CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-264

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	22-264 (N000)
Drug Name:	Invega SustennaTM (paliperidone palmitate) (b) (4)
Indication:	Schizophrenia
Applicant:	Johnson & Johnson
Dates:	Date of Document: 2/03/2009
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Review Priority:	Standard
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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The statistical reviewer agreed that Study 3007 was a positive study, where all three doses (25, 100 and 150 mg eq.) showed statistically significant effects in comparison with placebo on the primary endpoint, PANSS total scores. However, the efficacy findings on the PSP scores have not been replicated; thus this reviewer suggests that these findings not be included in the label. In addition, although 150 mg eq. performed numerically better than 100 mg eq., the numerical advantage was small and statistically indistinguishable (p=0.59); thus, it remains unclear whether 150 mg eq. would have an additional beneficial effect.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In response to the complete response letter for the original NDA application for paliperidone palmitate as a treatment of schizophrenia in adult patients, the sponsor included an additional efficacy study (Study 3007), which was designed to confirm the efficacy and safety of the paliperidone palmitate 25 and 100 mg eq. doses previously observed in the Phase 3 studies R092670-PSY-3003 (100 mg eq. dose) and R092670-PSY-3004 (25 and 100 mg eq. doses), to explore the efficacy and safety of a higher dose (paliperidone palmitate 150 mg eq.) and to examine a new dosing regimen used to increase the initial exposure to paliperidone (initial dose of 150 mg eq. in the deltoid muscle followed by either deltoid or gluteal injections at the target dose).

Study 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. Study medication was administered as 4 doses: an intial 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. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during the double-blind period. The primary endpoint is the change in the PANSS total score (sum of the scores of all 30 PANSS items) from the start of the double-blind treatment period (baseline) to the end of the double-blind treatment period (Day 92 or last post baseline assessment). Secondary endpoints included the changes from baseline to the end of the double-blind treatment period (Day 92 or last post baseline assessment) in the PSP and the CGI-S scores, where PSP was designated as a key secondary endpoint.

Based on statistically significant results shown on all three doses in comparison with placebo for the primary endpoint and on two higher doses for the key secondary endpoint, PSP scores, the sponsor concluded that 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 statistically significantly

more effective than placebo in improving the PANSS total score at end point in the 13-week double-blind study in subjects with schizophrenia. The sponsor even claimed that there was a dose response with respect to efficacy for the primary endpoint, with mean change in the PANSS total score at end point showing incrementally greater improvement across the 3 doses of paliperidone palmitate.

1.3 STATISTICAL ISSUES AND FINDINGS

The statistical reviewer basically 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. (b) (4)

Regarding the sponsor's dose response claim, although paliperidone palmitate 150 mg eq. seemed to perform numerically better than 100 mg eq. the observed difference between them appeared very small. With a p-value 0.59 for the comparison between these two treatment arms, it is not clear whether paliperidone palmitate 150 mg eq. would contribute any additional benefit.

2. INTRODUCTION

2.1 OVERVIEW

Paliperidone palmitate is the palmitate ester of paliperidone. The original new drug application for paliperidone palmitate (b) (4) was submitted by the sponsor on October 25 of 2007 for the treatment of schizophrenia in adults. In that submission, 4 phase 2/3 studies for subjects with acute psychosis were evaluated. It was determined that the efficacy of paliperidone palmitate (25 and 100 mg eq.) in treating patients with schizophrenia was demonstrated. However, due to some issues regarding the product quality, the NDA application was not approved.

To promote the use of higher initiation doses of paliperidone palmitate in a new dosing regimen and also explore the efficacy and safety of a higher dose (paloperidone palmitate 150 mg eq.), the sponsor conducted and included an additional efficacy study (Study 3007) along with this NDA re-submission. The sponsor also included their exploration for the effects of BMI on pharmacokinetics, clinical efficacy and clinical safety in this submission. They concluded that no consistent clinically remarkable difference was observed among the 3 BMI categories (normal, overweight, and obese) with regard to the overall pattern and incidences of treatment-emergent adverse events. They further concluded that at the highest recommended dose of 150 mg eq. paliperidone palmitate was generally safe and well tolerated across all BMI categories, supporting the safety and tolerability of the recommended dosing regimen.

2.2 DATA SOURCES

The sponsor's submission including study clinical report and study data is stored in the CDER electronic document room (EDR) with the following link: \\CDSESUB1\EVSPROD\NDA022264\0026.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Description of Protocol R092670-PSY-3007

This study was titled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects with Schizophrenia". There were 72 centers in 8 countries participated in this study. The 8 countries participating in the study included the United States (33 centers), Russia (11 centers), Romania (8 centers), the Ukraine (5 centers), Taiwan (5 centers), the Republic of Korea (4 centers), Malaysia (4 centers), and Serbia (2 centers).

3.1.1.1 Study Objectives

The primary objectives of this study were to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate (25, 100, and 150 mg eq.) administered i.m. after an initial dose of 150 mg eq. in the deltoid muscle followed by either deltoid or gluteal injections for a total of 13 weeks of treatment as compared with placebo in subjects with schizophrenia.

The secondary objectives were to:

- Assess the benefits in personal and social functioning (key secondary endpoint) associated with the use of paliperidone palmitate compared with placebo;
- Assess the global improvement in severity of illness associated with the use of paliperidone palmitate compared with placebo;
- Assess the dose-response and exposure-response relationships of paliperidone palmitate.

3.1.1.2 Study Design

Study R092670-PSY-3007 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response study designed to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate (25, 100, and 150 mg eq.) compared with placebo. Study medication was administered as 4 doses: an initial i.m. injection of placebo or paliperidone palmitate 150 mg eq. followed by 3 fixed i.m. doses of placebo or paliperidone palmitate [25, 100, or 150 mg eq.] on Days 8, 36, and 64. The initial dose of study medication was given in the deltoid muscle. Subsequent injections were given

either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during the double-blind period.

The study included a screening period of up to 7 days and a 13-week double-blind treatment period. The screening period included a washout of disallowed psychotropic medications. The entire study, including the screening period, lasted approximately 14 weeks.

It was planned that approximately 644 subjects (161 in each of 4 treatment groups) aged 18 years or older, with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of schizophrenia for at least one year before screening and severely symptomatic (Positive and Negative Syndrome Scale [PANSS] total score between 70 and 120, inclusive, at screening) would participate in the double-blind period of this study.

At the beginning of the double-blind treatment period, eligible subjects were randomly assigned in equal numbers to 1 of 4 treatment groups: paliperidone palmitate 25, 100, or 150 mg eq. or placebo. All subjects randomly assigned to active (paliperidone palmitate) treatment were given an injection of paliperidone palmitate 150 mg eq. in the deltoid muscle followed by 1 of 3 fixed doses of paliperidone palmitate (25, 100 or 150 mg eq.) on Days 8, 36, and 64. Subjects assigned to placebo received an injection of placebo in the deltoid muscle on Day 1, followed by injections of placebo on Days 8, 36, and 64 in either the deltoid or gluteal muscle. The choice of the injection site, deltoid or gluteal, for i.m. injections of study medication administered after Day 1 was at the discretion of the investigator.

Subjects were considered to have completed the study if they completed all assessments on Day 92 (Visit 12) of the double-blind period. The 13-week duration of the double-blind treatment period was intended to evaluate the efficacy and safety of paliperidone palmitate at approximate steady-state levels using the new initial 150 mg eq. dose regimen.

3.1.1.3 Efficacy Endpoints and Analyses

Efficacy assessments included PANSS, CGI-S, the Personal and Social Performance (PSP) scale, and the Sleep Visual Analog Scale (VAS).

The primary efficacy endpoint is the change in the PANSS total score (sum of the scores of all 30 PANSS items) from the start of the double-blind treatment period (baseline) to the end of the double-blind treatment period (Day 92 or last post baseline assessment).

Secondary endpoints included the changes from baseline to the end of the double-blind treatment period (Day 92 or last post baseline assessment) in the PSP and the CGI-S scores, where the PSP score at endpoint (LOCF) was designated as a key secondary variable.

Other endpoints included change in the Sleep VAS scores, onset of therapeutic effect, responder rate, changes from baseline to the end of the double-blind treatment period in the PANSS subscales and shifts in PSP.

For the change in PANSS total score at end point (LOCF), the least-squares (LS) means were estimated and compared between each active treatment group and placebo using an analysis of covariance (ANCOVA) model with treatment and country as factors, and baseline PANSS total score as a covariate. Dunnett's test was applied to adjust for multiple testing of the 3 doses versus placebo.

At end point, the interaction terms between treatment and country and between treatment and baseline PANSS total score were added to the primary ANCOVA model one at a time. If an interaction was observed to be statistically significant at the pre-specified 2-sided 0.10 significance level, then further evaluations were to be performed to assess and explain the nature of the interaction. Significant interactions were also to be examined using a 2-sided Gail-Simon test, with a 0.10 significance level. This is a likelihood ratio test for testing the presence of qualitative interaction (treatment effect is not consistent across subgroups).

For each time point (both LOCF and observed case), descriptive statistics were produced on the PANSS total score and change from baseline. In addition, to explore the course of treatment effect over time, ANCOVA models on both LOCF and observed case data were performed for each time point using the same factors as mentioned above for the primary efficacy analysis.

The analysis of the key secondary efficacy endpoint, the change in PSP score at end point (LOCF), was conducted by means of an ANCOVA model with treatment and country as factors, and the baseline PSP score as a covariate. The Dunnett-Bonferroni-based parallel gatekeeping approach (Xu et al. submitted) was used to adjust for multiple testing.

3.1.2 Efficacy Results for Study R092670-PSY-3007

3.1.2.1 Patient Population and Baseline Demographic Characteristics

Table 3.1 shows number of patients randomized in each treatment group for different study populations and patient disposition. Table 3.2 shows the demographic and baseline characteristics for the intent-to-treat analysis set. As shown in the table, the baseline characteristics and baseline PANSS total score appear similar among the treatment groups.

Table 3.1 Number of Subjects Randomly Assigned to Each Treatment Group

Reported are n (%)	Placebo (N=164)	R092670 25 mg eq. (N=160)	R092670 100 mg eq. (N=160)	R092670 150 mg eq. (N=160)	Total (N=652)
All Randomized	164 (100)	160 (100)	165 (100)	163 (100)	652 (100)
Safety	164 (100)	160 (100)	165 (100)	163 (100)	652 (100)
Intent-to-Treat	160 (98)	155 (97)	161 (98)	160 (98)	636 (98)
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 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)

Source: Sponsor's Tables 4 and 5 in CSR

Table 3.2 Demographic and Baseline Characteristics for ITT Analysis Set

	Placebo (N=160)	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)
Age (years) , Mean (SD)	39.9 (10.98)	39.5 (10.31)	38.8 (10.37)	39.4 (10.59)
Sex, n (%)				
Male	106 (66)	111 (72)	107 (66)	103 (64)
Female	54 (34)	44 (28)	54 (34)	57 (36)
Race, n (%)				
White	87 (54)	86 (55)	86 (53)	84 (53)
Black	49 (31)	42 (27)	51 (32)	50 (31)
Asian	24 (15)	24 (15)	22 (14)	22 (14)
American Indian or Alaskan native	0	2 (1)	0	2 (1)
Other	0	2 (1)	2 (1)	2 (1)
Weight (kg), Mean (SD)	78.2 (17.19)	80.8 (20.39)	77.2 (18.32)	78.2 (16.78)
Height (cm), Mean (SD)	170.5 (9.43)	173.1 (9.59)	170.7 (9.79)	171.2 (9.16)
Baseline PANSS Total, Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)

Source: Sponsor's Tables 6 and 7 in CSR

3.1.2.2 Sponsor's Results for Primary Efficacy Endpoint

Table 3.2 shows the sponsor's analysis results for PANSS Total score. Based on the intent-to-treat LOCF analysis of the primary efficacy variable using Dunnett's test to control for multiplicity, the improvement in all 3 paliperidone palmitate treatment groups reached statistical significance when compared with the placebo group.

Table 3.2 Analysis Results for PANSS Total Score on LOCF Data

Total 30 item Positive and Negative Syndrome Scale	Placebo (N=160)	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)
Change from Baseline				
N	160	155	161	160
Mean (SD)	-2.9 (19.26)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
Diff. of LS Means (SE)		-5.1 (2.01)	-8.7 (2.00)	-9.8 (2.00)
P-Value (Unadjusted)		0.0124	<0.0001	<0.0001
P-Value (Dunnett's Adjusted)		0.0335	<0.0001	<0.0001
95% C.I. (Unadjusted)		(-9.01,-1.10)	(-12.62, -4.78)	(-13.71, -5.85)

Source: Sponsor's Table 17. Note: the sponsor did not report unadjusted p-values.

The sponsor also performed some exploratory analyses for assessing palperidone palmitate dose response. Their results of the ANCOVA comparing mean change from baseline to endpoint in PANSS total score between the paliperidone palmitate groups are presented in Table 3.3. The sponsor claimed that there was a dose-response pattern with respect to the primary efficacy variable, with the mean decreases (improvement) in the PANSS total score at endpoint based on LOCF data.

Table 3.3 Sponsor's Pair-Wise Comparison Results for PANSS Total Score

Total 30 item Positive and Negative Syndrome Scale	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)
Change from Baseline			
Mean (SD)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
Unadjusted P-value (minus R092670 25 mg eq.)		0.071	0.019
Diff. of LS Means (SE)		-3.6 (2.01)	-4.7 (2.02)
95% CI		(-7.60; 0.31)	(-8.69; -0.77)
Unadjusted P-value (minus R092670 100 mg eq.)			0.588
Diff. of LS Means (SE)			-1.1 (2.00)
95% CI			(-5.01; 2.85)

Source: Sponsor's Table 18.

Note that for the primary endpoint, the sponsor also performed some sensitivity analyses including the worst rank analysis and two additional analyses based on longitudinal mixed effects model. All analysis results showed that three doses of paliperidone palmitate were all statistically significantly superior to placebo in improving the PANSS total scores.

3.1.2.3 Sponsor's Results for Secondary Efficacy Endpoints

Key Secondary Endpoint: Change in PSP Scores

Table 3.4 shows the sponsor's analysis results for change from baseline to end point in the PSP score. The sponsor stated in the clinical study report that 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 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 3.4 Sponsor's Analysis Results for PSP Scores on LOCF Data

Personal and Social Performance	Placebo (N=160)	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)
Change from Baseline				
N	157	153	156	157
Mean (SD)	1.7 (15.60)	2.9 (15.29)	6.1 (13.59)	8.3 (14.69)
Diff. of LS Means (SE)		1.0 (1.50)	4.4 (1.50)	6.2 (1.49)
P-Value (Unadjusted)		0.509	0.0036	<0.0001
P-Value[a] (D-B adjusted)		0.509	0.007	<0.001
95% C.I. (Unadjusted)		(-1.96, 3.95)	(1.43, 7.31)	(3.26, 9.12)

Source: Sponsor's Table 19 in CSR

[a] P-values were adjusted for multiplicity between PANSS Total Score and PSP, as well as different dose levels in comparison with placebo, using the Dunnett-Bonferroni-based parallel gate-keeping method.

Secondary Efficacy Endpoint: Change in CGI-S Scores

Table 3.5 shows the sponsor's analysis results for the change from baseline to end point in CGI-S scores. Note that the sponsor analyzed the CGI-S scores based on the ranked data. As shown in the table, they concluded that the improvement in the paliperidone palmitate 100 and 150 mg eq. groups reached statistical significance when compared with the placebo group at nominal significance level of 0.05. The paliperidone palmitate 25 mg eq. group was not statistically significantly superior to placebo. No multiplicity adjustment was applied for this analysis.

Table 3.5 Sponsor's Analysis Results for CGI-S Scores on LOCF Data

Clinical Global Impression-Severity Scale (CGI-S)	Placebo (N=160)	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)
Change from Baseline				
N	160	154	161	160
Median (Range)	0.0 (-3;2)	-1.0 (-3;2)	-1.0 (-4;2)	-1.0 (-4;3)
P-Value (minus Placebo)[a]		0.140	0.005	<0.0001

Source: Sponsor's Table 20 in CSR

[a] Based on analysis of covariance (ANCOVA) model on ranks with treatment (Placebo, R092670 25 mg eq., R092670 100 mg eq., R092670 150 mg eq.) and country as factors, and baseline value as a covariate.

3.1.2.4 Statistical Reviewer's Findings and Comments

1. The statistical reviewer confirmed the sponsor's analysis results for the primary endpoint and also two secondary endpoints. It was agreed that in comparison with placebo all three doses showed statistical significance on the primary endpoint and also the two higher doses showed statistically significant findings on the pre-specified key secondary endpoint. [redacted] (b) (4)

2. Although the sponsor claimed that Study 3007 showed a dose-response pattern, this reviewer would like to point out that the observed difference between R092670 100 mg eq. and 150 mg eq. is small. It is not clear whether 150 mg eq. had any additional beneficial effect in comparison with 100 mg eq.

3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review. Please refer the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

Tables 3.5 to 3.7 show this reviewer's exploratory subgroup analysis by gender, race and age. As observed from the tables for these basic demographic factors, none of subgroups had any dose which performed worse than placebo.

Table 3.5 FDA Results of Subgroup Analysis by Gender for PANSS Total Scores

Change from Baseline to Endpoint in PANSS Total Score	Placebo	R092670 25 mg eq.	R092670 100 mg eq.	R092670 150 mg eq.
Male, N	106	111	107	103
LS Mean Change (SE)	-6.63 (2.15)	-10.39 (2.03)	-14.61 (2.17)	-18.19 (2.12)
Unadjusted P-Value (vs. Placebo)		0.12	0.0010	<0.0001
Female, N	54	44	54	57
LS Mean Change (SE)	-5.51 (2.85)	-13.49 (3.17)	-14.56 (2.76)	-12.89 (2.91)
Unadjusted P-Value (vs. Placebo)		0.035	0.011	0.037

Table 3.6 FDA Results of Subgroup Analysis by Race for PANSS Total Scores

Change from Baseline to Endpoint in PANSS Total Score	Placebo	R092670 25 mg eq.	R092670 100 mg eq.	R092670 150 mg eq.
White, N	87	86	86	84
LS Mean Change (SE)	-9.00 (2.22)	-17.69 (2.22)	-17.93 (2.19)	-19.92 (2.25)
Unadjusted P-Value (vs. Placebo)		0.0014	0.001	<0.0001
Black, N	49	42	51	50
LS Mean Change (SE)	-5.39 (2.17)	-6.89 (2.33)	-11.88 (2.13)	-11.15 (2.14)
Unadjusted P-Value (vs. Placebo)		0.64	0.04	0.06
Asian, N	24	24	22	22
LS Mean Change (SE)	-1.41 (6.91)	-1.27 (7.67)	-14.84 (7.88)	-13.62 (7.96)
Unadjusted P-Value (vs. Placebo)		0.98	0.06	0.09
Other, N	.	3	2	4
LS Mean Change (SE)	.	-3.76 (9.26)	3.03 (12.14)	-24.94 (8.27)
Unadjusted P-Value (vs. Placebo)	.	.	.	.

Table 3.7 FDA Results of Subgroup Analysis by Age for PANSS Total Scores

Change from Baseline to Endpoint in PANSS Total Score	Placebo	R092670 25 mg eq.	R092670 100 mg eq.	R092670 150 mg eq.
Age <40, N	76	79	81	81
LS Mean Change (SE)	-4.26 (2.64)	-11.56 (2.45)	-16.40 (2.41)	-17.39 (2.60)
Unadjusted P-Value (vs. Placebo)		0.014	<0.0001	<0.0001
Age≥40, N	84	76	80	79
LS Mean Change (SE)	-7.35 (2.37)	-10.79 (2.54)	-12.90 (2.54)	-14.12 (2.44)
Unadjusted P-Value (vs. Placebo)		0.22	0.05	0.02

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Tables 3.8 and 3.9 show this reviewer's exploratory subgroup analysis results by the regional and weight factor. For the regional subgroup analyses, except 25 mg eq. of R092670 in Asia subgroup, all others showed that all doses performed numerically better than placebo. The observed drug effects from the North America seem to be smaller than those observed from the Eastern Europe. For the weight subgroup analyses, it is interesting to observe that in general the drug has stronger effect in patients with normal weight than those who are overweight or obese in comparison with placebo. Nevertheless, one should also note that the placebo responses among these three weight groups do not seem to be comparable.

Table 3.8 FDA Results of Subgroup Analysis by Region for PANSS Total Scores

Change from Baseline to Endpoint in PANSS Total Score	Placebo	R092670 25 mg eq.	R092670 100 mg eq.	R092670 150 mg eq.
North America, N	80	73	79	82
LS Mean Change (SE)	-5.32 (1.73)	-7.86 (1.80)	-8.94 (1.75)	-11.96 (1.71)
Unadjusted P-Value (vs. Placebo)		0.31	0.14	0.01
Eastern Europe, N	57	58	60	56
LS Mean Change (SE)	-8.80 (2.84)	-19.63 (2.83)	-22.61 (2.76)	-21.89 (2.87)
Unadjusted P-Value (vs. Placebo)		0.002	<0.0001	0.0002
Asia, N	23	24	22	22
LS Mean Change (SE)	2.43 (4.93)	2.56 (4.80)	-11.01 (5.05)	-9.79 (5.08)
Unadjusted P-Value (vs. Placebo)		0.98	0.06	0.09

Table 3.9 FDA Results of Subgroup Analysis by Weight for PANSS Total Scores

Change from Baseline to Endpoint in PANSS Total Score	Placebo	R092670 25 mg eq.	R092670 100 mg eq.	R092670 150 mg eq.
Normal (BMI<25), N	61	73	75	69
LS Mean Change (SE)	-3.75 (3.05)	-12.38 (2.83)	-15.07 (2.79)	-16.16 (2.93)
Unadjusted P-Value (vs. Placebo)		0.0101	0.0007	0.0003
Overweight (25≤BMI<30), N	59	40	53	53
LS Mean Change (SE)	-7.78 (2.78)	-8.05 (2.96)	-17.19 (2.83)	-21.14 (2.99)
Unadjusted P-Value (vs. Placebo)		0.9382	0.0037	<0.0001
Obese (BMI≥30), N	40	42	33	38
LS Mean Change (SE)	-5.63 (4.22)	-9.38 (4.03)	-10.51 (4.56)	-6.79 (4.16)
Unadjusted P-Value (vs. Placebo)		0.30	0.21	0.76

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The statistical reviewer basically 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. (b) (4) [redacted] (b) (4) paliperidone palmitate 150 mg eq. seemed to perform numerically better than 100 mg eq. the observed difference between them appeared very small. With a p-value 0.59 for the comparison between these two treatment arms, it is not clear whether paliperidone palmitate 150 mg eq. would contribute any additional benefit.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The statistical reviewer agreed that Study 3007 was a positive study, where all three doses (25, 100 and 150 mg eq.) showed statistically significant effects in comparison with placebo on the primary endpoint, PANSS total scores. (b) (4) [redacted] In addition, although 150 mg eq. performed numerically better than 100 mg eq., the numerical advantage was small and statistically indistinguishable (p=0.59); thus, it remains unclear whether 150 mg eq. would have an additional beneficial effect.

_____
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

Statistical Review and Evaluation
CLINICAL STUDIES

NDA/Serial Number:	NDA 22-264
Drug Name:	Paliperidone palmitate
Indication(s):	Treatment of schizophrenia and for the prevention of recurrence of symptoms of schizophrenia
Applicant:	Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
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Keywords: *Clinical studies, NDA review, endpoint analysis/LOCF, multi-center, drop-outs, treat.-by-center interaction*

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1. EXECUTIVE SUMMARY

In this submission, the sponsor has claimed for an approval of paliperidone palmitate (b) (4) to treat patients with schizophrenia and prevention of recurrence of symptoms of schizophrenia based on the efficacy findings of three phase III studies R092670-PSY-3003, R092670-PSY-3004, R092670-PSY-3001 and one phase II study SCH-201.

1.1. **Conclusions and Recommendations**

The efficacy findings of three short-term studies (PSY-3003, PSY-3004, and SCH-201) demonstrated that paliperidone palmitate 100 mg eq. was an effective dose for treating patients with schizophrenia. Paliperidone palmitate 25 mg eq. and 50 mg eq. in Study PSY-3004 and paliperidone palmitate 50 mg eq in Study SCH-201 were also effective doses for treating patients with schizophrenia. In Study PSY-3003, paliperidone palmitate 50 mg eq. and 150 mg eq. were not significantly efficacious as compared to placebo. As a result of a mismatch in the allocation of medication kits, only 30 subjects received paliperidone palmitate 150 mg eq in Study PSY-3003.

The efficacy findings of Study PSY-3001 established the effectiveness of monthly i.m. injections of paliperidone palmitate in preventing recurrence of symptoms of schizophrenia among adult subjects who had achieved satisfactory symptom control after an acute episode with doses in the flexible range of 25 to 100 mg eq. In accordance with protocol-specified criteria, the study PSY-3001 was stopped early for efficacy based on an interim analysis result. The rate of symptom recurrence was significantly lower, and the time to a recurrence event was significantly longer among the subjects continued on paliperidone palmitate compared with those switched to placebo.

1.2. Brief Overview of Reviewed Clinical Studies

1.2.1. Phase III Studies for Treatment of Schizophrenia

The studies PSY-3003 and PSY-3004 were Phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy of 3 fixed doses of paliperidone palmitate (50, 100, and 150 mg eq. in Study PSY-3003; and 25, 50, and 100 mg eq. in Study PSY-3004) compared to placebo. Study medication was administered as 4 doses: 2 doses separated by 1 week (Days 1 and 8) followed by 2 doses at 4-week (monthly) intervals (Days 36 and 64). Subjects randomly assigned to the study drug were to remain in the study for 28 days after the last injection on Day 64, with the end-of-study visit scheduled for Day 92 during the double-blind period.

Primary efficacy measure was the change in PANSS total score at the study endpoint, and it was analyzed using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline PANSS total score as a continuous covariate. The least squares (LS) adjusted means were estimated and compared for each treatment group versus placebo. The last

observation carried forward (LOCF) approach was used to impute missing data at the study endpoint.

1.2.2. Phase III Studies for Treatment of Schizophrenia

1.2.3. Prevention of Recurrence of Symptoms of Schizophrenia

A double-blind, placebo-controlled study (PSY-3001) was designed to address a question of recurrence prevention of long-acting injectable paliperidone palmitate versus injectable placebo. The study had a 33-week of open-label treatment (period of stabilization), and then a double-blind treatment period.

During open-label treatment, flexibly dosed paliperidone palmitate was given as an intramuscular injection into the gluteal muscle starting with 2 single doses of 50 mg eq. given 1-week apart followed by 1 injection monthly of 25, 50, or 100 mg eq., based on clinical needs. Dose was fixed during last 12 weeks of maintenance and the double-blind recurrence prevention. During the double-bind Phase, fixed doses of paliperidone palmitate (25, 50, or 100 mg eq.) or placebo administered monthly as a gluteal injection for variable duration.

The primary efficacy measure was the time to first recurrence of symptoms of schizophrenia during the double-blind recurrence prevention phase.

1.3. Statistical Issues and Findings

The LOCF ANCOVA and sensitivity analyses (available cases analyses at each visit, and MMRM analysis) demonstrated the efficacy of paliperidone palmitate (b) (4) to treat patients with schizophrenia and prevention of recurrence of symptoms of schizophrenia. However, there were more than 50% dropouts at each study. Although it is well known that dropout rates in psychiatric trials are relatively higher as compared to dropout rates in other therapeutic trials, a general question might be what percentage of dropouts is acceptable for a valid statistical inference on the efficacy of a study drug in psychiatric trials. For future NDA reviews of psychiatric drugs, it is important to have a consensus between the agency and industries on an acceptable percentage of dropouts regardless of using advanced statistical method in dealing with missing data.

2. INTRODUCTION

2.1. Overview

The sponsor has submitted this New Drug Application (NDA#022264) for an approval of paliperidone palmitate (b) (4) to treat the patients with schizophrenia and the prevention of recurrence of symptoms of schizophrenia. The submission contains data from double-blind, placebo-controlled studies (R092670-PSY-3003, R092670-PSY-3004, and R092670-SCH-201) designed to examine the efficacy of paliperidone palmitate in treating patients with schizophrenia. The submission also contains data from a double-blind, placebo-controlled study (R092670-PSY-3001) designed to examine the prevention of recurrence of symptoms of schizophrenia. Throughout this review, these studies are referred to as PSY-300x or SCH-201.

The studies PSY-3003 and PSY-3004 were Phase III, 13-week, double-blind, placebo-controlled studies, and designed to evaluate the efficacy of paliperidone palmitate 25, 50, 100, and 150 mg eq. doses. The study SCH-201 was a Phase II, 9-week, double-blind, placebo-controlled study, and designed to evaluate the efficacy of paliperidone palmitate 50 mg eq. and 100 mg eq. doses. The study PSY-3001 was a phase 3, double-blind, placebo-controlled, and designed to demonstrate recurrence prevention of long-acting injectable paliperidone palmitate. In this review, the efficacy findings of the four studies (PSY-3003, PSY-3004, SCH-201, and PSY-3001) will be reviewed. The short-term efficacy findings of the three studies (PSY-3003, PSY-3004, and SCH-201) will be reviewed first, and then the efficacy findings of the maintenance study (PSY-3001) will be reviewed.

Studies PSY-3003 and PSY-3004

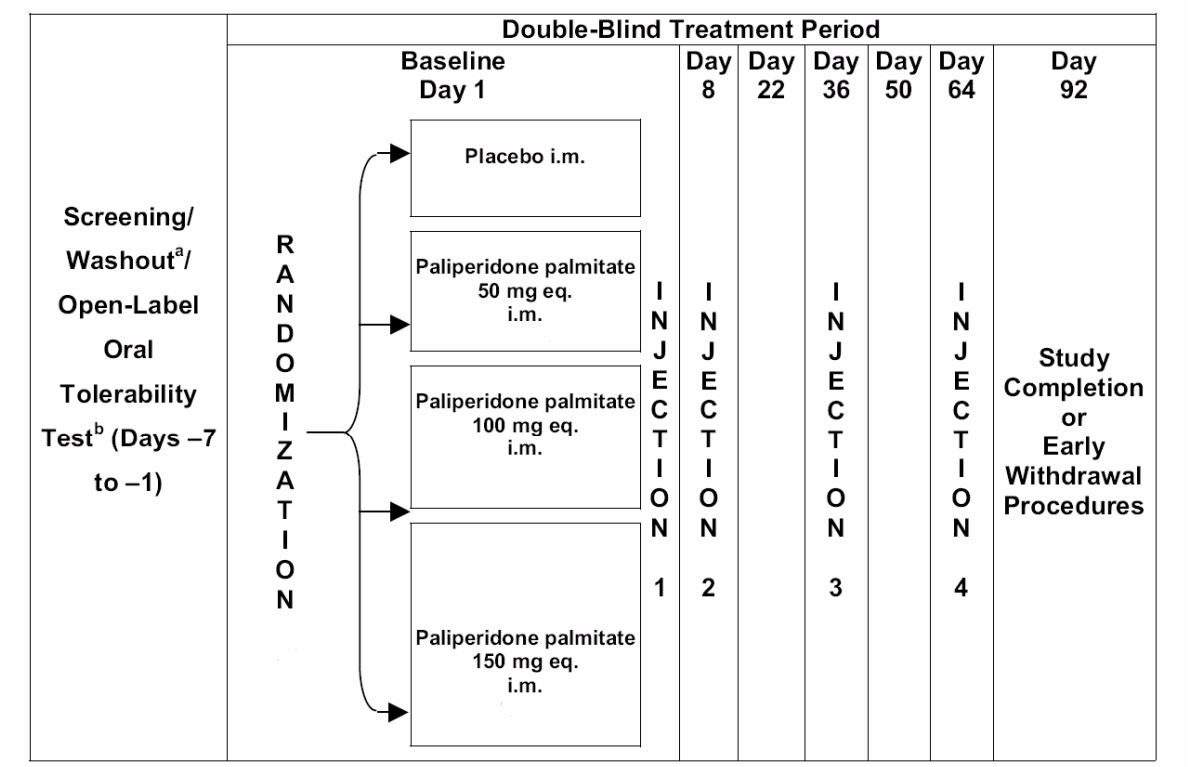
The studies PSY-3003 and PSY-3004 were Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy of 3 fixed doses of paliperidone palmitate (50, 100, and 150 mg eq. in study PSY-3003; and 25, 50, and 100 mg eq. in study PSY-3004) compared to placebo. Study medication was administered as 4 doses: 2 doses separated by 1 week (Days 1 and 8) followed by 2 doses at 4-week (monthly) intervals (Days 36 and 64). Subjects randomly assigned to the study drug were to remain in the study for 28 days after the last injection on Day 64, with the end-of-study visit scheduled for Day 92 during the double-blind period.

A diagrammatic representation of the study design for Study PSY-3003 is presented in Figure 1. The design of Study PSY-3004 was same as Figure 1, but the doses were 25, 50, 100 mg eq., and placebo.

In Study PSY-3003, subjects were enrolled from Korea, Malaysia, Taiwan, Ukraine, and USA. In Study PSY-3004, subjects were enrolled from Romania, Russia, South Africa, and USA.

The randomized subjects were from both genders, and aged at least 18 years with a DSM-IV diagnosis of schizophrenia for at least 1 year before screening and a PANSS total score between 70 and 120 at screening and baseline.

Figure 1. Study design



[a] Screening included a washout period of up to 5 days for subjects using any disallowed psychotropic medication.

[b] Subjects who did not have source documentation of previous exposure to 4 doses of risperidone or paliperidone received 3 mg/day of ER OROS paliperidone for 4 days before entering the double blind-treatment period.

Source: Study report

Endpoint Measures

In both studies, the primary efficacy measure was the change in the total PANSS score from the start of the double-blind treatment period (baseline) to the end of the double-blind treatment period (Day 92 or last post-randomization assessment).

Secondary endpoints were the changes from baseline to the end of the double-blind treatment period (Day 92 or last post-randomization assessment) in the CGI-S, PSP, and PANSS subscales for specific symptoms.

Primary Efficacy Analysis Data Set

Primary efficacy analysis data set included all subjects who were randomized, received at least 1 dose of double-blind study medication, whose dose of study medication did not change during the study, and who had both the baseline and at least 1 post baseline efficacy assessment (PANSS or CGI-S or PSP). The missing values of PANSS total scores at the study endpoint were imputed based on last observation carried forward (LOCF) approach.

Statistical Analysis Method

For the changes in PANSS total score at the study endpoint, the least squares (LS) adjusted means were estimated and compared for each treatment group versus placebo using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline PANSS total score as a covariate.

In Study PSY-3003, the paliperidone palmitate 50 mg eq. and 100 mg eq. doses were tested against placebo with a closed testing procedure using Dunnett's test at the 5% level. If both paliperidone palmitate 50 mg eq. and 100 mg eq. doses were significantly different from placebo, then the paliperidone palmitate 150 mg eq. dose was tested against placebo at the 5% level using a closed testing procedure using Dunnett's test at the 5% level. Otherwise, the closed testing procedure with Dunnett's test stopped after the comparisons of the paliperidone palmitate 50 mg eq. and 100 mg eq. doses to placebo.

In Study PSY-3004, the primary comparisons between each paliperidone palmitate dose group and the placebo group were done using Dunnett's test.

In the studies PSY-3003 and PSY-3004, an ANCOVA model with treatment and country as factors and baseline score as a covariate on the change from baseline to the study endpoint (LOCF) was used to analyze the secondary efficacy variables, PSP, CGI-S (ranks for change in CGI-S at the study endpoint), and the change in PANSS factors. No multiplicity adjustments were made for the secondary efficacy measures.

2.2. Data Sources

The SAS data sets are available at \\Cdsesub1\evsprod\NDA022264\0000\m5\datasets

3. STATISTICAL EVALUATION

3.1. Treatment of Schizophrenia-Phase III studies

3.1.1. Findings of the Studies PSY-3003 and PSY-3004

Disposition of Subjects - Study PSY-3003

In Study PSY-3003, 388 subjects were randomized (in a 1:1:1:1 ratio) to receive fixed doses of paliperidone palmitate 50 mg eq., 100 mg eq., 150 mg eq., or placebo. The randomized subjects were selected from 36 centers in 5 countries. There were 23 centers in the United States, 3

centers in Malaysia, 3 centers in the Republic of Korea, 4 centers in Taiwan, and 3 centers in Ukraine.

As a result of a mismatch in the allocation of medication kits, fewer subjects (only 30 subjects) received paliperidone palmitate 150 mg eq., and more subjects (135 subjects) received placebo than the original planned randomization schedule. All subjects in the paliperidone palmitate 50 mg eq. and 100 mg eq. arms received medication kits as planned according to the randomization schedule.

As specified in the statistical analysis plan (SAP) prior to database lock, a total of 39 subjects were excluded from the primary analysis. Among the 39 subjects, 31 subjects switched from active to placebo treatment (or vice versa) for 1 or more doses, and 9 subjects who did not receive any double-blind study medication or did not have both a baseline and at least one post baseline efficacy assessment.

Table 1 lists the subjects' withdrawal information. The percentages of withdrawal subjects were 63%, 50%, 45%, and 60% from placebo, 50 mg eq., 100 mg eq., and 150 mg eq, respectively. Majority of the randomized subjects from each group left the study due to lack of efficacy.

Table 1: Study Completion/Withdrawal Information --Studies PSY-3003 and PSY-3004

Study Id Subject Completed Treatment/trial Reason for Withdrawal/termination	Placebo (N=263) n (%)	R092670 25 mg eq. (N=131) 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 (a) (N=31) n (%)	Total Pali. Palmitate (N=612) n (%)
R092670-PSY-3003	136		94	97	30	31	221
Completed	51 (38)		47 (50)	53 (55)	12 (40)	24 (77)	112 (51)
Withdrawn	85 (63)		47 (50)	44 (45)	18 (60)	7 (23)	109 (49)
Lack of efficacy	48 (35)		25 (27)	26 (27)	13 (43)	3 (10)	64 (29)
Subject choice(subject withdrew consent)	12 (9)		7 (7)	9 (9)	2 (7)	2 (6)	18 (8)
Adverse event	13 (10)		8 (9)	2 (2)	2 (7)	0	12 (5)
Lost to follow-up	4 (3)		4 (4)	4 (4)	1 (3)	1 (3)	9 (4)
Other	8 (6)		3 (3)	3 (3)	0	1 (3)	6 (3)
R092670-PSY-3004	127	131	129	131			391
Completed	48 (38)	70 (53)	70 (54)	75 (57)			215 (55)
Withdrawn	79 (62)	61 (47)	59 (46)	56 (43)			176 (45)
Lack of efficacy	45 (35)	31 (24)	31 (24)	21 (16)			83 (21)
Subject choice(subject withdrew consent)	12 (9)	9 (7)	14 (11)	11 (8)			34 (9)
Lost to follow-up	10 (8)	8 (6)	4 (3)	13 (10)			25 (6)
Adverse event	8 (6)	8 (6)	2 (2)	6 (5)			16 (4)
Death	1 (1)	0	0	1 (1)			1 (<1)
Other	3 (2)	5 (4)	8 (6)	4 (3)			17 (4)

Note: 150 mg eq./Pbo - Subjects received various combinations of both 150 mg eq. and Placebo injections.
Source: Study Reports.

Disposition of Subjects - Study PSY-3004

In Study PSY-3004, 518 subjects were randomized (in a 1:1:1:1 ratio) to receive fixed doses of paliperidone palmitate 25 mg eq., 50 mg eq., or 100 mg eq. or placebo. The randomized subjects were from 38 centers in 5 countries -United States (19 centers), South Africa (2 centers), Bulgaria, Romania, and Russia (17 centers total in these 3 European countries).

Table 1 lists the subjects' withdrawal information. Among the 518 randomized subjects, 263 (51%) subjects completed the 13-week study. More subjects in the placebo group (35%) discontinued due to lack of efficacy than in the paliperidone palmitate treatment groups (16% to 24%). The rates for early withdrawal due to adverse events or for other reasons showed no apparent pattern of differences across the treatment groups.

Demographic Characteristics- Studies PSY-3003 and PSY-3004

In Study PSY-3003, the randomized subjects were predominately males (71% in the placebo group and 68% in the combined paliperidone palmitate groups). The mean age was 40.5 years (range, 18 to 68 years) for subjects in the placebo group and 39.2 years in the combined paliperidone palmitate groups (range, 18 to 68 years). There were 40% Whites, 39% Blacks, and 21% Asians or other racial origins. Demographic and baseline characteristics were similar across treatment groups.

In Study PSY-3004, the randomized subjects were predominantly males (62% of subjects in the placebo group and 68% of subjects in the combined paliperidone palmitate groups). The mean age was 41.1 years (range, 18 to 74 years) for subjects in the placebo group and 40.7 years (range, 18 to 68 years) for subjects in the combined paliperidone palmitate groups. There were 67% Whites, 29% Blacks, and 4% other race categories. Demographic and baseline characteristics were similar across treatment groups.

Across the two studies, the randomized subjects were similar in age, sex, and BMI category. The mean ages of subjects across the studies were similar and most subjects were males. Most subjects in Study PSY-3003 were either Whites (40%) or Blacks (39%), while most subjects in Study PSY-3004 were Whites (67%).

Sponsor's Results of the studies PSY-3003 and PSY-3004

Primary Efficacy Measure: PANSS Total Score-Change From Baseline to Endpoint

Table 2 shows the findings on the changes from baseline to endpoint in the PANSS total score by treatment group for the studies PSY-3003 and PSY-3004. In Study PSY-3003, the paliperidone palmitate 100 mg eq. group was statistically significantly superior to placebo for the mean change from baseline to endpoint in PANSS total score (p-value=0.019) under a closed testing procedure with Dunnett's test to adjust for multiplicity. The paliperidone palmitate 50 mg eq. group was not statistically significant. Since only the paliperidone palmitate 100 mg eq. group reached statistical significance relative to placebo, no statistical comparison was performed for the paliperidone palmitate 150 mg eq. group.

In Study PSY-3004, each of the paliperidone palmitate doses (25 mg eq., 50 mg eq., and 100 mg eq.) was statistically significantly superior to placebo for the mean change from baseline to endpoint in PANSS total score (p-value≤0.017) with a closed testing procedure using Dunnett's test to control for multiplicity.

Table 2**:** PANSS Total Score-Change From Baseline to Endpoint-LOCF for Studies PSY-3003 and PSY-3004: Primary Efficacy Analysis Set

		R092670			
	Placebo (N=257)	25 mg eq. (N=130)	50 mg eq. (N=221)	100 mg eq. (N=225)	150 mg eq. (N=30)
R092670-PSY-3003					
N	132		93	94	30
Mean baseline (SD)	92.4 (12.55)		89.9 (10.78)	90.1 (11.66)	92.2 (11.72)
Mean change (SD)	-4.1 (21.01)		-7.9 (18.71)	-11.0 (19.06)	-5.5 (19.78)
P-value (vs Placebo)[a]			0.193	0.019	
Diff. of LS Means (SE)			-3.5 (2.67)	-6.9 (2.65)	
R092670-PSY-3004					
N	125	129	128	131	
Mean baseline (SD)	90.7 (12.22)	90.7 (12.25)	91.2 (12.02)	90.8 (11.70)	
Mean change (SD)	-7.0 (20.07)	-13.6 (21.45)	-13.2 (20.14)	-16.1 (20.36)	
P-value (vs Placebo)[a]		0.015	0.017	<0.001	
Diff. of LS Means (SE)		-6.6 (2.46)	-5.9 (2.47)	-9.2 (2.45)	

[a] Based on ANCOVA model with treatment and country as factors, and baseline value as a covariate. Pairwise comparison: p-values associated with a closed testing procedure using Dunnett's test.
Source: Study report

Treatment by Country Interaction in exploratory Analysis

In Study PSY-3003, a treatment-by-country interaction was significant (p-value=0.040) for the primary efficacy variable. When the paliperidone palmitate 100 mg eq. group was compared to placebo, no significant treatment-by-country interaction was observed (p-value=0.197). When the paliperidone palmitate 50 mg eq. group was compared to placebo, the treatment-by-country interaction was found to be significant (p-value=0.018). The two doses of paliperidone palmitate were tested in comparison to placebo using the 2-sided Gail-Simon test, which showed there were insufficient evidences (p-value≥0.728) of the presence of a qualitative treatment-by-country interaction.

In Study PSY-3004, a treatment-by-country interaction was also significant for the mean change in PANSS total score (p-value=0.015). When either the paliperidone palmitate 25 mg eq. group or 100 mg eq. group was compared to placebo, no apparent treatment-by-country interaction was observed (25 mg eq.: p-value=0.13; 100 mg eq.: p-value=0.12). When the paliperidone palmitate 50 mg eq. group was compared to placebo, the treatment-by-country interaction was found to be significant (p-value=0.02). The three doses of paliperidone palmitate were tested in comparison to placebo using the 2-sided Gail-Simon test, which showed there were insufficient evidences (p≥0.660) of the presence of a qualitative treatment-by-country interaction.

Secondary Efficacy Variables

Personal and Social Performance(PSP) Scale- Change From Baseline to Endpoint

The changes from baseline to the study endpoint in the PSP score are presented by treatment group for the studies PSY-3003 and PSY-3004 in Table 3. In Study PSY-3004, the paliperidone palmitate 50 mg eq.

and 100 mg eq. groups were statistically significantly superior to placebo for the mean changes from baseline to endpoint in the PSP score (p-value≤0.004). Most subjects either remained in the same PSP category or improved (i.e., moved to a higher category at endpoint) during double-blind treatment. There were no apparent differences between the paliperidone palmitate groups and placebo with respect to the percentage of subjects who demonstrated an increase of at least one 10-point PSP category at endpoint.

In Study PSY-3004, improvements in the mean PSP score from baseline to endpoint were numerically larger in all paliperidone palmitate groups (25 mg eq., 50 mg eq., and 100 mg eq.,) compared to placebo. The improvement in each paliperidone palmitate group was not statistically superior to placebo (p-value≥0.257). Most subjects either remained in the same PSP category or improved (i.e., moved to a higher category at endpoint) during double-blind treatment.

Table 3: Personal and Social Performance Scale (PSP) - Change From Baseline to Endpoint-LOCF for Studies PSY-3003 and PSY-3004: Primary Efficacy Analysis Set)

	Placebo (N=257)	25 mg eq. (N=130)	50 mg eq. (N=221)	100 mg eq. (N=225)	150 mg eq. (N=30)
PSY-3003					
N	126		88	86	27
Mean baseline (SD)	49.0 (14.04)		51.0 (13.79)	51.4 (13.36)	46.7 (12.66)
Mean change (SD)	-1.2 (16.26)		4.2 (13.21)	4.8 (15.35)	0.6 (15.52)
P-value (vs Placebo)[a]			0.004	<0.001	
Diff. of LS Means (SE)			5.7 (1.99)	6.8 (2.00)	
PSY-3004					
N	118	119	121	119	
Mean baseline (SD)	48.0 (12.60)	47.7 (12.15)	46.3 (12.62)	45.9 (12.03)	
Mean change (SD)	3.6 (17.07)	6.5 (15.64)	6.8 (15.37)	7.4 (14.58)	
P-value (vs Placebo)[a]		0.262	0.262	0.257	
P-value (vs Placebo)[a]		0.154	0.189	0.110	
Diff. of LS Means (SE)		2.7 (1.92)	2.5 (1.91)	3.1 (1.92)	

[a] Based on ANCOVA model with treatment and country as factors, and baseline value as a covariate.
Source: Study Reports.

Clinical GIobal Impression-Severity (CGI-S) - Change From Baseline to Endpoint

The improvements measured by the median change from baseline to endpoint in the CGI-S score are presented by treatment group for the studies PSY-3003 and PSY-3004 in Table 4. In Study PSY-3003, improvements measured by the median change from baseline to endpoint in the CGI-S score were numerically larger in the paliperidone palmitate 50 mg eq. and 100 mg eq. groups compared to the placebo group, and the difference was significant for the 100 mg eq. group (p-value=0.010).

In Study PSY-3004, the 25 mg eq., 50 mg eq., and 100 mg eq. groups were statistically significantly superior to the placebo group for the change from baseline to endpoint in CGI-S score (p≤0.006).

Table 4: Clinical Global Impression - Severity Scale (CGI-S) - Change from Baseline to End Point-LOCF for Studies PSY-3003 and PSY-3004: Primary Efficacy Analysis Set.

	Placebo (N=257)	25 mg eq. (N=130)	50 mg eq. (N=221)	100 mg eq. (N=225)	150 mg eq. (N=30)
PSY-3003					
N	132		93	94	30
Median baseline (Range)	5.0 (2;7)		5.0 (2;6)	5.0 (2;6)	5.0 (3;6)
Median change (Range)	0.0 (-4;3)		-1.0 (-3;2)	-1.0 (-3;3)	0.0 (-4;1)
P-value (vs Placebo)[a]			0.069	0.010	
PSY-3004					
N	125	129	128	131	
Median baseline (Range)	4.0 (2;6)	5.0 (3;6)	5.0 (3;6)	4.0 (3;6)	
Median change (Range)	0.0 (-3;2)	-1.0 (-5;2)	-1.0 (-3;2)	-1.0 (-4;2)	
P-value (vs Placebo)[a]		0.003	0.006	0.002	

[a] Based on ANCOVA model on ranks with treatment and country as factors, and baseline value as a covariate.
Source: Study Report

Changes in PANSS Factor Scores

The mean changes from baseline to endpoint for the 5 PANSS factor scores and the LOCF ANCOVA analysis results for the studies PSY-3003 and PSY-3004 are provided in Table 5. In Study PSY-3003, the paliperidone palmitate 100 mg eq. group was statistically significantly superior to placebo for the mean change from baseline to endpoint for all 5 PANSS factor scores (p-value≤0.032) (unadjusted for multiplicity). The mean change from baseline to endpoint in disorganized thought and uncontrolled hostility/excitement was statistically significantly greater in the paliperidone palmitate 50 mg eq. group compared to placebo.

In Study PSY-30034, the three paliperidone palmitate groups were statistically significantly superior to the placebo group for both the positive and negative symptoms. The improvement in uncontrolled hostility/excitement was statistically significantly greater in the paliperidone palmitate 50 mg eq. and 100 mg eq. groups compared to the placebo group, while the improvement in the anxiety/depression factor reached statistical significance in favor of the paliperidone palmitate 25 and 100 mg eq. groups. No significant treatment difference was observed for disorganized thoughts for any of the three paliperidone palmitate groups compared to the placebo group.

Table 5: PANSS Factor Scores - Change From Baseline to Endpoint-LOCF: for Studies PSY-3003 and PSY-3004: Primary Efficacy Analysis set

PSY-3003	Placebo (N=132)	50 mg eq. (N=93)	100 mg eq. (N=94)	150 mg eq. (N=30)
Positive symptoms				
Mean baseline (SD)	27.7 (5.14)	26.5 (4.61)	26.5 (4.92)	27.6 (4.49)
Mean change (SD)	-1.4 (6.76)	-2.4 (5.71)	-3.5 (5.89)	-1.7 (5.63)
P-value(minus Placebo)[a]		0.270	0.012	
Negative symptoms				
Mean baseline (SD)	22.2 (4.46)	21.5 (4.63)	22.0 (4.88)	22.3 (4.99)
Mean change (SD)	-1.7 (6.04)	-1.9 (6.67)	-3.5 (4.94)	-2.7 (5.30)
P-value(minus Placebo)[a]		0.634	0.017	
Disorganized thoughts				
Mean baseline (SD)	21.0 (4.95)	21.7 (3.55)	21.2 (4.27)	20.9 (4.46)
Mean change (SD)	-0.8 (4.86)	-2.2 (4.47)	-2.2 (4.75)	-0.7 (5.13)
P-value(minus Placebo)[a]		0.031	0.032	
Uncontrolled hostility/excitement				
Mean baseline (SD)	9.8 (3.35)	9.1 (2.88)	9.4 (2.99)	9.7 (3.14)
Mean change (SD)	0.8 (4.75)	-0.1 (3.43)	-0.1 (4.21)	0.2 (3.65)
P-value(minus Placebo)[a]		0.020	0.027	
Anxiety/depression				
Mean baseline (SD)	11.6 (3.18)	11.1 (2.77)	11.1 (2.94)	11.7 (2.91)
Mean change (SD)	-1.0 (3.73)	-1.2 (3.49)	-1.7 (3.64)	-0.7 (3.14)
P-value(minus Placebo)[a]		0.201	0.009	

PSY-3004	Placebo (N=125)	25 mg eq. (N=130)	50 mg eq. (N=128)	100 mg eq. (N=131)
Positive symptoms				
Mean baseline (SD)	26.1 (4.88)	27.2 (5.01)	27.0 (4.76)	27.0 (4.77)
Mean change (SD)	-2.0 (6.72)	-5.0 (7.60)	-4.4 (6.42)	-5.5 (6.53)
P-value(minus Placebo)[a]		<0.001	0.010	<0.001
Negative symptoms				
Mean baseline (SD)	23.2 (4.67)	22.2 (5.33)	22.7 (5.75)	22.9 (5.05)
Mean change (SD)	-2.4 (5.19)	-3.8 (5.17)	-3.5 (6.41)	-3.9 (5.79)
P-value(minus Placebo)[a]		0.003	0.041	0.007
Disorganized thoughts				
Mean baseline (SD)	21.2 (4.52)	21.3 (4.46)	21.4 (4.92)	20.9 (4.31)
Mean change (SD)	-2.1 (4.98)	-2.7 (5.30)	-3.0 (5.10)	-3.1 (5.32)
P-value(minus Placebo)[a]		0.343	0.198	0.067
Uncontrolled hostility/excitement				
Mean baseline (SD)	9.0 (3.01)	9.4 (3.18)	9.6 (3.35)	9.1 (3.28)
Mean change (SD)	0.7 (4.27)	-0.3 (4.23)	-0.8 (4.54)	-1.1 (3.98)
P-value(minus Placebo)[a]		0.096	0.013	<0.001
Anxiety/depression				
Mean baseline (SD)	11.2 (3.34)	10.6 (3.29)	10.5 (2.82)	11.0 (3.28)
Mean change (SD)	-1.2 (3.22)	-1.7 (3.47)	-1.5 (3.38)	-2.3 (3.12)
P-value(minus Placebo)[a]		0.041	0.127	<0.001

[a] Based on ANCOVA model with treatment and country as factors, and baseline value as a covariate.
Source: Study report

3.1.2. FDA Reviewer's Data Analyses Findings and Comments

This reviewer re-analyzed the efficacy data of the studies PSY-3003 and PSY-3004 according to the protocol specified primary ANCOVA models. This reviewer also did sensitivity analyses on the primary efficacy measure using MMRM analysis (longitudinal analysis), and ANCOVA analysis on available cases at each post visit to check the robustness of efficacy findings of the two studies.

Studies PSY-3003 and PSY-3004

The reviewer's findings were similar to the sponsor's reported findings. The results of the MMRM analysis on the primary efficacy measure were also similar to the LOCF ANCOVA analysis (Table 6). In Study PSY-3003, the MMRM analysis demonstrated that the paliperidone palmitate 100 mg eq. was significantly superior (p-value=0.002) to placebo for the mean change from baseline to endpoint in PANSS total score. The paliperidone palmitate 50 mg eq. was not statistically significant (p-value=0.193). In the available cases ANCOVA analysis on the primary measure at each visit, the mean change from baseline in PANSS total score for each dose group was numerically higher than the mean change for the placebo group at each post visit, but the differences were not statistically significant.

In Study PSY-3004, the MMRM analysis findings were similar to the LOCF ANCOVA analysis findings (Table 6). The paliperidone palmitate group, 25 mg eq., 50 mg eq., and 100 mg eq., were statistically significantly (p-values= 0.003, 0.018, and <0.001) superior to placebo for the mean changes from baseline to endpoint in PANSS total score. In the available cases ANCOVA analysis on the primary measure at each visit, the mean change from baseline in PANSS total score for each dose group was numerically higher than the mean change for the placebo group at each post visit.

Table 6. Comparison of the LOCF ANCOVA and MMRM analyses results of the primary efficacy measure- Change from baseline to Endpoint in PANSS Total Score.

	Change from baseline to Endpoint in PANSS Total Score			
PSY-3003	LOCF ANCOVA Analysis		MMRM Analysis	
	LS MEAN Difference	P-value[§]	LS MEAN Difference	P-value[§]
50 mg - Placebo	-3.5	0.193	-3.6	0.193
100 mg - Placebo	-6.9	0.009	-8.6	0.002
PSY-3004				
25 mg - Placebo	-6.6	0.007	-8.7	0.003
50 mg - Placebo	-5.9	0.017	-6.9	0.018
100 mg - Placebo	-9.2	<0.001	-10.1	<0.001

[§] Unadjusted for multiplicity control for the familywise error rate

The reviewer also did exploratory analyses to find whether there was any qualitative interaction of treatment-by-country interaction in the studies PSY-3003 and PSY-3004. The exploratory analyses confirmed that there were no evidences of the presence of a qualitative interaction of treatment-by-country in interaction in the studies PSY-3003 and PSY-3004. In both studies, the significance of the treatment-by-country interaction were quantitative interactions, so it was not a concern in evaluating treatment efficacy of paliperidone palmitate.

The reviewer was also able to reproduce the sponsor's reported findings on the secondary efficacy measures of the studies PSY-3003 and PSY-3004.

In the protocols of the studies PSY-3003 and PSY-3004, the sponsor stated "Two secondary end points (changes from baseline at end point in CGI-S and in the PSP) will be analyzed for selected paliperidone palmitate dosages (those dosages that are significantly more effective compared with placebo according to the results of the primary analysis). The family-wise type I error rate, i.e., that the selected dosage is falsely declared superior to placebo for at least 1 of the secondary end points, will be controlled using a resampling approach that incorporates the correlation among the end points within each dosage group. The type I error rate within each dosage group comparison will be maintained at 0.05." However, in the study reports, the sponsor stated that no multiplicity adjustments were made for multiple comparisons in the analysis of other (except the primary measure) efficacy variables. (b) (4)

The reviewer did exploratory analyses on time to dropout (i.e., survival analysis) of the dropout subjects by the dose groups of paliperidone palmitate for the studies PSY-3003 and PSY-3004. In both studies, there were no differential patterns of dropouts over time among the dose groups of paliperidone palmitate.

3.2. Treatment of Schizophrenia-Phase II study

Study SCH-201

The study SCH-201 was a Phase II multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy of 2 fixed dosages of long-acting injections of paliperidone palmitate (50 mg eq. and 100 mg eq.) compared with placebo in subjects with schizophrenia. The study consisted of a screening period (maximum 5 days); a 7-day, open-label, oral run-in period; a 64-day double-blind treatment period, during which placebo and study drug injections were administered on Days 1, 8, and 36; and an end of study visit on Day 64 or at early withdrawal. The randomized subjects were from 30 centers of the USA (n=8), Russia (n=7), Bulgaria (n=4), Poland (n=4), Ukraine (n=4), and India (n=3).

The randomized subjects were from both genders, and aged between 18 and 65 years with a DSM-IV diagnosis of schizophrenia before screening and a PANSS total score between 70 and

120 at screening and between 60 and 120 on Day 1 (baseline) prior to start of double-blind treatment.

Endpoint Measures

The primary efficacy measure was the change in the total PANSS score from the start of the double-blind treatment period (baseline) to the last post-randomization assessment in the double-blind period.

Secondary endpoints were the changes from baseline to the end of the double-blind treatment period in the CGI-S and PANSS subscale scores for Positive Symptoms, Negative Symptoms, Disorganized Thoughts, Uncontrolled Hostility/Excitement, and Anxiety/Depression.

Primary Efficacy Analysis Data Set

Primary efficacy analysis data set included all subjects who were randomized, received at least 1 dose of double-blind study medication, whose dose of study medication did not change during the study, and who have the baseline and at least 1 post baseline efficacy assessment of PANSS. The missing values of PANSS total scores at the study endpoint were imputed based on last observation carried forward (LOCF) approach.

Statistical Analysis Method

For the change in PANSS total score at the study endpoint, the least squares (LS) adjusted means were estimated and compared for each treatment group versus placebo using an analysis of covariance (ANCOVA) model with treatment, center, and oral run-in treatment as factors and baseline PANSS total score as a covariate. The same primary analysis applied to total PANSS was also applied for each of these subscales.

3.2.1. Findings of Study SCH-201

Disposition of Subjects

Two hundred forty seven (247) subjects were randomized to placebo (N=84), paliperidone palmitate 50 mg eq. (N=79), or paliperidone palmitate 100 mg eq. (N=84) treatment groups. Forty-nine (49) randomized subjects from 6 sites [1] were excluded from the primary analyses of efficacy due to major deviations in study drug administration and in using the IVRS system. The primary efficacy analysis set was the intent-to-treat (ITT) population that included 197 randomized subjects who received at least 1 injection of double-blind treatment and had at least 1 postbaseline efficacy measurement.

[1] All subjects from 6 sites, 3 sites in the USA (701, 704, and 707) and 3 sites in India (301, 303, and 304), were prospectively (i.e. prior to database lock) 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

Table 7 lists the subjects' withdrawal information. The percentages of withdrawal subjects were 68%, 41%, and 39 from placebo, 50 mg eq,, and 100 mg eq., respectively. Lack of efficacy was the most common reason for discontinuation from double-blind treatment, and more subjects were withdrawn for this reason in the placebo group (43%) than in either paliperidone palmitate group (29% and 17% for 50 and 100 mg eq. dose groups, respectively). A higher percentage of subjects in the placebo group (10%) was also withdrawn from double-blind treatment as a result of adverse events compared with the withdrawns of paliperidone palmitate groups (4% and 2%).

Table 7: Study Completion/Withdrawal Information –Study SCH-201

	Placebo (N=84) n (%)	R092670 50 mg eq. (N=79) n (%)	R092670 100 mg eq. (N=84) n (%)	Total (N=247) n (%)
Completed	27 (32)	47 (59)	51 (61)	125 (51)
Withdrawn	57 (68)	32 (41)	33 (39)	122 (49)
Subject choice (subject withdrew consent)	8 (10)	4 (5)	11 (13)	23 (9)
Lost to follow-up	2 (2)	1 (1)	4 (5)	7 (3)
Adverse event	8 (10)	3 (4)	2 (2)	13 (5)
Lack of efficacy	36 (43)	23 (29)	14 (17)	73 (30)
Other[a]	3 (4)	1 (1)	2 (2)	6 (2)

[a] Includes noncompliance (n=4), sponsor decision (n=1), and unavailability of study drug injection.
Source: Study report

Demographic Characteristics

The randomized subjects were predominately males (62%) and whites (81%) with a median age of 40 years. The double-blind treatment groups were well matched in terms of age, sex, race, height, weight and BMI.

Sponsor's Results of the study SCH-201

Primary Efficacy Measure: PANSS Total Score-Change From Baseline to EndPoint

Table 8 shows the findings on the change from baseline to endpoint in the PANSS total scores by treatment groups. The paliperidone palmitate 50mg eq. and 100 mg eq. were statistically significantly superior to placebo for the mean change from baseline to endpoint in PANSS total score (p-value=0.001 and p-value<0.0001, respectively). The 100 mg eq. dose was associated with a larger mean reduction at endpoint in the total PANSS score (-7.8) compared with the 50 mg eq. dose (-5.2).

Table 8**:** PANSS Total Score-Change From Baseline to Endpoint-LOCF for Study SCH-201: Primary Efficacy Analysis Set

	Placebo (N=66)	R092670 50 mg eq. (N=63)	R092670 100 mg eq. (N=68)
Baseline			
N	66	63	68
Mean (SD)	87.8 (13.90)	88.0 (12.39)	85.2 (11.09)
Median (Range)	86.0 (55;118)	87.0 (64;120)	85.0 (66;118)
End point			
N	66	63	68
Mean (SD)	94.0 (24.84)	82.8 (24.48)	77.5 (21.42)
Median (Range)	91.0 (44;148)	76.0 (36;140)	77.0 (37;134)
Change from Baseline			
N	66	63	68
Mean (SD)	6.2 (18.25)	-5.2 (21.52)	-7.8 (19.40)
Median (Range)	9.0 (-40;52)	-8.0 (-64;52)	-9.0 (-47;53)
p-value(minus Placebo)[a,b]		0.001	<0.0001
Diff. of LS Means (SE)		-11.2 (3.41)	-14.0 (3.31)
90% CI		(-16.85;-5.57)	(-19.51;-8.58)

[a] Test for no difference between treatments from ANCOVA model with factors for treatment, oral run-in treatment and analysis center, and with baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Source; Study report

If the excluded randomized subjects (n=46) from the 6 sites were included in the primary analysis, the paliperidone palmitate 50 mg eq. and paliperidone palmitate 100 mg eq. remained statistically significantly superior to placebo with mean reductions from baseline to endpoint in the total PANSS score ($p<0.0001$ and $p<0.0001$, respectively).

Secondary Efficacy Variables

Clinical GIobal Impression-Severity (CGI-S) - Change From Baseline to EndPoint

The changes from baseline to endpoint in CGI-S were analyzed using an ANCOVA on a scale of 1 to 7 to the ratings from "not ill" to "extremely severe". Both the paliperidone palmitate 50 and 100 mg eq. doses were significantly superior to placebo in reducing CGI-S scores at endpoint (p-value=0.004 and p-value<0.001, respectively).

Changes in PANSS Factor Scores

The mean changes from baseline to endpoint for the 5 PANSS factor scores and the LOCF ANCOVA analyses results for the study SCH-201 are presented in Table 9. Paliperidone

palmitate 100 mg eq. dose was statistically significantly superior to placebo for the mean change from baseline to endpoint for all 5 PANSS factor scores (p-value≤0.006) (unadjusted for multiplicity). Paliperidone palmitate 50 mg eq. dose was statistically significantly superior to placebo for the mean change from baseline to endpoint for the four PANSS factor (except Uncontrolled hostility/excitement factors) scores (p-value≤0.012) (unadjusted for multiplicity). These findings were consistent with the results of the primary endpoint analysis.

Table 9: PANSS Factor Scores - Change From Baseline to Endpoint-LOCF: for Study SCH-201

	Placebo (N=66)	R092670 50 mg eq. (N=63)	R092670 100 mg eq. (N=68)
Positive symptoms			
Mean baseline (SD)	24.1 (5.64)	24.3 (4.98)	23.9 (5.06)
Mean change (SD)	1.7 (5.32)	-2.0 (6.81)	-2.9 (6.86)
p-value (vs. Placebo)[a,b]		0.001	<0.001
Negative symptoms			
Mean baseline (SD)	23.6 (4.70)	23.3 (4.88)	22.3 (4.42)
Mean change (SD)	0.3 (5.03)	-1.9 (5.12)	-2.6 (4.47)
p-value (vs. Placebo)[a,b]		0.010	<0.001
Anxiety/depression			
Mean baseline (SD)	9.3 (2.58)	9.7 (2.72)	9.4 (2.54)
Mean change (SD)	1.1 (2.98)	-0.6 (3.52)	-0.5 (2.90)
p-value (vs. Placebo)[a,b]		0.002	<0.001
Disorganized thoughts			
Mean baseline (SD)	22.3 (4.24)	22.6 (4.52)	21.5 (3.16)
Mean change (SD)	0.8 (4.89)	-1.5 (5.64)	-2.1 (4.64)
p-value (vs. Placebo)[a,b]		0.012	<0.001
Uncontrolled hostility/excitement			
Mean baseline (SD)	8.7 (3.26)	8.1 (2.35)	8.1 (2.74)
Mean change (SD)	2.1 (4.37)	0.8 (4.26)	0.4 (3.95)
p-value (vs. Placebo)[a,b]		0.080	0.006

[a] Test for no difference between treatments from ANCOVA model with factors for treatment, oral run-in treatment and analysis center, and with baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Source: Study report

3.2.2. FDA Reviewer's Data Analyses Findings and Comments

This reviewer re-analyzed the efficacy data of the study SCH-201 according to the protocol specified primary ANCOVA models. This reviewer also did sensitivity analyses on the primary efficacy measure using MMRM analysis (longitudinal analysis), and ANCOVA analysis on available cases at each post visit to check robustness of the efficacy findings of the study.

The reviewer's findings were similar to the sponsor's reported findings. The results of the MMRM analysis on the primary efficacy measure were also similar to the LOCF ANCOVA analysis (Table 10). The MMRM analysis demonstrated that paliperidone palmitate 50 mg eq. and 100 mg eq. were significantly superior to placebo for the mean change from baseline to endpoint in PANSS total score. In the available cases ANCOVA analysis on the primary measure at each visit, the mean change from baseline in PANSS total score for each dose group was numerically higher than the mean change for the placebo group at each post visit, and from day 43, both paliperidone palmitate 50 mg eq. and 100 mg eq. were significantly difference from placebo.

The reviewer was also able to reproduce the sponsor's reported findings on the secondary efficacy measures of the study.

Table 10. Comparison of the LOCF ANCOVA and MMRM analyses results of the primary efficacy measure- Change from baseline to Endpoint in PANSS Total Score.

	Change from baseline to Endpoint in PANSS Total Score			
SCH-201	LOCF ANCOVA Analysis		MMRM Analysis	
	LS MEAN Difference	P-value[§]	LS MEAN Difference	P-value[§]
50 mg - Placebo	-11.2	0.001	-13.6	0.002
100 mg - Placebo	-14.0	<0.001	-15.9	<0.0001

[§] Unadjusted for multiplicity control for the familywise error rate

The reviewer did exploratory analyses on time to dropout (i.e., survival analysis) of the dropout subjects by the dose groups of paliperidone palmitate. The withdrawals due to lack of efficacy were higher and occurred earlier during the course of double-blind treatment among placebo-treated subjects compared with the 2 paliperidone palmitate groups.

3.3. Prevention of recurrence of the symptoms of schizophrenia

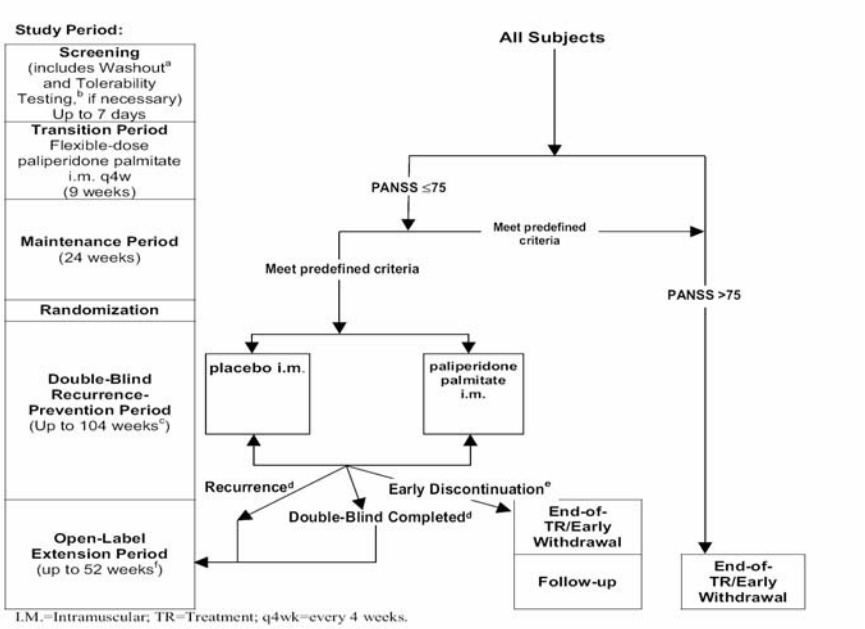
A single Phase 3 (Study PSY-3001), double-blind, placebo-controlled study was designed to address the question of recurrence prevention of long-acting injectable paliperidone palmitate versus injectable placebo. The study had a double-blind treatment period, after 33 weeks of open-label treatment (period of stabilization). A schematic for the design of Study PSY-3001 is provided at Figure-2.

During open-label treatment, flexibly dosed paliperidone palmitate was given as an intramuscular injection into the gluteal muscle starting with 2 single doses of 50 mg eq. given 1-week apart followed by 1 injection monthly of 25, 50, or 100 mg eq., based on clinical needs. Doses were fixed during last 12 weeks of maintenance and the double-blind recurrence prevention. During the double-bind Phase, fixed doses of paliperidone palmitate (25, 50, or 100 mg eq.) or placebo administered monthly as a gluteal injection for variable duration. The study was conducted across 56 centers in 9 countries. The countries were North America (United States and Mexico), Eastern Europe (Romania, Ukraine and Russia), Asia (Republic of Korea and Taiwan), and Rest of World (Costa Rica and South Africa).

The study PSY-3001 included 849 patients at the Open-Label Transition (TR) phase, and 681 patients at the Open-Label Maintenance (MA) phase. Among the 681 patients who met the inclusion criteria were randomized to double-blind recurrence prevention period (up to 104 weeks). It was expected that 384 subjects would be randomly assigned to either placebo or paliperidone palmitate treatment to ensure at least 136 recurrence events during the double-blind period.

Eligible subjects were from both genders between the ages of 18 and 65 years, with a diagnosis of either stable or symptomatic schizophrenia. To enter the DB phase, subjects had to first achieve and maintain symptom control during the TR/MA phase.

Figure 2: Study Design-PSY 3001



I.M.=Intramuscular; TR=Treatment; q4wk=every 4 weeks.

[a] Disallowed medications will be discontinued/washed-out during the screening period. Prior stable doses of oral antidepressant treatment may be continued.

[b] Subjects without source documentation of previous exposure to risperidone, Risperdal CONSTA, or paliperidone will receive 4 oral doses of ER OROS paliperidone before the first injection of study drug.

[c] The recurrence prevention period will last until the study is stopped for efficacy based upon an interim analysis performed when 68 recurrence events occur or when at least 136 recurrence events are observed.

[d] Subjects who experience a recurrence during the double-blind recurrence prevention period or remain recurrence free for the entire period (e.g., study is stopped for efficacy) will undergo End-of-Treatment/Early Withdrawal assessments and are eligible to enter the open-label extension period.

[e] Subjects who are withdrawn early from the recurrence prevention period for a reason other than a recurrence will have End-of-Treatment/Early withdrawal procedures done and, although they will not receive study treatment, they will be followed up every 4 weeks according to the Follow-up column in the Time and Events Schedule.

[f] Subjects completing or discontinuing early from the open-label extension period will have End-of-OLE/Early Withdrawal assessments done according to the Time and Events Schedule.

Source of the Fig: Study report

Endpoint Measures

The primary efficacy measure was the time to first recurrence of symptoms of schizophrenia during the double-blind recurrence prevention phase. Secondary measures included changes from baseline to the endpoint in PANSS total score, PANSS factor scores, CGI-S and PSP scale. The missing scores of the secondary measures at the endpoint were imputed based on last observation carried forward (LOCF) approach.

Analysis Data Set

The efficacy analysis of the primary and secondary efficacy measures for the transition and maintenance phases used the all treated analysis set, which included all subjects who received at least one dose of transition medication.

Statistical Analysis Method

For the primary measure, the cumulative distribution function of the time to recurrence was estimated by the Kaplan-Meier method, and treatments were compared using a 2-sided log-rank test. For the secondary measures, an ANCOVA model with treatment and country as factors and baseline score as a covariate on the change from baseline to endpoint (LOCF) was used.

According to the PSY-3001 study protocol, "An interim analysis based upon the primary endpoint will be conducted when 68 recurrence events have occurred. The actual number of subjects enrolled will depend on the time that it takes to obtain 136 recurrence events or to stop the study early on the basis of the interim analysis. ---- If the result of the interim analysis based on the primary endpoint is positive, enrollment in the study will be terminated and paliperidone palmitate will be declared superior to placebo in delaying recurrence. ----Otherwise, the study will continue until 136 events are obtained. When 136 events are obtained, the double-blind recurrence prevention period will be completed and a final analysis will be performed.--- the interim analysis will be performed at a significance level of 0.0106 when 68 events are obtained. If the result of the interim analysis is significant, the recurrence prevention period will be terminated and paliperidone palmitate will be declared superior to placebo in delaying recurrence. Otherwise, the recurrence prevention period will continue until a total of 136 events are obtained at which time the recurrence prevention period is completed and a final analysis will be performed at a significance level of 0.0448." An independent data monitoring committee conducted the interim analysis.

3.3.1. Findings of the study - Study PSY-3001

Disposition of Subjects

In the open-label transition phase, 849 subjects enrolled, and 681 (80%) completed the transition phase. Among the 681 subjects, 410 (60%) completed the open-label maintenance phase. The most common reasons for early withdrawal from both the open phases were withdrawal of consent, adverse event, and other. In addition, some subjects were discontinued due to failure in meeting eligibility criteria of the double-blind phase.

Double-blind Recurrence Prevention Phase – Intent-to-Treat Interim Analysis Set

In the double-blind Recurrence Prevention Phase, 410 subjects were randomized (206 subjects to placebo and 204 to paliperidone palmitate). Among these 410 subjects, 351 (86%) subjects completed the double-blind recurrence prevention phase and 59 (14%) discontinued as shown in Table 11. Of the 351 subjects who completed the double-blind phase, 126 (31%) experienced a recurrence event, including 95 (47%) in the placebo group and 31 (15%) in the paliperidone palmitate group, and 223 (54%) were participating in the double-blind phase at the time the study

was terminated. The percentages of withdrawals from the two groups were similar. The most common reasons 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).

Table 11: Double-Blind Treatment Completion/Withdrawal Information (Study PSY-3001: All Randomized Subjects Analysis Set)

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

[a] Study terminated based on the results of the interim analysis.
[b] Two subjects were randomized but did not receive any double-blind injection and were in the transition/maintenance phase when the study was terminated.
Source: Study report

Demographics Characteristics

More male (54%) than female (46%) subjects were randomized to the double-blind phase. The mean age at transition baseline was 39.1 years (range, 18 to 66 years); most subjects were Whites (65%), while 18% were Blacks, 15% were Asians, and 2% were from other races. The baseline psychiatric characteristics were similar across the treatment groups, and there were no notable differences between the subjects included in the double-blind phase.

Sponsor's Efficacy Results-Study PSY-3001

Primary Efficacy Analysis: Interim Analysis of Time to Recurrence

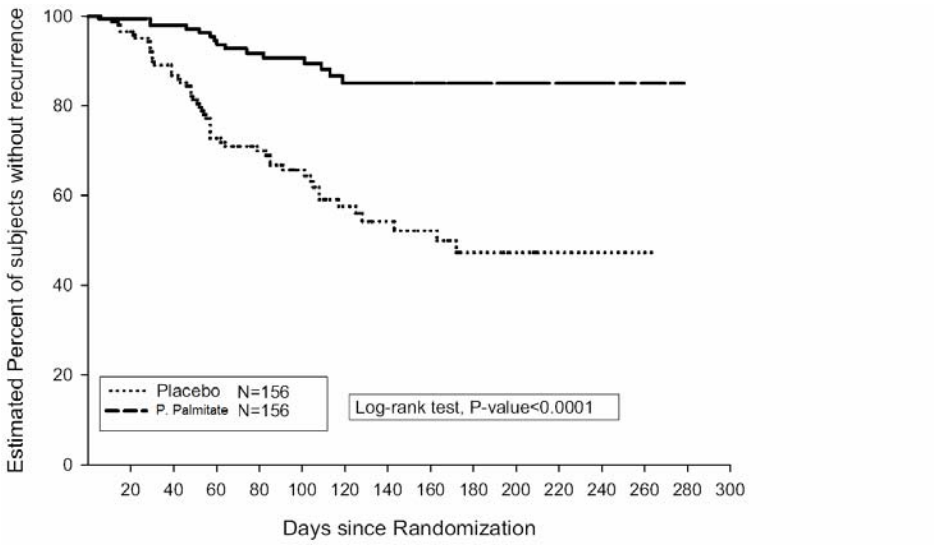
As specified in the protocol, the interim analysis of 312 subjects, conducted by the IDMC after 68 recurrence events had occurred, demonstrated a statistically significant difference in favor of paliperidone palmitate compared to placebo with regard to the time to a recurrence event as shown in Table 12. Among the 312 subjects, 53 (34%) subjects in the placebo group and 15 (10%) subjects in the paliperidone palmitate group experienced a recurrence event. There was a significant difference (p-value<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. This difference exceeded the threshold for significance (i.e., p-value <0.0106) resulting in the IDMC recommendation to terminate the study early. A Kaplan-Meier plot of time to recurrence by treatment group is shown in Figure 3. The time to recurrence for subjects in the placebo group was significantly shorter than for the paliperidone palmitate group.

Table 12: Number (%) of Subjects Experiencing Recurrence and Time to Recurrence (Days)- Interim Analysis (Study PSY-3001: Intent-to-Treat Interim Analysis Set)

Descriptive	Placebo	Paliperidone Palmitate	Total	Overall Chisq	Overall DF	Overall P-value[a]
Time to recurrence						
Double blind						
Number Assessed	156	156	312			
Number Censored (%)	103 (66.0)	141 (90.4)	244 (78.2)			
Number of Events (%)	53 (34.0)	15 (9.6)	68 (21.8)			
Statistical Test				29.411	1	<0.0001

[a] Log-rank test.
Source: Study Report

Figure 3: Kaplan-Meier Plot of Time to Recurrence - Interim Analysis (Study PSY-3001: Intent-to-Treat Analysis Set - Interim Analysis)



Secondary Efficacy Analysis

Based on the interim efficacy analysis, the study was terminated early with the recommendation of the IDMC. A secondary efficacy analysis was conducted on the time to recurrence data from all ITT subjects (n=408) through the time of study termination. A higher percentage of subjects in the placebo group (95 subjects or 47%) than the paliperidone palmitate group (31 subjects or 15%) experienced a recurrence event. There was a significant difference (p-value<0.0001, based on the log-rank test) between the treatment groups in the time to recurrence, in favor of paliperidone palmitate (i.e., subjects who continued treatment on paliperidone palmitate after

maintenance experienced a recurrence event later than subjects who received placebo). The secondary efficacy finding was consistent with the interim analysis (p-value<0.0001).

Efficacy Analysis on Secondary Measures

The mean changes from double-blind baseline to endpoint in PANSS total score, CGIS-S, and PSP scales are shown in Table 13. For the three secondary measures, the between-group difference was statistically significant (p-value<0.0001) in favor of paliperidone palmitate. Subjects who continued receiving paliperidone palmitate remained relatively stable in PANSS total score compared to subjects who were switched to placebo. There was a greater mean decrease in the PSP score (indicating worsening) from double-blind baseline to endpoint in the placebo group than the paliperidone palmitate group.

Table 13: Secondary efficacy measures: - Change From Double-Blind Baseline to Endpoint (Double-Blind)-LOCF (Study PSY-3001-Intent-to-Treat Final Analysis Set)

	Placebo (N=203)	Paliperidone Palmitate (N=205)
Change from Baseline in PANSS Total Score		
Mean (SD)	11.1 (16.65)	2.5 (12.23)
P-value (minus Placebo)[a]		<0.0001
Change from Baseline in CGIS-S scale		
Median (Range)	0.0 (-1;4)	0.0 (-1;3)
P-value (minus Placebo) [b]		<0.0001
Change from Baseline in PSP scale		
Mean (SD)	-7.2 (13.08)	-1.8 (10.76)
P-value (minus Placebo) [c]		<0.0001

[a] Based on Analysis of covariance (ANCOVA) model with treatment (Placebo, R092670) and country as factors, and baseline value as a covariate.
[b] Test for no difference between treatments from ANCOVA model on ranks with factors for treatment and country, and with baseline value as a covariate.
[c] Test for no difference between treatments (Placebo, R092670) from ANCOVA model with factors for treatment and country, and with baseline value as a covariate.
Source: Study report

3.3.2. FDA Reviewer's Data Analyses Findings and Comments

This reviewer re-analyzed the efficacy data of the study PSY-3001 according to the protocol specified primary survival (Kaplan-Meier) analysis. The reviewer also did a secondary survival analysis on the primary outcome measure at the end of the study. In addition, the reviewer did sensitivity analyses on the primary efficacy measure by considering the censored patients (who were censored before the time of interim analysis) as relapsed (i.e., having events) patients for both the interim sample (n=312) and ITT sample (n=408).

The reviewer's findings were similar to the sponsor's reported findings on the primary outcome measure. Both the interim analysis and the end of study analysis on the time to data demonstrated significant differences between the treatment groups in the time to recurrence in favor of paliperidone palmitate. The subjects who continued treatment on paliperidone palmitate

experienced recurrence later than subjects who switched to placebo. The sensitivity analysis on the interim data demonstrated significance (Log-rank test: p-value=0.043) of paliperidone palmitate with respect to delay time to recurrence as compared to placebo. The sensitivity analysis on the ITT subjects (n=408) demonstrated significance (Log-rank test: p-value<0.001) of paliperidone palmitate with respect to delay time to recurrence as compared to placebo.

The reviewer did exploratory analyses on time to censor (i.e., survival analysis) of the censored subjects by treatment groups. The analysis indicated that there was no differential patterns of censoring over time between the two groups.

4. SUBGROUP ANALYSES

4.1. Subgroup Analyses –Studies PSY-3003 and PSY-3004

The consistency (i.e., the same direction in treatment effects) across patient subgroups was assessed by analyzing the change from baseline to endpoint in the PANSS total score. Table 14 lists the subgroup analyses findings on the primary outcome measure- the change in PANSS total score. Subgroup analysis of the change from baseline in PANSS total score suggested that treatment with paliperidone palmitate at doses of 25, 50 or 100 mg eq. was effective numerically as compared to placebo in both PSY-3003 and PSY-3004 studies regardless of subjects' age (18-25, 26-50, ≥51 years), gender (male, female), race (White, Black, Asian, Other), and region (North America, Eastern Europe, and Asia).

Table 14: PANSS Total Score - Change From Baseline to Endpoint by subgroups (Age, Gender, Race, and Region)-LOCF (Studies-PSY-3003, and PSY-3004: Primary Efficacy Analysis Sets)

		Paliperidone Palmitate		
Age Group- PSY-3003	Placebo	50 mg eq.	100 mg eq.	150 mg eq.
18-25 years	(N=14)	(N=14)	(N=9)	(N=3)
Mean (SD)	1.9 (21.18)	-9.1 (17.93)	-3.8 (16.50)	5.0 (8.19)
26-50 years	(N=91)	(N=66)	(N=69)	(N=21)
Mean (SD)	-5.4 (19.75)	-7.3 (18.34)	-11.5 (19.37)	-9.4 (20.88)
≥51 years	(N=27)	(N=13)	(N=16)	(N=6)
Mean (SD)	-3.0 (24.96)	-9.4 (22.50)	-12.9 (19.27)	2.7 (16.95)

		Paliperidone Palmitate		
Age Group- PSY-3004	Placebo	25 mg eq.	50 mg eq.	100 mg eq.
18-25 years	(N=13)	(N=13)	(N=17)	(N=14)
Mean (SD)	-4.5 (13.74)	-14.6 (27.79)	-17.2 (17.52)	-20.4 (29.47)
26-50 years	(N=85)	(N=92)	(N=87)	(N=87)
Mean (SD)	-7.7 (20.78)	-13.5 (19.93)	-14.1 (20.45)	-15.6 (20.56)
≥51 years	(N=27)	(N=25)	(N=24)	(N=30)
Mean (SD)	-5.9 (20.80)	-13.2 (24.07)	-7.0 (20.18)	-15.5 (14.31)

		Paliperidone Palmitate			
Sex- PSY-3003	Placebo	25 mg eq.	50 mg eq.	100 mg eq.	150 mg eq.
Male	(N=94)		(N=65)	(N=61)	(N=22)
Mean (SD)	-5.2 (19.67)		-8.8 (18.91)	-11.4 (19.40)	-7.3 (21.24)
Female	(N=38)		(N=28)	(N=33)	(N=8)
Mean (SD)	-1.4 (24.06)		-5.8 (18.39)	-10.2 (18.69)	-0.8 (15.21)
Sex-PSY-3004					
Male	(N=78)	(N=85)	(N=94)	(N=85)	
Mean (SD)	-6.5 (19.00)	-12.7 (21.85)	-16.3 (18.51)	-14.7 (20.99)	
Female	(N=47)	(N=45)	(N=34)	(N=46)	
Mean (SD)	-7.9 (21.92)	-15.1 (20.85)	-4.5 (22.14)	-18.6 (19.09)	

Continuing Table 14.

Race- PSY-3003	Placebo	Paliperidone Palmitate 50 mg eq.	Paliperidone Palmitate 100 mg eq.	Paliperidone Palmitate 150 mg eq.
White	(N=51)	(N=35)	(N=35)	(N=20)
Mean (SD)	-6.2 (16.59)	-7.7 (15.87)	-8.3 (15.01)	-2.4 (16.33)
Black	(N=49)	(N=42)	(N=38)	(N=6)
Mean (SD)	-8.4 (20.30)	-7.5 (17.31)	-14.7 (18.52)	-13.3 (22.98)
Asian	(N=31)	(N=16)	(N=21)	(N=4)
Mean (SD)	5.8 (25.80)	-9.2 (27.47)	-8.8 (25.06)	-9.8 (31.60)

Race-PSY-3004	Placebo	Paliperidone Palmitate 25 mg eq.	Paliperidone Palmitate 50 mg eq.	Paliperidone Palmitate 100 mg eq.
White	(N=84)	(N=87)	(N=88)	(N=85)
Mean (SD)	-5.8 (21.50)	-11.4 (22.43)	-13.1 (19.89)	-16.8 (20.69)
Black	(N=35)	(N=38)	(N=33)	(N=41)
Mean (SD)	-10.8 (17.07)	-17.8 (19.75)	-15.3 (21.57)	-14.0 (19.09)
Asian	(N=1)	(N=2)	(N=3)	(N=1)
Mean (SD)	3.0 ( )	-26.5 (9.19)	7.0 (11.27)	-32.0 ( )
Other	(N=5)	(N=3)	(N=4)	(N=4)
Mean (SD)	-3.4 (15.03)	-14.0 (8.66)	-13.0 (14.17)	-17.8 (30.78)

Region- PSY-3003	Placebo	Paliperidone Palmitate 50 mg eq.	Paliperidone Palmitate 100 mg eq.	Paliperidone Palmitate 150 mg eq.
North America	(N=88)	(N=68)	(N=67)	(N=24)
Mean (SD)	-8.0 (18.69)	-6.2 (16.82)	-10.8 (17.75)	-3.8 (18.24)
Eastern Europe	(N=15)	(N=9)	(N=9)	(N=3)
Mean (SD)	-2.1 (15.21)	-18.6 (9.08)	-16.9 (12.94)	-9.0 (19.00)
Asia	(N=29)	(N=16)	(N=18)	(N=3)
Mean (SD)	6.6 (26.37)	-9.2 (27.47)	-8.9 (25.76)	-16.0 (35.54)

Region-PSY-3004	Placebo	Paliperidone Palmitate 25 mg eq.	Paliperidone Palmitate 50 mg eq.	Paliperidone Palmitate 100 mg eq.
Eastern Europe	(N=54)	(N=56)	(N=53)	(N=54)
Mean (SD)	-4.3 (23.17)	-13.9 (24.31)	-19.5 (19.09)	-20.9 (19.50)
Other	(N=71)	(N=74)	(N=75)	(N=77)
Mean (SD)	-9.0 (17.25)	-13.3 (19.15)	-8.7 (19.79)	-12.7 (20.38)

Source: Summary of efficacy report.

4.2. Subgroup Analyses –Study SCH-201

The consistency across patient subgroups was assessed by analyzing the change from baseline to endpoint in the PANSS total score. Table 15 lists the subgroup analysis findings on the primary outcome measure- the change in PANSS total score. Subgroup analysis of the change from baseline in PANSS total score suggested that treatment with paliperidone palmitate at doses of 50 and 100 mg eq. was effective numerically as compared to placebo regardless of subjects' age (18-25, 26-50, ≥51 years), gender (male, female), race (White, Black, Asian, Other), and geographic regions .

Table 15: PANSS Total Score - Change From Baseline to Endpoint by subgroups (Age, Gender, Race, and Region)-LOCF (Study-SCH-201: Primary Efficacy Analysis

		Paliperidone palmitate	
Age Group-SCH-201	Placebo	50 mg	100 mg
18-25 years	(N=8)	(N=3)	(N=12)
Mean (SD)	13.5 (8.1)	-33.6 (22.3)	-9.0 (17.2)
26-50 years	(N=48)	(N=51)	(N=50)
Mean (SD)	3.2 (19.3)	-5.1 (18.1)	-9.5 (20.1)
>=51 years	(N=10)	(N=9)	(N=6)
Mean (SD)	6.0 (9.6)	-10.3 (16.8)	-4 (10.0)
Sex-SCH-201			
Female	(N=27)	(N=22)	(N=26)
Mean (SD)	6.8 (15.7)	-5.6 (19.1)	-4.3 (21.3)
Male	(N=39)	(N=41)	(N=42)
Mean (SD)	3.4 (18.4)	-8.1 (18.8)	-11.8 (16.6)
Race-SCH-201			
White	(N=54)	(N=50)	(N=55)
Mean (SD)	5.9 (16.0)	-7.5 (20.3)	-8.4 (18.9)
Other	(N=12)	(N=13)	(N=13)
Mean (SD)	0.8 (22.6)	-6.3 (12.2)	-11.3 (18.7)
Country-SCH-201			
BULGARIA	(N=10)	(N=8)	(N=9)
Mean (SD)	-5.3 (17.4)	-10.3 (15.3)	-17.3 (16.6)
POLAND	(N=9)	(N=9)	(N=8)
Mean (SD)	7.6 (13.6)	1.3 (15.5)	7.25 (22.8)
RUSSIA	(N=16)	(N=17)	(N=19)
Mean (SD)	13.8 (16.4)	-9.8 (26.9)	-13.7 (20.7)
UKRAINE	(N=10)	(N=10)	(N=12)
Mean (SD)	7.3 (11.1)	-6.4 (19.4)	-4.1 (11.5)
USA	(N=21)	(N=19)	(N=20)
Mean (SD)	0.5 (19.1)	-8.1 (12.0)	-10.0 (16.5)

This table is produced by this reviewer.

4.3. Subgroup Analyses –Study PSY-3001

Table 16 lists the subgroup analysis findings on the primary outcome measure- incidence rates of recurrence of the symptoms of schizophrenia. The proportion of subjects who experienced recurrence events was higher in the placebo group than the paliperidone palmitate group in all age groups, with the greatest difference observed in the subjects aged >50 years. The recurrence event rates for male and female subjects were similar. The proportion of subjects who experienced recurrence events was higher in the placebo group than in the paliperidone palmitate group across the geographic regions.

Table 16: Incidence rates of Symptoms of Schizophrenia by subgroups (Age, Gender, Region, and Race)-LOCF (Studies-PSY-3001: Primary Efficacy Analysis Sets)

	Placebo	Paliperidone Palmitate
Age Group: 18-25		
Number of Assessed	25	29
Number of Censored (%)	17 (68.0)	22 (75.9)
Number of Events (%)	8 (32.0)	7 (24.1)
Age Group: 26-50		
Number of Assessed	143	147
Number of Censored (%)	75 (52.4)	126 (85.7)
Number of Events (%)	68 (47.6)	21 (14.3)
Age Group: >50		
Number of Assessed	35	29
Number of Censored (%)	16 (45.7)	26 (89.7)
Number of Events (%)	19 (54.3)	3 (10.3)
Sex: MALE		
Number of Assessed	111	109
Number of Censored (%)	63 (56.8)	89 (81.7)
Number of Events (%)	48 (43.2)	20 (18.3)
Sex: FEMALE		
Number of Assessed	92	96
Number of Censored (%)	45 (48.9)	85 (88.5)
Number of Events (%)	47 (51.1)	11 (11.5)
Region: NORTH AMERICA		
Number of Assessed	55	54
Number of Censored (%)	29 (52.7)	48 (88.9)
Number of Events (%)	26 (47.3)	6 (11.1)
Region: EASTERN EUROPE		
Number of Assessed	108	110
Number of Censored (%)	59 (54.6)	97 (88.2)
Number of Events (%)	49 (45.4)	13 (11.8)
Region: ASIA		
Number of Assessed	30	30
Number of Censored (%)	14 (46.7)	20 (66.7)
Number of Events (%)	16 (53.3)	10 (33.3)
Region: REST OF WORLD		
Number of Assessed	10	11
Number of Censored (%)	6 (60.0)	9 (81.8)
Number of Events (%)	4 (40.0)	2 (18.2)
Race: White		
Number of Assessed	133	133
Number of Censored (%)	72 (54.1)	115 (86.5)
Number of Events (%)	61 (45.9)	18 (13.5)
Race: Black		
Number of Assessed	36	36
Number of Censored (%)	19 (52.8)	33 (01.7)
Number of Events (%)	17 (47.2)	3 (8.3)
Race: Asian		
Number of Assessed	34	36
Number of Censored (%)	17 (50.0)	26 (72.2)
Number of Events (%)	17 (50.0)	10 (27.8)

Source: Study report

5. SUMMARY AND CONCLUSIONS

5.1. Collective Evidence of Efficacy

Submitted findings of the 4 multicenter, and adequately controlled trials demonstrate the efficacy of paliperidone palmitate in the prevention of symptom recurrence and treatment of schizophrenia.

5.1.1. Treatment of Schizophrenia

The efficacy of paliperidone palmitate in the treatment of schizophrenia was demonstrated in three short-term double-blind, placebo-controlled Phase III/II clinical studies. The study PSY-3003 (a Phase III) provided statistically significant evidence for the efficacy of paliperidone palmitate 100 mg eq. in reducing the severity schizophrenia. Paliperidone palmitate 50 mg eq. was numerically superior to placebo for the primary efficacy endpoint, but the difference was not statistically significant. Paliperidone palmitate 100 mg eq. was also statistically significantly efficacious as compared to placebo in all 5 PANSS factor scores. The change from baseline to endpoint in the CGI-S scale for the paliperidone palmitate 100 mg eq. group was statistically significantly different from the change in the placebo group.

The second Phase III study PSY-3004 provided evidence for the efficacy of paliperidone palmitate in the treatment of subjects with schizophrenia. The doses of 25 mg eq., 50 mg eq., and 100 mg eq. were statistically significantly different from placebo with respect to the change from baseline to endpoint in total PANSS score. All doses of paliperidone palmitate were statistically significantly different from placebo with respect to the change from baseline to endpoint in the five PANSS factor scores. The changes from baseline to endpoint in the CGI-S scale for all of the three paliperidone palmitate doses were statistically significantly different from the change in the placebo group.

The third Phase II study SCH-201 also provided evidence of the efficacy of paliperidone palmitate in the treatment of subjects with schizophrenia. Doses of 50 mg eq., and 100 mg eq. were statistically significantly different from placebo with respect to the change from baseline to endpoint in total PANSS score. All doses of paliperidone palmitate were statistically significantly different from placebo with respect to the change from baseline to endpoint in the five PANSS factor scores (except Uncontrolled hostility/excitement factor score). The changes from baseline to endpoint in the CGI-S scale for the two paliperidone palmitate doses were statistically significantly different from the change in the placebo group.

5.1.2. Prevention of Recurrence of Symptoms of Schizophrenia

The efficacy of paliperidone palmitate in preventing the recurrence of symptoms of schizophrenia was demonstrated in a double-blind, placebo-controlled Phase III clinical study in subjects at least 18 years of age. Before double-blind treatment, subjects had achieved symptom control during 33 weeks of open-label treatment with flexibly dosed paliperidone palmitate 25 mg eq., 50 mg eq., and 100 mg eq. There was a statistically significant difference 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. The efficacy of paliperidone palmitate in maintaining symptom control was also demonstrated by the secondary efficacy measures PANSS, CGI-S and PSP.

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/s/

Ohidul Siddiqui
6/19/2008 07:59:06 AM
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Peiling Yang
6/19/2008 08:54:18 AM
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Although I sign off this, I found that in Section 5.1 and 5.2 the conclusions about secondary endpoints were not fixed.

James Hung
6/19/2008 01:11:10 PM
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