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Established Name Paliperidone Palmitate
(Proposed) Trade Name Invega[®] Sustenna[™]
Therapeutic Class Atypical Antipsychotic
Applicant Johnson & Johnson

Formulation(s) Long-Acting Injection
Dosing Regimen Injection Every 4 Weeks
Indication(s) Acute Treatment of
Schizophrenia
Intended Population(s) Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the available data submitted to this New Drug Application (NDA) (including the data from this resubmission and from the original NDA), it is recommended that this NDA be granted an approval status.

Several major labeling recommendations have been made. Please refer to section 9.2 Labeling Recommendations for detailed comments. Final approval is contingent on satisfactory response to the agency's recommendations and mutual agreement on labeling as well as the conclusions of the CMC, pharmacology/toxicology, and clinical pharmacology reviewers.

1.2 Risk Benefit Assessment

Schizophrenia is a severe mental disorder affected about 1% of population world wide. Because schizophrenia is a life-long disorder, compliance with medication treatment is crucial in schizophrenia treatment. Numerous typical and atypical antipsychotics have been approved by FDA for the treatment of schizophrenia in the USA. Compared with the oral preparations, only a few long-acting antipsychotic injections are available in the USA: two typical antipsychotics—haloperidol decanoate and fluphenazine decanoate, and one atypical antipsychotic—Risperidal Consta. It is important to have more long-acting injectable antipsychotics available to patients who have compliance issues. In this NDA (including original submission and re-submission), paliperidone palmitate has demonstrated its efficacy in acute and maintenance treatment of schizophrenia in study PSY-3003, -3004, -3007, SCH-201, and PSY-3001. Study PSY-3001, 3003, -3004, and SCH-201 had been submitted to the original NDA on 25 October 2007, and Jing Zhang, MD. PhD. is the primary medical reviewer of the original submission.

The safety profile of paliperidone palmitate has been established by reviewing data from 16 completed paliperidone palmitate clinical trials (5 phase 3, 1 phase 2 and 10 phase 1) submitted to the original submission, and data from study PSY-3007, and the open-label extension phase of study PSY-3001 which were submitted to this resubmission. The safety evaluation demonstrated that the safety profile of paliperidone palmitate is similar to that of paliperidone ER, a marketed oral antipsychotic, for most parameters that were measured with the exception of injection site-related adverse events. No new or unexpected safety signals were identified.

Considering schizophrenia is a severe, and highly debilitating mental illness, it is believed that the benefit of having paliperidone palmitate available to schizophrenia

patients, especially to those who have appliance issues, justifies the risk of potential adverse events in the treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The safety profile of paliperidone palmitate is comparable to paliperidone ER, a marketed oral tablet formulation. No specific safety concern had been identified during the review. Risk Evaluation and Mitigation Strategies is not required at this time point.

1.4 Recommendations for Postmarket Requirements and Commitments

Long-Term Efficacy and Safety Study

The sponsor already conducted a positive long-term, relapse prevention study (study PSY-3001), which includes an initial 33 week open-label period (including a 24 week stabilization phase); a randomized, double-blind, placebo-controlled phase with varied duration; and followed by an optional 52 week open label extension phase. Therefore, no additional Phase 4 commitments are required at this time point.

Pediatric Study

With respect to conduct pediatric trials with paliperidone palmitate under PREA, the sponsor requested a full pediatric waiver based on following reasons:

- Lack of diagnostic stability earlier in the course of a psychotic illness in adolescence, and the need to finely titrate the dose of antipsychotic treatment in order to use the lowest possible dose while obtaining the best benefit-risk profile, make the use of an oral antipsychotic a more appropriate treatment choice than an long-acting injection (LAI) agent in this age group.
- Oral antipsychotics are the standard of care in adolescents with schizophrenia, and clinical guidelines recommend LAIs only in exceptional circumstances.
- Needle phobia and anticipatory distress, combined with the perception that LAI treatment is punitive or coercive, are likely to adversely affect a collaborative therapeutic relationship with a health-care professional and thus negatively impact on treatment adherence.
- Use of LAI atypical antipsychotic agents in adolescent patients is very limited, based on prescription data and postmarketing experience.

- For the reasons above, it would be impractical and unfeasible to recruit adequate numbers of adolescent patients with schizophrenia to successfully complete a clinical trial.
- The pharmacokinetics of oral paliperidone ER has been documented to be relatively similar in adolescents and adults.
- The pharmacokinetic (PK) profile of paliperidone palmitate in adolescents is expected to be relatively similar to the profile in adults so that additional studies in adolescents would not add value.

In addition, the sponsor is presently conducting a pediatric program with paliperidone ER tablets following the terms of FDA's written request. This program includes a PK study in adolescents, 10 to 17 years of age inclusive, (PALIOROS-PSZ-1001); a 6-week Phase 3 efficacy study including sparse PK sampling (R076477-PSZ-3001); and a long-term safety study (R076477-PSZ-3002). The efficacy and safety studies are currently ongoing. Upon completion of these studies, the sponsor should be able to extrapolate some useful PK, efficacy and safety information in pediatric population.

The sponsor's argument appears reasonable. It is recommended that a full waiver of pediatric studies with paliperidone palmitate covering age 0 to 17 for the indication of acute and maintenance treatment of schizophrenia to be granted.

2 Introduction and Regulatory Background

2.1 Product Information

Paliperidone (9-hydroxy-risperidone, R076477) is a mono-aminergic antagonist that exhibits the characteristic dopamine type 2 (D₂) and serotonin (5-hydroxytryptamine [5-HT]) type 2A (5HT_{2A}) antagonism of the newer, or second-generation, antipsychotic drugs. Paliperidone is the major active metabolite of risperidone (R064766) and is a racemic mixture of enantiomers R078543 (+) and R078544 (-).

2.2 Product Tables of Currently Available Treatments for Proposed Indications

Table 1 summarizes currently available antipsychotics for treatment of schizophrenia.

Table 1 Currently Available Antipsychotics for Treatment of Schizophrenia

Oral Preparations	Long-Acting Injections
Typical antipsychotics: <i>chlopromazine, mesoridazine, thioridazine, fluphenazine, perphenazine, trifluoperazine, haloperidol, thiothixene, molindone, loxapine, pimozide.</i> Atypical antipsychotics: <i>Clozapine, risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole, paliperidone, iloperidone.</i>	haloperidol decanoate, fluphenazine decanoate, Risperdal Consta.

2.3 Availability of Proposed Active Ingredient in the United States

INVEGA® (paliperidone) Extended-Release (ER) Tablets are approved in the U.S and the Europe for the treatment of schizophrenia. Paliperidone palmitate long-lasting injection has not been approved either in the U.S or Europe.

2.4 Important Safety Issues with Consideration to Related Drugs

Paliperidone is an active metabolite of risperidone, an approved atypical antipsychotic. An oral formulation of paliperidone (paliperidone ER) has been approved for marketing in the United States and the Europe. Similar to risperidone and paliperidone ER, paliperidone palmitate are associated with adverse events of increased serum prolactin levels, weight gain coupled with metabolic syndrome, and EPS-related adverse events. These safety issues have been addressed in the proposed labeling of paliperidone palmitate. There are has been no new safety issues generated on this topic from this submission.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

23 August 2000	Preclinical-Clinical Meeting with FDA for R092670
16 June 2004	CMC/Biopharmaceutics EOP2 meeting with FDA
28 September 2004	Preclinical/Clinical EOP2 Meeting with FDA and post follow-up information
12 October 2004	EOP2 CMC/Biopharm Meeting with FDA
7 December 2005	EOP2 pre-Phase 3 meeting with FDA for bipolar disorder

11 December 2006	Tele-conference with FDA regarding paliperidone palmitate injection
18 April 2007	Pre-NDA meeting with FDA
7 June 2007	CMC-Biopharmaceutics Pre-NDA meeting with FDA
25 October 2007	Original paliperidone palmitate NDA submission
25 February 2008	4-Month Safety Update
25 August 2008	Complete Response Letter from FDA
21 November 2008	Meeting with FDA to address the comments provided in the Complete Response Letter
3 February 2009	NDA 22264 re-submission

2.6 Other Relevant Background Information

Paliperidone ER has not been withdrawn from the market worldwide for any reason.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

During the course of the review, no problems with respect to data quality or integrity were identified.

3.2 Compliance with Good Clinical Practices

Study PSY-3007 was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

3.3 Financial Disclosures

(b) (6), a sub-investigator at study site# (b) (6), was a speaker for Janssen Products.

(b) (6) and (b) (6), MD, serve as sub-investigators at study site # (b) (6). (b) (6) and (b) (6), MD are couples. (b) (6) disclosed following financial arrangements/agreements: 1) received a \$250,000 research grant to study neurogenesis in rats receiving antipsychotics; 2) received a \$15,000 honoraria for ongoing consultation; 3) CME grants for the Department Grand Rounds Grants; 4) Grants for neurological test; and 5) received advisory board and speaker honoraria.

Since study PSY-3007 was a multi-center, double-blind study, the site # (b) (6) only enrolled (b) (6) patients out of the total of 636 subjects. It is less likely that those arrangements biased the study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

David Claffey, PhD., is the CMC reviewers for this submission. Please refer to his review for detailed CMC information.

4.2 Clinical Microbiology

No clinical microbiology study was deemed necessary.

4.3 Preclinical Pharmacology/Toxicology

Elzbieta Chalecka-Franaszek, PhD., is the pharmacology/toxicology reviewer for this submission. Please refer to her review for detailed pharmacology/toxicology information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Hao Zhu, PhD., is the primary clinical pharmacology reviewer for this submission. Please refer to his review for detailed clinical pharmacology information.

4.4.2 Pharmacodynamics

Hao Zhu, PhD., is the primary clinical pharmacology reviewer for this submission. Please refer to his review for detailed clinical pharmacology information.

4.4.3 Pharmacokinetics

Hao Zhu, PhD., is the primary clinical pharmacology reviewer for this submission. Please refer to his review for detailed clinical pharmacology information.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

PSY-3007 is the only study submitted to this resubmission. Table 2 summarizes study PSY-3007.

Table 2 Brief Summary of Study PSY-3007

Protocol No.	Region (Country)	Study Design	Study Treatments ^a and Duration	Subjects Included in Analysis of Efficacy
R092670-PSY-3007 (72 centers in 8 countries)	<u>North America</u> (United States) <u>Eastern Europe</u> (Romania, Russia, Serbia, the Ukraine) <u>Asia</u> (Malaysia, Republic of Korea and Taiwan)	Randomized, 13-week, Phase 3 double-blind, placebo-controlled, parallel-group, dose-response, 3 fixed doses of paliperidone palmitate. Study drug was administered as 4 doses: an initial i.m. injection of 150 mg eq. in the deltoid muscle on Day 1 followed by 1 of 3 fixed i.m. doses in either the deltoid or gluteal muscle on Days 8, 36, and 64. An end-of-study visit was scheduled for Day 92.	Placebo Paliperidone palmitate 25, 100, and 150 mg eq., deltoid and/or gluteal injection 7-day screening 13 weeks double-blind treatment	Placebo=160 Paliperidone palmitate 25 mg eq.=155 100 mg eq.=161 150 mg eq.=160 Total=636

5.2 Review Strategy

Material reviewed in this review cycle includes Clinical Study Report from PSY-3007, Clinical Summary, Clinical Overview, Safety Update, and the proposed labeling. The efficacy review was performed in consultation with the statistical reviewer, Yeh-Fong Chen, PhD. Please refer to her review for more detailed pertinent efficacy information.

5.3 Discussion of Individual Studies/Clinical Trials

Study PSY-3007 provides additional efficacy and safety information with regards to paliperidone palmitate in acute treatment of schizophrenia. PSY-3007 also provided some clinical evidence that supports a high starting dose regimen (starting with 150 mg followed by a 100 mg 1 week later, both deltoid injections) [REDACTED] (b) (4)

6 Review of Efficacy

Efficacy Summary

All 3 doses of paliperidone palmitate tested in study PSY-3007—25 mg, 100 mg and 150 mg eq.—were efficacious in adult subjects with schizophrenia who were experiencing acutely exacerbated schizophrenia as measured by change from baseline to end point in the PANSS total score. There was a dose response pattern in the primary efficacy endpoints—the PANSS total score.

A. Study PSY-3007 for the Acute Treatment of Schizophrenia in Adults

a. Rationale for Selection of Studies for Review

In this resubmission, only one study—PSY-3007—was submitted. Study PSY-3007 is a 13-week, randomized, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed doses, 25mg, 100 mg, and 150 mg eq. paliperidone palmitate, in subjects with schizophrenia. The primary endpoint of this study was the change in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to the end of the double-blind treatment period. The key secondary endpoint was the change in the Personal and Social Performance Scale (PSP) from baseline to the end of the double-blind treatment period.

The PANSS is a well known and validated rating scale used in numerous drug evaluation trials. The severity of neuropsychiatric symptoms of schizophrenia were

assessed using the 30-item PANSS scale which provides a total score (sum of the scores of all 30 items) and scores for 3 subscales, the positive subscale (7 items), the negative subscale (7 items), and the general psychopathology subscale (16 items), each rated on a scale of 1 (absent) to 7 (extreme).

The Personal and Social Performance Scale (PSP), is a validated scale to help clinicians assess the global functioning of a patient with Schizophrenia, and to track the progress of functioning over time, through repeat use of the scale. The ratings are based on the outcome of a structured clinical interview, divided into 4 categories a) socially useful activities, b) personal and social relationships, c) self-care, and d) disturbing and aggressive behaviors.

In general, study PSY-3007 is appropriately designed. The study length and the efficacy measures—the primary and the key secondary endpoints—are acceptable.

b. Study Summaries

i. Methods/Study Design/Analysis Plan

Study PSY-3007 was a 13-week, randomized, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed doses—25mg, 100 mg, and 150 mg eq.—of paliperidone palmitate in subjects with DSM-IV diagnosis of schizophrenia. The study included a screening period of up to 7 days and a 13-week double-blind treatment period.

This study was conducted from 08 March 2007 to 24 March 2008 in 72 centers which include 33 US centers and 39 non-US centers. The non-US centers are located in Korea, Malaysia, Romania, Russia, Serbia, Taiwan, and Ukraine. Three hundred fourteen subjects (Intent to treat, ITT) are from US and 322 subjects (ITT) are from non-US regions.

Overall Study Design

Study PSY-3007 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response study designed to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate (25, 100, and 150 mg eq.) compared with placebo (randomization ratio 1:1:1:1). Study medication was administered as 4 doses: an initial i.m. injection of placebo or paliperidone palmitate 150 mg eq. followed by 3 fixed i.m. doses of placebo or paliperidone palmitate [25, 100, or 150 mg eq.] on Days 8, 36, and 64. The initial dose of study medication was given in the deltoid muscle. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator.

The study included a screening period of up to 7 days and a 13-week double-blind treatment period. The screening period included a washout of disallowed psychotropic medications and oral tolerability testing for subjects without documented previous exposure to risperidone or paliperidone.

It was planned that 644 men and women (161 in each of 4 treatment groups) aged 18 years or older with a DSM-IV diagnosis of schizophrenia for at least one year and suffering from an acute episode (PANSS total score at screening between 70 and 120, inclusive) would be enrolled into this study. A total of 652 eligible subjects were randomized and received at least 1 dose of double-blind study medication (safety analysis set); 636 subjects had both baseline and post baseline efficacy data (intent-to-treat analysis set).

Doses and Administration

Paliperidone ER was supplied as a 6-mg capsule-shaped tablet for the oral tolerability test. Paliperidone palmitate was supplied as 25, 100, or 150 mg eq. injectable suspension. For the oral tolerability test, a 6-mg tablet of paliperidone ER (or the option of oral risperidone 3 mg/day for subjects in Malaysia) was administered daily for 4 to 6 days. On Day 1 of the double-blind treatment period, 150 mg eq. of paliperidone palmitate was injected in the deltoid muscle followed by 25, 100, or 150 mg eq. i.m. injections of paliperidone palmitate on Days 8, 36, and 64, injected into the deltoid or gluteal muscle at the investigator's discretion. Deltoid injections were administered using a 1.5-inch needle for subjects weighing ≥ 200 lb (≥ 90 kg) and a 1-inch needle for subjects weighing < 200 lb (< 90 kg). All gluteal injections were administered with a 1.5-inch needle.

The Primary and Secondary Endpoints

The primary efficacy endpoint was the change in the PANSS total score from Day 1 to end point (Day 92 or the last post baseline assessment in the double-blind treatment period). The primary comparison was between each paliperidone palmitate dose and placebo.

The key secondary endpoint was the change from baseline to end point in the PSP score.

Other secondary efficacy endpoints were the change in the Clinical Global Impression-Severity (CGI-S) scores from baseline to the end of the double-blind treatment period, the change from baseline in subject ratings of sleep quality and daytime drowsiness using a visual analogue scale (VAS), the onset of therapeutic effect, responder rate, and the change from baseline to end point in PANSS subscales and Marder factors.

Study Population

Key Inclusion Criteria:

- Male or female aged at least 18 years of age who meet diagnostic criteria for schizophrenia according to DSM-IV (disorganized type [295.10], catatonic type [295.20], paranoid type [295.30], residual type [295.60], or undifferentiated type [295.90]) for at least 1 year before screening.
- PANSS total score at screening of between 70 and 120, inclusive, and at baseline of between 60 and 120, inclusive;
- Body mass index (BMI) >17.0 kg/m²;
- Female subjects had to be:
 - Postmenopausal for at least 2 years, or
 - Surgically sterile or abstaining from sexual activity, or
 - Using an effective method of birth control if they were sexually active before study entry and for the duration of the study;
- Female subjects must have had a negative urine pregnancy test at baseline before receiving the first dose of study medication;

Key Exclusion Criteria

- Primary active DSM-IV Axis I diagnosis other than schizophrenia;
- DSM-IV diagnosis of active substance dependence within 3 months before screening (nicotine and caffeine dependence were not exclusionary);
- History of treatment resistance, defined as failure to respond to 2 adequate studies of different antipsychotic medications (a minimum of 4 weeks at the subject's maximum tolerated dose);
- Significant risk of suicidal, homicidal, or violent ideation or behavior as clinically assessed by the investigator;
- Known or suspected hypersensitivity or intolerance of risperidone, paliperidone, Intralipid™ (placebo) or any of their excipients;
- Treatment with any of the following disallowed therapies:
 - Injectable antipsychotic within 1 injection cycle before screening;

- Injection of RISPERDAL CONSTA within 6 weeks before screening;
 - Electroconvulsive therapy within 60 days before screening;
 - Injection of paliperidone palmitate within the 10 months before baseline;
 - Clozapine within 3 months before baseline;
 - Nonselective or irreversible monoamine oxidase inhibitor (MAOI) antidepressants within 30 days before screening;
 - Other antidepressant agents, unless subject had been on a stable dose for at least 30 days before screening;
 - Mood stabilizers, including lithium and all anticonvulsants, beta-blockers, and antiparkinsonian medication during the double-blind treatment period.
- History or presence of circumstances that could increase the risk of the occurrence of torsade de pointes or sudden death in association with the use of drugs that prolong the QTc interval.

Statistical Methods

All randomized subjects who received at least 1 dose of double-blind study drug and had both baseline and at least one post baseline efficacy measurement (PANSS, PSP, or CGI-S) during the double-blind treatment period were included in the intent-to-treat efficacy analyses. The overall type I error rate for testing all paliperidone palmitate doses versus placebo for both the primary endpoint (change in PANSS total score at end point) and the key secondary efficacy endpoint (change in PSP total score at end point) was controlled at the 2-sided 0.05 significance level.

The change from baseline in PANSS total score at each visit and at end point was analyzed using an analysis of covariance (ANCOVA) model. The last observation carried forward (LOCF) method was used. The model included treatment and country as factors and baseline PANSS total score as a covariate. Treatment effect was based on the difference in least-squares mean change. Dunnett's test was used to adjust for multiple comparisons of the 3 paliperidone palmitate dosages versus placebo. Unadjusted 2-sided 95% confidence intervals were presented for the difference in least-squares mean change of each paliperidone palmitate dosage group compared with placebo. Treatment-by-country and treatment-by-baseline PANSS total score interactions were explored using the same ANCOVA model as the one for the analysis of the primary endpoint. If either term was statistically significant at the predefined 2-sided significance level of 0.10, further evaluations of the effect of other covariates were to be performed to assess the nature of the interaction and identify possible causes. In addition, to address the dose-response relationship and to facilitate the discussion of dosage selection, an analysis to compare the 3 active paliperidone palmitate dosages with each other was performed without adjustment for multiple comparisons.

The number and percentage of subjects with treatment-emergent adverse events were summarized. Adverse events of potential clinical interest were summarized separately, including events related to EPS or changes in serum glucose or prolactin levels. Changes from baseline in clinical laboratory tests, vital sign measurements, ECGs, body weight, BMI, and EPS scale scores were summarized by treatment group. Prolactin levels were summarized by sex. Subjects with potentially abnormal values or changes in clinical laboratory tests, vital signs, orthostatic parameters, and ECG parameters were summarized based on predefined criteria. Frequency distributions were presented for the investigator's evaluation of the injection site, and descriptive statistics were presented for VAS scores corresponding to the subject's evaluation of injection pain.

ii. Results

Demographics

Demographic and baseline characteristics for the intent-to-treat analysis set are displayed in Table 3. The diagnosis and psychiatric history at baseline for the intent-to-treat analysis set are presented in Table 5. All demographic characteristics and baseline disease characteristics were roughly balanced across all treatment groups.

The majority of subjects were male (67%), especially in US region (77%) (see Table 4).

The age range was from 18 to 70 years, with the mean age being 39.4 years. Three (<1%) subjects were > 65 years of age.

Subjects were racially diverse, with 54% White, 30% Black, and 14% Asian. In non-US countries, subjects were either White (72%) or Asian (28%).

Using the WHO categorizations, 44% of subjects had a normal BMI, 32% were overweight, and 24% were obese. A higher proportion of subjects from U.S. centers were obese (38% compared with 11% for non-US subjects). The mean BMI at baseline was 28.83 kg/m² for U.S. subjects and 24.53 kg/m² for non-U.S. subjects (see Table 4).

Table 3 Demographic and Baseline Characteristics (ITT)

	Paliperidone Palmitate				
	Placebo (N=160)	25 mg eq. (N=155)	100 mg eq. (N=161)	150 mg eq. (N=160)	Total (N=636)
Age (years)					
N	160	155	161	160	636
Category, n (%)					
18-25	20 (13)	14 (9)	17 (11)	16 (10)	67 (11)
26-50	112 (70)	119 (77)	124 (77)	121 (76)	476 (75)
51-65	27 (17)	22 (14)	19 (12)	22 (14)	90 (14)
>65	1 (1)	0	1 (1)	1 (1)	3 (<1)
Mean (SD)	39.9 (10.98)	39.5 (10.31)	38.8 (10.37)	39.4 (10.76)	39.4 (10.59)
Median	40.5	39.0	39.0	39.0	40.0
Range	(19;67)	(20;63)	(18;70)	(18;69)	(18;70)
Sex, n (%)					
N	160	155	161	160	636
Male	106 (66)	111 (72)	107 (66)	103 (64)	427 (67)
Female	54 (34)	44 (28)	54 (34)	57 (36)	209 (33)
Race, n (%)					
N	160	155	161	160	636
White	87 (54)	86 (55)	86 (53)	84 (53)	343 (54)
Black	49 (31)	42 (27)	51 (32)	50 (31)	192 (30)
Asian	24 (15)	24 (15)	22 (14)	22 (14)	92 (14)
American Indian or Alaskan native	0	2 (1)	0	2 (1)	4 (1)
Other	0	1 (1)	2 (1)	2 (1)	5 (1)
Body mass index (kg/m²)					
N	160	155	161	160	636
Category, n (%)					
Normal <25	61 (38)	73 (47)	75 (47)	69 (43)	278 (44)
Overweight 25-<30	59 (37)	40 (26)	53 (33)	53 (33)	205 (32)
Obese ≥30	40 (25)	42 (27)	33 (20)	38 (24)	153 (24)
Mean (SD)	26.83 (5.129)	26.77 (5.378)	26.36 (5.234)	26.65 (5.209)	26.65 (5.228)
Median	26.45	25.60	25.70	25.80	25.80
Range	(16.7;39.9)	(16.2;39.9)	(17.3;47.0)	(16.4;39.9)	(16.2;47.0)

Table 4 Demographic and Baseline Characteristics by US and Non-US Regions (ITT)

	Age (years) Mean (SD)	Sex N (%)		Race N (%)				BMI (kg/m ²) Mean (SD)
		Male	Female	White	Black	Asian	Other	
US n=314	40.8 (10.32)	242 (77)	72 (23)	112 (36)	192 (61)	1 (<1)	9 (3)	28.83 (5.44)
Non-US n=322	38.0 (10.7)	185 (57)	137 (43)	231 (72)	0	91 (28)	0	24.53 (4.01)

Baseline Disease Characteristics

All subjects in the intent-to-treat analysis set had a primary Axis I diagnosis of schizophrenia as required by the protocol. The major subtype (88%) was schizophrenia, paranoid type. The mean age at diagnosis was 25.4 years old.

The PANSS total score at baseline ranged from 61 to 131, and the mean PANSS total score at baseline (SD) was 87.1 (11.21) points. Based on the CGI-S score, 49% of subjects were at least markedly ill as rated by the investigator.

Table 5 Diagnosis and Psychiatry History at Baseline (ITT)

	Paliperidone Palmitate				
	Placebo (N=160)	25 mg eq. (N=155)	100 mg eq. (N=161)	150 mg eq. (N=160)	Total (N=636)
Schizophrenia type, n (%)					
N	160	155	161	160	636
Paranoid (295.30)	135 (84)	137 (88)	146 (91)	140 (88)	558 (88)
Disorganized (295.10)	7 (4)	5 (3)	3 (2)	2 (1)	17 (3)
Catatonic (295.20)	1 (1)	1 (1)	0	0	2 (<1)
Undifferentiated (295.90)	16 (10)	10 (6)	10 (6)	18 (11)	54 (8)
Residual (295.60)	1 (1)	2 (1)	2 (1)	0	5 (1)
Age at diagnosis of schizophrenia (yrs)					
N	160	155	161	160	636
Mean (SD)	26.0 (8.12)	24.4 (7.04)	26.0 (9.37)	25.0 (7.86)	25.4 (8.16)
Median	23.5	23.0	24.0	23.0	23.0
Range	(13;51)	(13;48)	(6;68)	(8;50)	(6;68)
Baseline total PANSS					
N	160	155	161	160	636
Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)	87.1 (11.21)
Median	86.0	86.0	86.0	88.0	86.0
Range	(65;113)	(61;119)	(61;112)	(64;131)	(61;131)
Baseline CGI-S, n (%)					
N	160	154	161	160	635
Mild	2 (1)	3 (2)	8 (5)	3 (2)	16 (3)
Moderate	75 (47)	79 (51)	81 (50)	72 (45)	307 (48)
Marked	73 (46)	60 (39)	68 (42)	74 (46)	275 (43)
Severe	10 (6)	12 (8)	4 (2)	11 (7)	37 (6)

Patient Disposition

A total of 652 subjects were randomized, and 333 (51%) subjects completed the study (Table 6). A higher percentage of subjects in the paliperidone palmitate treatment groups completed the study (52% to 55%) compared with those assigned to the placebo group (43%). More subjects in the placebo group (27%) discontinued due to lack of efficacy than in the paliperidone palmitate treatment groups (14% to 19%). The rates for early withdrawal due to adverse events or reasons other than lack of efficacy showed similar incidences across treatment groups.

Table 6 Study Completion Withdrawal Information (all randomized)

	Paliperidone Palmitate				Total (N=652) n (%)
	Placebo (N=164) n (%)	25 mg eq. (N=160) n (%)	100 mg eq. (N=165) n (%)	150 mg eq. (N=163) n (%)	
Completed	71 (43)	83 (52)	89 (54)	90 (55)	333 (51)
Withdrawn	93 (57)	77 (48)	76 (46)	73 (45)	319 (49)
Lack of efficacy	45 (27)	31 (19)	28 (17)	23 (14)	127 (19)
Subject choice (subject withdrew consent)	26 (16)	23 (14)	28 (17)	30 (18)	107 (16)
Adverse event	11 (7)	10 (6)	10 (6)	13 (8)	44 (7)
Lost to follow-up	9 (5)	12 (8)	6 (4)	6 (4)	33 (5)
Pregnancy	0	0	1 (1)	0	1 (<1)
Other	2 (1)	1 (1)	3 (2)	1 (1)	7 (1)

Concomitant Medication Use

Benzodiazepine Use

According to the protocol, benzodiazepines could be used as rescue medications for agitation, anxiety, or sleep difficulties during the double-blind treatment period, with the dose and frequency of administration gradually tapered downward over the double-blind period. Benzodiazepine use during the double-blind treatment period is summarized for the intent-to-treat analysis set in Table 7.

During the double-blind treatment period, the majority of subjects in each treatment group received a benzodiazepine, primarily lorazepam. There was no noteworthy difference among the treatment groups with respect to benzodiazepine use during the double-blind treatment phase (55% to 62%).

Table 7 Benzodiazepine Received During the Double-Blind Phase

Generic Term Category	Paliperidone palmitate				Total (N=636) n (%)
	Placebo (N=160) n (%)	25 mg eq. (N=155) n (%)	100 mg eq. (N=161) n (%)	150 mg eq. (N=160) n (%)	
Total no. subjects with any benzodiazepines	97 (61)	96 (62)	89 (55)	94 (59)	376 (59)
Lorazepam	79 (49)	72 (46)	69 (43)	80 (50)	300 (47)
Diazepam	18 (11)	22 (14)	20 (12)	16 (10)	76 (12)
Clonazepam	13 (8)	7 (5)	6 (4)	10 (6)	36 (6)
Temazepam	5 (3)	10 (6)	5 (3)	10 (6)	30 (5)
Estazolam	1 (1)	1 (1)	2 (1)	1 (1)	5 (1)
Clorazepate	0	2 (1)	1 (1)	1 (1)	4 (1)
Bromazepam	0	0	1 (1)	0	1 (<1)
Flunitrazepam	1 (1)	0	0	0	1 (<1)
Midazolam	0	0	1 (1)	0	1 (<1)
Oxazepam	0	0	0	1 (1)	1 (<1)
Triazolam	0	0	1 (1)	0	1 (<1)

The duration in days of benzodiazepines (with at least 10 subjects in total) received by the subjects during the double-blind phase is presented in Table 8. The mean duration of lorazepam use (the primary benzodiazepine used in the study, 47% subjects) was similar among the paliperidone palmitate treatment groups (20.6 to 21.1 days) and placebo group (18.6 days). The median of the average total daily dose of lorazepam ranged from 1.92 mg to 2.0 mg across the 4 treatment groups, consistent with protocol dosing guidelines.

Table 8 Duration (Days) of Benzodiazepines (with at Least 10 Subjects in Total) Received During the Double-Blind Phase, ITT

	Clonazepam			Diazepam			Lorazepam			Temazepam		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Placebo	13	8.2	8.54	18	15.6	18.85	79	18.6	26.6	5	11.0	12.0
PP 25 mg eq.	7	38.6	36.93	22	23.5	28.52	72	20.9	27.59	10	9.9	3.5
PP 100 mg eq.	6	6.5	6.02	20	20.1	29.47	69	20.6	28.94	5	15.8	6.0
PP 150 mg eq.	10	27.0	29.51	16	10.9	14.29	80	21.1	28.67	10	23.2	10.5

PP: Paliperidone Palmitate

Since concomitant benzodiazepine use during the double-blind treatment phase, including the dose and duration and the type of benzodiazepine used, was relatively even distributed in all treatment groups, it is less likely the benzodiazepine use during this phase will affect the final efficacy outcome of the study.

Antipsychotic Drug Use

More subjects in placebo group used antipsychotic drugs (43 subjects, 26%) following the start of double-blind treatment compared with paliperidone palmitate treatment groups: 23 subjects (14%), 28 (17%), and 28 (17%) in the paliperidone palmitate 25 mg eq., 100 mg eq., and 150 mg eq. groups, respectively. Across all treatment groups, the most common of these drugs were risperidone (7%), haloperidol (3%), and quetiapine (3%). For most subjects, the additional antipsychotic drug was started after or within the 4-day period preceding the final PANSS evaluation or the final dose of the concomitant antipsychotic drug had been administered at least 1 week before the final PANSS evaluation.

For 5 subjects (placebo group: Subjects 081804 and 083710; 25 mg eq. group: Subject 083112; 100 mg eq. group: Subjects 082308 and 083705; 150 mg eq. group: Subject 080917), the concomitant antipsychotic medication was administered for more than 1 week before the final PANSS evaluation. In each of these 5 cases, the concomitant antipsychotic drug was started after the final dose of study drug, and each of these instances was recorded as a protocol deviation.

Since concomitant antipsychotic drug use during the double-blind treatment phase was relatively brief and evenly distributed in all treatment groups (slightly higher in the placebo treatment group), it is less likely the concomitant antipsychotic use during this phase will affect the final efficacy outcome of the study.

Important Protocol Deviations

One or more protocol deviations were recorded for 61 (10%) of the 636 subjects. The most common protocol deviation was receipt of excluded concomitant medications. The pattern of protocol deviations appeared similar across all treatment groups. No important protocol deviations were reported.

Efficacy Findings

Efficacy summaries are presented for the intent-to-treat analysis (ITT) data set, which included the 636 subjects who were randomly assigned to study treatment, received at least 1 dose of double-blind study medication, and had at least 1 post baseline efficacy assessment during the double-blind treatment period.

Primary Efficacy Analysis

The primary efficacy variable was the change from baseline to end point in the PANSS total score. Results of the primary efficacy analysis (LOCF analysis) are presented for each treatment group in Table 9.

Based on the intent-to-treat LOCF analysis of the primary efficacy variable using Dunnett’s test to control for multiplicity, the improvement measure by decrease in PANSS total score in all 3 paliperidone palmitate treatment groups reached statistical significance (25 mg eq.: p=0.034; 100 mg eq.: p<0.001; 150 mg eq.: p<0.001) when compared with the placebo group.

The LS mean difference from placebo was -5.1 for the paliperidone palmitate 25 mg eq. group, -8.7 for the paliperidone palmitate 100 mg eq. group and -9.8 for the paliperidone palmitate 150 mg eq. group.

Table 9 Change From Baseline to End Point in PANSS Total Score (LOCF, ITT)

	Placebo N=160	Paliperidone palmitate		
		25 mg eq. N=155	100 mg eq. N=161	150 mg eq. N=160
Baseline Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)
End point Mean (SD)	83.9 (21.44)	78.8 (19.88)	74.6 (18.06)	75.2 (18.59)
Δ from baseline Mean (SD)	-2.9 (19.26)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
P-value (minus placebo)		0.034	<0.001	<0.001

iii. Conclusion

Paliperidone palmitate, injected at a dose of 150 mg eq. into the deltoid muscle followed by 3 i.m. injections at fixed doses of 25 mg eq., 100 mg eq., or 150 mg eq. on Days 8, 36, and 64, was significantly more effective than placebo in improving the PANSS total score at end point (primary efficacy endpoint) in this 13-week double-blind study in subjects with schizophrenia.

The statistical reviewer, Yeh-Fong Chen, PhD. confirmed the sponsor’s analysis results for Study 3007. It was agreed that data supported the efficacy of paliperidone palmitate as a treatment for adult patients with schizophrenia.

c. Crosscutting Issues

i. Subgroup Analyses

Treatment-by-Age, Sex, or Race

Subgroup analysis on the data from Study PSY-3007 using the change in PANSS total score suggests that treatment with paliperidone palmitate was effective regardless of

subjects' age (18-25, 26-50, or ≥ 51 years), sex (male or female), or race (White, Black, Asian, or Other). These results are consistent with the results of subgroup analyses from the Phase 2/3 paliperidone palmitate studies, PSY-3003, PSY-3004, and SCH-201.

Treatment-by-Country Interactions

The distribution of the intent-to-treat analysis set by country was as follows: 49% U.S., 20% Russia, 8% Ukraine, 6% Taiwan, 6% Romania, 4% Malaysia, 4% Korea, and 1% Serbia.

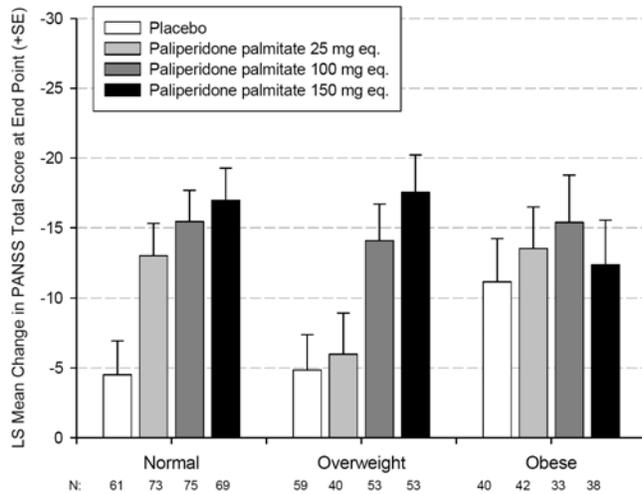
The treatment-by-country interaction ($p=0.273$) was not statistically significant at the pre-specified 0.10 significance level. However, US subjects were associated with relatively smaller mean change in PANSS total score from the baseline to the end point in all paliperidone palmitate treatment groups compared to that in overall ITT population. The placebo response measured by LS mean difference from baseline to endpoint in PANSS total score was -4.94 in US subjects and -2.9 in overall ITT populations.

Treatment-by-Baseline BMI (exploratory)

The distribution of pre-specified BMI categories based on the WHO classification (normal: <25 kg/m², overweight: >25 - <30 kg/m², and obese: ≥ 30 kg/m²) indicated a greater incidence of obese subjects enrolled in the U.S.; 38% of subjects from U.S. sites were categorized as being obese compared with 11% of subjects in other countries.

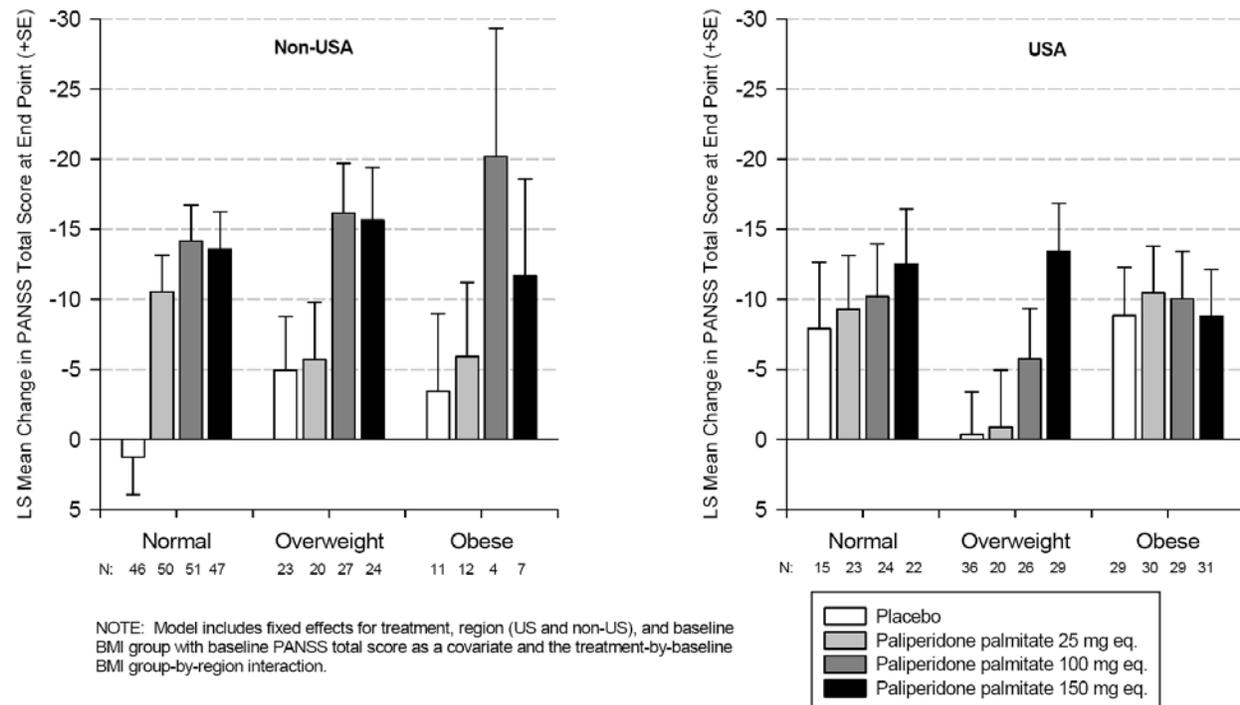
The statistical significance of the treatment-by-BMI group interaction term was 0.154. The placebo response in the obese subgroup was noticeably higher than the one for placebo-treated subjects in the normal or overweight subgroups (Figure 1).

Figure 1 Least-Squares Mean Changes in PANSS Total Score at Endpoint by Baseline BMI Group (ITT)



From the graphical inspection of the LS mean changes in PANSS total score at end point (Figure 2), the trend toward a smaller treatment effect relative to placebo among obese subjects was greatest for U.S. sites.

Figure 2 Least-Squares Mean Changes in PANSS Total Score at Endpoint by Baseline BMI Group and Region



ii. Dose Response

There was a dose-response pattern with respect to the primary efficacy variable, with the mean decreases (improvement) in the PANSS total score at end point (LOCF) incrementally increasing from -8.0 for the 25 mg eq. dose group to -11.6 for the 100 mg eq. group and to -13.2 for the 150 mg eq. dose group (Table 10). Although paliperidone palmitate 150 mg eq. group seemed to perform numerically better than 100 mg eq. group, the difference between two groups appeared very small with an unadjusted p-value 0.59.

Table 10 Change From Baseline to Endpoint in PANSS Total Score—Pairwise Comparisons between Paliperidone Palitate Groups (LOCF, ITT)

	Paliperidone palmitate		
	25 mg eq. N=155	100 mg eq. N=161	150 mg eq. N=160
Baseline Mean (SD)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)
End point Mean (SD)	78.8 (19.88)	74.6 (18.06)	75.2 (18.59)
Δ from baseline Mean (SD)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
P-value (minus 25 mg eq.)		0.071	0.019
P-value (minus 100 mg eq.)			0.588

iii. Key Secondary Endpoints

The key secondary efficacy variable was the change from baseline to end point in the PSP score. Results of the efficacy analysis (LOCF analysis) for this variable are presented for each treatment group in Table 11.

Based on the intent-to-treat LOCF analysis of this key secondary efficacy variable, using the Dunnett-Bonferroni-based parallel gatekeeping procedure to adjust for multiplicity, the improvement in the paliperidone palmitate 100 and 150 mg eq. treatment groups reached statistical significance (100 mg eq.: p=0.007; 150 mg eq.: p<0.001) when compared with the placebo group. The paliperidone palmitate 25 mg eq. treatment group was not found to be statistically significantly superior to placebo (p=0.509).

Table 11 Change from Baseline to End Point in PSP (LOCF, ITT)

	Placebo N=160	Paliperidone palmitate		
		25 mg eq. N=155	100 mg eq. N=161	150 mg eq. N=160
Baseline Mean (SD)	49.7 (12.33)	49.6 (12.52)	50.2 (12.78)	48.8 (12.99)
End point Mean (SD)	51.5 (16.93)	52.5 (16.01)	56.3 (14.72)	57.1 (15.23)
Δ from baseline Mean (SD)	1.7 (15.60)	2.9 (15.29)	6.1 (13.59)	8.3 (14.69)
P-value (minus placebo)		0.509	0.007	<0.001

The mean improvements in the PSP score showed a dose-related trend among the paliperidone palmitate treatment groups (25 mg eq.: 2.9; 100 mg eq.: 6.1; 150 mg eq.: 8.3).

iv. Effect Size

Compared with Other studies Submitted to This NDA

In the original submission dated on 25 October 2007, the acute efficacy of paliperidone palmitate at doses of 25, 50 and 100 mg eq. was demonstrated in 3 multiple center, fixed-dose, randomized, double-blind, placebo-controlled, and parallel-group studies—Study PSY-3003, -3004, and SCH-201. In this resubmission, the efficacy results from study PSY-3007 further confirmed the efficacy of paliperidone palmitate at doses 25, 100 mg eq. and provided the efficacy evidence of 150 mg eq. in the treatment of schizophrenia.

PSY-3003 was a 13-week study with 4 treatment groups (50, 100, 150 mg eq. paliperidone palmitate and placebo). By design, around 95 patients would be randomized in each treatment group. However, due to a medication kit allocation error, only 30 subjects have received 150 mg eq. paliperidone palmitate and 132 subjects have received placebo during the study. The randomization of 50 and 100 mg eq. treatment groups were not affected by the medication kit allocation error.

PSY-3004 was a 13-week study with 4 treatment groups (25, 50, 100 mg eq. paliperidone palmitate and placebo), around 130 patients randomized in each treatment group.

SCH-201 was a 9-week study with 3 treatment groups: 50, 100 mg eq. paliperidone palmitate and placebo. Around 65 patients were included in each treatment group.

The mean change from baseline to end point in PANSS total score was the primary efficacy end point of all aforementioned studies. The observed placebo-adjusted effect sizes from study PSY-3003, -3004, -3007, and SCH-201 are summarized in Table 12.

Table 12 Placebo-Adjusted Effect Sizes (Reduction in PANSS Total Score) from Study PSY-3003, -3004, -3007, and SCH-201

	Paliperidone palmitate			
	25 mg eq.	50 mg eq.	100 mg eq.	150 mg eq.
PSY-3007	-5.1		-8.7	-10.3
PSY-3003		-3.8	-6.9	-1.4
PSY-3004	-6.6	-6.2	-9.1	
SCH-201		-11.4	-14	

The placebo-adjusted effect sizes observed from Study PSY-3007 were comparable with those seen in study PSY-3003, and 3004 except in 150 mg eq. groups. There were larger placebo-adjusted effect sizes observed in study SCH-201 which might be caused by no placebo treatment effect at the endpoint. In SCH-201, the PANSS total scores at the endpoint in paliperidone palmitate treatment groups were comparable to those observed in other studies. However, the placebo group did worse (the PANSS total score became higher) at the endpoint. The mean changes in PANSS total score in placebo group at endpoint was 6.2 in study SCH-201 and was -4.1, -7.0, and -2.9 in study PSY-3003, -3004 and -3007 respectively.

Compared with other Long-Acting Injection Atypical Antipsychotic Trials

Risperdal Consta was the only FDA approved long-acting injection of atypical antipsychotics for marketing. Its acute efficacy in the original NDA 21436 has been demonstrated by a 12 week, randomized, double-blind, placebo-controlled, fixed-dose study (RIS-USA-121).

Olanzapine pamoate is a depot form of olanzapine which is under FDA's review (NDA 22173). The acute efficacy of Olanzapine pamoate has been demonstrated in an 8-week, randomized, placebo-controlled, fixed-dose study—Study JHGJZ.

The mean change from baseline to end point in PANSS total score was the primary efficacy end point for study RIS-USA-121 and HGJZ. The observed placebo-adjusted effect sizes from study RIS-USA-121, HGJZ and PSY-3007 are summarized in Table 13.

Table 13 Placebo-Adjusted Effect Sizes (Reduction in PANSS Total Score) from Study PSY-3007, RIS-USA-121, and HGJZ.

PSY-3007:			
	25 mg eq./4wk	100 mg eq./4wk	150 mg eq./4wk
Paliperidone palmitate	-5.1	-8.7	-10.3
RIS-USA-121 (NDA 21436):			
	25 mg/2wk	50 mg/2wk	75 mg/2wk
Risperdal Consta	-8.8	-11.1	-10.0
HGJZ (NDA 22173):			
	210 mg/2wk	405 mg/4wk	300 mg/2wk
Olanzapine Pamoate	-13.98	-14.47	-17.81

The effect sizes in study PSY-3007 were roughly comparable to those observed in Risperdal Consta study and were smaller than those observed in the olanzapine pamoate study. It is only a rough comparison because the study designs, study conditions, study medications and doses were very different. It is very difficult to do direct comparison about effect sizes between these studies without bias.

v. Long-term Efficacy

No long-term study was submitted to this submission. In the original submission, the long-term efficacy of paliperidone palmitate in treatment of schizophrenia was demonstrated in a relapse prevention study—Study PSY-3001.

vi. Pediatric Development

Up to date, there is no pediatric study conducted with paliperidone palmitate. However, the sponsor is presently conducting a comprehensive pediatric program with INVEGA (paliperidone Extended-Release [ER]) tablets following the terms of FDA’s written request as amended on August 29, 2007. This program includes a pharmacokinetic (PK) study in adolescents, 10 to 17 years of age inclusive, (PALIOROS-PSZ-1001); a 6-week Phase 3 efficacy study including sparse PK sampling (R076477-PSZ-3001); and a long-term safety study (R076477-PSZ-3002). The efficacy and safety studies are currently ongoing.

vii. Dose Recommendation and Its Justification

The sponsor proposed a new high starting dose regimen in their latest proposed labeling: initiate paliperidone palmitate with a dose of 150 mg on treatment day 1 and 100 mg one week later, both administered in the deltoid muscle. This regimen has not been formally tested in the clinical trials. The rationale for this regimen is to reach potential therapeutic range of paliperidone palmitate concentration rapidly for pharmacologic effect.

Clinical Evidences to Support the Regimen:

Early efficacy in treating schizophrenia is critical both for achieving control of psychotic symptomatology and for increasing the likelihood of continued patient adherence with the medication regimen, and thus, of diminishing the risk of drop-out. In double-blind, placebo-controlled, fixed-dose studies, the 150 mg eq. and 100 mg eq. doses of paliperidone palmitate showed consistent efficacy for multiple end points (change in PANSS total and subscale scores, CGI-S ratings, responder rate, discontinuation rate for efficacy). Starting paliperidone palmitate treatment with the dose most likely to provide benefit to the broadest population of patients is a rational strategy.

Based on clinical experience, the 150 mg eq. and 100 mg eq. doses of paliperidone palmitate are safe and well tolerated. In the fixed-dose studies in subjects with schizophrenia, the dose response for the incidence of treatment-emergent adverse events with paliperidone palmitate was relatively flat over the dose range of 25 to 150 mg eq.

In Study PSY-3007, there were 149 subjects in the PK database whose initiation regimen was 150 mg eq. deltoid injection on Day 1 and 100 mg eq. deltoid or gluteal dose on Day 8. Among these 149 subjects, 76 patients received the second injection in the deltoid muscle. This regimen was found to be safe and efficacious in this study.

In Study PSY-3005, where dosing was initiated in either the deltoid or gluteal muscle, there were no clinically relevant differences in the safety profile of paliperidone palmitate at doses of 50 to 100 mg eq. as a function of the injection site, despite the fact that initial plasma paliperidone concentrations were higher following injection in the deltoid muscle. Finally, data from Phase 1 studies and the Phase 3 studies, PSY-3003 and PSY-3007, did not reveal any appreciable increase in safety issues when high initial doses (up to 300 mg eq. in the Phase 1 studies and up to 150 mg eq. in the Phase 3 studies) of paliperidone palmitate were given.

PK Data to Support the Regimen

6 mg INVEGA is the recommended oral daily dose for paliperidone. Population-PK simulations indicate that the Day 1/8-150/100 mg eq. initiation regimen helps quickly achieve plasma drug levels that are similar to those observed with the 6 mg oral INVEGA daily regimen.

Trough values especially for the first month with 75/75 and 100/100 mg eq. Day 1/8 dosing shows that a greater proportion of subjects will not achieve target plasma levels. This is highlighted in Table 14 where the percentage of subjects above the target threshold of 7.5 ng/mL is presented. The results illustrate that the initiation regimen of 150/100 mg eq. on Day 1/8 provide the highest probability of producing potentially therapeutic plasma concentrations even on trough days.

Table 14 Percentage of Subjects above 7.5 ng/mL on Trough Days 8 and 36, for Various Initiation Regimens

Regimen	Day 8	Day 36
75/75 mg eq. Day 1/8 deltoid	64 %	68 %
100/100 mg eq. Day 1/8 deltoid	73 %	76 %
150/100 mg eq. Day 1/8 deltoid	84 %	84 %

The higher initiation regimen of 150/100 mg eq as compared to 100/100 mg eq or even 75/75 mg eq does not result in an appreciably different adverse event profile, suggesting that the higher earlier plasma concentrations are well tolerated. Higher paliperidone plasma concentrations can be achieved after injection in the deltoid muscle compared with the gluteal muscle during the initiation of treatment with paliperidone palmitate. Therefore, initiation of treatment with paliperidone palmitate is recommended in the deltoid muscle. After multiple injections, the difference between gluteal and deltoid is less apparent, and thus for continued treatment, the injection site can be switched between the deltoid and the gluteal muscle.

Comments from Pharmacometric Reviewer

Hao Zhu, PhD., is the primary pharmacometric reviewer, Office of Clinical Pharmacology. He reviewed and reanalyzed data submitted by the sponsor and concluded that the proposed regimen is acceptable based on following findings:

1. Starting treatment with 150 mg eq. paliperidone palmitate provides the benefit to reach the desirable exposure (i.e. median exposure between the steady state peak and trough concentration following 6 mg q.d. oral ER formulation) within one week. With 100 mg and 75 mg as the starting dose, the describable exposure can not be achieved until 1.5 – 2 weeks later.
2. The peak exposure obtained from using the sponsor proposed initial dosing regimen is below the exposure observed from dose of 150 mg eq. every 4 weeks. Dose of 150 mg eq. every 4 week had been tested in at least two clinical trials (PSY-3007 and PSY-3003) and had been well tolerated by patients.

I concur with the conclusions from Hao Zhu, PhD. From clinical point of view, the proposed starting dose regimen, initiate paliperidone palmitate with a dose of 150 mg on treatment day 1 and 100 mg one week later, both administered in the deltoid muscle, appears reasonably safe and is acceptable.

d. Efficacy Conclusion Regarding Schizophrenia Indication

Paliperidone palmitate at doses of 25 mg eq., 100 mg eq., or 150 mg eq. was significantly more effective than placebo in improving the PANSS total score at end point in this 13-week double-blind study in subjects with schizophrenia.

There was a dose-response pattern, but not statistically significant, with respect to efficacy for the primary endpoint.

The improvements in the PSP score from baseline to end point, the key secondary endpoint, were statistically superior to placebo for the paliperidone palmitate 100 mg eq. and 150 mg eq. groups.

The pre-specified treatment-by-country interaction ($p=0.273$) and treatment-by-baseline PANSS total score interaction ($p=0.206$) in the primary efficacy model were not found to be statistically significant at the pre-specified 0.10 significance level.

An exploratory analysis of the change from baseline in PANSS total score by BMI suggested that the paliperidone palmitate treatment effect relative to placebo was larger in subjects with a normal or overweight BMI classification compared with the response among obese subjects. The statistical significance of the treatment-by-BMI group interaction term was 0.154.

The statistical reviewer, Yeh-Fong Chen, PhD. confirmed the sponsor's analysis results for Study 3007. It was agreed that data supported the efficacy of paliperidone palmitate as a treatment for adult patients with schizophrenia. However, Yeh-Fong Chen, PhD. disagree with the sponsor's dose response claim although paliperidone palmitate 150 mg eq. seemed to perform numerically better than 100 mg eq. because the observed difference between them appeared very small (unadjusted p -value 0.59).

7 Review of Safety

Safety Summary

Overall, the safety and tolerability results from study PSY-007 were consistent with previous clinical studies involving paliperidone palmitate, and no new safety signals were detected. All 3 doses of paliperidone palmitate, including the highest dose of 150 mg eq., were well tolerated in the present study. A dose-related pattern with respect to the occurrence of safety findings was seen only for the increases in body weight and serum prolactin levels.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This resubmission only contains one study, PSY-3007. Summaries of treatment-emergent adverse events and other safety data are based on the 652 subjects who were randomly assigned to study treatment and received at least 1 dose of double-blind study medication, i.e., the safety analysis set.

7.1.2 Categorization of Adverse Events

Adverse Event

An adverse event can be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious Adverse Event

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Only one study was submitted in this resubmission package. No pooling of data was performed.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The actual number of injections received is summarized in Table 15 for the safety analysis set, and the duration (in days) of subject exposure to placebo or paliperidone palmitate is summarized in Table 16. The majority of subjects in the paliperidone palmitate treatment groups received all 4 injections of double-blind study medication (56% to 61%). The mean paliperidone palmitate exposure ranged from 65.1 to 67.3 days, and was similar across the 3 paliperidone palmitate treatment groups.

Table 15 Number of Injections of Double-Blind Study Medication (Safety Analysis Set)

	Paliperidone Palmitate			
	Placebo (N=164) n (%)	25 mg eq. (N=160) n (%)	100 mg eq. (N=165) n (%)	150 mg eq. (N=163) n (%)
Number of injections				
1	19 (12)	16 (10)	16 (10)	16 (10)
2	48 (29)	37 (23)	35 (21)	34 (21)
3	19 (12)	17 (11)	13 (8)	17 (10)
4	78 (48)	90 (56)	101 (61)	96 (59)

Table 16 Duration (Days) of Exposure to Study Medication (Safety Analysis Set)

	Paliperidone Palmitate			
	Placebo (N=164)	25 mg eq. (N=160)	100 mg eq. (N=165)	150 mg eq. (N=163)
Total exposure, days				
N	164	160	165	163
Category, n (%)				
≤ 7	11 (7)	9 (6)	7 (4)	9 (6)
8 - 35	48 (29)	35 (22)	37 (22)	29 (18)
36 - 63	18 (11)	15 (9)	13 (8)	20 (12)
64 - 91	23 (14)	28 (18)	24 (15)	25 (15)
≥ 92	64 (39)	73 (46)	84 (51)	80 (49)
Mean (SD)	58.1 (35.51)	65.1 (33.36)	67.3 (34.21)	67.2 (33.65)
Median	68.5	90.0	92.0	91.0
Range	(3;115)	(2;100)	(3;143)	(2;123)

Note: The duration of total exposure is calculated as the total number of days a subject remains in the study.

7.2.2 Explorations for Dose Response

Study PSY-3007 is a fixed-dose study. The safety data from each dose group were analyzed separately. A few adverse events (weight gain and increased serum prolactin levels) showed a dose response pattern. Akathisia also showed a dose-response pattern.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or In Vitro testing was deemed necessary.

7.2.4 Routine Clinical Testing

Safety assessments include deaths, adverse events (serious AEs and common AEs), safety laboratory tests (hematology, clinical chemistry and urinalysis), vital signs, body weight, ECG and plasma prolactin levels.

7.2.5 Metabolic, Clearance, and Interaction Workup

Atypical antipsychotics as a class are associated with metabolic syndrome. To explore metabolic effects of paliperidone palmitate, mean changes from baseline values for blood glucose, body weight, BMI, and waist circumference over time were studied.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Atypical antipsychotics are associated with increased prolactin levels, EPS, and metabolic syndrome. Plasma prolactin, glucose, insulin and lipid (cholesterol, triglycerides, LDL and HDL) levels were tested during the study. Body weight, BMI, waist circumference and EPS were assessed over time during the study.

7.3 Major Safety Results

7.3.1 Deaths

One subject died during the study. Subject 040712, a 46-year-old white female, received 2 injections of paliperidone palmitate 150 mg eq. (on Days 1 and 8). On Day 13, the subject was admitted to the hospital by ambulance with preliminary diagnoses of hypertension of III degree and hypertensive stroke. She had experienced a cerebrovascular accident, and was in a coma without spontaneous breathing and subsequently died on Day 22. An autopsy, performed on Day 23, confirmed the cause of death to be extensive brain infarction with brain edema and dislocation. Based on the

investigator's evaluation, the cerebrovascular accident may have been related to the study medication given the temporal relationship; however, there were also pre-existing risk factors for stroke, including extensive atherosclerosis noted at autopsy in the brain and kidney, hypertension with secondary LV hypertrophy, and first-degree AV block (an indication of pre-existing heart disease).

7.3.2 Nonfatal Serious Adverse Events

Table 17 summarizes the incidence of serious treatment-emergent adverse events by treatment group.

The number of subjects who experienced treatment-emergent serious adverse events was higher in the placebo group (14.0%) than in any of the paliperidone palmitate groups (25 mg eq.: 9.4%; 100 mg eq.: 13.3%; 150 mg eq.: 8.0%). Schizophrenia and psychotic disorder were the treatment-emergent adverse events most commonly reported as serious. Most other serious treatment-emergent adverse events were reported for only 1 subject.

During the double-blind treatment period, serious adverse events were experienced by 50 subjects who had been randomly assigned to treatment with paliperidone palmitate 25, 100, or 150 mg eq.. Forty-seven of the 50 subjects had serious adverse events coded to the system organ class of Psychiatric Disorders. Four subjects in the paliperidone palmitate groups had non-psychiatric serious adverse events during the study—syncope, diverticulitis, hemorrhoids and cerebrovascular accident (led to death).

Table 17 Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Paliperidone Palmitate				
	Placebo (N=164) n (%)	25 mg eq. (N=160) n (%)	100 mg eq. (N=165) n (%)	150 mg eq. (N=163) n (%)	Paliperidone (N=488) n (%)
Total no. subjects with serious AE	23 (14.0)	15 (9.4)	22 (13.3)	13 (8.0)	50 (10.2)
Psychiatric disorders	22 (13.4)	14 (8.8)	21 (12.7)	12 (7.4)	47 (9.6)
Schizophrenia	10 (6.1)	9 (5.6)	10 (6.1)	5 (3.1)	24 (4.9)
Psychotic disorder	7 (4.3)	3 (1.9)	7 (4.2)	4 (2.5)	14 (2.9)
Suicidal ideation	3 (1.8)	3 (1.9)	2 (1.2)	0	5 (1.0)
Anxiety	0	0	1 (0.6)	1 (0.6)	2 (0.4)
Depression	1 (0.6)	1 (0.6)	0	1 (0.6)	2 (0.4)
Suicide attempt	0	0	1 (0.6)	1 (0.6)	2 (0.4)
Agitation	1 (0.6)	1 (0.6)	0	0	1 (0.2)
Hallucination, auditory	0	1 (0.6)	0	0	1 (0.2)
Insomnia	0	1 (0.6)	0	0	1 (0.2)
Schizoaffective disorder	0	0	1 (0.6)	0	1 (0.2)
Schizophrenia, paranoid type	0	0	1 (0.6)	0	1 (0.2)
Acute psychosis	1 (0.6)	0	0	0	0
Delusional disorder, persecutory type	1 (0.6)	0	0	0	0
Homicidal ideation	1 (0.6)	0	0	0	0
Nervous system disorders	0	1 (0.6)	0	1 (0.6)	2 (0.4)
Cerebrovascular accident	0	0	0	1 (0.6)	1 (0.2)
Syncope	0	1 (0.6)	0	0	1 (0.2)
Gastrointestinal disorders	0	0	1 (0.6)	0	1 (0.2)
Haemorrhoids	0	0	1 (0.6)	0	1 (0.2)
Infections and infestations	0	1 (0.6)	0	0	1 (0.2)
Diverticulitis	0	1 (0.6)	0	0	1 (0.2)
General disorders and administration site conditions	1 (0.6)	0	0	0	0
Non-cardiac chest pain	1 (0.6)	0	0	0	0
Investigations	1 (0.6)	0	0	0	0
Electrocardiogram change	1 (0.6)	0	0	0	0

7.3.3 Dropouts and/or Discontinuations

Table 18 summarizes, by treatment group and MedDRA preferred term, the incidence of treatment-emergent adverse events that resulted in discontinuation during the double-blind treatment period.

The incidence of adverse events leading to study discontinuation was similar across treatment groups (6.7%, 6.3%, 6.1%, and 8.0% in the placebo and paliperidone palmitate 25, 100, and 150 mg eq. groups, respectively). The adverse events that led to

discontinuation that were reported by at least 2 subjects in any group were schizophrenia, psychotic disorder, suicidal ideation, and agitation.

There were no treatment-related patterns with respect to the individual treatment-emergent adverse events that led to discontinuation with 1 exception. Psychotic disorder led to the withdrawal of 6 subjects receiving paliperidone palmitate (1.2% in the combined paliperidone palmitate group); no subject receiving placebo was withdrawn for psychotic disorder.

Three of the non-serious adverse events that resulted in treatment discontinuation among subjects in the paliperidone palmitate treatment groups were injection site-related events, including single reports of injection site pain, injection site induration, and injection site swelling.

Table 18 Treatment-Emergent Adverse Events Leading to Study Discontinuation by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Paliperidone Palmitate				
	Placebo (N=164) n (%)	25 mg eq. (N=160) n (%)	100 mg eq. (N=165) n (%)	150 mg eq. (N=163) n (%)	Paliperidone (N=488) n (%)
Total no. subjects who discontinued due to AE	11 (6.7)	10 (6.3)	10 (6.1)	13 (8.0)	33 (6.8)
Psychiatric disorders	9 (5.5)	9 (5.6)	9 (5.5)	10 (6.1)	28 (5.7)
Schizophrenia	5 (3.0)	2 (1.3)	2 (1.2)	7 (4.3)	11 (2.3)
Psychotic disorder	0	3 (1.9)	2 (1.2)	1 (0.6)	6 (1.2)
Suicidal ideation	2 (1.2)	1 (0.6)	3 (1.8)	0	4 (0.8)
Agitation	0	2 (1.3)	0	0	2 (0.4)
Hallucination, auditory	1 (0.6)	1 (0.6)	0	1 (0.6)	2 (0.4)
Suicide attempt	0	0	1 (0.6)	1 (0.6)	2 (0.4)
Anxiety	0	0	0	1 (0.6)	1 (0.2)
Depression	1 (0.6)	1 (0.6)	0	0	1 (0.2)
Schizophrenia, paranoid type	0	0	1 (0.6)	0	1 (0.2)
Delusional disorder, persecutory type	1 (0.6)	0	0	0	0
Homicidal ideation	1 (0.6)	0	0	0	0
Insomnia	1 (0.6)	0	0	0	0
General disorders and administration site conditions	0	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Injection site induration	0	1 (0.6)	0	0	1 (0.2)
Injection site pain	0	0	0	1 (0.6)	1 (0.2)
Injection site swelling	0	0	1 (0.6)	0	1 (0.2)
Investigations	1 (0.6)	0	0	1 (0.6)	1 (0.2)
Aspartate aminotransferase increased	1 (0.6)	0	0	1 (0.6)	1 (0.2)
Alanine aminotransferase increased	1 (0.6)	0	0	0	0
Nervous system disorders	0	0	0	1 (0.6)	1 (0.2)
Cerebrovascular accident	0	0	0	1 (0.6)	1 (0.2)
Gastrointestinal disorders	1 (0.6)	0	0	0	0
Nausea	1 (0.6)	0	0	0	0
Vomiting	1 (0.6)	0	0	0	0

7.3.4 Significant Adverse Events

Paliperidone palmitate, same as other atypical antipsychotics, is associated to some significant AEs, such as increased plasma prolactin level, and metabolic syndrome. These AEs will be addressed in paliperidone palmitate labeling. No new significant AEs were identified from this re-submission.

7.3.5 Submission Specific Primary Safety Concerns

The safety profile of Paliperidone palmitate from this submission is consistent with the findings from the original submission dated on 25 October 2007. It is also comparable with that of paliperidone ER (oral tablets) which is a marketed drug. No submission specific primary safety concerns were identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All common treatment-emergent adverse events, i.e., events that occurred in at least 2% of subjects in any group, are presented by MedDRA system organ class and preferred term in Table 19.

Overall, treatment-emergent adverse events occurred at similar rates among the paliperidone palmitate (60.0% to 63.2%) and placebo (65.2%) groups. The most common adverse events were nervous system disorders and psychiatric disorders. Psychiatric disorders were reported at higher rates in placebo-treated subjects.

Among the most common treatment-emergent adverse events (>2% of subjects in any treatment group), events that occurred more frequently in the total paliperidone palmitate group (all 3 active dose groups combined) than in placebo-treated subjects (i.e., >1% difference between the incidence in the total paliperidone palmitate group and the placebo group) were: injection site pain (7.6% vs. 3.7%), dizziness (2.5% vs. 1.2%), sedation (2.3% vs. 0.6%), pain in extremity (1.6% vs. 0.0%), and myalgia (1.0% vs. 0.0%).

Table 19 Treatment-Emergent Adverse Events in ≥ 2% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Paliperidone Palmitate				Paliperidone (N=488) n (%)
	Placebo (N=164) n (%)	25 mg eq. (N=160) n (%)	100 mg eq. (N=165) n (%)	150 mg eq. (N=163) n (%)	
Total no. subjects with adverse events	107 (65.2)	101 (63.1)	99 (60.0)	103 (63.2)	303 (62.1)
Psychiatric disorders	63 (38.4)	48 (30.0)	54 (32.7)	45 (27.6)	147 (30.1)
Insomnia	27 (16.5)	19 (11.9)	16 (9.7)	21 (12.9)	56 (11.5)
Schizophrenia	19 (11.6)	13 (8.1)	13 (7.9)	13 (8.0)	39 (8.0)
Anxiety	11 (6.7)	8 (5.0)	10 (6.1)	9 (5.5)	27 (5.5)
Agitation	11 (6.7)	12 (7.5)	8 (4.8)	6 (3.7)	26 (5.3)
Psychotic disorder	8 (4.9)	7 (4.4)	7 (4.2)	5 (3.1)	19 (3.9)
Suicidal ideation	3 (1.8)	3 (1.9)	4 (2.4)	1 (0.6)	8 (1.6)
Nervous system disorders	27 (16.5)	28 (17.5)	35 (21.2)	33 (20.2)	96 (19.7)
Headache	12 (7.3)	17 (10.6)	11 (6.7)	10 (6.1)	38 (7.8)
Akathisia	8 (4.9)	2 (1.3)	8 (4.8)	9 (5.5)	19 (3.9)
Dizziness	2 (1.2)	1 (0.6)	7 (4.2)	4 (2.5)	12 (2.5)
Sedation	1 (0.6)	2 (1.3)	6 (3.6)	3 (1.8)	11 (2.3)
Somnolence	3 (1.8)	0	2 (1.2)	5 (3.1)	7 (1.4)
Tremor	4 (2.4)	1 (0.6)	3 (1.8)	2 (1.2)	6 (1.2)
Gastrointestinal disorders	28 (17.1)	18 (11.3)	23 (13.9)	29 (17.8)	70 (14.3)
Vomiting	5 (3.0)	4 (2.5)	4 (2.4)	4 (2.5)	12 (2.5)
Constipation	5 (3.0)	3 (1.9)	6 (3.6)	2 (1.2)	11 (2.3)
Toothache	2 (1.2)	2 (1.3)	3 (1.8)	5 (3.1)	10 (2.0)
Diarrhoea	4 (2.4)	1 (0.6)	4 (2.4)	4 (2.5)	9 (1.8)
Nausea	4 (2.4)	3 (1.9)	3 (1.8)	3 (1.8)	9 (1.8)
Dyspepsia	4 (2.4)	1 (0.6)	1 (0.6)	3 (1.8)	5 (1.0)
General disorders and administration site conditions	11 (6.7)	19 (11.9)	19 (11.5)	23 (14.1)	61 (12.5)
Injection site pain	6 (3.7)	14 (8.8)	10 (6.1)	13 (8.0)	37 (7.6)
Fatigue	1 (0.6)	1 (0.6)	4 (2.4)	2 (1.2)	7 (1.4)
Infections and infestations	13 (7.9)	21 (13.1)	19 (11.5)	19 (11.7)	59 (12.1)
Nasopharyngitis	4 (2.4)	6 (3.8)	3 (1.8)	3 (1.8)	12 (2.5)
Upper respiratory tract infection	3 (1.8)	2 (1.3)	3 (1.8)	6 (3.7)	11 (2.3)
Urinary tract infection	3 (1.8)	2 (1.3)	2 (1.2)	4 (2.5)	8 (1.6)
Musculoskeletal and connective tissue disorders	5 (3.0)	12 (7.5)	10 (6.1)	11 (6.7)	33 (6.8)
Pain in extremity	0	3 (1.9)	5 (3.0)	0	8 (1.6)
Musculoskeletal stiffness	2 (1.2)	1 (0.6)	2 (1.2)	4 (2.5)	7 (1.4)
Myalgia	0	1 (0.6)	0	4 (2.5)	5 (1.0)
Investigations	14 (8.5)	11 (6.9)	9 (5.5)	11 (6.7)	31 (6.4)
Alanine aminotransferase increased	4 (2.4)	2 (1.3)	1 (0.6)	2 (1.2)	5 (1.0)

7.4.2 Laboratory Findings

Mean Change from Baseline over Time

There were no clinically relevant mean changes from baseline to any time point during the double-blind period for laboratory analytes, including hematology, renal function, liver function, fasting blood glucose or insulin, serum lipid, and urinalysis parameters evaluated in this study. No treatment-related pattern was apparent for the mean changes from baseline to end point.

Individual Clinically Significant Abnormalities

For all laboratory parameters, 0 to 4 subjects per treatment group had treatment-emergent markedly abnormal results. One subject who received placebo and 1 subject who received paliperidone palmitate (100 mg eq. group) had a markedly abnormal elevation in liver enzymes (ALT). Only one subjects in paliperidone palmitate 25 mg eq. group had abnormally high plasma glucose level.

Serum Prolactin Levels

There was a mean decrease in prolactin in the placebo group compared with mean increases in the paliperidone palmitate treatment groups. The mean changes in prolactin levels from baseline to end point generally were larger among female subjects than for male subjects for all treatment groups. In male subjects, there is a dose-response pattern with regards to mean increase in prolactin levels (-16.43, 3.73, 8.43, and 13.15 ng/ml in placebo, 25, 100 and 150 mg eq. paliperidone palmitate respectively). In female subjects, the mean increase in prolactin level was -59.74, 9.34, 4.72, and 37.24 ng/ml in placebo, 25, 100 and 150 mg eq. paliperidone palmitate respectively.

Within each sex group, the percentage of subjects with treatment-emergent elevated prolactin levels at end point that were above the upper limit of the laboratory reference range (18.77 ng/mL for males and 24.2 ng/mL for females) was higher for the paliperidone palmitate groups (29% to 31% in male and 16% to 23% in female) than for the placebo group (4% in both sex).

7.4.3 Vital Signs

Mean Change from Baseline to Endpoint

Regardless of treatment, there were no clinically relevant mean changes from baseline to end point in vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate). There were small mean changes in standing and supine pulse rate at end point in

all paliperidone palmitate groups that were similar to those observed in the placebo group.

Individual Clinically Significant Abnormalities

Few subjects ($\leq 2\%$) across the placebo and paliperidone palmitate treatment groups had treatment-emergent abnormalities decreased in standing or supine systolic or diastolic blood pressure based on the pre-specified criteria.

Few subjects ($\leq 1\%$) across the placebo and paliperidone palmitate treatment groups had treatment-emergent decreases in standing or supine pulse rate.

Pulse rates of ≥ 100 bpm with an increase of ≥ 15 bpm were observed in 6% to 11% of subjects for standing measurements and in 2% to 5% for supine measurements across the treatment groups. No dose-related trend was seen with respect to the percentages of subjects with abnormal elevations in standing or supine pulse rate.

Orthostatic Changes in Blood Pressure and Pulse Rate

As assessed by orthostatic changes in blood pressure and pulse rate, treatment-emergent orthostatic hypotension during the double-blind period occurred in 1% to 2% of subjects across all 4 treatment groups.

None of the subjects with orthostatic hypotension based on blood pressure and pulse rate measurements had orthostatic hypotension reported as a treatment-emergent adverse event.

7.4.4 Electrocardiograms (ECGs)

No treatment-emergent abnormal QT intervals were observed during the double-blind period for any subject. An abnormally high PR interval value was recorded for 2 subjects in the placebo group and for 3 subjects across the paliperidone palmitate treatment groups.

Clinically significant findings related to abnormal ECG parameters were to be recorded as adverse events. The frequency of adverse events related to abnormal ECG findings was low ($\leq 1.2\%$ for the combined paliperidone palmitate group) and showed no apparent difference between the active dose groups and the placebo group.

Corrected QT Intervals

The primary method for calculation of heart rate corrected QT interval was QTcLD in this study. For completeness, QT was also corrected for heart rate using the traditional formulae of Fridericia (QTcF), Sagie (QTc), and Bazett (QTcB).

No subjects reported a maximum QTcLD value >500 ms or >480 ms.

Based on QTcLD, 1 subject each in the paliperidone palmitate 25 mg eq. group (Subject 082107, QTcLD value of 460 ms on Day 8) and 150 mg eq. group (Subject 010302, QTcLD value of 451 ms on Day 36) reported a maximum QTcLD value >450 to <480 ms.

Maximum increases between >30 and ≤60 ms in QTcLD intervals were reported in 3%, 4%, and 3% of paliperidone palmitate-treated subjects in the 25, 100, and 150 mg eq. groups, respectively, compared with 3% in the placebo group.

Based on QTcLD, no subject experienced an increase >60 ms.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials were required.

7.4.6 Immunogenicity

Immunogenicity study is not deemed as necessary.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A dose-related pattern with respect to the occurrence of safety findings was seen only for the increases in body weight and serum prolactin levels.

7.5.2 Time Dependency for Adverse Events

The time to first occurrence of an EPS-related adverse event suggests that most of these events occurred within the first month of treatment. There appeared to be no noteworthy differences between the treatment groups.

With regards to injection site pain, the average intensity of pain based on the subject's evaluation decreased over time for injections administered at either deltoid or gluteal sites in the 3 paliperidone palmitate treatment groups.

7.5.3 Drug-Demographic Interactions

By Sex

Two-thirds of the subjects in the safety analysis set were male (67%). The overall incidence of treatment-emergent adverse events was higher in female subjects (67%) than for male subjects (61%).

The common individual adverse events, i.e., those reported at the incidence of over 5%, which occurred more often (i.e., with a difference in incidence of $\geq 3\%$) among females were insomnia (16% vs. 11%), schizophrenia (11% vs. 8%), anxiety (8% vs. 5%). Injection site pain was reported in 8% of male subjects and 5% of female subjects.

The incidence of most other individual adverse events was distributed similarly between the 2 subgroups.

By Age

The largest subgroup of subjects (n=490) were between 26 and 50 years of age; 69 subjects were between 18 and 25 years, and 93 subjects were older than 50 years. The overall incidence of treatment-emergent adverse events was higher for the > 50 year old group (68%), followed by 63% for subjects in the 26-50 years, and the lowest incidence of 52% was observed for the 18-25 years subgroup.

Among common adverse events (those occurring at the incidence of over 5%) reported more frequently in the older (>50 years) subjects and the middle age (26-50 years) group, compared to the younger (18-25 years) subjects, were insomnia (15% and 13%, respectively, vs. 7%), schizophrenia (9% and 10%, respectively, vs. 4%), injection site pain (10% and 6% vs. 4%), headache (11% and 7% vs. 6%), psychotic disorder (6% and 4% vs. 3%).

The majority of other individual adverse events were distributed equally among the 3 age subgroups.

By Race

Subjects in the safety analysis set were 53% White, 31% Black, and 14% Asian, and 1% Other.

The overall rate of adverse events was highest among Asian subjects (73%) followed by Black (67%), and White (57%) subjects.

Adverse events reported more frequently by the Asian subjects, compared to the Black and White subjects, respectively, were those in Gastrointestinal Disorders System

Organ Class (SOC) (28% vs. 20% and 9%), including such common events as constipation (10% vs. 2% and 1%, respectively) and vomiting (6% vs. 2% and 1%, respectively); Infections and Infestations SOC (23% vs. 9% in each of the other 2 subgroups), including nasopharyngitis (9% vs. 1% in each of the other 2 subgroups) and upper respiratory tract infection (10% vs. 1% in each of the other 2 subgroups).

Asian and White subjects had higher rates of Psychiatric Disorders (37% and 34%, respectively), compared to Black subjects (27%), including such individual events as insomnia (17% and 14%, respectively, vs. 8%), and schizophrenia (8% and 12%, respectively, vs. 4%).

General Disorders and Administration Site Conditions were reported at the highest rate by Black subjects (17%) vs. 9% in White subjects and 4% in Asian subjects. Specifically, injection site pain was reported at the rates of 12% vs. 5% and 0% in these 3 respective racial subgroups. Black subjects experienced more adverse events in the Nervous System Disorders SOC (25%), compared to 15% in White subjects and 17% in Asian subjects. Musculoskeletal and Connective Tissue Disorders were also reported more frequently in Black subjects (9%) vs. 4% in each of the other subgroups.

7.5.4 Drug-Disease Interactions

No drug-disease interaction analysis was conducted in the submission.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not studied in this study. Please refer to clinical pharmacology review from Hao Zhu, PhD, for pertinent PK/PD information.

7.5.6 Other Safety Issues with Special Interests

Body Weight, Body Mass Index, and Waist Circumference

From baseline to end point, mean body weight, mean BMI, and mean waist circumference decreased in the placebo group and increased in the paliperidone palmitate treatment groups (Table 20).

The change from baseline to end point for mean body weight, mean BMI, and mean waist circumference showed a dose-related increase, with the largest mean increase seen in the paliperidone palmitate 150 mg eq. group (see Table 20).

Table 20 Body Weight, BMI and Waist Measurement: Change from Baseline to Endpoint (Safety Analysis Set)

	Placebo (n = 164)	Paliperidone palmitate		
		25 mg eq. (n = 160)	100 mg eq. (n = 165)	150 mg eq. (n = 163)
Weight (kg)				
N	143	137	144	145
Mean change (SD)	-0.2 (3.67)	0.4 (3.80)	0.7 (3.49)	1.4 (3.63)
Body mass index (kg/m²)				
N	143	137	144	145
Mean change (SD)	-0.1 (1.26)	0.1 (1.31)	0.3 (1.21)	0.5 (1.25)
Waist (cm)				
N	140	135	141	140
Mean change (SD)	-0.1 (3.91)	0.2 (4.04)	0.6 (3.96)	1.0 (4.20)

Weight increases from baseline of $\geq 7\%$ were more common among subjects in the paliperidone palmitate groups than in the placebo group. The proportion of subjects with an abnormal weight increase $\geq 7\%$ showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the paliperidone palmitate 25, 100, and 150 mg eq. groups, respectively.

Extrapyramidal Symptoms

The occurrence and severity of extrapyramidal symptoms were evaluated by monitoring subjects for EPS-related adverse events and by evaluating changes from baseline for extrapyramidal symptom rating scale scores and use of anti-EPS medications.

Extrapyramidal Symptom-Related Adverse Events

The EPS-related treatment-emergent adverse events are presented in Table 21.

Hyperkinesia (i.e., akathisia) was the most frequent category of EPS-related adverse events, and appeared to be associated with a dose-related pattern. However, akathisia was reported at a similar rate for the placebo (4.9%) and paliperidone palmitate 100 mg eq. (4.8%) and 150 mg eq. (5.5%) groups.

All but 1 of the EPS-related adverse events reported in placebo- or paliperidone palmitate-treated subjects were mild or moderate in intensity; musculoskeletal stiffness was reported as severe in a subject in paliperidone palmitate 150 mg eq. group. None of the EPS-related adverse events were serious, and no subject was discontinued due to an EPS-related event.

Most of these events occurred within the first month of treatment. There are no noteworthy differences between the treatment groups.

Table 21 Treatment-Emergent Extrapyramidal Symptom Related Adverse Events by MedDRA Preferred Term (Safety Analysis Set)

EPS Group Dictionary-derived Term	Paliperidone Palmitate				
	Placebo (N=164) n (%)	25 mg eq. (N=160) n (%)	100 mg eq. (N=165) n (%)	150 mg eq. (N=163) n (%)	Paliperidone (N=488) n (%)
Hyperkinesia	8 (4.9)	2 (1.3)	8 (4.8)	9 (5.5)	19 (3.9)
Akathisia	8 (4.9)	2 (1.3)	8 (4.8)	9 (5.5)	19 (3.9)
Parkinsonism	3 (1.8)	5 (3.1)	5 (3.0)	7 (4.3)	17 (3.5)
Musculoskeletal stiffness	2 (1.2)	1 (0.6)	2 (1.2)	4 (2.5)	7 (1.4)
Parkinsonism	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	4 (0.8)
Drooling	0	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Extrapyramidal disorder	0	1 (0.6)	0	0	1 (0.2)
Muscle rigidity	0	0	1 (0.6)	0	1 (0.2)
Muscle tightness	0	0	0	1 (0.6)	1 (0.2)
Nuchal rigidity	0	1 (0.6)	0	0	1 (0.2)
Tremor	4 (2.4)	1 (0.6)	3 (1.8)	2 (1.2)	6 (1.2)
Tremor	4 (2.4)	1 (0.6)	3 (1.8)	2 (1.2)	6 (1.2)
Dyskinesia	1 (0.6)	0	2 (1.2)	2 (1.2)	4 (0.8)
Dyskinesia	0	0	1 (0.6)	2 (1.2)	3 (0.6)
Movement disorder	0	0	1 (0.6)	0	1 (0.2)
Athetosis	1 (0.6)	0	0	0	0
Dystonia	1 (0.6)	3 (1.9)	0	0	3 (0.6)
Dystonia	1 (0.6)	2 (1.3)	0	0	2 (0.4)
Muscle spasms	0	1 (0.6)	0	0	1 (0.2)

Extrapyramidal Symptoms Rating Scales

The Simpson Angus Scale (SAS) is intended to measure the severity of specific EPS-related adverse events, including tremor, abnormal gait, rigidity (hypertonia), and salivation. The change from baseline in SAS global scores for each paliperidone palmitate group and the placebo group is assessed over time, including at end point. Median change in the SAS global scores was 0 at end point for all treatment groups, showing no change from baseline.

The Barnes Akathisia Rating Scale (BARS) includes an objective rating, and a global clinical rating of akathisia from 0 (absent) to 5 (severe). The global clinical rating score is rated separately, and is used as the primary measure of severity of akathisia during the study. Approximately 90% of subjects in each treatment group (range: 86.8% to 93.1%) scored 0 (absent) at end point in the global clinical rating score for akathisia from the BARS. There were no apparent differences between the treatment groups.

The total Abnormal Involuntary Movement Scale (AIMS) score, which rates the severity of abnormal involuntary movements, is a measure of dyskinesia, including tardive dyskinesia. The median baseline and end point scores, as well the median changes from baseline, were 0 in all treatment groups.

Use of Anticholinergic Medication

The percentage of subjects who required use of an anticholinergic medication during the study was low during the double-blind treatment period and similar across the placebo and paliperidone palmitate groups (11%, 12%, 13% and 13% in paliperidone palmitate 25, 100, 150 mg eq. and placebo group respectively).

Potentially Prolactin-Related Adverse Events

Like other drugs that antagonize dopamine D₂ receptors, paliperidone is associated with increases in prolactin levels. Changes in prolactin levels over time and the incidence of treatment-emergent prolactin level changes outside of laboratory reference ranges are described in Section 7.4.2 Laboratory Findings.

One male subject (0.9%) in the placebo group and 3 male or female subjects (0.6%) in the combined paliperidone palmitate 25, 100, and 150 mg eq. groups experienced potentially prolactin-related adverse events (galactorrhoea, loss of libido and ejaculation disorder). None of the potentially prolactin-related adverse events were serious or resulted in discontinuation of study treatment.

Two subjects in the paliperidone palmitate treatment groups with a potentially prolactin-related adverse event had a clinically significant prolactin level of >100 ng/mL.

Glucose-Related Adverse Events

No paliperidone palmitate-treated subject had a treatment-emergent glucose-related adverse event. Two subjects (1.2%) in the placebo group had a glucose-related adverse event (blood glucose increased and diabetes mellitus).

Injection Site Effects

Injection site pain and injection site erythema were the most common treatment-emergent injection site-related adverse events. Injection site pain was reported at a higher rate in the combined paliperidone palmitate group (7.6%) compared with the placebo group (3.7%); the incidence of injection site pain was similar among the 3 paliperidone palmitate dose groups (6.1% to 8.8%). Injection site erythema was reported at a similar rate for the placebo (1.8%) and paliperidone palmitate 25, 100, and 150 mg eq. groups (0.6% to 1.9%). Other injection site-related adverse events (i.e., injection site swelling, induration, irritation, mass, pruritis, and extravasation) were

reported by fewer than 1% of subjects in the combined paliperidone palmitate group. No other injection site-related treatment-emergent adverse event was reported among placebo-treated subjects.

All of the injection site-related adverse events were non-serious. Three subjects (0.6%) across the paliperidone palmitate groups were discontinued due to an injection site adverse event.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity study was not required for this submission.

7.6.2 Human Reproduction and Pregnancy Data

The safety of paliperidone palmitate or paliperidone for use during human pregnancy or women who are lactating has not been established.

One subject in study PSY-3007 was withdrawn from treatment due to pregnancy. Subject 083909 is a 34 year old woman, was confirmed to be pregnant on Day 20. One Day 36, the subject underwent an induced abortion. The subject was withdrawn from the study on Day 36 due to pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric patients were enrolled in this study. Therefore, the effect of paliperidone palmitate on growth was not established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential for overdose with paliperidone palmitate in this study was negligible due to the fact that the study drug was administered via i.m. injection by study drug administrator at each study site. No events of overdose with paliperidone palmitate were reported.

The pharmacologic profile of paliperidone palmitate indicates minimum abuse and dependence potential. This potential is further reduced due to the fact that paliperidone palmitate is an injectable formulation which is not readily available to patients.

This study was not designed to test withdrawal and rebound phenomenon of paliperidone palmitate.

7.7 Additional Submissions / Safety Issues

No additional submissions/safety issues were submitted to this resubmission.

8 Postmarket Experience

At the time of completion of this review, paliperidone palmitate was not marketed in any country.

9 Appendices

9.1 Literature Review/References

Literature Review/references submitted by the sponsor were located at Module 5.4 Literature References.

9.2 Labeling Recommendations

The major labeling recommendations have been summarized as following. The line-to-line labeling review can be found in the Complete Response Letter.

1. Initial Dosing Regimen

The sponsor proposed a new initial dosing regimen, initiate INVEGA SUSTENNA with a dose of 150 mg on Day 1 and 100 mg one week later, both administered in the deltoid muscle, in the latest proposed labeling. This regimen has not been formally tested in the clinical trials. This issue has been discussed in section 6 REVIEW OF EFFICACY/c. Crosscutting Issues/vii. Dose Recommendation and It Justification. From clinical point of view, the proposed regimen is reasonably safe and acceptable.

2. Missed Doses

The sponsor proposed a new subsection, 2.2 Missed Doses, intended to give prescribers more guidance regarding how to handle missing doses. Simulation data to support this revision were submitted to this NDA. Please refer to clinical pharmacology review for detailed discussion. From clinical point of view, this revision provided more guidance for missing dose circumstances which makes the labeling safer. The doses recommended following missed doses were safe. Therefore, the revision is acceptable.

(b) (4)

4. Dosage forms and strengths

In the proposed labeling, the dosage forms and strengths of INVEGA SUSTENNA were presented as “25 mg, 75 mg, 100 mg, and 150 mg paliperidone (as 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate)”. Based on the United States Pharmacopedia’s recommendation, the labeling should present the total strength of the salts or esters of the products, not the equivalent doses. In addition, to prevent dose confusion in future when the generic form of paliperidone palmitate become available, it is recommended that only the actual strength of paliperidone palmitate, 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate, will be presented in all paliperidone palmitate labelings. The information with regards to dose conversion between oral paliperidone ER and paliperidone palmitate, such as how many mg of paliperidone palmitate equates to how many mg of oral paliperidone ER, should be provided in the labeling to help prescribers switching.

5. Discontinuations Due to Adverse Reactions

The section 6.3 Discontinuations Due to Adverse Reactions has been updated and the safety data from PSY-3007 had been incorporated into the subsection. However, the numbers (discontinuation rates) seemed not matching well with the numbers obtained from the Clinical Study Reports of the four fixed-dose, double-blind, placebo-controlled studies. The sponsor needs to provide the data sources for these numbers, such as the analysis results, or tables.

6. Dose-Related Adverse Reactions

Besides AEs listed in this subsection, increased prolactin levels and weight gain are another two dose-related adverse events observed in the 4 short-term fixed-dose studies. The findings were consistent in the original submission and in this resubmission. Increased prolactin levels and weight gain were not included in the dose-related AE list in this subsection. It is recommended that these two adverse events are added to the AE list, or a justification should be provided.

7. PK of Paliperidone Palmitate versus paliperidone ER

(b) (4)



8. Clinical Studies

The whole section 14 CLINICAL STUDIES had been rewritten by the sponsor. Several major revisions had been made:

1) Data from study PSY-3007 were incorporated into the section;

2) [REDACTED] (b) (4)

[REDACTED] (b) (4)

4) [REDACTED] (b) (4)

Revision 1 (adding data from study PSY-3007) and 4 ([REDACTED] (b) (4)
[REDACTED]) are appropriate. These changes are acceptable. (b) (4)

9.3 Advisory Committee Meeting

No Advisory Committee Meeting is planned for this submission.

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

/s/

Jing Zhang
6/8/2009 07:42:43 PM
MEDICAL OFFICER

Gwen Zornberg
6/9/2009 05:27:51 PM
MEDICAL OFFICER

II concur with Dr. Zhang's recommendation to the Division
Director that an approval letter be issued for
paliperidone palmitate based on the favorable risk benefit
assessment contingent upon the findings of ONDQA &
OCP, as well as agreement on labeling.

CLINICAL REVIEW

Application Type NDA 22-264
Submission Number 000
Submission Code N

Letter Date 25 October 2007
Stamp Date 26 October 2007
PDUFA Goal Date 26 August 2008

Reviewer Name Jing Zhang, MD., PhD.
Review Completion Date 7 July 2008

Established Name Paliperidone Palmitate (b) (4)
(Proposed) Trade Name Pending
Therapeutic Class Atypical Antipsychotic
Applicant J & J PRD

Priority Designation S

Formulation Intramuscular Injection
Dosing Regimen 25, 50, 75 and 100 mg eq.
Indication Schizophrenia
Intended Population Adults

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Figure 1 Kaplan-Meier Plot of Time to Recurrence: PSY-3001, Interim Analysis, ITT 25

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this New Drug Application (NDA) be granted approvable status.

Additional information will be requested from the applicant regarding errors in adverse events reporting in study PSY-3001. Moreover, additional data will be required for labeling changes, to which the sponsor needs to respond (see section 9.4 *Labeling Review* for recommended labeling changes). Final approval is contingent on satisfactory response to the agency's requests and mutual agreement on labeling as well as the conclusions of the CMC, Pharmacology/Toxicology, and clinical pharmacology reviewers.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no additional recommendations.

1.2.2 Required Phase 4 Commitments

The sponsor already conducted a positive long-term, relapse prevention study (study PSY-3001), which includes an initial 33 week open-label period (including a 24 week stabilization phase); a randomized, double-blind, placebo-controlled phase with varied duration; and followed by an optional 52 week open label extension phase. Therefore, no additional Phase 4 commitments are required.

A full waiver of pediatric studies covering ages 0 to 17 for the indication of schizophrenia relapse prevention is recommended. However, for the acute treatment indication, adolescent studies covering ages 13 to 17, including a PK study, an efficacy and safety study, and a long-term safety study will be required if the adult indications are approved. No pediatric study for children ages 12 and under for the acute treatment indication is required. Requests for waivers and a deferral of pediatric studies will be presented to the Pediatric Review committee (PeRC).

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical efficacy and safety development program of paliperidone palmitate (R092670) includes 6 phase 2/3 studies. Table 1 summarizes the Phase 2/3 clinical studies submitted in support of the efficacy and safety of paliperidone palmitate.

Table 1 Studies Supporting the Efficacy and/or Safety of Paliperidone Palmitate

Protocol	Study Description	Study Treatments ^a	No. of Subjects ^b
Randomized, Controlled Recurrence Prevention Study in Adult Subjects with Schizophrenia			
R092670-PSY-3001	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter recurrence prevention study of variable duration preceded by an initial 33-week, open-label, transition/maintenance phase; gluteal injection.	Paliperidone palmitate (flexible dose 25 to 100 mg eq./4 weeks) Placebo (Double-blind phase only)	<i>Open-label transition phase</i> , n=849 <i>Open-label maintenance phase</i> , n=681 <i>DB phase</i> : Paliperidone, n=205 Placebo, n=203
Randomized, Controlled Fixed Dose Studies in Adult Subjects with Schizophrenia			
R092670-PSY-3003	13-week, Phase 3 randomized, double-blind, placebo-controlled, parallel group, multicenter dose response study; gluteal injection.	Placebo ^c Paliperidone palmitate ^c 50 mg eq./4 weeks 100 mg eq./4 weeks 150 mg eq./4 weeks	135 ^d 94 97 61 ^d
R092670-PSY-3004	13-week, Phase 3 randomized, double-blind, placebo-controlled, parallel group, multicenter dose response study; gluteal injection.	Placebo ^c Paliperidone palmitate ^c 25 mg eq./4 weeks 50 mg eq./4 weeks 100 mg eq./4 weeks	127 130 129 131
R092670-SCH-201	1-week oral run-in, 9-week randomized, double-blind, placebo-controlled, parallel group, multicenter dose response Phase 2 study; gluteal injection.	Placebo ^e Paliperidone palmitate ^e 50 mg eq./4 weeks 100 mg eq./4 weeks	84 79 84
R092670-PSY-3005	25-week, Phase 3, randomized, crossover study of safety and tolerability following i.m. injections into gluteal and deltoid muscle.	Paliperidone palmitate ^f 50 mg eq./4 weeks 75 mg eq./4 weeks 100 mg eq./4 weeks	249 82 81 86
Randomized, Non-inferiority Study in Adult Subjects with Schizophrenia			
R092670-PSY-3002	53-week, Phase 3 randomized, double-blind, parallel group, multicenter study; gluteal injection.	RISPERDAL [®] CONSTA [™] (flexible dose, 25 to 50 mg every 2 weeks) Paliperidone palmitate (flexible dose, 25 to 100 mg eq. every 4 weeks)	368 379

^a Doses of paliperidone palmitate are expressed as the paliperidone milligram equivalent (e.g., paliperidone palmitate 100 mg eq.; 156 mg of paliperidone palmitate is equivalent to 100 mg paliperidone). Placebo consisted of 20% Intralipid (200 ng/mL injectable emulsion matched by volume to corresponding injection of paliperidone palmitate).

^b Includes all subjects who were evaluable for safety.

^c Doses of paliperidone palmitate (and control) administered on Days 1, 8, 36, and 64.

^d As a result of an interactive voice response system (IVRS) programming error that resulted in an error in medication kit allocation, some subjects were assigned medication from the beginning of the study that did not match their original randomization code or were erroneously switched to a different medication (paliperidone palmitate to placebo or vice versa) at some time during the trial. Of the 61 subjects who received at least 1 dose of the 150 mg eq. dose, 31 received a combination of 150 mg eq. and placebo injections.

^e Doses of paliperidone palmitate (and control) administered on Days 1, 8, and 36.

^f Doses of paliperidone palmitate administered on Days 1, 8, 36 and at 4-week intervals thereafter.

Study PSY-3001 was a double-blind, parallel group, randomized withdrawal study designed to evaluate the efficacy and safety of paliperidone palmitate compared to placebo for the prevention of recurrence of symptoms of schizophrenia after a period of stabilization.

Studies PSY-3003 and PSY-3004 were 13-week, placebo-controlled, Phase 3 clinical trials designed to identify the effective and safe dose range for paliperidone palmitate in the treatment of schizophrenia.

Study SCH-201 was a randomized, 9-week, placebo-controlled, Phase 2 study of paliperidone palmitate in subjects with schizophrenia and encompassed 2 of the fixed doses used in the 13-week Phase 3 studies.

Study PSY-3005 compared the safety, tolerability and PK of paliperidone palmitate administered at fixed doses of 50, 75 and 100 mg eq. at 2 different i.m. injection sites (gluteus or deltoid). This Phase 3 cross-over study was undertaken following results of a Phase 1 study (R092760-USA-3) that found maximum plasma concentrations of paliperidone were approximately 50% higher after deltoid administration compared with gluteal administration, although total drug exposure was comparable between the 2 sites. Only safety data from this study were reviewed in this review. The PK data will be reviewed by the clinical pharmacology reviewer, John Duan PhD.

Study PSY-3002 was a non-inferiority trial examining the efficacy and safety of paliperidone palmitate, administered once monthly within a flexible dose range of 25 to 100 mg eq., and injectable risperidone (RISPERDAL® CONSTA™; flexible dose range of 25 to 50 mg, once every 2 weeks) in the treatment of schizophrenia. (b) (4)

While the agency does not consider non-inferiority studies to provide substantial evidence of efficacy, the efficacy data from this study were not reviewed in this review. However, the safety data from this study were reviewed in the integrated safety review.

1.3.2 Efficacy

The acute efficacy of paliperidone palmitate in the treatment of subjects with schizophrenia was demonstrated in three short-term, double-blind, placebo-controlled phase 2/3 clinical studies with respect to the change from baseline to endpoint in total PANSS score. Study PSY-3003 provided statistically significant evidence for the efficacy of paliperidone palmitate 100 mg eq. In study PSY-3004, all doses (25 mg eq., 50 mg eq., and 100 mg eq.) were demonstrated statistically to be superior to placebo. Study SCH-201 also provided statistically evidence of the efficacy of paliperidone palmitate at doses of 50 mg eq., and 100 mg eq.

The long-term efficacy of paliperidone palmitate in the prevention of recurrence of symptoms of schizophrenia was demonstrated in a randomized, double-blind, placebo-controlled, relapse prevention study, PSY-3001. There was a statistically significant difference between the treatment groups (flexible-dosed, ranged from 25 mg eq. to 100 mg eq.) in the time to recurrence

of symptoms in favor of paliperidone palmitate. Subjects who continued treatment on paliperidone palmitate experienced recurrence later than subjects who switched to placebo.

1.3.3 Safety

Safety data from 16 completed paliperidone palmitate clinical trials (5 phase 3, 1 phase 2 and 10 phase 1) were reviewed. The safety evaluation demonstrated that the safety profile of paliperidone palmitate is similar to that of paliperidone ER for most parameters that were measured with the exception of injection site-related adverse events. No new or unexpected safety signals were identified.

1.3.4 Dosing Regimen and Administration

[REDACTED] (b) (4)

The proposed dosing regimen has not been studied in controlled clinical trials. The sponsor proposed this dosing regimen based on the analysis of the relationship between BMI, PK, clinical efficacy and clinical safety. From the clinical point of view, the proposed the dosing regimen is reasonably safe in adults. However, the clinical pharmacological reviewer, John Duan, PhD, recommends a starting dose of 75 mg eq. instead of [REDACTED] (b) (4) mg eq. administered in the deltoid muscle. Please refer to the clinical pharmacological review for detailed information. More discussion regarding the rationale for the dosing recommendation also can be found in section 8.1 Dosing Regimen and Administration.

1.3.5 Drug-Drug Interactions

John Duan, PhD is the clinical pharmacology reviewer for this submission. Please refer to his review for detailed drug-drug interaction information.

1.3.6 Special Populations

No consistent differences with respect to efficacy or adverse events were observed between age groups, gender, race or geographic regions.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Paliperidone (9-hydroxy-risperidone, R076477) is a mono-aminergic antagonist that exhibits the characteristic dopamine type 2 (D₂) and serotonin (5-hydroxytryptamine [5-HT]) type 2A

(5HT_{2A}) antagonism of the newer, or second-generation, antipsychotic drugs. Paliperidone is the major active metabolite of risperidone (R064766) and is a racemic mixture of enantiomers R078543 (+) and R078544 (-).

2.2 Currently Available Treatment for Indications

Numerous typical and atypical antipsychotics have been approved by FDA for the treatment of schizophrenia in the USA. Compared with the oral preparations, only a few long-acting antipsychotic injections are available in the USA: two typical antipsychotics—haloperidol decanoate and fluphenazine decanoate, and one atypical antipsychotic—Risperidal Consta.

2.3 Availability of Proposed Active Ingredient in the United States

INVEGA[®] (paliperidone) Extended-Release (ER) Tablets are approved in the U.S and the Europe for the treatment of schizophrenia. Paliperidone palmitate long-lasting injection has not been approved either in the U.S or Europe.

2.4 Important Issues With Pharmacologically Related Products

Paliperidone is an active metabolite of risperidone, an approved atypical antipsychotic. An oral formulation of paliperidone (paliperidone ER) has been approved for marketing in the United States and the Europe. Similar to risperidone and paliperidone ER, paliperidone palmitate are associated with adverse events of increased serum prolactin levels, weight gain coupled with metabolic syndrome, and EPS-related adverse events. These safety issues have been addressed in the proposed labeling of paliperidone palmitate. There are has been no new safety issues generated on this topic from this submission.

2.5 Presubmission Regulatory Activity

23 August 2000	Preclinical-Clinical Meeting with FDA for R092670
16 June 2004	CMC/Biopharmaceutics EOP2 meeting with FDA
28 September 2004	Preclinical/Clinical EOP2 Meeting with FDA and post follow-up information
12 October 2004	EOP2 CMC/Biopharm Meeting with FDA
7 December 2005	EOP2 pre-Phase 3 meeting with FDA for bipolar disorder
11 December 2006	Tele-conference with FDA regarding paliperidone palmitate injection
18 April 2007	Pre-NDA meeting with FDA
7 June 2007	CMC-Biopharmaceutics Pre-NDA meeting with FDA

25 October 2007 Original paliperidone palmitate NDA submission

25 February 2008 4-Month Safety Update

2.6 Other Relevant Background Information

Paliperidone ER has not been withdrawn from the market worldwide for any reason.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Terrance Ocheltree, PhD, is the CMC reviewers for this submission. Please refer to his review for detailed CMC information.

3.2 Animal Pharmacology/Toxicology

Elzbieta Chalecka-Franaszek, PhD, is the pharmacology/toxicology reviewer for this submission. Please refer to her review for detailed review of the pharmacology/toxicology information.

3.3 Statistical Review and Evaluation

Ohidul I. Siddiqui, PhD, is the statistical reviewer for this submission. He re-analyzed efficacy data from studies PSY-3003, -3004, SCH-201 and PSY-3001 using the protocol specified primary ANCOVA models. In addition, he also conducted sensitivity analyses on the primary efficacy measure using MMRM analysis, and ANCOVA analysis on available cases at each study visit to check the robustness of efficacy findings of these studies. The findings were similar to the sponsor's reported findings. For details, please refer to the biometrics review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The efficacy data to support the acute efficacy of paliperidone palmitate in the treatment of schizophrenia were obtained from two phase 3 (PSY-3003, -3004) and one phase 2 (SCH-201) trials. The long-term efficacy data were obtained from study PSY-3001, a phase 3 relapse prevention study.

The safety data were collected from 16 completed paliperidone palmitate clinical trials, which consist of 5 phase 3 studies, 1 phase 2 study, and 10 phase 1 studies. Only safety data from phase

2/3 were reviewed in details in this review. In addition, a 4 Month Safety Update submitted on 25 February 2008 was also reviewed.

4.2 Tables of Clinical Studies

Table 1 (page 2) summarizes all phase 2/3 studies supporting the efficacy and/or safety claim of paliperidone palmitate.

4.3 Review Strategy

A list of the items examined during the course of the review is provided in Table 2. In the efficacy review, the efficacy data from each individual study (PSY-3001, -3003, -3004, and SCH-201) were reviewed separately. In the safety review, the data from studies PSY-3003 and -3004 were pooled for analyses due to similarity of the study design. The safety data from studies PSY-3001, -3002, -3005 and SCH-201 were reviewed individually.

Table 2 Items Utilized in the Course of the Review

Submission Date	Items Reviewed
25 October 2007	Clinical Study Report: PSY-3003, -3004, -3001, -3002, -3005, and SCH-201 Clinical Summary Clinical Overview Labeling
25 February 2008	4 Month Safety Update Updated Clinical Study Report of PSY-3001 Report of Post-marketing Experience of Paliperidone ER-Dec. 2006 to Dec. 2007 Revised Labeling

4.4 Data Quality and Integrity

During the course of the review, no problems with respect to data quality or integrity were identified. The Division of Scientific Inspection (DSI) has been consulted for study site inspection. At the time of completion of this review, the inspection results from DSI are still pending.

When the sponsor were in the process of closing the open label database for the Phase 3 study PSY-3001, they found additional adverse event (AE) information relevant to the double-blind, transition, and maintenance phases of the study that were not submitted in the original double-blind clinical study report (CSR) and database in the NDA.

J&J PRD developed and conducted a Quality Control (QC) plan to assess the accuracy of data entry in the PSY-3001 database. Based on the QC assessments from 100 specific samples, the sponsor concluded that there will be no impact on the conclusions from the primary efficacy analysis of time-to-recurrence and on the overall safety assessment (risk/benefit). More discussions can be found in section 7.2.8. Adequacy Assessment of Quality and Completeness of

Data. Additional requests from the division had been requested to further clarify the AE reporting errors in study PSY-3001. At the time of completion of this review, the responses are still pending.

4.5 Compliance with Good Clinical Practices

All studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

4.6 Financial Disclosures

Financial disclosures from studies PSY-3001, -3003, -3004, and SCH-201 were provided by the sponsor in the original submission. No investigators who participated in support of this NDA application hold disclosable financial arrangements with Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

John Duan PhD, is the clinical pharmacology reviewer for this submission. Please refer to his review for detailed pharmacokinetic information.

5.2 Pharmacodynamics

John Duan PhD, is the clinical pharmacology reviewer for this submission. Please refer to his review for detailed pharmacodynamic information.

5.3 Exposure-Response Relationships

Exposure-response relationship was studied in studies of PSY-3003, -3004 and SCH-201. The paliperidone palmitate 100 mg eq. dose was associated with larger mean reduction (-11.0, -16.1, and -7.8 in study PSY-3003, -3004 and SCH-201 respectively) at end point in the total PANSS score compared to the 50 mg eq. dose (-7.9, -13.2, and -5.2 in PSY-3003, -3004, and SCH-201 respectively).

There was a paliperidone palmitate 150 mg eq. arm in study PSY-3003 and a 25 mg eq. arm in study PSY-3004. In study PSY-3003, the 150 mg eq. dose did not demonstrated superiority compared to the 100 mg eq. dose (-5.5 vs. -11.0) in reduction in total PANSS score at endpoint. As a result of a mismatch in the allocation of medication kits, only 30 subjects received paliperidone palmitate 150 mg eq. dose. Thus, the result from the 150 mg eq. dose group is hardly to be interpreted. In study PSY-3004, the efficacy result from the 25 mg eq. dose group

was comparable to that of the 50 mg eq. dose group (-13.6 vs. 13.2 in reduction in the total PANSS score).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Paliperidone palmitate long-lasting injection is indicated for the treatment of schizophrenia and for the prevention of recurrence of symptoms of schizophrenia.

6.2 The Acute Indication—Efficacy Review on Study PSY-3003, PSY-3004 and SCH-201

6.2.1 Methods

The acute efficacy of paliperidone palmitate in the treatment of schizophrenia was demonstrated by two phase 3 studies and one phase 2 study. PSY-3003 and PSY-3004 were 13-week, double blind, placebo-controlled phase 3 studies designed to identify the effective and safe dose range for paliperidone palmitate. Study SCH-201 was a phase 2 study, which was a randomized, 9-week, fixed-dose, placebo-controlled study of paliperidone palmitate in subjects with schizophrenia.

The Clinical Study Reports for each individual study, the Clinical Overview, and the Clinical Summary are the major data source used for this efficacy review. The efficacy review was performed in consultation with the statistical reviewer, Ohidul I. Siddiqui, PhD.

6.2.2 General Discussion of Endpoints

The primary efficacy variable for study PSY-3003, PSY-3004 and SCH-201 was the change from baseline to endpoint in the Positive and Negative Syndrome Scale (PANSS) total score. The symptoms of schizophrenia were assessed using the 30-item PANSS scale. The PANSS is a well known and validated rating scale used in numerous drug evaluation trials. This scale, designed to assess the symptomatic change in the severity of symptoms in subjects with schizophrenia and other psychotic disorders, provides a total score (sum of the scores of all 30 items) and scores for 3 subscales, the positive subscale (7 items), the negative subscale (7 items), and the general psychopathology subscale (16 items).

6.2.3 Study Design

6.2.3.1 Investigators/Sites

PSY-3003 was conducted at 36 centers in 5 countries (Ukraine, Malaysia, Republic of Korea, Taiwan and the United States) from 30 June 2005 to 20 June 2006.

PSY-3004 was conducted at 38 centers in 5 countries (Bulgaria, Romania, Russia, South Africa and the United States) from 15 December 2004 to 1 March 2006.

SCH-201 was conducted at 30 centers in 6 countries (Bulgaria, Poland, Russia, Ukraine, India and the United States) from 27 October 2003 to 9 July 2004.

Table 3 summarizes number of sites in each country by study. A full list of clinical study sites and investigators for studies PSY-3003, -3004, and SCH-201 is included in Appendices 10.1.

Table 3 Number of Sites in Each Country by Study

Trial Number	SCH-201	PSY-3001	PSY-3003	PSY-3004
Country				
Bulgaria	3			3
Costa Rica		1		
India	3			
Korea		5	3	
Malaysia			3	
Mexico		3		
Poland	4			
Romania		9		4
Russia	7	8		10
South Africa		4		2
Taiwan		4	4	
Ukraine	4	10	3	
USA	8	18	23	21
Total Sites	29	62	36	40

6.2.3.2 Objectives

The primary objectives of these studies were to evaluate the efficacy and safety of fixed dose levels of paliperidone palmitate, when administered at 4-week (monthly) intervals after 2 initial doses given 1 week apart, as compared with placebo in subjects with schizophrenia.

6.2.3.3 Subjects

Key Inclusion Criteria:

- Men and women aged at least 18 years (18 to 65 years in SCH-201), met diagnostic criteria for schizophrenia (DSM-IV-TM) for at least one year before screening;

- PANSS total score at screening and baseline of 70 to 120;
- Body mass index (BMI) > 17.0 (15.0 to 35.0 in SCH-201) kg/m²;
- Female subjects were postmenopausal for at least 2 years, surgically sterile, or practicing an effective method of birth control before entry and throughout the study, and had a negative urine pregnancy test at baseline.

Key Exclusion Criteria:

- Primary active DSM-IV Axis I diagnosis other than schizophrenia;
- Decrease of at least 25% in the PANSS total score between screening and baseline;
- DSM-IV diagnosis of active substance dependence within 3 months before screening;
- History of treatment resistance, defined as a failure to respond to 2 adequate trials of different antipsychotic medications (a minimum of 4 weeks at a therapeutic dose);
- Relevant history of, or current presence of, any significant and/or unstable medical conditions, or abnormal laboratory parameters deemed to be clinically significant by the investigator;
- History of neuroleptic malignant syndrome (NMS);
- Significant risk of suicidal or violent behavior, as clinically assessed by the investigator;
- History of life-threatening allergic reaction; known or suspected hypersensitivity or intolerance to risperidone, paliperidone, Intralipid®, or any of their excipients (including egg yolks, soybean oil, phospholipids, and glycerol);
- Previously received an injection of paliperidone palmitate;
- Treatment with any of the following disallowed therapies:
 - Long lasting injection (LAI) antipsychotic within 60 days of screening;
 - Electroconvulsive therapy with 60 days before screening;
 - Nonselective/irreversible monoamine oxidase inhibitor (MAOI) antidepressants within 4 weeks before screening;
 - Other antidepressants unless at a stable dosage for 30 days before screening;
 - Beta-adrenergic blockers except when used to control hypertension and if the subject's blood pressure was stabilized before screening.
- Exposure to an experimental drug, experimental biologic or experimental medical device within 30 days before screening.

In addition to above exclusion criteria, following exclusion criteria were also applied to subjects in study SCH-201:

- Known sensitivity (e.g., rash) to phenytoin, carbamazepine, barbiturates, or lamotrigine;
- Received clozapine therapy within 3 months before screening;
- Received Risperdal Consta™ within 100 days before screening.

6.2.3.4 Overall Study Design

Study PSY-3003 and -3004

Study PSY-3003 and -3004 had almost identical study design. These two studies were multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose response studies.

These studies were comprised of a screening period of up to 7 days (including up to 5 days to wash out period and 4 days for tolerability testing, if needed) and a 13-week double-blind treatment period. At the start of the double-blind treatment period, each subject was randomly assigned to 1 of 4 treatment groups, 3 fixed doses of paliperidone palmitate (50, 100, or 150 mg eq. in study PSY-3003, and 25, 50, or 100 mg eq. in study PSY-3004) or placebo. Each subject received an i.m. injection in the gluteal muscle of paliperidone palmitate or placebo on Days 1, 8, 36, and 64. End-of-study assessments were scheduled for Day 92. Subjects were hospitalized for at least 7 days after the first injection of study medication and could be discharged from the study center on Day 8, 2 or more hours after receiving their second injection of study medication if, in the opinion of the investigator, they were ready for discharge.

Study SCH-201

This was a randomized, double-blind, placebo-controlled, multi-center study in subjects with schizophrenia. Subject enrollment included a screening period (maximum 5 days, including 3-day washout period); a 7-day, open-label, oral run-in period; and a 64-day double-blind treatment period. Total study duration was approximately 11 weeks. During the oral run-in period subjects received either ER OROS paliperidone (6 or 12 mg) or IR paliperidone (2 or 4 mg), Q.D. on each of the 7 oral run-in days. Eligible Subjects were randomized to placebo, paliperidone palmitate 50, or 100 mg eq. treatment groups in double-blind treatment phase. Paliperidone palmitate was administered as gluteal intramuscular injections on Days 1, 8, and 36. All subjects were hospitalized for at least 14 days, including the 7-day oral run-in period and the first 7 days of the double-blind treatment period.

6.2.3.5 Dose and Administration

In all three studies, paliperidone palmitate was administered as 2 doses separated by 1 week (Days 1 and 8) by gluteal intramuscular injection, and followed by injections every 4 weeks.

Table 4 summarizes paliperidone palmitate doses used in each study.

Table 4 Paliperidone Palmitate Doses Used in Study PSY-3003, PSY-3004 and SCH-201

Study	Placebo	25 mg eq.	50 mg eq.	100 mg eq.	150 mg eq.
PSY-3003	x		x	x	x
PSY-3004	x	x	x	x	
SCH-201	x		x	x	

Medication Kit Allocation Error in study PSY-3003

In study PSY-3003, 2 medication allocation files were incorrectly matched to the randomization file in the Interactive Voice Response System (IVRS) resulting in a mismatch between some of the medication kits to be assigned and the originally loaded randomization file provided by the Sponsor. The errors were discovered after all subjects had been randomized and dosed, but prior to the database lock.

The medication kit allocation error affected only subjects assigned to the placebo and paliperidone palmitate 150 mg eq. groups. Eighty-eight subjects were affected. Errors in medication kit allocation included

- Eleven subjects randomly assigned to placebo received paliperidone palmitate 150 mg eq. for all (6 subjects) or part (5 subjects) of their time in the study. The 6 subjects who received only paliperidone palmitate 150 mg eq. are included in the paliperidone palmitate 150 mg eq. group for analysis. The 5 subjects who received both paliperidone palmitate 150 mg eq. and placebo are included in the paliperidone palmitate 150 mg eq./Placebo group.
- Seventy-seven subjects randomly assigned to paliperidone palmitate 150 mg eq. received placebo for all (51 subjects) or part (26 subjects) of their time in the study. The 51 subjects who received only placebo are included in the placebo group for analysis. The 26 subjects who received both paliperidone palmitate 150 mg eq. and placebo are included in the paliperidone palmitate 150 mg eq./Placebo group. Subject 612222 was randomly assigned to paliperidone palmitate 150 mg eq., received one injection of placebo, followed by one injection of paliperidone palmitate 50 mg eq., followed by another injection of placebo. This Subject (612222) is included in the paliperidone palmitate 150 mg eq./Placebo group.

The medication kit allocation error was summarized in Table 5.

Table 5 Summary of Medication Kit Allocation Error in Study PSY-3003: All Randomized Subjects

Treatment group, n (%)	Intended Number of Subjects Per Randomization Code List (%) (N=388)	Number of Subjects by Actual Dose Received (%) (N=388)
N	388	388
Placebo	96 (25)	135 (35)
R092670 50 mg eq.	94 (24)	94 (24)
R092670 100 mg eq.	97 (25)	97 (25)
R092670 150 mg eq.	101 (26)	30 (8)
R092670 150 mg eq./pbo		31 (8)
Treatment not received		1 (<1)

6.2.4 Efficacy Findings

6.2.4.1 Disposition of Patients

Patient disposition in study PSY-3003, -3004 and SCH-201 is summarized in Table 6.

The study completion rates were low, around 50% in all three studies (48%, 51% and 51% in PSY-3003, -3004 and SCH-201 respectively).

More patients in paliperidone palmitate treatment groups completed the double-blind phase compared with the placebo groups in all three studies.

Lack of efficacy was the most common reason for discontinuation and more patients were withdrawn for this reason in the placebo groups than in paliperidone palmitate treatment groups in all three studies.

Higher or similar percentages of patients in the placebo groups were withdrawn from double-blind treatment as a result of adverse events compared to paliperidone palmitate treatment groups in all three studies.

Table 6 Patient Disposition: Study PSY-3003, -3004 and SCH-201, Double-Blind Phase

Study	Treatment group	n	Completed n (%)	Withdrawn n (%)					
				Lack of efficacy	Subject choice	Lost to follow-up	Adverse event	Death	Other
PSY-3003	Total	388	187 (48)	201 (52)	32 (8)	14 (4)	25 (6)	0	15(4)
	50 mg eq.	94	47 (50)	47 (50)	7 (7)	4 (4)	8 (9)	0	3 (3)
	100 mg eq.	97	53 (55)	44 (45)	9 (9)	4 (4)	2 (2)	0	3 (3)
	150 mg eq.	30	12 (40)	18 (60)	2 (7)	1 (3)	2 (7)	0	0
	150 mg/pbo	31	24 (77)	7 (23)	2 (6)	1 (3)	0	0	1 (3)
	Placebo	136	51 (38)	85 (63)	12 (9)	4 (3)	13 (10)	0	8 (6)
PSY-3004	Total	518	263 (51)	128 (25)	46 (9)	35 (7)	24 (5)	2(<1)	20(4)
	25 mg eq.	131	70 (53)	31 (24)	9 (7)	8 (6)	8 (6)	0	5 (4)
	50 mg eq.	129	70 (54)	31 (24)	14 (11)	4 (3)	2 (2)	0	8 (6)
	100 mg eq.	131	75 (57)	21 (16)	11 (8)	13 (10)	6 (5)	1 (1)	4 (3)
	Placebo	127	48 (38)	45 (35)	12 (9)	10 (8)	8 (6)	1 (1)	3 (2)
SCH-201	Total	247	125 (51)	73 (30)	23 (9)	7 (3)	13 (5)	0	6 (2)
	50 mg eq.	79	47 (59)	23 (29)	4 (5)	1 (1)	3 (4)	0	1 (1)
	100 mg eq.	84	51 (61)	14 (17)	11 (13)	4 (5)	2 (2)	0	2 (2)
	Placebo	84	27 (32)	36 (43)	8 (10)	2 (2)	8 (10)	0	3 (4)

6.2.4.2 Demographic Characteristics

Demographic characteristics at baseline in study PSY-3003, -3004 and SCH-201 were summarized in Table 7 by study.

The baseline demographic characteristics of all three studies at baseline were roughly similar and were balanced across the treatment groups in each individual study.

The majority of subjects were male (62% to 69%), and the mean ages of subjects were around 40 (39.3 to 40.8 years). Most of the population in study PSY-3004 and SCH-201 was the white (67% and 81%). In study PSY-3003, the white and the black had similar distribution (40% vs.

39%). The mean of BMI in study PSY-3003 was slightly higher, and study SCH-201 had the lowest overall BMI (mean).

Table 7 Demographic Characteristics at baseline: Study PSY-3003, -3004 and SCH-201

Study	Treatment group	n	Gender n (%)		Age (yrs) (Mean)	Race n (%)			BMI (kg/m ²) (Mean)
			Male	Female		White	Black	Other	
PSY-3003	Total	349	242 (69)	107 (31)	39.7	141 (40)	135 (39)	73 (21)	28.54
	50 mg eq.	93	65 (70)	28 (30)	39.1	35 (38)	42 (45)	16 (17)	28.78
	100 mg eq.	94	61 (65)	33 (35)	38.9	35 (37)	38 (40)	21 (22)	29.18
	150 mg eq.	30	22 (73)	8 (27)	40.7	20 (67)	6 (20)	4 (13)	28.51
	Placebo	132	94 (71)	38 (29)	40.5	51 (39)	49 (37)	32 (24)	27.92
PSY-3004	Total	514	342 (67)	172 (33)	40.8	344 (67)	147 (29)	23 (4)	27.5
	25 mg eq.	130	85 (65)	45 (35)	40.8	87 (67)	38 (29)	5 (4)	27.6
	50 mg eq.	128	94 (73)	34 (27)	39.0	88 (69)	33 (26)	7 (5)	27.3
	100 mg eq.	131	85 (65)	46 (35)	42.3	85 (65)	41 (31)	5 (4)	27.7
	Placebo	125	78 (62)	47 (38)	41.1	84 (67)	35 (28)	6 (5)	27.5
SCH-201	Total	197	122 (62)	75 (38)	39.3	159 (81)	33 (17)	5 (3)	25.5
	50 mg eq.	63	41 (65)	22 (35)	40.1	50 (79)	9 (14)	4 (6)	25.5
	100 mg eq.	68	42 (62)	26 (38)	37.3	55 (81)	13 (19)	0	25.1
	Placebo	66	39 (59)	27 (41)	40.5	54 (82)	11 (17)	1 (2)	25.9

6.2.4.3 Disease Characteristics

Key baseline disease characteristics are summarized in Table 8.

The baseline disease characteristics across all three studies were very similar and were roughly balanced across the treatment groups in each individual study.

All subjects had a primary Axis I diagnosis of schizophrenia as required by the protocol. The major subtype (81 to 90 %) was schizophrenia, paranoid type. The PANSS total score at baseline ranged from 70 to 120 in all three studies. The mean PANSS total scores in study PSY-3003, -3004 and SCH-201 at baseline were 91.1, 90.8 and 87, respectively. Based on the CGI-S score, majority of subjects were moderate and markedly ill as rated by the investigator.

Table 8 Baseline Disease Characteristics: Study PSY-3003, -3004 and SCH-201

Study	Treatment group	n	PANSS total (Mean)	CGI-S n (%)			Schizophrenia type n (%)		
				Moderate	Marked	Other*	Paranoid	Undifferentiated	Other**
SPY-3003	Total	349	91.1	149 (43)	152 (44)	48 (14)	283 (81)	51 (15)	15 (4)
	50 mg eq.	93	89.9	39 (42)	45 (48)	9 (10)	70 (75)	19 (20)	4 (4)
	100 mg eq.	94	90.1	38 (40)	41 (44)	15 (16)	79 (84)	11 (12)	4 (4)
	150 mg eq.	30	92.2	13 (43)	14 (47)	3 (10)	25 (83)	5 (17)	0
	Placebo	132	92.4	59 (45)	52 (39)	7 (5)	109 (83)	16 (12)	7 (5)
SPY-	Total	514	90.8	251 (49)	214 (42)	49 (10)	465 (90)	39 (8)	10 (2)

Study	Treatment group	n	PANSS total (Mean)	CGI-S n (%)			Schizophrenia type n (%)		
				Moderate	Marked	Other*	Paranoid	Undifferentiated	Other**
3004	25 mg eq.	130	90.6	59 (45)	61 (47)	10 (8)	120 (92)	9 (7)	1 (1)
	50 mg eq.	128	91.2	58 (45)	56 (44)	14 (11)	114 (89)	10 (8)	4 (3)
	100 mg eq.	131	90.8	67 (51)	48 (37)	16 (12)	116 (89)	12 (9)	3 (2)
	Placebo	125	90.7	67 (54)	49 (39)	9 (7)	115 (92)	8 (6)	2 (2)
SCH-201	Total	197	87.0	85 (43)	81 (41)	31 (16)	174 (88)	14 (7)	9 (5)
	50 mg eq.	63	88.0	27 (43)	27 (43)	9 (14)	56 (89)	4 (6)	5 (8)
	100 mg eq.	68	85.2	32 (47)	26 (38)	10 (15)	60 (88)	6 (9)	2 (3)
	Placebo	66	87.8	26 (39)	28 (42)	12 (18)	58 (88)	4 (6)	4 (6)

* Based on CGI-S score, the subjects were rated as very mild, mild, severe and extremely severe.

** Including Schizophrenia disorganized, catatonic and residual type.

6.2.4.4 Concomitant Medications

According to the protocol, benzodiazepines could be used as rescue medications for agitation, anxiety, or sleep difficulties during the double-blind treatment period, with the dose and frequency of administration gradually tapered downward over the double-blind period. During the double-blind treatment period in all three studies, the majority of subjects in each treatment group received benzodiazepines, primarily lorazepam. Concomitant benzodiazepine use was less in study SCH-201 (55%) compared to in study PSY-3003 and -3004 (79% and 71%, respectively). Concomitant benzodiazepine use was similar among the treatment groups in each individual study (76% - 83% in PSY-3003, 66% - 76% in PSY-3004, and 53% - 59% in SCH-201).

In study PSY-3003 and -3004, concomitant antipsychotic medication use was recorded for a minority of subjects during the double-blind period. For most of these subjects, the concomitant antipsychotic medication was started after the last dose of double-blind study medication, and the start date of concomitant antipsychotic drug administration coincided with the last day of the double-blind period.

In study SCH-201, a small number of the subjects received an antidepressant during the double-blind period, and the percentage of subjects using concomitant antidepressant therapy was higher for the paliperidone palmitate groups (6-8%) than for the placebo group (2%).

6.2.4.5 Efficacy Results

Primary Efficacy Analysis: Change from baseline in PANSS Total Score

The primary efficacy variable was the change from baseline to end point in the PANSS total score in all three studies.

Study PSY-3003

Based on the primary efficacy LOCF analysis of the primary efficacy variable with a closed testing procedure using Dunnett's test to adjust for multiplicity, the improvement in paliperidone

palmitate 100 mg eq. treatment group reached statistical significance ($p=0.019$) when compared with the placebo group. The paliperidone palmitate 50 mg eq. group was numerically superior to placebo for the primary endpoint, but the difference was not statistically significant ($p=0.193$). Since only the paliperidone palmitate 100 mg eq. treatment group achieved statistical superiority relative to placebo, no statistical comparison was performed for the paliperidone palmitate 150 mg eq. treatment group, as pre-specified in the SAP. The PANSS Total Score change from baseline to end point in study PSY-3003 is summarized in Table 9.

Table 9 PANSS Total Score Change from Baseline to End Point: PSY-3003, LOCF, ITT

	Placebo (n = 132)	Paliperidone palmitate		
		50 mg eq. (n = 93)	100 mg eq. (n = 94)	150 mg eq. (n = 30)
Baseline, Mean (SD)	92.4 (12.55)	89.9 (10.78)	90.1 (11.66)	92.2 (11.72)
End Point, Mean (SD)	88.2 (22.48)	82.0 (24.17)	79.1 (21.69)	86.7 (22.01)
Change from baseline, Mean (SD)	-4.1 (21.01)	-7.9 (18.71)	-11.0 (19.06)	-5.5 (19.78)
P-value (vs. PLA)		0.193	0.019	

The sensitivity longitudinal data analysis of the PANSS total score changes (observed case) corroborated the significant treatment effect of paliperidone palmitate 100 mg eq. treatment compared with placebo at the end of the 13-week treatment period.

Study PSY-3004

Based on the intent-to-treat LOCF analysis of the primary efficacy variable with a closed testing procedure using Dunnett's test to control for multiplicity, the improvement in all paliperidone palmitate treatment groups reached statistical significance (25 mg eq., $p=0.015$; 50 mg eq., $p=0.017$; and 100 mg eq., $p < 0.001$) when compared with the placebo group. The PANSS Total Score change from baseline to end point in study PSY-3004 is summarized in Table 10.

Table 10 PANSS Total Score Change from Baseline to End Point: PSY-3004, LOCF, ITT

	Placebo (n = 125)	Paliperidone palmitate		
		25 mg eq. (n = 129)	50 mg eq. (n = 128)	100 mg eq. (n = 131)
Baseline, Mean (SD)	90.7 (12.22)	90.7 (12.25)	91.2 (12.02)	90.8 (11.70)
End Point, Mean (SD)	83.7 (23.28)	77.1 (24.32)	78.0 (21.93)	74.7 (20.64)
Change from baseline, Mean (SD)	-7.0 (20.07)	-13.6 (21.45)	-13.2 (20.14)	-16.1 (20.36)
P-value (vs. PLA)		0.015	0.017	<0.001

Study SCH-201

Forty-six subjects from 6 sites, 3 sites in the USA (701, 704, and 707) and 3 sites in India (301, 303, and 304), were excluded from efficacy analyses because errors were made in drug administration due to incorrect use of the IVRS and deficiencies in following the study procedures. All subjects at these 6 excluded sites who were randomized to placebo received the correct treatment.

The efficacy results (excluding 6 sites) demonstrated that treatment with paliperidone palmitate 50 and 100 mg eq. was associated with mean reductions from baseline to end point in the total PANSS score that were significantly larger than the mean change seen in the placebo group (p=0.001 and p<0.0001, respectively). The 100 mg eq. dose was associated with a larger mean reduction at end point in the total PANSS score (-7.8) compared with the 50 mg eq. dose (-5.2). The efficacy results are summarized in Table 11.

Table 11 PANSS Total Score Change from Baseline to End Point: SCH-201, LOCF, ITT (Excluding 6 sites)

	Placebo (n = 66)	Paliperidone palmitate	
		50 mg eq. (n = 63)	100 mg eq. (n = 68)
Baseline, Mean (SD)	87.8 (13.90)	88.0 (12.39)	85.2 (11.09)
End Point, Mean (SD)	94.0 (24.84)	82.8 (24.48)	77.5 (21.42)
Change from baseline, Mean (SD)	6.2 (18.25)	-5.2 (21.52)	-7.8 (19.40)
P-value (vs. PLA)		0.001	<0.0001

6.2.4.6 Subgroup Analyses

Statistically significant treatment-by-country (in study PSY-3003 and -3004) and treatment-by-baseline PANSS total score (PSY-3003) interactions were seen in the primary efficacy model, although the results of the Gail-Simon test showed that there is insufficient evidence to indicate a qualitative interaction for any of the 3 doses of paliperidone palmitate in each individual study. Disparity in the distribution of baseline BMI and a difference in baseline PANSS total scores across countries were observed. Based on the exploratory analyses conducted by the sponsor, there appears to be a BMI effect on treatment and a difference in baseline PANSS total scores which helps explain the treatment-by-country interaction.

6.2.5 Clinical Microbiology

Clinical microbiology was not considered necessary for this product.

6.2.6 Efficacy Conclusions

Paliperidone palmitate, injected intramuscularly at a dose of 100 mg eq., in study PSY-3003, and 25, 50 and 100 mg eq. in study PSY-3004 at 4-week (monthly) intervals following 2 initial doses given 1 week apart, was significantly more effective than placebo in improving the PANSS total score at end point (LOCF) (primary efficacy end point) in these 13-week double-blind studies in subjects with schizophrenia.

In study SCH-201, results from the primary efficacy analysis demonstrated that paliperidone palmitate at doses of 50 and 100 mg eq. was more effective than placebo in reducing total PANSS scores in patients diagnosed with schizophrenia. The difference between each

paliperidone palmitate treatment group and placebo was statistically significant without adjusting for multiplicity.

6.3 The Long-Term Relapse Prevention Indication—Efficacy Review on Study PSY-3001

6.3.1 Method

The long-term efficacy (the prevention of recurrence of symptoms) of paliperidone palmitate in the treatment of schizophrenia has been demonstrated by study PSY-3001.

The Clinical Study Report of PSY-3001, the Clinical Overview and the Clinical Summary are the major data sources used for this efficacy review. The efficacy review was performed in consultation with the statistical reviewer, Ohidul I. Siddiqui, PhD.

6.3.2 General Discussion of Endpoints

The primary efficacy variable of Study PSY-3001 was the time to first recurrence of symptoms of schizophrenia during the double-blind recurrence prevention phase. The time to exacerbation of symptoms is a commonly used endpoint in long-term relapse prevention trials. Study PSY-3001 contains a 24-week maintenance phase and followed by a randomized, double-blind recurrence prevention phase. This design meets the agency's requirements for long-term relapse prevention trial. The results from this study can be used to support the sponsor's efficacy claim.

The criteria for recurrence are listed in Appendices 10.2.

6.3.3 Study Design

6.3.3.1 Investigators/Sites

Study PSY-3001 was conducted at 56 centers in 9 countries (Romania, Ukraine, Russia, Republic of Korea, Taiwan, Costa Rica, South Africa, Mexico and the United States) from 4 March 2005 to 20 Feb 2007.

Table 3 (page 10) summarizes number of sites in each country by study. A full list of clinical study sites and investigators for studies PSY-3001 is included in Appendices 10.1.

6.3.3.2 Objectives

The primary objectives of study PSY-3001 were to evaluate the efficacy of paliperidone palmitate compared with placebo in the prevention of recurrence of the symptoms of schizophrenia, and to assess the safety and tolerability of paliperidone palmitate in subjects with schizophrenia.

6.3.3.3 Subjects

Inclusion Criteria:

- Men and women aged 18 to 65 with DSM-IV-TM diagnosis of schizophrenia at least 1 year before screening;
- A total PANSS score below 120 at screening and baseline;
- Body mass index (BMI) of $\geq 15.0 \text{ kg/m}^2$;
- Female subjects were postmenopausal for at least 2 years, surgically sterile, or practicing an effective method of birth control before entry and throughout the study, and had a negative urine pregnancy test at baseline before receiving the first dose of study drug.

Exclusion Criteria:

- A primary, active DSM-IV-TM diagnosis other than schizophrenia;
- Active substance dependence within 3 months before screening;
- History of treatment resistance as defined by failure to respond to 2 adequate trials (minimum of 4 weeks at a therapeutic dose) of different antipsychotic medications;
- Relevant history or current presence of any significant or unstable medical conditions; abnormal laboratory parameters deemed to be clinically significant by the investigator;
- History of neuroleptic malignant syndrome (NMS);
- Significant risk of suicidal or violent behavior, as clinically assessed by the investigator;
- History of life-threatening allergic reaction; known or suspected hypersensitivity or intolerance to risperidone, paliperidone, Intralipid®, or any of their excipients (including egg yolks, soybean oil, phospholipids, and glycerol);
- Exposure to an experimental drug, experimental biologic or experimental medical device within 30 days before screening; previous enrollment in this study or history of having received a previous injection of paliperidone palmitate ;
- History of any malignancy within the previous 5 years, with the exception of basal cell carcinomas;
- Treatment with any of the following disallowed therapies:
 - 4-week interval LAI antipsychotic within 28 days before screening;
 - RISPERDAL CONSTA LAI antipsychotic within 5 weeks before screening;
 - Electroconvulsive therapy with 60 days before screening;
 - Nonselective/irreversible monoamine oxidase inhibitor antidepressants within 4 weeks before screening;
 - Other antidepressants unless at a stable dosage for 30 days before screening.
- Subjects involuntarily committed to psychiatric hospitalization.

6.3.3.4 Overall Study Design

This study is a randomized, double-blind (DB), placebo-controlled, parallel-group, multi-center study designed to evaluate the efficacy of paliperidone palmitate compared with placebo in preventing recurrence of schizophrenic symptoms in subjects with schizophrenia. The study consisted of 5 phases: screening/washout/tolerability phase (up to 7 days); a 9-week open-label transition (TR) phase (50 mg eq. on Days 1 and 8, and a flexible dose of 25, 50, or 100 mg eq. at

Week 5); a 24-week open-label maintenance (MA) phase (flexible dose of 25, 50, or 100 mg eq. at Weeks 9, 13, 17, and 21, with no further dose adjustments during the next 12 weeks); a randomized, DB, placebo-controlled recurrence prevention phase of variable duration (placebo or a fixed dose of paliperidone palmitate equivalent to the dose received at the end of the maintenance phase); and an optional 52-week open label extension for those subjects completing the placebo-controlled recurrence prevention phase or for those subjects who had received at least 1 injection of study drug when further randomization in the recurrence prevention phase was discontinued. Only the data collected from study start through the end of the DB recurrence prevention phase of the study are included in this submission and subsequently have been reviewed.

6.3.3.5 Dose and Administration

This study is a flexible-dosed, placebo-controlled recurrence prevention study. Paliperidone palmitate dose ranges from 25 mg eq. to 100 mg eq. in the double-blind phase. Subjects continued the doses received at the end of maintenance phase. Paliperidone palmitate was administered as 2 doses (50 mg each) separated by 1 week (Days 1 and 8) followed by the optimal dose on the subject's need every 4 weeks by gluteal intramuscular injection.

6.3.4 Efficacy Findings

6.3.4.1 Disposition of Patients

The double-blind treatment phase completion/withdrawal information is provided for all randomized subjects in Table 12.

In the open-label transition phase, 681 (80%) of 849 completed the transition phase. Among the 681 subjects, 410 (60%) completed the open-label maintenance phase. Of the 410 randomized subjects, 351 (86%) completed the double-blind recurrence prevention phase (including completers and patients who had recurrence) and 59 (14%) discontinued other than recurrence events. Similar percentages of subjects in the paliperidone palmitate group (15%) and the placebo group (14%) discontinued the double-blind recurrence prevention phase. The most common reasons for discontinuation were subject choice (6% in the paliperidone palmitate group versus 7% in the placebo group) and "other" (7% in the paliperidone palmitate group versus 5% in the placebo group). Five subjects (1%) discontinued due to adverse events, including 3 subjects in the paliperidone palmitate group and 2 subjects in the placebo group.

Of those 410 subjects who entered the double-blind phase, 126 (31%) experienced a recurrence event and 223 (54%) completed the entire course of study (these subjects were ongoing at the time the study was stopped and by protocol were considered completers). At the time the study was terminated by the sponsor, 69% of subjects randomized to paliperidone palmitate treatment were ongoing in the double-blind recurrence prevention phase compared with 39% in the placebo group. In contrast, 47% of the subjects randomized to placebo had experienced a recurrence event compared with 15% in the paliperidone palmitate group.

Table 12 Patient Disposition: PSY-3001, Double-Blind Recurrence Prevention Phase

	Paliperidone palmitate (N=206) n (%)	Placebo (N=204) n (%)	Total (N=410) n (%)
Completed	175 (85)	176 (86)	351 (86)
Completed entire double-blind phase	143 (69)	80 (39)	223 (54)
Recurrence during double-blind phase	31 (15)	95 (47)	126 (31)
Withdrawn	31 (15)	28 (14)	59 (14)
Subject choice	13 (6)	15 (7)	28 (7)
Adverse event	3 (1)	2 (1)	5 (1)
Other	15 (7)	11 (5)	26 (6)

6.3.4.2 Demographic Characteristics

Demographic characteristics of all treatment subjects in double-blind phase are summarized in Table 13.

More male (54%) than female (46%) subjects were randomized to double-blind treatment. The mean age of subjects at transition baseline was 39.1 years (range, 18 to 66 years); most subjects were white (65%), 18% were black, 17% were from other races. The treatment groups were generally well balanced with respect to demographic characteristics.

Table 13 Demographic Characteristics at baseline: PSY-3001, Double-Blind Phase

Treatment group	n	Gender n (%)		Age (yrs) (Mean)	Race n (%)			BMI (kg/m ²) (Mean)
		Male	Female		White	Black	Other	
Total	408	220 (54)	188 (46)	39.1	266 (65)	72 (18)	70 (17)	27.2
Paliperidone palmitate	205	109 (53)	96 (47)	38.8	133 (65)	36 (18)	36 (18)	27.2
Placebo	203	111 (55)	92 (45)	39.4	133 (66)	36 (18)	34 (17)	27.1

6.3.4.3 Disease Characteristics

Most subjects (84%) had a diagnosis of paranoid schizophrenia, while 11% had a diagnosis of undifferentiated schizophrenia. Most subjects (68%) had been hospitalized at least twice during their lifetime and prior to inclusion in the study, including a median of 3 prior hospitalizations for psychosis.

By study design, only those subjects who met the protocol-specified eligibility criteria with regard to symptom control were eligible for entry into the double-blind recurrence prevention phase. Consistent with this requirement, at double-blind baseline, the mean PANSS total score of subjects in the intent-to-treat analysis set was 52.6 (range, 30-83). Based on CGI-S score, most subjects' psychotic condition at double-blind baseline was mild (44%), very mild (36%), or not ill (5%), while 14% of subjects had a baseline CGI-S score of moderate or marked.

The 2 treatment groups (paliperidone palmitate and placebo) were well balanced with respect to disease severity and psychiatric diagnosis at double-blind baseline.

6.3.4.4 Concomitant Medications

During the double-blind treatment, 46% of subjects received at least one concomitant medication other than benzodiazepines. The most commonly used medication was zolpidem (8% of subjects) during the double-blind phases.

6.3.4.5 Efficacy Results

Since the study was terminated early because of the significant results of the interim analysis, the interim analysis is considered the primary analysis, as prespecified in the protocol. The final analysis of data, including events subsequent to interim analysis data cutoff on 25 September 2006, and up to the date of study completion on 16 February 2007, is considered confirmatory.

The efficacy data of the double-blind recurrence prevention phase used in this review include the data for the intent-to-treat (ITT) analysis set, defined as all randomized subjects who received at least one dose of double-blind study medication.

6.3.4.5.1 Primary Efficacy Analysis: Interim Analysis of Time to Recurrence

The primary efficacy variable for this study was the time to first recurrence of the symptoms of schizophrenia during the double-blind recurrence prevention phase. Results of the interim analysis of time to recurrence are provided in Table 14.

The interim analysis, conducted by the independent data monitoring committee (IDMC) after 68 recurrence events had occurred per protocol, demonstrated a statistically significant difference in favor of paliperidone palmitate, compared to placebo, with regard to the time to first recurrence.

A total of 312 subjects (156 randomized to placebo and 156 randomized to paliperidone palmitate) were included in the intent-to-treat analysis set for the interim analysis. All subjects remaining in the study and taking medication at the time of the 68th recurrence event (n=244) were censored at the date of the interim analysis.

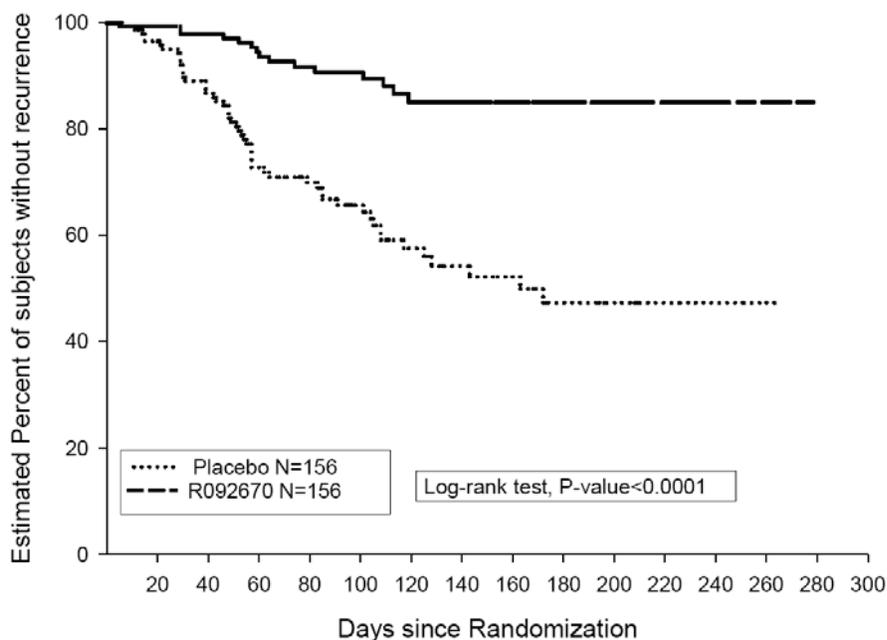
Overall, 53 (34%) subjects in the placebo and 15 (10%) subjects in paliperidone palmitate group experienced a recurrence event. There was a significant difference ($p < 0.0001$ based on the log-rank test) between the treatment groups in the time to recurrence in favor of paliperidone palmitate; subjects who continued treatment on paliperidone palmitate experienced recurrence later than subjects who switched to placebo.

Table 14 Number (%) of Subjects Experiencing Recurrence and Time to Recurrence (Days): PSY-3001, Interim Analysis, ITT

Descriptive ^a	Placebo	R092670	Total	Overall		
				Chisq	DF	P-value ^b
Time to recurrence						
<u>Double blind</u>						
Number of Assessed	156	156	312			
Number of Censored (%)	103 (66.0)	141 (90.4)	244 (78.2)			
Number of Events (%)	53 (34.0)	15 (9.6)	68 (21.8)			
25% Quantile (95% CI)	57.0 (49.0; 91.0)	NE	108.0 (83.0; 163.0)			
Median (95% CI)	163.0 (108.0; NE)	NE	NE			
75% Quantile (95% CI)	NE	NE	NE			
Statistical Test				29.411	1	<0.0001

A Kaplan-Meier plot of the time to recurrence is presented in Figure 1.

Figure 1 Kaplan-Meier Plot of Time to Recurrence: PSY-3001, Interim Analysis, ITT



6.3.4.5.2 Secondary Efficacy Analyses on Final Data Set

Results of the final analysis of time to recurrence of symptoms of schizophrenia by Kaplan-Meier estimate and log-rank test are presented in Table 15.

During the double-blind recurrence prevention phase, more subjects in the placebo group (95 or 47%) than in the paliperidone palmitate group (31 subjects or 15%) experienced a recurrence event. There was a significant difference ($p < 0.0001$ based on the log-rank test) between the treatment groups in the time to recurrence, in favor of paliperidone palmitate.

The significance of the difference between the treatment groups at the final analysis ($p < 0.0001$) was consistent with that at the interim analysis ($p < 0.0001$).

Table 15 Number (%) of Subjects Experiencing Recurrence and Time to Recurrence (Days): PSY-3001, Final Data Set, ITT

Descriptive ^a	Placebo	R092670	Total	Overall		
				Chisq	DF	P-value ^b
Time to recurrence						
<u>Double blind</u>						
Number of Assessed	203	205	408			
Number of Censored (%)	108 (53.2)	174 (84.9)	282 (69.1)			
Number of Events (%)	95 (46.8)	31 (15.1)	126 (30.9)			
25% Quantile (95% CI)	70.0 (55.0; 85.0)	NE (209.0; NE)	109.0 (85.0; 140.0)			
Median (95% CI)	172.0 (135.0; 235.0)	NE	NE (261.0; NE)			
75% Quantile (95% CI)	NE (261.0; NE)	NE	NE			
Statistical Test				53.482	1	<0.0001

6.3.4.6 Subgroup Analyses

Time to recurrence of symptoms of schizophrenia was evaluated by age group (18-25, 26-50, >50 years), by sex, by region, and by BMI category. Cox proportional hazard models were performed to individually assess the effect of these covariates.

Overall, the efficacy of paliperidone palmitate with regard to time to recurrence of symptoms of schizophrenia was consistent across the demographic subgroups defined by age, sex, BMI, and geographic region.

6.3.5 Clinical Microbiology

Clinical microbiology was not considered necessary for this product.

6.3.6 Efficacy Conclusions

Based on the interim analysis of the data, 53 (34%, ITT) subjects in placebo and 15 (10%, ITT) subjects in paliperidone palmitate group experienced a recurrence event during the double-blind recurrence prevention phase. There was a significant difference ($p < 0.0001$, based on the log-rank test) between the 2 treatment groups in the time to recurrence in favor of paliperidone palmitate; subjects who continued treatment on paliperidone palmitate experienced recurrence later than the

subjects who switched to placebo. This difference exceeded the prespecified threshold for significance (i.e., the p-value was less than 0.0106) resulting in the IDMC recommendation to stop the study early for efficacy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data collected in 16 clinical studies has been reviewed in this integrated safety review. These studies have been grouped into 3 categories according to similarities in study design, population, and status:

- Completed Phase 3 controlled double-blind studies in subjects with schizophrenia (5 studies): Studies PSY-3001, PSY-3002, PSY-3003, PSY-3004, and PSY-3005. The safety data from the double-blind phases of the two 13-week efficacy studies (PSY-3003, PSY-3004) are pooled; safety results for other Phase 3 studies (PSY-3001, PSY-3002, and PSY-3005) are provided individually due to the differences in study design. Safety data from these 5 studies were reviewed in detail in this safety review.
- Completed Phase 2 study SCH-201 in subjects with schizophrenia; this study was not pooled with Phase 3 studies due to differences in study design. Data from this study were reviewed in detail in this safety review.
- Completed Phase 1 studies in subjects with schizophrenia (10 studies). No pooling of safety data from these studies was performed due to the differences in study design, and permitted use of concomitant antipsychotics during the studies. Data from these studies were only used to detect deaths, serious or unexpected AEs in this safety review.

A total of 2,996 subjects with schizophrenia are included in the safety analyses of 6 controlled Phase 2/3 Studies. Of these, 2,282 subjects received at least one dose of paliperidone palmitate for a total exposure to paliperidone palmitate of 971.17 subject-years. In the 10 Phase 1 studies, 736 subjects with schizophrenia or schizoaffective disorder were included in the safety analysis set. Of these, 730 subjects received 1 or more doses of paliperidone palmitate.

7.1.1 Deaths

A total of 14 deaths (see Table 16) were reported during the drug development program, including 12 deaths in subjects treated with paliperidone palmitate, 1 death in a placebo-treated subject (pancreatic cancer) and 1 death in a subject receiving Risperdal Consta in study PSY-3002 (lung neoplasm malignant and pulmonary carcinoid tumor). A total of 13 treatment-emergent deaths were recorded in the controlled Phase 2/3 studies and 1 death was reported in Phase 1 studies. Thirteen cases were reported in the original NDA submission and one case was reported in the 4 Month Safety Update submitted on Feb. 25, 2008.

The 12 deaths in subjects treated with paliperidone palmitate included 6 deaths potentially associated with suicidality (4 confirmed suicides, 1 death resulting from a fall from a window coded as ‘accident’ and a post-study death (19 days after discontinuation) due to drug toxicity related to ingestion of a camphor-containing rubefacient). Other causes of death included cerebrovascular accident (suspected or confirmed stroke), acute myocardial infarction, foreign body aspiration (food aspiration) and cardiac arrhythmia. The cause of death was unknown in 1 subject. Although drug causality could not be excluded for some of the 12 deaths reported in subjects receiving paliperidone palmitate, there was no clear link to this long lasting injection (LAI) antipsychotic as the causative etiology in any of these cases based on the investigators assessment.

Table 16 Summary of Subjects Who Died in Paliperidone Palmitate Clinical Studies

Subject Number	Age (yrs) Sex	Dictionary-derived term Reported Term	Days of AE onset*	Protocol Phase	Onset Dose**
Phase 2/3 Studies					
Placebo-treated group					
650023 PSY-3004	66 male	Pancreatic carcinoma	66	DB	0
Paliperidone palmitate treatment group					
602017 PSY-3001	36 Male	Completed suicide	234	MA	100
604021 PSY-3001	53 Female	Completed suicide	220	MA	100
604062 PSY-3001	56 Female	Accident	135	MA	100
605026 PSY-3001	61 Male	Cerebrovascular accident	214	MA	100
618030 PSY-3002	56 Male	Acute myocardial infarction	99	DB	100
690052 PSY-3002	25 Female	Death (cause unknown)	196	DB	0
690096 PSY-3002	46 Female	Foreign body aspiration	49	DB	75
630094 PSY-3004	48 Male	Completed suicide	58	DB	100
604006 PSY-3005	25 Male	Completed suicide	81	DB	100
040712 PSY-3007	46 Female	Cerebrovascular accident	13	DB	150
Risperdal Consta treatment group					
690013 PSY-3002	53 Male	Lung neoplasm malignant	135	DB	50
Phase 1 Studies					
Paliperidone palmitate treatment group					
101015 PSY-1002	46 Male	Arrhythmia	239	Period 2	50

* Study day is in reference to the start of double-blind medication, except in Study PSY-3001, where it refers to the start of treatment in the transition phase.

** Doses included indicating subject's last exposure dose.

DB: double-blind phase
MA: maintenance phase

NOTE: In Study PSY-3001, Subject 607001 died from drug toxicity (verbatim: accidental ingestion) 19 days after discontinuation of study drug when she was withdrawn from the maintenance phase. In Study PSY-3005, Subject 603066 died due to aspiration of stomach contents prior to receiving his first dose of the study drug. These events are not listed in Table 16.

7.1.2 Other Serious Adverse Events

The types and rates of serious adverse events reported for subjects treated with paliperidone palmitate in Phase 2/3 studies are consistent with the safety profile of paliperidone ER. No new or unexpected serious adverse events were reported, and there was no evidence of an increase in serious adverse events reporting rates.

In the placebo-controlled, Phase 2/3 studies, the reporting rate for serious adverse events was the same or lower for therapeutic doses of paliperidone palmitate (25 to 100 mg eq., 5% to 13% across studies) than for placebo (7% to 18% across studies). There was no apparent dose relationship in the incidence of individual serious adverse events in subjects treated with paliperidone palmitate.

Schizophrenia and psychosis were the only adverse events reported as serious in more than 1% of subjects in the placebo or paliperidone palmitate groups in the Phase 2/3 studies, and such cases represent subjects hospitalized due to exacerbation of underlying disease. The majority of serious adverse events in all studies were judged by the investigator and Sponsor as either unrelated or doubtfully related to study treatment.

Across all Phase 2/3 studies, 5 of the 2,282 subjects receiving paliperidone palmitate had a serious adverse event(s) assessed by the investigators as probably drug related following medical review: extrapyramidal disorder (PSY-3001), orofacial dyskinesia (PSY-3002), dysphoria and tachycardia (PSY-3005), hypertension, tachycardia, syncope and chest discomfort (PSY-3004), and psychomotor hyperactivity (SCH-201).

Pooled PSY-3003 and PSY-3004 Data Set

Serious treatment-emergent adverse events were reported at a lower rate in the total paliperidone palmitate group (13%) than in the placebo group (18%) (Table 17). SAEs occurred at the highest rate (20%) in the paliperidone palmitate 150 mg eq. group. In other paliperidone palmitate treatment groups, the incidence of SAEs was lower compared to placebo treatment group. Fifteen (6%) subjects in the placebo group and 17 (3%) subjects in the paliperidone palmitate groups had treatment-emergent serious adverse events that resulted in discontinuation of treatment. Most of the serious adverse events that resulted in discontinuation of paliperidone palmitate therapy were psychiatric disorders.

Table 17 Treatment-Emergent Serious Adverse Events: Pooled PSY-3003 and -3004, Safety Analysis Set

Body System or Organ Class Dictionary-derived Term	Placebo (N=262) n (%)	R092670 25 mg eq. (N=130) n (%)	R092670 50 mg eq. (N=223) n (%)	R092670 100 mg eq. (N=228) n (%)	R092670 150 mg eq. (N=30) n (%)	R092670 150 mg eq./Pbo (N=31) n (%)	Total Pali Palmitate (N=611) n (%)
Total no. subjects with serious AE	48 (18)	18 (14)	33 (15)	21 (9)	6 (20)	5 (16)	78 (13)
Psychiatric disorders	43 (16)	16 (12)	26 (12)	20 (9)	5 (17)	5 (16)	67 (11)
Schizophrenia	21 (8)	6 (5)	12 (5)	9 (4)	1 (3)	3 (10)	28 (5)
Psychotic disorder	16 (6)	7 (5)	8 (4)	7 (3)	2 (7)	2 (6)	24 (4)
Suicidal ideation	4 (2)	0	1 (<1)	4 (2)	2 (7)	0	7 (1)
Hallucination, auditory	2 (1)	1 (1)	3 (1)	1 (<1)	0	0	5 (1)
Aggression	2 (1)	0	2 (1)	2 (1)	0	0	4 (1)
Agitation	2 (1)	0	0	3 (1)	0	0	3 (<1)
Hallucination	0	0	1 (<1)	1 (<1)	0	0	2 (<1)
Paranoia	2 (1)	1 (1)	1 (<1)	0	0	0	2 (<1)
Suicidal behaviour	0	1 (1)	0	0	1 (3)	0	2 (<1)
Suicide attempt	0	0	1 (<1)	1 (<1)	0	0	2 (<1)
Anxiety	1 (<1)	0	0	1 (<1)	0	0	1 (<1)
Completed suicide	0	0	0	1 (<1)	0	0	1 (<1)
Depressed mood	0	0	1 (<1)	0	0	0	1 (<1)
Depression	1 (<1)	0	1 (<1)	0	0	0	1 (<1)
Persecutory delusion	1 (<1)	0	0	0	0	0	0
Infections and infestations	2 (1)	0	3 (1)	1 (<1)	0	0	4 (1)
Bronchitis acute	0	0	0	1 (<1)	0	0	1 (<1)
Bronchopneumonia	0	0	1 (<1)	0	0	0	1 (<1)
Pneumonia	1 (<1)	0	1 (<1)	0	0	0	1 (<1)
Pulmonary tuberculosis	0	0	1 (<1)	0	0	0	1 (<1)
Cellulitis	1 (<1)	0	0	0	0	0	0
Cardiac disorders	1 (<1)	1 (1)	2 (1)	0	0	0	3 (<1)
Angina pectoris	0	0	1 (<1)	0	0	0	1 (<1)
Atrial fibrillation	0	0	1 (<1)	0	0	0	1 (<1)

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	Placebo (N=262)	R092670 25 mg eq. (N=130)	R092670 50 mg eq. (N=223)	R092670 100 mg eq. (N=228)	R092670 150 mg eq. (N=30)	R092670 150 mg eq./Pbo (N=31)	Total Pali Palmitate (N=611)
Body System or Organ Class Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiac disorders (continued)							
Cardiac failure congestive	0	0	1 (<1)	0	0	0	1 (<1)
Sinus arrhythmia	0	0	1 (<1)	0	0	0	1 (<1)
Tachycardia	0	1 (1)	0	0	0	0	1 (<1)
Palpitations	1 (<1)	0	0	0	0	0	0
Nervous system disorders	1 (<1)	1 (1)	1 (<1)	0	1 (3)	0	3 (<1)
Akathisia	0	0	0	0	1 (3)	0	1 (<1)
Convulsion	0	0	1 (<1)	0	0	0	1 (<1)
Syncope	0	1 (1)	0	0	0	0	1 (<1)
Grand mal convulsion	1 (<1)	0	0	0	0	0	0
Injury, poisoning and procedural complications	1 (<1)	1 (1)	1 (<1)	0	0	0	2 (<1)
Alcohol poisoning	1 (<1)	1 (1)	0	0	0	0	1 (<1)
Foreign body trauma	0	0	1 (<1)	0	0	0	1 (<1)
Metabolism and nutrition disorders	0	1 (1)	0	1 (<1)	0	0	2 (<1)
Hypoglycaemia	0	0	0	1 (<1)	0	0	1 (<1)
Hyponatraemia	0	1 (1)	0	0	0	0	1 (<1)
Gastrointestinal disorders	0	0	1 (<1)	0	0	0	1 (<1)
Pancreatitis acute	0	0	1 (<1)	0	0	0	1 (<1)
General disorders and administration site conditions	1 (<1)	1 (1)	0	0	0	0	1 (<1)
Chest discomfort	1 (<1)	1 (1)	0	0	0	0	1 (<1)
Chest pain	1 (<1)	0	0	0	0	0	0

See footnotes on the first page of the table.

(Continued)

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	Placebo (N=262)	R092670 25 mg eq. (N=130)	R092670 50 mg eq. (N=223)	R092670 100 mg eq. (N=228)	R092670 150 mg eq. (N=30)	R092670 150 mg eq./Pbo (N=31)	Total Pali Palmitate (N=611)
Body System or Organ Class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders	1 (<1)	0	1 (<1)	0	0	0	1 (<1)
Respiratory failure	0	0	1 (<1)	0	0	0	1 (<1)
Dyspnoea	1 (<1)	0	0	0	0	0	0
Social circumstances	0	0	1 (<1)	0	0	0	1 (<1)
Drug abuser	0	0	1 (<1)	0	0	0	1 (<1)
Vascular disorders	0	1 (1)	0	0	0	0	1 (<1)
Hypertension	0	1 (1)	0	0	0	0	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1)	0	0	0	0	0	0
Acute lymphocytic leukaemia	1 (<1)	0	0	0	0	0	0
Pancreatic carcinoma	1 (<1)	0	0	0	0	0	0

See footnotes on the first page of the table.

Study SCH-201

A total of 19 subjects experienced a treatment-emergent serious adverse event during the double-blind period. Of these, 6 subjects (7%) were receiving placebo, 8 subjects (10%) were receiving paliperidone palmitate 50 mg eq., and 5 subjects (6%) were receiving paliperidone palmitate 100 mg eq. Five subjects were discontinued from the study. Table 18 summarizes treatment-emergent SAEs in double-blind period.

Table 18 Treatment-Emergent Serious Adverse Events: Study SCH-201, Double-Blind Period, Safety Analysis Set

	Placebo (N=84) n (%)	R092670 50 mg eq. (N=79) n (%)	R092670 100 mg eq. (N=84) n (%)	Total R092670 (N=163) n (%)
Body System or Organ Class Dictionary-derived Term				
Total no. subjects with serious adverse event	6 (7)	8 (10)	5 (6)	13 (8)
Psychiatric disorders	5 (6)	8 (10)	3 (4)	11 (7)
Schizophrenia	2 (2)	5 (6)	2 (2)	7 (4)
Psychotic disorder	3 (4)	2 (3)	1 (1)	3 (2)
Depression	0	1 (1)	0	1 (1)
Suicidal ideation	0	1 (1)	0	1 (1)
Nervous system disorders	0	0	2 (2)	2 (1)
Psychomotor hyperactivity	0	0	1 (1)	1 (1)
Syncope	0	0	1 (1)	1 (1)
Investigations	1 (1)	0	0	0
Hepatic enzyme increased	1 (1)	0	0	0

Study PSY-3001

Treatment-emergent serious adverse events in the placebo group (12%) were reported at more than twice the incidence of the paliperidone palmitate group (5%) during the double-blind recurrence prevention phase. Schizophrenia (14 subjects), psychotic disorder (9 subjects), and suicidal ideation (4 subjects) were the only serious adverse events were reported in more than 1 subject across treatment groups. One subject had a treatment-emergent serious adverse event (myocardial infarction) that resulted in discontinuation of treatment. Table 19 summarizes the SAEs occurred in the double-blind phase in study PSY-3001.

Table 19 Treatment-Emergent Serious Adverse Events: Study PSY-3001, Double-Blind Phase, Safety Analysis Set

Body System or Organ Class	Placebo (N=203)	R092670 (N=205)	Total (N=408)
Dictionary-derived Term	n (%)	n (%)	n (%)
Total no. subjects with serious AE	25 (12)	10 (5)	35 (9)
Psychiatric disorders	23 (11)	8 (4)	31 (8)
Schizophrenia	10 (5)	4 (2)	14 (3)
Psychotic disorder	8 (4)	1 (<1)	9 (2)
Suicidal ideation	2 (1)	2 (1)	4 (1)
Aggression	1 (<1)	0	1 (<1)
Agitation	1 (<1)	0	1 (<1)
Anxiety	1 (<1)	0	1 (<1)
Hallucination	0	1 (<1)	1 (<1)
Hostility	1 (<1)	0	1 (<1)
Persecutory delusion	1 (<1)	0	1 (<1)
Schizophrenia, paranoid type	1 (<1)	0	1 (<1)
Infections and infestations	1 (<1)	1 (<1)	2 (<1)
Appendicitis	1 (<1)	0	1 (<1)
Cholecystitis infective	0	1 (<1)	1 (<1)
Blood and lymphatic system disorders	0	1 (<1)	1 (<1)
Lymphadenitis	0	1 (<1)	1 (<1)
Cardiac disorders	1 (<1)	0	1 (<1)
Myocardial infarction	1 (<1)	0	1 (<1)
Gastrointestinal disorders	1 (<1)	0	1 (<1)
Constipation	1 (<1)	0	1 (<1)
Injury, poisoning and procedural complications	0	1 (<1)	1 (<1)
Overdose	0	1 (<1)	1 (<1)
Respiratory, thoracic and mediastinal disorders	0	1 (<1)	1 (<1)
Acute respiratory failure	0	1 (<1)	1 (<1)

In Study PSY-3002, the rate of serious adverse events was 29% for the paliperidone palmitate group and 21% for the RISPERDAL CONSTA group. No difference was seen in Study PSY-3005 in the reporting rate for serious adverse events for the gluteal versus deltoid injection site (4% vs 5%, respectively).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall Profile of Dropouts

In each of the placebo-controlled Phase 2/3 studies, the overall rate of discontinuations due to adverse events in the paliperidone palmitate groups (range, 1% to 7%) was lower than the corresponding rate in the placebo group (range, <1% to 10%).

In the 13-week placebo-controlled studies PSY-3003 and PSY-3004 (pooled data set), the frequency of treatment-emergent adverse events leading to study drug discontinuation was lower in the paliperidone palmitate 50 mg eq. and 100 mg eq. groups (4% each) than in the placebo (8%), paliperidone palmitate 25 mg eq. (6%) or paliperidone palmitate 150 mg eq. (7%) groups.

During the double-blind period of study SCH-201, more subjects on placebo discontinued (10%) due to adverse events, in particular due to psychiatric disorders, compared with subjects in either of the paliperidone palmitate dose groups (3% in 50 mg eq. group and 2% in 100 mg eq. group).

In the long-term flexible dose study PSY-3001, 12% of subjects treated with open-label paliperidone palmitate experienced adverse events that resulted in discontinuation from the transition and maintenance phases. Discontinuation due to newly occurring adverse events was reported for 1% of subjects who were subsequently randomized to double-blind treatment with paliperidone palmitate.

In the long-term non-inferiority trial PSY-3002, the overall rate of discontinuations due to adverse events was similar for paliperidone palmitate (8%) and RISPERDAL CONSTA (6%). The higher rate of discontinuation due to psychiatric disorders in the paliperidone palmitate group than in the RISPERDAL CONSTA group (6% vs. 3%) is consistent with the similar imbalance in the rate of serious adverse events related to a psychiatric disorder, and appears to be associated with lower paliperidone plasma concentrations in the paliperidone palmitate group compared to active moiety plasma concentrations in the RISPERDAL CONSTA group.

In study PSY-3005, there was no clear relationship between the site of injection and the number of treatment-emergent adverse events leading to study drug discontinuation (4% gluteus, and 5% deltoid), and the number of treatment-emergent adverse events did not increase with the dosage of study drug.

The types and rates of adverse events leading to study discontinuation in subjects treated with paliperidone palmitate in Phase 2/3 studies are generally consistent with the corresponding events observed in the clinical trials of paliperidone ER. No new or unexpected adverse events resulting in treatment discontinuation were reported, and there was no noticeable increase in overall discontinuation rates due to adverse events.

7.1.3.2 Adverse events associated with dropouts

In all studies, the most common adverse events resulting in study discontinuation in both paliperidone palmitate treatment and placebo treatment groups are associated to subjects with psychiatric disorders, such as schizophrenia, agitation, auditory hallucination, suicidal ideation or attempt, aggression, and psychotic disorder.

7.1.3.3 Other significant adverse events

No other clinically significant adverse events were reported.

7.1.4 Other Search Strategies

No other search strategies were considered to be warranted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse events that occurred between the first and the last study-related procedures were reported. Adverse events were reported by the subject voluntarily or were collected by means of interviewing subjects in a non-directed manner.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events (verbatim terms) were coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA). The adverse event categorization was appropriate.

7.1.5.3 Incidence of common adverse events

Pooled PSY-3003 and PSY-3004

For the pooled 13-week, Phase 3 fixed-dose trials (PSY-3003/PSY-3004), adverse events occurred at similar rates for the paliperidone palmitate 25 mg eq., 50 mg eq. and 100 mg eq. (70% to 75%) and placebo (74%) groups, but at higher rates among subjects receiving paliperidone palmitate 150 mg eq. (83%) (Table 20). The small number of subjects in this group (n=30) makes it difficult to draw any definitive conclusions about the safety profile of this dose. The most common adverse events were CNS and psychiatric disorders, particularly schizophrenia and psychotic disorder. These were reported at higher rates in placebo-treated subjects. Few dose-related patterns were evident across the recommended dose range of 25 to 100 mg eq. Common adverse events that appeared to be reported at rates at least 3% higher for the paliperidone palmitate 100 mg eq. dose compared with paliperidone palmitate doses of either 25 or 50 mg eq. for pooled Studies PSY-3003/PSY-3004 included agitation (10% vs 4-10%),

headache (18% vs 11-12%), injection site pain (4% vs 0-1%) and injection site induration (3% vs 0-1%).

Table 20 Treatment-Emergent Adverse Events in ≥5% of Subjects in Any Treatment Group by MedDRA Preferred Term - Double-Blind Phase: Pooled PSY-3003, and -3004, Safety Analysis Set

	Placebo (N=262)	R092670 25 mg eq. (N=130)	R092670 50 mg eq. (N=223)	R092670 100 mg eq. (N=228)	R092670 150 mg eq. (N=30)	R092670 150 mg eq./Pbo (N=31)	Total Pali Palmitate (N=611)
Body System or Organ Class Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects with adverse events	195 (74)	98 (75)	155 (70)	165 (72)	25 (83)	27 (87)	443 (73)
Psychiatric disorders	111 (42)	53 (41)	79 (35)	77 (34)	12 (40)	7 (23)	221 (36)
Insomnia	34 (13)	20 (15)	27 (12)	29 (13)	3 (10)	1 (3)	79 (13)
Agitation	17 (6)	13 (10)	10 (4)	23 (10)	3 (10)	1 (3)	49 (8)
Psychotic disorder	30 (11)	9 (7)	15 (7)	17 (7)	3 (10)	2 (6)	44 (7)
Schizophrenia	32 (12)	11 (8)	19 (9)	13 (6)	1 (3)	4 (13)	44 (7)
Anxiety	20 (8)	11 (8)	12 (5)	7 (3)	2 (7)	2 (6)	32 (5)
Suicidal ideation	6 (2)	0	2 (1)	5 (2)	2 (7)	0	9 (1)
Nervous system disorders	61 (23)	38 (29)	58 (26)	73 (32)	15 (50)	16 (52)	184 (30)
Headache	37 (14)	14 (11)	27 (12)	40 (18)	8 (27)	15 (48)	89 (15)
Dizziness	4 (2)	8 (6)	5 (2)	9 (4)	1 (3)	2 (6)	23 (4)
Somnolence	5 (2)	5 (4)	11 (5)	6 (3)	0	1 (3)	22 (4)
Extrapyramidal disorder	6 (2)	6 (5)	7 (3)	3 (1)	1 (3)	0	17 (3)
Tremor	7 (3)	3 (2)	4 (2)	7 (3)	1 (3)	2 (6)	15 (2)
Sedation	4 (2)	2 (2)	5 (2)	4 (2)	3 (10)	0	14 (2)
Hypertonia	1 (<1)	1 (1)	3 (1)	2 (1)	3 (10)	1 (3)	9 (1)
Gastrointestinal disorders	51 (19)	20 (15)	47 (21)	45 (20)	12 (40)	12 (39)	124 (20)
Constipation	17 (6)	4 (3)	13 (6)	11 (5)	2 (7)	3 (10)	30 (5)
Nausea	12 (5)	5 (4)	11 (5)	9 (4)	4 (13)	3 (10)	29 (5)
Vomiting	11 (4)	7 (5)	12 (5)	7 (3)	3 (10)	2 (6)	29 (5)
Diarrhoea	4 (2)	0	8 (4)	4 (2)	4 (13)	2 (6)	16 (3)
Dyspepsia	8 (3)	2 (2)	3 (1)	7 (3)	0	2 (6)	12 (2)
Toothache	5 (2)	1 (1)	3 (1)	7 (3)	0	2 (6)	11 (2)

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	Placebo (N=262)	R092670 25 mg eq. (N=130)	R092670 50 mg eq. (N=223)	R092670 100 mg eq. (N=228)	R092670 150 mg eq. (N=30)	R092670 150 mg eq./Pbo (N=31)	Total Pali Palmitate (N=611)
Body System or Organ Class							
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders (continued)							
Stomach discomfort	3 (1)	2 (2)	2 (1)	2 (1)	2 (7)	0	8 (1)
Abdominal discomfort	3 (1)	0	5 (2)	1 (<1)	0	2 (6)	6 (1)
Flatulence	1 (<1)	0	0	0	2 (7)	1 (3)	2 (<1)
Investigations	26 (10)	12 (9)	31 (14)	18 (8)	3 (10)	5 (16)	64 (10)
Weight increased	0	5 (4)	10 (4)	4 (2)	0	2 (6)	19 (3)
General disorders and administration site conditions							
Injection site pain	1 (<1)	0	3 (1)	8 (4)	2 (7)	3 (10)	13 (2)
Injection site induration	1 (<1)	0	2 (1)	7 (3)	1 (3)	2 (6)	10 (2)
Pain	5 (2)	0	5 (2)	2 (1)	0	3 (10)	7 (1)
Pyrexia	4 (2)	1 (1)	1 (<1)	1 (<1)	0	2 (6)	3 (<1)
Infections and infestations							
Nasopharyngitis	24 (9)	9 (7)	27 (12)	21 (9)	4 (13)	6 (19)	61 (10)
	2 (1)	0	3 (1)	4 (2)	0	3 (10)	7 (1)
Skin and subcutaneous tissue disorders							
Rash	10 (4)	7 (5)	17 (8)	9 (4)	3 (10)	3 (10)	36 (6)
	2 (1)	2 (2)	3 (1)	1 (<1)	1 (3)	2 (6)	7 (1)
Pruritus generalised	0	0	0	0	2 (7)	0	2 (<1)
Respiratory, thoracic and mediastinal disorders							
Cough	15 (6)	6 (5)	15 (7)	11 (5)	2 (7)	7 (23)	34 (6)
	6 (2)	2 (2)	7 (3)	2 (1)	1 (3)	3 (10)	12 (2)
Nasal congestion	7 (3)	0	1 (<1)	4 (2)	0	2 (6)	5 (1)
Rhinorrhoea	2 (1)	0	2 (1)	1 (<1)	0	2 (6)	3 (<1)
Vascular disorders							
Hypertension	3 (1)	4 (3)	2 (1)	1 (<1)	2 (7)	3 (10)	9 (1)
	0	3 (2)	2 (1)	1 (<1)	1 (3)	2 (6)	7 (1)

See footnotes on the first page of the table.

Study SCH-201

The overall incidence of adverse events was similar for the paliperidone palmitate 50 and 100 mg eq. groups (60 to 65%) and placebo group (64%) (Table 21). As observed for PSY-3003 and PSY-3004, psychiatric disorders and nervous system disorders were the most common events, and overall reporting rates for these events were comparable across the treatment groups.

Table 21 Treatment-emergent Adverse Events in $\geq 5\%$ of Subjects in Any Treatment Group: Study SCH-201, Safety Analysis Set

Body System or Organ Class Dictionary-derived Term	Placebo	R092670 50 mg eq.	R092670 100 mg eq.	Total
	(N=84) n (%)	(N=79) n (%)	(N=84) n (%)	(N=163) n (%)
Total no. subjects with adverse events	54 (64)	51 (65)	50 (60)	101 (62)
Psychiatric disorders	33 (39)	28 (35)	25 (30)	53 (33)
Insomnia	14 (17)	17 (22)	12 (14)	29 (18)
Schizophrenia	2 (2)	6 (8)	4 (5)	10 (6)
Agitation	10 (12)	4 (5)	4 (5)	8 (5)
Psychotic disorder	8 (10)	4 (5)	1 (1)	5 (3)
Nervous system disorders	18 (21)	19 (24)	22 (26)	41 (25)
Headache	12 (14)	5 (6)	6 (7)	11 (7)
Extrapyramidal disorder	0	0	5 (6)	5 (3)
Gastrointestinal disorders	11 (13)	5 (6)	9 (11)	14 (9)
Constipation	1 (1)	1 (1)	4 (5)	5 (3)
Diarrhoea	4 (5)	0	2 (2)	2 (1)
Vomiting	4 (5)	1 (1)	0	1 (1)

Study PSY-3001

Due to the design of Study PSY-3001, only adverse events that newly appeared or worsened in severity after initiation of double-blind medication were considered treatment-emergent in the double-blind phase. Comparison of reporting rates for the open-label transition/maintenance and double-blind phases of PSY-3001 suggest that subjects who continue to receive paliperidone palmitate following a period of stabilization may have a lower incidence of new adverse events after that period of stabilization compared to those for whom treatment is newly initiated. During the double-blind phase of PSY-3001, adverse events were reported at similar rates for the paliperidone palmitate (38%) and placebo (44%) groups (Table 22). For most of the common adverse events, reporting rates were similar or lower in the paliperidone palmitate group compared with the placebo group. A notable exception was weight increased which was reported for 7% of subjects in the paliperidone palmitate group and 1% of subjects in the placebo group. In both treatment groups, most adverse events were considered to be mild or moderate in severity. There was no evidence of a withdrawal syndrome in subjects withdrawn from paliperidone palmitate treatment.

Table 22 Treatment-Emergent Adverse Events in $\geq 2\%$ of Subjects in Any treatment Group: Study PSY-3001, Safety Analysis Set

Body System or Organ Class Dictionary-derived Term	Placebo (N=203) n (%)	R092670 (N=205) n (%)
Total no. subjects with adverse events	89 (44)	78 (38)
Psychiatric disorders	53 (26)	24 (12)
Anxiety	12 (6)	10 (5)
Schizophrenia	15 (7)	6 (3)
Insomnia	13 (6)	6 (3)
Psychotic disorder	12 (6)	1 (<1)
Hallucination	4 (2)	3 (1)
Depression	5 (2)	0
Investigations	21 (10)	26 (13)
Weight increased	3 (1)	14 (7)
Blood glucose increased	3 (1)	4 (2)
Weight decreased	4 (2)	1 (<1)
Infections and infestations	18 (9)	18 (9)
Nasopharyngitis	6 (3)	8 (4)
Gastroenteritis viral	0	4 (2)
Nervous system disorders	10 (5)	19 (9)
Headache	6 (3)	6 (3)

Study PSY-3002

In the long-term non-inferiority trial PSY-3002, the incidences of all adverse events, as well as most adverse events of clinical interest (psychiatric, neurologic, cardiovascular, endocrine and metabolic) showed no clinically relevant differences between paliperidone palmitate and RISPERDAL CONSTA (76% vs. 78% respectively, TEAEs). A larger proportion of subjects in the paliperidone palmitate group had serious treatment-emergent adverse events, including psychiatric disorders, compared to the RISPERDAL CONSTA group. The higher incidence of serious psychiatric disorders and their greater severity in paliperidone palmitate-treated subjects appears to be associated with the lower initial plasma concentrations of paliperidone following injection of paliperidone palmitate compared to levels of active moiety following injection of RISPERDAL CONSTA.

Study PSY-3005

In Study PSY-3005, a safety and tolerability study with a crossover design, the incidence and severity of treatment-emergent adverse events was similar across treatment-sequence groups for gluteal and deltoid injections (63% vs 64% in Period 1 and 46% vs 51% in Period 2, TEAEs). There was no dosage-dependent increase in the proportion of subjects reporting a systemic (i.e.,

non-injection site related) treatment-emergent adverse event at either treatment initiation or following the switch of injection sites at Week 13.

7.1.5.4 Identifying common and drug-related adverse events

Events with a higher incidence in any of the dose groups compared to placebo and display a dose-response relationship were identified as adverse drug reactions. Adverse events with a higher incidence in all dose groups compared to placebo irrespective of a dose-response relationship (assessed based on relative differences, e.g., 2-fold) were identified as adverse drug reactions.

7.1.5.5 Additional analyses and explorations

Injection Site Effects

Local Injection Site Reactions and Systemic Post-injection Events

Adverse events suggestive of local injection site reactions were infrequently reported. Three subjects (<0.5%) with such events were identified during the open-label transition/maintenance phase of PSY-3001, and no subject had a local injection site reaction during the double-blind phase of this study. In the pooled Studies PSY-3003/PSY-3004, local injection site reactions were identified for 6 subjects (1%) receiving paliperidone palmitate and 2 (1%) receiving placebo. Injection site pain was the most commonly reported adverse event associated with drug administration in PSY-3002 and was reported at similar rates for paliperidone palmitate (3%) and RISPERDAL CONSTA (2%). In Study PSY-3005, the overall reporting rate for local injection site reactions did not differ as a function of injection site (4% gluteus, 6% deltoid).

Across all Phase 2/3 studies, none of the local injection site reactions were serious, and treatment was discontinued in only 1 subject as a result of the event (moderate injection site pain). Systemic post-injection events of clinical interest were identified in 8 subjects receiving injections of paliperidone palmitate, 4 subjects receiving placebo injections and 1 subject receiving injection of RISPERDAL CONSTA. None of these events were severe, serious or treatment limiting.

Injection Site Ratings

Based on investigator ratings, similar percentages of subjects had pain at the injection site for the paliperidone palmitate and placebo groups (approximately 15-20%) for PSY-3001 and pooled Studies PSY-3003/PSY-3004. Subject evaluations of injection site pain did not appreciably differ for placebo and paliperidone palmitate, and tended to lessen in intensity over time. Induration and swelling were reported for <5% of subjects (based on investigator ratings) in the placebo and paliperidone palmitate groups of Studies PSY-3003/3004 and PSY-3001, and the occurrence of redness was also similar for placebo and paliperidone palmitate (about 10% to 12%). Most ratings for each category were mild. The number of subjects with moderate or severe redness, pain, induration or swelling decreased as the studies progressed. In PSY-3002, ratings of pain,

redness, induration and swelling were similar for paliperidone palmitate and RISPERDAL CONSTA. There were no clinically meaningful differences in the proportions of subjects with pain, swelling or induration at the injection site for the deltoid versus gluteus injection sites in PSY-3005, although rates tended to be somewhat higher after deltoid administration for those given this injections at this site initially.

Extrapyramidal Symptoms

Reporting Rates of EPS-related Events

For the pooled Studies PSY-3003/PSY-3004, the proportion of subjects who experienced EPS-related adverse events was similar for paliperidone palmitate doses of 25, 50 and 100 mg eq. (11-12%) to that for placebo (10%). EPS-related adverse events tended to be more prominent in the 150 mg eq. dose group than in placebo group. Parkinsonism was the most frequent category of EPS-related adverse events in these studies, reported at a similar rate of 5% in the placebo group and at rates of 4% to 6% in the paliperidone palmitate 25, 50 and 100 mg eq. groups.

In Study SCH-201, parkinsonism was the most common category of EPS-related adverse events and was reported at a higher rate in the paliperidone palmitate 50 and 100 mg eq. groups (5% and 8%, respectively) compared with placebo (1%). Other categories of EPS-related events in Study SCH-201 were reported at similar rates in the placebo and combined paliperidone palmitate groups.

During the 33-week, open-label transition/maintenance phases of PSY-3001, EPS-related adverse events were reported for 9% of subjects receiving paliperidone palmitate, with akathisia (3%) and extrapyramidal disorder (2%) being the most common, and all others reported at a rate of 1% or less. In the double-blind phase of PSY-3001, the incidence of EPS-related adverse events in subjects maintained on paliperidone palmitate (5%) was lower compared to the preceding open-label phases but was higher than that reported in subjects switched to placebo (2%).

The reporting rate for these events did not differ markedly as a function of injection site in PSY-3005 (deltoid, 5%; gluteus, 8%), and in the noninferiority trial (PSY-3002), the reporting rate for most EPS-related adverse events was similar for paliperidone palmitate and RISPERDAL CONSTA.

Across the completed Phase 2/3 studies, most of the EPS-related adverse events were rated as mild or moderate in severity. Among the 2,282 subjects who received paliperidone palmitate across the completed Phase 2/3 studies, 5 subjects had a serious EPS-related adverse event (2 reports of akathisia, 1 report each of dystonia, psychomotor hyperactivity and extrapyramidal disorder) and 4 subjects (including 1 with serious extrapyramidal disorder) were discontinued as a result of the EPS-related event.

Tardive dyskinesia was reported for 2 subjects in the completed Phase 1, 2 and 3 studies, both of whom were treated with paliperidone palmitate (<0.1%). Neither event was serious or resulted in

treatment discontinuation, and both resolved. Oculogyration was reported in 3 (0.1%) subjects receiving paliperidone palmitate (and no subject receiving placebo) in the completed Phase 2/3 double-blind studies, all from Study PSY-3001. One of these events resulted in withdrawal of treatment.

Changes in Objective Extrapyramidal Symptom Rating Scales

Three well-validated, objective scales for the assessment of EPS, Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and Simpson Angus Scale (SAS) global scores, were used in the Phase 2/3 clinical studies. Assessment of EPS-related symptoms based on these rating scales was consistent with rates of reported EPS-related adverse events. There were no appreciable changes from baseline to end point on the BARS, AIMS or SAS global scores for the paliperidone palmitate treatment groups for any of the safety analysis sets, and comparisons with placebo for the pooled PSY-3003/PSY-3004, PSY-3001 (double-blind phase) and SCH-201 were not significant for any of these 3 scales.

7.1.6 Less Common Adverse Events

No less common adverse event of significant concern was identified in these studies.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Standard laboratory tests including hematology, clinical chemistry (including liver and renal function tests, serum lipid levels, glucose levels, and serum prolactin), and urinalysis testing were performed per protocol. Mean change from baseline to endpoint, treatment-emergent abnormalities at any time, and treatment-emergent potentially clinically significant abnormalities for each laboratory analyte were analyzed.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The clinical laboratory test results with paliperidone palmitate in all completed phase 2/3 studies were included in the analyses.

7.1.7.3 Standard analyses and explorations of laboratory data

Based on mean changes from baseline to end point and the occurrence of treatment-emergent markedly abnormal values, the results of chemistry (including fasting serum glucose), hematology, and urinalysis laboratory tests (with the exception of the increase in serum prolactin, which will be discussed separately in 7.1.7.4 Additional Analyses and Explorations) across Phase 2/3 studies did not show clinically relevant differences for paliperidone palmitate compared with those for placebo. There was no indication of long-term changes in laboratory analytes in the flexible dose studies. Slight decreases in platelet counts observed over time were

not considered clinically relevant; no unexpected adverse events suggestive of thrombocytopenia were reported in the clinical trials.

7.1.7.4 Additional analyses and explorations

Changes in Serum Prolactin Concentrations

Mean increases in prolactin concentrations from baseline were observed for adult subjects of both sexes with schizophrenia who received paliperidone palmitate. As expected, and consistent with the findings from clinical studies of paliperidone ER, the median increases in prolactin levels from baseline to end point were greater in females compared with male subjects who received paliperidone palmitate. Mean prolactin concentrations did not show clinically relevant changes from baseline for male or female subjects who received placebo in these studies.

The magnitude of the mean increases in prolactin concentrations at end point tended to be dose related. In the pooled PSY-3003/PSY-3004 studies, mean changes in prolactin concentrations for the paliperidone palmitate 25, 50, 100 and 150 mg eq. dose groups were 4.03, 6.94, 12.35 and 15.21 ng/mL, respectively, for male subjects and 9.28, 33.78, 42.15 and 62.33 ng/mL, respectively, for female subjects. Data from PSY-3005 also showed a larger mean increase in prolactin concentrations for paliperidone palmitate doses of 75 and 100 mg eq. compared with 50 mg eq. The proportions of subjects with a prolactin concentration above the upper limit of the normal range (but normal at baseline) showed a dose related pattern for the pooled PSY-3003/PSY-3004 studies but not for PSY-3005.

Data from Study SCH-201 suggest that the increase in serum prolactin with paliperidone palmitate is less than that for orally administered drug. Following the first injection of double-blind treatment in Study SCH-201, prolactin concentrations, which had been increased following the 7-day oral run-in treatment with paliperidone (ER or IR formulation), declined in all 3 treatment groups for both sexes. These mean reductions, however, were consistently larger in the placebo group than in the paliperidone palmitate groups.

In Study PSY-3001, gradual mean increases from baseline in prolactin concentrations were apparent throughout the open-label transition and maintenance phases. During the double-blind phase, mean prolactin concentrations continued to show a gradual rise. The mean increase in prolactin concentrations from transition baseline to end of the maintenance phase was 9.8 ng/mL among male subjects and 25.3 ng/mL for female subjects; in subjects maintained on paliperidone palmitate, the mean increase from double-blind baseline at end point was 3.7 ng/mL for males and 12.7 ng/mL for females.

In the non-inferiority study, PSY-3002, the mean increase in prolactin concentrations was similar for paliperidone palmitate (6.9 and 22.5 ng/mL for males and females) and RISPERDAL CONSTA (9.1 and 22.4 ng/mL, respectively) groups. The proportion of male and female subjects with abnormally high prolactin concentrations, however, was larger in the RISPERDAL CONSTA group (53% and 51%) than in the paliperidone palmitate group (31% and 42%).

Although mean elevations in serum prolactin were consistently apparent with paliperidone palmitate treatment, these changes were not reflected in a higher reporting rate of potentially prolactin-related adverse events (amenorrhea, gynecomastia, and events related to sexual dysfunction). Across the completed Phase 2/3 studies, the incidences of potentially prolactin-related adverse events was 1% in the placebo groups, 4% in the RISPERDAL CONSTA group, and ranged from 1% to 3% in the paliperidone palmitate groups. None of these adverse events were serious, most were mild or moderate in severity, and 2 resulted in treatment discontinuation (dysmenorrhea, erectile dysfunction). Only a minority of subjects with a potentially prolactin-related adverse event had a clinically significant serum prolactin concentration of > 100 ng/mL.

Glucose-Related Adverse Events

A clinical review for potentially remarkable glucose-related adverse events was conducted by the sponsor. Events suspicious for an alteration in glucose metabolism were reviewed, as were all verbatim and MedDRA preferred terms for subjects with a post baseline glucose concentration of > 6.9 mmol/L or 126 mg/dL (consistent with the criteria set forth by the expert committee on the diagnosis and classification of diabetes mellitus). Across all Phase 2/3 studies, glucose-related adverse events were infrequent (1% to 3%), which is consistent with the low incidence of markedly abnormal glucose concentrations and absence of clinically meaningful changes in mean glucose concentrations. In Studies PSY-3001 (double-blind phase), pooled PSY-3003/PSY-3004 and SCH-201, the incidence of glucose-related adverse events in the paliperidone palmitate groups was similar to that in the placebo group. Glucose-related adverse events were reported at a higher rate for RISPERDAL CONSTA (4%) than for paliperidone palmitate (2%) in Study PSY-3002. Most of the glucose-related adverse events were mild or moderate in intensity, did not result in withdrawal of study treatment and were not serious. One paliperidone palmitate-treated subject with a history of diabetes was withdrawn during the transition/maintenance phase of Study PSY-3001 for serious diabetes mellitus, and a subject in the 100 mg eq. paliperidone palmitate group of PSY-3004 with a history of non-insulin dependent diabetes was hospitalized for hypoglycemia (did not result in withdrawal).

7.1.7.5 Special assessments

No special assessments were warranted in these studies.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Supine and standing vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate), orthostatic vital sign changes, body weight, and BMI were evaluated for changes over time. Data for individual subjects were evaluated based on the occurrence of treatment-emergent vital sign- or weight-related adverse events and the occurrence of treatment-emergent abnormal findings based on protocol pre-specified criteria.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The vital sign data from all completed phase 2/3 studies were included in the analyses.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Regardless of treatment in all phase 2/3 studies, there were no clinically relevant mean changes from baseline to end point in vital signs. There were no clinically relevant differences between the paliperidone palmitate and placebo groups with regard to mean changes from baseline in blood pressure values, or mean change from baseline in supine or standing blood pressure values over time.

At the time of observed maximum plasma concentration (15-20 days), there was no significant change in vital sign parameters from the screening/baseline values in all phase 2/3 studies.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

In pooled double-blind studies of PSY-3003 and -3004, standing pulse rates of ≥ 100 bpm with an increase of ≥ 15 bpm, which represented the most common vital sign abnormality in all studies, were observed at the incidence of 9% in the paliperidone palmitate total treatment group, compared to 12% in the placebo group. In other placebo-controlled studies, these incidences were similar for the 2 groups (PSY-3001: paliperidone palmitate, 5%; placebo, 3%; SCH-201: paliperidone palmitate, 13%; placebo, 15%).

In these placebo-controlled Phase 2/3 studies, the placebo-treated subjects had a higher incidence of abnormal elevations in supine pulse rate values, compared with paliperidone palmitate-treated subjects.

In study PSY-3002, standing pulse rates of ≥ 100 bpm with an increase of ≥ 15 bpm were reported for 11% of paliperidone palmitate-treated subjects and 13% of subjects treated with RISPERDAL CONSTA. Other vital sign abnormalities were reported at lower rates and equally distributed between the 2 treatment groups.

The incidence of orthostatic hypotension assessed by orthostatic changes in blood pressure and pulse rate was low. In placebo-controlled Phase 3 studies, this incidence did not exceed 2% for either paliperidone palmitate or placebo. In the long-term non-inferiority trial PSY-3002, it was reported at a low incidence of 3% for both paliperidone palmitate and RISPERDAL CONSTA.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Most of the adverse events associated with vital sign abnormalities, including cases of orthostatic hypotension as an adverse event, were reported at the incidences of 2% or less and were mild or

moderate in severity. Serious adverse events related to vital sign abnormalities or discontinuations due to adverse events associated with vital sign abnormalities were reported in isolated cases.

7.1.8.4 Additional analyses and explorations

Body Weight and BMI

Treatment with paliperidone palmitate, like that observed with paliperidone ER, results in modest increases in body weight and BMI, and the magnitude of these changes appears similar with the 2 formulations. In the 13-week Phase 3 studies, body weight and BMI showed small mean decreases of -0.6 kg and -0.2 kg/m² from baseline to end point in the placebo group (pooled Studies PSY-3003/PSY-3004). A dose-related increase was seen for both parameters in the paliperidone palmitate groups, with mean increases in body weight ranging from 0.4 to 1.4 kg and those for BMI ranging from 0.2 to 0.5 kg/m². The proportion of subjects showing a weight increase of $\geq 7\%$ also increased relative to placebo (2%) in a dose-related manner, ranging from 6% to 10% for paliperidone palmitate doses of 25 to 100 mg eq. groups, but not further increase was apparent with the 150 mg eq. dose (4%). No dose relationship was seen, however, in Study PSY-3005 with respect to either mean weight changes or the percentage of subjects with a weight increase of $\geq 7\%$.

The mean changes in body weight and BMI over the 33-week open-label transition/maintenance phases of PSY-3001 (0.7 and 0.2 kg/m²) were consistent with those for doses of 50-100 mg eq. for PSY-3003/PSY-3004, as was the percentage of subjects with a weight increase of $\geq 7\%$ (12%). Increases in body weight were also apparent during the double-blind phase among subjects who remained on paliperidone palmitate (mean increase relative to double-blind baseline of 0.2 kg and 0.1 kg/m²). The weight gain seen with paliperidone palmitate tended to resolve following discontinuation of treatment; subjects switched to placebo in the double-blind phase of PSY-3001 showed mean decreases in body weight (-1.0 kg) and BMI (-0.3 kg/m²).

During the 53-week treatment period for Study PSY-3002, increases of $\geq 7\%$ in body weight were reported at similar rates in paliperidone palmitate (14%) and RISPERDAL CONSTA (15%) groups. Similar rates of abnormal weight increases were also observed in subjects treated with paliperidone palmitate in PSY-3005 (13%). There were no clinically relevant differences between injection sites in PSY-3005 with regard to mean changes in body weight or BMI or rates of abnormal weight increases.

A common finding in the Phase 3 studies was that mean changes in body weight and BMI with paliperidone palmitate were larger for subjects with a normal BMI (<25 kg/m²) at baseline than for those who were overweight or obese.

While adverse events of weight increase were reported for 2% to 7% of subjects in the paliperidone palmitate 25 to 100 mg eq. groups across the completed Phase 2/3 studies, none of these events were reported as serious. Two subjects across the Phase 2/3 studies were withdrawn for weight increased: 1 subject in the paliperidone palmitate group of the double-blind phase of

PSY-3001 and 1 subject receiving RISPERDAL CONSTA (preferred term, overweight) in PSY-3002.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Twelve-lead ECGs were obtained from treated subjects in all Phase 2/3 studies; care was taken to record ECGs at approximately the same time of day at each specified visit to minimize possible diurnal variation and food effects. ECGs were read and interpreted by a central facility blinded to the actual treatment received by subjects. Special attention was paid to the QT interval corrected for heart rate. QTc limits were in accordance with International Conference on Harmonisation (ICH) E14 guidelines. Results for QT were corrected for heart rate using the traditional formulae of Bazett (QTcB), Fridericia (QTcF), and Sagie (QTcI).

No specific QT study with paliperidone palmitate was conducted by the sponsor. However, the effects of paliperidone ER on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), and multi-center QT study in adults with schizophrenia. No QT study is recommended.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The ECG data from all completed paliperidone palmitate phase 2/3 studies were analyzed and were included in this review.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Mean changes from baseline in the linear-derived corrected QT interval (QTcLD) in the paliperidone palmitate groups were not significantly different from those for placebo in the pooled Studies PSY-3003/PSY-3004 (25 mg eq., +0.2 ms; 50 mg eq., +1.1 ms; 100 mg eq., -0.3 ms; 150 mg eq., -3.1 ms, and placebo +0.5 ms). No dose-related pattern was apparent with regard to mean increases in QTcLD in subjects receiving paliperidone palmitate. In a long-term non-inferiority trial PSY-3002, the mean changes in QTcLD from average pre-dose values were -0.4 ms for paliperidone palmitate and +1.4 ms for RISPERDAL CONSTA.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Across all Phase 2/3 studies, the maximum increases from baseline in the QTcLD were below 30 msec for the majority of subjects, and no subject receiving paliperidone palmitate had a maximum increase of 60 msec or longer from their average pre-dose QTcLD value. Maximum

increases in the QTcLD of 30-60 msec were reported at similar rates (at or below 5%) for subjects receiving paliperidone palmitate and placebo (PSY-3001, pooled PSY-3003/PSY-3004, SCH-201) and paliperidone palmitate and RISPERDAL CONSTA (PSY-3002).

Treatment-emergent abnormal ECG parameters (PR, QRS, QT and RR intervals) were observed at incidences not exceeding 2% in all treatment groups for the Phase 2/3 studies. Abnormal increases in heart rate in the paliperidone palmitate group (total) were recorded at similar rates to that for placebo in PSY-3001 (6% to 8%) and pooled PSY-3003/PSY-3004 studies (12% to 14%) and to RISPERDAL CONSTA (12% to 13%) in PSY-3002. There were also no differences in the incidence of ECG parameters outside clinically important limits between the placebo and paliperidone palmitate groups for the PSY-3001 and the pooled PSY-3003/PSY-3004 studies, or as a function of injection site of administration in PSY-3005.

7.1.9.3 Marked outliers and dropouts for ECG abnormalities

Of the 2,282 adult subjects with schizophrenia receiving paliperidone palmitate in the completed Phase 2/3 studies, one had a QTcLD value exceeding 500 msec (507 msec) and 1 additional subject had a maximum post dose QTcLD value above 480 msec (483 msec). Both cases were clinically unremarkable, and in neither subject was the QTcLD elevation associated with any cardiovascular adverse events. Both subjects had marked bradycardia (heart rate <50 bpm), and thus, the QTcLD may represent an overcorrection of the true effect.

QTc interval prolongation was infrequently reported by the investigators as an adverse event. Across the completed Phase 2/3 studies, 12 paliperidone palmitate-treated subjects (<1% of 2,282 subjects) and 7 placebo-treated subjects (1% of 549 subjects) had QT interval prolongation or QT interval abnormal reported as an adverse event. For 2 of the paliperidone palmitate-treated subjects, these events were reported on the first day of study, prior to the first injection of paliperidone palmitate, and appear to be associated with oral tolerability study medication. None of the reported events were serious and only one resulted in treatment discontinuation.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were conducted.

7.1.10 Immunogenicity

Human immunogenicity study was not required.

7.1.11 Carcinogenicity

Human Carcinogenicity study was not required.

7.1.12 Special Safety Studies

Suicidality Related Adverse Events

A careful and systematic approach was taken by the sponsor in the analysis of suicide-related events for subjects treated with paliperidone palmitate. In addition to evaluating reports of MedDRA preferred terms related to suicide (completed suicide, suicide attempt, suicidal behavior, suicidal ideation), all adverse event verbatim terms for full or partial word combinations possibly suggestive of self-injurious behavior and investigator comments on the CRF pages were reviewed to identify any other adverse events that could possibly be associated with suicidality.

There were 4 reports of completed suicide among the 3,012 subjects receiving paliperidone palmitate in any of the completed clinical studies (Phase 1, 2 or 3) included in this submission (2 in Study PSY-3001, 1 in PSY-3004 and 1 in PSY-3005) compared to none in the 549 subjects treated with placebo. In addition, 1 subject in Study PSY-3001 died after falling from a window, with the cause of death listed as an accident and a second subject in this study died post-study from drug toxicity (verbatim term, accidental ingestion) 19 days after completing the maintenance phase. The rate of completed suicide, even including these latter 2 subjects, is low (0.2%) and consistent with that reported for paliperidone ER during clinical development.

Overall, across Phase 2/3 studies, suicidality-related events (based on MedDRA terms) were uncommon, and most of the reported cases were of suicidal ideation. In the pooled Phase 3 placebo-controlled studies (PSY-3003/3004), the risk of suicidal ideation per 100 patient-years of exposure was lower in paliperidone palmitate-treated subjects (8.1) compared to placebo (15.0). There was no suggestion of any relationship of suicidality-related events to the dose of paliperidone palmitate for the pooled PSY-3003 and PSY-3004 studies or in PSY-3005.

A search of all adverse event verbatim terms and investigator comments possibly suggestive of self-injurious behavior revealed some additional cases. Across all completed Phase 2/3 studies, a total of 61 of the 2,282 subjects (3%) receiving paliperidone palmitate experienced a suicidality-related adverse event or had an event suggestive of potential self-injurious behavior. A thorough clinical review of all cases by the Sponsor indicated that the majority of suicidality-related events and potential self-injurious behavior were associated with the underlying disease process and were unlikely to be related to paliperidone palmitate treatment. None were assessed by the Sponsor as probably drug related.

Thus, based on the sponsor's study, there is no new safety signal regarding suicidality for paliperidone palmitate. The incidence of suicidality-related events in subjects treated with paliperidone palmitate in Phase 2/3 studies are generally consistent with the observations from clinical trials of paliperidone ER.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The pharmacologic profile of paliperidone indicates that the abuse and dependence potential of paliperidone is minimal. This potential is further reduced due to the fact that paliperidone

palmitate is an injectable formulation not readily available to patients and not available in retail pharmacies.

Due to the long-acting nature of the paliperidone palmitate formulation, a systematic approach to evaluation of withdrawal events via a checklist or other standardized questionnaire was not performed in the clinical development program.

The randomized withdrawal design of study PSY-3001 was used to search for withdrawal-related symptoms upon discontinuation of paliperidone palmitate. A clinical review of discontinuation related adverse events was focused on somatic symptoms common to withdrawal in psychiatric subjects. The incidence of newly emergent somatic symptoms observed during review is low and does not show evidence of a withdrawal syndrome or rebound phenomenon in subjects who abruptly discontinue paliperidone palmitate.

7.1.14 Human Reproduction and Pregnancy Data

The safety of paliperidone palmitate or paliperidone for use during human pregnancy or women who are lactating has not been established.

Across all studies, 7 pregnancies were reported in subjects enrolled in paliperidone palmitate clinical trials, including 5 cases in subjects who were treated with paliperidone palmitate, 1 subject in a mixed treatment placebo/paliperidone palmitate 150 group, and 1 subject in RISPERDAL CONSTA group. Two cases were reported in Phase 1 study PSY-1004 and 5 cases in Phase 3 studies PSY-3002 and PSY-3003. Of the 7 cases, there were 2 deliveries (healthy babies in both cases), 3 elective abortions, and 2 spontaneous abortions.

No new safety concerns have been revealed with regard to paliperidone palmitate exposure during pregnancy.

7.1.15 Assessment of Effect on Growth

No pediatric patients were enrolled in these studies. Therefore, the effect of OP Depot on growth was not studied.

7.1.16 Overdose Experience

The potential for overdose with paliperidone palmitate in these studies was negligible due to the fact that study drug was administered via i.m. injection by the study drug administrator at each study center. No events of overdose with paliperidone palmitate were reported.

7.1.17 Postmarketing Experience

At the time of the writing of this review, paliperidone palmitate was not marketed in any country.

A Periodic Safety Update Review (PSUR) for paliperidone ER the reporting period 20 December 2006 through 19 December 2007 did not identify any new safety signals. No changes to the reference safety information for paliperidone ER are warranted at this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 23 summarizes the studies included in paliperidone palmitate integrated safety review.

Table 23 Summary of Studies Included in the Integrated Safety Review

Analysis Set Protocol No.	Study Design
PHASE 3 DOUBLE-BLIND CONTROLLED STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
Pooled Double-Blind Studies Analysis Set	
R092670-PSY-3003	Randomized, DB, PC, PG, dose-response fixed dose efficacy and safety study Dose: 50, 100, and 150 mg eq., gluteal injection (F013 formulation) Duration: 14 weeks No. Subjects Evaluable for Safety: 387 Treated with paliperidone palmitate: 252
R092670-PSY-3004	Randomized, DB, PC, PG, dose-response fixed dose efficacy and safety study Dose: 25, 50, and 100 mg eq., gluteal injection (F011/F013 formulation) ^a Duration: 14 weeks No. Subjects Evaluable for Safety: 517 Treated with paliperidone palmitate: 390
Other Phase 3 Double-Blind Studies	
R092670-PSY-3002	Randomized, DB, PC, PG comparative study of flexibly dosed paliperidone palmitate (25, 50, 75, or 100 mg eq.) administered every 4 weeks and flexibly dosed RISPERDAL [®] CONSTA [™] (25, 37.5, or 50 mg) administered every 2 weeks Dose: 25, 50, 75, or 100 mg eq., gluteal injection (F011/F013 formulation) Duration: 54 weeks No. Subjects Evaluable for Safety: 747 Treated with paliperidone palmitate: 379
R092670-PSY-3005	Randomized CO safety and tolerability study of paliperidone palmitate injected in the deltoid or gluteus muscle ^b Dose: 50, 75, and 100 mg eq., deltoid and gluteal injection (F013 formulation) Duration: 26 weeks No. Subjects Evaluable for Safety: 249 Treated with paliperidone palmitate: 249
R092670-PSY-3001 ^c	Randomized, DB, PC, PG recurrence prevention study Dose: 25, 50, 75, or 100 mg eq., gluteal injection (F011/F013 formulation) Duration: 33-week OL transition and maintenance phases followed by a variable duration DB phase No. Subjects Evaluable for Safety: 849 Treated with paliperidone palmitate: 849
COMPLETED PHASE 2 DOUBLE-BLIND STUDY IN SUBJECTS WITH SCHIZOPHRENIA	
Study R092670-SCH-201	
R092670-SCH-201	Randomized, DB, PC efficacy and safety study Dose: 50 and 100 mg eq., gluteal injection (F011* formulation) ^a Duration: 11 weeks No. Subjects Evaluable for Safety: 247 Treated with paliperidone palmitate: 163

Analysis Set Protocol No.	Study Design
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
Single Dose Studies	
R092670-BEL-1	Dose: 50 mg eq., single gluteal injection (pilot depot formulation F001) Duration: 8 weeks No. Subjects Evaluable for Safety: 9
R092670-BEL-2	4 parallel groups Dose: 50 mg eq (F002 or F004), 100 mg eq. (F004) or 150 mg eq. (F004) single gluteal injection (depot formulation F002 or F004) Duration: 12 weeks No. Subjects Evaluable for Safety: 29
R092670-INT-12	PK, tolerability and safety parallel group study of the depot formulation 4 parallel groups Dose: 25, 50, 100, or 150 mg eq. single gluteal injection (F011*) ^a Duration: 85 days No. Subjects Evaluable for Safety: 48
R092670-PSY-1002	OL, parallel group, randomized study of in vitro/in vivo correlation of paliperidone palmitate long-acting formulations and the comparability of the F011 and F013 formulations Dose: 50 mg eq. single gluteal injection (F011 or F013) (different release rates) Duration: 18 weeks or 36 weeks No. Subjects Evaluable for Safety: 143
R092670-PSY-1004	OL, parallel group, randomized dose proportionality PK study of paliperidone palmitate injection in the deltoid or gluteal muscle Dose: 25, 50, 100, or 150 mg eq. single injection (gluteal vs. deltoid), (F013) Duration: 18 weeks No. Subjects Evaluable for Safety: 201
Multiple Dose Studies	
R092670-USA-3	Dose: repeated i.m. injections (2 doses) of 25 mg eq. (gluteal vs. deltoid), 150 mg eq. (gluteal vs. deltoid) (F011*) ^a , 1 week apart Duration: 64 days No. Subjects Evaluable for Safety: 83
R092670-BEL-4	Dose: 50 mg eq. (4 to 6 injections), 100 mg eq.(6 injections) or 150 mg eq.(6 injections) (consecutive monthly gluteal injections) (F004) Duration: 36 weeks No. Subjects Evaluable for Safety: 54
R092670-INT-11	DB comparative PK, tolerability and safety study of paliperidone palmitate formulations originating from 2 different production methods. Dose: 50 mg eq. and 150 mg eq. (F004 and F011*) ^a Repeated 4-week injections in gluteal muscle, total of 4 i.m. injections (2 injections per formulation), 2 parallel groups. Duration: 169 days No. Subjects Evaluable for Safety: 60
R092670-BEL-7	PK, tolerability and safety study Repeated initial day 1 and day 8 followed by monthly maintenance doses: 100 mg eq. + 3x 50 mg eq., 200 mg eq.+ 3x 100 mg eq., 300 mg eq.+ 3x 150 mg eq., 50 mg eq. + 4x 50 mg eq., 150 mg eq. + 4x 150 mg eq. (F004) Duration: 18 weeks No. Subjects Evaluable for Safety: 60
R092670-PSY-1001	OL, parallel group, randomized, multiple-dose PK study of paliperidone palmitate injections in the deltoid vs. gluteal muscle Dose: 100 mg eq. (F013), repeated dose 4 injections (deltoid vs. gluteal) Duration: 176 days No. Subjects Evaluable for Safety: 49

7.2.1.2 Demographics

Across all phase 2/3 studies, the majority of subjects were male (54% to 68%) in different studies. The mean ages of subjects were around 40 (39.1 to 42.8 years across studies). Most of the population in these studies was the White (56% to 92%). Study PSY-3001, PSY-3003 and PSY-3004 included more Asian population (8% to 12%) because these studies included several Asian sites.

The baseline demographic characteristics of all phase 2/3 studies at baseline were similar and were roughly balanced across the treatment groups in each individual study.

7.2.1.3 Extent of exposure (dose/duration)

A total of 2,996 subjects with schizophrenia are included in the safety analyses of 6 controlled Phase 2/3 Studies. Of these, 2,282 subjects received at least one dose of paliperidone palmitate, 346 were randomized to placebo, and 368 received RISPERDAL CONSTA. Of the 2,282 subjects, two-thirds (1,536 subjects, 67%) were exposed to at least 12 weeks of treatment, 712 (31%) were exposed to at least 6 months (i.e., ≥ 28 weeks) of treatment and 288 (13%) were exposed to 1 year or more of treatment with paliperidone palmitate, for a total exposure to paliperidone palmitate of 971.17 subject-years. The median exposure to the study drug was 97.0 days (range, 2 to 639 days) for the total paliperidone palmitate group. A total of 1,128 subjects were treated with paliperidone palmitate using a flexible dosing regimen (PSY-3001 and PSY-3002), and subjects exposed to longer durations of treatment came mainly from these studies.

In the 10 Phase 1 studies, 736 subjects with schizophrenia or schizoaffective disorder were included in the safety analysis set. Of these, 730 subjects received 1 or more doses of paliperidone palmitate.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were conducted to evaluate the safety of paliperidone palmitate for this submission.

7.2.2.2 Postmarketing experience

At the time of the writing of this review, paliperidone palmitate was not marketed in any country.

7.2.2.3 Literature

A search of the worldwide literature on safety following the direct administration of paliperidone, or after exposure to 9-OH-risperidone following the administration of risperidone, and the correlation between exposure to paliperidone/9-OH-risperidone and safety from 01 August 2006 to 06 June 2007 was done. This search revealed 25 pertinent publications. A review of these publications indicated that published data are consistent with the safety results obtained during clinical trials carried out by J&JPRD during the development of paliperidone ER tablets, and support the conclusion that paliperidone ER was generally tolerated.

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate to evaluate the efficacy and safety of paliperidone palmitate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Elzbieta Chalecka-Franaszek, PhD is the pharmacology/toxicology reviewer for this submission. Please refer to her review for detailed animal and /or In Vitro testing information.

7.2.5 Adequacy of Routine Clinical Testing

Generally speaking, routine clinical testing in this submission was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

John Duan, PhD is the clinical pharmacology reviewer for this submission. Please refer to his review for detailed metabolic, clearance and interaction workup information.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Overall evaluation for potential adverse events for paliperidone palmitate was adequate. No further study is recommended at this time.

7.2.8 Adequacy Assessment of Quality and Completeness of Data

When the sponsor were in the process of closing the open label database for the Phase 3 study PSY-3001, they became aware of additional adverse event (AE) information relevant to the double-blind, transition, and maintenance phases of the study that were not submitted in the original double-blind clinical study report (CSR) and database in the NDA.

An external Contract Research Organization managed the data entry and data validation for this study. After the additional adverse event information was discovered, J&JPRD developed and conducted a Quality Control (QC) plan to assess the accuracy of data entry in the PSY-3001 database. The QC review has been completed. In the pre-defined QC plan, 8 critical domains: AE, DEMOG, DISPOSIT, RECURRENCE, RANDOM, PANSS, MEDKIT and EXPOSURE as well as all other domains were reviewed for accuracy. Based on the evaluation of a subset of 100 subjects, the error rate exceeded the preset thresholds of an error rate below 0.05% in the 8 critical domains, and below 0.5% in all other domains.

The sponsor stated that based on the QC assessments from this sample of subjects, there is no anticipated impact on the primary efficacy variable (time-to-recurrence) as the discrepancies observed in the RECUR (recurrence) database were mainly related to the reasons for recurrence (in 4 subjects). Furthermore, no new SAEs or deaths have been recorded in any phase up to and including the double-blind phase as compared with the data included in the original NDA filed on October 25, 2007. All expedited safety is reported through our global Benefit Risk Management division via a separate reporting process and database system called "SCEPTRE" and is independent of the affected study database.

Based on the QC assessments from this specific sample of 100 subjects, the sponsor concluded that there will be no impact on the conclusions from the primary efficacy analysis of time-to-recurrence and on the overall safety assessment (risk/benefit). The updated safety data from study PSY-3001 will not be available until December 2008.

7.2.9 Additional Submissions, Including Safety Update

The sponsor submitted a 4 Month Safety Update on February 25, 2008. This Safety Update focuses on safety results from the ongoing long-term open-label extension of the double-blind Phase 3 study PSY-3001 through the cutoff of 25 October 2007. In addition, blinded key safety listings (deaths, serious adverse events, and discontinuations due to adverse events) are presented for 2 ongoing double-blind Phase 3 studies R092670-PSY-3006 and R092670-PSY-3007, and for one ongoing Phase 1 study R092670-PSY-1008.

No deaths were reported as of the cutoff date of 25 October 2007 in the open-label extension of Study PSY-3001.

One death was reported in the ongoing double-blind Phase 3 Study R092670-PSY-3007. The subject's treatment assignment was unblinded by the Sponsor at the time of preparation of this Safety Update; the subject had been randomized to paliperidone palmitate 150 mg group. She died from stroke on Day 22 after receiving 2 injections on Day 1 and Day 8. An autopsy confirmed the cause of death to be extensive brain infarction. This case has been discussed in integrated safety review.

The types and rates of serious adverse events reported for subjects treated with paliperidone palmitate in study PSY-3001 are consistent with the safety profile of paliperidone ER and with the safety data reported in the Summary of Clinical Summary of NDA 22-264. No new or unexpected serious adverse events were reported, and there was no evidence of an increase in serious adverse events rates.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Other than injection site-related adverse events, the profile of drug-related adverse events in paliperidone palmitate is consistent with that of paliperidone ER. No important limitations of data were found.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Study PSY-3003 and PSY-3004 have almost identical study design. Therefore, the safety data from these two studies were pooled and analyzed as one data set. The safety data from other phase 2/3 studies were analyzed and reviewed individually.

7.4.1.2 Combining data

The safety data from study PSY-3003 and PSY-3004 were combined.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The placebo-controlled, fixed dose design of Phase 2/3 Studies PSY-3003 and PSY-3004 allow examination of dose relationships for paliperidone palmitate with respect to safety-related findings. Few dose-related trends were evident; those safety findings that appeared to be more common with the 100 mg eq. dose of paliperidone palmitate than with lower doses were:

- higher reporting rates for headache, agitation, injection site induration, injection site pain, and the EPS-related adverse event, hypertonia; these events were not generally serious or treatment-limiting,
- modest increases in body weight and BMI, and
- increases in serum prolactin concentrations that were not accompanied by a similar dose-related trend in reporting rates of potentially prolactin-related adverse events.

Data from Study PSY-3005, which included 3 fixed doses of paliperidone palmitate (50, 75 and 100 mg eq.) showed similar dose-related trends for adverse event of injection site pain and increases in serum prolactin concentrations (among females).

7.4.2.2 Explorations for time dependency for adverse findings

No explorations for time dependency for adverse findings were conducted in these studies.

7.4.2.3 Explorations for drug-demographic interactions

Although some gender-, race-, age- and geographic region-associated differences in adverse event rates were observed in some studies or analysis sets, the results did not suggest that administration of paliperidone palmitate at the doses used in the Phase 2/3 trials was associated with a clinically increased risk in any of the subgroups evaluated. No consistent clinically remarkable differences were observed among 3 BMI categories (normal, overweight, and obese) with regard to the overall pattern and incidences of adverse events. At the highest recommended dose of 100 mg eq., paliperidone palmitate was generally safe and well tolerated across all BMI categories.

7.4.2.4 Explorations for drug-disease interactions

No explorations for drug-disease interactions were conducted in these studies.

7.4.2.5 Explorations for drug-drug interactions

John Duan, PhD is the clinical pharmacology reviewer for this submission. Please refer to his review for detailed drug-drug interaction information.

7.4.3 Causality Determination

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below.

Attribution Definitions

Not related

An adverse event which is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen of all phase 2/3 studies is summarized in Table 24. Paliperidone palmitate was administered by intramuscular injection as 2 doses separated by 1 week (Days 1 and 8) followed by injections every 4 weeks.

Table 24 Summary of Paliperidone Palmitate Dose Regimen in the Phase 2/3 Studies

Study	Placebo	25 mg eq.	50 mg eq.	75 mg eq.	100 mg eq.	150 mg eq.
PSY-3003	x		x		x	x
PSY-3004	x	x	x		x	
SCH-201	x		x		x	
PSY-3001*	x	x.....x				
PSY-3005			x	x	x	
PSY-3002	Risperdal Consta**	x.....x				

*: The double-blind phase

**.: Risperdal Consta doses ranged from 25 mg to 50 mg every two weeks (flexible dosed) by intramuscular injection.

To achieve potential therapeutic blood concentrations more quickly, the sponsor proposed a dosing regimen with a dose of (b) (4) mg eq. administered in the deltoid muscle on treatment days 1 and 8, followed by a monthly (every 4 weeks) dose within the dose range of (b) (4) mg eq. to (b) (4) mg eq. based on individual factors. The monthly doses can be administered in either the deltoid or gluteal muscle.

The (b) (4) mg eq. injection in the gluteal muscle has been systematically evaluated in Phase 3 trials but the recommended initiation-dosing regimen as described above has not been studied in Phase 3 trials. Therefore, various simulations of PK profiles were performed by the sponsor to support the recommended initiation of treatment with (b) (4) mg eq. dose by deltoid injection.

Simulations of PK profiles by the sponsor demonstrated that the initial two deltoid injections of 100 mg eq. helped attain potential therapeutic concentrations rapidly with exposures that were similar to the maximum steady-state level achieved at one year with the 100 mg eq. gluteal injections. Furthermore, even if the injection site is not changed to the gluteal muscle after the second dose, the concentrations at steady-state from the deltoid injection will not be substantially higher than from gluteal injections. The median peak at steady-state for repeated gluteal and deltoid injections (administered on day 36 and beyond) were 31 and 34 ng/mL respectively. More information regarding this issue can be found in the clinical pharmacology review.

In the clinical pharmacological review, John Duan PhD. pointed out that the currently proposed initial dosing regimen may generate exposures comparable to that of 7.5 mg ER tablets QD dosing, which is 24%-34% higher than the recommended paliperidone ER dose of 6 mg QD, although it is lower than the maximum recommended oral dose of 12 mg QD. He recommended a starting dose of 75 mg eq. administered by deltoid injection on treatment days 1 and 8 instead of (b) (4) mg eq. which is proposed by the sponsor.

The efficacy and safety of treatment with 100 mg eq. dose of paliperidone palmitate has been demonstrated in double-blind, placebo-controlled, fixed-dose trials. In study PSY-3003, -3004, and SCH-201, the dose response for the incidence of treatment-emergent adverse events with paliperidone palmitate was relatively flat over the dose range of 25 to 100 mg eq. The rates of discontinuation due to adverse events as well as rates of serious adverse events were similar for 100 mg eq. to those seen for lower doses of 25 and 50 mg eq.

In summary, based on data provided by the sponsor, the starting doses of either 75 mg eq. recommended by the clinical pharmacological reviewer or (b) (4) mg eq. proposed by the sponsor administered by deltoid injection on treatment days 1 and 8, seem to be safe in adult schizophrenia population from the clinical point of view.

8.2 Drug-Drug Interactions

John Duan, PhD is the clinical pharmacology reviewer for this submission. Please refer to his review for detailed drug-drug interaction information.

8.3 Special Populations

Although some gender-, race-, age- and geographic region-associated differences in adverse event rates were observed in some studies or analysis sets, the results did not suggest that administration of paliperidone palmitate at the doses used in the Phase 2/3 trials was associated with a clinically increased risk in any of the subgroups evaluated.

8.4 Pediatrics

J&JPRD requested a full waiver of pediatric studies for the indications of acute and maintenance treatment of schizophrenia. Given the finding that childhood onset schizophrenia may present with symptoms quite different from those of adult onset schizophrenia, it would be important to systemically study the efficacy and safety of treatment within pediatric population. However, the very low incidence of schizophrenia diagnosis prior to the age 12 make it very unlikely that it would be possible to conduct a sufficiently large study of this age group within a reasonable time. Therefore, the sponsor's request to waive pediatric studies on children aged 12 or under for the indications of acute schizophrenia treatment is reasonable. A full waiver of pediatric study covering children age of 0 to 12 for the acute treatment indication is recommended. Adolescent studies for the acute treatment indication including a PK study, an efficacy and safety study, and a long-term safety study will be required if the adult indications are approved.

Schizophrenia is less common overall in children and adolescents than in adults. Compliance issues are less common in pediatric populations than in adult populations. Paliperidone palmitate is unlikely to be used in a substantial number of pediatric patients for the indication of relapse prevention. Therefore, a full waiver of pediatric studies covering age range from 0 to 17 year old for the indication of relapse prevention is recommended.

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacologic Drug Advisory Committee.

8.6 Literature Review

See section 7.2.2.3 Literature.

8.7 Postmarketing Risk Management Plan

Postmarketing Risk Management Plan has been submitted along with this NDA package and is under review by the Office of Safety Evaluation. Please refer to their review for details.

8.8 Other Relevant Materials

No other relevant materials were provided.

9 OVERALL ASSESSMENT

9.1 Conclusions

Paliperidone palmitate, injected intramuscularly at a dose of 100 mg eq., in study PSY-3003, and 25, 50 and 100 mg eq. in study PSY-3004 at 4-week (monthly) intervals following 2 initial doses given 1 week apart, was statistically significantly more effective than placebo in improving the PANSS total score at end point (LOCF) (primary efficacy end point) in these 13-week double-blind studies in subjects with schizophrenia.

In study SCH-201, paliperidone palmitate at doses of 50 and 100 mg eq. was more effective than placebo in reducing total PANSS scores in patients diagnosed with schizophrenia. The difference between each paliperidone palmitate treatment group and placebo was statistically significant without adjusting for multiplicity.

In study PSY-3001, there was a statistically significant difference between the treatment groups (flexible-dosed, ranged from 25 mg eq. to 100 mg eq.) in the time to recurrence of symptoms in favor of paliperidone palmitate. Subjects who continued treatment on paliperidone palmitate experienced recurrence later than subjects who switched to placebo.

The safety evaluation from 16 completed paliperidone palmitate clinical trials (5 phase 3, 1 phase 2 and 10 phase 1) demonstrated that the safety profile of paliperidone palmitate is similar to that of paliperidone ER for most parameters that were measured with the exception of injection site-related adverse events. No new or unexpected safety signals were identified.

9.2 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this New Drug Application (DNA) be granted approvable status.

Additional information will be requested from the applicant regarding errors in adverse events reporting in study PSY-3001. Moreover, additional data will be required for labeling changes, to which the sponsor needs to respond (see section 9.4 *Labeling Review* for recommended labeling changes). Final approval is contingent on satisfactory response to the agency's requests and mutual agreement on labeling as well as the conclusions of the CMC, Pharmacology/Toxicology, and clinical pharmacology reviewers.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no additional recommendations.

9.3.2 Required Phase 4 Commitments

No additional Phase 4 commitments are required.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

HIGHLIGHTS OF PRESCRIBING INFORMATION

Warnings and Precautions

The proposed labeling indicates AEs of **dysphagia, priapism, disruption of body temperature regulation, antiemetic effect, increased sensitivity in patients with Parkinson's disease or these with dementia with Lewy bodies, and diseases or conditions that could affect metabolism or hemodynamic response** have been removed from the list of warnings and precautions in section of the highlights of prescribing information. All these AEs were discussed in section 5. Warnings and Precautions in the main body of the labeling. It is found that the

changes mentioned above had been made in the current approved paliperidone ER labeling. The AE profile of paliperidone palmitate is similar to that of paliperidone ER. No new safety issue had been identified in this submission. Therefore, the changes mentioned above were considered as a resolved issue and the changes are acceptable.

2. Dosage and Administration

2.1 Recommended dosing

(b) (4)



6. Adverse Reactions

(b) (4)



9.5 Comments to Applicant

There are no comments to applicant at this time.

10 APPENDICES

10.1 List of Principle Investigators and Study Sites

ALPHABETICAL LIST OF INVESTIGATORS

Appended is a list of principal investigators supplied with the drug substance or drug product by the applicant or known to have investigated the drug and who participated in the key efficacy studies for paliperidone palmitate that pertain to this NDA. Investigators are listed alphabetically by investigator's last name and grouped by study.

Detailed in Table 1 are all of the clinical studies in which the listed investigators participated.

Table 1: List of Studies Included in Alphabetical List of Investigators

Study Identifier	Study Title
R092670-SCH-201 Mod.5.3.5.1\R092670-SCH-201	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate The Efficacy and Safety of 50 and 100 mg-eq of Paliperidone Palmitate in Subjects With Schizophrenia
R092670-PSY-3001 Mod.5.3.5.1\R092670-PSY-3001	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Subjects With Schizophrenia
R092670-PSY-3003 Mod.5.3.5.1\R092670-PSY-3003	A Randomized, Crossover Study to Evaluate the Overall Safety and Tolerability of Paliperidone Palmitate Injected in the Deltoid or Gluteus Muscle in Subjects With Schizophrenia
R092670-PSY-3004 Mod.5.3.5.1\R092670-PSY-3004	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq, 50 mg eq, and 100 mg eq) of Paliperidone Palmitate in Subjects With Schizophrenia

List of Investigators

Investigator(s)	Current Address	Study Identifier
Study R092670-PSY-3001		
Alexandrovsky, Yuri, M.D., Ph.D.	Serbsky National Research Center 47, Volokolamskoe shosse, Moscow 123367 Russia	R092670-PSY-3001
Badescu, Alexandra, M.D.	CMD.TA "Nicolae Kretzulescu" Str. Mihai Voda Nr.17 050042 Bucuresti Romania	R092670-PSY-3001
Beckett, Louise, M.D. (new name is Louise Thurman, M.D.)	IPS Research 1111 North Lee Suite 400 Oklahoma City, OK 73103 U.S.A.	R092670-PSY-3001
Belz, Irving, M.D. (retired) Sneed, Jonathan, D.O.	Tri-Country Mental Health Mental Retardation Services 1020 Riverwood Court, Building 5 Conroe, TX 77304 U.S.A.	R092670-PSY-3001
Bitensky, Valeryy, M.D., Ph.D.	Odessa Satte Medical University, Department of Psychiatry Odessa Regional Clinical Mental Hospital Str. Ac. Vorobjeva 9 Odessa, 65006 Ukraine	R092670-PSY-3001
Braunon, Guy, M.D.	Brentwood Research Institute 1002 Highland Ave Suite 400 Shreveport, LA 71101 U.S.A.	R092670-PSY-3001
Brar, Saroj, M.D.	Inc. 2012-W-25 Suite 405 Cleveland, OH 44113 U.S.A.	R092670-PSY-3001
Brenner, Ronald, M.D.	Neurobehavioral Research, Inc. 371 Central Avenue Lawrence, NY 11559 U.S.A.	R092670-PSY-3001

List of Investigators

Investigator(s)	Current Address	Study Identifier
Brown, David, M.D.	Community Clinical Research, Inc. 8334 Cross Park Drive Austin, TX 78754 U.S.A.	R092670-PSY-3001
	Community Clinical Research, Inc. 12151 Hunters Chase Austin, TX 72729 U.S.A.	
Chaganti, Surendra, M.D.	MedClin Research, Inc. 2639 Miami St. Suite S-20 St. Louis, MO 63118 U.S.A.	R092670-PSY-3001
Chan, Hung-Yu M.D.	Taoyuan Psychiatric Center 71 Long-Shou Street, Taoyuan city 330 Taiwan	R092670-PSY-3001
Chirita Vasile, , M.D., Ph.D.	Spitalul Universitar de Psihiatrie "Socola" Sos Bucium Nr. 36 700282 Iasi, Jud. Iasi Romania	R092670-PSY-3001
Chiu, Nan-Ying M.D.	Department of Psychiatry, Chunghua Christian Hospital 135 Nanshao Street, Changhua city 500, Taiwan	R092670-PSY-3001
Demchenko, Vladislav, M.D., Ph.D.	Kiev City Psycho- Neurological Hospital #2 8 Miropolskaya Str. Kiev, 02660, Ukraine	R092670-PSY-3001
DeSilva, Himasiri, M.D.	Clinical Innovations 801 N. Tustin Avenue Suite 600 Santa Ana, CA 92705 U.S.A.	R092670-PSY-3001
Gabos-Grecu, Iosif, M.D.	Spitalul Clinic Judetean de Urgenta Targu Mures Clinica Psihiatrie 1 Str. Gh.Marinescu Nr. 38 540139 Tg. Mures Romania	R092670-PSY-3001

Clinical Review
 Jing Zhang, MD., PhD.
 Original NDA 22,264
 Paliperidone palmitate long-lasting injection

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10.2 Appendix to Integrated Review of Efficacy

Recurrence criteria for study PSY-3001

Recurrence was defined by sponsor as any one of the following:

- Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or
- For the PANSS total score:
 - 1) Increase of 25% in the PANSS total score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was >40, or
 - 2) A 10-point increase in the PANSS total score from randomization for 2 consecutive assessments separated by 3 to 7 days if the score at randomization was ≤40, or
- Deliberate self-injury and/or violent behavior resulting in suicide or in clinically significant injury to the subject or another person or property damage, or
- Suicidal or homicidal ideation and aggressive behavior that was clinically significant (in frequency and severity) in the investigator's judgment, or

- For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility) or G8 (uncooperativeness):
 - 1) A score ≥ 5 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above PANSS items if the maximum score for the above PANSS items was ≤ 3 at randomization, or
 - 2) A score ≥ 6 after randomization for 2 consecutive assessments separated by 3 to 7 days on any of the above PANSS items if the maximum score for the above PANSS items was 4 at randomization.

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this page is the manifestation of the electronic signature.**

/s/

Jing Zhang
7/7/2008 11:55:30 AM
MEDICAL OFFICER

Gwen Zornberg
7/7/2008 02:12:12 PM
MEDICAL OFFICER

Based on Dr. Zhang's review of the safety and efficacy data, I concur in recommending to the Division Director that an approvable action be issued. We recommend a deferral on schizophrenia studies in adolescents (ages 13-17 years) & a waiver in children.