MEMORANDUM

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

DATE: August 25, 2006

FROM: Ni A. Khin, M.D.
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TO: File NDA 21-999 (This overview should be filed with the 11-30-2005 original submission.)

SUBJECT: Recommendation of Approvable Action for Paliperidone Extended Release OROS Oral Tablets for the Treatment of Schizophrenia

1. BACKGROUND

Paliperidone is a major active metabolite of risperidone which is an atypical antipsychotic agent approved in the treatment of schizophrenia. Both risperidone and paliperidone are centrally active dopamine D2 and 5-HT_{2A} antagonists. The proposed dose range in schizophrenia is 3 to 12 mg once daily.

IND 65,850 for paliperidone OROS was originally submitted on September 25, 2002. Several meetings were held at EOP2 with the sponsor for preclinical, CMC, OCP and clinical issues (4/25/2003, 6/20/2003, 12/12/2003). The discussions included:

- preclinical program requirements on genotoxicity data
- description of the relationship between paliperidone exposure achieved with OROS paliperidone administration compared to paliperidone exposure achieved with risperidone
- adequacy of cardiovascular safety monitoring plan including conducting a specific ECG study
- requirement for an NDA.

A pre-NDA meeting was held with the sponsor on 3/23/2005. The meeting focused on the format and contents of the NDA.

The sponsor submitted the above referenced NDA on November 30, 2005. This NDA has been reviewed by Fanghui Kong, Ph.D., from the Office of Biostatistics (review dated 08/08/2006), and Karen Brugge, M.D., Medical Officer, DPP (review dated 07/23/06; 8/18/06). The CMC reviewer for this NDA is Chhagan Tele Ph.D. The Office of Clinical Pharmacology (OCP) reviewer is Ron Kavanaugh, Ph.D. The pharmacology/toxicology reviewer is Elzbieta Chalecka-Franaszek, Ph.D. At the time of completion of this memo, the Chemistry, the pharmacology/ toxicology and the clinical pharmacology reviews are not finalized.

2.0 CHEMISTRY

I am not aware of any CMC concerns that would preclude an approvable action on this NDA.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues that would preclude an approvable action for this NDA.

4.0 CLINICAL PHARMACOLOGY

I am not aware of any clinical pharmacology concerns that would preclude an approvable action for this NDA.

Paliperidone has an elimination half-life of approximately 23 hours. Steady state is reached 4-5 days. The Cmax and AUC values were increased by 42% and 46%, respectively, in the fed state compared with administration of paliperidone under fasting condition. The plasma protein binding of paliperidone is 74%. Cytochrome P450 isozymes (CYP2D6 and CYP3A4) seem to be involved in metabolism of paliperidone. In-vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the drugs metabolized by Cytochrome P450 isozymes. The pharmacokinetics does not appear to be affected by age, race, gender, smoking status or hepatic impairment. The elimination half-life of paliperidone is prolonged (41-50 hrs) in subjects with impaired renal function.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 4 short-term, double-blind, placebo-controlled trials in patients with schizophrenia. Three studies (R076477-SCH-303, R076477-SCH-304, R076477-SCH-305) were the 6-week, double-blind, placebo and active controlled (Olanzapine 10 mg), parallel-group, fixed-dose studies designed to evaluate the efficacy and safety of paliperidone ER. The doses of paliperidone ER used were 6, 9, and 12 mg in study 303; 6 and 12 mg in study 304; and 3, 9, and 15 mg in study 305. Study R076477-SCH-302 was a 6-week, double-blind, placebo controlled, flexible dose of paliperidone ER in elderly patients with schizophrenia.

The sponsor indicated that results of the 3 pivotal clinical studies, either considered individually or pooled, demonstrated that all doses of paliperidone ER OROS tested were superior to placebo on the primary efficacy variable. The sponsor also indicated that paliperidone ER did not differ from olanzapine in a pooled analysis of the 3 phase 3 fixed dose studies in adults and the results from olanzapine group was used for assay sensitivity analysis.

I would briefly describe the results of each of these paliperidone studies pertinent to efficacy claim in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

Study R076477-SCH-303

This was a randomized, double-blind, placebo and active controlled, parallel-group, 6-week, fixed-dose study comparing paliperidone ER (at fixed doses of 6, 9, 12 mg/day, given on a qd basis in the morning), olanzpine (at a fixed dose of 10 mg, given on a qd basis in the morning), and placebo. The study was conducted at 53 centers in 11 countries (Eastern and Western European; Asia) in adult (age 18 or older) patients meeting DSM-IV criteria for schizophrenia. All subjects were hospitalized for the first 14 days of double-blind treatment. The total number of subjects enrolled in this study was 628 in which 374 subjects in paliperidone treatment group. The ITT samples for paliperidone (6, 9, 12 mg), olanzapine and placebo were 123, 122, 129, 128 and 126, respectively. The subjects enrolled were mostly white, mean age was 37 yrs, and had approximately an equal distribution of male and female subjects. There seemed to be no significant differences in demographic characteristics among the treatment group. A total of 415 subjects (66%) completed the study. The number of subjects who discontinued from the study for were 35%, 30%, 22%, 30% and 54%, in paliperidone (6, 9, 12 mg), olanzapine and placebo group, respectively. The most common reason for early withdrawal was lack of efficacy.

The efficacy assessment included the PANSS and the CGI-S, administered weekly. The primary end point phase was the change in the total score of the PANSS from baseline to the last post-randomization assessment in the double-blind treatment period. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with Dunnett's procedure to adjust for multiple doses. Dr. Kong confirmed the primary efficacy results. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on PANSS Total Scores for Study 303 (LOCF):

	Mean Baseline PANSS (SD)	Change from Baseline Mean (SD)	P-values (vs. placebo)
Paliperidone ER OROS 6mg	94.3 (10.48)	-17.9 (22.23)	<0.001
Paliperidone ER OROS 9mg	93.2 (11.9)	-17.2 (20.23)	<0.001
Paliperidone ER OROS 12mg	94.6 (10.98)	-23.3 (20.12)	<0.001
Placebo	94.1 (10.74)	-4.1 (23.16)	

There does not seem to have an advantage of the 9 mg over 6 mg dose. However, the sponsor states that a statistically significant difference in mean change was seen between the paliperidone 12 mg and the other 2 doses 6 and 9 mg, p-values of 0.046 and 0.037, respectively.

Comment:

Both Drs. Brugge and Kong considered this a positive study for paliperidone, and I agree with them.

Study R076477-SCH-304

This was a randomized, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, 6-week, fixed-dose study comparing paliperidone ER (at fixed doses of 6, 12 mg/day, given on a qd basis in the morning), olanzpine (at a fixed dose of 10 mg, given on a qd basis in the morning), and placebo. The study was conducted at 45 centers in the U.S. in adult (age 18 or older) patients meeting DSM-IV criteria for schizophrenia. All subjects were hospitalized for the first 14 days of double-blind treatment. The total number of subjects enrolled in this study was 432 in which 222 subjects in paliperidone treatment group. The ITT samples for paliperidone (6, 12 mg), olanzapine and placebo were 111, 111, 105 and 105, respectively. The subjects were mostly male, slightly above 50% were black and mean age was 42 yrs. There seemed to be no significant differences in demographic characteristics among the treatment group. A total of 193 subjects (43%) completed the study. The number of subjects who discontinued from the study were 54%, 52%, 55% and 66%, in paliperidone (6, 12mg), olanzapine and placebo group, respectively. The most common reason for early withdrawal was lack of efficacy.

The efficacy assessment included the PANSS and the CGI-S, administered weekly. The primary end point was the change in the total score of the PANSS from baseline to the last post-randomization assessment in the double-blind treatment period.

The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with Dunnett's procedure to adjust for multiple doses. Dr. Kong confirmed the primary efficacy results. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on PANSS Total Scores for Study 304 (LOCF):

	Mean Baseline PANSS (SD)	Change from Baseline Mean (SD)	P-values (vs. placebo)
Paliperidone ER OROS 6mg	92.3 (11.96)	-15.7 (18.89)	0.006
Paliperidone ER OROS 12mg	94.1 (11.42)	-17.5 (19.83)	<0.001
Placebo	93.6 (11.71)	-8.0 (21.48)	

The 12 mg dose exhibited a numerically greater mean decrease in PANSS total scores compared with the 6 mg dose, but this difference is not statistically significant.

Comment:

Both Drs. Brugge and Kong considered this a positive study for paliperidone, and I agree with them.

Study R076477-SCH-305

This was a randomized, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, 6-week, fixed-dose study comparing paliperidone ER (at fixed doses of 3, 9, 15 mg/day, given on a qd basis in the morning), olanzpine (at a fixed dose of 10 mg, given on a qd basis in the morning), and placebo. The study was conducted at 74 centers in 14 countries in North America, Eastern Europe, Asia, Isreal, Mexico and South Africa in adult (age 18 or older) patients meeting

DSM-IV criteria for schizophrenia. All subjects were hospitalized for the first 14 days of double-blind treatment. The total number of subjects enrolled in this study was 605 in which 359 subjects in paliperidone treatment group. The ITT samples for paliperidone (3, 9, 15 mg), olanzapine and placebo were 123, 123, 113, 126 and 120, respectively. The subjects were about 65-75% male, approximately 50% white and mean age was 38 yrs. There seemed to be no significant differences in demographic characteristics among the treatment group.

A total of 365 subjects (59%) completed the study. The number of subjects who discontinued from the study were 45%, 38%, 29%, 31% and 62%, in paliperidone (3, 9, 15 mg), olanzapine and placebo group, respectively. The most common reason for early withdrawal was lack of efficacy.

The efficacy assessment included the PANSS and the CGI-S, administered weekly. The primary end point phase was the change in the total score of the PANSS from baseline to the last post-randomization assessment in the double-blind treatment period.

The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with Dunnett's procedure to adjust for multiple doses. Dr. Kong confirmed the primary efficacy results. He also applied MMRM as a sensitivity analysis. The results are as follows:

Efficacy Results on PANSS Total Scores for Study 305 (LOCF):

	Mean Baseline PANSS (SD)	Change from Baseline Mean (SD)	P-values (vs. placebo)
Paliperidone ER OROS 3mg	91.6 (12.66)	-15.0 (19.61)	<0.001
Paliperidone ER OROS 9mg	93.9 (11.9)	-17.2 (20.23)	<0.001
Paliperidone ER OROS 15mg	94.6 (10.98)	-23.3 (20.12)	<0.001
Placebo	94.1 (10.74)	-4.1 (23.16)	

A statistically significant difference in mean change was seen between the paliperidone 3 mg and the 15 mg group (p=0.021); a numerical difference was observed between the 9 and the 15 mg groups, with a trend in p=0.074.

Comment:

I agreed with both Drs. Brugge and Kong that this study be considered a positive study for paliperidone.

Study R076477-SCH-302

This was a 6-week, double-blind, placebo controlled, multicenter study using flexible dose (3 to 12 mg/day) of paliperidone ER in elderly with schizophrenia. A total of 114 subjects were enrolled in this study; 76 subjects in paliperidone group and 38 subjects in placebo group. The study population was predominantly female (73%); mean age was 69.7 yrs (range 64-81 yrs). The results showed a trend for greater improvement based on the PANSS scores.

Because the study was intended mainly for the safety and tolerability of the paliperidone in elderly patients and was comprised of a small sample size, Dr. Kong did not include this study in his efficacy analysis. I agree with Dr. Brugge's conclusion that the result are difficult to interpret due to the small sample size in this study.

5.1.3 Comments on Other Important Clinical Issues

Evidence Bearing on the Dose-Response for Efficacy

All 3 positive studies involved fixed paliperidone ER doses. The doses included were: 6, 9 and 12 mg in study 303; 6 and 12 mg in study 304; and 3, 9 and 15 mg in study 305. The studies were not optimally designed to study dose-response. Dr. Brugge has recommended a target dose of 6 mg/day mainly based on the fact that there was more support for this dose than for the 3 mg dose. I would prefer targeting the 3 mg dose, with the possibility of titration. The labeling should include information regarding the demonstrated efficacy compared to adverse events profile of the drug at higher doses. It is noted that risperidone labeling provides specifications on dose adjustment in the dosing and administration section of the labeling. We should provide the same for paliperidone labeling. We should ask the sponsor to conduct a fixed dose study in this patient population to give a better understanding in the lowest effective dose, the dose titration schedule and interval. We should obtain the sponsor's commitment to conduct this as a phase IV study.

Subgroup Analyses

Exploratory subgroup analyses were done by the sponsor and the Statistical Reviewer to detect subgroup interactions on the basis of gender, age and race.

As Dr. Kong pointed out in his review, the majority of study subjects (87%) were white and over 70% of the study subjects were between age 25 and 50. Dr. Brugge noted that there was a numerical improvement on the primary efficacy variable for each paliperidone treatment group compared to placebo. Because of the small sample size, the results are difficult to interpret for these smaller subgroups.

The gender did not seem to have an effect on the significance level of the treatment on the primary efficacy endpoint, i.e, no treatment and gender interaction in all 3 studies (303, 304 and 305).

Mean effect size, as measured by difference between drug and placebo, were comparable between males and females in all these studies although the sample size, as Dr. Kong notes in his review that, was considerably larger in the male group in studies 304 and 305.

Overall, there is no clear indication of subgroup differences in response based on these variables. The effect size observed in these positive studies seemed similar to that seen in other schizophrenia trials.

Secondary Efficacy Variables

In the proposed labeling, the sponsor intends to claim efficacy evaluation using the PANSS factors and the Personal and Social Performance (PSP) scale. Although the results from these secondary efficacy measures were reported to be positive, these were not pre-specified outcome measures.

Therefore, we should not accept the sponsor's proposal to include these two variables in the labeling unless the sponsor could provide documentation that the studies were prospectively planned to include such claim.

[redacted]

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses of all 3 fixed-dose studies supported the efficacy claim of paliperidone ER OROS in the treatment of schizophrenia in all of the dose groups tested. The sponsor has not adequately explored the lower end of the dose response curve for paliperidone. We should obtain the sponsor's commitment to conduct a study to identify the minimal effective dose and dose titration/adjustment as a phase IV study. The issue of [redacted]

5.2 Safety Data

5.2.1 Satety Database

Dr. Brugge's safety review of this NDA was based on an integrated database covering 37 clinical trials in the drug development program for paliperidone. This included:

1) clinical pharmacology studies comprised of 27 phase 1/2a studies
   - 17 pooled trials of healthy adults
   - 3 pooled trials of schizophrenia patients
   - unpooled data from 7 other trials
2) clinical efficacy and safety phase 3 studies
   - 4 completed phase 3 double-blind studies in subjects with schizophrenia
   - 1 ongoing phase 3 double-blind relapse prevention study
   - 5 ongoing phase 3 open-label extension studies

Dr. Brugge's safety review included data from the original submission and also a 4-month safety update, with a cut-off date of 05/31/2005 (8/31/2005 for deaths and SAEs) and 11/1/2005, respectively.

The program included 592 paliperidone exposed subjects out of 1048 subjects enrolled in the clinical pharmacology trials and 1523 paliperidone exposed subjects in the phase 3 safety/efficacy trials, representing 507.59 patient-years of exposure.

The patient distribution for the sample was as follows:

- 383 subjects with schizophrenia or schizoaffective disorder in phase 1/2a studies; and
- 1039 schizophrenia patients (out of 1796 enrolled) in the 4 completed phase 3 double-blind treatment; 1167 patients then received open-label ER OROS paliperidone

- 462 schizophrenia patients had been enrolled in the ongoing phase 3 double-blind relapse prevention study (study 301)

The ICH criteria for duration of drug exposure were met for ≥6 months and ≥12 months, with n=687 exposed for ≥29 weeks and n=228 exposed for >52 weeks based on the total duration of paliperidone exposure table provided in the safety report update by the sponsor.

There were no deaths reported in the paliperidone treatment group in the phase 3 double-blind studies. Serious adverse events were available from these trials. There were no post-marketing data since paliperidone ER OROS is not marketed any country in the world.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). In the double-blind studies, the AEs of tachycardia, akathesia, and EPS occurred more frequently in subjects who received paliperidone. However, there are several AEs that, while not strictly meeting these criteria, did appear at a higher rate for paliperidone mostly at high doses vs. placebo: dystonia, hypertonia, orthostatic hypotension, headaches and hypersalivation.

5.2.2.2.1 Extrapyrimidal Symptoms

Pooled data from the three placebo-controlled, fixed dose studies also suggested evidence of treatment emergence and dose-relatedness for EPS with the higher doses of paliperidone. Compared to the EPS rate of 2.3% in placebo group, the percentage of subjects with EPS were 4.7%, 2.1%, 6.9%, 7.4% for 3 mg, 6 mg, 9 mg and 12 mg dose groups of paliperidone, respectively.

5.2.2.2.2 Akathesia

Similarly, the rate of akathesia was 3.9% in placebo group, the percentage of subjects who experienced akathesia were 3.97%, 3.0%, 8.1%, 9.5% for 3 mg, 6 mg, 9 mg and 12 mg dose groups of paliperidone, respectively.

5.2.2.2 Mortality in Elderly

Two subjects who participated in the elderly study 302 died in the course of the study. Subject 200308 died from coma due to subdural hygroma; subject 200718 died from cardiac arrest due to lung cancer. Both of these subjects were assigned to placebo. The sponsor's proposal of this topic in the paliperidone labeling that include information from the Boxed Warning and the Warning sections of risperidone labeling on increased mortality and cerebrovascular AE including stroke in elderly patients with dementia related psychosis seems reasonable.

5.2.2.3 Orthostatic Hypotension

Orthostatic hypotension was observed with greater frequency in subjects who received paliperidone ER OROS consistent with the known pharmacology of risperidone and paliperidone. Specifically, pooled data from the three placebo-controlled, fixed dose studies showed the incidence rate of orthostatic hypotension in placebo group was 0.8% while the percentage of patients who experienced orthostasis in paliperidone groups were 2.4%, 1.3%, 2.4% and 3.7%, with 3 mg, 6 mg, 9 mg and 12 mg dose, respectively.

5.2.2.4 Vital Sign Changes

As expected based on its alpha-blocking activity, ER OROS paliperidone was associated with a higher incidence of abnormally high supine and standing pulse rates compared to placebo. These findings were consistent with the higher incidence of adverse events of tachycardia in subjects who received ER OROS paliperidone versus placebo. Based on the results from the short-term, fixed-dose, placebo-controlled trials, the percentages of subjects with tachycardia were 2.4%, 7.2%, 7.3%, 7.4% with the 3, 6, 9 and 12 mg paliperidone treated group, respectively, while the rate was 2.8% in the placebo group.

A mean increase from baseline in heart rate (both standing and supine tachycardia) was observed. It was time-dependent and dose-dependent with greatest effects generally observed in the high dose group (15 mg). The mean increase observed in this group for supine heart rate was 6.8±12.9 bpm on Day 6 (ranging up to a maximum individual-subject increase of 128 bpm) compared to 0.6+11 bpm in placebo group. The 15 mg paliperidone treated group generally showed higher mean increases of standing heart rate up to 7 bpm (SD of ±14 or ±15) on Days 3 and 4 with little to no change in the placebo group (mean change of 1.5 to -0.8).

5.2.2.5 ECG and QTc Findings

ECG data were available from the three fixed-dose, placebo-controlled, phase 3 studies. ECG data were available from the phase 1/2a PK studies as well. In addition, the sponsor conducted a cardiovascular safety study (study R076477-SCH-1009).

Study R076477-SCH-1009
This was a double-blind, placebo and active controlled (moxifloxacin 400 mg), randomized study in subjects with schizophrenia or schizoaffective disorder (total N=141). Study subjects were randomized to paliperidone immediate release (IR) or the positive control, moxifloxacin, on Day 1. All subjects received a single dose of placebo on Day 1 in the paliperidone IR treatment group, and on Days 1 to 7 in the moxifloxacin treatment group. In the paliperidone IR treatment group (N=72), subjects received paliperidone 4 mg/day q.d. on Day 2, 6 mg/day q.d. on Day 3, and 8 mg/day q.d. on Days 4 through 8. In the moxifloxacin treatment group, subjects received moxifloxacin 400 mg on Day 8. Both groups were followed off treatment on Days 9 and 10.

Day-averaged QTcLD showed a LS mean difference of 5.5±1.09 ms (90% CI 3.66-7.25) at Day 8 for the paliperidone IR group and a difference of 4.3±0.84ms (90% CI 2.88-5.64) at Day 8 for the moxifloxacin 400 mg group, compared to placebo at Day 1. None of the paliperidone IR subjects showed a QTc increase of greater than 60 ms. None of the paliperidone IR subjects showed

prolonged QT values exceeding 450 ms for males and 470 ms for females except that QTcB was prolonged in 7 out of 72 paliperidone IR subjects. Paliperidone increases the heart rate be noted.

The formulation used in study SCH-1009 was the immediate release formulation of paliperidone. It should be noted further that the Cmax ss for paliperidone IR 8 mg qd is 113 ng/mL, approximately 2.5 times the Cmax ss for paliperidone ER 12 mg qd, i.e., 45 ng/mL.

I note in Dr. Brugge's review that 1 subject (201102), a 23 year old male with no cardiac history who received 12 mg paliperidone ER in study 303 was reported as an adverse dropout due to abnormal ECG (QTcF of 454 msec on Day 6).

There is a greater incidence of AV block in the 15 mg paliperidone group (4.4%) compared to placebo (1.4%). In the elderly study 302 using flexible doses of paliperidone, First degree AV block was observed in 3% (2 subjects out of 76 paliperidone) compared to no events in placebo subjects.

Recently, DPP has sent a consult to the Division of Cardiorenal Products to comment on whether study SCH-1009 is an adequate basis for estimating the QT effects of paliperidone. We are awaiting their input on the QT data from study SCH-1009, along with the QT findings from the phase 3 clinical studies with paliperidone, a sufficient basis for concluding that paliperidone ER, at the doses recommended, is adequately safe. We also asked for any need for additional QT data before reaching a conclusion about the cardiovascular safety of paliperidone ER.

5.2.2.6 Syncope

In the original submission (N000), results of the short-term phase 3 trial dataset noted that syncope was reported in 1 subject (<1%) in each treatment group of paliperidone including the placebo.

In response to the questions raised by Dr. Brugge regarding subjects with potential vital sign related events and for the safety update review, the sponsor provided an amendment submission (N007). In this amendment, the sponsor reported that a total of 49 subjects (3%) who were asymptomatic at baseline (out of 1682 subjects) in the pooled double-blind studies were identified as symptomatic during treatment (paliperidone ER OROS 3%, 32/963; placebo 2%, 7/355; olanzapine 3%, 10/364). The sponsor concluded that 12 of these 49 subjects may have confounding cause (e.g., concomitant medication or medical condition) including 7 of 32 subjects in paliperidone group, 3 of 7 placebo subjects and 2 of 10 olanzapine subjects). The sponsor also noted that the remaining subjects, there was insufficient information to draw conclusion. On this list of 49 symptomatic subjects, 10 subjects were listed to have experienced syncope: 7 subjects out of 963 in paliperidone group (0.73%); 1 subject out of 355 subjects (0.28%) in placebo group; and 2 subjects out of 364 in olanzapine group (0.55%). I acknowledge Dr. Brugge's concerns of vital sign related events. Based on these numbers of events, Dr. Brugge's recommendation that the sponsor be asked to provide more description (line listings and narratives) on cases using various vital sign cutoffs, as listed in her review, seems unnecessary at this time.

We are awaiting an input from the Cardiorenal whether they have any concerns on possible QT effect of drug, and if any, would have contributed in causing syncope.

5.2.2.7 Neuroleptic Malignant Syndrome

Neuromuscular malignant syndrome (NMS) was not reported for any subjects in the completed Phase 3 trials (-302 through -305) or for the ongoing OL studies (-701 through -705). According to the sponsor, NMS and increased blood creatine phosphokinase (CPK) were reported for 1 subject (100057) in the ongoing "prevention of recurrence" trial, Study -301 after receiving 3 weeks of blinded study drug. NMS was resolved following discontinuation of treatment. Dr. Brugge noted that, based on her review of case narratives, there may be an additional case. NMS is one of the subsections in the Warnings section of the proposed labeling. The language is similar to the risperidone labeling. It seems acceptable to me.

5.2.2.8 Tardive Dyskinesia

There were 2 reports of tardive dyskinesia (1 during the double-blind and 1 during the open-label paliperidone ER OROS treatment). It appears acceptable as the description of TD in the proposed labeling is almost identical to that of risperidone.

5.2.2.9 Abnormal Laboratory Tests

5.2.2.9.1.1 Hyperglycemia and Lipid Profiles

The sponsor reported that the effects of ER OROS paliperidone on the results of chemistry and hematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not show clinically relevant differences from those of placebo. Hyperglycemia and diabetes mellitus is described under Precautions of risperidone and so as for some other antipsychotic drugs. The sponsor's report on hyperglycemia and diabetes mellitus in paliperidone treated subjects (1%) has not revealed any new or unexpected findings. Given the fact that paliperidone is the major metabolite of risperidone, I have no objection of the sponsor's proposal to use most of the language from risperidone in the paliperidone labeling.

5.2.2.9.1.2 Hyperprolactinemia

Dose dependent group mean increases in prolactin levels were observed with greater frequency in subjects who received paliperidone ER OROS in the phase 3 fixed dose dataset. Phase 1/2a results with schizophrenia patients revealed similar mean Prolactin level increases in Pal groups (OROS and non-OROS groups compared) to Risperidone treatment (i.e., mean levels of 32.1 and 37.0 ng/ml were observed in the high dose OROS Pal and the risperidone groups, respectively). The Agency has requested the sponsor to make revisions to the precaution section regarding hyperprolactinemia associated with risperidone. The sponsor has recently submitted a response to the risperidone NDA supplement on this issue and is under review. Given the finding that prolactin levels among paliperidone treated subjects generally is similar to those observed during treatment with risperidone, we would modify the language in paliperidone accordingly.

5.2.2.9.1.3 CPK

Dr. Brugge noted in her review that elevations in CPK levels were observed in phase 3 trials. However, she pointed out that these elevations were inconsistent across treatment groups, varied widely among subjects and showed large fluctuations over time within a given subject. There were

no other serious events associated with CPK elevations except for two cases of NMS as described before. In her review dated 8/18/06, Dr. Brugge provided her review of additional information by the sponsor on this topic including the elevated CPK levels from the phase 1 trials. She noted that if the sponsor cannot provide convincing data to explain that these elevations are not drug-related, labeling should include [redacted] She also noted that since CPK elevations can occur in acutely psychotic patients for non-drug related reasons, the highly variable CPK elevations observed in patients in the phase 3 trials are difficult to interpret.

5.2.2.10 Weight Gain

Mean body weight and BMI showed dose-related increases during double-blind treatment with ER OROS paliperidone. In the 6-week, double-blind Phase 3 trials (R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305), mean weight increases were 0.6 kg for subjects who received 3 or 6 mg/day, 1.0 kg for subjects who received 9 mg/day, and 1.1 kg for subjects who received 12 mg/day of ER OROS paliperidone. Weight increases were infrequently reported as adverse events.

5.2.2.11 Suicidality

The sponsor has provided the methodology in their effort to identify subjects with suicidality that was reported in the CRFs. In the pooled double-blind phase 3 studies, the incidence of suicide related AEs listed 7 subjects in paliperidone treatment group (N=1039), 4 subjects in the placebo group (N=355), and 5 subjects in the olanzapine treatment group (N=364). I acknowledge Dr. Brugge's comments and discussion of this topic in her assessment of quality and completeness of data. She pointed out that there was a note in the table for not including several subjects in the subject listing if the investigator reported symptom as part of overall clinical condition or investigator denied suicidality. She questioned on whether or not there should be additional search term to find existence of other uncaptured subjects. It is known that the risk of suicide is high among patients with schizophrenia and some apparent suicide may be in response to the psychotic illness (in case of command hallucinations). The sponsor's proposed language on this topic in one of subsections in the Precaution section of the labeling seems adequate at this time.

5.2.3 Additional Concern of a Food Effect

Results from the study R076477-P01-1008 showed food effects in which approximately 42-46% increase in the Cmax and AUC were observed in the fed compared to the fasted state. As pointed by Dr. Brugge in her review, food effects were observed on PK data may in turn increase in mean systolic BP (i.e., 13.5 mmHg in the fed to-be-marketed [redacted] Pal treatment condition at 36 hours postdose) that began at approximately 29 or 30 hours post-dose that was less prominent in the fasted conditions in Phase I studies. Group mean increase in heart rate to a similar extent in fasted and fed treatment conditions was also observed that occurred near the same time as the increased BP.

Risperidone and Paliperidone used mostly in PK studies were an immediate release formulation while the to-be-marketed formulation of paliperidone is an extended release oral OROS formulation which was also used in the phase 3 clinical studies stated above. It should be noted further that the Cmax ss for paliperidone IR 8 mg qd is 113 ng/mL, approximately 2.5 times the Cmax ss for paliperidone ER 12 mg qd, i.e., 45 ng/mL. Labeling will need to be clear in noting this issue. Based on my discussion with the biopharm reviewer (final review not yet available at this time), Dr.

Kavanaugh stated that the food effect is likely due to the OROS formulation and such food effect results can be addressed adequately in the labeling.

As stated before, recently, DPP has sent a consult to the Division of Cardiorenal Products to comment on results of study SCH-1009 and also, the approximately 50% increase in paliperidone ER Cmax with food a cause for concern regarding the cardiovascular safety of paliperidone. Based on the available data and the cardiorenal input, we may be able to decide whether the proposed labeling for paliperidone ER adequately reflect the cardiovascular risks associated with this drug.

5.2.4 Conclusion Regarding Safety of Paliperidone ER in Schizophrenia

Overall, this submission revealed safety findings of paliperidone consistent with the previously observed safety profile of risperidone. While I acknowledge safety signals raised by the clinical reviewer based on her review of the safety information provided in this submission, the questions imposed to the sponsor to address these issues is deemed unnecessary. We are waiting to receive a consultative report by the Division of Cardiorenal Products on whether there is sufficient QTc and related data, based on the submitted results from the phase 3 placebo-controlled trials and the QT study R076477-SCH-1009, to conclude that paliperidone is reasonably safe. The safety items considered by the Division as needed in prescribing information would be adequately reflected in the labeling.

6.0 WORLD LITERATURE

The sponsor indicated that they discovered 273 publications in their literature search and they noted that their full-text review of 88 of these selected articles revealed no new or remarkable clinical information that affect conclusions about the relevance to the safety of paliperidone. Dr. Brugge reviewed the reference list and some findings were described in her review. She concluded that the safety information of paliperidone are generally not unexpected given they seemed similar to the safety profile of drugs in this class.

7.0 FOREIGN REGULATORY ACTION

To my knowledge, paliperidone is not approved for any indication in any country at this time. We will ask for an update on the regulatory status of paliperidone for the treatment of schizophrenia in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 study sites. DSI recommended that data from these inspected sites appear acceptable. Inspectional findings did not seem to raise any major concern on integrity of study data.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified. Our proposed labeling should be included in the action letter.

10.2 Foreign Labeling

At this time, I am not aware that paliperidone is approved for the treatment of schizophrenia anywhere else.

10.3 Action Letter

The approvable letter includes draft labeling and request for phase IV commitment.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that paliperidone ER OROS is effective and appears reasonably safe in the treatment of schizophrenia. I recommend that we issue an approvable action letter. Addendum to this memo will be generated if conclusion changes upon receipt of the consultative report by the Division of Cardiorenal Products. We may consider approval of this NDA contingent on satisfactory responses to the concerns raised by various disciplines, if any, and a mutual agreement between the sponsor and the Agency on language in the labeling.

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/s/

Ni Aye Khin
8/31/2006 03:41:43 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Division of Cardiovascular and Renal Products

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Division of Psychiatry Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8/8/06		21-999		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Paliperidone		schizophrenia	PDUFA date is 9/30/06

NAME OF FIRM: Johnson & Johnson

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: see attached

SIGNATURE OF REQUESTOR
Steven D. Hardeman, R.Ph.
CPMS
Division of Psychiatry Products
WO Room 4390

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☒ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Reason for Request:

We would appreciate your input and recommendations about QT findings for paliperidone, particularly those reported from study SCH-1009). Specific questions are included in attached document.

Comments/Specific Instructions:

This is a new NDA for paliperidone extended release oral tablets. Please note that this application has been submitted electronically and may be accessed by the EDR. The link is \\Cdsesub1\evsprod\n021999\0000\ Should you have any questions, please contact Steve Hardeman, CPMS, at 301-796-1081. The PDUFA due date for this NDA is September 30, 2006. Dr. Karen Brugge is the medical officer for this NDA. Please see more detailed questions that are attached.

Cardiology Consult Request

NDA: 21-999
Paliperidone ER in treatment of schizophrenia

Paliperidone is a major active metabolite of risperidone which is an atypical antipsychotic agent approved in the treatment of schizophrenia. Both risperidone and paliperidone are centrally active dopamine D2 and 5-HT_{2A} antagonists.

In this NDA for paliperidone, the sponsor has included the results from the following studies:

1) Study R076477-SCH-1009: cardiovascular safety study

This was a double-blind, placebo and active controlled (moxifloxacin 400 mg), randomized study in subjects with schizophrenia or schizoaffective disorder (total N=141). Study subjects were randomized to paliperidone immediate release (IR) or the positive control, moxifloxacin, on Day 1. All subjects received a single dose of placebo on Day 1 in the paliperidone IR treatment group, and on Days 1 to 7 in the moxifloxacin treatment group. In the paliperidone IR treatment group (N=72), subjects received paliperidone 4 mg/day q.d. on Day 2, 6 mg/day q.d. on Day 3, and 8 mg/day q.d. on Days 4 through 8. In the moxifloxacin treatment group, subjects received moxifloxacin 400 mg on Day 8. Both groups were followed off treatment on Days 9 and 10. [Note: Please note the differences in formulations: risperidone is an immediate release formulation while the to-be-marketed formulation of paliperidone is an extended release oral OROS formulation which was also used in the phase 3 clinical studies stated above. The formulation used in study SCH-1009 was the immediate release formulation of paliperidone. It should be noted further that the Cmax ss for paliperidone IR 8 mg qd is 113 ng/mL, approximately 2.5 times the Cmax ss for paliperidone ER 12 mg qd, i.e., 45 ng/mL.]

Table 12 (Day-averaged QTcLD) showed a LS mean difference of 5.5±1.09 ms (90% CI 3.66-7.25) at Day 8 for the paliperidone IR group and a difference of 4.3±0.84ms (90% CI 2.88-5.64) at Day 8 for the moxifloxacin 400 mg group, compared to placebo at Day 1. None of the paliperidone IR subjects showed a QTc increase of greater than 60 ms. None of the paliperidone IR subjects showed prolonged QT values exceeding 450 ms for males and 470 ms for females except that QTcB was prolonged in 7 out of 72 paliperidone IR subjects. [Note: Paliperidone increases the heart rate.]

2) Phase 3 clinical studies (conducted with paliperidone ER):

- Study R076477-SCH-303 (Europe): a 6-week, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, fixed-dose (6, 9, 12 mg of paliperidone ER) study to evaluate the efficacy and safety of paliperidone ER. Total N=629; N=375 in paliperidone group
- Study R076477-SCH-304 (all U.S. sites): a 6-week, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, fixed-dose (6, 12 mg of paliperidone ER) study to evaluate the efficacy and safety of paliperidone ER. Total N= 439, N=224 in paliperidone group
- Study R076477-SCH-305: a 6-week, double-blind, placebo and active controlled (olanzapine 10mg), parallel-group, fixed-dose (3, 9, 15 mg of paliperidone ER) study to evaluate the efficacy and safety of paliperidone ER. Total N=614; N=364 in paliperidone group
- Study R076477-SCH-302: a 6-week, double-blind, placebo controlled, flexible dose of paliperidone ER in elderly with schizophrenia. Total N=114; N=76 in paliperidone group

The sponsor indicates that paliperidone ER did not differ from olanzapine or placebo in a pooled analysis of the 3 phase 3 studies in adults.

3) Pivotal BE food effect study:

- Study R076477-P01-1008: The results showed food effects in which approximately 42-46% increase in the Cmax and AUC were observed in the fed compared to the fasted state.

The proposed paliperidone ER dosing regime is 6 mg administered daily in the morning with the recommended daily dose range of 3 to 12 mg.

Questions:

1. Is study SCH-1009 an adequate basis for estimating the QT effects of paliperidone?
2. Are the QT data from study SCH-1009, along with the QT findings from the phase 3 clinical studies with paliperidone, a sufficient basis for concluding that paliperidone ER, at the doses recommended, is adequately safe?
3. Is there any need for additional QT data before reaching a conclusion about the cardiovascular safety of paliperidone ER?
4. Is the roughly 50% increase in paliperidone ER Cmax with food a cause for concern regarding the cardiovascular safety of paliperidone?
5. Does the proposed labeling for paliperidone ER adequately reflect the cardiovascular risks associated with this drug?

Reference:

QT study full report: Mod5.3.5.4\R076477-SCH-1009

- Module 5.3.5.4\R076477-SCH-1009\Section7.2.1.1
- Table 12: Day-Averaged QTcLD: Least Square Mean Differences From Day 1
- Table 15: Number of subjects with a maximum change in QTc interval of 30 to 60 ms or >60 ms. (Attachment 3.4)
- Table 16: Number of subjects with a maximum QTc interval that was borderline or prolonged (Attachment 3.5)
- Attachment 3.6: Number (%) of Subjects With a Maximum QTc Interval of 450 ms or Greater by Study Day and Time Postdose.

Tabular Listing of all studies and linkage:
\\Cdsesub1\evsprod\n021999\0000\m5\52-tab-list

Phase 3 clinical study reports:
\\Cdsesub1\evsprod\n021999\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5351-stud-rep-contr

Pivotal BE food effect study report: Mod5.3.1.2\R076477-P01-1008

Proposed labeling (word version): \\Cdsesub1\evsprod\n021999\0000\m1\us

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/s/

Steve Hardeman
8/10/2006 01:16:34 PM

CLINICAL REVIEW

Application Type:	NDA 21-999
Submission Number Code and Materials Reviewed:	N005 (sections not previously reviewed in the original NDA review), N007, N006 (sections as specifed in the review), Responses to other Questions, as specified in the review
Letter Dates:	6/15, 06, 6/27/06, 6/15/06, respectively and see review f or additional dates
Reviewer Name	Karen Brugge, MD
Review Completion Date	8/18/06
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

I. Introduction and Background

The following subsections summarize the sponsor's responses to inquiries (that were not included in the original NDA review). The final section of this review summarizes a section found in the 210-safety update report submission under this NDA in which the sponsor added new information to 15 narratives (the section reviewed in the 210 safety update report, as specified later in this introductory and background section).

Reviewer comments are italicized and are followed by reviewer recommendations (italicized) in the case that the Agency grants an approvable action on this NDA.

Questions and comments are conveyed to the sponsor that can be found in an 8/2/06 documents submitted in DFS under this NDA. The following summarizes the sources of information continue responses to questions conveyed to the sponsor that are summarized in this review, unless otherwise specified:

- Sections of N005 (some sections of this submission were previously reviewed in summarized in the original review of this NDA).
- Results from an EKG study, Study SCH-1009, found in N007 (dated 6/27/06).
- E-mailed responses dated 7/15/06, 7/21/06, and 7/26/06 in response to Questions 2, 3, and Questions 4 and 5, respectively (these questions were conveyed to the sponsor in an e-mail communication dated 6/28/06 which is included in the 8/2/06 correspondence document submitted under the NDA in DFS).
- New information was added to narratives of 15 subjects that were found in appendix 3.6 of the Summary of Clinical Safety Section (SCS) starting on page 1709 of the SCS in the 210 SUR N006 submission.

Before summarizing the sponsor's response to inquiries, the next section provides information about a subject with serious adverse events (SAEs) leading to an early withdrawal (adverse dropout also referred to as ADO), in which the subject's past history was described in the original review as including a history of one of the SAEs (psychogenic polydipsia), yet the subject's narrative indicates that this subject did not have a history of this condition.

II. Subject 500108

This section of this review describes a subject with hyponatremia (sodium level of 117 mmol, serum osmolality of 240; 275-295 within normal limits of which units were not found) that resolved within 2 days with treatment) and psychogenic polydipsia, convulsion and pneumonia aspiration reported as SAEs and that lead to early cessation of Pal treatment in a subject with no past history of any related events. This subject was previously described in the review of the NDA but had indicated that this subject had a past history of psychogenic polydipsia. The narrative indicates specifically that this subject did not have a prior history of this condition.

Reviewer Comment

The overall conclusion of this subject does not change from that previously described in the review of the original NDA submission. Psychogenic polydipsia was likely to be the diagnosis. However, in the absence of additional clinical information (e.g. results of a diagnostic work-up

to rule out other causes, such as urine osmolality) the etiology of the hyponatremia is not certain. Psychogenic polydipsia is reported to occur in this patient population and can lead to the type of complications that this patient developed. This event also appears to be an isolated case.

III. N007 Amendment Submission Response to a Request Regarding Subjects with Potential Vital Sign Related Events

N007 provides a response to a request for information on any subject with symptomatic bradycardia, tachycardia, hypotension, orthostatic hypotension and syncope. The sponsor was given examples of subjects and comments about our concerns in identifying subjects, as follows (copied from an 8/2/06 DFSed Telecon/e-mailed correspondence document under NDA 21999 N000):

> "Syncope and potential pro-arrhythmic effects: Patient 300541 in study 304 is described as having sinus pauses of up to 8 seconds but a description of this subject could not be found in the pro-arrhythmic section of the SCS or in any other in-text section of the SCS.
>
> Subject 201805 in Study -303 (a 33 year old male) had 12 mg daily Pal treatment discontinued on Day 7 who had an SAE of tachycardia that was first noted on Day 4 and reached a HR of 120 bpm supine (124 bpm standing) compared to 71 bpm (per ECG) at baseline (84 bpm supine at baseline). The subject also developed "hypotension" in which Day 4 BP was 100/65 mmHg, supine (115/75 standing) compared to 135/65 mmHg, supine at baseline and decreased further to 85/55 mmHg, supine, on Day 6 (80/50 standing). Supine BP of 115/80 mmHg and HR of 93 bpm on day 7. The tachycardia prolonged his hospitalization. Tachycardia was reported to resolve by 12 days and hypotension by 3 days without treatment. ALT was also reported to be "increased" during the study.
>
> Subject 201803 in Study -303 (33 year old male) had a SAE of tachycardia with increased heart rate first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline values while BP generally did not change from baseline vales. This subject was not described as having orthostatic hypotension (on page 146 of the CSR). His baseline supine and standing heart rates were 72 and 76 bpm, respectively compared to supine and standing heart rates of 106 and 130, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days. Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days, then the subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG heart rate of 73 bpm on that day.
>
> We are interested in a listing of patients that were asymptomatic at baseline but who went on to have syncope, symptomatic bradycardia or tachycardia or symptomatic hypotension. Would it be possible for you to make a listing of these patients (with whether they were SAE, DAE or both along with their verbatim and thesaurus term) and a page number reference to the narrative?"

Response and Reviewer Comments: *The sponsor's response (in N008) was confusing regarding the methodology they employed for generating summary tables that show the incidence of subjects they identified. The in-text summary tables did not provide subject numbers but only the incidence of subjects in only the Phase III datasets (we asked for results of all safety datasets).*

Attached to their response were approximately 1000 pages of appendices of line listings that were difficult to understand in conjunction with their explanation of methods they employed for generating these listings. The only narrative information provided was of selected serious adverse events (SAEs) and adverse dropouts (ADO) that were captured by their special search of cases. These narratives were included among the narratives of SAEs and ADOs provided in the original NDA submission. The sponsor's summary of their search results are difficult to interpret, as in the following example.

The following is an example of an in-text summary table that is followed by their comments and conclusions regarding this table.

Table 1: Number of Subjects With a Symptomatic Vital Sign/Heart Rate Abnormality of Inte
Pooled Double-Blind Studies
(Studies R076477-SCH-303, SCH-304, and SCH-305: Safety Analysis Set)

Abnormality	Placebo (N=355)	Total Paliperidone (N=963)	Olanzapine (N=364)	To (N=1
Total number of subjects with any abnormality	7	32	10	4
Symptomatic bradycardia	3	7	6	1
Symptomatic hypotension	1	7	0	8
Symptomatic orthostatic hypotension	0	4	0	4
Symptomatic tachycardia	2	16	2	2
Syncope	1	7	2	1

Note: Some subjects had an abnormality in more than one category
Cross Reference: Attachment 2.5.

Per the predefined criteria, a total of 49 distinct subjects out of 1,682 (3%) subjects in the pooled double-blind studies were identified as symptomatic during treatment but asymptomatic at baseline/screening (ER OROS paliperidone 3%, 32/963; placebo 2%, 7/355; olanzapine 3%, 10/364). The data for these 49 subjects identified with a symptomatic abnormality underwent additional clinical review to assess causality. For 12 of these 49 subjects identified as symptomatic, there may have been a cause for the abnormality other than study drug (e.g., concomitant medication or medical condition), including 7 of 32 subjects treated with ER OROS paliperidone, as well as 3 of 7 placebo subjects and 2 of 10 olanzapine subjects. For the remaining subjects, there was insufficient information to draw conclusions.

The basis for the sponsor's conclusions is not clear, since the rationale for conclusions cannot be found in their response (as in the above example, corresponding subject numbers and relevant narrative information that correspond to conclusions such as the conclusion that there may have been a non-drug-related cause of the symptoms of 12 out of 49 subjects could not be found in the submission). The type of relevant information that would have been helpful but that could not be found on the subjects include information such a clinical data, the differential diagnosis and work-up of a given subject, potential risk factors and other information relevant to the potential etiologies). It is also not clear why information was insufficient on the other subjects and why this information was not obtained or provided. Only the narratives of selected ADOs or SAEs were provided and information was limited in some of these narratives sometimes (e.g. a

description of "syncope," the discharge summary and other key relevant information in subject 300541). The following table lists the subjects that had narratives which were the subjects that were reported as ADOs or having SAEs (copied from the N008 submission).

Table 2: Subjects Identified With a Symptomatic Vital Sign/Heart Rate Abnormality for Whom a Narrative Was Previously Submitted: Studies R076477-SCH-303, SCH-304, and SCH-305

Study	Subject Number	Treatment Group	Event Identified Per Methodology[a]	Reason for the Narrative Submitted in NDA 21-999\0000\ Mod 2.7.4	Completion/ Withdrawal Information
SCH-304	300541	ER OROS PAL 12 mg/day	Syncope, Symptomatic bradycardia	D/C due to exacerbation of psychosis (Day 5). SAEs dizziness and hypotension (Day 5), and bradycardia and delay in pulse (coded to heart rate irregular) (Day 6)	Withdrawn on Day 6
SCH-305	500102	ER OROS PAL 9 mg/day	Symptomatic hypotension	D/C due to dizziness, impaired memory, nausea, headache, (Day 1) and SAE tachycardia (Day 3)	Withdrawn on Day 12
SCH-305	500518	Placebo	Symptomatic bradycardia	D/C due to hyponatremia (Day 14) and SAE rule out primary polydipsia (coded to polydipsia) (Day 15)	Withdrawn on Day 16
SCH-303	200966	Olanzapine 10 mg/day	Syncope	D/C due to elevated serum ALT values and elevated serum AST values	Withdrawn on Day 17
SCH-304	300137	Olanzapine 10 mg/day	Syncope	D/C due to SAEs QT prolonged and electrolyte disturbance	Withdrawn on Day 11
SCH-305	501519	Olanzapine 10 mg/day	Symptomatic bradycardia	D/C due to sedation	Withdrawn on Day 36

ALT = alanine aminotransferase, AST = aspartate aminotransferase, D/C = discontinued, SAE = serious adverse event

[a] Please see Attachment 1 for the detailed description of methodology.

The appendices of the sponsor's response were over 1300 pages long. The undersigned reviewer conducted a word search in the PDF submission for "syncope." Over approximately 40 pages within the appendices were found to have this term.

Reviewer Recommendation

It is recommended that the sponsor be asked to provide a line listing of subjects in each treatment group in each study of each safety dataset (Phase I-III) with syncope (reported as a verbatim or preferred term) in all safety datasets that includes the following information:

- *Subject number*
- *Verbatim and preferred terms*
- *Whether or not the subject was an ADO or SAE with corresponding verbatim and preferred terms*
- *A hyperlink and specification of exact location of a narrative description of the subject.*

It is recommended that the sponsor provide a narrative description of each of the above subjects that includes any clinically relevant information (e.g. diagnostic test results, clinical data, risk factors, and other information) regarding potential etiologies of the

syncopal event and that provides a clinical interpretation of the event (e.g. including differential diagnosis) with data to support to conclusions (e.g. results of a diagnostic work-up, vital sign data, risk factors). The narrative information should also include a discharge summary of any subject to was hospitalized due to any type of adverse event (i.e. adverse events or clinical findings that led to hospitalization, prolonged hospitalization, or transferred to a specialized unit, or an emergency room evaluation).

A request for the above information (line-listings and narratives) is recommended for each of the following types of events:

- *Any subject with heart rate below 50 bpm (or had a related AE reported, such as bradycardia) during treatment (with normal values at baseline).*
- *Any subject with a systolic blood pressure below 100 (or had a related AE, such as low blood pressure) during treatment (with normal values at baseline) that did not have orthostatic hypotension.*
- *Any subject with a systolic blood pressure below 100 (or had a related AE, such as low blood pressure) during treatment (with normal values at baseline) that also had orthostatic hypotension.*
- *Any subject with sinus pause, PR prolongation or AV block or a related arrhythmia (even reported as an AE or as reported by EKG assessment) during treatment (that was not present at baseline).*
- *Any subject with tachycardia (with a heart rate over 120 bpm are reported as a related AE, such as tachycardia, sinus tachycardia, as examples) in the absence of concurrent orthostatic hypotension (that was not present at baseline).*

IV. Sections of N005 Responding to Inquiries of Elevations of CPK Levels

The following paragraphs provide background information regarding the potential drug effect on CPK levels in which comments are provided from the perspective of the undersigned reviewer and therefore is provided in a televised text.

The sponsor was asked about a potential CPK signal observed in high versus low OROS treated Phase I subjects that showed a greater mean elevation after a high dose of OROS Pal compared to levels obtained after receiving a low-dose of OROS Pal (refer to the original NDA review for details under section 7.1.7.3.1). Schizophrenia Phase III trials (double-blind, short-term trials and open-label longterm trials) showed highly variable CPK levels across treatment groups, across subjects and fluctuate came levels over time such that results were difficult to interpret. While these observations could be reflecting elevations related to the patient population rather than being drug-related, highly variable and fluctuating CPK levels can lead to difficulties in detecting a potential drug effect (as discussed previously in the original NDA review).

The sponsor was asked about the above potential signal in healthy subjects in Phase I trials (found in the safety dataset of 17-Phase I pooled studies, as described in the review of the original NDA submission). The sponsor was also asked to provide descriptive statistical results

and incidence of outliers for other treatment conditions (e.g. placebo, risperidone), since this information could not be found in the original NDA submission (as described in the original NDA review).

Response: The sponsor's response indicates that only some of the Phase I trials collected post-dose CPK data and that Phase I trials with placebo or risperidone treatment conditions were not among these trials (i.e. CPK data was not collected in trials with a placebo or risperidone treatment condition).

The Phase I trials that included post-treatment CPK assessments, had blood samples collected at the following time-points (these trials were cross-over trials generally involving several single-dose treatment periods and between-treatment-period washout intervals of at least several days):

- Screening
- End-of-study visit (at 5 days post-dose for Studies –P01-1008 and P01-1007 and at 4-8 days post-dose for other studies).
- Prior to dosing on selected treatment days in a few of the trials (trials generally employed a multiple day washout period)
- One study also had a 48 hour post-dose laboratory assessment for Period 1 only (Study –P01-1006).

A total of 177 subjects in the pooled Phase I dataset had CPK levels at a time-point after dosing.

The following summarizes the grouping of subjects by treatment condition for the Phase I safety dataset that included subjects receiving high and low dose OROS pal and/or IR pal as follows (copied from the submission):

Treatment Group	Description
Placebo	All placebo treatments
Paliperidone IR:	All immediate-release (IR) treatments, including intravenous (i.v.) injection, ^{14}C labeled oral solution, oral solutions and tablets with racemic mixtures, oral solutions of (+) and (-) enantiomers
Paliperidone Other:	All experimental formulations containing paliperidone doses of 2 to 6 mg (includes osmotic modules, paliperidone flat and ascending profiles, coated OROS, [redacted]OROS, and al[redacted] formulations)
Paliperidone OROS, Low Dose:	All 3 to 6 mg paliperidone doses using Phase 1 (or SLOW OROS – 2 mg tablets) Phase 3, and commercial to-be-marketed ER OROS paliperidone formulations
Paliperidone OROS, High Dose:	All 9 to 15 mg paliperidone doses using Phase 1 (or SLOW OROS – 2 mg tablets), Phase 3, and commercial to-be-marketed ER OROS paliperidone formulations; a first day of placebo in a 1-week paliperidone group in Study R076477-SCH-101 followed by 12 mg paliperidone OROS
Risperidone:	All 2 to 8 mg oral risperidone treatments, including risperidone ascending profiles, osmotic modules, oral solutions, and IR tablets

The incidence of outliers on high CPK levels in the combined safety dataset was as follows:

- 1% of low dose OROS pal subjects (1/76 subjects)
- 3 % of high dose OROS pal subjects (4/123 subjects)
- 0 IR Pal treated subjects met outlier criteria, while noting that the dose given to these subjects was generally lower than the low and high dose OROS treatment conditions, as shown in the previous table (1-3 mg of which a few subjects received drug intravenously). Furthermore, only 21 subjects received the IR Pal treatment.

The sponsor provided narrative descriptions for the above 5 subjects who were outliers on high CPK levels (Attachment 1 of this review provides a copy of these narratives). CPK level values were also provided for each assessment time-point for each of these subjects, which will be shown later.

The sponsor concludes that there were related events that "could explain the abnormality" in each of the 5 subjects, such that elevations in CPK levels did not appear to be drug-related in these cases.

Since the above 5 subjects came from either Study –P01-1008 or Study –P01-1010 the following additional information about these 2 trials is provided below:

- The majority of High and Low dose ER Pal subjects in the Phase I safety dataset came from either or both of these 2 trials as follows (copied from a section of the sponsor's table):

Treatment group	Study
PALI OROS low dose (n=76)	P01-1006 (n=20) P01-1007 (n=4) P01-1010 (n=49) SIV-101 (n=3)
PALI OROS high dose (n=127)	P01-1008 (n=80) P01-1010 (n=47)

- The study design of each of these 2 trials is shown in the table below (copied from a summary table that was provided by the sponsor).

Study	Study design/enrolment status
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. Subj. 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. Subj. enrolled: 50 Treated with Paliperidone: 50

Reviewer Comment. *The sponsor used a cut-off criterion of >990 U/l. The rationale for selecting this cutoff criterion for a healthy Phase I subject population cannot be found in their response. Such a remarkably abnormal value may not be the optimal cut-off criterion for a generally healthy population for detecting a potential drug-related effect.*

It is also not clear if greater group mean CPK values in the high OROS compared to the low OROS and the IR Pal groups would still be revealed if data from the above outlier subjects were excluded from the analyses. In any case, the incidence of outliers was higher in the High dose compared to the low dose OROS Pal conditions and suggests a dose-dependent effect of Pal on CPK levels (as previously described in the review of the original NDA).

Higher group mean CPK values were also observed in the high OROS group compared to the IR Pal, as previously described. This observation may be also reflecting the dose-dependent drug effect, since the IR Pal condition involved lower single dose levels (1-3 mg) than were given to a number of subjects in the low OROS condition (3-6 mg). It is also important to note that the IR pal condition used shorter acting formulations, including an intravenous route of administration in some subjects, in contrast to the longer acting, oral OROS treatment condition. Therefore, these other confounding variables may have also influenced treatment group differences on CPK

values. Another consideration is in the small sample size of the IR pal condition which consisted of only 21 subjects. Finally, it is not clear if the above positive findings are reproduceable.

While several subjects may have had events that might account for the CPK levels at least a role of Pal is possible for at least the following reasons (see Attachment 1 of this review for a copy of the individual-subject narrative descriptions):

- *Subject 101017 had "chest pain (muscular)" thought to account for the elevations in CPK, yet it is not clear from the narrative whether or not this muscular-related event was drug-related (e.g. muscular pain may have occurred due to a dystonic like or other extrapyramidal related event which in turn, could be associated with elevations in CPK). Several adverse dropouts due to extrapyramidal side effects reported in Phase I subjects could have been associated with elevations in CPK.*
- *While a few subjects also had abnormally high CPK levels at baseline, these baseline values did not meet outlier criteria, yet remarkable CPK values (values that met outliers criteria including values of up to 8240 U/l) were revealed after these subjects received multiple single-dose treatment periods and they generally received the higher dose level treatment conditions (e.g. 12 and 15 mg dose-levels). One exception is subject 101038 in which this subject met outlier criteria after a single treatment period. Yet, the highest dose level (15 mg) was given on this first treatment period, while lower doses were given on subsequent treatment periods. Laboratory CPK results for each time-point in each subject is shown later in this review.*
- *Attachment 1 of this review provides the narrative descriptions of the 5 subjects.*
- *Although the washout interval between treatment periods was for several days (as previously described), it is not clear how soon after treatment the CPK values increased, since CPK levels were not obtained until the next treatment prior to dosing for that given treatment period. One might also expect a possible lag in the rise of CPK levels following dosing, as can be observed with some drugs that induce elevations and liver function tests, based on the experience of the undersigned reviewer.*
- *Given the above comment of a potential lag period that the undersigned reviewer has observed with some drugs inducing elevations in liver function tests, it is also notable that 4 out of the 5 subjects also showed elevations in liver functions tests (the above subject with muscular chest pain did not have elevated liver functions test values). Yet, several of these subjects also had other AEs that suggested the possibility of a systemic illness (e.g. one subject had "common cold" AE reported).*
- *A clear reason for elevated CPK and elevations in LFTs in the 4 out of 5 subjects showing these abnormalities could not be found in the narrative descriptions (e.g. a diagnostic work-up with results such as a alcohol abuse, viral hepatitis based on CBC and hepatitis antigen, antibody work-up, among others).*

Individual subject CPK levels over time for each of the 5 above subjects who met the outliers criteria for elevated CPK are shown below (as copied from the submission; see Attachment 1 for narratives and for treatment conditions for each of the following corresponding treatment periods):

Outpat [redacted] 1091AB: Subjects with Treatment-Emergent Markedly Abnormal Laboratory Values - Phase 1/2a Studies
(continued)

Analysis Set: Safety
Analysis Group: Healthy Volunteers-SD
Lab Type: Chemistry
Param: Creatine kinase, U/L
Marked Abnormal Range (Unit): M/A - 990 (U/L)

Markedly Abnormal Sex Flag	Study Id	Subject Number	Actual Date of Sample	Actual Time of Sample	Scs Treatment Group	Scs Visit	Lab Visit Type	Reported Value	Change	
Male	R076477-PO1-1008	100843	09Sep2004	11:40	NONE	Screening	Scheduled	76		N
			15Sep2004	8:07	NONE	Baseline	Scheduled	62		N
			28Sep2004	8:02	PALI OROS HIGH DOSE	Post dose	Scheduled	68	7	N
			05Oct2004	7:30	PALI OROS HIGH DOSE	Post dose	Scheduled	8246	8184	H
			12Oct2004	9:01	PALI OROS HIGH DOSE	Post dose	Scheduled	239	177	N
	R076477-PO1-1010	101012	30Jul2004	11:14	NONE	Screening	Scheduled	434		N
			09Aug2004	9:21	NONE	Baseline	Scheduled	822		N
			19Aug2004	9:22	PALI OROS HIGH DOSE	Post dose	Scheduled	489	-333	N
			30Aug2004	9:11	PALI OROS HIGH DOSE	Post dose	Scheduled	577	-245	N
			31Aug2004	16:23	PALI OROS HIGH DOSE	Post dose	Unscheduled	263	-559	N
			09Sep2004	9:13	PALI OROS HIGH DOSE	Post dose	Scheduled	596	-226	N
			20Sep2004	9:15	PALI OROS LOW DOSE	Post dose	Scheduled	3045	2223	H
			24Sep2004	9:19	PALI OROS LOW DOSE	Post dose	Scheduled	433	-389	N
		101015	04Aug2004	15:03	NONE	Screening	Scheduled	222		N
			10Aug2004	8:30	NONE	Baseline	Scheduled	82		N
			20Aug2004	8:30	PALI OROS LOW DOSE	Post dose	Scheduled	76	-6	N
			31Aug2004	8:30	PALI OROS LOW DOSE	Post dose	Scheduled	77	-5	N
			10Sep2004	8:30	PALI OROS HIGH DOSE	Post dose	Scheduled	89	7	N
			21Sep2004	8:30	PALI OROS HIGH DOSE	Post dose	Scheduled	2885	2803	H
			23Sep2004	8:41	PALI OROS HIGH DOSE	Post dose	Unscheduled	1756	1674	H
			25Sep2004	8:36	PALI OROS HIGH DOSE	Post dose	Scheduled	1178	1096	H
		101017	30Jul2004	15:40	NONE	Screening	Scheduled	240		N
			10Aug2004	8:40	NONE	Baseline	Scheduled	133		N
			20Aug2004	8:40	PALI OROS HIGH DOSE	Post dose	Scheduled	94	-39	N
			31Aug2004	8:40	PALI OROS HIGH DOSE	Post dose	Scheduled	143	10	N
			10Sep2004	8:40	PALI OROS HIGH DOSE	Post dose	Scheduled	3394	3261	H
			21Sep2004	8:40	PALI OROS LOW DOSE	Post dose	Scheduled	135	2	N
Male	R076477-PO1-1010	101017	25Sep2004	9:05	PALI OROS LOW DOSE	Post dose	Scheduled	132	-1	N
		101038	11Aug2004	10:15	NONE	Screening	Scheduled	140		N
			13Aug2004	9:29	NONE	Baseline	Scheduled	128		N
			23Aug2004	9:25	PALI OROS HIGH DOSE	Post dose	Scheduled	3173	3045	H
			03Sep2004	9:25	PALI OROS HIGH DOSE	Post dose	Scheduled	470	342	N
			13Sep2004	9:25	PALI OROS LOW DOSE	Post dose	Scheduled	151	23	N
			24Sep2004	9:20	PALI OROS HIGH DOSE	Post dose	Scheduled	117	-11	N
			28Sep2004	11:44	PALI OROS LOW DOSE	Post dose	Scheduled	178	50	N

It is also important to note that it is not clear why elevations were sometimes observed after longterm term treatment in subjects in the open-label trials (e.g. consider lack-of-efficacy in which subjects become acutely psychotic and agitated for example, or drug-related adverse events or other potential events that may account for this observation).

In conclusion, the sponsor's response does not provide adequate assurance that a potential OROS Pal-related signal for elevations in CPK does not exist. Refer to the original NDA review for further comment on this potential signal relevant to the Phase III patient population. Also the original NDA review describes subjects with elevations in CPK and LFTs (liver function tests) that may or may not be inter-related.

Reviewer Recommendation. *As previously advised in the original NDA review, it is recommended that this issue be resolved before considering a final approval action on this NDA (in the case the Agency grants an approvable action). If the sponsor cannot provide convincing data to explain non-drug-related reasons for elevations in CPK in their trials, it is also recommended that labeling inclu* [redacted]

[redacted] *As recommended in the review of the original NDA submission this subsection under Warning and Precautions should be included for describing elevations observed in liver function tests in some subjects of the Phase I-III trials. This section should also indicate that sometimes these elevations were also associated with elevations in CPK.*

V. Selected Responses to Inquiries about ECG Study –SCH-1009

Results and Reviewer Comments.
Refer to the review of the original NDA for details on the ECG Study SCH-1009. The sponsor was asked several questions about results from this study. The most revealing results were provided in their response that included the following information (some of this information was provided in recent e-mails from the sponsor of which a submission under the NDA is pending at the time of this writing):

- *Raw mean and least square mean QT and QTc interval values of each gender in each treatment group were requested for data-points that correspond to data points shown in the sponsor's Tables 108 and 109 found in the CSR of this study that summarize their results (also shown in the clinical review of the original NDA under Section 7.1.12 A).*
- *The sponsor was also asked to provide least square mean values for QTc interval (of each treatment group as shown in Tables 108 and 109) based on their statistical analyses of results (only results of QTcLD could be found in the original NDA, but not for QTcF, QTlc or others as described in the review of the original NDA for details).*

The most remarkable QTc prolongation effects were generally observed at approximately 1 ½ hour post-dose on Day 2 (first day of Pal treatment which was given as 4 mg IR), Day 4 (first day of the 8 mg dose-level), Day 8 (after 4 days of 8 mg/day) in the Pal group. The maximal group mean increases (from the averaged pre-dose values) that were generally observed at these time-points were approximately 10-12 msec for raw group mean QTcLD, QTlc, and QTcF in male and female subgroups with some exceptions as shown in tables below (results of QTcB were not requested since this was considered least informative, for reasons discussed in the review of the original NDA). These results of raw group mean values were generally similar to results of least square group mean values of QTc (QTcF and QTcLD) but maximal group mean increases (also observed at the 1/12 hour post-dose time-point on Days 2, 4 and 8) were generally lower than the corresponding raw group mean QTc values (least square mean values were generally approximately one millisecond less than the raw group mean values).

Gender differences can also be seen when examining the results shown in the tables below. Males appear to show greater maximal mean changes when examining tables showing results by multiple post-dose time-points that include time-points near Tmax. However, females appear to show a greater duration of QTc prolongation when examining the averaged QTc mean increases on a given treatment day or when examining the data by multiple post-dose time-points (refer to the tables below).

The Sponsor's Summary Tables Provided in Their Response

The following is a copy of sections of the sponsor's summary tables for the raw QTc mean changes at various post-dose time-points during treatment in the Pal group (the results of the moxifloxacin group are not shown) for each gender (as provided in a 6/29/06 e-mail from the sponsor, the sponsor was asked to submit results as an amendment under the NDA, of which remains pending at the time of this writing). These results correspond to the results of Table 109 in the CSR and shown in Section 7.1.12 of the review of the original NDA (this table as found in the original NDA only showed results of least square mean changes in QTcLD which were not provided for each gender subgroup within each treatment group and were not provided for other methods for calculating QTc).

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcLD (ms)
Treatment Arm: IR Paliperidone
Sex: Male

	Day 2 (PALI 4 mg)		Day 3 (PALI 6 mg)		Day 4 (PALI 8 mg)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	0.3 (1.41)	(-2.10; 2.69)	-0.5 (1.30)	(-2.68; 1.74)	0.2 (1.35)	(-2.07; 2.49)
30min	4.1 (2.05)	(0.64; 7.58)	3.1 (1.70)	(0.21; 5.96)	5.9 (1.65)	(3.15; 8.74)
1h	4.9 (1.70)	(1.99; 7.73)	5.5 (1.59)	(2.79; 8.16)	6.4 (1.58)	(3.75; 9.08)
1h30min	10.4 (2.03)	(7.02; 13.87)	8.2 (1.83)	(5.11; 11.28)	11.5 (2.22)	(7.78; 15.27)
2h	6.0 (1.71)	(3.08; 8.86)	5.8 (2.07)	(2.31; 9.30)	7.5 (1.81)	(4.44; 10.56)
2h30min	3.8 (1.49)	(1.23; 6.27)	4.5 (1.37)	(2.16; 6.79)	5.5 (1.63)	(2.77; 8.29)
3h	4.1 (1.86)	(0.99; 7.29)	4.2 (1.77)	(1.23; 7.21)	8.1 (2.33)	(4.12; 11.99)
3h30min	3.9 (1.59)	(1.21; 6.57)	0.9 (1.79)	(-2.17; 3.89)	5.2 (1.61)	(2.48; 7.91)
4h	3.1 (1.85)	(-0.02; 6.24)	3.1 (1.70)	(0.23; 5.99)	4.3 (1.55)	(1.71; 6.95)
6h	1.8 (1.72)	(-1.11; 4.72)	-0.8 (1.86)	(-3.89; 2.39)	1.5 (1.49)	(-1.04; 3.99)
12h	2.1 (1.31)	(-0.16; 4.28)	-0.9 (1.70)	(-3.81; 1.93)	1.3 (1.69)	(-1.61; 4.12)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcLD (ms)
Treatment Arm: IR Paliperidone
Sex: Male

	Day 8 (PALI 8 mg)		Day 9 (Posttreatment)		Day 10 (Posttreatment)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	1.7 (1.54)	(-0.93; 4.28)	1.2 (2.06)	(-2.33; 4.64)	0.1 (1.52)	(-2.51; 2.63)
30min	6.8 (1.76)	(3.78; 9.72)	5.6 (1.78)	(2.63; 8.64)	7.0 (1.58)	(4.33; 9.67)
1h	7.8 (1.51)	(5.26; 10.35)	5.1 (1.73)	(2.17; 8.00)	2.3 (1.75)	(-0.67; 5.23)
1h30min	11.7 (1.81)	(8.66; 14.79)	5.4 (2.28)	(1.59; 9.30)	3.1 (2.28)	(-0.80; 6.91)
2h	9.1 (1.63)	(6.38; 11.90)	5.6 (1.88)	(2.44; 8.78)	1.4 (1.88)	(-1.81; 4.53)
2h30min	7.5 (1.91)	(4.32; 10.77)	1.5 (1.87)	(-1.65; 4.68)	0.1 (1.60)	(-2.57; 2.85)
3h	7.8 (1.97)	(4.51; 11.16)	3.2 (1.70)	(0.33; 6.06)	0.9 (1.76)	(-2.12; 3.84)
3h30min	4.6 (2.31)	(0.71; 8.51)	3.8 (1.84)	(0.65; 6.85)	1.0 (1.56)	(-1.64; 3.64)
4h	5.8 (1.44)	(3.38; 8.23)	1.9 (1.39)	(-0.48; 4.21)	2.2 (1.66)	(-0.64; 4.97)
6h	4.0 (1.59)	(1.35; 6.71)	1.8 (1.64)	(-1.02; 4.52)	0.3 (1.53)	(-2.33; 2.83)
12h	3.7 (1.40)	(1.34; 6.08)	3.6 (1.60)	(0.88; 6.30)	3.2 (1.56)	(0.54; 5.81)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcLD (ms)
Treatment Arm: IR Paliperidone
Sex: Female

	Day 2 (PALI 4 mg)		Day 3 (PALI 6 mg)		Day 4 (PALI 8 mg)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	4.9 (3.04)	(-0.88; 10.63)	2.6 (3.55)	(-4.10; 9.35)	2.4 (3.50)	(-4.26; 9.01)
30min	7.2 (2.50)	(2.14; 12.20)	2.0 (3.01)	(-3.84; 7.84)	3.3 (4.39)	(-5.24; 11.82)
1h	5.1 (3.90)	(-2.27; 12.52)	-1.1 (5.36)	(-11.28; 9.03)	1.9 (3.81)	(-5.33; 9.08)
1h30min	2.1 (3.22)	(-4.11; 8.40)	0.1 (4.43)	(-8.26; 8.51)	1.0 (4.68)	(-7.87; 9.87)
2h	2.1 (2.55)	(-2.81; 7.10)	-0.6 (3.51)	(-7.28; 6.03)	6.1 (4.82)	(-3.00; 15.25)
2h30min	1.6 (3.71)	(-5.40; 8.65)	2.1 (4.65)	(-6.69; 10.94)	-0.1 (5.18)	(-10.21; 9.92)
3h	3.5 (2.80)	(-1.81; 8.81)	-3.6 (3.63)	(-10.50; 3.25)	2.9 (5.30)	(-7.45; 13.16)
3h30min	1.4 (2.96)	(-4.24; 6.99)	-4.6 (2.32)	(-9.02; -0.23)	-5.3 (4.04)	(-13.14; 2.56)
4h	2.0 (3.37)	(-4.38; 8.38)	-2.8 (3.05)	(-8.53; 3.03)	-2.7 (4.71)	(-11.87; 6.44)
6h	2.6 (5.40)	(-7.60; 12.85)	-3.5 (4.94)	(-12.86; 5.86)	0.6 (5.35)	(-9.51; 10.76)
12h	1.0 (1.76)	(-2.34; 4.34)	-0.4 (2.33)	(-4.79; 4.04)	1.8 (2.48)	(-2.94; 6.44)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcLD (ms)
Treatment Arm: IR Paliperidone
Sex: Female

	Day 8 (PALI 8 mg)		Day 9 (Posttreatment)		Day 10 (Posttreatment)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	6.4 (3.95)	(-1.11; 13.86)	5.8 (4.34)	(-2.48; 13.98)	3.8 (2.86)	(-1.68; 9.18)
30min	8.0 (3.49)	(1.22; 14.78)	1.1 (4.57)	(-7.75; 10.03)	8.0 (5.45)	(-2.59; 18.59)
1h	9.4 (4.63)	(0.61; 18.14)	-0.1 (4.04)	(-7.78; 7.53)	1.8 (3.86)	(-5.57; 9.07)
1h30min	7.4 (4.69)	(-1.52; 16.27)	2.8 (4.34)	(-5.47; 10.97)	1.3 (3.79)	(-5.93; 8.43)
2h	7.9 (3.58)	(1.10; 14.65)	3.1 (3.88)	(-4.40; 10.69)	3.0 (1.69)	(-0.20; 6.20)
2h30min	8.4 (4.48)	(-0.10; 16.85)	2.0 (3.74)	(-5.09; 9.09)	1.8 (3.33)	(-4.55; 8.05)
3h	7.0 (5.58)	(-3.57; 17.57)	4.3 (5.01)	(-5.25; 13.75)	5.3 (2.85)	(-0.15; 10.65)
3h30min	6.6 (3.61)	(-0.31; 13.46)	5.1 (4.92)	(-4.19; 14.44)	3.6 (3.45)	(-2.92; 10.17)
4h	5.5 (4.57)	(-3.15; 14.15)	-2.6 (4.46)	(-11.23; 6.09)	0.5 (2.99)	(-5.16; 6.16)
6h	8.1 (4.79)	(-0.96; 17.21)	-1.1 (9.00)	(-18.63; 16.35)	3.9 (4.33)	(-4.33; 12.08)
12h	4.0 (2.12)	(-0.02; 8.02)	4.8 (1.68)	(1.57; 7.93)	8.9 (1.87)	(5.22; 12.49)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment Arm: IR Paliperidone
Sex: Male

	Day 2 (PALI 4 mg)		Day 3 (PALI 6 mg)		Day 4 (PALI 8 mg)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	0.6 (1.37)	(-1.76; 2.88)	-0.6 (1.44)	(-3.02; 1.84)	0.7 (1.43)	(-1.68; 3.15)
30min	3.7 (1.95)	(0.42; 7.02)	2.4 (1.66)	(-0.38; 5.21)	5.6 (1.76)	(2.61; 8.56)
1h	5.0 (1.73)	(2.10; 7.95)	5.7 (1.63)	(2.95; 8.44)	6.6 (1.62)	(3.90; 9.38)
1h30min	10.6 (2.00)	(7.26; 14.02)	7.6 (1.86)	(4.49; 10.79)	11.6 (2.20)	(7.89; 15.33)
2h	6.3 (1.65)	(3.49; 9.07)	5.7 (2.11)	(2.15; 9.29)	8.0 (1.88)	(4.82; 11.18)
2h30min	3.6 (1.45)	(1.14; 6.03)	4.1 (1.29)	(1.88; 6.23)	5.6 (1.62)	(2.87; 8.35)
3h	3.9 (1.72)	(0.95; 6.77)	3.7 (1.69)	(0.84; 6.55)	7.7 (2.29)	(3.83; 11.59)
3h30min	3.6 (1.58)	(0.97; 6.30)	0.9 (1.70)	(-1.99; 3.76)	5.0 (1.49)	(2.51; 7.54)
4h	3.0 (1.79)	(-0.05; 5.99)	3.1 (1.72)	(0.20; 6.02)	4.4 (1.68)	(1.58; 7.26)
6h	2.5 (1.89)	(-0.72; 5.67)	-0.3 (1.96)	(-3.59; 3.04)	2.4 (1.64)	(-0.33; 5.22)
12h	2.1 (1.41)	(-0.26; 4.49)	-1.1 (1.63)	(-3.87; 1.64)	1.2 (1.72)	(-1.68; 4.14)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment Arm: IR Paliperidone
Sex: Male

	Day 8 (PALI 8 mg)		Day 9 (Posttreatment)		Day 10 (Posttreatment)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	1.9 (1.69)	(-0.96; 4.78)	1.5 (2.18)	(-2.20; 5.17)	-0.3 (1.60)	(-3.02; 2.42)
30min	6.5 (1.83)	(3.44; 9.62)	5.5 (1.90)	(2.29; 8.71)	6.6 (1.76)	(3.61; 9.56)
1h	8.5 (1.60)	(5.79; 11.21)	5.4 (1.80)	(2.35; 8.43)	2.0 (1.92)	(-1.27; 5.22)
1h30min	11.5 (1.88)	(8.33; 14.67)	5.3 (2.45)	(1.17; 9.44)	2.3 (2.49)	(-1.87; 6.54)
2h	9.4 (1.53)	(6.81; 11.97)	5.2 (1.97)	(1.87; 8.52)	0.8 (2.08)	(-2.70; 4.31)
2h30min	7.8 (1.58)	(5.16; 10.49)	0.9 (1.88)	(-2.31; 4.03)	-0.9 (1.64)	(-3.69; 1.85)
3h	7.4 (1.76)	(4.44; 10.40)	2.0 (1.64)	(-0.76; 4.76)	-0.4 (1.83)	(-3.46; 2.73)
3h30min	4.7 (2.22)	(0.98; 8.47)	3.2 (1.78)	(0.22; 6.23)	0.3 (1.55)	(-2.34; 2.89)
4h	5.6 (1.50)	(3.07; 8.15)	1.3 (1.43)	(-1.14; 3.69)	1.8 (1.79)	(-1.19; 4.86)
6h	5.2 (1.73)	(2.30; 8.14)	2.0 (1.88)	(-1.15; 5.21)	0.4 (1.72)	(-2.54; 3.26)
12h	4.0 (1.47)	(1.51; 6.49)	4.1 (1.68)	(1.25; 6.93)	3.0 (1.73)	(0.04; 5.90)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment Arm: IR Paliperidone
Sex: Female

	Day 2 (PALI 4 mg)		Day 3 (PALI 6 mg)		Day 4 (PALI 8 mg)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	4.8 (2.97)	(-0.87; 10.37)	4.3 (2.94)	(-1.32; 9.82)	2.9 (3.10)	(-2.99; 8.74)
30min	6.3 (1.87)	(2.56; 10.11)	2.0 (3.06)	(-3.95; 7.95)	3.1 (3.98)	(-4.60; 10.89)
1h	4.8 (3.94)	(-2.71; 12.21)	-0.3 (5.01)	(-9.73; 9.23)	3.0 (3.20)	(-3.07; 9.07)
1h30min	2.1 (3.07)	(-3.82; 8.10)	0.4 (4.32)	(-7.80; 8.55)	1.6 (3.96)	(-5.88; 9.13)
2h	1.1 (2.74)	(-4.18; 6.46)	0.1 (2.66)	(-4.91; 5.16)	6.5 (3.95)	(-0.98; 13.98)
2h30min	0.8 (3.36)	(-5.62; 7.12)	3.0 (3.67)	(-3.96; 9.96)	-0.3 (4.98)	(-9.97; 9.40)
3h	3.1 (3.06)	(-2.66; 8.91)	-3.1 (3.29)	(-9.35; 3.10)	2.1 (4.55)	(-6.70; 10.98)
3h30min	0.9 (3.21)	(-5.21; 6.96)	-4.1 (2.08)	(-8.07; -0.18)	-5.1 (3.94)	(-12.80; 2.52)
4h	2.1 (3.40)	(-4.32; 8.57)	-1.6 (2.52)	(-6.40; 3.15)	-3.0 (4.48)	(-11.70; 5.70)
6h	3.6 (5.89)	(-7.53; 14.78)	-3.3 (5.07)	(-12.86; 6.36)	1.4 (5.65)	(-9.33; 12.08)
12h	2.0 (2.20)	(-2.16; 6.16)	-0.1 (2.75)	(-5.34; 5.09)	2.5 (2.56)	(-2.36; 7.36)

Table ECG.06B: ECG: Descriptive statistics on QT/QTc Differences from Day 1 on Days 2,3,4,8,9 and 10 at each Timepoint by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment Arm: IR Paliperidone
Sex: Female

	Day 8 (PALI 8 mg)		Day 9 (Posttreatment)		Day 10 (Posttreatment)	
Time	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)	Mean(SE)	(90% CI LL;90% CI UL)
Predose	7.4 (3.78)	(0.21; 14.54)	7.4 (3.74)	(0.30; 14.45)	5.0 (2.43)	(0.40; 9.60)
30min	8.4 (3.01)	(2.57; 14.29)	1.4 (3.77)	(-5.90; 8.76)	8.1 (5.43)	(-2.40; 18.69)
1h	10.3 (4.21)	(2.27; 18.23)	0.5 (4.05)	(-7.17; 8.17)	1.9 (4.29)	(-6.26; 10.01)
1h30min	7.5 (4.35)	(-0.75; 15.75)	3.0 (4.17)	(-4.91; 10.91)	1.1 (3.80)	(-6.07; 8.32)
2h	8.4 (3.69)	(1.39; 15.36)	3.4 (3.40)	(-3.18; 10.04)	2.5 (1.61)	(-0.56; 5.56)
2h30min	8.8 (4.18)	(0.83; 16.67)	2.0 (3.62)	(-4.85; 8.85)	1.6 (3.41)	(-4.83; 8.08)
3h	6.6 (5.34)	(-3.50; 16.75)	4.3 (5.13)	(-5.47; 13.97)	4.9 (3.08)	(-0.96; 10.71)
3h30min	7.3 (3.75)	(0.15; 14.35)	5.3 (5.21)	(-4.63; 15.13)	3.1 (3.68)	(-3.85; 10.10)
4h	6.1 (4.42)	(-2.25; 14.50)	-2.7 (4.50)	(-11.46; 6.03)	0.3 (3.12)	(-5.66; 6.16)
6h	9.3 (4.85)	(0.07; 18.43)	-0.4 (9.67)	(-19.22; 18.36)	4.0 (4.56)	(-4.64; 12.64)
12h	4.3 (2.20)	(0.08; 8.42)	5.8 (1.45)	(3.01; 8.49)	9.9 (2.02)	(5.94; 13.78)

The following is a copy of sections of summary tables provided in the 6/29/06 e-mail showing only the Pal group least square mean changes in QTcF (previous tables showed raw group mean changes) subdivided by gender for post-dose time-points during treatment days corresponding to Table 109 of the CSR (Table 109 was also shown in Section 7.1.12 of the review of the NDA which only included results of QTcLD and not for other QTc results such as QTcF and QTlc).

Note gender differences in the tables below. While males appeared to show a slightly numerically greater peak mean increase in QTc than females (examine the 1 ½ hour post-dose time-points on Days 2, 4 and 8), females appeared to show a more sustained QTc prolongation effect than males (examine Day 8 pre-dose values and values at subsequent time points for each gender). Results of QTcLD are not shown but were generally similar to results of QTcF shown below.

Table ECG.06C: Least Square Mean Differences from Day 1 on Days 2, 3, 4, 8, 9 and 10 at Each Time Point by Sex While Adjusting for Other Potential Confounding Factors (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment: IR Paliperidone
Sex: Male

Time	Day 2 LSMean diff. (SE)	Day 2 (90% CI LL;90% CI UL)	Day 3 LSMean diff. (SE)	Day 3 (90% CI LL;90% CI UL)	Day 4 LSMean diff. (SE)	Day 4 (90% CI LL;90% CI UL)
Predose	0.2 (2.42)	(-3.86; 4.17)	-1.0 (2.42)	(-5.01; 3.02)	0.3 (2.42)	(-3.69; 4.35)
30min	3.2 (2.39)	(-0.82; 7.12)	1.8 (2.39)	(-2.12; 5.82)	5.0 (2.39)	(1.04; 8.98)
1h	4.5 (2.39)	(0.49; 8.43)	5.1 (2.39)	(1.15; 9.09)	6.1 (2.39)	(2.10; 10.04)
1h30min	10.1 (2.39)	(6.10; 14.04)	7.1 (2.39)	(3.10; 11.04)	11.0 (2.39)	(7.07; 15.01)
2h	5.7 (2.39)	(1.74; 9.68)	5.2 (2.39)	(1.18; 9.12)	7.4 (2.39)	(3.46; 11.40)
2h30min	3.0 (2.39)	(-0.96; 6.98)	3.5 (2.39)	(-0.48; 7.45)	5.0 (2.39)	(1.07; 9.01)
3h	3.3 (2.39)	(-0.68; 7.26)	3.1 (2.39)	(-0.85; 7.09)	7.2 (2.41)	(3.18; 11.16)
3h30min	3.1 (2.39)	(-0.90; 7.04)	0.3 (2.39)	(-3.65; 4.29)	4.5 (2.39)	(0.49; 8.43)
4h	2.4 (2.39)	(-1.57; 6.37)	2.5 (2.39)	(-1.43; 6.51)	3.8 (2.39)	(-0.12; 7.82)
6h	1.9 (2.39)	(-2.07; 5.87)	-0.8 (2.39)	(-4.82; 3.12)	1.9 (2.39)	(-2.10; 5.84)
12h	1.7 (2.41)	(-2.32; 5.67)	-1.8 (2.42)	(-5.80; 2.24)	0.8 (2.41)	(-3.21; 4.78)

See footnotes on the first page of the table.

Table ECG.06C: Least Square Mean Differences from Day 1 on Days 2, 3, 4, 8, 9 and 10 at Each Time Point by Sex While Adjusting for Other Potential Confounding Factors (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment: IR Paliperidone
Sex: Male

Time	Day 8 LSMean diff. (SE)	Day 8 (90% CI LL;90% CI UL)	Day 9 LSMean diff. (SE)	Day 9 (90% CI LL;90% CI UL)	Day 10 LSMean diff. (SE)	Day 10 (90% CI LL;90% CI UL)
Predose	1.5 (2.42)	(-2.51; 5.52)	1.1 (2.44)	(-2.96; 5.12)	-0.7 (2.44)	(-4.75; 3.33)
30min	6.0 (2.39)	(1.99; 9.93)	4.9 (2.39)	(0.96; 8.90)	6.0 (2.39)	(2.04; 9.98)
1h	7.9 (2.39)	(3.96; 11.90)	4.8 (2.39)	(0.85; 8.79)	1.4 (2.39)	(-2.57; 5.37)
1h30min	10.9 (2.39)	(6.96; 14.90)	4.7 (2.39)	(0.77; 8.70)	1.8 (2.39)	(-2.21; 5.73)
2h	8.8 (2.39)	(4.85; 12.79)	4.6 (2.39)	(0.65; 8.59)	0.2 (2.39)	(-3.73; 4.20)
2h30min	7.1 (2.41)	(3.07; 11.05)	0.3 (2.41)	(-3.65; 4.33)	-1.5 (2.39)	(-5.46; 2.48)
3h	6.8 (2.39)	(2.88; 10.82)	1.4 (2.39)	(-2.54; 5.40)	-0.9 (2.39)	(-4.90; 3.04)
3h30min	4.2 (2.39)	(0.18; 8.12)	2.7 (2.39)	(-1.32; 6.62)	-0.3 (2.39)	(-4.26; 3.68)
4h	5.0 (2.39)	(1.07; 9.01)	0.7 (2.39)	(-3.26; 4.68)	1.3 (2.39)	(-2.71; 5.23)
6h	4.7 (2.39)	(0.68; 8.62)	1.5 (2.39)	(-2.51; 5.43)	-0.2 (2.39)	(-4.18; 3.76)
12h	3.6 (2.41)	(-0.43; 7.55)	3.6 (2.42)	(-0.37; 7.66)	2.5 (2.41)	(-1.46; 6.52)

See footnotes on the first page of the table.

Table ECG.06C: Least Square Mean Differences from Day 1 on Days 2, 3, 4, 8, 9 and 10 at Each Time Point by Sex While Adjusting for Other Potential Confounding Factors (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment: IR Paliperidone
Sex: Female

	Day 2		Day 3		Day 4	
Time	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)
Predose	3.3 (4.19)	(-3.66; 10.18)	2.8 (4.19)	(-4.16; 9.68)	1.4 (4.19)	(-5.53; 8.31)
30min	4.5 (4.62)	(-3.13; 12.11)	-0.5 (4.38)	(-7.71; 6.74)	0.7 (4.38)	(-6.57; 7.89)
1h	3.3 (4.19)	(-3.66; 10.18)	-1.7 (4.19)	(-8.66; 5.18)	1.5 (4.19)	(-5.41; 8.43)
1h30min	1.4 (4.38)	(-5.88; 8.58)	-1.1 (4.19)	(-8.03; 5.81)	0.1 (4.19)	(-6.78; 7.06)
2h	0.4 (4.38)	(-6.88; 7.58)	-1.4 (4.19)	(-8.28; 5.56)	5.0 (4.19)	(-1.91; 11.93)
2h30min	-0.7 (4.19)	(-7.66; 6.18)	1.5 (4.19)	(-5.41; 8.43)	-1.1 (4.38)	(-8.31; 6.15)
3h	1.6 (4.19)	(-5.28; 8.56)	-4.6 (4.19)	(-11.53; 2.31)	1.4 (4.38)	(-5.88; 8.58)
3h30min	-0.6 (4.19)	(-7.53; 6.31)	-5.6 (4.19)	(-12.53; 1.31)	-5.9 (4.38)	(-13.16; 1.29)
4h	0.6 (4.19)	(-6.28; 7.56)	-3.1 (4.19)	(-10.03; 3.81)	-3.8 (4.38)	(-11.02; 3.44)
6h	2.1 (4.19)	(-4.78; 9.06)	-4.7 (4.19)	(-11.66; 2.18)	-0.1 (4.19)	(-7.03; 6.81)
12h	0.5 (4.19)	(-6.41; 7.43)	-1.6 (4.19)	(-8.53; 5.31)	1.0 (4.19)	(-5.91; 7.93)

See footnotes on the first page of the table.

Table ECG.06C: Least Square Mean Differences from Day 1 on Days 2, 3, 4, 8, 9 and 10 at Each Time Point by Sex While Adjusting for Other Potential Confounding Factors (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)

Parameter: QTcF (ms)
Treatment: IR Paliperidone
Sex: Female

	Day 8		Day 9		Day 10	
Time	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)	LSMean diff. (SE)	(90% CI LL;90% CI UL)
Predose	5.9 (4.19)	(-1.03; 12.81)	5.9 (4.19)	(-1.03; 12.81)	3.5 (4.19)	(-3.41; 10.43)
30min	5.9 (4.38)	(-1.29; 13.17)	-1.1 (4.38)	(-8.29; 6.17)	5.7 (4.38)	(-1.57; 12.89)
1h	8.8 (4.19)	(1.84; 15.68)	-1.0 (4.19)	(-7.91; 5.93)	0.4 (4.19)	(-6.53; 7.31)
1h30min	6.0 (4.19)	(-0.91; 12.93)	1.5 (4.19)	(-5.41; 8.43)	-0.4 (4.19)	(-7.28; 6.56)
2h	6.9 (4.19)	(-0.03; 13.81)	2.6 (4.38)	(-4.59; 9.86)	1.0 (4.19)	(-5.91; 7.93)
2h30min	7.3 (4.19)	(-0.34; 14.18)	0.5 (4.19)	(-6.41; 7.43)	0.1 (4.19)	(-6.78; 7.06)
3h	5.1 (4.19)	(-1.78; 12.06)	2.8 (4.19)	(-4.16; 9.68)	3.4 (4.19)	(-3.53; 10.31)
3h30min	5.8 (4.19)	(-1.16; 12.68)	3.8 (4.19)	(-3.16; 10.68)	1.6 (4.19)	(-5.28; 8.56)
4h	4.6 (4.19)	(-2.28; 11.56)	-3.5 (4.38)	(-10.74; 3.72)	-1.2 (4.19)	(-8.16; 5.68)
6h	7.8 (4.19)	(0.84; 14.68)	-1.2 (4.38)	(-8.45; 6.01)	2.5 (4.19)	(-4.41; 9.43)
12h	2.8 (4.19)	(-4.16; 9.68)	4.3 (4.19)	(-2.66; 11.18)	9.1 (4.38)	(1.84; 16.29)

See footnotes on the first page of the table.

The following tables show QTcF mean changes by treatment day of each of the above gender by treatment groups. Note that females tend to show a slightly greater maximal numerical QTc increase than males (observed on Day 8 of treatment). This gender difference was greater with Moxifloxacin treatment (on Day 8) than with Pal treatment.

Table ECG.05B: ECG: Descriptive statistics on Differences from Day 1 in Day Averaged QT/QTc by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)
Parameter: QTcF (ms)
Sex: Female

Treatment Arm	Visit	Treatment Group	N	Mean (SE)	Mean Difference (SE)	90% Confidence Interval on Mean Difference
IR Paliperidone	Day 1	Placebo	8	402.5 (5.64)		
	Day 2	Pali 4mg IR q.d.	7	407.3 (6.38)	3.0 (2.77)	(-2.38; 8.38)
	Day 3	Pali 6mg IR q.d.	8	400.9 (5.04)	-1.6 (2.58)	(-6.52; 3.27)
	Day 4	Pali 8mg IR q.d.	7	405.3 (5.48)	1.0 (3.42)	(-5.64; 7.64)
	Day 8	Pali 8mg IR q.d.	8	409.6 (6.31)	7.1 (3.07)	(1.31; 12.94)
	Day 9	Posttreatment	8	405.6 (5.52)	3.1 (4.34)	(-5.09; 11.34)
	Day 10	Posttreatment	8	406.6 (5.32)	4.1 (2.35)	(-0.32; 8.57)
Moxifloxacin	Day 1	Placebo	11	401.4 (4.12)		
	Day 2	Placebo	11	401.6 (3.38)	0.3 (1.22)	(-1.94; 2.49)
	Day 3	Placebo	11	403.2 (3.00)	1.8 (2.49)	(-2.70; 6.34)
	Day 4	Placebo	11	402.5 (2.70)	1.1 (2.22)	(-2.94; 5.12)
	Day 8	MOXI 400 mg	11	411.0 (2.77)	9.6 (2.06)	(5.90; 13.38)
	Day 9	Posttreatment	11	405.2 (2.33)	3.8 (2.38)	(-0.50; 8.14)
	Day 10	Posttreatment	11	402.6 (2.12)	1.3 (2.44)	(-3.15; 5.70)

Table ECG.05B: ECG: Descriptive statistics on Differences from Day 1 in Day Averaged QT/QTc by Sex (STUDY R076477-SCH-1009: Per-Protocol Analysis Set)
Parameter: QTcF (ms)
Sex: Male

Treatment Arm	Visit	Treatment Group	N	Mean (SE)	Mean Difference (SE)	90% Confidence Interval on Mean Difference
IR Paliperidone	Day 1	Placebo	36	383.9 (2.43)		
	Day 2	Pali 4mg IR q.d.	36	387.2 (2.41)	3.3 (1.16)	(1.31; 5.24)
	Day 3	Pali 6mg IR q.d.	36	385.1 (2.24)	1.2 (1.29)	(-1.02; 3.35)
	Day 4	Pali 8mg IR q.d.	36	387.5 (2.10)	3.6 (1.08)	(1.75; 5.41)
	Day 8	Pali 8mg IR q.d.	36	389.5 (2.03)	5.6 (1.09)	(3.75; 7.42)
	Day 9	Posttreatment	36	386.9 (2.62)	2.9 (1.28)	(0.75; 5.09)
	Day 10	Posttreatment	36	385.3 (2.33)	1.4 (1.31)	(-0.82; 3.60)
Moxifloxacin	Day 1	Placebo	47	389.3 (2.27)		
	Day 2	Placebo	47	389.2 (2.20)	-0.0 (0.63)	(-1.08; 1.04)
	Day 3	Placebo	47	387.3 (2.12)	-1.9 (0.88)	(-3.42; -0.45)
	Day 4	Placebo	47	387.9 (2.26)	-1.4 (0.99)	(-3.05; 0.28)
	Day 8	MOXI 400 mg	47	392.5 (2.07)	3.3 (1.18)	(1.27; 5.24)
	Day 9	Posttreatment	47	389.6 (1.98)	0.3 (1.11)	(-1.57; 2.17)
	Day 10	Posttreatment	47	387.3 (2.13)	-1.9 (1.19)	(-3.91; 0.08)

It is noteworthy to show results of some individual subject QTcLD values against Pal plasma levels that were found in Attachment 4.3 of the CSR of Study SCH-1009 (found in the original NDA submission). Only a few selected subjects are shown below. Note that some subjects appear to show a lag in peak QTc values several hours after Cmax and may show a secondary increase in QTc values at 12 hours post-dose (it is not clear how high QTc increases after the 6 hour post-dose time-point since only a 12 and 24 hour post-dose assessment was collected thereafter on selected treatment days). Also compare results across treatment days below. While examining these figures, it is also important to note that some apparent changes in QTc

over time could be reflecting test-retest variance in values independent of treatment and plasma levels.

Note that the upper line in the figures corresponds to QTc interval and the lower line shows plasma levels.

Figure PK/PD 25: Individual Paliperidone Plasma Concentration and QTcLD in Function of Time

[R076477-SCH-1009] page 2 of 63

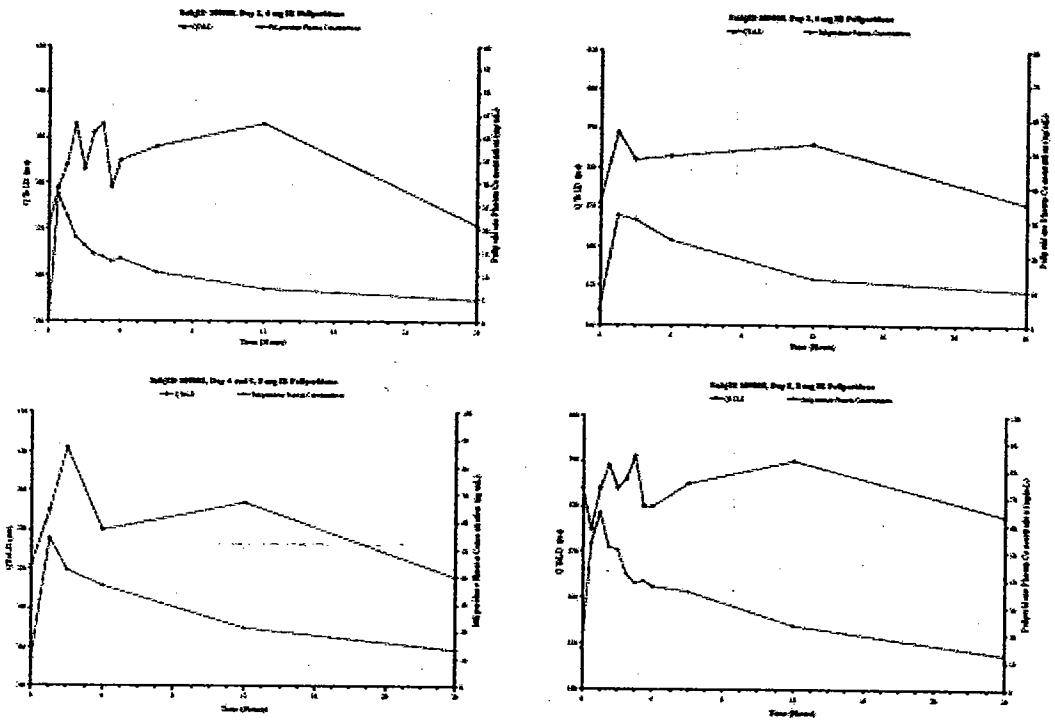


Figure PK/PD 25: Individual Paliperidone Plasma Concentration and QTcLD in Function of Time

[R076477-SCH-1009] page 6 of 63

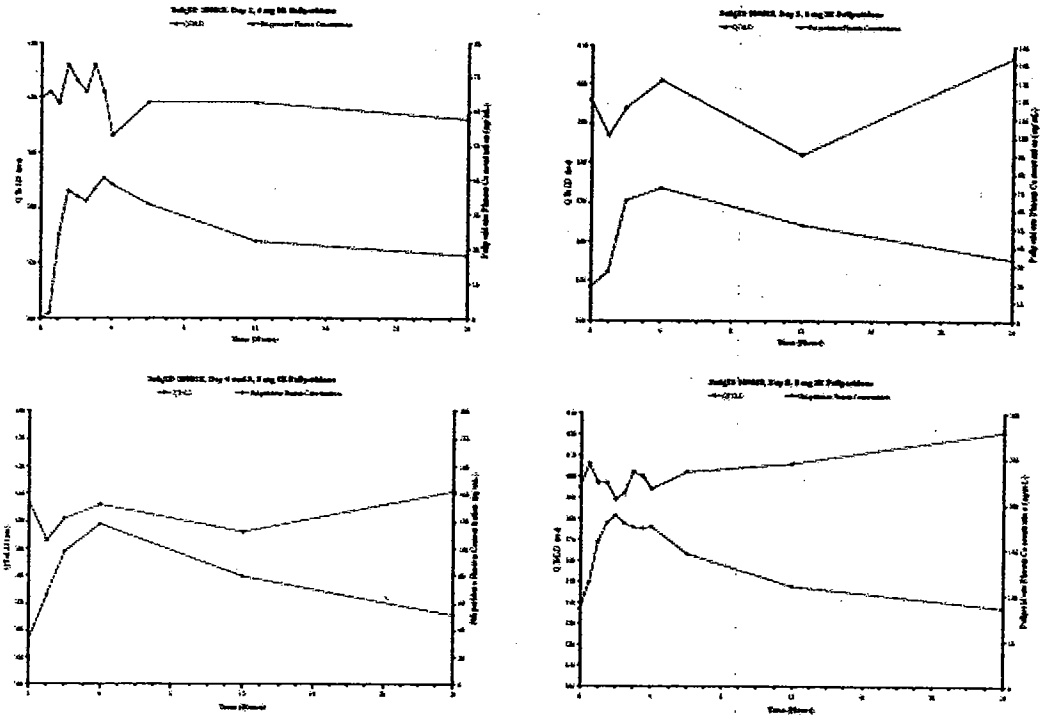
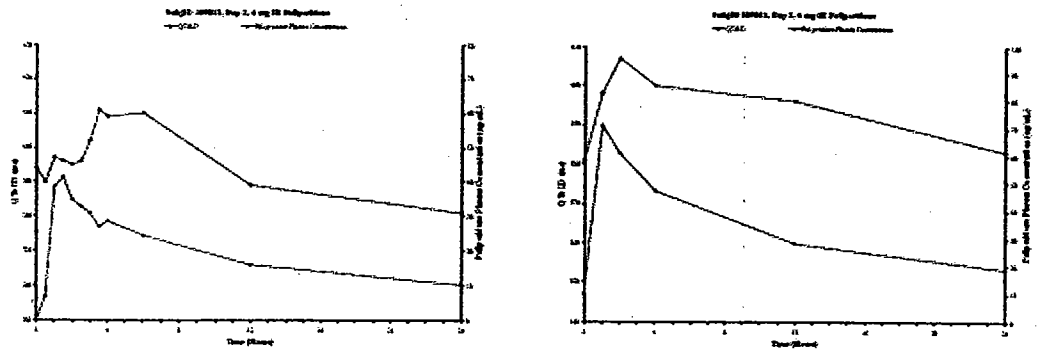
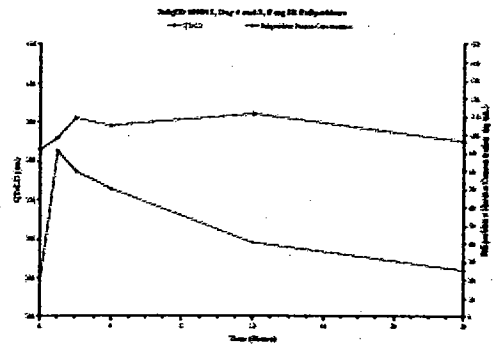
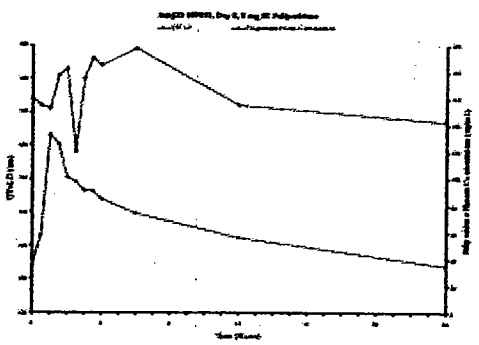


Figure PK/PD 25: Individual Paliperidone Plasma Concentration and QTcLD in Function of Time

[R076477-SCH-1009] page 4 of 63







Reviewer Recommendations. *Given QTc interval prolongation effects (described in the original NDA review), consultative input from the Cardiorenal Division in the Agency will be obtained. Recommendations for questions for the consultant and for information to be provided for the consultant were e-mailed to Dr. Ni Khin on 8/7/06 (upon her 8/7/06 e-mailed request). These recommendations are copied in Attachment 2 of this review. OCPB input on questions and on information to provide for the consultant was also recommended with respect to PK and PK-pharmacodynamic relationships (specifically regarding effects on the cardiovascular system).*

VI. 7/15/06-Response to 6/28/06-Question 2 on the Phase III Formulation

The sponsor was asked to verify if all Phase III trials used the [redacted] formulation [redacted] The sponsor indicated that trials used 3 and 9 mg F016 and F017 formulations, respectively. These formulations differed [redacted] by only the absence of color coating, printing excipients and "minor adjustments" in the amount of other "excipients" (e.g. polyethylene glycol and others). The sponsor provided additional CMC related information on the quantitative composition of Phase III formulations in their 7/15/06 e-mailed response (the corresponding NDA amendment submission is pending at this time).

Reviewer Comment and Recommendations
It appears that there were minor differences, according to the sponsor's overall explanation. However, since the information is CMC related and some of the differences could impact on PK, it is recommended that input from CMC and OCPB be obtained (it is recommended that these consultants be provided with their 7/15/06 response and asked if these minor differences are a significant CMC or OCPB related concern).

VII. 7/21/06 Response to 6/28/06 Question 3 on a Subject with Syncope and "Pauses" on Holter Monitoring and on a Young Female Subject who Suddenly Died in an Open-Label Extension Study (Subjects 300541 and 100963).

The above subjects were described in the review of the original NDA in Section 7. The sponsor was asked to provide more information in these subjects. Subject 100963 was found by the

undersigned reviewer in a Safety Alert Report submitted under the OROS Pal IND (as previously described in the original review).

Reviewer Comments

Little new information on the above subjects could be found in the sponsor's response (see Attachment 3 of this review sent in a 7/21/06 e-mail from the sponsor of which the NDA amendment submission is pending at this time). The information provided in their response does not change the undersigned reviewer's conclusion that events are suspicious of a drug-related etiology and considered to be likely (in the absence of any clear or probable non-drug-related etiology). Refer to the original NDA review for additional comments about these individual subjects and for recommendations. A few additional comments relevant to potential etiologies are made below based on the information in their response.

Subject 300541

Subject 300541 (had syncope, pauses on holter monitoring and other events including AEs leading to an ADO and SAEs, as provided in the original NDA review). The verbatim term syncope was reported as an AE, but the nature and description of "syncope" could not be found in the sponsor's response. The subject was also reported to have events of fainting and dizziness. Refer to Attachment 3 for details on this subject.

The following are reviewer comments that were not previously provided in the original NDA review and are based on the sponsor's response.

It appears that concomitant lorazepam probably played little to no a role in the adverse events in this subject for the following reasons. Lorazepam was last given on Day 4 and adverse events first occurred on Day 5, with additional events occurring on Day 6. Furthermore these events resolved within 2-4 days of Pal treatment cessation.

Vital signs and ECG assessments results on Day 5 of 12 mg Pal treatment (when fainting, hypotension, syncope and other events were reported) could not be found in the sponsor's response. Therefore, the onset of bradycardia and sinus pauses reported on Day 6 could have occurred sooner. Furthermore, bradycardia and sinus pauses could explain the AEs that reported on Day 5.

Although anterior fascicular block found at baseline could have played a role are suggested in underlying condition in this subject, the subject was not reported to have any past history or cardiac disorders are events similar to those observed during paliperidone treatment (e.g. no history of hypotensive episodes, fainting, sinus pauses, heart rates lower than 60 and as low as 38 bpm as were reported on Day 6). Additionally, resolution of the events after cessation of pal treatment together with the nature of the events, as well as the timing of events relative to treatment onset are consistent with at least a major role of Pal treatment.

Subject was reported as an ADO due to "exacerbation of psychosis" on Day 6 and Pal treatment was discontinued on Day 5 for this reason, rather than due to SAEs and other cardiovascular system adverse events (e.g. syncope, hypotension, among others). The sponsor provided the

following additional information with respect to the reason for discontinuation as follows (copied from their response):

NOTE The following description is included because this subject's reason for discontinuation differed from the process described later in the document:
The subject was discontinued due to the adverse event of "exacerbation of psychosis", described as not related by the investigator. During the investigator meeting investigators were trained about what to do in the event a subject had an exacerbation of symptoms associated with their underlying schizophrenia diagnosis. They were instructed to differentiate between symptoms caused by the disease and those potentially caused by the drug. If in their clinical judgment the symptoms were caused by the disease (e.g. were consistent with past exacerbations) and were thus a result of the drug not working (e.g. lack of efficacy), they were to indicate the reason for withdrawal as "lack of efficacy". If their clinical judgment was that the drug was causing the symptoms, they were instructed to list the reason for withdrawal as the adverse event of exacerbation. While these instructions would have suggested this subject should have been discontinued due to "lack of efficacy", it is ultimately up to the investigator to select the reason for discontinuation.

See recommendations below.

Subject 100963

See Attachment 3 of this review for details on this 23 year old female who suddenly died after week 16 of 12 mg daily Pal during an OL extension trial (Study -701). Little new information was provided. However, the sponsor's response specified that trihexyphenidyl 2 mg was prescribed for EPS (this drug was given on the day preceding her death). Information on starting date and treatment regimen could not be found, although this subject had no evidence of EPS on her last study visit.

As previously described in the review of the original NDA, her death occurred about one month after she was last seen at a scheduled study visit during OL treatment of 12 mg Pal/day. She did not show up for her next study visit and had developed AEs 2 days later followed by death on the day after her initial reported symptoms.

In the absence of any clear etiology or risk factors (bronchospam or pulmonary embolism were considered in the differential diagnosis and the subject was a nonsmoker) or underlying conditions (no concomitant illnesses could be found in narrative descriptions), Pal treatment is highly suspected to be involved with events leading to death in this subject.

Although this subject had already received Pal treatment for months adverse effects of pal (including QT prolongation, cardiovascular effects, among others) are described in chronically treated subjects (as described in the original NDA review). Furthermore, limitations with the OL longterm safety data are inherent in the ability to detect potential safety signals (e.g. the absence of a placebo group is a major limitation, refer to the original NDA review for more examples and further discussion).

Reviewer Recommendations

It is recommended that events in subject 300541 and 100963 be described under [redacted]

NDA review) under Warning and Precautions in labeling. A description of subject 100963 is recommended for these subsections since a role of cardiovascular and ECG effects cannot be ruled out and could at least contribute to events that ensued in this subject. A summary of the events of this subject should also be included under the Seizures section in proposed labeling, since the subject appeared to have a seizure. Also consider describing the events of this subject under the "Dysphagia" subsection of labeling, while noting that the subject vomited prior to an episode suggestive of seizure. In any case a differential diagnosis (as described by the undersigned reviewer in the original NDA review) should be included in the description in labeling, as well as a comment that events leading to death and the cause of death remains unclear, as well as noting that no autopsy was performed on this subject.

Given the explanation on the reason for discontinuation of Pal treatment and early study withdraw provided in the sponsor's response (as previously shown in this review) the following concern should be considered. It is not clear if there are additional subjects with clinically remarkable events concurrent with an ADO due to "exacerbation of schizophrenia" that could be drug-related and involving another organ system (e.g. the cardiovascular system). It is recommended that this issue be resolved before granting a final approval on this NDA and that the methodology for AE reporting be included in labeling. Consider asking the sponsor if there are any other Pal subjects in the Phase III short-term double-blind trials with "exacerbation of schizophrenia" reported as an ADO who had concurrent remarkable clinical events (reported as SAEs, ADOs, or as meeting clinically remarkable outlier criteria). If so, then it is recommended that the sponsor provide a line listing of these subjects that includes the following information: subject number, verbatim and preferred ADO, SAE and AE terms, the value of any clinical parameter that met outlier criteria, and a hyperlink to a narrative description (that is included in the submission).

Another concern regarding reporting methods for reporting "lack-of-efficacy" versus "exacerbation of schizophrenia" (as previously described) on results on disposition under the "lack-of-efficacy" and it's potential relevance to assessing the efficacy of the drug. In the case of the subject above, it is reasonable to consider that any psychotic symptoms in the first several days of treatment would not be due to a lack-of-efficacy since treatment was only recently initiated. However, such subjects later in treatment (over at least the final 3-4 weeks of treatment) may not be as easily distinguishable. This issue should be resolved before granting a final approval action on this NDA. In addition to the sponsor providing a response to this potential issue, consider asking for the incidence of early withdrawals due to" lack-of-efficacy" and the incidence of ADOs due to "exacerbation of schizophrenia" for each treatment week of the 6-week DB phase of the short-term Phase III safety dataset (Studies -303, 304 and 305, combined) and to identify and describe any ADOs due to this reason that also had adverse events

(that were not related to symptoms at the time of the ADO, such as cardiovascular related AEs, extrapyramidal side effects or others), abnormal clinical measures or clinical abnormalities during the time or just before the onset of symptoms leading to the ADO of exacerbation of schizophrenia. The sponsor could also be asked to provide the investigator's rationale for reporting each of these ADO as an "exacerbation of the disorder" rather than as "lack-of-efficacy." This may require that the sponsor contact the investigator if they do not already have this information.

VIII. 7/26/06-Response to 6/28/06-Questions 4 and 5 on Selected Subjects

The sponsor was asked the following question (Question 4) and responded in a 6/2/06 e-mail

4. **FDA Comment - The following paliperidone subjects are some examples which lead us to wondering if we are missing subjects who were adverse dropouts (ADOs), such as subjects who withdrew from the study for reasons related to AEs or due to clinical abnormalities (e.g. subjects who withdrew consent due to AEs, subjects who were withdrawn due to noncompliance in which their noncompliance was due to AEs or subjects that withdrew early for other reasons related to AEs)?**

Sponsor's Response to Question 4 and Reviewer Comments.
It appears that the sponsor did not provide any new information on individual subjects that were provided for them as examples as subjects that lead to our overall question, copied above. An example of how the sponsor responded is provided below (copied from their response regarding one of the subjects we identified as an example).

a. **FDA Comment** - Subject 503018: This subject cannot be found in line listings of SAEs or ADOs. The narrative indicates that the elevations in LFTs were not reported as AEs. Please clarify and provide the rationale for how events of elevated LFTs were actually reported in subjects and clarify why the drug was stopped and why the subject was noncompliant.

J&JPRD Response - Subject 503018 (SCH-305) was randomized to receive paliperidone ER 15 mg/day. When clarification was sought from the site to assist in this response, the investigator recently provided the following explanation regarding elevations in AST (154 U/L), ALT (323 U/L) and GGT (175 U/L) observed in the laboratory assessments obtained on Day 15 of the study. The subject was discharged from the hospital on day 15 and continued to receive medication. After reviewing the laboratory results of the sampling on Day 15, the investigator referred the subject to his primary care provider (PCP) who repeated the tests at a local laboratory on Day 18. The PCP instructed the subject to stop taking the study drug at that time. The results from the local laboratory demonstrated a normal AST 25 IU/L (normal range 0-40 IU/L) and still elevated, but lower, ALT of 91 IU/L (normal range 0-40 IU/L) on Day 18. GGT was not included in the panel. The primary care provider believed the LFT abnormalities were related to stomach cramps, reported in the subjects medical history at the beginning of the study, reported as an AE on Day 1 and observed by the site in the days prior to the subject's hospital discharge. Other than the AE of abdominal cramps, the investigator reported no other AEs and no SAEs for this subject during the study. The subject presented for his next scheduled visit on Day 23 and informed the site he had not taken the study drug for the past 5 days. Although the site envisioned study continuation, per the protocol specifications, any subject missing 4 or more consecutive doses must be withdrawn for non-compliance. Therefore, the site withdrew the subject due to "non-compliance".

Additional Reviewer Comments and Recommendations
It is not clear why the above subject was noncompliant and if the subject had been asked why they were noncompliant and if this type of information was being recorded by the investigator. It is also not clear if subjects that withdrew consent or became noncompliant or did not return (and

so dropped out), among other early withdrawals (not reported as ADOs) were asked why. It is also not clear if this information was recorded.

Direct inquiry to the patient about their reasons for becoming noncompliant or withdrawing consent (as examples) might reveal that their early withdraw was due to a potential drug-related reasons (e.g. a given subject could have been feeling sick due to elevations in liver function tests or became non-compliant because of their elevated liver function tests and they were also concerned that continuing treatment could lead to further elevations).

The sponsor did not appear to conduct an inquiry of the investigator and/or subjects as to why the subjects withdrew early (e.g. withdrew consent or became noncompliant) for at least the subjects we identified as examples of subjects that also developed AEs or clinical abnormalities just before and during the time of their early withdraw from the study.

The sponsor also did not appear to conduct a search for additional subjects similar to the examples that were provided for them (e.g. search for subjects who withdrew consent or became noncompliant or withdrew for unspecified or unclear reasons who had AEs or other clinical abnormalities when they withdrew or required treatment for clinical abnormalities when they withdrew).

Some of these patients may have been severely psychotic to the extent that communication with them may have been difficult but it is not clear from the narrative information on these subjects if this was the case. A follow-up inquiry of these subjects might be revealing if the given subject eventually improved enough to be able to communicate adequately. Inquiry of the investigator might also be revealing.

Response to Question 5 and Reviewer Comments
The sponsor was also asked the following question which was the main part of Question 5 in the 6/28/06 e-mail sent to the sponsor (refer to the DFS communications document dated 8/2/06 in DFS for specific communications with the sponsor).

b. **FDA Comment** - Are there any other SAEs that occurred after treatment cessation that were preceded by AEs that led to the SAE that were not captured in the Phase III database (of double-blind and open-label drugs)?

The following example leading to the above question was provided and is provided in this review given the serious nature of the AEs in this subject.

e. **FDA Comment** - Subject 100057: This subject is recorded on the narrative summary table as only having an SAE and is not checked off as being an adverse dropout but is checked off as an SAE (see the "premature discontinued" column on page 1773)? Please clarify why this subject was not considered an ADO.

J&JPRD Response - Subject 100057 (SCH-301) experienced the non-serious adverse events verbatim "restlessness (akathisia)" on Day 4 and "EPS symptoms: muscle stiffness in the entire body" on Day 15 and was treated with benztropine beginning on Day 15. On Day 20 the subject was discharged from the hospital, as allowed by the protocol, and returned for a study visit on Day 22 reporting side effects he "could not tolerate" (restlessness and inability to sleep). The subject was withdrawn from the study and despite the presence of continued adverse events the reason listed by the investigator was subject choice. This investigator designation of reason withdrawn determines who is included in the discontinuation due to adverse events category. On Day 22 the subject had laboratory samples taken and body temperature was recorded as 36.4c. The results of the laboratory samples were reported to the investigative site 2 days later, containing an elevated creatine kinase of 2201 U/L. The subject was contacted and instructed to go to the emergency room immediately, but he did not agree to go until the following day. He was diagnosed with neuroleptic malignant syndrome and elevated creatine kinase. On Day 25 the CK elevation reportedly persisted, but the NMS was considered recovered without sequelae.

The serious adverse event of neuroleptic malignant syndrome was reported by the site as beginning 3 days after the subject was withdrawn from the study (subject's final date in the

R076477-SCH-301 study was the date of withdrawal). Additionally, the event was initially incorrectly identified as occurring in the open label extension phase of the study (R076477-SCH-701). This error was discovered during the data reconciliation process, at which time discussions with the site were held. The site maintained that the start date of the event was after the subject was discontinued from study SCH-301 (as that was when the laboratory values were available and the diagnosis was made) so this date was maintained in the database. As a rule, data for all subjects from their respective study start date through their study end date are summarized. For this subject the reported event occurred after the subject's study end date, thus this event was not included in the summaries. Because this event was recorded as occurring post study, the reason for discontinuation was not queried and the subject was not included in the list of discontinuations due to adverse events, however given the potential clinical importance of the event, a description was included in the submission documents (e.g. 120 day safety update subject narratives).

The sponsor provided the following response to the above question about whether there were other subjects in response to question 5.

To evaluate the question of whether there were other SAEs occurring after subjects discontinued the study that were preceded by AEs potentially leading to the SAE, a review of the clinical and pharmacovigilance databases was performed for Studies R076477-SCH-301, SCH-302, SCH-303, SCH-304, SCH-305, SCH-701, SCH-702, SCH-703, SCH-704, and SCH-705. All SAEs occurring after a subject discontinued the study were reviewed and are included in Attachment 1. These events are divided into those reported only in the pharmacovigilance database (e.g. reported to the company via a CIOMS form) and those found in both the clinical and pharmacovigilance database (e.g. reported to the company via both a CRF page and a CIOMS form). The table was populated with information from the CIOMS reports, patient profiles and previously submitted written narratives. It includes the date and reason a subject discontinued, the date and description of the SAE occurring after discontinuation, and a description and dates for all AEs reported during that study.

The sponsor found only one additional subject (subject 501411) who had the "persisting AE of agitation" who discontinued "due tot lack of efficacy" but later had the SAE of schizophrenia reported at post-study.

Attachment 1 is a listing of subjects with SAEs reported on a date that followed the day of premature study discontinuation in subjects in Phase III trials (this list included subjects who withdrew early due to a variety of reasons such as the withdraw of consent, lack-of-efficacy, ADO's, among others). Most SAE's that occurred after study discontinuation were SAEs of schizophrenia or other psychiatric-related events that appeared to be primarily associated with discontinuation of treatment or lack-of-efficacy or related to their psychiatric condition (based on the timing of these SAEs relative to the timing of treatment discontinuation and by the nature and/or the timing of AE's or ADOs that preceded the post-study SAEs). Other post-study SAEs occurred in placebo subjects. Some subjects had adverse events that began at baseline or resolved prior to study discontinuation or resolved prior to the date of the post- study SAE.

The following additional subject was found by the undersigned reviewer in the sponsor's listing (Attachment 1 of their response):

*Subject 200710 had to **AEs of pneumonia and hydrothorax leading to discontinuation on Day 40 of paliperidone treatment after the dose was recently increased** on Day 36 (from 6 mg daily to 9 mg daily). According to the line-listing hypotension was also reported as an AE on Day 40 ("there were no blood pressure values available for this day," according to that described in the narrative). The hypotension resolved in two days. The AEs of **hydrothorax and pneumonia***

were upgraded to SAEs on Day 44 when the subject was admitted to a general hospital *for treatment of her condition. Treatment included furosemide, an antibiotic, and other medications. Her condition resolved by Day 63 when the subject was discharged from the general hospital. This subject had a history of arteriosclerosis (cardiac and cerebral), QTc prolongation, and intraventricular conduction defect. The timing of the onset of the AE's relative to a recent increase in the dose of paliperidone is suspicious of a role of Pal at least in initial events leading to the more serious complications of hydrothorax and pneumonia), as discussed in more detail below. This female subject also had multiple risk factors for these type of events since she was elderly (65 years old) with concomitant conditions as previously described. Therefore, potential effects of Pal may have played a role together with her pre-existing conditions and risk factors.*

Hemodynamic effects of paliperidone were previously described in the review of NDA 2199. These effects could play a role in subsequent complications in patients with underlying concomitant illnesses and/or risk factors, such as in the above-described subject and in other subjects described in the review of the original NDA.

The incidence of respiratory infection was reported in 3.5% of subjects in the 15 mg paliperidone group to 0.6% of subjects in the placebo group in the primarily non-elderly Phase 3 trials (pooled dataset). Refer to approved Risperdal® labeling for a similar safety signal. Patients, such as the above patient who was elderly with a pre-existing arteriosclerotic disease, are more likely to develop more serious complications due to a less severe Pal-induced AE.

In light of the above comments, it is noteworthy that subject 200214 died of bronchopneumonia in an OL extension trial (a 70 year old male subject). This subject had multiple major medical conditions and complications such that it is difficult to determine whether or not Paliperidone treatment played a role (based on the information provided in the narrative and as described in the review of the original NDA which includes a copy of the narrative).

A few additional SAEs/ADOs were due to respiratory related events in Phase III trials, as described in the review of the original NDA.

The following is a final comment about this additional subject found in the sponsor's listing that was provided in response to question 5 and the potential concern that this subject was not adequately captured in the information found in the original NDA submission. Despite that SAEs were not reported until after treatment cessation and were not found in line listing of SAEs in open-label trials in the original NDA submission, these adverse events were still captured as AE's leading to early discontinuation (and in the sponsor's line listing for ADO's in the original NDA 21999 submission).

Reviewer Recommendations*: the above described subject provides further support for recommendations provided in the review of the original NDA 21999, regarding a lower dose and a more gradual dose increase to be employed in elderly patients and in patients with concomitant illnesses. Given the hemodynamic as well as EKG-related effects of paliperidone described in the original review of NDA 21999 patients with concomitant illnesses involving the*

cardiovascular system may be a particular risk for these drug effects in contributing the development of more serious medical complications (e.g. angina, or other complications as observed in the above subject). In turn, less serious adverse events (e.g. AE's of respiratory infection) associated with paliperidone may pose a greater risk for more serious events (e.g. pneumonia) in some patients, such as the patient described above. The risk for pneumonia should also be addressed under Warnings/Precautions in sections relevant to the elderly and to patients with concomitant illnesses.

IX. A Review of New Information Provided in Narratives of 15 Subjects Provided in the 210-Day Safety Update Report

The 210-Day Safety Update report (SUR) included narratives of 15 subjects in ongoing open label trials that had been previously provided in the four-month safety update report submission under this NDA. Information was added to these narratives in the more recent 210-Day SUR, was primarily of additional SAEs reported in subjects that were previously reported to have other SAEs or ADOs or elevated liver function tests. Most of the added SAEs were psychiatric related events that were typically schizophrenia-related or other psychiatric symptoms that are commonly reported in this patient population. Other newly reported SAEs did not reveal any unexpected drug-related events or involved subjects that were previously described in the review of the original NDA submission in which the added information did not change the overall conclusions. However, the following subject is a possible exception. Subject 500501 was described in the review of the original NDA since this subject developed elevated liver function tests including elevated CPK. The elevated liver function tests were reported as AE's leading to early study withdraw in the original NDA submission. The sponsor has now upgraded these AE's to SAEs. The sponsor explains that this change was made as a result of new information, which provided liver function test values that remained elevated on Day 180 (9 mg/day of paliperidone was discontinued on Day 173) and a further increase in CPK levels of 760 U/l while showing no "evidence of myglobinuria (i.e. positive blood on urine dipstick in the absence of RBC's on microscopy)," and "no evidence of hyperkalemia at any time during the study."

Reviewer Recommendations

The new information provided in the narratives did not reveal any new or unexpected findings that were not previously described in the review of the original NDA submission. However, the additional information on subject 500501 again shows concurrent elevations of CPK with elevations in liver function tests. As previously described the subject had no previous history of liver disease and a non-drug-related etiology could not be identified. Although elevations continued until at least seven days post-treatment cessation it is not uncommon for a drug-induced elevation in liver function tests to lag behind cessation of treatment, among drugs believed to have this adverse effect. Furthermore, paliperidone has a long half-life. Therefore, as previously concluded in the review of the original NDA submission, a potential safety signal for elevations in liver function tests during paliperidone treatment in some subjects is suggested and a may also be associated with elevations in CPK. It is not clear how high liver function test values would have been reached in those subjects who were ADOs due to this adverse event. As

previously recommended, a section under warnings and precautions that describes this potential safety signal is advised for labeling, unless the sponsor can provide convincing evidence that such a potential signal does not exist.

Attachment 1 Narrative descriptions of high CPK outliers

Protocol: R076477-P01-1008; Subject: 100843

Subject 100843 was a white 30-year old male randomized to receive ER OROS paliperidone 15 mg (fasted Phase 3 formulation) during Period 1, 15 mg ER OROS paliperidone (fasted commercial formulation) during Period 2, and 15 mg ER OROS paliperidone (fed commercial formulation) during Period 3. This subject completed all 3 periods of the study.

Cmax levels registered during each treatment period were: period 1: 37.8 ng/mL, period 2: 31.0 ng/mL and period 3: 22.5 ng/mL. The washout period between trial medication administration was 10-14 days.

The laboratory results from the sample obtained at the pre-dose Period 3 visit showed a CK value of 8246 U/L (upper limit of normal 170 U/L in this study) compared to a value of 76 U/L during screening. At the study end the value was 239 U/L. No adverse event was reported regarding this abnormality. The results of the laboratory sample from the pre-dose Period 3 visit also demonstrated elevated ALT and AST values (96 U/L and 215 U/L respectively) compared to values of 32 U/L and 25 U/L respectively, during screening. At study end point values were normalized at 69 U/L and 44 U/L respectively (upper limit of normal 72 and 59 respectively, in this study). This finding of elevated ALT and AST values was reported as a mild, doubtfully related adverse event.

Other adverse events reported around the time of these laboratory abnormalities, included "headache" (2 days after the Period 3 pre-dose assessments) and "sore throat", "night sweats", "nasal congestion" and "dry mouth" (all 3 days after the Period 3 pre-dose assessments).

Given the proximity to these adverse events to the increased CK ALT and AST values, it was likely that all were part of to illness the subject was experiencing at that time. The increase in CK levels at 1 timepoint during the study is thus probably due to other factors than trial medication.

Protocol: R076477-P01-1010; Subject: 101012

Subject 101012 was a black 22-year old male with a medical history of "congenital jaundice hemolytic or hepatic" randomized to receive ER OROS paliperidone 12 mg during Period 1, ER OROS paliperidone 9 mg during Period 2, ER OROS paliperidone 15 mg during Period 3, ER OROS paliperidone 6 mg during Period 4 and ER OROS paliperidone 3 mg during Period 5. This subject completed all 5 periods of the study. The washout in between trial medication administration was at least 9 days.

Cmax levels corresponded to 12.6 ng/mL during period 1, 7.62 ng/mL during period 2, 21.2 ng/mL during period 3, 9.80 ng/mL during period 4 and 3.34 ng/mL during period 5.

The laboratory results form the sample obtained at the pre-dose Period 1 visit demonstrated a CK of 822 U/L (upper limit of normal 545 U/L in this study) compared to 434 U/L during screening. At the pre-dose Period 3 visit the CK was 577 U/L and was reported as a mild, doubtfully related adverse event of "elevated creatine kinase". A re-test the following day had returned to the normal range (263 U/L). At the pre-dose Period 5 visit the CK was 3045 U/L and was reported as a mild doubtfully related adverse event. At the end of the study the CK had returned to the normal range, 433 U/L.

Given the CK abnormality prior to the first dose of ER OROS paliperidone and the return to normal after receiving the highest dose (e.g. pre-dose Period 3 was abnormal and normalized the following day after the 15 mg dose) it is unlikely the paliperidone was causally related to the elevation.

Protocol: R076477-P01-1010; Subject: 101015

Subject 101015 was a white 19-year old male randomized to receive ER OROS paliperidone 6 mg during Period 1, ER OROS paliperidone 3 mg during Period 2, ER OROS paliperidone 9 mg during Period 3, ER OROS paliperidone 15 mg during Period 4 and ER OROS paliperidone 12 mg during Period 5. This subject completed all 5 periods of the study. The washout in between trial medication administration was at least 9 days.

Cmax levels were 13.2 ng/mL in period 1, 2.36 ng/mL during period 2, 12.8 ng/mL during period 3, 27.8 ng/mL during period 4 and 16.3 ng/mL during period 5.

The laboratory results from the sample obtained at the pre-dose Period 5 visit demonstrated a CK of 2885 U/L (upper limit of normal 545 U/L in this study) compared to a value of 222 U/L during screening. A re-test the following day showed a value of 1756 U/L and a value at study end was 1178 U/L. Also at this visit the AST value was elevated to 62 U/L (upper limit of normal 42 in this study)/ A repeat test the following day was 61 U/L and at the end of the study 56 U/L. Neither of these abnormalities was reported as an adverse event.

Overlapping with these abnormal laboratory results was an adverse event of "common cold" beginning two days prior to the pre-dose Period 5 visit and continuing for 3 days after the visit.

Given the proximity to the adverse event "common cold" it is likely the increased CK was related to this illness.

Protocol: R076477-P01-1010; Subject: 101017

Subject 101017 was a white 27-year old male randomized to receive ER OROS paliperidone 12 mg during Period 1, ER OROS paliperidone 9 mg during Period 2, ER OROS paliperidone 15 mg during Period 3, ER OROS paliperidone 6 mg during Period 4 and ER OROS paliperidone 3 mg during Period 5. This subject completed all 5 periods of the study. The washout in between trial medication administration was at least 9 days.

Cmax levels were 18.2 ng/mL in period 1, 11.1 ng/mL during period 2, 20.1 ng/mL during period 3, 6.38 ng/mL during period 4 and 2.23 ng/mL during period 5.

The laboratory results from the sample obtained at the pre-dose Period 4 visit demonstrated a CK of 3394 U/L (upper limit of normal 545 U/L in this study) compared to a value of 240 U/L during screening. At the pre-dose Period 5 and end of study visits the levels were within the normal range (135 and 132 U/L respectively). Also at the per-dose 4 visit the ALT and AST were elevated (54 U/L and 90 U/L respectively) compared to values during screening of 27 and 32 U/L respectively. At the pre-dose Period 5 visit both had normalized with ALT 34 U/L and AST 35 U/L (upper limit of normal 53 and 42 U/L respectively). None of these abnormalities was reported as an adverse event.

No other adverse events were reported around the time of these abnormalities, but a comment in the Case Report Form said the "subject had been stressing his muscles thus CK was elevated predose"

Protocol: R076477-P01-1010; Subject: 101038

Subject 101038 was an asian 22 year-old male randomized to receive ER OROS paliperidone 15 mg during Period 1, ER OROS paliperidone 12 mg during Period 2, ER OROS paliperidone 3 mg during Period 3, ER OROS paliperidone 9 mg during Period 4 and ER OROS paliperidone 6 mg during Period 5. This subject completed all 5 periods of the study. The washout in between trial medication administration was at least 9 days.

Cmax levels were 34.6 ng/mL in period 1, 16.1 ng/mL during period 2, 7.58 ng/mL during period 3, 14.2 ng/mL during period 4 and 11.3 ng/mL during period 5.

The laboratory results from the sample obtained at the pre-dose Period 2 visit demonstrated a CK of 3173 U/L (upper limit of normal 545 in this study) compared to a value of 140 U/L during screening. At the pre-dose Period 3 visit this had normalized to 470 U/L. Also at pre-dose Period 2 the AST was elevated at 50 U/L (upper limit of normal 42 U/L) and LDH at 300 U/L (upper limit of normal 227 U/L). At the pre-dose Period 3 visit both AST and LDH had normalized (33 U/L and 156 U/L respectively).

At the time of the initial abnormalities the adverse events of mild doubtfully related "chest pain (muscular)", mild doubtfully related "elevated AST", mild doubtfully related "elevated creatine kinase" and mild doubtfully related "elevated LDH" were reported.

Given the timing of the adverse event muscular chest pain, the elevated CK value was likely related to this event.

Attachment 3 Recommendations for a Cardiorenal Consult Request (3 pages)
Recommendations for questions for the consultant and of information to be provided for the consultant were e-mailed to Dr. Ni Khin on 8/7/06 (upon her 8/7/06 e-mailed request) and are copied below. OCPB input on questions and on information to provide for the consultant was also recommended with respect to PK and PK-pharmacodynamic relationships (specifically regarding effects on the cardiovascular system).

1) is there sufficient information to recommend a maximum dose-level for adequacy safety based on hemodynamic and QT effects and for higher risk populations, while taking into account potential PK-PD interactions and PK effects (such as the food effect)?
2) If so, then please recommend a maximum dose-level, starting dose-level and recommended titration of the dose in healthy patients and in special populations with respect to adequate cardiovascular system safety (while noting that from an efficacy standpoint a 6 mg starting dose is probably best, while the some subjects may respond to the 3 mg daily dose-level).
3) Please recommend any key cardiovascular system findings that they think we should consider for description under Warnings/Precautions and any additional comments relevant to safety with respect to key findings (see Section 9 of the Clinical review).

I recommend (as in the above) that cardiorenal not only assess QT effects but also vital sign effects, not only because they could be inter-related or vital sign effects could influence QT results, but also because of the following. The overall hemodynamic effects of the drug (which could or could not be related to QT effects) are likely to lead to further clinically remarkable complications such as ischemia or other effects (e.g. consider drug effects on cardiac output) that were sometimes observed in ADOs or SAEs of young subjects that appeared to be healthy or could exacerbate pre-existing conditions as discussed in my review is the above sections).

Given the above Qs I have drafted recommended comments for the consult form, as requested (italicized text below).

Paliperidone NDA proposes treatment of this drug for schizophrenia at doses ranging from 3-12 mg. QT prolongation, other ECG and vital effects were observed in Phase III trials (used up to 15 mg/day), and in longterm open-label (OL) trials (using 3-12 mg daily flexible dose) with results suggestive of greater effects after approximately 6-12 months of OL treatment. Paliperidone (Pal) is a major active metabolite of risperidone (of which risperidone is also active, as described in Risperdal labeling). Yet, QT prolongation effects were not observed in Risperidone trials and vital sign effects described in labeling were quite limited with risperidone (as described in labeling for Risperdal). Risperdal is an immediate release formulation while [redacted] Pal is a longer acting (OROS) formulation. Pal also shows food effects (in contrast to Risperdal which is not described in labeling as showing food effects). ECG and vital sign effects of Pal vary over time as described in the clinical review (in some cases could be reflecting a PK-PD interaction effect or a Pal-interaction effect with underlying physiological-cardiovascular changes related to potential confounding variables or other factors). Also consider potential dynamic effects of Pal induced vital and ECG changes (e.g. under conditions of challenging the cardiovascular system in addition to potential static or absolute effect drug effects). The potential PK-QT relationship was further explored in an ECG study described in the NDA (Study -SCH-1009) which used an immediate-release Pal formulation in order to achieve up to "supra-therapeutic" plasma levels. However, note that this study had an uptitration phase (as subjects were monitored) and that QT prolongation effects appeared to "recur" or become greater upon an increase in dose-level and after

multiple dosing at a given dose level (they examined QT after 4 days on the highest daily dose level of 8 mg daily after a titration phase using a starting dose of 4 mg). More recent results (provided in response to an inquiry about this study), showed the following. Pal group mean QTc (QTcF and QTcLD) increases (from the averaged baseline values) of approximately 10-12 msec at that was generally near 1 1/2 hours post-dose on the ECG assessment day when treatment was initiated (4 mg) and on subsequent test days when the daily dose-level was increased or after multiple daily dosing at a fixed dose-level (only the highest 8 mg daily dose-level was examined for a MD effect at a given fixed dose-level). Gender differences may also exist. Study SCH-1009 did not examine vital sign drug effects and consequently the PK-vital sign drug effect relationship was not examined, as well. Food effect studies (section 7.1.12 of the clinical review) included multiple post-dose vital sign assessments and showed possible drug-effects (e.g. between fed versus fasted conditions but a placebo group was not included). Phase III trials also included fewer, yet multiple post-dose time-points showing effects a specific time-points (as described in Section 7.1.8 of the clinical review). ECG effects were also observed a certain time-points (as described in ECG related sections of the clinical review). Also note observations in the elderly Phase III trial (Study -302 that included a potential signal for AV block AEs and blood pressure changes, and other findings). Also note remarkable subjects in Section 7.1.3.3 of the clinical review, including a subject with syncope and sinus pause (nature of the syncope, etc is unclear) and other remarkable subjects.

Please contact Dr. Karen Brugge and (Ron can insert his name if he wishes) for any questions on the above or questions with locating key information.

Additional New QT prolongation Results:
Refer to a response e-mail to our inquiry about Study -1009 (3 e-mails sent on 6/29/06 from one of the sponsor's personnel Beth Getere-Douglass attached below). Note that these responses are similar to tables 109 and 108 provided in the clinical review of Section 7.1.12 A of the clinical review of the NDA) and provide similar results by gender, as requested. See the clinical review for additional information (as listed below). Also see figures of individual subjects (of QTcLD and plasma levels over time) in Appendix 4.3 of the original NDA (in the CSR for Study -1009) which shows peak QTcLD intervals in some subjects occurring near Cmax or after Cmax is achieved (this could be reflecting a delayed effect of Cmax). Also some subjects showed an additional rise in QTcLD values a number of hours (e.g. 12 hours post-dose in Subject 109088 on page 315 in Attachment 4.3 of the CSR) after Cmax is achieved (very few assessment time-points were conducted after the initial 4 hour-post-dose time-period such that it is not clear how high QTcLD would have reached in a given subject).



FW: Outstanding SCH-1009 Qs &.. | FW: Outstanding SCH-1009 Qs &.. | RE: Outstanding SCH-1009 Qs &..

Other recommended sections of the clinical review and other sources: :
It is suggested that the consultant start with reading the following sections of the Clinical review: Sections I and 9, Section 7 (the overview section that starts on page 70), Section 7.1.3.3 (and also section 7.1.1, 7.1.2, 7.1.3 for summary tables of deaths, ADOs and SAEs), Section 7.1.4, 7.1.8 (vital sign results) and 7.1.9 (ECG results). Sections 7.2.9 (includes more longterm exposure info on QT and related observations in a 120-Day SUR), section 7.1.12 which focuses on the ECG study (-SCH-1009) and food effect studies with vital sign info (that had no meaningful ECG results as I recall due to ECGs only occurring at baseline and sometimes a end-of-study assessment days post-dose). These sections also provide tables and figures with results. Section 5 of the clinical review also shows some PK results, as

provided by the sponsor that may be useful (but also refer to information provided by the OCPB reviewer, Dr. Ronald Kavanagh).

Also refer to olanzapine labeling (which has hemodynamic and related sections under Warnings/Precautions including findings of bradycardia and sinus pause and other findings). Also refer to Risperdal labeling which does not describe cardiovascular system findings observed with paliperidone despite that paliperidone is the major active metabolite of risperidone (while noting that risperidone is also an active compound).

Attachment 4 Sponsor's Response to a Request for More Information on Subjects 300541 and 100963

Subject 300541 (SCH-304) was a 50-year-old white male with a medical history of asthma, intermittent headaches, agitation, and insomnia. The physical examination at screening was normal. There was no relevant history of bradycardia, hypotension, dizziness, or syncope. His weight was 131.5 kg (body mass index 39.3 kg/m2).

At baseline, the ECG was reported as abnormal but not clinically important, showing left anterior fascicular block and a heart rate of 61 beats per minute (bpm). Blood pressure at baseline was 114/84 mmHg (standing) and 112/82 mmHg (supine); his pulse rate was 82 bpm (standing) and 82 bpm (supine).

On Day 5, while receiving paliperidone 12 mg/day, the subject was reportedly hypotensive, dizzy and fainted. The serious adverse events of *dizziness* (dizziness-verbatim) and *hypotension* (hypotension-verbatim) and non-serious adverse events of *syncope* (syncope-verbatim) and *psychotic disorder* (exacerbation of psychosis-verbatim) were reported on Day 5. The case record form does not contain further description of the actual syncope and no vital signs information or other descriptive information is available for Day 5. Study medication was stopped on Day 5 reportedly as a result of the exacerbation of psychosis ("requiring too much lorazepam": CIOMS). Lorazepam (1-7 mg/day) had been used during screening and throughout the first 4 days of double-blind treatment.

On Day 6 the subject was withdrawn from the study due to the adverse event "exacerbation of psychosis" and treatment with lithium 300 mg twice daily was initiated and on Day 7 aripiprazole 15 mg b.i.d. was added.

On Day 6 the subject was hospitalized and diagnosed with bradycardia (this term reportedly included the diagnosis of "pulse delay", both terms were reported as serious adverse events). His standing pulse rate of 38 bpm (40 bpm supine); his supine and standing blood pressures were 110/72 mmHg and 112/72 mmHg, respectively. A computed tomography scan revealed no acute intracranial process and no bleed, a chest x-ray was unremarkable, a basic metabolic profile, cardiac enzymes, T4 and thyroid stimulating hormone were all within normal limits. An ECG revealed normal sinus rhythm, left anterior fascicular block (present at baseline), possible lateral infarct of undetermined age, ventricular rate 67 bpm, PR interval 168 ms, QRS duration 100 ms and QT/QTc 408/431 ms (correction method not reported). A holter monitor reportedly demonstrated "several pauses including an 8-second pause". No further information was reported as the subject signed out/eloped from the hospital.

The dizziness, hypotension and syncope resolved in 2 days, the exacerbation of psychosis resolved in 13 days, and the bradycardia and delay in pulse resolved in 4 days.

The investigator assessed the serious adverse events "dizziness" and "hypotension" to be moderate in severity and possibly related to the study medication. The "exacerbation of psychosis" was rated mild and not related to study medication, the "syncope" mild and possibly related, while the serious adverse events "bradycardia" and "delay in pulse" were considered severe and possibly related to the study medication.

The subject had no prior symptoms of bradycardia, dizziness, or syncope, though there were ECG abnormalities at baseline. Dizziness, hypotension and psychosis have been reported with the use of paliperidone, although these events could also be due to the subject's underlying condition including anterior fascicular block, a potential signal of underlying cardiac disorders. This subject received 5 doses of 12 mg paliperidone; no re-challenge was performed. Therefore a causal relationship between the adverse events "syncope" and "exacerbation of psychosis" and the serious adverse events "dizziness" and "hypotension" and the intake of paliperidone is difficult to assess, but not possible to exclude. The lorazepam received throughout screening and the first four days of double-blind may also have played a role in the symptoms.

NOTE The following description is included because this subject's reason for discontinuation differed from the process described later in the document:
The subject was discontinued due to the adverse event of "exacerbation of psychosis", described as not related by the investigator. During the investigator meeting investigators were trained about what to do in the event a subject had an exacerbation of symptoms associated with their underlying schizophrenia diagnosis. They were instructed to differentiate between symptoms caused by the disease and those potentially caused by the drug. If in their clinical judgment the symptoms were caused by the disease (e.g. were consistent with past exacerbations) and were thus a result of the drug not working (e.g. lack of efficacy), they were to indicate the reason for withdrawal as "lack of efficacy". If their clinical judgment was that the drug was causing the symptoms, they were instructed to list the reason for withdrawal as the adverse event of exacerbation. While these instructions would have suggested this subject should have been discontinued due to "lack of efficacy", it is ultimately up to the investigator to select the reason for discontinuation.

b) Subject 100963: Please provide more complete information on this subject (include relevant information that may help to determine the etiology). Please also provide a hospital report (e.g. discharge summary) on this subject who died in transit to another hospital and any autopsy report (if one was performed). We are also wondering why this subject was prescribed trihexyphenidyl (e.g. "as needed" for what)?

Subject 100963 (SCH-301/701) was a 23-year old female non-smoker, who received primarily paliperidone ER 12 mg and had completed approximately 12 of the 14 weeks of run-in/stabilization in the recurrence prevention study at the time the study was stopped early on the basis of positive efficacy at the interim analysis. The subject was enrolled in the open-label extension and treated with paliperidone ER 12 mg and trihexyphenidyl for EPS treatment and prophylaxis. At the last recorded open-label extension visit (Week 16 in the open-label extension), the subject was experiencing no new symptoms, had no delusions or hallucinations and sleep and appetite were reportedly normal. PANSS total score was 40, CGI-S was 3 ("mild") and AIMS/BARS/SAS scores were all 0. Her score on the Personal and Social Performance (PSP) scale was an 80 (100 indicating the highest functioning). Blood pressure on that date was 116/80 mmHg supine, 112/80 mmHg standing, and heart rate was 80 bpm supine and 84 bpm standing. ECG showed a heart rate of 81 bpm, QRS axis was 78, rhythm was normal sinus rhythm, and repolarization pattern was normal. The subject failed to show up for her next appointment after she had been treated without tolerability issues for approximately 28 weeks and the investigative site made multiple attempts to contact her.

Approximately 5 weeks later, the site was able to obtain information from a relative and learned the subject had died around the time of the missed appointment. Initially, the family refused to provide further information to the site. Subsequently, the site obtained the following information. On the day of her death, the subject's mother described her as anxious, agitated and complaining of breathlessness. The mother gave her a dose of trihexyphenidyl 2 mg (prescribed for EPS). The subject later reportedly vomited, shortly thereafter experienced "severe convulsive movements of the entire body" and became unconscious. She was taken initially to a nearby practitioner who directed them to a hospital where she was examined and found to be unresponsive to painful stimuli and had only deep tendon reflexes present. She was maintained in the hospital for 3 hours on IV fluids and demonstrated a gradual fall in her blood pressure. She received oxygen and phenytoin. She experienced no further convulsions. Laboratory results showed a random plasma glucose of 102 mg/dL, sodium 126 mmol/L, potassium 3.1 mmol/L and chloride 99 mmol/L. Neither an ECG nor an EEG was performed. A decision was made for her to be transferred to a second "better equipped center". She reportedly died on route to the second facility. No autopsy was performed and as the subject lived in a very rural region of India, there is reportedly no death registry, thus no death certificate is available. Also there is no hospital record or discharge summary available.

The treating physician did not believe there were signs of drug use, overdose or poisoning of any kind, but no specific tests were obtained. Her clinical diagnosis was postictal stupor/postictal coma, with bronchospasm and pulmonary thrombo-embolism considered in the differential diagnosis.

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/s/

Karen Brugge
8/18/2006 04:26:23 PM
MEDICAL OFFICER

Ni Aye Khin
8/31/2006 03:11:07 PM
MEDICAL OFFICER
See memo to file for additional comments.