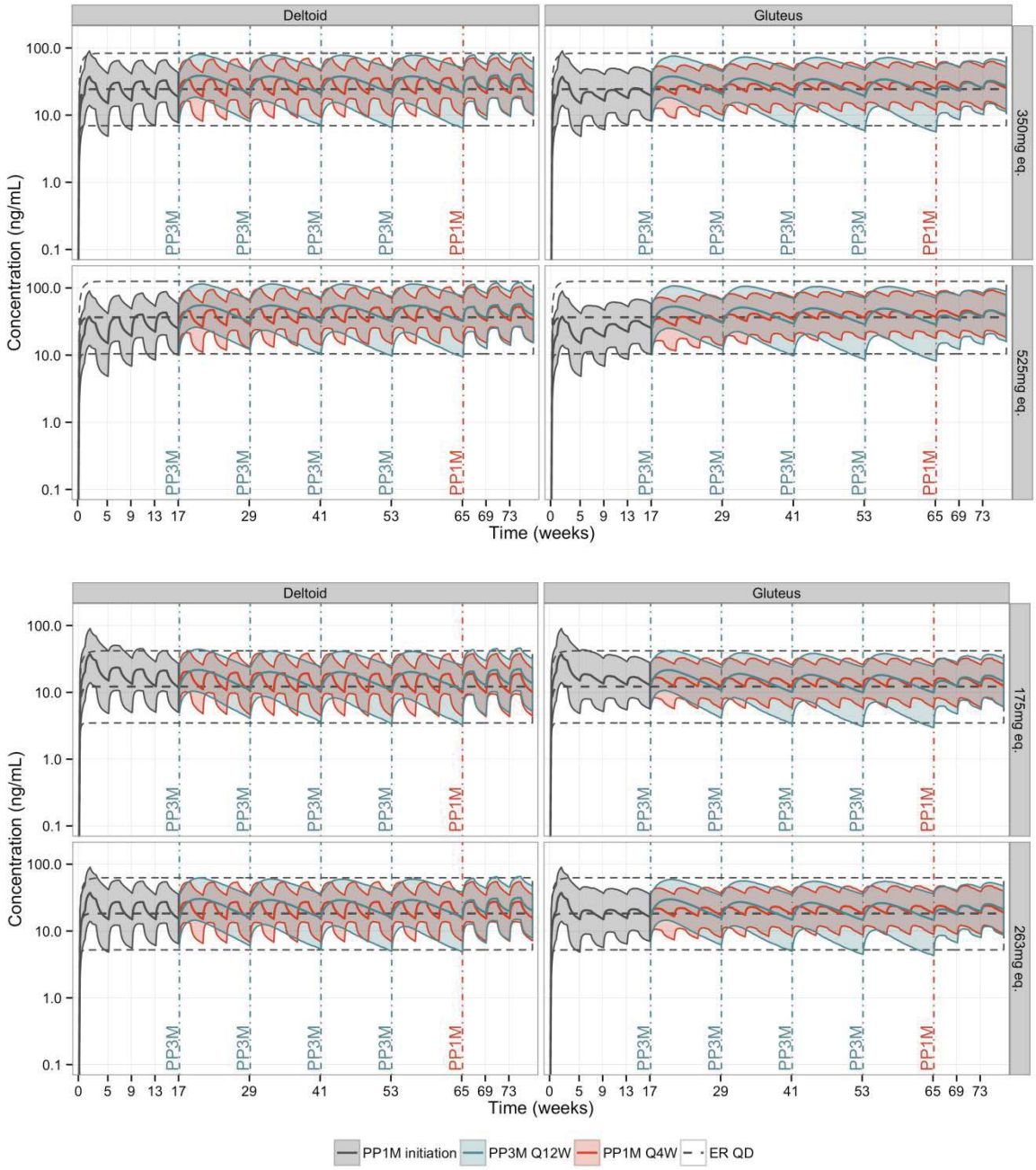
Figure 11. Simulated paliperidone plasma concentrations versus time. The full line and the shaded areas represent the median, and the 90% prediction intervals.



Note: *The solid lines and shaded areas represent the median paliperidone concentrations and 90% prediction intervals. Black and grey colors represent the PP1M initiation phase, red and blue colors represent the PP1M and PP3M maintenance regimens, respectively, and the thick and thin dashed lines represent the median paliperidone concentrations and 90% prediction interval following treatment with ER.*

Source: *Figure 12 and figure 13 report: REP-1-JAN-PAL-PMX-1*

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3.2.7 Simulation of dosing windows and managing missed doses

3.2.7.1 Dosing frequency margin of the regular treatment schedule

The applicant performed simulations to evaluate the management of missed doses. Results of applicant's simulation of delayed doses (up to three weeks) shown marginal decrease in exposure. Similarly, administering doses up to three weeks before schedule resulted in marginally increase Cmax values, **Table 14**.

Table 14. Median C_{min} and C_{max} when switching from PP1M to PP3M at Week 17, ±1 week, and dosing windows around the regularly scheduled 12-week dosing interval, ±1, ±2 and ±3 weeks, after subjects reached apparent steady-state on treatment with PP3M deltoid injections

Type	Parameter	Dose	Default	±1 week	±2 weeks	±3 weeks
Switching to PP3M	C_{min} (ng/mL)	175 mg eq.[a]	11.6	10.2		
	C_{max} (ng/mL)	525 mg eq.[b]	58.2	60.2		
Maintenance PP3M	C_{min} (ng/mL)	175 mg eq.[a]	11.0	10.3	9.7	9.0
	C_{max} (ng/mL)	525 mg eq.[b]	56.4	57.1	58.0	58.8

[a] +X week simulations were performed with the lowest PP3M dose strength of 175 mg eq. to simulate a worst-case scenario (ie, largest % drop in C_{min}) since the lowest dose has the shortest apparent $t_{1/2}$.
[b] -X week simulations were performed with the highest PP3M dose strength of 525 mg eq. to simulate a worst-case scenario (ie, largest % increase in C_{max}).
C_{max}: maximum concentration; C_{min}: minimum concentration; PP1M: paliperidone palmitate 1-month formulation; PP3M: paliperidone palmitate 3-month formulation

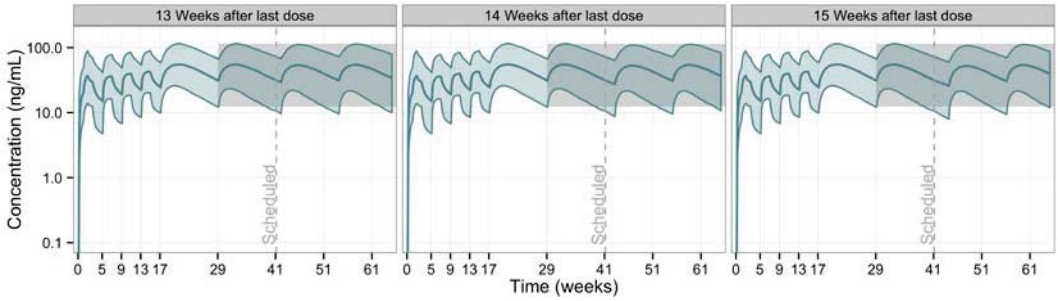
Source: Table 8 report: REP-1-JAN-PAL-PMX-1

Reviewer´s comments: The applicant proposes that paliperidone can be administered ±2 weeks every 3 months. The simulations support applicant´s recommendations.

3.2.7.2 Missed dose: up to 4 months

Applicant´s simulations shows that paliperidone PP3M formulation can be reinitiated at the regular dosing interval and dose strength if a scheduled dose was missed by less than 4 months, **Figure 12.**

Figure 12. Missed dose simulations when less than 4 months had elapsed since the last 525 mg eq. deltoid injections of PP3M.



Source: Figure 14 report: REP-1-JAN-PAL-PMX-1

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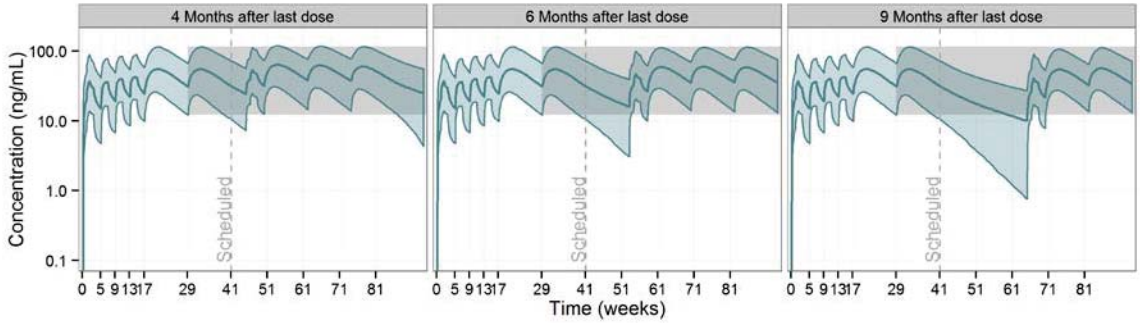
3.2.7.3 Missed dose: between 4 and 9 months

Applicant´s simulations shows that paliperidone PP3M formulation can be reinitiated with a PP1M deltoid injection of 100 mg eq. on Day 1 and a second PP1M deltoid injection of 100 mg eq. on Day 8, followed by 525 mg eq. PP3M dosing every 12 weeks if a scheduled dose was missed by between 4 and 9 months, **Figure 13.**

Figure 13. Missed dose simulations when 4 to 9 months had elapsed since the last 525 mg eq. deltoid injections of PP3M.



Source: Figure 15 report: REP-1-JAN-PAL-PMX-1

Reviewer´s comments: The applicant´s simulations are based on a 525 mg maintenance regimen. The applicant has provided results from simulations with other dosing regimens.

Table 15. Re-initiation regimen after missing between 4 and 9 months of PP3M

Last PP3M Dose	Administer PP1M two doses one week apart		Then administer PP3M
	Day 1 →	**Day 8 →**	**1 month after Day 8**
273 mg [175 mg eq.]	78 mg →	78 mg →	273 mg
410 mg [263 mg eq.]	117 mg →	117 mg →	410 mg
546 mg [350 mg eq.]	156 mg →	156 mg →	546 mg
819 mg [525 mg eq.]	156 mg →	156 mg →	819 mg

Source: Adapted from applicant's proposed labeling

3.2.7.4 Missed dose: more than 9 months

Applicant´s simulations shows that paliperidone PP3M formulation can be reinitiated with a PP1M deltoid injection of 150 mg eq. on Day 1 and a second PP1M deltoid injection of 100 mg eq. on Day 8, followed by 3 additional 150 mg eq. PP1M injections, followed by 525 mg eq. PP3M dosing every 12 weeks if a scheduled dose was missed by more than 9 months, **Figure 14.**

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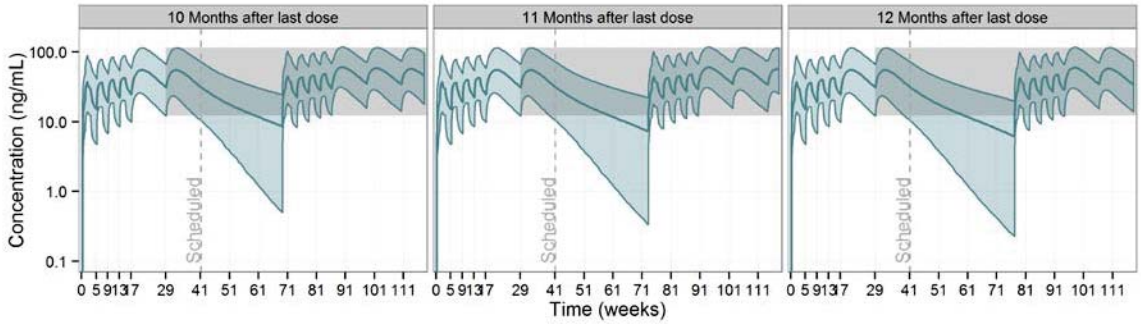
Figure 14. Missed dose simulations when more than 9 months had elapsed since the last 525 mg eq. deltoid injections of PP3M.



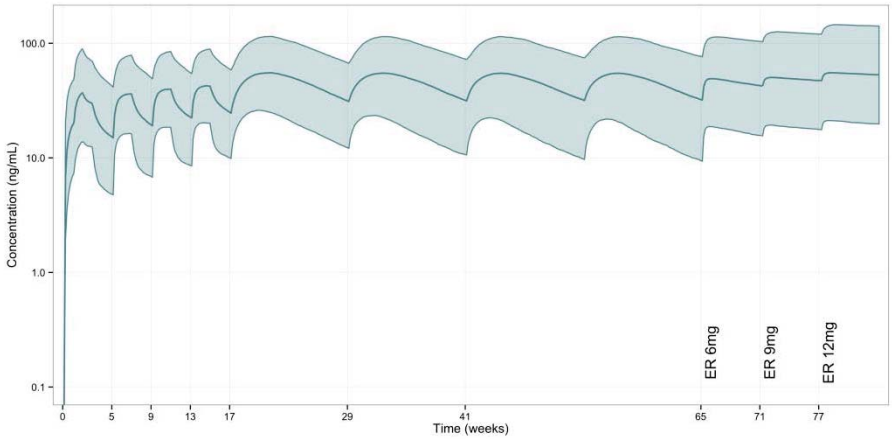
Source: Figure 15 report: REP-1-JAN-PAL-PMX-1

Reviewer´s comments: The applicant´s simulations are based on a 525 mg maintenance regimen. The applicant has provided results from simulations with other dosing regiments.

3.2.8 Simulation of transition from PP3M formulation to oral ER formulation

Applicant performed simulation to evaluate the proposed regimen when transitioning from PP3M formulation and oral ER formulation, **Figure 15.** The proposed transition regimen is shown in **Table 16**.

Figure 15. Transition from PP3M (525 mg eq.) to oral paliperidone ER



Source: Figure 16 report: REP-1-JAN-PAL-PMX-1

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Table 16. PP3M doses and once-daily paliperidone extended-release conversion regimens needed to attain similar paliperidone exposures

	Weeks since last PP3M dose		
Last PP3M Dose	≥ 3 months to ≤ 18 weeks	> 18 weeks to ≤ 24 weeks	> 24 weeks
	Doses of oral paliperidone extended-release tablets		
273 mg [175 mg eq.]	3 mg	3 mg	3 mg
410 mg [263 mg eq.]	3 mg	3 mg	6 mg
546 mg [350 mg eq.]	3 mg	6 mg	9 mg
819 mg [525 mg eq.]	6 mg	9 mg	12 mg

Source: Adapted from applicant's proposed labeling

Reviewer´s comment: The applicant has submitted similar results for other dosing regimens.

4 REVIEWER'S ANALYSIS

4.1 Introduction

This reviewer has initiated three analyses. The first analysis investigates the probability of treatment failure if a healthcare provider fails to administer the full dose of the PP3M paliperidone product. The details of this analysis are disused in section **1.1.4**. The second analysis investigates the probability of dose dumping in patients with paliperidone plasma concentrations > 125 ng/mL. The details of this analysis are discussed in section **1.1.5**.

The third analysis was undertaken to confirm the results of the sponsor's simulations. The applicant has used NONMEM to analyze the available data. But, simulations that support the applicant´s conclusions where conducted in R. Translation of a NONMEM model to R is not straightforward and the applicant has not provided validation of the R implementation of the NONMEM model. Furthermore, this reviewer was not able to run the applicant´s R code. Thus, a reviewer initiated analysis was undertaken to confirm that mild renal impairment results in only 16% increase in Cmax at steady state.

4.2 Objectives

Analysis objectives are to confirm applicant's simulations of paliperidone exposure in patients with mild renal impairment.

4.3 Methods

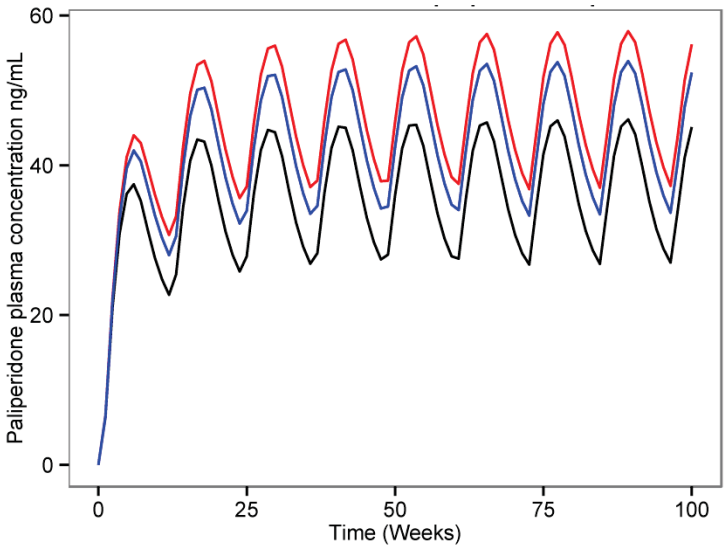
Applicant´s model was implemented in Berkley Madonna, version 8.3.18. Simulations were conducted in three typical individuals using applicant´s final parameter estimates. The typical individuals were males, with study median BMI and injection volume. All doses (525 mg eq.) were administered in the deltoid muscle. The three individuals had CRCL values of 115 mL/min (study median), 65 mL/min, and 50 mL/min.

Reference ID: 3748068

4.4 Results

Results of the simulations are shown in **Figure 16**. The applicant estimates that, on average, steady state Cmax will increase by 16% in patients with mild renal impairment. The simulations show that Cmax at steady state will increase from 46 ng/mL to 53.9 ng/mL as CRCL decreases from the study median 115 mL/min to 65 mL/min. The estimated percent increase of 17% corresponds well with the applicant´s own estimate. However, the absolute numbers differ between the reviewer and the applicant. The applicant estimates an increase from 55.1ng/mL to 64.1 ng/mL in subjects with mild renal impairment compared to subjects with normal renal function. There are several reason for possible difference: error in translation of the NONMEM model to R or to Berkley Madonna, or because of the difference between typical prediction and the mean prediction. Typical prediction is obtained from simulations with the typical fixed effects estimates of a nonlinear mixed effects model (the reviewers approach), while the mean prediction is obtained from the mean profile following a large number of Monte-Carlo simulations (the applicant's approach). Whatever the reason, this reviewer believes the applicant simulations and estimates of increase in exposure to be acceptable. However, the reviewer doses not agree with applicant´s conclusions [redacted] (b) (4) A 16 or 17% percent increase in exposure does not motivate a dosing restriction. This is further exemplified by the relative modest increase in exposure of 26% in a patient with CRCL of 50 mL/min compared to the typical patient. Furthermore, 6 subjects with mild renal impairment received the 525 mg eq. dose in the phase 3 trial without any noticeable difference in safety compared to other subjects in that dose group, Table 2.

Figure 16. The influence of renal impairment on paliperidone PP3M exposure in the typical patients with normal renal function (blue), a patient with CRCL of 65 mL/min (blue), and a patient with CRCL of 50 mL/min (red).



Reference ID: 3748068

5 LISTING OF DATA, CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
TTE.csv	Time to event data analysis filed used for COX.R model, derived from applicants adtte.xpt file	Paliperidone_NDA207946_DR\FDA Reviews\Data
COX.R	Cox model used to generate **Figure 2**	Paliperidone_NDA207946_DR\FDA Reviews\Code
PP3M model mmd	Berkley Madonna model used to generate **Figure 16**	Paliperidone_NDA207946_DR\PPK Analyses\BM_models
BMsim	Output from PP3M model.mmd	Paliperidone_NDA207946_DR\PPK Analyses\BM_models\BMsimulation

6 REFERENCESES

1. Bergstrand, M., Hooker, A. C., Wallin, J. E. & Karlsson, M. O. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *The AAPS journal* **13**, 143–151 (2011).
2. Jonsson, EN & Karlsson, MO Automated covariate model building within NONMEM. *Pharmaceutical research* (1998).doi:10.1023/A:1011970125687
3. Khandelwal, A., Harling, K., Jonsson, E. N., Hooker, A. C. & Karlsson, M. O. A fast method for testing covariates in population PK/PD Models. *AAPS J* **13**, 464–72 (2011).

Reference ID: 3748068

Report #: R092670PSY3012 Study Period: 4/26/12 – 4/9/14
EDR Link: \\cdsesub\EVSPROD\nda207946\0000\m5

Title: A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3-Month Formulation for the Treatment of Subjects with Schizophrenia (pharmacokinetic analysis)

Objective: This report deals with the non-compartmental and statistical analysis of the bioanalytical results derived from trial R092670PSY3012, which was a randomized, double-blind, parallel group, placebo controlled, multicenter study designed to determine the efficacy and safety of paliperidone palimitate with a 3-month injection interval (PP3M) in adults 18 to 70 years of age with schizophrenia.

Study Design: After enrollment, there were three treatment phases: the Transition Phase, the Maintenance Phase, and the Double-blind Phase. In the Transition Phase, all subjects received paliperidone palmitate with a 1-month injection interval (PP1M). Subjects who were not switching from other long acting injectable (LAI) antipsychotics received the first injection of 150 mg eq. PP1M on Day 1 and the second injection of 100 mg eq. PP1M on Day 8, both in the deltoid muscle. Injections on Day 36 and on Day 64 were to be given in either the deltoid or gluteal muscle and were to be flexibly dosed (50, 75, 100, or 150 mg eq.). At Day 92, subjects received the same dose of PP1M that was administered at Day 64. Those subjects who completed the Transition Phase of the study, and who met the prospectively defined criteria, entered the Maintenance Phase. At the start of the 12-week Maintenance Phase (Day 120 [Week 17]), subjects received a single injection of PP3M [using a 3.5-fold multiple of the final PP1M dose received on Day 92]. Subjects who met specific stabilization criteria entered the Double-blind Phase at Week 29 (Day 204). Subjects that entered the Double-Blind Phase were randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP3M or placebo. Subjects assigned to PP3M in the Double-blind Phase received the same dose of study drug that was administered on Day 120 of the Maintenance Phase; the dose remained fixed throughout the Double-blind Phase. Blood samples were collected for population PK analysis to further explore the PK of paliperidone after treatment with PP3M. An overview of the dosing administration schedule and the PK blood sampling schedule in the Transition, Maintenance and Double-blind Phases of the study are provided in the table below.

A total of 1768 samples were taken from 508 subjects during the Transition Phase. On Day 1, 434 subjects had their first administration of 150 mg eq. PP1M, followed by a 100 mg eq. PP1M dose on Day 8 for 429 subjects. Subjects who were stable on PP1M, other LAIs or Risperdal Consta (2-weekly regimen) had their first administration of PP1M on Day 8 (see administration schedule). Flexible dosing (50 – 150 mg eq.) was allowed on Day 64 and Day 92. On Day 99, the individual paliperidone palmitate dose were fixed resulting in 9, 38, 188 and 169 subjects receiving 50, 75, 100 and 150 mg eq. PP1M, respectively.
A total of 1303 samples were taken from 186 subjects receiving active treatment during the Double-blind Phase. Pharmacokinetic parameters of paliperidone were available for 3, 6, 34 and 24 subjects in the 175, 263, 350 and 525 mg eq. dose groups, respectively.

A total of 1124 samples were taken from 397 subjects during the Maintenance Phase. Subjects were divided over dose groups including 9, 36, 188 and 164 subjects in dose groups of 175, 263,350 and 525 mg eq. PP3M respectively.

Dosing Administration Schedule

	Transition Phase					Maintenance Phase			Double-blind Phase			
Visit	2	3	4	5	6	8	9	10	11	12	13	Every 12 weeks
Day	1[a]	8[a]	36	64	92	120	148	176	204	232	260	
PP1M Dose	150 mg eq.	100 mg eq.	50-150 mg eq.	50-150 mg eq.	50-150 mg eq.	--	--	--	--	--	--	--
Muscle	D	D	D or G	D or G	D or G	D or G			D or G			D or G
Flexible or Fixed	Fixed	Fixed	Flexible	Flexible	Fixed [b]	Fixed [c]	--	--	Fixed [c]	--	--	Fixed [c]
PP3M/ Placebo Dose	--	--	--	--	--	X	--	--	X	--	--	X

D=deltoid muscle; G=gluteal muscle; PP1M=paliperidone palmitate 1 month formulation; PP3M=paliperidone palmitate 3 month formulation

[a] For subjects who are stable on PP1M, will have their last dose on Day -21and their first study dose on Day 8, which is the same dose as their last PP1M injection (50, 75, 100, or 150 mg eq. D/G). For subjects who are stable on other LAIs will have their last dose on Day -21, Day -14, Day -7 or Day 1 for 4-weekly, 3-weekly, 2-weekly or once a week regimens respectively and their first dose of 150 mg eq. PP1M on Day 8. For subjects who are stable on Risperdal Consta (2-weekly regimen) will have their last dose on Day -7 and their first dose of 50, 75, 100 mg eq. PP1M corresponding to 25, 37.5 and 50 mg of Risperdal Consta respectively on Day 8.

[b] Dose on this visit should be the same as given on Visit 5 (Day 64)

[c] The dose of PP3M given will be a 3.5-fold multiple of the PP1M dose given on Visit 6 (Day 92)

PK Sampling Schedule

Period	Screening	Transition						Maintenance			Double-Blind									
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Visits every 4 weeks[a]	Visits every 8 weeks[a]	Visits every 12 weeks[a]	Week 54 PK	Week 55 PK	EOS/ Early WD Visit
Week	-3 to -1		1	5	9	13	14	17	21	25	29	33	37	41						
Day	-21 to -1	1	8	36	64	92	99	120	148	176	204	232	260	288						
Window (days)		NA	± 3	± 7	± 7	± 7	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	NA
Study drug administration																				
Administer study medication		X[b]	X	X	X	X		X			X			X			X			
Pharmacokinetic Procedures																				
PK Sample collection [c]		X			X	X	X	X	X	X	X	X	X	X	X			X[d]	X[d]	X

[a] After Visit 14 (Week 41), visits will take place every 4 weeks. Assessments listed for every 12 weeks will be performed at Week 41, Week 53, Week 65, etc. Assessments listed for every 8 weeks will be performed at Week 37, Week 45, Week 53, Week 61, etc. The assessments in these columns will be performed mutually inclusive of each other.

[b] Day 1 injection of PP1M does not apply to subjects who are being switched from another depot antipsychotic (including Risperdal CONSTA), or stable subjects who are continuing on current treatment with PP1M at enrollment.

[c] Venous samples of 4 mL should be obtained prior to dose administration on each PK day. Unscheduled PK samples may be obtained at the Investigator's discretion for cases of severe or serious adverse events that may be potentially related to unexpected increases in plasma concentrations of study drug.

[d] PK samples should be obtained 10 days (Week 54) and 20 days (Week 55) after study drug injection at Week 53.

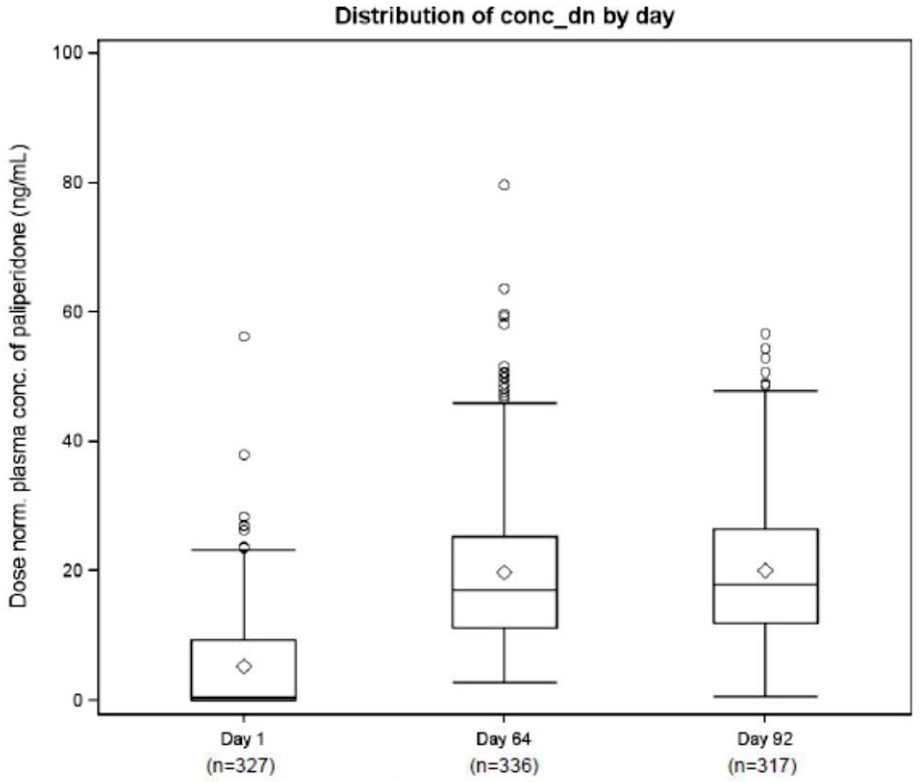
Bioanalytical Methods Used

Study	Matrix	Analyte	Concentration range (ng/mL)	Method
Study-3012	Plasma	Paliperidone	0.10 – 250	LC-MS-MS
	Plasma	Prohibited antipsychotics	0.1-100 (olanzapine, risperidone, haloperidol, trifluoperazine 0-1000 (aripiprazole, chlorpromazine, quetiapine)	LC-MS-MS

Results

Paliperidone predose dose normalized plasma concentrations after administration of PP1M at 50, 75, 100 or 150 mg eq. on Day 64 and on Day 92 were comparable as indicated in the box plot below.

Box Plot of Dose Normalized (to 100 mg eq.) Predose Plasma Concentrations of Paliperidone after administration of PP1M at 50 mg eq., 75 mg eq., 100 mg eq., or 150 mg eq. during the Transition Phase

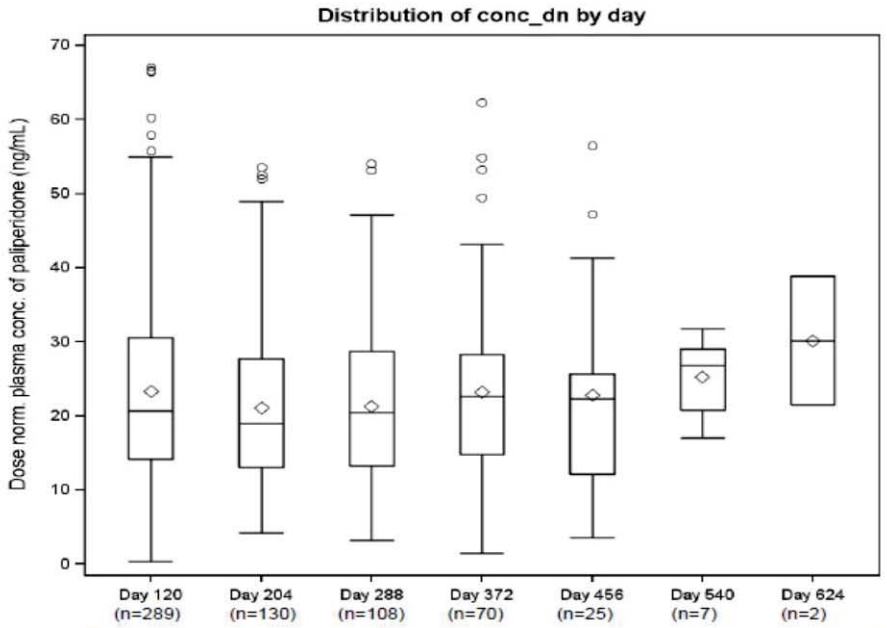


Boxes: 25th percent quartile, median, 75th percent quartile; Whiskers: min and max within 1.5xIQR; Diamond arithmetic mean; Circles: individual values outside 1.5xIQR

Pre-dose Plasma Concentration of Paliperidone after PP1M Injection – Transition Phase

Plasma Concentrations Paliperidone (n, mean ± SD)	PP1M, 50 mg eq.				PP1M, 75 mg eq.				PP1M, 100 mg eq.				PP1M, 150 mg eq.			
	n	mean	±	SD	n	mean	±	SD	n	mean	±	SD	n	mean	±	SD
$C_{Day\ 1}$, ng/mL	-	-	±	-	-	-	±	-	-	-	±	-	327	7.79	±	11.5
$C_{Day\ 64,\ Week\ 9}$, ng/mL	9	17.4	±	10.5	27	21.5	±	9.06	155	21.6	±	11.9	145	23.0	±	14.0
$C_{Day\ 92,\ Week\ 13}$, ng/mL	6	13.9	±	5.61	28	20.7	±	8.24	148	21.7	±	11.0	135	24.6	±	13.0
$C_{Day\ 99,\ Week\ 14}$, ng/mL	7	23.1	±	12.2	25	29.7	±	14.1	137	32.7	±	16.7	117	39.1	±	20.5

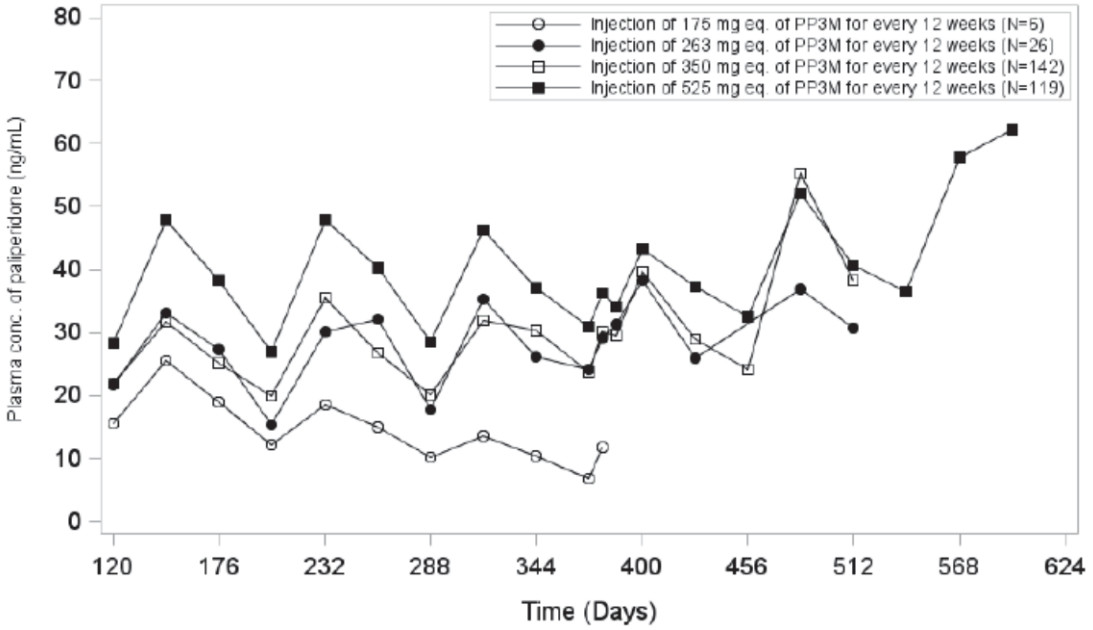
Box Plot of Dose Normalized (to 350 mg eq.) Pre-dose Plasma Concentrations of Paliperidone after administration of PP3M at 175 mg eq., 263 mg eq., or 525 mg eq. during Maintenance and Double Blind Phase



Boxes: 25th percent quartile, median, 75th percent quartile; Whiskers min and max values within 1.5xIQR; Diamond arithmetic mean; Circles: individual values outside 1.5xIQR

Paliperidone predose plasma concentrations after administration of PP3M at 175, 263, 350 and 525 mg eq. were similar on Day 120, 204, 288, 372, and 456. On Day 540 and Day 624 a higher plasma concentration can be observed but there was a decrease in the number of subjects.

Median Plasma Concentration Time Profiles of Paliperidone after administration of PP3M at 175 mg eq., 263 mg eq., 350 mg eq., or 525 mg eq. during the Maintenance and Double-Blind Phase



Pharmacokinetic Parameters of Paliperidone after administration of PP3M on Day 372 (Week 53) at 175, 263, 350 or 525 mg eq. during the Double Blind Phase

Pharmacokinetics of Paliperidone (n, mean ± SD, t_{max}: median [range])	**PP3M, 175 mg eq.**				**PP3M, 263 mg eq.**				**PP3M, 350 mg eq.**				**PP3M, 525 mg eq.**			
	n	mean		SD	n	mean		SD	n	mean		SD	n	mean		SD
$C_{predose}$, ng/mL	3	8.23	±	4.82	6	25.8	±	11.0	40	25.9	±	14.7	29	29.5	±	14.1
C_{max}, ng/mL	3	15.7	±	4.28	6	38.5	±	8.04	34	41.5	±	21.7	24	45.9	±	16.4
t_{max}, days	3	8.94 (6.93-19.86)			6	28.36 (0.00-54.96)			34	27.86 (0.00-54.99)			24	25.92 (0.00-54.90)		
AUC_{τ}, ng.h/mL	3	22635	±	5511	6	60660	±	14062	34	62893	±	30514	24	70793	±	25850
C_{avg}, ng/mL	3	11.2	±	2.73	6	30.7	±	6.43	34	32.0	±	15.6	24	35.1	±	13.1
Peak–to-trough-ratio	3	2.52	±	1.94	6	1.63	±	0.54	34	1.91	±	0.96	21	2.59	±	3.89
DN- C_{max}, ng/mL	3	31.3	±	8.56	6	51.2	±	10.7	34	41.5	±	21.7	24	30.6	±	10.9
DN- AUC_{τ}, ng.h/mL	3	45270	±	11022	6	80726	±	18714	34	62893	±	30514	24	47195	±	17233

Based on dose normalized Cmax and AUC, the pharmacokinetic parameters does not appear to be dose proportional except between 175 and 525 mg eq. However, a definite conclusion cannot be drawn because of the small number of patients for 175 and 263 mg-eq. and the variability in the data.

Peak to Trough Ratios of Paliperidone after administration of PP1M on Day 92 during the Transition Phase, PP3M on Day 120 during the Maintenance Phase and PP3M on Day 372 during the Double-Blind Phase

Peak-to-trough ratios of Paliperidone	Day 92, Transition Phase, PP1M	Day 120, Maintenance Phase, PP3M	Day 372, Double-blind Phase, PP3M
N	292	124	27
Mean	1.44	1.95	2.18
SD	0.60	1.08	1.64
%CV	41.9	55.4	75.2
gMean	1.36	1.76	1.89

The peak to trough ratios were similar between PP3M during the maintenance and the double blind phases. However, the number of patients in each phase varied considerably and the variability was large.

Safety Summary

The sponsor reported that the following subjects (Table below) with plasma paliperidone higher than 125 ng/mL were checked for adverse events (AEs).

List of Subjects with Paliperidone Concentration higher than125 ng/mL checked for AEs after or just before the observed High Concentration

CRF ID	AE[a] (start day – stop day)	Grade / SAE	Severity	Relationship	Last received treatment	Scheduled sampling day	plasma concentration (ng/mL) mean (min-max)
60011507	Weight increased (Day 65 – NR)	NA/N	Moderate	Very likely	PP3M, 525 mg eq.	Day 148	142 53.8 (8.53–167)
	Dry mouth (Day 106 – NR)	NA/N	Mild	Probable	PP3M, 525 mg eq.	Day 568	137 70.9 (40.5-137)
	Dental Caries[b] (Day 311 – Day 311)	NA/N	Mild	Not related			
60013809	Weight increased (Day 88 – NR)	NA/N	Severe	Probable	PP1M, 150 mg eq.	Day 99	136 39.1 (8.83-136)
	Upper respiratory tract infection (Day 146 – Day 152)	NA/N	Moderate	Not related	PP3M, 525 mg eq.	Day 148	137 53.8 (8.53–167)
60017109	Weight decreased (Day 148 – NR)	NA/N	Mild	Possible	PP3M, 525 mg eq.	Day 232	165 51.8 (10.4-123)
60017110	Weight increased (Day 202 – NR)	NA/N	Mild	Possible	PP3M, 525 mg eq.	Day 232	139 51.8 (10.4-123)
	Insomnia (Day 244 – NR)	NA/N	Mild	Possible			
	Anxiety (Day 253 – NR)	NA/N	Mild	Possible			
60017817	Insomnia (Day 141 – Day 178)	NA/N	Mild	Not related	PP3M, 525 mg eq.	Day 148	125 53.8 (8.53–167)
60017820	-	-	-	-	PP3M, 525 mg eq.	Day 176	176 45.6 (2.95-176)
60522206	Insomnia (Day 3 – NR)	NA/N	Moderate	Not related	PP3M, 525 mg eq.	Day 232	137 51.8 (10.4-123)
	Influenza (Day 227 – 262)	NA/N	Mild	Not related			
	Influenza (Day 265 – 274)	NA/N	Moderate	Not related			
	Influenza (Day 283 – 293)	NA/N	Mild	Not related			
	Bronchitis (Day 310 – 316)	NA/N	Mild	Not related			

CRF ID	AE[a] (start day – stop day)	Grade / SAE	Severity	Relationship	Last received treatment	Scheduled sampling day	plasma concentration (ng/mL) mean (min-max)
60522302	Blood pressure increased (Day 293 – Day 300)	NA/N	Mild	Not related	PP3M, 525 mg eq.	Day 148	152 53.8 (8.53–167)
	Hypertension (Day 300 – NR)	NA/N	Mild	Not related			
63800708	-	-	-	-	Placebo, 0 mg	Day 316	131 12.2 (BQL-131)
63801202	Anxiety (Day 340 – Day 341)	NA/N	Mild	Possible	PP3M, 525 mg eq.	Day 148	167 53.8 (8.53–167)
					PP3M, 525 mg eq.	Day 176	139 45.6 (2.95-176)
63802504	Weight increased (Day 155 – NR)	NA/N	Mild	Possible	PP3M, 525 mg eq.	Day 148	160 53.8 (8.53–167)
	Insomnia (Day 209 – Day 215)	NA/N	Mild	Possible			
	Insomnia (Day 245 – Day 264)	NA/N	Moderate	Possible			
	Hyperglycaemia (Day 295 – NR)	NA/N	Mild	Not related			

BQL = Below quantification limit, NA = Not available, NR = Not recovered

a AEs occurring after first occurrence of paliperidone plasma concentration ≥125 ng/mL, or AEs occurring before first occurrence of paliperidone plasma concentration ≥125 ng/mL and resolving thereafter or any unresolved AEs.

b This AE was resolved before the scheduled sampling day 568.

The sponsor reported that 14 samples, a plasma paliperidone concentration ≥ 125 ng/mL was observed. Twelve of these samples were obtained after treatment with 525 mg eq. PP3M. None of the subjects in this treatment group experienced a serious or severe AE. Four subjects experienced one or more moderate AEs. For Subject 60011507) the moderate AE (weight increased) was very likely related and for Subject 63802504 the moderate AE (insomnia) was possibly related to drug administration. All other AEs were mild and considered possible or not related.

The sponsor reported that subject 60013809 experienced a severe AE (severe weight increase) which was probably related to drug administration. This subject received 150 mg eq. PP1M.

Summary and Conclusions of Pharmacokinetic analysis

Paliperidone predose plasma concentrations after administration of PP1M (Transition Phase) at 75 or 100 mg eq. appeared to be similar to paliperidone predose plasma concentrations after administration of the corresponding PP3M doses of 263 and 350 mg eq. (Maintenance and Double-blind Phase) respectively. Paliperidone predose plasma concentrations after administration of PP3M at 175 mg eq. appeared to be somewhat lower compared to paliperidone predose plasma concentrations after administration of the corresponding PP1M dose of 50 mg eq. Paliperidone predose plasma concentrations after administration of PP3M at 525 mg eq. appeared to be somewhat higher compared to paliperidone predose plasma concentrations after administration of the corresponding PP1M dose of 150 mg eq. Overall, steady-state conditions were maintained after switching from the PP1M formulation to the PP3M formulation.

Reviewer Comments: Reviewer agrees with sponsor's pharmacokinetic conclusions. Pre-dose plasma concentration was similar between the maintenance and double blind phase except for the highest dose (525mg-eq.). There was no consistent pattern in the plasma concentration-time profiles of the 14 subjects that concentrations ≥ 125 ng/mL were observed. Most subjects had concentrations ≥ 125 ng/mL at single time points but were

not sustained. The pharmacokinetic data from this study was incorporated in the population PK modeling and simulation analysis. Refer to the Pharmacometric review in Appendix for further evaluation of the pharmacokinetics of paliperidone after multiple PP3M injection.

Report # R092670PSY1005 **Study Period**: 2/29/2008 – 10/26/2009
EDR Link:
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m5
Title: A Single-Dose, Open-Label, Randomized, Parallel-Group Study to Assess the Pharmacokinetics, Safety and Tolerability of a Paliperidone Palmitate 3-Month Formulation in Subjects With Schizophrenia

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

The secondary objectives were (1) to evaluate the relative bioavailability of the paliperidone palmitate formulations after deltoid and gluteal injection compared with a 1 mg immediate release (IR) formulation of paliperidone; (2) to explore the dose-proportionality of paliperidone palmitate after gluteal and deltoid injection; and (3) to investigate the effect of the volume of injection, suspension strength, particle size and milling technique (dry versus wet) on the PK of paliperidone (Panels A and C).

Study Design: This was a multicenter, randomized, open-label, parallel-group study in 4 panels (A, B, C, and D). Each panel comprised of 2 sequential single-dose treatment periods (Period 1 and Period 2). The study agent injection was followed by a 96-hour observation period in Period 1 and a 364-day observation period (544-day in Panel D and those who consented in Panel B) in Period 2. Successive study agent administration was separated by a washout period of at least 7 and no more than 21 days. An interim analysis was conducted after 63 subjects in Panel A completed their Day 196 assessments in Period 2 to evaluate the PK and safety. Recruitment into Panel B was to start only if the F015 formulation exhibited a local tolerability and safety profile that was acceptable and comparable to the 1-month formulation. Subjects were enrolled in Panel C once enrollment in Panel A was completed. An interim analysis was conducted after 25 subjects completed their Day 196 visit assessments in Panel C. In Panel B, interim analyses were conducted after a minimum of 15 subjects per treatment group completed their Day 196 assessments in Period 2 and after all subjects per treatment group completed their Day 364 to evaluate the pharmacokinetics and safety. In Panel D, an interim analysis was conducted after at least 10 subjects who received 525 mg eq. F015 injection (either deltoid or gluteal) completed Day 84 of Period 2 to evaluate the PK and safety. Another interim analysis was conducted when all subjects, assigned to one of the 525 mg-eq. treatments, completed the study (Day 544 of Period 2) and all other subjects completed at least Day 364 of Period 2.

Panel A: Seventy-four subjects were randomized in Panel A of the study; however, 72 subjects received the study agent.
Panel B: One hundred twenty nine subjects were randomized in Panel B of the study; however,

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128 subjects received the study agent.
Panel C: Twenty-five subjects were enrolled in Panel C of the study.
Panel D: One hundred subjects were randomized in Panel D of the study.
A total of 328 subjects were randomized in the 4 panels of the study, of which 325 subjects received the study agent.

Period 1:
Panels A and C: 1 mg paliperidone IR solution in the gluteal muscle.
Panels B and D: 1 mg paliperidone IR solution in the deltoid or gluteal muscle.
Batch numbers and expiry dates: 07F04/F024, 31 May 2008; 08A30/F024, 31 December 2008; 10A27/F024, December 2010; and 11K02/F024, November 2012.

Period 2:

All subjects received a long-acting paliperidone palmitate formulation. The 3-month injection interval formulation F015 used in Panels A, B, and D had a particle size dv50 of approximately 7 µm and a concentration of 200 mg eq./mL. The 3-month injection interval formulation F016 used in Panel C had a particle size dv50 of approximately 7 µm (same as in the other panels) and a concentration of 100 mg eq./mL (same as paliperidone palmitate 1 month formulation [PP1M] but less concentrated than the other panels). The injection was given in the same muscle but at the opposite side (left or right) as in Period 1.
The following study agents were administered in Period 2:

Panel A: a single i.m. injection of 1.5 ml of the following formulations of paliperidone palmitate:
200 mg eq./mL F015, manufactured by a wet milling technique, injected in the gluteal muscle (batch number, expiry date: 07K21/F015, 31 December 2008).
200 mg eq./mL F015, manufactured by a dry milling technique, injected in the gluteal muscle (batch number, expiry date: 07L11/F015, 31 December 2009).

After Panel A, all formulations of paliperidone palmitate were produced by the wet milling technique.

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

75 mg eq. F015 injected in the gluteal muscle.
150 mg eq. F015 injected in the gluteal muscle.
450 mg eq. F015 injected in the gluteal muscle.
300 mg eq. F015 injected in the deltoid muscle.
450 mg eq. F015 injected in the deltoid muscle.
Batch number and expiry date: 10A08/F015, 31 January 2012.

Panel C: a single 1.5 ml i.m. injection of 100 mg eq./mL F016 of paliperidone palmitate, manufactured by a wet milling technique, injected in the gluteal muscle (batch number, expiry date: 07L04/F016, 31 December 2009).

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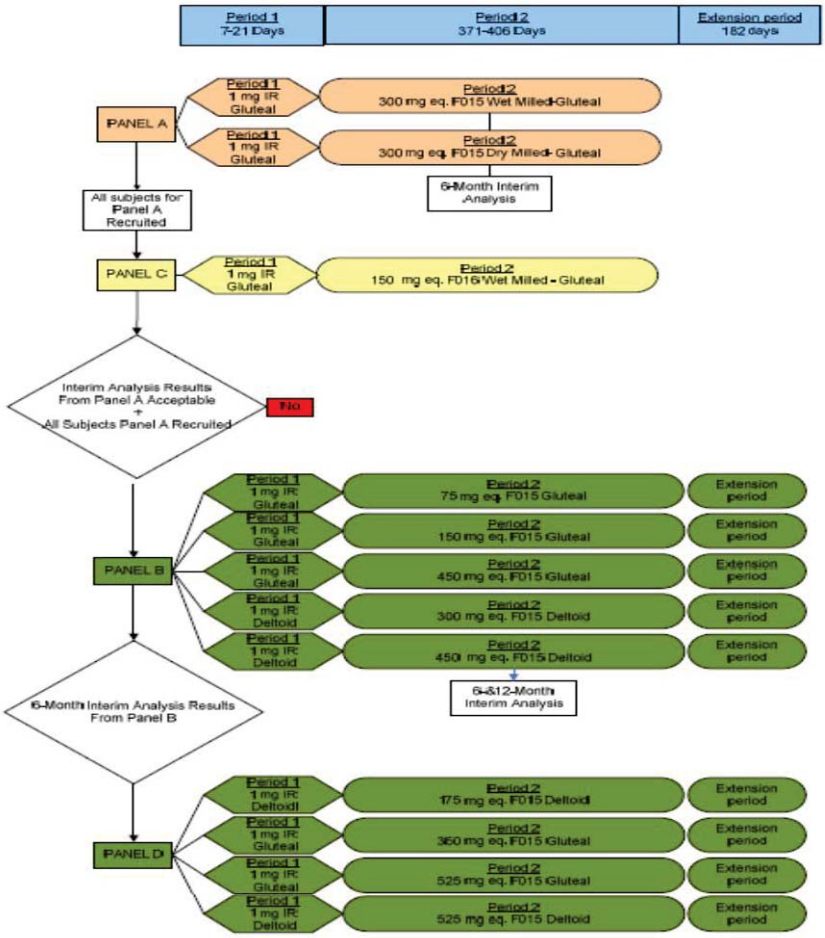
Panel D: a single i.m. injection of 1 of the following doses of Paliperidone Palmitate:
525 mg eq. F015 injected in the gluteal muscle.
525 mg eq. F015 injected in the deltoid muscle.
350 mg eq. F015 injected in the gluteal muscle.
175 mg eq. F015 injected in the deltoid muscle.
Batch number and expiry date: 11J26/F015, 30 November 2013.

Subjects were to be first enrolled in Panels A and C. Once the interim analyses of these panels were available, subjects then enrolled in Panel B. After the interim analysis of Panel B, Panel D was started to study higher doses, as well as other clinically relevant dose administrations.
As the aim was to develop a 3-month formulation, the key parameter for Panel A and C was the t1/2. In Panels B and D, the interest was to document the PK profile and explore exposure for different doses and injection sites. The parameters of interest therefore were AUC and Cmax.

Figure 1: Study Flow Chart



Sampling Times (PK, plasma): Serial PK blood samples for determination of paliperidone

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and/or paliperidone palmitate were collected for a 96-hour observation period in Period 1 and a 364- or 544-day observation period in Period 2.

-
- **Analytical Method:**

Table 1: Bioanalytical Methods used

Study ID (Location)	Matrix	Analyte	Concentration range	Method
R092670-PSY-1005 Mod5.3.3.2	plasma	paliperidone	0.100-250 ng/mL	LC-MS/MS
	plasma	paliperidone	0.100-250 ng/mL	LC-MS/MS
	plasma	paliperidone	0.0100-1.00 ng/mL	Qualified LC-MS/MS
	plasma	paliperidone palmitate	0.200-100 ng/mL	LC-MS/MS
	Plasma	paliperidone enantiomers	0.200-100 ng/mL	LC-MS/MS
	Plasma	risperidone and paliperidone (screening samples)	0.100-250 ng/mL	Qualified LC-MS/MS

Table 2: Treatment Groups

Panel	Period 1	Period 2
A	1 mg paliperidone IR solution in the gluteal muscle	300 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the gluteal muscle
	1 mg paliperidone IR solution in the gluteal muscle	300 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a dry milling technique in the gluteal muscle
B	1 mg paliperidone IR solution in the gluteal muscle	75 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the gluteal muscle
	1 mg paliperidone IR solution in the gluteal muscle	150 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the gluteal muscle
	1 mg paliperidone IR solution in the gluteal muscle	450 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the gluteal muscle
	1 mg paliperidone IR solution in the deltoid muscle	300 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the deltoid muscle
	1 mg paliperidone IR solution in the deltoid muscle	450 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the deltoid muscle
C	1 mg paliperidone IR solution in the gluteal muscle	150 mg eq. 3-month formulation paliperidone palmitate F016 manufactured by a wet milling technique in the gluteal muscle
D	1 mg paliperidone IR solution in the gluteal muscle	525 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the gluteal muscle
	1 mg paliperidone IR solution in the deltoid muscle	525 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the deltoid muscle
	1 mg paliperidone IR solution in the gluteal muscle	350 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the gluteal muscle
	1 mg paliperidone IR solution in the deltoid muscle	175 mg eq. 3-month formulation paliperidone palmitate F015 manufactured by a wet milling technique in the deltoid muscle

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- **Results:**

Pharmacokinetic Evaluation

Table 3: Subject Demographic Characteristics

Subject Demographic Characteristics (Panel A)

	Paliperidone 300 mg Gluteal ([redacted] (b) (4)	Paliperidone 300 mg Gluteal [redacted] (b) (4)	Total
Treated/completed/withdrawn AE/Withdrawn other	39/20/3/16	33/28/0/5	72/48/3/21
Male/Female	28/11	24/9	33/32
Age [Median (range)] yrs	42 (22, 60)	44 (29, 55)	43 (22, 60)
Weight [Mean (SD)] kg	78.05 (16.5)	77.07 (15.24)	77.60 (15.98)
BMI [mean (SD)] kg/m^2	26.37 (4.39)	26.25 (4.67)	26.32 (4.50)
Race [White/AA]	12/22	20/11	32/33

Table 4: Subject Demographics Characteristics (Panel B)

	75 mg-eq F015 [redacted] (b) (4) Gluteal	150 mg-eq F015 [redacted] (b) (4) Gluteal	300 mg eq. F015 [redacted] (b) (4) Deltoid	450 mg-eq. F015 [redacted] (b) (4) - Gluteal -	450 mg-eq F015 [redacted] (b) (4) Deltoid	Total
Treated/completed/withdrawn AE/Withdrawn other	25/19/1/5	27/21/0/6	26/21/0/5	25/21/2/2	25/22/1/2	128/104/4/20
Male/Female	15/10	15/12	16/10	15/10	14/11	75/53
Age [Median (range)] yrs	44 (24,63)	42 (25,55)	44.5 (25, 62)	45 (25,58)	38 (22,57)	43 (22,63)
Weight [Mean (SD)] kg	76.73 (14.11)	79.10 (16.20)	80.43 (13.09)	76.40 (12.41)	80.30 (14.33)	78.61 (13.99)
Race [White/AA/other]	18/3/4	17/3/7	19/2/5	13/6/6	14/3/8	81/17/30
BMI [mean (SD)] kg/m^2	27.68 (3.91)	27.75 (4.29)	27.66 (4.26)	27.60 (4.41)	27.97 (4.11)	27.73 (4.14)

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Table 5: Subject Demographic Characteristics (Panel C)

Treated/completed/withdrawn AE/Withdrawn other	25/22/0/3
Male/Female	18/7
Age [Median (range)] yrs	43 (25, 57)
Weight [Mean (SD)] kg	67.12 (12.18)
Race [White/AA/other]	8/1/12
BMI [mean (SD)]	24.18 (3.53)

Table 6: Subject Demographic Characteristics (Panel D)

	175 mg eq F015 (b) (4) Deltoid	350 mg eq. F015 (b) (4) Gluteal	525 mg eq. F015 (b) (4) Gluteal	525 mg eq. F015 (b) (4) Deltoid	Total
Treated/completed/withdrawn AE/Withdrawn other	26/14/0/12	24/17/0/7	25/21/1/3	25/19/0/6	100/71/1/28
Male/Female	19/7	18/6	17/8	17/8	71/29
Age [Median (range)] yrs	41 (23, 64)	46.5 (27, 62)	43 (22, 63)	38 (21, 56)	41 (21, 64)
Weight [Mean (SD)] kg	79.89 (13.12)	79.98 (18.02)	76.21 (15.68)	74.84 (14.91)	77.73 (15.41)
Race [White/AA/other]	19/0/0	10/0/0	18/0/0	16/0/0	63/0/0
BMI [mean (SD)]	27.44 (4.01)	27.35 (4.56)	26.17 (4.32)	25.50 (4.21)	26.62 (4.29)

Table 7: Relative Bioavailability: Summary of the Statistical Analysis of Dose-Normalized AUC∞ of Paliperidone After Administration of PP3M Compared to 1 mg Paliperidone IR, Study

Reference ID: 3748068

Test treatment	n	LS means		LS means ratio, %	90% CI, % [a]
		1 mg paliperidone IR (reference)	Test treatment		
Panel A and C					
300 mg eq. F015 (b) (4) gluteal	14	243	142	58.31	32.56 - 104.41
300 mg eq. F015 gluteal	21	195	84.1	43.08	30.09 - 61.67
150 mg eq. F016 gluteal	18	242	210	87.04	75.59 - 100.23
Panel B and D					
75 mg eq. F015, gluteal	13	254	285	112.26	102.41 - 123.07
150 mg eq. F015, gluteal	10	257	256	99.64	81.27 - 122.16
350 mg eq. F015, gluteal	16	236	274	116.44	106.08 - 127.82
450 mg eq. F015, gluteal	11	243	262	107.84	97.86 - 118.84
525 mg eq. F015, gluteal	18	251	263	104.81	94.58 - 116.14
175 mg eq. F015, deltoid	22	257	276	107.25	100.65 - 114.29
300 mg eq. F015, deltoid	15	249	261	105.04	96.84 - 113.93
450 mg eq. F015, deltoid	14	253	269	106.43	96.90 - 116.90
525 mg eq. F015, deltoid	20	233	260	111.32	104.56 - 118.53

[a] 90% confidence intervals

Dose-normalized to 1 mg. LS=least-squares.

The low relative bioavailability of F015 and F016 in Panels A and C of the study was due to incomplete dosing of the active ingredient resulting from inadequate shaking of syringes before injection in some subjects. This incomplete shaking led to significant quantities of medication being left in the syringe due to investigational product not being resuspended prior to injection. Therefore, PP3M paliperidone PK exposure information obtained in Period 2 for those subjects in Panels A and C are not reliable (i.e., underestimated). The calculated Frel values (ratio of AUC $_{0-\infty}$ obtained in Period 2 vs AUC $_{0-\infty}$ in Period 1, after correction for the difference in dose) for those subjects was less than 100%, not due to a difference in actual relative bioavailability, but because a lower than intended dose was administered in some subjects. The sponsor decided to develop the formulation with (b) (4)

Panel A and C

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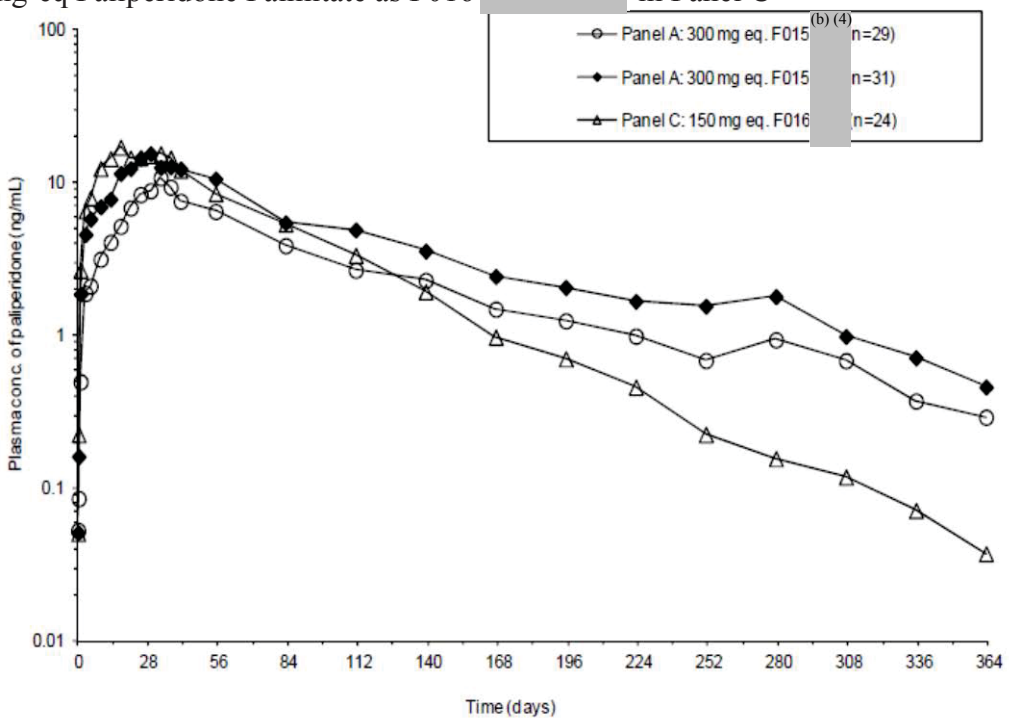
Figure 2: Semi-Logarithmic median plasma concentration-time profiles of Paliperidone after administration of 300 mg eq. Paliperidone as F015 (b) (4) and F015 (b) (4) in Panel A and 150 mg-eq Paliperidone Palmitate as F016 (b) (4) in Panel C



The decline in plasma concentrations of paliperidone was comparable for the F015 formulation (Panel A) with the (b) (4) technique and the (b) (4) technique. For the F016 formulation (Panel C) the decline was faster compared to the F015 formulation.

Table 8: Summary of the Key Pharmacokinetic Parameters of Paliperidone after administration of 1 mg Paliperidone IR (Period 1), Paliperidone Palmitate (F016) and Paliperidone Palmitate F015 (Period 2) (Panels A and C)

Reference ID: 3748068

PK of paliperidone	150 mg eq. F016 (b) (4) (Panel C)			300 mg eq. F015 (b) (4) (Panel A)			300 mg eq. F015 (b) (4) (Panel A)		
	N	Mean	Median (min-max)	N	Mean	Median (min-max)	N	Mean	Median (min-max)
Period 1: 1 mg Paliperidone IR									
C_{max}, ng/mL	24	12.4	10.9 (4.24 - 27.6)	32	10.4	8.65 (4.32 - 22.8)	35	9.52	7.60 (3.56 - 21.8)
t_{max}, days	24		0.53 (0.45 - 6.08)	32		1.00 (0.48 - 4.00)	35		1.00 (0.50 - 4.00)
AUC_{∞}, ng.h/mL	23	242	232 (117 -232)	31	223	188 (93.8 - 648)	33	203	194 (65.1 - 513)
Period 2: 150 mg or 300 mg eq. Paliperidone Palmitate									
C_{max}, ng/mL	24	19.4	18.6 (4.38 – 42.0)	30	15.6	11.6 (2.08 - 66.7)	32	23.7	17.8 (0.927 - 89.8)
t_{max}, days	24		21.02 (12.98 – 42.00	30		33.01 (13.00 - 193.05)	32		27.57 (4.11 - 222.00)
AUC_{last}, ng.h/mL	22	31047	30552 (12770 - 60210)	26	34843	28929 (5642 - 118207)	18	44712	49334 (1626 - 92292)
$F_{rel, AUClast}$, %*	22	90.1	82.8(46.8 - 215)	25	58.7	60.7 (7.54 - 146)	17	69.9	73.7 (1.06 - 159)

The median paliperidone Cmax and AUClast in Period 2 after administration of 300 mg eq. F015 (b) (4) were higher as compared to 300 mg eq. F015 (b) (4) The %CV for Cmax and AUClast were, respectively, 56.4% and 40.6% after administration of 150 mg eq. F016 (b) (4) 90.3% and 81.5% after administration of 300 mg eq. F015 (b) (4) and 82.0% and 48.1% after administration of 300 mg eq. F015 (b) (4)

Table 9: Summary of the Statistical Analysis of the PK Parameters of Paliperidone after Administration of Paliperidone Palmitate, 150 mg eq. F016 (b) (4), 300 mg eq. F015 (b) (4) (Test) and 300 mg eq. F015 (b) (4) Compared to 1 mg Paliperidone IR (Reference) (Panels A and C)

Test treatment	Parameter	N	LSmeans 1 mg Pali IR (reference)	LSmeans Test treatment	LSmeans ratio, %	90% CI,% [a]
150 mg eq. (F016) (b) (4)	$AUC_{last, DN}$, ng.h/mL*	22	228.9	190.2	83.08	71.81 - 96.11
	$AUC_{\infty, DN}$, ng.h/mL	18	241.5	210.2	87.04	75.59 - 100.23
300 mg eq. (F015) (b) (4)	$AUC_{last, DN}$, ng.h/mL*	17	230.8	122.6	53.10	33.35 - 84.56
	$AUC_{\infty, DN}$, ng.h/mL	14	243.2	141.8	58.31	32.56 - 104.41
300 mg eq. (F015) (b) (4)	$AUC_{last, DN}$, ng.h/mL*	25	197.7	81.85	41.39	30.03 - 57.05
	$AUC_{\infty, DN}$, ng.h/mL	21	195.3	84.13	43.08	30.09 - 61.67

[a] 90% confidence intervals.

The formulations (PP3M) are not equivalent to the 1 mg Paliperidone IR.

The sponsor decided to develop the F015 formulations with (b) (4)

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Panel B
Figure 2: Mean (±SD) Linear and Semi-Logarithmic Plasma Concentration-Time Profiles of Paliperidone, Period 2

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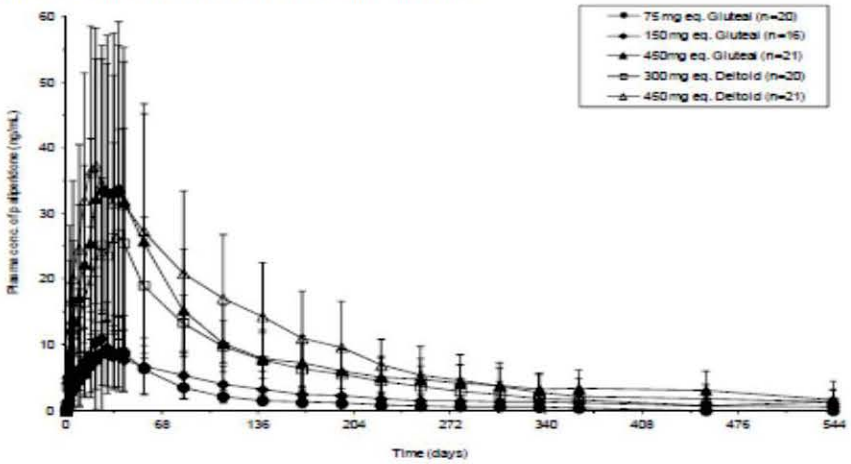
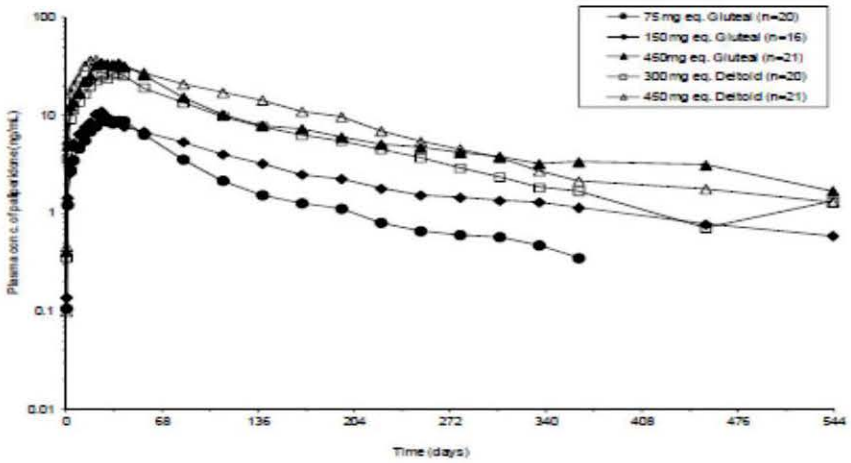
Period 2: 75 mg eq. F015 injected in the gluteal muscle
Period 2: 150 mg eq. F015 injected in the gluteal muscle
Period 2: 450 mg eq. F015 injected in the gluteal muscle
Period 2: 300 mg eq. F015 injected in the deltoid muscle
Period 2: 450 mg eq. F015 injected in the deltoid muscle





Reference ID: 3748068

Figure 3: Median Linear and Semi-Logarithmic Plasma Concentration-Time Profiles of Paliperidone- Dose Normalized to 350 mg-eq, Period 2

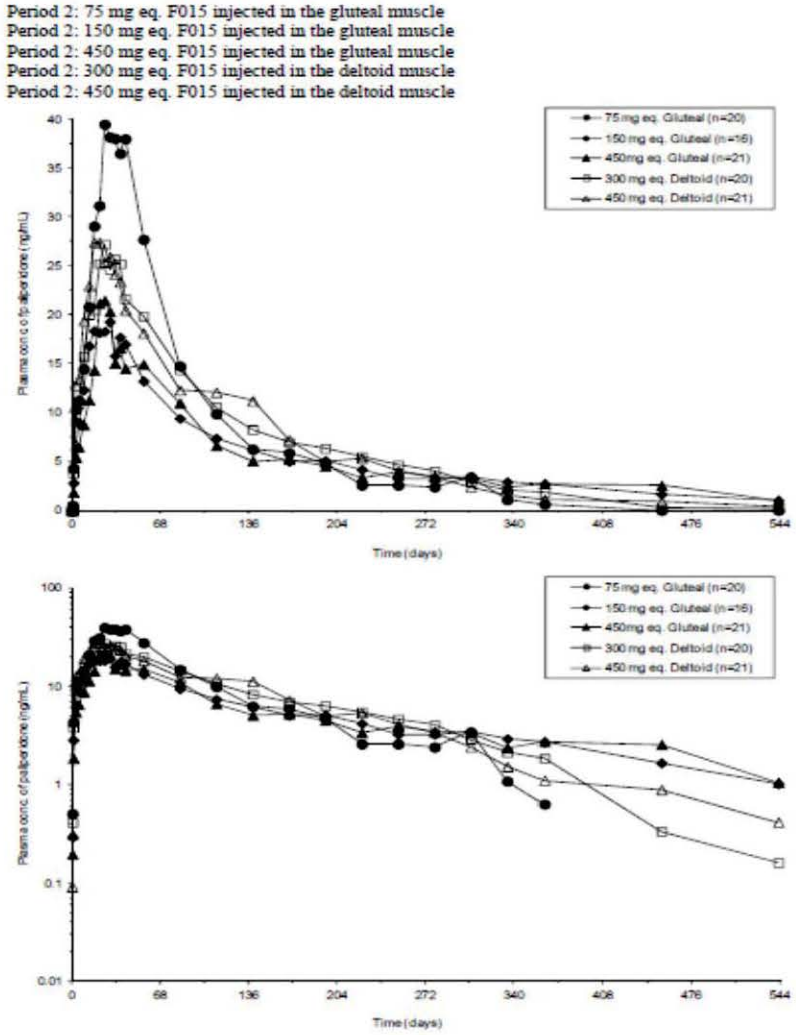


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Figure 4: Period 2: Cmax by BMI category, dose normalized to 350 mg eq.

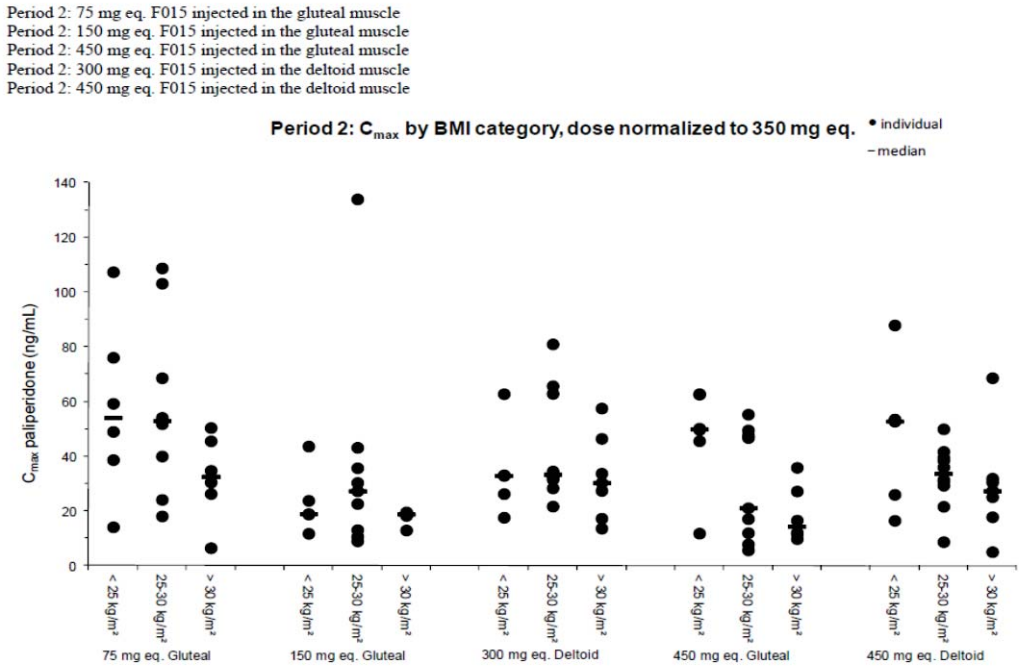
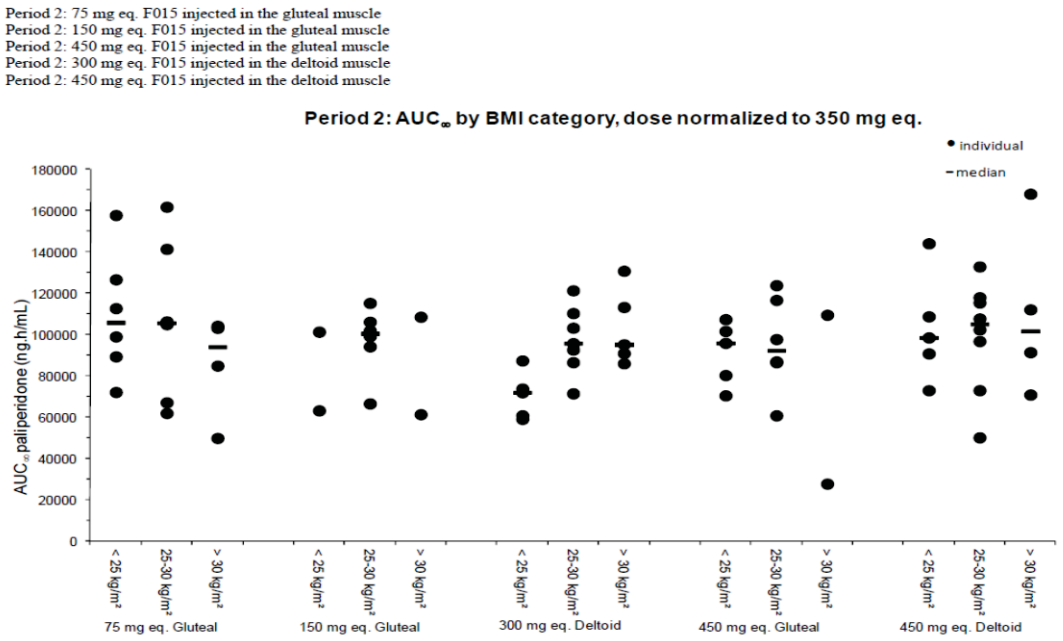


Figure 5: AUC $_{0-\infty}$ by BMI category, dose normalized to 350 mg eq



Median plasma concentrations of paliperidone increased with dose after administration of 75 mg eq., 150 mg eq., and 450 mg eq. in the gluteal muscle, and similarly after administration

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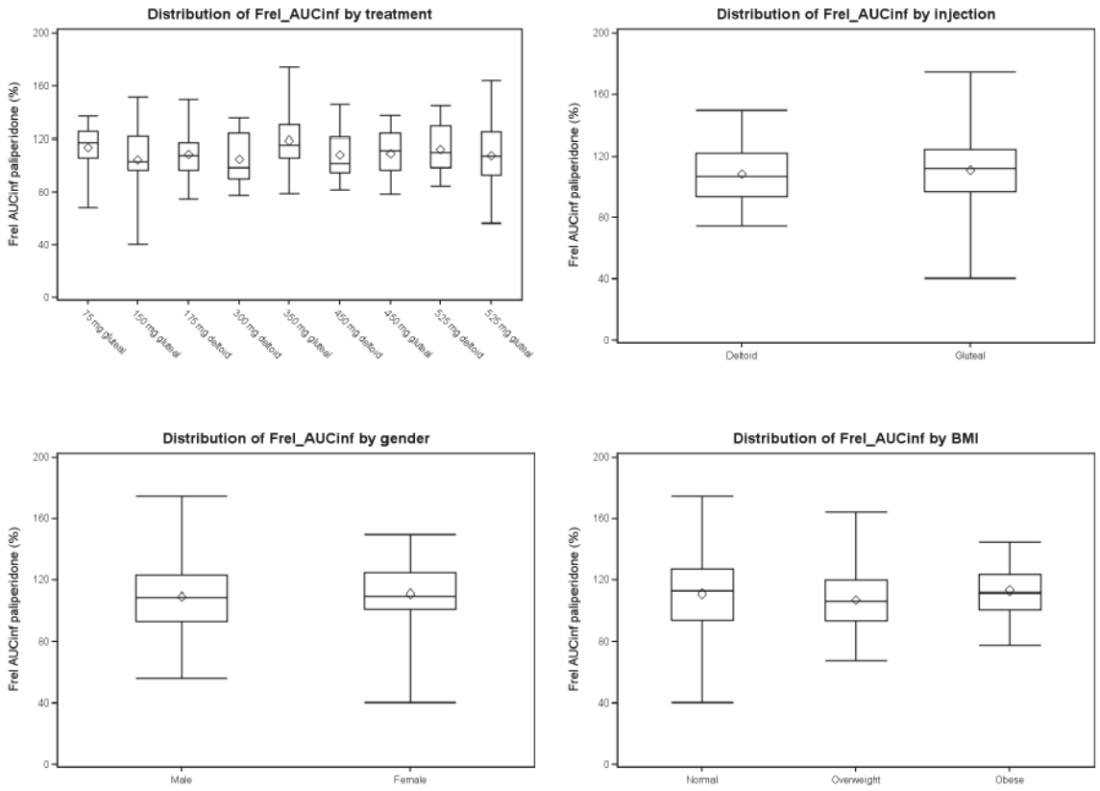
of 300 mg eq. and 450 mg eq. in the deltoid muscle, reaching a median Tmax of 29, 28 and 28 days for dose groups 75 mg eq., 150 mg eq., and 450 mg eq. in the gluteal muscle, respectively; and 37 and 24 days for dose groups 300 mg eq. and 450 mg eq. in the deltoid muscle, respectively. In general, the maximum plasma concentration of paliperidone increased with dose. The median peak plasma concentrations of paliperidone after administration of 450 mg eq. paliperidone palmitate in the deltoid muscle was higher compared to that after administration of 450 mg eq. paliperidone palmitate in the gluteal muscle. The Cmax and AUC of paliperidone do not appear to differ with respect to BMI. The median relative bioavailability estimated as the AUC∞ ratios of Treatment Period 2/Treatment Period 1 (Frel,AUC∞) was comparable between the dose groups and ranged between 101.78% after administration of 450 mg eq. in the deltoid muscle to 117.65% after 75 mg eq. in the gluteal muscle.

Figure 6: Box Plots of Relative Bioavailability after Administration of PP3M by Treatment, Injection Site,
Sex, BMI and Race



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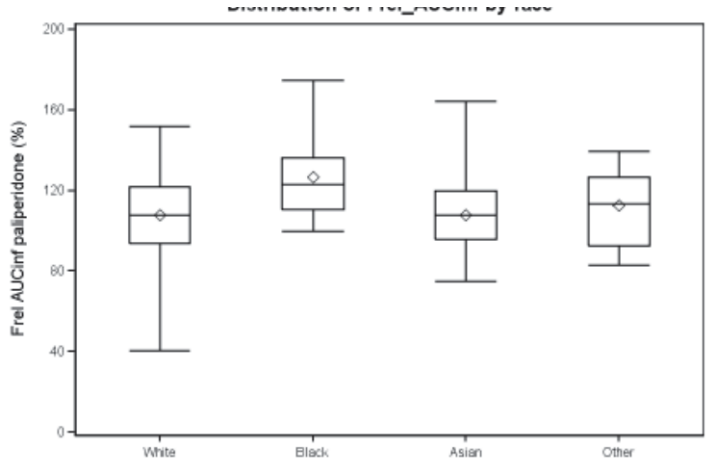

Table 10: Summary of the Key Pharmacokinetic Parameters of Paliperidone after administration of 1 mg Paliperidone (Period 1) and 75 mg eq, 150 mg eq and 450 mg eq Paliperidone Palmitate in the Gluteal Muscle

Pharmacokinetics of paliperidone (Panel B, F015)	75 mg eq. Gluteal			150 mg eq. Gluteal			450 mg eq. Gluteal		
Period 1: 1 mg Pali IR	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	21	11.4	12.3 (0.586-19.6)	21	10.7	10.5 (3.95-16.1)	22	10.8	11.6 (0.906-14.6)
t_{max}, h	21		1.00 (0.45-4.00)	21		1.00 (0.45-12.00)	22		1.00 (0.48-6.00)
AUC_{last}, ng.h/mL	21	230	244 (10.8-408)	21	241	233 (107-421)	22	231	243 (17.2-346)
AUC_{∞}, ng.h/mL	20	256	263 (25.2-440)	21	257	264 (111-444)	22	246	251 (19.8-376)
$t_{1/2}$, h	20	26.2	25.0 (17.2-39.9)	21	24.4	22.3 (18.4-42.0)	22	24.3	23.6 (15.9-38.7)
Period 2	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	20	10.8	10.1 (1.39-23.3)	18	12.2	8.33 (3.86-57.4)	21	40.3	35.0 (7.31-80.7)
t_{max}, days	20		29.00 (16.98-113.99)	18		27.51 (8.09-41.00)	21		28.00 (13.00-54.98)
$AUC_{12months}$ ng.h/mL	16	20352	21133 (11666-34464)	13	30662	28412 (14659-49307)	20	92597	93608 (34078-154371)
$AUC_{18months}$ ng.h/mL	14	21342	21577 (13047-34616)	10	35154	36811 (20711-49307)	17	107055	110699 (54659-186494)
AUC_{∞}, ng.h/mL	16	22007	22214 (10671-34683)	10	39323	42963 (26283-49399)	13	115241	123273 (35579-159235
$t_{1/2}$, days	18	83.0	44.9 (26.9-341.5)	10	96.6	79.6 (27.7-198.9)	15	120.5	81.5 (21.2-349.5)
$F_{rel,\ AUC12months}$ %	14	103.62	109.48 (67.96-135.67)	13	81.08	81.38 (32.06-122.39)	17	84.22	94.25 (31.45-126.55)
$F_{rel,\ AUC18months}$ %	12	107.80	111.93 (67.96-135.67)	10	88.43	86.72 (37.13-122.39)	16	96.42	97.66 (41.16-137.32)
$F_{rel,\ AUC\infty}$, %	13	113.92	117.65 (68.20-137.61)	10	104.37	103.33 (40.64-151.63)	11	109.36	111.61 (78.67-138.06)

Table 11: Summary of the Key Pharmacokinetic Parameters of Paliperidone after Administration of 1 mg Paliperidone (Period 1) and 300 mg eq. and 450 mg eq Paliperidone Palmitate in the Deltoid Muscle (Period 2) (Panel B)

Reference ID: 3748068

Pharmacokinetics of paliperidone (Panel B, F015)	300 mg eq. Deltoid			450 mg eq. Deltoid		
Period 1: 1 mg Pali IR	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	20	12.3	12.5 (8.30-17.2)	23	12.6	12.4 (6.43-17.0)
t_{max}, h	20		0.75 (0.48-4.02)	23		0.92 (0.45-3.00)
AUC_{last}, ng.h/mL	20	240	237 (189-303)	23	272	264 (131-612)
AUC_{∞}, ng.h/mL	20	256	252 (198-332)	19	262	256 (135-397)
$t_{1/2}$, h	20	25.4	25.4 (15.6-36.5)	20	25.2	23.6 (16.2-45.1)
Period 2	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	20	32.4	28.0 (11.7-69.4)	22	45.0	40.1 (6.49-113)
t_{max}, days	20		34.00 (13.00-83.12)	22		23.98 (12.99-51.07)
$AUC_{12months}$, ng.h/mL	17	72959	74065 (45401-106437)	19	119012	122682 (22679-216062)
$AUC_{18months}$, ng.h/mL	12	75884	76193 (49856-117544)	16	132017	138021 (34360-216062)
AUC_{∞}, ng.h/mL	17	78166	77925 (50607-112132)	17	132645	131651 (64417-216177)
$t_{1/2}$, days	17	77.7	73.5 (28.3-177.8)	18	85.9	71.8 (24.5-226.5)
F_{rel}, $AUC_{12months}$, %	16	100.07	99.99 (50.41-128.22)	16	94.72	97.63 (37.34-145.85)
F_{rel}, $AUC_{18months}$, %	11	107.08	108.18 (68.14-143.88)	13	97.68	95.63 (56.58-143.05)
$F_{rel, AUC\infty}$, %	15	106.61	102.60 (77.70-136.12)	14	108.43	101.78 (81.84-145.99)

Table 12: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Paliperidone after administration of Paliperidone Palmitate Treatment Groups (Test) compared to 1 mg Paliperidone IR (Reference) (Panel B)

Panel B (F015)			LSmeans			
Test treatment	Parameter	N	1 mg Pali IR (reference)	Test treatment	LSmeans ratio, %	90% CI,% [a]
75 mg eq. F015 Gluteal	$AUC_{12months, DN}$, ng.h/mL	14	248	252	101.66	92.18 - 112.12
	$AUC_{18months, DN}$, ng.h/mL	12	249	265	106.14	96.21 - 117.09
	$AUC_{\infty, DN}$, ng.h/mL	13	254	285	112.26	102.41 - 123.07
150 mg eq. F015 Gluteal	$AUC_{12months, DN}$, ng.h/mL	13	254	193	75.99	62.32 - 92.67
	$AUC_{18months, DN}$, ng.h/mL	10	269	225	83.67	67.30 - 104.03
	$AUC_{\infty, DN}$, ng.h/mL	10	257	256	99.64	81.27 - 122.16
300 mg eq. F015 Deltoid	$AUC_{12months, DN}$, ng.h/mL	16	248	242	97.48	87.44 - 108.67
	$AUC_{18months, DN}$, ng.h/mL	11	242	254	104.78	92.78 - 118.34
	$AUC_{\infty, DN}$, ng.h/mL	15	249	261	105.04	96.84 - 113.93
450 mg eq. F015 Deltoid	$AUC_{12months, DN}$, ng.h/mL	16	250	226	90.55	78.47 - 104.49
	$AUC_{18months, DN}$, ng.h/mL	13	269	256	95.19	84.56 - 107.15
	$AUC_{\infty, DN}$, ng.h/mL	14	253	269	106.43	96.90 - 116.90
450 mg eq. F015 Gluteal	$AUC_{12months, DN}$, ng.h/mL	17	242	188	77.73	64.63 - 93.50
	$AUC_{18months, DN}$, ng.h/mL	16	235	217	92.18	79.94 - 106.30
	$AUC_{\infty, DN}$, ng.h/mL	11	243	262	107.84	97.86 - 118.84

[a] 90% confidence intervals.
DN=dose normalized to 1 mg.

Median values of Cmax and AUC $_{0-\infty}$ for paliperidone in Period 2 increased proportionally with dose, except for the 75 mg eq. gluteal dose group for which median dose normalized Cmax (but not AUC $_{0-\infty}$) was higher compared to the other dose groups. The inter-subject %CV for

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Cmax was slightly lower in the dose groups with deltoid muscle injection (range between 49.1% and 54.4%) as compared to the groups with gluteal muscle injection (range between 59.4% and 99.2%). The inter-subject %CV for $AUC_{0-\infty}$ was similar across the dose groups and ranged between 22.0% and 31.7%. Median Tmax values were comparable for all dose groups (ranging from 27.51 to 29.00 days) with gluteal muscle injection. For the groups with the deltoid muscle injection, the Tmax ranged from 23.98 days (450 mg eq.) to 34.00 days (300 mg eq.)

Panel D

Figure 7: Mean (±SD) Linear and Semi-Logarithmic Plasma Concentration-Time Profiles of Paliperidone

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Period 2: i.m. injection with 175 mg eq. paliperidone palmitate F015 injected in the deltoid muscle
Period 2: i.m. injection with 350 mg eq. paliperidone palmitate F015 injected in the gluteal muscle
Period 2: i.m. injection with 525 mg eq. paliperidone palmitate F015 injected in the deltoid muscle
Period 2: i.m. injection with 525 mg eq. paliperidone palmitate F015 injected in the gluteal muscle

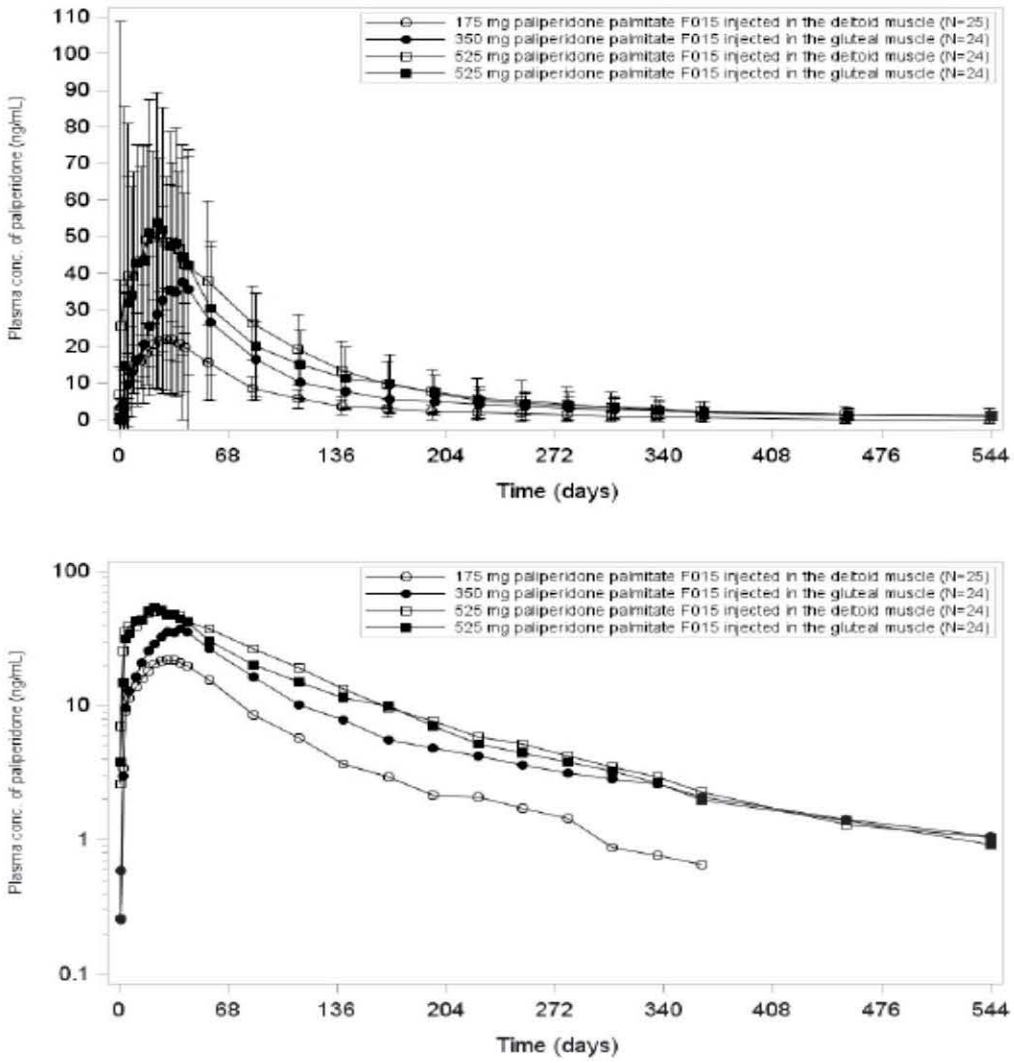

Figure 8: Scatter Plots of Pharmacokinetic Parameters of Paliperidone – by BMI Category

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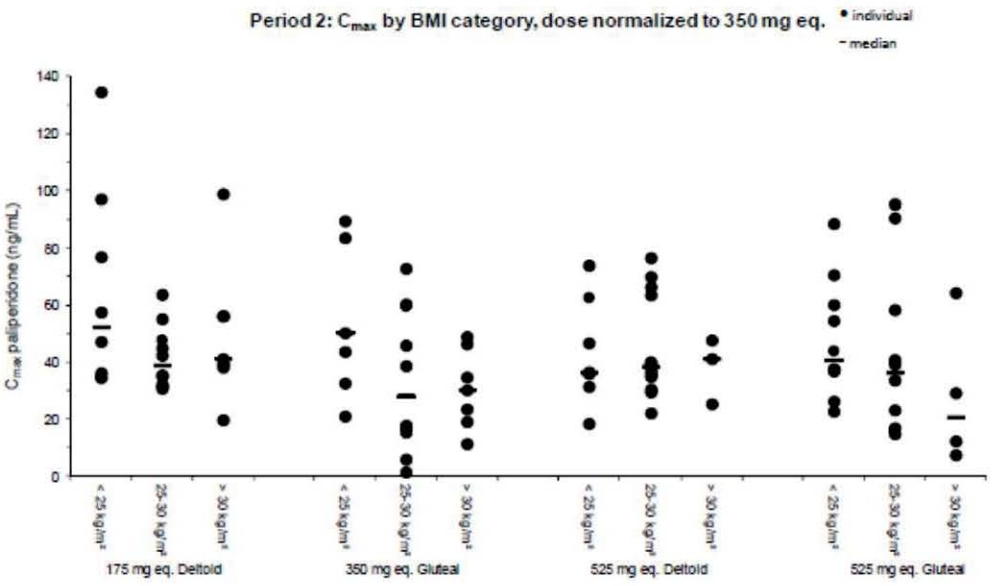

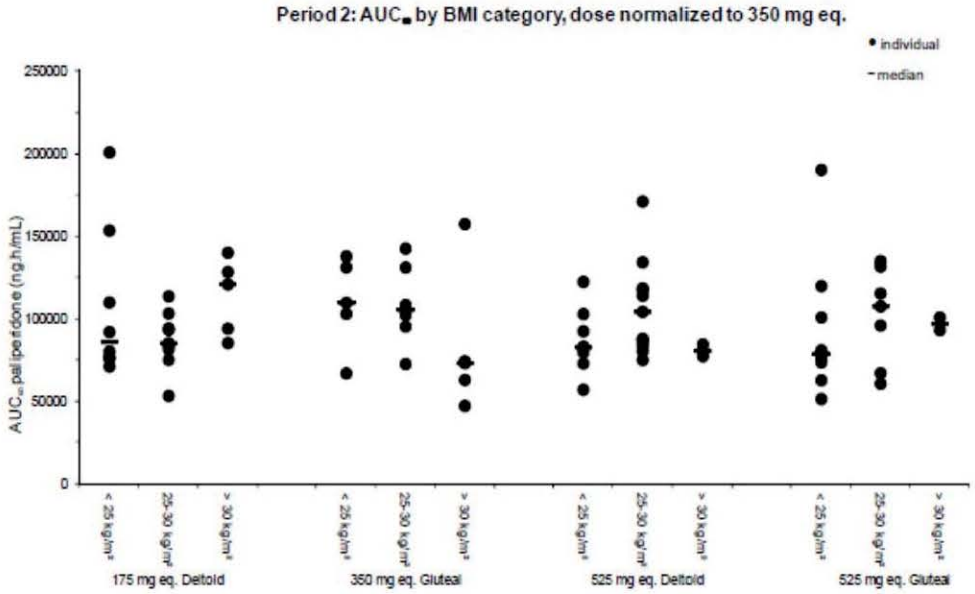

Table 13: Summary of the Key Pharmacokinetic Parameters of Paliperidone after Administration of 1 mg Paliperidone (Period 1) and 175 mg eq, and 525 mg eq. Paliperidone Palmitate in the

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Deltoid Muscle (Period 2) (Panel D)

Pharmacokinetics of paliperidone (Panel D, F015)	175 mg eq. Deltoid			525 mg eq. Deltoid		
Period 1: 1 mg Pali IR	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	26	11.6	11.6 (7.99-16.5)	24	12.0	11.6 (7.08-21.3)
t_{max}, h	26		1.00 (0.47-3.92)	24		0.75 (0.48-3.00)
AUC_{last}, ng.h/mL	26	241	234 (128-409)	24	234	230 (134-428)
AUC_{∞}, ng.h/mL	26	258	247 (138-449)	23	240	245 (138-353)
$t_{1/2}$, h	26	24.6	24.5 (18.3-33.8)	24	25.2	24.1 (16.4-52.3)
Period 2	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	25	25.8	21.2 (9.85-67.3)	24	80.0	57.9 (27.6-416)
t_{max}, days	25		23.99 (5.00-56.10)	24		24.51 (0.99-54.99)
$AUC_{12months}$, ng.h/mL	18	49993	44149 (26712-99648)	20	136074	124672 (85817-221565)
$AUC_{18months}$, ng.h/mL	14	46806	45391 (26712-70029)	18	141127	125429 (85817-244079)
AUC_{∞}, ng.h/mL	22	50407	46480 (26773-100550)	22	144173	128969 (85887-257003)
$t_{1/2}$, days	22	56.6	51.7 (19.7-143.1)	22	60.7	56.9 (21.3-115.2)
F_{rel}, $AUC_{12months}$, %	18	107.47	106.07 (73.82-148.55)	18	107.92	103.29 (60.42-144.68)
F_{rel}, $AUC_{18months}$, %	14	106.74	109.07 (74.47-135.22)	16	163.07	160.11 (126.19-217.02)
$F_{rel, AUC\infty}$, %	22	108.77	107.94 (74.85-149.89)	20	112.72	109.98 (84.83-144.77)

The median peak plasma concentrations of paliperidone after administration of 525 mg eq. paliperidone palmitate in the deltoid muscle were slightly higher compared to that after administration of 525 mg eq. paliperidone palmitate in the gluteal muscle. Median values of Cmax and $AUC_{0-\infty}$ for paliperidone in Period 2 increased proportionally with dose. The inter-subject %CV for Cmax was 50.5% and 94.7% for the 175 mg eq. and 525 mg eq. deltoid dose groups respectively and 87.5% and 59.7% for the 350 mg eq. and 525 mg eq. gluteal dose groups respectively. The inter-subject %CV for AUC∞ was 32.5% and 26.4% for the 175 mg eq. and 525 mg eq. deltoid dose groups respectively and 32.3% and 34.8% for the 350 mg eq. and 525 mg eq. gluteal dose groups respectively.

Table 14: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Paliperidone after administration of Paliperidone Palmitate Treatment Groups (Test) compared

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to 1 mg Paliperidone IR (Reference)(Panel D)

Panel D (F015) Test treatment	Parameter	N	LSmeans 1 mg Pali IR (reference)	LSmeans Test treatment	LSmeans ratio, %	90% CI,% [a]
175 mg eq. F015 Deltoid	$AUC_{12months, DN}$, ng.h/mL	18	257	272	105.85	98.35 - 113.92
	$AUC_{18months, DN}$, ng.h/mL	14	247	260	105.59	98.12 - 113.63
	$AUC_{\infty, DN}$, ng.h/mL	22	257	276	107.25	100.65 - 114.29
350 mg eq. F015 Gluteal	$AUC_{12months, DN}$, ng.h/mL	17	236	232	98.32	84.87 - 113.89
	$AUC_{18months, DN}$, ng.h/mL	17	233	252	107.97	96.02 - 121.41
	$AUC_{\infty, DN}$, ng.h/mL	16	236	274	116.44	106.08 - 127.82
525 mg eq. F015 Deltoid	$AUC_{12months, DN}$, ng.h/mL	18	233	246	105.44	96.06 - 115.73
	$AUC_{18months, DN}$, ng.h/mL	16	236	253	107.16	99.23 - 115.71
	$AUC_{\infty, DN}$, ng.h/mL	20	233	260	111.32	104.56 - 118.53
525 mg eq. F015 Gluteal	$AUC_{12months, DN}$, ng.h/mL	23	255	214	84.14	70.95 - 99.78
	$AUC_{18months, DN}$, ng.h/mL	20	244	232	95.24	82.07 - 110.52
	$AUC_{\infty, DN}$, ng.h/mL	18	251	263	104.81	94.58 - 116.14

[a] 90% confidence intervals.
DN=dose normalized to 1 mg.

Table 15: Summary of key Pharmacokinetic Parameters after Administration of PP3M in Study R092670-PSY-1005- By Treatment, Panels B and D

Dose	75 mg eq. Gluteal			150 mg eq. Gluteal			350 mg eq. Gluteal			450 mg eq. Gluteal			525 mg eq. Gluteal		
Parameter (t_{max}: median [range])	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median
C_{max}, ng/mL	20	10.8 (59.4)	10.1	18	12.2 (99.2)	8.33	24	44.0 (87.5)	36.7	21	40.3 (63.8)	35.0	24	63.8 (59.7)	56.3
t_{max}, days	20	29.00 (16.98-113.99)		18	27.51 (8.09-41.00)		24	31.03 (5.00-84.08)		21	28.00 (13.00-54.98)		24	23.01 (2.00-41.00)	
AUC_{∞}, ng.h/mL	16	22,007 (31.7)	22,214	10	39,323 (22.0)	42,963	16	101,244 (32.3)	102,894	13	115,241 (28.8)	123,273	18	145,611 (34.8)	142,201
$t_{1/2}$, days	18	83.0 (100.1)	44.9	10	96.6 (69.3)	79.6	19	94.7 (77.3)	77.4	15	120.5 (77.3)	81.5	20	91.8 (72.6)	68.5
$F_{rel, AUC\infty}$, %	13	113.92 (16.4)	117.65	10	104.37 (27.6)	103.33	16	118.93 (21.4)	115.91	11	109.36 (17.2)	111.61	18	107.80 (23.6)	107.41
Dose	-			**175 mg eq. Deltoid**			**300 mg eq. Deltoid**			**450 mg eq. Deltoid**			**525 mg eq. Deltoid**		
Parameter (t_{max}: median [range])	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median	n	Mean (%CV)	Median
C_{max}, ng/mL	-	-	-	25	25.8 (50.5)	21.2	20	32.4 (49.1)	28.0	24	45.0 (54.4)	40.1	24	80.0 (94.7)	57.9
t_{max}, days	-	-		25	23.99 (5.00-56.10)		20	34.00 (13.00-83.12)		22	23.98 (12.99-51.07)		24	24.51 (0.99-54.99)	
AUC_{∞}, ng.h/mL	-	-	-	22	50,407 (32.5)	46480	17	78,166 (22.3)	77925	17	132,645 (28.0)	131651	22	144,173 (26.4)	128,969
$t_{1/2}$, days	-	-	-	22	56.6 (57.7)	51.7	17	77.7 (50.1)	73.5	18	85.9 (65.8)	71.8	22	60.7 (47.7)	56.9
$F_{rel, AUC\infty}$, %	-	-	-	22	108.77 (17.0)	107.94	15	106.61 (17.8)	102.60	14	108.43 (20.4)	101.78	20	112.72 (16.2)	109.98

Dose proportionality

Figure 9: Linear Regression Model of Paliperidone Individual Dose Normalized (to 350 mg eq.) Cmax and $AUC_{0-\infty}$ after administration of Paliperidone Palmitate in the Deltoid or the Gluteal Muscle

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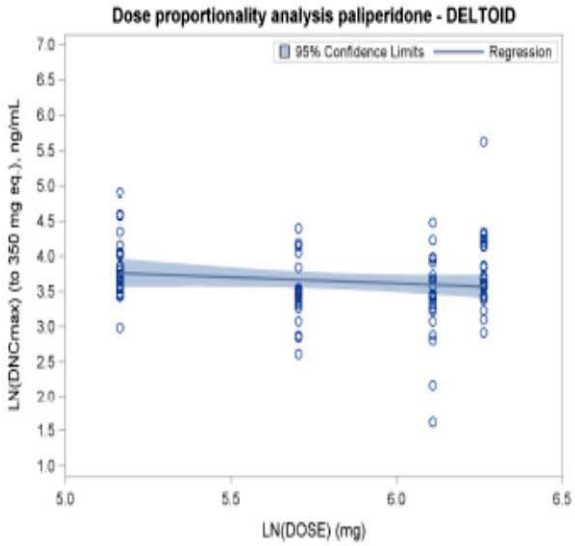

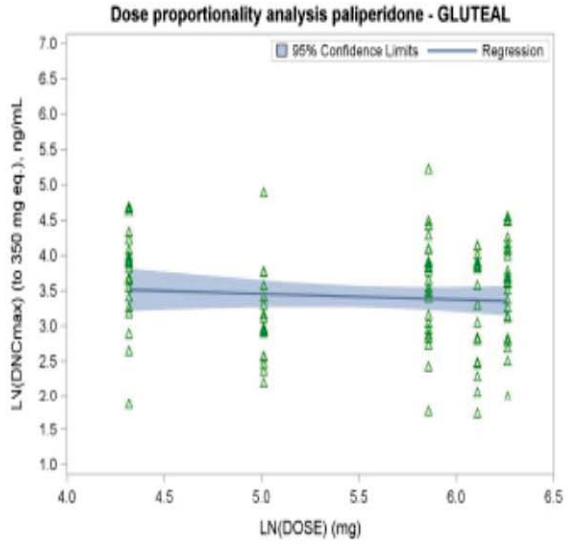

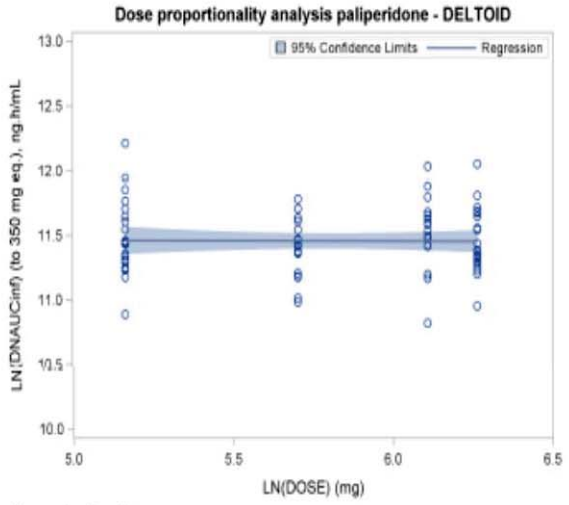

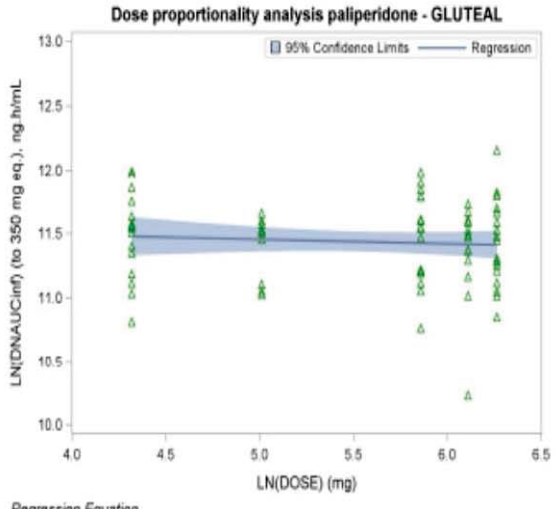

A proportional increase in $AUC_{0-\infty}$ with dose was observed because the $AUC_{0-\infty}$ slopes were not significantly different from zero for both the deltoid (slope -0.004, p=0.95) and gluteal (slope -0.033, p=0.52) injection sites as well as the deltoid and gluteal injection sites combined (slope -0.021, p=0.58), Similarly, for Cmax the slopes were not significantly different from zero for both the deltoid (slope -0.177, p=0.18) and gluteal (slope -0.081, p=0.45) injection sites as well as the deltoid and gluteal injection sites combined (slope -0.064, p=0.43),

The plasma concentrations of the R078543(+) enantiomer were consistently higher than those for the R078544(-) enantiomer. The median ratio of R078543(+)/R078544(-) plasma concentrations was 2.50 and 2.38, two days after i.m. administration of 175 mg eq. in the deltoid muscle and 525 mg eq. in the gluteal muscle respectively, decreasing to approximately a range of 1.72 to 1.94 and 1.49 to 1.82 respectively from 4 days post-dosing and onwards, for both injection sites and doses. The mean and median R078543(+)/R078544(-) PK parameter ratios after i.m. injections of paliperidone palmitate (F015) are 1.81 and 1.83 and 1.86 and 1.90, for

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$AUC_{0-\infty}$ and Cmax, respectively after injection of 175 mg eq. in the deltoid muscle. After injection of 525 mg eq. in the gluteal muscle mean and median ratios were 1.65 and 1.63 and 1.67 and 1.72 for AUC∞ and Cmax, respectively.

Pharmacokinetic Summary
After i.m. injection of 75-525 mg-eq. paliperidone palmitate (F015) in the gluteal or deltoid muscle, paliperidone palmitate is slowly absorbed, reflected by a Tmax of approximately 23 to 34 days and an apparent half-life of approximately 2-4 months; the half-life was similar in the gluteal and deltoid dose groups, except for the 75 mg eq. gluteal dose group where the half-life was smaller compared to the other dose groups. After a single i.m. injection of paliperidone palmitate (F015) in the gluteal or deltoid muscle, the paliperidone $AUC_{0-\infty}$ and Cmax increased dose-proportionally in the 75-525 mg-eq. range. The LSmeans of Cmax of paliperidone was higher after injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (27%) increase over all dose levels whereas there was no difference between both injection sites for $AUC_{0-\infty}$. After i.m. administration of paliperidone palmitate, a low incidence of low paliperidone palmitate concentrations was observed.
Some subjects in Panel B (Period 2), the $\%AUC_{0-\infty}$,extrapolated was above 20% of total AUC due to the continued release of paliperidone palmitate up to and beyond the last sampling point (3 out of 21 subjects in the 75 mg eq. gluteal dose group, 2 out of 14 subjects in the 150 mg eq. gluteal dose group, 2 out of 21 in the 450 mg eq. deltoid dose group and 2 out of 15 subjects in the 450 mg eq. gluteal dose group) requiring exclusion from the descriptive statistics. Therefore descriptive statistics on $AUC_{0-\infty}$ may be biased downwards.
After i.m. administration of paliperidone palmitate (F015), a low incidence of low paliperidone palmitate concentrations was observed (0.8%, 0%, 0% and 3.7% of the measured samples in Panel A, B, C and D respectively with a concentration of paliperidone palmitate <19.2 ng/mL)

Safety: Was there any death or serious adverse events? ☑ Yes ☐No ☐ NA
One death occurred in Panel B of study. The sponsor reported that the subject died due to metastatic melanoma, which was considered by the investigator not to be related to the study agent. One or more treatment-emergent SAEs were reported in 9 subjects in Panel A, 14 subjects in
Panel B, 1 subject in Panel C, and 11 subjects in Panel D. Majority of the SAEs were in the psychiatric disorders SOC. Three subjects withdrew from Panel A due to TEAEs of anxiety, suicidal ideation, and hypertension, 3 subjects withdrew from Panel B due to TEAEs of psychotic disorder, metastatic malignant melanoma, muscle spasticity, and dysphemia (each reported in 1 subject), and 1 subject withdrew from Panel D due to TEAE of psychotic disorder. No subjects withdrew from Panel C of the study due to TEAEs.
The sponsor reported that the most commonly reported TEAEs were In Panel A were headache and insomnia (each reported in 5.6% subjects) in Period 1; and headache and nasopharyngitis (each reported in 13.6% subjects), and toothache (6.1%) in Period 2. In Panel B were headache (4.7%), anxiety and constipation (each reported in 3.1% subjects) in Period 1; nasopharyngitis (12.5%); headache (11.7%); anxiety (10.0%); insomnia, diarrhea, toothache, and weight increased (each reported in 7.5% subjects), abdominal pain and back pain (each reported in 6.7% subjects), weight decreased and tachycardia (each reported in 5.8% subjects), and depression, psychotic disorder, and schizophrenia in Period 2 (each reported in 5% subjects). In Panel C was headache (8.0%) in Period 1; and upper respiratory tract infection (25.0%), headache (16.7%),

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constipation (12.5%), vomiting, dystonia, injection site warmth, back pain, and diabetes mellitus (each reported in 8.3% subjects) in Period 2. In Panel D was insomnia and anxiety (each 3.0%) in Period 1; and nasopharyngitis (10.2%), headache (7.1%), back pain (6.1%); dizziness, and weight increased (each reported in 5.1% subjects) in Period 2.

Conclusion:

After i.m. injection of 75-525 mg-eq. paliperidone palmitate (F015) in the gluteal or deltoid muscle, paliperidone palmitate is slowly absorbed, reflected by a Tmax of approximately 23 to 34 days and an apparent half-life of approximately 2-4 months; the half-life was similar in the gluteal and deltoid dose groups, except for the 75 mg eq. gluteal dose group where the half-life was slightly lower compared to the other dose groups. After a single i.m. injection of paliperidone palmitate (F015) in the gluteal or deltoid muscle, the paliperidone AUC∞ and Cmax increased dose-proportionally in the 75-525 mg-eq. range.

- **Reviewer's comments:** The reviewer agrees with the sponsor's conclusions.

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/s/

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