	Region: Rest of World		Region: Western Europe	
	Total Pali <=6 months (N=57)	Total Pali >6 months (N=95)	Total Pali <=6 months (N=52)	Total Pali >6 Months (N=99)
Weight (kg)				
N	45	32	42	40
Mean baseline (SD)	59.2 (12.69)	57.9 (12.27)	74.0 (19.28)	73.4 (16.27)
Mean change (SD)	1.5 (3.12)	3.6 (5.55)	1.1 (4.72)	1.3 (4.14)
Weight percent change (%)				
N	45	32	42	40
Mean baseline (SD)	59.2 (12.69)	57.9 (12.27)	74.0 (19.28)	73.4 (16.27)
Mean change (SD)	3.0 (5.70)	7.0 (10.57)	1.8 (7.45)	1.8 (5.38)
Body mass index (kg/m2)				
N	45	32	42	39
Mean baseline (SD)	22.1 (4.30)	21.7 (4.45)	26.0 (6.14)	26.2 (5.65)
Mean change (SD)	0.6 (1.14)	1.4 (2.24)	0.4 (1.75)	0.3 (1.44)

Baseline is double-blind baseline.
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Table 79: Number of Subjects With Abnormal Weight Values at End Point
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	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=476) 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=754) n (%)
Weight classification	73	64	158	240	80	54	311	358
Decrease >= 7%	4 (5)	5 (8)	5 (3)	18 (8)	4 (5)	1 (2)	13 (4)	24 (7)
Increase >= 7%	8 (11)	8 (13)	25 (16)	49 (20)	15 (19)	19 (35)	48 (15)	76 (21)
Weight classification (OL)	74	64	158	240	80	54	312	358
Decrease >= 7%	3 (4)	5 (8)	1 (1)	14 (6)	5 (6)	4 (7)	9 (3)	23 (6)
Increase >= 7%	6 (8)	8 (13)	11 (7)	31 (13)	3 (4)	8 (15)	20 (6)	47 (13)

Note: Percentages calculated with the number of subjects per parameter as denominator.
Weight classification: relative to baseline(DB)
Weight classification (OL): relative to base(OPEN)
tsfvs10_t1.rtf generated by tsfvs10.sas.

7.2.9.2 210-Day Safety Update Report

The following table (provided in the 210-Day Safety Update Report dated 6/15/06) shows updated information on duration of Pal exposure in subjects in the ongoing integrated OL trial dataset.

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Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 1 February 2006
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

	— Pla/Pali — (N=236)	— Pali/Pali — (N=686)	— Olan/Pali — (N=249)	— Total — (N=1171)
Total duration of study medication (day)				
N	236	686	249	1171
Category, n (%)				
Week 1-4	35 (15)	4 (1)	44 (18)	83 (7)
Week 5-8	17 (7)	41 (6)	18 (7)	76 (6)
Week 9-12	17 (7)	58 (8)	16 (6)	91 (8)
Week 13-16	5 (2)	48 (7)	13 (5)	66 (6)
Week 17-20	5 (2)	36 (5)	6 (2)	47 (4)
Week 21-24	20 (8)	22 (3)	11 (4)	53 (5)
Week 25-28	18 (8)	14 (2)	11 (4)	43 (4)
Week 29-32	4 (2)	70 (10)	5 (2)	79 (7)
Week 33-36	5 (2)	13 (2)	3 (1)	21 (2)
Week 37-40	9 (4)	17 (2)	12 (5)	38 (3)
Week 41-44	18 (8)	27 (4)	15 (6)	60 (5)
Week 45-48	4 (2)	46 (7)	9 (4)	59 (5)
Week 49-52	43 (18)	34 (5)	53 (21)	130 (11)
> week 52	36 (15)	256 (37)	33 (13)	325 (28)
Mean (SD)	211.5 (136.79)	264.8 (134.87)	207.8 (144.02)	241.9 (139.80)
Median	202.0	302.0	238.0	272.0
Range	(1;391)	(26;437)	(2;392)	(1;437)

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Reviewer Comment. *Only a small number of additional subjects were exposed to over 6 moths of Pal treatment in the more recent 210-Day report (dated 6/15/06) compared to the number of subjects that received this longer term duration of treatment previous 120-Day SUR (see the table below copied form the 120-Day SUR). Given that the sample sizes between the 2 SURs are similar with only a few more additional subjects in the more recent report, a review of the 210-Day report was not conducted at this time for the purpose of this review. Furthermore, this SUR was provided late in the review cycle but is information that can be reviewed if the Agency grants an Approvable action on this NDA.*

Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 1 November 2005
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

	— Pla/Pali — (N=236)	— Pali/Pali — (N=685)	— Olza/Pali — (N=249)	— Total — (N=1170)
Total duration of study medication (day)				
N	236	685	249	1170
Category, n (%)				
Week 1-4	35 (15)	4 (1)	44 (18)	83 (7)
Week 5-8	17 (7)	41 (6)	18 (7)	76 (6)
Week 9-12	17 (7)	58 (8)	16 (6)	91 (8)
Week 13-16	5 (2)	48 (7)	13 (5)	66 (6)
Week 17-20	5 (2)	36 (5)	6 (2)	47 (4)
Week 21-24	20 (8)	22 (3)	11 (4)	53 (5)
Week 25-28	30 (13)	14 (2)	23 (9)	67 (6)
Week 29-32	13 (6)	99 (14)	13 (5)	125 (11)
Week 33-36	7 (3)	45 (7)	9 (4)	61 (5)
Week 37-40	4 (2)	31 (5)	7 (3)	42 (4)
Week 41-44	19 (8)	23 (3)	24 (10)	66 (6)
Week 45-48	9 (4)	27 (4)	15 (6)	51 (4)
Week 49-52	36 (15)	44 (6)	34 (14)	114 (10)
> week 52	19 (8)	193 (28)	16 (6)	228 (19)
Mean (SD)	195.4 (126.82)	247.0 (126.33)	188.8 (131.15)	224.2 (130.23)
Median	183.0	237.0	169.0	218.0
Range	(1;391)	(26;453)	(2;379)	(1;453)

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Deaths. No new deaths were reported in the 210-Day SUR.

SAEs in the Integrated OL Safety Dataset. A comparison by the undersigned reviewer of the summary table below enumerating SAEs as of the new 2/1/06 cut-off date to the 120-Day SUR table (shown previously in this review) on each of the following selected SAE terms revealed no new SAEs for these terms: cardiac disorder SAEs, completed suicide, suicide attempt, convulsion, grand mal convulsion, transient ischemic attack, investigations SAEs. Syncope was not reported as an SAE in any subject. 1 new subject had an SAE of suicide attempt (in the DB Placebo/OL Pal > 6 month subgroup) as of the more recent 2/1/06 cut-off date that does not appear on the sponsor's summary table in the 120-Day SUR. This additional subject does not alter the overall incidence in this subgroup (1%).

The sponsor provides a list of 46 new subjects with SAEs, ADOs and/or with AST or ALT of over 3 times the ULN that were not reported in the 120-Day SUR since they occurred between the 11/1/05 cut-off date for the 120-Day SUR and the 2/1/06 cut-off date for the 210-Day SUR.

These new subjects and other section of the 210-Day SUR have not yet been reviewed since this submission was received late in the review cycle (see Section 4.3 regarding the review strategy).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This topic was addressed under each appropriate section.

7.4 General Methodology

See previous sections regarding concerns on methodology.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

See Section 7.1 where this topic is discussed.

Reviewer Comment. *See sections below. See Section 7.1 for pooled safety dataset methods. Specific limitations to safety datasets are discussed in detail in appropriate sections of this review that describe the results and the interpretation of results.*

7.4.1.2 Combining data

This topic is addressed above.

7.4.2 Explorations for Predictive Factors

See the following subsections. Also refer to Section 6 for subgroup analyses of efficacy data on the basis of age, gender and ethnic origin.

7.4.2.1 Explorations for dose dependency for adverse findings

Refer to the summary table of AEs in Section 7.1.5 showing the incidence of AEs for each Preferred Term for each treatment group. The incidence of several AEs appeared to be dose-dependent, as shown in summary tables provided in this review. Dose-dependent effects on other clinical parameters were also previously addressed in sections on each respective clinical parameter. Refer to the last section of this review for recommendations.

7.4.2.2 Explorations for time dependency for adverse findings

Examination safety parameters obtained at multiple time points were previously described and results were previously discussed in subsections of 7.1.

7.4.2.3 Explorations for drug-demographic interactions

Reviewer comments on results described below. *The results of only the placebo controlled, completed, short-term Phase III dataset analyses are described since these trials are completed, involved patients with schizophrenia and the trials were placebo controlled. The elderly Phase III trial, Study -302 had an insufficient sample size with the age-range skewed to over 65 year olds and within a rather narrow age-range. Consequently, results of an analyses on the basis of demographic subgroupings are considered difficult to interpret.*

Results of a Subgroup Analysis of Safety Parameters on the Basis of Origin Results on the basis of origin are difficult to interpret due to insufficient sample size of non-Caucasians. The sponsor analyses the incidence of AEs of each treatment group for the Short-term Phase III trial dataset (-303, -304 and -305) of "black" and "white" subgroups, since the number of subjects in other racial or ethnic groups were small. The incidence of AEs was numerically greater in the "black" subgroup compared to the "white" subgroups in each treatment group (75% and 65%, respectively in the placebo group, 75% and 70%, respectively in the Pal group and 70% and 67%, respectively in the olanzapine group).

Reviewer Comment. *These results suggest an absence of a drug by racial subgroup (between "black" and "white" subgroupings) interaction effect on the incidence of AEs. However, results are only considered preliminary since it is not clear if the results are reproduceable.*

Results of a Subgroup Analyses of Safety Parameters on the Basis of Age.
The sponsor subdivided subjects in each treatment group of the short-term Phase III trial dataset into 4 age-groups: 18-25 year olds, 26-50 year olds, 51-65 year olds and over 65 year olds. The sponsor selected these age-groups as an attempt to differentiate early onset schizophrenia (in the youngest age-group) from late onset and chronic schizophrenia (over 50 year olds). See reviewer comments below. The oldest age-group only had 10 subjects, therefore the sponor provided results for only the 3 younger age groups. See reviewer comments below which discuss the results and relevant issues.

Reviewer Comment. *It is speculative that the older age-groups represents a late-onset subgroup of patients, since a subgroup of these patients may have had an onset in early adulthood years. The incidence of AEs for the 3 youngest age-groups only differed by approximately 3-5% within each treatment group. These differences are not considered by the undersigned as clinically remarkable, particularly since it is know if findings are reproduceable.*

Results of a Subgroup Analyses of Safety Parameters on the Basis of Gender The following outlines the results on the incidence of AEs in males and females, respectively, in each treatment subgroup of the Phase III short-term trial dataset:

- Placebo subjects: 71% and 56%, respectively
- Olanzapine (72% and 64%)
- Paliperidone (68% and 77%)

Reviewer comment. *The results are difficult to interpret and to ascertain the clinical significance on the basis of overall incidence of AEs. However, the sponsor notes that the most frequently reported AEs in women compared to men who were assigned to DB Pal treatment in the Phase III trial dataset were the following: nervous system AEs, including extrapyramidal system AEs, gastrointestinal AEs and tachycardia (and sinus tachycardia).*

7.4.2.4 Explorations for drug-disease interactions

Explorations of potential drug-disease interactions could not be found in the SCS.

Reviewer's Comments. *As for most explorations in this section of the review, trials were not designed specifically to examine effects of each factor discussed in this section of the review, including the potential role of concomitant disorders. It is likely that concomitant disorders, as well as specific concomitant medications have significant effects on specific organ system effects, such as cardiovascular drug effects. Phase III trials included subjects with a past history of various medical disorders, however subjects had to be generally medically stable and meet specific eligibility criteria regarding their medical status and baseline clinical assessments.*

Drug class labeling for approved drugs generally has a section to address potential drug-disease interactions. Refer to the final section of this review for recommendations.

7.4.2.5 Explorations for drug-drug interactions

Potential drug-drug interactions on the safety profile of Pal were not systematically examined, as described in section 6.3.

Reviewer's Comments. *Drug class labeling for approved drugs generally has a section to address potential drug-disease interactions. Refer to the final section of this review for recommendations.*

7.4.3 Causality Determination

The above results of exploratory analyses are only preliminary observations such that causality cannot be inferred. Safety results of other sections and the potential role of Pal are previously discussed in this review.

8 ADDITIONAL CLINICAL ISSUES

See the final section of this review for any clinical issues that are recommended as issues that need to be address.

8.1 Dosing Regimen and Administration

See the final section of this review regarding the proposed treatment and any issues.

8.2 Drug-Drug Interactions

See the previous section 7.4.2.5 which covers this topic and the final section of this review for comments and recommendations relevant to this topic.

8.3 Special Populations

A Phase III study in elderly patients was conducted (Study -302) and efficacy and safety results on this study were previously described in Sections 6 and 7, respectively, in this review.

See the final section of this review for additional comment and recommendations relevant to this topic.

8.4 Pediatrics

The sponsor refers to meeting minutes of a 4/25/03 End-of-Phase II meeting in which the sponsor states the Division granted a waiver from performing studies patients ≤12 years old and a deferral for studies of 13-17 year old patients until their adult Phase III program is completed, as described in the section of the NDA submission entitled "Pediatric Use Information."

Reviewer comment and conclusion: *A pediatric waiver for the younger age-group is appropriate for the schizophrenia indication since schizophrenia is a disorder of the adult population with an age of onset that is generally in the young adult or adolescent (as considered by the majority of the clinical community and in accordance with the DSM-IV R). Furthermore, childhood psychotic-related disorders, as indicated in the DSM-IV R do not include Schizophrenia. A deferral for the adolescent population is reasonable and appropriate since Paliperidone is not currently approved for schizophrenia.*

8.5 Advisory Committee Meeting

An Advisory Committee (AC) meeting is to be held in September of 2006 on this NDA.

Reviewer Comment. *Given that risperidone is already on the market together with safety related concerns (e.g. QT prolongation) together with significant food effects and the need to establish a maximal (not-to-exceed dose-level) AD input is recommended. Not only do these issues exist but also relative to the benefit: risk ratio and as it compares to Risperdol.® The advantages of having Pal available to those of risperidone are not clear and do not appear to be clearly addressed in the submission. Moreover the advantages need to weighed against the risk relative to risperidone.*

8.6 Literature Review

Refer to Section 7.1.18. No new or remarkable information was revealed in the sponsor's search and review.

8.7 Postmarketing Risk Management Plan

A postmarketing risk plan cannot be found in the submission. Although, the sponsor maintains a postmarketing surveillance program for their approved formulations and is required by CRF codes to submit postmarketing reports (according the regulations).

8.8 Other Relevant Materials

This was already discussed.

9 OVERALL ASSESSMENT

This section reflects the opinions of the undersigned reviewer and from a clinical perspective, unless otherwise specified.

9.1 Conclusions

Pivotal Phase III trials were positive for establishing adequate efficacy, pending confirmation by the Office of Biometrics. The recommended dose in proposed labeling is also reasonable from an efficacy standpoint. However, there are several key issues that primarily pertain to establishing an adequately safe, yet efficacious dose range of Pal. Extensive experience with the already marketed Risperdol® provides some support in favor of the adequate safety of Pal. Yet, some key issues specific to Pal need to be resolved, such as a food effect on plasma levels, QT prolongation effects observed in Phase III trials and in a QT Prolongation study, among other safety findings that were not revealed in the Phase III trials of risperidone that supported approval for Risperdal® (as described in labeling).

Input from the Office of Clinical Pharmacology and Biopharmacy (OCPB) is critical in determining an adequately safe dose and treatment regimen and regarding other related issues (as outlined in the next subsection). Ultimately the risk: benefit ratio relative to the already available risperidone needs to be addressed. An Advisory Committee will be held in September of 2006.

A synopsis of key safety findings is provided under Section 7 of this review.

See key issues and recommendations in the next section below.

9.2 Recommendation on Regulatory Action

It is recommended that this NDA, be given an approvable action, from a clinical perspective.

The basis of this recommendation is discussed in the previous section and as follows. Although key issues remain unresolved that are relevant to safety, the dose-range found to be efficacious is sufficiently wide that given issues are resolved (as outline below), it is likely that an adequately

safe treatment regimen can be identified (with input from primarily OCPB given the food effect, QT prolongation effects and other safety signals). For example the 3 and 6 mg dose-levels appear to show adequate safety in clinical trials (as long the food effect is not an issue from a PK-safety perspective and given that labeling includes adequate information as recommended below). The critical issue is in identifying a maximum end of the dose-range for adequately safe treatment which remains unclear given the safety issues (the sponsor is proposing 3 to 12 mg under Dosage and Administration for labeling). OCPB input is critical for reasons specified below.

If an approvable action is granted at the Agency level on this NDA, then recommendations are provided below starting with a recommendation that impact on both safety and efficacy, followed by safety specific recommendations and efficacy-related recommendations follow, thereafter.

Recommendations that impact on both safety and efficacy:

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

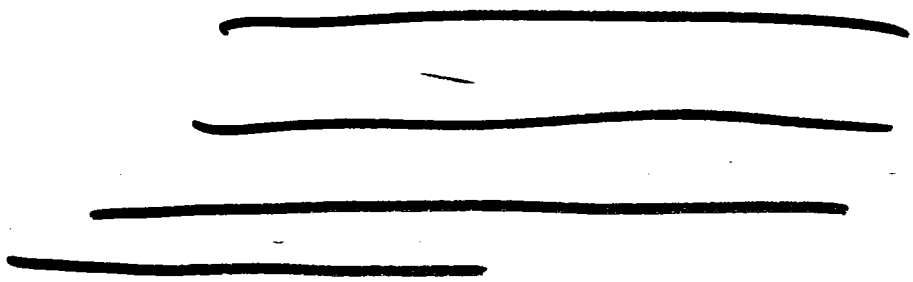
Safety Related Recommendations

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

1. A food effect on the pharmacokinetic (PK) properties of Pal was observed in two Phase I trials, as described in Section 5 of this review. This issue needs to be resolved with respect to recommendations for an adequately safe, yet efficacious treatment regimen. OCPB input is critical and recommended.
2. Food effects on PK and safety (in Phase I food effect studies described in Sections 5 for PK effects, 7.1.12 C and Section 7.1.3.3 for safety findings)
3. Several cardiovascular-related findings need to be addressed from a dose-level perspective that include a signal for
    - QT prolongation (based on Phase III data, updated longterm OL extension trial data provided in the 120-Day SUR, results of Study –SCH-1009),
    - Results on heart rate (based on ECG and vital sign results), and other hemodynamic effects were observed (based on results in Section 7). Subjects with clinically remarkable events related to hemodynamic Pal effects are also described in Section 7.1.3.3 of this review.
    - Potential PR interval prolongation effects as suggested by the following observations:

- A greater incidence of adverse events (AEs) of ° AV block in the 15 mg (highest-dose) Pal group compared to placebo (4.4%, 1.4%, respectively)
- Similar findings in the small elderly Phase III trial (3% and 0% in the Pal and placebo groups, respectively) that used a flexible dose design (3-12 mg/day),
- A small group mean increase in PR interval in Pal compared to placebo groups in Phase III trials (the magnitude of this increase was clinically unremarkable).

4. I



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

subjects and showed large fluctuations over time within a given subject. Furthermore, baseline levels were elevated in some subjects and in some treatment groups. Consequently, it is difficult to detect a potential drug signal in a population with highly variable CPK levels at baseline. CPK elevations were also observed in Phase I trials of generally healthy subjects (who did not have schizophrenia) that appeared to be dose-dependent in subjects treated with the OROS formulation.

The sponsor does not describe any serious events associated with CPK elevations except for one subject (and possibly another with NMS that was found by the undersigned review; subjects 100057 and 200213). Additional subjects with elevated CPK were however, found by the undersigned reviewer that also had elevations in LFTs (as described in Section 7.1.3.3 of this review). There may be additional subjects with clinically remarkable events associated with CPK elevations since results of a special data analyses for revealing a potential drug-related signal could not be found in the Summary of Clinical Safety (SCS) section of the submission which provided the integrated summary of safety in clinical drug trials. Therefore, it is not clear to the undersigned if CPK elevations were associated with dystonia or other drug-related adverse effects. Another consideration is that CPK elevations reflective of the patient population would be expected to occur primarily in the acutely psychotic patient, yet elevations were also revealed during longterm OL Pal treatment (in the Phase III OL extension trials). This potential safety signal should be adequately resolved.

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

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The proposed Risk Management program cannot be found in the submission. In accordance with the Clinical Reviewer MAPP, a postmarketing studies and surveillance plan should be described here. Sponsors generally conduct ongoing postmarketing surveillance for safety signals and maintain a database. Sponsors of approved NDAs are also required to submit Periodic Safety Update reports according to regulations. If the Agency deems this NDA to be approvable consideration to obtaining input from the Office of Surveillance and Epidemiology is recommended.

9.3.2 Required Phase 4 Commitments

It is recommended that the sponsor address key issues as discussed in this review (as previously outlined and described in the final section of this review), before considering required Phase 4 commitments on this NDA.

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

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

- Other safety issues and PK issues may require further examination depending on the sponsor's responses to issues and on OCPB input.

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

Since elevations in LFTs were observed in some Pal subjects further study in this area should be considered such as employing a challenge test to determine if elevations can be elicited using methods that would be adequately safe. For example consider a study examine the effects of coadminstration of olanzapine (refer to labeling describing LFT elevations in some subjects on this drug). Polypharmacy involving multiple antipsychotic medications is not uncommon among clinicians treating patients with schizophrenia.

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

9.3.3 Other Phase 4 Requests

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

9.4 Labeling Review

If an approvable action is granted at the Agency level on this NDA, then the following paragraphs are comments and recommendations regarding labeling.

3 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*4

Preclinical Team. It is common clinical practice to treat patients for years, given the chronicity of this disorder.

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

cc: IND; HFD 130/N Khin/K Brugge/K Kiedrow/T Laughren/

APPENDIX

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Table Series 10.1 Schedule of Events of Phase III Trials (as provided by the sponsor)

Table 3: Time and Events Schedule
(Protocol R076477-SCH-303)

		Screening	Baseline	Double-Blind Treatment Phase								Post-Study Visit
	Visit	1	2	3	4	5	6	7	8	9	10	11
	Week	-1				1	2	3	4	5	6	7
Procedures	Day			1	4	8	15	22	29	36	43	50
Screening												
Inclusion/exclusion criteria		X	X									
Medical history		X										
Psychiatric evaluation		X										
Height		X										
Hemoglobin A_{1c}			X									
Oral glucose tolerance test		X										
Efficacy												
Positive and Negative Syndrome Scale (PANSS)		X	X		X	X	X	X	X	X	X	
Personal and Social Performance Scale (PSP)			X								X	
Clinical Global Impression Scale – Severity (CGI-S)			X		X	X	X	X	X	X	X	
Symptoms and Quality of Life in Schizophrenia Scale (SQLS)			X			X	X		X		X	
Sleep Visual Analog Scale (VAS)			X			X	X		X		X	
Safety												
Abnormal Involuntary Movement Scale (AIMS)			X			X	X	X	X	X	X	
Barnes Akathisia Rating Scale (BARS)			X			X	X	X	X	X	X	
Simpson Angus Scale (SAS)			X			X	X	X	X	X	X	
Clinical laboratory tests (fasting)[a]		X	X				X			X[b]	X	X
Vital signs		X	X	X[c]	X[c]	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X[d]	X[d]		X[e]	X[e]	X[f]		X	X[f]	X	X
Physical examination, body weight, temperature		X									X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review			X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sample[g]							X			X	X[h]	
Pharmacogenomic blood sample[i]			X									
Pregnancy test in females[j]		X									X	X
Administrative												
Informed consent		X										
Pharmacogenomic informed consent			X									
Hospitalization			X	X	X	X	X					
Randomization to treatment group[k]			X									
Dispense study drug				X	X	X	X	X	X	X		
Study drug accountability					X	X	X	X	X	X	X	

[a] Hematology, serum chemistry, and urinalysis. Laboratory samples were drawn in the fasting state.
[b] Prolactin levels only.
[c] Vital sign measurements were also obtained on Days 2, 3, 5, and 6.
[d] Three ECGs were recorded pretreatment, 2 recordings during screening (Days –5 to –1) and 1 recording at baseline.
[e] On Days 4 and 8, ECG recordings were obtained at 4, 10, and 22 hours after dosing.
[f] On Days 15 and 36, ECGs were recorded before blood samples were obtained for pharmacokinetic assessments (immediately predose, 1 to 2 hours after dosing, and 4 hours after dosing).
[g] Samples were obtained predose, 1 to 2 hours after dosing, and at least 4 hours after dosing.
[h] Sample was obtained only if a subject was withdrawn from the study before Visit 9.
[i] If blood sample was not collected at baseline (Visit 2), sample was collected at any time before Visit 10.
[j] Serum pregnancy test at screening (Visit 1) and post-study visit (Visit 11); urine pregnancy test at end of double-blind treatment phase (Visit 10).
[k] Contacted IVRS at baseline for randomization assignment.

Table Series 10.1, continued. Schedule of Events of Phase III Trials (as provided by the sponsor), continued.

Table 3: Time and Events Schedule
(Protocol R076477-SCH-304)

		Screening	Baseline	Double-Blind Treatment Phase								Post-Study Visit
	Visit	1	2	3	4	5	6	7	8	9	10	11
	Week	-1				1	2	3	4	5	6	7
Procedures	Day			1	4	8	15	22	29	36	43	50
Screening												
Inclusion/exclusion criteria		X	X									
Medical history		X										
Psychiatric evaluation		X										
Height		X										
Hemoglobin A_{1c}			X									
Oral glucose tolerance test		X										
Efficacy												
Positive and Negative Syndrome Scale (PANSS)		X	X		X	X	X	X	X	X	X	
Personal and Social Performance Scale (PSP)			X								X	
Clinical Global Impression Scale – Severity (CGI-S)			X		X	X	X	X	X	X	X	
Symptoms and Quality of Life in Schizophrenia Scale (SQLS)			X			X	X		X		X	
Sleep Visual Analog Scale (VAS)			X			X	X		X		X	
Safety												
Abnormal Involuntary Movement Scale (AIMS)			X			X	X	X	X	X	X	
Barnes Akathisia Rating Scale (BARS)			X			X	X	X	X	X	X	
Simpson-Angus Scale (SAS)			X			X	X	X	X	X	X	
Clinical laboratory tests (fasting)[a]		X	X				X			X[b]	X	X
Vital signs		X	X	X[c]	X[c]	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X[d]	X[d]		X[e]	X[e]	X[f]		X	X[f]	X	X
Physical examination, body weight, temperature		X									X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review			X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sample[g]							X			X	X[h]	
Pharmacogenomic blood sample[i]			X									
Pregnancy test in females[j]		X									X	X
Administrative												
Informed consent		X										
Pharmacogenomic informed consent			X									
Hospitalization			X	X	X	X	X					
Randomization to treatment group[k]			X									
Dispense study drug				X		X	X	X	X	X		
Study drug accountability					X	X	X	X	X	X	X	

[a] Hematology, serum chemistry, and urinalysis. Laboratory samples were drawn in the fasting state.
[b] Prolactin levels only.
[c] Vital sign measurements were also obtained on Days 2, 3, 5, and 6.
[d] Three ECGs were recorded pretreatment, 2 recordings during screening (Days –5 to –1) and 1 recording at baseline.
[e] On Days 4 and 8, ECG recordings were obtained at 4, 10, and 22 hours after dosing.
[f] On Days 15 and 36, ECGs were recorded before blood samples were obtained for pharmacokinetic assessments (immediately predose, 1 to 2 hours after dosing, and 4 hours after dosing).
[g] Samples were obtained predose, 1 to 2 hours after dosing, and at least 4 hours after dosing.
[h] Sample was obtained only if a subject was withdrawn from the study before Visit 9.
[i] If blood sample was not collected at baseline (Visit 2), sample was collected at any time before Visit 10.
[j] Serum pregnancy test at screening (Visit 1) and post-study visit (Visit 11); urine pregnancy test at end of double-blind treatment phase (Visit 10).
[k] Contacted IVRS at baseline for randomization assignment.

Table Series 10.1, continued. Schedule of Events of Phase III Trials (as provided by the sponsor), continued.

Table 3: Time and Events Schedule
(Protocol R076477-SCH-302)

	Screening	Baseline	Double-Blind Treatment Phase								Post-Study Visit
Visit	1	2	3	4	5	6	7	8	9	10	11
Week	-1				1	2	3	4	5	6	7
Procedures / Day			1	4	8	15	22	29	36	43	50
Screening											
Inclusion/exclusion criteria	X	X									
Medical history	X										
Psychiatric evaluation	X										
Height	X										
Hemoglobin A_{1c} (HbA_{1c})		X									
Oral glucose tolerance test	X										
Efficacy											
Positive and Negative Syndrome Scale (PANSS)	X	X		X	X	X	X	X	X	X	
Personal and Social Performance Scale (PSP)		X								X	
Clinical Global Impression Scale – Severity (CGI-S)		X		X	X	X	X	X	X	X	
Schizophrenia Quality of Life Scale (SQLS)		X			X	X		X		X	
Sleep Visual Analog Scale (VAS)		X			X	X		X		X	
Safety											
Abnormal Involuntary Movement Scale (AIMS)		X		X	X	X	X	X	X	X	
Barnes Akathisia Rating Scale (BARS)		X		X	X	X	X	X	X	X	
Simpson Angus Scale (SAS)		X		X	X	X	X	X	X	X	
Clinical laboratory tests (fasting)[a]	X	X				X			X[b]	X	X
Vital signs	X	X	X[c]	X[c]	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X[d]	X[d]		X[e]	X[e]	X[f]		X	X[f]	X	X
Physical examination, body weight, temperature	X									X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sample[g]						X			X	X[h]	
Pharmacogenomic blood sample[i]		X									
Administrative											
Informed consent	X										
Pharmacogenomic informed consent	X										
Hospitalization		X	X	X	X	X					
Randomization to treatment group[j]		X									
Dispense study drug			X	X	X	X	X	X	X		
Study drug accountability				X	X	X	X	X	X	X	

[a] Hematology, serum chemistry, and urinalysis. Laboratory samples were drawn in the fasting state.
[b] Prolactin levels only.
[c] Vital sign measurements were also obtained on Days 2, 3, 5, and 6.
[d] Three ECGs were recorded pretreatment, 2 recordings during screening (Days –5 to –1) and 1 recording at baseline.
[e] On Days 4 and 8, ECG recordings were obtained at 4, 10, and 22 hours after dosing.
[f] On Days 15 and 36, ECGs were recorded before blood samples were obtained for pharmacokinetic assessments (immediately predose, 1 to 2 hours after dosing, and 4 hours after dosing).
[g] Samples were obtained predose, 1 to 2 hours after dosing, and at least 4 hours after dosing.
[h] Sample was obtained only if a subject was withdrawn from the study before Visit 9.
[i] If blood sample was not collected at baseline (Visit 2), the sample was collected at any time before Visit 10.
[j] Contacted IVRS at baseline for randomization assignment.

Table Series 10.2 Outlier Criteria Employed for Clinical Parameters (as provided by the sponsor) for Completed Phase III Trials (-303, -304 and -305).

Criteria for Identification of Markedly Abnormal Clinical Laboratory Analyte Values

Study R076477-SCH-304

Output DLAB06: Criteria for Identification of Markedly Abnormal Clinical Laboratory Analyte Values

Laboratory Parameter	Clinically Significant Low in STD Unit	Clinically Significant High in STD Unit
SODIUM (mmol/l)	125	155
POTASSIUM (mmol/l)	3	5.8
CHLORIDE (mmol/l)	94	112
BICARBONATE (mmol/l)	15.1	34.9
GLUCOSE (mmol/l)	2.2204	16.653
AST (SGOT) (U/L)	N/A	250
ALT (SGPT) (U/L)	N/A	200
UREA NITROGEN (mmol/l)	N/A	17.85
CREATININE (umol/l)	N/A	265.2
LDL (mmol/l)	2.30154	4.1376
HDL (mmol/l)	0.9051	N/A
CHOLESTEROL (mmol/l)	N/A	7.758
TRIGLYCERIDES (mmol/l)	N/A	5.715
CREATINE KINASE (U/L)	N/A	990
WBC (giga/l)	2.5	15
RBC (tera/l)--FEMALE	3	5.5
RBC (tera/l)--MALE	3	6.4
HEMOGLOBIN (g/l)	80	190
HEMATOCRIT (l)--FEMALE	0.29	0.5
HEMATOCRIT (l)--MALE	0.24	0.55
PLATELETS (giga/l)	100	600
RETICULOCYTES (%)--FEMALE	0.9	4.4
RETICULOCYTES (%)--MALE	1	3.8
NEUTROPHILS (%)	30	90
LYMPHOCYTES (%)	10	60
MONOCYTES (%)	N/A	20
EOSINOPHILS (%)	N/A	10
BASOPHILS (%)	N/A	6
ALBUMIN (g/l)	24	60
ALKALINE PHOSPHATASE (U/L)	N/A	250
CALCIUM (mmol/l)	1.497	2.994
GGT (U/L)	N/A	300
LDH (U/L)	N/A	500
PHOSPHORUS (mmol/l)	0.71038	2.61549
BILIRUBIN (umol/l)	N/A	51.3
PROTEIN (g/l)	50	N/A
URIC ACID (umol/l)	89.22	594.8
HAEMOGLOBIN A1C (%)	4.3	6.1
DIRECT BILIRUBIN (umol/l)	N/A	6.84

Note: The same limits apply to both male and female unless gender is indicated
N/A=Not applicable

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Table Series 10.2, continued Outlier Criteria Employed for Clinical Parameters (as provided by the sponsor) for Study -302

Attachment 8.3.1: Criteria for Markedly Abnormal Laboratory Values

	Markedly Abnormal Limits	
Laboratory Test	Low	High
Albumin (g/dL)	2.4	6.0
Alkaline phosphatase (µ/L)	N/A	250
Alanine transaminase (SGPT) (µ/L)	N/A	200
Aspartate transaminase (SGOT) (µ/L)	N/A	250
Bicarbonate (mEq/L)	15.1	34.9
Blood urea nitrogen (mg/dL)	N/A	50
Calcium (mg/dL)	6	12
Chloride (mEq/L)	94	112
Cholesterol (mg/dL)	N/A	300
Creatine kinase (µ/L)	N/A	990
Creatinine (mg/dL)	N/A	3
Gamma glutamyl transferase (µ/L)	N/A	300
Glucose (mg/dL)	40	300
HDL (mg/dL)	30	N/A
LDH (µ/L)	N/A	500
LDL (mg/dL)	98	224
Phosphorus (mg/dL)	2.2	8.1
Potassium (mEq/L)	3.0	5.8
Sodium (mEq/L)	125	155
Total bilirubin (mg/dL)	N/A	3.0
Total protein (g/dL)	5	N/A
Triglycerides (mg/dL)	N/A	500
Uric acid (mg/dL)	1.5	10
Hematocrit (%)-- female	28	50
-- male	24	55
Hemoglobin (g/dL)	8	19
Neutrophils (%)	30	90
Monocytes (%)	N/A	20
Eosinophils (%)	N/A	10
Basophils (%)	N/A	6
Lymphocytes (%)	10	60
Platelet count ($x10^3/\mu L$)	100	600
Red blood cell count ($x10^6/\mu L$) -- female	3.0	5.5
-- male	3.0	6.4
Reticulocytes (%)-- female	0.9	4.4
-- male	1.0	3.8
White blood cell count ($x10^3/\mu L$)	2.5	15.0

Note: The same limits apply to both males and females unless gender is indicated;
N/A = Not applicable.

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Table Series 10.2, continued Outlier Criteria Employed for Clinical Parameters (as provided by the sponsor)

Table 75: Criteria for Treatment-Emergent Abnormal Vital Signs, Orthostatic Changes, and Body Mass Index

Parameter	Outside of normal limit if ... Abnormally low		Abnormally high
Vital signs:			
Pulse (bpm)	A decrease from baseline of ≥ 15 to a value ≤ 50		An increase from baseline of ≥ 15 to a value ≥ 100
Systolic blood pressure (mm Hg)	A decrease from baseline of ≥ 20 to a value ≤ 90		An increase from baseline of ≥ 30 to a value ≥ 180
Diastolic blood pressure (mm Hg)	A decrease from baseline of ≥ 15 to a value ≤ 50		An increase from baseline of ≥ 15 to a value ≥ 105
Body weight (kg)	A decrease from baseline of ≥ 7%		An increase from baseline of ≥ 7%
Orthostatic changes in:			
Systolic blood pressure (mm Hg)	>15		
Diastolic blood pressure (mm Hg)	< -30		
Pulse (bpm)	< -10		
	Normal	Overweight	Obese
Body mass index (BMI)	< 25	25 - <30	≥ 30

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Table 84: Criteria for Abnormal Electrocardiographic Findings

ECG parameter		Abnormally low	Abnormally high
HR (bpm)		≤ 50	≥ 100
PR interval (msec)		--	≥ 210
QRS interval (msec)		≤ 50	≥ 120
QT interval (msec)		≤ 200	≥ 500
QTc value (msec)	**Classification**	**Adult Males**	**Adult Females**
	Normal	≤ 430	≤ 450
	Borderline	431 – 450	451 – 470
	Prolonged	> 450	> 470
		Adult Males and Females	
Clinically significant value	No	< 500	
	Yes	≥ 500	
Change from baseline	No concern	< 30	
	Concern	30 – 60	
	Clear concern	> 60	
QTc Classification[a]	Normal	<450	
	≥450	≥450 and <480	
	≥480	≥480	

[a] Classification based on ICH E14 Guideline (reference 4).

Table 10.3 Study Schedule for Study SCH-1009

TIME AND EVENTS SCHEDULE

Study Procedure	Screening Period			Randomization Period: Treatment Phase						Post-treatment Phase		End of Study/ Early Withdrawal
Day:	−14 to −3[a]	−2	−1	1	2	3	4	5 to 7	8	9	10	
Screening/Administrative Procedures												
Informed consent	X											
Inclusion/exclusion criteria	X											
Medical, psychiatric histories	X											
Psychiatric evaluation	X											
Physical examination	X											X
Body weight	X											
Height	X											
Prior medication	X											
Urine drug screening[b]	X	X										
Alcohol test		X										
Randomization to treatment group				X								
Hospitalization[c]		X	X	X	X	X	X	X	X	X	X	
Discharge from hospital											X	
Study Drug Administration[d]												
Administer oral study medication (paliperidone, moxifloxacin, or placebo)				X	X	X	X	X	X			
Study drug accountability				X	X	X	X	X	X			
Pharmacodynamic Procedures												
12-lead electrocardiogram[e]	X		X	X	X	X	X	X[a]	X	X	X	X[f]
Pharmacokinetic Procedures												
Documentation of meal time and content[g]			X	X	X	X	X	X	X	X	X	
Blood sample collection[e]				X	X	X	X	X[a]	X	X	X	
Pharmacogenomic Procedures												
Informed consent	X	(X)										
Blood sample collection				X								
Safety Procedures												
Vital signs[h]	X	X	X									X
Clinical laboratory tests	X	X										X
Pregnancy test in women[i]	X	X										X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X

NOTE: Footnotes are provided on the following page. (Continued)

Table 10.3 Study Schedule for Study SCH-1009, continued.

TIME AND EVENTS SCHEDULE (CONTINUED)

[a] All medications that subjects are currently taking at enrollment must be washed out. A minimum washout period of 5 days prior to study start will be adequate except in the case of certain medications (see Section 4.3).
[b] All subjects will be tested for drugs of abuse at both screening and Day –2. Subjects who test positive for drugs of abuse at screening must have a negative test when re-tested on Day –2 prior to randomization.
[c] Subjects may also be hospitalized during the washout period, based on the clinical judgment of the investigator.
[d] Study medication (paliperidone, moxifloxacin, and placebo) will all be identical in appearance, in order to preserve the blind.
[e] Specific times for dosing, electrocardiogram (ECG), and pharmacokinetic sampling are provided in Table 1 in Section 9.1.1. On Days 5, 6, and 7, pharmacokinetic blood sampling will only be predose; on Day 5, ECG recording will only be predose.
[f] A single ECG will be performed upon early withdrawal if no ECG has been performed that day.
[g] Caffeine/methylxanthine-containing beverages or foods (including chocolate) are not allowed within 2 hours prior to each ECG recording. High-fat- and high-sugar-containing foods must be minimized. Meals must be scheduled so that subjects will have at least 30 minutes of rest prior to an ECG recording, and conditions in the unit must be modified so that both physical and emotional stress are minimized prior to ECG recording.
[h] Supine blood pressure, pulse, and oral temperature.
[i] Serum test will be performed at screening and end of study/early withdrawal; urine test will be performed on Day –2.

Table 10.4 PK Blood Sampling and ECG Assessment Time-points for Study SCH-1009.

R076477 (paliperidone): Clinical Protocol R076477-SCH-1009

Table 1: Schedule for ECG Recordings and Pharmacokinetic Sampling

Study Day	Hour (Target)	Time Relative to Dosing (hours)[a]	Study Drug Administration	12-Lead ECG[b]	Pharmacokinetic Sampling[c]
Day –1	08:00	–24		X	
Days 1 and 2	08:00	0	X	X[d]	X[d]
	08:30	0.5		X	X
	09:00	1		X	X
	09:30	1.5		X	X
	10:00	2		X	X
	10:30	2.5		X	X
	11:00	3		X	X
	11:30	3.5		X	X
	12:00	4		X	X
	14:00	6		X	X
	20:00	12		X	X
Days 3 and 4	08:00	0	X	X[d]	X[d]
	08:30	0.5		X	
	09:00	1		X	X
	09:30	1.5		X	
	10:00	2		X	X
	10:30	2.5		X	
	11:00	3		X	
	11:30	3.5		X	
	12:00	4		X	X
	14:00	6		X	
	20:00	12		X	X
Day 5	08:00	0	X	X[d]	X[d]
Days 6 and 7	08:00	0	X		X[d]
Day 8	08:00	0	X	X[d]	X[d]
	08:30	0.5		X	X
	09:00	1		X	X
	09:30	1.5		X	X
	10:00	2		X	X
	10:30	2.5		X	X
	11:00	3		X	X
	11:30	3.5		X	X
	12:00	4		X	X
	14:00	6		X	X
	20:00	12		X	X
Day 9	08:00	24		X	X
	08:30	24.5		X	
	09:00	25		X	
	09:30	25.5		X	
	10:00	26		X	
	10:30	26.5		X	
	11:00	27		X	
	11:30	27.5		X	

(Continued)

Table 10.4 PK Blood Sampling and ECG Assessment Time-points for Study SCH-1009, continued.

Study Day	Hour (Target)	Time Relative to Dosing (hours)[a]	Study Drug Administration	12-Lead ECG[b]	Pharmacokinetic Sampling[c]
Day 9 (continued)	12:00	28		X	
	14:00	30		X	
	20:00	36		X	X
Day 10	08:00	48		X	X
	08:30	48.5		X	
	09:00	49		X	
	09:30	49.5		X	
	10:00	50		X	
	10:30	50.5		X	
	11:00	51		X	
	11:30	51.5		X	
	12:00	52		X	
	14:00	54		X	
	20:00	60		X	X

[a] Time on Day –1 is relative to the Day 1 dosing; time on Days 1 to 7 is relative to that day's dosing; time on Days 8, 9, and 10 is relative the Day 8 dosing.
[b] Triplicate 10-sec recordings collected at 60-sec intervals.
[c] Within 5 min after each triplicate ECG recording, where applicable.
[d] Predose.

Table 10.5 Visit Windows of Phase I-III Trials

Table Ia: Time Intervals for ECG, Lab, Vitals and EPS Scales Visits for R076477-SCH-303, 304, and 305

Variable	Scheduled Visit Number	Time Interval (Label on ouput)	Time Interval (Day)[a]	Target Time Point (Day)
ECG	1,2	Baseline	≤ 1	1
	4	Day 4: 4H pst-ds	2-6[b]	4
	4	Day 4: 10H pst-ds	2-6[b]	4
	4	Day 4: 22H pst-ds	2-6[b]	4
	5	Day 8: 4H pst-ds	7-11[b]	8
	5	Day 8: 10H pst-ds	7-11[b]	8
	5	Day 8: 22H pst-ds	7-11[b]	8
	6	Day 15: pre-ds	12-22	15
	6	Day 15: 1-2H pst-ds	12-22	15
	6	Day 15: 4H pst-ds	12-22	15
	8	Day 29	23-32	29
	9	Day 36: Pre-ds	33-39	36
	9	Day 36: 1-2H pst-ds	33-39	36
	9	Day 36: 4H pst-ds	33-39	36
	10	Day 43	40-end of DB	43
Labs	1,2	Baseline	≤1	1
	6	Day 15	2-29[c]; 2-32[d]	15
	9	Day 36	33-39[d]	36
	10	Day 43	30-end of DB[c] 40-end of DB[d]	43
SAS/BARS/AIMS	1,2	Baseline	≤ 1	1
	5	Day 8	2-11	8
	6	Day 15	12-18	15
	7	Day 22	19-25	22
	8	Day 29	26-32	29
	9	Day 36	33-39	36
	10	Day 43	40-end of DB	43
Vital Signs	1,2	Baseline	≤ 1	1
	3	Day 2	2	2
	3	Day 3	3	3
	4	Day 4	4	4
	4	Day 5	5	5
	4	Day 6	6	6
	5	Day 8	7-11	8
	6	Day 15	12-18	15
	7	Day 22	19-25	22
	8	Day 29	26-32	29
	9	Day 36	33-39	36
	10	Day 43	40-end of DB	43

[a] Relative to the first day of double-blind study drug administration
[b] Time point will be assessed based on the scheduled elapsed time (EGPTMNUM) in the data set.
[c] Applicable to all laboratory tests except for prolactin.
[d] Only for prolactin that is assessed at Day 36.

Table 10.5 series, continued.

Table 1b: Time Intervals for ECGs and Lab Visits for R076477-SCH-302

Variable	Scheduled Visit Number	Time Interval (Label on ouput)	Time Interval (Day)[a]	Target Time Point (Day)
ECG	1,2	Baseline	≤ 1	1
	4	Day 4: 4H pst-ds	2-6[b]	4
	4	Day 4: 10H pst-ds	2-6[b]	4
	4	Day 4: 22H pst-ds	2-6[b]	4
	5	Day 8: 4H pst-ds	7-11[b]	8
	5	Day 8: 10H pst-ds	7-11[b]	8
	5	Day 8: 22H pst-ds	7-11[b]	8
	6	Day 15	12-22	15
	8	Day 29	23-35	29
	10	Day 43	36-end of DB	43
Labs	1,2	Baseline	≤1[c,d]	1
	6	Day 15	2-29[c], 2-32[d]	15
	9[f]	Day 36[d]	33-39[d]	15
	10	Day 43	30-end of DB[c], 40-end of DB[d]	43

[a] Relative to the first day of double-blind study drug administration
[b] Time point will be assessed based on the scheduled elapsed time (EGPTMNUM) in the data set.
[c] Applicable to all laboratory tests except for prolactin.
[d] Only for prolactin that is assessed also at Visit 9 (Day 36).

Table 10.5 series, continued.

Table 2a: Time Intervals for Double-Blind Data Summarized in Open-Label Studies

Analysis	Time interval label in R076477-SCH-304	Time interval label in R076477-SCH-704
Double-blind	Baseline	Baseline (DB)
	Day 1	Day 1 (DB)
	Day 1 LOCF	Day 1 (DB) LOCF
	Day 4	Day 4 (DB)
	Day 8	Day 8 (DB)
	Day 8 LOCF	Day 8 (DB) LOCF
	Day 15	Day 15 (DB)
	Day 15 LOCF	Day 15 (DB) LOCF
	Day 22	Day 22 (DB)
	Day 22 LOCF	Day 22 (DB) LOCF
	Day 29	Day 29 (DB)
	Day 29 LOCF	Day 29 (DB) LOCF
	Day 36	Day 36 (DB)
	Day 36 LOCF	Day 36 (DB) LOCF
	Day 43	Day 43 (DB)
	Day 43 LOCF	Day 43 (DB) LOCF
	End point	End point (DB)

Table 10.5 series, continued.

Table 2b: Time Intervals for Open-Label Studies

Variable	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
Vital Signs	Open-label	101	Base (open)	-14 to 1	1
		102	Day 4	2 to 6	4
		103	Week 1 (open)	7 to 11	8
		104	Week 2 (open)	12 to 18	15
		105	Week 3 (open)	19 to 25	22
		106	Week 4 (open)	26 to 43	29
		107	Week 8 (open)	44 to 71	57
		108	Week 12 (open)	72 to 99	85
		109	Week 16 (open)	100 to 127	113
		110	Week 20 (open)	128 to 155	141
		111	Week 24 (open)	156 to 183	169
		112	Week 28 (open)	184 to 211	197
		113	Week 32 (open)	212 to 239	225
		114	Week 36 (open)	240 to 267	253
		115	Week 40 (open)	268 to 295	281
		116	Week 44 (open)	296 to 323	309
		117	Week 48 (open)	324 to 351	337
		118	Week 52 (open)	352 to 370	365
		119	Week 53 (open)	>370	372
Labs	Open-label	101	Base (open)	-14 to 1	1
		111	Week 24 (open)	2 to 267	169
		118	Week 52 (open)	268 to 370	365
		119	Week 53 (open)	>370	372
ECG	Open-label	101	Base (open)	-14 to 1	1
		102	Day 4	2 to 6	4
		103	Week 1 (open)	7 to 11	8
		104	Week 2 (open)	12 to 18	15
		106	Week 4 (open)	19 to 43	29
		107	Week 8 (open)	44 to 85	57
		109	Week 16 (open)	86 to 141	113
		111	Week 24 (open)	142 to 225	169
		115	Week 40 (open)	226 to 337	281
		118	Week 52 (open)	338 to 370	365
		119	Week 53 (open)	>370	372

[a] Day 1 is the day of the first dose in open-label study.

Table 10.6 series. Phase I Dose Group Classifications for the Phase I Safety Dataset Selected by the Sponsor for Presenting Data Described in the Summary of Clinical Safety section of the Submission and is Summarized in Section 7 of this Review

To make the diverse Phase 1/2a treatments comparable, they were classified in 6 treatment groups as indicated in Tables 3 and 4. All results will be summarized by these groups, unless specified otherwise. The 6 treatment groups, in order of their appearance in all summaries, are:

a. Placebo: all placebo treatments.

b. Pali IR: all Immediate Release treatments, including IV injection, oral solutions with C14 label, (+) and (-) enantiomers, oral solutions and tablets with racematic mixtures.

c. Pali other: all experimental formulations with doses between 2 and 6 mg paliperidone, including the osmotic modules, the paliperidone flat and ascending profiles, the coated OROS in R076477-P01-101, the [redacted] OROS in ALZA C-2002-034 and all [redacted] formulations.

d. Pali OROS low dose: all 3 to 6 mg doses with OROS formulations, including 2 mg tablets ([redacted] OROS or Phase 1 formulation), and 3 and 6 mg ER OROS paliperidone.

e. Pali OROS high dose: all 9 to 15 mg doses using Phase 1 (2 mg tablets), Phase 3 [redacted] OROS formulations and a first day of placebo in a one week paliperidone group in the R076477-SCH-101 study, followed by 12 mg paliperidone OROS (as in the original clinical study report).

f. Risperidone: all 2 to 8 mg oral risperidone treatments, including risperidone ascending profiles, osmotic modules, oral solutions and IR tablets.

Table 10.6 series, continued. Dose Group Classifications for the Phase I Safety Dataset ..., continued.

Per summary, there will be 3 tables for the pooled phase 1/2a analyses, excluding overall totals, unless otherwise specified:

- Healthy young subjects, excluding ER OROS treatments, but including columns: (a), (b), (c), sum of (b) and (c), (f).
- Healthy young subjects receiving ER OROS paliperidone, with the columns: (d), (e), sum of (d) and (e).
- Subjects with schizophrenia with the columns: (b), (e) and (f).

Table 3: Pooled Phase 1 Studies in Healthy Young Subjects

Protocol Number	Study Treatment Label	SCS Treatment Group
Alza C-2001-032	RIS 2mg OSM MOD	risperidone
	RIS 2mg OS	risperidone
	PAL 2mg OSM MOD	pali other
	PAL 2mg OS	pali IR
Alza C-2001-039	PAL 5.5mg ASCEND (3.5 ASC+2IR)	pali other
	PAL 4.5mg FLAT (2.5 FLAT+2IR)	pali other
	PAL 4mg IR(2*2mg)	pali IR
	PLACEBO	placebo
Alza C-2002-019	RIS 6mg ASCEND (4mg ASC+2IR)	risperidone
	PAL 6mg ASC-4 (4mg ASC+2IR)	pali other
	PAL 4mg ASC-2 (2mg ASC +2IR)	pali other
	RIS 4mg IR-2 (2*2mg IR)	risperidone
	PLACEBO	placebo
Alza C-2002-034	PAL 4mg [redacted] OROS Fasted	pali other
	PAL 4mg [redacted] OROS Fasted	pali OROS low dose
	PAL 4mg [redacted] OROS Fed	pali OROS low dose
	PAL 2mg IR Fasted	pali IR low dose
Alza C-2003-044	PAL 6mg OROS	pali OROS low dose
	PAL 9mg OROS	pali OROS high dose
	PAL 12mg OROS	pali OROS high dose
	PAL 15mg OROS	pali OROS high dose
Alza C-2004-006	PAL 12mg OROS Fasted	pali OROS high dose
	PAL 15mg OROS Fasted	pali OROS high dose
	PAL 15mg OROS Fasted	pali OROS high dose
	PAL 15mg OROS Fed	pali OROS high dose
R076477-BEL-1	PAL 0.5mg OS Fasted	pali IR
	PAL 0.5mg TAB Fasted	pali IR
	PAL 0.5mg TAB Fed	pali IR
R076477-P01-101	PAL 2.5mg [redacted] Fasted	pali other
	PAL 2.5mg [redacted] Fed	pali other
	PAL 4mg coated OROS Fasted	pali other
	PAL 4mg coated OROS Fed	pali other
	PAL 2mg OS Fasted	pali IR
R076477-P01-102	PAL 2.5mg [redacted]-1 Fasted	pali other
	PAL 2.5mg [redacted]-1 Fed	pali other

Table 10.6 series, continued. Dose Group Classifications for the Phase I Safety Dataset ..., continued.

Protocol Number	Study Treatment Label	SCS Treatment Group
	PAL 2.5mg [redacted] -2 Fasted	pali other
	PAL 2.5mg [redacted] -2 Fed	pali other
	PAL 2mg OS Fasted	pali IR
R076477-P01-103	PAL 1mg C14 OS	pali IR
R076477-P01-1006	PAL 3mg OROS, Fasted in Jap.	Pali OROS low dose
	PAL 3mg OROS, Fed in Jap.	Pali OROS low dose
R076477-P01-1007	PAL 1mg OS	pali IR
	PAL 3mg OROS	pali OROS low dose
	PAL 1mg IV	pali IR
	PAL(+) 1mg OS	pali IR
	PAL(-) 1mg OS	pali IR
R076477-P01-1008	PAL 15mg OROS Phase 3, fasted	pali OROS high dose
	PAL 15mg OROS [redacted], fasted	pali OROS high dose
	PAL 15mg OROS [redacted] fed	pali OROS high dose
R076477-P01-1010	PAL 3mg OROS	pali OROS low dose
	PAL 6mg OROS	pali OROS low dose
	PAL 9mg OROS	pali OROS high dose
	PAL 12mg OROS	pali OROS high dose
	PAL 15mg OROS	pali OROS high dose
R076477-SIV-101	PAL 6mg OROS	pali OROS low dose
R076477-SWE-1	PAL 1mg	pali IR
RIS-BEL-28	RIS IR 1mg	risperidone
	PAL IR 1mg	pali IR
	PLACEBO	placebo

Table 4: Pooled Phase 1/2a Studies in Subjects with Schizophrenia

Protocol Number	Study Treatment Label	SCS Treatm. Group
R076477-INT-1	PAL 1mg TAB	pali IR
	PAL 2-4mg TAB	pali IR
	PAL 2-8mg TAB	pali IR
R076477-SCH-101	PLAC/PAL 12mg OROS	pali OROS high dose
	PAL 12mg OROS	pali OROS high dose
	RIS IR 2-4mg	risperidone
R076477-SCH-102	PAL 9-15mg OROS	pali OROS high dose
	RIS IR 1-8mg	risperidone

ATTACHMENTS

Appears This Way
On Original

Attachment 1. Questions to the Sponsor (refer to DFS).

Questions Conveyed to the Sponsor
(a response to Question 1 was e-mailed, pending submission under the NDA) and
Outstanding Questions
(responses to Question 2-4 are pending at the time of this writing)

-----Original Message-----
From: Brugge, Karen [mailto:karen.brugge@fda.hhs.gov]
Sent: Wednesday, June 28, 2006 10:46 AM
To: Martynowicz, Jadwiga [PRDUS]
Cc: sochalsk@prdus.jnj.com; Khin, Ni Aye; Kiedrow, Keith
Subject: RE: Outstanding SCH-1009 Qs & Miscellaneous

Hi Heddie,

Thanks for your responses and we look forward to your response to the syncope-related Q.

This e-mail is a follow-up to your last response regarding SCH-1009 (see Q1 below), 2 new questions that we were hoping you could help us with (see Q 2 and 3), and examples of dropouts that we said we would be sending you (Q 4). Q 5 below is related to our examples of dropouts but is regarding subject 100057 who had adverse events ("muscle stiffness over the entire body" and other AEs during treatment that were followed by a serious adverse event (SAE) of neuroleptic malignant syndrome within days of treatment cessation that was not captured in the SAE database. Thanks for your assistance on getting the answers to our questions.

1. We received the most recent response about Study -1009-related Qs (forwarded with this e-mail). Just to be sure we don't miss anything, it looks like there is only 1 outstanding Q on this study which is the following about gender (we recently discussed this outstanding Q with you and I then sent you a follow-up e-mail from which I've copied key sections below for your convenience).

The raw mean QT and QTc values (for each method except for Bazett's) of each treatment condition by gender over time (similar to how results are presented in Tables 108 and 109 in the CSR but with groups subdivided by gender and including results of all treatment conditions in both tables). Would you provide these results? It would also be helpful to do the same using the least square mean results for QTcLD based on the analyses that was conducted in reply to our inquiry. Would you also conduct a similar analyses with least square mean results for QTcF and provide the results?

2. We would like to verify if all Phase III trials (-303, -304, -305, -302 and open label trials -702, -703, -704 and -705) used the [redacted]' formulation. If not please clarify.

3. Would you send us more information about the following subjects that would be helpful regarding potential etiologies of these events?

a) Subject 300541 was described in the Clinical Study Report for Study -304 section of the submission as having "pauses" on holter monitor after presenting with syncope, hypotension and bradycardia. Please provide more complete information on this subject (include a

description of the actual syncope that occurred and other relevant information that may help to determine the etiology).

b) A safety alert report submission N182 under IND 65850 for oral ER tablets (OROS) dated 4/3/06 was adescription of a sudden death (after at least 3 months of 12 mg Pal daily in the OL study -701, and was receiving trihexyphenidyl, 2 mg given as needed) in a healthy 24 year old female (subject [redacted]). Please provide more complete information on this subject (include relevant information that may help to determine the etiology). Please also provide a hospital report (e.g. discharge summary) on this subject who died in transit to another hospital and any autopsy report (if one was performed). We are also wondering why this subject was prescribed trihexyphenidyl (e.g. "as needed" for what)?

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

a) Subject 503018 in Study -305 in the original NDA submission was withdrawn due to noncompliance" after 4 days of stopping the study drug (drug stopped on Day 20 and withdrew "due to noncompliance" on Day 24) who had abnormal LFTs on Day 15 and "onward" (elevations of up to approximately 5 times the ULN, first observed on Day 15). Values normalized on Day 29 (9 days post-treatment cessation). This subject was found in the narrative section of subjects but was not checked off in the narrative summary table (preceding the narratives) as having either an SAE or as "premature discontinued." This subject cannot be found in line listings of SAEs or ADOs. The narrative indicates that the elevations in LFTs were not reported as AEs. Please clarify and provide the rationale for how events of elevated LFTs were actually reported in subjects and clarify why the drug was stopped and why the subject was noncompliant.

b. Subject 201803 in Study -303 (33 year old male) had a serious adverse event of tachycardia with increased heart rate first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline values. His baseline supine and standing heart rate values (HR) were 72 and 76 bpm, respectively compared to supine and standing HRs of 106 bpm and 130 bpm, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days. Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days. The subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG HR of 73 bpm on that day. Why did this subject withdraw consent? This subject was also not checked off under the "premature discontinued" column in the narrative summary table (preceding the narratives) and could not found in the line listings for premature discontinuations in Appendix 2.7.4.3.8.2.1 in the original NDA (in the SCS).

c. Subject 100232 (an ADO due to prolonged QT) is described in the narrative (page 1790 of the SUR) as not being included in the "interim analyses." Please clarify this comment and if this pertains to how this subject was captured in the safety database (e.g. in enumerating ADOs in SUR summary tables or line listings).

d. Subject 300011 withdrew "due to lack of efficacy" and is described in the narrative of the N000 submission as follows:

The subject received paliperidone 12 mg/day; she was discharged from the inpatient hospitalization portion of this study on Day 12 (source: CIOMS). Her symptoms had significantly improved and she was eager to be discharged. At her outpatient therapy on Day 15, she reported that the voices had returned on Day 13 and that she wanted to kill herself (source: follow-up SAE reports). The serious adverse event schizophrenia (increase of symptoms of schizophrenia verbatim) was reported on Day 15; the serious adverse event suicidal ideation (suicide ideation-verbatim) was reported on Day 17 (source: SAE follow-up forms). She went to the emergency room after experiencing a return of hallucinations and wanting to "kill herself." She was admitted to an adult psychiatric unit (source: CIOMS). She took paliperidone 12 mg/day on Day 15 but admitted that there may have been times that she forgot to take the medication (source: SAE follow-up forms). Study medication was held on Day 16, given on Day 17 and then permanently stopped.

She is not checked off in the narrative summary table under "premature discontinued." Was this subject captured in the line listings and summary tables enumerating ADOs (e.g. in Table 34 of the SCS)? If not why and how is this subject different that other subjects with psychotic-related events that were captured in Table 34? Please clarify.

e) Subject 100057 also had AEs that he could not tolerate on the same day of having study medication stopped "permanently on Day 22 as the subject withdrew consent." Refer to the narrative on page 1815. The following are excerpts from the narrative (also see Item II below describing this subject as well):

The subject was discharged from the hospital portion of the study on Day 20. At the scheduled Day 22 visit, he reported side-effects that he "could not tolerate" (restlessness and inability to sleep) (source: CIOMS). Study medication was permanently stopped on Day 22 as the subject withdrew consent. Vital signs were within normal limits but slightly higher than at earlier readings (138/91 mmHg standing; 141/72 mmHg supine); temperature was 36.4 degrees. Laboratory analyses on Day 22 (end of study) revealed a creatine kinase (CK) of 2201 U/L (reference range: 18-198 U/L); all other laboratory values were reported within the normal range. At baseline (Day -2), the baseline creatine kinase value was 186 U/L. The serious adverse events "elevated CK" and "neuroleptic malignant syndrome (acute EPS side effects)" were reported on Day 24 and Day 25, respectively; the elevated CK was considered life threatening.

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

Q 5. Why is subject 100057 (an SAE during run-in phase of study -301 found in the narratives) not listed in line listings of SAEs for this study (Appendix 3.5.1) and does not appear to be included in the in-text summary tables of SAEs in the SUR (e.g. Table 31)?

We note a comment about the reason provided as a footnote in the narrative summary table (on page 1773 of the SUR) yet it is still confusing for the following reasons. The subject had SAE of neuroleptic

malignant syndrome reported only 2 days study after the drug was stopped, but was preceded by related AEs that included "muscle stiffness over the entire body" that the subject "could not tolerate" on Day 22. The subject withdrew consent on this same study visit (Day 22). Please clarify why this SAE was not captured in the database.

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

Questions Conveyed to the Sponsor (some responses were received by e-mail and are pending submission to the NDA at the time of this writing)

-----Original Message-----
From: Geter-Douglass, Beth [PRDUS]
Sent: Thursday, June 29, 2006 2:56 PM
To: Karen. Brugge (E-mail)
Cc: Ni. khin (E-mail); Ochalski, Stefan [PRDUS]; Martynowicz, Jadwiga [PRDUS]; Keith. Kiedrow (E-mail)
Subject: RE: Outstanding SCH-1009 Qs & Miscellaneous --EMAIL #1a of 2

Dear Dr. Brugge,

On behalf of Heddie Martynowicz who is on vacation this week, I am acknowledging receipt of your June 28 e-mail with additional questions regarding NDA 21-999.

I am also providing J&JPRD's response to the outstanding question "b" regarding SCH-1009 that was originally sent on June 21 and referred to below as Question #1. Responses to the new questions will be provided to you shortly.

Please find attached the following tables for question "b":

- tecg05b: equivalent for table 108 for each QTc parameter with raw means (descriptive statistics) by gender **Given that this file is too large to send with the others, I will send separately]**
- tecg06b: equivalent for table 109 for each QTc parameter with raw means (descriptive statistics) by gender[Geter-Douglass, Beth [PRDUS]] **Given that this file is too large to send with the others, I will send separately]**

In addition we have for completeness:

- tecg05a: table 108 for each QTc parameter (LSMeans) **[attached]**
- tecg06a: table 109 for each QTc parameter (LSMeans) **[attached]**

Lastly, the LS mean results by gender **[Given that this file is too large to send with the others, I will send separately]**

- tecg06c

Best Regards,
Beth

Beth Geter-Douglass, Ph.D.
Associate Director, Regulatory Affairs
J&J Pharmaceutical Research and Development
609-730-4409 (phone)
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609-369-0743 (cell)

Initial Set of Questions Sent to the Sponsor in May of 2006 (See Sponsor's Teleconference Meeting minutes on the following pages that followed this initial request)

We are moving along on the paliperidone review and we also recently received the safety update. We have run into a fairly time-consuming search problem that we were hoping you could help us with. In the original submission there is a line listing of patients with Deaths, Serious Adverse Events (SAE) and Discontinuations due to Adverse Events (DAE) that we found in an appendix to the Summary of Clinical Safety section (SCS). The listing does not provide page numbers or hyperlinks to the exact location for each subject. In-text sections of the SCS sometimes refers to subjects having potentially remarkable safety findings but often does not provide subject numbers and/or exact locations to narratives. Sometimes a hyperlink is provided but it generally goes to a summary table or listing (often a lengthy appendix to the SCS) in which we cannot find the subject number and/or exact location of a narrative of the specific subject in the hyperlinked section.

- So, for the open-label combined-trials safety-dataset, study 301, study 701, would it be possible for you to generate a list of the patients with Deaths, SAE, and DAE along with their verbatim and thesaurus term with a page number reference to the narrative (please make the listing comprehensive to include all deaths, SAEs, DAEs through the cut-off date used for the safety update report submission)?

We also are having trouble reconciling the cases described in the narrative text of the Safety summary with the cases in the datasets. It is common for the cases to be briefly described and enumerated, but there is no way for us to reconcile the descriptions with the actual cases. We are looking at liver effects and syncope and need some help.

- Drug effects on the liver is something that we always look closely at and we have a case that appears to be significant that we could not find described in in-text sections of the SCS (Subject 503018 in the 15 mg Pal group was a 44 year old male with no history or abnormal baseline values suggestive a pre-existing liver disorder who developed approximately 8 times the ULN of ALT and approximately 5 times the ULN of AST with about almost 4 times the ULN of GGT on Day 15 of Pal that resolved to normal values after 9 days (on Day 29) following Pal cessation on Day 20.)

  There are also several patients who had elevated LFTs at baseline and it is difficult to dissect those away from patients who had normal LFTs at baseline and elevations. Would you be able to provide a listing of patients who had normal ALT, AST and bilirubin at baseline who went on to have AST or ALT of >3x and >8X normal along with their bilirubin values when these elevations occurred?

- Syncope and potential pro-arrhythmic effects: Patient 300541 in study 304 is described as having sinus pauses of up to 8 seconds but a description of this subject could not be found in the pro-arrhythmic section of the SCS or in any other in-text section of the SCS.

Subject 201805 in Study -303 (a 33 year old male) had 12 mg daily Pal treatment discontinued on Day 7 who had an SAE of tachycardia that was first noted on Day 4 and reached a HR of 120 bpm supine (124 bpm standing) compared to 71 bpm (per ECG) at baseline (84 bpm supine at baseline). The subject also developed "hypotension" in which Day 4 BP was 100/65 mmHg, supine (115/75 standing) compared to 135/65 mmHg, supine at baseline and decreased further to 85/55 mmHg, supine, on Day 6 (80/50 standing). Supine BP of 115/80 mmHg and HR of 93 bpm on day 7. The tachycardia prolonged his hospitalization. Tachycardia was reported to resolve by 12 days and hypotension by 3 days without treatment. ALT was also reported to be "increased" during the study.

Subject 201803 in Study -303 (33 year old male) had a SAE of tachycardia with increased heart rate first noted on Day 7 of 6 mg daily of Pal treatment compared to baseline values while BP generally did not change from baseline vales. This subject was not described as having orthostatic hypotension (on page 146 of the CSR). His baseline supine and standing heart rates were 72 and 76 bpm, respectively compared to supine and standing heart rates of 106 and 130, respectively on Day 8 of treatment. Metoprolol treatment was started on Day 10 and given for 11 days. Tachycardia resolved by 14 days. Paliperidone treatment was over 21 days, then the subject withdrew from the study on Day 22 "due to consent withdrawn" with an ECG heart rate of 73 bpm on that day.

We are interested in a listing of patients that were asymptomatic at baseline but who went on to have syncope, symptomatic bradycardia or tachycardia or symptomatic hypotension. Would it be possible for you to make a listing of these patients (with whether they were SAE, DAE or both along with their verbatim and thesaurus term) and a page number reference to the narrative?

Follow-up Teleconference Minutes (Sponsor's Version) of a 5/15/06 Teleconference between the Sponsor and Team Leader Dr. Paul Andreason and Reviewer Dr. Karen Brugge (with some Responses in a N005 6/15/06 Submission)

-----Original Message-----
From: Martynowicz, Jadwiga [PRDUS] [mailto:JMartyn1@PRDUS.JNJ.com]
Sent: Monday, May 15, 2006 9:23 PM
To: Kiedrow, Keith
Subject: NDA 21-999: Summary of 15 May 2006 Teleconference

Dear Keith,

Thank you for arranging this teleconference. As promised, here is our summary of key outcomes from the meeting. Please share with Drs. Brugge and Andreason and let me know if there are any differences in understanding.

Attendees from FDA: Paul Andreason, MD; Karen Brugge, MD; Keith Kiedrow, PharmD.

Attendees from J&JPRD: Peter Briscoe, MD; Denise Brown; Jackie Brown; Linda Carter; William Clayton; Joseph Donato, Beth Geter-Douglass, PhD, Michelle Kramer, MD, Pilar Lim, PhD; Heddie Martynowicz, MS; Anna Mendlin, PhD; Wayne Napoliello, Paul Sokol.

* We agreed that FDA Medical Reviewers may contact J&JPRD at anytime with further questions resulting from their ongoing review of the NDA. The primary contact will be Heddie Martynowicz. Contact information for Heddie is provided below:

Tel: 609-730-7028
Cell: 609-509-1043
Fax: 609-730-3091
Email: jmartyn1@prdus.jnj.com

* J&JPRD will update and combine the tables currently provided in front of the narrative sections of the 4-month Safety Update to add the following information for each subject: verbatim and thesaurus terms and page numbers for each narrative included in the 4-month Safety Update through the cut-off date of November 1, 2005. The resulting comprehensive table will be organized as follows: R076477-SCH-R076477-301, R076477-SCH-701 and followed by pooled open-label trials (R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705).

* FDA clarified that the data displays requested below are needed to complete their standard safety assessment:
* An incidence table by treatment group will be provided for subjects in the double-blind studies that were included in the original NDA (R076477-SCH-303, R076477-SCH-304 and R076477- SCH-305) with ALT and/or AST values >3 times the upper limit of normal (who had normal AST, ALT and bilirubin values at baseline). A separate incidence table will be provided for the elderly study (R076477-SCH-302).
* A listing of subjects with ALT and/or AST values >8 times the

upper limit of normal (who had normal AST, ALT and bilirubin values at baseline) and existing narratives previously submitted to the NDA will be provided for all safety datasets including those submitted in the original NDA as well as those included in the 4-month Safety Update through the November 1, 2005 cutoff date.

* A listing of those subjects with syncope, symptomatic bradycardia, symptomatic tachycardia or symptomatic hypotension (asymptomatic at baseline) will be provided for all safety datasets including those submitted in the original NDA as well as those included in the 4-month Safety Update through the November 1, 2005 cutoff date. For those subjects with SAE's, deaths or discontinuations due to adverse events, existing narratives previously submitted to the NDA will be provided for ease of review. The methodology used for selecting subjects for this listing will be described.

* The above items will be provided to FDA as soon as each response becomes available and will be submitted as Review Aides. The timelines for providing FDA responses to these requests are in preparation.

* The same requests will be applied to the 7-month Safety Update. However, the information will be limited to only the new safety data available after the cutoff date of the 4-month Safety Update.

Thank you for a very informative and productive discussion. I am looking forward to working with you, Dr. Brugge and Dr. Andreason in addressing any further questions/requests and facilitating completion of FDA's review of this NDA. In addition, please note that J&JPRD is willing to assist in addressing questions as they arise from any of the other FDA Review Teams.

Best regards,

Heddie

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The Sponsor's Minutes of 5/23/06 Teleconference with Some Responses in a N005 6/15/06 and Submission

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Regulatory Affairs **Record of Contact**

EDMS-PSDB-5573941

Date of Contact: 23 May 2006 **Date of Report:** 25 May 2006

Health Authority/Division:
Center for Drug Evaluation and
Research/Division of Psychiatry Products

Product: R076477 (RWJ16232411) (paliperidone)
NDA No.: 21-999

Health Authority Contact:
Name: Keith Kiedrow, Ph.D.
Title: Project Manager

Prepared by:
Name: Heddie Martynowicz, MS
Title: Director, Regulatory Affairs

Health Authority Attendee(s):
Name: Paul Andreason, MD
Title: Psychopharmacology Team Leader

Name: Karen Brugge, MD
Title: Medical Reviewer

Company Attendee(s):
Name: Heddie Martynowicz, MS
Title: Director, Regulatory Affairs

Subject: QUESTIONS RECEIVED VIA TELEPHONE FROM DRS. ANDREASON AND BRUGGE ON 23 May 2006 REGARDING NDA 21-999 AND FOLLOW-UP E-MAIL FROM DR. BRUGGE

1. **Vital signs**: Study 1009: Did you collect vital signs at Tmax in this study? If no, do we have information from any other Ph 1 study (preferably with the to be marketed formulation) where we may have collected vital signs and EKGs at Tmax.

2. **Confounding factor analysis**: Study 1009: Looking for role of confounding variables, such as gender, concomitant medication or pre-existing cardiac condition. This info is not found in SCS. Also would like to see raw mean results presented in Table 109 in SCS.

3. **Logic for laboratory data displays in the SCS**: We provide in the SCS incidence of outliers for a variety of laboratory parameters. However, this list is not comprehensive. FDA wants to understand why we chose to present only those and not the other laboratory parameter in the SCS. Is it because there were no outliers in those parameters? If this is not the case where can they find the rest of the data?

4. **Suicidality**: SCS Section 2.1.6.1.1 provides a search of all terms that may be indicative of suicidality. FDA is having a hard time reconciling this list with cases included elsewhere. They want to understand what patients where excluded and why. They make references to cases described on p.109, 104, 96, 95 and specific references to patients from 304 study: 300397 and 300301. They don't understand why these cases should be excluded from list and dismissed, as terms are suggestive of suicidality. And they don't see info of any pre-existing suicidality at study entry.

5. **CPK**: We mention in the SCS that we have observed inconsistent elevations in CPK in our Ph 3 schizophrenia data. We also offer an explanation that this is indicative of the

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EDMS-PSDB-5573941

schizophrenia population (not due to extra pyramidal effects of the drug or other effect of the drug). However, when looking at the Ph 1 data, FDA notes that there are also elevations in healthy subjects and that the greatest increases in CPK occur in the paliperidone high dose group. FDA is looking at the SCS, which includes information from 17 pooled phase 1 studies. In this section, there are various subgroups within that data set, including placebo, low dose OROS, high dose OROS and other. FDA wants to understand why there are elevations in healthy subjects? They are looking for pooled information (a) descriptive statistical results and (b) incidence of outliers for these subgroups from the pooled data set. FDA is particularly interested in seeing results for the placebo group.

Follow-up e-mail from Dr. Brugge to Ms. Martynowicz on 23 May 2006:

I just found a few examples in which I cannot find results in summary tables on a clinical parameter for a given treatment condition (in this case it's the IR Paliperidone treatment condition) for the Phase I healthy subject (pooled) safety dataset. See appendix 2.7.4.3.1 as an example on page 3611 in which creatine kinase results are not shown for placebo treatment condition/group and also for some other treatment conditions/groups. Note that these groups have results for other parameters but not for all parameters. Look at page 3627 in Appendix 2.7.4.3.2 for another example where creatine kinase and other parameters are not shown for the "Pali IR" subgroup but results on some other parameters are shown.

A Question to Which a Response was Submitted (N007 6/27/06)

During the 15 May 2006 teleconference, the FDA requested the following information:

> Please provide a listing of subjects with symptomatic bradycardia, tachycardia, hypotension, orthostatic hypotension, and syncope (asymptomatic at baseline) for all safety datasets through November 1, 2005. For those subjects with serious adverse events, deaths, or discontinuations due to adverse events, it was agreed that existing narratives previously submitted to the NDA would be provided with the response to this request.

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

/s/

Karen Brugge
7/21/2006 07:43:58 PM
MEDICAL OFFICER

Ni Aye Khin
8/31/2006 02:59:57 PM
MEDICAL OFFICER
I agree that this NDA be considered approvable; see memo to file for additional comments.