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APPLICATION NUMBER:

21-999

STATISTICAL REVIEW(S)

Memorandum

NDA/Serial Number:	21-999
Drug Name:	ER OROS Paliperidone
Indication:	Schizophrenia
Applicant:	Johnson & Johnson Pharmaceuticals
Date:	October 17, 2006
Review Priority:	Priority
Biometrics Division:	Biometrics I (HFD-710)
Statistical Reviewer:	Fanhui Kong, PhD
Project Manager:	Keith Kiedrow

1. BACKGROUND

Reference is made to the sponsor's NDA application submitted on November 30, 2005, claiming the effectiveness of ER OROS paliperidone for the treatment of adults with schizophrenia based on the primary endpoint of PANSS total score. The Agency issued an Approvable Letter on September 29, 2006. In this re-submission, in addition to addressing the Agency's concerns raised in the Approval Letter, the sponsor seeks to claim the effectiveness of the treatment on the key secondary endpoint of Personal and Social Performance Scale (PSP) total score in the label. They also seek to claim the efficacy results of the primary endpoint [redacted]

2. REVIEW OF SPONSOR's RE-SUBMISSION

In this section, we summarize the responses provided by the sponsor regarding the Agency's decision of deleting the reference to the secondary endpoint and to the [redacted] from the Approval Letter.

To respond to the efficacy comment of the Agency "*We have deleted reference to any secondary outcomes because these were not prospectively designated as key secondaries and properly addressed in the SAP*", the sponsor points out:

a. Prior to database lock of the first completed Phase 3 study (Study 304), the sponsor conducted two teleconferences with the Agency on January 13, 2005 and February 2, 2005 and the Agency agreed that a single secondary endpoint was acceptable for inclusion in the label for the NDA submission.

b. In the Briefing Document of the March 23, 2005 preclinical and clinical pre-NDA meeting submitted to FDA on May 24, 2005 (SN139), the sponsor proposed a two stage procedure to control the Type I error rate: "The overall type I error rate for the comparisons of paliperidone and placebo based on the family of primary endpoint comparisons and the family of secondary endpoint comparisons will be controlled at the 0.05 level. The analysis will be performed in 2 stages. The first stage involves the primary endpoint. Dunnett's method will be used to identify effective doses and to adjust for multiplicity testing of the 2 (or 3) paliperidone doses against placebo. The second stage involves the analysis of the secondary endpoints." They also specified the key secondary endpoint: change from baseline to endpoint in Personal and Social Performance Scale (PSP).

c. In the statistical analysis plans (SAP) for Phase 3 studies (Studies 303, 304 and 305), which they claimed to be finalized prior to the respective database lock for each study, they specified the secondary endpoint of PSP and further detailed the two stage procedure: "Dunnett's test will be performed for the change from baseline to endpoint in the PSP. The model will include all paliperidone treatment groups regardless of the significance level observed in the primary analysis. Upon completion of the primary analysis on the PANSS and the secondary analysis on the PSP, whatever doses achieve statistical significance based on the secondary endpoint will be considered as having the secondary benefit only if the corresponding doses were significant for the primary endpoint. If none of the doses are significant for the secondary endpoint but at least one dose is significant for the primary endpoint, only the effective doses as defined by the primary endpoint will be identified."

In addition, the sponsor objects to the Agency's decision of deleting [redacted]. They argue that such a plan was submitted to the Agency in the Briefing Document of the March 23, 2005 preclinical and clinical pre-NDA meeting submitted to the Agency on May 24, 2005 (SN 139) and was also in the meeting minutes of the March 23, 2005 preclinical and clinical pre-NDA meeting dated May 19, 2005. So the sponsor suggests that [redacted] was prespecified and discussed with the Agency, at which time the Agency did not object. So they propose to retain the text describing the findings based on [redacted]

3. REVIEWER'S REEVALUATION

We have carefully re-examined the meeting minutes and documents submitted by the sponsor related to these two issues in these studies and have the following comments.

Regarding the sponsor's suggestion of [redacted] and claiming the findings based on the [redacted] on the primary endpoint, it needs to be pointed out that this is not in line with the general practice of the Agency so it cannot be accepted. We typically allow sponsors to include exploratory results of [redacted] in the section of the Integrated Analysis of Efficacy in the NDA Study Report. However, this is irrelevant to labeling claims.

In the teleconferences of January 13, 2005 and February 22, 2005, the Agency allowed the sponsor to claim one key secondary endpoint along with the primary endpoint of PANSS total score. During the discussion, the Agency suggested to use PSP as the key secondary endpoint. They also agreed with a hierarchical approach of analyzing both the primary and key secondary endpoints using the Dunnett's method for all dose groups to control overall Type I error. The labeling claims for the secondary endpoint were allowed only for the doses for which the results were positive on both the primary and secondary endpoint. The corresponding SAP was submitted in the Appendix of the Study Report. The

SAP was not reviewed by the Agency although the sponsor claims that it was finished before the database lock of the studies.

The efficacy results on the change from baseline of the PSP total score of LOCF data are reviewed and verified using the data sets provided by the sponsor, see Table 1. Table 1 indicates that treatment effect on the change from baseline of the PSP total score at the endpoint is quite significant on all dose levels. Since this score was observed only at the last visit, there are no corresponding efficacy results for previous visit times.

Table 1: Statistical Comparisons between Treatment and Placebo for the Key Secondary Endpoint PSP Total Score in Fixed-Dose Studies 303, 304, and 305–LOCF ITT Population

Study		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Study 303	(N=126)		(N=123)	(N=122)	(N=129)	
N[a]	120		119	118	129	
Change from Baseline Diff of LS Means (SE) P-Value [b,c]			8.9 (1.32) <0.001	7.7 (1.32) <0.001	10.7 (1.27) <0.001	
Study 304	(N=105)		(N=111)		(N=111)	
N[a]	89		95		91	
Change from Baseline Diff of LS Means (SE) P-Value [b,c]			8.6 (1.23) 0.01		6.3 (1.27) 0.21	
Study 305	(N=120)	(N=123)		(N=123)		(N=113)
N[a]	109	113		116		107
Change from Baseline Diff of LS Means (SE) P-Value [b,c]		6.8 (1.35) <0.001		7.2 (1.31) <0.001		10.5 (1.38) <0.001

a: The number of observations available in the LOCF data set for the PSP Total Score.
b: Test for no difference between treatments from ANCOVA model with treatment and analysis center as factors, and baseline value as a covariate. Olanzapine data were excluded from the model.
c: Pairwise comparison: p-values associated with Dunnett's procedure.
Note: Positive change in score indicates improvement.
Source: Reviewer.

4. STATISTICAL CONCLUSION

We agree that the sponsor has shown that the PSP total score was prespecified as the key secondary endpoint along with the corresponding statistical analysis method. Therefore, such results can be claimed in the label. On the other hand, [redacted] the labeling is not in line with the general practice of the Agency, so it cannot be accepted.

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-999
Drug Name: ER O	ROS Paliperidone
Indication(s):	Schizophrenia
Applicant:	Johnson & Johnson Pharmaceuticals
Date(s):	November 30, 2005
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD-710)
Statistical Reviewer:	Fanhui Kong
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Keywords: ANCOVA, MMRM, LOCF, Dunnett's Method, Schizophrenia.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this submission, the sponsor conducted 4 short-term ER OROS paliperidone studies between February 2004 and May 2005 in North America, Europe, Asia, Mexico, Israel and South Africa. Three pivotal studies were evaluated in this review. The primary objectives of the studies were to evaluate the efficacy and safety of ER OROS paliperidone compared with placebo in subjects with schizophrenia and to identify the effective dose range. The primary efficacy measure was the change from baseline in PANSS total score.

The analysis results support the claim of the effectiveness of ER OROS paliperidone in the treatment of schizophrenia in all dose groups of the three pivotal studies. The efficacy results were supported by pre-specified analyses of nonparametric methods, mixed-effects models repeated measures analysis (MMRM) and worst rank analysis. Together these results support the claim of ER OROS paliperidone in the treatment of schizophrenia.

1.2 Brief Overview of Clinical Studies

Four short-term ER OROS paliperidone studies were submitted for the evaluation of the efficacy of ER OROS paliperidone in doses of 3 mg to 15 mg/day in the treatment of patients with schizophrenia. The studies were conducted between February 2004 and May 2005 in North America, Europe, Asia, Mexico, Israel and South Africa. Three fixed-dose studies (Studies 303, 304, and 305) were pivotal and one flexible-dose study (Study 302) was not. All the studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in adults with schizophrenia, with a double-blind treatment period of 6 weeks. Olanzapine was also used as an active comparator in the pivotal studies. The primary objectives of the pivotal studies were to evaluate the efficacy and safety of ER OROS paliperidone compared with placebo in subjects with schizophrenia and to identify the effective dose range. The primary efficacy measure was the change from baseline of PANSS total score. In the data analysis, all the three pivotal efficacy studies were highly positive on the reduction of the primary efficacy measure in LOCF analyses.

After the screening period, subjects were treated during a double-blind period in arms with doses of ER OROS paliperidone ranging from 3 to 15 mg/day, placebo, and the comparator olanzapine for 6 weeks. In the pooled data of the pivotal studies 303, 304 and 305, a total of 1692 subjects were randomized to trial treatments. Of those, 1665 subjects were included in the ITT analysis data sets, including 351 subjects in the placebo group, 955 subjects in the ER OROS paliperidone dose groups (3 mg, 6 mg, 9 mg, 12 mg, and 15 mg), and 359 subjects in the olanzapine 10 mg dose group. The majority of the patients were white. In Studies 304 and 305, the majority were male. The average age was 37 in Study 303, 42 in Study 304 and 38 in Study 305.

1.3 Statistical Issues and Findings

Pivotal efficacy studies 303, 304 and 305 were all 6-week, phase 3, multicenter, randomized, double blind, placebo-controlled, fixed-dose studies with treatment arms of ER OROS paliperidone 3 mg to 15

mg dose groups and placebo. The primary efficacy analyses on the change from baseline in PANSS total score were performed using ANCOVA with LOCF data. Statistical significance levels were adjusted by Dunnett's method.

The analysis results supported the efficacy claim of ER OROS paliperidone in the treatment of schizophrenia in all the dose groups of the three studies. The efficacy results were supported by pre-specified analyses of nonparametric methods, mixed-effects model repeated measures analysis and worst rank analysis. Together these results supported the claim of ER OROS paliperidone in the treatment of schizophrenia.

2. INTRODUCTION

2.1 Overview

In this submission, 4 short-term (6 week) studies were submitted for the evaluation of the efficacy and safety of ER OROS Paliperidone in doses of 3 to 15 mg/day in the treatment of schizophrenia in adult outpatients (Table 2.1).

Table 2.1: Studies Supporting the Efficacy and Safety of ER OROS Paliperidone in the Treatment of Schizophrenia

Protocol	Study Description	Study Treatments	No. of Subjects[a]
Completed Controlled, Fixed-Dose Studies in Adult Subjects with Schizophrenia			
R076477-SCH-303	6-week, randomized, double-blind, placebo- and active-controlled, parallel group, multicenter dose response study.	Placebo	126
		ER OROS Paliperidone	
		6 mg/day	123
		9 mg/day	122
		12 mg/day	130
		Olanzapine 10 mg/day	128
R076477-SCH-304	6-week, randomized, double-blind, placebo- and active-controlled, parallel group, multicenter dose response study.	Placebo	106
		ER OROS Paliperidone	
		6 mg/day	112
		12 mg/day	112
		Olanzapine 10 mg/day	109
R076477-SCH-305	6-week, randomized, double-blind, placebo- and active-controlled, parallel group, multicenter dose response study.	Placebo	123
		ER OROS Paliperidone	
		3 mg/day	127
		9 mg/day	124
		15 mg/day	113
		Olanzapine 10 mg/day	127
Completed Controlled Flexible-Dose Study in Elderly Subjects with Schizophrenia			
R076477-SCH-302	6-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study.	Placebo	38
		ER OROS Paliperidone (flexible dose 3 to 12 mg/day)	76

a: Includes all subjects who were evaluable for safety.

Source: Page 14 of sponsor's Summary of Clinical Efficacy.

Three of the studies were fixed-dose studies (Studies 303, 304, and 305) and one was flexible-dose study (Study 302). All of these studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in adults (Study 302 for elderly) with schizophrenia, with a double-blind treatment period of 6 weeks. Study 302 not pivotal. It was conducted only for the safety and tolerability of the treatment in elderly patients with only a small sample size, therefore its efficacy analysis will not be evaluated in this review. Only the efficacy results of Studies 303, 304, and 305 are evaluated in this review.

These studies were conducted between February 2004 and May 2005 (March 39, 2004 to January 25, 2005 for Study 303, February 17, 2004 to December 22, 2004 for Study 304, and May13, 2004 to May 24, 2005 for Study 305) in North America (US and Canada), Eastern and Western Europe, Asia, Mexico, Israel and South Africa. In the pooled data of pivotal Studies 303, 304 and 305, a total of 1692 subjects were randomized to trial treatment. Of those, 1665 subjects were included in the ITT analysis data sets, including 351 subjects in the placebo group, 955 subjects in the ER OROS paliperidone dose groups (3 mg, 6 mg, 9 mg, 12 mg, and 15 mg), and 359 subjects in the olanzapine 10 mg dose group. The numbers of subjects in all studies are given in Table 2.1.

2.2 Data Sources

The electronic study reports and electronic SAS transport data sets for the studies are provided in \\Cdsesub1\evsprod\n021999\0000\m2 and \\Cdsesub1\evsprod\n021999\0000\m5.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The pivotal efficacy studies were all 6-week, multicenter, randomized, double-blind, placebo- and active-controlled. Each was designed to evaluate the efficacy and safety of ER OROS paliperidone compared with placebo in subjects with schizophrenia and to identify the effective dose range. Olanzapine 10 mg/day was included as an active control in the studies. Eligible subjects were randomly assigned to receive fixed dosages in the morning of ER OROS paliperidone (range of 3 to 15 mg/day), olanzapine 10 mg, or placebo (Table 2.1). Subjects were assigned to either 1 of 5 treatment groups (3 fixed doses of ER OROS paliperidone, olanzapine 10 mg, or placebo) in Studies 303 and 305, or 1 of 4 treatment groups (2 fixed doses of ER OROS paliperidone, olanzapine 10 mg, or placebo) in Study 304. No dose adjustment was permitted during the double-blind phase (except for the first-week titration in the 15 mg dose group in Study 305 per protocol). Randomization was balanced using permuted blocks of treatment and was stratified by study center.

Eligible subjects were $\geq$ 18 years of age, with a DSM-IV diagnosis of schizophrenia for at least 1 year, and were experiencing active symptoms at the time of enrollment with a PANSS total score at screening and baseline of 70 to 120 points (inclusive). The change from baseline to the endpoint (Day 43) in PANSS total score was the primary variable. Secondary variables included changes from baseline to the endpoint in PSP scale, CGI-S, and SQLS scale. The tests were two sided and the overall significance level for each study was α=0.05.

3.1.1 Dispositions

The number of subjects randomly assigned to each treatment group and those included in the ITT analysis data set are shown in Table 3.1. In Study 303, 630 subjects were randomized to trial treatments, and of these, 628 subjects were included in the ITT analysis data set, including 374 subjects in the ER OROS paliperidone dose groups (6 mg, 9 mg, and 12 mg) and 126 subjects in placebo. In Study 304, 444 subjects were randomized to trial treatments, and of these, 432 subjects were included in the ITT analysis data set, including 222 subjects in the ER OROS paliperidone dose groups (6 mg and 12 mg) and 105 subjects in placebo. In Study 305, 618 subjects were randomized to trial treatments, and of these, 605 subjects were included in the ITT analysis data set, including 359 subjects in the ER OROS paliperidone dose groups (3 mg, 9 mg, and 15 mg) and 120 in placebo.

Table 3.1: Number of Subjects Randomly Assigned by Group in Each Study

		ER OROS PAL						Olanzapine
	Placebo (N=360)	3 mg (N=127)	6 mg (N=235)	9 mg (N=247)	12 mg (N=242)	15 mg (N=115)	Total (N=966)	10 mg (N=366)
Study Numbers	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Study R076477-SCH-303								
All Randomized	127 (35)	0	123 (52)	122 (49)	130 (54)	0	375 (39)	128 (35)
Intent-to-Treat	126 (35)	0	123 (52)	122 (49)	129 (53)	0	374 (39)	128 (35)
Study R076477-SCH-304								
All Randomized	110 (31)	0	112 (48)	0	112 (46)	0	224 (23)	110 (30)
Intent-to-Treat	103 (29)	0	111 (47)	0	111 (46)	0	222 (23)	105 (29)
Study R076477-SCH-305								
All Randomized	123 (34)	127 (100)	0	125 (51)	0	115 (100)	367 (38)	128 (35)
Intent-to-Treat	120 (33)	123 (97)	0	123 (50)	0	113 (98)	359 (37)	126 (34)

Source: Table 7 on Page 35 of sponsor's Summary of Clinical Efficacy.

3.1.2 Demographic Characteristics

The patient baseline demographic characteristics appear in Tables 3.2 to 3.4 for these three studies. There seemed to be no significant differences among treatment groups in the demographic characteristics. The majority of the patients were white. In Studies 304 and 305, the majority were male. The average age was 37 in Study 303, 42 in Study 304 and 38 in Study 305.

Table 3.2 Baseline Demographic Characteristics for Study 303--ITT Population

		ER OROS PAL			Olanzapine	
	Placebo (N=126)	6 mg (N=123)	9 mg (N=122)	12 mg (N=129)	10 mg (N=128)	Total (N=628)
Age (years)						
N	126	123	122	129	128	628
Category,n (%)						
18-25	15 (12)	17 (14)	15 (12)	22 (17)	25 (20)	94 (15)
26-50	96 (76)	94 (76)	87 (71)	93 (72)	89 (70)	459 (73)
51-65	13 (10)	11 (9)	19 (16)	13 (10)	12 (9)	68 (11)
>65	2 (2)	1 (1)	1 (1)	1 (1)	2 (2)	7 (1)
Mean (SD)	37.9 (10.89)	37.0 (10.23)	38.5 (11.41)	36.0 (10.61)	36.3 (11.21)	37.1 (10.89)
Median	36.5	37.0	38.5	34.0	35.0	35.0
Range	(19;71)	(19;66)	(19;67)	(19;66)	(18;71)	(18;71)
Sex, n (%)						
N	126	123	122	129	128	628
Male	66 (52)	61 (50)	72 (59)	69 (53)	60 (47)	328 (52)
Female	60 (48)	62 (50)	50 (41)	60 (47)	68 (53)	300 (48)
Race, n (%)						
N	126	123	122	129	128	628
White	106 (84)	106 (86)	105 (86)	111 (86)	111 (87)	539 (86)
Asian	1 (1)	0	0	0	1 (1)	2 (<1)
Other	19 (15)	17 (14)	17 (14)	18 (14)	16 (13)	87 (14)
Ethnicity, n (%)						
N	126	123	122	129	128	628
Hispanic or Latino	3 (2)	6 (5)	6 (5)	5 (4)	7 (5)	27 (4)
Native American (American Indian)	0	0	0	1 (1)	0	1 (<1)
Neither Hispanic/Latino nor Native American	123 (98)	117 (95)	116 (95)	123 (95)	121 (95)	600 (96)

Source: Table 7 on Page 67 of sponsor's Clinical Study Report R076477-SCH-303.

Table 3.3 Baseline Demographic Characteristics for Study 304--ITT Population

	Placebo (N=105)	ER OROS PAL 6 mg (N=111)	ER OROS PAL 12 mg (N=111)	Olanzapine 10 mg (N=105)	Total (N=432)
Age (years)					
N	105	111	111	105	432
Category, n (%)					
18-25	8 (8)	10 (9)	13 (12)	11 (10)	42 (10)
26-50	74 (70)	79 (71)	80 (72)	72 (69)	305 (71)
51-65	23 (22)	21 (19)	18 (16)	20 (19)	82 (19)
>65	0	1 (1)	0	2 (2)	3 (1)
Mean (SD)	42.3 (10.73)	42.1 (10.22)	41.4 (10.74)	40.5 (11.04)	41.6 (10.67)
Median	43.0	43.0	43.0	40.0	43.0
Range	(20;64)	(19;73)	(19;64)	(19;76)	(19;76)
Sex, n (%)					
N	105	111	111	105	432
Male	82 (78)	76 (68)	77 (69)	84 (80)	319 (74)
Female	23 (22)	35 (32)	34 (31)	21 (20)	113 (26)
Race, n (%)					
N	105	111	111	105	432
White	50 (48)	46 (41)	45 (41)	44 (42)	185 (43)
Black	53 (50)	64 (58)	65 (59)	56 (53)	238 (55)
Asian	0	0	0	4 (4)	4 (1)
Other	2 (2)	1 (1)	1 (1)	1 (1)	5 (1)
Ethnicity, n (%)					
N	105	111	111	105	432
Hispanic or Latino	7 (7)	11 (10)	8 (7)	7 (7)	33 (8)
Native American (American Indian)	3 (3)	3 (3)	3 (3)	3 (3)	12 (3)
Neither Hispanic/Latino nor Native American	95 (90)	97 (87)	100 (90)	95 (90)	387 (90)

Source: Table 7 on Page 66 of sponsor's Clinical Study Report R076477-SCH-304.

Table 3.4 Baseline Demographic Characteristics for Study 305--ITT Population

	Placebo (N=120)	ER OROS PAL 3 mg (N=123)	ER OROS PAL 9 mg (N=123)	ER OROS PAL 15 mg (N=113)	Olanzapine 10 mg (N=126)	Total (N=605)
Age (years)						
N	120	123	123	113	126	605
Category, n (%)						
18-25	22 (18)	24 (20)	26 (21)	17 (15)	18 (14)	107 (18)
26-50	83 (69)	84 (68)	87 (71)	84 (74)	95 (75)	433 (72)
51-65	15 (13)	15 (12)	10 (8)	12 (11)	13 (10)	65 (11)
Mean (SD)	37.3 (10.94)	36.3 (10.98)	36.2 (10.88)	37.6 (9.84)	36.5 (10.18)	36.8 (10.56)
Median	36.5	35.0	35.0	38.0	36.0	36.0
Range	(18;61)	(19;64)	(18;60)	(18;62)	(18;61)	(18;64)
Sex, n (%)						
N	120	123	123	113	126	605
Male	83 (69)	78 (63)	79 (64)	73 (65)	96 (76)	409 (68)
Female	37 (31)	45 (37)	44 (36)	40 (35)	30 (24)	196 (32)
Race, n (%)						
N	120	123	123	113	126	605
White	61 (51)	61 (50)	65 (53)	50 (44)	60 (48)	297 (49)
Black	26 (22)	25 (20)	22 (18)	27 (24)	29 (23)	129 (21)
Asian	27 (23)	30 (24)	28 (23)	29 (26)	30 (24)	144 (24)
Other	6 (5)	7 (6)	8 (7)	7 (6)	7 (6)	35 (6)
Ethnicity, n (%)						
N	120	123	123	113	126	605
Hispanic or Latino	5 (4)	5 (4)	7 (6)	3 (3)	7 (6)	27 (4)
Native American (American Indian)	1 (1)	0	0	0	0	1 (<1)
Neither Hispanic/Latino nor Native American	114 (95)	118 (96)	116 (94)	110 (97)	119 (94)	577 (95)

Source: Table 7 on Page 65 of sponsor's Clinical Study Report R076477-SCH-305.

3.1.3 Patient Discontinuation

In Study 303, 630 subjects were randomized and 415 (66%) completed the 6-week double-blind phase, as shown in Table 3.5. The most common reason for early withdrawal was lack of efficacy: 40% in the placebo group, 16%, 16% and 10% in the ER OROS paliperidone 6 mg, 9 mg and 12 mg group, respectively.

In Study 304, 444 subjects were randomized and 192 (43%) completed the 6-week double-blind phase, as shown in Table 3.5. The most common reason for early withdrawal was lack of efficacy: 35% in the placebo group, 23% and 14% in the ER OROS paliperidone 6 mg and 12 mg group, respectively. The second most common reason for early withdrawal was subject withdrawal consent: 15% in the placebo group, 17% and 19% in the ER OROS paliperidone 6 mg and 12 mg group, respectively.

In Study 305, 618 subjects were randomized and 365 (59%) completed the 6-week double-blind phase, as shown in Table 3.5. The most common reason for early withdrawal was lack of efficacy: 44% in the placebo group, 24%, 18% and 12% in the ER OROS paliperidone 3 mg, 9 mg and 15 mg group, respectively.

Table 3.5 Number (%) of Subjects Who Discontinued Treatment During the Double-Blind Period by Primary Reason for Withdrawal

Study		ER OROS PAL					Olanzapine
Reason	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	10 mg
Study 303	(N=127)		(N=123)	(N=122)	(N=130)		(N=128)
Total withdraw	69 (54)		43 (35)	36 (30)	29 (22)		38 (30)
Lack of efficacy	51 (40)		20 (16)	19 (16)	13 (10)		19 (15)
Subject withdrawal consent	7 (6)		9 (7)	11 (9)	8 (6)		5 (4)
Adverse event	9 (7)		8 (7)	4 (3)	8 (6)		9 (7)
Lost to follow-up	2 (2)		1 (1)	2 (2)	0		2 (2)
Death	0		0	0	0		1 (1)
Non-compliance	0		0	0	0		1 (1)
Other	0		5 (4)	0	0		1 (1)
Study 304	(N=110)		(N=112)		(N=112)		(N=110)
Total withdraw	73 (66)		61 (54)		58 (52)		60 (55)
Lack of efficacy	39 (35)		26 (23)		16 (14)		24 (22)
Subject withdrawal consent	17 (15)		19 (17)		21 (19)		17 (15)
Adverse event	5 (5)		8 (7)		6 (5)		8 (7)
Lost to follow-up	4 (4)		8 (7)		10 (9)		6 (5)
Non-compliance	3 (3)		0		3 (3)		2 (2)
Other	5 (5)		0		2 (2)		3 (3)
Study 305	(N=123)	(N=127)		(N=125)		(N=115)	(N=128)
Total withdraw	76 (62)	57 (45)		47 (38)		33 (29)	40 (31)
Lack of efficacy	54 (44)	31 (24)		23 (18)		14 (12)	16 (13)
Subject withdrawal consent	13 (11)	17 (13)		18 (14)		8 (7)	11 (9)
Adverse event	5 (4)	3 (2)		6 (5)		4 (3)	5 (4)
Lost to follow-up	0	1 (1)		0		2 (2)	3 (2)
Non-compliance	0	1 (1)		0		2 (2)	1 (1)
Other	4 (3)	4 (3)		0		3 (3)	4 (3)

Source: Tables 8, 9, 10 of sponsor's Summary of Clinical Efficacy.

3.1.4 Baseline Disease Characteristics

Across the individual studies, the baseline psychiatric diagnosis and history were similar. All subjects were diagnosed with schizophrenia, and the most common diagnosis was paranoid schizophrenia. At baseline, the mean PANSS total scores were similar and CGI-S scores indicated that most subjects were at least markedly ill.

3.1.5 Statistical Issues and Results

The primary efficacy analysis was performed on the change from baseline of the PANSS total score at the end of the double blind phase (Day 43) in the ITT population, defined as all the subjects who were randomized, received at least 1 dose of study medication, and had a least 1 post-baseline efficacy assessment (PANSS, PSP, CGI-S, SQLS, or sleep VAS). The primary comparison was between each ER OROS paliperidone dose group and placebo. Data from olanzapine group were excluded from efficacy analysis. Data from the centers with fewer than 5 subjects in the ITT analysis data set (i.e., small centers) were pooled with that from larger centers within the same country (see Appendix 2.2 of the sponsor's Clinical Study Report of Studies 303, 304, and 305). Statistical significance was tested at an overall significance level of 0.05 (2-sided) in each study. LOCF was used as the primary analysis for the missing observations of the dropout patients. The analysis of covariance (ANCOVA) with treatment and site as factors and the baseline PANSS score as a covariate was used to test treatment effect. Using this model, estimated least squares (LS) means of the difference, p-values that adjusted for multiple comparisons using the Dunnett procedure, and Dunnett-adjusted 95% confidence intervals (CI) were presented for the difference in change between each ER OROS paliperidone treatment group and placebo. The efficacy results using LOCF analysis are depicted in Table 3.5.

As a sensitivity analysis, MMRM was applied for the primary efficacy measure. It was used as an exploratory analysis to evaluate the change of treatment effect over time. It could give reliable results if the patient dropouts were non-informative, with dropouts only depending on the observed outcome values, not on the unobserved values. However, this assumption cannot be directly verified. Nevertheless, positive results in the MMRM analysis support the effectiveness claim of the treatment.

Because subjects dropped out early for lack of efficacy, a worst rank analysis was performed for robust interpretation of the primary efficacy data. In this analysis, withdrawal from the study due to "lack of efficacy" indicates no improvement or a worsening of condition, thus leading to informatively missing data at the endpoint. Subjects who discontinued due to "lack of efficacy" were assigned a rank that represents a "worst-rank score" relative to those actually observed. These ranks reflected the relative ordering of the actual times to discontinuation.

The normality and equal variance assumptions underlying the primary ANCOVA model were assessed graphically for the total PANSS at endpoint. Residuals from the primary ANCOVA model would be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution were presented. According to SAP, if either the equal variance or the normality assumption appeared to be grossly violated, other sensitivity analyses, such as rank-based methods, would be performed.

Table 3.5: Statistical Comparisons between Treatment and Placebo for Primary Efficacy Variable PANSS Total Score in Fixed-Dose Studies 303, 304, and 305–LOCF ITT Population

Study		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Study 303	(N=126)		(N=123)	(N=122)	(N=129)	
Baseline						
N	126		123	122	129	
Mean (SD)	94.1 (10.74)		94.3 (10.48)	93.2 (11.90)	94.6 (10.98)	
Change from Baseline Mean (SD)	-4.1 (23.16)		-17.9 (22.23)	-17.2 (20.23)	-23.3 (20.12)	
P-Value (minus Placebo)[a,b]			<0.001	<0.001	<0.001	
Diff of LS Means (SE)			-13.7 (2.63)	-13.5 (2.63)	-18.9 (2.60)	
95% CI			(-19.91,-7.53)	(-19.65,-7.25)	(-25.07,-12.82)	
Study 304	(N=105)		(N=111)		(N=111)	
Baseline						
N	105		110		111	
Mean (SD)	93.6 (11.71)		92.3 (11.96)		94.1 (11.42)	
Change from Baseline Mean (SD)	-8.0 (21.48)		-15.7 (18.89)		-17.5 (19.83)	
P-Value (minus Placebo) [a,b]			0.006		<0.001	
Diff of LS Means (SE)			-7.0 (2.36)		-8.5 (2.35)	
95% CI			(-12.27, -1.81)		(-13.75,-3.32)	
Study 305	(N=120)	(N=123)		(N=123)		(N=113)
Baseline						
N	120	123		123		112
Mean (SD)	93.9 (12.66)	91.6 (12.19)		93.9 (13.20)		92.4 (12.36)
Change from Baseline Mean (SD)	-2.8 (20.89)	-15.0 (19.61)		-16.3 (21.81)		-19.9 (18.41)
P-Value (minus Placebo) [a,b]		<0.001		<0.001		<0.001
Diff of LS Means (SE)		-11.6 (2.35)		-12.9 (2.34)		-17.2 (2.40)
95% CI		(-17.17,-6.09)		(-18.42,-7.38)		(-22.82,-11.51)

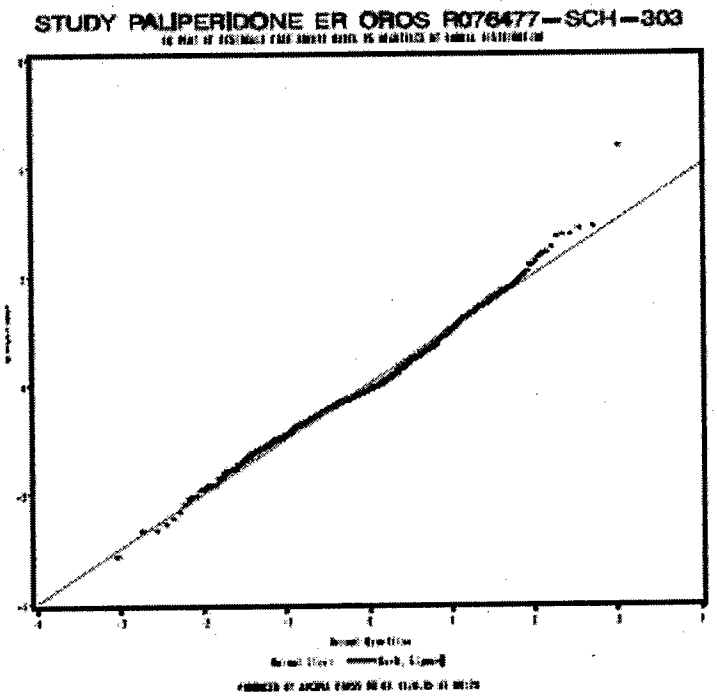
a: Test for no difference between treatments from ANCOVA model with treatment and analysis center as factors, and baseline value as a covariate. Olanzapine data were excluded from the model.
b: Pairwise comparison: p-values associated with Dunnett's procedure.
Note: Negative change in score indicates improvement.

Source: Tables 15 in sponsor's Clinical Study Report of Studies 303, 304 and 305.

In the data analysis, all the efficacy results of the primary endpoint between ER OROS paliperidone and placebo in LOCF analyses were statistically significant. These results were also verified by the reviewer using the data sets submitted by the sponsor. The normality assumption for the primary endpoint of the total PANSS score was assessed with the QQ plots of the residuals from the ANCOVA model on its change from baseline. The QQ plots indicate that the normality assumption was reasonable. For Study

303, the plot is given in Figure 3.1. The homoscedasticity was assessed through the plot of residuals against predicted values from ANCOVA model on the change from baseline in PANSS total score at the end point using LOCF data. No heteroscedasticity was found from the plots.

Figure 3.1: QQ plot of residuals from ANCOVA model on the change from baseline in PANSS total score at the end point - ITT LOCF



Source: Page 3289 from sponsor's Clinical Study Report R074677-SCH-303

As one of the sensitivity analyses, nonparametric ANCOVA was performed, using the rank of the change from baseline in PANSS score as the response, with treatment and site as factors and ranked baseline score as a covariate. Nonparametric ANCOVA analyses using LOCF data gave *p*-values below 0.001 (<0.01 in Study 304) for ER OROS paliperidone versus placebo in Studies 303 and 305 for all the dose groups. The corresponding Wilcoxon rank sum test gave *p*-values below 0.01. These supported the claim of the effectiveness of the ER OROS paliperidone in the treatment of schizophrenia. Such nonparametric analyses results do not depend on model assumptions.

In longitudinal studies, patient dropout raises concerns on the reliability and interpretation of efficacy results. As the pre-specified primary analysis, it's hard to directly assess the LOCF analysis results due to the high dropout rates as indicated above. In general, if the mean of the outcome measure is stable over the whole study period, the LOCF procedure may be reliable. Otherwise, it could produce very unreliable results.

The results of the worst rank analysis showed that ER OROS paliperidone groups were statistically significantly better than placebo (p-values below 0.001 for all the dose groups in Studies 303 and 305; p-value = 0.015 and <0.001 for dose groups 6 mg and 12 mg in Study 304.).

In all three studies, the MMRM analysis gave statistically significant efficacy results for the primary endpoint for the ER OROS paliperidone groups versus placebo. P-values were below 0.0001 for all the dose groups of Studies 303 and 305, and p-values were below 0.01 for the dose groups of Study 304 (p-values without multiplicity adjustment). These results supported the effectiveness of ER OROS paliperidone in the treatment of schizophrenia in the improvement of the PANSS total score.

In conclusion, the protocol specified primary analyses using LOCF procedure in fixed dose Studies 303, 304 and 305 gave positive efficacy results supporting the claim of the effectiveness of ER OROS paliperidone in the treatment of schizophrenia. These results were supported by pre-specified analyses of nonparametric methods, random-effects model repeated measures analysis and worst rank analysis. Together these results supported the effectiveness of ER OROS paliperidone in the treatment of schizophrenia.

The sponsor intended to claim the treatment effect of OROS paliperidone in each PANSS factor and the PSP scale. However, these secondary endpoints were not pre-specified for inclusion in labeling. Results of these hypothesis-generating analyses can only be considered exploratory.

3.2 Evaluation of Safety

See medical review for detail.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The treatment effects in each sex and treatment group are depicted in Table 4.1.The effect of sex on the treatment effect was explored by testing the significance of the treatment effect at a nominal level of 0.05 after the adjustment of sex alone, and sex by treatment interaction on the change from baseline of PANSS score. Sex was statistically significant in Study 303, but not the interaction between sex and treatment. However, it was not significant in Studies 304 and 305, nor was the treatment and sex interaction. Sex did not seem to have a dramatic effect on the significance level of the treatment on the primary efficacy endpoint.

Table 4.1 Treatment Effect by Sex on the effect size in Studies 303, 304 and 305 (LOCF Analysis)

		ER OROS PAL				
Study	**Placebo**	**3 mg**	**6 mg**	**9 mg**	**12 mg**	**15 mg**
Study 303						
Male	N=66		N=61	N=72	N=69	
Mean Eff. Size	-1.86		-15.43	-16.64	-20.42	
Female	N=60		N=62	N=50	N=60	
Mean Eff. Size	-6.53		-20.29	-18.04	-26.62	
Study 304						
Male	N=82		N=75		N=77	
Mean Eff. Size	-7.77		-13.47		-15.73	
Female	N=23		N=35		N=34	

Mean Eff. Size	-8.83		-20.54		-21.56	
Study 305						
Male	N=83	N=78		N=79		N=72
Mean Eff. Size	-3.65	-15.18		-15.37		-20.90
Female	N=37	N=45		N=44		N=40
Mean Eff. Size	-0.76	-14.62		-18.0		-18.13

Source: FDA analysis.

The sample size was considerably larger in the male group in Studies 304 and 305. The above table suggests that the treatment effect sizes were comparable between males and females in all this studies. But the ER OROS paliperidone treatment groups were not significantly better than placebo at nominal significance level of 0.05 in the female group of Study 304, due to the small sample size and small differences of the least squared means between each treatment group and placebo.

To consider the treatment effect in different ethnic groups, we note that there were about 87% white in all the studies. As for the treatment effect in age groups, we note that the vast majority of the patients were middle aged. More than 70% of the patients were between 25 and 50, and more than 98% were between the age of 18 and 65.

4.2 Other Special/Subgroup Populations

Not available.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Studies 303, 304 and 305 were all 6-week, phase 3, multicenter, randomized, double blind, placebo-controlled, fixed-dose studies with treatment arms of ER OROS paliperidone 3 mg to 15 mg dose groups and placebo. The primary efficacy analyses on the change from baseline of PANSS total score were performed using ANCOVA with LOCF data. Statistical significance levels were adjusted by Dunnett's method.

The analysis results support the efficacy claim of ER OROS paliperidone in the treatment of schizophrenia in all the dose groups of the three studies. The efficacy results were also supported by pre-specified analyses of nonparametric methods, mixed-effects model repeated measures analysis and worst rank analyses. Together these results support the claim of ER OROS paliperidone in the treatment of schizophrenia.

5.2 Conclusions and Recommendations

The analysis results supported the claim of the effectiveness of ER OROS paliperidone in the treatment of schizophrenia in all the dose groups of the three studies (Studies 303, 304 and 305). The efficacy results were also supported by pre-specified analyses of nonparametric methods, mixed-effects model repeated

measures analysis and worst rank analyses. Together these results support the claim of ER OROS paliperidone in the treatment of schizophrenia.

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