Seizures in a few subjects (at least subjects 200986, 500108) are described in Section 7.1.3.3 I of this review. It is not clear if there are other subjects (e.g. there may be subjects with seizure but believed to have syncope for example, so that an accurate count is difficult to determine). Subjects with reported seizure or syncope are listed in SAE and ADO summary tables in this review and several subjects are described in Section 7.1.3.3. I, including one additional ***patient that had seizures prior to death*** *(subject [redacted] reported in a Safety Alert Report under the Pal OROS IND).*

Common AEs (5% in any group) in Phase III trials were generally similar for drugs in the drug class as described in Section 7.1.5 except for the incidence of 1°AV block which occurred in 4.4% at the highest dose-level (15 mg Pal) compared to 1.4% of placebo. See findings on PR prolongation below.

Potentially Unexpected Safety Signals Based on Safety Results of Phase III trials
Note that all mean changes discussed below are relative to baseline values unless otherwise specified.

Unexpected hemodynamic/cardiovascular or cardiac effects:
Dose-dependent QT prolongation effects *of Paliperidone. Such an effect is not described in Risperdal® labeling. However, there are other drugs in this drug-class with this effect.*

QTc group mean increases were observed in pal groups compared to placebo in the DB Phase III studies. These mean increases:

- *Did not appear to occur at all assessment time-points (primarily only observed on the days having more frequent post-dose assessments following daily administration).*
- *Appeared to occur near Tmax,*
- *Appeared to also be influenced by confounding variables (primarily based on results of Study SCH-1009 with supporting evidence from the Phase III trial results).*

The ***greatest group mean increases was a mean increase of 7.2 ±25 msec in QTraw*** *(median increase of 11.0 msec) at the 12 month assessment time-point in the subgroup with the longest continuous Pal exposure (in OL Phase III extension trials based on results in the 120-Day SUR in Section 7.2.9.1). Note the following:*

- *This subgroup was the group in the OL pal trials that was previously exposed to DB Pal in the 6-week lead-in Phase III trials that had over 6 months of continuous Pal treatment (DB and OL treatment).*
- *This subgroup also had the largest sample size at assessment time-points over the last 6-12 months of OL Pal treatment in the 1-year OL trials (as found in the 120-Day Safety Update Report).*

- *Since heart rate was not generally altered during chronic treatment (-2.9 to 0.1 bpm over the 6-12 months of treatment in this subgroup) these results (and those above) are based on QTraw mean changes.*
- *QTcLD mean change (which appears to be the sponsor's preferred method of correcting for QT values) was 3.2±14 msec at 12 months of OL Pal treatment in this subgroup.*
- *Other time-points during the last 6-12 months of OL pal treatment also showed group mean increases in QTraw and QTcLD interval in this group that were generally found to be numerically greater than values at earlier OL time-points.*

QT mean appeared to be influenced by Cmax, Tmax and by confounding variables (based on results of Phase III trials and Study –SCH-1009).

Results on the incidence of outliers on QTcLD (results on QTraw outliers or scatterplots could generally not be found) also suggest the following:

- *A greater effect over chronic treatment in which the above DB Pal/OL Pal treatment group showed an incidence of 11% of 30-60 msec QTcLD interval shifts in the over 6 month exposure subgroup compared to 5% in the ≤ 6 month exposure subgroup. These results are limited by the absence of placebo group (as are the results on mean and median changes) but could be reflecting a real signal and warrant further exploration.*
- *2.5% of DB-Pal/OL-Pal subjects had QTcLD values of 450 msec or greater in OL trials (in the 120-Day SUR) and 1.9% of all DB Pal subjects of DB Phase III trials met this outlier criterion in QTcLD (1.4% of Placebo subjects exceeded 450 msec in DB trials). Fewer subjects had QTcLD values of over 480 msec.*

None of the subjects had a QT or QTcLD value of 500 msec or greater in DB and OL Phase III trials.

Several Pal subjects had QTc prolongation reported that generally also had other hemodynamic or related events that were sometimes SAEs or ADOs that included non-elderly and elderly subjects.

- *2 ADOs due to QTc prolongation (QTcB over 450 msec) on day 4 were reported in Pal subjects of the elderly Phase III trial (subjects 200514 and 200119) in which one of these subjects also had QTcF of over 500 msec (QTcB is likely to be misleading yet it is not clear what QTcF was in the other subject).*
- *A 65 year old female (200614) was reported to hae QTcLF and QTcF of 450-454 msec on Day 5 after a daily dose increase of Pal from 6 to 9 mg who also had a "mild ventricular arrhythmia." This subject completed the study without sequelea.*

Time-dependent effects on increasing supine heart rate that occurred in the absence of concurrent orthostatic vital sign changes and clinically remarkable subjects with this event that could be reflecting the influence of confounding variables including PK proporties:

- *Refer to drug class labeling and Olanzapine labeling for descriptions of tachycardia with the focus on tachycardia associated with orthostatic hypotension under Precautions.*
- *A group mean increase of up to 6.8±13 bpm was observed in the 15 mg Pal group compared to almost no change in mean heart rate (at supine) in the placebo group (smaller mean increases were observed in lower dose Pal groups) or in the 10 mg/day Olanzapine group in the short-term Phase III trials.*
- *Pal effects on vital signs appears to be strongly influenced not only by Cmax levels, but also to confounding variables that are time-dependent, as suggested by safety results from the Phase III trials (see Section 7).*

*2 **food effect Single-Dose Phase I studies (using either 12 mg or 15 mg Pal Phase III or [redacted] formulations) employed more frequent vital sign assessments** over a longer post-dose time period than was employed in Phase III trials that **revealed:***

- ***Food effects on PK and in turn on mean increase in systolic BP (13.5 mmHg in the fed [redacted] 15 mg Pal treatment condition at 36 hours post-dose)** that began at approximately 29 or 30 hours post-dose that was less prominent in the fasted conditions in both Phase I studies (in one study subjects were released from bed rest at 30 hours post-dose but the other study had an ambulatory condition that also showed this food effect on increased BP).*
- ***Group mean increase in heart rate to a similar extent in fasted and fed treatment conditions** was also observed that occurred near the same time as the increased BP. Other vital sign changes were observed in these trials.*
- *Refer to Section 7.1.12 C for additional safety findings and Section 7.1.3.3. E for clinically remarkable subjects.*

SAEs and ADOs involving supine tachycardia (without orthostatic hypotension found in the narrative) associated with other related events, such as ECG changes, symptoms such as dyspnea and/or other vital sign changes that were strongly suspicious of Pal induced events given the timing and nature of the events and the baseline status of the subjects. Example of these events are as follows (see Section 7.1.3.3 for additional observations):

- *Subject 200973 (a 28 year old male taking 6 mg Pal/day) reported as an ADO with SAEs who had sinus tachycardia, non-specific ST wave changes with dyspnea and increased blood pressure, reported.*
- *Subject 500603 was an 18 year old (in the 9 mg Pal group) who was an ADO with SAEs of similar events to those of the previously described subject.*

A potential small (clinically remarkable) group mean increase in supine systolic BP (sBP)** also appeared to be observed **in the 15 mg Pal group (4±12.9 mmHg)** that was **not observed in lower dose Pal groups or in the placebo group in Phase III trials.
Some clinically remarkable Pal subjects had various hemodynamic changes that sometimes included increased blood pressure:

- *Subject 100201 had a history of hypertension that appeared to be well controlled by an antihypertensive agent prior to Pal treatment. This subject appeared to show an exacerbation of hypertension during Pal treatment (requiring the addition of*

antihypertensive drugs and increases in the dose) that led to an ADO (due to high blood pressure).

- *Subject 200601: a 30 year old male who developed a systolic blood pressure of approximately 170 mmHg during the first 7 days of Pal treatment when vital sign effects appear to be the greatest (he had a past history of hypertension but was not taking antihypertensives and appeared to have normal vital signs at baseline).*

Potentially greater vital sign changes in subjects receiving over 6 months of treatment compared to subjects receiving less than 6 moths of treatment in OL Pal Extension Trials, *as follows (based on the incidence of outliers for each of the following parameters, as found in the 120-Day SUR):*

- *Decreased supine systolic BP (4-5% incidence in > 6 month exposure subgroups compared to 0-1% incidence in ≤ 6 month exposure subgroups in the OL Pal long-term trials).*
- *Increased supine heart rate of generally over 10% in > 6 month exposure subgroups compared to 0-4% incidence in ≤ 6 month exposure subgroups,*
- *Increased standing systolic BP may also show this pattern but exposure subgroup differences were small.*

The above observations are limited by the absence of a placebo group. Also, subjects that are monitored longer and more frequently have a greater chance of meeting outlier criteria. Yet, the incidence of outliers in the opposite direction (e.g. for increased supine systolic BP, decreased supine heart rate) did not show this pattern for more outliers in the > 6 month exposure subgroup and the incidence was generally smaller than was observed in the above outlier categories. Consequently, the findings suggest a real effect over time.

Sinus pause, hypotension and bradycardia *were observed in Subject 300541 and sudden death in subject [redacted] (reported in a safety alert report under the IND for this drug). Approved labeling for olanzapine describes 3 normal volunteers in Phase I trials who had hypotension, bradycardia and sinus pauses following either oral olanzapine (in 1 case) or intramuscular olanzapine (in 2 cases).*

Episodes of hypotension and widely fluctuating BP occurred in a elderly subject *(200302)* ***who also developed NSST wave changes (first noted on Day 4)*** *who was hypertensive at baseline (the subjects was in the elderly Phase III trial receiving 9 mg Pal daily) who developed unstable angina and was an SAE and ADO due to "acute coronary syndrome." While this subject was likely to have pre-existing coronary disease the timing and nature of the vital sign related events are suspicious of being Pal related (at least partly related). Note the greater incidence of AEs of hypotension and AEs of hypertension in the elderly Phase III study, as shown below which was greater in Pal compared to placebo subjects.*

PR prolongation *was observed in Phase III trials but was not clinically remarkable in the magnitude of this effect. The largest group mean increase (from baseline) was 4.3 msec was at the highest dose-level (in the 15 mg Pal group) on Day 8 of DB treatment compared to -0.1 to 1.7 mean change at previous time-points and compared 0.5 to -1.9 mean changes in the placebo group during the DB phase in short-term Phase III trials. The 15 mg group was the only one to*

have a dose increase which occurred on Day 8 (from 12 mg daily to 15 mg daily). Therefore, these observations could be reflecting an effect of increasing the dose, in additional to an effect of dose-level. This drug effect is a noteworthy finding given the following related observations, suggesting a similar drug effect in other subjects and studies:

- ***Events in subject 300541 (12 mg Pal group)** described below of **hypotension, bradycardia (38 and 40 bpm at standing and supine), dizziness and possibly syncope, and multiple "pauses" of up to 8 seconds** found by holter monitoring) that also appeared to have an underlying cardiac disease (detected by ECG findings).*
- *1° AV-Block reported in 4.4% of 15 mg pal subjects compared to 1.4% placebo subjects in the short-term Phase III trial dataset,*
- *3% of Pal (2/76 subjects) and 0% of Placebo (0/38 subjects) in the small elderly Phase III study -302 (using flexible dose design of 3-12 mg daily).*

***Small, clinically unremarkable Pal group mean decreases in platelet count, hemoglobin, and reticulocyte count** (see above item 10 for an outline of results on decreased platelet and Section 7.1.7 of this review). The large variance (e.g. between subject and within subject over time) on platelet count can potentially be a limitation in detecting a potential drug effect in the clinical trials (as is the case with CPK levels described below).*

Clinically Remarkable Subjects with Elevations in LFTs (and in some cases elevations of CPK also occurred that were sometimes associated with elevations in GGT).

***Inconsistent Elevations of CPK were observed in Phase III trials** (across treatment groups, sometimes also observed in the placebo group, with dramatic fluctuations over time within a given subject). This observation could be due to non-drug-related reasons, since elevated CPK is not uncommon in the schizophrenia population, as the sponsor concludes (e.g. acute patients can be highly agitated, hyperactive, be receiving multiple IM injections, among other potential factors). The sponsor also concludes that individual elevations in CPK were generally not due to AEs (e.g. extrapyramidal symptoms). However, results of data analyses to support this conclusion could not be found in the SCS of the submission or in CSRs. Furthermore, when baseline values vary across subjects, groups and over time (as observed in the Phase III trials) it can be difficult to detect a potential drug effect on the given parameter. Morever, **Phase I trials of healthy subjects (who were not psychiatric patients) also revealed a greater group mean increase in CPK in high-dose OROS pal subjects (9 to 15 mg) than in the low dose OROS Pal subjects (3 to 6 mg).** Also CPK elevations were sometimes observed in subjects of Phase III and possibly Phase I trials with elevations with LFT in which other etiologies of CPK elevations could not be found in the narrative, as described, below. Elevations were also observed in the OL Phase III trials after chronic treatment. It would appear that a patient population (e.g. indirect) effect on CPK would no longer account for CPK elevations after long-term treatment in a more stable population. Consequently, CPK results are difficult to interpret and require further explanation. A response to an inquiry about the findings in Phase I trials was recently received, late in the review cycle, such that the submission (N005) has not been fully reviewed at the time of this writing.*

The following incidence of AEs in the elderly Phase III trial (Study -302) that are notable (a 6-week, flexible dose, parallel group study using 3-13 mg/day of Pal compared to a placebo group):

- *Incidence of sinus tachycardia and tachycardia AEs were 0% in placebo (for each AE) compared to 5% of each AE in the Pal group.*
- *QT prolongation was reported in 7% of Pal subjects compared to 3% of placebo subjects.*
- *The following were observed in the elderly trial but not the sort-term Phase III trials that were primarily of non-elderly patients (the incidence of Pal and placebo groups are shown):*
    - *Hypertension (5%, 3%, respectively)*
    - *Hypotension (5%, 0%): one cannot assume that hypotension in these subjects was orthostatic hypotension.*
    - *1° AV block in 3% (2 out of 76 Pal subjects) compared to 0 placebo subjects (out of 38 subjects).*

Some additional potentially clinically remarkable subjects are described in Section 7.1.3.3 (subjections C and I) of this review. There is also a subsection on syncope describing additional subjects with syncope not described above.

Potential Formulation (OROS) Related Adverse Events
The sponsor does not report any events related to gastrointestinal obstruction with respect to potential OROS formulation-related AEs. However, the undersigned reviewer found one subject with duodenal rupture (subject 201333) and another with gastrointestinal hemorrhage (subject 501122) described in Section 7.1.3.3.Q of this review that had this event reported on Day 37 (in the 6 mg Pal group of one of the short-term Phase III trials) who required surgery. A past medical history or concomitant medications to explain this event could not be found in the narrative. Therefore, the role of the OROS formulation is suspected (in the absence of alternative explanations or clear risk factors in this subject).

7.1 Methods and Findings

The safety data from clinical trials is outlined below (trials are summarized in Section 4.2 of this review) which provided the safety results described in Section 7 of this review.

Safety results from the N000 submission are described in Section 7.1 of this review, while safety results provided in the Safety Update Report (SUR) are described in Section 7.2.9 of this review in accordance with the Clinical Review MAPP.

In summary, the majority of safety data in the N000 submission that is relevant to the sponsor's proposed indication and recommended daily dose-range (3-12 mg with a starting daily dose of 6 mg) as described in proposed labeling is the following. Safety data came from three 6-week Phase III Trials (Studies -303, -304 and -305 of almost entirely non-elderly subjects) provided the bulk of integrated safety over short-term 6-week exposure of Pal treatment in these placebo

controlled, DB trials. A small 6-week Phase III Trial of elderly subjects (-302) provided unpooled data (placebo controlled, DB study). Limited longterm safety data came from ongoing open-label (OL) trials (-702, -703, -704, -705) of which the data was pooled. Most subjects in these trials had 6 months or less of exposure. These results are described in Section 7.1 of this review.

The 120-Day SUR provided the majority of longterm safety data (integrated) that included up to 1 year of OL Pal exposure that waswithin the ICH guidelines. These results came from primarily the ongoing OL extension trials (-702, -703, -704, and -705, pooled data). Section 7.2.9 of this review provides the results from this pooled dataset.

Safety Data Provided in the Original N000 Submission

I. Short Term Phase III Safety Data:

Pooled data from 3 Pivotal 6-week Phase III Trials (Studies -303, -304, -305): the safety data from these DB, placebo controlled, fixed dose, trials of primarily non-elderly schizophrenia patients were pooled given the similarity in study design and study population. The daily dose-levels of Paliperidone that was examined in a parallel group design for each study were as follow: 6, 9 and 12 mg/day in Study -303, 6 and 12 mg/day in Study -304, and 3, 9 and 15 mg/day in Study -305 and each study had an active control group: 10 mg/day of Olanzapine.

See Section 4 and Section 6 for a summary of the study design in these trials. Note that the 15 mg group was started on 12 mg daily for one week before receiving 15 mg daily which was given for the remainder of the DB phase. Dosing was to occur in the morning. Subjects were not monitored with respect to timing or content of meals.

Data from 1 elderly Phase III schizophrenia, flexible dose (3-12 mg daily), 6-week, placebo controlled trial (Study -302): safety data from this study were analyzed as an individual study (unpooled).

Reviewer Comment: The main focus of the review was on the completed Phase III trials and the integrated longterm safety dataset provided from Phase III OL extension trials (below).

II. Limited and Blinded Safety Data from an Ongoing Phase III "prevention of recurrence" Trail (Study -301) and the Open-Label Extension Trial (Study -701)

Limited Blinded Data (only listings of deaths and SAEs) from 1 Ongoing Phase III "prevention of recurrence" trial (Study -301): this study has an 8-week OL-run-in phase, then a 6-week OL stabilization phase, followed by a placebo controlled, DB treatment phase (1:1 of placebo or Paliperidone treatment). Treatment was flexible during the OL run-in and DB treatment phases (3 to 15 mg daily) but was fixed during the OL stabilization phase (at the dose identified during the stabilization phase).

Since this study is ongoing and has a DB phase in which study drug remains blinded, a Clinical Study Report (CSR) was not provided in the submission and only listings of deaths and SAEs (but not ADOs) are provided (as of 8/31/05) in which only COMIS forms, instead of narratives are provided for reported SAEs between cut-off dates of 5/31/05 and 8/31/05.

As described below, this study was completed in time for safety data to be included in the Safety Update Report submission.

Limited and unpooled data is provided for an Ongoing Study -701, an OL Extension Trial to the "Prevention of Recurrence" Study -301. Study -301 was completed in time for safety data from this trial and from -701 to be included in Safety Update Report submission (as described below).

The sponsor was asked to clarify the rationale for the breakdown (subcategorization) of dose groups into "low" versus "high" dose groups and the following was their response (copied from their N001, 1/10/06 response submission):

> "While all the safety data is important, the lowest doses tested (ER OROS paliperidone ≤6 mg) were believed to provide more relevant safety information for the population of interest in the submission (patients with schizophrenia) than the higher doses, thus both groups were included, but a distinction was made between the two. The terms "low" and "high" have been selected to differentiate the lowest doses of the ER OROS paliperidone from the higher doses and should not be considered a reflection of their perceived clinical benefit."

III. Longterm Safety Data in 6-12 Month Open-Label Extension Trials in Which Most Subjects had 6 Months or Less Pal Exposure

Pooled data from 4 Ongoing Phase III OL Extension Studies -702, -703, -704, -705

Since these studies are ongoing CSRs are not provided. Safety results on clinical parameters and incidence of AEs (using data from the last assessment on or before the May 31, 2005 cut-off date) is provided for 2 subgroup of subjects, categorized on the basis of total duration of Pal treatment (includes duration of exposure in the given 6-week DB lead-in study combined with OL exposure during the given OL Extension trial):

- ≤ 3 month exposure subgroup and
- > 3 month exposure subgroup

Since the studies are ongoing CSRs are not provided.

See section 4 of this review for a summary of the trial design and treatment.

See Table series 10.6 in the appendix of this review for a more information on how dose-groups were pooled by the sponsor.

Reviewer Comment. *Clarification on methods for categorizing subjects into low and high dose groups (as above) and the rationale for this breakdown was provided upon request in a 1/11/06 N001 submission (see methods in Table series 10.6) and the following rationale was provided:*

> "Healthy volunteers are known to tolerate this class of drugs less well than patients with schizophrenia. While all the safety data is important, the lowest doses tested (ER OROS paliperidone ≤6 mg) were believed to provide more relevant safety information for the population of interest in the submission (patients with schizophrenia) than the higher doses, thus both groups were included, but a distinction was made between the two."

Results supporting the above conclusion could not be found the sponsor's response submission. It is generally believed that healthy volunteers are more vulnerable to some effects of the drug (e.g. risk for dystonic reactions), it is not clear to the undersigned reviewer that this applies to all adverse drug effects (e.g. QT prolongation). Furthermore, the schizophrenia population has greater morbidity and is reported to be at greater risk of mortality than the general population. Consequently, the risk for some adverse drug effects (e.g. weight gain, lipid profile effects, cardiovascular effects) or secondary effects (clinically remarkable complications secondary to primary drug effects such as a potential complication of ischemia or risk for ischemia, for example) could be greater in the schizophrenia population than in the generally population.

Pooled from 3 Phase I/IIa trials of schizophrenia patients. See Section 4 of this review for a description of these 3 Trials. These studies included at least 100 Pal treated subjects.

Unpooled data from 7 "Other Phase I/IIa trials." These studies were not pooled due to unique study designs that were employed, such as a special study population PK trials (e.g. patients with renal impairment), or examining drug-drug interactions, or a study designed to yield "supratherapeutic plasma levels" to examine cardiovascular safety in patients with schizophrenia or schizoaffective disorders (Study –SCH-1009). Since study -1009 was a focused clinical safety study Study –1009 the results of this study are summarized under subsection 7.1.12 of this review.

IV. 1-Year Longterm Safety Information for Phase III OL Pal Trials Provided in 120-Day Safety Update Report

Refer to a separate section of this review for a description of safety datasets in the 120-Day Safety Update Report, in accordance with the clinical review MAPP (Section 7.2.9). The majority of safety data reviewed in this

V. Narratives and CRFs in the N000 and in the 3/29/06 120-Day Safety Update Report Submissions:

The sponsor reports deaths, SAEs and ADOs using two cut-off dates, 5/31/2005 and 8/31/2005. Narratives and CRFs are provided for deaths (SAEs and ADOs) occurring by the former cut-off date, while Safety reports (CIOMS forms) are provided for deaths (SAEs and ADOs) that occurred from 6/10/05 through 8/31/05. CRFs are provided for each narrative of deaths, ADOs and SAEs of the completed Phase I-III trials and for ongoing OL extension trials (-702 through -705). Narratives and CRFs were provided for Studies -301 and OL extension trials, -701-705 studies in the 120-Day SUR.

The majority of the longterm safety data (exposures of up to 6 and 12 months within ICH guidelines) was provided in the 120-Day Safety Update Report Submission (SUR, letter date 3/29/06) provided the narratives and CRFs of deaths, SAEs and ADOs for the more recently "Prevention of Recurrence" trial, Study -301 and for open-label trials (Studies -701-705) using the cur-off date of 11/1/05 (narratives or narrative summary tables generally included hyperlinks to the CRFs). Safety (CIOMS) reports were provided for SAEs and ADOs at the cut-off-dates of 11/2/05-12/31/05.

VI. Other datasets or datasources:

Section 7 also provides safety information from the literature and postmarketing data on Risperdol® as provided in the sponsor's N000 submission.

In accordance with the Clinical Review MAPP Section 4 summarizes the study design and overall numbers of subjects for each trial outlined above, and Seciton 7.2 enumerates subjects by treatment and by treatment duration (also provides some information on disposition and number of completers). To avoid redundancy, this information is not repeated in this section.

VII. Subjects Included for Safety Analyses for each Safety Dataset.

It is important to note that safety data analyzed for a given safety dataset were from subjects that were in the ITT safety population (defined as subjects receiving at least one dose of study medication using an LOCF approach for a given clinical parameter when examining group mean change or treatment endpoint values for given parameter and using a 5/31/05 cut-off date).

VIII. Coding Systems for AEs.

MEDRA System: Results on SAEs, ADOs, deaths and AEs described in the SCS are using the MEDRA system and events are reported using the Dictionary Term, unless otherwise specified.

WHO System : This system was used in the CSRs of at least the pivotal Phase III trials that were reviewed.

Reviewer Comment on AE Categorization Systems. *It appears that the SCS adopted the MedRA system which was more recently deemed by the Agency as the more acceptable method AE categorization, to the knowledge of the undersigned.*

IX. Schedule of Safety Assessments.

This topic will be discussed in relevant subsections below. Also refer to the Study Schedules provided in the Table Series 10.1 in the appendix of this review. Subsections below described time-points for specific clinical parameters.

X. Time-Windows of Safety Assessments for Each Study Visit

Visit/assessment time-windows were provided in the 2.7.4 SCS module of the original submission starting on page 265 of the Statistical Analyses Plan section of the SCS. Since these time-windows are important for interpreting safety data, a copy of the sponsor's tables showing the time intervals for each visit for each study is provided in the Table Series 10.5 in the appendix of this review.

Reviewer Comment and Caveat. *It is not clear if the above time-window tables reflect true time-windows or were provided in the case that assessments varied to the extent shown in the tables.*

Actual assessment time-points were likely to vary widely and vary widely relative to dosing across subjects at least for time-points when patients were outpatients. Subjects in the short-term Phase III and OL Phase III trials were outpatients, except for at least the first two weeks of

DB treatment in the short-term Phase III trials. Subjects were required to be inpatients during the first 2 weeks of DB treatment in the short-term trials and were outpatients thereafter, unless it was clinically indicated to prolong hospitalization or readmit a given subject. However, on PK assessment days subjects were generally inpatients (e.g. when PK sampling was conducted over multiple time-points on a given treatment day).

XI. Miscellaneous Topics

Exposure. This topic no longer appears before the safety results but instead, appears in Section 7.2.1 which follows the safety results and is entitled "Description of Primary Clinical Data Sources (Populations Exposed and Extend of Exposure) Used to Evaluate Safety." This major change in organization is in accordance to the MAPP for this review.

Demographic Features. According the MAPP, this topic is no longer covered here, but instead is provided after the safety results subsections in Section 7.2.1.2, entitled "Demographics."

XII. An Important Note to the Reader on Subsections 7.1.2-7.1.9

The Summary of Clinical Safety section (SCS) of the NDA generally did not describe individual subjects with SAEs or who had AEs leading to cessation of treatment in the in-text sections on the serious adverse events and adverse dropouts and in sections on the incidence of potentially clinically significant outliers. However, descriptions of individual subjects were found in some of the safety sections of CSRs of each short-term Phase III trial or were found upon review by the undersigned review of selected narratives. Also refer to Section 7.2.8 of this review regarding potential concerns with capturing clinically remarkable subjects or events.

Subsections on SAEs, ADOs and AEs (sections 7.1.2-3 and 7.1.5) of this review focus on the the incidence of SAEs, ADOs and AEs, respectively. Section 7.1.3.3. focuses on potentially clinically remarkable subjects covering specific organ system topics (and includes some ADOs and SAEs). The sponsor conducted special search strategies for potentially remarkable events which is provided under Section 7.1.4 of this review. These subsections on potential clinically remarkable events is not considered a comprehensive overview of such events and of all subjects with these type of event for reasons described in Section 7.2.8 of this review. Subsections on clinical parameters focus on results on the incidence of outliers and descriptive statistical results (sections 7.1.7-9).

7.1.1 Deaths

The following deaths include newly reported deaths in the 120-day SUR submission. Section 7.2.9 of this review describes safety results provided in the SUR in accordance with the Clinical

- 2 completed suicides (1 of these deaths occurred between [redacted] after the 5/31/05 cut-off date, such that the CIOMS report was provided instead of the CRF in the N000 submission)
  - Subject 200416 in Study -703 died after an overdose of venlafaxine and lorazepam on Day 238 of treatment (Day 1 corresponds to Day 1 of the 6-week DB lead-in Study -303).
  - Subject 20156 in Study -703 completed suicide described in the SUR as a 41 year old female who completed suicide by falling from the 3rd floor.
- Subject 200214: Bronchopneumonia in a 70 year old male subject. This OL Pal treated subject is discussed in more detail below.

Reviewer Comment and Conclusions on Reported Deaths. *No deaths occurred in the 4 completed Phase III trials, a few deaths occurred in the "prevention relapse" Phase III trial (Study -3010 which is ongoing and in the OL extension trials. No deaths occurred in the Phase I/II trials. The deaths in Pal treated subjects were primarily related to suicidality (except 1 death was reported as bronchopneumonia). Completed suicide was reported in one placebo subject, noting that the sample size of Pal exposure far exceeds the total number of subjects exposed to placebo in these trials.*

Suicidality, including successful suicide or lethal attempts is not uncommon in this patient population. The completed suicides reported in trials, as above, could have been associated with in part, due to lack-of-efficacy of the blinded study drug (placebo or paliperidone) and/or to the underlying pre-existing condition. Suicidality is also believed by psychiatric professionals to be associated with improvement of symptoms in some patients, such as in a subject who develops more insight that they have schizophrenia which can occur in patients who improve with treatment and as they realize the serious, debilitating and chronic nature of their illness. Off-label treatment with antidepressant medications, as well as the addition of other therapeutic modalities are generally provided to the treatment regimen in such patients to target suicidality and related symptomatology, as well as addressing social factors. It is well known that patients with schizophrenia are at risk of suicidality which may increase as symptoms improve. It is also part of good clinical practices to monitor patients for suicidality and to treat patients accordingly. The sponsor also provides a special safety section on this topic that will be summarized under subsection 2.6.1.

Suicides were only reported in subjects in the longer-term, 6-12 month OL trials, including Study -301 which involved several months of treatment, but were not reported in any of the short-term trials that included placebo, Pal and other active treatment groups. Not only were subjects of the longer term trials (OL trials and study -301) followed over months of treatment in which more events are likely to occur, but also the sample size of subjects in these studies was large in which all of these subjects received OL Pal (except for a short DB phase in Study -301). In contrast to these longer term trials of OL Pal subjects, the sample size of placebo controlled subjects in the shorter-term trials Phase III studies (combined) is much smaller. Consequently it is not surprising that no suicides occurred in the small number of placebo subjects that were included in the short term trials. Both the sample size and the duration of the shorter-term DB

studies were probably insufficient to generate a baseline suicide signal that is known to exist in this patient population.

Finally, the only DB treated subject in DB placebo controlled trials that completed suicide was a placebo treated subject, as reported in a subsequent 120-day SUR submission (subject 100846 in the longer term, Study -301 which was a "prevention of recurrence" study that included a short phase of DB placebo controlled treatment).

One death of "gun shot wound" was also reported in a subject on blinded study drug (the "completed suicide" or other terms related to suicidality were not used as the reported term for this subject). If the gun shot wound were not related to suicidality but rather indirectly due to homicidality or agitation, then this event alone does not provide adequate evidence for a drug-related safety signal for homicidality and is the type of event that is not unexpected for the patient population (homicidality and agitation can commonly occur in patients with schizophrenia and can lead to violent behaviors in some patients). Also refer to Section 9 for additional comments and recommendations regarding suicidality. The sponsor also provides a special safety section on this topic (of agitation and of suicidality) that will be summarized under subsection 7.1.4 of this review. Additionally suicidality is discussed in other sections of this review (e.g. see Section 7.1.3.3 focusing on subjects with specific types of clinically significant adverse events which includes a topic on suicidality).

Death due to bronchopneumonia (as above) occurred in one subject. Since this is an isolated case among a large number of exposed subjects, this finding alone does not provide adequate basis for suspecting a drug-related signal. Furthermore, the clinical scenario was very complicated by this patient's extensive past medical history and concomitant medications suggesting that his death was due to pre-existing multiple conditions. Yet, a role of Pal is serious considered in this case because of Pal's cardiovascular effects including QT prolongation to which this patient was likely at greater risk in experiencing from both a PK perspective (may have had higher Cmax, AUC exposure secondary to other factors that may have altered PK), as well as from a PD perspective (likely to have greater vulnerability to adverse effects given his baseline condition). The narrative does not describe vital sign results on this subject but his risk for myocardial ischemia and reduced cardiac output may have been increased (the first reported AE during treatment was myocardial ischemia on Day 8) secondary to Pal effects on the cardiovascular system (e.g. tachycardia, blood pressure changes that are more likely to occur early in treatment). Although QT prolongation was not reported until Day 111 the timing of assessments relative to dosing and the frequency of assessments can impact on capturing potentially maximal QT prolongation effects. Therefore, it is difficult to determine if QT prolongation was drug-related or related to his underlying history of QT prolongation. This single complicated subject is not alone sufficient evidence that Pal is not adequately safe. However, this review does raise the issue of a potential role of Pal in subjects at risk for cardiovascular and cardiac-related events that is discussed further in other relevant sections.

Refer to Section 9 for further reviewer comment and recommendations.

Narrative description of Subject 200214 copied from the 210-Day SUR submission (with selected words bolded by the undersigned reviewer).

Subject 200214 (Study R076477-SCH-702) was a **70-year-old man** who completed **double-blind treatment with placebo** before entering **the open-label extension, where he received ER OROS paliperidone 6 mg/day for the first week and 9 mg/day for another 15 weeks.** This subject had a history of prolonged QTc, and **pretreatment QTcLD values up to 464 ms** upon entering the double-blind study. Other **relevant medical history** included **chronic bronchitis, hypertension, ischemic disease in leg, cholelithiasis, and paresis nerve peroneus.** The subject was a **current smoker with a 40-year history** of smoking.

At **open-label baseline prior to receiving ER OROS paliperidone, the ECG was suggestive of myocardial ischemia.** During the open-label extension, the subject had adverse events of **myocardial ischemia on Day 8 of the open-label study**, a fungal infection of the foot on Day 19 of open-label treatment, and osteoarthritis on Day 20 of open-label treatment; all of these events were persisting when study drug was discontinued. **Concomitant medications** included acetylsalicylic acid for ischemic heart disease, potassium carbonate and mycoseptin (itraconazole) for foot mycosis, piracetam for prevention of vascular dementia, pentoxifylline for vasodilation of peripheral blood vessels, allopurinol to prevent **hyperuricemia, felodipine for hypertension**, and nimesulide for hip arthiritis.

Two ECGs were performed on **Day 111** of open-label treatment (the last day of study drug intake), and both revealed prolonged QTcLD intervals (503 and 513 ms) (Appendix 7.2.10). **Study medication was discontinued because of this adverse event,** which the investigator considered of doubtful relationship to study drug. **The following day, the subject's QTcLD value was 478 ms.** A laboratory evaluation performed on Day 112 of open-label treatment showed normal values for relevant laboratory parameters, including potassium (4.8 mmol/L; normal range, 3.40 to 5.40 mmol/L).

The subject died of bronchopneumonia on [redacted] **4 days after receiving the last dose of study medication** (see Section 2.1.2).

The QTcLD prolongation in this subject with a history of cardiovascular disorder and QTc prolongation was observed after 111 days of treatment with ER OROS paliperidone. The QTcLD values decreased within 24 hours despite the fact that t_{max} would have been reached 1 day after the last drug intake, it is therefore unlikely that this event is causally related to paliperidone.

7.1.2 Other Serious Adverse Events

This section describes serious adverse events (SAEs) as of the August 31, 2005 cut-off date, as reported in the N000 submission.

SAEs and ADOs provided in the 120-Day SUR was the primary source of review for the long term safety data which comes from ongoing OL trials. However, other sections on clinical safety parameters provide results as provided in the original NDA with updated results from the 120-

Day SUR that were provided in Section 7.2.9 of this review (in accordance with the Clinical Reviewer MAPP). Note that ICH guidelines for 6 month exposure were met in the OL dataset provided in the original NDA while ICH guidelines for 12 month exposure was met in the updated OL dataset in the 120-day SUR reported. Study -301 was completed in time for inclusion of safety data from this SUR, as well. Therefore, refer to section 7.2.9 of this review for a complete and updated information on SAEs and ADOs for Study -301 (and the OL extension study -701), as well as for the longer term safety dataset from OL extension trials. Only summary tables of SAEs and ADOs of ongoing Phase III trials are provided in subsections 7.1.2 and 7.1.3, respectively.

Descriptions of selected subjects (based on narratives) is not described in this section of the review since more complete and updated information was provided in the SUR submission. Also selected subjects are described in section 7.1.3.3 in order to provide a more comprehensive presentation of clinically remarkable subjects.

Some Potential Caveats Specific to the Phase III DB Dataset
Note that the most studies were conducted in a confined study unit (e.g. in most Phase I studies) or patients were hospitalized for at least 14 days during the DB phase of the Phase III trials. Thus, SAEs reported during these periods of hospitalization may reflect an under-representation of SAEs in an outpatient population (SAEs that would otherwise result in hospitalization in an outpatient setting that may not be considered as SAEs in an inpatient setting). However, subjects were not required to be hospitalized after the initial 14-day period of the 8-week DB treatment phase of Phase III trials, unless it was clinically indicated. Furthermore, OL extension studies generally did not require hospitalization or confinement to a study unit. Finally, the overall number of paliperidone subjects was large in Phase III trials including trials involving 6-12 months duration (with 506 subject who had 6 months exposure as of the 5/31/05 cut-off date).

Also note that the 15 mg treatment group (employed in only 1 Phase III study) started subjects on 12 mg daily for one week before they received their assigned 15 mg daily dose-level for the remainder of the 6-week DB phase.

A Summary of Results on the Incidence of SAEs in Clinical Trials and Reviewer Comments and Conclusions
The following summarizes the sponsor's results (from the undersigned reviewer's perspective) based on the results found in the SCS sections on SAEs which focused on the incidence of events and as shown later in the subsection.

The incidence of SAEs for any given type of event (by Preferred Term category) ranged from 0% to 1% in treatment groups in each of the safety datasets of completed Phase I-III trials with few exceptions as follows:

- *Psychotic disorder (3 to 5%) and schizophrenia (3%) in paliperidone subjects of ongoing OL paliperidone non-placebo controlled extension trials. These SAEs occurred among 391 subjects who received 3 months or less of treatment and among*

776 subjects who received 3-12 months of treatment. The majority of these subjects received at least 6 months of treatment.

The incidence in placebo treated subjects on a given type of event (by Preferred Term category) in safety datasets of placebo controlled, parallel group, trials was similar to that of the paliperidone subjects. The SAEs that had an incidence that was numerically less that that of of the placebo subjects only showed a between-group differences of only 1or 2% (when comparing each Pal group to and placebo subjects).

The majority of SAEs (by Preferred Terms) in all Phase I-III trial safety datasets (includes ongoing trials) were either expected events given the study population or were expected given the known safety profile of Ris® (refer to approved labeling) and for the drug class (e.g. tachycardia associated with orthostatic hypotension, extrapyramidal system related AEs).

Psychotic-related SAEs are expected for the patient population. The incidence between placebo and pal groups and across dose-levels in the Phase III trials for these type of SAEs were similar (as shown in a summary table provided later in this section). It is also notable that psychotic related SAEs did not appear to be greater in the 3 mg Pal group (the lowest dose-level) than in the other Pal groups (at 6, 9, 12 and 15 mg) or compared to the placebo group. Refer to Section 6 for results and comments related to subject disposition and for the incidence of subjects who dropped out early due to lack of efficacy.

Several SAEs were isolated events (by Preferred Term). Generally, such isolated SAEs are not considered as adequate evidence for suspecting an new, unexpected, clinically remarkable drug effect on the basis of the given isolated case, alone (e.g. this applies to an isolated SAE which occurred in only 1 subject in a paliperidone group in a given safety dataset that was not observed in other paliperidone groups, or was also observed in placebo or olanzapine subjects, or occurred in a low dose paliperidone group and not at higher dose-levels in the fixed dose trials, combined).

There can be exceptions in which an isolated SAE may be highly suspicious of a drug effect on the basis of a given event that cannot be accounted for by other non-drug-related factors or on the basis of supporting evidence obtained elsewhere (e.g. based on other safety data described in this review, the potential for a similar safety signal suggested by similar events reported for related drugs, among other considerations). An effort was made by the undersigned reviewer to find such cases. Refer to section 7.1.3.3 of this review for a discussion of individual subjects that may fall under this category.

Refer to the final section of this review for further comments and recommendations.

The remainder of this subsection is to provide results of the incidence of SAEs in clinical safety datasets, as presented in the SCS which are the basis of conclusions and comments above.

Completed Phase III Trials -302, -303, -304 and -305.

The table below summarizes SAEs (dictionary term) in the 3 pivotal Phase III 6-week trials, as provided by the sponsor.

Table 31: Serious Adverse Events
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
Body System or Organ Class	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects with serious AE	23 (6)	7 (6)	15 (6)	13 (5)	14 (6)	6 (5)	55 (6)	22 (6)
Psychiatric disorders	18 (5)	6 (5)	9 (4)	10 (4)	7 (3)	5 (4)	37 (4)	18 (5)
Psychotic disorder	7 (2)	3 (2)	3 (1)	4 (2)	2 (1)	2 (2)	14 (1)	6 (2)
Schizophrenia	8 (2)	2 (2)	3 (1)	2 (1)	5 (2)	1 (1)	13 (1)	6 (2)
Agitation	0	0	4 (2)	2 (1)	1 (<1)	0	7 (1)	2 (1)
Suicidal ideation	1 (<1)	1 (1)	2 (1)	1 (<1)	1 (<1)	1 (1)	6 (1)	2 (1)
Aggression	1 (<1)	0	1 (<1)	0	2 (1)	0	3 (<1)	2 (1)
Acute psychosis	0	0	0	1 (<1)	0	0	1 (<1)	0
Anxiety	1 (<1)	0	0	0	0	1 (1)	1 (<1)	0
Depression	0	0	0	1 (<1)	0	0	1 (<1)	0
Hallucination, auditory	0	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Schizophrenia, paranoid type	0	0	1 (<1)	0	0	0	1 (<1)	0
Suicide attempt	1 (<1)	0	0	1 (<1)	0	0	1 (<1)	2 (1)
Hallucination	1 (<1)	0	0	0	0	0	0	0
Impaired self-care	0	0	0	0	0	0	0	1 (<1)
Sleep disorder	0	0	0	0	0	0	0	1 (<1)
Cardiac disorders	0	0	2 (1)	1 (<1)	3 (1)	0	6 (1)	2 (1)
Tachycardia	0	0	1 (<1)	1 (<1)	2 (1)	0	4 (<1)	1 (<1)
Bradycardia	0	0	0	0	1 (<1)	0	1 (<1)	0
Sinus tachycardia	0	0	1 (<1)	0	0	0	1 (<1)	0
Cardio-respiratory arrest	0	0	0	0	0	0	0	1 (<1)
Investigations	2 (1)	0	1 (<1)	0	2 (1)	2 (2)	5 (1)	1 (<1)
Blood creatine phosphokinase increased	0	0	1 (<1)	0	0	0	1 (<1)	0
Blood glucose increased	0	0	0	0	0	1 (1)	1 (<1)	0
Blood lactate dehydrogenase increased	0	0	1 (<1)	0	0	0	1 (<1)	0
Blood pressure increased	0	0	0	0	1 (<1)	0	1 (<1)	0
Electrocardiogram QT corrected interval prolonged	0	0	0	0	1 (<1)	0	1 (<1)	0

Table 31: Serious Adverse Events (continued)
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
Body System or Organ Class	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Investigations (continued)								
Heart rate irregular	0	0	0	0	1 (<1)	0	1 (<1)	0
Weight increased	0	0	0	0	0	1 (1)	1 (<1)	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	0	1 (<1)
Electrocardiogram T wave abnormal	1 (<1)	0	0	0	0	0	0	0
Liver function test abnormal	1 (<1)	0	0	0	0	0	0	0
Nervous system disorders	0	0	1 (<1)	0	3 (1)	1 (1)	5 (1)	0
Akathisia	0	0	0	0	0	1 (1)	1 (<1)	0
Convulsion	0	0	0	0	1 (<1)	0	1 (<1)	0
Dizziness	0	0	0	0	1 (<1)	0	1 (<1)	0
Dystonia	0	0	0	0	1 (<1)	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Gastrointestinal disorders	0	0	1 (<1)	1 (<1)	0	0	2 (<1)	0
Duodenal perforation	0	0	1 (<1)	0	0	0	1 (<1)	0
Gastrointestinal haemorrhage	0	0	0	1 (<1)	0	0	1 (<1)	0
Metabolism and nutrition disorders	1 (<1)	0	0	2 (1)	0	0	2 (<1)	1 (<1)
Diabetes mellitus	0	0	0	1 (<1)	0	0	1 (<1)	0
Hypoglycaemia	0	0	0	1 (<1)	0	0	1 (<1)	0
Water intoxication	0	0	0	1 (<1)	0	0	1 (<1)	0
Electrolyte imbalance	0	0	0	0	0	0	0	1 (<1)
Polydipsia	1 (<1)	0	0	0	0	0	0	0
Vascular disorders	0	0	0	1 (<1)	1 (<1)	0	2 (<1)	0
Hypotension	0	0	0	1 (<1)	1 (<1)	0	2 (<1)	0
General disorders and administration site conditions	0	1 (1)	0	0	0	0	1 (<1)	0
Drug ineffective	0	1 (1)	0	0	0	0	1 (<1)	0
Immune system disorders	0	0	1 (<1)	0	0	0	1 (<1)	0
Anaphylactic reaction	0	0	1 (<1)	0	0	0	1 (<1)	0
Infections and infestations	0	0	0	0	1 (<1)	0	1 (<1)	0
Cellulitis	0	0	0	0	1 (<1)	0	1 (<1)	0

Renal and urinary disorders	0	0	0	1 (<1)	0	0	1 (<1)	0
Renal failure acute	0	0	0	1 (<1)	0	0	1 (<1)	0
Renal impairment	0	0	0	1 (<1)	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	1 (<1)	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Chronic obstructive airways disease exacerbated	0	0	0	0	1 (<1)	0	1 (<1)	0
Aspiration	0	0	0	0	0	0	0	1 (<1)
Chronic obstructive pulmonary disease	1 (<1)	0	0	0	0	0	0	0
Social circumstances	0	0	1 (<1)	0	0	0	1 (<1)	0
Drug abuser	0	0	1 (<1)	0	0	0	1 (<1)	0
Injury, poisoning and procedural complications	1 (<1)	0	0	0	0	0	0	3 (1)
Drug toxicity	0	0	0	0	0	0	0	1 (<1)
Overdose	0	0	0	0	0	0	0	1 (<1)
Thermal burn	1 (<1)	0	0	0	0	0	0	0
Treatment noncompliance	0	0	0	0	0	0	0	1 (<1)

Cross-reference: Appendix 2.7.4.3.8.1.1.

Detailed Description of Selected SAEs

The following are descriptions of SAEs (some also were ADOs) that are not described elsewhere in this review but are of SAEs previously discussed as occurring in the Phase III trials. These descriptions are based on in-text information found in the CSRs of each of the 3 short-term Phase III trials. These SAEs are described under subheadings that correspond with those previously discussed.

Suicidality.

In study -304 Pal subjects 300306 and 300376 are described who abused cocaine with another substance (marijuana in one subject and alcohol in the other subject). One subject had a history of substance abuse. It is not clear from the description if the other subject had a history of substance abuse. These drugs are known to be associated with increased risk for suicidality and depressive symptoms. It is important to note that subjects were reported to have no history of suicidality. One of these 2 subjects (300306) also had a recent and significant stressor (death of a cousin) that occurred prior to his reported suicidal ideations. Suicidality resolved with "treatment." Both subjects had suicidal ideations but actual suicidal attempts are not described. It is likely that the suicidality in these subjects was related to the abuse or use of substances combined with other non-drug-related factors (stressors, underlying risk factors known to exist for this patient population).

Another subject (S300011) had suicidal ideation (suicidal attempt is not described), along with increased psychosis. Pal treatment was discontinued due to lack of efficacy. The subject's events resolved with "treatment." This subject, as well as the above subjects did not have a history of suicidality. The suicidality in S300011 is likely to be related to exacerbation of psychosis (due to lack of efficacy) and given that suicidality is common in this population.

See section 7.1.4.6 for a special search for suicidality related AEs conducted by the sponsor.

Elderly Phase III Study -302. Only 2 out of 76 Paliperidone subjects had SAEs in the elderly Phase III trial, Study -302 (3%; dictionary term of acute coronary syndrome in 1 subject and mania in another subject) in contrast to 8/38 placebo subjects (8%) in this trial (1 of these subjects had cardiac arrest reported

Ongoing Phase III Trial -301.
Study drug is still blinded in the ongoing placebo controlled Phase III "prevention of recurrence" Study -301 involving an 8-weeks OL-run-in phase, then a 6-week OL stabilization phase, followed by a DB treatment phase of variable duration in patients with schizophrenia.

This study was ultimately completed prior to the 120-Day SUR submission and unblinded safety results from this study were provided in the SUR. See section 7.2.9 for the incidence of SAEs and ADOs in treatment groups in this study.

Reviewer comment. *Study drug remains blinded such that the interpretation of results are difficult.*

The 2 most prominent signals are suicidality (including attempts and one completed suicide) and psychotic-related events. These events are not unexpected for the study population and were also observed in clinical trials of Risperidone (refer to approved labeling). However, the study drug assignment remains blinded so that actual incidence in actively treated subjects and a comparison to placebo treatment cannot be determined.

The subject with thrombocytopenia is described in Section 7.1.3.3. of this review.

The following summarizes reported SAEs as of the May 31, 2005 cut-off date among a total of 41 subjects with SAEs (see Section 7.2.9 for unblinded and updated information:

- 31 with psychotic related AEs (e.g. pscychotic disorder, worsening of schizophrenia, among others
- 4 suicide-related SAEs (one is a previously listed completed suicide under section 7.1.2, a suicide attempt, and suicidal ideation and an ADO reported as an SAE of a suicide attempt that was an overdose).
- 1 neuroleptic malignant syndrome SAE associated with increased creatine phosphokinase (CPK) of which "no additional information is available at this time."

- SAEs that resulted in ADOs (occurring in 1 subject each): overdose suicide attempt, as mentioned above, cholelithiasis, phlebothrombosis, thrombocytopenia and 1 subject that had SAEs of hypertensive crisis, non-cardiac chest pain and tachycardia.

The following summarizes reported SAEs between June 1, 2005 and August 31, 2005(only COMIS forms are provided for these subjects):

9 subjects with SAEs: 1 of whom died of completed suicide (see subsection on deaths) and the remaining 8 subjects had psychotic-related symptoms or conditions, that the sponsor indicated as being the result of an exacerbation of their underlying condition.

Ongoing Phase III Open Label Trials -701, -702, -703, -704, and -705.

Note the following: *Safety results from the OL extension trial dataset were provided for treatment subgroups by duration of exposure as follows:*

- *Treatment groups were subdivided on the basis of DB treatment assignment in the lead-in studies as follows: DB Placebo/OL Pal, DB Pal/OL Pal, DB olanzapine/OL Pal and total OL Pal subjects (which consists of all subjects independent of DB treatment assignment).*
- *Each of the above treatment groups were subdivided on the basis of duration of exposure as follows: into ≤ 3 month and > 3 month exposure subgroups in the N000 submission (and into ≤ 6 month and > 6 month subgroups in the 120-Day SUR as shown in Section 7.2.9 of this review).*

The following table summarizes results on SAEs in ongoing OL extension trials -702, -703, -704, and -705, as of the 5/31/05 cut-off date (while results of OL extension trial -701 are provided thereafter in this subsection). See section 7.2.9 for an updated incidence of SAEs and ADOs in treatment groups in these trials, combined.

Table 33: Serious Adverse Events Through 31 May 2005
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)

Total no. subjects with serious adverse events	15 (14)	8 (6)	19 (11)	48 (10)	20 (19)	22 (15)	54 (14)	78 (10)
Psychiatric disorders	11 (10)	6 (5)	14 (8)	41 (8)	18 (17)	18 (13)	43 (11)	65 (8)
Psychotic disorder	6 (6)	2 (2)	7 (4)	15 (3)	6 (6)	10 (7)	19 (5)	27 (3)
Schizophrenia	2 (2)	1 (1)	3 (2)	19 (4)	8 (8)	6 (4)	13 (3)	26 (3)
Depression	0	2 (2)	1 (1)	3 (1)	0	2 (1)	1 (<1)	7 (1)
Suicidal ideation	2 (2)	1 (1)	1 (1)	5 (1)	0	0	3 (1)	6 (1)
Agitation	2 (2)	0	1 (1)	4 (1)	7 (7)	0	10 (3)	4 (1)
Suicide attempt	1 (1)	1 (1)	0	2 (<1)	0	1 (1)	1 (<1)	4 (1)
Hallucination, auditory	0	0	0	2 (<1)	0	0	0	2 (<1)
Acute psychosis	0	0	0	1 (<1)	0	0	0	1 (<1)
Completed suicide	0	0	0	0	0	1 (1)	0	1 (<1)
Delusion	0	0	1 (1)	1 (<1)	0	0	1 (<1)	1 (<1)
Depressed mood	0	0	0	1 (<1)	0	0	0	1 (<1)
Insomnia	0	0	0	1 (<1)	2 (2)	0	2 (1)	1 (<1)
Paranoia	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Aggression	3 (2)	0	0	0	3 (3)	0	5 (1)	0
Confusional state	0	0	0	0	1 (1)	0	1 (<1)	0
Delusional disorder, persecutory type	0	0	1 (1)	0	0	0	1 (<1)	0
Disorientation	0	0	1 (1)	0	0	0	1 (<1)	0
Self-injurious ideation	0	0	0	0	1 (1)	0	1 (<1)	0
Infections and infestations	0	0	1 (1)	4 (1)	0	2 (1)	1 (<1)	6 (1)
Nasopharyngitis	0	0	0	2 (<1)	0	0	0	2 (<1)
Bronchitis acute	0	0	0	1 (<1)	0	0	0	1 (<1)
Pneumonia	0	0	0	0	0	1 (1)	0	1 (<1)
Pulmonary tuberculosis	0	0	0	0	0	1 (1)	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
Nervous system disorders	1 (1)	2 (2)	3 (2)	3 (1)	1 (1)	0	5 (1)	5 (1)
Dizziness	0	0	0	3 (1)	0	0	0	3 (<1)
Dystonia	0	1 (1)	0	0	0	0	0	1 (<1)
Ischaemic stroke	0	1 (1)	0	0	0	0	0	1 (<1)
Akathisia	0	0	0	0	1 (1)	0	1 (<1)	0
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

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.3.8.1.3.

Table 33: Serious Adverse Events Through 31 May 2005 (continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

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On Original

Injury, poisoning and procedural complications	1 (1)	1 (1)	1 (1)	2 (<1)	0	1 (1)	2 (1)	4 (1)
Fall	0	0	0	1 (<1)	0	0	0	1 (<1)
Intentional misuse	0	0	0	1 (<1)	0	0	0	1 (<1)
Overdose	0	0	0	0	0	1 (1)	0	1 (<1)
Road traffic accident	0	1 (1)	0	0	0	0	0	1 (<1)
Accidental overdose	0	0	1 (1)	0	0	0	1 (<1)	0
Alcohol poisoning	1 (1)	0	0	0	0	0	1 (<1)	0
General disorders and administration site conditions	0	0	0	3 (1)	1 (1)	0	1 (<1)	3 (<1)
Chills	0	0	0	1 (<1)	0	0	0	1 (<1)
Cyst	0	0	0	1 (<1)	0	0	0	1 (<1)
Pyrexia	0	0	0	1 (<1)	0	0	0	1 (<1)
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Investigations	0	0	0	2 (<1)	0	0	0	2 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	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)
Metabolism and nutrition disorders	0	0	1 (1)	1 (<1)	0	0	1 (<1)	1 (<1)
Diabetes mellitus	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	0	0	1 (1)	0	1 (<1)
Benign neoplasm of skin	0	0	0	0	0	1 (1)	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	0	0	1 (1)	0	0	1 (1)	1 (<1)	1 (<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)
Cardiac disorders	1 (1)	0	2 (1)	0	2 (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
Gastrointestinal disorders	1 (1)	0	0	0	0	0	1 (<1)	0
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Social circumstances	0	0	0	0	1 (1)	0	1 (<1)	0
Drug abuser	0	0	0	0	1 (1)	0	1 (<1)	0

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.3.8.1.3.

SAEs in the Ongoing OL Extension study -701 (as of 5/31/2005):
2 subjects receiving OL Paliperidone had psychotic related SAEs ("recurrence of schizophrenia" and "exacerbation of paranoid schizophrenia").

The following are additional SAEs between cut-off dates of [redacted] for all of the above OL extension trials -701 through -705 (only the CIOMS forms are provided by the sponsor for these more recent SAEs):

- 1 subject died who committed suicide (see previous section on deaths).
- 1 subject died of bronchopneumia (see previous section on deaths).
- Most of the remaining SAEs (27 subjects) were hosptitalizations due to pshchotic-related symptoms/conditions. Other SAEs were "unrelated medical conditions," and "less frequently, SAEs of "drug-related" events such as extrapyramidal symptoms and syncope.

Section 7.2.9 of this review provides updated safety information on SAEs and ADOs from the -701 trial.

Phase I/IIa Studies.
Reviewer Comment. *Few SAEs were reported among all Phase I/IIa trials and did not reveal any new or unexpected findings from that previously described in this review. 1 subject had myocardial infarction. Respiratory distress associated with extrapyramidal symptoms is not unexpected and is described in labeling.*

17 Healthy Subject Phase I/IIa Studies. No SAEs were reported among the 17 healthy subject Phase I/IIa studies (275 paliperidone treated subjects and 222 subjects treated with other formulations or medications in the ITT population of these trials combined).

3 Schizophrenia Phase I/IIa Trials. Only 3 subjects had SAEs (psychotic-related events, of which 1 subject was receiving risperidone treatment) in the 3 schizophrenia Phase I/IIa studies (out of 111 Paliperidone subjects, 34 immediate-release (IR) paliperidone subjects, and 55 risperidone subjects in the ITT population).

7 Other Phase I/IIa Trials. Reported SAEs were as follows:

3 IR paliperidone subjects: dystonia in 1 subject, extrapyramidal disorder and respiratory distress in another subject, and myocardial infarction in the third subject (the former two subjects had treatment discontinued). Subject numbers could not be found for these subjects.

A search for "respiratory distress" and "myocardial infarction" among the Phase I/II narratives in the appendix to the SCS revealed the following 2 narratives (coped from the submission):

Subject 109047 (extrapyramidal disorder, respiratory distress), a 46-year-old man with schizoaffective disorder, enrolled in the study with a

history of asthma, hypertension, anxiety, insomnia, and suicide attempt by drug overdose. Prestudy, the subject received quetiapine for the treatment of psychosis which was discontinued on Day -13 of the screening period. During the screening period, the subject received lorazepam for anxiety, paracetamol for headache, and zolpidem tartrate for insomnia. The subject was randomly assigned to the IR paliperidone treatment group. No adverse events were reported after administration of placebo on Day 1 or after administration of 4 mg IR paliperidone on Day 2. After administration of 6 mg IR paliperidone on Day 3, the subject experienced severe respiratory distress and extrapyramidal disorder involving a swollen tongue and neck spasms, both considered by the investigator to be of very likely relationship to study drug. Diphenhydramine hydrochloride 50 mg and benztropine mesylate 2 mg were administered for the treatment of the extrapyramidal disorder that resolved in 3 hours; oxygen was administered for respiratory distress, which resolved 1 hour later. The subject was taken to the emergency room as a precaution, but was not admitted in the hospital. The subject was discontinued from the study due to respiratory distress and the extrapyramidal disorder. The subject remained at the study hospital 3 days after discontinuation from the study for stabilization. These events were reported as serious.

7.1.3 Dropouts and Other Significant Adverse Events

Reviewer summary and comment. *Results on the incidence of the incidence of ADOs were generally similar to results of SAEs (see reviewer summary and comments under 7.1.2) with 0-1% incidence observed in Paliperidone and placebo groups (by Peferred Term categories) with a few exceptions described in paragraphs that follow. The majority of events were not unexpected and/or showed a similar incidence between placebo and paliperidone groups and did not show a clear or consistent dose-dependent effect, similar to that observed with SAEs. As observed with SAEs, a few isolated ADOs occurred in paliperidone subjects that do not provide a basis for suspecting an unexpected or new drug-related event on the basis of these observations alone (e.g. the Preferred Term ADO occurred in only 1 subject who was in a paliperidone group but was not observed in other paliperidone groups, or was also observed in placebo or olanzapine subjects, or occurred in a low dose paliperidone group and not at higher dose-levels in the fixed dose trials, combined).*

The short term efficacy trial of elderly subjects (Study -302) was an exception regarding the above observations. 3% of Paliperidone subjects were ADOs due to QT prolongation and an additional Paliperidone subject was an ADO due to acute coronary syndrome while none of the placebo subjects had any cardiac-related events leading to ADOs. However, the sample size was small (only needed 2 subjects to have an incidence of 3%).

Adverse Dropouts.
This section describes adverse dropouts (ADOs), otherwise referred to premature withdrawal from the study due to an AE (the sponsor used August 31, 2005 as the reporting cut-off date).

Reviewer Comment and Conclusions on ADOSs in Clinical Trials.
Group differences on the incidence of ADOs are generally not apparent, as the incidence in any given group is small. Nervous system disorder ADOs showed a slightly greater incidence in Pal subjects than placebo subjects but the difference is only by 1 to 2%, which could be due to chance alone given the number of dependent variables. Refer to Section 7.1.3.3 describing potentially clinically remarkable subjects.

Completed Phase III Trials -303, -303 and -305.
The table below summarizes ADOSs in the 3 pivotal Phase III 6-week trials, as provided by the sponsor.

Table 34: Adverse Events Leading to Study Discontinuation
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
Body System or Organ Class Dictionary-derived Term	Placebo (N=355) n (%)	3 mg (N=127) n (%)	6 mg (N=235) N (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=113) n (%)	Total (N=963) n (%)	10 mg (N=364) n (%)
Total no. subjects who discontinued due to AE	18 (5)	3 (2)	15 (6)	10 (4)	13 (5)	4 (4)	45 (5)	20 (5)
Nervous system disorders	0	1 (1)	3 (1)	4 (2)	6 (2)	1 (1)	15 (2)	4 (1)
Dizziness	0	0	0	1 (<1)	1 (<1)	1 (1)	3 (<1)	0
Akathisia	0	0	0	2 (1)	0	0	2 (<1)	0
Headache	0	0	0	1 (<1)	1 (<1)	0	2 (<1)	0
Sedation	0	0	1 (<1)	0	1 (<1)	0	2 (<1)	1 (<1)
Tremor	0	0	1 (<1)	1 (<1)	0	0	2 (<1)	0
Convulsion	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Dystonia	0	0	0	0	1 (<1)	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Memory impairment	0	0	0	1 (<1)	0	0	1 (<1)	0
Parkinsonism	0	0	0	0	1 (<1)	0	1 (<1)	0
Somnolence	0	0	0	1 (<1)	0	0	1 (<1)	2 (1)
Syncope	0	1 (1)	0	0	0	0	1 (<1)	0
Psychiatric disorders	9 (3)	0	5 (2)	3 (1)	3 (1)	1 (1)	12 (1)	7 (2)
Psychotic disorder	1 (<1)	0	1 (<1)	2 (1)	2 (1)	1 (1)	6 (1)	2 (1)
Agitation	4 (1)	0	1 (<1)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)
Anorgasmia	0	0	0	1 (<1)	0	0	1 (<1)	0
Impulsive behaviour	0	0	1 (<1)	0	0	0	1 (<1)	0
Schizophrenia	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Suicidal ideation	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0
Aggression	0	0	0	0	0	0	0	1 (<1)
Hostility	0	0	0	0	0	0	0	1 (<1)
Insomnia	2 (1)	0	0	0	0	0	0	1 (<1)
Psychomotor agitation	1 (<1)	0	0	0	0	0	0	0
Suicide attempt	0	0	0	0	0	0	0	1 (<1)

Investigations	3 (1)	2 (2)	2 (1)	1 (<1)	3 (1)	1 (1)	9 (1)	6 (2)
Electrocardiogram QT corrected interval prolonged	1 (<1)	0	1 (<1)	0	1 (<1)	0	2 (<1)	0
Hepatic enzyme increased	0	1 (1)	1 (<1)	0	0	0	2 (<1)	0
Alanine aminotransferase increased	0	0	0	1 (<1)	0	0	1 (<1)	3 (1)
Blood glucose increased	0	0	0	0	0	1 (1)	1 (<1)	0
Blood pressure increased	0	0	0	0	1 (<1)	0	1 (<1)	0
Electrocardiogram ST-T change	0	1 (1)	0	0	0	0	1 (<1)	0

Cross-reference: Appendix 2.7.4.3.8.2.1.

(continued)

Table 34: Adverse Events Leading to Study Discontinuation (continued)
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	Total	10 mg
Body System or Organ Class	(N=355)	(N=127)	(N=235)	(N=246)	(N=242)	(N=113)	(N=963)	(N=364)
Dictionary-derived Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Investigations (continued)								
Transaminases increased	0	0	0	0	1 (<1)	0	1 (<1)	0
Aspartate aminotransferase increased	0	0	0	0	0	0	0	3 (1)
Body temperature increased	1 (<1)	0	0	0	0	0	0	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	0	2 (1)
Hepatic enzyme abnormal	1 (<1)	0	0	0	0	0	0	0
Liver function test abnormal	0	0	0	0	0	0	0	1 (<1)
Gastrointestinal disorders	0	0	4 (2)	2 (1)	1 (<1)	0	7 (1)	0
Nausea	0	0	1 (<1)	1 (<1)	1 (<1)	0	3 (<1)	0
Abdominal pain upper	0	0	0	1 (<1)	0	0	1 (<1)	0
Dry mouth	0	0	1 (<1)	0	0	0	1 (<1)	0
Duodenal perforation	0	0	1 (<1)	0	0	0	1 (<1)	0
Vomiting	0	0	1 (<1)	0	0	0	1 (<1)	0

Cardiac disorders	2 (1)	0	2 (1)	2 (1)	2 (1)	0	6 (1)	2 (1)
Tachycardia	1 (<1)	0	0	1 (<1)	2 (1)	0	3 (<1)	1 (<1)
Sinus tachycardia	0	0	1 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Bundle branch block left	0	0	0	1 (<1)	0	0	1 (<1)	0
Palpitations	0	0	1 (<1)	0	0	0	1 (<1)	0
Bradycardia	1 (<1)	0	0	0	0	0	0	0
General disorders and administration site conditions	0	0	0	1 (<1)	0	1 (1)	2 (<1)	0
Asthenia	0	0	0	1 (<1)	0	0	1 (<1)	0
Feeling abnormal	0	0	0	0	0	1 (1)	1 (<1)	0
Vascular disorders	1 (<1)	1 (1)	0	1 (<1)	0	0	2 (<1)	0
Hypotension	0	1 (1)	0	0	0	0	1 (<1)	0
Ischaemia	0	0	0	1 (<1)	0	0	1 (<1)	0
Hypertension	1 (<1)	0	0	0	0	0	0	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
Immune system disorders	0	0	1 (<1)	0	0	0	1 (<1)	0
Anaphylactic reaction	0	0	1 (<1)	0	0	0	1 (<1)	0
Infections and infestations	0	0	1 (<1)	0	0	0	1 (<1)	0
Amoebic dysentery	0	0	1 (<1)	0	0	0	1 (<1)	0
Metabolism and nutrition disorders	1 (<1)	0	0	1 (<1)	0	0	1 (<1)	2 (1)
Water intoxication	0	0	0	1 (<1)	0	0	1 (<1)	0
Diabetes mellitus	0	0	0	0	0	0	0	1 (<1)
Electrolyte imbalance	0	0	0	0	0	0	0	1 (<1)
Hyponatraemia	1 (<1)	0	0	0	0	0	0	0
Polydipsia	1 (<1)	0	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	1 (1)	1 (<1)	0
Dysuria	0	0	0	0	0	1 (1)	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	1 (1)	1 (<1)	0
Dyspnoea	0	0	0	0	0	1 (1)	1 (<1)	0
Social circumstances	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0
Drug abuser	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0
Injury, poisoning and procedural complications	1 (<1)	0	0	0	0	0	0	1 (<1)
Overdose	0	0	0	0	0	0	0	1 (<1)
Thermal burn	1 (<1)	0	0	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	0	0	0	1 (<1)
Galactorrhoea	0	0	0	0	0	0	0	1 (<1)
Skin and subcutaneous tissue disorders	1 (<1)	0	0	0	0	0	0	0
Rash	1 (<1)	0	0	0	0	0	0	0

Cross-reference: Appendix 2.7.4.3.8.2.1.

A description of selected ADOs that were also SAEs in the short-term Phase III, completed trials (that were selected from in-text descriptions found in the CSRs) were covered in the previous section of this review on SAEs. The following are selected ADOs that were not SAEs that were revealed from a review of CSRs (in-text sections) in an effort to reveal potentially remarkable or new safety findings.

ADO associated with Elevated Liver Enzymes.

Elderly Phase III Study -302. The following table shows the incidence of ADOs in the elderly Study -302.

Table 35: Adverse Events Leading to Study Discontinuation (Study R076477-SCH-302)

Body System or Organ Class Dictionary-derived Term	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
Total no. subjects who discontinued due to AE	3 (8)	5 (7)
Infections and infestations	1 (3)	2 (3)
Bronchopneumonia	0	1 (1)
Pneumonia	1 (3)	1 (1)
Investigations	0	2 (3)
Electrocardiogram QT corrected interval prolonged	0	2 (3)
Cardiac disorders	0	1 (1)
Acute coronary syndrome	0	1 (1)
Respiratory, thoracic and mediastinal disorders	0	1 (1)
Hydrothorax	0	1 (1)
Gastrointestinal disorders	1 (3)	0
Diarrhoea	1 (3)	0
Nervous system disorders	1 (3)	0
Status epilepticus	1 (3)	0

Cross-reference: Appendix 2.7.4.3.8.2.1.

Reviewer comment. *3% of Paliperidone subjects were ADOs due to QT prolongation and an additional Paliperidone subject was an ADO due to acute coronary syndrome while none of the placebo subjects had any cardiac-related events leading to ADOs. However, the study is small and only 2 subjects yields a 3% incidence in Paliperidone subjects.*

Ongoing Phase III Trial -301.
Study drug is still blinded in the ongoing placebo controlled Phase III "prevention of recurrence" Study -301 involving an 8-weeks OL-run-in phase, then a 6-week OL stabilization phase, followed by a DB treatment phase of variable duration in patients with schizophrenia (among

This study was ultimately completed prior to the 120-Day SUR submission and unblinded safety results from this study were provided in the SUR. See section 7.2.9 for the incidence of SAEs and ADOs in treatment groups in this study.

Ongoing Phase III Open Label Trials -702, -703, -704, and -705.
The following table summarizes results of Studies -702 through -705 (as provided by the sponsor, as of their cut-off date for the N000 submission). Refer to Section 7.2.9 for updated information from these ongoing trials.

Table 36: 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 ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Total no. subjects with adverse events	7 (7)	3 (2)	15 (8)	23 (5)	17 (16)	4 (3)	39 (10)	30 (4)
Psychiatric disorders	3 (3)	2 (2)	8 (4)	17 (3)	9 (8)	4 (3)	20 (5)	23 (3)
Depression	0	0	0	4 (1)	0	2 (1)	0	6 (1)
Insomnia	0	0	0	3 (1)	2 (2)	1 (1)	2 (1)	4 (1)
Schizophrenia	0	0	0	3 (1)	3 (3)	1 (1)	3 (1)	4 (1)
Suicidal ideation	1 (1)	0	1 (1)	3 (1)	2 (2)	0	4 (1)	3 (<1)
Anxiety	0	1 (1)	0	0	1 (1)	1 (1)	1 (<1)	2 (<1)
Hallucination, auditory	0	0	0	2 (<1)	0	0	0	2 (<1)
Psychotic disorder	2 (2)	0	3 (2)	1 (<1)	3 (3)	1 (1)	8 (2)	2 (<1)
Suicide attempt	0	0	0	2 (<1)	0	0	0	2 (<1)
Acute psychosis	0	0	0	1 (<1)	0	0	0	1 (<1)
Depressed mood	0	0	0	0	0	1 (1)	0	1 (<1)
Homicidal ideation	0	0	0	1 (<1)	0	0	0	1 (<1)
Hostility	0	0	0	1 (<1)	0	0	0	1 (<1)
Paranoia	0	1 (1)	1 (1)	0	0	0	1 (<1)	1 (<1)
Aggression	0	0	0	0	1 (1)	0	1 (<1)	0
Agitation	0	0	2 (1)	0	2 (2)	0	4 (1)	0
Confusional state	0	0	2 (1)	0	0	0	2 (1)	0
Delusion	0	0	1 (1)	0	1 (1)	0	2 (1)	0
Disorientation	0	0	1 (1)	0	0	0	1 (<1)	0
Nervous system disorders	1 (1)	1 (1)	4 (2)	2 (<1)	2 (2)	1 (1)	7 (2)	4 (1)
Akathisia	0	0	1 (1)	1 (<1)	0	1 (1)	1 (<1)	2 (<1)
Dyskinesia	0	1 (1)	0	0	0	0	0	1 (<1)
Dystonia	0	0	0	1 (<1)	0	0	0	1 (<1)
Extrapyramidal disorder	0	0	1 (1)	0	0	1 (1)	1 (<1)	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
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	0	1 (1)	1 (1)	2 (<1)	2 (2)	0	3 (1)	3 (<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)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.3.8.2.2.

(continued)

Table 36: 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 ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Investigations (continued)								
Blood prolactin increased	0	1 (1)	0	0	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	0	0	0	1 (<1)	0	0	0	1 (<1)
Gamma-glutamyltransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Weight increased	0	1 (1)	0	0	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	0	2 (<1)	0	0	0	2 (<1)
Erectile dysfunction	0	0	0	2 (<1)	0	0	0	2 (<1)
Gastrointestinal disorders	1 (1)	0	0	1 (<1)	3 (3)	0	4 (1)	1 (<1)
Dysphagia	0	0	0	1 (<1)	0	0	0	1 (<1)
Constipation	0	0	0	0	1 (1)	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
Injury, poisoning and procedural complications	1 (1)	0	1 (1)	1 (<1)	0	0	2 (1)	1 (<1)
Intentional misuse	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (1)	0	0	0	1 (<1)	0
Self mutilation	1 (1)	0	0	0	0	0	1 (<1)	0
Musculoskeletal and connective tissue disorders	1 (1)	0	0	1 (<1)	2 (2)	0	3 (1)	1 (<1)
Muscle rigidity	0	0	0	1 (<1)	0	0	0	1 (<1)
Arthralgia	0	0	0	0	1 (1)	0	1 (<1)	0
Joint stiffness	1 (1)	0	0	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	0	1 (<1)	0	0	0	1 (<1)
Acne	0	0	0	1 (<1)	0	0	0	1 (<1)
Cardiac disorders	1 (1)	0	3 (2)	0	2 (2)	0	6 (2)	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
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	0	0	1 (1)	0	0	0	1 (<1)	0
Hepatitis A	0	0	1 (1)	0	0	0	1 (<1)	0
Metabolism and nutrition disorders	0	0	1 (1)	0	0	0	1 (<1)	0
Anorexia	0	0	1 (1)	0	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (1)	0	0	0	1 (<1)	0
Dyspnoea	0	0	1 (1)	0	0	0	1 (<1)	0
Social circumstances	0	0	1 (1)	0	1 (1)	0	2 (1)	0
Alcohol use	0	0	1 (1)	0	0	0	1 (<1)	0
Drug abuser	0	0	0	0	1 (1)	0	1 (<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

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Appendix 2.7.4.3.8.2.2.

Phase I/IIa Studies.

Reviewer Comment. *Refer to Section 7.1.3.3 for a description of potentially clinically remarkable subjects and section 7.2.12 for additional safety information from selected Phase I studies.*

17 Healthy Subject Phase I/IIa Studies. The following outlines the incidence of ADOs among the 17 healthy-subject Phase I/IIa studies (275 paliperidone treated subjects and 222 subjects treated with other formulations or medications in the ITT population of these trials combined).

- 9% of subjects receiving a "high dose" level which corresponds to 3 and 6 mg dose-levels (out of N=200 receiving the high dose level)
- 1% of subjects receiving the "low" dose, corresponding to 9, 12xx? and 15 mg dose-levels (N=152)
- 1% of subjects receiving single doses of other Paliperidone formulations
- 2% of risperidone treated subjects
- No placebo subjects

Dystonia (n=7), anxiety (n=2) and akathisia (n=2) were ADOs that occurred in more than 1 subject who received Paliperidone. Each event resulting in ADOs in subjects receiving other non-OROS paliperidone formulations did not occur in more than 1 subject.

Schizophrenia Phase I/IIa Trials. The following summarizes ADOs in the 3 schizophrenia Phase I/IIa studies (out of 111 Paliperidone subjects, 34 immediate-release (IR) paliperidone subjects, and 55 risperidone subjects in the ITT population) placebo subjects:

- 1 (3%) of IR paliperidone treated subjects was an ADO
- 4% of the Paliperidone high dose (OROS) treated subjects which included AEs of agitation, akathisia, psychotic disorder and hypertension that led to the ADOs in these subjects.
- 7% of risperidone treated subjects

The above high-dose paliperidone and risperidone ADOs occurred among 4 subjects.

7 Other Phase I/IIa Trials. Reported ADOs were as follows:

- A total of 18 subjects (5% out of 400 total subjects) were ADOs in the 7 trials.
- 14 out of the above 18 ADOs occurred in subjects receiving IR or ER OROS Paliperidone and were primarily due to nervous system disorder AEs (most commonly EPS).
- Each of the following AEs resulted in ADOs in 1 paliperidone treated subject (IR or ER OROS): ECG abnormality, T-wave abnormality, orthostatic hypotension, hypotension and postural dizziness.

7.1.3.1 Overall profile of dropouts

See previous section on adverse dropouts.

7.1.3.2 Adverse events associated with dropouts

This topic was previously discussed in sections on SAEs and ADOs.

7.1.3.3 Other significant adverse events

Reviewer Comments on Identifying Potentially Clinically Remarkable Subjects

A description of individual subjects (SAEs, ADOs, clinically remarkable AEs, clinically remarkable outliers on clinical parameters or other clinically remarkable observations in a given subject) could generally not be found in most in-text subsections of the SCS with a few exceptions. The SCS had a section focusing on special search strategies to identify AEs of interest of which results are summarized in Section 7.1.4 of this review. The sponsor's subsection on special search strategies in the SCS (Section 2.1.6) focused primarily on enumerating AEs of interest (to provide the incidence for each group). A discussion of potentially remarkable individual subjects in each special safety topic was generally limited and often did not provide subject numbers. It was difficult to reconcile the summary tables in these sections and summary tables on the incidence of SAEs, ADOs (in section that focused on SAEs and ADOs) with line listings and narratives found in the appendices of the SCS, since subject numbers to match these tables could not be found and the number of subjects was large (given the patient population that is known to have greater morbidity than the general population). A listing of at least ADOs and SAEs corresponding to summary tables could not be found. Sections of the SCS focusing on the incidence of outliers on clinical parameters often provided a few

statements on the number of ADOs and/or SAEs (but subject numbers could not be found) or a summary statement about potentially remarkable subjects (but subject numbers could not be found). Line listings of SAEs and ADOs could be found in appendices of the SCS and were helpful (were organized by study and treatment groups), listings to match the summary tables, but due to reasons above, it was difficult to reconcile these line listings with various in-text key safety sections in the SCS.

In addition to the above difficulties in identifying clinically remarkable subjects (e.g. in in-text sections of the SCS), additional concerns with capturing potentially clinically remarkable subjects is discussed in Section 7.2.8 in this review (on "Quality and Completeness of Data").

Most clinically remarkable subject described in this review were either found by review of CSRs (which generally only briefly described some subjects and did not always provide subject numbers) or upon review of line listings (of SAEs, ADOs for primarily completed Phase III trials and OL trials in the integrated longterm safety dataset) that were provided in appendices of SCS and narratives (of SAEs and ADOs). This was conducted as an effort to find clinically remarkable drug-related findings that were either unexpected due to the severe nature of a given event or in the type of event that occurred (e.g. refer to Section 7.1.2 describing several individual subjects).

An effort has been made to present individual subjects found not only in the original submission but in the 120-Day SUR submission line listings of SAEs and ADOs, as specified below.

A. Orthostatic Hypotension

Studies 303, 304 and 305 had no SAEs or ADOs of orthostatic hypotension. However, the following subjects are examples of clinically remarkable events associated with orthostatic hypotension that were found in various sections of CSRs of these studies and are noted below:

- *Subject 300541 in the 12 mg Pal group in Study -304 had SAEs of hypotension and other related events of **syncope, pauses on holter monitor and bradycardia.** This subject also had the AE of **orthostatic hypotension** as previously described in this subsection.*
- *Subject 200014 in the 6 mg Pal group of Study -303 had **"postural hypotension"** on Days 3 and 43 and met outlier criteria on Day 43. He had a **"sudden fall (accidental)"** on Day 17 leading to injury (a wound on the right arm). He was a 46 year old man with no prior meidal history or concomitant medications described in the description of this subject found on page 122 of the CSR.*
- *Subject 500102 in Study 305 (in the 9 mg Pal group) met outlier criteria for orthostatic hypotension **who withdrew early due to "dizziness, nausea, amnesia, headache and tachycardia".** Subject 50124 also is described under events of somnolence who also had tachycardia ("pulse=100-160 on minor activity") who **met outlier criteria for orthostatic hypotension** among other AEs (nausea, headache and amnesia).*
- *Subject 5000630 in the 9 mg Pal group of Study -305 was previously described as having AEs, but was not described as having SAEs or AEs leading to an ADO. Yet this subject was reported to have **syncope and episodes of tachycardia on Days 4 and 5 of treatment**, as*

*well as **episodes of orthostatic hypotension prior to and during DB treatment**, while also receiving concomitant lorazepam during the study.*

Also, subject 502318 in the 3 mg Pal group in Study -305 was found in an in-text section of the SCS on the topic of potential proarrhtyhmic AEs who had AEs of hypotension and syncope (Preferred term which was reported verbatim as "swoon") that led to an ADO on Day 3 but was not considered as SAEs. It is not clear if this subject has orthastatic hypotension as well, but this subject had similar events prior to Pal treatment.

B. Tachycardia in the Absence of Orthostatic Hypotension and Vital Sign Effects

Current labeling for Ris® generally describes the safety signal of tachycardia as occurring in association with orthostatic hypotension under Precautions. A clear distinction between tachycardia (or increased heart rate) associated with orthostatic hypotension versus tachycardia (or increased heart rate) in the absence of concurrent orthostatic hypotension cannot be found in approved labeling for Ris® and is not clearly addressed in the sponsor's proposed labeling, in the opinion of the undersigned. Yet, there were SAEs and ADOs due to or associated with tachycardia (or increased heart rate). Also refer to sections of this review on vital sign and ECG results from the Phase III clinical trials showing increases in supine heart rate and other related findings.

The examples below were of subjects that were found in in-text safety sections of the CSR of Study -303 (starting on page 143 of the CSR) or upon review of narratives. A few subjects did not have SAEs but were ADOs who had tachycardia in the absence of orthostatic hypotension. The following key features are noted in these 5 Pal subjects who received 6, 9 or 12 mg/day of Pal (these were the dose-levels employed in Study 303):

- ***A number of subjects below were generally healthy, had an unremarkable past medical history (PMH) and no concomitant medications and were young adults (between 23 and 33 years old).***
- *All subjects developed an **increase in heart rate in supine heart rate or by ECG** compared to baseline (on vital sign and ECG assessments).*
- *All subjects were **not described as having orthostatic hypotension (either as an AE or based on vital signs).***
- ***Several** subjects had additional vital sing or ECG changes: **became hypertensive or showed increased blood pressure, along with increased heart rate** during Pal treatment compared to baseline vital sign values (and/or ventricular rate ECG values).*
- *At least one subject had a **decrease in blood pressure** and increased heart rate (subject 201805) during Pal treatment compared to baseline heart rate with a positive dechallenge on these parameters. A decrease in blood pressure in the absence of orthostatic hypotension is an unexpected event.*
- *Subjects **generally showed a resolution of vital sign changes upon dechallenge** (within days after Pal treatment cessation).*

- *Almost all subjects **were first reported with a vital sign event by Day 4 or 5 of treatment** (one subject had vital sign changes noted on Day 7). **See Section 7.1.9** for a discussion of **time-dependent increases in heart rate recorded by ECG at multiple time-points.***
- *Some subjects **were ADOs or had SAEs of tachycardia.***
- ***A few subjects also showed QTc prolongation** that were generally first observed **on Day 6 or 7.***
- *These subjects are described below (most of these subjects were found on pages 144-146 of the CSR of 303). First the subject is summarized and then a more detailed description follows the summary:*
  - *Subject 200973 (generally healthy, unremarkable PMH, no concomitant medications, diazepam 5 mg/day as rescue medication on Days 1-4) was a 28 year old male. On **Day 4 of 6 mg Pal** treatment this subject had the **SAE of sinus tachycardia** and **AEs of dyspnea, increased BP** (compared to baseline). Additionally **non-specific ST wave changes (NSST)** were found on ECG that were absent upon a repeat ECG (on Day 4). While this subject had intermittent NSST wave changes, first observed at baseline, the timing of the adverse events (on Day 4) are probably drug-related in that Pal-induced tachycardia may have triggered an increase in BP to maintain cardiac output and this subject appeared to be at risk of angina given the AE of dyspnea and NSST wave changes associated with these events.*
    *The following provides more details on subject 200973. He was reported as an **ADO on Day 4** (in the **6 mg Pal group**) due to **sinus tachycardia that** was also reported **as an SAE.** The subject also had **"breathlessness," "palpitations," and increased BP** (130/40 compared to 118/80 at baseline) **on Day 4** (according to the narrative). Heart rate on Day 4 was 140 bpm (per ECG) compared to 74 bpm (per ECG) at baseline (the 4 and 10 hour post-dose ECGs showed increased heart rates). Sinus tachycardia was reported as an SAE on Day 4 due to prolonged hospitalization. The subject was monitored in an intensive care unit for 2 days and was treated with a 10 mg dose of propanalol. Pal was also discontinued on Day 4. In addition to the above events, **intermittent non-specific T (NSST)-wave abnormalities** were revealed at baseline and on the first scheduled (on-treatment) ECG assessment at 4 hours post-dose of Pal **on Day 4**, but were not observed in **a repeat Day 4 ECG (sinus tachycardia with normal repolarization)**. On Day 11 (7 days post-treatment) ECG heart rate was 57 bpm. Blood pressure values were not found in the CSR-in-text description and the subject was not reported as having AEs associated with abnormal BP. Vital sign values returned to normal after discontinuing Pal treatment.*
  - *Subject 200974 was a 49 year old male subject (generally healthy, unremarkable PMH and no concomitant medications) in the **9 mg Pal group** who was reported as an **ADO** due to **"bundle branch block left, sinus tachycardia."***

In summary, while this subject may have had a pre-existing cardiac condition (as may be suggested by his baseline ECG repolarization findings), the timing of the heart rate and blood pressure changes during treatment (on Day 4) and resolution of these changes which occurred upon dechallenge (see more details below) is suspicious of Pal-induced effects on vital signs.

The following provides details on vital sign changes observed in this subject: ***increased BP and HR*** *first reported* ***on Day 4*** *(110 bpm supine, 120 bpm standing and ECG ventricular rate of* ***125 bpm at 4 hours post-dose compared to 73 bpm (per ECG) at baseline.*** *His heart rate* ***approached baseline values on Day 8 (4 days after cessation of 9 mg/day of Pal). His blood pressure was only 92/70 mmHg (supine) and 110/70 (standing) on Day 8 (heart rate was 90 bpm).***

This subject had ***left anterior fascicular block on ECG at baseline****, during treatment and at post-treatment. This ECG finding was probably not drug-related.*

- *Subject 201022 (generally healthy, unremarkable PMC and no concomitant medications) was in the 12 mg Pal group (45 year old male). The subject was reported as an* ***ADO of "dyspepsia, tachycardia (twice), electrocardiogram QT interval prolonged, blood pressure increased." Pal was stopped on Day 7 (Day 4 Pal treatment was held for that day due to "QT interval prolonged.".*** *Reported* ***SAEs included increased blood pressure, tachycardia and prolonged QT interval (according to the narrative).***

While undiagnosed underlying cardiovascular pathology appears to have existed in this subject, a role of Pal is suspected in exacerbating an underlying hypertension by inducing increased heart rate and possibly by a small unremarkable QT prolongation effect and given the timing of the events (see more details in the next paragraph). It is not clear if this subject had angina since ECG assessment results could not found in the narrative or CSR description of this subject on Day 2 when he had dyspepsia. This subject was eventually treated with ranitidine (after Pal treatment was discontinued) suggesting that the clinician treating this subject considered the adverse event to be unrelated to the cardiovascular related events.

The following provides more details on this subject. On Day 2 he has "mild dyspepsia" ("burning in chest-verbatim"). ECG and vital sign measures could not be found in the narrative for Day 2 despite that angina can present clinically with the complaint of this nature (e.g. dyspepsia, indigestion). ***Increased heart rate and blood pressure*** *were* ***first noted on Day 4,*** *as well as the* ***SAE of "prolonged QTc interval) on Day 4 (QTcB of 468 msec compared to 396 msec on per-dose Day 1 ECG, QTcF=419 msec).*** *The subject* ***complained of palpitations*** *and* ***heart rate increased to 124 bpm compared to 71 at baseline*** *and* ***supine BP increased to 180/114 mmHg*** *(standing was 170/110 mmHg)* ***compared to supine BP of 134/90 mmHg at baseline*** *(130/90 standing).* ***At 9-days (Day 16) after discontinuing pal treatment HR and BP returned to baseline values*** *(supine BP was 130/90 and HR was normal). QTcF, QTc sagie derived or linear derived values were not provided in the description of this subject on page 145 of the CSR, but the narrative had QTcF value of 419 msec on Day 4. QTcB changes were probably an over representation of potential QT prolongation effects since heart rate was increased (such that QTcB values would be expected to be falsely high). It was believed by the "local cardiologist" that the patient had "essential hypertension" and that he had ECG findings revealing "concentric left ventricular hypertrophy." BP on Day 16 (9 days post-dose) had decreased to 130/90 mmHg and HR was normal and with treatment (enalapril) BP ranged from 120-126/80-84 on Days 23.*

- *Subject 201102 was a **12 mg Pal subject** (a 23 year old male with no cardiac-related history) in Study 303 **did not have any SAEs reported** but was reported as an **ADO due to "ECG specific abnormal"** (QTcB ≥ 500 msec **on Day 6**, as well as **increased QTcF, QTLc and QTcLD of up to approximately 450 msec).***

In summary this was a young male with an unremarkable PMH who developed increases in BP and HR by Day 5. QTc prolongation (including QTcF of 454 msec) was also observed. The increases in heart rate, QTc and possibly increased BP appeared to be Pal related. While evidence for a viral illness with one day of fever (Day 5) may have played a role in the HR and BP changes, a positive rechallenge on HR was observed and is strong evidence for a Pal induced effect. Since BP values were not found in the narrative or CSR descriptions, after Day 5 (that included days during rechallenge and dechallenge of Pal treatment) it is difficult to assess the role of Pal on BP. However, in the absence of this information a Pal induced effect or role of Pal in increased BP is considered to be likely. QTc increases relative to BL values that resolved upon dechallenge is also strong evidence for a Pal effect. Although successive ECGs were obtained during the rechallenge of Pal treatment, it is difficult to interpret QTc results in reference to the rechallenge dose that was given for reasons described below.

*The following are more details on the this subject. The CSR (on page 155 in another section of the CSR that focuses on QT interval results) as indicated an **over 60 msec prolongation of QTcLD on Day 6** compared to the baseline value (pre-treatment average value). This subject was also described in more detail on page 156-7 of the CSR as also developing **increased HR and increased BP first noted on Day 5** of treatment **(130 bpm HR and 140/90 mmHg BP at supine, 140 bpm HR and 142/90 mmHg at standing compared to baseline values of 77bpm and 120/84 BP at supine and 90 bpm HR and 122/84 mmHg at standing).** "No ECG was available" when these vital signs were obtained on Day 5. However, on Day 6 an ECG showed QTc prolongation (for any QTc method employed) from **approximately 370 to 375 msec (pre-treatment average) for QTcF, QTlc and QTcLD to approximately 440 to 450 msec for QTc F, QTlc, and QTcLD at 4 hours post-dose on Day 6. QTcB** at this time-point was **505 msec compared to 387 msec at pre-treatment** (given increased HR this value is considered an over-exaggerated estimate of the actual magnitude of QT interval prolongation). **QTc interval values (for all QTc methods) returned to baseline** values **on the ninth day (Day 16 of the study) after stopping Pal treatment and HR was only 67 bpm (near baseline values).** BP values could not be found in the sponsor's description in the CSR on page 157.*

The following additional information was found in the narrative of this subject. This subject also had fever on Day 5 with tremor (hands), and glossitis and baseline CBC showed elevated lymphocytes, "decreased" neutrophils and elevated glucose. While tachycardia was first observed on Day 5 in "sinus tachycardia" was observed several days after resolution of the fever (resolved in 1 day). Furthermore, according to the narrative Pal was held on Day 6 and resumed on Day 7 while HR was 140 bpm on Day 5, then 115 bpm on Day 6, and then increased again on Day 7 to 144 bpm (Day 6 and 7 values were obtained by ECG). Therefore, a positive rechallenge on tachycardia was observed in this subject. Blood pressure values for these days (Days 6

and 7 or thereafter) could not be found in the CSR description or the narrative of this subject. Results of QTcF over Days 6 and 7 are more difficult to interpret in determining if there is a positive rechallenge effect since QTc Pal effects appear to be greatest near approximately 22 hours post-dose (near Tmax) and since the exact timing of ECG assessments relative to dosing on these days could not be found in the CSR and narrative descriptions.

- *Subject 201805 in Study -303 (a 33 year old male with an unremarkable PMH, no concomitant medications but "remarkable" ALT elevation and triglyceride elevation at baseline) had 12 mg daily Pal treatment* ***discontinued on Day 7 (ADO) who had an SAE of tachycardia*** *that was* ***first noted on Day 4.*** *This subject also had* ***hypotension*** *on Day 4.*

  Given the timing of the vital sign events of hypotension and tachycardia relative to treatment, along with a positive dechallenge that was observed, these events are likely to be Pal related (see details below).

  The following are more details. On Day 4 ***HR reached to 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). According to the narrative, the* ***"hypotension was reported on Day 5." "Paliperidone was discontinued and blood pressure normalized the following day."*** *Supine BP of 115/80 mmHg and HR of 93 bpm were observed 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 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 HRs were 72 and 76 bpm, respectively compared to supine and standing HRs 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 HR of 73 bpm on that day.*

Tachycardia occurred after some subjects in the longterm OL trials as well. The following are some subjects found in the 120-Day SUR Submission:

- *Subject 200303: This subject was a* ***generally healthy 37 year old male (unremarkable PMH)*** *subject in OP Study -703 who* ***previously received DB olanzapine (in the 6-week lead-in Study*** *-303) who developed* ***tachycardia*** *initially reported as an AE* ***while receiving 9 mg daily*** *on Days 1-3 which was then decreased to 3 mg daily on Day 4.* ***On Day 5 tachycardia*** *was reported* ***as an SAE*** *and the subject* ***was hospitalized (HR was 140 bpm). Study drug was temporarily discontinued*** *and* ***resumed on Day 7 at the 3 mg daily*** *dose-level. Orthostatic hypotension was not described. No other clinically-related information*

could be found in the narrative. However this subject developed intermittent episodes of "acute paranoia" that lead to gradual increases of Pal and temporary resolution of the paranoia. The narrative does not a recurrence of tachycardia associated with subsequent increases in the Pal dose.

A discussion of vital sign or ECG changes that were observed after subjects were switched from DB Olanzapine (10 mg/day) to OL pal is provided in sections on vital sign and ECG changes in this review.

The following describes in more detail the changes in the dose after resuming Pal treatment and additional information. The tachycardia resolved after 13 days at this low dose-level but the patient developed "acute paranoia" and was hospitalized. He was receiving diazepam intermittently during the study. After resuming the dose at 3 mg daily on Day 7, the dose was increased to a daily dose of 6 mg (on Day 30) due to paranoia, and to 6 mg on Day 34 with resolution of acute paranoia until Day 64 upon which the subject was hospitalized for "acute paranoid ideas." The daily dose was increased to 12 mg on Days 71-74 and decreased again to 9 mg. It is not clear why the dose was decreased. However, the subject received 9 mg daily on Days 75-79 until he withdrew consent on Day 79.

- *Subject 500603: This subject was a generally healthy 18 year old (Malaysian) with an unremarkable PMH and taking no concomitant medications who developed an* ***SAE of tachycardia on Day 4 of OL 9 mg daily of Pal in Study -705 that persisted with an abnormal ECG of NST-wave abnormalities and "sinus tachycardia at 106 bpm," noted on Day 15. He was not hospitalized but also had "inability to walk for a distance or to exert himself in view of breathlessness and lethargy." Ultimately this subject was reported as an ADO on Day 22 due to these AEs.*** *Dyspnea was first reported on Day 13 and the "cardiology interpretation stated that the precordial leads on the Day 15 ECG were not valid." There is no mention of a repeat ECG on this study day, but an ECG on Day 22 was "within normal limits." This subject also reportedly received 9 mg daily of DB Pal in a 6-week lead-in Study that lead to early discontinuation on Day 23 due to "lack of efficacy." The narrative did not provide an vital sign information during this initial Pal exposure.*
- *Subject 200601: This* ***30 year old male subject*** *had a* ***history of hypertension and tachycardia but no concomitant antihypertensive agents*** *or other medications. He* ***developed transient tachycardia*** *early* ***during DB olanzapine*** *treatment in the lead-in 6-week study (****on Days 4-6*** *of DB treatment).* ***These events reappeared on Day 6 of OL Pal (at 9 mg/day) with a HR of 150 bpm (reported as an SAE) and BP of 170/100 which led to an ADO on Day 7. The events resolved by Days 8 or 9 without treatment.*** *This subject also had psychotic-related AEs, as well as a potential underlying condition (history of tachycardia and hypertension) that may have contributed to the degree of cardiovascular changes this subject. It is possible that this patient's history of tachycardia and hypertension were associated with past treatment with antipsychotic medications (but this is speculation), since it appears that he did not require antihypertensive treatment and the narrative did not describe abnormal vital signs at screening or at baseline. Furthermore, the AEs of high BP and HR resolved upon dechallenge of Pal treatment. Consequently, the AEs in this subject are likely to at least, in part, be related to antipsychotic drug treatment.*

Tachycardia in Phase I Subjects and Potential Food Effects.

Additional subjects were found to have tachycardia (in which orthostatic hypotension was not reported) and dyspnea among young Phase I male subjects. These events occurred after these subjects were given their first and only SD of 15 mg Pal after a high fat meal (that occurred on the next day after treatment). This was the first and last dose given to these subjects, since they were also ADOs. A subsection E below describes these subjects (see the subsection entitled "Potential Food Effects on Cardiovascular and Respiratory Related Events in Phase I trials"). Also refer to Seciton 7.1.12 C for related safety results from 2 Phase I food effect studies using SDs of 12 mg or 15 mg of the Phases III, [redacted] formulations.

Increased BP

Some of the previously described subjects had events that included increased blood pressure. The following subjects were in the "prevention relapse" Study -301 and were found as examples of additional examples of subjects with potentially clinically noteworthy increases in BP (found in the 120-Day SUR, as this study was completed after N000 and before this SUR):

- *Subject 100121 (**ADO due to "blood pressure increased"**) had a progressive increase of blood pressure during Pal treatment that did not resolve with the addition of clonidine to his usual pre-study, antihypertensive regimen of benazepril HCl. Pal at the 9 mg daily dose level was discontinued after 21 days of treatment (Day 21 of the run-in phase) due to "elevated blood pressure which was persisting." This subject had a history of hypertension that was being treated with benazepril HCl that appeared to well controlled given his baseline vital sign values obtained (124/72 mmHg at standing). A progressive increase in standing BP (of up to 140/84) was observed despite the addition of clonidine treatment and despite multiple increases in the dose. A role of Pal in inducing poorly controlled hypertension is suspected on the basis of the narrative information found on this subject.*

Refer to the last section of this review for further comment and recommendations regarding hemodynamic drug effects and potential drug effects.

C. Cardiovascular Related Events Associated with Syncope

The following are examples of subjects with syncope who also had clinically remarkable vital sign or ECG related events or other clinically remarkable events. Syncope was sometimes associated with known drug effects, such as orthostatic hypotension but also included cases of potentially unexpected drug related adverse effects, such as the possibility of sinus pause.

The following subject was found in an in-text section of a CSR of one of the Phase III trials: ***Subject 300541:*** ***"Pauses" of up to 8 seconds on holt monitoring of S300541.*** *This subject had* ***SAEs of "hypotension"*** *(110/72 mmHg at supine) and* ***"dizziness."*** *This subject also developed* ***"syncope"*** *which was reported as an AE. A description of his syncope cannot be found in the narrative or in-text CSR description of this subject. This subject also had* ***bradycardia*** *(40 bpm at supine, 38 bpm at standing) and met outlier criteria for orthostatic hypotension. EKG showed* ***a possible lateral infarct of undetermined age, left anterior fascicular block and heart rate of 67 bpm,*** *while cardiac enzyme levels were normal. Holter monitoring revealed "several pauses" lasting up to 8 seconds. These events occurred early in Pal treatment (Days 5 and/or 6*

of 12 mg daily treatment) near the time when peak cardiovascular drug effects were revealed by descriptive statistical results of vital sign and ECG data by treatment group, as described later in this review. The subject was withdrawn from the study on Day 6, but it is reported that the reason was due to "exacerbation of schizophrenia." Yet, cardiovascular events and SAEs occurred on Days 5 and 6 and were assessed by the investigator as being "possibly" drug-related. These cardiovascular adverse events also resolved within 2 to 4 days after treatment cessation, which is strongly suggestive of drug-related events. This subject was ***not described as having any pre-existing conditions or concomitant medications*** *that could potentially account for these events. However, the subject was male and 50 years old which are risk factors for cardiovascular disease.*

The following description of Subject 300541 was found in the narrative on pages 2555-6 of an appendix of the SCS:

[redacted]

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Subject 300541 (paliperidone, preferred term: dizziness, hypotension, syncope, psychotic disorder, bradycardia (twice); [redacted] was a 50-year-old white man with a diagnosis of paranoid schizophrenia. The medical history included asthma, intermittent headaches, agitation, and insomnia. The physical examination at screening was normal. There was no relevant history of bradycardia, dizziness, or syncope.

Laboratory values at screening showed elevated alanine aminotransferase, aspartate aminotransferase, C-peptide, and gamma-glutamyl transferase. The subject discontinued aripiprazole and lithium carbonate on Day -5. Lorazepam 1 to 7 mg "as needed" was given daily between Day –5 and Day 4. Concomitant medications at baseline were benzatropine mesylate 1 mg twice daily, salbutamol inhaler, and rofecoxib 25 mg/day.

On screening Day –4, the ECG, reported as abnormal but not clinically important, showed left anterior fascicular block and a heart rate of 76 beats per minute (bpm). Blood pressure on screening Day –6 was 124/78 mmHg (standing) and 122/76 mmHg (supine); his pulse rate was 92 bpm (standing) and 90 bpm (supine). His weight was 131.5 kg (body mass index 39.3 kg/m^2).

On Day 5, while receiving paliperidone 12 mg/day, the subject experienced the serious adverse events of *dizziness* (dizziness-verbatim) and *hypotension* (hypotension-verbatim) and non-serious adverse events of *syncope* (syncope-verbatim) and *psychotic disorder* (exacerbation of psychosis-verbatim). No vital signs information is available for this day. Study medication was stopped on Day 5 as a result of the exacerbation of psychosis (requiring too much lorazepam: CIOMS); treatment with lithium 300 mg twice daily was initiated on Day 6 and aripiprazole 15 mg b.i.d. on Day 7. The subject was withdrawn from the study on Day 6 due to the adverse event "exacerbation of psychosis".

On Day 6, serious adverse events of *bradycardia* (bradycardia-verbatim) and *heart rate irregular* (delay in pulse-verbatim) were reported. He was hospitalized due to a standing pulse rate of 38 bpm (40 bpm supine); his supine

and standing blood pressures were 110/72 mmHg and 112/72 mmHg, respectively. An ECG obtained on Day 5 showed normal sinus rhythm, left anterior fascicular block, and a possible lateral infarct of undetermined age, with a ventricular rate of 67 beats per minute. His cardiac isoenzymes were reported as normal. A Holter monitor demonstrated several pauses including one 8-second pause. A computed tomography scan of the head revealed no acute intracranial process and no bleed (source: CIOMS). A cardiology consultation was requested but the subject eloped before he could be evaluated (source: SAE follow-up forms). The dizziness, hypotension and syncope resolved in 2 days, the exacerbation of psychosis resolved in 13 days, and the bradycardia and delay in pulse resolved in 4 days.

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

In many instances it is difficult to differentiate adverse events from preexisting disorders. Even though there were ECG abnormalities at baseline, the subject had no prior symptoms of bradycardia, dizziness, or syncope. Dizziness, hypotension and psychosis have been reported with the use of paliperidone, although these events could also be due to the subject's underlying condition including heart block which may signal underlying cardiac disorders. This subject received 5 doses of 12 mg paliperidone; no rechallenge was performed. Therefore a causal relationship between the adverse events "syncope" and "exacerbation of psychosis" and the serious adverse events "dizziness" and "hypotension" and the intake of paliperidone is difficult to assess, but not totally excludable.

Bradycardia and delay in pulse have also been reported with the use of paliperidone. These serious adverse events occurred at the same time the study medication was stopped, the sponsor considered that a causal relationship between the serious adverse events "bradycardia" and "delay in pulse" and the use of paliperidone could not be excluded.

(Manufacturer's Control No.: US-JNJFOC-20040900273(5)).

This subject is listed in a listing of subjects meeting outlier criteria on page 308 of a 475 page table in an appendix of the SCS on page 4350 (which is page 308 of the 475 page table) and listed as having:

- *Standing and supine HRs of 38 and 40 bpm, respectively on Day 6 of the study*
- *Compared to standing and supine heart rates of 80-92 and 90-76 bpm, respectively on previous assessments (includes: 2 baseline assessments and assessments on Days 2, 3, and 4).*

Additional Reviewer comments on the above subject: Sinus pauses (and bradycardia and hypotension) have been previously reported for at least a related drug, olanzapine (following IM treatment in 2 subjects and oral olanzapine in 1 subject as described in approved labeling, in 2 Phase I trials of normal healthy subjects in which telemetry monitoring was employed). It is notable that these types of events may have occurred in this subject at a time-point when plasma levels were dramatically rising or near Tmax. Another concern is that drug levels of Pal can be dramatically affected by food intake, among other potential factors that may impact on PK of Pal. However other factors, aside from PK factors, that may influence cardiovascular drug effects need to be considered that may at least playing a role. That is, drug effects on the cardiovascular system are not likely to be solely dependent on drug level or to be static effects. Instead, drug effects may be strongly influenced by non-drug-related dynamic physiological changes in the cardiovascular system in the healthy patient, as well as in the patient with pre-

existing cardiovascular conditions (e.g. consider diurnal fluctuations in the cardiovascular system, consider a patient with an already compromised cardiac output who then develops drug-induced tachycardia that may lower cardiac output further and trigger hypertensive compensatory episodes or hypotensive episodes, among other considerations). An apparent time-dependent (which could be related to either PK factors and/or physiological dynamic related factors) was observed in cardiovascular related clinical parameters as described later in this review. Furthermore, some of these effects appeared to be dose-dependent (see results on vital signs and ECGs in this review).

Refer to the final section of this review for further comment and recommendations. .

The following subject was in an OL trial and was reported in a safety alert report under the Paliperidone IND (ER OROS) is described below because the subject was a young generally healthy female who died suddenly without having any known non-drug-related reason to explain her death.

A Summary of Events and Death in Subject [redacted] *based on information from a Safety Alert Report under IND658850.*

A sudden death associated with syncope and possible seizure after at least 3 months of OL Pal treatment (12 mg/day) in Study -701 *was reported in a Safety Alert Report under the Paliperidone IND (IND 65850 for the OROS Pal formulation, a N184 4/3/06 submission). See a description of this subject below. The following are reviewer comments about this subject. In the opinion of the undersigned reviewer the events leading to death were likely to be related to the study drug, since the subject was healthy, and was only receiving trihexyphenidyl as needed, was a nonsmoker and was not described as having pre-existing conditions or abnormalities or risk factors to explain the cause of sudden death. Clinical data on this subject are limited, but the clinical presentation (in the absence of other clear causes) is highly suggestive of a Pal related adverse events that led to death. Possible diagnostic considerations are the following: pulmonary embolism versus cardiorespiratory arrest secondary to an arrhythmia, versus aspiration of emesis and bronchospasm, together with slightly low potassium and sodium levels, among other cardiac and/or CNS related events that may lead to sudden death. While the subject could have had a dystonic reaction leading to compromise to her airway, she scored 0 on SAS and BARS at her last study visit approximately one month before the day of her death. It is not clear why she was given trihexyphenidyl (perhaps it was being used off-label for agitation, but this is only speculative).*

The following is a more detailed description of events that ensued in subject [redacted] *based on information in the safety alert report. The subject had schizophrenia who suddenly died after over 3 months of receiving 12 mg daily of OROS Pal in the OL extension trial -701 (which followed a "prevention of recurrence" trial, Study -301). She was last assessed in the OL study on 12/7/05 and was not exhibiting acute psychotic features, was sleeping and eating well, and had normal vital signs and a negative urine pregnancy test. The mother of the patient was contacted about changing the date of her next study visit (scheduled for* [redacted] *, but the mother could not change the date). On* [redacted] *the patient was noted by the mother to*

*become **"very anxious, agitated and complained of breathlessness."** The mother **gave her a 2 mg trihexyphenidyl tablet**, according to instructions. No other information could be found as to why this concomitant medication was prescribed and her AIMS, SAS and BARS scores were all 0 at her last study visit within the previous month (on 12/7/05). "Within some time" after receiving this drug the subject **"started vomiting" then, "within no time"** the subject was reported to have **"severe convulsive movements of the entire body" and became "unconsciousness."** She was **evaluated at a hospital at approximately** [redacted] **that day and was observed** over approximately **3 hours before being transported (while "deteriorating") to another hospital but the patient died in transit. During the 3 hours during hospitalization** the internist found her in a **"stuperous" state, unresponsive to pain, while DTRs were "present."** Her **blood pressure was "reported to gradually fall"** (vital sign measures could not be found). An ECG and EEG were not performed. Laboratory values were as follows: glucose was normal, **potassium was low at 3.1 (NR 3.5-5.2 mM), sodium was low at 126 (NR: 134-145 mM).** No other assessments could be found in the safety alert report submission. The patient is "presumed" to have not undergone an autopsy. **The differential diagnoses by the investigator included: convulsion, bronchospasm and respiratory failure, rule out pulmonary embolism. The treating physician in the patients 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."***

Additional cases of syncope were found by the undersigned reviewer that were not reported as SAEs (as specified below) that strongly suggest Pal induced effects:

- **Copied from the narrative found in the 120-Day SUR**
  Subject 100140 (paliperidone dosage at onset of event: 12 mg/day; syncope; [redacted] was a 27-year-old white man with a diagnosis of paranoid schizophrenia. At screening, the subject's medical history noted 4 prior hospitalizations for psychosis. During the double-blind study, the subject received placebo for 12 days before entering the open-label study. Adverse events reported during the double-blind study were "aggression" and "exacerbation of symptoms (increase in psychosis)." During double-blind, the subject received lorazepam as a rescue medication. During the open-label study, the subject received paliperidone 12 mg/day for 65 days. On open-label Day 1, the subject's blood pressure was 118/74 mmHg, with a pulse rate of 70 beats per minute (bpm); vital signs were stable throughout the study. On open-label Day 65, the serious adverse event "syncope" was reported when the subject fainted while on a trip with his group home. He was admitted to the hospital for observation with a diagnosis of syncope. Paliperidone was discontinued at that time. A cardiac evaluation was performed on an unspecified date but the results were still pending. The syncope resolved in 7 days and was considered by the investigator to be severe and possibly related to study medication. On Day 67, the subject was withdrawn from the study due to the serious adverse event. (Manufacturer's Control No. US-JNJFOC-20050802498(2)
- *Subject 500630: The following subject did not have SAEs and was not an ADO but is described here in this review, because the subject had **syncope** associated with*

***tachycardia** and **orthostatic hypotension** which were reported as AEs. Subject 500630 (30 year old female) in the 9 mg Pal group of Study 305 had the AE of syncope (verbatim term: "fainting attack" considered to be mild on Day 4 (this was not an SAE). This subject also had episodes of orthostatic hypotension (met outlier criteria including assessments prior to the DB phase) and was receiving concomitant lorazepam (1 to 6 mg po daily). This subject had episodes of tachycardia on Days 4 and 5 of DB treatment (returned to normal on Day 8). Sinus tachycardia revealed by ECG assessments on Days 4 and 5 was considered "clinically significant." However, subsequent ECG assessments were interpreted as normal and the subject completed the study on Day 44 without requiring treatment for her AEs.*

The timing and nature of these events (early in the first week of treatment) is generally consistent with results showing Pal effects on cardiovascular related clinical parameters described later in this review.

- *Subject 500407 (55 year old male) in the 15 mg Pal group of Study 305 did not have an SAE or AEs leading to an ADO but is described here due to an AE of **"syncope"** on Day 34 (of moderate severity, "resolved in 1 day") and **borderline QTc interval values** during ECG assessments on Day 4 (10 hours post-dose time-point), Day 7 (22 hours post-dose time-point), Day 35 (1-2 hours post-dose) and Day 42. None of the QTc values reached 450 msec or greater and the subject completed the study on Day 42. The timing and nature of these events is generally consistent with results on Pal effects on related clinical parameters described later in this review.*
- *Subject 502318 in Study -305 had AEs of **hypotension and syncope** (Preferred term which was reported verbatim as "swoon") that led to an ADO on Day 3 and that spontaneously resolved within several days after treatment cessation. These events were not considered as SAEs. This subject had similar events at baseline, suggesting that the events could be at least partly related to a pre-existing condition.*

A search for AEs of syncope among the narrative section (an appendix) of the SCS for SAEs and ADOs revealed additional subjects with SAEs or AEs due to an ADO of syncope, that were not found elsewhere in in-text sections of the SCS (as described in this review). The following were 2 notable events given the nature of the events and that alternative non-drug-related explanations for these events could not be found or described in the narratives or CIOMS forms found on these subjects:

- *Patient number 103772/1000140: this subject was a healthy 28 year old male with schizophrenia in the OL Study -701 who had no concomitant medications and had **syncope after approximately 2 months of 12 mg Pal daily.** This event led to hospitalization. A "cardiac work-up" was conducted and "resulting are pending." There was no additional information that could be found this subject (information was found in a CIOMS report, since this event occurred past a May 31, 2005 cut-off deadline in this ongoing trial.*
- *Subject 700015 in a Phase I study (-P01-1007) who had **syncope for 60 seconds** that occurred upon standing after 3 hours and 48 minutes after receiving 1 mg IR Pal. This 52 year old healthy woman (with an unremarkable past history and no*

concomitant medications described in the narrative) continued to have "extreme dizziness" and nausea for 4 hours post treatment. She was able to continue the remaining 4 treatment conditions in this Phase I study without recurrence of syncope or orthostatic hypotension. One possible consideration is that Phase I trials generally involve

Additional SAEs and/or ADOs of syncope found in the 120-Day SUR and/or in OL Trials

- *Subject 200986: this subject was previously described who had a 5 minute episode of loss of consciousness (**grand mal convulsion reported as an SAE and lead to an ADO**) that was not followed by a post-ictal state of which **it is not clear if whether or not this subject had a seizure versus another type of syncopal event**. Information on the subject is limited. This subject is described in more detail under the subsection on seizures below (subsection I).*

Response to an Inquiry of Any Cases of Syncope

Since a description of subject 300541 (with sinus pauses) and others could not be found in the in-text sections of the SCS in the submission, including a section that focused on events of syncope and other potentially pro-arrthmic-related events, the sponsor was asked to provide listings and narratives of subjects with symptomatic bradycardia, tachycardia, hypotension, orthostatic hypotension or syncope (who were asymptomatic at baseline) using their November 1, 2005 cut-off date (since this was the cut-off date for the original submission).

A response to this inquiry was recently received, but since it was received late in the review cycle (N006, 6/27/06) then results will be described in an amendment review or in a review of a response to an approvable action (if the Agency takes an approvable action on this NDA).

Also see related subsections below on Seizures, Dizziness and ischemia-related events, as well as the previous subsection for potentially related events..

D. Dizziness

2 ADOs due to dizziness occurred in Study 305 (500102 and 5011244 in the 9 mg and 15 mg pal groups respectively), as described below.

- *Subject 501244 in the **15 mg Pal group** of Study 305 was an obese 41 year old male with **"fuzzy thinking," dyspnea and dizziness the led to treatment cessation on Day** 7. Vital signs were normal on Day 7.*
- *Subject 500102 in the **9 mg Pal group** in Study 305 **withdrew early due to "dizziness, nausea, amnesia, headache and tachycardia" with tachycardia reported as an SAE.** This subject also had mild somnolence as an AE. **Tachycardia was described as a"pulse=100-160 on minor activity."** This subject also **met outlier criteria for orthostatic hypotension.***

See previously described subjects with seizures and syncopal episodes (or in some cases appeared to be near-syncopal episodes based on the verbatim term provided).

The CSR of Study 303 indicates that there were no SAEs due to dizziness but:

- *One **ADO occurred in a 12 mg treated subject due to "dizziness" on Day 29** (subject 201526). This subject had **dizziness and epigastric abdominal pain starting on day 15** and was also reported to have **AEs of "first degree AV block" and "blurred vision."** It is not clear if angina was ruled out and if there were other non-drug-related causal factors that existed in this subject.*

E. Potential Food Effects on Cardiovascular and Respiratory Related Events in Phase I Subjects

*While the focus of this section of the review is primarily on Phase III trials, it is important to consider the remarkable food effect observed with Pal (based on Phase I studies, as previously described in this review). Upon review of line-listings of SAEs and ADOs of Phase I trials and review of selected narratives the following subjects were found as having **ADOs of dyspnea and tachycardia (2 subjects) or postural hypotenision and dizziness (in 1 subject)** that were also associated with other AEs as described below. These subjects were in the food effect Study – P01-1008 which used the 15 mg SD level of Pal in a crossover study design. While there were no SAEs reported in this study, one caveat to consider is that Phase I trials are generally conducted on-site (not as outpatients). Consequently if an AE that may have resulted in hospitalization and therefore would be reported as an SAE in an outpatient study may not necessarily be reported in an inpatient study setting (such as the setting of most Phase I trials). The following describes the ADOs with cardiovascular related events:*

- *Subject 100813 was a 29 year old generally healthy male who was reported as an **ADO due to sinus tachycardia in the morning of Day 2 of Period 1 following 15 mg Pal** given **after ingestion of a high-fat breakfast.** **Dyspnea** was reported by the subject 4 hours later which was treated with oxygen (4 L/min). Both events resolved within 30 and 17 hours, respectively. This subject developed additional AEs on the evening before Day 2: "moderate anxiety" that was treated with 5 mg diazepam PRN, "mild impaired concentration," "mild diarrhea," and "mild dry mouth."*
- *Subject 100824: was a 27 year old generally healthy male who was reported as an **ADO due to dizziness** at the same time of the onset of events in the subject described above (subject 100813) which was **in the morning of Day 2 of Period 1 after 15 mg Pal given in the fed state** (as with the previously described subject). The subject had an episode of **orthostatic hypotension** approximately 3.5 hours prior to the dizziness. The dizziness was treated with oxygen (4 L/min). This subject also had **chest pain** (an ECG result cannot be found in the narrative), as well as **abnormal vision** (mild intensity) and abdominal pain (the latter was treated with diazepam 5 mg PRN).*
- *Subject 100811 was a 19 year old, generally healthy, male who was reported as an **ADO due to dystonia** who also had **"moderate dyspnea," "mild tachycardia," and "mild abnormal vision" in the afternoon of Day 2 of Period 1 after 15 mg Pal given after consuming a high-fat breakfast.** The subject received procyclidine, 5 mg PRN and diazepam (2.5-5mg PRN). These drugs were given i.v. for the dystonia and the dyspnea was treated with oxygen (4L/min) and 1-2 puffs of salbutamol. It is possible that the dyspnea and tachycardia were related to the subject experiencing dystonia (a drug-related event).*

See sections 7.1.8.3.1on vital signs in fed versus fasted conditions and 7.1.12 C for safety results of Phase I studies that examined food effects since the potential for food effects on safety variables were not examined in the Phase II/III trials.

Reviewer Comments on Safety Findings in Phase I Healthy Control Subjects. *It is generally believed that antipsychotic-drug-naïve subjects (who are more likely to participate in Phase I trials of healthy volunteers) have greater risk for some known drug-class effects, such as dystonia. Yet, a recently diagnosed patient with schizophrenia with no prior antipsychotic exposure may also be potentially similar to the healthy subject with respect to risk for adverse drug effects. Furthermore, the schizophrenic population has greater morbidity and is believed by many to have greater risk for mortality than is observed in the general population. Furthermore, patients with concomitant illnesses and elderly are also more vulnerable. Consequently, events occurring in Phase I studies can be useful in understanding drug effects that may be relevant to the schizophrenia patient population, particularly since these trials are generally conducted in more controlled conditions than conditions employed in Phase III studies.*

F. Ischemia-related Events

The sponsor conducted a special search of ischemia-related AEs in which results were primarily provided as the incidence of cases in Phase III safety datasets (as described in Section 7.1.4.5 of this review). The following individual cases that are at least suggestive of ischemia related events were found by the undersigned reviewer upon review of selected narratives or of safety sections of the CSRs for the short-term, placebo controlled Phase III trials.

Subject 502217: This subject was a 49 year old female who developed ***"ischemia" with "possible endocardial injury"*** *revealed* ***by ECG on Day 6 of Pal treatment (9 mg/day)*** *that led to an* ***ADO on Day 9*** *and* ***treatment by a cardiologist, as well as at least 3 weeks of hospitalization.***

In summary, the timing of the onset of these events (within approximately 1 week of treatment) together with vital sign and ECG results described later in this review is suspicious of a role of Pal treatment in exacerbating an undiagnosed cardiac disorder (e.g. coronary artery disease). This review describes vital sign and other cardiovascular related effects that occur near approximately the time when steady state levels are expected to achieve and effects near Tmax. Although, subject 502217 had a history of hypertension and a baseline ECG showing NSST wave changes and incomplete right bundle branch block, she had no previous history of angina and the timing of these events occurred within approximately 1 week of Pal. Her condition continued after cessation Pal treatment, despite receiving multiple cardiac medications that included isosorbide dinitrate 20 mg BID (an "internist-cardiologist" was consulted. Despite this treatment regimen which started on Day 9 the ECG abnormalities persisted (as assessed on Day 17). A failure of the "ST depression, possible endocardial injury in the inferiror leads (II,III and AVF)" that were first observed on Day 6 of Pal treatment, despite treatment with isosorbide dinitrate is highly suspicious of myocardial infarction (MI or

at least endocardial infarction). Although, results of a cardiac work-up to rule out an MI could not be found in the narrative of this subject (e.g. enzyme levels could not be found).

The following are more details on this subject. This subject (in the 9 mg Pal group of Study 305) who ***had abnormal ECGs of "ischemia"*** *during Pal treatment that was reported as an* ***ADO due to "ischemia" on Day 9 of Pal.*** *She was not described as having any abnormal vital sign parameters but had borderline hypertension (140/85) on Day 6 of Pal treatment. An ECG assessment* ***on Day 6*** *of treatment showed* ***ST depression, and "possible endocardial injury inferior leads" and "incomplete right bundle branch block."*** *Ischemia was reported as an AE on Day 8. Study drug was stopped on Day 9 due to "inferior ischemia."*
The above ECG abnormalities were also noted on an ECG assessment on Day 17 (8 days after the day of Pal treatment cessation). The baseline ECG showed non-specific ST wave abnormalities with "incomplete right bundle branch block." Other baseline safety assessments were generally within normal limits or did not reveal any clinically remarkable except that GGT was reported to be elevated at baseline. No other information to explain these events could be found in the narrative for this subject (e.g. a description of cardiac enzyme levels and post treatment cessation ECG results could not be found other than a comment that "a slight improvement occurred in the ECG" at the time of discharge from the hospital 3 weeks after discontinuing study drug).

Subject 200302 in the elderly Phase III trial (study -302) had the ***SAE and ADO of "acute coronary syndrome" on Day 16 (on 9 mg Pal/day).***

In summary, this subject, who is described in more detail below, appeared to have pre-existing cardiovascular disease and potentially undiagnosed coronary artery disease (and undiagnosed angina). One of the pre-dose ECGs of this subject showed NSST wave changes with isolated premature ventricular contractions while other pre-dose assessments were normal, which suggests that this patient had undiagnosed coronary artery disease and possibly undiagnosed angina. This elderly woman had an unremarkable PMH but had baseline/screening BP of 150/60 and 165/90 (so she appeared to have undiagnosed hypertension).

During Pal treatment, this subject developed hypotensive episodes (it is not clear if she had orthostatic hypotension, as well) and exhibited wide fluctuations in vital signs that apparently did not appear to exist at baseline (hypotensive episodes were first noted during treatment rather than prior to treatment in the narrative description found on this subject and as described later). She was also receiving rescue lorazepam treatment (1-3 mg/day) that may have played a role.

The hypotensive episodes (that fluctuated with hypertensive episodes) appeared to be followed by NSST wave changes on Days 4 and 5 prior to initiating an antihypertensive agent that was started on Day 6 of Pal. A role of this antihypertensive agent in exacerbating the hypotensive episodes should also be considered in events that later occurred (she was diagnosed with "acute coronary syndrome" of "unstable angina" on Day 16 that lead to transfer to a cardiology unit). It is important to note that the recommended starting dose of the antihypertensive agent given to this subject (felodipine) is 2.5 mg, daily for elderly patients (according to Micromedix; the subject was in Greece). This subject was started on a daily dose of 5 mg (as described below).

A role of Pal in inducing hypotensive episodes in a patient with an underlying and undiagnosed cardiovascular condition is suspected given the timing of events relative to Pal treatment. Since this patient was likely to have compromised cardiac output (undiagnosed), her vulnerability and sensitivity to cardiovascular effects of Pal were likely to be greater than in a patient without underlying cardiovascular disease. Any Pal induced changes in vital signs were likely to further compromise cardiac output and hypotensive episodes. Ultimately an antihypertensive agent was given that may have interacted with Pal to further exacerbate this subject's already compromised cardiovascular system. The timing of the events (hypotensive episodes and ECG changes began early in treatment prior to initiating an antihypertensive agent. This timing is suspicious of a role of Pal, given that vital sign and ECG effects appear within the first week of treatment and as described later in this review. Finally, a role of Pal is not surprising from a mechanistic standpoint.

See sections below in this review on vital sign and ECG changes observed within the first week of treatment. Also see previously described subjects with vital sign events occurring within one week of treatment.

The following are more details on the above subject (as found in the narrative of this subject):

"Subject 200302 (paliperidone 6-9 mg, preferred term: acute coronary syndrome; [redacted] was a 66-year-old white woman with a diagnosis of paranoid schizophrenia. Her medical history and physical examination at screening were normal. The CIOMS reported a history of hypertension (diagnosed at age 62). There was no history of cardiovascular disorders. Laboratory values at screening (Day –6) showed increased lactate dehydrogenase; no screening values were provided for red blood cell count or hemoglobin. Baseline laboratory values showed increased lactate dehydrogenase and decreased hemoglobin. She discontinued haloperidol 15 mg on Day –11, lorazepam 8 mg on Day –7 and biperidin 4 mg/day and quetiapine 400 mg/day on Day -5. The subject received rescue medication lorazepam 1 to 3 mg/day on Day 1 and Day 8. There were no concomitant medications reported at baseline. At screening (Day -6), the ECG showing normal sinus rhythm with monomorphic isolated ventricular premature beats and non-specific T-wave abnormality was read as abnormal, not clinically significant. The baseline ECG (Day -1) was read as normal sinus rhythm and normal repolarization pattern. On Day 4, the ECG was read as normal sinus rhythm and non-specific T wave abnormalities, a second ECG on Day 4 and the ECG of Day 5 were read as normal sinus rhythm with non-specific T wave depression. The ECG on Day 8, 9 and Day 15 were read as normal sinus rhythm and non-specific T wave abnormalities, not clinically significant.
At screening (Day -6), the subject's blood pressure was 165/90 mmHg (standing) and 160/90 mmHg (supine); her pulse rate was 76 bpm (standing) and 72 bpm (supine). Her weight was 65 kg (body mass index 27.8 kg/m2). At baseline, standing blood pressure was 150/60 mmHg and pulse rate was 76 bpm, the supine blood pressure was 140/60 mmHg and pulse rate was 80 bpm.

The subject's standing blood pressure during the study ranged from 95/55 mmHg to 175/90 mmHg and standing pulse rate ranged from 78 to 108 bpm. Supine blood pressure during the study ranged from 110/60 mmHg to 175/70 mmHg and supine pulse rate ranged from 79 to 94 bpm. Felodipine 5 mg/day was started on Day 6 for hypertension.
The subject complained of breast pain on Day 16 while receiving paliperidone 9 mg/day. An ECG was abnormal and she was transferred to the cardiology unit of the general hospital on Day 16 for unstable angina. The subject was diagnosed with *acute coronary syndrome* (acute coronary syndrome-verbatim). Paliperidone 9 mg/day was permanently stopped on Day 16. The acute coronary syndrome was considered serious (life threatening) (source: CIOMS).
The subject received treatment on Day 23 with acetylsalicylic acid 100 mg/day, clopidogrel 15 mg/day, diltiazem 60 mg t.i.d., ferric hydroxide polymaltose complex 100 mg/day, folic acid 30 mg/day, isosorbide mononitrate 20 mg b.i.d., omeprazole 20 mg/day, and perindopril 4 mg/day. Lorazepam 8 mg and temazepam 20 mg were given; she then received risperidone 4 mg b.i.d. The subject was released from the cardiology clinic on Day 23 having recovered without sequelae. She had no complaint of chest pain and an ECG was normal (source: CIOMS).
The acute coronary syndrome was considered resolved in 8 days. The investigator considered the acute coronary syndrome as severe and doubtfully related to study medication.
The subject received paliperidone 6-9 mg/day for 16 days and prematurely discontinued from the study on Day 23 as a result of the serious adverse event acute coronary syndrome.
Angina pectoris has not been reported with the use of paliperidone. The subject's cardiovascular history was unremarkable, except for hypertension since the age of 62. The event occurred on Day 16 of treatment with paliperidone 9 mg/day. The subject was permanently discontinued from the study and no rechallenge was performed. Taking these facts into consideration, a causal relationship between the serious adverse event and the intake of paliperidone cannot be excluded. (Manufacturer's Control No.: GR-JNJFOC-20050406978)."

Additional Subjects of Potential Ischemia-Related Events during Pal Treatment in OL Trials:

- *Subject 500603: This subject was previously described under Subsection B (on tachycardia in the absence of concurrent orthostatic hypotension).*
    - *This subject was a generally healthy 18 year old (Malaysian) with an unremarkable PMH and taking no concomitant medications. This subject had an* ***SAE of tachycardia on Day 4 of OL 9 mg daily of Pal in Study -705 that persisted and was possibly associated with abnormal ECG of NST-wave abnormalities, dyspnea upon exertion and lethargy that was eventually reported as an ADO on Day 22 due to these AEs.*** *See details in the previous description in which this subject had previously received 9 mg daily of DB Pal, but was withdrawn from this 6-week lead-in study due to "lack of efficacy." The*

cardiologist considered the ECG to have invalidly placed precordial leads. The narrative does not describe a repeat ECG performed on this day. Given the young age of this subject and unremarkable PMH the events are likely to be drug related. The subject's ethnicity (Malyasian) may also be a contributory factor (refer to Section 7.1.12 of a Phase I study in Asian (Japanese) and Caucasian subjects.

- *Subject 500849: This subject was a 22 year old generally healthy male with an unremarkable PMH and no concomitant medications described in the narrative (and no abnormal ECGs) who had* ***intermittent NSTW abnormalities on ECG*** *on Day 15 and 36 ECG assessments (normal on Day 29)* ***during DB olanzapine treatment (10 mg/day)****. The* ***Day 36 abnormalities persisted when he was switched to OL Pal (9mg/day)*** *that resulted in* ***an ADO on Day 2 of OL Pal.***

  The narrative does not specify this subject's vital signs, if an ECG changes were only found on some of the leads, if any diagnostic evaluations were conducted (e.g. stress test), if events resolved upon dechallenge or other clinically relevant information. However, given the young age of the subject and unremarkable PMH in the absence of concomitant medications, this ECG event is likely to be drug-related and the potential of ischemia or conduction changes need to be considered.
- *Subject 201139: This* ***40 year old woman had an unremarkable PMH and no concomitant medications*** *who* ***developed "exercised induced ischemia" on Day 7 of 9 mg daily OL Pal treatment*** *in Study -703* ***reported as an ADO*** *that was then treated with deplatt A and pantoprazole with outcome of the event reported as "unknown."*

  The subject had no AEs on a lower dose of Pal, given during the DB 6-week lead-in study (at 6 mg/day). It is possible this subject had an underlying, yet undiagnosed condition but in the absence of other information (which could not be found in the narrative) a role of the study drug is considered probable since it occurred shortly after receiving a higher dose of Pal than she previously received and given the known cardiovascular effects of Pal. Even if she had undiagnosed cardiovascular disease a contributory role of Pal is suspicious given that the event occurred within days after receiving the higher dose-level of Pal.
- *Subject 300347: This 44 year old male subject had* ***no past history of cardiovascular disease of bundle branch block (BBB) and concomitant medications were not reported.*** *He had the* ***SAE of "abnormal ECG (BBB)" reported on Day 57 of 9 mg daily of OL Pal*** *in Study -704 (he previously received DB placebo in the lead-in phase). "Study medication was stopped and he did not require hospitalization." He also had* ***"sinus tachycardia," SST changes "possibility secondary to QRS abnormalities, "prolonged QTc (Bazett) interval of 495 msec"*** *and a* ***QTcF of 444 msec****. Standing and supine* ***pulse were 120 and 117 bpm,*** *respectively. QTc Bazett's is not an appropriate method when HR is increased.*

  It appears that this subject developed sinus tachycardia and the possibility of ischemia should be considered (but information is limited on this subject), along with conduction defect. BBB is not atypical in the general population and this subject may have had an undiagnosed, underlying condition. However, given the information as presented in the narrative, at least a role of Pal treatment is suspected. He was later on Day 65 "withdrawn from the study because of incarceration."

- *Subject 501572 (found in the 120-Day SUR): This subject is a 46 year old woman with an unremarkable PMH and normal assessment on screening (no concomitant medications reported) who had* ***"heart attack" ("myocardial infarction) reported as an SAE while receiving OL Pal (9 mg/day)*** *that resulted in an* ***ADO and hospitalization****. She first had "coronary and aortic atherosclerosis, heart failing and ischemic heart disease" reported on Day 32 of the OL Pal treatment.* ***Her Pal dose had been increased from 6 mg daily.*** *However, she had received the higher 9 mg daily dose on Days 1-14 of OL treatment due to "mild anxiety" on Day 14. She also received 9 mg daily of Pal in the DB lead-in study. She was discharged from the hospital on Day 62 after receiving multiple heart medications "having recovered without sequelea" and was discharged on clopidogrel and isosorbide mononitrate.*

  While an undiagnosed coronary artery disease may have been a pre-existing condition (not clear how this was ultimately diagnosed since diagnostic testing and results were not found in the narrative), a role of Pal appears to be likely as a potential contributory factor in exacerbating a potential underlying condition after the Pal dose had been increased. Although, she previously had received this dose without an SAE of "heart attack," it is possible that a combination of factors (along with potentially undiagnosed underlying heart disease) including a dose increase of Pal contributed to her SAE.

The following Phase I subjects were found in Phase I/II line-listings and narratives (copied from the narrative descriptions):

Subject 101116 (myocardial infarction), a 79-year old white man in the elderly subject group with no prior clinically significant medical history of cardiovascular problems or physical abnormalities showed signs of an inferior myocardial infarction on the ECG recording 5 days following the final repeated dose of ER OROS paliperidone. The adverse event resolved within 17 days, without treatment intervention or hospitalization. The subject was seen in the hospital and was prescribed Aspirin cardio 80 mg q.d. as prophylaxis. The event was considered possibly related to the study drug by the investigator. Subject was referred and seen by the cardiologist 55 days after the end of the study. Upon completion of a stress test the subject was told to continue his aspirin cardio. The subject will be followed up in a year by the cardiologist.

Reviewer Comment. *This subject was likely to have undiagnosed cardiovascular disease, yet a role of Pal in leading to this significant cardiac event since it's not clear form the narrative what previous ECG, vital sign and laboratory measures showed or other relevant information (e.g. results of a diagnostic work-up). This patient could have developed episodes of altered vital signs induced by Pal that further compromised his cardiac output or he may have had undiagnosed congestive heart failure that was further compromised with episodes of ischemia such that by the time of his fifth dose he had an unstable condition and ultimately suffered myocardial infarction (cardiac enzyme results could not be found in the narrative).*

The following additional subject in Study -301 was found in the 120-Day SUR (this study was recently completed prior to this SUR):

- *Subject 100067 had the* ***SAEs of "hypertension urgency," "chest pain" (a "heaviness in her chest" with "tingling in her left arm") and tachycardia on Day 21*** *of DB treatment of 9 mg daily of Pal (she completed run-in and stabilization phases with the first AE of "elevated blood pressure" on Day 14 of DB treatment. These events* ***recurred on Day 21 (chest pain tachycardia and hypertension), along with non-specific STT-wave changes (not previously observed) with "short" QT and QRS intervals on an emergency room ECG assessment that lead to Pal treatment cessation.*** *While this subject had risk factors, including controlled hypertension and diabetes she had not previously reported history of cardiac related events (such as no history of angina). Another non-drug-related factor is that the subject may have "possibly missed doses" of her ongoing antihypertensive agent since Day 18 of the DB phase. Nevertheless a potential contributory role of the drug is considered given that there was no reported history of angina in this subject.*

G. QT prolongation

See sections later in this review describing QT prolongation effects that ~~appear~~ to exist near Tmax, at least early in treatment that appear to resolve over time (but this is unclear since ECG assessments after several weeks of treatment were conducted less frequently and not tightly controlled to capturing peak levels with the daily dosing regimen). However, a small numerical QT prolongation appears to exist after over 6 months of treatment described under section 7.2.9.1 of this review (results in the 120-Day SUR) that appears to be supported by results on the incidence of outliers that were found in the 210-Day SUR (under Section 7.2.9.2 of this review). However, outlier results in a longterm OL study are more difficult to interpret since the longer and more frequently a subject is monitored the more likely outliers will be detected (due to background noise alone). Since the sponsor did not look at outliers for low QT values then it is not possible to determine if outliers were also increased over time with low values which would support a non-drug-related trend on the incidence of outliers over time in these OL trials.

Previous subsection describes subjects that had QT prolongation reported among with other cardiovascular related events, such as the following previously described subjects:

- *Subject 201022 under Subsection B (on tachycardia in the absence of concurrent orthostatic hypotension) in a 12 mg Pal subject who had QTc prolongation reported on Day 4 of QTcB of 486 msec which was normal at baseline (along with increased HR). The subject was an ADO due to SAEs of increased HR and BP on Day 7. See a description below, as found in the CSR of Study -303 which provided more details on QT results at multiple time-points.*
- *Subject 201102 in the 12 mg Pal group who had QTcF of 450 msec on Day 6 that resulted in an ADO see below which has the description found in the CSR of Study -303 and provides more details on QT values at various time-points.*

Upon review of the CSRs for these 3 short-term Phase III trials the following subjects were noted:

- *Only 1 subject (a **12 mg Pal subject** in Study 303) had a QTcLD interval that increased from a normal value at baseline **(QTcLD pre-treatment average value of 408.3 msec) to 456 msec on Day 8** (found on page 153 of the CSR. No other information could be found on the subject including the subject number.*
- *One **12 mg Pal subject** in Study 303 (20112) was only 23 year old male with no remarkable medical conditions, no concomitant medication or other potential conditions to account for the following event). This subject was an **ADO due to "ECG specific abnormal (QTcB ≥ 500 msec on Day 6)** and was described in the CSR (on page 155) as showing an **over 60 msec prolongation of QTcLD on Day 6** compared to the baseline value (pre-treatment average value). This subject is described in more detail on page 156-7 of the CSR as also developing **increased HR and increased BP first noted on Day 5** of treatment **(130 bpm HR and 140/90 mmHg BP at supine, 140 bpm HR and 142/90 mmHg at standing compared to baseline values of 77bpm and 120/84 BP at supine and 90 bpm HR and 122/84 mmHg at standing).** "No ECG was available" when these vital signs were obtained on Day 5. However, on Day 6 an ECG showed QTc prolongation (for any QTc method employed) from **approximately 370 to 375 msec (pre-treatment average) for QTcF, QTlc and QTcLD to approximately 440 to 450 msec for QTc F, QTlc, and QTcLD at 4 hours post-dose on Day 6. QTcB** at this time-point was **505 msec compared to 387 msec at pre-treatment** (given increased HR this value is considered an over-exaggerated estimate of the actual magnitude of QT interval prolongation). **QTc interval values (for all QTc methods) returned to baseline** values **on the ninth day (Day 16 of the study) after stopping Pal treatment and HR was only 67 bpm (near baseline values).** BP values could not be found in the sponsor's description in the CSR on page 157. This subject was previously described under Section 7.1.2.*
- *Subject 201022 in Study 303 was previously described under Section 7.1.2 who was in the 12 mg Pal group (45 year old male and no other conditions or medications to account for the adverse events). The subject was an **ADO on Day 7** who was reported to have **SAEs of hypertension and tachycardia.** Increased heart rate and blood pressure were **first noted on Day 4,** as well as the **SAE of "prolonged QTc interval) on Day 4 (QTcB of 486 msec compared to 396 msec on pre-dose Day 1 ECG). Heart rate increased to 124 bpm compared to 71 at baseline** and **supine BP increased to 180/114 mmHg** (standing was 170/110 mmHg) **compared to supine BP of 134/90 mmHg at baseline** (130/90 standing). **At 9-days (Day 16) after discontinuing pal treatment HR and BP returned to baseline values** (supine BP was 130/90 and HR was normal). QTcF, QTc sagie derived or linear derived values were not provided in the description of this subject on page 145 of the CSR. QTcB changes were probably an over representation of potential QT prolongation effects since heart rate increased (such that QTcB values would be expected to be falsely high). Yet, consideration should be given to a small Pal effect on increasing QT interval in this subject.*

- *The CSR of Study 305 only describes one subject (subject 500424) in the section on QT interval results who was in the 3 mg Pal group and was an ADO due to "ECG abnormality [STT]". It appears from a description of this subject found in Seciton 6.4.3.1 of the CSR that this subject had an abnormal ECG at baseline as well.*
- *Subject 500407 in Study -305 had QTcB prolongation reported as an AE and syncope as an AE (other QT values could not be found in the narrative) is described under Section C on Cardiovascular related events associated with syncope.*
- *Subject 300444: an ADO due to QTc prolongation in Study -304 after 7 days of 6 mg Pal treatment with Day 5 QTcB of 502 msec (compared to 464 msec at baseline) and QTcF of 456 msec (baseline value not found) who also had a HR of 106 on day 5. Prolonged QTcB resolved by Day 8 (468 msec).*

The CSRs of the short-term trials had section on QT prolongation that included a description of several subjects with QTc interval increases during Pal treatment but were not reported as ADOs or SAEs. Some of these subjects showed normal values and baseline and showed increases during treatment. Only 2 subjects increased from normal at baseline to prolonged during Pal treatment (prolonged is defined as over 450 msec in males or over 470 msec in females) while 6 subjects showed normal values at baseline and had borderline values during treatment (defined as over 430 msec in males and over 450 msec in females). The increase in QT interval often occurred within approximately one week of treatment and generally following a daily dose increase to 9 mg in several subjects. Although there were 2 subjects showing elevations near Day 40 of treatment.

"Mild" AE of ventricular arrhythmia along with the AE of QT prolongation was reported in one of the subjects (200614) found in the CSRs, as above. These events occurred on Day 15 on the day of a daily dose increase from 6 mg to 9 mg, daily, as described in the CSR. This 65 year old female subject did not have any past medical history or concomitant medication to explain these events. Furthermore, the predose QTc average values were normal and then increased to the following values on Day 15: 451 to 454 msec for QTcLD, QtcF and QTlc intervals and 471 msec for QTcB interval. Despite these events, the subject completed the study without subsequent QT interval or vital sign related events and had normal vital signs throughout the study.

Subjects in the elderly Phase III trial:
2 ADOs occurred in the elderly Phase III trial (-302) that included events of QTcB prolongation (subjects 200514 and 200119) of over 450 msec. One of the subjects had QTcF values of over 500 msec. The QT prolongation was reported on Day 4 of 6 mg daily in these subjects (one had increased heart rate).

Subjects in OL Trials:

- *Subject 201418 was found in a 120-Day SUR in which the role of Pal in QT prolongation (QTcLD of 549 after approximately 6 months of OL 9 mg/day Pal treatment) is unclear, as described in section 7.2.9.2 of this review.*
- *Subject 200214 was previously described who died form what appeared to be due to multiple factors in which Pal may have played a role and in which QT prolongation*

was also reported among other events prior to death (see section 7.1.1 on deaths for details).

- ***Other cases may have existed but due to the late date of the 210-Day SUR submission in the review cycle very little of this submission was reviewed.***

Additional subjects in a recently completed Study -301 found in the SUR:

- ***QTc prolongation of up to 461 msec (QTcL and QTcLd)*** *lead to an* ***ADO*** *in Subject 100232 on Day 57 of 9 mg Pal daily during the run-in phase of Study -301. QT prolongation resolved upon treatment cessation. QTc prolongation was reported to resolve in 22 days in the narrative description (page 1790 of the SUR) but it is not clear if any previous ECG assessments were conducted following treatment cessation. Furthermore, risperidone was initiated after 3 days of stopping Pal treatment (no ECG value is found in the narrative). The narrative provides limited information on ECG values over time. In the absence of more information, a role of the study drug cannto be ruled out. This subject (a 56 year old generally healthy white male) had a history of bradycardia (52-56 bpm during screening). Bradycardia can influence QT interval values but may also pose a potential risk for development of QT prolongation. Even when QT was corrected for low heart rate the value was still clinically prolongated (QTcB of 458 msec on Day 57 while HR was 57 bpm). The subject was not included in the "interim analyses." Refer to the last section of this review for further comment and recommendations regarding QT interval effects.*
- *Subject 100767 was a 31 year old, generally healthy male with unremarkable PMH, on no concomitant medications, normal baseline ECG who also had* ***QTc prolongation on Day 8 at 10 hours post-dose after 12 mg Pal, increased from 9 mg daily on previous study days that lead to an ADO on Day 16.*** *QTcB, QTcL and QTcLD showed a "borderline" prolongation of up to 467 msec for QTcB (heart rate values could not be found in the narrative). QTc prolongation was intermittent which is not surprising since QT effects were found to be time-dependent in the short-term trials. While the investigator considered the QTc prolongation to be moderate in severity and "probably" drug-related the prolongation "did not resolve." QTc values after Pal treatment cessation could not be found in the narrative.*
- *Subject 100336 was an* ***ADO due to prolonged QRS complex on Day 10*** *(but not on the Day 4 ECG assessment) while receiving* ***12 mg Pal treatment*** *(in the run-in phase)* ***that resolved upon dechallenge*** *(based on a Day 17 ECG assessment). This initial study phase used a flexible dose design (a description of what the starting dose in this trial cannot be found in the submission but could have been 9 mg daily which was the starting dose in the OL extension trials -702-705). It is not clear in the narrative when the dose of Pal was increased in this subject. This 50 year old woman was generally healthy with an unremarkable PMH. Concomitant medications were sertraline from Day -4 through Day 10 and rescue lorazepam treatment during the study. This subject had an abnormal ECG at baseline that did not involve "QRS" prolongation or "heart block" (baseline ECG showed nonspecific T-wave abnormalities, low voltage QRS and an RSR' pattern in V1).*
- *Subject 100320 was an* ***ADO due to T-wave inversion on ECG on Day 4 (at 4 hours, 10 hours and 22 hours post-dose assessment time-points) of 9 mg daily of Pal (in the***

run-in phase). *The subject also had* ***low blood pressure in the absence of tachycardia (118/81 mmHg and 84 bpm at standing compared to baseline standing values of 136/80 mmHg and 82 bpm).*** *This 53 year old WM had a history of an old MI with ECG findings with this history, along with nonspecific ST wave changes at baseline. However, at post-dose time-points early in treatment that appear to be characteristic for drug-induced hemodynamic effects (refer to previous sections of this review for time-dependent changes on ECG parameters), this subject developed T wave inversion and a new RSR' pattern on the V1 lead "suggestive of myocardial ischemia." Therefore Pal was discontinued on Day 6 and ECG changes resolved in 10 days. "Mild tachycardia" was reported as an AE 7 days after the last Pal dose (100 bpm standing and 106 bpm supine). Although a pre-existing condition could explain ECG changes, the ECG changes occurred at early in treatment at time-points that are characteristic of time-dependent drug effects (on ECG parameters) observed in the short-term phase III trials at this daily dose-level as previously described in this review. Furthermore, the event resolved upon dechallenge and given the long half life of Pal, it is not surprising that resolution did not occur until 10 days post-dose. The development of a decreased systolic blood pressure in the absence of tachycardia at the post-dose time-points early in treatment is also highly suspicious of drug-induced hemodynamic effects. The absence of tachycardia is also noteworthy since tachycardia would be expected at these time-points. Tachycardia was reported as an AE after 7 days of Pal treatment cessation and was reported to persist (while ECG changes resolved, 10 days post Pal cessation). It is important to note that the subject was taking mirtazapine as a concomitant medication at baseline, which could potentially influence findings but would not explain the timing of ECG and vital sign changes during Pal treatment.*

H. Potential Cerebrovascular-Related and/or Additional Potential Cardiovascular Related SAEs and Other Clinically Remarkable Events

Grand mal Convulsion (SAE) was reported in a 23 year old patient who was found to have a positive MRI for an "old lacuner infarct in the left thalamic nucleus" in S300676. *The description of this subject (below) is consistent with a seizure (tonic clonic) and the EEG was positive (as described below). No pre-existing condition or concomitant medication or other etiological factors can be found in the description of this subject other than the positive MRI finding. However, it is not clear how a 23 year old would have an "old lacunar infarct" and it is not clear to the undersigned that the seizure was not the result of at least a drug-related excacerbation of an underlying condition (e.g. possible cardiovascular or cerebrovascular system effects or a possible effect on seizure threshold or some other effect).*

See a more detailed description below found on pages 131-132 of the CSR for Study -304:

Subject 300676, 23-year-old white man, ER OROS paliperidone 6 mg group: This subject had no past history nor family history of seizure or epilepsy. On Day 5, the subject experienced a "grand mal convulsion". The tonic-clonic seizure lasted about 45 seconds; he hit his head, sustaining a 2 cm laceration to his left forehead when he fell, bit his tongue and shook violently. He was not incontinent, but was incoherent, lethargic, and

somewhat unresponsive after the seizure. Intravenous treatment with fosphenytoin sodium was initiated. The subject was scheduled to have an electroencephalogram (EEG); prior to the EEG, he apparently experienced another tonic-clonic seizure. There was no convulsive activity noted during the EEG. This report showed a diffuse slowing and triphasic waveform that suggested an underlying metabolic encephalopathy with a structural lesion and probably represented continuous seizure activity. On Day 6, a magnetic resonance imaging revealed evidence of an old lacunar infarct in the left thalamic nucleus, otherwise the examination was normal. Treatment with aripiprazole, atenolol, and phenytoin was initiated on Day 6. The grand mal convulsion, which the investigator considered serious, resulted in the discontinuation of study medication and premature discontinuation from the study. The investigator assessed the grand mal convulsion as severe and possibly related to study medication. The adverse event was considered to have resolved in 1 day with treatment. It should be noted that the subject was receiving concomitant pantoprazole; convulsions have been reported in <1% of subjects receiving this medication.

Additional subjects found in the 120-Day SUR or in OL Trials:

- *Subjects 201452 and 300166 were 54 and 53 year old, female and male subjects, respectively that had an unremarkable PMH except for mild hypertension (no antihypertensive agent found in the narrative) in the former subject and hypercholesterolemia in the latter subject. Both subjects previously received DB placebo in the lead-in study but developed "ischemic stroke" (an SAE) and "aphasia" on Day 10 of 9 mg Pal daily in subject 201452 and "transient ischemic attack" (as an SAE) on Day 40 of 9 mg daily of Pal. Vital sign, ECG data and other related clinical information cannot be found in the narratives of these subjects (e.g. diagnostic tests to rule in or out atherosclerotic disease such as evidence for carotid stenosis). Therefore at least a potential role of study drug is suspicious in the absence of information related to potential etiology aside form the possibility of an undiagnosed underlying condition (e.g. atherosclerotic disease related to either hypertension or hypercholesterolemia given their PMH of these known risk factors for atheroslerotic disease).*

  Subject 201452 was hospitalized and the following medications were initiated fenofibrate, magnesium sulfate, and piracetam. It appears that he continued OL pal treatment through Day 299 of the study. The "ischemic stroke" was reported as resolved within 9 days and the aphasia resolved in 48 days since their initial onset and after initiating pharmacotherapy.

  Subject 300166 received Pal treatment intermittently (on Days 12 for unclear reasons and Days 41-42 that coincided with the SAE) and ultimately the subject withdrew from the study "due to noncompliance with study medication." Perhaps the Day 12 dose was missed due to noncompliance (but this is not clearly stated in the narrative). CT and MRI were reported as showing "no acute disease" or as "negative," respectively (day of neuroimaging was not found in the narrative). The events in this subject resolved withing 3 days of their onset.

- *Subject 200179: This 65 year old female had "confusional" state leading to an ADO on Day 27 of OL pal (6 mg/day). This subject had a history of "cardio sclerosis and cerbro sclerosis," and had completed 43 days of DB pal at the same dose. A description of vital sign, ECG results or other related clinical information could not be found in the narrative. Therefore, at least a contributory role of Pal needs some consideration.*
- *Subject 300129: Developed dizziness and fell on Day 170 of OL 6 mg/day Pal in Study -704 reported as an SAE.*

I. Seizures or Syncope

Another subject (S300693) in Study -304 had a "possible" seizure who had a history of alcohol abuse and recent abuse of alcohol and recent cessation of lorazepam administration for extrapyramidal disorders. It is not clear if this subject actually had a seizure and if this subject did it was likely related to alcohol withdrawal (along with recent cessation of lorazepam).

See additional subjects of syncope described under subsection C on cardiovascular related SAEs Associated with Syncope and under a subsection on potential cerebrovascular-related events (subsection H).

Additional subject found in the 120-Day Safety Update Report and/or in OL Trials:

- *Subject 200986: This was a 30 year old female with an unremarkable PMH and no concomitant medications reported in the narrative who had an SAE of "generalized tonic-clonic convulsion" reported on Day 13 of OL 9 mg daily of Pal in Study -703 that resulted in an ADO. She had a "sudden onset of tremulousness of hands and feet followed by a fall...frothing at the mouth, and loss of consciousness lasting...about 5 minutes" without "incontinence, injury, tongue biting or postictal confusion reported." An EEG 2 days later was WNL and the subject was lost to follow-up. The narrative does not described any vital sign or ECG results, laboratory results or other clinically relevant information that would lead to potential etiologies. Furthermore, it is not clear if this subject experienced a seizure or some other type of syncopal episode. The absence of a post-ictal state is highly suggestive of a non-seizure related syncopal episode. Although this subject had already received DB Pal (12 mg/day) in the 6-week lead-in study, at least a role of Pal is suspect in the absence of clinical information that would suggest potential non-drug-related etiologies.*
- *Subject 500108 (SAE and ADO): had convulsion reported, hyponatermia, psychogenic polydipsia, aspiration pneumonitis and exacerbation of schizophrenia reported. This subject had undifferentiated schizophrenia who had a history of psychogenic polydipsia. Psychogenic polydipsia has been reported in this patient population which can lead to these other events of hyponatremia, convulsion and aspiration pneumonitis.*

J. Suicidality and Other Mood-related Event (e.g. agitation, aggression, depression).

This topic is covered under Section 7.1.4.6 of this review, based on the sponsor search for suicidality and other related events. A slightly larger incidence of suicidality was found for suicidality in the 15 mg Pall group compared to other treatment groups and placebo, as described in Section 7.1.4.6. Agitation, mood changes, and aggression are expected events of the patient population and in the presence of lack of efficacy of placebo and/or study drug. Section 7.1.4.7 discusses the sponsor's results on their special search for aggression or agitation related AEs that failed to reveal a greater incidence in these events in Pal subjects compared to placebo subjects.

The following descriptions is regarding subjects with suicidality who did not appear to have a clear risk factor for suicidality (aside from schizophrenia) that were found by the undersigned reviewer and are not discussed in Section 7.1.4.6:

A few Pal subjects had suicidality who did not have a clear risk factor for suicidality (e.g. was not reported to abuse substances and did not experience a recent major stressor) other than the known risk associated with this patient population. Many of these subjects were exhibiting signs of experiencing a poor response to Pal treatment or lack of efficacy that would suggest that suicidality was related to their underlying condition together with failure the Pal treatment in adequately relieving these patients of their symptoms of schizophrenia, as described in the following:

- *In Study -304 the CSR described the following subjects who had no reported co-existing or pre-existing conditions that are known to increase risk for suicidality (other than the presence of schizophrenia, of which suicidality more frequently occurs than in the general population):*
  - *Subject 300011in the 12 mg Pal group had SIs along with "increase of symptoms of schizophrenia" with hallucinations and as reported as "wanting to kill herself." This subject was hospitalized and withdrawn on Day 19 from the study due to lack of efficacy.*
- *In Study -305 the CSR described the following subjects who had no reported co-existing or pre-existing conditions that are known to increase risk for suicidality (other than schizophrenia):*
  - *3 mg Pal subjects (500625, 50128): One subject (50128) completed the study which the SI occurred on Day 44 and resolved within 1 day before completing the study on Day 45. This subject's CGI was score was rated as severe at baseline and marked on Day 45, suggesting poor to no Pal treatment response to this low dose-level. The SI in the other subject (50625) was transient (reported on Day 28 and resolved in 4 days). He chose to withdraw from the study several days later after he also reported AEs of palpitation, tremor, lethargy and ambivalence on whether or not to continue in the study. This subject also showed evidence of little to no response to this low dose level of Pal treatment (rated on CGI as moderate at baseline and on Day 36, the day of early withdrawal from the study).*
  - *Two 15 mg Pal subjects in Study -305 who had no reported co-existing or pre-existing conditions that are known to increase risk for suicidality had SIs. One subject (500514) who also had intermittent anxiety (as an AE), completed the study. This*

subject's who had a CGI score that did not change from baseline to Day 43 (assessed as "moderate" on these study days). The other 15 mg Pal subject also had SIs (500623) who also had hallucinations, was "unable to stay calm" and had insomnia with "vague" SIs. He took 9 study drug tablets "and then another 3 tablets"(a 60 mg dose "to calm himself" according to that described on page 141 of the CSR). The patient was hospitalized and received sulpiride and zuclophenotixol acetate. He then improved. He chose to withdraw from the study after about a week following resolution of his AEs, although his CGI score was assessed as marked on the day of withdrawal (Day 23 and also marked at baseline). CGI score was assessed as moderate on Days 4, 8 and 15. The etiology of these SIs are likely to be associated with a lack of efficacy and the known risk of sucidality in this patient population.

- *Only 1 Pal subject is described in the CSR of Study -303:*
  - *This subject (201559) had "cut is arm superficially" and only required topical treatment on Day 23 of 9 mg Pal treatment. This subject withdrew from the study on Day 30 due to lack of efficacy and had CGI ratings of severe at baseline, marked on Day 15 and severe on Day 22 and throughout there remainder of the study, prior to early withdrawal.*

Several placebo subjects also had SIs that could not be accounted for by a pre-existing condition or risk factor other than the presence of schizophrenia (as previously discussed).

3 completed suicides were reported in Study -305 in the 120-Day SUR:

- *2 placebo subjects (500447 and 50130) and*
- *1 subject who withdrew from the study during screening procedures, prior to the DB phase (and was not assigned a subject number).*

K. Elevated CPK

The following enumerates SAEs and ADOs in Pal subjects, according to the summary tables (shown later in this section of the review for completed Phase III trials and as shown later in Section 7.2.9 in the 120-Day Update report, as provided by the sponsor):

- *1 SAE and no ADOs in Short Term Phase III trials: elevated CPK in a 6 mg Pal subject who had a diagnosis of amebic dysentery (S 200969) in Study 303.*
- *None in the Elderly Phase III Study -302*
- *1 SAE and 1 ADO in the 120Day SUR summary table (on the basis of the line listing found in the 120--Day report the ADO and SAE appear to have occurred in a single subject, number 500501 who also had elevated LFTs as described in subsection M on this topic (was in the OL Extension Trials and occurred after over 6 months of exposure of DB Pal/OL Pal treatment).*
- *Study -301 and OL Extension Study -701: reported one subject with NMS and elevated CPK (10057 described in the next subsection).*

The event of elevated CPK alone is not surprising given the study population and the known safety profile for the drug class. The explanation that the sponsor provides (that can be found in

the SCS) for this safety signal on elevated CPK levels is that this type of an event can commonly occur in this patient population.

However, this review describes clinically remarkable elevations in CPK that was observed in multiple trials including Phase I trials (see the section on laboratory parameter results in this review for a description of Phase I results on CPK) that needs to be addressed.

Phase I trials had a number of subjects with dystonic-like related ADOs or SAEs ("muscle spasms," muscular chest pain, dystonic reactions that were sometimes associated with laryngeal or respiratory system involvement). The narratives generally did not include CPK values.

One narrative was found of a subject in a Phase II schizophrenia trials had a dystonic reaction associated with CPK of 607 U/L (in Subject 100040 in Study -SCH-1010).

Only 1 and possibly another subject appeared to have NMS could be found in the SCS and among SAEs and ADOs in the 120-Day SUR. Subjects with rhabdomyolisis, fever associated with elevated CPK, or extrapyramidal side effects associated with CPK were also not found in the SCS (or in SAEs, ADOs in the 120-Day SUR).

L. Neuroleptic Malignant Syndrome

One case of markedly elevated CPK levels in which NMS was reported (in Paliperidone subject) was subject 100057 who was in a "prevention of recurrence" study (found in the 120-Day SUR). This subject first developed "muscle stiffness in the entire body" on Day 15 of Pal treatment while receiving 12 mg daily (the next to the highest dose-level employed in Phase I-III trials). By Day 22 this subject had marked CPK elevation (temperature was 36.4°C).

At least one other subject may have had NMS who was found in a review of the CSR of completed, short-term Phase III trials. Subject 200213 (in Study -303) was in the 12 mg Pal group (the next highest dose-level employed in primarily non-elderly Phase III trials) and was 66 years old (a potential risk factor) who developed fever (reported as an AE) and "dystonia focalis," "hypersalivations," "blurred speech" on day 3 of treatment ("after 2 doses" upon which treatment appeared to be discontinued at this time). Post-dose laboratory values were not available and the only post-dose temperature was on Day 4 (36.8 degrees C) as described on page 117 of the CSR. The subject was reported to be withdrawn from the study on Day 4 "due to dystonia." The patient received neostigmine injections for 1 day and oral pyridostigmine treatment for 2 days. The "investigator confirmed that the patient did not have NMS." A description of a differential diagnosis and the diagnostic work-up to rule out NMS cannot be found in the narrative. Therefore, it is the opinion of the undersigned clinical reviewer that the conclusion that this patient had NMS cannot be made in the absence of actual clinical data. The clinical description of this subject (fever, dystonia) is suspicious of an NMS-like presentation.

M. Elevated CPK with Concurrent Elevations in LFTs

This subsection describes subjects with elevated CPK that also had elevations in LFTs. A discussion of additional and potentially remarkable subjects with elevated LFTs follows this subsection.

It is notable that some schizophrenia subjects in Phase III trials and some Phase I healthy volunteer subjects showed elevations of LFTs that were also associated with elevations in CPK.

Elevations in LFTs (enzymes) can nonspecific and not always involving the liver. However, at least one of the subjects described below also had elevations in GGT (Subject 501245 in an OL Phase III trial, a copy of the narrative is below) who developed markedly elevated CPK and other LFT values who was an ADO due to choleliathisis (she showed evidence for cholangiitis) that may or may not be drug-related (she had multiple risk factors suggesting an undiagnosed underlying condition and she had already received months of treatment prior to developing this condition). This subject is described in more detail in the next subsection on elevated LFTs.

Subject 500501 is also mentioned in the next subsection (a copy of the narrative is provided below in this subsection) who had elevated LFTs and CPK (up to 688 U/L) similar to the above patient. However, the LFT and CPK elevations were not as marked and fever or elevated WBC or eosinihpilia were not described in the narrative (although mention of laboratory results on these parameters could not be found). The elevated laboratory parameters were first noted on Day 169 of Pal treatment and lead to an ADO on Day 174. No past history or risk factors were described in this 33 year old Asian male patient in one of the OL Phase III trials.

Subject 501320 (also listed in the next section on elevated LFTs) during DB olanzapine treatment in one of the Phase III trials that "persisted" during this study, but were also reported during OL extension trial (-705) of Pal treatment (9 mg/day). These laboratory changes lead to an ADO after 3 days of OL Pal treatment. Although the subject had some elevations in LFTs, values increased during the DB olanzapine and OL Pal treatment phase, along with elevations in CPK that were not observed at baseline (CPK elevations of up to 454 U/l during Pal treatment and CPK of 279 was reported during olanzapine treatment). While these events appeared to be related to olanzapine further increases appeared to be related to Pal treatment.

Copies of the narratives of the above subjects are provided below.

Copies of Narratives of the above subjects:

Subject 500501 (paliperidone dosage at onset of event: 9 mg/day; alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine phosphokinase increased gamma-glutamyltransferase increased; [redacted] was a 33-year-old Asian man with a diagnosis of undifferentiated schizophrenia. His medical history and physical examination results at screening were within normal limits; no history of liver disease or hepatic symptoms was noted. The subject was assigned to receive paliperidone 15 mg/day during the double-blind study, which he completed on Day 35. He received paliperidone 9 mg/day during the

open-label extension study On Day 169, the subject experienced a mild "elevated ALT" 60 U/L (reference range: 6-43 U/L), a mild "elevated AST", 37 U/L (reference range: 11-36 U/L), a mild "elevated CK level", 484 U/L (reference range: 18-198 U/L), and a mild "elevated GGT", 211 U/L (reference range: 10-61 U/L), all of which were persistent. The investigator believed that it was possible for the elevated CK level to be related to the study medication but found it doubtful that the elevated ALT, AST, and GGT were related. The subject had a creatine kinase retest performed at a local laboratory on Day 174 and the results were 688 U/L. No history of liver disease was specified. The study medication was permanently stopped after Day 173 and the subject was withdrawn from the study on Day 174 due to the adverse event. He was referred to an internist for further evaluation (source: CIOMS). (Manufacturer's Control Number: KR-JNJFOC-20050502675(2)).

"Subject 501320 (paliperidone dosage at onset of event: 9 mg/day; hepatic enzyme increased; [redacted]) was a 28-year-old black man with a diagnosis of paranoid schizophrenia. His medical history included a full-remission of poly substance abuse and a nonspecific T-wave abnormality; there was no history of liver disease reported. His physical examination results at screening were within normal limits. The subject was randomly assigned to receive olanzapine 10 mg/day during the double-blind study. Adverse events reported included non-serious events of "moderate elevated liver enzymes" and moderate "elevated CK" increased on Day 44; both events persisted and were considered by the investigator to be probably related to study medication. He completed the study on Day 44 and entered the open-label extension study. The subject received paliperidone 9 mg/day during the open-label study. On Day 1, the non-serious events of moderate "elevated liver enzymes" and moderate "elevated CK" were reported. Laboratory data at double-blind screening revealed elevations in alanine aminotransferase (ALT) 49 U/L (reference range: 6-43 U/L), creatine kinase 279 U/L (reference range: 18-198 U/L) and gamma glutamyl transferase (GGT) 118 U/L (reference range: 10-61 U/L). At double-blind baseline elevations were noted in ALT of 60 U/L, aspartate aminotransferase (AST) 41 U/L (reference range 11-36 U/L) and GGT 114 U/L. On Day 1 laboratory data included ALT 73 U/L, AST 52 U/L, GGT 249 U/L and CK 454 U/L. The subject was not treated and the events resolved within 9 days. The investigator believed that the events were probably related to the study medication. Study medication was stopped on Day 3; on Day 4, the subject was withdrawn from the study due to the event of increased hepatic enzymes."

"Subject 501245 (paliperidone dosage at onset of event: 9 mg/day; cholelithiasis; [redacted]) was a 58-year-old black woman with a diagnosis of paranoid schizophrenia. Her medical history included elevated

triglycerides and diabetes; physical examination was noncontributory to the adverse events. The subject was randomly assigned to receive paliperidone 9 mg/day during the double-blind study. "Nausea", "yeast infection," "abnormal ECG," "headache," "fatigue," and "middle insomnia" were reported as adverse events during double-blind; concomitant medications included clotrimazole, acetylsalicylic acid, amantadine, metformin and multivitamins. The subject completed double-blind and entered the open-label extension study on Day 43. The subject received paliperidone 9 mg/day during the open-label extension study including 9 days without study medication. On Day 192, the alanine aminotransferase (ALT) was slightly elevated at 56 U/L (reference range: 6-34 U/L). The ALT remained elevated on Day 204 at 51 U/L, and 57 U/L on Day 311. The ALT on Day 367 was within normal limits. On Day 295, the serious adverse event "cholelithiasis" was reported. Study medication was temporarily stopped on Day 295 as the subject reported nausea and then confusion, when she stopped taking her study medication (source: CIOMS). She was admitted to the hospital on Day 298 (source: CIOMS) for confusion and right upper quadrant abdominal pain (for the last week), which she attributed to eating spicy foods. Her temperature in the emergency room was 101.7° (later reported to be 99.1°). Diagnostic studies revealed a negative chest x-ray and ECG showed normal sinus rhythm (source: CIOMS). Laboratory results showed sodium 136, potassium 3.4, chloride 96, CO2 30, BUN 14, creatinine 1.2, total protein 7.3, albumin 3.4, glucose 184, phosphorus 1.9, urate 8.2, bilirubin 6.4, alkaline phosphatase 219, CK 938, LDH 543, AST 346, ALT 821, triglycerides 530, total cholesterol 177, TSH 3.91, free T-4 1.1, urine pregnancy test negative, WBC 5.2, hematocrit 32%, MCV 94, platelets 300,000, segs 74%, (no units or ranges provided). A consultation was obtained because of the elevated liver function tests; the subject had no history of liver disease or any family history, no known hepatitis, no history of intravenous drug use, blood transfusion, GERD, ulcers or pancreatitis. The subject denied any abdominal pain but reported that she had nausea without emesis for 1 week after eating greasy food. The subject reported never being a heavy drinker and last drank alcohol 2 years ago (source: CIOMS). Metformin was stopped during the hospitalization. Laboratory analyses showed amylase and lipase to be within normal limits, total bilirubin 3.3, direct bilirubin 1.8, alkaline phosphatase 191, CPT 282, AST 150, and ALT 550 (no units or ranges provided). The physician assessed that the subject's liver function tests exhibited both a cholestatic and hepatocellular pattern. Moreover, given the subject's history of symptoms starting after a greasy meal and dark urine with bile, this likely representedcholestatic disease, possibly caused by gallstones. An abdominal ultrasound was ordered to better evaluate the subject (unknown results). The subject recovered without sequelae and was discharged from the hospital on Day 304 (source: CIOMS). Paliperidone 9 mg/day was resumed on Day 304. The investigator considered the cholelithiasis severe and doubtfully related to study medication. The serious adverse event of cholelithiasis resolved in 9 days. The subject completed the study on Day 367. The other adverse events reported