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*APPLICATION NUMBER:*

**22-043**

**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: 22-043 (N000)  
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Indication: Schizophrenia  
Applicant: Johnson & Johnson Pharmaceutical  
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Biometrics Division: Biometrics I, HFD-710  
Statistical Reviewer: Yeh-Fong Chen, Ph.D.  
Concurring Reviewers: Peiling Yang, Ph.D.  
James Hung, Ph.D.  
Medical Division: Division of Psychiatry Drug Products, HFD-130  
Clinical Team: Clinical Reviewer: Karen Brugge, M.D.  
Clinical Team Leader: Mitchell Mathis, M.D.  
(Deputy Director and also  
Acting Team Leader)  
Project Manager: Keith Kiedrow, Pharm. D., LT USPHS

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## 1. EXECUTIVE SUMMARY

### 1.1 CONCLUSIONS AND RECOMMENDATIONS

After evaluation, this reviewer agreed with the sponsor that the only submitted Study R076477-SCH-301 is a positive study which supports the efficacy of ER OROS Paliperidone in maintaining clinical stability for adult patients with schizophrenia who had achieved satisfactory symptom control after an acute episode.

### 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this submission, the sponsor submitted a single study (R076477-SCH-301) to support the effectiveness of ER OROS paliperidone, within a flexible dose range of 3 to 15 mg/day, in maintaining clinical stability for adult patients with schizophrenia who had achieved satisfactory symptom control after an acute episode.

Study R076477-SCH-301 was a randomized withdrawal study with eight weeks-open-label run-in and six weeks-stabilization phases, followed by the double-blind phase. The duration of double-blind phase was determined based on the time of study termination since the study was designed to be terminated by reaching a pre-specified number of recurrence events. The primary efficacy endpoint was the time to first recurrence during the double-blind phase.

One interim analysis was planned and conducted. According to both the interim and final analysis results, the sponsor concluded that data supports the ER OROS paliperidone's maintenance efficacy. The sponsor further stated that during the double-blind phase of up to 11 months, the rate of symptom recurrence was significantly lower and that the time to a recurrence event was significantly longer, among subjects maintained on ER OROS paliperidone compared with those switched to placebo.

### 1.3 STATISTICAL ISSUES AND FINDINGS

This reviewer confirmed the sponsor's analysis results for the primary endpoint and agreed that the data supported the ER OROS paliperidone's maintenance efficacy.

Regarding the secondary endpoints, first, none of them were prospectively specified and agreed as a 'KEY' secondary endpoint, so they should not be considered for labeling inclusion. Second, all of the secondary endpoints were based on the change from baseline to the endpoint visit. Since patients left when they had recurrences, the analysis results for this type of endpoints in the randomized withdrawal trial are actually confounded with the outcomes of the primary endpoint. Thus, the analysis results for this type of endpoints are not interpretable.

This reviewer noticed that the length of double-blind phase following the stabilization phase was mentioned in the sponsor's draft labeling. Since the majority of patients left the study very early and actually only 50% of patients stayed till the end of double-blind phase, the description of length of the double-blind period should be removed to avoid any misinterpretation.

## **2. INTRODUCTION**

### **2.1 OVERVIEW**

Paliperidone has been developed as an extended-release (ER) formulation. The efficacy of ER OROS paliperidone, administered once daily in adults at fixed doses of 3 mg, 6 mg, 9 mg, 12 mg and 15 mg, in the treatment of schizophrenia was demonstrated in the 3 Phase III trials (R076477-SCH-303, R076477-SCH-304, R076477-SCH-305). Another 6-week, double-blind Phase III study (R076477-SCH-302) in elderly subjects with schizophrenia also supported the finding of efficacy of ER OROS paliperidone.

The controlled Phase III study, R076477-SCH-301, included in this NDA submission was to support the effectiveness of ER OROS paliperidone, within a flexible dose range of 3 to 15 mg/day, in maintaining clinical stability for adult patients with schizophrenia who had achieved satisfactory symptom control after an acute episode. The study was conducted in the USA, Latvia, Lithuania, Romania, Turkey, and India.

Study R076477-SCH-301 was a randomized withdrawal study with eight weeks-open-label run-in and six weeks-stabilization phases, followed by the double-blind phase. The duration of double-blind phase was determined based on the time of study termination since the study was designed to be terminated by reaching a pre-specified number of recurrence events. The primary efficacy endpoint was the time to first recurrence during the double-blind phase.

Based on both interim and final analysis results, the sponsor concluded that during the double-blind phase of up to 11 months, the rate of symptom recurrence was significantly lower, and the time to a recurrence event was significantly longer, among subjects maintained on ER OROS paliperidone compared with those switched to placebo.

### **2.2 DATA SOURCES**

The electronic submission of this NDA was stored in the CDER's network by the following directory: "\\Cdsub1\evsprod\NDA022043"

### **3. STATISTICAL EVALUATION**

#### **3.1 EVALUATION OF EFFICACY**

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

##### **3.1.1 Description of Study R076477-SCH-301**

This study was entitled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with an Open-Label Extension Evaluating Extended Release OROS<sup>®</sup> Paliperidone in the Prevention of Recurrence in Subjects with Schizophrenia." It was conducted in the USA, Latvia, Lithuania, Romania, Turkey, and India.

##### **3.1.1.1 Study Objectives**

The primary objectives of this study were to evaluate the efficacy of ER OROS paliperidone compared with placebo in the prevention of the recurrence of the symptoms of schizophrenia, and to assess the safety and tolerability of ER OROS paliperidone in subjects with schizophrenia.

Secondary objectives included evaluation of the improvement on psychotic symptoms (based on Positive and Negative Syndrome Scale [PANSS]), the global improvement in severity of illness (based on Clinical Global Impression Severity Scale [CGI-S]), the change in social functioning (based on Personal and Social Performance Scale [PSP]), the change in quality of life (based on Symptoms and Quality of Life Scale in Schizophrenia [SQLS]), the subjective sleep measures (based on Visual Analog Scale [VAS]) associated with the use of ER OROS paliperidone compared with placebo and determination of genes/genotypes that may be related to the response or metabolism of ER OROS paliperidone.

##### **3.1.1.2 Study Design**

Study R076477-SCH-301 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study designed to evaluate the efficacy of flexibly dosed ER OROS paliperidone (3 to 15 mg, administered once daily) in the prevention of the recurrence of the symptoms of schizophrenia and to evaluate the safety and tolerability of ER OROS paliperidone compared with placebo. Subjects eligible for participation in the study were men and women between the ages of 18 and 65 years, with a diagnosis of schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition (DSM-IV) criteria.

The study consisted of 5 phases: screening (up to 5 days); an 8-week open-label run-in phase; a 6-week open-label stabilization phase; double-blind treatment phase of variable duration; and an optional 52-week open-label extension. Only the data collected from study start through the end of the double-blind phase of the study are included in this study report.

The 5-day screening phase allowed for the washout of psychotropic medications (including antipsychotic and antiparkinson medications); this did not include antidepressants and benzodiazepines. Patients who had received a stable dose of an antidepressant or benzodiazepine for at least 3 months before the start of the study could continue receiving the stable dose during the double-blind phase.

During the 8-week open-label run-in phase, the investigator identified the tolerated dose for subjects. Subjects were hospitalized from the first day of the run-in phase for a minimum of 14 full days to allow investigators to closely monitor safety. In order to enter the stabilization phase, subjects had to show tolerance for the ER OROS paliperidone treatment and satisfy the following requirements for at least 2 consecutive weeks before stabilization: 1) stable dosage of ER OROS paliperidone and 2) control of acute symptoms, defined as PANSS total score of  $\leq 70$ , PANSS scores on individual items of  $\leq 4$  (moderate or less), and a CGI-S score of  $\leq 4$  (moderately ill or better).

The 6-week open-label stabilization phase allowed for identification of subjects who maintained control of their acute psychotic symptoms on a stable dosing regimen. The dose received by each subject during the last 2 weeks of the run-in phase was maintained throughout stabilization. Those subjects who remained on that stable dose and continued to meet the aforementioned eligibility criteria with regard to symptom control were eligible for entry into the double-blind phase.

Subjects who entered the double-blind phase were randomly assigned, in a 1:1 ratio, to receive flexibly dosed ER OROS paliperidone (3 to 15 mg/day, starting at the dose maintained during stabilization) or placebo. Further dose adjustments during the double-blind phase were allowed based on safety and efficacy considerations.

Subjects who either experienced a recurrence or remained recurrence-free for the entire double-blind phase were considered to have completed the double-blind phase of the study and were eligible to enter the 52-week open-label extension phase.

### 3.1.1.3 Efficacy Measures and Statistical Analyses

#### Primary Efficacy Variable

The primary efficacy variable was the time to the first recurrence event during the double-blind phase.

Recurrence was defined as any one of the following:

- Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or
- For PANSS:
  - Increase of 25% in the total PANSS score from randomization for 2 consecutive days if the score at randomization was  $> 40$ , or
  - A 10-point increase in the total PANSS score from randomization for 2 consecutive days if the score at randomization was  $\leq 40$ , or
- Deliberate self-injury and/or violent behavior resulting in clinically significant injury to the subject or another person or property damage, or
- Suicidal or homicidal ideation and aggressive behavior that was clinically significant (in frequency and severity) in the investigator's judgment, or
- For CGI-S:
  - A score of  $\geq 4$  after randomization for 2 consecutive days if CGI-S score was  $\leq 3$  at randomization, or
  - A score of  $\geq 5$  after randomization for 2 consecutive days if CGI-S was 4 at randomization, or
- For PANSS items P1 (delusions), P2 (conceptual disorganization), P3(hallucinatory behavior), P6 (suspiciousness/persecution), P7(hostility) or G8 (uncooperativeness):
  - A score  $\geq 5$  after randomization for 2 consecutive days on any of the above PANSS items if the maximum score for the above PANSS items was  $\leq 3$  at randomization, or
  - A score  $\geq 6$  after randomization for 2 consecutive days on any of the above PANSS items if the maximum score for the above PANSS items was 4 at randomization.

#### Secondary Efficacy Variables

The secondary efficacy endpoints included changes from randomization to the end of the double-blind phase in the PANSS total and subscales, CGI-S, Sleep VAS, PSP, and SQLS-R4.

### Primary Efficacy Assessment

For the primary analysis, time to recurrence was defined as the time between randomization to treatment in the double-blind phase and the first documentation of a recurrence. Subjects who met any of the recurrence criteria were considered to have had a recurrence events. All other subjects were considered censored as of their last day in the double-blind phase. This included subjects who completed the study without experiencing a recurrence, subjects who discontinued study medication without a recurrence, or subjects who withdrew from the study without documentation of recurrence. Subjects who died while on medication without documentation of recurrence (i.e., their death was not related to worsening of schizophrenia symptoms) were also censored at the time of death.

For the interim analysis, the cut off date was defined as the date when the 43<sup>rd</sup> recurrence event (50% of the planned recurrence events) was observed, and unblinded efficacy data were assessed by the IDMC. Efficacy results were monitored with accepted statistical techniques to control the overall type I error rate at 5% level. Wang and Tsatis group sequential boundary of 0.2 was used by the IDMC to guide recommendations about early termination for efficacy. The type I error probability allocated to the interim analysis is approximately 0.01. The corresponding significance level for the final analysis became 0.0451.

The cumulative distribution function of the time to recurrence was estimated by the Kaplan-Meier method, time to recurrence was summarized (number of events, number of censored subjects, median, 25<sup>th</sup> and 75<sup>th</sup> percentile of time to events) and treatment differences were compared using a 2-sided log-rank test. The estimate of the hazards ratio and its 95% confidence interval was based on the Cox proportional hazards model with treatment as the only covariate.

In addition, Cox proportional hazards model with treatment, region, and baseline BMI as covariates was performed.

### Secondary Efficacy Assessment

Secondary efficacy variables were assessed for the run-in/stabilization phases based on the change from run-in baseline, defined as pre-(run-in) treatment day closest to (and including) Day 1 of the run-in phase. For the double-blind phase, the evaluation was based on change from double-blind baseline, defined as the pre-(double-blind) treatment visit closest to (and including) the first day of double-blind medication, i.e., Day 1 of double-blind phase.

Analyses of double-blind data involving changes from double-blind baseline to end point visit and from baseline to each assessment time point used the last observation carried forward (LOCF) approach. If a subject had no data at the end of double-blind phase, the last available observation in chronological order to the target day was used. In addition, the LOCF approach was employed for each assessment time point to assist

in inferring the effect of the dropout pattern on efficacy. For each time point for both observed case and LOCF data, descriptive statistics including number of subjects evaluated, mean, and standard deviation were produced on the PANSS total score and change from the double-blind baseline. Using an analysis of covariance (ANCOVA) model with treatment and analysis center and double-blind baseline PANSS total score as a covariate, the change from baseline to end point visit for the ER OROS paliperidone treatment group was compared to the change of the placebo group for the double-blind phase. Using this model, estimated least squares means of the difference, p-values, 95% confidence intervals (CIs) were presented for the average change of each ER OROS paliperidone treatment group versus placebo.

For the CGI-S, PSP, SQLS, and sleep VAS total scores, descriptive statistics of the numerical values and changes from baseline were presented at each assessment time point and end point visit for each study phase. At each assessment time point during the double-blind phase, except baseline, the p-values for testing a difference between ER OROS and placebo were produced using an ANCOVA model on the change from baseline (on the ranked data for CGI-S) with factors for treatment and analysis center, and with baseline score as a covariate.

In addition, PSP scores were grouped into 10-point increment categories, and a shift table of the change from baseline to end point was generated.

For the PANSS, CGI-S, and VAS, only descriptive summaries for the change from baseline over time were presented for the run-in and stabilization phases. For the PSP, descriptive summaries were presented for the stabilization phase only, since no PSP data were collected at the run-in baseline.

**Reviewer's Note:** The analysis results for the change from baseline on the PANSS Total, CGI-S, PSP, ... depended on patients' recurrence status and time of having recurrence, so the results may not be interpretable. In this review, among all secondary endpoints only sponsor's analysis results on the PANSS Total and CGI-S are reported.

### 3.1.2 Efficacy Results for Study R076477-SCH-301

#### 3.1.2.1 Patient Disposition and Study Completion/Withdrawal Information

##### **Patient Disposition**

Overall, 530 subjects with schizophrenia were enrolled in the run-in phase as of August 1 2005, when the enrollment was stopped based on results of the interim analysis. These 530 enrolled subjects were included in the all treated analysis set.

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Of the 530 enrolled subjects, 207 were randomized into the double-blind phase of the study (ratio 1:1), including 102 subjects randomized to placebo and 105 subjects randomized to ER OROS paliperidone. The intent-to-treat analysis set for the final analysis included 205 subjects. Two of the 207 randomized subjects were not included in the intent-to-treat analysis set, including one (randomized to placebo) who was lost to follow-up and had no post-randomization efficacy assessment and the other one who did not receive any double-blind medication after randomization.

At the time of the interim efficacy analysis, 113 subjects were randomized into the double-blind phase of the study and received at least 1 dose of double-blind study medication, including 55 subjects randomized to placebo and 58 subjects randomized to ER OROS paliperidone. However, based on the requirement of intent-to-treat analysis set the interim analysis only included 111 subjects (55 randomized to placebo and 56 randomized to ER OROS paliperidone) at the time of the interim analysis data cutoff (May 13, 2005). Since two randomized subjects did not provide any efficacy data by May 13, 2005, they were not included in this analysis set.

#### Study Completion/Withdrawal Information

##### Run-In Phase (8 weeks)

Table 3.1 shows the run-in phase completion/withdrawal information for this study. As shown in the table, of the 530 enrolled subjects, 347 (65%) completed the run-in phase and 183 (35%) subjects discontinued. The most common reason for early withdrawal was subject choice, which was accounted for 15% of subjects. Additional reasons included other (7%), lost to follow-up (5%), and adverse event (4%).

At the time the study was stopped, 35 subjects (7% of the 530 enrolled subjects) were participating in the run-in phase, and these patients were considered completers for the run-in phase.

Table 3.1 Run-In Completion/Withdrawal Information for Study R076477-SCH-301

	ER OROS PAL (RUST) (N=530) n (%)
<b>Total enrolled in run-in phase</b>	<b>530</b>
Completed run-in phase	347 (65)
Completed entire course of study*	35 (7)
Continued to stabilization phase	312 (59)
Withdrawal from run-in phase	183 (35)
Subject choice (subject withdrew consent)	78 (15)
Adverse event	22 (4)
Lost to follow-up	27 (5)
Subject failed criteria to enter stabilization phase	16 (3)
Study medication not taken according to protocol	1 (<1)
Other	39 (7)

Enrolled in run-in = those who received at least one non-zero dose of run-in medication.

Percent relative to all subjects enrolled in the run-in phase.

\* Study stopped based on the results of interim analysis.

Source: Sponsor's Table 6 in the clinical study report.

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### Stabilization Phase (6 weeks)

Table 3.2 shows the stabilization phase completion/withdrawal information for this study. As shown in the table, of the 312 subjects enrolled in the stabilization phase, 263 (84%) completed stabilization, and 49 (16%) subjects discontinued. The most common reasons for early withdrawal were subject choice (5%) and subject failed criteria to enter stabilization phase or double-blind phase (5%). The sponsor specifically pointed out that the percentage of withdrawals from stabilization phase (16%) was less than half of that from run-in phase (35%). They also mentioned that this situation was consistent with expected drop-out rates for stabilized versus acute patients.

Table 3.2 Stabilization Completion/Withdrawal Information for Study R076477-SCH-301.

	ER OROS PAL (RL/ST) (N=530) n (%)
<b>Total enrolled in stabilization phase</b>	<b>312</b>
Completed stabilization phase	263 (84)
Completed entire course of study*	56 (18)
Randomized to the double-blind phase	207 (66)
Withdrawal from stabilization phase	49 (16)
Subject choice (subject withdrew consent)	16 (5)
Adverse event	5 (2)
Lost to follow-up	6 (2)
Subject failed criteria to enter stabilization phase	5 (2)
Subject failed criteria to enter double-blind phase	9 (3)
Other	8 (3)

Enrolled in stabilization - those who received at least one non-zero dose of stabilization medication  
Percent relative to all subjects enrolled in the stabilization phase

\* Study stopped based on the results of interim analysis

Source: Sponsor's Table 7 in the clinical study report.

### Double-Blind Phase- Final Analysis

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Table 3.3 shows the double-blind treatment completion and withdrawal information for the study. As shown in the table, of the 207 randomized subjects, 179 (86%) completed the double-blind phase and 28 (14%) discontinued. Of the 179 (86%) subjects who completed, 75 (36%) experienced a recurrence event and 104 (50%) completed the entire course of the study. At that time the study was terminated by the sponsor, and most subjects randomized to the ER OROS paliperidone group (59%) were ongoing in the double-blind phase, compared to 41% in the placebo group. In contrast, over one-half (51%) of the subjects randomized to placebo had experienced a recurrent event, compared to only 22% in the ER OROS paliperidone group.

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Table 3.3 Double-Blind Treatment Completion/Withdrawal Information for Study R076447-SCH-301

	Placebo (N=102) n (%)	ER OROS PAL (N=105) n (%)	Total (N=207) n (%)
<b>Completed</b>	94 (92)	85 (81)	179 (86)
Experienced recurrence	52 (51)	23 (22)	75 (36)
Completed entire course of study <sup>a</sup>	42 (41)	62 (59)	104 (50)
<b>Withdrawn</b>	8 (8)	20 (19)	28 (14)
Subject choice(subject withdrew consent)	0	12 (11)	12 (6)
Adverse event	1 (1)	3 (3)	4 (2)
Death *	1 (1)	0	1 (<1)
Lost to follow-up	3 (3)	2 (2)	5 (2)
Study med. not taken according protocol	0	1 (1)	1 (<1)
Other	3 (3)	2 (2)	5 (2)

(a) Study stopped based on the results of interim analysis

\* There were 2 deaths in the double-blind phase. One death was attributed to worsening of psychotic symptoms and was considered as a recurrence event (included among the 75 subjects with recurrence)

Source: Sponsor's Table 9 in the clinical study report.

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### 3.1.2.2 Interim Efficacy Analysis for Primary Endpoint- Time to Recurrence

The interim analysis, conducted by the IDMC after 43 recurrence events had occurred, demonstrated a statistically significant difference in favor of ER OROS paliperidone, compared to placebo, with regard to the number of recurrence events and time to a recurrence event. The sponsor's results for the interim analysis of time to recurrence are provided in Table 3.4 and their Kaplan-Meier plot of the time to recurrence is presented in Figure 3.1. As shown in the table, a total of 111 subjects (55 randomized to placebo and 56 randomized to ER OROS paliperidone) were included in the intent-to-treat analysis set for the interim analysis. All subjects remaining in the study and taking medication at the time of the 43<sup>rd</sup> recurrence event were censored at the date of the interim analysis.

The sponsor's results (Table 3.4) showed that overall, 29 (53%) subjects in the placebo and 14 (25%) subjects in ER OROS paliperidone group experienced a recurrence event. There was a statistically significant difference (p-value=0.0053 based on the log-rank test) between the treatment groups in the time to recurrence in favor of ER OROS paliperidone. This difference exceeded the threshold for statistical significance (i.e., the p-value was less than 0.0102) resulting in the IDMC recommendation to stop the study early based entirely on efficacy data.

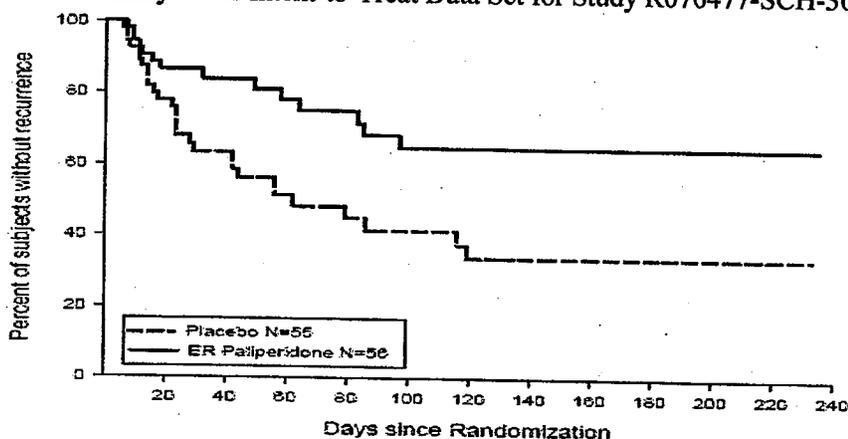
Table 3.5 summarize the types and reasons for recurrence events for subjects who experienced a recurrence in the interim analysis based on the intent-to-treat analysis set. As shown in the table, predominant reasons for recurrence in subjects included in the interim efficacy analysis were an increase in the PANSS total score and an increase in the CGI severity score. Most subjects in both treatment groups who experienced a recurrence were clinically managed without the need for psychiatric hospitalization.

Table 3.4 Sponsor's Summary Statistics of Time to Recurrence for Interim Analysis for Study R076477-SCH-301

Descriptive	Placebo	ER OROS PAL	Overall-P-value
Time to Recurrence			
Number of Assessed	55	56	
Number Censored (%)	26 (47.3)	42 (75.0)	
Number Recurred (%)	29 (52.7)	14 (25.0)	
25% Quantile (95% C.I.)	23.0 (14.0; 42.0)	83.0 (32.0; NE*)	
Median (95% C.I.)	62.0 (42.0; 119.0)	NE** (97.0; NE*)	
75% Quantile (95% C.I.)	NE* (116.0; NE*)	NE*	
Log-Rank Test			0.0053

\*NE means not estimable. \*\* NE means not estimable. This NE was resulted from less than 50% of subjects experienced a recurrence event. Source: Sponsor's Table 27 in the clinical study report.

Figure 3.1. Sponsor's Kaplan-Meier Plot of Time to Recurrence from the Interim Analysis for Intent-to-Treat Data Set for Study R076477-SCH-301



Source: Sponsor's Figure 4 in the clinical study report.

Table 3.5 Frequency Distribution of Recurrence Type and Reasons for Interim Analysis for Study R076477-SCH-301

Type of Recurrence/ Reason	Placebo (N=55)	ER OROS PAL (N=56)
Psychiatric hospitalization	8	4
PANSS		
Increase of 25% in the Total PANSS score	22	13
10 point increase in Total PANSS score	21	10
Suicidal or homicidal ideation	1	3
CGI-S		
CGI-S $\geq 4$ (moderately ill) for 2 Days	1	0
CGI-S $\geq 5$ (markedly ill) for 2 Days	1	0
PANSS items, P1, P2, P3, P6, P7, G8		
Score $\geq 5$ for 2 Days	10	7
	10	7

Note: PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness).

Source: Sponsor's Table 28 in the clinical study report.

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### 3.1.2.3 Final Efficacy Analyses for Primary Endpoint- Time to Recurrence

The study was stopped because of the positive results of the interim efficacy analysis in favor of ER OROS and the recommendation of the IDMC. The final analysis includes data from all subjects in the intent-to-treat analysis set through study termination. According to the sponsor, the final analysis of time to recurrence data was considered supportive per protocol. However, now that the occurred final recurrence events (75) was actually close to the originally planned number of events (86) for the final analysis, the efficacy evaluation should be mainly based on the final analysis.

#### Time to recurrence by Kaplan-Meier estimate and log-rank test

Sponsor's results of the final analysis of time to recurrence of symptoms of schizophrenia by Kaplan-Meier estimate and log-rank test are presented in Table 3.6. The Kaplan-Meier plot of the time to recurrence is shown in Figure 3.2.

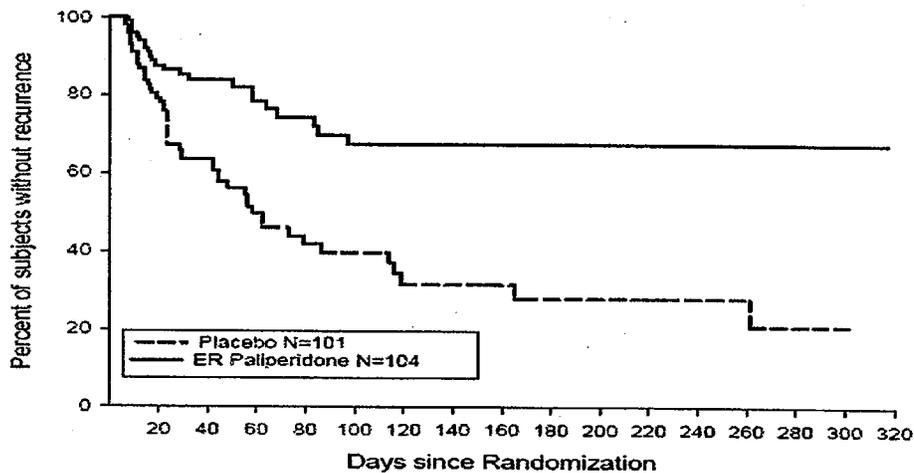
Table 3.6 Sponsor's Summary Statistics of Time to Recurrence for Final Analysis for Study R076477-SCH-301

Descriptive	Placebo	ER OROS PAL	Overall-P-value
Time to Recurrence			
Number of Assessed	101	104	
Number Censored (%)	49 (48.5)	81 (77.9)	
Number Recurred (%)	52 (51.5)	23 (22.1)	
25% Quantile (95% C.I.)	23.0 (15.0; 29.0)	68.0 (50.0; NE*)	
Median (95% C.I.)	58.0 (44.0; 114.0)	NE*	
75% Quantile (95% C.I.)	261.0 (116.0; NE*)	NE*	
Log-Rank Test			<0.001

\*NE means not estimable.

Source: Sponsor's Table 29 in the clinical study report.

Figure 3.2: Sponsor's Kaplan-Meier Plot of Time to Recurrence for the Final Analysis for Study R076477-SCH-301



Source: Sponsor's Figure 5 in the clinical study report.

According to Table 3.6, during the double-blind phase, twice as many subjects in the placebo group than in the ER OROS paliperidone group experienced a recurrence event. There was a statistically significant difference ( $p < 0.001$  based on the log-rank test) between the treatment groups in the time to recurrence, in favor of ER OROS paliperidone. The result at the final analysis ( $p < 0.001$ ) was consistent with that at the interim analysis ( $p = 0.0053$ ).

### Recurrence Type and Reasons

Table 3.7 shows the types and reasons for recurrence events for subjects who experienced a recurrence by treatment group. As shown in the table, predominant reasons for recurrence were an increase in the PANSS total score and an increase in the CGI severity score. More subjects in the placebo group than in the ER OROS paliperidone group who experienced a recurrence were hospitalized for exacerbation of their schizophrenic symptoms. Most subjects in both treatment groups who experienced a recurrence were clinically managed without resorting to hospitalization.

Table 3.7. Frequency Distribution of Recurrence Type and Reasons for Final Analysis for Study R076477-SCH-301

Type of Recurrence Reason	Placebo (N=101)	ER OROS PAL (N=104)
	n	n
Psychiatric hospitalization	13	6
Psychiatric hospitalization	13	6
PANSS	41	19
Increase of 25% in the Total PANSS score	37	14
10 point increase in Total PANSS score	4	5
Deliberate self-injury, violent behavior	2	0
Deliberate self-injury, violent behavior	2	0
Suicidal or homicidal ideation	4	0
Suicidal or homicidal ideation	4	0
CGI-S	38	18
CGI-S $\geq 4$ (moderately ill) for 2 Days	34	16
CGI-S $\geq 5$ (markedly ill) for 2 Days	4	2
PANSS items, P1, P2, P3, P6, P7, G8	18	11
Score $\geq 5$ for 2 Days	18	10
Score $\geq 6$ for 2 Days	0	1

Note: PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness).

The number of recurrence events in the placebo group were 52 and in ER OROS PLA were 23.

Subject may have more than 1 reason for recurrence

Source: Sponsor's Table 30 in the clinical study report.

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### 3.1.2.4 Sensitivity Analysis for Primary Endpoint

The sponsor performed the sensitivity analysis for patients who discontinued the double-blind phase for reasons other than recurrence. In this analysis, subjects who met the criteria for recurrence (during double-blind phase and during post-treatment follow-up, if any) were considered to have had a recurrence event at the time of first documentation of recurrence; subjects who did not have a recurrence were considered censored at the time of the last contact. It was stated in the study report that this sensitivity analysis was in agreement with the results of the final analysis.

The sponsor also performed the Cox regression analysis for the time to recurrence of symptoms of schizophrenia by using treatment as a covariate. Based on the analysis results, the sponsor stated in the study report that there was a significant difference between the treatment groups in the time to recurrence in favor of ER OROS paliperidone (hazard ratio=2.83, 95% CI=1.73 to 4.63; p<0.001).

### 3.1.2.5 Sponsor's Analysis Results for Secondary Endpoints

**Reviewer's Note:** As mentioned earlier, the following sponsor's analysis results for the change from baseline type of endpoints should be interpreted with caution due to the nature of confounding with the primary endpoint.

#### Change in Positive and Negative Syndrome Scale (PANSS) Total Score

Table 3.8 shows the sponsor's analysis results for the mean (SD) change from the double-blind phase baseline to the end point visit. As shown in the table, the mean (SD) change from the double-blind phase baseline to end point visit (LOCF) in PANSS total score was 15.1 (19.10) points in the placebo group and 6.0 (13.62) in the ER OROS paliperidone group. The difference between the placebo group and the ER OROS paliperidone group was statistically significant.

Table 3.8 Sponsor's Analysis Results for PANSS Total Score for Study R076447-SCH-301

	Placebo (N=101)	ER OROS PAL (N=104)
<b>Double-blind baseline</b>		
N	101	104
Mean (SD)	53.4 (10.56)	51.0 (11.38)
Median (Range)	56.0 (30;70)	53.0 (30;89)
<b>End point (double-blind)</b>		
N	101	104
Mean (SD)	68.5 (22.30)	57.0 (18.12)
Median (Range)	65.0 (31;114)	55.0 (30;113)
<b>Change from Baseline</b>		
N	101	104
Mean (SD)	15.1 (19.10)	6.0 (13.62)
Median (Range)	12.0 (-17;68)	2.0 (-17;50)
<b>P-value (minus Placebo)<sup>a,b</sup></b>		
Diff. of LS Means (SE)		<0.001
95% CI		-8.8 (2.14) (-12.99;-4.54)

<sup>a</sup> Analysis of covariance (ANCOVA) model with treatment (placebo, ER OROS PLA) and analysis center as factors, and baseline value as a covariate.

<sup>b</sup> Comparison with placebo without multiplicity adjustment.

Source: Sponsor's Table 32 in the clinical study report.

#### Clinical Global Impression-Severity Scale (CGI-S)

Tables 3.9 and 3.10 show the sponsor's analysis results for CGI-S scale. As shown in the tables, the baseline (double-blind phase) CGI-S scores were similar across treatment groups. At the end point visit, there were 27.6% more subjects in the ER OROS paliperidone group (73.1%) than in the placebo group (45.5%) with severity scores of 'mild', 'very mild', or 'not ill'.

At end point visit, twice as many subjects in the placebo group than in the ER OROS paliperidone group (22 [21.8%] subjects versus 10 [9.6%] subjects) had a CGI-S rating of at least markedly severe ('marked' or 'severe' or rating of  $\geq 5$ ). This finding is consistent with the higher percentage of subjects with a recurrence event and an increase of PANSS total score at end point visit in the placebo group compared with the ER OROS paliperidone group.

Table 3.9 Sponsor's Frequency Tabulation of CGI-Severity Score in Double-Blind Phase for Study R076477-SCH-301

	----- Placebo -----			--- ER OROS PAL ---		
	n	%	Cum.%	n	%	Cum.%
<b>Clinical global impression</b>						
Double-blind baseline						
Not ill	5	5.0	5.0	6	5.8	5.8
Very mild	33	32.7	37.6	38	36.5	42.3
Mild	54	53.5	91.1	49	47.1	89.4
Moderate	9	8.9	100.0	11	10.6	100.0
Marked	0	0.0	100.0	0	0.0	100.0
Severe	0	0.0	100.0	0	0.0	100.0
-----	-----			-----		
Total	101			104		
End point (double-blind)						
Not ill	3	3.0	3.0	5	4.8	4.8
Very mild	21	20.8	23.8	34	32.7	37.5
Mild	22	21.8	45.5	37	35.6	73.1
Moderate	33	32.7	78.2	18	17.3	90.4
Marked	16	15.8	94.1	8	7.7	98.1
Severe	6	5.9	100.0	2	1.9	100.0
-----	-----			-----		
Total	101			104		

Source: Sponsor's Table 35 in the clinical study report.

Changes from baseline to the end point visit in CGI-S scores are summarized by treatment group in Table 3.10. As shown in the table, from baseline (double-blind phase), there was worsening in the severity of subjects' psychosis in the placebo group while the psychotic condition of subjects in the ER OROS paliperidone group remained stable.

Table 3.10 Sponsor's LOCF Analysis Results for Change from Double-Blind Baseline to Endpoint Visit in CGI-Severity Scale for Study R076477-SCH-301

	Placebo (N=101)	ER OROS PAL (N=104)
<b>Double-blind baseline</b>		
N	101	104
Median (Range)	3.0 (1:4)	3.0 (1:4)
<b>End point (double-blind)</b>		
N	101	104
Median (Range)	4.0 (1:6)	3.0 (1:6)
<b>Change from Baseline</b>		
N	101	104
Median (Range)	1.0 (-2:4)	0.0 (-2:3)
<b>P-value (minus Placebo)<sup>a,b</sup></b>		<0.001

Note: The analysis of variance uses ranked data.

<sup>a</sup> Test for no difference between treatments from ANCOVA model with factors for treatment and analysis center, and with baseline value as a covariate.

<sup>b</sup> Comparison with placebo without multiplicity adjustment.

Source: Sponsor's Table 36 in the clinical study report.

### 3.1.2.6 Statistical Reviewer's Findings and Comments

1. This reviewer confirmed the sponsor's analysis results for the primary endpoint. Although the protocol amendment INT-2 specified that "if the result of the interim analysis is significant, the study will be stopped and the interim analysis will be considered the primary analysis. Succeeding events after the decision to stop will be included in a secondary analysis", this review focused on the sponsor's final analysis results since the number of events at the final analysis (Total 75 events) was not very far from the sponsor's originally planned number of events (Total 86 events). According to the final analysis results for the primary endpoint, time to the first recurrence event, the efficacy of paliperidone in the prevention of recurrence in patients with schizophrenia was demonstrated.
2. The submitted Study (R076477-SCH-301) included many secondary endpoints which were based on the change from baseline to the endpoint scores. The sponsor also included the significant findings in this type of secondary endpoints in the draft labeling. This reviewer wishes to emphasize that these secondary endpoints (with positive findings) were not qualified to be described in the labeling since they were not pre-planned and also the analysis results for this type of endpoints in the randomized withdrawal trial can not be meaningfully interpreted because they were confounded with patients' time and status of having recurrence.
3. This reviewer noticed that the draft labeling included the description of the length of the double-blind phase following the stabilization phase. Since the majority of patients left the study very early and only 50% of patients stayed till the end of the double-blind phase (See Table 3.3 and Figure 3.2), this description of length should be removed to avoid any misinterpretation.

### 3.2 EVALUATION OF SAFETY

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

### 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor performed the efficacy subgroup analysis for the primary endpoint, time to recurrence of symptoms of schizophrenia by age group (18-25, 26-50 and 51-60 years), by sex and by geographic region (Eastern Europe, North America, the rest of world). This reviewer confirmed the sponsor's analysis results.

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#### 4.1 GENDER, RACE AND AGE

##### Gender

Table 3.11 shows the sponsor's subgroup analysis for gender. As shown in the table, the results with regard to the number of recurrence events were consistent for male and female subjects.

**Table 3.11 Sponsor's Analysis Results for Gender for Study R076477-SCH-301**

Number (%) of Recurrence	Placebo	ER OROS PAL	Total
<b>Male</b>			
Number of assessed	63	58	121
Number of censored (%)	35 (55.6)	44 (75.9)	79 (65.3)
Number failed (%)	28 (44.4)	14 (24.1)	42 (34.7)
<b>Female</b>			
Number of assessed	38	46	84
Number of censored (%)	14 (36.8)	37 (80.4)	51 (60.7)
Number failed (%)	24 (63.2)	9 (19.6)	33 (39.3)

Source: Sponsor's Attachment 5.1.1.3.1.2 in the clinical study report.

##### Age

Table 3.12 shows the sponsor's subgroup analysis for age. As shown in the table, the proportion of subjects who experienced recurrence events was higher in the placebo group than in the ER OROS paliperidone group in subjects aged 18-25 years or 26-50 years, but not in the 51-60 years age group. However, these results do not appear to be of significance, considering the smaller sample size in each of the demographic subcategories.

**Table 3.12 Sponsor's Analysis Results for Age for Study R076477-SCH-301**

Number (%) of Recurrence	Placebo	ER OROS PAL	Total
<b>Age Group: 18-25</b>			
Number of assessed	13	14	27
Number of censored (%)	7 (53.8)	9 (64.3)	16 (59.3)
Number failed (%)	6 (46.2)	5 (35.7)	11 (40.7)
<b>Age Group: 26-50</b>			
Number of assessed	77	70	147
Number of censored (%)	34 (44.2)	57 (81.4)	91 (61.9)
Number failed (%)	43 (55.8)	13 (18.6)	56 (38.1)
<b>Age Group: 51-65</b>			
Number of assessed	11	20	31
Number of censored (%)	8 (72.7)	15 (75.0)	23 (74.2)
Number failed (%)	3 (27.3)	5 (25.0)	8 (25.8)

Source: Sponsor's Attachment 5.1.1.3.2.1 in the clinical study report.

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**Race**

The sponsor did not perform the subgroup analysis by race, so this reviewer performed the analysis and results are shown in Table 3.13. As shown in the table, for all different race groups (except Asian), the placebo group had higher rate of recurrence than the ER OROS PAL group.

**Table 3.13 Reviewer's Analysis Results for Race for Study R076477-SCH-301**

Number (%) of Recurrence	Placebo	ER OROS PAL	Total
<b>White</b>			
Number of assessed	61	62	123
Number of censored (%)	20 (32.8)	45 (72.6)	65 (52.8)
Number failed (%)	41 (67.2)	17 (27.4)	58 (47.2)
<b>Black</b>			
Number of assessed	9	8	17
Number of censored (%)	4 (44.4)	6 (75.0)	10 (58.8)
Number failed (%)	5 (55.6)	2 (25.0)	7 (41.2)
<b>Asian</b>			
Number of assessed	0	3	3
Number of censored (%)	0 (0)	2 (66.7)	2 (66.7)
Number failed (%)	0 (0)	1 (33.3)	1 (33.3)
<b>Other</b>			
Number of assessed	31	31	62
Number of censored (%)	25 (80.7)	28 (90.3)	53 (85.5)
Number failed (%)	6 (19.4)	3 (9.7)	9 (14.5)

**4.2 OTHER SPECIAL/SUBGROUP POPULATIONS**

The sponsor also performed the subgroup analysis by three different regions (Eastern Europe, North America and the rest of world) and this reviewer confirmed the sponsor's analysis results. As shown in Table 3.14, for all three regions, the proportion of subjects who experienced recurrence events in the placebo group was higher than in the ER OROS paliperidone group.

**Table 3.14 Sponsor's Analysis Results for Region for Study R076477-SCH-301**

Number (%) of Recurrence	Placebo	ER OROS PAL	Total
<b>Eastern Europe</b>			
Number of assessed	49	48	97
Number of censored (%)	16 (32.7)	37 (77.1)	53 (54.6)
Number failed (%)	33 (67.3)	11 (22.9)	44 (45.4)
<b>North America</b>			
Number of assessed	23	26	49
Number of censored (%)	10 (43.5)	17 (65.4)	27 (55.1)
Number failed (%)	13 (56.5)	9 (34.6)	22 (44.9)
<b>The Rest of World</b>			
Number of assessed	29	30	59
Number of censored (%)	23 (79.3)	27 (90.0)	50 (84.7)
Number failed (%)	6 (20.7)	3 (10.0)	9 (15.3)

Source: Sponsor's Attachment 5.1.1.3.1.3 in the clinical study report.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

This reviewer confirmed the sponsor's analysis results for the primary endpoint and agreed that the data supported the ER OROS paliperidone's maintenance efficacy.

Regarding the secondary endpoints, first, none of them were prospectively specified and agreed as a 'KEY' secondary endpoint, so they should not be considered for labeling inclusion. Second, all of the secondary endpoints were based on the change from baseline to the endpoint visit. Since patients left when they had recurrences, the analysis results for this type of endpoints in the randomized withdrawal trial are actually confounded with the outcomes of the primary endpoint. Thus, the analysis results for this type of endpoints are not interpretable.

This reviewer noticed that the length of double-blind phase following the stabilization phase was mentioned in the sponsor's draft labeling. Since the majority of patients left the study very early and actually only 50% of patients stayed till the end of double-blind phase, the description of length of the double-blind period should be removed to avoid any misinterpretation.

### 5.2 CONCLUSIONS AND RECOMMENDATIONS

After evaluation, this reviewer agreed with the sponsor that the only submitted Study R076477-SCH-301 is a positive study which supports the efficacy of ER OROS Paliperidone in maintaining clinical stability for adult patients with schizophrenia who had achieved satisfactory symptom control after an acute episode.

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Yeh-Fong Chen, Ph.D.  
Mathematical Statistician

cc: NDA 22-043  
HFD-130/Dr. Laughren  
HFD-130/Dr. Mathis  
HFD-130/Dr. Brugge  
HFD-130/Mr. Kiedrow  
HFD-700/Dr. Nevius  
HFD-700/Ms. Patrician  
HFD-710/Dr. Mahjoob  
HFD-710/Dr. Hung  
HFD-710/Dr. Yang

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Peiling Yang  
3/8/2007 10:34:39 AM  
BIOMETRICS

James Hung  
3/9/2007 03:02:37 PM  
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