CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-999

MEDICAL REVIEW

M E M O R A N D U M

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

DATE: 19 December 2006

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

TO: File NDA 21-999 (This overview should be filed with the 10-20-06 response submission.)

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

1.0 PURPOSE

The purpose of this memo to file is to provide an interim update for NDA 21,999 since the Division issued an approvable letter to the sponsor dated 9/29/2006. The sponsor responded to this letter on 10/20/06. Please see the approvable memos from Drs. Khin and Laughren for a more detailed evaluation of the data that supported the original approvable action.

1.1 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.

2.0 CHEMISTRY

The chemists have identified no CMC concerns that would preclude an approval action on this NDA. CMC concerns about stability as listed in the approvable letter dated 9/29/2006 have been addressed and the data submitted support an [redacted] month initial expiry for the drug product.

3.0 PHARMACOLOGY

The pharmacologists have identified no pharmacology/toxicology issues that would preclude an approval action for this NDA.

4.0 CLINICAL PHARMACOLOGY

The clinical pharmacologists have not identified no areas of concern that would preclude an approval action for this NDA. Clinical Pharmacology and Biopharmaceutics found the originally proposed dissolution specifications unacceptable and proposed new specifications which have

been accepted by the sponsor. [redacted]

5.0 CLINICAL

5.1 Efficacy Data

Efficacy was determined from four 6-week, double-blind, randomized, parallel group, placebo-controlled trials in patients with acute exacerbations of schizophrenia. The primary endpoint was change from baseline in PANNS total score and the secondary endpoint was change from baseline in the Personal and Social Performance scale (PSP). Dosing was without regard to meals.

All doses in all 4 studies were statistically significantly superior to placebo on the PANSS. Paliperidone ER was also superior to placebo on PSP from these trials, and this is noted in labeling.

[redacted]

5.2 SAFETY

The safety data for this NDA were derived from a total of 2115 subjects/patients exposed to paliperidone ER across 37 clinical trials. Negotiations with the sponsor since the issuance of the approvable letter have focused on the potential for paliperidone ER to produce QT interval prolongation.

5.2.1 QT Prolongation

Although there is no signal from the phase 3 trials, paliperidone ER has a modest QT effect as judged from the sponsor's thorough QT study (SCH-1009). We consulted the Division of Cardiorenal Products (DCRP) for assistance in interpreting the results of this study and verification of corrected QT interval calculations from ECGs submitted to FDA's ECG warehouse. DCRP suggested language for the QT Prolongation section of labeling and recommended this language be included under Warnings because of the identified moderate risk (Pbo-subtracted QTcLD increase from baseline = 12.3 msec). We agree with this recommendation and have included this language under the Warnings section of labeling. The sponsor suggested that language describing [redacted]

5.2.2 Neonatal Effects

The sponsor had included labeling language under the Pregnancy which described the potential for extrapyramidal symptoms in the neonate. We consulted OND's Pregnancy Labeling Team (PLT) for their advice on this issue and recommendations for labeling. PLT provided general language describing the potential effects of maternal antipsychotic use on the neonate, and this language was accepted by the sponsor and incorporated into labeling.

5.0 PHASE 4 COMMITMENTS

Four phase 4 commitments were asked of the sponsor in the approvable letter of 9/29/2006. The sponsor has successfully argued that our initially-requested proton-pump inhibitor drug interaction study would not likely yield valuable information given that the OROS delivery system of the drug is not expected to be affected by gastric pH. The sponsor has agreed to the other three phase 4 commitments in the approvable letter. We should also include the deferred pediatric studies under PREA to be postmarketing study commitments.

6.0 LABELING AND ACTION LETTER

6.1 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.

6.2.1 Foreign Labeling

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

7.0 CONCLUSIONS AND RECOMMENDATION

Sufficient data have been submitted to support the conclusion that paliperidone ER is effective and acceptably safe in the treatment of schizophrenia. We have identified three phase 4 commitments which were conveyed to the sponsor in the approvable letter dated 9/29/2006, and these continue to apply. I recommend that we approve this application.

Memorandum

To: File, NDA 21-999

From: Robert Temple, MD

Date: December 19, 2006

Subject: Approval of Paliperidone Extended Release Oros Oral Tablets for the treatment of schizophrenia

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Based on primary, secondary and tertiary reviews of safety and effectiveness, as well as reviews by chemistry, toxicology and clinical pharmacology, and DSI inspection, I agree that paliperidone has been shown to be effective in the acute treatment of schizophrenia. Maintenance treatment has not yet been studied. While the data stand on their own (3 placebo and active control dose-response studies and over 2000 patients in multiple dose trials), the fact that paliperidone is the principal active metabolite of risperidone means that there is an unusually large experience pertinent to this NME.

Doses from 3-15 mg per day were studied, with higher doses numerically somewhat better through 12 mg, but I agree with the recommended 6 mg (including elderly patients with normal renal function) starting dose and 12 mg maximum recommended dose, as well as elicitation of an agreement to explore lower doses further. There were only a few persuasively dose-related adverse events: akithesia, dystonia, extra-pyramidal disorder, somnolence, hypertonia, orthostatic hypotension, and salivary hypersecretion. Weight gains of $\geq$ 7% were increased in the 9 and 12 mg dose groups.

Despite the impression that risperidone had no material effect on QT, a relatively high dose of paliperidone IR showed a 12 msec effect. The concentrations expected with up to 12 mg ER should be lower, approximately those associated with a QT effect of about 6 msec. These data have led to a QT warning, but not to second line status, the risperidone experience is apparently benign. There were no patients in trials with QTc > 500 msec. The safety update review by Dr. Brugge did not describe any impressive prolongations.

I note late difficulties in agreeing on wording about the [redacted] and that the approved labeling will be silent on this. Most labeling for psychiatric drugs is silent on this point, so that I don't think the omission renders labeling false, but I believe this represents a needless loss of data. I note Dr. Mathis' discussion of this point and wonder whether we are over-refining our analyses. I start with knowing that the drug is effective, giving me a "prior" that it must work [redacted] This deserves further discussion, including good biometrics representation; the labeling can be promptly amended if we can agree on language.

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/s/

Robert Temple
12/19/2006 05:45:27 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies
Addendum to QT Study Review

NDA	21999
Brand Name	[redacted]
Generic Name	Paliperidone
Sponsor	Johnson & Johnson
Indication	Treatment of schizophrenia
Dosage Form	Oral
Therapeutic Dose	3-12 mg once daily
Duration of Therapeutic Use	Chronic Use
Review Classification	Standard
Clinical Division	Division of Psychiatry Products

1.0 GOAL OF THE REVIEW

This review serves as an addendum to a prior QT study review. The purpose of this review was to evaluate a subset of ECGs submitted to the ECG warehouse as part of study RO76477-SCH-1009

2.0 ECG ANALYSIS

A subset of at approximately 30-50 ECG tracings were reviewed to verify the Sponsor's QT measurements. This reviewer focused on those tracings with poor T-wave signal and low and high-frequency noise.

From this reviewer's perspective, the QT measurements appear to have been made appropriately.

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/s/

Shari Targum
12/1/2006 03:45:59 PM
MEDICAL OFFICER

Norman Stockbridge
12/1/2006 05:24:12 PM
MEDICAL OFFICER

Application Type	NDA 21-999 Response to an Approvable Letter
Submission Number Code	N0014
Letter Date	10/20/06
Received	10/20/06
PDUFA Goal Date	12/20/06
Reviewer Name	Karen Brugge, MD
Review Completion Date	11/17/06
Established Name	Paliperidone
(Proposed) Trade Name	[redacted]
Therapeutic Class	Atypical Antipsychotic
Applicant	Johnson & Johnson
Priority Designation	Standard
Formulation	Extended Release OROS® oral tablets
Indication	Schizophrenia
Intended Population	Adults with Schizophrenia

I. The Purpose of this Review and Background Information

The Purpose of This Review.

The purpose of this review is to assist the Team Leader and Director of the Division of Psychiatry Products in the regulatory processing of NDA [redacted]

Recommendations in this review are being provided from a clinical perspective. This NDA was given an Approvable Action as deemed by the Agency. This review focuses on the sponsor's responses to each Clinical item in the Approvable Letter that was deemed by the Agency as clinical issues that still need to be addressed before a final approval action may be granted. This review also focuses on labeling revisions of clinical sections of labeling that differ from labeling that was deemed by the Agency as acceptable labeling.

Other outstanding items that fall under other disciplines (as specified in the Approvable letter) and sections of labeling involving other disciplines are under review by the other disciplines (at the time of this writing). These are additional outstanding issues that need to be addressed before a final approvable action may be considered.

Each clinical item is copied from the Approvable Letter below (bolded text), followed by a summary of the sponsor's response. Note that the order of clinical issues, items E and F (F covers labeling) below is reversed from the order in which they appear in the Approvable letter, such that labeling may be addressed lastly in this review.

Background Information

The sponsor is seeking approval of Paliperidone OROS extended release tablets (Pal) for treatment of schizophrenia based on 3 positive 6-week Phase III trials conducted on patients with schizophrenia (that were generally in the acute episode). Refer to the original clinical review of NDA 21999 for details.

[redacted]

II. Clinical Items in the Approvable Action Letter and a Summary of the Sponsor's Responses

A. Clinical

Please submit the ECG data for study SCH-1009 to FDA's ECG warehouse so the QT measurements on these ECGs can be verified.

Summary of the Sponsor's Response
The sponsor provided the information as requested in the Action Letter and as requested by the QT team that was consulted regarding QT prolongation effects of Pal.

Reviewer Comment. *It is recommended that QT input be obtained on QT data submitted under the NDA, as the QT Team has requested.*

B. Foreign Regulatory Update/Labeling

We require a review of the status of all paliperidone actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If paliperidone has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for paliperidone along with English translations when needed.

Summary of the Sponsor's Response
Pal (ER tablet) is not approved in any country. "No negative action has been taken" with any of the sponsor's pending applications submitted to foreign countries (as listed in the submission, as of 10/2/06).

C. World Literature Update
Prior to the approval of paliperidone, we require an updated report on the world archival literature pertaining to the safety of paliperidone. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of paliperidone. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The NDA 21-999 Page 4 report should emphasize clinical data, but new findings in pre-clinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Summary of the Sponsor's Response
The sponsor summarized methodology of their updated search (for literature published between 4/1/06 and 7/31/06; note that 3/31/06 was the cut-off date used for literature search in the 210-SUR submission).

The following are listings of databases searched and search terms employed in the search, respectively (as copied from the submission)

Medline	Embase	Psych Info	Derwent Drug	Biosis
SciSearch	Chemical	Int Pharm Abs	File	Previews
Adis Clinical	Abstracts	ExtraMed	Life Sciences	Fedrip
Trials Insight	Conference		Collection	Pharmline
	Papers Index		JICST-Eplus	

The following primary search terms were included in the database search:

9-hydroxyrisperidone	9-hydroxy-risperidone	CAS Registry Number
9-OH-risperidone	paliperidone	144598-75.4

The sponsor explains that [redacted] conducted the search (assisted by J&JPRD Global Information Center) and that [redacted] reviewed the articles.

Only 3 out of 12 articles that were found in their search had safety data. According to the sponsor daily doses ranging from 3 mg to 15 mg were "safe in schizophrenia subjects up to 6 weeks."

Reviewer Comment.
Footnotes found in summaries of the above 3 articles (3 abstracts) provided in Attachment 1 of the submission indicated that the data in these abstracts "were extracted" from short-term Phase III trials -302, -303 and -305. Safety results from these trials were previously reviewed. Therefore, no new safety information could be found in the current submission.

The sponsor also provided results of updated reviews of the literature in previous NDA 21999 submissions; the 120-Day and 210-Day SUR submissions. This information was not previously reviewed as follows. The 210-SUR submission arrived late in the review cycle and was therefore not reviewed in the original and addendum clinical reviews of NDA 21999. Only clinical trial safety data provided in the 120-Day SUR was reviewed and summarized in the clinical review of NDA 2199. Consequently, the below subsection summarizes the results of the literature reviews described by the sponsor in these previous SUR submissions.

Summary of Literature Reviews in the 120-Day and 210-Day SUR submissions

The SURs used the same search terms and search databases as were employed for the current approvable response submission. A description of personnel that reviewed the search term results and articles could no be found in these previous submissions. Only a few publications with Pal were found which contained results from previously reviewed Phase III 6-week schizophrenia trials. Therefore, new information on Pal could not be found, that was not already described in the original review of NDA 21999. Risperidone studies that had safety information in reference to 9-OH-resperidone were summarized

and did not provide any new clinically remarkable safety observations that were not already described in the previous clinical reviews of NDA 21999. Several PK Risperidone-drug interaction studies were summarized that included results on PK properties of 9-OH-respiridone that the sponsor concluded did not provide any new information relevant to safety.

OCPB input is recommended regarding PK studies found in the sponsor's reviews of the literature that are included in the original and updated submissions under NDA 21999.

D. Safety Update

Our assessment of the safety of paliperidone is based on our review of all safety information provided in your original and subsequent submissions, including your safety update of December 31, 2005. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

Reviewer Comment. *Newly submitted information summarized below does not change previously conveyed conclusions and recommendations provided in previous clinical reviews of NDA 21999.*

A Summary of the Sponsor's Response
The sponsor provides narratives for 5 subjects with newly reported SAEs since the reporting cut-off date for 210-Day SUR submission (these 5 SAEs that occurred between 3/31/06 and 8/31/06). The subjects are as follows: subjects 100323 and 100772 in Study R076477-SCH-701, subjects 500132, 500547, and 500655 in Study R076477-SCH-705.

Four of the 5 newly reported subjects with SAEs were SAEs of psychotic related events (e.g. schizophrenia) during OL treatment in which narrative descriptions did not describe any other unrelated events (e.g. potential drug effects on another organ system that may have lead to these psychiatric related events). The fifth subject (500547) was a 57 year old female patient (that appeared to be generally healthy) and was not receiving any concomitant medications. She developed dyspnea on Day 327 of OL treatment that was evaluated in the emergency room. This event was believed to be due to anxiety (ECG and "other unspecified tests...failed to show any organic findings..."). Therefore the subject was treated with diazepam for 5 days and the event resolved during the emergency room visit. Study medication was discontinued by the investigator on Day 338 (one day after a study visit during which no abnormalities on physical examination, ECG or vital signs were reported).

Reviewer Comment. *The reason why study medication was stopped in subject 50047 cannot be found in the narrative. Perhaps, cessation of treatment was related to lack of efficacy but this is only speculation on the part of the undersigned reviewer.*

Update on a Sudden Death during OL Treatment of 12 mg daily of Pal (Study -70)
The sponsor also provided updated information on a 23 year old female subject (100963 or [redacted] on the CIOMS form) with an unremarkable past medical history who died within hours after she became "breathless, anxious and agitated." This subject was given 2 mg trihexyphenidyl by her mother after developing these symptoms, "as per instruction" (2 mg BID was prescribed for extrapyramidal side effects of "masked facies"). She subsequently had "convulsions" and "loss of consciousness" for unclear reasons and died hours later after being seen in an emergency room, while she was being transported to another hospital. Refer to the clinical review and addendum clinical review of NDA 21999 for more details regarding this subject.

It appears that the new information being provided is the following:

- *The sponsor now reports that the investigator has more recently changed the terms used for the cause of death from "convulsion, bronchospasm, and respiratory failure" (as specified in the 210-Say SUR) to "convulsion" and "pulmonary embolism" (as specified in the current response to the Approvable letter submission and as found in a recent safety alert update report submitted under the IND). The SAE terms (and terms used for the cause of death) for this subject are now convulsion and pulmonary embolism since the investigator more recently suspected pulmonary embolism on the basis of the previously reported symptoms of breathlessness, anxiety and agitation that were described in past submissions as preceding the convulsion and loss of consciousness.*

Note that in the sponsor's proposed labeling (discussed later in this review), "bronchospasm" does not appear in the "Other Events Observed During the Premarketing..." section of labeling, while pulmonary embolism is now listed in this section.

No other new information from that previously described in the past clinical reviews of NDA 21999 can be found in the current updated description and narrative provided for this subject. The following are additional comments about the cause of death and differential diagnosis of this subject. As previously described in the original review the differential diagnoses by the investigator included: convulsion, bronchospasm and respiratory failure, rule out pulmonary embolism. The treating physician in the patient's home town did not suspect drug overdose, poisoning (did not have any "signs or symptoms" of poisoning) and "his clinical diagnosis was: posticital stupor/postictal coma." The narrative also indicates that the treating physician gave a clinical diagnosis of "postictal stupor/postictal coma." "The investigator maintained that this event was probably related to study medication." While pulmonary embolism is a possible diagnosis it is not clear that this event actually occurred. Furthermore, other etiologies could have been due to an arrhythmia (e.g. secondary to QT prolongation), bronchospasm or other underlying events that could have been drug-related. An autopsy was not performed and other clinically relevant information (such as ECG results) was limited or could not be found in the narrative of this subject.

In conclusion no new clinical data (e.g. any diagnostic test results or autopsy results) on the above subject can be found that differs from clinical data that were previously described in the clinical review and clinical addendum review of NDA 21999 (other than the impression of the investigator on the cause of death). Consequently information on the above subject provided in the current submission does not change previous conclusions and recommendations conveyed by the undersigned reviewer in past clinical reviews of NDA 21999.

A Summary of Safety Results of Clinical Trials in the Previous 210-SUR Submission

The 210-SUR of NDA 21999 was not previously reviewed except for selected information that was summarized in previous clinical reviews of NDA 21999. [redacted]

Review Strategy of Updated Safety Information

For the purpose of the current review of this approvable response submission, only updated results of deaths, serious adverse events (SAEs) and adverse dropouts (ADOs) are reviewed and summarized (rather than providing more detailed safety results such as on clinical parameters). [redacted]

The clinical review of the original NDA 21999 (that include 120-Day SUR safety results) described the bulk of longterm safety data. This longterm data was primarily of the integrated OL extension trial safety dataset in which the sponsor had met ICH guidelines for exposure including 6 month and 12 month exposure (refer to results in the clinical review of the original NDA 21999 review). Only a few of the 6-12 month OL extension trials were ongoing since a review of the 120-Day SUR was completed and summarized in previous NDA 21999 reviews. Furthermore, limitations with OL data are inherent (as discussed in previous reviews).

In conclusion, for the purposes of the current review only updated information on deaths, SAEs and ADOs in ongoing trials (as summarized later) were reviewed and summarized below.

A more comprehensive review of other clinical safety results from selected safety datasets is currently being conducted [redacted]

Reviewer Conclusions on Results Described Below. *The safety results described below did not reveal any new, clinically remarkable findings that alter conclusions and recommendations that were previously conveyed in the original and addendum clinical reviews of NDA 21999.*

[redacted] Longterm Safety Results Relevant to the Current NDA 219999

As previously discussed the safety results on deaths, SAEs and ADOs below were also provided in the 210-Day SUR submitted under NDA 21999 [redacted]

The following summarizes the study design of open-label (OL) extension trials from which safety updated information was provided which includes ongoing trials and trials completed since the 120-Day SUR submission under NDA 21999. Other trials were previously completed in which deaths, SAEs and ADOs were previously provided and included in previous clinical reviews of NDA 21999.

OL Extension Trials: A brief summary of each OL Pal Extension trial is outlined below. All OL trails were conducted on patients with schizophrenia who previously participated in short-term efficacy Phase III trials. Each OL trial used a flexible dose design that generally allowed dose adjustments (generally in 3 mg intervals) to maximize efficacy while minimizing adverse events:

- Study -701 (non-elderly patients) used a 3-15 mg daily flexible-dose-level with a starting daily dose of 9 mg. This study is an OL extension trial that followed the maintenance treatment Phase III study -301. Study -301 was a pivotal maintenance trial [redacted] and was completed in time for inclusion of death, SAE and ADO information in the previously reviewed 120-Day SUR NDA 219999 submission.
- Elderly Study -702 used a 3-12 mg daily flexible-dose-level (3, 6, 9, or 12 mg/day) with a starting daily dose of 6 mg. This small 6-month OL extension trial followed the small, elderly, 6-week Phase III efficacy trial -302.
- Studies -703, -704 and -705 (almost all non-elderly patients). These studies used a 3-12 mg daily flexible-dose-level (3, 6, 9, or 12 mg/day), except for Study -305 which included a maximum daily dose level of 15 mg. The starting daily dose in these trials was 9 mg. In summary these trials included generally healthy adults, almost all non-elderly subjects with schizophrenia who had previously participated in a 6-week double-blind, placebo controlled, active (olanzapine) controlled, parallel group Phase III trial (Studies -302, -303, -304 and -305).

Pooled and Unpooled Safety Datasets that were Reviewed

The following summarizes the pooled and un-pooled safety datasets that are the focus of the safety review from which results described in sections below were obtained:

- Integrated OL Extension Trial Safety dataset (-702, -703, -704 and -705, combined).
- A Completed Extension OL Elderly Trial -702.
- A Completed Extension OL Study -701 that followed the maintenance treatment Study -301.

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

- Status of OL trials as described in the submission are outlined below:
  - Study -705 is ongoing
  - Studies -702, -703 and -704 are now completed
- CSRs provided:
  - CSRs are provided for -701, -702 and -704 (since they were completed before the 2/1/06 cut-off date).
  - Study -703 was completed shortly after the cut-off date such that a CSR was not provided for this study. The CSR of Study -704 was provided but was not reviewed as described in the following.
- CSRs that were not reviewed:
  - The CSR of Study -701 was not reviewed. This study is the extension OL 12-month trial that followed Study -301. [redacted] included safety results from Study -701 that were selected for the purpose of this review and are summarized below. [redacted]
  - The CSR of Study -704 was not reviewed since the integrated OL trial safety database was reviewed and is considered to be more informative than a single OL trial that is a subset of the integrated safety dataset that the sponsor analyzed. Given the larger sample size and limitations inherent with data from OL trials, the integrated safety dataset is considered to be more likely to reveal a potential safety signal than a single trial from the integrated safety dataset.
  - Selected sections of the CSR of -702 were reviewed as described in sections below since this trial focused on a special population (elderly patients).

Updated Safety Information on Deaths, SAEs and ADOs
Excerpts on deaths, SAEs and ADOs described below are copied from Section 7 of the [redacted]

Deaths

Reviewer Comment. *To the knowledge of the undersigned reviewer and based on the information reviewed in the [redacted] submission, there are no newly reported deaths in clinical trials of Pal that were are not already described in the original and addendum clinical reviews of NDA 21999.*

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

Subject number (Study number)	Age (Years) Sex	Dictionary-derived Term Reported Term	Day of AE Onset[a]	Action Taken with Treatment	Relationship to Study Drug[b]
Double-Blind Study					
Treatment Group: ER OROS paliperidone (post run-in phase)					
100744 (R076477-SCH-301)	36 Male	Completed suicide death (suicide - strangulation by hanging)	72	None	Very likely
Treatment Group: Placebo					
100068 (R076477-SCH-301)	47 Male	Gun shot wound multiple gunshot wounds	174	None	Not related
100846 (R076477-SCH-301)	50 Male	Completed suicide suicide	152	None	Not related
Phase 3 Open-Label Extension Studies					
Treatment Group: Pla/Pali, ≤6 months					
200214 (R076477-SCH-702)	70 Male	Bronchopneumonia Bronchopneumonia	157[c]	None	Not related
Treatment Group: Pali/Pali, >6 months					
201516 (R076477-SCH-703)	42 Female	Completed suicide fall from 3rd floor	283	None	Not related
Treatment Group: Olan/Pali, >6 months					
200416 (R076477-SCH-703)	31 Female	Completed suicide suicide with medication[d]	238	None	Not related

[a] Study day is in reference to the start of double-blind medication, except for Subject 100744 (start of run-in phase).
[b] Relationship based on assessment of investigator.
[c] Subject was withdrawn from the study due to a serious adverse event (electrocardiogram QT corrected interval prolonged) and died of non-treatment-emergent bronchopneumonia 4 days after receiving the last dose of study medication.
[d] Subject ingested venlafaxine and lorazepam.

Between the cut-off dates of 2 February 2006 through 31 March 2006 an additional death was reported to occur in subject 100963 who was a 24 year old female with an unremarkable medical history who was only receiving trihexyphenidyl for extrapyramidal symptoms. The subject was lost to follow-up after receiving several months of 12 mg of paliperidone, daily during Study -701. She had experienced anxiety, dyspnea, vomiting followed by a seizure and ultimately cardiorespiratory arrest. A non-drug-related etiology could not be found in the narrative and an autopsy was not performed.

Reviewer Comment. *Subject 100963 was previously described in the original review of NDA 21999 and in an addendum review under NDA 21999 (subject [redacted] and 100963 are the same subject). 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.

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

Other Serious Adverse Events

The following summary tables of the OL extension trials have updated information (as provided by the sponsor). Separate updated tables for each of the recently completed OL trials, studies -701 and -702 are also shown below (as provided by the sponsor).

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

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

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

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

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=36) n (%)	Total Pali >6 months (N=199) n (%)
Total no. subjects with serious adverse events	3 (8)	7 (4)
Psychiatric disorders	1 (3)	6 (3)
Schizophrenia	0	3 (2)
Delusion	0	1 (1)
Suicide attempt	1 (3)	0
Injury, poisoning and procedural complications	0	2 (1)
Alcohol poisoning	0	1 (1)
Tibia fracture	0	1 (1)
Nervous system disorders	1 (3)	0
Syncope	1 (3)	0
Reproductive system and breast disorders	1 (3)	0
Varicocele	1 (3)	0

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

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

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Total no. subjects with serious adverse events	17 (17)	13 (9)	40 (19)	57 (12)	33 (31)	14 (10)	90 (22)	84 (11)
Psychiatric disorders	12 (12)	10 (7)	35 (17)	44 (9)	30 (28)	11 (8)	77 (19)	65 (9)
Psychotic disorder	7 (7)	2 (1)	14 (7)	20 (4)	12 (11)	5 (4)	33 (8)	27 (4)
Schizophrenia	2 (2)	2 (2)	15 (7)	15 (3)	13 (12)	3 (2)	30 (7)	21 (3)
Depression	0	2 (1)	1 (<1)	4 (1)	2 (2)	1 (1)	3 (1)	7 (1)
Suicidal ideation	2 (2)	1 (1)	3 (1)	4 (1)	0	0	5 (1)	5 (1)
Agitation	2 (2)	1 (1)	3 (1)	2 (<1)	5 (5)	1 (1)	10 (2)	4 (1)
Hallucination, auditory	0	0	0	4 (1)	0	0	0	4 (1)
Acute psychosis	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Anxiety	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Completed suicide	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Depressed mood	0	0	0	2 (<1)	0	0	0	2 (<1)
Suicide attempt	1 (1)	2 (1)	2 (1)	0	1 (1)	0	4 (1)	2 (<1)
Aggression	2 (2)	1 (1)	0	0	4 (4)	0	6 (1)	1 (<1)
Alcoholism	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Confusional state	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Delusion	0	0	2 (1)	1 (<1)	0	0	2 (<1)	1 (<1)
Insomnia	0	1 (1)	1 (<1)	0	2 (2)	0	3 (1)	1 (<1)
Paranoia	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia, paranoid type	0	0	0	1 (<1)	0	0	0	1 (<1)
Self-injurious ideation	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Infections and infestations	0	0	1 (<1)	8 (2)	1 (1)	1 (1)	2 (<1)	9 (1)
Nasopharyngitis	0	0	0	2 (<1)	0	0	0	2 (<1)
Bronchitis acute	0	0	0	1 (<1)	0	0	0	1 (<1)
Cellulitis	0	0	0	1 (<1)	0	0	0	1 (<1)

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

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Infections and infestations (continued)								
Measles	0	0	0	1 (<1)	0	0	0	1 (<1)
Perianal abscess	0	0	0	1 (<1)	0	0	0	1 (<1)
Pulmonary tuberculosis	0	0	0	0	0	1 (1)	0	1 (<1)
Sinusitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Urinary tract infection	0	0	0	1 (<1)	0	0	0	1 (<1)
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	0	0	0	0	1 (1)	0	1 (<1)	0
Nervous system disorders	1 (1)	2 (1)	4 (2)	5 (1)	1 (1)	0	6 (1)	7 (1)
Akathisia	0	0	0	2 (<1)	1 (1)	0	1 (<1)	2 (<1)
Dizziness	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Dystonia	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Ischaemic stroke	0	1 (1)	0	0	0	0	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Transient ischaemic attack	1 (1)	0	0	0	0	0	1 (<1)	0
General disorders and administration site conditions	0	0	1 (<1)	4 (1)	1 (1)	0	2 (<1)	4 (1)
Pyrexia	0	0	0	2 (<1)	0	0	0	2 (<1)
Cyst	0	0	0	1 (<1)	0	0	0	1 (<1)
Irritability	0	0	0	1 (<1)	0	0	0	1 (<1)
Chills	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0

See footnotes on the first page of the table.

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Injury, poisoning and procedural complications	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	0	4 (1)	4 (1)
Alcohol poisoning	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Fall	0	0	0	1 (<1)	0	0	0	1 (<1)
Road traffic accident	0	1 (1)	0	0	0	0	0	1 (<1)
Traumatic haematoma	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Overdose	0	0	0	0	1 (1)	0	1 (<1)	0
Investigations	1 (1)	0	0	2 (<1)	0	0	1 (<1)	2 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Metabolism and nutrition disorders	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Diabetes mellitus	0	0	0	1 (<1)	0	0	0	1 (<1)
Hyponatraemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Hypokalaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Benign neoplasm of skin	0	0	0	0	0	1 (1)	0	1 (<1)
Colon neoplasm	0	0	0	1 (<1)	0	0	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	0	0	1 (<1)	1 (<1)	0	1 (1)	1 (<1)	2 (<1)
Asthma	0	0	0	0	0	1 (1)	0	1 (<1)
Dyspnoea	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood and lymphatic system disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Anaemia	0	0	0	1 (<1)	0	0	0	1 (<1)

See footnotes on the first page of the table.

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Gastrointestinal disorders	1 (1)	1 (1)	0	0	0	0	1 (<1)	1 (<1)
Crohn's disease	0	1 (1)	0	0	0	0	0	1 (<1)
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Hepatobiliary disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Cholelithiasis	0	0	0	1 (<1)	0	0	0	1 (<1)
Cardiac disorders	1 (1)	0	2 (1)	0	3 (2)	0	5 (1)	0
Bundle branch block	1 (1)	0	0	0	0	0	1 (<1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Sinus tachycardia	0	0	0	0	1 (1)	0	1 (<1)	0
Tachycardia	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Social circumstances	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

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

The sponsor also specifies that 3 additional subjects had SAEs in the OL extension trials (of the combined OL extension trial dataset) since the cut-off date for the above summary table and prior to the 4/1/06 cut-off date. One of these subjects is subject 10096 who died (a 24 year old female with an unremarkable PMH who developed agitation, coma, convulsion and dyspnea and died during OL 12 mg daily Pal treatment). This subject was previously described under the section on deaths. The other 2 subjects had SAEs of

"exacerbation of schizophrenia" and "psychotic disorder and suicidal ideation," respectively.

Additional SAEs are described below.

Reviewer Comment.
No new clinically remarkable findings were revealed that change conclusions and recommendations that were previously described in the reviews of NDA 21999. The following are additional reviewer comments. .

OL Safety Dataset (Studies -701, through -705).
Results shown above are generally similar to results of the 120-Day SUR of NDA 21999 that were previously shown in the review of NDA 21999.

Newly reported SAEs (between November 1, 2005 in February 1, 2006), since the time of the four month safety update report were provided in the 210-Day safety update report of NDA 21999 (in the SCS section and line listing found in the appendix on page 1710 of this section) are identical to those provided in [redacted] the SCS of the current submission is identical to the SCS of the 210-Day SUR submission under NDA 21999, as specified on page 3 of the "Reviewer's Guide for [redacted] ; the line listing reviewed started on page 1710 of the 210-Day safety update report under NDA 21-999).

New SAEs reported before the most recent 4/1/06 cut-off date (3 subjects, as previously described) included 1 death that was also described in the review of NDA 21999. Information found on the other 2 subjects fail to shed any clinically new and remarkable findings that differ from those previously described in the review of NDA 21999.

Most SAEs in the line-listing (starting on page 1710 of the 210-Day SUR under NDA 21999) of newly reported SAEs were due to psychosis related SAEs and a few due to suicidal related SAEs. Few of these subjects had SAE and/or ADO Preferred or verbatim terms that included non-psychiatric related terms that might be considered unrelated to the psychiatric related event (e.g. none of these subjects had a cardiovascular related event reported as an ADO or SAE in addition to the psychiatric related SAE).

Psychiatric-related symptoms reported as SAE's and/or ADOs are expected for this patient population. However, it is theoretically possible to have exacerbation of symptoms secondary to underlying drug-related adverse effects (that could theoretically include non-psychiatric related adverse effects that may not be clearly expressed by an acutely psychotic or agitated patient). A description of such patients (i.e. patients of SAE's that could be reflecting a drug-related adverse effect) could not be found in in-text sections of the SCS section of this submission. The line listing that was found in the 210-Day safety update report under NDA 21999 (starting on page 1710) specified preferred

and verbatim terms for each ADO and SAE in a given subject. This line listing was reviewed. Subjects were found in this line listing that had a psychiatric-related SAE or ADO that had non-psychiatric-related verbatim terms reported either as an ADO or SAE term. The following subjects are noted:

- *Subject 100312 in Study -701 had SAE's of fracture of the left tibia (reported on Day 140 of the open-label extension phase, leading hospitalization) and "aggressive behavior" (reported during placebo double-blind treatment, with exacerbation of schizophrenia also reported SAE). "No information was available regarding the cause of the injury." However, given the events occurring during placebo treatment, it appears that this subject exhibits aggressive behaviors during an acute psychotic state which can increase the risk for injury. These events are not an uncommon event in this patient population. Exacerbation of schizophrenia was reported again as an SAE and was the event that led to an ADO in the subject.*
- *Subject 201432 had "exacerbation of schizophrenia" reported as an SAE who also had high fasting insulin levels, gastritis, candidiasis and high fasting c-peptide reported. These events were listed as SAEs in line listing but were indicated in a footnote as not being reported as serious but were instead "referenced to the clinical safety form." Several of these adverse events could be drug-related (e.g. diabetic mellitus-like adverse events are known to be associated with this drug-class) that may have contributed to worsening of schizophrenia.*
- *Subject 500772 with SAE's of akathisia, anxiety and irritability. Akathisia is known to occur with drugs in this drug-class and could lead to anxiety and irritability.*
- *Subject 501413 had confusion reported as an SAE (which could reflect a nonpsychiatric adverse effect). Agitation and acute psychotic episode were also reported as verbatim terms. Patients often appear to be confused while acutely psychotic and/or agitated. Information is limited in the narrative (e.g. does not mention results of a any possible neurological examination that might have been conducted while the patient was hospitalized, results of clinical parameters or diagnostic tests, and other relevant information such as orientation to person, time and place). These SAEs resolved as the patient continued OL treatment. However another psychotic episode was reported as an SAE (but confusion was not mentioned as an AE or SAE). This event lead to hospitalization which occurred over 200 days after the episode of confusion.*

The following non-psychiatric related SAEs are notable since a convincing or clear non-drug-related etiology could not be found and the events may reflect a new and remarkable drug-related effect on safety:

- *Subject 500501 had SAEs related to elevated LFTs (transaminases and GGT), as well as markedly elevated CPK (for unclear reasons). The subject was generally healthy (no non-drug-related etiology or risk factors were found in the narrative). These events were first noted on Day 160 of OL Pal (9 mg/day). LFTs remained elevated after 1 week of treatment cessation that may suggest a*

non-drug-related event, but levels were only provided for this one 1-week post treatment cessation time-point and LFT changes can sometimes lag behind changes in treatment. Elevations in LFT and CPK were previously described in this subject (refer to the original clinical review of NDA 21999 for details).

The following are additional comments regarding SAEs of Study -702 since this was the OL extension trial of elderly patients with schizophrenia (the study followed the elderly Phase III 6-week efficacy DB, placebo controlled trial, Study -302). Efficacy and safety results of Study -302 were previously described in the review of NDA 21999. However, Study -702 was ongoing at that time [redacted] *provides the CSR for this OL elderly trial. A key difference on methodology of Study -702 (aside from the elderly age-group selected for the study) in contrast to the other OL extension trials (-703, -704, and -705) is that Study -702 involved 6 months of OL Pal treatment rather than a 12 month treatment phase.*

Reviewer Comment and Results of a Completed Elderly OL Extension Trial
The previously shown table of SAEs for this elderly 6-month OL trial failed to show any remarkably new SAEs that were not previously observed or described in clinical reviews of NDA 21999 submission (and amendment submissions submitted prior to the PDUFA deadline for the first review cycle). A review of narratives also revealed that no new and clinically remarkable findings could be found that were not previously described in reviews of NDA 21999. The following are some additional comments on a few subjects.

The one subject 200326 who had multiple medical conditions and developed SAEs of anemia, pyrexia, nasopharyngitis leading to hospitalization had already completed the 6-week DB treatment phase and 20 days of OL Pal. This subject continued OL Pal during treatment of these SAEs. The SAEs resolved and completed OL Pal treatment in the study, such that a role of Pal is unlikely).

The subject that died 200214 was previously described under NDA 21999. This subject had a history of QT prolongation. The SAE and ADO of QTc prolongation was reported during OL treatment. The subject developed cough diagnosed as bronchopneumonia 2 days after the last dose and then died 4 days after the last dose. The "cause of death was reported as bronchopnuemia" and an autopsy was not performed. Other SAEs did not shed any new clinically remarkable findings that differ from those described in previous reviews of NDA 21999.

Dropouts and Other Significant Adverse Events

The following summary tables of OL trials provide updated information since the 120-Day SUR NDA 21999 submission since they include ongoing trials (tables were provided by the sponsor).

Table 39: Treatment-Emergent Adverse Events Leading to Study Discontinuation
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=11) n (%)	Pla/Pali >6 months (N=69) n (%)	Pali/Pali <=6 months (N=3) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali(NO DB)/Pali <=6 months (N=23) n (%)	Pali(NO DB)/Pali >6 months (N=60) n (%)
Total no. subjects with adverse events	3 (27)	5 (7)	0	1 (1)	3 (13)	0
Psychiatric disorders	1 (9)	2 (3)	0	1 (1)	1 (4)	0
Anxiety	0	1 (1)	0	0	0	0
Depression	0	1 (1)	0	0	1 (4)	0
Schizophrenia	0	1 (1)	0	0	0	0
Suicidal ideation	0	0	0	1 (1)	0	0
Suicide attempt	1 (9)	0	0	0	0	0
Investigations	0	2 (3)	0	0	0	0
Electrocardiogram QT corrected interval prolonged	0	1 (1)	0	0	0	0
Electrocardiogram QT prolonged	0	1 (1)	0	0	0	0
Nervous system disorders	2 (18)	1 (1)	0	0	1 (4)	0
Dyskinesia	1 (9)	1 (1)	0	0	0	0
Dizziness	0	0	0	0	1 (4)	0
Syncope	1 (9)	0	0	0	0	0
Tremor	1 (9)	0	0	0	0	0
Gastrointestinal disorders	0	0	0	0	1 (4)	0
Vomiting	0	0	0	0	1 (4)	0
Reproductive system and breast disorders	0	0	0	0	1 (4)	0
Amenorrhoea	0	0	0	0	1 (4)	0

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

Table 39: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=36) n (%)	Total Pali >6 months (N=199) n (%)
Total no. subjects with adverse events	6 (17)	6 (3)
Psychiatric disorders	2 (6)	3 (2)
Anxiety	0	1 (1)
Depression	1 (3)	1 (1)
Schizophrenia	0	1 (1)
Suicidal ideation	0	1 (1)
Suicide attempt	1 (3)	0
Investigations	0	2 (1)
Electrocardiogram QT corrected interval prolonged	0	1 (1)
Electrocardiogram QT prolonged	0	1 (1)
Nervous system disorders	3 (8)	1 (1)
Dyskinesia	1 (3)	1 (1)
Dizziness	1 (3)	0
Syncope	1 (3)	0
Tremor	1 (3)	0
Gastrointestinal disorders	1 (3)	0
Vomiting	1 (3)	0
Reproductive system and breast disorders	1 (3)	0
Amenorrhoea	1 (3)	0

See footnotes on the first page of the table.
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The following table is of the elderly OL extension trial (-702), as provided by the sponsor.

Table 22: Treatment-Emergent Adverse Events Leading to Study Discontinuation by MedDRA Preferred Term During the Open-Label Phase
(Study R076477-SCH-702: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali (N=30) n (%)	Pali/Pali (N=58) n (%)	Total (N=88) n (%)
Total no. of subjects who discontinued due to an adverse event	3 (10)	3 (5)	6 (7)
Investigations	1 (3)	1 (2)	2 (2)
Electrocardiogram QTc interval prolonged	1 (3)	0	1 (1)
Weight decreased	0	1 (2)	1 (1)
Psychiatric disorders	0	2 (3)	2 (2)
Confusional state	0	2 (3)	2 (2)
General disorders and administration site conditions	0	1 (2)	1 (1)
Fatigue	0	1 (2)	1 (1)
Infections and infestations	1 (3)	0	1 (1)
Pneumonia	1 (3)	0	1 (1)
Metabolism and nutrition disorders	0	1 (2)	1 (1)
Anorexia	0	1 (2)	1 (1)
Musculoskeletal and connective tissue disorders	1 (3)	0	1 (1)
Joint stiffness	1 (3)	0	1 (1)
Nervous system disorders	1 (3)	0	1 (1)
Tremor	1 (3)	0	1 (1)

Table 40: Treatment-Emergent Adverse Events Leading to Study Discontinuation
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Total no. subjects with adverse events	10 (10)	6 (4)	29 (14)	12 (3)	18 (17)	8 (6)	57 (14)	26 (3)
Psychiatric disorders	4 (4)	5 (4)	18 (9)	7 (1)	10 (9)	5 (4)	32 (8)	17 (2)
Depression	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	1 (1)	4 (1)	5 (1)
Psychotic disorder	2 (2)	0	2 (1)	1 (<1)	3 (3)	2 (1)	7 (2)	3 (<1)
Anxiety	0	1 (1)	0	0	1 (1)	1 (1)	1 (<1)	2 (<1)
Insomnia	0	0	3 (1)	1 (<1)	1 (1)	1 (1)	4 (1)	2 (<1)
Paranoia	0	2 (1)	1 (<1)	0	0	0	1 (<1)	2 (<1)
Acute psychosis	0	0	0	0	0	1 (1)	0	1 (<1)
Delusion	0	1 (1)	2 (1)	0	1 (1)	0	3 (1)	1 (<1)
Depressed mood	0	0	0	0	0	1 (1)	0	1 (<1)
Depressive symptom	0	1 (1)	0	0	0	0	0	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia	0	0	2 (1)	1 (<1)	3 (3)	0	5 (1)	1 (<1)
Suicidal ideation	1 (1)	0	1 (<1)	1 (<1)	2 (2)	0	4 (1)	1 (<1)
Aggression	0	0	0	0	1 (1)	0	1 (<1)	0
Agitation	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Alcoholism	0	0	0	0	1 (1)	0	1 (<1)	0
Confusional state	0	0	3 (1)	0	0	0	3 (1)	0
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Hallucination, auditory	0	0	1 (<1)	0	0	0	1 (<1)	0
Homicidal ideation	0	0	1 (<1)	0	0	0	1 (<1)	0
Hostility	0	0	1 (<1)	0	0	0	1 (<1)	0
Suicide attempt	0	0	1 (<1)	0	0	0	1 (<1)	0
Nervous system disorders	1 (1)	1 (1)	6 (3)	1 (<1)	2 (2)	3 (2)	9 (2)	5 (1)
Akathisia	0	0	2 (1)	0	0	2 (1)	2 (<1)	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyskinesia	0	1 (1)	0	0	0	0	0	1 (<1)
Extrapyramidal disorder	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)

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

Table 40: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Nervous system disorders (continued)								
Hypertonia	0	0	0	0	0	1 (1)	0	1 (<1)
Mental impairment	0	0	0	0	0	1 (1)	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dizziness	0	0	0	0	2 (2)	0	2 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Dystonia	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Tremor	1 (1)	0	0	0	0	0	1 (<1)	0
Investigations	1 (1)	1 (1)	1 (<1)	3 (1)	2 (2)	0	4 (1)	4 (1)
Weight increased	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Alanine aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood prolactin increased	0	1 (1)	0	0	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Gamma-glutamyltransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram T wave abnormal	0	0	0	0	1 (1)	0	1 (<1)	0
Hepatic enzyme increased	0	0	0	0	1 (1)	0	1 (<1)	0
Weight decreased	0	0	1 (<1)	0	0	0	1 (<1)	0
Reproductive system and breast disorders	0	0	2 (1)	1 (<1)	0	1 (1)	2 (<1)	2 (<1)
Erectile dysfunction	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Galactorrhoea	0	0	0	0	0	1 (1)	0	1 (<1)
Retrograde ejaculation	0	0	1 (<1)	0	0	0	1 (<1)	0

See footnotes on the first page of the table.

Table 40: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
Injury, poisoning and procedural complications	1 (1)	0	2 (1)	1 (<1)	0	0	3 (1)	1 (<1)
Traumatic haematoma	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Self mutilation	1 (1)	0	0	0	0	0	1 (<1)	0
Metabolism and nutrition disorders	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Hyponatraemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Anorexia	0	0	1 (<1)	0	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyspnoea	0	0	1 (<1)	0	0	0	1 (<1)	0
Cardiac disorders	1 (1)	0	3 (1)	0	2 (2)	0	6 (1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Myocardial ischaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Palpitations	0	0	0	0	1 (1)	0	1 (<1)	0
Sinus tachycardia	1 (1)	0	0	0	1 (1)	0	2 (<1)	0
Tachycardia	0	0	1 (<1)	0	0	0	1 (<1)	0
Eye disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Vision blurred	0	0	0	0	1 (1)	0	1 (<1)	0
Gastrointestinal disorders	1 (1)	0	1 (<1)	0	3 (3)	0	5 (1)	0
Constipation	0	0	0	0	1 (1)	0	1 (<1)	0
Dysphagia	0	0	1 (<1)	0	0	0	1 (<1)	0
Nausea	0	0	0	0	1 (1)	0	1 (<1)	0
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Vomiting	0	0	0	0	2 (2)	0	2 (<1)	0

See footnotes on the first page of the table.

Table 40: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=418) n (%)	Total Pali >6 months (N=755) n (%)
General disorders and administration site conditions	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Fatigue	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Infections and infestations	1 (1)	0	1 (<1)	0	0	0	2 (<1)	0
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	1 (1)	0	0	0	0	0	1 (<1)	0
Musculoskeletal and connective tissue disorders	1 (1)	0	1 (<1)	0	2 (2)	0	4 (1)	0
Arthralgia	0	0	0	0	1 (1)	0	1 (<1)	0
Joint stiffness	1 (1)	0	0	0	0	0	1 (<1)	0
Muscle rigidity	0	0	1 (<1)	0	0	0	1 (<1)	0
Muscle twitching	0	0	0	0	1 (1)	0	1 (<1)	0
Skin and subcutaneous tissue disorders	0	0	1 (<1)	0	0	0	1 (<1)	0
Acne	0	0	1 (<1)	0	0	0	1 (<1)	0
Social circumstances	0	0	2 (1)	0	2 (2)	0	4 (1)	0
Alcohol use	0	0	1 (<1)	0	0	0	1 (<1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Vascular disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Hypertension	0	0	0	0	1 (1)	0	1 (<1)	0

See footnotes on the first page of the table.
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Reviewer Comments.

Study -701

Updated results fail reveal any new clinically remarkable findings that differ from results described in reviews of NDA 21999 (the review of the original NDA submission and the addendum review).

The following subjects are noted and were not previously noted in the review of the original NDA 21999 submission:

- *Subject 100756: this 44-year-old female was an ADO due to QTc prolongation (severe) of up to 462 and 460 milliseconds for QTc F and QTc LD, respectively. QTc prolongation for QTc F was first noted during the run-in phase, apparently on Day 57 while receiving 15 mg of paliperidone (QTc B was noted sooner during Pal treatment, but is not considered an accurate calculation method for QT since a heart rate was not described as being abnormally low). Pal treatment was terminated due to QT prolongation. QTcLD normalized while QTcF decreased to 451 milliseconds on Day 7 after cessation of Pal.*

  QT prolongation this subject is likely to be drug-related due to the following reasons. A non-drug-related etiology was not identified. Also the timing of this event that resolved after treatment cessation, as well as QT prolongation effects observed with Pal (as revealed in Phase three trials and in an EKG study which is described in the review of the original NDA 21999),

Pooled OL Trials (-702,-703,-704,-705)
No new clinically remarkable findings were revealed that differ from results previously described in the review and addendum review of NDA 21999.

Newly reported ADOs since the time of the four month safety update report were provided in the 210-Day safety update report of NDA 21999 (in the SCS section and line listing found in the appendix of this section, starting on page 1710). [redacted]

See previous comments on psychiatric related SAEs that also apply to psychiatric related AEs leading to ADOs.

The following non-psychiatric related ADOs are described, since a clear non-drug-related etiology could not be found and the event(s) may reflect a new, potentially remarkable drug-related effect on safety:

- *Subject 501535 had increased hepatic enzymes reported as an AE leading to an ADO who had abnormal values at baseline. However, the subject showed more marked elevations in GGT during DB olanzapine and OL pal treatment and had treatment discontinued on Day 5 of OL Pal (9 mg/day). Levels remained elevated on Day 6. No other information could be found in the narrative regarding any subsequent levels, non-drug-related etiologies or risk factors. Additional cases of subjects with elevated LFTs and ADOs due to elevated LFTs were previously described in the previous clinical reviews of NDA 21999.*
- *Subject 100921(previously received placebo in the lead-in study) had QTc prolongation leading to an ADO, that did not appear to be drug-related since similar QTc values were observed during placebo treatment in the lead-in study.*
- *Subject 100943 had junction nodal rhythm that lead to an ADO that was first noted on Day 42 of 9 mg Pal daily (during the run-in phase) that was not reported at baseline or upon treatment cessation ("resolved" post-treatment-cessation). A cardiologist in the central laboratory read the same ECG and reported it as normal. Paliperidone treatment was discontinued after two days of 12 mg of daily paliperidone during the open-label these study-701 due to "nodal rhythm" that was reported "as persisting." Incomplete right bundle branch block was reported at baseline and at post treatment cessation. Ranitidine was given on Day 42 for dyspepsia. This subject was a 30 year old healthy female with a past medical history of anemia and respiratory infection.*

The role of Pal is considered probable in the absence of more information. Despite a normal reading by the cardiologist on Day 42, the event was considered persisting several days later, in which EKG results that lead to this conclusion could not be found in the narrative description. The description of a cardiology work-up of the patient during or following the study or any mention of holter monitoring (which would have been helpful at least following treatment cessation) could not be found in the narrative description of this subject.

A higher incidence of first degree AV block compared to placebo was previous observed in the 15 mg Pal treated subjects in the integrated 6-week Phase III trial safety dataset and in elderly Pal treated subjects in the 6-week Phase III Study -302.

- *Subject 500501 had SAE's involving elevated liver function tests and elevated CPK that lead to an ADO of this subject. This subject was previously described under the above section on SAE's and was also previously described in past clinical reviews of NDA 21999.*
- *Subject 500507 had elevations in liver function tests, but these elevations are also observed at baseline with no further increase observed during olanzapine and paliperidone treatment (this subject received double-blind olanzapine during Study-305 followed by open label paliperidone during Study-705). Since the LFT elevations persisted, the subject was withdrawn prematurely due to AEs of elevated LFTs (an ADO). His LFTs declined upon dechallenge. This subject was not previously described in the original clinical review of NDA 21999. However, similar cases were previously described.*
- *Subject 501535 had hepatic enzymes increased (ALT, AST, and GGT) reported as an ADO who had abnormal levels at baseline but had markedly greater elevations in gamma-glutamyltransferase levels during double-blind olanzapine treatment (on Day 21 of the double-blind lead-in Study-305). The subject continued to show elevations after five days of open label treatment with 9 mg, daily of paliperidone in Study-705 and was therefore discontinued from the study on Day 6.*

  This subject had an unremarkable past medical history, did not receive concomitant medications and an etiology for these events, or a potential etiology and other relevant information (e.g. mention or results of a diagnostic work-up) could not be found in the narrative description. This subject was not previously described in the original clinical review of NDA 21999. However, other subjects with elevated LFTs and ADOs due to hepatic-related AEs were previously described in past clinical reviews of NDA21999.

Psychiatric-related ADOs that were also associated with non-psychiatric related SAE's or ADOs are previously discussed in the section on SAEs above.

Results and Reviewer Comments of Elderly OL Trial -702

The summary table of ADOs, as previously shown, includes isolated ADOs of anorexia and joint stiffness but these isolated cases do not change overall conclusions on safety or on the overall safety profile of Paliperidone in this population, as previously discussed in the review of NDA 21999. Additional ADOs are described below, that do not change the overall safety profile as previously described in clinical reviews of NDA 21999.

Due to the unexpected ADOs of confusion in 2 subjects (200321 and 200719), a review of the narratives of these subjects was conducted. It appears these subjects had a pre-existing condition that was likely to at least play a role in the development of confusion.

However, a clear diagnosis of dementia (e.g. with supporting diagnostic testing) could not be found in the narratives. These subjects are described in more detail later. One consideration is a possible role of Pal exacerbating underlying dementia-like conditions in these elderly subjects. Pal is not indicated for dementia and the sponsor is only seeking a schizophrenia indication. Furthermore, proposed labeling includes a drug class section on risk of mortality with patients with dementia.

A review of the narrative of an atypical ADO of joint stiffness (subject 200412) was also conducted. This event occurred in a women receiving thyroid replacement hormone for hypothyroidism. She developed tremor in the same arm where she developed stiffness (in the elbow). Consequently a role of Pal is likely since tremor is an expected extrapyramidal side effect that in turn was likely to contribute to the joint stiffness. A role of the patient's age, along with thyroid disease may also have contributed to this AE.

The sponsor's in-text description of the ADO due to anorexia (subject 200309 as found in the CSR) did not describe any other abnormalities in this subject other than anorexia and weight loss. This subject was not reported to have any pre-existing condition. Although acute psychosis, as well as the patient's age could be factors involved with this AE, a role of Pal is suggested since a non-drug-related etiology cannot be clearly identified.

The sponsor provided in-text descriptions of selected subjects in the CSR of -702. These descriptions are summarized below. Some of these subjects were previously noted above.

DB-Placebo/OL-Pal Treated Subjects with ADOs in Study -702.
These subjects previously received DB Placebo in the 6-week Phase III lead-in study to the OL Pal Extension Study -702:

- **Subject 200214:** with the SAE of QTc prolongation. This subject was previously described in this review as a subject who died with cause of death, reported as bronchopneumonia.
- **Subject 200412:** a 71-year old female who had a medical history of hypothyroidism being treated with levothyroxine sodium and had joint stiffness and tremor on OL Pal treatment Day 15 leading to an ADO on Day 21. Comments on this subject were previously provided.
- **Subject 200713:** a 66-year old male with pneumonia leading to an ADO on Day 31 of OL al had a history of pulmonary tuberculosis, pneumonia (twice) and chronic bronchitis.

DB-Pal/OL-Pal Treated Subjects with ADOs in Study -702
These subjects previously received DB Pal in the 6-week Phase III lead-in study to the OL Pal Extension Study -702:

- **Subject 200309**, had ADOs of anorexia and decreased weight (from 41 kg prior to treatment to 41 kg on Day 73 of OL treatment when Pal was stopped). This subject was previously noted.
- **Subject 200321:** a 74-year old female with a history "noted dementia-like symptoms, but no formal diagnosis" and was receiving 4 mg BID of galantamine for "dementia-like symptoms," and dihydroergotamine (2 mg/day) for mild hypotension. The dose of during the OL phase due to "moderate hypotension." During OL treatment events of confusion, fatigue, insomnia and hypotension (this resolved with an increase in dihydroergotamine to 2.5 mg bid). Confusion and fatigue worsened and the confusion lead to the ADO. This subject was previously noted.
- **Subject 200719** a 65-year old female who had a history of "cerebrosclerosis." She had an AE of insomnia that persisted and later developed confusion which worsened such that Pal treatment was stopped. The subject was previously noted.

E. Post Approval (Postmarketing) Clinical Commitments
We note that in the one study that included a 3 mg dose of paliperidone ER, that dose was shown to be effective. Thus, you have not fully evaluated the lower end of the dose response curve. Therefore, you should conduct a study to better explore for a minimal effective dose in phase IV.

The sponsor agrees to this commitment as follows (as copied from their response submission):

J&JPRD agrees to perform a study to better assess the lower end of the dose response curve and can perform an efficacy study of 1.5 mg paliperidone ER tablets in subjects with schizophrenia as a Phase 4 commitment. The Sponsor proposes to submit a protocol for such a study to the Agency for review within 3 months after approval. We estimate a study report could be submitted by December 2010.

Reviewer Comments. *The sponsor has adequately responded to this item in the Approvable letter on Phase IV commitment. Once the sponsor submits a protocol the Division can provide feedback on the study design, as deemed appropriate.*

F. Labeling
Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Sponsor's Response and Reviewer Comments
The purpose of this labeling review is to address the sponsor's proposed changes in clinical sections of labeling that differ from labeling provided in the Approvable Action Letter. Therefore this review does not repeat past issues and recommendations that were previously raised in past clinical reviews under NDA 21999 (the original and addendum reviews). The draft-annot-labeling-text.pdf file in the current submission was used to review clinical sections of labeling changes proposed by the sponsor as specified in this pdf file (the sponsor used track changes to denote changes made from the version provided in the Approvable letter).

Proposed modifications of clinical labeling sections are generally presented in this review in the order in which they appear in the sponsor's proposed labeling, unless there are related sections that appear elsewhere in labeling on a given topic or issue being discussed in this review.

Other labeling changes that are proposed by the sponsor are under review by other disciplines (these reviews are pending at the time of this writing).

31 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

G. Conclusions and Additional Recommendations

Safety results described in this review failed to reveal any safety-related observations that would change conclusions and recommendations in the original review of NDA 21999.

The sponsor has also adequately responded to the Clinical items in the Approvable Action letter but has made revisions in labeling that differ from labeling in the Approvable Letter. See specific labeling recommendations in the Labeling section of this review.

In addition to labeling recommendations, the following are additional recommendations.

Word-for-Word Comparisons between Labeling Versions are Recommended

In addition to labeling issues raised in this review, it is also recommended that word-for-word comparisons be conducted between the sponsor's proposed labeling and the Approvable Action letter version of labeling. The "draft-annot-labeling-text.pdf" file was used for purposes of this review. If differences are found in any of the above word-to-word comparisons then it is recommended that the sponsor be notified of these differences and inquired about them. In the opinion of the undersigned reviewer, a convincing rationale would need to be provided for any differences that are found unless they are minor editorial differences that do not impact on the content of the information and would not be expected to alter the interpretation of the information being conveyed from a clinical perspective.

It is also recommended that word-to-word comparisons of drug class labeling sections under Warnings and Precautions of the sponsor's proposed labeling be made with corresponding sections of approved drugs (e.g. Risperdol®). If differences are found then it is recommended that labeling be revised to match standard language for the drug class, unless the sponsor provides a convincing rationale for changing drug class labeling language.

Karen Brugge, M.D.
Medical Reviewer,
FDA CDER ODE1 DPP HFD 130

cc: IND; HFD 130/N Khin/K Brugge/K Kiedrow/T Laughren/M Mathis/F Fanhui/P Yang/B Rosloff/R Baweja/R Kavanagh/T Oliver/C Tele/E Chalecka-Franaszek

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

Table 8: Treatment-Emergent Adverse Events With at Least 2% Incidence in Any Paliperidone Treatment Group (3 or 6 or 9 or 12 or 15) and Where the Incidence > Placebo by MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Placebo (N=551) n (%)	ER ORDO Paliperidone					Olanzapine
		3 mg (N=137) n (%)	6 mg (N=135) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=113) n (%)	10 mg (N=354) n (%)
Nervous system disorders	96 (17.4)	34 (24.8)	68 (28.8)	99 (40.2)	110 (45.5)	47 (41.6)	123 (33.8)
Akathisia	14 (2.5)	5 (3.6)	7 (3.0)	20 (8.1)	23 (9.5)	11 (9.7)	7 (1.9)
Dizziness	14 (2.5)	7 (5.1)	11 (4.7)	11 (4.5)	12 (5.0)	7 (6.2)	19 (5.2)
Dystonia	2 (0.4)	1 (0.7)	3 (1.3)	8 (3.3)	9 (3.7)	1 (0.9)	1 (0.3)
Extrapyramidal disorder	8 (2.3)	6 (4.4)	5 (2.1)	17 (6.9)	18 (7.4)	9 (8.0)	6 (1.6)
Headache	42 (11.8)	14 (11.0)	29 (12.3)	34 (13.8)	35 (14.5)	20 (17.7)	35 (9.6)
Hypertonia	4 (1.1)	3 (2.4)	3 (1.3)	10 (4.1)	8 (3.3)	4 (3.5)	5 (1.4)
Parkinsonism	0	0	1 (0.4)	5 (2.0)	3 (1.2)	2 (1.8)	2 (0.5)
Sedation	15 (3.7)	1 (0.8)	12 (5.1)	8 (3.3)	15 (6.2)	2 (1.8)	24 (6.6)
Somnolence	12 (3.4)	6 (4.7)	8 (3.4)	17 (6.9)	11 (4.5)	7 (6.2)	47 (12.9)
Tremor	12 (3.4)	4 (3.1)	6 (2.6)	11 (4.5)	8 (3.3)	3 (2.7)	8 (2.2)
Psychiatric disorders	111 (31.3)	35 (26.0)	39 (23.1)	61 (24.8)	57 (23.6)	33 (29.2)	96 (26.4)
Anxiety	29 (8.2)	12 (9.4)	15 (6.6)	14 (5.7)	11 (4.5)	9 (8.0)	21 (5.8)
Sleep disorder	2 (0.6)	1 (0.8)	1 (0.4)	2 (0.8)	1 (0.4)	4 (3.5)	4 (1.1)
Suicide ideation	4 (1.1)	2 (1.6)	2 (0.9)	1 (0.4)	1 (0.4)	3 (2.7)	3 (0.8)
Respiratory, thoracic and mediastinal disorders	14 (3.9)	8 (6.3)	13 (4.7)	13 (5.3)	10 (4.1)	11 (9.7)	21 (5.8)
Cough	4 (1.1)	4 (3.1)	4 (1.7)	7 (2.8)	4 (1.7)	3 (2.7)	6 (1.6)
Nasal congestion	3 (0.8)	1 (0.8)	3 (1.3)	2 (0.8)	2 (0.8)	3 (2.7)	3 (0.8)
Vascular disorders	10 (2.8)	5 (3.9)	8 (3.5)	9 (3.7)	15 (6.2)	6 (5.3)	14 (3.8)
Orthostatic hypotension	3 (0.8)	3 (2.4)	3 (1.3)	6 (2.4)	9 (3.7)	3 (2.7)	6 (1.6)

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/s/

Karen Brugge
11/20/2006 11:20:25 AM
MEDICAL OFFICER

Mitchell Mathis
11/21/2006 06:26:57 PM
MEDICAL OFFICER

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 22, 2006

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

SUBJECT: Recommendation for approvable action for paliperidone ER tablets for schizophrenia (short-term efficacy only)

TO: File NDA 21-999
[Note: This overview should be filed with the 11-30-05 original submission of this NDA.]

1.0 BACKGROUND

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

Paliperidone ER was developed under IND 65,850. We held a number of meetings with the sponsor of this IND during the development of paliperidone ER, and had planned on taking it to the PDAC. However, as we neared the end of the review cycle, we decided that there were no critical review issues that needed input from the PDAC.

2.0 CHEMISTRY

I am not aware of any CMC issues at this point that would preclude an approvable action for this NDA.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approvable action for this NDA. We are relying on the carcinogenicity data for the parent drug,

risperidone, because of adequate exposure to paliperidone and its metabolites in those studies. There was a question about possibly different human metabolites seen with paliperidone administration compared to what is seen with risperidone administration, however, to my knowledge, this concern has been addressed and we do not believe there are any new metabolites with paliperidone administration.

4.0 BIOPHARMACEUTICS

Paliperidone ER is an OROS formulation of paliperidone that reaches Cmax in about 24 hours and has an average elimination half-life of approximately 23 hours. Thus, steady state is reached in about 4-5 days. There is a substantial food effect, with Cmax and AUC values increased by roughly 50% in the fed state. However, the clinical trials with paliperidone ER were carried out without regard to food intake. Paliperidone ER has minimal peak-trough fluctuations compared to immediate release risperidone. Although both 2D6 and 3A4 appear to have some role in metabolizing paliperidone ER, it is not extenisively metabolized in the liver. Rather, it is substantially cleared unchanged in the urine.

I am not aware of any biopharmaceutics issues at this point that would preclude an approvable action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application focused on 4 short-term (6-week), double-blind, randomized, parallel group, placebo-controlled trials in patients with acutely exacerbated schizophrenia. The primary endpoint was change from baseline on the PANSS total score. Treatment group sizes in the adult studies ranged from 105 to 128 patients per group. Three studies were fixed-dose, active controlled (olanzapine 10 mg) studies in adults (303, 304, and 305) and the fourth was a flexible-dose study (3-12 mg/day) in elderly schizophrenic patients (302). Study 304 was conducted entirely in the US. Dosing was always AM, without regard to meals.

The fixed paliperidone ER doses in the adult studies were as follows:

Study #	Dose Groups			
303		6 mg	9 mg	12 mg
304		6 mg		12 mg
305	3 mg		9 mg	15 mg

In summary, for the adult studies, all doses studied were statistically significantly superior to placebo, and the effect sizes were typical of those seen with effective antipsychotic drugs. There was a slight numerical advantage to the higher doses compared to the lower doses, and in some but not all comparisons, these differences were statistically significant. Thus, unlike the data for risperidone, there may be some advantage to higher doses compared to lower doses. As can be seen, there are data from only 1 trial supporting the 3 mg/day dose.

The elderly flexible-dose study showed a trend for drug superiority, but was likely underpowered.

5.1.3 Comment on Other Important Clinical Issues Regarding the Paliperidone ER Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

As noted, there was a numerical trend for dose response, and some statistical evidence to support dose response as well. The sponsor has proposed 6 mg/day as the target dose, with the possibility of titration within a range of 3-12 mg/day, at the judgment of the clinician. Dr. Brugge has agreed with this proposal, while Dr. Khin has suggested targeting 3 mg/day. Given the fact that there is some support for dose response, and more data for doses in the 6-12 mg/day range than the 3 mg/day dose, I am inclined to accept 6 mg/day as the target dose for now. However, I agree with Dr. Khin that the sponsor should be asked to commit to a fixed dose study at the lower end of the dose response curve to better establish efficacy at the lower end.

Secondary Efficacy Variables

In their proposed labeling, the sponsor has added results from the PANSS factors as well as from the PSP (Personal and Social Performance) scale. Even if declared in the protocol as key secondaries, we would not have accepted the PANSS factors because they are redundant with the total score. However, we did in fact communicate to the sponsor in an earlier meeting that the PSP would be acceptable as a key secondary, since we consider it a reasonable measure of functional improvement. Oddly, however, the sponsor did not clearly specify the PSP as a key secondary, nor provide a clearly defined analysis plan for addressing the PSP and multiple doses. Thus, they will not be permitted to include the results from either secondary outcome in their labeling.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of gender, because there were not sufficient data to explore differences based on age or race. There was no indication of any difference in effectiveness based on gender.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive schizophrenia trials.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy in this NDA, [redacted]

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of paliperidone ER in the treatment of schizophrenia.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for this NDA were derived from a total of n=2115 subjects/patients exposed to paliperidone ER across 37 clinical trials comprising the total paliperidone ER program. The patient breakdown included n=592 paliperidone ER-exposed subjects/patients in 27 phase 1/2 trials, and n=1523 paliperidone ER-exposed patients in 10 phase 3 trials. This represents about 508 patient-years of exposure. They easily satisfied ICH criteria for long-term exposure.

5.2.2 Common Adverse Event Profile for Paliperidone ER in Schizophrenia

The profile of common and drug-related adverse events included: tachycardia; akathisia; EPS; dystonia; hypertonia; orthostatic hypotension; and hypersalivation. Thus, paliperidone ER has an adverse event profile quite similar to that seen for risperidone, as would be expected.

5.2.3 Adverse Events of Particular Interest

5.2.3.1 Orthostatic Hypotension and Syncope

Paliperidone ER has alpha-adrenergic blocking activity, thus, it is no surprise that there is drug-related and dose-related orthostatic hypotension seen with this drug, as is the case with risperidone. However, the effect is modest. As an adverse event, orthostatic hypotension was seen in 2% of drug-treated patients in the pool of adult phase 3 trials compared to 1% of placebo (higher at the higher doses, e.g., 4% at 12 mg). As a measured orthostatic change, it was observed in 7% of drug-treated vs 4% of placebo-treated patients. Syncope was also a drug-related event (0.8% in drug vs 0.3% in placebo). The sponsor has proposed a Precautions

statement similar to the statement in risperidone labeling to address this concern, and I think this is adequate.

5.2.3.2 Tachycardia

It is also no surprise that there is drug-related and dose-related tachycardia seen with this drug, as is the case with risperidone. As an adverse event, tachycardia was dose-related, with rates of about 7% at the higher doses in the pool of adult phase 3 trials compared to 3% of placebo patients. There was also a dose-related mean increase in heart rate, i.e., about 7 bpm at the higher doses vs about 2 bpm in placebo-treated patients. Tachycardia is clearly noted in labeling as a drug-related effect.

5.2.3.3 QTc Increases

Although there is not a QTc signal emerging from the phase 3 trials with paliperidone ER, which included extensive ECG monitoring, there is a modest signal emerging from the sponsor's thorough QT study (SCH-1009) involving an immediate release formulation of paliperidone (on the order of a 10 msec increase from baseline at exposures that are likely to be seen at the higher recommended doses of paliperidone ER). Given the roughly 50% increase in paliperidone exposures when the ER formulation is given with a high fat meal, the Division of Cardiorenal Products (DCRP) has recommended that paliperidone ER not be given with food. However, the data from study SCH-1009 seem to suggest a plateau of the exposure response curve for QTc effect:

Paliperidone IR Dose	Exposure	QTc Increase from Baseline
4 mg	35 ng/ml	9.3 msec
8 mg	113 ng/ml	10.9 msec

Given that the expected Cmax ss for the 12 mg paliperidone ER dose (the maximum recommended dose) is only 45 ng/ml, a 50% increase with a high fat meal would yield an exposure well below the exposure seen with 8 mg IR. Thus, I am not inclined to recommend dosing only in the fasted state. Furthermore, this advice would be virtually impossible to implement with this population. The currently proposed Dosage and Administration section alerts prescribers to the increased exposure occurring with a high fat meal, and I think this is sufficient.

I do agree with DCRP's recommendation that the language in labeling regarding QTc prolongation be revised and relocated to Warnings. The sponsor relied on a day-averaged value for QTc increase, which underestimates the effect at peak concentration, a more appropriate measure. Our proposed language for this statement will alert prescriber's to a possible risk of torsade de pointes and/or sudden death with this drug, and will warn against certain situations that may increase this risk.

One puzzling fact is that we have not seen a signal for a similar degree of QTc prolongation with the parent drug, risperidone, even in a similarly thorough QT study (study 54 conducted by Pfizer), even though the expected levels of paliperidone would be similar to those observed in study SCH-1009.

5.2.3.4 Hyperprolactinemia

As expected, paliperidone ER elevates prolactin, and in fact, the extent of elevation seen with this drug is very similar to that seen with risperidone. Given that risperidone is an outlier among atypical antipsychotics in terms of its potential for elevating prolactin, and we have recently asked the sponsor to strengthen the labeling for risperidone regarding this effect. I agree with Dr. Khin that we need to ask the sponsor to adopt similar language for paliperidone ER.

5.2.4 Other Concerns of Dr. Brugge

5.2.4.1 CPK Elevations

Dr. Brugge seems concerned about some paliperidone-treated patients with CPK increases. However, the placebo-controlled trial data reveal no signal for drug-related CPK increases, and I do not agree that the sponsor needs to do more to evaluate this concern.

5.2.4.2 Suicidality

Dr. Brugge argues that more should be done to evaluate suicidality with paliperidone ER, however, her concern is not supported by the available data. In the pool of placebo-controlled phase 3 trials, the risk of suicidality using an approach that seems quite reasonable to me is about 1% for both drug and placebo. Thus, I agree with Dr. Khin that the sponsor's proposal to include the standard suicidality language for antipsychotic drugs is reasonable.

5.2.4.3 Food Effect

Dr. Brugge also argues that more needs to be done to evaluate the impact of a food effect, however, I don't agree. I think the food effect (approximately 50% increase in Cmax and AUC in the fed state) has been well-characterized and also adequately studied, in the sense that drug was given without regard to food intake in the clinical program. Thus, the adverse event profile observed reflects the conditions of use, and that profile has been well-characterized in labeling, in my view.

5.2.4.4 "Hemodynamic Effects"

Dr. Brugge repeatedly raises concerns about "hemodynamic" effects of paliperidone, however, it isn't clear what she means by this, beyond the quite predictable hypotensive effects, the tachycardia, and the demonstrated modest QTc effect. She recommends a number of phase 4 commitments to address these concerns, including drug interaction studies with other drugs that

prolong the QTc, tread mill tests, tilt table tests, chronic open label challenge studies with higher than recommended doses of paliperidone, among others. I don't see any merit in any of these studies, and I will not be making such recommendations. I feel that the observed effects of paliperidone on blood pressure, heart rate, and the QTc can be adequately characterized in labeling.

5.2.3.5 Gastrointestinal Problems Related to OROS Capsule

Dr. Brugge has noted a very small but clinically meaningless reduction in hemoglobin with paliperidone ER as possible evidence for a signal of risk due to need to clear the capsule shell through the gastrointestinal tract. She also notes 2 cases of possible interest regarding this concern, one a ruptured duodenum and the other a GI bleed. She wants to extensively describe these cases under the standard precautionary language in labeling regarding this risk, but I disagree. The OROS formulation is well-known and has been available for years, and these minimal risks are well-known and well-characterized by the sponsor's proposed language.

5.2.3.6 Transaminase Elevations

There was no signal for mean increase in transaminase levels for the placebo-controlled trials with paliperidone. There were several outliers ($\geq$ 3XULN) in the controlled trials and in open label extensions, several of which were discontinued due to these increases. In her proposed labeling comments, Dr. Brugge notes a case of both transaminase increase and bilirubin increase, but says nothing about the case in her review. We further explored this case (CRF ID:501245) and discovered that the patient also had alkaline phosphatase elevation and was diagnosed as "cholilithiasis."

Based on these findings, Dr. Brugge has recommended routine monitoring for LFTs, i.e., q 2 weeks for the first month, then monthly, etc. I don't think there is a reasonable basis for requesting such monitoring and I won't make this recommendation.

5.2.3.7 Seizures

Dr. Brugge wants to modify the sponsor's proposed labeling language for seizures. They had pooled data from the 4 placebo-controlled 6-week studies, which yield similar risks of seizure in drug and placebo patients. She wants to focus only on the 3 adult studies, which eliminates the placebo patient. She also wants to add mention of a seizure that occurred in a long-term open extension. I have no objection to the sponsor's approach or their proposed language. The one seizure occurring in an entirely different setting is not relevant to this language.

5.2.3.8 Use in Elderly Patients

Dr. Brugge wants the labeling modified regarding dosing in the elderly out of concern that renal function may be compromised and there may be other vulnerabilities in elderly patients. Although the data accumulated in elderly patients in the development program has generally not

revealed any difference in pharmacokinetics of paliperidone in elderly patients with relatively normal renal function, nor has it revealed any consistent difference in the adverse event profile, I generally agree that caution is needed in elderly patients. Thus, I have recommended 3 mg/day as the starting dose in elderly patients. Otherwise, I think the sponsor's proposed Geriatric Use section adequately reflects the data accumulated.

5.2.3.9 Risk:Benefit vs Risperidone

Dr. Brugge argues that the sponsor needs to make a case that the risk:benefit ratio for paliperidone must be superior to that for risperidone in order to justify approval of paliperidone. There is, of course, no such provision in the law or regulations, and I disagree with this requirement.

5.2.5 Conclusions Regarding Safety of Paliperidone ER in the Treatment of Schizophrenia

I agree with Dr. Khin that the adverse event profile for paliperidone ER is quite similar to that seen for risperidone, and can be adequately characterized in labeling. The one finding of some concern is the modest increase in QTc, and I agree with the Division of Cardiorenal Products that these findings should be noted in Warnings.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would adversely affect conclusions about the safety of paliperidone ER in the treatment of schizophrenia.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, paliperidone ER is not approved anywhere at this time for the treatment of schizophrenia.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

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

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included an extensively modified version of labeling with the approvable letter.

10.2 Foreign Labeling

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

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for phase 4 commitments.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that J&J has submitted sufficient data to support the conclusion that paliperidone ER is effective and acceptably safe in the treatment of schizophrenia. However, before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, I recommend that we issue the attached approvable letter along with our proposal for labeling, in anticipation of final approval.

cc:
Orig NDA 21-999
ODE-I/RTemple
HFD-130
HFD-130/TLaughren/MMathis/NKhin/KBrugge/KKiedrow/SHardeman

DOC: Paliperidone_Laughren_AE_Memo.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
9/22/2006 08:32:03 AM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: NDA Review

NDA	# 21,999 (N000)
Brand Name	[redacted]
Generic Name	Paliperidone
Sponsor	Johnson & Johnson
Indication	Treatment of schizophrenia
Dosage Form	Oral (capsules)
Therapeutic Dose	3-12 mg once daily
Duration of Therapeutic Use	Chronic
Review Classification	Standard NDA Review
Date Consult Received	August 8, 2006
Date Consult Due	September 1, 2006
Clinical Division	Division of Psychiatry Products
PDUFA Date	September 30, 2006

1.0 RECOMMENDATIONS

2.0 ANSWERS TO REVIEW TEAM QUESTIONS

2.1 **Is Study SCH-1009 an adequate basis for estimating the QT effects of paliperidone?**

2.1.1 **Response:** Yes. Study SCH-1009 is an adequate basis for estimating the QT effects of paliperidone.

2.2 **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?**

2.2.1 **Response:** The QT data are consistent with a QT signal for paliperidone. While the sponsor has claimed that the peak plasma concentrations at steady-state with 8 mg IR paliperidone (mean 113 ng/ml) were more than twice as high as that achieved by the highest dose of ER OROS paliperidone (12 mg: mean 45 ng/ml), the clinical pharmacology reviewer has found that concentrations achieved in the QT study (given the variability) appear to overlap with clinical doses. The extent of the signal in the QT study suggests that a low QT risk is present.

2.3 **Is there any need for additional QT data before reaching a conclusion about the cardiovascular safety of paliperidone ER?**

2.3.1 **Response:** We would have liked to verify that the QT measurements were made appropriately. In order to do this, we ask that the sponsor submit the ECGs to the ECG warehouse.

2.4 **Is the roughly 50% increase in paliperidone ER Cmax with food a cause for concern regarding the cardiovascular safety of paliperidone?**

2.4.1 **Response:** Given the known food effect, the labeling should specify that the drug should be administered without food.

2.5 **Does the proposed labeling for paliperidone ER adequately reflect the cardiovascular risks associated with this drug?**

2.5.1 **Response:** No. In fact, we do not agree with the description of study results in the proposed labeling. Please see Section 6.0 of this review for a more detailed discussion of the proposed labeling.

2.0 GOAL OF THE REVIEW

The purpose of this review is to provide input and recommendations about QT findings for paliperidone based on study SCH-1009

3.0 BACKGROUND

3.1. Indication: Paliperidone ER is being proposed for the treatment of schizophrenia.

3.2. Drug Class: Paliperidone is a major active metabolite of risperidone, which is approved in the treatment of schizophrenia. Both risperidone and paliperidone are centrally active dopamine D2 and 5-HT_{2A} antagonists.

3.3. Regulatory Classification: NDA # 21-999 for paliperidone is currently under review in the Division of Psychiatry Products.

3.4. Market approval status

Paliperidone is not approved for use for any indication in the United States. However, risperidone has been available in the US for over 10 years.

3.5. Clinical Pharmacology

According to the protocol, the Tmax of IR paliperidone is 2.0 + 1.1 hours with a terminal half-life of about 1 day.

4.0. SPONSOR'S SUBMISSION

4.1. Thorough QT study

4.1.1. Synopsis

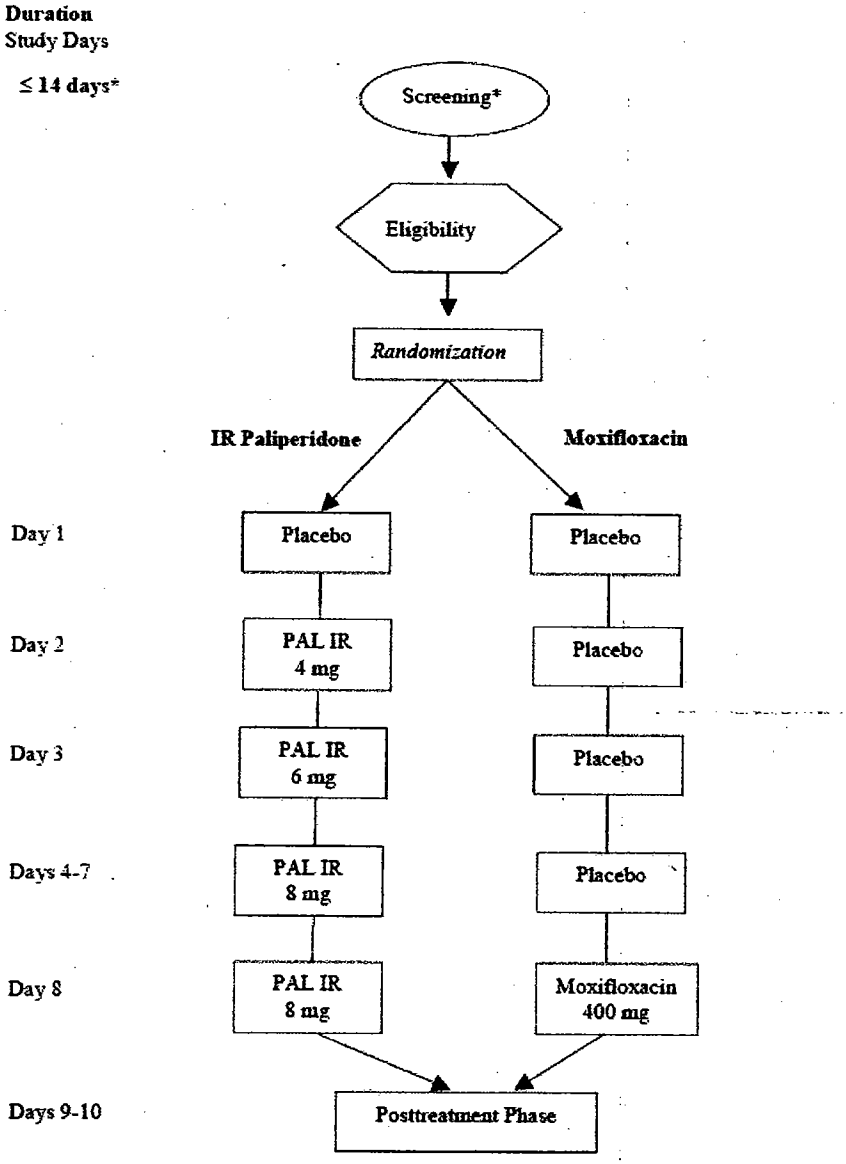
4.1.1.1. Title: A Placebo- and Positive-Controlled, Randomized Study Evaluating QT and QTc Intervals Following Administration of Immediate-Release Paliperidone in Subjects with Schizophrenia or Schizoaffective Disorder (Feb. 2-May 26, 2005)

4.1.1.2. Protocol Number: RO76477-SCH-1009

4.1.1.3. Primary Objective: To assess the cardiovascular safety of paliperiodne in schizophrenic or schizoaffective patients, with particular attention to the length of the QT/QTc interval.

4.1.2. Design: This was a randomized, double-blind, placebo and active-controlled study in patients with schizophrenia or schizoaffective disorder. The IR formulation of paliperidone was utilized in this study. A diagram of the study design is shown below:

Figure 1: Study Design for Protocol R076477-SCH-1009



* Included a 5-day washout period (Days -5 to -1) during which all prestudy medications were discontinued.

4.1.2.1. Justification for design provided: The sponsor did not provide a justification of the study design (other than justifying single-dose moxifloxacin).

4.1.3. Population: Patients with schizophrenia and schizoaffective disorder, aged 18-50 years, with normal screening 12-lead ECG. Patients with electrolyte disorders, risk factors for torsades de pointes, and significant cardiovascular history were excluded from the study.

4.1.3.1. Justification for dose provided: The dosage of 8 mg/day IR paliperidone was expected to provide plasma concentrations higher than those associated with the highest dosage (150 mg-equivalent Q 4 weeks) being considered for use in the paliperidone palmitate program. The IR formulation was chosen because of more predictable plasma concentrations and a shorter time to steady state, and the expectation that the IR dosage would cover the entire concentration range for the highest planned dosages of bother formulations in current clinical development.

4.1.4. Study Schedule and Timing of Samples

Study Day	**0**	**1, 2, 3, 4**	**5-7**	**8**	**9-10**
Intervention	No treatment	Dosing	Dosing	Dosing	Posttreatment
12-Lead ECGs	Record ECGs### (Baseline)	Record ECGs###	Single ECG pre-dose only	Record ECGs###	Record ECGs #
PK Samples for drug	None collected	Collected###	Pre-dose only	Collected###	Collected *
Meal Instructions	1 hour before first ECG	1 hour before 1st ECG	Not stated	1 hour before 1st ECG	1 hour before 1st ECG

###0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12 hours post dose
#Day 9: 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 30 and 36 hours after the Day 8 dose.
Day 10: 48, 48.5, 49, 49.5, 50, 50.5, 51, 51.5, 52, 54, and 60 hours after the Day 8 dose.
* 24, 36, 48 and 60 hours after the Day 8 dose.

4.1.5. QT Measurement: Standard 12-Lead ECGs were obtained while subjects were recumbent. ECGs were read centrally; readers were blinded to time and treatment. The QT was calculated from lead 2.
The primary correction method was QTcLD, calculated with linear regression technique.

4.1.6. Controls: The Sponsor used both placebo and positive (moxifloxacin) controls.

4.1.7. Blinding: Paliperidone, over-encapsulated moxifloxacin (to match paliperidone) and placebo were identical in appearance in order to preserve blinding.

4.1.8. Baseline: The Sponsor planned to collect time-matched baseline QTc values on the day prior to initiating dosing (Day -1) of the study for each treatment.

4.1.9. Endpoints: The primary evaluation was based on individual linear correction method, calculated with linear regression.
4.1.10. Safety assessments: adverse events, laboratory tests, and vital signs.

4.1.11. Results
Patient Disposition: A total of 141 patients were randomized to IR paliperidone 8 mg (n=72) or moxifloxacin 400 mg (n=69). All 141 patients were included in the safety

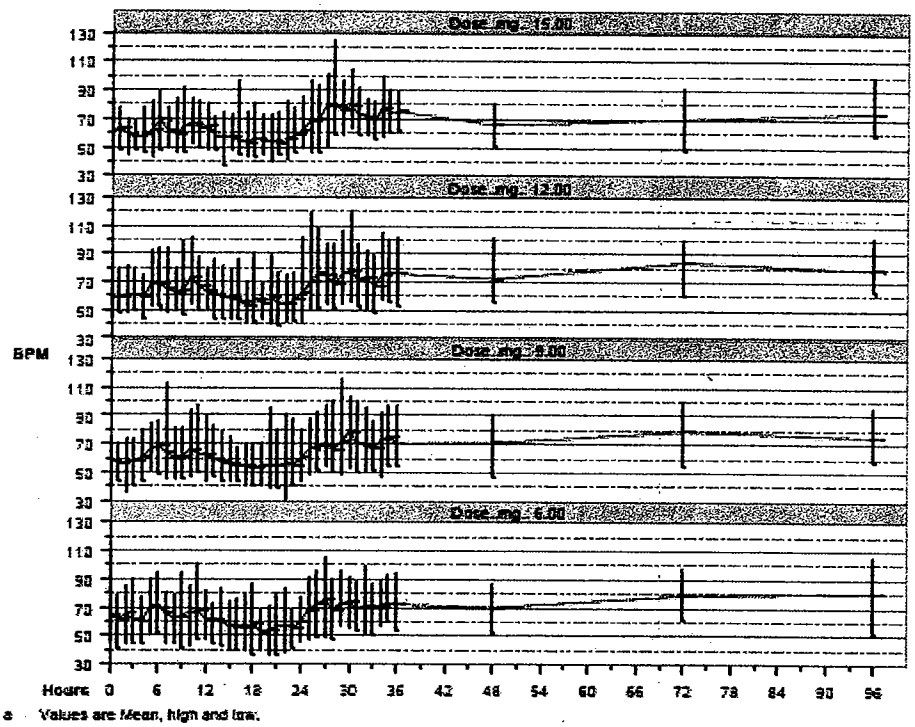
analysis set. The pharmacodynamic analysis set included 44 paliperidone and 58 moxifloxacin patients who received at least 1 dose of study medication and completed the ECG assessments on Days 9 and 10; eight subjects were excluded due to significant protocol deviations. Twenty-four patients discontinued prematurely from paliperidone (8 due to adverse events (AE) and 8 patients discontinued prematurely from moxifloxacin (1 due to AE).

Baseline characteristics: The safety analysis population was 79% male and 55% Black; the mean age was 39 years.

Effect on Heart Rate:

From the graph below, there appears to be little or no effect on heart rate.

Figure 78 Effect of Single Doses of Paliperidone OROS on Heart Rate over Time by Dosage Heart Rate – Study Alza-044[a]



a Values are Mean, High and low.

(Source: OCPB Review: Dr. Kavanagh)

12-lead ECGs: No ECGs were submitted to the ECG warehouse. Therefore, this reviewer is unable to verify that the QT measurements were appropriate.

Analysis of Central Tendency:

The primary ECG variable was the difference in day-averaged QTcLD between IR paliperidone 8 mg at steady state (Day 8) and placebo (Day 1). This analysis produced the following result (below):

Table 12: Day-Averaged QTcLD: Least Square Mean Differences From Day 1
(Study R076477-SCH-1009: Pharmacodynamic Analysis Set)

Treatment Arm	Visit	Treatment Group	LSMean (SE)	LSMean Difference (SE)	90% CI on LSMean Difference[a,b]
IR Paliperidone (N=44)	Day 1	Placebo	387.6 (2.22)		
	Day 2	4 mg IR q.d.	390.6 (2.23)	3.0 (1.10)	(1.18; 4.79)
	Day 3	6 mg IR q.d.	388.1 (2.22)	0.6 (1.09)	(-1.23; 2.36)
	Day 4	8 mg IR q.d.	390.5 (2.23)	2.9 (1.10)	(1.13; 4.75)
	Day 8	8 mg IR q.d.	393.0 (2.22)	5.5 (1.09)	(3.66; 7.25)
	Day 9	Posttreatment	390.5 (2.22)	3.0 (1.09)	(1.18; 4.77)
	Day 10	Posttreatment	389.8 (2.22)	2.2 (1.09)	(0.45; 4.05)
Moxifloxacin (N=58)	Day 1	Placebo	391.8 (1.87)		
	Day 2	Placebo	391.8 (1.87)	-0.0 (0.84)	(-1.40; 1.36)
	Day 3	Placebo	390.6 (1.87)	-1.2 (0.84)	(-2.59; 0.17)
	Day 4	Placebo	391.1 (1.87)	-0.7 (0.84)	(-2.09; 0.67)
	Day 8	400 mg q.d.	396.1 (1.87)	4.3 (0.84)	(2.88; 5.64)
	Day 9	Posttreatment	393.1 (1.87)	1.3 (0.84)	(-0.10; 2.65)
	Day 10	Posttreatment	390.8 (1.87)	-1.0 (0.84)	(-2.38; 0.38)

[a] The 2-sided 90% confidence intervals around the mean difference in day-averaged QTcLD during and after paliperidone treatment compared with day-averaged QTcLD on during placebo treatment (Day 1) was constructed using the estimated least-squares means and variances from the mixed models with treatment as a fixed effect and subject as a random effect.

[b] The mean effect of IR paliperidone 8 mg at steady-state (Day 8) on QTc-interval was considered "negative" if the 2-sided 90% confidence interval excluded 10 ms. Assay sensitivity was confirmed, i.e., moxifloxacin 400 mg had a positive effect on QTc interval if the 2-sided 90% confidence interval excluded 0 ms.

It will be noted that LSM Differences from Day 1 for both paliperidone and moxifloxacin were low. However, the day-averaged analysis does not take into account the time course of effect or effects at peak concentrations of drug.

An analysis of LSM Change from baseline in QTcLD by time post-dose yielded the following results:

Table 80 Least Squates Mean Change from Baseline ± SE and (90% CI) in QTcLD by Time Post-Dose – Study SCH-1009

Time Postdose	Day 2	Day 3	Day 4	Day 5	
	PAL 4 mg	PAL 6 mg	PAL 8 mg	PAL 8 mg	Moxi 400 mg
n	44	44	44	44	58
Predose	0.70 ± 1.66 (-2.00 - 3.45)	0.40 ± 1.66 (-2.36 - 3.11)	1.00 ± 1.66 (-1.77 - 3.68)	2.50 ± 1.66 (-0.27 - 5.18)	-1.1 ± 1.5 (-3.55 – 1.39)
0.5 h	4.70 ± 1.66 (2.02 - 7.46)	2.80 ± 1.65 (0.07 - 5.49)	5.50 ± 1.65 (2.75 - 8.17)	6.90 ± 1.65 (4.21 - 9.62)	3.3 ± 1.49 (0.83 – 5.72)
1.0 h	4.90 ± 1.64 (2.22 - 7.60)	4.30 ± 1.64 (1.58 - 6.96)	5.60 ± 1.64 (2.90 - 8.28)	8.10 ± 1.64 (5.40 - 10.78)	1.8 ± 1.49 (-0.60 - 4.21)
1.5 h	9.30 ± 1.65 (6.56 - 11.98)	6.70 ± 1.64 (4.04 - 9.42)	9.60 ± 1.64 (6.92 - 12.31)	10.90 ± 1.64 (8.24 - 13.62)	3.7 ± 1.49 (1.24 -6.16)
2.0 h	5.50 ± 1.65 (2.76 - 8.18)	4.60 ± 1.64 (1.94 - 7.33)	7.30 ± 1.64 (4.56 - 9.94)	8.90 ± 1.64 (6.22 - 11.60)	3.5 ± 1.49 (1.05 - 5.95)
2.5 h	3.40 ± 1.64 (0.67 - 6.06)	4.00 ± 1.64 (1.35 - 6.74)	4.70 ± 1.65 (1.98 - 7.40)	7.50 ± 1.65 (4.83 - 10.24)	5.5 ± 1.49 (3.05 – 7.97)
3.0 h	4.00 ± 1.64 (1.33 - 6.71)	2.80 ± 1.64 (0.10 - 5.49)	7.20 ± 1.66 (4.52 - 9.97)	7.70 ± 1.64 (4.99 - 10.37)	6.1 ± 1.49 (3.64 – 8.53)
3.5 h	3.40 ± 1.64 (0.74 - 6.12)	-0.10 ± 1.64 (-2.83 - 2.56)	3.70 ± 1.65 (0.95 - 6.37)	5.00 ± 1.64 (2.29 - 7.67)	4.7 ± 1.49 (2.26 -7.18)
4.0 h	2.90 ± 1.64 (0.22 - 5.60)	2.00 ± 1.64 (-0.65 - 4.74)	3.20 ± 1.65 (0.52 - 5.93)	5.80 ± 1.64 (3.06 - 8.44)	5.7 ± 1.5 (3.25 – 8.19)
6.0 h	2.00 ± 1.64 (-0.74 - 4.65)	-1.30 ± 1.64 (-3.94 - 1.44)	1.30 ± 1.64 (-1.37 - 4.01)	4.80 ± 1.64 (2.08 - 7.46)	5.0 ± 1.49 (2.57 – 7.47)
12.0 h	1.80 ± 1.65 (-0.86 - 4.55)	-1.10 ± 1.66 (-3.82 - 1.63)	1.30 ± 1.65 (-1.45 - 3.96)	3.60 ± 1.65 (0.93 - 6.35)	3.5 ± 1.5 (1.07 – 6.01)

(Source: OCPB Review: Dr. Kavanagh)

It can be seen that at peak concentrations, the upper bound of the 90% CI crosses 10 msec for paliperidone IR (all doses and Study Days).

- A concern was raised about the study design: since Day 1 is placebo for both groups, the investigator will know that Day 1 is placebo and, therefore, the study will not be "double-blind" (perhaps single-blind) for Day 1. However, this premise is not fundamentally different from a "no-treatment" baseline.

- A more straighforward design would have been a three-arm parallel study, using paliperidone, placebo and moxifloxacin arms.

- We analyzed the data, considering Day 1 as the baseline measurements and we compared the baseline adjusted QT effect of the drug to the corresponding baseline adjusted QT intervals of placebo in the positive control arm; i.e., PAL IR 4 mg (6 mg, 8 mg) with Day 2 (Day 3, Days 4-7) placebo in the moxifloxacin arm. We realize that this analysis might yield inconsistence results between the drug-placebo comparison and the moxifloxacin-placebo comparison since it is a two group comparison for the drug and placebo and one group comparison for the moxifloxacin and placebo; however, at least our results are based on a double-blinded design.

- Our results for the drug at Day 8 are provided in the following Table 1. As can be seen from this table, at multiple time points, the one-sided 95% upper confidence intervals are above 10 msec, which have already demonstrated assay sensitivity of the study. The upper bound crosses the threshold of regulatory concern and is consistent with results from the clinical pharmacology review.

Table 1 The mean difference of double delta of the drug and placebo at Day 8

Time	# of Subj. PALI D8	Mean Delta QTcF PALI D8	# of Subj. Placebo D4	Mean Delta QTcF Placebo D4	Double Delta	SD	95%CI LOW	95%CI HIGH
0	49	3.31	59	0.27	3.04	2.12	-0.45	6.53
0.5	50	6.32	61	-0.28	6.6	2.63	2.27	10.93
1	51	7.94	61	-2.36	10.3	2.1	6.85	13.75
1.5	50	10.02	59	-2.46	12.48	2.21	8.85	16.11
2	50	9.2	61	-2.75	11.95	1.84	8.92	14.98
2.5	49	7.49	60	-2.83	10.32	2.23	6.66	13.98
3	49	7.22	61	-0.28	7.5	2.03	4.15	10.85
3.5	49	4.57	60	-1.2	5.77	2.34	1.91	9.63
4	49	5.1	59	-1.71	6.81	1.82	3.82	9.8
6	49	5.96	60	0.32	5.64	1.92	2.48	8.8
12	48	3.35	59	-0.8	4.15	1.98	0.89	7.41

- The results of double delta analysis for moxifloxacin are provided in Table 2. At 2.5 hour after dosing, the lower bound is greater than 5 msec, which indicates that at least at one time point, the mean difference of baseline adjusted moxifloxacin and baseline adjusted placebo is at least 5 msec. The assay sensitivity was demonstrated by moxifloxacin's QTcF effect. We should point out though we did not adjust for α when comparing multiple time points for moxifloxacin. If we perform some α adjustment scheme, for instance, using the most conservative Bonferroni adjustment, the lower bound at 2.5 hour for moxifloxacin will be less than 5 msec. Note that since the drug itself also demonstrated QT prolongation

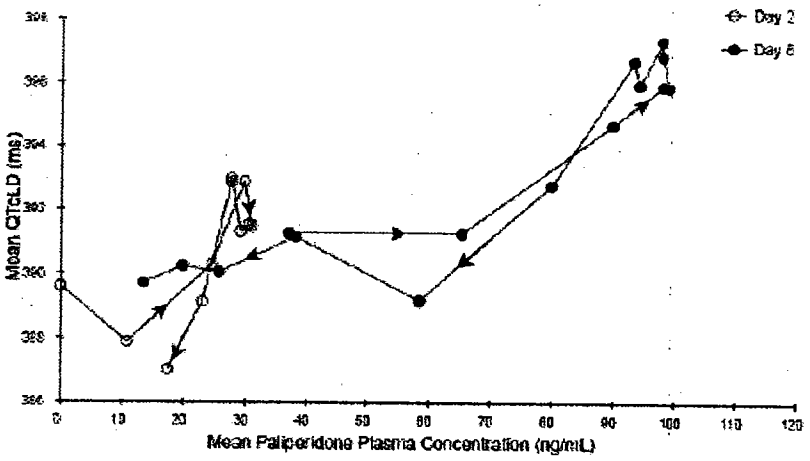
(producing even stronger signal than that from moxifloxacin), the role of moxifloxacin in this study seems not that important.

Table 2 Then mean difference of double delta of moxifloxacin and placebo

Time	# of Subj. Moxi D8	Mean Delta QTcF Moxi D8	Mean Delta QTcF Placebo D4	SD of Delta QTcF Placebo D4	Double Delta	SD	95%CI LOW	95%CI HIGH
0	59	-0.8	0.27	11.8	-1.07	1.05	-2.79	0.65
0.5	61	3.56	-0.28	16.4	3.84	1.8	0.87	6.8
1	61	1.52	-2.36	11.7	3.89	1.52	1.38	6.39
1.5	60	3.78	-2.46	11.46	5.66	1.57	3.09	8.24
2	61	3.56	-2.75	10.42	6.31	1.27	4.23	8.39
2.5	60	5.82	-2.83	13.87	8.65	1.6	6.02	11.28
3	61	6.39	-0.28	10.17	6.67	1.17	4.75	8.59
3.5	60	4.83	-1.2	10.41	6.03	1.79	3.09	8.98
4	59	6.08	-1.71	8.92	7.8	1.42	5.46	10.14
6	61	5.87	0.32	8.45	5.92	1.42	3.58	8.26
12	59	3.58	-0.8	10.35	4.88	1.18	2.93	6.83

A hysteresis plot of mean QTcLD vs. mean paliperidone plasma concentrations suggested a concentration-QTc relationship as well as a lack of hysteresis.

Figure 70 Hysteresis Plots of Mean QTcLD versus Mean Paliperidone Plasma Concentration – Study SCH-1009



(Source: OCPB Review: Dr. Kavanagh)

It should be noted that the QT study was performed with the IR formulation, which has been associated with higher exposures than the proposed marketed formulation (OROS).

According to the clinical pharmacology reviewer (Dr. Kavanagh), there appears to be "overlap of the concentrations associated with QT effect in the controlled QT study and the peak concentrations likely to be seen with clinical dosing of the OROS formulation, even without accounting for the elderly who have slightly higher peak concentrations and patients with organ dysfunction that might result in higher exposures than is typical."

Outlier Analysis:

Table 15: Number of Subjects With a Maximum Change in QTc Interval of 30 to 60 ms or ≥60 ms
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)			Placebo/Moxifloxacin (N=69)		
	Total	QTc Interval ↑ (ms)		Total	QTc Interval ↑ (ms)	
Parameter	n (%)	30-60	>60	n (%)	30-60	>60
QTcLD	19 (26)	19	0	12 (17)	12	0
QTcF	19 (26)	19	0	11 (16)	11	1
QTlc	20 (28)	20	0	13 (19)	13	0
QTcB	59 (82)	59	1	26 (38)	26	0

Number of subjects with a maximum increase in QTc of 30-60 ms or >60 ms at any time during the study relative to time-matched QTc intervals on Day 1 (placebo).

Cross-reference: Attachment 3.4.

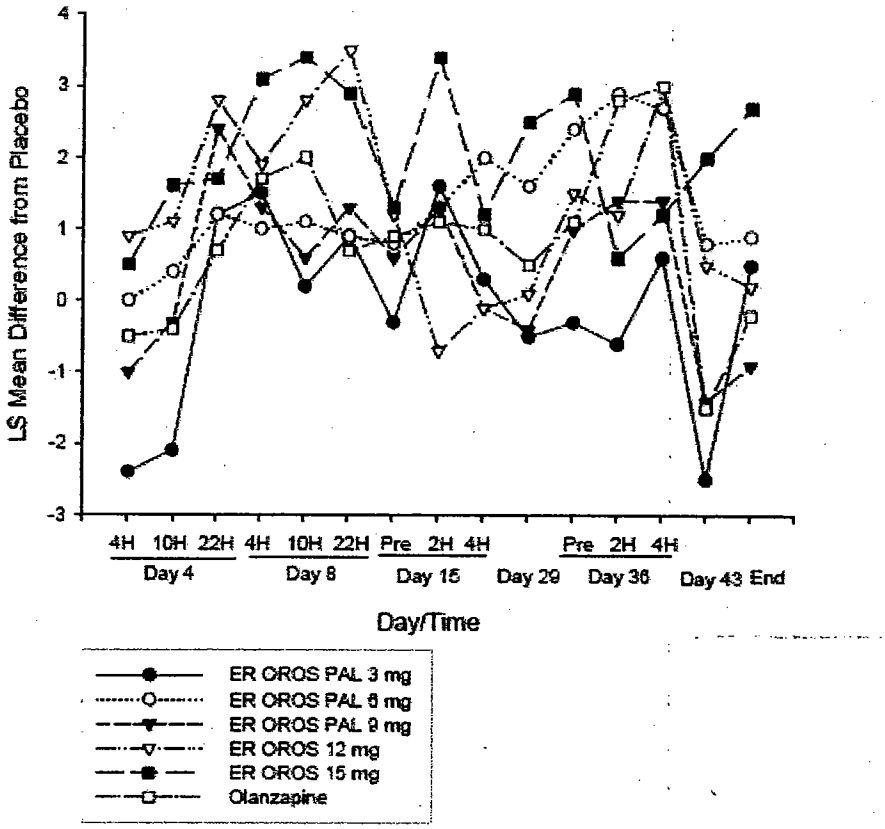
Table 17: Number of Subjects With Absolute QTc Prolongation ≥450 ms, ≥480 ms, or >500 ms
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)					Placebo/Moxifloxacin (N=69)				
		Maximum QTc Interval (ms)					Maximum QTc Interval (ms)			
	n	Normal	≥450	≥480	>500	n	Normal	≥450	≥480	>500
QTcLD	72	72	0	0	0	69	69	0	0	0
QTcF	72	72	0	0	0	69	69	0	0	0
QTlc	72	72	0	0	0	69	69	0	0	0
QTcB	72	63	8	1	0	69	63	6	0	0

4.2. Phase 3 Studies:

In the safety review, the sponsor analyzed means and mean changes in QTc over time for double-blind studies R076477-SCH-303, R0767477-SCH-304, and R076477-SCH-305 (Double-blind studies analysis set). In this analysis set, 12-lead ECGs were recorded at screening and baseline; on Days 4 (4, 10, 22 hours post-dosing), 8 (4, 10, 22 hours post-dose), 15 (pre-dose and 2, 4 hours post-dose), 29, 36 (pre-dose and 2, 4 hours post-dose), and 43 (or at endpoint) and at the poststudy visit (Day 50). According to the sponsor, the LSM differences from placebo were small (< 4 msec).

Figure 9: Least-Square Mean Difference (Treatment - Placebo) for QTcLD
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)



Note: LS Mean difference is based on the ANCOVA model with factors for treatment, baseline (average predose), study, analysis center (nested within study).

Reviewer Comment: While the sponsor's analysis did not result in a signal, this analysis did not include a measurement of assay sensitivity. In addition, we are unable to verify that the QT measurements were made appropriately.

5.0. REVIEWERS' ASSESSMENT

- The QTcLC effects at peak concentration, which cross the upper bound of 10 msec, as well as the hysteresis plot for the mean change in QTcLD vs. plasma concentration, are consistent with a QT signal.
- The sponsor has claimed that peak steady-state concentrations of 8 mg IR paliperidone are more than twice the concentrations of the highest dose of OROS 15 mg paliperidone. However, the clinical pharmacology reviewer has concluded that overlap is present between concentrations in the QT study and concentrations seen with the OROS formulation.
- We conclude that, based on the available information, that a QT signal is present, although the risk for a torsade de pointes event is probably low in the targeted

range. However, labeling should include safety information in order to limit patient exposure (see below, Section 6.0).

6.0. PROPOSED LABELING: The proposed labeling includes the following: Under Clinical Pharmacology:

Electrophysiology

[redacted]

6.1. Reviewer Comments/Labeling Recommendations:

We do not agree with the above labeling. The sponsor's day-averaged correction does not fairly portray QTc effects at peak concentrations. Instead, QTc effects at peak concentrations should be included. For the three fixed-dose efficacy studies, the sponsor did not include a demonstration of assay sensitivity; we do not know if those studies were able to detect a positive signal.

Our best assessment, given the available information, is that there is a low QT risk. Therefore, we recommend that the following cautionary information be included in labeling:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shari Targum
9/12/2006 05:53:49 PM
MEDICAL OFFICER

Joanne Zhang
9/13/2006 09:31:26 AM
BIOMETRICS

Norman Stockbridge
9/13/2006 11:04:21 AM
MEDICAL OFFICER