

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-043

MEDICAL REVIEW(S)

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

DATE: November 21, 2007

FROM: Gwen L. Zornberg, M.D., Sc.D.
Acting Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Paliperidone Extended Release Oros Oral Tablets for the treatment of schizophrenia

TO: File NDA 21-999 SN001
Safety and PLR Format Supplement
Related NDA 22-043 (Maintenance treatment of schizophrenia)

REVIEWERS: Clinical, Karen Brugge, M.D.; Stephen Grant, M.D. Interdisciplinary Review Team for QT Studies; Clinical Pharmacology, Ron Kavanaugh, Ph.D.; Division of Psychiatry Products Safety Group, Lisa Jones, M.D.

1.0 BACKGROUND

Paliperidone, a major metabolite of risperidone with antagonist activity at dopamine D₂ receptors, was approved for treatment of schizophrenia by the FDA on 19 December 2006. The fact that paliperidone is the major active metabolite of risperidone means that there is an unusually large pool of safety experience to draw from. In the thorough QT/QTc study submitted under the original NDA, a high dose of paliperidone was associated with a 12 msec prolongation effect. There were no patients with QTc > 500 msec reported. Dr. Laughren agreed with the IRT QT recommendation that the language in labeling regarding QTc prolongation be revised and relocated to Warnings.” While found to be a “modest signal” “Our proposed language for this statement will alert prescribers to a possible risk of torsade de pointes and/or sudden death with this drug, and will warn against certain situations that may increase this risk.” The combined data led to a QT warning, but not second line status with extensive risperidone experience that has remained benign.

This supplement to the NDA seeks three changes to labeling focused on particular safety concerns in concert with revising the structure into PLR format.

In this submission dated 26 January 2007, the primary proposal for labeling changes stems from analyses of a thorough QT/QTc study (paliperidone 12 mg and 18 mg qd)

RO76477-SCH-1014 conducted by the sponsor. This study had not been submitted for review to the Division of Psychiatry Products (DPP) and was completed therefore without recommendations from the Interdisciplinary Review Team for QT Studies of the FDA.

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Finally, minor changes are proposed to the 7.2 Potential for Other Drugs to Affect INVEGA™ section of labeling based on the review by Clinical Pharmacology of the results of the Phase I pharmacokinetics study RO76477-SCH-1016.

2.0 CHEMISTRY

There were no supplemental quality assessment issues to address beyond those reviewed in the context of the NDA application that would preclude an approval action for this safety supplement.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approval action for this safety supplement.

4.0 BIOPHARMACEUTICS

Based on the Clinical Pharmacology review of the drug-drug interaction study entitled: "A Randomized, Open-Label, Single-Center, Crossover Study of the Potential Effects of Paroxetine on the Pharmacokinetics of a Single Dose of Paliperidone Extended-Release in Healthy Men", which was a 2-way cross-over study in 57 healthy volunteers in the fasted condition (ages 18-55 years) who were either CYP2D6 extensive or ultra-rapid metabolizers by genotype included in this safety supplement regarding treatment of schizophrenia, Dr. Kavanaugh "finds the sponsor's proposed labeling changes acceptable" and recommends changes to paliperidone labeling regarding drug-drug interactions with the commonly used antidepressant, paroxetine.

The findings demonstrated an approximately 10% increase in paliperidone C_{max} and a 20% increase in unbound AUC in the presence of paroxetine 20 mg qd. However, paroxetine may be dosed at up to 60 mg daily so a larger effect will be expected. In addition, paroxetine may cause cardiac toxicity and thus use may increase or complicate any assessment of cardiac toxicity due to paliperidone. Changes to labeling were recommended by Dr. Kavanaugh as follows:

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I am not aware of any Clinical Pharmacology issues at this point that would preclude an approval action for the changes above to subsection 7.2 of the Drug Interactions section of Invega™ labeling.

5.0 CLINICAL DATA

5.1 Safety Data

5.1.1 Clinical Data Sources for Safety Review

Dr. Brugge consulted the Interdisciplinary Review Team for QT Studies who

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based on findings from the Risperdal and Invega™ database searches, Dr. Brugge noted information regarding the database search could not be identified and that at least one death occurred in the paliperidone treated population attributed to pulmonary thromboembolism. Dr. Brugge noted also that in her past reviews of the paliperidone database, there were clinically unremarkable changes in platelet count and other hematological parameters. In light of the uncertainty, a DPP safety group consultation was sought. Dr. Lisa Jones, in her review dated 28 September 2007,

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On page 9 of her review, Dr. Brugge observed that the rationale was not provided when the sponsor deleted patients who had been exposed paliperidone in the Phase 2/3/4 clinical studies. Many of the adverse events that are unlikely to be drug related have been removed in keeping with the 2006 Guidance. In view of the recommendations by

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A number of changes to labeling including section changes discussed by Dr. Brugge will follow in the new PLR format according to Guidance and in consultation with SEALD.

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5.2. Conclusions Regarding the Safety of Paliperidone

The adverse drug reaction profile for paliperidone in PLR labeling will remain largely unchanged since approval of the NDA.

5.3 Clinical Sections of Labeling

We have made modifications to the sponsors' proposed Abilify labeling that has been converted to PLR format for the first time in the context of the approval of the pediatric schizophrenia and bipolar disorder indications.

6.0 WORLD LITERATURE

The sponsor reported that they reviewed the literature and found no relevant articles that would adversely affect conclusions about the safety of paliperidone with respect to abnormal QT prolongation or TTP in the treatment of patients diagnosed with schizophrenia. There is inadequate patient exposure experience available to be able to draw any reasonable conclusions regarding the rates of this rare potentially fatal drug reaction in the absence of spontaneous reports.

7.0 INTERDISCIPLINARY REVIEW TEAM FOR QT STUDIES

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These designs flaws and others rendered the data uninterpretable by Dr. Grant who recommended that the sponsor submit the study protocol to the FDA prior to conducting an additional study in the effort to support labeling changes.

8.0 LABELING AND APPROVABLE LETTER

We will include a modified version of the new PLR version of labeling with the approvable letter.

9.0 CONCLUSIONS AND RECOMMENDATIONS

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I agree with Dr. Kavanaugh's recommendations on changes to labeling for the drug-drug interaction with paroxetine. I recommend that this language describing the findings of the study will be incorporated into labeling, which will be re-formatted into structured product labeling, Physician Labeling Rule (PLR) format. In addition, I recommend that

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As noted on page 18 of Dr. Brugge's review, the paliperidone labeling will be revised into PLR format in concert with consultation by the SEALD team.

Moreover, class labeling is being required for all D₂ antagonist antipsychotic drugs as suited to each label with regard to dystonias as adverse drug reactions. I recommend that the sponsor add this language into labeling tailored to the style and substance of the present language.

Dystonia

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Before we can take an approval action, we need to reach an agreement on labeling. A number of adverse events in paliperidone labeling that are considered to be adverse events unrelated to drug exposure will be removed from labeling in keeping with the 2006 Guidance. Thus, I recommend that we issue the approvable letter along with our proposal for labeling, in anticipation of final approval of the Clinical Pharmacology changes in the first version of the Invega™ label in PLR format.

cc:

Orig NDA 21-999

NDA 22-043

HFD-130

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130/TLaughren/MMathis/GZornberg/KBrugge/LJones/AHughes/KKiedrow/SHardeman

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/s/

Gwen Zornberg
11/21/2007 12:12:26 PM
MEDICAL OFFICER

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

DATE: April 26, 2006

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for paliperidone ER tablets for the longer-term (maintenance) treatment of schizophrenia

TO: File NDA 22-043
[Note: This overview should be filed with the 6-27-06 original submission of this NDA.]

1.0 BACKGROUND

Paliperidone ER is an extended release formulation of paliperidone, an atypical antipsychotic (5HT₂ and D₂ receptor antagonist). It is the major active metabolite of risperidone and has essentially the same pharmacological profile as risperidone which is approved for the treatment of schizophrenia and bipolar mania. Paliperidone ER is already approved (as of 12-19-06) for the short-term (acute) treatment of schizophrenia. This NDA seeks a claim for the longer-term (maintenance) treatment of schizophrenia, in a dose range of 3 to 12 mg/day.

2.0 CHEMISTRY

The only CMC issue for this NDA would have been environmental assessment. However, the sponsor sought and was granted a categorical exclusion for EA. Thus, CMC recommends approval of this application from a CMC standpoint.

3.0 PHARMACOLOGY

Since the claim being sought is for the approved formulation of paliperidone ER, there were no pharm/tox issues for review.

4.0 BIOPHARMACEUTICS

Since the claim being sought is for the approved formulation of paliperidone ER, there were no OCP issues for review, and no new biopharm data were submitted as part of this application.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our review of this application focused on a single flexible-dose (3-15 mg/day) randomized withdrawal study (SCH-301). There was an 8-week, open-label run-in phase, a 6-week stabilization phase, and a double-blind randomized phase (drug vs placebo) to observe for relapse. The primary endpoint was time to relapse (the definition of relapse was quite complicated, but reasonable, in my view). The end of the trial was defined in terms of a prespecified number of relapses, and there was a planned interim analysis based on reaching half that number (i.e., 43). There were no prespecified key secondary endpoints. There were 51% relapses on placebo compared to only 22% on drug. The primary analysis of time to relapse was the log-rank test. Since the interim analysis was positive, enrollment was stopped at that point. However, patients already randomized were continued until they experienced relapse, dropped out for other reasons, or completed the study. The results on the final analysis were entirely consistent with the interim analysis, i.e., in both cases, highly significant. The results were generally robust to differences in gender, age, race, and geographic distribution. The sponsor has, in my view, provided sufficient evidence to support a limited claim of maintenance efficacy for paliperidone ER in the treatment of schizophrenia. We have made a number of changes to labeling regarding the description of the efficacy results. I agree with Dr. Mathis that we can defer the requirement for adolescent maintenance data until after we have seen the data from the planned adolescent acute study.

5.2 Safety Data

The additional safety experience with paliperidone ER available from study 301 and extension phases from earlier studies is incrementally quite small compared to the safety database we had available for our original review of this drug, and I agree with Dr. Mathis that no new, important safety information about this drug has been revealed in this NDA for maintenance treatment. As Dr. Mathis points out in his memo for this NDA, the primary reviewer, Dr. Karen Brugge, has repeatedly made statements in her review that attest to this fact, i.e., no new, important safety information was revealed that would impact on our decision about this application or about labeling. Thus, I agree with Dr. Mathis that this application can be approved without any need for substantive changes to labeling with regard to the safety of this drug. I also agree with Dr. Mathis that Dr. Brugge's various recommendations for additional consultation on this NDA (e.g., OCP, biometrics, QT team) are not justified and will not be sought.

5.3 Clinical Sections of Labeling

As noted, we have made several modifications to the sponsor's proposed labeling, particularly regarding the description of the efficacy results, and we have now reached agreement with the sponsor on final labeling.

6.0 WORLD LITERATURE

The sponsor provided a literature update during the review cycle for this NDA that included only 3 additional papers, none of which contributed any new safety information, according to Dr. Brugge.

7.0 FOREIGN REGULATORY ACTIONS

It is my understanding that paliperidone ER is not approved anywhere outside the US at this time for the treatment of schizophrenia.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVAL LETTER

10.1 Labeling

As noted, we have reached agreement with the sponsor on final labeling.

10.2 Foreign Labeling

Paliperidone ER is not approved anywhere at this time for the treatment of schizophrenia.

10.3 Approval Letter

The approval letter includes the agreed upon final labeling.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that J&J has submitted sufficient data to support the conclusion that paliperidone ER is effective and acceptably safe in the maintenance treatment of schizophrenia. We have reached agreement with the sponsor on final labeling. Thus, we will issue an approval letter for this application, with the agreed upon final labeling.

cc:

Orig NDA 22-043

HFD-130

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/s/

Thomas Laughren
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MEDICAL OFFICER

MEMORANDUM

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

DATE: 23 April 2007

FROM: Mitchell V. Mathis, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 22-043/N000 (This overview should be filed with the 6/27/2006 submission.)

SUBJECT: Recommendation of Approval Action for Paliperidone ER for the Maintenance Treatment of Schizophrenia

1.0 BACKGROUND

Paliperidone ER is approved for the acute treatment of schizophrenia. Paliperidone (6-OH risperidone) is the pharmacologically active major metabolite of risperidone. The sponsor is seeking approval for the indication of maintenance treatment of schizophrenia with this application.

Paliperidone ER was developed under IND 65850 and the development program included several meetings with the Division (including EOP2/pre-NDA).

This sNDA has been reviewed by Karen Brugge, M.D., Medical Officer, DPP, Yeh-Fong Chen, Ph.D., Office of Biostatistics, and Tele Chhagan, Ph.D, Chemistry.

2.0 CHEMISTRY

The chemists have recommended approval with a categorical exclusion from environmental assessment.

3.0 PHARMACOLOGY

Paliperidone ER is an approved product and so there are no pending pharmacology review issues.

4.0 CLINICAL PHARMACOLOGY

The clinical pharmacologists have no new information to review for this application.

5.0 CLINICAL DATA

5.1 Overview of Studies

A single study (SCH-301) was submitted to support the effectiveness of paliperidone ER in the maintenance treatment of schizophrenia. This was a flexible dose (3 mg – 15mg) randomized withdrawal study with an eight week open-label run-in phase followed by a six week stabilization phase, followed by a double-blind randomization phase (placebo vs. drug) and an optional open-label extension phase. The primary efficacy endpoint was time to first recurrence during the double-blind phase.

5.1.1 Primary Efficacy Variable/Definition of Recurrence

The primary efficacy variable for this single study was time to first recurrence 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 treatment of schizophrenic symptoms).
- 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 ≤ 40.
- Deliberate self-injury and/or violent behavior resulting in clinically significant injury to the subject or another person or property.
- Clinically significant suicidal or homicidal ideation and aggressive behavior.
- For CGI-S:
 - A score of ≥ 4 after randomization for 2 consecutive days if CGI-S score was ≤ 3 at randomization, or
 - A score of ≥ 5 after randomization for 2 consecutive days if CGI-S was 4 at randomization.
- For PANSS items P1 (delusions), P2 (conceptual disorganization), P3(hallucinatory behavior), P6 (suspiciousness/persecution), P7(hostility) or G8 (uncooperativeness):
 - A score ≥ 5 after randomization for 2 consecutive days on any of the above PANSS items if the maximum score for those items was ≤ 3 at randomization, or
 - A score ≥ 6 after randomization for 2 consecutive days on any of the above PANSS items if the maximum score for those items was 4 at randomization.

5.1.2 Primary Efficacy Assessment

The primary efficacy endpoint was time to first recurrence during the double-blind phase. Subjects who met any of the recurrence criteria above were considered to have had a recurrence. The duration of the double-blind phase was determined based upon the time required to reach a pre-specified number of recurrence events. An interim analysis was planned on the date of the 43rd recurrence event, which was when 50% of the estimated recurrences were anticipated to have occurred.

5.1.3 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. No key secondary variables were identified in the protocol.

5.1.4 Study Design

The study was entitled, “A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with an Open Label Extension Evaluating Extended Release OROS Paliperidone in the Prevention of Recurrence in Subjects with Schizophrenia.” It was a multi-centered study conducted in the US, Latvia, Lithuania, Romania, Turkey, and India. The primary objective was to compare drug versus placebo in the prevention of recurrence of the symptoms of schizophrenia.

The study evaluated the safety and efficacy of flexibly-dosed paliperidone ER (3 mg to 15 mg, given once a day). Subjects were men and women with a DSM-IV diagnosis of schizophrenia between the ages of 18 and 65 years.

There were 5 phases to the study: screening (5 days); 8 week open-label run-in, 6 week open-label stabilization, a double-blind treatment phase of variable duration (based upon recurrence of disease), and a maximum of 52 weeks of open-label extension.

Benzodiazepines and antidepressants were continued during the 5 day washout phase. During the run-in, the optimal dose was established for each patient based upon the control of acute symptoms (PANSS Total Score of 70 or less). The open-label stabilization phase allowed identification of subjects who had maintained control on a stable dosing regimen, and then that dose was fixed during the last two weeks of this phase. Those subjects remaining stable were eligible to enter the double-blind portion of the study where they were randomized 1:1 to continue drug or receive placebo. Subjects who experienced a recurrence (defined above) or remained recurrence-free for the entire double-blind period of the study were considered to have completed the study and were eligible to enter the open-label phase (see Table 1).

A total of 530 subjects with schizophrenia were enrolled in the run-in phase. Of these, 207 were randomized into the double-blind phase of the study.

Table 1: Double-Blind Treatment Completion/Withdrawal Information for Study 301

	Placebo (N=102) n (%)	ER OROS PAL (N=105) n (%)	Total (N=207) n (%)
Completed	94 (92)	85 (81)	179 (86)
Experienced recurrence	52 (51)	23 (22)	75 (36)
Completed entire course of study ^a	42 (41)	62 (59)	104 (50)
Withdrawn	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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5.2 Efficacy Data

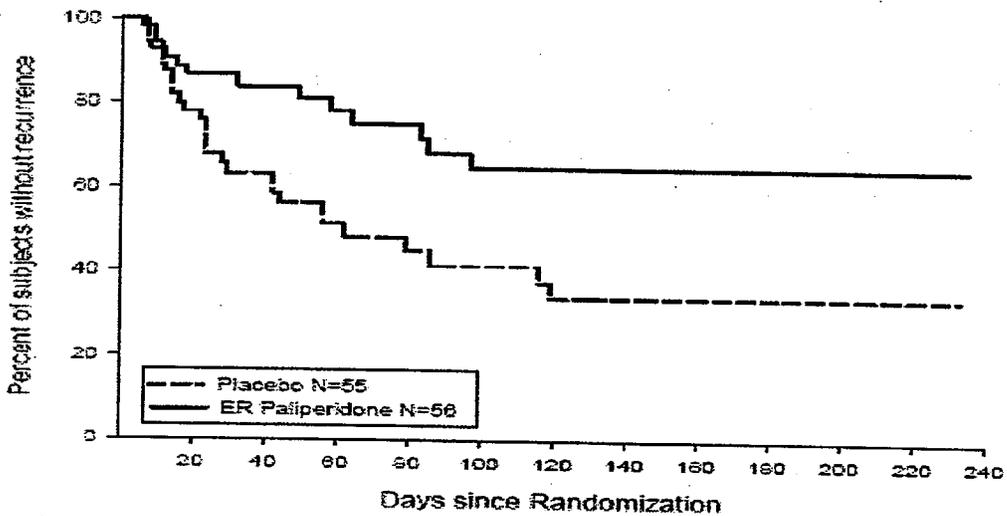
5.2.1 Summary of Studies Pertinent to Efficacy Claim

As shown in Table 1 above, of the 207 randomized subjects, 179 (86%) completed the double-blind phase and 24 (14%) discontinued. Of the 179 completers, 75 (36%) experienced a recurrence event

and 104 (50%) completed the entire course of the study. Over half (51%) of the subjects randomized to placebo experienced a recurrence event compared to only 22% in the paliperidone ER group. The time course of recurrence events is demonstrated in Figure 1.

Figure 1: Kaplan-Meier Plot of Time to Recurrence from the Interim Analysis for ITT Data Set for Study 301

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

Table 2 lists the types and reasons for recurrence events by treatment group. The 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 the drug group were hospitalized.

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Table 2: Frequency Distribution of Recurrence Type and Reason for Final Analysis

Type of Recurrence Reason	Placebo	ER OROS PAL
	(N=101)	(N=104)
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.

Change in PANSS Total Score

Table 3 is a summary of the sponsor's analysis results for the mean (SD) change from the double-blind phase baseline to the endpoint visit in PANSS total score. The mean change from baseline to endpoint visit (LOCF) was 15.1 points in the placebo group and 6.0 in the treatment group. This difference was statistically significant.

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Table 3: Analysis Results for PANSS Total Score

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

^a Analysis of covariance (ANCOVA) model with treatment (placebo, ER OROS PAL) and analysis center as factors, and baseline value as a covariate.

^b Comparison with placebo without multiplicity adjustment.

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

Change in CGI-Severity Scale

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Changes from baseline to endpoint visit in CGI-S scores are summarized by treatment group in Table 4. As can be seen from the table, the placebo group experienced worsening from baseline in severity, while the paliperidone ER treatment group remained stable.

Table 4: LOCF Analysis Results—Change from Double-Blind Baseline to Endpoint Visit in CGI-S Scale

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

Note. The analysis of variance uses ranked data.

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

^b Comparison with placebo without multiplicity adjustment.

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

Findings by Subgroup

Efficacy analyses based upon age, gender, and geographic region (Eastern Europe, North America, and Other) for the primary endpoint were consistent with the combined results.

5.3 Conclusions Regarding Efficacy Data

I agree with Drs. Brugge and Chen that the sponsor has submitted a single positive study to support the efficacy of paliperidone in maintaining clinical stability in adult patients with schizophrenia.

6.0 Safety Data

6.1 Safety Findings from the Placebo-Controlled Trials

The controlled trial safety database for paliperidone ER includes patients who participated in the double-blind acute phases of the trials submitted to N21999 (paliperidone ER for acute treatment of schizophrenia), in addition to those subjects from the current NDA (Study 301). I agree with Dr. Brugge that the safety results do not yield any new or clinically remarkable findings to alter our conclusions that paliperidone ER is reasonably safe to use in schizophrenic patients.

6.1.2 Safety Findings and Issues of Particular Interest

6.1.2.1 Common and Drug-Related Adverse Events

Adverse events with an incidence of at least 2% in the treatment group that were also at least twice that seen with the placebo group included: anxiety, somnolence, akathisia, headache, back pain, postural hypotension, tachycardia, amenorrhea, respiratory system disorders, and musculoskeletal system disorders. I agree with Dr. Brugge that these results are generally similar in type and frequency to those of the earlier controlled trials of paliperidone ER.

6.1.2.2 Adverse Events Leading to Dropout

Dr. Brugge identified no new clinically remarkable events leading to dropout from Study 301.

6.1.2.3 Serious Adverse Events (SAEs) in Clinical Trials

Treatment-Emergent Serious Adverse Events for study 301 are identical to the information provided in the Safety Update Report for NDA21-999 (see page 59 of Dr. Brugge's review). The same is true of safety results from the open-label trial results and from the extension trial datasets (see pages 60-64 of Dr. Brugge's review). I agree with Dr. Brugge's conclusion that no new clinically remarkable findings were revealed.

QT Interval Prolongation

Paliperidone ER was found (N21999) to cause a modest increase in the QTc interval and has been labeled accordingly. There are some suggestions that this effect persists in the open-label trial data, but I agree with Dr. Brugge that it is not possible to assess this from non-controlled datasets. At any rate, what is known with certainty about the effects of paliperidone ER on QT prolongation is already prominently labeled in this approved product.

6.1.2.4 Laboratory Findings

I agree with Dr. Brugge that laboratory findings from Study 301 are generally similar to what is already known (and labeled) about paliperidone ER.

6.1.2.5 Vital Signs Findings

I agree with Dr. Brugge that no new clinically remarkable findings with regard to vital signs were identified in study 301.

6.2 Conclusion Regarding Safety

I agree with Dr. Brugge that no new safety concerns have been identified from Study 301 that were not addressed during the review of paliperidone ER for the acute treatment of schizophrenia.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was not presented to the PDAC.

8.0 DSI INSPECTIONS

Data from two sites (Latvia and Lithuania) were inspected by DSI and found to be acceptable.

9.0 LABELING AND ACTION LETTER

9.1 Final Draft of Labeling

The sponsor's proposed labeling is not consistent with other drugs in the class approved for maintenance treatment of schizophrenia and will require some modification. Of particular importance to labeling will be to accurately describe the stabilization period prior to double-blind randomization. We will modify labeling to reflect our understanding of the trial data and provide our modified version to the sponsor.

9.2.2 DMETS

INVEGA® is an approved product with the approved trade name.

10.0 Phase 4 Commitments

Schizophrenia is not a disease of children and we should grant a waiver for study in children.

We should consider deferring the requirement to study paliperidone ER for the maintenance of clinical stability in adolescents with schizophrenia until after data from the paliperidone ER acute treatment of adolescent schizophrenics program are submitted for review.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that paliperidone ER is effective and reasonably safe in the maintenance of clinical stability in adult patients with schizophrenia.

We should defer the PREA requirement to study this drug for this indication in children, for the reasons cited in section 10 above.

Annotated Draft Labeling as revised by the Division should be attached to the Action Letter.

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/s/

Mitchell Mathis
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MEDICAL OFFICER
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CLINICAL REVIEW

Application Type Supplemental NDA
Submission Number 22043
Submission Code N000

Letter Date 6/27/06
Stamp Date 6/27/06
PDUFA Goal Date 4/27/06

Reviewer Name Karen Brugge
Review Completion Date 3/9/07

Established Name Paliperidone
(Proposed) Trade Name INVEGA™
Therapeutic Class Atypical Antipsychotic
Applicant Johnson and Johnson PH

Priority Designation Standard

Formulation OROS oral
Dosing Regimen 6-12 mg daily oral treatment range
Indication Maintenance Treatment of
Schizophrenia
Intended Population Patients with Schizophrenia

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1 EXECUTIVE SUMMARY

The Purpose of This Review.

This review and summary are to assist the Team Leader and Director of the Division of Psychiatry Products in the regulatory processing of NDA 22-043. The summary provides a brief overview of the Clinical review of this NDA (refer to the review for more complete and detailed clinical information and clinical recommendations).

Information, comments and recommendations in this review are provided from a clinical perspective.

Proposed Indication and Treatment

The proposed indication is for [redacted] in patients with Schizophrenia (in adults). b(4)

A pivotal Phase III Study -301 was conducted to support the proposed claim. Safety results from this study, along with results of open-label extension trials (pooled and unpooled datasets) were also provided as the Phase III long-term safety database. These results are intended by the sponsor to support the adequate safety of their proposed maintenance treatment claim.

OROS Paliperidone (Pal) is approved for the treatment of schizophrenia by demonstrating efficacy of Pal in the acute treatment of schizophrenia in three 6-week, placebo controlled, fixed-dose trials in patients with this disorder (as specified in labeling under the Indications and Usage section as approved on 12/19/06 under NDA21999).

The recommended treatment for schizophrenia in approved labeling is a daily oral dose of 6 mg of Pal to be taken in the morning with or without food. The Dosage and Administration section of approved labeling also notes a food effect (that exposure to Pal can be increased or decreased by the presence or absence of food, respectively). It is also noted that patients may benefit from lower or higher doses within a recommended daily dose range of 3 to 12 mg (once daily).

1.1 Recommendation on Regulatory Action

It is recommended that an Approvable Action be granted on NDA22043, from a clinical perspective.

In accordance with the Clinical Review MAPP, the basis for this overall recommendation is provided under Section 1.3 below. Section 1.3 summarizes the clinical trials, the results from the pivotal efficacy Study -301 and safety results from Phase III studies. Section 1.3 also provides conclusions on safety and efficacy. As described in Section 1.3 Pal is adequately safe and efficacious, from a clinical perspective and as specified in this review (in Section 1.3 and in Section 9 of this review).

Recommendations and issues are provided that are considered by the undersigned reviewer as issues that need to be resolved before considering a final approval action on the NDA. These issues pertain to labeling based on the sponsor's safety and efficacy results with respect to describing the results, the proposed claim and on the proposed treatment regimen (as discussed and outline in Sections 9.2 and 9.4 of this review)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The proposed Risk Management program cannot be found in the submission. Sponsors maintain a world-wide safety database and are required to submit annual reports or periodic safety reports, as specified in the regulations.

1.2.2 Required Phase 4 Commitments

The Pediatric section of this review discusses plans for pediatric adolescent trials (Section 8.4).

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

See subsections 1.3.1 below. In accordance with the MAPP on the clinical review template subsections below provide the following information, as specified:

- Subsection 1.3.1 provides an overview of the clinical trials intended to support the proposed indication (the clinical program)
- Subsections 1.3.2. and 1.3.3 summarize the efficacy and safety results, respectively from the clinical trials, as well as provide key conclusions (Section 7 of this review describes safety results in more detail).

Key efficacy and safety-related issues and recommendations were previously outlined under Section 1.2 and are also provided in Section 9 of this review.

1.3.1 Brief Overview of Clinical Program

See Section 1 for the overview of the proposed indication and of the Phase III efficacy and safety database submitted under NDA22043.

Phase III Pivotal Efficacy Studies

The following summarizes the efficacy results intended by the sponsor to support their proposed indication.

Only one pivotal Phase III longer term trial was conducted to support the proposed claim. Study -301 was conducted on non-elderly adults with schizophrenia (met DSM-IV criteria and criteria for acute symptoms). The protocol involved stabilizing subjects on an initial flexible-dose OL treatment phase (3, 6, 9, 12 and 15 mg daily dose-levels) over 6-weeks. This treatment phase allowed for dose adjustment to optimize efficacy and tolerability. Then subjects who were stabilized (which was defined by prespecified criteria) were continued on their achieved, fixed, dose-level over an 8 week period (using an OL fixed dose design). Subjects who remained stable (based on prespecified criteria) in the protocol, were eligible to enter the DB treatment phase.

A total of 113 subjects met eligibility criteria for entry into the DB phase. These subjects were randomized (1:1) to either placebo or Pal treatment (3-15 mg/daily using a flexible dose design). Subjects were monitored on efficacy assessments throughout the study and were monitored for recurrence during the DB phase. Recurrence was defined on the basis of the subject's mental status, using specific criteria for defining a recurrence (as specified in the protocol).

Time-to-recurrence was the primary efficacy variable. The primary efficacy analysis involved an Interim Analysis after 43 recurrence event occurred (50% of planned recurrence events). The Kaplan-Meier method was employed for statistical analyses, along with a 2-sided log-rank test to compare the treatment groups on time-to-recurrence. Additional analyses were conducted, as well as analysis of secondary efficacy variables.

Phase III Safety Trials

Phase III safety results provided under NDA22043 were updated from results that were previously described in clinical reviews under NDA21999, since a number of trials were ongoing.

The bulk of the Phase III safety data provided in NDA22043 was an integrated safety dataset from longterm OL extension trials (Studies -702, -703, -704 and -705). These extension trials followed 6-week, DB, placebo controlled efficacy studies that supported approval of NDA21999 for the schizophrenia indication. OL Pal treatment during the extension trials was given to subjects for up to 12 months except for the small elderly study, Study -702. This smaller extension study employed a 6 month treatment duration. The trials used a flexible dose design using daily doses of 3, 6, 9, 12, except for Study -705 which had a maximum daily dose-level of 15 mg maximum.

Several of the OL studies remain ongoing at the time of the cut-off dates for the NDA22043 submissions (N000 and N0001). As of a 2/1/2006 cut-off date, the following outlines the exposure to Pal treatment among subjects included in the integrated OL trial safety dataset:

- 441 safety subjects who received at least 6 months of Pal treatment and
- 755 safety subjects receiving over 6 months

The sponsor met ICH guidelines for 6 month and 12 month exposure with Pal (over 100 subjects had 52 weeks of OL Pal treatment in the integrated OL trials).

1.3.2 Efficacy

See the previous subsection for a summary of the study design of the pivotal Phase III efficacy trial, Study -301.

A significantly longer time-to-recurrence was observed in the Pal group compared to the placebo group ($p < 0.01$) during the DB treatment phase of Study 301.

In conclusion Study -301 is a positive study.

See the previous Section 1.1 for key efficacy-related issues and recommendations. Section 9 of this review also describes these issues and provides recommendations. Section 6 of this review provides details on the study design and efficacy results of Study -301.

1.3.3 Safety

See Section 1.3.1 for a summary of the Phase III safety database.

Safety results summarized in this review (as submitted to N000-002 under NDA22043) do not yield any new and clinically remarkable findings that alter overall conclusions and recommendations that were previously provided for this drug for this patient population under NDA21999 (as provided in the original clinical and addendum clinical reviews of NDA21999 for the schizophrenia indication).

NDA 21999 was approved on 12/19/06.

Pal is in the same drug class as several other previously approved drugs for the maintenance claim for treatment of schizophrenia. Pal is a major active metabolite of one of these approved drugs (risperidone). Consequently, there is extensive pre-marketing and postmarketing experience with drugs in the same drug class as Pal and with the precursor to Pal (risperidone).

Therefore, Paliperidone is adequately safe, from a clinical perspective within the recommended dose range of up to 12 mg daily (as appears in approved labeling) and for longer-term treatment, as specified in recommendations for labeling (as discussed in detail in Section 9 of this review).

Section 7 of this review focuses on safety results in greater detail.

1.3.4 Dosing Regimen and Administration

The Dosage and Administration section of the sponsor's proposed annotated labeling (in the N000 submission) does not include any changes from the approved version of labeling under NDA21999. Study -301 and the safety database used daily dose-levels comparable to the recommended treatment regimen for treatment of acute patients with schizophrenia (in approved labeling under NDA21999).

See Section 1 for further comment and for recommendations relevant to this section of labeling. Section 9 of this review also provides recommendations.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not systematically evaluated in Phase III trials. This topic was previously addressed under NDA21999 (refer to the OCPB review for details). Section 8.2 of this review provides further comments on this topic.

1.3.6 Special Populations

Phase III trials did not systematically evaluate special populations. A small OL Study -702 provided some limited safety results on elderly patients. Sections 8.3 and 8.4 of this review provide further comment on this topic and regarding the pediatric patient population.

NDA21999 previously addressed the topic of Pal treatment in special populations (refer to the OCPB review for details and for limited safety results of a small, short-term Phase III trial in elderly patients, Study -302 in the clinical review of NDA21999).

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2 INTRODUCTION AND BACKGROUND

The Purpose of this Clinical Review. The purpose of this clinical review is to assist the Team Leader and Director of the Division of Psychiatry Products (DPP) in the regulatory processing of NDA 22-043. Information, comments and recommendations in this review are provided from a clinical perspective.

Proposed Indication. The sponsor is seeking approval of Paliperidone OROS® oral formulation (Pal) for a maintenance treatment of schizophrenia.

Note to the Reader and a Brief Overview of the Organization of this Review.

A reviewer MAPP was followed for this review which involves having multiple headings with redundancy across sections. An effort has been made by the undersigned reviewer to minimize this redundancy without jeopardizing the flow of the content. Figures and tables provided in this review were generally obtained from the NDA submission.

The following provides some comments intended to aid the reader.

All sections, subsections (which are numbered) and the order and placement of these sections and subsections in this review are according to the required template. However, please note the following:

- Note that “Clinical Microbiology” appears under a subsection on efficacy (Section 6.1.6) but this topic is not relevant to efficacy and is not relevant to this review.
- In order to avoid redundancy between various subsections, subsection(s) that are related or redundant are cross-referenced (rather than repeating the same information under multiple subsections).

Italicized text in this review generally appears in various places throughout this review and is generally intended to denote comments, conclusions and recommendations being made by the undersigned reviewer (from a clinical perspective), unless otherwise specified (or if a given section is clearly intended for providing reviewer comments, conclusions and/or recommendations). Sometimes sections include reviewer comments/conclusions that are embedded with the sponsor’s results. These sections generally present the results, as found in the submission (unless otherwise specified). These sections that contain some of the sponsor’s results embedded with reviewer comments are also italicized.

Guide to the Reader

Since the template has a number of sections enhancing the length of this review the reader is guided to the following sections for a comprehensive summarization of key efficacy and safety results, reviewer comments, and conclusions with recommendations:

- Sections 1 and 9

- Section 7.1.1 “Reviewer’s Overview of Key Safety Findings” was inserted by the undersigned reviewer in order to facilitate the reader in providing the main conclusions of safety results that are described in greater detail in sections that follow Section 7.1.1 (it is the understanding of the undersigned reviewer that adding a new section is permitted).

2.1 Product Information

The pharmacologically active compound in Pal is 6-OH Risperidone which is the major metabolite of risperidone (Ris). The OROS® formulation is considered as a slow release formulation. Pal was recently approved on 12/19/2006 for treatment of schizophrenia under NDA21999 (refer to approved labeling for details).

Ris is marketed (as Risperdol®) as a tablet formulation which is a more immediate release formulation compared to Pal. Risperdol® is approved for the treatment schizophrenia.

2.2 Currently Available Treatment for Indications

Pal is in a drug class of atypical antipsychotic agents and several drugs in this drug class are approved for treatment of schizophrenia, as well as for other psychiatric indications. Several of these drugs including Risperdol® are also approved for maintenance treatment of schizophrenia.

2.3 Availability of Proposed Active Ingredient in the United States

See section 2.1 above describing Ris which is approved for treatment of schizophrenia and maintenance treatment of schizophrenia.

2.4 Important Issues With Pharmacologically Related Products

See the previous sections and other safety related sections of this review. Also refer to current approved labeling for drugs in this drug class. Refer to the Approval Action letter for NDA21999 regarding any postmarketing commitments on Pal. The final section of this review provides recommendations to any new and clinically remarkable safety findings that were not previously described in past clinical reviews of NDA21999 (see Section 4.3 for the review strategy).

2.5 Presubmission Regulatory Activity

Pal was developed under IND 65850. The sponsor has had several meetings with the Division (EOP II, Pre-NDA meetings) under IND 65850. Any meeting minutes and/or communications with the sponsor regarding trials under their IND are found in DFS (under IND65850) and are not summarized in this review.

This review does not discuss and summarize past key clinical issues under IND65850 (unless otherwise specified), since the focus of this review is on the actual data submitted under

NDA22043 for assessing adequate efficacy and safety for the proposed efficacy claim. See section 4 of this review for the review strategy of the NDA22043.

2.6 Foreign Marketing Experience

Information on foreign marketing and postmarketing safety information cannot be found in the current submission other than a comment in Module 2.7.4 that Pal is not approved in any country.

Under NDA 21999 (a 10/20/06 response to an approvable letter) the sponsor indicates that Pal (extended release tablet) is not approved in any country and that several foreign applications have been submitted (countries and submission dates are specified). None of these pending applications have had a negative action.

Past clinical reviews cover foreign marketing information and postmarketing information (only on Ris, since Pal was not approved in any country). These previously reviews were a review of a response submission to an approvable action letter on NDA 21999 and a review of the original 11/30/05 NDA 21999 submission, which covered each topic, respectively. The original NDA219999 clinical review covers the topic of world-wide postmarketing safety information on risperidone (which was first approved in 1992 in the United Kingdom and is also approved by the Agency for US marketing).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

This submission is a supplemental NDA for a new efficacy claim. The undersigned reviewer is not aware of any key CMC issues identified by the CMC review Team at the time of this writing.

3.2 Animal Pharmacology/Toxicology

This topic is not applicable since preclinical information is not provided, since this is a supplemental NDA for an efficacy claim.

3.3 Biometrics

A Biometric review of this NDA is underway at the time of this writing. Any potential Biometric-related issues are discussed in Sections 6 and 9 of this review where efficacy results of the pivotal maintenance trial, Study -301 are described. Also see the last section of this review for further comment and recommendations.

3.4 Division of Scientific Investigation (DSI)

The undersigned reviewer is not aware of any key DSI issues identified by the DSI review Team at the time of this writing.

3.4 Clinical Pharmacology and Biopharmaceutics (OCPB)

The undersigned reviewer is not aware of any key OCPB issues identified by the OCPB review Team at the time of this writing.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The following items were utilized during the course of this clinical review:

Documents Utilized in Clinical Review	
LETTER DATE	DESCRIPTION
6/27/06	NDA 22-043 N000: electronic submission with Module 2.7.4 providing safety results and Clinical Study Report of the pivotal Phase III efficacy trial, Study -301. Narrative and CRFs were included. Refer to sections below and Section 7 in this review for details on information reviewed that was included in the submission. The sponsor used a 2/1/06 cut-off date for: <ul style="list-style-type: none"> • Results of safety data analyses in Module 2.7.4 • For providing Clinical Study reports (CSRs) of completed Phase III (non-pivotal) trials (Studies -702 and -704 and for Phase I Study P01-1012). Study -703 was completed after the cut-off date, and Studies -701 and -705 are ongoing. Therefore, CSRs were not provided for these latter trials. • For providing narratives and CRFs for Deaths, Serious adverse events and adverse dropouts and deaths. CIOMS forms (clinical safety reports) were provided for deaths and serious adverse events in ongoing OL phase III Extension trials that were reported after 2/1/06 and by 3/31/06 (according to Section 2.1.3.3 of Module 2.7.4.
10/27/2006	N001: 120-Day Safety Update Report (SUR) as described in Section 7.2.9.1 of this review.
12/21/2006	N002: response to clinical inquiries
1/26/2007	N003: This submission (provided late in the review cycle) was not reviewed, as discussed in more detail in Sections 1 and 9 of this review.

N000 and N001 Submissions

See the next section regarding clinical trials included in the submission and Sections 4.3 and 7 for review strategies for the N000-001 submissions.

N003 Submission

N003 was not reviewed, as discussed in sections 1 and 9 of this review.

N002 Submission

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 Paliperidone OROS oral

This is a response to inquiries and some sections of this review include some information obtained from this 12/21/06 submission, as specified accordingly.

4.2 Tables of Clinical Studies

Completed Trials as of the 2/1/06 Cut-off Date

Tables below (tables or sections of tables were copied from the submission) were either found in Module 5.2 (only a listing of completed trials were included in this table) or were found in the Summary of Clinical Safety (SCS) Module 2.7.4 (included ongoing trials).

Tabular Listing of All Studies – R076477

Protocol Number Study Identifier ^a Principal Investigator (Country) Start/End Dates	Study Description/Design	Subjects Evaluated ^b Sex (M/F) Age (yr): median [mean] (range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Batch/Formulation Numbers	Study Status Type of Report Location of Study Report (CRFs and CRTs) or Publication
Controlled Clinical Studies Relevant to the Proposed Indication: Key Efficacy Trials				
R076477-SCH-301 EDMS-PSDB-3176970 K. Yadalam (US) Start: 13 April 2004 End: 31 August 2005	Randomized, DB, PC, parallel- group study of efficacy and safety	305 121M/84F 38 [38.2] (19-63) 123/17/65	PAL Treatment Group: Flexible dosing: 3 mg/day to 15 mg/day Batch Nos: 3-mg tablets: 03110/ F022; 03J01/ F022; 04E05/ F022; 05A03/ F022; MV0301019/ F016; MV033871B / F016 9-mg tablets: 05123/ F023; 03G14/ F023; 03J13/ F023; 04E04/ F023; 05A10/ F023; MV0301025/ F017; MV0406657/ F017	Completed Full Report Mod 5.3.5.1/R076477-SCH-301 (CRF) (CRT)
Clinical Studies Relevant to the Proposed Indication: Supportive Studies				
R076477-SCH-702 EDMS-PSDB-5139270 T. Andreas (International) OL phase: Start: 21 September 04 End: 15 November 05	OL efficacy, safety and tolerability in geriatric subjects	88 24M/64F 68 [69] (64-81) 87/~/1	OL extension (24 wk): ER OROS PAL flexible dosing 3 - 12 mg/day Batch Nos: 3 mg capsules: MV0301019/ F016; MV0332875/ F016; 0426911/ F015 9 mg capsules: MV0301025/ F017; MV0406657/ F017; 0426912/ F017	Completed Full Report Mod 5.3.5.4/R076477-SCH-702 (CRF) (CRT)
Clinical Studies Relevant to the Proposed Indication: Supportive Studies (Continued)				
R076477-SCH-704 EDMS-PSDB-5497233 A. Lowy (U.S.) OL phase: Start: 18 March 04 End: 20 December 05	OL efficacy, safety and tolerability in subjects with schizophrenia	303 149M/54F 43 [41.5] (20-76) 180/99/4	OL extension (53 wk): ER OROS PAL flexible dosing 3 - 12 mg/day Batch Nos: 3 mg: MV0301019/F016, MV0307085/ F016, MV0333801/F016 9 mg: MV0301025/F017, MV0406657/F017	Completed Full report Mod 5.3.5.4/R076477-SCH-704 (CRF) (CRT)

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 Paliperidone OROS oral

			<u>Bioavailability Studies</u>	
PALOROS-P01-1012	Single-dose, randomized, OL	74	Treatment A:	Completed
EDMS-PSDS-5082229	3x-crossover study to evaluate	74M/0F	12 mg ER OROS PAL,	Full Report
D. Morrison	the effect of food and posture on		TBM formulation,	
(US)	the PK of ER OROS PAL in	24 (18-55)	after a high-fat breakfast	ModS.3.1.1/PALIOROS-P01-1012
Start: 30 August 2005	healthy men	64/8/2	1x 12 mg tablet	(CRF)
End: 1 December 2005			Treatment B:	(CRT)
			12 mg ER OROS PAL,	
			TBM formulation, fasted, ambulant	
			1x 12 mg tablet	
			Treatment C:	
			12 mg ER OROS PAL,	
			TBM formulation,	
			fasted, 36-hour confinement, supine	
			1x 12 mg tablet	
			Batch No.:	
			12 mg: 0406338; F049	

Key: B=black; DB=double-blind; ER=extended release; F=female; M=male; O=open-label; PAL=paliperidone; PC=placebo-controlled; PK=pharmacokinetics; TBM=to-be-marketed; US=United States; W=white.
 * The sponsor is Johnson & Johnson Pharmaceutical Research & Development (J&JPRD).
 † Number of subjects evaluated for safety.
 ‡ Racial information captured as white, Asian, or other, therefore black subjects are included with "other."

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See Section 6 of this review for more information on treatment given in each phase of Study 301.

Ongoing Trials as of the 2/1/06 Cut-off Date

The trials below were included in the submission of which clinical study reports (CSRs) were not provided since they were completed after cut-off date for the N000 submission (Study -703) or are ongoing trials (-701 and -705). Although a CSR was not provided for Study -703, the sponsor indicates that all safety data from this study was included in the NDA submission since the study was completed (according to that described on page 11 of the Clinical Overview).

Additional Trials that Were Ongoing at the Time of the Reporting Cut-off Date

<u>OPEN-LABEL PHASE 3 EXTENSION STUDIES IN SUBJECTS WITH SCHIZOPHRENIA</u>	
R076477-SCH-701	A 52-week open-label extension of the relapse prevention study (Study R076477-SCH-301) in subjects with schizophrenia
	No. Subjects Enrolled as of 1 Feb 2006: 235
	Ongoing
R076477-SCH-703	A 52-week open-label extension to evaluate ER OROS paliperidone in the treatment of subjects with schizophrenia who completed the 6-week double-blind phase or discontinued due to lack of efficacy after a minimum of 21 days of double-blind treatment in Study R076477-SCH-303
	No. Subjects Enrolled as of 1 Feb 2006: 473
	Ongoing [†]
R076477-SCH-705	A 52-week open-label extension to evaluate ER OROS paliperidone in the treatment of subjects with schizophrenia who completed the 6-week double-blind phase or discontinued due to lack of efficacy after a minimum of 21 days of double-blind treatment in Study R076477-SCH-305
	No. Subjects Enrolled as of 1 Feb 2006: 407
	Ongoing

[†] Enrollment as of 1 February 2006.
[‡] This study was ongoing as of 1 February 2006 but was completed shortly after that date. Complete data from all 473 subjects who participated in this extension are included in this submission. The final study report had not been written by the time of this submission.

Treatment Regimens in OL Studies

Since the above tables do not specify the treatment regimens for each OL Pal Extension Trial this information is summarized as follows. All OL extension trials used a flexible dose design that generally allowed dose adjustments of 3 mg intervals to maximize efficacy and minimize adverse events):

- Study -701 (non-elderly patients) used a 3-15 mg daily dose-level with a starting daily dose of 9 mg.
- Elderly Study -702 used a 3-12 mg daily dose-level with a starting daily dose of 9 mg.
- Studies -703, -704 and -705 (almost all non-elderly patients) used a 3-12 mg daily dose-level with a starting daily dose of 9 mg, except that Study 705 used a 3-15 mg daily dose-level.

OL treatment was immediately started at 9 mg daily of Pal in all OL trials which was started after completion of the DB placebo controlled 6-week Phase III lead-in studies (-302, -303, -304 and -305). Note that DB treatment was abruptly stopped before starting OL 9 mg/day of Pal. Previous DB treatment was placebo, 10 mg/day olanzapine or Pal (at 3-15 mg daily; 3, 6, 9, 12, or 15 mg daily).

4.3 Review Strategy

Efficacy Results: Efficacy results of the pivotal Phase III trial, Study -301 were reviewed as described in more detail in Section 6 of this review. Primarily in-text sections of the CSR of this study were reviewed on sections relevant to study design methods and efficacy results, as described in Section 6 of this review. Refer to Section 9 of this review for any key issues relevant to efficacy that were revealed upon review of this information.

Safety Results: The key objective in reviewing safety results was to determine if any new clinically remarkable findings could be found that were not previously described in past clinical reviews under NDA 21999 (the review and addendum review of NDA 21999 and in the response to the approvable action review that was more recently completed).

The above approach in reviewing safety results is employed for this review, since the bulk of short-term and longterm safety results were previously reviewed under NDA 21999. The bulk of long-term safety results came from integrated data from OL extension trials that includes ongoing trials as outlined below:

- The bulk of safety data was previously reviewed under NDA 21999 and included integrated safety data from several ongoing longterm OL extension trials, some of which were more recently completed. It is notable that the sponsor met ICH guidelines for longterm exposure as described in the original clinical review of NDA21999.
- Module 2.7.4 in the current NDA 22043 submission is identical to the 210-SUR of NDA 219999 and provides some updated safety information from the integrated OL extension-trial dataset (updated since the 120-Day SUR under NDA21999). Updated

results from unpooled safety datasets from OL trials are also provided in the current NDA22043.

- A 120-Day SUR was provided under this maintenance claim NDA (NDA22043) which contains the most complete and updated safety results for the integrated OL trial safety dataset.

Refer to Section 7 of this review for more details of the safety datasets provided and reviewed in the original NDA 22043. This section provides more details on the review strategy and summarizes safety results that were reviewed. Section 7 also provides a discussion on some of the key limitations of the safety information provided. See Section 7.2.9.1 for more comments regarding the 120-Day SUR submission and for a summary of the safety results that were reviewed in this SUR. The final section (Section 9) of this review summarizes any key issues relevant to safety and provides recommendations, accordingly.

The following outlines summarize safety information that was reviewed.

Pooled and Unpooled Safety Datasets in the Original NDA 22043 submission that were reviewed for specific safety information as summarized in various subsections of Section 7 of this review (Section 7 summarizes the safety results that were reviewed for each dataset and provides more details on the rationale for specific aspects of the review strategy under appropriate subsections accordingly):

- Completed Study -301: Safety results (in-text sections of the CSR, unless otherwise specified) were reviewed for this study since this was a pivotal maintenance treatment trial.
- Ongoing Study -701 (the OL extension trial of Study -301): results on deaths, SAEs and ADOs were reviewed for this study as described under Section 7 (based on primarily in-text information found in Module 2.7.4 unless otherwise specified in this review). Additional safety information for this study was not reviewed for the following reasons. The integrated OL extension trial safety results involved a larger number of subjects. Furthermore, Study -701 has not been completed. Hence, the review of additional safety information from the much smaller sample size of subjects in Study -701 would not be expected to be as informative as results from a large integrated safety dataset. The interpretation of results from OL trials is compromised by the inherent limitations associated with studies of this nature.
- Integrated-OL extension trial safety dataset from ongoing and completed (Studies -702, -703, -704, -705 of which Studies 704 and 705 are ongoing): the safety results from this dataset (primarily from in-text sections of Module 2.7.4) were reviewed since the integrated results are considered to be more informative for longterm safety information than results from unpooled studies (i.e. from a given, single small OL trial).
- The safety results of Study -702 (as found primarily in selected in-text sections of the CSR) were reviewed since this study was the only elderly Phase III trial.

Results of the following CSRs that were provided but were not reviewed for reasons that follow:

- Studies -702 and -704 of which CSRs were provided: these studies were recently completed OL extension trials. Results of these studies were pooled with the integrated OL trial safety dataset in Module 2.7.4 of the submission. New information would not be expected from the review of the individual CSRs, particularly given that OL studies are limited by the OL study design as previously discussed (also see Section 7 of this review for more details).
- Results of Phase I study –P01-1012 were submitted but selected results from this study were previously reviewed under NDA 21999 and the study was also reviewed by Dr. Ronald Kavanagh, as the OCPB reviewer for NDA21999.

In-text sections of Module 2.7.4 and of selected CSRs that correspond to sections of this review and as specified in this review were reviewed. However, in some cases additional information was reviewed as outlined below.

Narratives, CIOMS forms, and Case Report Forms (CRFs):

Narratives were provided for subjects with SAEs (includes subjects that died), ADOs and for subjects with abnormal liver function tests (that met prespecified criteria, as described in relevant sections of this review). CIOMS forms were provided for more recently reported subjects (as specified using specified cut-off dates). This information was reviewed as follows:

- Narratives and CIOMS forms on selected subjects were reviewed, as described under Section 7 were reviewed (this information was provided in appendices or attachments to Module 2.7.4).
- A spot check of arbitrarily selected CRFs comparing arbitrarily selected information between the selected CRFs and narratives was conducted as part of an assessment on the accuracy and completeness of the information provided. See Sections 4.4 and 7.2.8 of this review for details and further comment.

Additional Information that was Reviewed

The following outlines additional information that was reviewed:

- Some information that was found in appendices to primarily Module 2.7.4 were reviewed, as specified in corresponding sections of Section 7 of this review.
- Section 7 of this review also summarizes results from the literature and other results from other datasources that were found in the submission and as described in subsections of Section 7.
- Section 7.2.9.1 summarizes results in the 120-Day SUR (which also specifies the materials reviewed and details on the review strategy for this more recent submission).
- Responses to questions provided in N002.

N003 was not reviewed as discussed in Sections 1 and 9 of this review.

Final Comments on the Review Strategy

As a final note, as previously discussed in Section 2.5 of this review, this review does not discuss and summarize past key clinical issues under IND65850 (unless otherwise specified). Instead this review focuses on the actual data submitted under NDA22043 for assessing adequate efficacy and safety for the proposed claim.

Team Leader and Deputy Director of DPP, Mitch Mathis, MD concurred with the review strategy for NDA 22043 (N000-003) and as described in this review.

4.4 Data Quality and Integrity

DSI has not conveyed any key concerns at the time of this writing.

A spot check comparison between Case Report Form (CRFs) and narratives revealed the following observations (and as described in more detail in a paragraph below):

- *A number of Data Clarification Form (DCF) entries were generally found. However, the clarified information that was found, together with information in the CRF, generally matched the information that was found in the narrative (based on the arbitrarily selected items that were compared, as described in more detail later).*
- *Information on some clinical safety parameters (e.g. ECG and laboratory data) could not be found in the CRFs. Yet, this information was sometimes found in the narratives. It is not clear why some of the safety parameter information was not included in the CRFs.*

Reviewer Conclusions

DSI has not reported any key concerns at the time of this writing and narrative/CRF spot checks do not reveal any key issues on quality and integrity of the data. Therefore, observations noted in this section and under Sections 4.5 and 7.2.8 of this review), generally do not alter conclusions previously conveyed in the review of NDA219999 (refer to the review of NDA21999 for details on potential concerns previously noted that are relevant to the current NDA22043).

Additional Comments on Comparisons between Narratives and CRFs on Clinical Parameter Data

See details on the methods for making spot check comparisons between selected narratives and CRFs below. The following are comments regarding clinical parameter data that could not be found in selected CRFs, based on these spot check comparisons:

- *QT values for a subject with QT prolongation (100767) could not be found in the CRF but were described in the narrative.*
- *Laboratory data on a subject with elevated LFTs (reported as AEs in subject 501320) could not be found in the CRF but was included in the narrative.*

It is noted that while other clinical safety parameter information could not be found in the CRFs, vital sign data was found in the CRFs. It is not clear why the CRFs did not include all clinical parameter data obtained from the given subject. However, clinical parameter data is generally found in other sections of the submission. SAS datasets were also provided that include efficacy data (and generally include additional data) from the pivotal efficacy trial (Study 301) and that

were used by the Biometric Team. The Biometric Team did not convey any key issues regarding the SAS datasets with respect to efficacy.

Methods for Conducting Spot Check Comparisons between CRFs and Narratives

A spot check on comparing CRFs to narratives of arbitrarily selected subjects was conducted as follows:

- Sections of the CRFs and narratives for a given subject were arbitrarily selected for making these comparisons (arbitrarily selected sections generally included AE verbatim terms, dates of AEs relative to treatment and a few other arbitrarily selected sections).
- The arbitrarily selected subjects for the document comparisons were:
 - Subject 501320 of Study -705,
 - Subject 201690 of Study -703 and
 - Subject 100767 of Study -301 (some basic demographic information was also compared between the CRF and narrative for this subject).

4.5 Compliance with Good Clinical Practices

DSI has not conveyed any key concerns at the time of this writing.

4.6 Financial Disclosures

The sponsor provides a list of investigators of the pivotal Study -301 and the OL extension trial of this study, Study -701. The investigators listed are specified as investigators that did not enter into any financial arrangement, as indicated in item 1 (which is checked off) of Form FDA 3454 (4/06). Items 2 and 3 were not checked off on the form.

Financial information for Study P01-1012 was also found in the submission but this study was a Phase I study previously submitted under NDA 21999.

Upon request, the sponsor verified that the financial information provided in the original NDA 22043 submission (as summarized above) is complete (as specified in the December 21, 2006 response to inquires submitted under NDA 22043).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

NDA 21999 provided pharmacokinetic and related information of Pal that was reviewed by the OCPB. This previously submitted NDA was approved on 12/19/2006.

The following is key information on PK properties, as provided by the sponsor under NDA 21999 (copied from the clinical review of NDA 21999 of which the clinical review was conducted by the undersigned reviewer of the current NDA 22043):

- T_{max} is approximately 24 hours
- The PK of Pal is dose-proportional across the proposed clinical dose range of 3 mg to 12 mg daily.
- T_{1/2} = approximately 23 hours
- Steady state levels are achieved within 4-5 days of daily treatment in most subjects
- Fluctuation indices with daily treatment of 12 mg Pal and 4 mg immediate-release formulation of risperidone are 38% and 125%, respectively, at steady state.
- Absolute oral bioavailability is 28%
- C_{max} and AUC values increase by 42% and 46%, respectively in a high-fat/high-caloric fed state compared to a fasting state following a SD of 15 mg Pal in healthy subjects confined to bed for 36 hours.
- Plasma protein binding is 74%, primarily to alpha-1-acid glycoprotein and albumin.
- *In vitro* studies show some slight displacement of protein bound Pal to the free fraction (at 50 ng/ml) at high therapeutic concentrations of diazepam, sulfamethazine, warfarin and carbamazepine.
- Administration of radiolabeled IR Pal (1 mg) yields 59% of the dose unchanged in the urine with approximately 80% of radioactivity found in urine and 11% in the feces.
- The following 4 metabolic pathways were identified *in vivo* (accounting for no more than 6.5% of the above 1 mg dose): dealkylation, hydroxylation, dehydrogenation and benzisoxazole scission.
- While *in vitro* studies suggest a role of CYP2D6 and CYP3A4 in Pal metabolism, *in vivo* studies show a limited role of these isozymes.

Also refer to approved labeling for Pal (NDA 219999 for a schizophrenia indication).

Reviewer Comments:

Food effects on PK are observed. Accumulation also occurs with multiple dosing. In light of the proposed maintenance treatment claim for longterm treatment, input from OCPB regarding potential OCPB-related issues with chronic treatment is recommended. See the last section of this review for further comments.

5.2 Pharmacodynamics

The *in vitro* pharmacodynamic properties of Pal (as described in the submission) generally appear to be similar to that of risperidone. Sections on pharmacodynamic properties of Pal on efficacy and safety in clinical trials are addressed later in this review.

5.3 Exposure-Response Relationships

Refer to Sections 6 and 7 for dose-response relationship information on efficacy and safety, respectively.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor is seeking a maintenance treatment claim for the schizophrenia indication.

6.1.1 Methods

Study -301 (a “prevention of recurrence” trial) as the basis for their proposed claim.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint is time-to-recurrence. The study design of Study -301, including a more detailed description of primary, secondary efficacy variables and statistical analyses are provided in the next subsection. Section 9 of this review discusses any key limitations or issues relevant to the primary efficacy variable, efficacy results, to the proposed claim and proposed labeling.

6.1.3 Study Design

The study had the following phases:

- Screening phase,
- Run-in OL phase: 8-week open-label (OL) Pal flexible-dose (3 to 15 mg/day) run-in phase,
- Stabilization OL phase: 6-week fixed dose, OL Pal stabilization phase, as described later
- DB Treatment Maintenance Phase: A placebo-controlled, fixed dose DB treatment maintenance phase

Figure 1 in the CSR provides a flow chart of the above phases.

Eligibility Criteria required that subjects be 18-65 year old, generally healthy patients with schizophrenia (DSM-IV criteria used) for at least one year before screening and have an acute episode defined as a PANSS total score of 70-120. Additional key criteria included:

- Hospitalization for at least the first 14 days of the run-in phase.
- Prohibited medications and washout periods are specified (see next paragraph for more details on concomitant and prohibited medications).

- Subjects cannot have an other Axis I diagnosis (based on DSM-IV criteria) and cannot have Axis I diagnosis of Substance Dependence within 6 months of screening (except for nicotine and caffeine)
- Previous history of a lack of response to Ris (as defined in the protocol)

The CSR has a section on eligibility criteria listing the above and additional criteria.

Treatment in OL and DB Phases

Treatment during the run-in and stabilization phases was open-label (OL).

A flexible dose design was used for the run-in and DB phases as follows:

- Flexible dose range was 3-15 mg daily (3, 6, 8, 9, 12 or 15 mg daily) given orally and was to be taken in the morning (before 10:00 am and preferably at the same time each day) and without regard to food intake.
- In the run-in phase only, a starting dose in the run-in phase was to be 9 mg daily.
- In the DB phase the starting dose was the dose received at the end of the stabilization phase.
- The dose in the run-in and DB phases could be adjusted. Dose increases could occur at intervals of no greater than every 7 days and at daily-dose-level increments of no more than 3 mg. Although, note the entry criteria for the stabilization phase, outlined below. One criterion outlined below, requires that subjects must be on a stable dose over the last 2 weeks of the run-in phase.

Fixed Treatment during the Stabilization Phase

See entry criteria for the stabilization phase outlined below that requires 2 weeks of stability on a fixed daily dose level during the run-in phase of the study. The treatment for the stabilization phase was a fixed dose at the daily dose-level given to the subject over the last 2 weeks of the run-in phase.

Entry criteria into the stabilization phase required that subjects meet the following criteria over the last 2 weeks of the run-in phase:

- Maintain a stable (fixed dose) of Pal and
- Score on efficacy scales as follows:
 - Score ≤ 70 on the Positive and Negative Syndrome Scale (PANSS) total,
 - ≤ 4 on the Clinical Global Impression scale-severity (CGI-S; score of 4 or less corresponds to a rating of moderately ill or better),
 - ≤ 4 on each of the following individual PANSS items: P1 [delusions], P2 [conceptual disorganization], P3 [hallucinatory behavior], P6 [suspiciousness/persecution], P7 [hostility] and G8 [uncooperativeness] of ≤ 4 (moderate or less).

Entry criteria into the DB phase:

- Subjects must show symptom control as defined by using the above cut-of scores that were employed for entry into the stabilization phase. Subject must meet these criteria throughout the stabilization phase.
- Subjects must be maintained on a stable dose during the 6-week stabilization phase.

DB Phase

Upon entry into the DB phase, eligible subjects were randomized to either placebo or Pal (1:1). Subjects continued the DB phase until one of the three following conditions was met:

- The subject met criteria for “recurrence” (as defined later).
- The subject withdrew from the study prematurely
- The study was terminated (an interim analysis was conducted as described later)

Prohibited and Allowed Concomitant Medications:

Prohibited and allowed concomitant medications were specified in the eligibility criteria and in Section 3.8 (in the CSR). The following oral medications were permitted during the study:

- Nonsteroidal anti-inflammatory drugs for headaches and other types of pain.
- Antihypertensive agents, as specified.
- Benzotropine 1 to 2 mg BID or biperiden 2 mg TID (or equivalent agents) for the treatment of EPS, as specified.
- Beta-adrenergic blockers for treatment emergent akathisia.
- Antidepressants (except MAOI) were permitted during the DB phase in subjects on a stable dosage for 3 months before baseline (the dose nor the antidepressant agent could not be changed).
- Benzodiazepine for agitation, anxiety, or insomnia, as specified (includes allowing subjects who were on a stable dose \geq 3 months prior to the study to continue treatment on their stable dose, allows for doses of up to 2 mg/day lorazepam or equivalent dose of diazepam as needed, during the study as specified).

Safety and Efficacy Assessments

See Table Series 10.1 in the appendix of this review for the Time and Events Schedule (as provided by the sponsor). This table includes safety and efficacy assessments and time-points for each assessment.

The PANSS and CGI-S were the most frequently conducted efficacy measures in which subjects were assessed as follows and a shown in the study schedule in Table Series 10.1 of this review:

- Weekly over the first 4 weeks of the run-in phase and of the DB phase.
- Every 2 weeks:
 - On weeks 6 and 8 of the run-in phase,
 - Throughout the stabilization phase and
 - For a 4-week period of the DB phase that corresponded to weeks 18, 20 and 22 of the study.
- Every 4 weeks for the remainder of the DB phase (after study week 22).

Repeat Efficacy Assessments Were Conducted on the Next Day When a Recurrence was Suspected

If a "recurrence" was suspected on a given assessment day then the PANSS and CGI-S assessments were repeated on the following day. A suspected recurrence was defined on the basis of the PANSS score or on the basis of the CGI-S score as defined below:

1. Suspicion of a recurrence on the basis of the PANSS score was defined by at least one of the following criteria that must be met on a given scheduled assessment day:
 - An increase in the total PANSS score from randomization by either 25% or
 - An increase by 10 points if the score at randomization was ≤ 40 , or
 - "A maximum score of ≤ 3 at randomization for the PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 suspiciousness/persecution), P7 (hostility) or G8 (uncooperativeness); and a score of ≥ 5 post-randomization on any of these items, or P7 (hostility) or G8 (uncooperativeness) scores ≥ 5 postrandomization on any of these items, or
 - "A subject who has a maximum score of 4 at randomization for the above PANSS items scores ≥ 6 post-randomization on any of the above PANSS items."
2. Suspicion of a recurrence on the basis of the CGI-S score was defined by at least one of the following criteria that must be met on a given scheduled assessment day (copied from the submission):
 - A CGI-S ≤ 3 at randomization and ≥ 4 at post-randomization or,
 - A CGI-S of 4 at randomization and ≥ 5 at post-randomization

See the next subsection for a definition of recurrence.

Primary Efficacy Variable

The time to "recurrence" was the primary efficacy variable. Recurrence was defined as the following (copied from the submission):

- 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 ≤ 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

Continued on the next page,

Recurrence-event Criteria (continued from the previous page):

- For CGI-S:
 - A score of ≥ 4 after randomization for 2 consecutive days if CGI-S score was ≤ 3 at randomization, or
 - A score of ≥ 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 ≥ 5 after randomization for 2 consecutive days on any of the above PANSS items if the maximum score for the above PANSS items was ≤ 3 at randomization, or
 - A score ≥ 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.

The time to recurrence was defined as the time between randomization to double-blind treatment and the first documentation of recurrence (with recurrence defined as above).

Interim Analyses.

The Data Monitoring Committee

Interim analysis was conducted that involved an "independent expert group," referred by sponsor as the Independent Data Monitoring Committee (IDMC). This committee was to perform the following functions:

- Monitor for safety and
- Provide recommendations on stopping, modifying or continuing the study on the basis of safety or positive efficacy results, as revealed by the interim efficacy analyses.

Time-point for Interim Analyses and Datasets Analyzed

The interim efficacy analysis was to be conducted by the IDMC after 43 recurrence events that occurred (50% of the planned recurrence events). Results of this analysis are shown in the next subsection of this review. All other subjects that were remaining in the study (and also taking the study drug) at the time of the 43rd recurrence event were censored (at the date of the interim analysis). Censored subjects also included:

- Subjects who completed the study
- Subjects who discontinued the study drug (without a recurrence event) and
- Subjects who discontinued the study drug without documentation of a recurrence.

The intent-to-treat analysis (ITT) dataset was the dataset used analyses of results for each of the following analyses:

- The interim analysis using a cutoff date of May 13, 2005, when 43 recurrence events occurred (see above regarding subjects that were censored for the primary analysis)

- Secondary analyses which included analyses on the primary efficacy variable for the final analysis. These analyses included data through the date of study completion which was on August 31, 2005.

The ITT data set is defined as randomized subjects who received at least one dose of double-blind treatment and at least one post-baseline assessment related to recurrence criteria.

Statistical Test Employed

The following outlines several key statistical tests that were employed:

- The Kaplan-Meier method was employed to estimate the cumulative distribution function of the time to recurrence.
- The 2-sided log-rank test was employed to compare treatment groups on time to recurrence.
- The Cox proportional hazards model was also employed with treatment as a covariate to estimate that hazards ratio and the 95% confidence interval.
- An additional analysis was conducted using a Cox proportional hazards model with treatment, region, and baseline BMI as covariates.

Secondary analyses were conducted as described in section 3.11.1.1 of the CSR. Some of the results of these analyses are shown in the next subsection of this review.

Enumeration of Subjects in Each Dataset Analyzed

The following table enumerates subjects in each dataset analyzed (as provided in the CSR).

Table 5: Number of Subjects in Each Analysis Set
 (Study R076477-SCH-301)

	Run-In/Stabilization		Double-Blind		Total N (%)
	RI/ST PAL	ER OROS PAL	Placebo	ER OROS PAL	
	n (%)	n (%)	n (%)	N (%)	
Interim Analysis					
Interim Analysis randomized subjects	NA	N=55	N=58	N=113	
Interim Analysis Intent-to-Treat	NA	55 (100)	56 (97)	111 (98)	
Final Analysis	N=530	N=102	N=105	N=207	
All treated subjects	530 (100)	NA	NA	NA	
All randomized subjects	NA	102 (100)	105 (100)	207 (100)	
Intent-to-Treat	NA	101 (99)	104 (99)	205 (99)	
Safety	NA	102 (100)	104 (99)	206 (99)	

All treated subjects are those who received at least one non-zero dose of run-in medication.

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6.1.4 Efficacy Findings

In accordance with the Clinical Review MAPP demographic and other baseline features of the study population are described in this section. However, the extent of drug exposure is also relevant this topic is also covered in this section. Furthermore, the disposition is also critical to interpreting efficacy results. Therefore, the results on disposition and extent of exposure are included in subsections below. Efficacy results are not provided until Section 6.1.4, in accordance with the MAPP.

6.1.4.1 Extent of Exposure

The following tables summarize the extent of exposure to the study drug in each phase of Study - 301 (copied from the CSR section of the submission).

Table 17: Extent of Exposure to Run-In Medication
 (Study R076477-SCH-301: All Treated Analysis Set)

RI ER OROS PAL (N=530)	
Treatment duration, days^a	
N	530
Category, n (%)	
≤ 7	32 (6)
8-14	34 (6)
15-21	34 (6)
22-28	21 (4)
29-35	23 (4)
36-42	15 (3)
43-49	22 (4)
50-56	221 (42)
≥ 57	128 (24)
Mean (SD)	44.7 (18.33)
Median	56.0
Range	(1;63)
Mean dose (days on drug only)	
N	530
Mean (SD)	10.5 (2.31)
Median	10.5
Range	(3;15)
Mode dose (days on drug only)	
N	523
Mean (SD)	10.8 (2.98)
Median	9.0
Range	(3;15)

^a Treatment duration excludes days off study drug.
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Table 18: Extent of Exposure to Run-In Medication During the Run-In Phase:
 the First 6 Weeks versus the Last 2 Weeks
 (Study R076477-SCH-301: Run-in Completer Analysis Set)

	RI ER OROS PAL (N=312)	
	The First 6 Weeks of Run-In Phase	The Last 2 Weeks of Run-In Phase
Mean dose (days on drug only)		
N	312	312
Mean (SD)	10.4 (2.46)	11.2 (3.10)
Median	10.5	12.0
Range	(3;14)	(3;15)
Mode dose (days on drug only)		
N	312	312
Mean (SD)	10.7 (3.21)	11.2 (3.10)
Median	9.0	12.0
Range	(3;15)	(3;15)

Note: Completers include only subjects who received run-in medication for 8 weeks

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Figure 3: Subject Distribution by Mode Dose of ER OROS Paliperidone Over Time During the Run-In Phase

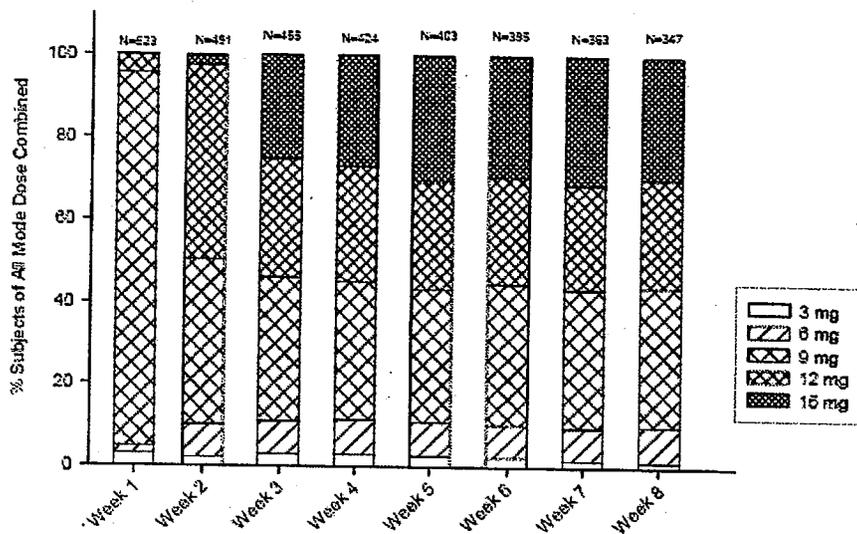


Table 21: Distribution of Changes From Maximum Run-In Dose to the Final Run-In Dose
 (Study R076477-SCH-301: Run-in Completer Analysis Set)

----- RI/ST ER OROS PAL -----						
(N=312)						
Maximum Dose	3 mg	6 mg	9 mg	12 mg	15 mg	Total
Final Dose						
3 mg	0	0	4	1	0	5
6 mg	0	1	26	2	0	29
9 mg	0	0	87	17	1	105
12 mg	0	0	0	76	5	81
15 mg	0	0	0	0	92	92
Total	0	1	117	96	98	312

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**Table 22: Extent of Exposure to Stabilization Medication
 (Study R076477-SCH-301: All Treated Analysis Set)**

RI ER OROS PAL (N=312)	
Treatment duration, days²	
N	312
Category, n (%)	
≤ 7	2 (1)
8-14	15 (5)
15-21	15 (5)
22-28	15 (5)
29-35	15 (5)
36-42	172 (55)
43-48	73 (23)
≥ 49	5 (2)
Mean (SD)	38.2 (9.68)
Median	42.0
Range	(3;63)
Mean dose (days on drug only)	
N	312
Mean (SD)	11.2 (3.12)
Median	12.0
Range	(3;15)
Mode dose (days on drug only)	
N	312
Mean (SD)	11.2 (3.13)
Median	12.0
Range	(3;15)

²Treatment duration excludes days off study drug.
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**Table 23: Frequency Distribution of Daily Dosage (Mode) During the
 Stabilization Phase
 (Study R076477-SCH-301: All Treated Analysis Set)**

RI ER OROS PAL (N=312)	
Mode dose (days on drug only)^a	
N	312
Category, n (%)	
3 mg	5 (2)
6 mg	29 (9)
9 mg	102 (33)
12 mg	81 (26)
15 mg	95 (30)

^aDose most frequently taken during the stabilization phase.
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**Table 24: Extent of Exposure to Double-Blind Study Medication – Interim Analysis
 (Study R076477-SCH-301: Interim Analysis Safety Analysis Set)**

Analysis Set: Safety	Placebo (N=55)	ER OROS PAL (N=58)
Treatment Duration, Days		
N	55	58
Category, n (%)		
≤ 7	4 (7)	8 (14)
8-14	8 (15)	5 (9)
15-21	6 (11)	7 (12)
22-28	9 (16)	4 (7)
29-42	5 (9)	4 (7)
43-56	3 (5)	4 (7)
57-70	4 (7)	3 (5)
71-98	5 (9)	5 (9)
99-126	3 (5)	3 (5)
127-154	3 (5)	8 (14)
155-182	2 (4)	1 (2)
183-210	2 (4)	3 (5)
211-238	1 (2)	3 (5)
Mean (SD)	57.5 (57.11)	70.2 (67.33)
Median	30.0	45.0
Range	(5;233)	(1;235)
Mean Dose (days on drug only)		
N	55	58
Mean (SD)	0.0 (0.00)	10.4 (3.50)
Median	0.0	9.0
Range	(0;0)	(3;15)
Mode Dose (days on drug only)		
N	55	56
Mean (SD)	0.0 (0.00)	10.4 (3.43)
Median	0.0	9.0
Range	(0;0)	(3;15)

Treatment Duration: Excludes days off drug.

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**Table 25: Extent of Exposure to Double-Blind Study Medication by
 Randomized Treatment Group
 (Study R076477-SCH-301: Safety Analysis Set)**

	Placebo (N=102)	ER OROS PAL (N=104)
Treatment duration, days^a		
N	102	104
Category, n (%)		
<= 7	9 (9)	7 (7)
8-14	16 (16)	13 (13)
15-21	15 (15)	9 (9)
22-28	11 (11)	11 (11)
29-42	10 (10)	11 (11)
43-56	10 (10)	10 (10)
57-70	8 (8)	7 (7)
71-98	5 (5)	9 (9)
99-126	7 (7)	7 (7)
127-154	2 (2)	3 (3)
155-182	2 (2)	3 (3)
183-210	0	4 (4)
211-238	3 (3)	6 (6)
239-266	1 (1)	0
267-294	2 (2)	1 (1)
>=295	1 (1)	3 (3)
Mean (SD)	56.1 (66.29)	74.1 (78.08)
Median	28.5	44.5
Range	(5;299)	(3;330)
Mean dose (days on drug only)		
N	102	104
Mean (SD)	0.0 (0.00)	10.8 (3.31)
Median	0.0	9.9
Range	(0;0)	(3;15)
Mode dose (days on drug only)		
N	102	104
Mean (SD)	0.0 (0.00)	10.8 (3.50)
Median	0.0	10.5
Range	(0;0)	(3;15)

^a Treatment duration excludes days off study drug.
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Table 26: Frequency Distribution of Daily Dosage (Mode) During the Double-Blind Phase
 (Study R076477-SCH-301: Safety Analysis Set)

	Placebo (N=102)	ER OROS PAL (N=104)
Mode dose (days on drug only)^a		
N	102	104
Category, n (%)		
0 mg	102 (100)	0
3 mg	0	4 (4)
6 mg	0	9 (9)
9 mg	0	39 (38)
12 mg	0	23 (22)
15 mg	0	29 (28)

^a This dose represents the dose that is most frequently taken during the double blind phase
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The sponsor notes that 95% of subjects in the OL phase were treatment compliant (defined as taking at least 1 tablet daily) and 94% and 99% of placebo and Pal subjects in the DB phase were treatment compliant. Any subject who missed 4 or more consecutive days of treatment or a total of 7 days of treatment during the DB phase were required to have their study-drug discontinued.

6.1.4.2 Disposition, Demographic and Baseline Features

The following tables summarize the disposition of subjects in each study phase (as provided in the CSR). Reviewer comments follow these tables.

Table 6: Run-In Completion/Withdrawal Information
 (Study R076477-SCH-301: All Treated Analysis Set)

	ER OROS PAL (RI/ST) (N=530) n (%)
Total enrolled in run-in phase	530
Completed run-in phase	347 (65)
Completed entire course of study ^a	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.

^a Study stopped based on the results of interim analysis.
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Table 7: Stabilization Completion/Withdrawal Information
 (Study R076477-SCH-301: All Treated Analysis Set)

	ER OROS PAL (R1ST) (N=530) n (%)
Total enrolled in stabilization phase	312
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

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Table 8: Interim Analysis Treatment Completion/Withdrawal Information
 (Study R076477-SCH-301: Interim Analysis Safety Analysis Set)

	Placebo (N=55) n (%)	ER OROS PAL (N=58) n (%)	Total (N=113) n (%)
Completed the double-blind phase	29 (53)	14 (24)	43 (38)
Experienced recurrence	29 (53)	14 (24)	43 (38)
Ongoing	21 (38)	30 (52)	51 (45)
Withdrawn from the double-blind phase	5 (9)	14 (24)	19 (17)
Subject choice (subject withdrew consent)	0	8 (14)	8 (7)
Adverse event	0	3 (5)	3 (3)
Death	1 (2)	0	1 (1)
Lost to follow-up	1 (2)	1 (2)	2 (2)
Other	3 (5)	2 (3)	5 (4)

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**Table 9: Double-Blind Treatment Completion/Withdrawal Information
 (Study R076477-SCH-301: All Randomized Subjects Analysis Set)**

	Placebo (N=102) n (%)	ER OROS PAL (N=105) n (%)	Total (N=207) n (%)
Completed	94 (92)	85 (81)	179 (86)
Experienced recurrence	52 (51)	23 (22)	75 (36)
Completed entire course of study ^a	42 (41)	62 (59)	104 (50)
Withdrawn	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)
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Reviewer Comments on Disposition of Subjects

Comments on the "Other" Category for Early Dropouts

Note the number and incidence of subjects who withdrew for "other" reasons in each phase of Study 301. The sponsor clarified in a 12/21/06 response submission that this category of early study dropouts was due primarily to lack-off efficacy and consisted of only a few subjects. The DB treatment groups showed a similar incidence of subjects in this category. A few subjects were withdrawn early due to other reasons that generally appear to be appropriate reasons for early withdraw. Examples of these additional early dropouts included a subject who had persisting bradycardia (first observed at screening/baseline that continued on Day 2), subjects with protocol violations (e.g. the investigator found that the subject did not comply with eligibility criteria due to use of prohibited substances, the subject failed to disclose prior panic attacks, among other protocol violations) and others.

Comments on the Incidence in Each Category for Early Dropouts across DB Treatment Groups

The DB treatment groups generally showed a similar distribution and incidence of subjects within in each disposition category except for the following:

- A 14% or 11% incidence of Pal subjects were in the withdrawn category of "subject choice" in the interim analysis and final analysis datasets, respectively, while 0 placebo subjects withdrew for this reason in each dataset for the DB phase.
- A slightly greater incidence of ADOs occurred in the Pal group than in the placebo group.

Comments on the Category of Subjects in the Withdrawn Category of "Subject Choice"

Given the above observation on the incidence of subjects withdrawing due to "subject choice" the sponsor was inquired about this category of subjects. In a 12/21/06 response submission the sponsor provided the following information regarding dropouts by subject choice:

- *The sponsor was not able to provide more specific reasons for withdraw for subjects in the "subject choice" category, since CRFs only specified that the given subject withdrew consent and provided no other information as to the reason.*
- *The sponsor provided the following additional information regarding the 12 Pal subjects who withdrew consent in the DB phase that were included in the final analysis dataset:*
 - *7 subjects did not show "worsening in either the PANSS total score or CGI score from DB baseline."*
 - *5 of the subjects showed worsening on the PANSS total score (from DB baseline) but the score at DB treatment endpoint was lower than the score at run-in baseline (i.e. showed improvement relative to the pre-treatment value).*

The sponsor had censored these subjects for their primary analysis, in accordance with their statistical analysis plan. It is not clear to the undersigned reviewer, if efficacy results were dramatically impacted by the above observations or impacted among the 8 DB Pal subjects who withdrew consent in the interim analysis dataset (and were censored). Therefore, the undersigned reviewer contacted the Biometric Reviewer, Yeh-Fong Chen regarding these subjects. Dr. Chen conducted a preliminary analysis of the data (final analysis dataset) in which Dr. Chen included the 12 Pal subjects in the preliminary analyses of the final analysis dataset as events of recurrence. This conservative approach was selected as a preliminary analysis to determine if the study would no longer be positive. The reanalysis still yielded a significantly positive study ($p < 0.01$).

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 Paliperidone OROS oral

Table 10: Demographic and Baseline Characteristics
 (Study R076477-SCH-30): All Treated Analysis Set

	All Treated		Intent-to-Treat		Total Intent-to- Treat (N=205)
	RIER OROS PAL (N=530)	Not Randomized to DB (N=323)	Placebo (N=101)	ER OROS PAL (N=104)	
Age (years)					
N	530	323	101	104	205
Category, n (%)					
<18	1 (<1)	1 (<1)	0	0	0
18-25	75 (14)	47 (15)	13 (13)	14 (13)	27 (13)
26-50	383 (72)	235 (73)	77 (76)	70 (67)	147 (72)
51-65	71 (13)	40 (12)	11 (11)	20 (19)	31 (15)
Mean (SD)	37.9 (10.54)	37.7 (10.57)	37.5 (10.36)	39.0 (10.65)	38.2 (10.51)
Median	38.0	38.0	37.0	39.5	38.0
Range	(17;64)	(17;64)	(19;62)	(19;63)	(19;63)
Sex, n (%)					
N	530	323	101	104	205
Male	362 (68)	240 (74)	63 (62)	58 (56)	121 (59)
Female	168 (32)	83 (26)	38 (38)	46 (44)	84 (41)
Race, n (%)					
N	530	323	101	104	205
White	283 (53)	160 (50)	61 (60)	62 (60)	123 (60)
Black	76 (14)	58 (18)	9 (9)	8 (8)	17 (8)
Asian	6 (1)	3 (1)	0	3 (3)	3 (1)
Other	165 (31)	102 (32)	31 (31)	31 (30)	62 (30)
Ethnicity, n (%)					
N	530	323	101	104	205
Hispanic or Latino	55 (10)	33 (10)	11 (11)	11 (11)	22 (11)
Native American (American Indian)	3 (1)	3 (1)	0	0	0
Neither Hispanic/Latino nor Native American	472 (89)	287 (89)	90 (89)	93 (89)	183 (89)
Weight (kg)					
N	529	322	101	104	205
Mean (SD)	75.3 (22.83)	75.7 (23.35)	75.9 (24.38)	72.6 (17.57)	74.2 (21.21)
Median	72.0	72.3	72.0	72.0	72.0
Range	(32;174)	(32;163)	(35;174)	(33;114)	(33;174)
Height (cm)					
N	529	322	101	104	205
Mean (SD)	169.1 (9.93)	169.7 (10.23)	168.7 (10.11)	167.8 (8.73)	168.3 (9.43)
Median	169.0	170.0	168.5	168.3	168.5
Range	(131;205)	(131;203)	(143;188)	(142;191)	(142;191)

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 Paliperidone OROS oral

Table 10: Demographic and Baseline Characteristics (Continued)
 (Study R076477-SCH-301: All Treated Analysis Set)

	All Treated		Intent-to-Treat		Total Intent-to-Treat (N=205)
	RI ER OROS PAL (N=530)	Not Randomized to Double-Blind (N=323)	Placebo (N=101)	ER OROS PAL (N=104)	
Body mass index (kg/m²)					
N	529	322	101	104	205
Category, n (%)					
Normal <25	271 (51)	170 (53)	50 (50)	50 (48)	100 (49)
Overweight 25-<30	132 (25)	69 (21)	27 (27)	36 (35)	63 (31)
Obese ≥30	126 (24)	83 (26)	24 (24)	18 (17)	42 (20)
Mean (SD)	26.1 (7.21)	26.1 (7.21)	26.5 (7.85)	25.7 (5.82)	26.1 (6.89)
Median	24.8	24.5	25.1	25.0	25.0
Range	(14;66)	(14;60)	(15;66)	(16;42)	(15;66)
Does subject currently smoke?, n (%)					
N	529	322	101	104	205
Yes	270 (51)	185 (57)	42 (42)	42 (40)	84 (41)
No	259 (49)	137 (43)	59 (58)	62 (60)	121 (59)
Diabetes, n (%)					
N	530	323	101	104	205
No	503 (95)	301 (93)	99 (98)	101 (97)	200 (98)
Yes	27 (5)	22 (7)	2 (2)	3 (3)	5 (2)
Hypertension, n (%)					
N	530	323	101	104	205
No	480 (91)	282 (87)	97 (96)	100 (96)	197 (96)
Yes	50 (9)	41 (13)	4 (4)	4 (4)	8 (4)
Dyslipidemia, n (%)					
N	530	323	101	104	205
No	503 (95)	303 (94)	100 (99)	98 (94)	198 (97)
Yes	27 (5)	20 (6)	1 (1)	6 (6)	7 (3)
Cardiovascular disease, n (%)					
N	530	323	101	104	205
No	519 (98)	316 (98)	99 (98)	102 (98)	201 (98)
Yes	11 (2)	7 (2)	2 (2)	2 (2)	4 (2)

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Table 11: Diagnosis and Psychiatric History at Baseline
 (Study R076477-SCH-301: All Treated Analysis Set)

	All Treated		Intent-to-Treat		Total Intent-to-Treat (N=205)
	RIE OROS PAL (N=530)	Not Randomized to Double-Blind (N=323)	Placebo (N=101)	ER OROS PAL (N=104)	
Schizophrenia type, n (%)					
N	530	323	101	104	205
Paranoid (295.30)	434 (82)	263 (81)	81 (80)	38 (35)	169 (82)
Disorganized (295.10)	13 (2)	7 (2)	4 (4)	2 (2)	6 (3)
Catatonic (295.20)	7 (1)	5 (2)	2 (2)	0	2 (1)
Undifferentiated (295.90)	72 (14)	45 (14)	14 (14)	13 (13)	27 (13)
Residual (295.60)	4 (1)	3 (1)	0	1 (1)	1 (<1)
Age at diagnosis of schizophrenia (yrs)					
N	529	322	101	104	205
Mean (SD)	25.8 (8.69)	25.4 (8.31)	25.8 (9.37)	27.1 (9.17)	26.5 (9.27)
Median	24.0	23.5	23.0	25.0	23.0
Range	(1;52)	(1;52)	(1;51)	(13;51)	(1;51)
Run-in baseline Total PANSS					
N	530	323			
Mean (SD)	92.1 (11.48)	91.3 (11.65)			
Median	93.0	89.0			
Range	(70;132)	(70;132)			
Run-in baseline CGI-S, n (%)					
N	530	323			
Mild	6 (1)	5 (2)			
Moderate	260 (49)	166 (51)			
Marked	214 (40)	121 (37)			
Severe	50 (9)	31 (10)			
Double-blind baseline Total PANSS					
N			101	104	205
Mean (SD)			53.4 (10.56)	51.0 (11.38)	52.2 (11.02)
Median			56.0	53.0	54.0
Range			(30;70)	(30;89)	(30;89)

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Table 11: Diagnosis and Psychiatric History at Baseline (Continued)
 (Study R076477-SCH-301: All Treated Analysis Set)

	All Treated		Intent-to-Treat		Total Intent-to-Treat (N=205)
	RI ER OROS PAL (N=530)	Not Randomized to Double-Blind (N=323)	Placebo (N=101)	ER OROS PAL (N=104)	
Double-blind baseline CGI-S, n (%)					
N			101	104	205
Not ill			5 (5)	6 (6)	11 (5)
Very mild			33 (33)	38 (37)	71 (35)
Mild			54 (53)	49 (47)	103 (50)
Moderate			9 (9)	11 (11)	20 (10)
Time since last psychotic episode (Days)					
N	517	314	98	103	201
Mean (SD)	476.4 (759.05)	455.7 (711.85)	539.2 (910.04)	482.3 (752.06)	510.0 (831.22)
Median	198.0	199.5	182.0	209.0	196.0
Range	(3;5894)	(3;5894)	(7;4517)	(21;4823)	(7;4823)
Prior hospitalizations for psychosis					
N	384	231	74	78	152
Mean (SD)	2.3 (1.20)	2.7 (1.20)	2.9 (1.20)	2.9 (1.17)	2.9 (1.18)
Median	3.0	3.0	3.0	3.0	3.0
Range	(1;4)	(1;4)	(1;4)	(1;4)	(1;4)
Prior hospitalization, n (%)					
N	530	323	101	104	205
None	146 (28)	92 (28)	27 (27)	26 (25)	53 (26)
Once	82 (15)	53 (16)	14 (14)	15 (14)	29 (14)
Twice	76 (14)	50 (15)	13 (13)	13 (13)	26 (13)
Three times	66 (12)	38 (12)	13 (13)	17 (16)	28 (14)
Four times or more	160 (30)	90 (28)	36 (36)	33 (32)	69 (34)

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Reviewer Comments on Demographic Features

Treatment groups of the DB phase were generally similar on demographic features and in baseline psychiatric status.

6.1.4.3 Concomitant Medications and Illnesses

The following tables summarize concomitant use of antidepressants and medications for adverse effects (as specified in the tables) during the study (as provided in the CSR). Reviewer comments follow these tables.

Table 13: Antidepressant Medication Received During the Double-Blind Phase
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set)

Generic Term Category	Placebo (N=101)	ER OROS PAL (N=104)	Total (N=205)
	n (%)	n (%)	n (%)
Total no. subjects with any antidepressant medication	5 (5)	3 (3)	11 (5)
Fluoxetine	3 (3)	1 (1)	4 (2)
Sertraline	2 (2)	0	2 (1)
Amitriptyline	0	1 (1)	1 (<1)
Clomipramine	1 (1)	0	1 (<1)
Doxepin	1 (1)	0	1 (<1)
Escitalopram	0	1 (1)	1 (<1)
Fluvoxamine	1 (1)	0	1 (<1)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Table 14: Anti-EPS and Antihistamines Therapies Taken on the Day of Randomization and at the End of Double-Blind Phase (Analysis Set: Intent-to-Treat)

Psychotropic Drug Category Generic Term Category	Placebo (N=101) n (%)	ER OROS PAL (N=104) n (%)	Total (N=205) n (%)
Anti-EPS and Antihistamines on the Day of Randomization			
Total no. Subjects with anti-EPS or antihistamines therapy	24 (24)	28 (27)	52 (25)
Anti-EPS	23 (23)	28 (27)	51 (25)
Trihexyphenidyl	19 (19)	19 (18)	38 (19)
Biperiden	3 (3)	6 (6)	9 (4)
Benzatropine	1 (1)	2 (2)	3 (1)
Amantadine	0	1 (1)	1 (<1)
Antihistamines	1 (1)	0	1 (<1)
Loratadine	1 (1)	0	1 (<1)
Anti-EPS and Antihistamines at the End of Double-Blind Phase			
Total no. Subjects with anti-EPS or antihistamines therapy	24 (24)	28 (27)	52 (25)
Anti-EPS	22 (22)	28 (27)	50 (24)
Trihexyphenidyl	18 (18)	19 (18)	37 (18)
Biperiden	3 (3)	6 (6)	9 (4)
Benzatropine	1 (1)	3 (3)	4 (2)
Amantadine	0	1 (1)	1 (1)
Antihistamines	2 (2)	0	2 (1)
Cyproheptadine	1 (1)	0	1 (<1)
Loratadine	1 (1)	0	1 (<1)

Note: Percentages calculated with the number of subjects in each group as a denominator.

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According to the sponsor 65% of ITT subjects (among 530 total subjects) received benzodiazepines during the OL treatment phase of the study at an average daily dose of 2.0 mg lorazepam and 14.3 mg for diazepam.

During the DB phase 16% of placebo subjects and 9% of Pal subjects received benzodiazepines at an average daily dose of 23.5 mg and 12.5 mg for the placebo and Pal groups, respectively.

The incidence of the use of other concomitant medications (for each specific generic drug name) was provided in Attachments 3.5.1 and 3.8 for the OL and DB phases, respectively that revealed the following commonly used concomitant medications in each study phase as specified below (common is defined as an incidence $\geq 5\%$ in OL pal and DB Pal treated subjects):

- OL phase:
 - Benzotropine
 - Biperidine
 - Paracetamol
 - Propranolol
 - Trihexyphenidyl
- DB Phase (with incidence in placebo and Pal groups provided in parentheses):
 - Biperidine (3%, 7%)
 - Paracetamol (2%, 6%)
 - Propranolol (5%, 4%)

- o Trihexyphendiyl (20%, 19%)

Reviewer Comments. Treatment groups of the DB phase were generally similar on concomitant medication use except for use of benzodiazepines which were used in more subjects and at a higher mean daily dose-level in the placebo group compared to the Pal group, which is consistent with a therapeutic effect of Pal over placebo. The use of anti-EPS drugs was slightly greater in Pal compared to placebo subjects. The use of concomitant medications other than benzodiazepines and antidepressant medications was reported by the sponsor to occur in 52% of subjects in the DB ITT population. DB treatment groups were generally similar in the incidence of concomitant use of these other medications (for each drug listed by generic name), including commonly used medications (as previously defined) except for the use of paracetamol which would not be anticipated to alter efficacy or safety results.

6.1.5 Efficacy Results

Reviewer Comment on Results

As shown in tables and figures below (as provided by the sponsor) the study revealed significantly longer time to recurrence in the Pal group compared to the placebo group. The median time to recurrence (i.e. in which 50% of subjects had a recurrence event) was 62 days for the placebo group. This value was not estimated for the Pal group since fewer than 50 subjects in this group had a recurrence event at the time of the interim analysis.

Table 27: Summary Statistics of Time to Recurrence - Double-Blind Phase - Interim Analysis
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set)

Descriptive ^a	Placebo	ER OROS PAL	Overall		
			Chisq	DF	P-value ^b
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% CI)	23.0 (14.0; 42.0)	33.0 (32.0; NE)			
Median (95% CI)	62.0 (42.0; 119.0)	NE ^c (97.0; NE)			
75% Quantile (95% CI)	NE ^d (116.0; NE)	NE ^d			
Statistical Test			7.7713	1	0.0053

^a Based on Kaplan-Meier product limit estimates.

^b Log rank test.

^c Less than 50% of subjects experienced a recurrence event.

^d Less than 75% of subjects experienced a recurrence event.

NE = not estimable

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Figure 4: Kaplan-Meier Plot of Time to Recurrence (Interim Analysis)
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set - Interim Analysis)

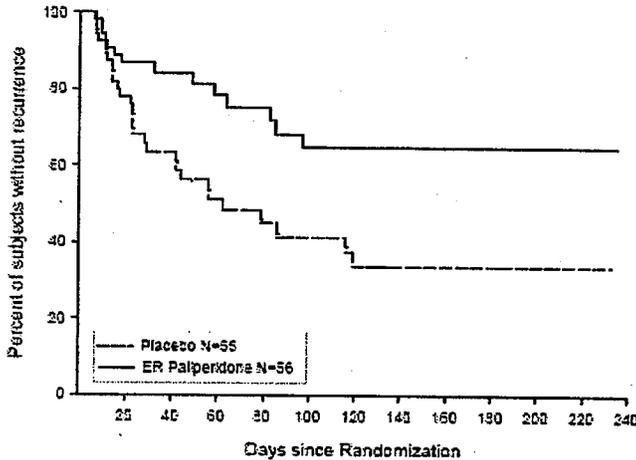


Table 28: Frequency Distribution of Recurrence Type and Reasons - Interim Analysis
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set - Interim Analysis)

Type of Recurrence: Reason	Placebo (N=55)	ER OROS PAL (N=56)
	n	n
Psychiatric hospitalization	8	4
Psychiatric hospitalization	8	4
PANSS	22	13
Increase of 25% in the Total PANSS score	21	10
10 point increase in Total PANSS score	1	3
Suicidal or homicidal ideation	1	0
Suicidal or homicidal ideation	1	0
CGI-S	23	12
CGI-S ≥ 4 (moderately ill) for 2 Days	20	12
CGI-S ≥ 5 (markedly ill) for 2 Days	3	0
PANSS items, P1, P2, P3, P6, P7, G8	10	7
Score ≥ 5 for 2 Days	10	7

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

Subject may have more than 1 reason for recurrence.

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Secondary Efficacy Result

Reviewer Comments on the Full Interim Analysis on Time-to-Recurrence

Secondary efficacy results of the final analysis on the primary efficacy variable, the time-to-recurrence also showed a significantly greater proportion of Pal subjects who did not have a recurrence event compared to the placebo subjects (the analysis conducted on all ITT subjects through the time when the study was terminated).

The following tables were provided by the sponsor.

Table 29: Number (%) of Subjects Experiencing Recurrence and Time to Recurrence – Final Analysis
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set)

Descriptive ^a	Placebo	ER OROS PAL	Overall		
			Chisq	DF	P-value ^c
Time to recurrence					
Number of Assessed	101	104			
Number Censored (%)	49 (48.5)	51 (77.9)			
Number Recurred (%)	52 (51.5)	23 (22.1)			
25% Quantile (95% CI)	23.0 (15.0; 29.0)	68.0 (50.0; NE)			
Median (95% CI)	53.0 (44.0; 114.0)	NE ^b			
75% Quantile (95% CI)	261.0 (116.0; NE)	NE ^d			
Statistical Test			18.709	1	<0.001

^aBased on Kaplan-Meier product limit estimates.

^bLog rank test.

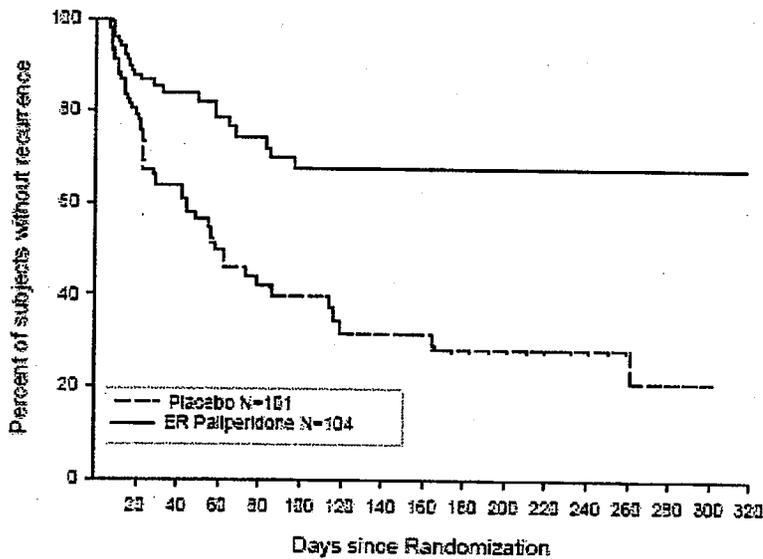
^cLess than 50% of subjects experienced a recurrence event.

^dLess than 75% of subjects experienced a recurrence event.

NE = not estimable

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Figure 5: Kaplan-Meier Plot of Time to Recurrence (Final Analysis)
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set)



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Table 30: Frequency Distribution of Recurrence Type and Reasons - Final Analysis
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set)

Type of Recurrence Reason	Placebo	ER OROS PAL
	(N=101)	(N=104)
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 25.
 Subject may have more than 1 reason for recurrence
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Reviewer Comment on Results of Secondary Efficacy Variables
 Results on secondary efficacy variables are described in the CSR with selected summary tables and figures shown below (as provided by the sponsor). These results were generally consistent with a greater proportion of placebo subjects with a recurrence event compared to the Pal group.

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Table 32: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Double-Blind Baseline to End Point (Double-Blind)-LOCF (Study R076477-SCH-301: Intent-to-Treat Analysis Set)

	Placebo (N=101)	ER OROS PAL (N=104)
Double-blind baseline		
N	101	104
Mean (SD)	53.4 (10.56)	51.0 (11.38)
Median (Range)	56.0 (30;70)	53.0 (30;89)
End point (double-blind)		
N	101	104
Mean (SD)	58.5 (22.30)	57.0 (18.12)
Median (Range)	65.0 (31;114)	55.0 (30;113)
Change from Baseline		
N	101	104
Mean (SD)	15.1 (19.10)	6.0 (13.62)
Median (Range)	12.0 (-17;68)	2.0 (-17;50)
P-value (minus Placebo)^{a,b}		
Diff. of LS Means (SE)		<0.001
95% CI		-8.8 (2.14)
		(-12.99; -4.54)

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

^b Comparison with placebo without multiplicity adjustment.

Note: Negative change in score indicates improvement; positive change in score indicates worsening.

One subject in the ER OROS paliperidone group, Subject 100018, had a double-blind baseline score of 89; this was recorded as a protocol deviation.

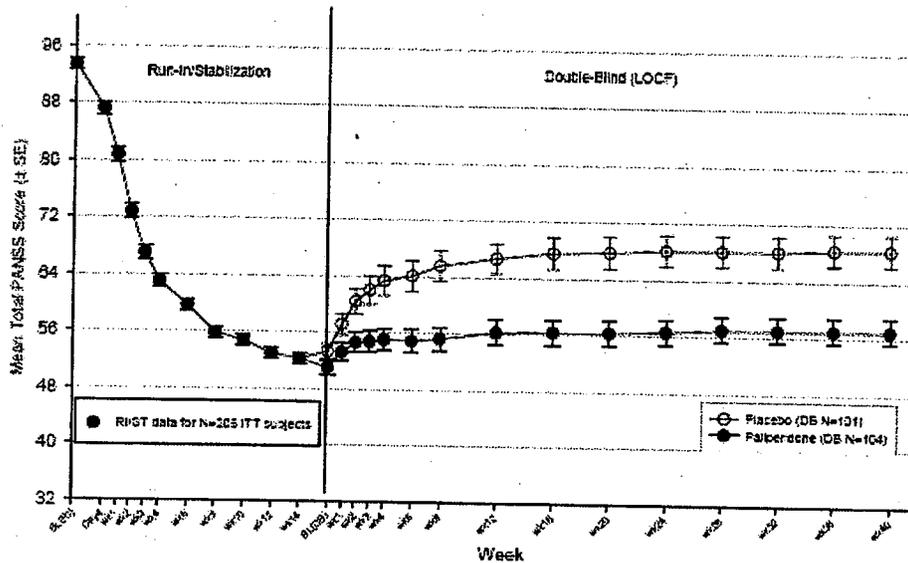
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The table above (Table 32) shows a numerical mean increase in the Pal group on the PANSS total score (from baseline to treatment endpoint of the DB phase). This observation would appear to suggest a degree of worsening of symptoms. However, upon examination of Figure 6 the observed group mean increase appears to reflect an increase over the first few weeks upon randomization from OL Pal treatment to DB placebo or Pal treatment (LOCF ITT Analysis Set).

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**Figure 6: Mean PANSS Total Scores Over Time:
 Run-In, Stabilization, and Double-Blind Phases
 Study R0764770-SCH-301 (Intent-to-Treat Analysis Set)**



The distribution and frequency of subjects across CGI-S score categories are consistent efficacy among the DB Pal treated subjects compared to the DB placebo treated subjects during the DB phase, as shown in a table below (as provided by the sponsor). The CSR describes results of additional secondary analyses that were generally similar to results on secondary variables described in this review.

Table 33: Frequency Tabulation of CGI-Severity Score During the Run-In and Stabilization Phases (Study R076477-SCH-301: All Treated Analysis Set)

	-- RI ER OROS PAL --		
	n	%	Cum.%
Clinical global impression			
Baseline (Run-in phase)			
Not ill	0	0.0	0.0
Very mild	0	0.0	0.0
Mild	6	1.1	1.1
Moderate	260	49.1	50.2
Marked	214	40.4	90.6
Severe	50	9.4	100.0

Total	530		
End point (Stabilization phase.)			
Not ill	15	4.8	4.8
Very mild	103	33.1	37.9
Mild	131	42.1	80.1
Moderate	50	16.1	96.1
Marked	9	2.9	99.0
Severe	3	1.0	100.0

Total	311		

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Table 34: Frequency Tabulation of CGI-Severity Score for Double-Blind Intent-to-Treat Subjects During the Run-In and Stabilization Phases (Study R076477-SCH-301: Intent-to-Treat Analysis Set)

	-- RI ER OROS PAL --		
	n	%	Cum.%
Clinical global impression			
Baseline (Run-in phase)			
Not ill	0	0.0	0.0
Very mild	0	0.0	0.0
Mild	1	0.5	0.5
Moderate	92	44.9	45.4
Marked	93	45.4	90.7
Severe	19	9.3	100.0

Total	205		
End point (Stabilization phase.)			
Not ill	11	5.4	5.4
Very mild	71	34.6	40.0
Mild	103	50.2	90.2
Moderate	20	9.8	100.0
Marked	0	0.0	100.0
Severe	0	0.0	100.0

Total	205		

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Table 36: Frequency Tabulation of CGI-Severity Score - Double-Blind Phase
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set)

	----- Placebo -----			--- ER OROS PAL ---		
	n	%	Cum.%	n	%	Cum.%
Clinical global impression						
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		

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Table 36: Clinical Global Impression Severity Scale (CGI-S) - Change From Double-Blind Baseline to End Point (Double-Blind)-LOCF
 (Study R076477-SCH-301: Intent-to-Treat Analysis Set)

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

Note: The analysis of variance uses ranked data.

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

^b Comparison with placebo without multiplicity adjustment.

Note: Positive change in score indicates worsening (negative change indicates improvement).

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Subgroup Analyses on the Basis of Age, Gender and "Race"

Reviewer Comment. The samples sizes of the DB treatment groups and within each subgroup category (age, gender and "race" categories) was insufficient to examine the potential influence of these demographic features on efficacy.

6.1.6 Clinical Microbiology

This topic is not relevant to this section of the review and is not relevant to the review.

6.1.7 Efficacy Conclusions

Reviewer Conclusions and Comments.

Study -301 is a positive study.

See previous sections for some caveats and/or limitations of the study. Additional limitations are generally inherent in a study of this nature and every study has limitations, as well as strengths. Despite potential limitations, the study design is considered by the undersigned reviewer to be adequate for reasons discussed in the last section (Section 9) of this review.

Section 9 of this review discusses key issues relevant to this study and relevant to proposed labeling. Recommendations are also provided in Section 9.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

See section 4 of this review for:

- A summary table of the clinical trials and
- For the review strategy on the selection of safety data and sections of the submission that were reviewed. More comments about specific aspects on the review strategy for a particular set of information (or section of the submission) are provided below or in corresponding subsections of Section 7 of this review.

See sections 7.1.1, 1 and 9 of this review for a summary overview, comments and conclusions (with recommendations provided in Sections 1 and 9) regarding safety results described in this review and in more detail in sections that follow Section 7.1.1 of this review.

The following provides details on safety datasets from clinical trials and as summarized previously in Section 4 of this review.

Pooled and Unpooled Safety Datasets that Were Reviewed as Specified

The following safety datasets are the focus of the safety review from which results described in sections below were obtained:

A) Unpooled Safety Datasets that were Reviewed as Specified

- **The Pivotal Maintenance Treatment Phase III Study -301** was previously described under Sections 4 and 6 of this review. Module 2.7.4 provided results from this study. Study -301 was a pivotal maintenance trial conducted for NDA 22043 and was completed in time for inclusion of death, SAE and ADO information in the previously reviewed 120-Day SUR NDA 21999 submission. The current submission provides the CSR for this study. Selected sections of the CSR for this study were also reviewed as described in corresponding subsections below.
- **Ongoing OL Extension Study -701 (non-elderly patients) that followed Study -301**: this study used a 3-15 mg daily flexible-dose-level with a starting daily dose of 9 mg. This

study is an OL extension trial that followed the maintenance treatment Phase III study - 301. Deaths, SAEs and ADOs were reviewed (in Module 2.7.4 of the submission) as described in corresponding sections of this review.

- A Completed Extension OL Elderly Trial -702. This trial was a 6 month OL flexible dose extension trial that followed an elderly 6-week, DB, placebo controlled Study - 302. Study -702 was completed before the 2/1/06 cut-off date such that a CSR was provided for this study. Selected sections of the CSR of -702 were reviewed as described in corresponding subsections below since this trial focused on a special population (elderly patients).

B) Pooled Safety Datasets that were Reviewed as Specified

- The Integrated OL Extension Trial Safety dataset (-702, -703, -704 and -705, combined): Refer to Section 4 of this review for details on the study design. See section 7.2 of this review for information on demographic features and sample sizes of the subjects in these trials. Key aspects of these OL Extension trials are outlined below:
 - The trials included generally healthy adults (primarily non-elderly) with schizophrenia who had previously participated in a 6-week double-blind, placebo controlled, active (olanzapine) controlled, parallel group Phase III trial (Studies - 302, -303, -304 and -305).
 - Study -302 was the lead-in study to Study -702 and this lead-in study was a small elderly trial.
 - The other 6-week lead-in trials had almost all non-elderly subjects.
 - The OL extension trials were 12 months of OL flexible dose Pal except for the elderly Study -702 which was 6 months.

The OL extension trials used a flexible dose design (3, 6, 9, or 12 mg/day, except for Study -705 that used an additional higher daily dose level of 15 mg). The daily starting dose was 9 mg in these trials.

Treatment Regimens in Study -301 and in OL Studies

Subjects in study 301 were receiving a daily dose ranging from 3-15 mg (3, 6, 9, 12 or 15 mg daily) except for placebo treated subjects in the DB phase of the study. Refer to Section 6 of this review for details on treatment in each phase of this maintenance treatment study (for the run-in, stabilization and DB phases, respectively).

All OL extension trials used a flexible dose design that generally allowed dose adjustments of 3 mg intervals to maximize efficacy and minimize adverse events):

- Study -701 (non-elderly patients) used a 3-15 mg daily dose-level with a starting daily dose of 9 mg.
- Elderly Study -702 used a 3-12 mg daily dose-level with a starting daily dose of 9 mg.
- Studies -703, -704 and -705 (almost all non-elderly patients) used a 3-12 mg daily dose-level with a starting daily dose of 9 mg (except Study -705 included an additional higher daily dose-level of 15mg).

OL treatment was immediately started at 9 mg daily of Pal in all OL trials which was started after completion of the DB placebo controlled 6-week Phase III lead-in studies (-302, -303, -304 and -305). Note that DB treatment was abruptly stopped before starting OL 9 mg/day of Pal. Previous DB treatment was either placebo, 10 mg/day olanzapine or Pal (at 3-15 mg daily; 3, 6, 9, 12, or 15 mg daily).

Treatment subgroups Analyzed in the Integrated OL Safety Dataset

The sponsor provided safety results from the integrated OL safety datasets after subdividing the major OL treatment groups in into subgroups on the basis of:

- Previous DB treatment group assignment during the lead-in study (placebo, Pal or olanzapine) and
- The total duration of Pal treatment (includes DB Pal treatment for subjects assigned to the DB Pal group of the lead-in study).

Consequently, safety results were presented for the following treatment subgroups:

- DB Placebo/OL Pal \leq 6 month (pal exposure) group
- DB Placebo/OL Pal $>$ 6 month (pal exposure) group
- DB Pal/OL Pal \leq 6 month (pal exposure) group
- DB Pal/OL Pal $>$ 6 month (pal exposure) group
- DB Olanzapine/OL Pal \leq 6 month (pal exposure) group
- DB Olanzapine/OL Pal $>$ 6 month (pal exposure) group

Reviewer Comment on the above Subgroupings:

Limitations with interpreting results from subgroups based on Pal exposure, as above, are discussed in corresponding sections later in this review.

Status of the Integrated OL Extension Trial Database in the Previous NDA 21999 and in the Current NDA 22043

The bulk of short-term and longterm safety results were previously reviewed under NDA 21999. Some of the extension trials were ongoing or remain ongoing, as of the cut-off date for NDA22043. The bulk of long-term safety results come from the integrated data from OL extension trials described in this review and in the past NDA21999 review as outlined below:

- The bulk of safety data was previously reviewed under NDA 21999 and included integrated safety data from several ongoing longterm OL extension trials, some of which were more recently completed. It is notable that the sponsor met ICH guidelines for longterm exposure as described in the original clinical review of NDA21999.
- Module 2.7.4 in the current NDA 22043 submission is identical to the 210-SUR of NDA 219999 and provides some updated safety information from the integrated OL extension-trial dataset (updated since the 120-Day SUR under NDA21999). Updated results from unpooled safety datasets from OL trials are also provided in the current NDA22043.

The review of the response to the approvable action letter (RAAL) submission under NDA21999 includes updated results on SAEs as described in the 210-Day SUR under this IND. Since, the 210-Day SUR submission of NDA21999 is identical to Module 2.7.4 of NDA 22043 safety results on deaths, SAEs and ADOs, as specified in corresponding sections below include the same summary tables and almost the same text summary that appears in the review of the RAAL of NDA21999 (as specified in corresponding sections below).

The Status of OL Extension Trials and Individual CSRs That Were Provided but Were Not Reviewed

Since some of the OL extension trials were previously ongoing (at the time of NDA21999) and some trials are now completed for inclusion of CSRs in NDA22043 (that were not previously provided) the following summarizes in more detail the status of the OL extension trials.

- Status of OL trials as described in the submission are outlined below:
 - Study -701 -705 are ongoing
 - Studies -702, -703 and -704 are now completed
- CSRs provided:
 - CSRs are provided for -702 and -704 (since they were completed before the 2/1/06 cut-off date).
 - Study -703 was completed shortly after the cut-off date such that a CSR was not provided for this study. The CSR of Study -704 was provided but was not reviewed as described for reasons that follow (see the next bulleted item).
- CSRs that were not reviewed:
 - The CSR of Study -704 was not reviewed. This data from this study was included in the integrated OL trial safety database which was reviewed and is considered to be more informative than a single OL trial. Given the larger sample size and limitations inherent with data from OL trials, the integrated safety dataset is considered to yield more interpretable results of a potential safety signal than results of a smaller single OL trial.
 - Selected sections of the CSR of -702 were reviewed as described in sections below since this trial focused on a special population (elderly patients).

As previously discussed in Section 4 of this review, Dr. Mitch Mathis concurs with the clinical review strategy employed for NDA22043.

Data Sources that were Reviewed for Deaths, SAEs and ADOs

The results on deaths, SAEs and ADOs below were found in in-text sections of Module 2.7.4, unless otherwise specified in sections below (Module 2.7.4 of NDA 22043 is identical to the 210-SUR of NDA 21999, as previously indicated).

Safety Assessments and Assessment Schedule for Each Study

See subsections below for various clinical parameter results. Tables Series 10.1 in the appendix of this review provides the schedule of safety assessments of Study -704, one of the OL Extension trials and Study -301.

Outlier Criteria on Clinical Parameters

Table Series 10.2 in the appendix of this review provide outlier criteria employed for each clinical parameter (as provided by the sponsor).

7.1.1 Reviewer's Overview of Key Safety Findings of NDA22043

The safety results of clinical trials described in the current NDA22043 (N000, N001 and N002) are derived from the completed maintenance-treatment efficacy Study 301 and from Phase III OL trials, as described in Section 7 of this review (and includes the 120-SUR updated information from OL trials as described under Section 7.2.9.1 of this review).

No new and clinically remarkable safety findings were revealed by results described in this review that differ from observations described in past clinical reviews of NDA 21999. These results generally do not change previous conclusions and recommendations provided under NDA21999. NDA21999 was recently approved.

One potentially notable observation is regarding the longterm OL trial safety results that suggest a possible trend for QT prolongation effects after chronic treatment with Pal that may appear generally after at least 6 to 12 months of treatment that were generally not observed at previous time-points during OL treatment. This finding is noted since QT prolongation was clearly shown in a focused ECG study with IR Pal (Study -1009) as previously summarized in the review of NDA 21999. Furthermore, QT prolongation is believed to be associated with development of torsade de pointe and sudden death. Consequently, the QT results of chronically exposed subjects are noteworthy. Refer Section 7.1.10.3 for ECG results and Section 7.2.9.1 of this review for updated results. Refer to Section 9 of this review for an overview of key findings relevant to EKG results. Section 9 also provides overall conclusions and recommendations relevant to safety. Sections below describe safety results in detail.

Other potentially new observations were:

- Not clinically remarkable or*
- Were observations in which the results were not consistent (e.g. across groups, across comparable dependent variables, across studies) or*
- Were of results that were difficult to interpret (e.g. on the basis of comparing subgroups categorized by duration of exposure rather than examining results of all subjects in a treatment group over time, on the basis of OL trial results, and other factors).*

The QT team was consulted regarding QT results of a focused ECG study, Study -1009 under NDA21999. QT Team input resulted in a QT section under Warnings in approved labeling under NDA21999. Approved labeling also indicates that food affects on PK, as described under Dosage and Administration. See Section 9 for further comments on this topic.

Submission N003 was not reviewed. See Sections 1 and 9 of this review for further comment.

7.1.2 Deaths

Safety results in summary tables in this subsection are identical to summary table results provided in the review of the response to the approvable letter submission (RAAL) of NDA21999, as previously discussed. Text descriptions of these results are also almost identical to the text descriptions that appear in the review of the RAAL of NDA 21999 for these same results.

Reviewer Comment. To the knowledge of the undersigned reviewer and based on the information found in the original NDA 22043 submission, there are no newly reported deaths in clinical trials of Pal (-301, -701 through -705) that were not already described in the original and addendum clinical reviews of NDA 21999.

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Table 32: Deaths Through 1 February 2006
 (Studies R076477-SCH-301, -701, -702, -703, -704, and -705)

Subject number (Study number)	Age (Years) Sex	Dictionary-derived Term Reported Term	Day of AE Onset ^a	Action Taken with Treatment	Relationship to Study Drug ^b
Double-Blind Study:					
Treatment Group: ER OROS paliperidone (post run-in phase)					
100744 (R076477-SCH-301)	36 Male	Completed suicide death (suicide - strangulation by hanging)	72	None	Very likely
Treatment Group: Placebo					
100868 (R076477-SCH-301)	47 Male	Gun shot wound multiple gunshot wounds	174	None	Not related
100846 (R076477-SCH-301)	50 Male	Completed suicide suicide	152	None	Not related
Phase 3 Open-Label Extension Studies					
Treatment Group: Pla/Pali, ≤6 months					
200214 (R076477-SCH-702)	70 Male	Bronchopneumonia Bronchopneumonia	157 ^c	None	Not related
Treatment Group: Pali/Pali, >6 months					
201516 (R076477-SCH-703)	42 Female	Completed suicide fall from 3rd floor	283	None	Not related
Treatment Group: Olan/Pali, >6 months					
200416 (R076477-SCH-703)	31 Female	Completed suicide suicide with medication ^d	238	None	Not related

^a Study day is in reference to the start of double-blind medication, except for Subject 100744 (start of run-in phase).

^b Relationship based on assessment of investigator.

^c Subject was withdrawn from the study due to a serious adverse event (electrocardiogram QT corrected interval prolonged) and died of non-treatment-emergent bronchopneumonia 4 days after receiving the last dose of study medication.

^d Subject ingested venlafaxine and lorazepam.

Between the cut-off dates of 2 February 2006 through 31 March 2006 an additional death was reported to occur in subject 100963 who was a 24 year old female with an unremarkable medical history who was only receiving trihexyphenidyl for extrapyramidal symptoms. A non-drug-related etiology could not be found in the narrative and an autopsy was not performed.

Reviewer Comment. Subject 100963 was previously described in the original review of NDA 21999 and in an addendum review under NDA 21999 (subject and 100963 are the same subject). She became "very anxious, agitated and complained of breathlessness" followed by having a seizure with vomiting and ultimately cardiorespiratory arrests (bronchospasm or pulmonary embolism were included in the differential diagnosis). She was a nonsmoker who had no known risk factors reported, and did not have a history suggestive of similar events of this nature, according to the information in the narrative. No concomitant illnesses could be found

b(6)

in the narrative. Consequently, in the absence of any clear etiology, risk factors, or underlying conditions, Pal treatment is highly suspected to be involved with events leading to death in this subject.

This subject had already received Pal treatment for months without prior related events (based on information found in the sponsor's response and in the safety alert report on this subject). Adverse effects of pal including QT prolongation, cardiovascular effects, among other observations are described in chronically treated subjects (refer to past clinical reviews of NDA 21999). However, limitations with the OL longterm safety data are inherent (refer to the original NDA 21999 review for details).

7.1.3 Other Serious Adverse Events

Results of Study -301

The following tables for Study -301 (as provided by the sponsor) are identical to the information provided in the 4-month SUR of NDA21999 and were summarized in the review of the 4 month SUR submission (refer to the review of the original NDA 21999 review).

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Table 33: Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term - Run-In and Stabilization Phases (Study R076477-SCH-301: All Treated Analysis Set)

Body System or Organ Class Dictionary-derived Term	ER OROS PAL (RI/ST) (N=530) n (%)
Total no. subjects with serious AE	30 (6)
Psychiatric disorders	25 (5)
Schizophrenia	10 (2)
Psychotic disorder	8 (2)
Agitation	4 (1)
Aggression	2 (<1)
Suicidal ideation	2 (<1)
Depression	1 (<1)
Hallucination	1 (<1)
Intentional self-injury	1 (<1)
Paranoia	1 (<1)
Suicide attempt	1 (<1)
Injury, poisoning and procedural complications	2 (<1)
Injury	1 (<1)
Intentional overdose	1 (<1)
Blood and lymphatic system disorders	1 (<1)
Thrombocytopenia	1 (<1)
Gastrointestinal disorders	1 (<1)
Swollen tongue	1 (<1)
Hepatobiliary disorders	1 (<1)
Cholelithiasis	1 (<1)
Nervous system disorders	1 (<1)
Akathisia	1 (<1)
Dyskinesia	1 (<1)
Tremor	1 (<1)
Social circumstances	1 (<1)
Social problem	1 (<1)

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**Table 34: Treatment-Emergent Serious Adverse Events by Preferred Term - Double-Blind Phase
 (Study R076477-SCH-301: Safety Analysis Set)**

Body System or Organ Class Dictionary-derived Term	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	Total (N=206) n (%)
Total no. subjects with serious AE	16 (16)	8 (8)	24 (12)
Psychiatric disorders	15 (15)	6 (6)	21 (10)
Schizophrenia	10 (10)	5 (5)	15 (7)
Psychotic disorder	4 (4)	0	4 (2)
Agitation	0	1 (1)	1 (<1)
Completed suicide ^a	1 (1)	0	1 (<1)
Suicidal ideation	1 (1)	0	1 (<1)
Injury, poisoning and procedural complications	1 (1)	1 (1)	2 (1)
Gun shot wound ^a	1 (1)	0	1 (<1)
Treatment noncompliance	0	1 (1)	1 (<1)
Vascular disorders	0	2 (2)	2 (1)
Hypertension	0	1 (1)	1 (<1)
Venous thrombosis	0	1 (1)	1 (<1)
Cardiac disorders	0	1 (1)	1 (<1)
Tachycardia	0	1 (1)	1 (<1)
Musculoskeletal and connective tissue disorders	0	1 (1)	1 (<1)
Musculoskeletal chest pain	0	1 (1)	1 (<1)

^a This event resulted in death of subject (see Section 2.1.2).
 tsfae106_tsfae05.rtf generated by tsfae05.sas.

Results from Pooled and Unpooled OL Extension Trial Datasets

Safety results in summary tables in this subsection on OL trial results are identical to summary table results provided in the review of the RAAL of NDA21999, as previously discussed (as provided by the sponsor). Text descriptions of these results are also almost identical to the text descriptions that appear in the review of the RAAL of NDA 21999 for these same results. However, it is noted here that Studies -701 and -705 are ongoing studies, while other studies were completed as of the cut-off date used for including safety data in the results shown below. Text below is modified, accordingly to reflect that these studies are ongoing.

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Results of Study -701

See the sponsor's summary table below.

**Table 35: Serious Adverse Events Through 1 February 2006
 (Open-Label Study R076477-SCH-701: Safety Analysis Set)**

Body System or Organ Class Dictionary-derived Term	Pia/Pali <=6 months (N=11) n (%)	Pia/Pali >6 months (N=69) n (%)	Pali/Pali <=6 months (N=2) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali/NO DB/Pali <=6 months (N=23) n (%)	Pali/NO DB/Pali >6 months (N=60) n (%)
	Total no. subjects with serious adverse events	2 (18)	3 (4)	0	3 (4)	1 (4)
Psychiatric disorders	1 (9)	3 (4)	0	2 (3)	0	1 (2)
Schizophrenia	0	3 (4)	0	2 (3)	0	0
Delusion	0	0	0	0	0	0
Suicide attempt	1 (9)	0	0	0	0	1 (2)
Injury, poisoning and procedural complications	0	1 (1)	0	1 (1)	0	0
Alcohol poisoning	0	0	0	1 (1)	0	0
Tibia fracture	0	1 (1)	0	0	0	0
Nervous system disorders	1 (9)	0	0	0	0	0
Syncope	1 (9)	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	1 (4)	0
Varicocele	0	0	0	0	1 (4)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

**Table 36: Serious Adverse Events Through 1 February 2006 (Continued)
 (Open-Label Study R076477-SCH-701: Safety Analysis Set)**

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=36) n (%)	Total Pali >6 months (N=199) n (%)
	Total no. subjects with serious adverse events	3 (8)
Psychiatric disorders	1 (3)	6 (3)
Schizophrenia	0	5 (3)
Delusion	0	1 (1)
Suicide attempt	1 (3)	0
Injury, poisoning and procedural complications	0	2 (1)
Alcohol poisoning	0	1 (1)
Tibia fracture	0	1 (1)
Nervous system disorders	1 (3)	0
Syncope	1 (3)	0
Reproductive system and breast disorders	1 (3)	0
Varicocele	1 (3)	0

See footnotes on the first page of the table.
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Results of the Elderly OL Extension Study -702

The following table summarizes the results from this study.

Table 21: Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term During the Open-Label Phase (Study R076477-SCH-702: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pia/Pali (N=30) n (%)	Pali/Pali (N=58) n (%)	Total (N=88) n (%)
Total no. of subjects with serious adverse event	2 (7)	3 (5)	5 (6)
Psychiatric disorders	1 (3)	2 (3)	3 (3)
Psychotic disorder	1 (3)	1 (2)	2 (2)
Schizophrenia	0	1 (2)	1 (1)
Blood and lymphatic system disorders	0	1 (2)	1 (1)
Anaemia	0	1 (2)	1 (1)
General disorders and administration site conditions	0	1 (2)	1 (1)
Pyrexia	0	1 (2)	1 (1)
Infections and infestations	0	1 (2)	1 (1)
Nasopharyngitis	0	1 (2)	1 (1)
Investigations	1 (3)	0	1 (1)
Electrocardiogram QTc interval prolonged	1 (3)	0	1 (1)

Results from the Integrated OL Extension Trial Dataset

Study 705 of the pooled dataset is ongoing. See the summary table below.

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 Supplemental NDA 22-043 N000-N002
 Paliperidone OROS oral

Table 36: Serious Adverse Events Through 1 February 2006
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	<=6 months (N=99) n (%)	>6 months (N=137) n (%)	<=6 months (N=309) n (%)	>6 months (N=377) n (%)	<=6 months (N=108) n (%)	>6 months (N=141) n (%)	<=6 months (N=416) n (%)	>6 months (N=755) n (%)
Total no. subjects with serious adverse events	17 (17)	13 (9)	46 (19)	37 (12)	33 (31)	14 (10)	90 (22)	84 (11)
Psychiatric disorders	12 (12)	10 (7)	35 (17)	44 (9)	30 (28)	11 (8)	77 (19)	65 (9)
Psychotic disorder	7 (7)	2 (1)	14 (7)	20 (4)	12 (11)	5 (4)	33 (8)	27 (4)
Schizophrenia	2 (2)	3 (2)	15 (7)	15 (3)	13 (12)	3 (2)	30 (7)	21 (3)
Depression	0	2 (1)	1 (<1)	4 (1)	3 (2)	1 (1)	3 (1)	7 (1)
Suicidal ideation	2 (2)	1 (1)	3 (1)	4 (1)	0	0	5 (1)	5 (1)
Agitation	2 (2)	1 (1)	3 (1)	2 (<1)	5 (5)	1 (1)	10 (2)	4 (1)
Hallucination, auditory	0	0	0	4 (1)	0	0	0	4 (1)
Acute psychosis	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Anxiety	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Completed suicide	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Depressed mood	0	0	0	1 (<1)	0	0	0	2 (<1)
Suicide attempt	1 (1)	2 (1)	2 (1)	0	1 (1)	0	4 (1)	2 (<1)
Aggression	2 (2)	1 (1)	0	0	4 (4)	0	6 (1)	1 (<1)
Alcoholism	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Confusional state	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Delusion	0	0	2 (1)	1 (<1)	0	0	1 (<1)	1 (<1)
Insomnia	0	1 (1)	1 (<1)	0	3 (3)	0	3 (<1)	1 (<1)
Paranoia	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia, paranoid type	0	0	0	1 (<1)	0	0	0	1 (<1)
Self-injurious ideation	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Infections and infestations	0	0	1 (<1)	3 (2)	1 (1)	1 (1)	2 (<1)	9 (1)
Nasopharyngitis	0	0	0	2 (<1)	0	0	0	2 (<1)
Bronchitis acute	0	0	0	1 (<1)	0	0	0	1 (<1)
Celutitis	0	0	0	1 (<1)	0	0	0	1 (<1)

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 36: Serious Adverse Events Through 1 February 2006 (Continued)
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	<=6 months (N=99) n (%)	>6 months (N=137) n (%)	<=6 months (N=309) n (%)	>6 months (N=377) n (%)	<=6 months (N=108) n (%)	>6 months (N=141) n (%)	<=6 months (N=416) n (%)	>6 months (N=755) n (%)
Infections and infestations (continued)								
Measles	0	0	0	1 (<1)	0	0	0	1 (<1)
Perianal abscess	0	0	0	1 (<1)	0	0	0	1 (<1)
Pulmonary tuberculosis	0	0	0	0	0	1 (1)	0	1 (<1)
Stomatitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Urinary tract infection	0	0	0	1 (<1)	0	0	0	1 (<1)
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	0	0	0	0	1 (1)	0	1 (<1)	0
Nervous system disorders	1 (1)	2 (1)	4 (2)	5 (1)	1 (1)	0	6 (1)	7 (1)
Akathisia	0	0	0	2 (<1)	1 (1)	0	1 (<1)	2 (<1)
Dizziness	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Dysomnia	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Ischaemic stroke	0	1 (1)	0	0	0	0	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Transient ischaemic attack	1 (1)	0	0	0	0	0	1 (<1)	0
General disorders and administration site conditions	0	0	1 (<1)	4 (1)	1 (1)	0	2 (<1)	4 (1)
Pyrexia	0	0	0	2 (<1)	0	0	0	2 (<1)
Cyst	0	0	0	1 (<1)	0	0	0	1 (<1)
Irritability	0	0	0	1 (<1)	0	0	0	1 (<1)
Chills	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0

See footnotes on the first page of the table.

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 Paliperidone OROS oral

Table 36: Serious Adverse Events Through 1 February 2006 (Continued)
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pia/Pali	Pia/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	<=6 months (N=99) n (%)	>6 months (N=137) n (%)	<=6 months (N=309) n (%)	>6 months (N=477) n (%)	<=6 months (N=108) n (%)	>6 months (N=141) n (%)	<=6 months (N=416) n (%)	>6 months (N=755) n (%)
Injury, poisoning and procedural complications								
Alcohol poisoning	1 (1)	1 (1)	2 (1)	3 (3)	1 (1)	0	4 (1)	4 (1)
Fall	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Road traffic accident	0	0	0	1 (<1)	0	0	0	1 (<1)
Traumatic haematoma	0	1 (1)	0	0	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Overdose	0	0	0	0	1 (1)	0	1 (<1)	0
Investigations								
Blood creatine phosphokinase increased	1 (1)	0	0	2 (<1)	0	0	1 (<1)	2 (<1)
Electrocardiogram QT corrected interval prolonged	0	0	0	1 (<1)	0	0	0	1 (<1)
	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Metabolism and nutrition disorders								
Diabetes mellitus	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Hypoaemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Hypocalcaemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Benign neoplasm of skin	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Colon neoplasm	0	0	0	0	0	1 (1)	0	1 (<1)
0	0	0	0	1 (<1)	0	0	0	1 (<1)
Respiratory, thoracic and mediastinal disorders								
Asthma	0	0	1 (<1)	1 (<1)	0	1 (1)	1 (<1)	2 (<1)
Dyspnoea	0	0	0	0	0	1 (1)	0	1 (<1)
Pneumonia aspiration	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
0	0	0	1 (<1)	0	0	0	0	1 (<1)
Blood and lymphatic system disorders								
Anaemia	0	0	0	1 (<1)	0	0	0	1 (<1)
0	0	0	1 (<1)	0	0	0	0	1 (<1)

See footnotes on the first page of the table.

Table 36: Serious Adverse Events Through 1 February 2006 (Continued)
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pia/Pali	Pia/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	<=6 months (N=99) n (%)	>6 months (N=137) n (%)	<=6 months (N=309) n (%)	>6 months (N=477) n (%)	<=6 months (N=108) n (%)	>6 months (N=141) n (%)	<=6 months (N=416) n (%)	>6 months (N=755) n (%)
Gastrointestinal disorders								
Crohn's disease	1 (1)	1 (1)	0	0	0	0	1 (<1)	1 (<1)
Peptic ulcer	0	1 (1)	0	0	0	0	0	1 (<1)
1 (1)	0	0	0	0	0	0	1 (<1)	0
Hepatobiliary disorders								
Cholelithiasis	0	0	0	1 (<1)	0	0	0	1 (<1)
0	0	0	1 (<1)	0	0	0	0	1 (<1)
Cardiac disorders								
Bundle branch block	1 (1)	0	2 (1)	0	2 (2)	0	5 (1)	0
Myocardial infarction	1 (1)	0	0	0	0	0	1 (<1)	0
0	0	1 (<1)	0	0	0	0	1 (<1)	0
sinus tachycardia	0	0	0	0	1 (1)	0	1 (<1)	0
Tachycardia	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Social circumstances								
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
0	0	1 (<1)	0	2 (2)	0	3 (1)	0	

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Additional SAEs Prior to the 4/1/06 Cut-off Date

The sponsor also specifies that 3 additional subjects had SAEs in the OL extension trials (of the combined OL extension trial dataset) since the cut-off date for the above summary table and prior to the 4/1/06 cut-off date.

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