CLINICAL REVIEW

Application Type	NDA 21-999
Submission Number Code	N000
Letter Date	11/30/05
Stamp Date	11/30/05
PDUFA Goal Date	9/30/06
Reviewer Name	Karen Brugge, MD
Review Completion Date	7/21/06
Established Name	Paliperidone
(Proposed) Trade Name	[redacted]
Therapeutic Class	Atypical Antipsychotic
Applicant	Johnson & Johnson
Priority Designation	Standard
Formulation	Extended Release OROS® oral tablets
Proposed Dosing Regimen	6 mg administered daily in the morning, may benefit from lower or higher doses within the recommended daily dose range of 3 mg to 12 mg once, daily.
Indication	Schizophrenia
Intended Population	Adults with Schizophrenia

1 EXECUTIVE SUMMARY

The Purpose of This Review.

[redacted] 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).

Recommendations in this review are being provided from a clinical perspective. Reviews from other disciplines are pending at the time of this writing.

Proposed Indication and Treatment
The proposed indication is Schizophrenia in the acute episode (in adults).

The sponsor proposes a daily oral dose of 6 mg of OROS Paliperidone (Pal) to be taken in the morning. Proposed labeling also specifies 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

An approvable action is recommended from a clinical perspective.

All comments and recommendations below are provided from a clinical perspective (in the opinion of the undersigned reviewer).

Pivotal Phase III trials were positive for establishing adequate efficacy, pending confirmation by the Office of Biometrics. The recommended dose in proposed labeling is also reasonable from an efficacy standpoint. However, there are several key issues that primarily pertain to establishing an adequately safe, yet efficacious dose range of Pal. Extensive experience with the already marketed Risperdol® provides some support in favor of the adequate safety of Pal. Yet, some key issues specific to Pal need to be resolved, such as a food effect on plasma levels, QT prolongation effects observed in Phase III trials and in a QT Prolongation study, among other safety findings that were not revealed in the Phase III trials of risperidone that supported approval for Risperdal® (as described in labeling). Input from the Office of Clinical Pharmacology and Biopharmacy (OCPB) is critical in determining an adequately safe dose and treatment regimen, as outline below. OCPB input is recommended for other issues, as outlined below. Ultimately the risk: benefit ratio relative to the already available risperidone needs to be addressed. An Advisory Committee will be held in September of 2006.

If an approvable action is granted at the Agency level on this NDA, then recommendations are provided below starting with a recommendations that impact on both safety and efficacy,

followed by safety specific recommendations and efficacy-related recommendations follow, thereafter.

Recommendations that impact on both safety and efficacy:

1. The recommended starting dose and dose-range appears to be reasonable from an efficacy perspective but there are safety issues that also impact on dose, as described below. Therefore, these safety issues need to be addressed, as well before a recommended dose range can be made.
2. It is not clear if the to-be-marketed formulation was used in all pivotal efficacy trials (this question was conveyed to the sponsor and a response is pending at the time of this writing). OCPB input may be needed if a different formulation was used.

Safety Related Recommendations

If an approvable action is granted at the Agency level on this NDA, then the following outline contains comments and recommendations regarding safety (refer to Sections 7 and 9 of this review for an outline of safety findings, including those that are the basis of issues below):

1. A food effect on the pharmacokinetic (PK) properties of Pal was observed in two Phase I trials, as described in Section 5 of this review. This issue needs to be resolved with respect to recommendations for an adequately safe, yet efficacious treatment regimen. OCPB input is critical and recommended.
2. Food effects on PK and safety (in Phase I food effect studies described in Sections 5 for PK effects, 7.1.12 C and Section 7.1.3.3 for safety findings)
3. Several cardiovascular-related findings need to be addressed from a dose-level perspective that include a signal for
    a. QT prolongation (based on Phase III data, updated longterm OL extension trial data provided in the 120-Day SUR, results of Study –SCH-1009),
    b. Results on heart rate (based on ECG and vital sign results), and other hemodynamic effects were observed (based on results in Section 7). Subjects with clinically remarkable events related to hemodynamic Pal effects are also described in Section 7.1.3.3 of this review.
    c. Potential PR interval prolongation effects as suggested by the following observations:
        i. A greater incidence of adverse events (AEs) of ° AV block in the 15 mg (highest-dose) Pal group compared to placebo (4.4%, 1.4%, respectively)
        ii. Similar findings in the small elderly Phase III trial (3% and 0% in the Pal and placebo groups, respectively) that used a flexible dose design (3-12 mg/day),
        iii. A small group mean increase in PR interval in Pal compared to placebo groups in Phase III trials (the magnitude of this increase was clinically unremarkable)
4. [redacted]

5. OCPB input is recommended regarding dosing recommendations in light of QT prolongation and other adverse effects and the potential PK-pharmacodynamic (PD) interactions (as well as other factors impacting PK such as a food effect, drug-drug interactions and others). Effects on QT and vital sign appear to be influenced by Cmax and Tmax (e.g. not only absolute levels but also perhaps how quickly levels are rising) and by other confounding variables (due to observations of direct or indirect time-dependent effects observed in Phase III trials and in Study –SCH-1009).
6. A more gradual dose adjustment (with a lower starting dose and longer interval between dose increments) and a lower maximum dose-level (not-to-exceed level) should be recommended for elderly patients and any other special populations, pending input from OCPB. It is noted that Risperdal® labeling provides specifications on dose adjustment in this section of labeling, although the recommendation is not specific to a given dose-level or maximum dose-level. This recommendation is being made on the basis of the following:
    a. Safety findings in the elderly trial (-302), as outline in Sections1.1, 7 and 9 of this review,
    b. Multiple concomitant medications and diseases are common in the elderly
    c. The elderly are generally considered to have greater vulnerability to adverse effects (e.g. cardiovascular, ECG, CNS and other effects)
    d. The elderly are more predisposed to alterations in PK (towards greater plasma levels),
    e. There is the additional concern of a food effect on PK
    f. A safety signal was revealed for increased risk of mortality in elderly patients with dementia being treated with atypical antipsychotics in longterm clinical drug trials (as described in drug class labeling of approved atypical antipsychotic agents). The role of age in this signal remains unclear.
7. Elevations in CPK levels were observed in treatment groups in Phase III trials. However, these elevations were inconsistent across treatment groups and may be reflective of the patient population rather than being drug-related. Yet, CPK levels varied widely across subjects and showed large fluctuations over time within a given subject. Furthermore, baseline levels were elevated in some subjects and in some treatment groups. Consequently, it is difficult to detect a potential drug signal in a population with highly variable CPK levels at baseline. CPK elevations were also observed in Phase I trials of generally healthy subjects (who did not have schizophrenia) that appeared to be dose-dependent in subjects treated with the OROS formulation.

    The sponsor does not describe any serious events associated with CPK elevations except for one subject (and possibly another with NMS that was found by the undersigned review; subjects 100057 and 200213). Additional subjects with elevated CPK were however, found by the undersigned reviewer that also had elevations in LFTs (as described in Section 7.1.3.3 of this review). There may be additional subjects with

clinically remarkable events associated with CPK elevations since results of a special data analyses for revealing a potential drug-related signal could not be found in the Summary of Clinical Safety (SCS) section of the submission which provided the integrated summary of safety in clinical drug trials. Therefore, it is not clear to the undersigned if CPK elevations were associated with dystonia or other drug-related adverse effects. Another consideration is that CPK elevations reflective of the patient population would be expected to occur primarily in the acutely psychotic patient, yet elevations were also revealed during longterm OL Pal treatment (in the Phase III OL extension trials). This potential safety signal should be adequately resolved.

8. It is recommended that the specific methodology for dose adjustments during the OL trials (-702, -703, -704, and -705) be clarified (these trials used a flexible dose design). This information is relevant to longterm safety and may influence recommendations for dosage and administration in labeling.
9. Attachment 1 of this review lists questions raised to the sponsor to which some responses were received and other responses are pending at the time of this writing that should be resolved before considering a final approval action on this NDA (since some responses arrived late in the review cycle a review of these responses is pending, unless otherwise specified in this review).
10. Section 7.2.8 (on quality and completeness of data) discusses concerns related to identifying potentially clinically remarkable subjects with a specific type of AE (e.g. syncope, suicidality, among others). These issues should be adequately resolved. See Attachment 1 that includes some questions related to this concern (as described in the pervious item).
11. Once efficacy and safety related issues can be adequately addressed, then the sponsor would need to provide a convincing justification that the benefit: risk ratio of Pal outweighs that of Risperdol® (Ris).
12. Input from other disciplines is pending at the time of this writing.

Section 9 of this review provides key recommendations for labeling if an approvable action is granted at the Agency level on this NDA.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The proposed Risk Management program cannot be found in the submission. In accordance with the Clinical Reviewer MAPP, a postmarketing studies and surveillance plan should be described here. Sponsors generally conduct ongoing postmarketing surveillance for safety signals and maintain a database. Sponsors of approved NDAs are also required to submit Periodic Safety Update reports according to regulations. Input from the Office of Surveillance and Epidemiology is a consideration, as well, if the Agency grants an Approvable Action.

1.2.2 Required Phase 4 Commitments

It is recommended that the sponsor address key issues, as discussed in this review (and as outlined above) before considering Phase 4 commitments.

The following are some considerations for studies that should enhance our understanding of cardiovascular effects of Pal:

- Conduct cardiovascular challenge tests (at baseline and during treatment) in double-blind, placebo controlled studies of patients with schizophrenia while monitoring vital signs and ECG (and in some cases with telemetry monitoring) using the following challenge paradigms for each given study:
  - Challenge subjects with a commonly used drug in the population that is known to have some degree of QT prolongation effects using adequately safe doses that would allow for detecting a signal while assuring adequate safety (e.g. the undersigned reviewer is the primary reviewer on the escitalopram NDA 21323 in which a pimozide-escitalopram interaction study revealed greater QT effects with this combination than with either of the two drugs alone.
  - Challenge subjects with a tread mill stress test (using methods for an adequately safe study).
  - Challenge subjects with a tilt table test
- Challenge subjects on longterm OL Pal (over 6 months to up to a year of treatment) with a higher daily dose of Pal (that is adequately safe) to determine if vital sign and QT effects can be elicited after a single dose and after subsequent multiple daily doses until at least steady state levels are achieved (subjects should undergo monitoring prior to starting the OL Pal treatment and throughout OL treatment to allow for pre-challenge and pre-Pal comparisons on cardiovascular parameters).
- Conduct a food challenge (food effect) study in patients with schizophrenia to examine the role of food effects on safety parameters (input from OCPB is recommended on this recommendation).
- Conduct studies to better characterize drug-drug and drug-disease interactions on cardiovascular effects and other relevant safety parameters.
- Other safety issues and PK issues may require further examination depending on the sponsor's responses to issues and on OCPB input.

There is the belief that antipsychotic drug treatment may be associated with or induce a metabolic syndrome (e.g. weight gain, abnormal lipid profile, hyperglycemia and other changes) that may increase risk for morbidity and possibly mortality in this population. Also consider a role of potential alterations in the endocrine system that may yet to be revealed or are known to exist (e.g. increased prolactin levels). Therefore, further study in this area should be considered.

Since elevations in LFTs were observed in some Pal subjects further study in this area should be considered such as employing a challenge test to determine if elevations can be elicited using methods that would be adequately safe. For example consider a study examine the effects of coadminstration of olanzapine (refer to labeling describing LFT elevations in some subjects on

this drug). Polypharmacy involving multiple antipsychotic medications is not uncommon among clinicians treating patients with schizophrenia.

Phase III clinical trials using the OROS® formulation did not appear to test stools for bleeding and to monitor for excretion of capsules. A small group mean decrease in HgB was also observed that in itself is not clinically remarkable, yet could be reflecting a real drug-related effect (e.g. gastrointestinal bleeding perhaps due to retention of capsules). There was one subject with duodenal rupture and another subject with gastrointestinal hemorrhage reported in Phase III trials. It is recommended that consideration be given to studies focusing on a potential effect on OROS versus an effect of Pal on HgB and gastrointestinal bleeding, while also closely monitoring for signs and symptoms for GI complications, monitoring stools for occult blood and retention of capsules which were not systematically evaluated in Phase III trials.

1.2.3 Other Phase 4 Requests

See the previous section in which key issues first need to be addressed that can impact on the nature of Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Paliperidone (an extended release oral OROS® formulation) is in the drug class of atypical neuroleptic agents and is a major active metabolite of risperidone. Risperidone is approved for treatment of Schizophrenia. Paliperidone and risperidone are atypical antipsychotic agents and are in the chemical class of benzisoxazole derivatives.

Three pivotal multicenter, placebo controlled, active controlled, randomized, double-blind (DB), fixed dose-response, parallel group trials were conducted to establish efficacy of oral paliperidone administration for the treatment of Schizophrenia (Studies R076477-SCH-303, R076477-SCH-304, R076477-SCH-305). The daily oral doses among these trials ranged from as high as 15 mg daily (in Study R076477-SCH-305) and as low as 3 mg in Study R076477-SCH-303. The 15 mg treatment group was started on 12 mg daily for the first seven days of treatment following by 15 mg daily for the remainder of the DB phase. The active control groups in these trials received olanzapine (10 mg daily). Two studies included subjects from the United States while the third study was conducted in eastern and western European countries, as specified in the submission.

A total of 1665 subjects were in the intent-to-treat (ITT) population (defined as a randomized subject with at least one dose of study drug and at least one post-baseline efficacy assessment) of which 351 subjects received placebo, 955 subjects received paliperidone (extended release OROS® formulation) and 359 subjects received active control drug (10 mg daily of olanzapine). Subjects were 18 to 65 year old (a few subjects over 65 years old) generally healthy men and women with Schizophrenia for at least one year using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Subjects were required to have a Positive

and negative Symptom Scale total score of 70 to 120 at baseline and were inpatients for at least 14 days during the study.

An additional Phase III trial (R076477-SCH-302) was conducted on elderly patients using a flexible dose design (3-12 mg daily of paliperidone. Other aspects of the study design of this trial were generally similar to that employed in three above described pivotal trials of non-elderly adults. The ITT population consisted of 114 total subjects of which 76 subjects received paliperidone and 38 subjects received placebo.

Safety was assessed in the 3 pivotal trials, as well as in additional Phase I, II and III trials. Section 7 of this review provides more details on safety.

1.3.2 Efficacy

Pivotal Trials

Each pivotal Phase III trial (Studies R076477-SCH-303, R076477-SCH-304, R076477-SCH-305) was positive for efficacy. Refer to the previous section for a description of these studies and enumeration of subjects. The primary efficacy measure was the mean change from baseline to treatment endpoint on the Positive and negative Symptom Scale (PANSS) total score (a standard measure for Phase III trials for establishing efficacy in treating schizophrenia). Greater improvement was observed with paliperidone treatment compared to placebo treatment. Improvement was demonstrated for all dose levels examined (3, 6, 9, 12 and 15 mg daily doses administered in the morning).

Results on secondary variables in each of these short-term Phase III trials were also generally consistent with findings on the primary efficacy variable.

The elderly Study -302 showed at least trends for greater improvement. This study was small such that failure to show significant group differences may be due to insufficient sample size. Due to the small sample size in this study, the results are difficult to interpret.

Key Issues Relevant to Efficacy and Proposed Labeling
See Section 1.1 above. The last section of this review also addresses key issues.

1.3.3 Safety

See key safety issues under Section 1.1. Section 7 of the review provides a detailed discussion of safety findings.

In addition to pivotal DB Phase III trials and a small DB Phase III elderly trial, the safety results were also provided for ongoing longterm open-label trials that were extension trials to the short-term (6-week) DB Phase III trials. The results of the OL trials provided longterm safety results for 6 and 12 month exposures within ICH guidelines within the dose-range being recommended for treatment in proposed labeling.

Study –SCH-1009 provided results on QT prolongation effects of a non-OROR (more immediate release) formulation of Pal. This review also describes results of a few other Phase I trials that provided some safety results in fed and fasted treatment conditions, as the effect of food on PK was examined and conducted more frequent vital sign assessments, than was employed in the Phase III trials.

Section 7 describes safety findings.

1.3.4 Dosing Regimen and Administration

The sponsor proposes a daily oral dose of 6 mg to be taken in the morning. Proposed labeling also specifies that patients may benefit from lower or higher doses within a recommended daily dose range of 3 to 12 mg (once daily).

See Section 1.1 for comments relevant to dosing and administration with respect to key safety issues and food effects.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not systematically evaluated in Phase III trials. See section 1.1 for comments and recommendations on potential drug-drug interactions relevant to key safety related issues.

1.3.6 Special Populations

See Section 1.1 for comments and recommendations relevant to the elderly population and relevant to key safety findings in a small Phase III trial on elderly patients. This topic is covered in various sections of this review.

2 INTRODUCTION AND BACKGROUND

Note to the Reader: 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 Purpose of this Clinical Review (copied from Section 1). The purpose of this clinical review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-999. The information in this review and recommendations are provided from a clinical perspective.

Proposed Indication (also in Section 1). The sponsor is seeking approval of Paliperidone OROS® oral formulation (Pal) for the treatment of schizophrenia in adult patients.

A Brief Overview of the Organization of this Review. The undersigned reviewer has attempted to follow the required Clinical Reviewer Template MAPP which was finalized approximately one year ago. Since the organization of this review, as required by the MAPP is generally new to the regulatory reading audience 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 some subsections such as clinical microbiology (section 6.1.5) appear under efficacy but is not relevant to this review.
- In order to avoid redundancy between various subsections, related subsection(s) are referenced, rather than repeating the same information under multiple subsections.

Italicized text in this review appears in various places throughout this review and is intended to denote comments, conclusions and recommendations being made by the undersigned reviewer (from a clinical perspective), unless otherwise specified. Sometimes a result section has both reviewer comments/conclusions embedded with the sponsor's results. These sections generally present the results found in the submission (unless otherwise specified). Consequently, these sections that contain some of the sponsor's results along with reviewer comments are also italicized.

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. 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 and other psychiatric indications. See the previous section regarding Ris which is one of these approved drugs and is metabolized primarily to 9-OH Ris which is the active compound in Pal.

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 is metabolized primarily to 9-OH Ris which is the active compound in Pal. Pal is not approved for the market in the United States.

2.4 Important Issues With Pharmacologically Related Products

See the previous section and other safety related sections of this review, as well as current approved labeling for drugs in this drug class and the final section of this review.

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. The sponsor provides copies of meeting minutes in the submission.

2.6 Foreign Marketing Experience

Section 5.11 of Module 2.5 of the submission specifies that "ER OROS paliperidone has not been marketed in any country to date."

The sponsor does provide 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, as previously described.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC information is provided in the submission and is under review by the CMC Team at the time of this writing. The CMC reviewer, has no major CMC issues at the time of this writing or at the time of the mid-cycle review meeting.

3.2 Animal Pharmacology/Toxicology

The submission contains preclinical information which is under review by the Pharmacology Reviewer at the time of this writing.

3.3 Other Disciplines: Division of Scientific Investigations (DSI) and Biometric Disciplines

DSI is involved with this NDA and results are pending at the time of this writing.

The NDA is also under review by Biometrics 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	
DATE	DESCRIPTION (electronic submissions unless indicated otherwise).
11/30/05	NDA 21-999 N000: the submission included Narratives hyperlinked to CRFs (were generally hyperlinked from the narrative or from tables listing narratives) for completed Phase I-III trials for serious adverse events (SAEs) and adverse dropouts (ADOs) using a cut-off date of 5/31/05. Safety (CIOMS) reports (of SAEs and ASDOs) were provided at the cut-off dates of 6/1/05-8/31/05 120-Day Safety Update Report Submission (N0002, letter date 3/29/06 and stamp date 3/29/06): Narratives of SAEs and ADOs were provided for the more recently completed Study -301 and for open-label trials (Studies -701-705) using the cur-off date of 11/1/05 (narratives or narrative summary tables generally included hyperlinks to the CRFs). Safety (CIOMS) reports were provided for SAEs and ADOs at the cut-off-dates of 11/2/05-12/31/05 This submission contained the bulk of longterm safety data from ongoing open label trials in which ICH guidelines for 6 and 12 month exposure was met. N0001 letter dated 1/10/06 response to pre-filing questions. <u>Additional Submissions with Clinical Information that were Received Late in the Review Cycle of which Some are in Response to Inquiries</u> The following submissions either have not been reviewed or not have been fully reviewed, since they were received late in the review cycle or contained only non-clinical information: • N007 6/27/06: responses to clinical inquiries • N006 6/15/06: 210-Safety Update Report and new Food Effect Phase I trial Results • N005 letter dated 6/15/06: responses to clinical inquiries • N004: letter dated 5/26/06: no clinical information could be found (CMC related) • N003: no clinical information could be found (CMC related) Not all information from these submission are described or were fully reviewed since some submissions were only submitted with 1-2 months of the internal reviewer deadline which is 7/22/06.

4.2 Tables of Clinical Studies

Tables in this section provide an overview of trials, study design and the number of subjects, as specified. More detailed information on the enumeration of subjects for efficacy and safety analyses is provided in Sections 6 and 7.2.1 of this review (in accordance with the Clinical Reviewer MAPP). In addition to information required by the Clinical Reviewer MAPP, Section 7.2.1 also provides the enumeration of subjects that completed key trials. Other subsections of 7.2 provide additional exposure information as required by the Clinical Reviewer MAPP.

Completed and Ongoing Phase III Trials
Phase III trials included:

- 3 pivotal Phase III trials of primarily non-elderly adult patients using a 6-week double-blind (DB) phase (Studies R06477-SCH-303, R06477-SCH-304, R06477-SCH-305). The sponsor specifies these 3 trials as providing results to support their proposed efficacy claim. These adult trials had very few elderly subjects.
- An elderly Phase III trial of patients using the 6-week DB phase (Study R06477-SCH-302). This trial was a small flexible dose trial that was otherwise almost identical in study design to the above 3 Phase III trials.
- Ongoing Phase III Trials include 1 ongoing Phase III trial on "prevention of recurrence" (Study R06477-SCH-301) and ongoing open-label (OL) extension phases of 6-12 months duration that are being conducted for longterm safety data. These longer term OL phases are extension phases (trials R06477-SCH-701, -702, -703, -704 and -705) that followed the 6-week double-blind phases of the 3 pivotal Phase III trials (Studies R06477-SCH-303, R06477-SCH-304, R06477-SCH-305), of one elderly Phase III trial (Study R06477-SCH-302) and of a Phase III trial on "Prevention of recurrence (Study R06477-SCH-301).

Since a food effect was observed in Phase I trials, it is important to note that dosing in the Phase III short-term trials (-302, -303, -304, -305) was to occur in the morning. The timing and content of meals (and the timing relative to dosing) were not monitored in the Phase III trials.

This review will generally be referring to trials by the last set of hyphenated digits of the trial number (e.g. -302 for Study R06477-SCH-302).

All tables below were provided in the submission with some additional information added by the undersigned reviewer for clarification purposes or to provide more detailed information (all of these additions are denoted by italics).

COMPLETED PHASE 3 DOUBLE-BLIND STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
Analysis Set Protocol No.	Study Design/Enrollment Statusa
Double-Blind Studies Analysis Set	
R076477-SCH-303 Western and Eastern Europe	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of paliperidone ER (6, 9, and 12 mg/day) and olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 629 Treated with Paliperidone: 375
R076477-SCH-304 United States	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 2 fixed dosages of paliperidone ER (6 and 12 mg/day) and olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 439 Treated with Paliperidone: 224
R076477-SCH-305 North America (includes the United States), Eastern Europe, Asia, Isreal, Mexico and South Africa	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of paliperidone ER (3, 9, and 15 mg/day)band olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. *Reviewer Comment: the 15 mg group received 12 mg daily over the first week of DB treatment, followed by 15 mg daily thereafter during the DB phase.* Double-blind: Completed No. Subjects Evaluable for Safety: 614 Treated with Paliperidone: 364
Study R076477-SCH-302	
R076477-SCH-302 Easter Europe, South Africa and Greece	A randomized, 6-week double-blind, placebo-controlled study to evaluate the safety and tolerability of flexible doses of paliperidone ER in the treatment of geriatric subjects with schizophrenia. *Reviewer comment inserted here (based on information found on page 43-44 in the SCS): the flexible daily dose level used in this trial was 3 to 12 mg. Subjects were started on 6 mg daily over the first week and if tolerated, this dose daily dose was increased to 9 mg daily. Subjects that could not tolerate the 6 mg daily dose-level could have their dose decreased to 3 mg daily at any time during the first week. Dose increments could not occur more frequently that every 7 days, in increments of no greater than 3 mg daily. The lowest dose permitted was 3 mg daily.* Double-blind: Completed No. Subjects Evaluable for Safety: 114 Treated with Paliperidone: 76

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
a Enrollment as of 31 May 2005.
b Subjects in the 15 mg/day group received 12 mg/day on Days 1-7 and 15 mg/day for the rest of the double-blind phase.

	ONGOING DOUBLE-BLIND PHASE 3 STUDY
R076477-SCH-301	A randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension evaluating paliperidone ER in the prevention of recurrence in subjects with schizophrenia. *Reviewer comment inserted here: the trial involved an 8-week OL-run-in phase, then a 6-week OL stabilization phase, followed by a placebo controlled, DB treatment phase (1:1 of placebo or Paliperidone treatment). Treatment was flexible during the OL run-in and DB treatment phases (3 to 15 mg daily) but was fixed during the OL stabilization phase (at the dose identified during the stabilization phase).* Double-blind: Ongoing No. Subjects Enrolled as of 31 May 2005: 462 *Reviewer Comment inserted here: This study was completed in time for unblinded data to be provided in the 120-Day SUR.*

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005. [b]Subjects in the 15 mg/day group received 12 mg/day on Days 1-7 and 15 mg/day for the rest of the double-blind
se.

Ongoing Open-Label Extension Trials (Studies -702, -703, -704, -705)

The following table summarizes the ongoing extension phases (referred to as Studies -702, -703, -704, -705) to the completed 6-week double-blind pivotal (-303, -304, -305) and elderly Phase III (-302) trials. These studies used a flexible daily dose of 3 to 12 mg (dose levels of 3, 6, 9 or 12 mg/day), except Study -705 used a maximum allowable daily dose of 15 mg (3, 6, 9, 12 or 15 mg/day). Study –702 was conducted on elderly subjects, while the other OL studies were conducted on almost exclusively non-elderly adults.

Analysis Set Protocol No.	Study Design/Enrollment Status[a]
ONGOING OPEN-LABEL PHASE 3 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
Open-Label Studies Analysis Set	
R076477-SCH-702	A 26-week open-label extension to evaluate the safety and tolerability of flexible doses of ER OROS paliperidone in geriatric 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-302 *Starting dose was 9 mg and a flexible dose design was employed (3, 6, 9, or 12 mg/day) as described on page 45 of the SCS.* No. Subjects Enrolled as of 31 May 2005: 88 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 *Reviewer comment: Starting dose was 9 mg and a flexible dose design was employed (3, 6, 9, or 12 mg/day) as described on page 45 of the SCS.* No. Subjects Enrolled as of 31 May 2005: 473 Ongoing

R076477-SCH-704	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-304 *Reviewer comment: Starting dose was 9 mg and a flexible dose design was employed (3, 6, 9, or 12 mg/day) as described on page 45 of the SCS.* No. Subjects Enrolled as of 31 May 2005: 203 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 *Reviewer comment: Starting dose was 9 mg and a flexible dose design was employed (3, 6, 9, or 15 mg/day) as described on page 45 of the SCS.* No. Subjects Enrolled as of 31 May 2005: 403 Ongoing
Study R076477-SCH-701	
R076477-SCH-701	A 52-week open-label extension evaluating ER OROS paliperidone for the prevention of recurrence in subjects with schizophrenia who experienced a recurrence event or remained recurrence free during the double-blind phase of Study R076477-SCH-301 No. Subjects Enrolled as of 31 May 2005: ~36[b] Ongoing

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005. [b]Number based on unaudited enrollment information.

Phase I/II trials.

The next set of tables summarize Phase I/II trials categorized as trials conducted on healthy subjects, studies on patients with schizophrenia, and "Other Phase I studies."

Continued on the next page

Summary Tables of Each Set of Phase I/II Trials.

Protocol No. (Formulation)	Study Design/Enrollment Status*
	PHASE I/Ia STUDIES IN HEALTHY ADULT SUBJECTS
R076477-P01-103 *Absorption, metabolism, elimination* (IR)	SD, OL in healthy males (CYP2D6 EMs and PMs) / oral dose, 1 mg ^{14}C PAL IR/ mass balance, metabolic pathways of paliperidone and excretion of PAL and its metabolites in urine and feces. No. Subjects Enrolled: 5 Treated with Paliperidone: 5
R076477-P01-1007 *Absolute bioavailability and enantiomer disposition* (IR and ER)	SD, OL, randomized, 5-way CO in healthy males and females (CYP2D6 EMs and PMs) / oral dose, 1 mg IR PAL, 1 mg PAL i.v., 3 mg PAL ER, 1 mg R078543 solution, 1 mg R078544 solution (fasting) / absolute BA of IR and PAL ER, enantiomer disposition and interconversion. No. Subjects Enrolled: 20 Treated with Paliperidone: 20
R076477-P01-1008 *Final bioequivalence and food effect* (ER)	SD, OL, randomized, 3-way CO in healthy males / single oral doses of 15 mg (9+3+3 mg) PAL ER, 15 mg PAL ER tablet (fed or fasting) / BE of Phase 3 formulation (9+3+3 mg) *vs.* highest strength (15 mg) of commercial formulation, food effect on highest strength commercial formulation. No. Subjects Enrolled: 80 Treated with Paliperidone: 80
R076477-P01-1010 *Dose proportionality* (ER)	SD, OL, randomized, 5-way CO in healthy males / oral dose, 3, 6, 9, 12 or 15 mg PAL ER tablet (fasting) / dose proportionality. No. Subjects Enrolled: 50 Treated with Paliperidone: 50
RIS-BEL-28 *PK in healthy subjects* (IR)	SD, DB, randomized, PC, 3-way CO in healthy males (CYP2D6 EMs and PMs) / oral dose, 1 mg IR RIS, 1 mg IR PAL, placebo / plasma and urine PK, relative BA, PD (prolactin). No. Subjects Enrolled: 9 Treated with Paliperidone: 9
R076477-BEL-1 *Relative bioavailability and food effect* (IR)	SD, OL, randomized, 3-way CO in healthy males and females / oral dose, 0.5 mg IR PAL tablet (fed or fasting), 0.5 mg IR PAL solution (fasting) / relative BA of tablet *vs.* oral solution, food effect on tablet. No. Subjects Enrolled: 12 Treated with Paliperidone: 12
ALZA C-2001-032 *Colonic absorption* (IR and Pilot ER)	SD, OL, randomized, 4-way CO in healthy males and females / oral dose, 3 mg osmotic module RIS, 2 mg RIS oral solution, 3 mg osmotic module PAL and 3 mg PAL oral solution / PK. No. Subjects Enrolled: 16 Treated with Paliperidone: 16
ALZA C-2001-039 *Dose zipping* (IR and Pilot ER)	MD, DB, randomized, PC, 4-way CO in healthy males and females / oral doses over 2 days of 5.5 mg PAL Ascend, 4.5 mg PAL Flat, 4 mg IR PAL, placebo / PK, evaluate PD (orthostatic hypotension and prolactin). No. Subjects Enrolled: 27 Treated with Paliperidone: 27
ALZA C-2002-019 *Dose zipping* (IR and Pilot ER)	MD, DB, randomized, PC, 5-way CO in healthy males and females / oral doses over 2 days of 6 mg RIS (RIS Ascend-6), 6 mg PAL (PAL Ascend-4), 4 mg PAL (PAL Ascend-2), 4 mg IR RIS (IR-2), placebo / PK, PD (orthostatic hypotension, prolactin). No. Subjects Enrolled: 30 Treated with Paliperidone: 30

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v. = intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
* Enrollment as of 31 May 2005.

Protocol No. (Formulation)	Study Design/Enrollment Status[a]
	PHASE 1/2a STUDIES IN HEALTHY ADULT SUBJECTS (continued)
ALZA C-2002-034 *Relative bioavailability and food effect* (IR and ER)	SD, OL, randomized, 4-way CO in healthy males and females / oral dose, 2x2 mg [redacted] OROS (fasting), 2x2 mg [redacted] OROS (= PAL ER, Phase 1 formulation) (fed or fasting), 2 mg IR PAL (fasting) / PK, BA of OROS formulations, food effect on PAL ER formulation, compare PD (orthostatic hypotension). No. Subjects Enrolled: 32 Treated with Paliperidone: 32
ALZA C-2003-044 *Pilot dose proportionality* (ER)	SD, OL, 4-period sequential in healthy males / oral dose, 6, 9, 12 and 15 mg PAL ER (3 and 9 mg tablets, Phase 3 formulation) / dose proportionality. No. Subjects Enrolled: 30 Treated with Paliperidone: 30
ALZA C-2004-006 *Tolerability* (ER)	SD, OL, randomized, sequential, parallel group in healthy males / oral dose, 12 mg and 15 mg PAL ER (fasting) (Group 1), or 15 mg PAL ER (fed or fasting) (Group 2), (3 and 9 mg tablets, Phase 3 formulation) / PK, dose proportionality, food effect, tolerability. No. Subjects Enrolled: 40 Treated with Paliperidone: 40
R076477-P01-101 *PK/PD* (Alternative ER formulations)	SD, OL, randomized, 5-way CO in healthy males and females / oral dose, 2 mg-eq. ER [redacted] PAL (2.5 mg [redacted] fed or fasting), 2 mg-eq. coated PAL ER (2x2 mg tablets, fed or fasting), 2 mg IR PAL (fasting) / PK of [redacted] food effect, compare PD (orthostatic hypotension). No. Subjects Enrolled: 35 Treated with Paliperidone: 35
R076477-P01-102 *PK/PD* (Alternative ER formulations)	SD, OL, randomized, 5-way CO in healthy males and females / oral dose, 2.5 mg [redacted] ER PAL [redacted] formulation 1 (fed or fasting), 2.5 mg [redacted] ER PAL [redacted] formulation 2 (fed or fasting), 2 mg IR PAL / relative BA o [redacted] formulations, food effect, compare PD (orthostatic hypotension). No. Subjects Enrolled: 35 Treated with Paliperidone: 35
R076477-SWE-1 *PET* (IR)	SD, OL, PET / oral dose, 1 mg IR PAL (fasting) in healthy males / PK, D_2+ $2HT_{2A}$receptor occupancy, relationship PK-PD. No. Subjects Enrolled: 3 Treated with Paliperidone: 3
R076477-SIV-101 *PET* (ER)	SD, OL, PET in healthy males and females / oral dose, 6 mg (3x2 mg) PAL ER / PK, D_2receptor occupancy, relationship PK-PD. No. Subjects Enrolled: 4 Treated with Paliperidone: 4
R076477-P01-1006 *Food effect in Japanese* (ER)	SD, OL, randomized, 2-way CO in healthy Japanese males and females / oral dose of 3 mg PAL ER (fed or fasting) / food effect in Japanese subjects. No. Subjects Enrolled: 20 Treated with Paliperidone: 20

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005.

Protocol No. (Formulation)	Study Design/Enrollment Status[a]
PHASE 1/2a STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R076477-INT-1 *PK in target population* (IR)	MD, OL, randomized, parallel group in subjects with chronic schizophrenia (M/F) / once daily doses of 1, 4, or 8 mg IR PAL / steady-state PK, dose proportionality. No. Subjects Enrolled: 34 Treated with Paliperidone: 34
PAL-SCH-101 *Orthostatic tolerability* (ER)	MD, DB, randomized, PC and AC, parallel group in subjects with schizophrenia (M/F) / placebo on Day 1 and 12 mg/day PAL ER on Days 2-6, 12 mg/day PAL ER on Days 1-6, 2 mg IR RIS on Day 1 and 4 mg/day IR RIS on Days 2-6 / PK, PD (orthostatic hypotension, prolactin), enantiomer disposition. No. Subjects Enrolled: 113 Treated with Paliperidone: 75
R076477-SCH-102 *Dose proportionality and exposure comparison* (ER)	MD, OL, randomized, parallel group in subjects with schizophrenia or schizoaffective disorder (M/F) / 9 mg q.d. PAL ER on Days 8-14 and 15 mg q.d. PAL ER on Days 15-21, dose escalation up to 7 mg b.i.d. IR RIS on Days 8-14 and 8 mg b.i.d. IR RIS on Days 15-21/ dose proportionality, enantiomer disposition, comparison steady-state PK of PAL after PAL treatment *vs.* RIS treatment. No. Subjects Enrolled: 62 Treated with Paliperidone: 36

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005.

Continued on the next page

OTHER PHASE 1/2a STUDIES	
Pharmacodynamic Studies	
R076477-SCH-1010 *Sleep* (ER)	DB, PC, randomized in subjects with schizophrenia-related insomnia (M/F) / 9 mg/day PAL ER, placebo / relationship between PK and PD (sleep architecture). No. Subjects Enrolled: 42 Treated with Paliperidone: 21
R076477-SCH-1009 *Cardiovascular safety* (IR)	DB, PC, AC, randomized in subjects with schizophrenia or schizoaffective disorder (M/F) / placebo on Day 1 and 4 mg q.d. Day 2, 6 mg q.d. Day 3, 8 mg q.d. IR PAL Day 4-8; placebo on Days 1-7 and 400 mg moxifloxacin on Day 8 / influence of paliperidone on ECG parameters, relationship between PK and ECG parameters. No. Subjects Enrolled: 141 Treated with Paliperidone: 72
Studies in Special Populations	
R076477-REI-1001 *Renal impairment* (ER)	SD, OL, parallel group in subjects with severe, moderate and mild renal impairment and with normal renal function (M/F) / oral dose of 3 mg PAL ER (fasting) / plasma and urine PK in renally impaired subjects *vs.* healthy subjects, PPB, enantiomer disposition. No. Subjects Enrolled: 47 Treated with Paliperidone: 47
PALIOROS-SCH-1011 *Elderly PK* (ER)	SD and MD, OL in male and female healthy elderly subjects (> 65 years) and young subjects (18-45 years) / single oral dose of 3 mg PAL ER on Day 1 and 3mg/day PAL ER on Days 6-12 (fasting) / PK in elderly subjects *vs.* young subjects, enantiomer disposition. No. Subjects Enrolled: 60 Treated with Paliperidone: 60

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005.

Continued on the next page

	OTHER PHASE 1/2a STUDIES (continued)
Studies in Special Populations (continued)	SD, OL, parallel group in male and female subjects with moderate hepatic
R076477-SCH-1008 *Hepatic impairment* (IR)	impairment and with normal hepatic functions/ oral dose, 1 mg IR PAL (fasting) SD of PK in subjects with hepatic impairment *vs.* healthy subjects, PPB, enantiomer disposition. No. Subjects Enrolled: 20 Treated with Paliperidone: 20
R076477-P01-1005 *Japanese vs.Caucasian PK* (ER)	SD and MD, DB, PC, randomized in male and female healthy Caucasian and Japanese subjects / SD of 3 mg PAL ER on Day 1, MD of 3 mg/day PAL ER on Days 5-11, and SD 6 mg PAL ER on day 19, placebo (fasting) / SD and MD PK in Japanese subjects *vs.* Caucasians, enantiomer disposition. No. Subjects Enrolled: 60 Treated with Paliperidone: 48
Drug-Drug Interaction Study	
Renal DDI (ER)	R076477-P01-1004 SD, OL, randomized, 2-way crossover in healthy males / single oral dose of 6 mg PAL ER on Day 1, 200 mg trimethoprim b.i.d. on Days 1-8 with single oral dose of 6 mg PAL ER on Day 5 (fasting) / effect of trimethoprim on plasma and urine PK of PAL ER, enantiomer disposition. No. Subjects Enrolled: 30 Treated with Paliperidone: 30

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = position emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.
[a]Enrollment as of 31 May 2005.

4.3 Review Strategy

The main focus of this review was on the Summary of Clinical Safety section of the NDA (module 2.7.4) which provides integrated safety of summary information and on the review of sections of the NDA that focus on efficacy results from the placebo controlled, double-blind Phase III trials of Pal that examined efficacy (primarily Studies -303, -304 and -305, as well as the small elderly trial, Study -302).

A special safety study focusing on potential QT interval effects of IR Pal was also reviewed (Study –SCH-1009), since this is a key safety study relevant to assessing the adequate safety of Pal.

The rationale for the review of any additional data (e.g. vital sign information from a Phase study, Study –P01-1005) is provided in the appropriate section of this review where the given study and data is described.

The 120-Day Safety Update Report (SUR) provided updated data from the integrated OL extension trial dataset (and other ongoing trials). Since this longterm OL dataset was the major source for longterm treatment data and met ICH guidelines for 6 and 12 month exposure in this

SUR submission, the focus of the review of this submission was on safety findings from this dataset and on SAEs and ADOs (primarily from the longterm integrated OL dataset). Former, Team Leader Dr. Paul Andreason and the current Team Leader, Dr. Ni Khin concurred with this review strategy.

A number of questions arose during the course of this review that resulted in additional response submissions from the sponsor that came in late in the review cycle. Most of this information has not been reviewed at the time of this writing but will be reviewed either before the PDUFA date for this submission or after receipt of an approvable response (if an approvable action is taken by the Agency on this NDA). Dr. Ni Khin concurred with this review plan regarding the sponsor's responses that were received late in the review cycle.

4.4 Data Quality and Integrity

Reviewer Comments and Conclusions
The following summarizes findings relevant to this section of the review while a more detailed description is provided afterwards:

- *DSI investigation results are pending*
- *Comparisons between CRFs and Narratives (of selected sections and of 3 arbitrarily selected subjects) revealed adequate quality given that Data Correction Forms were included in the CRFs.*

See section 7.2.8 for a discussion of potential concerns with the quality and completeness of the data.

Detailed Description of Comparisons between CRFs and Narratives
The following outlines arbitrarily selected comparisons between narratives and CRFs (comparisons on AE terms were made between the documents to see if any AE terms were deleted or were not accurately described as an AE leading to an ADO or as an SAE):

- Subject 10903 in Study –SCH-1009: had the above described omission in the CRF of whether or not the bradykinesia that lead to early withdrawal was an SAE, but this omission was ultimately found and documented as not being an SAE according to a DCF found in the CRF. This subject was also arbitrarily selected for a comparison between concomitant medications listed in the CRF with those listed in the narrative. The CRF listed Ativan as concomitant drug while mention of this drug was not found in the narrative (either as a brand or generic name). These differences or omissions did not dramatically impact on the overall interpretation of the key observation of bradykinesia, particularly since the DCF was filed with key information.
- Subject 100811 in Study –P01-1008: AEs of drowsiness and nasal congestion were listed in the CRF but could not be found in the narrative. However, these AEs are considered minor deletions with respect to the overall clinical impression of the dystonia that lead to early withdrawal in this subject.

- Subject 300376 in Study -304: The narrative had "drug abuse and "suicidal ideation reported as SAEs on Day 17 but these terms could not be found in the AE section (domain) of the CRF (which had terms of nasal congestion, insomnia and tinea corpis found). However, a DCF found in the CRF of this subject had the following information, as well as additional information that was found in the narrative but not in the AE section (located by a hyperlink to this section) of the CRF that was reviewed:

ORIGINAL

J&J PRD — **DCF 3413 - 0** — Data Correction Form

Trial:	R076477-SCH- 304	Subject:	300376	Subject Initials:	[redacted]
Main Invest:	[redacted]	Book:		Date:	08-Feb-2005
Created By:	[redacted]	Country/site:	USA-03	Sender Name:	[redacted]

Page(s)	Item	Query	Answer/Comment
111	sAE / AE	1)In regards to DCF 3187, you specified the reason for with drawal as other, SAE resulting in hospitalisation ([redacted] However, we can not find an AE with a serious code= YES with hospitalisation in the CRF. According to protocol all hospitalisations require that an SAE form is send to [redacted] Please provide the required info on the adverse event for which the patient withdrew from the study and send an SAE form for the hospitalisation to [redacted] Thank you	Relapse of [specify event] Substance abuse start date = [redacted] stop date = continued. severity = 3 Severe action taken = 4 stopped drug therapy started = ... relation to trail medication = 2 doubtful outcome = continued If applicable: n/a therapy:... start date... end date ..... regimen (or total daily dose in case of RESCUE medication)..... route... given for AE: YES indication:[specify event]..... Report follows this page.

4.5 Compliance with Good Clinical Practices

DSI investigation is underway at the time of this writing.

4.6 Financial Disclosures

This section summarizes financial disclosure information.

Reviewer's comments and conclusions: *Some investigators had financial interest or funding (in at least 2 investigators), while the majority of principal investigators did not have disclosable*

financial information. Approximately 34 sub-investigators were not contacted or did not provide information (as described below). Potential bias in the pivotal Phase III trials was minimized by the study design employed which involved a double-blind, multi-center study design and involved multiple investigators. Sites were also independently monitored. Despite difficulties with contacting sub-investigators, the sponsor generally provided information for the principal investigators, as described below.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The following is key information on pharmacokinetic (PK) properties, as provided by the sponsor:

- Tmax 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 ½ = 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. See the following figure for comparisons between these drugs on their steady-state concentration profiles (as provided by the sponsor).
- Absolute oral bioavailability is 28%
- Cmax 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.

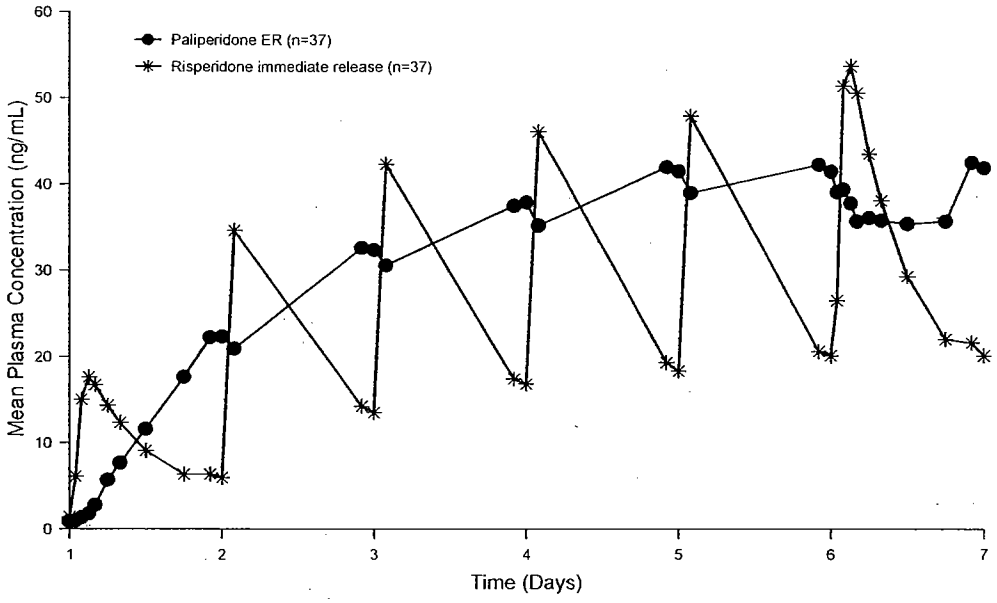


Figure 1.
Steady-state concentration profile following administration of 12 mg paliperidone administered as six 2 mg extended-release tablets once daily for 6 days (paliperidone concentrations are represented) compared with risperidone immediate-release administered as 2 mg once daily on Day 1 and 4 mg once daily on Days 2 to 6 (paliperidone+risperidone concentrations are represented).

As previously listed above, a dramatic food effect on PK was observed in subjects confined to bed for up to 36 hours. The 210-Day SUR provided new results on fed versus fasted effects on PK and examining potential postural effects in the food effect on PK (confined to the bed versus ambulatory). A food effect was demonstrated in both ambulatory and non-ambulatory conditions using the 12 mg single dose-level. The fed state involved a breakfast of 2 eggs, buttered toast (2 pieces), 2 strips of bacon, milk and hash brown fried potatoes before the single morning dose. The figure and table below were copied from the 210-SUR showing key results of this study.

Continued on the next page

Figure 2: Mean Paliperidone Plasma Concentration-Time Profiles After Single-Dose Administration of 12 mg ER OROS Paliperidone in Fed Ambulant, Fasted Ambulant and Fasted Supine Condition
(Study PALIOROS-P01-1012)

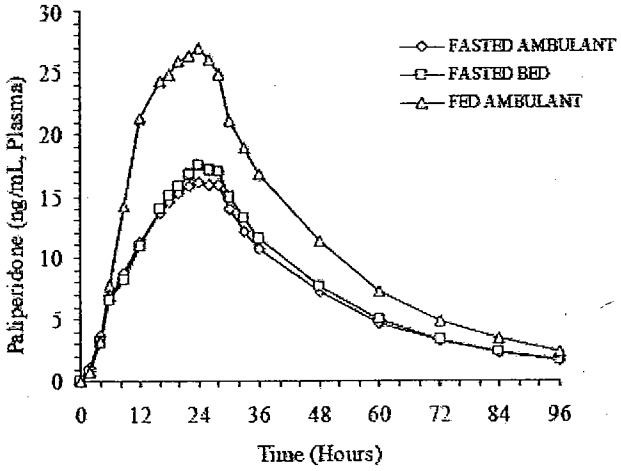


Table 2: Pharmacokinetic Parameters (Mean ± SD) After ER OROS Paliperidone, 12 mg Single Dose
(Study PALIOROS-P01-1012)

PK parameter	Fed, Ambulant[a] (Treatment A)	Fasted, Ambulant[a] (Treatment B)	Fasted, Bed[a] (Treatment C)	Ratio, % (90% CI)[b] A/B	Ratio, % (90% CI)[b] C/B
N	58	59	62	57	57
t_{max}, h	20.00 (9.00 – 28.00)	22.00 (6.00 – 28.00)	24.00 (6.00 – 28.00)	-	-
C_{max}, ng/mL	29.2 ± 15.9	17.4 ± 7.21	18.6 ± 7.59	159.56 (144.21–176.54)	106.08 (95.89–117.36)
AUC_{last}, ng/mL.h	1102 ± 558	685 ± 297	720 ± 303 *	155.51 (140.49–172.13)	103.92 (93.90–115.02)
AUC_{∞}, ng/mL.h	1179 ± 606	741 ± 330	775 ± 331 *	153.94 (139.11–170.36)	103.71 (93.73–114.75)
$t_{1/2}$, h	21.1 ± 3.1	21.9 ± 3.3	21.7 ± 3.3 *	-	-

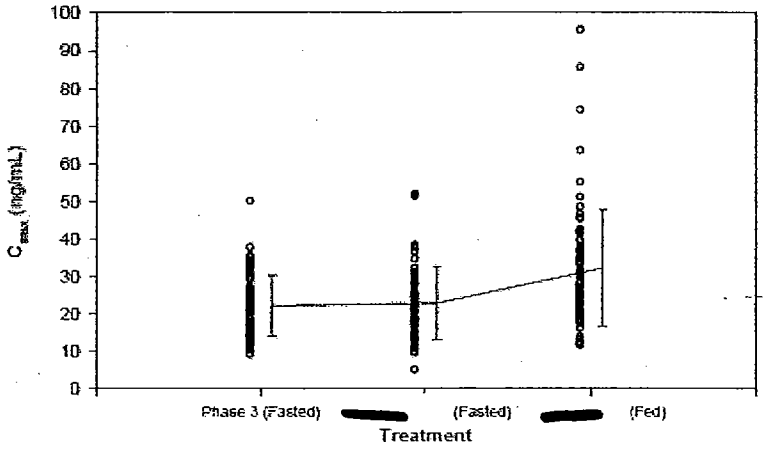
[a] data presented as arithmetic mean ± SD; t_{max} presented as median (range)
[b] ratio of geometric means with 90% confidence intervals; for statistical analysis: data were analyzed on logarithmic scale, and transformed back to original scale
* n=60

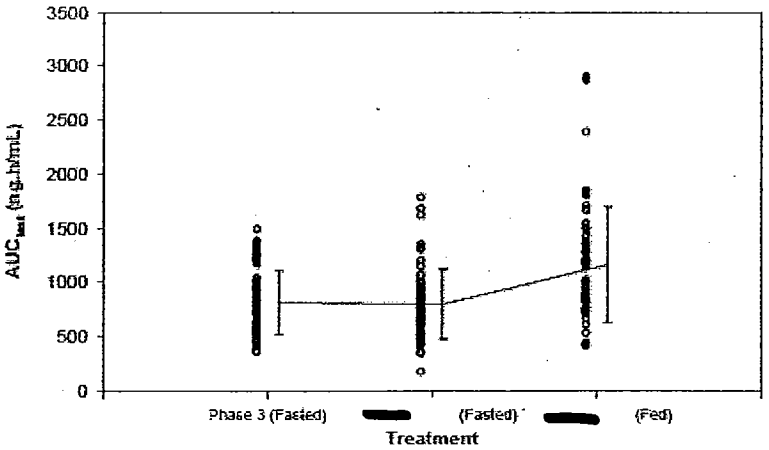
The following figures are of individual subject PK values in the first food effect study conducted which used the 15 mg single dose-level of OROS Pal (Study P01-1008). Subjects were confined to be for up to 36 hours.

Figure PK 5: Individual and Mean Bioavailability Parameters of Paliperidone by Treatment

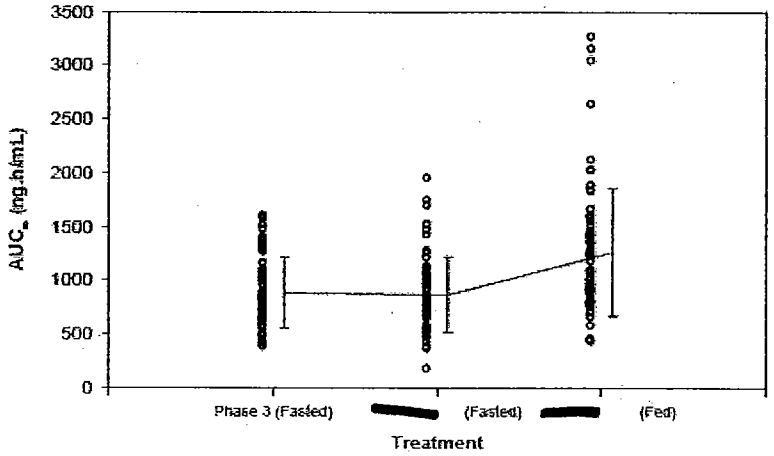
R076477-P01-1008 page 1 of 2

Treatment A: Single oral dose of 15 mg ER OROS paliperidone Phase 3 formulation in the fasted state
Treatment B: Single oral dose of 15 mg ER OROS paliperidone [redacted] in the fasted state
Treatment C: Single oral dose of 15 mg ER OROS paliperidone [redacted] after a high-fat breakfast
Open circles: individual values ; Solid line: arithmetic mean, SD as error bars





Treatment A: Single oral dose of 15 mg ER OROS paliperidone Phase 3 formulation in the fasted state
Treatment B: Single oral dose of 15 mg ER OROS paliperidone [redacted] in the fasted state
Treatment C: Single oral dose of 15 mg ER OROS paliperidone [redacted] after a high-fat breakfast
Open circles: individual values ; Solid line: arithmetic mean, SD as error bars



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✓ Trade Secret / Confidential

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Figure PK 4: Overlay Plasma Concentration-Time Profiles of Paliperidone

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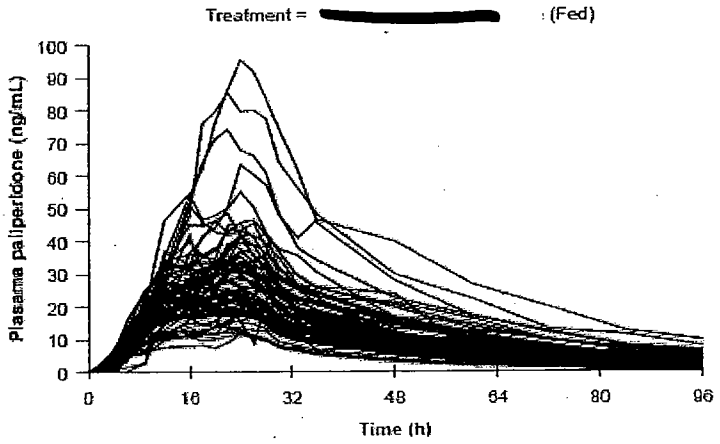
Treatment C: Single oral dose of 15 mg ER OROS paliperidone [redacted] after a high-fat breakfast
Top: linear-linear scale ; bottom: log-linear scale



A QT prolongation study will be described later, that showed QT prolongation effects of the immediate release (IR) Pal formulation (Study SCH-1099). However, for comparisons with previously results a figure is shown below of individual subject plasma profiles over treatment days. Before presenting this figure the following outlines treatment given to these subjects (copied from the CSR):

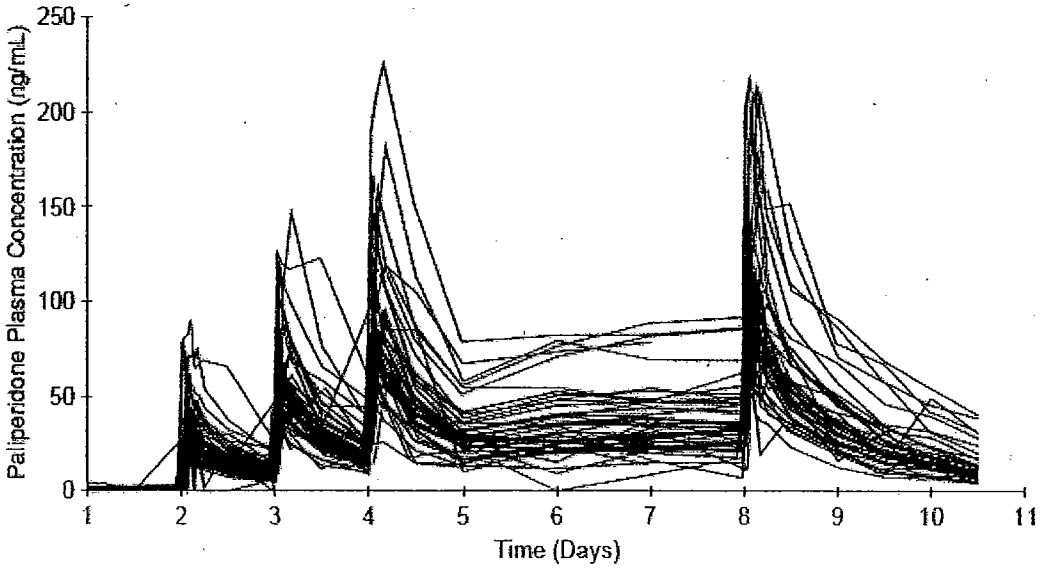
- Four placebo capsules on Day 1;
- Two paliperidone 2 mg capsules and 2 placebo capsules on Day 2;
- Three paliperidone 2 mg capsules and 1 placebo capsule on Day 3;
- Four paliperidone 2 mg capsules on Days 4 through 8.

Subjects in the moxifloxacin group received once daily doses as follows:

- Four placebo capsules on Days 1 to 7;
- One moxifloxacin capsule (over encapsulated 400 mg tablet) and 3 placebo capsules on Day 8.

Compare levels from subjects in this QT study (levels are shown in the figure below) to levels shown in previous figures of Pal (OROS formulation) since QT prolongation effects and food effects were observed (Section 7.1.12 A in this review describes QT prolongation results of Study -1009 which was conducted in patients with schizophrenia).

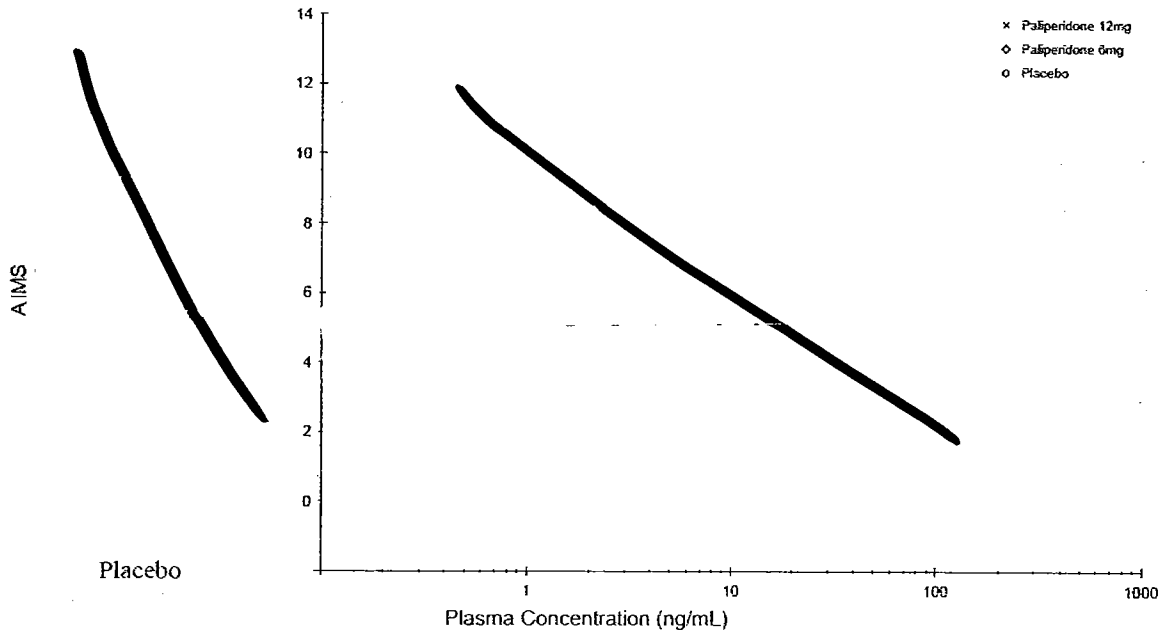
Figure 3: Overlay Plasma Concentration-Time Profiles of Paliperidone on Days 1 through 10 (Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



The following scatterplot is shown (found in the CSR of -304) in order to see the individual subject range of plasma levels observed in subjects in a pivotal 6-week Phase III trial that had the 12 mg daily dose-level. This dose-level is being shown, since the sponsor is recommending this dose as the maximum recommended daily dose in proposed labeling. Dosing was to occur in the mornings in Phase III trials without monitoring food intake and it appears from the protocol description that only the first half of non-elderly subjects, along with all elderly subjects of which there were only a few, were to have PK sampling conducted on selected days (Days 15 and 36 at 1 to 2 hours post-dose and at least 4 hours post-dose). The protocol describes population PK analyses to be conducted on the PK data from Phase III trials.

Figure PKPD 1: Scattterplots of AIMS Versus Plasma Concentration of Paliperidone and Olanzapine
R076477-SCH-304

Page 1 of 2



was preformed prior to administration.
concentrations are represented on a logarithmic scale.
ent: 6 mg ER OROS paliperidone q.d., 12 mg ER OROS paliperidone q.d. or placebo.

PK in Special Populations.

According to the sponsor studies fail to show a need for dose adjustment in patients with hepatic impairments, whereas a reduction in dose is recommended for patients with moderate and severe renal impairment. Dose adjustment is also not needed on the basis of gender or race, according to the sponsor.

Studies of the elderly show a 20% lower clearance rate of Pal at steady state compared to that observed in younger adults (18-45 year olds). However, the sponsor claims that population PK studies failed to reveal a need for dose adjustment.

Reviewer Comment on the Food Effect. *While the above and proposed labeling is subject to OCPB input (pending at this time) the above large food effects of Pal is notable. In the opinion of the undersigned reviewer a food effect is a significant issue from a clinical safety perspective given the cardiovascular effects of the drug as described later in this review. The sponsor includes the following language in labeling regarding this finding:*

[redacted] Clinical trials establishing the safety and efficacy of [redacted] were carried out in subjects without regard to the timing of meals."

The potential for a large food effect exists in the patient population that needs to be adequately characterized in the opinion of the undersigned. Furthermore, proposed labeling (as above) does not in the opinion of the undersigned reviewer, adequately address the issue of a food effect and that the patient population can be subject to this effect. OCPB input is recommended on determining an adequately maximum recommended dose-level and regarding how labeling should describe potential food effects if the NDA were ultimately deemed by the Agency as approved. See the final section of this review for further comment and recommendations.

Reviewer Comment on the Elderly Population. *The sponsor claims a dose adjustment is not needed for elderly yet in the opinion of the undersigned a lower starting dose and a more gradual increase in dose (when clinically indicated) should be recommended for the elderly than is being recommended for the non-elderly healthy patient population, similar to that found in approved labeling for Risperdol,® as described in the following (similar to that found in approved labeling). Refer to the last section of this review for further comment and recommendations.*

[redacted]

Section 7 of this review will describe some safety findings suggestive of an age-group effect among elderly on some of the cardiovascular parameters. This population is also likely to be at greater risk of adverse effects of Pal on not only QT prolongation effects and other cardiovascular effects, but also on adverse effects involving other organ systems. Finally Phase III trials had very few elderly patients and the elderly Study -302 was small, such that safety findings are only considered as preliminary results. Furthermore, subjects in this elderly trial received Pal using a flexible dose design with only 3 mg daily-dose increments permitted in

which the dose could not be increased more frequently at weekly intervals. This is contrasted to the fixed dose Phase III trials of almost all non-elderly adults that used daily doses as high as 15 mg. Therefore, a more gradual dose adjustment as well as a lower starting dose than recommended for the non-elderly population should be recommended in labeling, along with a clear description of the treatment regimen employed in this study and it's limitation in examining safety (primarily due to the small sample size as well as other limitations inherent in the elderly population).

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 proposed indication is for treatment of Schizophrenia.

6.1.1 Methods

Summary of Study Design. Three pivotal multicenter, placebo controlled, active controlled, randomized, double-blind (DB), fixed dose-response, parallel group trials were conducted to establish efficacy of oral paliperidone administration for the treatment of Schizophrenia (Studies R076477-SCH-303, R076477-SCH-304, R076477-SCH-305). The daily doses among these trials ranged from as high as 15 mg daily (in Study R076477-SCH-305) to as low as 3 mg in Study R076477-SCH-303. The 15 mg treatment group was started on 12 mg daily for the first seven days of treatment followed by 15 mg daily for the remainder of the DB phase. The active control groups in these trials received olanzapine (10 mg daily). Double-blind treatment was given for 6 weeks.

The following table summarizes the 3 pivotal efficacy Phase III trials, as well as a summary of a small study of elderly subjects the preliminarily examines efficacy.

Table 2: Phase 3 Multicenter, Double-Blind Placebo-Controlled Studies Providing the Basis of Efficacy for ER OROS Paliperidone in Subjects With Schizophrenia

Protocol No.	Region (Country)	Study Design	Daily Dose and Study Duration	Subjects Included in Analysis of Efficacy
Fixed-Dose Studies in Subjects (≥18 years of age) with Schizophrenia				
R076477-SCH-303 Key Efficacy Study	Western Europe (France, Greece, the Netherlands and Spain) Eastern Europe (Bulgaria, Croatia, Estonia, Poland, Russia, Slovakia) India	Randomized, 6-week DB, placebo- and active-controlled, parallel group, dose-response, 3 fixed dosages of ER OROS paliperidone (6, 9, and 12 mg/day) and olanzapine (10 mg/day).	Placebo ER OROS Paliperidone 6 mg/day 9 mg/day 12 mg/day Olanzapine 10 mg/day 5-day screening 6-wk DB phase	Placebo=126 Paliperidone 6 mg=123 Paliperidone 9 mg=122 Paliperidone 12 mg=129 Olanzapine=128 Total=628
R076477-SCH-304 Key Efficacy Study	United States	Randomized, 6-week DB, placebo- and active-controlled, parallel group, dose-response, 3 fixed dosages of ER OROS paliperidone (6 and 12 mg/day) and olanzapine (10 mg/day).	Placebo ER OROS Paliperidone 6 mg/day 12 mg/day Olanzapine 10 mg/day 5-day screening 6-wk DB phase	Placebo=105 Paliperidone 6 mg=111 Paliperidone 12 mg=111 Olanzapine=105 Total=432
R076477-SCH-305 Key Efficacy Study	North America (United States and Canada) Eastern Europe (Ukraine, Bulgaria, Romania, and Poland) Asia (Hong Kong, Malaysia, Republic of Korea, Singapore, and Taiwan) Israel, Mexico, and South Africa	Randomized, 6-week DB, placebo- and active-controlled, parallel group, dose-response, 3 fixed dosages of ER OROS paliperidone (3, 9, and 15 mg/day) and olanzapine (10 mg/day).	Placebo ER OROS Paliperidone 3 mg/day 9 mg/day 15 mg/day Olanzapine 10 mg/day 5-day screening 6-wk DB phase	Placebo =120 Paliperidone 3 mg=123 Paliperidone 9 mg=123 Paliperidone 15 mg=113 Olanzapine =126 Total=605
Flexible-Dose Safety and Tolerability Study in Elderly Subjects (≥65 years) with Schizophrenia				
R076477-SCH-302 Supportive Efficacy Study	Eastern Europe (Czech Republic, Russia, Slovakia, and Ukraine Other (South Africa and Greece)	Randomized, 6-week DB, placebo-controlled study of flexible doses of ER OROS paliperidone (2:1 ratio of active drug to placebo).	Placebo ER OROS Paliperidone Flexible doses (3 mg to 12 mg/day) 5-day screening 6-wk DB phase	Placebo = 38 Paliperidone 3-12 mg =76 Total =114

Investigators. The sponsor provided a listing of investigators in the N000 submission.

Subjects. A total of 1665 subjects were in the intent-to-treat (ITT) population. The ITT population is defined as a randomized subject who received at least one dose of study drug and had at least one post-randomization efficacy assessment. The following provides an enumeration of ITT subjects by DB study drug assignment (among the 3 pivotal Phase III trials, combined):

- 351 subjects received placebo
- 955 subjects received paliperidone (extended release OROS® formulation)
- 359 subjects received active control drug (10 mg daily of olanzapine)

The following are some of the key eligibility criteria:

- Subjects were 18 years and older adults, generally healthy men and women with Schizophrenia for at least one year using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).
- Subjects were required to have a Positive and negative Symptom Scale total score of 70 to 120 at baseline and were inpatients for at least 14 days during the study.

The following are some key exclusionary criteria:

- Subjects with a history of severe gastrointestinal narrowing were excluded.
- Subjects with a history of failing to respond to risperidone for acute psychosis on at least 2 occasions were excluded (must be documented that failure to respond occurred with adequate doses and durations of treatment or due to failure to tolerate an effective dose).
- Subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values of over twice the upper limit of normal (ULN).

Refer to Sections 4.1 for more details on the enumeration of subjects.

An additional 6-week Phase III trial (R076477-SCH-302) was conducted on elderly patients using a flexible dose design (3-12 mg daily of paliperidone. Other aspects of the study design of this trial were generally similar to that employed in three above described pivotal trials of non-elderly adults. The ITT population consisted of 114 total subjects of which 76 subjects received paliperidone and 38 subjects received placebo. Section 4.1 provides more details enumerating subjects in each treatment group.

Section 6.1.3 describes the actual study design of the above trials in more detail.

Section 6.1.2 describes additional key aspects of the study design of the 6-week DB Phase III trials.

6.1.2 General Discussion of Endpoints

The primary efficacy measure was the mean change from baseline to treatment endpoint on the Positive and negative Symptom Scale (PANSS) total score. This dependent variable is generally considered as a standard measure for Phase III trials for establishing efficacy in treating schizophrenia. Additional comments on the efficacy endpoints are discussed under subsequent sections (or were previously discussed), as well as in the final section of this review which also provides recommendations relevant to efficacy.

6.1.3 Study Design

Section 6.1.1 provides the overall study design and shows a table specifying dose-levels employed. Additional key aspects of the study design of Phase III trials are described below. This section is also intended to include reviewer comments on the study design (in accordance with the Clinical Reviewer MAPP). Sections below that contain reviewer comments are italicized.

Pivotal Phase III Non-Elderly Schizophrenia Trials (Studies -303, -304, and -305)
Screening of subjects occurred within a maximum of 5 days from baseline upon which subjects were randomized to study drug. Daily dose-levels of paliperidone among the 3 pivotal trials were 3, 6, 9, 12 and 15 mg. See previous sections for which studies examined which dose-levels and for the number of subjects in the various treatment groups.

The dose-levels chosen for the pivotal trials were selected on the basis of the following key points, according to the sponsor:

- Risperidone is reported to be equipotent to paliperidone (the basis for this conclusion is not clear to the undersigned reviewer) and the recommended daily dose of risperidone for treatment of schizophrenia is between 2 and 6 mg in approved labeling.
- The mean bioavailability of paliperidone is approximately 33% of that of risperidone, such that a daily dose of 6 to 18 mg of paliperidone was anticipated to be effective, given the 2 to 6 mg daily dose range for risperidone (as above).
- D_2 receptor occupancy of 70 to 80% is hypothesized as being associated with efficacy and was reportedly achieved by doses between 4.5 and 9 mg in a PET scan study conducted as part of the sponsor's development program.

Key eligibility criteria were previously described under Section 6.1.1. One key criterion that is provided in more detail here is that to be eligible for randomization to DB treatment patients had to score within 70-120 on the PANSS total rating at both screening and baseline visits and could not show 25% or greater improvement on the PANSS total score between these 2 visits. Patients who did not meet these criteria were excluded from the study.

Elderly Phase III Trial (Study -302)
This study was almost identical in study design to the previously described pivotal trials except for the follow major differences:

- The age of subjects was restricted to ≥ 65 years old
- Subjects were randomized to either Pal or placebo groups (2:1) for the 6-week DB phase
- A flexible dose regimen was employed at a daily dose-level of 3 to 12 mg of Pal.
- The Pal group started at a daily dose level of 6 mg which could down adjusted to the 3 mg daily dose-level over the first week of DB treatment. However, the daily dose level could not be increased until after the first week of treatment. After the first week of treatment dose increases could be made no more frequently that every 7 days at daily-

dose-level increments of no greater than 3 mg. The dose could be decreased at anytime to a daily dose of no lower than 3 mg. Dose adjustments were made at the clinical discretion of investigators to optimize efficacy, while minimizing adverse effects.

Concomitant medications.
Psychotropic medications were discontinued at screening over a maximum of a 5 day period prior to baseline (prior to randomization to double-blind treatment) and were also prohibited during the DB treatment phase except for the following:

- Patients on a stable dose of benzodiazepines or an antidepressant were continued on their usual regimen during the study at a fixed dose (no dose adjustments were allowed).
- Rescue treatment with benzodiazepines was permitted for agitation, anxiety or sleep difficulties within pre-specified treatment restrictions and
- Rescue benztropine treatment for extrapyramidal symptoms (EPSE) were permitted within pre-specified dosing restrictions.

Section 6.1.4 provides the incidence of the more common concomitant medications used during the study.

Reviewer Comments on the Study Design.
The 6-week duration of the double-blind treatment phase and other aspects of methodology are generally a standard approach for establishing efficacy of a study drug in the treatment of patients with acute schizophrenia. Generally, Phase III trials of this nature only employ a minimum cut-off score on the PANSS total or on a comparable measure. As a result of using this upper limit in the sponsor's Phase III trials, the studies excluded more severely symptomatic patients. Section 6.1.4 shows baseline results that show an adequate proportion of subjects who scored in the severe category on the CGI-S, while few subjects had the highest score on the CGI-S.

Efficacy Assessment Schedule
Efficacy assessments were conducted at screening, baseline, and generally on a weekly basis during the DB phase of each of the 3 pivotal Phase III non-elderly trials and the Phase III elderly trial.

The primary efficacy variable was previously described and further discussion of statistical methods for this variable and secondary variables are provided in the next subsection.

Secondary variables are listed below.

- Mean change from baseline to treatment endpoint in PANSS subscales and on additional scales as follows:

- PANSS subscale for positive symptomatology which includes severity ratings of symptoms that commonly appear in the acute phase such as hallucinations, bizarre behaviors, among others.
- PANSS subscale for negative symptomatology which are severity ratings of symptoms that commonly continue during non-acute (chronic) phases of schizophrenia such as social withdrawal, motor retardation and others.
- Additional PANSS subscales (see Section 6.1.2 for complete listing in a summary table on efficacy results).
- Personal and Social Performance Scale (PSP): a clinician rating scale that has been previously used in psychiatric patients in rehabilitation facilities. Subjects are rated on difficulties in self-care, with work and study, personal and social relationships and aggressive behaviors over a 1-month period. The total score can range from 0 (absent) to a maximum score of 100 (very severe).

- Median change in Clinical Global Impression-Severity Scale (CGI-S) which is a standard scale employed in Phase III trials for examining efficacy in treating a given psychiatric disorder. The clinician rates the overall severity of the patient's psychiatric condition at a given time-point in the study. This scale is intended to provide an overall clinical rating of the severity of the patient's clinical presentation of their psychiatric disorder.
- Visual Analogue Scales (VAS) were employed for self-ratings of quality of sleep and daytime drowsiness, each, over the past 7 nights.
- Additional secondary variables were included.

Table 3: Visit Schedule for Efficacy Assessments Performed in the Four Phase 3 Clinical Studies Providing the Basis of Efficacy for ER OROS Paliperidone in Subjects With Schizophrenia

				Double-Blind Treatment Phase						
	Week	-1			1	2	3	4	5	6
Procedures	Day			4	8	15	22	29	36	43
Investigator-Rated Efficacy Assessment										
Positive and Negative Syndrome Scale (PANSS)		X	X	X	X	X	X	X	X	X
Personal and Social Performance Scale (PSP)			X							X
Clinical Global Impression Scale – Severity (CGI-S)			X	X	X	X	X	X	X	X
Subject Self-Rated Efficacy Assesament										
Symptoms and Quality of Life in Schizophrenia Scale (SQLS)			X		X	X		X		X
Sleep Visual Analog Scale (VAS)			X		X	X		X		X

Refer to Table series 10.2 in the appendix of this review for the study schedules for the 3 pivotal, primarily non-elderly trials and for the elderly trial (Studies 303, 304 and 305 and Study 302, respectively).

Reviewer Comment. *A description of key secondary variables cannot be found in efficacy sections of pivotal Phase III trials in Module 2.7.3 (Summary of Clinical Efficacy) or in efficacy sections of the Clinical Study Reports. Documentation of declaring key secondary variables (a priori) cannot be found by the undersigned reviewer or by the Biometrics Reviewer at the time of this writing. Yet the sponsor's proposed labeling includes a description of most secondary*

variables in pivotal trials. Refer to Section 9 for further comment and recommendations on this issue.

Primary and Secondary Efficacy Analyses
The primary efficacy variable was mean change from baseline to treatment endpoint on the Positive and negative Symptom Scale (PANSS) total score.

The primary analysis was conducted on the last-observation-carried-forward (LOCF) dataset of the ITT population (as previously defined). Each paliperidone group was compared to the placebo group on the primary efficacy variable. The statistical test for the primary analyses was an ANCOVA model. Treatment and analysis center were the independent variables in this model and the baseline PANSS total score was a covariate. Dunnett's procedure was used to adjust for multiple comparisons between the placebo group and each paliperidone group. The observed cases (OC) dataset was used for additional secondary analyses for examining effects on the primary efficacy variable at each time-point of the treatment phase.

Each paliperidone group that was found to show "superiority" over placebo on the above primary analyses was also compared on secondary efficacy variables using ANCOVA (on mean change from baseline to treatment endpoint) except for the CGI-S (in which an ANCOVA on the ranks of change was employed). Adjustment for multiple comparisons was conducted by using an unconditional re-sampling algorithm. Treatment group comparisons on the PSP were conducted using this algorithm for adjusting for multiple comparisons. Additionally group comparisons on the PSP were conducted using the Dunnett's procedure.

No adjustments for multiple comparisons were employed for group comparisons on the VAS sleep scores.

6.1.4 Baseline Characteristics of the Study Population (Demographics, Concomitant Medication Use, Medical and Psychiatric Conditions)

Disposition of the Subjects. Refer to Table 4.2.1 in Sections 4.2 above, for enumeration of subjects in various study populations (enrolled, randomized, ITT Safety, completers and others). The disposition of subjects in the 3 pooled pivotal trials is shown in the table below (as copied from the submission).

Continued on the next page

Table 8: Study Completion/Withdrawal Information
(Study R076477-SCH-303: All Randomized Subjects)

	Placebo (N=127) n (%)	ER OROS PAL 6 mg (N=123) n (%)	ER OROS PAL 9 mg (N=122) n (%)	ER OROS PAL 12 mg (N=130) n (%)	Olanzapine 10 mg (N=128) n (%)	Total (N=630) n (%)
Completed	58 (46)	80 (65)	86 (70)	101 (78)	90 (70)	415 (66)
Withdrawn	69 (54)	43 (35)	36 (30)	29 (22)	38 (30)	215 (34)
Lack of efficacy	51 (40)	20 (16)	19 (16)	13 (10)	19 (15)	122 (19)
Subject choice (subject withdrew consent)	7 (6)	9 (7)	11 (9)	8 (6)	5 (4)	40 (6)
Adverse event	9 (7)	8 (7)	4 (3)	8 (6)	9 (7)	38 (6)
Lost to follow-up	2 (2)	1 (1)	2 (2)	0	2 (2)	7 (1)
Death	0	0	0	0	1 (1)	1 (<1)
Study medication non-compliance	0	0	0	0	1 (1)	1 (<1)
Other	0	5 (4)	0	0	1 (1)	6 (1)

Cross-reference: Mod5.3.5.1\R076477-SCH-303\Table 6.

Table 9: Study Completion/Withdrawal Information
(Study R076477-SCH-304: All Randomized Subjects)

	Placebo (N=110) n (%)	ER OROS PAL 6 mg (N=112) n (%)	ER OROS PAL 12 mg (N=112) n (%)	Olanzapine 10 mg (N=110) n (%)	Total (N=444) n (%)
Completed	37 (34)	51 (46)	54 (48)	50 (45)	192 (43)
Withdrawn	73 (66)	61 (54)	58 (52)	60 (55)	252 (57)
Lack of efficacy	39 (35)	26 (23)	16 (14)	24 (22)	105 (24)
Subject choice (subject withdrew consent)	17 (15)	19 (17)	21 (19)	17 (15)	74 (17)
Lost to follow-up	4 (4)	8 (7)	10 (9)	6 (5)	28 (6)
Adverse event	5 (5)	8 (7)	6 (5)	8 (7)	27 (6)
Study medication non-compliance	3 (3)	0	3 (3)	2 (2)	8 (2)
Other	5 (5)	0	2 (2)	3 (3)	10 (2)

Cross-reference: Mod5.3.5.1\R076477-SCH-304\Table 6.

Table 10: Study Completion/Withdrawal Information
(Study R076477-SCH-305: All Randomized Subjects)

	Placebo (N=123) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 9 mg (N=125) n (%)	ER OROS PAL 15 mg (N=115) n (%)	Olanzapine 10 mg (N=128) n (%)	Total (N=618) n (%)
Completed	47 (38)	70 (55)	78 (62)	82 (71)	88 (69)	365 (59)
Withdrawn	76 (62)	57 (45)	47 (38)	33 (29)	40 (31)	253 (41)
Lack of efficacy	54 (44)	31 (24)	23 (18)	14 (12)	16 (13)	138 (22)
Subject choice (subject withdrew consent)	13 (11)	17 (13)	18 (14)	8 (7)	11 (9)	67 (11)
Adverse event	5 (4)	3 (2)	6 (5)	4 (3)	5 (4)	23 (4)
Lost to follow-up	0	1 (1)	0	2 (2)	3 (2)	6 (1)
Study medication non-compliance	0	1 (1)	0	2 (2)	1 (1)	4 (1)
Other	4 (3)	4 (3)	0	3 (3)	4 (3)	15 (2)

Cross-reference: Mod5.3.5.1\R076477-SCH-305\Table 6.

The disposition of subjects in the elderly Phase III trial are shown below (copied from the submission).

Table 5: Study Completion/ Withdrawal Information
(Study R076477-SCH-302 Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)	Total (N=114) n (%)
Completed	26 (68)	64 (84)	90 (79)
Withdrawn	12 (32)	12 (16)	24 (21)
Lack of efficacy	6 (16)	3 (4)	9 (8)
Adverse event	3 (8)	5 (7)	8 (7)
Subject choice (subject withdrew consent)	1 (3)	2 (3)	3 (3)
Death	1 (3)	0	1 (1)
Study medication non-compliance	0	1 (1)	1 (1)
Other[a]	1 (3)	1 (1)	2 (2)

[a] These included discontinuation on Day 36 due to personal circumstances for the subject in the paliperidone group and discontinuation on Day 32 due to lack of study medication at the site for the subject in the placebo group.
Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec4.1

Demographic Features

Treatment groups among the 3 pivotal trials were generally similar on demographic features (distribution of subjects on the basis of gender or ethnicity and on mean or median age, as well as age range). However, some differences were observed across individual studies, as noted by the sponsor. For example Study -303 (conducted in the US) had a numerically greater distribution of subjects in the overweight or obese categories than in the within-the-normal category compared to the distribution of subjects among these categories in the other 2 trials. Study -303 also had approximately an equal distribution of male and female subjects (52% males), while the other two trials had approximately 70% males. Some differences across ethnic groups were also observed.

Reviewer Comments on Demographic Differences Across Studies. *The differences in demographic features across studies are likely to be reflecting direct or indirect geographical differences in where the studies were conducted, among other factors. Since the observed differences varied from one study to another rather than following a consistent pattern, while efficacy was demonstrated in all 3 trials, as discussed later, it is not likely that demographic differences could account for consistent results on efficacy.*

The study population of each pivotal trial had a mean age of approximately 36 to 39 years old and the majority of subjects were "White" (44 to 69%) and male (59 to 67%). Few subjects in the pivotal trials were elderly (ages ranged from 18 to 76 years old).

The tables below summarize demographic features in pooled studies.

Table 11: Demographic and Baseline Characteristics: Pooled Data
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL					Olanzapine
	Placebo (N=351)	3 mg (N=123)	6 mg (N=234)	9 mg (N=245)	12 mg (N=240)	15 mg (N=113)	10 mg (N=359)
Age (years)							
N	351	123	234	245	240	113	359
Category, n (%)							
18-25	45 (13)	24 (20)	27 (12)	41 (17)	35 (15)	17 (15)	54 (15)
26-50	253 (72)	84 (68)	173 (74)	174 (71)	173 (72)	84 (74)	256 (71)
>50	53 (15)	15 (12)	34 (15)	30 (12)	32 (13)	12 (11)	49 (14)
Mean (SD)	39.0 (11.04)	36.3 (10.98)	39.4 (10.51)	37.4 (11.18)	38.5 (10.99)	37.6 (9.84)	37.6 (10.94)
Median	39.0	35.0	40.0	36.0	39.5	38.0	37.0
Range	(18;71)	(19;64)	(19;73)	(18;67)	(19;66)	(18;62)	(18;76)
Sex, n (%)							
N	351	123	234	245	240	113	359
Male	231 (66)	78 (63)	137 (59)	151 (62)	146 (61)	73 (65)	240 (67)
Female	120 (34)	45 (37)	97 (41)	94 (38)	94 (39)	40 (35)	119 (33)
Race, n (%)							
N	351	123	234	245	240	113	359
White	217 (62)	61 (50)	152 (65)	170 (69)	156 (65)	50 (44)	215 (60)
Black	79 (23)	25 (20)	64 (27)	22 (9)	65 (27)	27 (24)	85 (24)
Asian	28 (8)	30 (24)	0	28 (11)	0	29 (26)	35 (10)
Other	27 (8)	7 (6)	18 (8)	25 (10)	19 (8)	7 (6)	24 (7)
Region, n (%)							
N	351	123	234	245	240	113	359
North America	147 (42)	40 (33)	111 (47)	45 (18)	111 (46)	37 (33)	150 (42)
Western Europe	33 (9)	21 (17)	15 (6)	34 (14)	17 (7)	17 (15)	36 (10)
Eastern Europe	126 (36)	33 (27)	91 (39)	122 (50)	94 (39)	31 (27)	128 (36)
Asia	45 (13)	29 (24)	17 (7)	44 (18)	18 (8)	28 (25)	45 (13)
Body mass index (kg/m2)							
N	350	123	234	245	240	113	356
Category, n (%)							
Normal <25	168 (48)	68 (55)	90 (38)	137 (56)	104 (43)	61 (54)	178 (50)
Overweight25-<30	93 (27)	30 (24)	75 (32)	77 (31)	81 (34)	25 (22)	95 (27)
Obese >=30	89 (25)	25 (20)	69 (29)	31 (13)	55 (23)	27 (24)	83 (23)
Mean (SD)	26.8 (6.20)	25.7 (5.74)	27.2 (6.34)	25.0 (5.10)	26.8 (6.24)	26.7 (7.71)	26.7 (7.04)
Median	25.7	24.2	26.6	24.4	25.9	24.5	24.9
Range	(16;53)	(15;45)	(15;65)	(16;56)	(13;50)	(17;57)	(15;61)

Continued on the next page

The following table summarizes baseline and past psychiatric history as found in the submission.

Table 12: Diagnosis and Psychiatric History at Baseline: Pooled Data
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL					Olanzapine
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	10 mg
	(N=351)	(N=123)	(N=234)	(N=245)	(N=240)	(N=113)	(N=359)
Schizophrenia type, n (%)							
N	351	123	234	245	240	113	359
Paranoid (295.30)	281 (80)	90 (73)	204 (87)	195 (80)	199 (83)	85 (75)	299 (83)
Disorganized (295.10)	14 (4)	7 (6)	3 (1)	13 (5)	9 (4)	6 (5)	8 (2)
Catatonic (295.20)	0	1 (1)	1 (<1)	1 (<1)	1 (<1)	1 (1)	1 (<1)
Undifferentiated (295.90)	49 (14)	24 (20)	20 (9)	31 (13)	26 (11)	18 (16)	47 (13)
Residual (295.60)	7 (2)	1 (1)	6 (3)	5 (2)	5 (2)	3 (3)	4 (1)
Age diagnosis of schizophrenia (yrs)							
N	350	121	232	241	240	111	356
Mean (SD)	26.3 (9.57)	25.7 (8.23)	25.8 (8.49)	26.6 (8.49)	25.5 (8.98)	25.2 (7.77)	25.3 (8.74)
Median	24.0	24.0	24.0	24.0	23.0	25.0	23.0
Range	(3;60)	(2;52)	(5;53)	(8;57)	(9;62)	(1;53)	(8;67)
Baseline total PANSS							
N	351	123	234	245	240	113	359
Mean (SD)	93.9 (11.68)	91.6 (12.19)	93.4 (11.20)	93.6 (12.55)	94.4 (11.16)	92.3 (12.33)	93.7 (11.75)
Median	93.0	92.0	92.0	93.0	94.0	91.0	93.0
Range	(70;120)	(71;123)	(70;123)	(67;136)	(70;121)	(65;120)	(67;147)
Baseline CGI-S, n (%)							
N	351	123	234	245	240	113	359
Very mild	1 (<1)	0	0	0	1 (<1)	1 (1)	0
Mild	7 (2)	3 (2)	5 (2)	7 (3)	3 (1)	2 (2)	9 (3)
Moderate	138 (39)	54 (44)	88 (38)	102 (42)	82 (34)	46 (41)	122 (34)
Marked	171 (49)	50 (41)	109 (47)	108 (44)	123 (51)	51 (45)	185 (52)
Severe	34 (10)	16 (13)	32 (14)	26 (11)	31 (13)	13 (12)	41 (11)
Extremely severe	0	0	0	2 (1)	0	0	2 (1)
Prior antipsychotic use, n (%)							
N	351	123	234	245	240	113	359
Atypical antipsychotics	232 (66)	79 (64)	170 (73)	146 (60)	168 (70)	63 (56)	234 (65)
Typical antipsychotics	173 (49)	68 (55)	81 (35)	138 (56)	87 (36)	62 (55)	168 (47)
Prior hospitalization[a], n (%)							
N	351	123	233	245	240	113	358
None	41 (12)	18 (15)	26 (11)	37 (15)	24 (10)	11 (10)	38 (11)
Once	89 (25)	35 (28)	52 (22)	34 (14)	60 (25)	23 (20)	83 (23)
Twice	56 (16)	19 (15)	40 (17)	44 (18)	41 (17)	28 (25)	70 (20)
Three times	47 (13)	20 (16)	35 (15)	39 (16)	41 (17)	15 (13)	46 (13)
Four times or more	118 (34)	31 (25)	80 (34)	91 (37)	74 (31)	36 (32)	121 (34)

[a] Prior hospitalization for psychosis, excluding the current hospitalization.

Table 16: Diagnosis, Psychiatric History, and Symptom Severity at Baseline
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Schizophrenia type, n (%)								
N	355	127	235	246	242	113	963	364
Paranoid (295.30)	285 (80)	93 (73)	205 (87)	195 (79)	201 (83)	85 (75)	779 (81)	304 (84)
Disorganized (295.10)	14 (4)	7 (6)	3 (1)	14 (6)	9 (4)	6 (5)	39 (4)	8 (2)
Catatonic (295.20)	0	1 (1)	1 (<1)	1 (<1)	1 (<1)	1 (1)	5 (1)	1 (<1)
Undifferentiated (295.90)	49 (14)	25 (20)	20 (9)	31 (13)	26 (11)	18 (16)	120 (12)	47 (13)
Residual (295.60)	7 (2)	1 (1)	6 (3)	5 (2)	5 (2)	3 (3)	20 (2)	4 (1)
Age at diagnosis of schizophrenia (yrs)								
N	354	125	233	242	242	111	953	361
Mean (SD)	26.3 (9.57)	25.8 (8.19)	25.8 (8.49)	26.5 (8.56)	25.5 (8.96)	25.2 (7.77)	25.8 (8.51)	25.2 (8.76)
Median	24.0	24.0	24.0	24.0	23.0	25.0	24.0	23.0
Range	(3;60)	(2;52)	(5;53)	(8;57)	(9;62)	(1;53)	(1;62)	(8;67)
Baseline total PANSS								
N	355	127	235	246	242	113	963	364
Mean (SD)	93.8 (11.67)	91.3 (12.14)	93.3 (11.21)	93.7 (12.61)	94.3 (11.18)	92.3 (12.33)	93.3 (11.84)	93.7 (11.73)
Median	93.0	92.0	92.0	93.0	94.0	91.0	93.0	93.0
Range	(70;120)	(71;123)	(70;123)	(67;136)	(70;121)	(65;120)	(65;136)	(67;147)
Baseline CGI-S, n (%)								
N	355	127	235	246	242	113	963	364
Very mild	1 (<1)	0	0	0	1 (<1)	1 (1)	2 (<1)	0
Mild	7 (2)	3 (2)	5 (2)	7 (3)	3 (1)	2 (2)	20 (2)	9 (2)
Moderate	141 (40)	56 (44)	88 (37)	102 (41)	82 (34)	46 (41)	374 (39)	123 (34)
Marked	172 (48)	51 (40)	110 (47)	108 (44)	125 (52)	51 (45)	445 (46)	189 (52)
Severe	34 (10)	17 (13)	32 (14)	27 (11)	31 (13)	13 (12)	120 (12)	41 (11)
Extremely severe	0	0	0	2 (1)	0	0	2 (<1)	2 (1)
Prior antipsychotic use, n (%)								
Atypical antipsychotics	235 (66)	81 (64)	171 (73)	147 (60)	170 (70)	63 (56)	632 (66)	238 (65)
Typical antipsychotics	175 (49)	69 (54)	81 (34)	138 (56)	87 (36)	62 (55)	437 (45)	169 (46)
Prior hospitalization,[a] n (%)								
N	355	127	235	246	242	113	963	364
None	41 (12)	18 (14)	26 (11)	37 (15)	24 (10)	11 (10)	116 (12)	38 (10)
Once	89 (25)	35 (28)	53 (23)	34 (14)	61 (25)	23 (20)	206 (21)	83 (23)
Twice	57 (16)	20 (16)	40 (17)	44 (18)	41 (17)	28 (25)	173 (18)	70 (19)
Three times	48 (14)	22 (17)	35 (15)	40 (16)	42 (17)	15 (13)	154 (16)	48 (13)
Four times or more	120 (34)	32 (25)	81 (34)	91 (37)	74 (31)	36 (32)	314 (33)	125 (34)

[a] Prior hospitalization for psychosis, excluding the current hospitalization.

Reviewer Comment about Severity and Acuity of Schizophrenia in the Study Population.
The sponsor was inquired about the cut-off criteria on the range of allowed PANSS total scores in the eligibility criteria. A N0001 submission responded to an inquiry about the rationale for selected the range of 70-120 that appears to be acceptable in that the population studied appears to consistent of an adequate proportion of acutely ill patients, as described below. Furthermore, statistical methods also included baseline PANSS score as a covariate in the ANCOVA model.

The following explanation for the selection of an upper limit of 120 units on the PANSS was found in the N0001 response submission (dated 1/11/06):

"The upper limit of 120 was chosen to balance the severity of symptoms with the likelihood of the patient being able to provide informed consent."

The following are comments found in section 4.3.1.2 of module 2.5 regarding the acuity and severity of Schizophrenic patients in the 3 primarily non-elderly clinical trials (-303, -304 and -305)

" Both the mean PANSS total scores and the subjects' psychiatric history indicated that the study populations were quite ill. All subjects were currently experiencing an acutepsychotic episode, established by clinical assessment and corroborated by PANSS total scores of 70 to 120, inclusive, after washout of existing antipsychotic medication.
Baseline mean PANSS total scores ranged from 91.6 to 94.4 across the pooled treatment groups, and approximately 60% of subjects (n=994, 60%) were at least markedly ill at randomization as rated by the investigator using the CGI-S. (Mod 2.7.3\Sec 3.1.2) The most common diagnosis among the pooled intent-to-treat analysis set was paranoid schizophrenia (n=1353, 81%), which is consistent with epidemiological data on the relative prevalence of schizophrenia subtypes."

The population included a range of severity in symptomatology with a sufficient proportion of subjects with the "markedly ill" range. Furthermore, the primary analysis included the baseline PANSS score as a covariate in the ANCOVA model. But few subjects were rated as "extremely severe" on the CGI-S. [redacted] *). See the final section of this review for further comment and recommendations.*

Continued on the next page

The following tables summarize demographic and psychiatric baseline information on subjects of the elderly trial, Study -302 (copied from the CSR).

Table 7: Demographic and Baseline Characteristics
(Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)	Total (N=114)
Age (years)			
N	38	76	114
Category, n (%)			
64-69	23 (61)	43 (57)	66 (58)
70-75	13 (34)	19 (25)	32 (28)
>75	2 (5)	14 (18)	16 (14)
Mean (SD)	69.1 (3.34)	70.1 (4.95)	69.7 (4.49)
Median	68.0	68.0	68.0
Range	(65;76)	(64;81)	(64;81)
Sex, n (%)			
N	38	76	114
Male	11 (29)	20 (26)	31 (27)
Female	27 (71)	56 (74)	83 (73)
Race, n (%)			
N	38	76	114
White	38 (100)	75 (99)	113 (99)
Other	0	1 (1)	1 (1)
Ethnicity, n (%)			
N	38	76	114
Neither Hispanic/Latino nor Native Amer.	38 (100)	76 (100)	114 (100)
Weight (kg)			
N	38	76	114
Mean (SD)	66.8 (10.22)	65.6 (12.94)	66.0 (12.07)
Median	68.0	64.8	66.1
Range	(44;89)	(45;101)	(44;101)
Height (cm)			
N	38	76	114
Mean (SD)	162.1 (7.38)	161.6 (9.05)	161.7 (8.50)
Median	162.3	162.0	162.0
Range	(137;175)	(145;180)	(137;180)
Body mass index (kg/m^2)			
N	38	76	114
Category, n (%)			
Normal <25	19 (50)	45 (59)	64 (56)
Overweight 25-<30	13 (34)	19 (25)	32 (28)
Obese >=30	6 (16)	12 (16)	18 (16)
Mean (SD)	25.6 (4.87)	25.2 (5.15)	25.3 (5.04)
Median	25.0	24.2	24.4
Range	(17;41)	(17;43)	(17;43)

Table 8: Diagnosis and Psychiatric History at Baseline
(Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)	Total (N=114)
Schizophrenia type, n (%)			
N	38	76	114
Paranoid (295.30)	33 (87)	64 (84)	97 (85)
Disorganized (295.10)	1 (3)	1 (1)	2 (2)
Catatonic (295.20)	0	1 (1)	1 (1)
Undifferentiated (295.90)	2 (5)	3 (4)	5 (4)
Residual (295.60)	2 (5)	7 (9)	9 (8)
Age at diagnosis of schizophrenia (yrs)			
N	36	71	107
Mean (SD)	38.8 (11.71)	37.3 (13.71)	37.8 (13.04)
Median	37.5	34.0	36.0
Range	(21;66)	(13;71)	(13;71)
Baseline PANSS total score			
N	38	76	114
Mean (SD)	94.3 (9.00)	91.8 (9.69)	92.6 (9.50)
Median	93.0	92.5	93.0
Range	(79;117)	(75;119)	(75;119)
Baseline CGI-S, n (%)			
N	38	76	114
Mild	0	1 (1)	1 (1)
Moderate	16 (42)	31 (41)	47 (41)
Marked	18 (47)	40 (53)	58 (51)
Severe	4 (11)	4 (5)	8 (7)
Prior psychotropic use, n (%)			
N	38	76	114
Yes	37 (97)	71 (93)	108 (95)
No	1 (3)	5 (7)	6 (5)
Prior hospitalization*, n (%)			
N	38	76	114
None	2 (5)	3 (4)	5 (4)
Once	5 (13)	3 (4)	8 (7)
Twice	4 (11)	11 (14)	15 (13)
Three times	7 (18)	8 (11)	15 (13)
Four times or more	20 (53)	51 (67)	71 (62)

* Prior hospitalization for psychosis, excluding the current hospitalization.

Study Drug Exposure. This topic is discussed in Section 7 on safety.

Conconmitant Medication Use.
10% of subjects in the pooled Phase III efficacy trails (-303, -304 and -305) continued antidepressant medication. Treatment groups were generally comparable on previous psychotroptic medication such that subjects were also comparable on psychotropic medications discontinued according to the protocol (based on in-text description of results in section 1.4.2.1. of Module 2.7.4).

The incidence of rescue medication use within a give treatment group generally ranged from as low as 54% to as high as 78% across the 3 pivotal trials. Lorazepam was the most commonly used rescue medication. A clear relationship between dose of paliperidone and use of rescue

medications was not revealed by the sponsor (based on in-text description of results in section 1.4.2.1. of Module 2.7.4).

Anticholinergic agents were the most frequently used drug for treatment of EPSEs in which 12% to 19% of subjects in a given treatment group received anticholinergic treatment during the DB trials, pooled.

The table below summarizes the incidence of use of other concomitant medications in the study.

Table 21: Other Concomitant Medication Received During the Double-Blind Phase in ≥ 5% of Subjects in Any Treatment Group
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

Generic Term Category	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
No. subjects with any concomitant therapy	201 (57)	66 (52)	137 (58)	128 (52)	164 (68)	66 (58)	561 (58)	192 (53)
Paracetamol	70 (20)	18 (14)	50 (21)	37 (15)	61 (25)	18 (16)	184 (19)	58 (16)
Ibuprofen	34 (10)	5 (4)	20 (9)	12 (5)	26 (11)	7 (6)	70 (7)	29 (8)
Biperiden	11 (3)	4 (3)	7 (3)	29 (12)	23 (10)	6 (5)	69 (7)	12 (3)
Benzatropine	16 (5)	6 (5)	10 (4)	8 (3)	20 (8)	8 (7)	52 (5)	12 (3)
Maalox	14 (4)	5 (4)	7 (3)	4 (2)	12 (5)	3 (3)	31 (3)	15 (4)
Magnesium	12 (3)	3 (2)	8 (3)	7 (3)	7 (3)	6 (5)	31 (3)	14 (4)
Trihexyphenidyl	6 (2)	3 (2)	2 (1)	12 (5)	7 (3)	6 (5)	30 (3)	6 (2)
Metformin	14 (4)	3 (2)	5 (2)	6 (2)	13 (5)	1 (1)	28 (3)	4 (1)
Propranolol	7 (2)	4 (3)	6 (3)	4 (2)	3 (1)	8 (7)	25 (3)	4 (1)
Diphenhydramine	13 (4)	2 (2)	11 (5)	0	6 (2)	1 (1)	20 (2)	11 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.2.5.1.

In the elderly Study -302, the following tables show the mot commonly used rescue medications and concomitant use of antidepressant medications among the subjects (copied from the submission).

Table 9: Duration (Days) of The Most Frequently Used Rescue Medication Received During the Double-Blind Phase
(Study R076477-SCH-302: Safety Analysis Set)

	N	Mean	SD	Med	Min	Max
Rescue Medication						
DIAZEPAM						
Placebo	3	7.0	2.00	7.0	5	9
ER OROS PAL	11	5.5	4.11	5.0	1	13
LORAZEPAM						
Placebo	7	4.7	4.75	3.0	1	14
ER OROS PAL	6	14.3	14.31	10.5	3	41

Table 10: Antidepressant Medications Received During the Double-Blind Phase (Study R076477-SCH-302: Safety Analysis Set)

Medication Generic Term	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)	Total (N=114) n (%)
Total no. subjects with any antidepressant medication	0	10 (13)	10 (9)
Amitriptyline	0	6 (8)	6 (5)
Sertraline	0	2 (3)	2 (2)
Mirtazapine	0	1 (1)	1 (1)
Venlafaxine hydrochloride	0	1 (1)	1 (1)

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

68% of placebo subjects and 61% of Pal subjects used other concomitant drugs in the elderly Study -302. The following drugs were the most commonly used among all subjects (used in over 5% of all subjects):

- Biperiden (17% of all subjects)
- Biperiden hydrochloride (5% of all subjects)
- Aspirin (7% of all subjects)
- Furosemide (6% of all subjects).

Concomitant Illness. The following table shows the incidence of specified major medical conditions as shown by the sponsor.

Table 15: Demographic and Baseline Characteristics (continued)
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo	ER OROS PAL 3 mg	ER OROS PAL 6 mg	ER OROS PAL 9 mg	ER OROS PAL 12 mg	ER OROS PAL 15 mg	Total Paliperidone	Olanzapine 10 mg
Does subject currently smoke?, n (%)								
N	355	127	234	346	242	113	963	364
Yes	224 (63)	66 (52)	152 (65)	128 (52)	162 (67)	62 (55)	570 (59)	237 (65)
No	131 (37)	61 (48)	82 (35)	118 (48)	80 (33)	51 (45)	392 (41)	127 (35)
Diabetes, n (%)								
N	355	127	235	346	242	113	963	364
Yes	18 (5)	4 (3)	9 (4)	8 (3)	17 (7)	3 (3)	41 (4)	11 (3)
No	337 (95)	123 (97)	226 (96)	238 (97)	225 (93)	110 (97)	922 (96)	353 (97)
Hypertension, n (%)								
N	355	127	235	346	242	113	963	364
Yes	46 (13)	7 (6)	28 (12)	17 (7)	28 (12)	14 (12)	94 (10)	35 (10)
No	309 (87)	120 (94)	207 (88)	329 (93)	214 (88)	99 (88)	869 (90)	329 (90)
Dyslipidemia, n (%)								
N	355	127	235	346	242	113	963	364
Yes	18 (5)	4 (3)	9 (3)	9 (4)	11 (5)	6 (3)	38 (4)	12 (3)
No	337 (95)	123 (97)	227 (97)	237 (96)	231 (95)	107 (95)	925 (96)	352 (97)
Cardiovascular disease, n (%)								
N	355	127	235	346	242	113	963	364
Yes	8 (2)	3 (2)	4 (3)	3 (1)	6 (3)	3 (3)	18 (2)	6 (2)
No	347 (98)	124 (98)	231 (98)	243 (99)	236 (98)	111 (98)	945 (98)	358 (98)

The following table is regarding Study -302.

Table 7: Demographic and Baseline Characteristics (Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)	Total (N=114)
Current smoker, n (%)			
N	37	76	113
Yes	10 (27)	20 (26)	30 (27)
No	27 (73)	56 (74)	83 (73)
Diabetes, n (%)			
N	38	76	114
Yes	3 (8)	11 (14)	14 (12)
No	35 (92)	65 (86)	100 (88)
Hypertension, n (%)			
N	38	76	114
Yes	11 (29)	29 (38)	40 (35)
No	27 (71)	47 (62)	74 (65)
Dyslipidemia, n (%)			
N	38	76	114
Yes	0	2 (3)	2 (2)
No	38 (100)	74 (97)	112 (98)
Cardiovascular disease, n (%)			
N	38	76	114
Yes	17 (45)	32 (42)	49 (43)
No	21 (55)	44 (58)	65 (57)

Cross-reference: Attachments 2.1.1 and 2.1.2.

6.1.5 Efficacy Findings

Each pivotal Phase III trial (Studies R076477-SCH-303, R076477-SCH-304, R076477-SCH-305) was positive for efficacy on the primary efficacy variable (mean change from baseline to treatment endpoint on the PANNS-total score).

Results of the primary and secondary efficacy variables form each trial is shown below (copied from the submission).

Continued on the next page

Table 4: Overview of Efficacy Change From Baseline to End Point LOCF Results for Study R076477-SCH-303: Intent-to-Treat Analysis Set

Efficacy Variable	Placebo (N=126)	ER OROS PAL 6 mg (N=123)	ER OROS PAL 9 mg (N=122)	ER OROS PAL 12 mg (N=129)
PANSS total score (primary variable) (n)	126	123	122	129
Mean change (SD)	-4.1 (23.16)	-17.9 (22.23)*	-17.2 (20.23)*	-23.3 (20.12)*
PSP (n)	120	119	118	129
Mean change (SD)	0.5 (15.51)	9.1 (15.52)*,#	8.1 (14.46)*,#	11.5 (15.98)*,#
CGI-S (n)	126	122	122	129
Median change (Range)	0.0 (-4;2)	-1.0 (-4;2)#	-1.0 (-4;1)#	-1.0 (-5;1)#
SQLS (n)	120	120	120	121
Mean change (SD)	-4.9 (16.64)	-8.3 (14.75)	-12.9 (17.92)#	-13.4 (18.95)#
PANSS Factor Scores (n)	126	123	122	129
Mean change (SD)				
Positive symptoms	-2.1 (6.98)	-6.6 (7.40)†	-6.2 (6.87)†	-8.2 (6.64)†
Negative symptoms	-1.0 (5.85)	-4.2 (6.17)†	-3.5 (5.43)†	-5.0 (5.98)†
Disorganized thoughts	-0.9 (5.70)	-3.5 (5.05)†	-3.1 (4.73)†	-4.6 (5.14)†
Uncontrolled hostility/excitement	0.5 (4.48)	-1.4 (4.28)†	-1.8 (3.83)†	-2.4 (3.44)†
Anxiety/depression	-0.6 (3.97)	-2.1 (3.29)†	-2.6 (3.42)†	-3.0 (3.38)†
Quality of Sleep (n)	119	121	120	126
Mean change (SD)	1.0 (35.49)	13.5 (33.84)†	10.5 (31.21)†	12.2 (32.54)†
Daytime Drowsiness (n)	119	121	120	126
Mean change (SD)	-5.8 (30.26)	-2.4 (24.27)	-7.2 (30.73)	-6.4 (29.88)

* Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Dunnett's procedure to adjust for multiple comparisons.
# Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using unconditional randomization resampling algorithm to adjust for multiple comparisons.
† Denotes a statistically significant ($p<0.05$) improvement with no adjustment for multiple comparisons.
Note: A comparison between the olanzapine 10 mg group and the ER OROS paliperidone groups in terms of the primary efficacy variable showed no statistically significant between-group differences.
Cross-reference: Mod5.3.5.1\R076477-SCH-303\Synopsis Efficacy Results.

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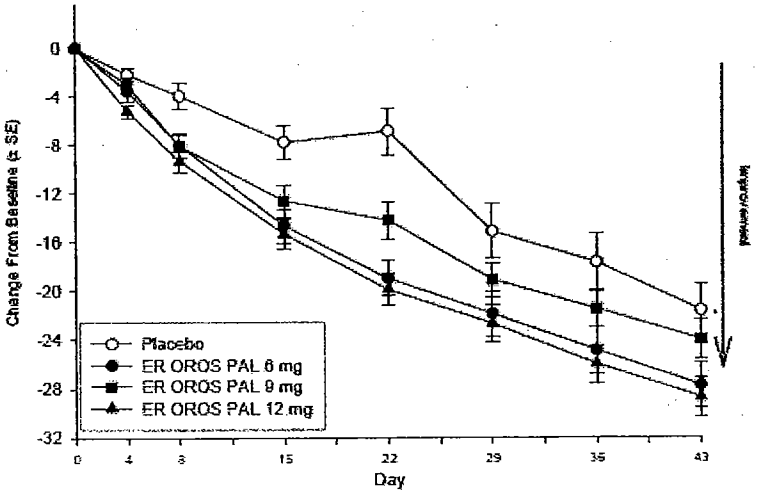
Figure 7: Change From Baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score Over Time – Observed Case
(Study R076477-SCH-303: Intent-to-Treat Analysis Set)



Placebo:	125	123	114	109	73	54	58
PAL 6 mg:	123	116	110	101	90	83	81
PAL 9 mg:	121	117	110	106	91	87	86
PAL 12 mg:	128	122	123	121	106	97	90

Cross-reference: Attachment 5.1.1

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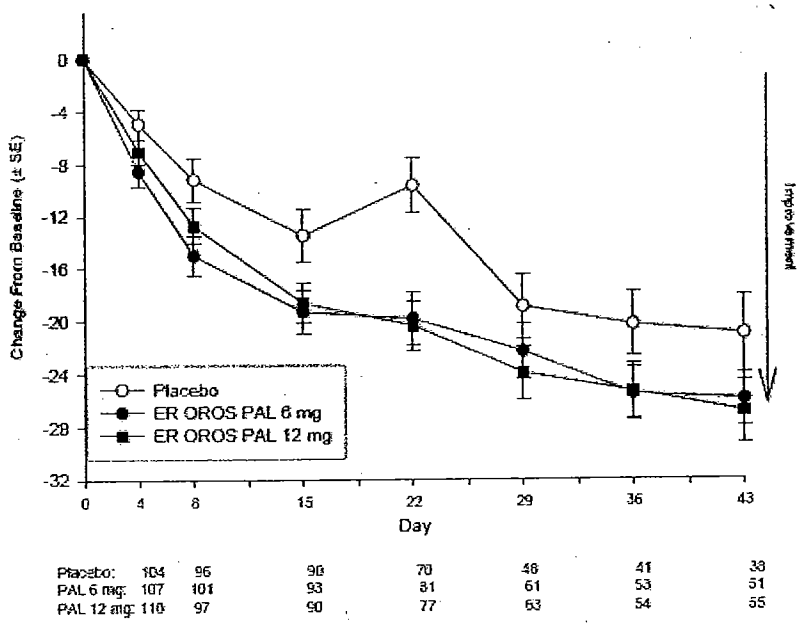
Table 5: Overview of Efficacy Change From Baseline to End Point LOCF Results for Study R076477-SCH-304: Intent-to-Treat Analysis Set

Efficacy Variable	Placebo (N=105)	ER OROS PAL 6 mg (N=111)	ER OROS PAL 12 mg (N=111)
PANSS total score (primary variable) (n)	105	110	111
Mean change (SD)	-8.0 (21.48)	-15.7 (18.89)*	-17.5 (19.83)*
PSP (n)	88	93	91
Mean change (SD)	2.9 (13.04)	8.8 (13.92)*,#	6.6 (13.06)
CGI-S (n)	105	111	111
Median change (Range)	0.0 (-4;2)	-1.0 (-4;1)#	-1.0 (-3;1)#
SQLS (n)	100	107	107
Mean change (SD)	-3.3 (16.31)	-6.7 (16.62)	-5.7 (14.19)
PANSS Factor Scores (n)	105	111	111
Mean change (SD)			
Positive symptoms	-2.9 (7.07)	-5.2 (5.95)†	-6.0 (6.68)†
Negative symptoms	-2.2 (6.59)	-4.4 (5.87)†	-3.9 (5.56)†
Disorganized thoughts	-1.7 (5.13)	-2.7 (4.33)	-3.7 (4.98)†
Uncontrolled hostility/excitement	0.3 (3.90)	-1.2 (3.92)†	-1.5 (3.91)†
Anxiety/depression	-1.5 (4.36)	-2.3 (3.67)	-2.4 (3.75)
Quality of Sleep (n)	101	106	107
Mean change (SD)	-3.3 (36.16)	8.3 (33.40)†	6.8 (35.03)†
Daytime Drowsiness (n)	101	107	107
Mean change (SD)	-2.6 (29.93)	0.9 (31.57)	1.2 (31.96)

* Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Dunnett's procedure to adjust for multiple comparisons.
# Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using unconditional randomization resampling algorithm to adjust for multiple comparisons.
† Denotes a statistically significant ($p<0.05$) improvement with no adjustment for multiple comparisons.
Note: A comparison between the olanzapine 10 mg group and the ER OROS paliperidone groups in terms of the primary efficacy variable showed no statistically significant between-group differences.
Cross-reference: Mod5.3.5.1\R076477-SCH-304\Synopsis Efficacy Results.

Figure 7: Change From Baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score Over Time – Observed Case (Study R076477-SCH-304: Intent-to-Treat Analysis Set)



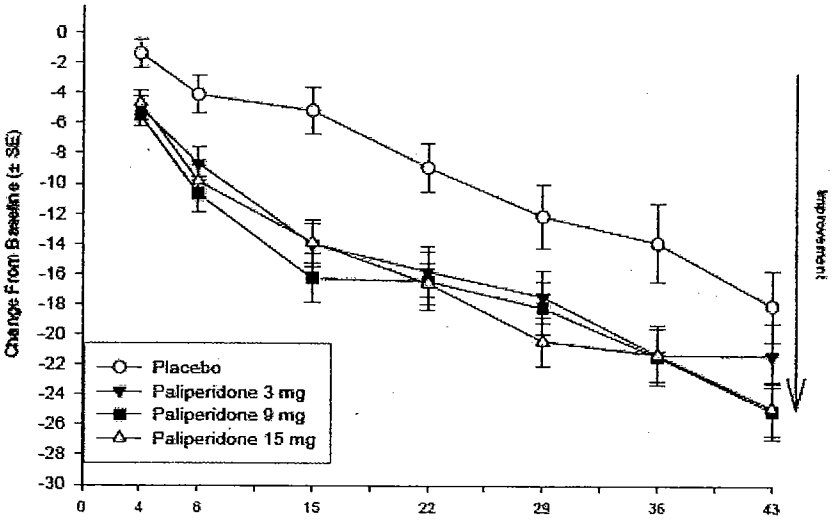
Cross-reference: Attachment 5.1.1

Table 6: Overview of Efficacy Change From Baseline to End Point LOCF Results for Study R076477-SCH-305: Intent-to-Treat Analysis Set

Efficacy Variable	Placebo (N=120)	ER OROS PAL 3 mg (N=123)	ER OROS PAL 9 mg (N=123)	ER OROS PAL 15 mg (N=113)
PANSS total score (primary variable) (n)	120	123	123	112
Mean change (SD)	-2.8 (20.89)	-15.0 (19.61)*	-16.3 (21.81)*	-19.9 (18.41)*
PSP (n)	109	113	116	107
Mean change (SD)	-1.5 (15.82)	8.3 (17.11)*,#	7.6 (14.20)*,#	12.2 (15.65)*,#
CGI-S (n)	120	123	123	113
Median change (Range)	0.0 (-5;2)	-1.0 (-4;1)#	-1.0 (-4;2)#	-1.0 (-5;1)#
SQLS (n)	114	116	116	112
Mean change (SD)	-3.8 (13.40)	-7.4 (14.77)#	-6.7 (15.93)	-7.5 (16.45)
PANSS Factor Scores (n)	120	123	123	113
Mean change (SD)				
Positive symptoms	-2.1 (6.90)	-5.0 (6.89)†	-6.0 (7.74)†	-6.9 (6.87)†
Negative symptoms	-1.0 (5.52)	-3.8 (5.27)†	-3.9 (5.36)†	-4.2 (5.30)†
Disorganized thoughts	-0.2 (5.34)	-3.4 (5.06)†	-3.4 (5.47)†	-3.9 (4.46)†
Uncontrolled hostility/excitement	1.2 (4.68)	-1.1 (3.61)†	-1.2 (4.48)†	-2.3 (3.34)†
Anxiety/depression	-0.7 (3.46)	-1.8 (3.35)†	-1.9 (3.72)†	-2.6 (2.87)†
Quality of Sleep (n)	115	118	120	113
Mean change (SD)	3.6 (35.99)	9.0 (34.52)	12.3 (34.88)†	11.3 (33.17)
Daytime Drowsiness (n)	115	118	119	113
Mean change (SD)	-0.5 (29.69)	-2.9 (28.10)	-0.9 (33.85)	-3.8 (34.47)

* Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Dunnett's procedure to adjust for multiple comparisons.
# Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using unconditional randomization resampling algorithm to adjust for multiple comparisons.
† Denotes a statistically significant ($p<0.05$) improvement with no adjustment for multiple comparisons.
A comparison between the olanzapine 10 mg group and the ER OROS paliperidone groups in terms of the primary efficacy variable showed no statistically significant between-group differences.
Cross-reference: Mod5.3.5.1\R076477-SCH-305\Synopsis Efficacy Results.

Figure 7: Change From Baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score Over Time – Observed Case (Study R076477-SCH-305: Intent-to-Treat Analysis Set)



Placebo:	118	111	99	90	87	49	47
PAL 3 mg:	122	119	112	105	82	78	70
PAL 9 mg:	122	114	108	108	95	85	77
PAL 15 mg:	112	108	105	102	91	84	82

Cross-reference: Attachment 5.1.1

The study of elderly patients (Study -302) showed numerical trends for greater improvement on the PANSS-total score in the Pal group than observed in the placebo group as shown in the summary table and figure below (copied from the submission).

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Table 15: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Change From Baseline to End Point-LOCF (Study R076477-SCH-302: Intent-to-Treat Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)
Baseline		
N	38	76
Mean (SD)	94.3 (9.00)	91.8 (9.69)
Median (Range)	93.0 (79;117)	92.5 (75;119)
End point		
N	38	76
Mean (SD)	84.4 (14.55)	77.3 (14.98)
Median (Range)	84.0 (46;119)	76.5 (44;122)
Change from Baseline		
N	38	76
Mean (SD)	-9.9 (15.00)	-14.6 (14.64)
Median (Range)	-8.5 (-39;26)	-14.5 (-44;22)
Diff. of LS Means (SE) [a,b]		-5.5 (2.20)
95% CI		(-9.85;-1.12)

[a] Analysis of covariance from ANCOVA model with factors for treatment, age group and analysis center, and with baseline value as a covariate.
[b] Comparison with Placebo
Note: Negative change in score indicates improvement.

The following figure shows results on the primary variable by dose-level for each of the 3 short-term pivotal trials and for pooled data (as copied from the submission).

Table 18: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point-LOCF for Each Study and the Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305): Intent-to-Treat Analysis Set)

		ER OROS PAL			
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
R076477-SCH-303	(N=126)		(N=123)	(N=122)	(N=129)	
N	126		123	122	129	
Mean baseline (SD)	94.1 (10.74)		94.3 (10.48)	93.2 (11.90)	94.6 (10.98)	
Mean change (SD)	-4.1 (23.16)		-17.9 (22.23)	-17.2 (20.23)	-23.3 (20.12)	
P-value (vs. Placebo)[a,b]			<0.001	<0.001	<0.001	
Diff. of LS Means (SE)			-13.7 (3.63)	-13.5 (2.63)	-18.9 (2.60)	
95% CI			(-19.91;-7.53)	(-19.65;-7.25)	(-25.07;-12.82)	
R076477-SCH-304	(N=105)		(N=111)		(N=111)	
N	105		110		111	
Mean baseline (SD)	93.6 (11.71)		92.3 (11.96)		94.1 (11.42)	
Mean change (SD)	-8.0 (21.48)		-15.7 (18.89)		-17.5 (19.83)	
P-value (vs. Placebo)[a,b]			0.006		<0.001	
Diff. of LS Means (SE)			-7.0 (2.56)		-8.5 (2.35)	
95% CI			(-12.27;-1.81)		(-13.75;-3.32)	
R076477-SCH-305	(N=120)	(N=123)		(N=123)		(N=113)
N	120	123		123		112
Mean baseline (SD)	93.9 (12.66)	91.6 (12.19)		93.9 (13.20)		92.4 (12.36)
Mean change (SD)	-2.3 (20.89)	-15.0 (19.61)		-16.3 (21.81)		-19.9 (18.41)
P-value (vs. Placebo)[a,b]		<0.001		<0.001		<0.001
Diff. of LS Means (SE)		-11.6 (2.35)		-12.9 (2.34)		-17.2 (2.40)
95% CI		(-17.17;-6.09)		(-18.42;-7.38)		(-22.82;-11.51)

Table, continued.

Table 18: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point-LOCF for Each Study and the Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305): Intent-to-Treat Analysis Set)

	Placebo	ER OROS PAL 3 mg	ER OROS PAL 6 mg	ER OROS PAL 9 mg	ER OROS PAL 12 mg	ER OROS PAL 15 mg
Pooled Data: Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305						
	(N=351)	(N=123)	(N=234)	(N=245)	(N=240)	(N=113)
N	351	123	233	245	240	112
Mean baseline (SD)	93.9 (11.68)	91.6 (12.19)	93.4 (11.22)	93.6 (12.55)	94.4 (11.16)	92.4 (12.36)
Median baseline (Range)	93.0(70;120)	92.0 (71;123)	92.0 (70;123	93.0 (67;136)	94.0 (70;121)	91.0 (65;120)
Mean end point (SD)	89.1 (24.59)	76.6 (21.08)	76.5 (21.04)	76.8 (22.18)	73.7 (20.47)	72.5 (19.12)
Median end point (Range)	90.0 (30;164)	76.0 (30;140)	74.0 (30;138)	75.0 (30;176)	71.0 (31;157)	72.0 (30;121)
Mean change (SD)	-4.8 (21.95)	-15.0 (19.61)	-16.9 (20.70)	-16.8 (21.00)	-20.6 (20.15)	-19.9 (18.41)
Median change (Range)	-3.0 (-71;49)	-14.0 (-75;27)	-19.0 (-92;47)	-18.0 (-79;68)	-21.0 (-77;44)	-20.0 (-84;25)
P-value (vs. Placebo) [c,d]		<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-11.1 (2.27)	-11.0 (1.70)	-11.8 (1.65)	-14.5 (1.69)	-16.6 (2.34)
95% CI		(-15.61;-6.68)	(-14.31;-7.63)	(-15.00;-8.54)	(-17.82;-11.18)	(-21.23;-12.06)

[a] Based on ANCOVA model with treatment (placebo and ER OROS paliperidone arms in each protocol) and analysis center as factors, and baseline value as a covariate.
[b] Pairwise comparison: p-values associated with Dunnett's procedure.
[c] Based on ANCOVA model with protocol, treatment (placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[d] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.
Cross-reference: Mod5.3.5.1\R076477-SCH-303\Table 15, Mod5.3.5.1\R076477-SCH-304\Table 15, and Mod5.3.5.1\R076477-SCH-305\Table 15.

Subgroup Analyses of Pooled Phase III trials (303, 304 and 305)

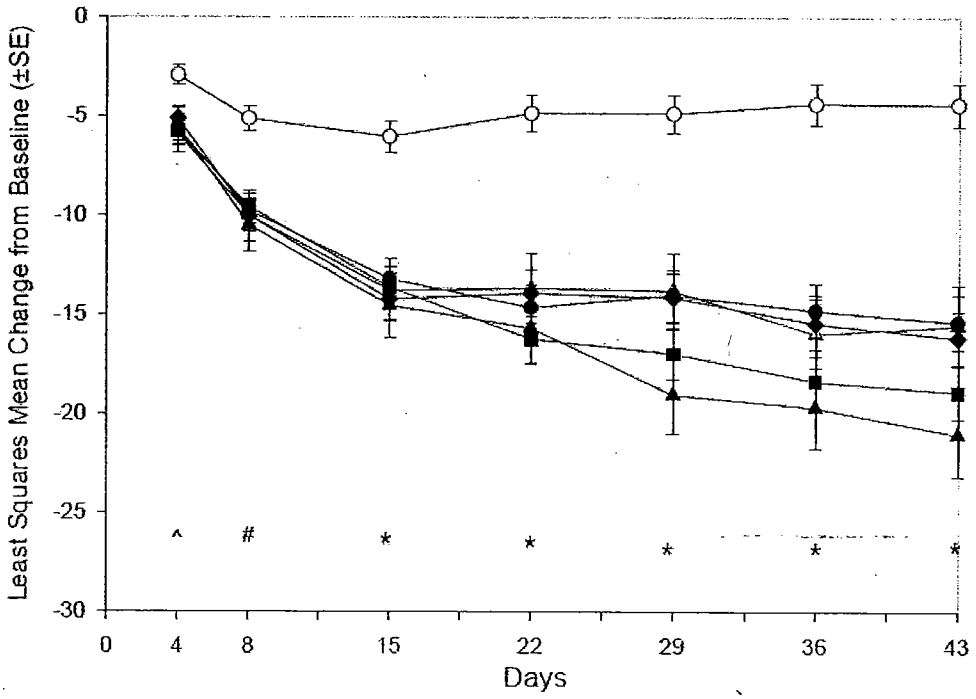
The sponsor examined efficacy results for 3 age-subgroups (18-25, 26-50 and over 50 year old age subgroups). These age-groupings were chosen in an effort to differentiate early onset schizophrenia (18-25 year olds) from late onset or chronic schizophrenia (over 50 year olds).

Reviewer Comment on Efficacy by Dose-level

Refer to previous Figures of each pivotal trial of the OC dataset results over time. These figures show little treatment group differences among Pal groups. The sponsor conducted a dose-level by effect analyses of pooled data of the LOCF dataset that suggests a dose-dependent effect on the primary efficacy variable. Similar analyses of the OC dataset could not be found in the submission. Yet upon visual examination of the above figures of the OC dataset clear or consistent differences among Pal dose-levels within any given study is not observable, even when comparing the lowest dose-level to the highest dose level.

The following shows results of pooled data using the LOCF dataset, as found in the submission which is more difficult to interpret.

Figure 2: Onset of Effect: Changes From Baseline in LS Means (±SE) for PANSS Total Score – LOCF: Pooled Data
(Studies R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305: Intent-to-Treat Analysis Set)



	N	Baseline Mean Total Score
Placebo	351	93.9
Paliperidone 3 mg	123	91.6
Paliperidone 6 mg	233	93.4
Paliperidone 9 mg	245	93.6
Paliperidone 12 mg	240	94.4
Paliperidone 15 mg	112	92.4

Comparisons of paliperidone vs placebo based on an Analysis of Covariance (ANCOVA) model with treatment, protocol, and analysis center as factors and baseline score as covariate.

^: 3 mg, 6 mg, 9 mg and 12 mg: All nominal p-values <= 0.05. Maximum was 0.021 (3 mg vs placebo). The observed nominal p-value was 0.071 between 15 mg and placebo.

*: **All Doses:** All nominal p-values <= 0.001.

#: **All Doses:** All nominal p-values <= 0.01. Maximum is 0.003 (3 mg vs placebo).

While efficacy between placebo and each Pal group is consistent when looking at either the OC or LOCF dataset consistent or clear differences between the Pal groups is not revealed for the OC dataset and LOCF datasets. Unlike the OC dataset, examination of the LOCF dataset shows some possible separation across treatment groups at the more extreme ends of the dose range. At least trends for greater effect may be observed when comparing the highest daily dose levels (e.g. the 15 mg or 12 mg dose-levels) to the lowest daily dose-level (3 mg). But this is only observed with the LOCF dataset and not with the OC dataset. When interpreting these results it is important to note that the OC dataset shows efficacy obtained over real time and across dose levels for only subjects who remain on the drug while the LOCF dataset does not show efficacy over real time but rather shows efficacy up to the time-point when subjects either dropped out early combined with subjects that completed the study. Therefore, the results of the LOCF dataset do not actually reflect effects over real time and do not show reflect results in the subjects that remain on the drug (which is clinically relevant information). Yet the LOCF dataset shows effects in as observed in a larger sample size early in treatment before subjects drop out due to lack of efficacy or for other reasons. A problem with pooling data is that it is difficult to interpret results across independent studies regarding an examination of dose-dependent effects and in turn with data from independent trials, pooled. Not all studies examined the same dose-levels. Such that the effect size in one dose-level in one study compared to a different dose-level used in another study is difficult to interpret. If this NDA is ultimately approved at the Agency level, then it is recommended that a figure of each study (by dose-level across time on the mean change on the PANSS total score) be provided and described in labeling for the OC dataset and results of the LOCF data set be described in which the primary endpoint be referred to as the mean change from baseline to treatment endpoint for subjects who stopped treatment early combined with subjects who completed treatment (in which the value of the last efficacy assessment was carried forward). It is recommended that the terms LOCF and OC be clearly defined in labeling. See the final section of this review for recommendations.

Reviewer Comment on Age Subgroup Analyses. *At least a greater numerical improvement on the primary efficacy variable was generally observed in Pal groups compared to the placebo group within each age-subgroup. However, one cannot assume that the over 50 year old age-group represent new onset (late onset) schizophrenia. Furthermore, subgroupings resulted in small sample sizes for the younger and older age-groups such that interpretation of results is difficult.*

Gender subgroups were also analyzed for efficacy in male and female subgroups.

Reviewer Comment on Gender Subgroup Analyses. *Each gender subgroup generally showed significantly greater or numerically greater efficacy in each Pal groups compared to the placebo group ($p<0.001$ without correcting for multiple comparisons).*

Geographical region sub-groupings were analyzed for efficacy.

Reviewer Comment on Efficacy Results for Geographical Region Subgroups *At least a greater numerical improvement on the primary efficacy variable was generally observed for each Pal group compared to placebo groups within each geographical-subgroup. However, several geographical region subgroups had small sample sizes such that results are difficult to interpret for at least these smaller subgroups.*

Geographical region sub-groupings were analyzed for efficacy.

Reviewer Comment on Efficacy Results for Subgroupings based on Race or Ethnicity *At least a greater numerical improvement on the primary efficacy variable was generally observed for each Pal group compared to placebo groups within each subgroup. However, many subgroups had small sample sizes such that results are difficult to interpret for at least these smaller subgroups.*

0Results of the above subgroup analyses are shown below (copied from the submission).

Table 28: PANSS Total Score- Change From Baseline to End Point by Age-LOCF: Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Age Group: 18-25	(N=45)	(N=24)	(N=27)	(N=41)	(N=35)	(N=17)
Baseline (N)	45	24	27	41	35	17
Mean (SD)	94.1 (12.22)	96.5 (11.81)	95.8 (9.48)	94.1 (12.58)	96.7 (11.55)	93.4 (16.44)
Median (Range)	94.0 (71;120)	95.5 (72;119)	95.0 (80;117)	92.0 (72;136)	98.0 (72;120)	88.0 (71;117)
End Point (N)	45	24	27	41	35	17
Mean (SD)	90.2 (28.15)	80.1 (21.12)	80.0 (20.90)	73.6 (19.88)	79.4 (25.51)	70.1 (20.81)
Median (Range)	93.0 (38;164)	80.0 (30;117)	77.0 (37;122)	71.0 (34;122)	74.0 (39;157)	68.0 (33;100)
Baseline Change (N)	45	24	27	41	35	17
Mean (SD)	-4.0 (24.46)	-16.4 (16.33)	-15.8 (19.72)	-20.4 (22.81)	-17.3 (23.16)	-23.2 (21.29)
Median (Range)	-6.0 (-71;44)	-14.5 (-59;10)	-17.0 (-80;15)	-22.0 (-73;35)	-16.0 (-55;44)	-17.0 (-84;6)
P-value (vs. Placebo) [a,b]		0.278	0.021	0.019	0.007	0.046
Diff. of LS Means (SE)		-7.0 (6.40)	-14.6 (6.24)	-12.6 (5.31)	-17.3 (6.28)	-14.4 (7.13)
95% CI		(-19.66;5.70)	(-27.02;-2.27)	(-23.17;-2.12)	(-29.76;-4.83)	(-28.55;-0.26)
Age Group: 26-50	(N=253)	(N=84)	(N=173)	(N=174)	(N=173)	(N=84)
Baseline (N)	253	84	172	174	173	83
Mean (SD)	94.0 (11.82)	89.8 (12.18)	93.7 (11.56)	93.5 (12.89)	94.4 (11.46)	91.9 (11.61)
Median (Range)	94.0 (70;120)	89.0 (71;123)	93.0 (70;123)	93.0 (67;131)	94.0 (70;121)	90.0 (65;118)
End Point (N)	253	84	172	174	173	83
Mean (SD)	89.2 (24.21)	74.2 (20.55)	76.6 (21.85)	78.4 (23.25)	72.5 (20.08)	73.6 (18.61)
Median (Range)	91.0 (30;164)	74.0 (30;125)	75.5 (30;138)	77.0 (30;176)	70.0 (31;129)	73.0 (30;121)
Baseline Change (N)	253	84	172	174	173	83
Mean (SD)	-4.8 (21.66)	-15.6 (21.01)	-17.1 (21.83)	-15.1 (20.62)	-21.9 (20.06)	-18.4 (17.44)
Median (Range)	-3.0 (-71;49)	-14.5 (-75;27)	-19.5 (-92;47)	-17.0 (-79;68)	-22.0 (-77;37)	-19.0 (-72;25)
P-value (vs. Placebo) [a,b]		<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-11.8 (2.82)	-11.4 (2.04)	-10.7 (2.00)	-16.3 (2.04)	-15.3 (2.82)
95% CI		(-17.35;-6.26)	(-15.44;-7.43)	(-14.63;-6.79)	(-20.26;-12.25)	(-20.88;-9.81)
Age Group: >50	(N=53)	(N=15)	(N=34)	(N=30)	(N=32)	(N=12)
Baseline (N)	53	15	34	30	32	12
Mean (SD)	93.1 (10.70)	93.8 (10.89)	89.6 (10.12)	93.5 (10.69)	91.6 (8.44)	94.0 (11.73)
Median (Range)	91.0 (72;118)	95.0 (77;113)	87.5 (73;117)	93.0 (73;113)	92.0 (78;120)	92.0 (79;120)
End Point (N)	53	15	34	30	32	12
Mean (SD)	87.4 (23.56)	84.7 (22.63)	73.3 (16.54)	72.1 (17.82)	74.1 (15.33)	68.3 (21.02)
Median (Range)	86.0 (41;139)	83.0 (48;140)	70.0 (47;107)	70.5 (30;108)	72.5 (32;103)	65.0 (42;103)
Baseline Change (N)	53	15	34	30	32	12
Mean (SD)	-5.7 (21.47)	-9.1 (15.93)	-16.4 (15.37)	-21.4 (19.92)	-17.4 (16.68)	-25.8 (20.58)
Median (Range)	-4.0 (-68;35)	-11.0 (-32;27)	-19.5 (-40;25)	-19.5 (-75;19)	-17.0 (-60;11)	-28.5 (-59;12)
P-value (vs. Placebo) [a,b]		0.891	0.037	0.275	0.178	0.091
Diff. of LS Means (SE)		-1.3 (9.64)	-10.8 (5.10)	-6.8 (6.19)	-7.3 (5.36)	-16.1 (9.42)
95% CI		(-20.50;17.84)	(-20.94;-0.67)	(-19.11;5.50)	(-17.93;3.38)	(-34.84;2.62)

[a] Based on ANCOVA model with protocol, treatment (placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.

Table 37: PANSS Total Score - Change From Baseline to End Point by Geographic Region-LOCF: Pooled Data (R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
North America	(N=147)	(N=40)	(N=111)	(N=45)	(N=111)	(N=37)
Baseline (N)	147	40	110	45	111	36
Mean (SD)	94.2 (12.31)	95.1 (12.94)	92.3 (11.96)	96.1 (13.23)	94.1 (11.42)	94.8 (12.15)
Median (Range)	95.0 (70;120)	93.5 (74;123)	91.0 (70;119)	94.0 (72;131)	94.0 (70;120)	96.5 (70;113)
End Point (N)	147	40	110	45	111	36
Mean (SD)	87.5 (23.59)	77.7 (22.81)	76.6 (20.15)	85.8 (23.95)	76.5 (20.21)	80.7 (18.60)
Median (Range)	89.0 (33;139)	76.5 (37;125)	75.0 (33;138)	85.0 (36;176)	75.0 (40;157)	82.5 (44;109)
Baseline Change (N)	147	40	110	45	111	36
Mean (SD)	-6.7 (20.58)	-17.5 (23.23)	-15.7 (18.89)	-10.3 (24.94)	-17.5 (19.83)	-14.2 (16.19)
Median (Range)	-4.0 (-71;35)	-15.5 (-75;21)	-17.0 (-80;30)	-7.0 (-79;54)	-18.0 (-65;44)	-15.0 (-59;12)
P-value (vs. Placebo) [a,b]		0.004	0.004	0.224	<0.001	0.014
Diff. of LS Means (SE)		-11.7 (3.99)	-7.0 (2.44)	-4.7 (3.87)	-8.5 (2.43)	-10.1 (4.08)
95% CI		(-19.50;-3.83)	(-11.80;-2.21)	(-12.30;2.89)	(-13.32;-3.76)	(-18.14;-2.08)
Western Europe	(N=33)	(N=21)	(N=15)	(N=34)	(N=17)	(N=17)
Baseline (N)	33	21	15	34	17	17
Mean (SD)	93.7 (13.86)	93.0 (12.49)	93.5 (13.02)	93.1 (16.42)	92.4 (11.86)	94.6 (14.62)
Median (Range)	93.0 (71;120)	92.0 (72;113)	93.0 (73;117)	89.5 (70;136)	92.0 (74;109)	88.0 (74;120)
End Point (N)	33	21	15	34	17	17
Mean (SD)	81.7 (27.35)	77.7 (27.75)	79.3 (24.67)	72.9 (21.11)	69.8 (22.08)	61.7 (20.26)
Median (Range)	83.0 (30;164)	78.0 (30;140)	73.0 (43;127)	70.0 (34;117)	66.0 (32;118)	61.0 (30;93)
Baseline Change (N)	33	21	15	34	17	17
Mean (SD)	-12.0 (24.49)	-15.2 (23.81)	-14.1 (16.52)	-20.1 (19.64)	-22.5 (24.40)	-32.9 (22.71)
Median (Range)	-12.0 (-71;44)	-14.0 (-70;27)	-20.0 (-36;18)	-17.0 (-73;22)	-22.0 (-62;33)	-25.0 (-84;5)
P-value (vs. Placebo) [a,b]		0.994	0.229	0.095	0.023	0.010
Diff. of LS Means (SE)		0.0 (5.90)	-8.3 (6.86)	-8.2 (4.86)	-15.3 (6.62)	-16.5 (6.27)
95% CI		(-11.64;11.73)	(-21.88;5.29)	(-17.83;1.44)	(-28.38;-2.15)	(-28.92;-4.09)
Eastern Europe	(N=126)	(N=33)	(N=91)	(N=122)	(N=94)	(N=31)
Baseline (N)	126	33	91	122	94	31
Mean (SD)	94.5 (10.28)	92.6 (9.08)	94.4 (10.27)	93.8 (10.97)	94.5 (10.87)	92.6 (11.13)
Median (Range)	93.5 (70;120)	93.0 (76;109)	94.0 (73;123)	93.0 (67;129)	94.0 (71;121)	90.0 (78;118)
End Point (N)	126	33	91	122	94	31
Mean (SD)	94.1 (25.19)	78.2 (14.69)	74.9 (22.10)	76.7 (20.71)	71.4 (20.55)	75.6 (16.81)
Median (Range)	95.0 (41;164)	78.0 (38;115)	70.0 (30;131)	74.5 (30;152)	70.5 (31;137)	71.0 (42;121)
Baseline Change (N)	126	33	91	122	94	31
Mean (SD)	-0.4 (22.35)	-14.4 (13.11)	-19.4 (23.81)	-17.2 (19.08)	-23.2 (19.32)	-16.9 (17.25)
Median (Range)	0.5 (-68;49)	-14.0 (-43;23)	-20.0 (-92;47)	-20.0 (-75;68)	-23.0 (-77;36)	-16.0 (-48;25)
P-value (vs. Placebo) [a,b]		<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-16.2 (4.46)	-18.1 (2.84)	-17.0 (2.53)	-22.0 (2.82)	-19.4 (4.54)
95% CI		(-24.97;-7.46)	(-23.69;-12.52)	(-21.99;-12.04)	(-27.55;-16.46)	(-28.31;-10.45)
Asia	(N=45)	(N=29)	(N=17)	(N=44)	(N=18)	(N=28)
Baseline (N)	45	29	17	44	18	28
Mean (SD)	91.2 (11.56)	84.5 (11.67)	94.8 (9.77)	90.6 (12.35)	97.1 (10.82)	87.6 (11.72)
Median (Range)	89.0 (72;117)	81.0 (71;106)	96.0 (79;112)	91.0 (68;117)	101.5 (77;111)	87.0 (65;109)
End Point (N)	45	29	17	44	18	28
Mean (SD)	85.4 (21.98)	72.5 (19.80)	82.0 (17.83)	71.0 (22.88)	72.4 (19.47)	64.9 (16.28)
Median (Range)	83.0 (34;124)	73.0 (34;113)	82.0 (55;122)	71.0 (32;122)	80.0 (32;102)	68.0 (32;90)
Baseline Change (N)	45	29	17	44	18	28
Mean (SD)	-5.8 (21.53)	-12.0 (17.43)	-12.8 (16.93)	-19.6 (21.98)	-24.7 (21.03)	-22.7 (15.77)
Median (Range)	-9.0 (-53;35)	-11.0 (-41;23)	-18.0 (-38;14)	-18.5 (-60;35)	-15.0 (-74;0)	-24.5 (-44;12)
P-value (vs. Placebo) [a,b]		0.022	0.614	<0.001	0.015	<0.001
Diff. of LS Means (SE)		-10.7 (4.63)	-2.8 (5.58)	-14.4 (3.82)	-13.5 (5.49)	-20.5 (4.64)
95% CI		(-19.88;-1.57)	(-13.83;8.20)	(-21.94;-6.84)	(-24.38;-2.69)	(-29.63;-11.30)

[a] Based on ANCOVA model with protocol, treatment (Placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.

[b] Comparisons with placebo without multiplicity adjustment.

Note: Negative change in score indicates improvement.

Table 31: PANSS Total Score- Change From Baseline to End Point by Sex-LOCF: Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Sex: Male	(N=231)	(N=78)	(N=137)	(N=151)	(N=146)	(N=73)
Baseline (N)	231	78	136	151	146	72
Mean (SD)	94.3 (12.09)	90.5 (11.63)	92.6 (10.99)	93.7 (12.43)	92.9 (11.38)	93.1 (12.91)
Median (Range)	93.0 (70;120)	90.5 (71;123)	92.0 (70;119)	93.0 (67;136)	94.0 (70;120)	94.0 (70;120)
End Point (N)	231	78	136	151	146	72
Mean (SD)	89.7 (25.44)	75.3 (20.55)	78.3 (20.98)	77.8 (24.04)	74.9 (20.58)	72.2 (19.46)
Median (Range)	91.0 (31;164)	75.0 (30;140)	77.0 (33;131)	77.0 (30;176)	71.5 (31;137)	72.5 (30;121)
Baseline Change (N)	231	78	136	151	146	72
Mean (SD)	-4.6 (21.82)	-15.2 (18.68)	-14.3 (18.64)	-16.0 (22.34)	-17.9 (19.85)	-20.9 (19.58)
Median (Range)	-3.0 (-71;49)	-14.0 (-75;27)	-16.0 (-61;30)	-17.0 (-79;68)	-19.0 (-77;37)	-20.0 (-84;25)
P-value (vs. Placebo)[a,b]		<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-11.0 (2.93)	-9.5 (2.26)	-10.3 (2.15)	-12.6 (2.21)	-16.3 (2.98)
95% CI		(-16.80;-5.28)	(-13.91;-5.03)	(-14.55;-6.12)	(-16.95;-8.28)	(-22.19;-10.49)
Sex: Female	(N=120)	(N=45)	(N=97)	(N=94)	(N=94)	(N=40)
Baseline (N)	120	45	97	94	94	40
Mean (SD)	93.2 (10.86)	93.5 (13.02)	94.4 (11.52)	93.3 (12.80)	96.7 (10.46)	91.1 (11.33)
Median (Range)	94.0 (70;119)	94.0 (71;119)	94.0 (72;123)	93.5 (70;125)	95.0 (72;121)	89.5 (65;118)
End Point (N)	120	45	97	94	94	40
Mean (SD)	88.0 (22.94)	78.9 (22.03)	74.0 (20.98)	75.3 (18.84)	71.9 (20.27)	73.0 (18.74)
Median (Range)	88.5 (30;156)	77.0 (37;125)	70.0 (30;138)	74.0 (32;121)	70.5 (32;157)	70.5 (33;108)
Baseline Change (N)	120	45	97	94	94	40
Mean (SD)	-5.2 (22.28)	-14.6 (21.34)	-20.4 (22.93)	-18.0 (18.69)	-24.8 (20.01)	-18.1 (16.19)
Median (Range)	-2.0 (-54;46)	-15.0 (-69;27)	-22.0 (-92;47)	-19.5 (-64;35)	-23.5 (-70;44)	-19.5 (-45;22)
P-value (vs. Placebo)[a,b]		0.004	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-11.8 (4.12)	-12.9 (2.88)	-14.9 (2.85)	-16.5 (2.89)	-15.7 (4.27)
95% CI		(-19.89;-3.69)	(-18.60;-7.27)	(-20.54;-9.34)	(-22.16;-10.81)	(-24.08;-7.28)

[a] Based on ANCOVA model with protocol, treatment (placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.

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Table 34: PANSS Total Score- Change From Baseline to End Point by Race-LOCF: Pooled Data (Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set)

		ER OROS PAL				
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Race: White	(N=217)	(N=61)	(N=152)	(N=170)	(N=156)	(N=50)
Baseline (N)	217	61	151	170	156	50
Mean (SD)	95.2 (11.59)	93.6 (10.41)	93.7 (10.45)	94.2 (11.63)	94.4 (10.89)	94.1 (11.84)
Median (Range)	95.0 (70;120)	94.0 (72;119)	93.0 (73;123)	93.0 (67;129)	94.0 (71;121)	93.5 (78;120)
End Point (N)	217	61	151	170	156	50
Mean (SD)	92.1 (25.11)	81.9 (20.56)	76.2 (21.88)	77.6 (20.23)	73.2 (20.53)	75.6 (17.81)
Median (Range)	94.0 (33;164)	78.0 (38;140)	72.0 (30;138)	76.5 (30;152)	71.0 (31;137)	72.5 (42;121)
Baseline Change (N)	217	61	151	170	156	50
Mean (SD)	-3.1 (22.39)	-11.7 (18.00)	-17.5 (21.54)	-16.6 (18.51)	-21.2 (20.30)	-18.5 (17.72)
Median (Range)	-1.0 (-71;89)	-11.0 (-69;27)	-20.0 (-92;47)	-19.0 (-75;68)	-22.0 (-77;37)	-18.0 (-55;25)
P-value (vs. Placebo) [a,b]		0.002	<0.001	<0.001	<0.001	<0.001
Diff. of LS Means (SE)		-10.4 (3.25)	-14.3 (2.17)	-13.8 (2.05)	-18.3 (2.17)	-17.1 (3.45)
95% CI		(-16.75;-3.97)	(-18.52;-10.01)	(-17.78;-9.72)	(-22.54;-14.03)	(-23.83;-10.28)
Race: Black	(N=79)	(N=25)	(N=64)	(N=22)	(N=65)	(N=27)
Baseline (N)	79	25	64	22	65	26
Mean (SD)	91.7 (11.71)	92.6 (10.92)	92.2 (13.31)	94.4 (15.93)	93.7 (11.93)	94.8 (12.73)
Median (Range)	91.0 (70;117)	90.0 (74;119)	91.0 (70;117)	93.0 (72;136)	94.0 (70;120)	96.0 (70;117)
End Point (N)	79	25	64	22	65	26
Mean (SD)	83.1 (23.32)	72.6 (21.88)	75.9 (19.97)	82.5 (24.69)	75.6 (20.85)	75.1 (23.02)
Median (Range)	85.0 (30;132)	76.0 (30;117)	77.0 (33;113)	80.5 (34;117)	76.0 (43;157)	81.0 (30;109)
Baseline Change (N)	79	25	64	22	65	26
Mean (SD)	-8.6 (21.09)	-20.0 (20.62)	-16.3 (19.86)	-11.8 (28.78)	-18.1 (19.72)	-19.7 (23.71)
Median (Range)	-6.0 (-71;28)	-17.0 (-70;7)	-15.0 (-80;25)	-7.0 (-73;35)	-20.0 (-65;44)	-17.0 (-84;9)
P-value (vs. Placebo) [a,b]		0.545	0.096	0.818	0.055	0.318
Diff. of LS Means (SE)		-3.2 (5.31)	-5.8 (3.49)	1.3 (5.52)	-6.8 (3.51)	-5.3 (5.31)
95% CI		(-13.69;7.25)	(-12.71;1.04)	(-9.60;12.14)	(-13.67;0.16)	(-15.79;5.16)
Race: Asian	(N=28)	(N=30)		(N=28)		(N=29)
Baseline (N)	28	30		28		29
Mean (SD)	89.7 (11.80)	85.1 (11.86)		88.1 (12.13)		88.2 (11.90)
Median (Range)	88.5 (72;116)	82.0 (71;106)		86.5 (68;117)		87.0 (65;109)
End Point (N)	28	30		28		29
Mean (SD)	90.1 (23.86)	73.0 (19.64)		70.0 (22.73)		66.2 (17.48)
Median (Range)	89.5 (43;124)	73.0 (34;113)		68.5 (32;122)		69.0 (32;103)
Baseline Change (N)	28	30		28		29
Mean (SD)	0.4 (21.28)	-12.1 (17.13)		-18.1 (20.14)		-21.9 (16.00)
Median (Range)	-4.0 (-43;35)	-12.5 (-41;23)		-18.0 (-60;35)		-24.0 (-44;12)
P-value (vs. Placebo) [a,b]		0.014		<0.001		<0.001
Diff. of LS Means (SE)		-12.2 (4.88)		-17.7 (4.92)		-22.1 (4.87)
95% CI		(-21.94;-2.55)		(-27.41;-7.89)		(-31.76;-12.44)
Race: Other	(N=27)	(N=7)	(N=18)	(N=25)	(N=19)	(N=7)
Baseline (N)	27	7	18	25	19	7
Mean (SD)	93.9 (10.78)	98.6 (21.61)	94.6 (9.55)	95.0 (14.89)	96.3 (11.07)	88.6 (13.82)
Median (Range)	92.0 (75;117)	110.0 (73;123)	95.5 (79;112)	97.0 (71;131)	101.0 (77;111)	84.0 (71;109)
End Point (N)	27	7	18	25	19	7
Mean (SD)	80.9 (20.61)	60.7 (17.87)	81.0 (17.81)	74.0 (30.12)	71.7 (19.17)	66.3 (14.10)
Median (Range)	80.0 (34;119)	55.0 (42;86)	80.5 (55;122)	74.0 (38;176)	78.0 (32;102)	62.0 (53;93)
Baseline Change (N)	27	7	18	25	19	7
Mean (SD)	-13.0 (18.68)	-37.9 (24.35)	-13.6 (16.72)	-21.0 (29.05)	-24.6 (20.44)	-22.3 (11.32)
Median (Range)	-10.0 (-53;19)	-32.0 (-75;-12)	-21.0 (-38;14)	-18.0 (-79;54)	-16.0 (-74;0)	-18.0 (-44;-10)
P-value (vs. Placebo) [a,b]		0.009	0.923	0.097	0.080	0.231
Diff. of LS Means (SE)		-27.7 (10.28)	-0.6 (6.49)	-9.8 (5.86)	-11.6 (6.54)	-13.8 (11.46)
95% CI		(-48.13;-7.25)	(-13.53;12.27)	(-21.51;1.81)	(-24.60;1.40)	(-36.62;8.95)

[a] Based on ANCOVA model with protocol, treatment (placebo, ER OROS PAL 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) and analysis center within protocol as factors, and baseline value as a covariate.
[b] Comparisons with placebo without multiplicity adjustment.
Note: Negative change in score indicates improvement.

6.1.6 Clinical Microbiology

No information on "clinical microbiology" was provided.

6.1.7 Efficacy Conclusions

Reviewer Conclusions and comments: *The results of pivotal Phase III studies are positive for showing greater improvement on the primary efficacy variable in Pal groups compared to placebo groups. The elderly Study -302 shows at least trends for greater improvement. The elderly study was small such that failure to show significant group differences may be due to insufficient sample size. Due to the small sample size in this study, the results are difficult to interpret.*

The results shown in Table 39 did not show that results were corrected for multiple comparisons between each Pal dose-level and placebo subjects. However, at least numerical trends for greater efficacy in Pal groups at all dose-levels examined compared to placebo was observed. Therefore, a daily dose-level as low as 3 mg may be beneficial to at least, some patients. The final section of this review of this review provides for further comment regarding proposed treatment regimen and dose-levels for the proposed indication.

See previous reviewer comments in this Section addressing other potential issues relevant to efficacy findings.

Refer to Section 9 for reviewer conclusions, comments and recommendations relevant to efficacy for this NDA.

7 INTEGRATED REVIEW OF SAFETY

To aid the reader the following provides an overview of safety findings which is followed by more detailed reviewer comments and summary of each safety variable followed by the sponsor's data (some of the data could only be found in multipaginated tables with as many as 50 or more pages in some cases, such that only sections of these summary tables are displayed or results are summarized rather than being displayed).

Several Safety Signals Consistent with Known Drug Class Effects were Observed in Phase III Trials:

1. *Orthostatic hypotension and tachycardia associated with orthostatic hypotension.*
2. *Hyperprolactinemia*
3. *Subjects that developed hyperglycemia*
4. *Lipid profile effects*
5. *Weight gain*
6. *Somnolence*
7. *Extrapyramidal system effects*
8. *Neuroleptic Malignant Syndrome (NMS): one subject with NMS was reported although there may be at least one additional subject (subjects 100057, 200213)*

Suicidality (includes a few completed suicides) that is known to be inherent in the schizophrenia population but occurred with an incidence of 3% in the 15 mg Pal group compared to 0-1% in

lower dose Pal groups (except that the 3 mg group had an incidence of 2%) and placebo. It is not clear if this is a real dose dependent effect due to the following reasons:

- *Due to the relatively smaller sample size of the 15 mg group compared to most other treatment groups,*
- *Due to multiple between group comparisons,*
- *The between group difference between this group and placebo is small,*
- *The lowest dose group had an incidence of 2%, which is inconsistent with a real signal, since the 3, 6, 9 and 12 mg group had a lower incidence and is only 1% less than the incidence in the 15 mg group*
- *Among other considerations, such as those described in Section 7.2.8 of this reveiw discussing challenges and potential concerns with identifying and enumerating subjects with suicidality.*

Risperdal® labeling describes ADOs of suicide attempt in 1.2% of Risperidone treated subjects compared to 0.6% placebo subjects in their clinical trials for the schizophrenia indication (under Adverse Reactions). Risperdal® has a suicide subsection under Precautions (indicating the risk of suicide that is known to exist in this patient population and the need for close monitoring but only describes the ADOs of suicidality under the Adverse Reactions section).

One subject with Thrombotic Thrombocytopenic Purpura is described in a subsection in Risperdal® labeling under Precuations.

The following observations are noted:

- *Thrombocytopenia was reported as an SAE (100847) in a subject in Study -301 (a "prevention relapse trial). Decreased platelet count was first noted on Day 71 of Pal treatment (12 mg daily). The subject was given the diagnosis of pancytopenia (based on CBC) secondary to a nutritional deficiency. This subject recovered after Pal cessation and nutritional supplementation. In the absence of diagnostic tests (e.g a bone marrow biopsy and B12, folate levels) the role of Pal is unclear.*
- *Clinically unremarkable decreases in group mean values of HgB and platelet count were observed in Pal treatment groups (and not in placebo subjects) in Phase III trials (as described below).*
- *Platelet count appears to show greater decreases with 6-12 month continuous antipsychotic treatment (compared to shorter treatment durations), but the magnitude of these mean decreases is clinically unremarkable (observed in Phase III OL extension trials that is primarily based on updated results in the 120-Day SUR).*
- *Decreased platelet count with chronic treatment appears to be greatest in the group of OL Pal subjects (in the OL extension trials) that previously received DB Olanzapine treatment (in the DB Phase III lead-in studies). But the magnitude of the decrease was clinically unremarkable (primarily based on updated results in the 120-Day SUR).*
- *The most prominent signal for low platelet count was in a small elderly short-term Phase III trial showing an incidence of 8% and 3% in 3-12 mg flexible dose Pal group and placebo group, respectively. However, the sample size was quite small (approximately 30 or more placebo subjects and approximately 70 or more Pal subjects)*