during the study were "sore throat," "increased triglycerides," "hypokalemia," "rash on chin," "pinched nerve" and "diarrhea" (3 times)."

**N. Elevated LFTs**

*The following enumerates SAEs and ADOs of an elevated LFT were reported in Pal subjects (according to summary tables later in this section for the completed DB Phase III Short-Term trials and in summary tables provided in the 120-Day SUR shown in Section 7.2.9 for OL Studies and Studies -301 and -701):*

- *DB Phase III Short-Term Trials (-302, -303, -304, -305) in which subject numbers were found in a line listing in the SCS:*
  - *1 SAE of increased LDH in a subject in the 6 mg Pal group in Study -303 (the line listings show a subject 200969 who also had increased CPK as an SAE who was diagnosed with amebic dysentery).*
  - *4 ADOs of which 3 subjects had abnormal baseline values:*
    - *1 ADO of increased transaminases in a subject (201445) in the 12 mg Pal group in Study -303 who had abnormal values at baseline.*
    - *2 ADOs of increased hepatic enzyme: in a 3 mg subject (that appeared to be drug-related as described below in subject 500853 that was found in the line listings) and a 6 mg Pal subject (subject 201684 who had abnormal baseline values but was receiving risperidone prior to be receiving Pal)*
    - *1 ADO of increased ALT in a 9 mg Pal subject in Study -303 who had abnormal values at baseline.*
- *OL Extension Trials (-702,-703, -704, -705) in which subject numbers were found in line listings in the 120-Day SUR*
  - *Only 1 SAE of a liver function related event (cholelithiasis) can be found in the summary table enumerating SAEs. The LL shows that subject 501245 with cholelithiasis (with fever and leukocytosis) reported as an SAE and leading to an ADO that appeared to be possibly related to an underlying, undiagnosed condition, but this is not certain (in the absence of critical diagnostic data such as ultrasound results; see the previously provided narrative in the above subseciton).*
  - *ADOs of*
    - *1 subject with increased AST, ALT, GGT (GGT was elevated to greater extent than AST and ALT with values of upt to 211 U/l reported in the narrative) and CPK reported as AEs leading to the ADO in a DBPal/OLPal subject in the over 6 month treated subgroup in Study -705 (Subject 500501, according to the line listing in the 120-Day SUR). According to the line-listing on SAEs this subject also had elevated CPK of up to 688 U/l reported as an SAE (as already described above in more detail). These events were first observed on day 169 of OL Pal treatment (9 mg/day). This subject was a 33 year old with unremarkable PMH and no concomitant medications reported in the narrative and the outcome of these events after early treatment cessation cannot be found in the narrative. Therefore, in the absence of a non-drug-related explanation for*

*these elevations a role or cause of the study drug is suspected. See the narrative information provided in subsection M above.*

- *1 subject with increased hepatic enzyme in the ≤ 6 month DB Olanz/ OL Pal group (according the LL subject 501320 was an ADO due to "elevated liver enzymes"). This subject had elevated LFTs (GGT, AST and ALT) as well as elevated CPK after completing DB olanzapine treatment (in the 6-week lead-in study) but they increased further (up to 5 x ULN for GGT and CPK reach 454 U/L while other LFTs also increased to a lesser extent) on Day 1. Pal was discontinued on Day 3 and these events resolved by 9 days post Pal cessation. These events appeared to be olanzapine related but may have been further increased by Pal. The narrative of this subject was provided under the previous subsection.*
- *An additional ADO was found in the LL (not in the summary table) of cholelithiasis in subject 501245 that was also reported as an SAE.*

- *Study -301 had 1 subject (subject 100737) with an SAE of cholelithiasis that lead to an ADO after only 1 day of treatment in the run-in phase.*

  *Cholelithiasis was reported in a 47 year old female (100737 subject) after only 1 day of treatment in the run-in phase that lead to an ADO. This type of event is not uncommon in a 47 year old female and is not likely to be drug-related given that the event occurred only after one day of a 9 mg Pal dose. Cholelithiasis was reported in a 47 year old female (100737 subject) after only 1 day of treatment in the run-in phase that lead to an ADO. This type of event is not uncommon in a 47 year old female and is not likely to be drug-related given that the event occurred only after one day of a 9 mg Pal dose. However, the narrative does not provide any laboratory values (e.g. eosinophil count to determine if eosinophilia was present which would suggest a drug-related cholangitis secondary to an allergic response to the study drug). The 120-Day SUR narrative indicates that an ultrasound revealed cholilthiasis. Therefore, it is unlikely that this event was drug-related.*

*The sponsor provided narratives for subjects with greater than 3 times the upper limit of normal on ALT or AST but these narratives were generally not reviewed since there were SAEs, ADOs and clinical parameter sections on LFTs that were considered more informative (since many subjects with greater than 3 times of the upper limit of normal had abnormal values at baseline and since the incidence of outliers on LFTs was provided in other sections with results described in this review).*

*At least some of the below cases are considered likely to be drug-related as described below. Yet, descriptions of individual subjects could generally not be found in any in-text section of the SCS. Given that cases of concern were revealed by the undersign reviewer that were not found in the in-text sections of the SCS the sponsor was inquired about outliers on LFTs, as discussed below.*

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

*Inquiry on Remarkable LFT Outliers with a Response Received in a Recent N005 submission with Review of Results Pending:*
*Since some remarkable cases were found in at least one subject involving up to approximately 8 times the upper limit of normal (ULN) of AST and elevations in other LFTs during 15 mg Pal treatment. This subject could not be found in line listings of SAEs or ADOs or in in-text sections on LFTs in the SCS (this subject, 5013018, is described below). Due to concerns of missing other remarkable cases the sponsor was asked to provide more information about outliers on LFTs (e.g. using specific cut-off criteria for subjects with normal values at baseline and other specifications).*

*The results of a N005 response to our inquiry was submitted and are summarized in section 7.1.7.3.3 in this review.*

*Since most narratives describing elevations in GGT (and/or CPK) did not mention laboratory results on WBC and differential it may be informative to ask the sponsor about any cases of elevated LFTs with eosinophilia. Cholangitis (with increased GGT and also generally increased alkaline phosphatase) in the presence of eosinophilia would be highly suspicious of a drug-related event.*

*In addition to the previous described subjects with elevations in LFT (and/or CPK) the following subjects are noted.*

***The following are subjects found with elevations in LFTs (±CPK elevations):***

- *The following subject was found in the narratives (which were provided for subjects with greater than 3 times the ULN of LFTs) but the subject was not listed as an ADO or an SAE. Subject 503018 in the* ***15 mg Pal group*** *in Study -305 was a 44 year old male with no history or abnormal baseline values suggestive a pre-existing liver disorder who developed approximately* ***8 times the ULN of ALT and approximately 5 times the ULN of AST*** *with about* ***almost 4 times the ULN of GGT on Day 15 of Pal that resolved to normal values after 9 days (on Day 29) following Pal cessation on Day 20.*** *The subject received 12 mg daily of Pal for 7 days (during a titration period) followed by 12 days at the 15 mg daily dose-level.*

***The marked elevation in LFTs in the above subject is likely to be drug-related*** *given the patient's unremarkable past history and normal baseline LFTs, the marked increase in LFTs after a few weeks of a high dose of Pal that resolved upon dechallenge. The elevated LFTs were not reported as AEs and the subject withdrew from the study 4 days after Pal was stopped (on Day 20, LFTs were elevated from Day 15, "onward" and normalized on Day 29). The narrative doesn't say why Pal was stopped on Day 20 and the subjects was not listed as an ADO. The narrative says he withdrew from the study on Day 24 "due to non-compliance." This subject was found in the narratives, but a description of this subject could not be found in in-text sections in the SCS or in in-text sections of the Study Report for Study 305 (e.g. sections in the SCS and Study report on individuals meeting outlier criteria or on "individual subject changes" on laboratory*

*parameters such as Section 3.2.1 on page 160). Concomitant medications reported at baseline: amfebutamone hydrochloride 400 mg and lisinopril 10 mg/day.*

*One subject (*500853) *was an ADO in Study -305 due to* ***elevated liver enzyme levels of up to 5 times the ULN on ALT on Day 14 that remained elevated through Day 19*** *of treatment (over 4 times ULN), along with elevations in AST and GGT. These events led to early discontinuation of Pal on Day 20. This subject was in a low dose group (3 mg Pal/day) and resolved about one week after treatment cessation. ALT increased up to 214 U/l (6-43 U/l within normal limits) and AST reached 76 U/l (11-36 WNL) and GGT was slightly elevated (72 U/l with 10-61 WNL).*

***This ADO is likely to be drug-related*** *given no pre-existing condition or concomitant medications to explain these elevations and given resolution of these elevations upon dechallenge. It is noteworthy that this subject was in the lowest dose Pal group (only 3 mg/day). Therefore, it is possible that an unidentified underlying condition may have at least in part contributed to the elevations in LFTs.*

*A copy of the narrative of the above subject and of others are provided in the latter part of this subsection.*

*The following provides more information on previously mentioned subjects who had baseline LFT abnormalities who were ADOs due to abnormal LFTs:*

*Study -303 describes 3 Pal subjects (201684, 201518 and 201445) who were ADOs due to non-serious liver-related events (occurred in 1 subject in each of the following Pal groups: 3 mg, 6 mg and 12 mg groups). All three subjects had abnormal LFTs (liver enzyme levels) at baseline and/or screening assessments and all three showed a further elevation or similar abnormal levels during DB Pal treatment that resulted in early treatment cessation. One of these subjects also had "fever" and "bronchial process." LFT elevations in this subject (201518) and subject 201445 did not exceed 3 times the upper limit of normal and one sucject was discintued on Day 1 of the DB phase.*

*Among the above 3 subjects (ADOs) with abnormal baseline LFTs, subject 201684 had the most remarkable LFT increases from approximately 2 times the ULN on ALT and AST at baseline to approximately 10 times the ULN on ALT and approximately 5 times the ULN on AST (GGT<2 times the ULN) on Day 17 of treatment (6 mg/day of Pal). This subject was on risperidone prior to the study (Day -4). A copy of the narrative is provided below and the following summarizes findings. Study drug was discontinued on Day 24 as levels remained high and LFTs started to decrease from previous values on Day 25. This subject was a 22 year old female subject who had abnormal levels at baseline but had no remarkable history that would explain her abnormal LFTs (as described on page 136 of the CSR). Clearly from the baseline values this subject had a pre-existing and undiagnosed condition. Yet these elevations could have been exacerbated by Pal treatment as suggested by decreasing levels upon treatment cessation and she was receiving Risperidone prior to the study and until Day -4.*

*Copies of Narratives of a few of the above subjects are provided below, so as to provide some more detail of the progression of the events and diagnostic work-up if any (of which some of the examples below also provide the investigator's or other clinical interpretations of which some may differ from the above interpretation by the undersigned reviewer). Key events described in these narratives were previously discussed above.*

*Although this subject was only receiving 3 mg Pal daily Pal-induced elevations in LFTs is suspected:*

**Subject 500853 (paliperidone; preferred term: hepatic enzymes increased;**
[redacted] ) was a 27-year-old man with a diagnosis of schizophrenia, undifferentiated type. The medical history and screening physical examination were normal; no history was reported of hepatic disorder or alcoholism. The subject discontinued haloperidol 7.5 mg/day, orphenadrine 100 mg/day; rescue medication lorazepam 1 mg/day was given only on Day -5. No concomitant medications were reported at baseline. At screening Day -2, laboratory values were unremarkable; the baseline (Day-1) laboratory values were normal. The hepatic enzymes at screening and baseline were within normal limits.
On Day 14 while receiving paliperidone 3 mg/day, *hepatic enzymes increased* (increased liver enzymes-verbatim) were reported as an adverse event. Elevations were present in the following hepatic enzymes: alanine aminotransferase (ALT) 214 U/L (reference: 6-43 U/L), aspartate aminotransferase (AST) 71 U/L (reference: 11-36 U/L), and gamma glutamyl transpeptidase (GGT) 72 U/L (reference range 10-61 U/L).
On Day 19 the ALT was 171 U/L, the AST was 76 U/L, and the GGT was 58 U/L (within normal limits). On Day 27 (post study Day 7), the ALT remained elevated at 44 U/L, the AST was normal at 23 U/L and the GGT at 40 U/L was within normal limits.
Study medication was discontinued on Day 20 due to the increased liver enzymes, which resolved in 25 days. The investigator considered the increased liver enzymes to be moderate in severity and very likely related to study medication.
The subject received paliperidone 3 mg/day for 20 days and was withdrawn from the study on Day 20 due to the increased liver enzymes.
The ALT, AST and GGT were elevated at Day 14. The GGT returned to normal on Day 19, while the ALT and AST were further elevated. The subject was withdrawn from the study on Day 20 due to the increased liver enzymes. The AST returned to normal on Day 27 and the ALT remained elevated. As increased hepatic enzymes have been reported with the use of paliperidone, the sponsor considered that a causal relationship between the elevated hepatic enzymes and the use of the study medication in this subject cannot be excluded.

*The following subject was previously described as having abnormal baseline LFTs but showed greater elevations on Pal:*

**"Subject 201684 (paliperidone; preferred term: hepatic enzymes increased;**
[redacted] ) was a 22-year-old white woman with a diagnosis of

paranoid schizophrenia. The medical history and screening physical examination were non-contributory to the adverse event. There was no history of hepatic disorder. The subject discontinued risperidone 2 mg/day on Day -4. Diazepam 10 to 15 mg/day was given as a rescue medication from Day 1 through Day 10. At screening, laboratory values were unremarkable for the relevant parameters; hepatic enzymes were within normal limits.
At baseline, elevations were noted for alanine aminotransferase (ALT 71 U/L; reference: 6 to 34 U/L) and aspartate aminotransferase (AST 50 U/L; reference: 9 to 34 U/L). Despite the ALT elevations twice the upper limit of normal (a protocol violation), the subject entered the study.
On Day 17, while receiving paliperidone 6 mg/day, an adverse event of *hepatic enzymes increased* (liver enzymes increase-verbatim) was reported. At this time, ALT was 376 U/L, AST was 164 U/L, gamma-glutamyltransferase (GGT) was 60 U/L (reference: 4 to 49 U/L), and lactic dehydrogenase (LDH) was 228 U/L (reference: 53 to 234 U/L). Study medication was unchanged.
On Day 22, ALT was 320 U/L, AST 164 U/L, GGT 59 U/L, and LDH 232 U/L. Study medication was discontinued on Day 24 as a result of the increased liver enzymes.
On Day 25, ALT was 230 U/L, AST 80 U/L, GGT 54 U/L, and LDH 173 U/L. The investigator assessed the liver enzymes increase as moderate in severity and doubtfully related to the study medication. The adverse event was ongoing at the time of study discontinuation.
The subject received paliperidone 6 mg/day for 24 days and was withdrawn from the study on Day 25 due to this adverse event.
ER OROS Paliperidone: MODULE 2.7 Clinical Summary; 2.7.4 Clinical Safety
The adverse event, "hepatic enzymes increased" was reported on Day 17. However, ALT and AST were increased at baseline. Although increased hepatic enzymes have been reported with the use of paliperidone, the sponsor considered a causal relationship between the adverse event, "hepatic enzymes increased", and the use of the study medication in this subject unlikely."

**O. Remarkable Glucose-Related SAEs.**

*It is noteworthy that elevated levels of glucose, which is expected for the drug class (as described in labeling of approved atypical antipsychotic agents). Many of the patients with elevated glucose levels or other related abnormal laboratory measures (e.g. elevated insulin levels) had pre-existing diabetes mellitus or abnormal glucose (and insulin levels in some paitents) at baseline. Some patients had risk factors for diabetes mellitus (e.g. obesity). Most events of hyperglycemia resolved in these patients (e.g. after cessation of Pal).*

*Although hyperglycemia is already described in proposed labeling (as is the standard for drug class labeling for this drug class) it may be informative to ask the sponsor about any cases where hyperglycemia did not resolve upon dechallenge. Yet it may still be difficult to interpret results since some patients may have had undiagnosed diabetes or undetected diabetes prior to treatment which would be difficult to determine in retrospect.*

*Weight gain is known to be associated with this drug class and was observed with Pal which can increase risk for diabetes.*



*The following subjects were some examples of SAEs due to hyperglycemia and/or other events that were found upon review of some of the short-term trial CSRs:*
*The CSR of Study -305 describes the following SAEs in Pal subjects. SAEs of diabetes mellitus and hypoglycemia were reported in a subject (S501122). This subject subsequently developed SAEs of "renal failure acute" and "GI hemorrhage" which were reported on Day 40 of the DB phase (in the 9 mg Pal group) who was hospitalized. This 45 year old female subject had a history of diabetes, hypertension and was overweight at baseline. She also had elevated OGTT glucose levels at baseline, as well as elevated cholesterol and triglyceride levels. While a role of Pal is possible, this subject had pre-existing conditions that at least contributed to these events.*

*S501300 had hyperglycemia as an SAE and ADO on Day 11 of the DB Phase who was obese, 36 year old male and had increased appetite and weight gain during 15 mg Pal daily. This subject had elevated glucose and insulin levels at screening. Hyperglycemia resolved after cessation of treatment.*

*See section 7.1.4.13 for a special search for glucose related AEs conducted by the sponsor.*

**P. SAEs of Hyponatremia or "Water Intoxication"**

*SAEs of hyponatremia were reported in a few subjects in both placebo and Pal groups.*

*The Pal subject in Study -305 with this SAE (501136) had a previous history of seizure due to hyponatremia and was reported to have "water intoxication" on Day 18 on Day 18 of 9 mg/day Pal that resolved with treatment within 3 days. Study drug was discontinued on Day 19 due to extrapyramidal related AEs. Electrolyte levels were normal in this subject except for a low potassium on Day 20.*

*The following subject was found in a line listing of OL subjects in the 120-Day SUR who was previously listed under Subsection I on Seizures:*

- *Subject 500108 (SAE and ADO): had convulsion reported, hyponatermia, psychogenic polydipsia, aspiration pneumonitis and exacerbation of schizophrenia reported. Psychogenic polydipsia has been reported in this patient population which can lead to these other events of hyponatremia, convulsion and aspiration pneumonitis.*

**Q. SAEs of Duodenal Perforation or Gastrointestical Hemorrhage**

*Because of the formulation (OROS) it is important to describe any potential cases of duodenal perforation. See below.*

*1 SAE of Duodenal Perforation and 1 SAE of Gastrointestinal Hemorhage in a 6 mg and 9 mg Pal Subject, respectively were reported with subject descriptions as follows in which the etiology of these events are not clear:*

- *See the description of subject 501122 in Study -305 (in the 9 mg Pal group) above who had diabetes mellitus who had SAEs of "diabetes mellitus," "renal failure acute," and "GI hemorrhage." This subject had a history of pre-existing conditions (diabetes mellitus, hypertension, overweight, among other conditions) that can lead to these type of events, although the role of the study drug is possible given the events of hyperglycemia known to be associated with this drug class as described in labeling of approved drugs. The etiology of GI hemorrhage is not clear based on the sponsor's description found in the CSR. This subject had multiple conditions that complicated the clinical picture.*
- *The CSR of Study 303 describes one Pal subject (201333) with "ruptured duodenum" on Day 37 of 6 mg Pal treatment (in a 47 year old male) that required surgery and required early study withdrawal. This subject is not described as having any concomitant medications or any remarkable medical conditions or clinical abnormalities. Therefore the etiology of this serious and remarkable clinical event cannot be determined.*

*The potential role of the OROS formulation is unclear in the above cases. The former subject had multiple serious medical conditions and one might suspect that this patient had a pre-existing undiagnosed GI disorder (obese, diabetes, renal failure, and others). However, the OROS capsules may have exacerbated and undiagnosed underlying condition. The latter subject is less clear.*

*The other subject is less clear, but could be an isolated case. Labeling should include standard language as was used for Concerta® as follows (copied from approved labeling) but should also include a comment on the total number of subjects in all clinical trials in the development program who had any evidence of GI rupture or GI hemorrhage and described the number of days and daily dose (with number of capsules received daily), which would be the above subject.*

**"Potential for Gastrointestinal Obstruction**

Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients)."

*See the last section of this review for recommendations.*

**R. Anaphylactic Reaction and Steven Johnson's Syndrome**

*Only 1 SAE of anyphylactic reaction was reported but was treatable with diphenydramine but the subject had a recurrence, so the study drug had to be discontinued. The sponsor did not describe any cases of Steven Johnson's syndrome that could be found in in-text sections or reported as SAEs or ADOs..*

**S. Thrombocytopenia Cases:**

*A clinically unremarkable numerical mean decrease in platelet count observed almost consistently in all trials. There were not ADOs or SAEs of thrombocytopenia that could be found in Phase III trials except for the following that appeared to have an underlying etiology. Although a bone marrow biopsy was not performed on this subject and other key diagnostic test were not mentioned to confirm the diagnosis. This subject is described below.*

*100847 Study -301 as on page 1824 of SCS: This subject is a 41 year old who developed low platelet count (as low as 80, 000/mm$^{3)}$ days after starting OL Pal during the stabilization phase if study -301 (Day 15 in this study phase and Day 71 in the study involving OL Pal). The subject was receiving 12 mg of Pal daily (as described in the narrative provided in the Safety update report submission under this NDA). This SAE was worked up by a hematologist. The subject also had high reticulocyte count, megaloblastic and macrocytic anemia and decreased WBC from 9400 at baseline to 5400 during OL Pal treatment (hematology values on all parameters including platelet count were generally normal at baseline. He was not receiving concomitant medications and his hematology work-up was negative (no jaundice, hepatomegaly or splenamegaly, no schistocytes on peripheral smear or elevated bilirubin and no lymphadenopathy or evidence on physical examination for cancer. Bone marrow and B12 and folate levels were not obtained but the patient was treated with multiple vitamins (iron, folate, and others) and thyroid extract. Hematology parameters showed improviement with this treatment as the patient was continued on OL Pal with the dose titrated up to 12 mg daily. Platelet count increased to 260,000. mm$^3$ on a date that appears to be after multivitamin treatment was initiated and whiel the patient was continued on Pal. The patient also had elevated LDH. The hematologist suspected a nutritional deficiency in this 54 kg male subject with schizophrenia as follows (as copied from the CIOMS Report on this subject on page 2088 of the SCS):*

> A hematoglist's evaluation revealed the appetite of the patient increased along with behavioral improvement while on study medication. Subsequently the subject started complaining of lethargy, weakness, anorexia and shortness of breath. A complete blood count showed mild pancytopenia and elevated LDH. The pancytopenia subsequently improved after receiving B12 injections along with folic acid 1 mg intramuscularly for 10 days. The hematologist also reported

"The peripheral blood picture, pancytopenia, elevated LDH and prompt response to B12 and folate is consistent with B12/folate deficiency. I feel this is nutritional B12/folate deficiency. In India, this is a very common problem, hence B12/folate levels and bone marrow is not routinely performed in all cases. It is done only if the patient does not respond to B12 and folate. I do not feel this is drug induced marrow suppression or drug induced impaired absorption of B12/folate. The development of B12/folate deficiency and commencement of the drug is purely coincidental".

**T. Miscellanious SAEs or ADOs**

*The following is an additional remarkable SAE to which the etiology is unknown that was found by the undersigned reviewer (that did not fall under previous categories):*

- *Subject 201422: This 56 year old female is described because she had an **SAE of "traumatic hematoma"** that required **"subcranial evacuation"** and was associated with "complications." This SAE was reported **on Day 255 of OL Pal (9 mg/day)** and **lead to an ADO**, as well as hospitalization and surgical intervention. She also had the SAE of "schizophrenia aggravated" that required continued hospitalization after she recovred "with uspecified seqeuelea on Day 269." This subject had **AEs of "arterial hypertension (3 times)" and "increase weight" during OL treatment.** She had received placebo during the DB 6-week lead-in study. Without additional information at least a role of Pal is suspected.*

*Additional SAEs or ADOs from Phase I Trials*

*The following are noted since they may suggest a new finding not previously described and not described in drug class labeling of approved antipsychotic agents.*

**Narrative for Discontinuation Due to Adverse Event**
**R076477-SCH-1010**
**CRF ID: 100040**
**Country: Romania**
**Study medication: ER OROS paliperidone**
**Subject 100040 (dystonia)**, a 34-year-old white man with residual-type schizophrenia and an otherwise unremarkable medical history, was randomized to the ER OROS paliperidone group. His baseline PANSS score was 50 and the CGI–S indicated mild disease severity. Prior to the study, he was taking clozapine 200 mg once daily which was stopped on Day -5. The subject presented with mild diarrhea on Day -1 which resolved the same day with furazolidone treatment. On Day 2 of the study, the subject experienced mild oculogyric crisis and moderate severity **laryngeo-pharyngeal dystonia** which resolved the same day after treatment with diazepam and trihexyphenidyl. The subject withdrew from the study on Day 2 due to the adverse events and clozapine therapy was resumed on Day 4 for treatment of psychosis. At baseline (Day -10), his serum chloride level was 107 mmol/L (normal range: 94 and

112 mmol/L). By Day 5, the value had increased to 113 mmol/L. A concurrent creatine kinase level was also elevated (607 U/L; normal range: 18-198 U/L). With exception of low serum cholesterol values (3.02 and 3.64 mmol/L; normal range: 3.88-6.83 mmol/L), all other serum chemistry values were within normal limits. No follow-up laboratory information is available.

### 7.1.4 Other Search Strategies

The following subsections are special search strategies conducted by the sponsor.

#### 7.1.4.1. Sponsor's Results of AEs of "Common" AEs of "Interest"

The sponsor analyzed common AEs of "interest" of which findings are summarized in subsections below. The sponsor conducted this analyses on completed short term Phase III trials (Studies -303, -304, -305, short-term, placebo-controlled, fixed, parallel group 6-week trials using multiple dose-levels) and on the ongoing OL extension trials (-702, -703, -704, -705). The sponsor also provides results from the elderly short-term, flexible-dose (3 to 12 mg/day), placebo controlled Phase III trial, Study -302.

All results described in this section including any descriptions of related SAEs and ADOs are using a 5/31/05 cut-off date for ongoing studies (the longterm OL studies).

An analyses of AEs of "interest" were not conducted for the ongoing placebo controlled "prevention of recurrence" study (-301) and for the ongoing OL extension trial (-701 of which Study -301 is the lead-in study).

***Reviewer Comment and Caveat to Results Described in Subsections 7.1.4.1-12.***
*Please refer to previous sections of this review for a description of additional cases found by the undersigned reviewer (primarily provided in Section 7.1.3.3 of this review). Also see previous comments on questions that the sponsor was asked to clarify on other cases (see Attachment 1 and Section 7.2.8 ).*

*The sponsor has responded to some of questions about potentially clinically remarkable subjects (e.g. listing all subject with syncope, questions about capturing subjects with suicidality)), while responses to other questions relevant to finding potentially clinically remarkable subjects are pending at the time of this writing. Responses received late in this review cycle have not yet been reviewed (see Section 4.1 for a listing and Attachment 1 for questions asked).*

*Refer to the last section of this review for more comments and recommendations.*

*One additional comment about results provided below is that the results of ongoing OL trials are difficult to interpret. Therefore, the OL trial results are generally not described in this review, unless the undersigned reviewer found results that might suggest a new signal not was observed in the short-term trials.*

### 7.1.4.2. Search for Tachycardia-related AEs

***Reviewer Comments.*** *Results are similar to that described in the subsection below of "Common AEs" (section 7.1.5) in which a drug-related signal for tachycardia was found.*

*The following summarize the sponsor's results:*

- *An incidence of 9 to 14% of tachycardia was observed in paliperidone groups (3, 6, 9, 12 and 15 mg daily dose-levels) compared to 7% in the placebo group in fixed dose, placebo controlled, parallel group, short term Phase III trials of almost all non-elderly patients (included AEs of increased heart rate, sinus tachycardia, tachycardia and tachycardia paroxysm).*
- *The elderly short-term Phase III Trial (-302) showed a 16% incidence of tachycardia in Pal subjects (flexible daily dose of 3 to 12 mg) compared to 0 placebo subjects.*
- *The sponsor also conducted "life table" analyses of AEs of interest, including tachycardia. Based on these analyses the sponsor reports that tachycardia was reported by most subjects within 2 weeks of treatment in short-term DB Phase III trials and within the first month of OL treatment in the OL extension trials.*

### 7.1.4.3. Search for Orthostatic Hypotension-related AEs

The incidence of orthostatic hypotension reported as an AE and of outliers on vital sign parameters (meeting criteria for orthostatic hypotension) are described under appropriate sections in this review (refer to Sections 7.1.5 and 7.1.8, respectively).

***Reviewer Comment.*** *Orthostatic hypotension is known as an adverse effect of atypical antipsychotic drugs and is generally described under Precautions in approved drugs in this drug class.*

*It is noteworthy that orthostatic hypotension as defined by objective vital measures occurs with a greater incidence and a greater difference in the incidence between Paliperidone and placebo groups (as high as 11% in the high-dose 15 mg group compared to only 4% of placebo subjects) than the incidence when orthostatic hypotension is reported as an AE (4% in the 15 mg compared to 1% placebo). This observation may suggest that many subjects meeting outlier criteria for orthostatic hypotension did not have symptoms and were therefore not considered by investigators to have a clinically significant event, such that the event was not reported as an AE.*

*The sponsor also describes results of a safety pharmacology Phase I study (-SCH-101) but since this study did not include a placebo group results are difficult to interpret. It is noteworthy that the incidence of orthostatic hypotension AEs that were elicited upon direct inquiry of the subjects (55% and 79% for the OROS and IR treatment conditions) were higher than AEs reported by the investigator (28% and 56% for each respective treatment condition). A greater incidence observed upon direct inquiry versus reported as an AE is not surprising to the undersigned*

*reviewer given that this observation has also been reported among placebo subjects in some past trials of other drugs that used a placebo controlled study design.*

*The results from the fixed dose, short-term Phase III dataset also shows at least trends for a dose-dependent effect with a greater incidence at higher dose-levels compared to lower dose-levels.*

*See Section 7.1.3.3 for potentially clinically remarkable subjects and section 7.1.8 for vital sign results.*

*Results of dose-dependent and time-dependent effects on the basis of vital sign results for orthostatic changes are discussed in Section 7.18 of this review.*

*See recommendations for labeling and further comment under the last section of this review.*

**7.1.4.4. Search for "Proarrythmic" Potential AEs**

The incidence of "proarrythmic" related AEs involved a search for AEs of seizure, syncope, ventricular fibrillation and flutter, ventricular tachycardia, torsade de pointes and AEs "consistent with sudden death." The sponsor explains that these terms were selected in accordance with ICH E14 (a guidance document for evaluation potential QT prolongation effects).

The following outlines results of the short-term Phase III trial safety dataset:

- No Paliperidone subjects had sudden death related AEs.
- Seizures (convulsion or grand mal convulsion were reported in one 12 mg Pal subject (<1% in this 12 mg group) and one 6 mg Pal subject (<1%) and in no other treatment groups (including 0 out of 355 Placebo subjects and 0 subjects in the 3 mg, 9 mg and 15 mg Pal groups with a total of 286 subjects in these 3 Pal groups).
- Syncope was reported in 1 subject (less than 1% of subjects) in each treatment group including the placebo group (generally 1-3 subjects per treatment group of 127 to 355 subjects/group).

The sponsor had ECG data of all of the above subjects reviewed. The sponsor had vital sign data reviewed for subjects with syncope. The following observations were described in the SCS based on this review of ECG and vital sign data from these subjects:

- None of the 10 Pal subjects had QTcLD values of over 450 msec or an increase from baseline of greater than 60 msec at time-points near or at the time of the AE.
- Among the 8 Pal subjects with syncope, none had orthostatic hypotension based on postural vital sign data but 2 of these 8 subjects had the following abnormal vital signs:
  - Subject 300649 in the 6 mg group was a 36 year old female a standing HR of 120 bpm, supine BP of 90/50 mmHg. That day she had AEs of syncope, diaphoresis, hypoglycemia and dizziness (Day 2) which spontaneously resolved as she continued in the study.

- Subject 502318 in the 3 mg group was a 40 year old women with syncope and hypotension at baseline and on Day 2 (standing BP of 100-70).

No Pal subjects of the elderly Phase III trial, -302 had "proarrhythmic" related AEs (out of 76 total Pal subjects compared to 2 out of 38 placebo subjects (5%) with a proarrhythmic related AE).

The OL dataset showed only 2 subjects out of over 1000 subjects with a proarrhythmic related AE (syncope in 1 subject and seizure in another) in these Pal OL extension ongoing trials. These 2 subjects did not have a QTcLD of over 450 msec at or near the time of the AE or an increase by over 60 msec and vital signs were within normal limits in the subject with syncope (vital sign data was reviewed by the sponsor in subjects with syncope).

***Reviewer Comment.*** *It is not clear from the description found in the SCS why the above OL subjects had syncope and seizure and the nature of these events is also unclear. A subject number for these subjects cannot be found.*

*See Section 7.1.3.3 of this review for descriptions of additional subjects, including a subject with SAEs of hypotension and dizziness and had AEs of syncope and bradycardia. Holter monitoring revealed episodes of "pauses" of up to 8 seconds long in one subject 300541 that was found in the CSR of Study -304.*

*The sponsor was asked about subjects with syncope in Phase III trials (as discussed in other sections of this review) and a response was recently received late in the review cycle (so will be reviewed at a later date, as previously discussed).*

**7.1.4.5. Search for Ischemia-related AEs**

Only 2 Pal subjects out of over 900 Pal subjects (<1% in their respective Pal 6 mg and 12 mg treatment groups) had an ischemia related AE (myocardial ischemia in each subject), and none of the 355 placebo subjects had this type of AE (upon a review of AEs with MedRA terms listed in Appendix 2.7.4.3.11 of the SCS that were identified as ischemia related AEs, according to the sponsor).

One elderly Pal subject in the elderly Phase III trial (Study -302) had "acute coronary syndrome" (out of 76 Pal subjects) and no placebo subjects had an ischemia related AE (out of 38 subjects). The "acute coronary syndrome" was reported as an ADO and an SAE (refer to Section 7.1.2 on SAEs). It should be noted that 1 placebo subject had "cardiac arrest" reported (refer to Section 7.1.2 on SAEs).

Seven out of 1167 (1%) of OL subjects had ischemia related AEs in the OL extension trials in which these subjects were reported as having an ADO and/or SAE due to an ischemia-related

AE. 5 of these 7 subjects had cardiac-related AEs of ischemia. The remaining 2 subjects had stroke-related AEs of ischemia ("ischemic stroke" or "transient ischemic attack").

***Reviewer Comment.*** *The incidence of the above events are not unexpected for the study population. Refer to Section 7.1.3.3 of additional individual subjects with ischemia related events that were found upon review of CSRs of the three pivotal Phase III trials that were not found in the in-text sections of SCS including the section on ischemia related events.*

**7.1.4.6. Search for Suicidality-related AEs.**

***Reviewer comment.*** *Based on results described below the incidence of suicidality is generally expected for the study population and Pal treatment groups showed a similar incidence to placebo in the pooled dataset from short term non-elderly Phase III trials, except that the high dose Pal group (15 mg) showed an incidence of 3% compared to 1% of placebo and almost all lower dose Pal groups (except the 3 mg group had an incidence of 2%). It is difficult to determine if this finding is a real finding versus an artifact (e.g. due to multiple group comparisons on multiple dependent errors resulting in a Type I error). However, since the greatest incidence was observed in the highest dose group and since there is only one dataset of placebo controlled, fixed dose trials with only one study using this high dose-level, then this result should be taken as a possible true positive finding at this time. The sponsor conducted a review of CRFs of SAEs (CIOMS forms, as described later) and found CRFs of subjects in which the investigator had comments related to suicidality but did not report an AE of suicidality. Upon inquiry by the sponsor the investigators who had these particular subjects verified they "judged that no suicidality-related AE should be recorded."*

*The sponsor summary table is shown below.*

Table 40: Treatment-Emergent Suicidality Adverse Events By MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

| Suicidality Group Dictionary-derived Term | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) n (%) | ER OROS PAL 6 mg (N=235) N (%) | ER OROS PAL 9 mg (N=246) n (%) | ER OROS PAL 12 mg (N=242) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects with suicidality-related AE** | 5 ( 1) | 2 ( 2) | 2 ( 1) | 2 ( 1) | 1 (<1) | 3 ( 3) | 5 ( 1) |
| Suicidality | 5 ( 1) | 2 ( 2) | 2 ( 1) | 2 ( 1) | 1 (<1) | 3 ( 3) | 5 ( 1) |
| Suicidal ideation | 4 ( 1) | 2 ( 2) | 2 ( 1) | 1 (<1) | 1 (<1) | 3 ( 3) | 3 ( 1) |
| Suicide attempt | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 2 ( 1) |

*It is important to note that the 10 Pal subjects with suicidality AEs in the short-term Phase III trial dataset had no history of suicidal ideation or suicide attempts. Yet, none of the placebo subjects of these trials that had suicidality who had a positive history for suicidality (as found upon review of the CSRs of these trials). Perhaps this reflects the subjects found by the sponsor that were not captured in the results that included some subjects with suicidality that was*

*believed to be due to the overall condition (e.g. were reported as SAEs due to "exacerbation of schizophrenia") as described in more detail below (also see Section 7.2.8 of this review).*

*The results of the OL trials are difficult to interpret since there was no placebo control group employed. However the overall incidence of suicidality (3% or less) in the Paliperidone treatment subgroups is not unexpected for this study population (based on the duration of treatment at the time the data were analyzed in these ongoing trials). 6 additional subjects in OL trials had suicidality described in the CRFs (according to the sponsor) but were not reported as having suicidality related AEs since the investigator consider the events as part of an exacerbation of their psychotic disorder and were reported as such. Even if these 6 additional subjects were reported as having suicidal related AEs and were counted as such, the incidence of suicidal related AEs in the OL subjects (a total of 31 subjects out of over 1100 total subjects, 2.8% is well within the expected incidence of suicidality for this study population).*

*The Safety Alert forms reviewed (CIOMS reports) by the sponsor's personnel revealed some subjects were found to have comments of suicidality in their CIOMS reports (but not reported as suicidal as an AE or separate SAE term). Upon inquiry with the investigator by the sponsor's personnel, these subjects were considered by the investigator to either not have suicidality or were subjects with suicidality that was believed to be part of the their overall clinical condition (and suicidality was not reported as an AE or SAE), as described in more detail under Section 7.2.8 of this review. Refer to Section 7.2.8 of potential concerns related to these findings. Despite these concerns the overall interpretation of the sponsor's results do not appear to be impacted (e.g. in favor of Pal over Placebo) with respect to a potential suicidality signal. The cases that the sponsor identified by a review CIOMS forms as being uncaptured included placebo, as well as Pal subjects and the number of subjects was small enough such that if these cases had been included in the sponsor results, then the overall interpretation of the results would not have been altered (e.g. the 15 mg group would still have a similar overall higher numerical incidence compared to placebo subjects).*

*See the final section of this review for further comment.*

Results of the sponsor's analysis on suicidality events are described in more detail, below.

The completed short-term fixed-dose Phase III trials of almost all non-elderly subjects (pooled dataset) showed an incidence of 1% or less in placebo and paliperidone groups while a 3% incidence was reported in the high dose group (15 mg), while the 3 mg (low dose) group showed an incidence of 2%. Olanzapine group showed an incidence of 1%. Suicide attempt was only reported in 1 placebo subject, 1 9 mg Pal subject and in 2 olanzapine subjects (each of these groups had an incidence of 1% or less).

Methods of the sponsor's analyses on suicidality related events are described in more detail below.

The following describes the sponsor methods, but also provides details on some subjects that had comments of suicidality in the subject's CRF were not included in the sponsor's enumeration of suicidal-related cases (only CIOMS Safety Alert forms used for reporting SAEs) were reviewed by the clinical team for comments related to suicidality in which suicidality was not reported as an AE or SAE. In summary these cases were excluded because the investigator either "denied suicidality" or "reported the symptom as part of [the] overall clinical condition" such that suicidal ideation was not reported as an AE or as an SAE (but instead another SAE term was used such as exacerbation of schizophrenia for reporting the subject).

The sponsor determined the incidence of "suicide-related" AEs coded under MedRA preferred terms of completed suicide, suicidal ideation and suicide attempt (which were to be reported as SAEs). Note that these results likely reflect events as of the May 31, 2005 cut-off date. However, additional SAEs and deaths related to suicidality were reported in some trials after the 5/31/05 cut-off date but before the 8/31/05 cut-off date (used for deaths and SAEs and in some studies ADOs, of ongoing trials).

> "AEs coded under MedRA preferred terms related to suicidality were analyzed, as described in the following on page 107 of the SCS (copied verbatim): Suicide-related adverse events—coded under MedDRA preferred terms of completed suicide, suicide attempt, and suicidal ideation—were examined. Suicidality-related adverse events were to be reported as serious adverse events. Investigator comments were reviewed to identify suicidality associated with any other adverse events that were coded under other (non-suicidality) MedDRA preferred terms, and that the investigator did not deem reportable as suicidality-related adverse events."

Upon inquiry about the above methods the sponsor indicated that their clinical team reviewed selected CRFs (of SAEs) as follows (copied verbatim from their 5/23/2006 response):

> "During the conduct of Studies R076477- SCH-302, R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305, each serious adverse event (SAE) was reviewed by the clinical team for references to *suicidality, aggression or agitation.* If any of these terms were included in the investigators description of an event and not included as a separate adverse event (AE) on the Case Report Form (CRF) a Data Clarification Form (DCF) was sent to the site asking whether this term should be reported as an AE. If the site indicated it should not be added as an AE, the reply from the site to the DCF was entered in the Comments section of the database."

The following table shows the subject numbers of the above reviewed CRFs and bolded subject numbers indicates which subjects were enumerated as having a suicidal-related AE (as provided in a 5/23/06 response to our inquiry). Note that Appendix 2.7.4.3.8.3.1 of the SCS, referenced below, lists subject numbers of CRFs reviewed and Table 40 (referenced in the footnote to the

table) was the table in the SCS showing the incidence of suicidality-related AEs in the short-term Phase III trial dataset:

**Table 2:** Subject Listing by Treatment Group for Subjects Included in Appendix 2.7.4.3.8.3.1 in the SCS for Pooled Double-Blind Studies (R076477- SCH-302, R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305)

| Placebo | 3mg | 6mg | 9mg | 12mg | 15mg | OLZ |
|---|---|---|---|---|---|---|
| 300619 | 501329 | 300381 | 501339 | 201519 | **500623** | **200028** |
| **500405** | | | | 300301 | 501295 | 300692 |
| 500447 | | | | | | 300397 |
| 501270 | | | | | | 500464 |
| | | | | | | 500672 |

- Bolded = those included in the SCS Table 40 and in the appendix 2.7.4.3.8.3.1

**Table 5:** Subject Listing From Appendix 2.7.4.3.8.3.1 With Rationale for Non-Inclusion in Table 40 for Double-Blind Studies (R076477- SCH-302, R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305)

| Subject # | Treatment Group | Included/Not Included in Table 40 | Rationale if Not Included as an AE |
|---|---|---|---|
| 200028 | Olanzapine 10 mg | Included | |
| 201519 | ER OROS PAL 12 mg | Not Included | Investigator denied suicidality |
| 300692 | Olanzapine 10 mg | Not Included | Investigator denied suicidality |
| 300381 | ER OROS PAL 6 mg | Not Included | Investigator reported symptom as part of overall clinical condition |
| 300301 | ER OROS PAL 12 mg | Not Included | Investigator reported symptom as part of overall clinical condition |
| 300397 | Olanzapine 10 mg | Not Included | Investigator denied suicidality |
| 300619 | Placebo | Not Included | Investigator reported symptom as part of overall clinical condition |
| 500405 | Placebo | Included | |
| 500447 | Placebo | Not Included | Suicide occurred after subject left the study and was not reported as an AE. No details available on this event. |
| 500464 | Olanzapine 10 mg | Not Included | Investigator reported symptom as part of overall clinical condition |
| 500672 | Olanzapine 10 mg | Not Included | Investigator denied suicidality |
| 500623 | ER OROS PAL 15 mg | Included | |
| 501295 | ER OROS PAL 15 mg | Not Included | Investigator denied suicidality |
| 501329 | ER OROS PAL 3 mg | Not Included | Investigator denied suicidality |
| 501270 | Placebo | Not Included | Investigator reported symptom as part of overall clinical condition |
| 501339 | ER OROS Pal 9 mg | Not Included | Investigator reported symptom as part of overall clinical condition |

**Table 6:** Subject Listing From Appendix 2.7.4.3.8.3.2 With Rationale for Non-Inclusion in Table 41 for Open-Label Extension Studies (R076477- SCH-701, R076477-SCH-702, R076477-SCH-703, R076477-SCH-704 and R076477-SCH-705)

| Subject # | Treatment Group | Included/Not Included in Table 41 | Rationale if Not Included as an AE |
|---|---|---|---|
| 300453 | Pali/Pali | Not Included | Investigator denied suicidality |
| 300623 | Olan/Pali | Not Included | Investigator denied suicidality |
| 300493 | Pali/Pali | Not Included | Investigator reported symptom as part of overall clinical condition |
| 300494 | Pali/Pali | Not Included | Investigator reported symptom as part of overall clinical condition |
| 300579 | Pali/Pali | Not Included | Investigator denied suicidality |
| 300098 | Pla/Pali | Included | |
| 300518 | Pali/Pali | Included | |
| 500108 | Pali/Pali | Not Included | Investigator denied suicidality |
| 500303 | Pali/Pali | Included | |

*The CRFs that were reviewed for any suicide related comments. However, it appears that only selected CRFs were reviewed based on an inquiry to the sponsor of the investigator as to why a suicide related AE was not reported in subjects with CRFs containing comments related to suicidality, the investigators verified that suicidality-related AEs should not be reported in these particular subjects (4 out of 393 placebo subjects, 6 out of 1039 paliperidone subjects and 4 our of 364 olanzapine subjects).*

*The largest treatment group difference between Pal and placebo group reported in the SCS (that excluded un-reported cases) was 3% in the 15 mg group compared to 1% in the placebo group. Yet none of the 15 mg Pal subjects were among cases of suicidality that were not captured in these results (this specifically pertains to subjects that had suicidality described in the CIOMS form but that the investigator believed it to be part of the overall condition and were not reported using a term of suicidality and were not captured in this database as a suicidal event). Furthermore, several placebo subjects were found to fall under the category of un-captured cases. Additionally, consider all cases identified by the sponsor as uncpatured cases independent of the reason for these cases not being reported as cases of suicidality (e.g. cases in which the investigator denied suicidality after being inquired about comments in the CIOMS). If all such cases were included in the sponsor's results, then only one 15 mg subject out of a total of 113 subjects would be added to their enumeration of suicidality related cases. Consequently, if this single subject were counted among suicidality cases in this 15 mg group then the incidence would have been 3.5% which is not substantially different from 3%. In conclusion, the cases identified as not being captured in the sponsor's results on suicidality would not have altered overall conclusions if they had been included in the results (based on results provided in a 6/15/06 N005).*

*See sections 7.2.8 and the final section of this review for further comments and recommendations.*

## 7.1.4.7. Search for Aggression or Agitation Related AEs.

***Reviewer Comment.*** *The sponsor's search for aggression and agitation MedRA preferred terms (aggression, hostility, homicidal ideation, agitation and psychomotor agitation) failed to show a greater incidence of these AEs in any given Paliperidone group (ranging from 3% to 7% in any given group) compared to placebo (10%) in the short-term Phase III trial dataset of almost all non-elderly subjects. Similar results were observed for each type of AE in the Phase III dataset, as well as for the elderly Phase III Study -302 (for aggression and agitation-related AEs combined, and for each individual AE). Results of OL trials are difficult to interpret, as previously discussed but the overall incidence of 8% and 3% in the less than 3 month and 3 month and over Pal subgroups are not unexpected for this patient population and given that these studies are longterm trials of up to one year. As previously discussed the sponsor's subgrouping of subjects by duration of treatment is not a subgrouping to reflect the onset of these AEs relative to dosing but rather indicate how long a given subject has been on treatment at the time that safety data were analyzed in these ongoing trials (using a 5/31/05 cut-off date).*

## 7.1.4.8. Search for Somnolence Related AE

***Reviewer Comment.***
*The table below (copied from the SCS) shows at least trends for a greater incidence of somnolence in all Pal groups compared to placebo except for the lowest dose Pal group (3 mg group).*

**Table 66:** Treatment-Emergent Adverse Events of Somnolence By MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

| Somnolence Group Dictionary-derived Term | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) n (%) | ER OROS PAL 6 mg (N=235) n (%) | ER OROS PAL 9 mg (N=246) n (%) | ER OROS PAL 12 mg (N=242) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects with somnolence-related AE** | 25 ( 7) | 7 ( 6) | 22 ( 9) | 24 ( 10) | 26 ( 11) | 10 ( 9) | 70 ( 19) |
| **Somnolence** | 25 ( 7) | 7 ( 6) | 22 ( 9) | 24 ( 10) | 26 ( 11) | 10 ( 9) | 70 ( 19) |
| Hypersomnia | 0 | 0 | 0 | 0 | 0 | 1 ( 1) | 0 |
| Lethargy | 0 | 1 ( 1) | 2 ( 1) | 0 | 0 | 0 | 0 |
| Sedation | 13 ( 4) | 1 ( 1) | 12 ( 5) | 8 ( 3) | 15 ( 6) | 2 ( 2) | 24 ( 7) |
| Somnolence | 12 ( 3) | 6 ( 5) | 8 ( 3) | 17 ( 7) | 11 ( 5) | 7 ( 6) | 47 ( 13) |

*Elderly subjects in Study -302 also showed a greater incidence of somnolence-related AEs (9%) in Pal subjects compared to placebo subjects (5%).*

According to the sponsor, the above AEs in Pal subjects were not reported as SAEs or ADOs except for 3 subjects (each subject was in the 6 mg, 9 mg and 12 mg groups respectively) who were ADOs due to these AEs (refer to Section 7.1.3 on ADOs later in this review).

**7.1.4.9. Search for Prolactin Related AEs**

***Reviewer Comments.*** *It is not clear to the undersigned reviewer if all AEs listed in the sponsor's summary table (below) were actually prolactin related AEs. However, the results described in the SCS are not unexpected for this study drug or for the drug class and labeling in approved drugs in this drug class include a description of the known effects of these drugs on prolactin levels under Precautions. However, labeling for Risperdol® states that the "clinical significance of elevated serum prolactin levels is unknown for most patients." Refer to the final section of this review for recommendations in describing results of AEs that may be prolactin related that were reported with a greater incidence (twice that of placebo) in the 2 highest daily dose-levels of Pal (12 and 15 mg) examined in the pooled, fixed-dose, Phase III trials and as described in the next paragraph, below.*

*The incidence of subjects with any given AE identified by the sponsor as prolactin related (for the 3 Phase III short-term studies, pooled dataset) was 1% in the placebo group and in Pal groups at the lower dose-levels (3 mg, 6 mg and 9 mg), while the incidence was greater at the higher dose-level Pal groups of 12 mg (2%) and 15 mg (4%). These results are not shown in the summary table shown in this subsection (but were described in the SCS). Since the higher Pal dose-levels showed twice the incidence observed in lower-dose Pal groups and compared to the placebo group the results provide some evidence for a dose-dependent effect of Pal on these types of events. According to the sponsor, none of the prolactin-related AEs in the pooled Phase III short-term trial dataset were reported as SAEs and 1 AE was reported as an ADO (galactorrhea).*

The following summary table was provided by the sponsor (prolactin-related AEs were not found by the sponsor for the elderly Study -302).

Table 58: Number of Subjects With Treatment-Emergent Potentially Prolactin Related Adverse Events by MedDRA Preferred Term and Sex
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

| | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) n (%) | ER OROS PAL 6 mg (N=235) n (%) | ER OROS PAL 9 mg (N=246) n (%) | ER OROS PAL 12 mg (N=242) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|---|---|---|
| **Male** | 235 | 81 | 137 | 152 | 148 | 73 | 245 |
| Erectile dysfunction | 1 (<1) | 0 | 1 (1) | 0 | 0 | 1 (1) | 1 (<1) |
| **Female** | 120 | 46 | 98 | 94 | 94 | 40 | 119 |
| Amenorrhoea | 0 | 0 | 1 (1) | 1 (1) | 0 | 0 | 1 (1) |
| Menstruation irregular | 0 | 0 | 1 (1) | 0 | 0 | 0 | 0 |
| **Both** | 355 | 127 | 235 | 246 | 242 | 113 | 364 |
| Anorgasmia | 0 | 0 | 0 | 1 (<1) | 1 (<1) | 1 (1) | 0 |
| Breast discharge | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Breast pain | 0 | 0 | 0 | 0 | 0 | 1 (1) | 0 |
| Galactorrhoea | 0 | 1 (1) | 0 | 0 | 1 (<1) | 1 (1) | 1 (<1) |
| Hypertrophy breast/gynaecomastia | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Libido decreased | 0 | 0 | 0 | 0 | 0 | 1 (1) | 0 |
| Loss of libido | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Sexual dysfunction | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |

Note: Percentages calculated with the number of subjects per sex as denominator.

Table 59: Treatment-Emergent Potentially Prolactin Related Adverse Events by MedDRA Preferred Term and Sex
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

| | 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 (%) |
|---|---|---|---|---|---|---|
| **Male** | 64 | 73 | 97 | 278 | 74 | 84 |
| Erectile dysfunction | 1 (2) | 0 | 0 | 4 (1) | 0 | 4 (5) |
| **Female** | 43 | 55 | 81 | 227 | 32 | 59 |
| Amenorrhoea | 0 | 2 (4) | 1 (1) | 7 (3) | 0 | 1 (2) |
| Menstruation irregular | 0 | 3 (5) | 0 | 1 (<1) | 0 | 1 (2) |
| **Both** | 107 | 128 | 178 | 505 | 106 | 143 |
| Anorgasmia | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Blood prolactin increased | 0 | 1 (1) | 0 | 1 (<1) | 0 | 0 |
| Breast pain | 0 | 0 | 0 | 2 (<1) | 0 | 0 |
| Breast tenderness | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Galactorrhoea | 0 | 1 (1) | 0 | 4 (1) | 0 | 1 (1) |
| Hyperprolactinaemia | 0 | 1 (1) | 0 | 0 | 0 | 0 |
| Hypertrophy breast/gynaecomastia | 0 | 0 | 0 | 2 (<1) | 0 | 0 |
| Libido decreased | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Loss of libido | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Sexual dysfunction | 0 | 0 | 0 | 4 (1) | 0 | 0 |

Note: Percentages calculated with the number of subjects per sex as denominator.

## 7.1.4.10. Search for Gastrointestinal Obstruction and Related AEs

Since Pal was given as "non-deformable" tablet (OROS formulation) the sponsor determine the incidence of AEs related to gastro-intestinal obstruction (GIO AEs, using MedRA terms listed in Appendix 2.7.4.3.11 in the SCS).

None of the subjects in any of the 4 short term, completed, Phase III trials or in the ongoing OL trials had a GIO AE.

***Reviewer Comment.***
*The undersigned reviewer found one subject with an SAE of ruptured duodenum previously described under Section 7.1.3.3 of this review. A description of this subject could not be found in in-text sections of the SCS but was found in line listings and narratives in appendices to the SCS.*

**7.1.4.11. Search for Neuromuscular Malignant Syndrome Related AEs**

Neuromuscular malignant syndrome (NMS) was not reported for any subjects in the completed Phase III trials (-302 through -305) or for the ongoing OL studies (-701 through -705). According to the sponsor, NMS and increased blood creatine phosphokinase (CPK) were reported for 1 subject (100057) in the ongoing "prevention of recurrence" trial, Study -301 after receiving 3 weeks of blinded study drug (remains blinded). While this 34 year old male's symptoms have resolved "at this time" his CPK remains elevated. NMS was not reported in any of the Phase I/II studies.

***Reviewer Comment.*** *At least one additional subject considered by the undersigned as likely to have had AEs of NMS was previously described, along with the above subject 100057 under Section 7.1.3.3 of this review.*

*See results on laboratory parameters later in this review showing inconsistent elevations in CPK in Phase III trials and results in Phase I trials suggesting a dose-dependent signal for elevated CPK in Phase I trials using the OROS Pal formulation.*

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

**7.1.4.12. Search for Extrapyramidal Side Effect Related AEs**

The following results were found in the SCS.

**Table 45: Treatment-Emergent Extrapyramidal Symptom (EPS) Related Adverse Events (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)**

| EPS Group<br>Dictionary-derived Term | Placebo (N=355)<br>n (%) | ER OROS PAL 3 mg (N=127)<br>n (%) | ER OROS PAL 6 mg (N=235)<br>N (%) | ER OROS PAL 9 mg (N=246)<br>n (%) | ER OROS PAL 12 mg (N=242)<br>n (%) | ER OROS PAL 15 mg (N=113)<br>n (%) | Olanzapine 10 mg (N=364)<br>n (%) |
|---|---|---|---|---|---|---|---|
| **Total No. with any EPS-related adverse event** | 39 ( 11) | 16 ( 13) | 24 ( 10) | 62 ( 25) | 63 ( 26) | 27 ( 24) | 31 ( 9) |
| **Dyskinesia** | 12 ( 3) | 6 ( 5) | 6 ( 3) | 19 ( 8) | 21 ( 9) | 10 ( 9) | 7 ( 2) |
| Dyskinesia | 3 ( 1) | 0 | 1 (<1) | 1 (<1) | 4 ( 2) | 1 ( 1) | 1 (<1) |
| Extrapyramidal disorder | 8 ( 2) | 6 ( 5) | 5 ( 2) | 17 ( 7) | 18 ( 7) | 9 ( 8) | 6 ( 2) |
| Muscle twitching | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Tardive dyskinesia | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| **Dystonia** | 4 ( 1) | 1 ( 1) | 3 ( 1) | 13 ( 5) | 11 ( 5) | 2 ( 2) | 3 ( 1) |
| Dystonia | 2 ( 1) | 1 ( 1) | 3 ( 1) | 9 ( 4) | 9 ( 4) | 1 ( 1) | 1 (<1) |
| Muscle spasms | 1 (<1) | 0 | 0 | 1 (<1) | 2 ( 1) | 1 ( 1) | 1 (<1) |
| Oculogyration | 0 | 0 | 0 | 5 ( 2) | 0 | 0 | 0 |
| Trismus | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 1 (<1) |
| **Hyperkinesia** | 14 ( 4) | 5 ( 4) | 7 ( 3) | 20 ( 8) | 24 ( 10) | 11 ( 10) | 8 ( 2) |
| Akathisia | 14 ( 4) | 5 ( 4) | 7 ( 3) | 20 ( 8) | 23 ( 10) | 11 ( 10) | 7 ( 2) |
| Hyperkinesia | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Restless legs syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<1) |
| **Parkinsonism** | 8 ( 2) | 4 ( 3) | 6 ( 3) | 18 ( 7) | 15 ( 6) | 7 ( 6) | 8 ( 2) |
| Bradykinesia | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Cogwheel rigidity | 1 (<1) | 0 | 0 | 0 | 0 | 1 ( 1) | 0 |
| Drooling | 1 (<1) | 0 | 2 ( 1) | 1 (<1) | 0 | 2 ( 2) | 1 (<1) |
| Hypertonia | 4 ( 1) | 3 ( 2) | 3 ( 1) | 10 ( 4) | 8 ( 3) | 4 ( 4) | 5 ( 1) |
| Hypokinesia | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Muscle rigidity | 0 | 1 ( 1) | 0 | 3 ( 1) | 1 (<1) | 0 | 0 |
| Musculoskeletal stiffness | 2 ( 1) | 0 | 0 | 0 | 2 ( 1) | 0 | 0 |
| Parkinsonism | 0 | 0 | 1 (<1) | 5 ( 2) | 3 ( 1) | 2 ( 2) | 2 ( 1) |
| **Tremor** | 12 ( 3) | 4 ( 3) | 6 ( 3) | 11 ( 4) | 8 ( 3) | 3 ( 3) | 8 ( 2) |
| Tremor | 12 ( 3) | 4 ( 3) | 6 ( 3) | 11 ( 4) | 8 ( 3) | 3 ( 3) | 8 ( 2) |

**Figure 2:** Simpson-Angus Rating Scale (SAS): Change From Baseline to End Point
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

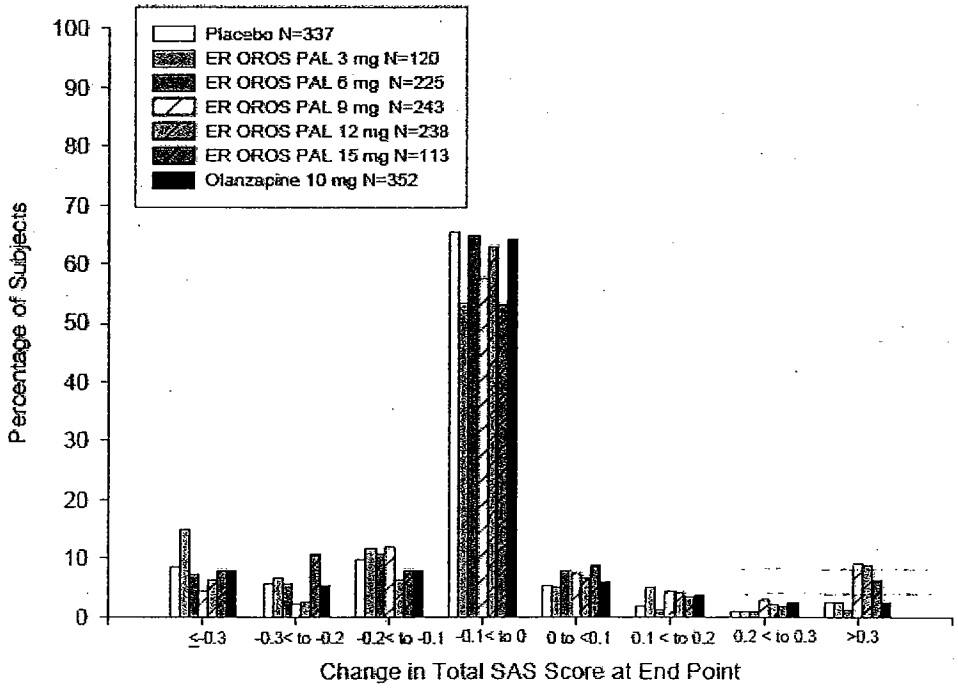
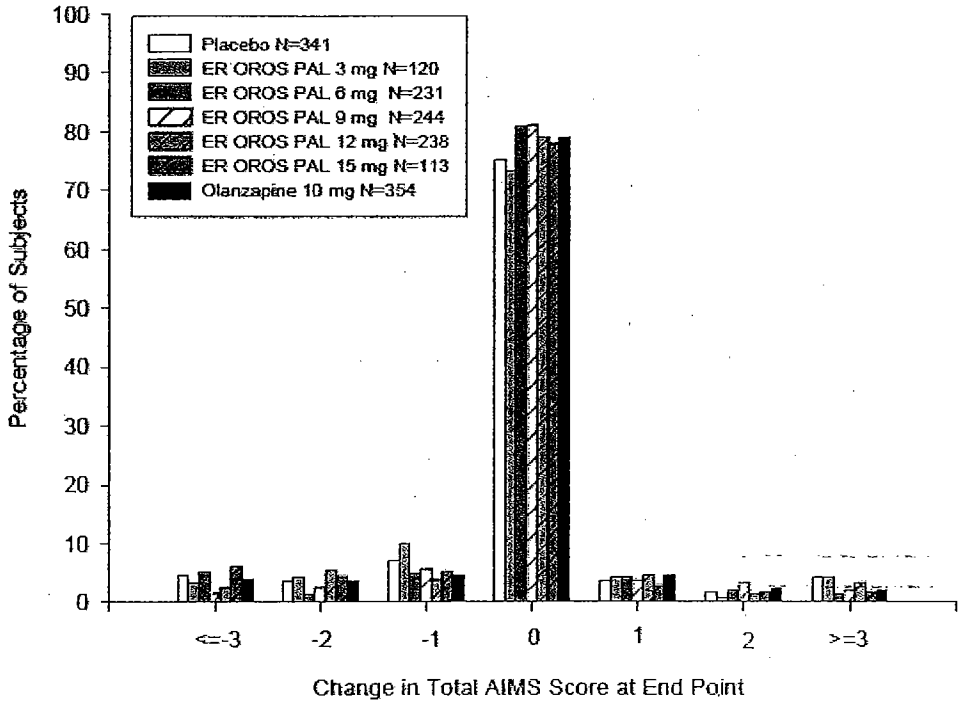



**Table 46:** Summary of BARS Global Clinical Rating Score at End Point
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

| | | | | ER OROS PAL | | | | Olanzapine |
|---|---|---|---|---|---|---|---|---|
| | 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 (%) |
| **Global clinical rating of akathisia** | | | | | | | | |
| End point | | | | | | | | |
| Absent | 278 ( 81.0) | 104 ( 85.2) | 204 ( 87.9) | 203 ( 83.2) | 189 ( 79.1) | 89 ( 78.8) | 789 ( 83.1) | 316 ( 88.5) |
| Questionable | 43 ( 12.5) | 10 ( 8.2) | 18 ( 7.8) | 23 ( 9.4) | 29 ( 12.1) | 15 ( 13.3) | 95 ( 10.0) | 25 ( 7.0) |
| Mild akathisia | 14 ( 4.1) | 7 ( 5.7) | 6 ( 2.6) | 15 ( 6.1) | 14 ( 5.9) | 8 ( 7.1) | 50 ( 5.3) | 13 ( 3.6) |
| Moderate akathisia | 6 ( 1.7) | 1 ( 0.8) | 3 ( 1.3) | 3 ( 1.2) | 6 ( 2.5) | 1 ( 0.9) | 14 ( 1.5) | 2 ( 0.6) |
| Marked akathisia | 2 ( 0.6) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.4) | 0 ( 0.0) | 1 ( 0.1) | 1 ( 0.3) |
| Severe akathisia | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.4) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.1) | 0 ( 0.0) |

**Figure 3: Abnormal Involuntary Movement Scale (AIMS): Change From Baseline to End Point (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)**




The following results on the incidence of concomitant medication (including antihistamine drugs) use for EPSE were also provided for each treatment group (for Phase III -303 through -305, combined) in the SCS:

- 3 mg Pal (14%)
- Pal 6 mg (13%)
- 9 mg Pal (22%),
- 12 mg Pal (24%),
- 15 mg Pal (21%)
- Placebo (14%)
- Olanzapine (12%).

## 7.1.4.13 Search for Glucose Related AEs

***Reviewer Comment.*** *It is well known and is described under Precautions of Risperdol® and other drugs in this drug class, that hyperglycemia and diabetes mellitus has been reported in treated subjects such that the sponsor has not revealed any new or unexpected findings.*

*In summary, the fixed dose, short-term Phase III dataset showed a 1% incidence in each treatment group (Pal groups, Olanzapine and placebo) except for 2% in the lowest dose Pal group (3 mg). Two SAEs are also described by the sponsor in this section of the SCS (on page 130) of Subject 501300 in the 15 mg group with no prior history of hyperglycemia who developed this event during treatment that resolved upon dechallenge (this subject was also an ADO due to this event). Subject 501122 in the 9 mg group had a history of diabetes mellitus who had AEs of "diabetes mellitus" and "hypoglycemia." While the former described subject was likely to have a drug-related event the events of the latter subject are less clear regarding their relationship to Pal treatment.*

*Open label trials failed to show any new remarkable findings. This dataset showed an incidence of 0% in most OL subgroups except for the > 3month Placebo (DB lead-in study treatment)/Paliperidone (OL treatment) subgroup (2%) and <1% in the > 3month Paliperidone/Paliperidone group.*

### 7.1.5. Common Adverse Events

This section focuses on the incidence of common AEs which includes summary tables that were provided by the sponsor.

This section begins with a summary and interpretation of results as provided in the opinion of the undersigned reviewer (as denoted by italicized text). Summary tables of the incidence of common AEs follow thereafter (as provided by the sponsor that were primarily found in the SCS of the submission).

In accordance with the MAPP, results on the incidence of AEs on the basis of gender, age and ethnic subgroupings are provided under subsection 7.1.5.6.

***Reviewer Comment and Summary.*** *The summary AE tables of completed Phase III trials of primarily non-elderly subjects (of pooled data from Studies -303, -304 and -305, shown in this section) reveal results that are expected (for at least one of the following reasons):*

- *Given the known effects of Risperidone*
- *Given the known Drug class or*
- *Given the known mechanism of action of the drug (at the receptor level) or*
- *Were findings that are expected for the study population.*

*Some AEs failed to show consistent or remarkable evidence for a drug-related effect.*

*The following are notable or possible exceptions to the above conclusions (most of the following AEs occurred in at least 2% of subjects in a given Paliperidone group with at least twice the incidence observed in placebo and suggested a consistent drug-related effect based on the pattern of the incidence across dose-levels of Pal):*

*a) Cardiac related events, as follows.*

- *Tachycardia or sinus (s) tachycardia. While some AEs could be tachycardia due to orthostatic hypotension (an expected event), one cannot assume that all events were due to this expected drug-related adverse effect. See a discussion of evidence for drug induced supine tachycardia described under the section on vital signs (section 7.1.8) and SAEs involving tachycardia that could not be explained by the presence of orthostatic hypotension.*
- *1°Atrioventricular block (AV block) occurred in 4.4% of 15 mg Pal subjects compared to 1.4% of placebo subjects which is an unexpected event. Note later in this review results on potential PR prolongation effects that appeared to be of a clinically unremarkable magnitude.*
- *QT prolongation is unexpected for the study drug but is observed to varying degress with other antipsychotic drugs of primarily other drug classes but has been reported with some atypical antipsychotic agents. QT prolongation (as an investigation AE) was reported with an incidence in the 3 mg, 12 and 15 mg Pal groups that was at least twice that of placebo subjects but was not common (most groups had an incidence of <2% with only the 3 mg group being the exception with an incidence of 2.4%).*

*b) Suicidal ideation occurred in 2.7% of 15 mg Pal subjects compared to 1.1% of placebo subjects, 1.6% of 3 mg Pal subjects and less than 1% of subjects in each of the other Pal groups (6, 9 and 12 mg groups). Depression and anxiety or other potentially related psychiatric AEs did not show evidence for drug-related effects based on the incidence of these AEs shown in the sponsor's summary table, but sleep disorder did show drug-related effects on the incidence of this AE. See the results of the sponsor's special search strategy for AEs of suicidality described under Section 7.1.4 in this review.*

*c) The following infection-related or respiratory-related AEs shown an unexpectedly greater incidence in at least the 15 mg Pal group compared to placebo (and the incidence was at least twice that of placebo):*

- *Upper respiratory tract infection and urinary tract infection in 3.5% and 2.7% of the 15 mg group, for each AE, respectively compared to 0.6% of placebo subjects (for each AE) and generally less than 1% of subjects given lower Pal dose-levels.*
- *Respiratory related AEs of cough occurred in approximately 2 or 3% of Pal subjects at each dose-level compared to 1.1% of placebo subjects, nasal congestion was reported in 3% of 15 mg Pal subjects compared to <1% in the lower dose Pal groups and in placebo subjects.*

*Tachycardia, upper respiratory infection, coughing, rhinitis and other related AEs did show evidence of drug-related effects based on the incidence of these AEs in summary tables of Schizophrenia short term trials (used 10 and 16 mg daily dose-levels) and Bipolar short term trials (used 1-6 mg daily dose-levels) in approved labeling for Risperdol.®*

*While tachycardia is included in summary tables of adverse events in approved Risperdol® labeling, tachycardia is described in Risperdol® labeling as being associated with orthostatic hypotension under Precautions, similar to approved labeling for other antipsychotic drugs in*

*this drug class. However, refer to previous descriptions of SAEs and/or ADOs of tachycardia, independent of orthostatic hypotension under Sections 7.1.2 and 7.1.3.*

*Common AEs in the Elderly Phase III Trial (Study -302).*
*The placebo controlled elderly Phase III trial generally showed similar findings, in which the following unexpected findings to the undersigned are noted (see the above discussion of tachycardia as described in approved Risperdol® labeling):*

- *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 placebo subjects).*

*Common AEs in OL Trials*
*Results of the longer term OL trials (-702 through-705) are difficult to interpret since there was not a placebo group. Also comparisons between results of subgroups on the basis of Pal exposure of 3 months or less, and exposure of over 3 months are difficult to interpret since these results do not reflect the timing of reported AEs relative to dosing. Instead these subgroups only reflect the overall incidence of AEs for subjects subdivided into these subgroups on the basis of duration of treatment at the time the data was analyzed for these ongoing OL trials. Common AEs for describing results of OL trials is defined as ≥ 5% incidence in either the ≤ 3 month or > 3 month Total Pal subgroups. This 5% cut-off level was selected by the undersigned reviewer for describing these results, since exposure in the OL was longterm.*

*Common AEs in the OL trial dataset were generally expected AEs for the study population, the study drug or the drug class while also taking into account the nature of the longterm trial (in which the longer the trial the greater the incidence of a given AE is likely to occur than in the short term trials). The following findings were unexpected to the undersigned reviewer:*

- *Tachycardia and/or sinus tachycardia were common unexpected AEs (if they occurred independent of an orthostatic tachycardia). However, tachycardia was reported in Risperdol® approved labeling and is on this basis not an unexpected event. It is difficult to determine if the incidence of tachycardia AEs was dose-dependent for several reasons. Firstly, the event is reported either as sinus tachycardia or tachycardia rather than having these AEs combined. Yet, another problem is distinguishing AEs of tachycardia associated with orthostatic hypotension from tachycardia that is not associated with orthostatic hypotension.*

- *Depression and agitation and anxiety AEs were common but not unexpected for the study population. See section 7.1.4 for "other search strategies" of related AEs. A potential signal for AEs of suicidality may exist at the 15 mg Pal dose-level based on the incidence observed in the pooled short term Phase III trials that employed multiple dose-levels and a placebo control group in a parallel group study design (as previously mentioned).*
- *Nasopharyngitis which was reported more commonly in Pal subjects compared to placebo subjects of the short term Phase III trials was a common AE in the OL longterm trials.*

*Some drug-related AEs were reported in <5% of subjects in the pooled OL trial dataset, such as AEs related to extrapyramidal side effects among others.*

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

The following table provides the incidence of AEs as specified (copied from the submission).

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

| | | ER OROS Paliperidone | | | | | Olanzapine |
|---|---|---|---|---|---|---|---|
| Body System or Organ Class<br>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 (%) | 10 mg (N=364) n (%) |
| **Total no. subjects with adverse events** | 235 (66.2) | 91 (71.7) | 156 (66.4) | 171 (69.5) | 184 (76.0) | 87 (77.0) | 252 (69.2) |
| **Cardiac disorders** | 43 (12.1) | 22 (17.3) | 37 (15.7) | 45 (18.3) | 41 (16.9) | 15 (13.3) | 52 (14.3) |
| Atrioventricular block first degree | 5 (1.4) | 2 (1.6) | 0 | 6 (2.4) | 2 (0.8) | 5 (4.4) | 4 (1.1) |
| Bundle branch block | 6 (1.7) | 4 (3.1) | 3 (1.3) | 7 (2.8) | 1 (0.4) | 1 (0.9) | 9 (2.5) |
| Sinus arrhythmia | 0 | 3 (2.4) | 2 (0.9) | 2 (0.8) | 1 (0.4) | 0 | 2 (0.5) |
| Sinus tachycardia | 15 (4.2) | 11 (8.7) | 9 (3.8) | 10 (4.1) | 17 (7.0) | 8 (7.1) | 20 (5.5) |
| Tachycardia | 10 (2.8) | 3 (2.4) | 17 (7.2) | 18 (7.3) | 18 (7.4) | 2 (1.8) | 13 (3.6) |
| **Eye disorders** | 6 (1.7) | 3 (2.4) | 2 (0.9) | 8 (3.3) | 8 (3.3) | 2 (1.8) | 3 (0.8) |
| Oculogyration | 0 | 0 | 0 | 5 (2.0) | 0 | 0 | 0 |
| Vision blurred | 4 (1.1) | 1 (0.8) | 1 (0.4) | 0 | 5 (2.1) | 0 | 1 (0.3) |
| **Gastrointestinal disorders** | 58 (16.3) | 25 (19.7) | 47 (20.0) | 44 (17.9) | 62 (25.6) | 28 (24.8) | 62 (17.0) |
| Abdominal pain upper | 2 (0.6) | 1 (0.8) | 6 (2.6) | 5 (2.0) | 4 (1.7) | 2 (1.8) | 2 (0.5) |
| Diarrhoea | 8 (2.3) | 1 (0.8) | 2 (0.9) | 3 (1.2) | 6 (2.5) | 2 (1.8) | 6 (1.6) |
| Dry mouth | 2 (0.6) | 3 (2.4) | 8 (3.4) | 2 (0.8) | 7 (2.9) | 4 (3.5) | 5 (1.4) |
| Dyspepsia | 14 (3.9) | 3 (2.4) | 6 (2.6) | 5 (2.0) | 12 (5.0) | 6 (5.3) | 13 (3.6) |
| Nausea | 19 (5.4) | 8 (6.3) | 9 (3.8) | 10 (4.1) | 10 (4.1) | 2 (1.8) | 8 (2.2) |
| Salivary hypersecretion | 1 (0.3) | 0 | 1 (0.4) | 3 (1.2) | 10 (4.1) | 3 (2.7) | 0 |
| Toothache | 4 (1.1) | 2 (1.6) | 5 (2.1) | 6 (2.4) | 5 (2.1) | 2 (1.8) | 11 (3.0) |
| Vomiting | 17 (4.8) | 2 (1.6) | 6 (2.6) | 9 (3.7) | 12 (5.0) | 8 (7.1) | 5 (1.4) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **General disorders/ administration site conditions** | 19 ( 5.4) | 7 ( 5.5) | 10 ( 4.3) | 16 ( 6.5) | 17 ( 7.0) | 8 ( 7.1) | 16 ( 4.4) |
| Asthenia | 3 ( 0.8) | 2 ( 1.6) | 1 ( 0.4) | 5 ( 2.0) | 5 ( 2.1) | 1 ( 0.9) | 2 ( 0.5) |
| Fatigue | 5 ( 1.4) | 2 ( 1.6) | 2 ( 0.9) | 4 ( 1.6) | 5 ( 2.1) | 0 | 6 ( 1.6) |
| Pyrexia | 4 ( 1.1) | 1 ( 0.8) | 1 ( 0.4) | 5 ( 2.0) | 4 ( 1.7) | 1 ( 0.9) | 5 ( 1.4) |
| **Infections and infestations** | 28 ( 7.9) | 11 ( 8.7) | 30 (12.8) | 21 ( 8.5) | 27 (11.2) | 19 (16.8) | 24 ( 6.6) |
| Nasopharyngitis | 10 ( 2.8) | 4 ( 3.1) | 5 ( 2.1) | 4 ( 1.6) | 6 ( 2.5) | 3 ( 2.7) | 5 ( 1.4) |
| Upper respiratory tract infection | 2 ( 0.6) | 1 ( 0.8) | 2 ( 0.9) | 3 ( 1.2) | 2 ( 0.8) | 4 ( 3.5) | 1 ( 0.3) |
| Urinary tract infection | 2 ( 0.6) | 1 ( 0.8) | 2 ( 0.9) | 2 ( 0.8) | 0 | 3 ( 2.7) | 2 ( 0.5) |
| **Investigations** | 42 (11.8) | 22 (17.3) | 31 (13.2) | 32 (13.0) | 34 (14.0) | 18 (15.9) | 75 (20.6) |
| Blood insulin increased | 2 ( 0.6) | 3 ( 2.4) | 3 ( 1.3) | 2 ( 0.8) | 1 ( 0.4) | 1 ( 0.9) | 3 ( 0.8) |
| Blood pressure increased | 2 ( 0.6) | 3 ( 2.4) | 1 ( 0.4) | 1 ( 0.4) | 3 ( 1.2) | 2 ( 1.8) | 1 ( 0.3) |
| Blood triglycerides increased | 1 ( 0.3) | 2 ( 1.6) | 1 ( 0.4) | 0 | 0 | 3 ( 2.7) | 4 ( 1.1) |
| Electrocardiogram QT corrected interval prolonged | 9 ( 2.5) | 4 ( 3.1) | 9 ( 3.8) | 7 ( 2.8) | 12 ( 5.0) | 4 ( 3.5) | 10 ( 2.7) |
| Electrocardiogram T wave abnormal | 4 ( 1.1) | 3 ( 2.4) | 2 ( 0.9) | 4 ( 1.6) | 2 ( 0.8) | 2 ( 1.8) | 2 ( 0.5) |
| Heart rate increased | 2 ( 0.6) | 4 ( 3.1) | 2 ( 0.9) | 1 ( 0.4) | 3 ( 1.2) | 0 | 2 ( 0.5) |
| Weight increased | 5 ( 1.4) | 1 ( 0.8) | 0 | 4 ( 1.6) | 4 ( 1.7) | 3 ( 2.7) | 15 ( 4.1) |
| **Musculoskeletal and connective tissue disorders** | 17 ( 4.8) | 5 ( 3.9) | 10 ( 4.3) | 13 ( 5.3) | 21 ( 8.7) | 6 ( 5.3) | 18 ( 4.9) |
| Back pain | 3 ( 0.8) | 1 ( 0.8) | 2 ( 0.9) | 3 ( 1.2) | 5 ( 2.1) | 0 | 6 ( 1.6) |
| Pain in extremity | 4 ( 1.1) | 0 | 2 ( 0.9) | 0 | 5 ( 2.1) | 3 ( 2.7) | 2 ( 0.5) |

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

| | | ER OROS Paliperidone | | | | | Olanzapine |
|---|---|---|---|---|---|---|---|
| | Placebo | 3 mg | 6 mg | 9 mg | 12 mg | 15 mg | 10 mg |
| **Body System or Organ Class** | (N=355) | (N=127) | (N=235) | (N=246) | (N=242) | (N=113) | (N=364) |
| Dictionary-derived Term | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Nervous system disorders | 96 (27.0) | 34 (26.8) | 68 (28.9) | 99 (40.2) | 110 (45.5) | 47 (41.6) | 123 (33.8) |
| Akathisia | 14 ( 3.9) | 5 ( 3.9) | 7 ( 3.0) | 20 ( 8.1) | 23 ( 9.5) | 11 ( 9.7) | 7 ( 1.9) |
| Dizziness | 14 ( 3.9) | 7 ( 5.5) | 11 ( 4.7) | 11 ( 4.5) | 12 ( 5.0) | 7 ( 6.2) | 19 ( 5.2) |
| Dystonia | 2 ( 0.6) | 1 ( 0.8) | 3 ( 1.3) | 9 ( 3.7) | 9 ( 3.7) | 1 ( 0.9) | 1 ( 0.3) |
| Extrapyramidal disorder | 8 ( 2.3) | 6 ( 4.7) | 5 ( 2.1) | 17 ( 6.9) | 18 ( 7.4) | 9 ( 8.0) | 6 ( 1.6) |
| Headache | 42 (11.8) | 14 (11.0) | 29 (12.3) | 34 (13.8) | 35 (14.5) | 20 (17.7) | 35 ( 9.6) |
| Hypertonia | 4 ( 1.1) | 3 ( 2.4) | 3 ( 1.3) | 10 ( 4.1) | 8 ( 3.3) | 4 ( 3.5) | 5 ( 1.4) |
| Parkinsonism | 0 | 0 | 1 ( 0.4) | 5 ( 2.0) | 3 ( 1.2) | 2 ( 1.8) | 2 ( 0.5) |
| Sedation | 13 ( 3.7) | 1 ( 0.8) | 12 ( 5.1) | 8 ( 3.3) | 15 ( 6.2) | 2 ( 1.8) | 24 ( 6.6) |
| Somnolence | 12 ( 3.4) | 6 ( 4.7) | 8 ( 3.4) | 17 ( 6.9) | 11 ( 4.5) | 7 ( 6.2) | 47 (12.9) |
| Tremor | 12 ( 3.4) | 4 ( 3.1) | 6 ( 2.6) | 11 ( 4.5) | 8 ( 3.3) | 3 ( 2.7) | 8 ( 2.2) |

The following table provides the incidence of common AEs in the elderly Phase III trial (as provided by the sponsor).

Table 27: Incidence of Common[a] Treatment-Emergent Adverse Events (Study R076477-SCH- 302)

| Body System or Organ Class<br>Dictionary-derived Term | Placebo (N=38)<br>n (%) | ER OROS PAL (N=76)<br>n (%) |
|---|---|---|
| **Total no. subjects with adverse events** | 27 ( 71) | 51 ( 67) |
| **Nervous system disorders** | 9 ( 24) | 22 ( 29) |
| Somnolence | 2 ( 5) | 7 ( 9) |
| Dizziness | 0 | 5 ( 7) |
| Extrapyramidal disorder | 4 ( 11) | 4 ( 5) |
| Headache | 1 ( 3) | 4 ( 5) |
| **Cardiac disorders** | 5 ( 13) | 20 ( 26) |
| Sinus tachycardia | 0 | 7 ( 9) |
| Tachycardia | 0 | 5 ( 7) |
| **Psychiatric disorders** | 10 ( 26) | 11 ( 14) |
| Insomnia | 4 ( 11) | 7 ( 9) |
| Agitation | 2 ( 5) | 2 ( 3) |
| Anxiety | 2 ( 5) | 2 ( 3) |
| **Vascular disorders** | 2 ( 5) | 8 ( 11) |
| Hypertension | 1 ( 3) | 4 ( 5) |
| Hypotension | 0 | 4 ( 5) |
| **Gastrointestinal disorders** | 7 ( 18) | 7 ( 9) |
| Nausea | 2 ( 5) | 2 ( 3) |
| Vomiting | 2 ( 5) | 1 ( 1) |
| **Investigations** | 5 ( 13) | 7 ( 9) |
| Electrocardiogram QT corrected interval prolonged | 1 ( 3) | 5 ( 7) |
| Electrocardiogram T wave inversion | 2 ( 5) | 1 ( 1) |
| **General disorders and administration site conditions** | 2 ( 5) | 5 ( 7) |
| Asthenia | 2 ( 5) | 4 ( 5) |

[a] Includes treatment-emergent adverse reported in at least 5% of the subjects in either treatment group.
Cross-reference: Appendix 2.7.4.3.2.1.

The following observation from a table found in the appendix of the SCS for this elderly trial is noted, since a similar potential drug-related signal was observed in the completed Phase III trials of primarily non-elderly subjects. 1° AV block in 3% (2 out of 76 Pal subjects) compared to 0 placebo subjects (out of 38 placebo subjects). This event was not shown in the sponsor in-text summary table in the SCS but rather in Appendix 2.7.4.3.1 of the SCS.

**Ongoing Phase III Trial -301.**
Since the trial is ongoing and blinded, results were not described.

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

The following table summarizes the incidence of common (≥5% in any given treatment group) AEs, as provided by the sponsor.

**Table 29: Incidence of Common[a] Treatment-Emergent Adverse Events**
**(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** | 68 ( 64) | 98 ( 77) | 93 ( 52) | 350 ( 69) | 68 ( 64) | 109 ( 76) | 229 ( 59) | 557 ( 72) |
| **Nervous system disorders** | 26 ( 24) | 62 ( 48) | 40 ( 22) | 181 ( 36) | 20 ( 19) | 68 ( 48) | 86 ( 22) | 311 ( 40) |
| Akathisia | 5 ( 5) | 19 ( 15) | 9 ( 5) | 48 ( 10) | 4 ( 4) | 18 ( 13) | 18 ( 5) | 85 ( 11) |
| Headache | 4 ( 4) | 11 ( 9) | 11 ( 6) | 54 ( 11) | 8 ( 8) | 20 ( 14) | 23 ( 6) | 85 ( 11) |
| Somnolence | 4 ( 4) | 9 ( 7) | 4 ( 2) | 32 ( 6) | 2 ( 2) | 17 ( 12) | 10 ( 3) | 58 ( 7) |
| Extrapyramidal disorder | 6 ( 6) | 13 ( 10) | 6 ( 3) | 24 ( 5) | 3 ( 3) | 9 ( 6) | 15 ( 4) | 46 ( 6) |
| Dizziness | 1 ( 1) | 7 ( 5) | 4 ( 2) | 21 ( 4) | 4 ( 4) | 6 ( 4) | 9 ( 2) | 34 ( 4) |
| Hypertonia | 1 ( 1) | 6 ( 5) | 1 ( 1) | 15 ( 3) | 3 ( 3) | 9 ( 6) | 5 ( 1) | 30 ( 4) |
| Tremor | 4 ( 4) | 5 ( 4) | 3 ( 2) | 15 ( 3) | 0 | 9 ( 6) | 7 ( 2) | 29 ( 4) |
| Dystonia | 3 ( 3) | 8 ( 6) | 1 ( 1) | 4 ( 1) | 1 ( 1) | 3 ( 2) | 5 ( 1) | 15 ( 2) |
| **Psychiatric disorders** | 24 ( 22) | 41 ( 32) | 39 ( 22) | 160 ( 32) | 33 ( 31) | 60 ( 42) | 96 ( 25) | 261 ( 34) |
| Insomnia | 9 ( 8) | 18 ( 14) | 16 ( 9) | 53 ( 10) | 12 ( 11) | 20 ( 14) | 37 ( 9) | 91 ( 12) |
| Anxiety | 5 ( 5) | 7 ( 5) | 9 ( 5) | 37 ( 7) | 10 ( 9) | 10 ( 7) | 24 ( 6) | 54 ( 7) |
| Depression | 3 ( 3) | 12 ( 9) | 1 ( 1) | 30 ( 6) | 1 ( 1) | 12 ( 8) | 5 ( 1) | 54 ( 7) |
| Psychotic disorder | 6 ( 6) | 6 ( 5) | 11 ( 6) | 31 ( 6) | 10 ( 9) | 14 ( 10) | 27 ( 7) | 51 ( 7) |
| Schizophrenia | 2 ( 2) | 4 ( 3) | 6 ( 3) | 31 ( 6) | 8 ( 8) | 8 ( 6) | 16 ( 4) | 43 ( 6) |
| Agitation | 6 ( 6) | 2 ( 2) | 8 ( 4) | 13 ( 3) | 9 ( 8) | 5 ( 3) | 23 ( 6) | 20 ( 3) |
| **Infections and infestations** | 9 ( 8) | 16 ( 13) | 10 ( 6) | 88 ( 17) | 12 ( 11) | 24 ( 17) | 31 ( 8) | 128 ( 16) |
| Nasopharyngitis | 2 ( 2) | 5 ( 4) | 3 ( 2) | 28 ( 6) | 4 ( 4) | 6 ( 4) | 9 ( 2) | 39 ( 5) |
| **Cardiac disorders** | 16 ( 15) | 28 ( 22) | 17 ( 10) | 64 ( 13) | 14 ( 13) | 22 ( 15) | 47 ( 12) | 114 ( 15) |
| Tachycardia | 2 ( 2) | 8 ( 6) | 7 ( 4) | 25 ( 5) | 3 ( 3) | 9 ( 6) | 12 ( 3) | 42 ( 5) |
| Sinus tachycardia | 7 ( 7) | 10 ( 8) | 2 ( 1) | 18 ( 4) | 5 ( 5) | 6 ( 4) | 14 ( 4) | 34 ( 4) |
| Bundle branch block | 5 ( 5) | 3 ( 2) | 2 ( 1) | 7 ( 1) | 5 ( 5) | 2 ( 1) | 12 ( 3) | 12 ( 2) |

Note: Percentages calculated with the number of subjects in each group as denominator.
[a]Adverse events occurring in ≥5% of subjects in any treatment group.

*See recommendations in the final section of this review regarding the above AEs.*

"Significant" AEs were previously described in a subsection on "Other Significant" AEs (Section 7.1.3.3) and results of a search for specific AE terms in either the study report or in subject narratives were previously described in Section 7.1.4.

#### 7.1.5.1 Eliciting adverse events data in the development program

The above sections are in reference to spontaneous reported AEs, as is standard procedure. Any special rating scales that might be considered as elicited AEs are also described, elsewhere, in the appropriate subsection of this review.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Categorization and preferred terminology is based on the MedRA system. Several categorization and preferred term systems exist of which MedRA is one (e.g. WHO system is another).

***Reviewer Comments.*** *Each AE categorization system has its inherent limitations. The MedRA system is now considered the preferred categorization system by the Agency at this time, to the knowledge of the undersigned reviewer.*

#### 7.1.5.3 Incidence of common adverse events

See Section 7.1.5

#### 7.1.5.4 Common adverse event tables

See Section 7.1.5

#### 7.1.5.5 Identifying common and drug-related adverse events

See Section 7.1.5

#### 7.1.5.6 Additional analyses and explorations

See Section 7.4.2 of this review for additional analyses of AEs by demographic features, for drug-drug interactions and other analyses.

### 7.1.6 Less Common Adverse Events

The focus of this review is on common AEs, AEs of special interest, SAEs and ADOs as described in previous sections which include less common AEs.

### 7.1.7 Laboratory Findings

***A Caveat on Group and Time-point Comparisons on a Given Clinical Parameter.*** *Results of statistical group or time-point comparisons or in-text description of statistical results on clinical parameters could not be found in the SCS. Therefore, group and time-point comparisons described in this review on any given clinical parameter are based on numerical comparisons,*

*unless otherwise specified (results on clinical parameters that were found in the SCS and are described in this review did not include statistical comparisons).*

#### 7.1.7.1 Overview of laboratory testing in the development program

See study schedules in Table series 10.1 in the appendix of this review.

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See sections below and Section 7.1 for a description of datasets analyzed and described in this review.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

See below.

##### 7.1.7.3.1 Analyses focused on measures of central tendency

See Table Series 10.1 for schedule of assessments in Phase III trials.

Routine laboratory and urinalysis assessments were planned at the following time-points for the completed short-term non-elderly and elderly Phase III trials:

- At screening
- Baseline and on
- Days 15, 43 with DB treatment given on Days 1-42.
- Study Endpoint scheduled for 7 days after the last day of DB treatment (on Day 50 or upon early withdrawal)

Routine laboratory and urinalysis assessments were planned at the following time-points for the OL Extension Trials:

- Baseline of the OL Extension Trial
- Weeks 12, 24, 52 with OL Pal treatment planned for one year (weeks 1-52) for Studies -703 through -705 and for 6 months in Study -702.
- Study Endpoint

Results on each clinical parameter showing mean changes from baseline to each assessment time-point were found in appendices of the SCS (the SCS provided mean change from baseline to endpoint for selected parameters).

***Reviewer Comments and Caveats on Overall Potential Limitations Found Upon Review of Results that were Found in the SCS***

*Results of statistical group and/or time-point comparisons could not be found in the sponsor's summary tables that were found in the SCS or in the more complete tables found in the appendix (as shown later in this review). Therefore, reviewer comments on group or time-point differences are based on numerical comparisons.*

*Descriptive statistical results on several urinalysis parameters either could not be found or were only found for a small subgroup of subjects (could not be found in the SCS or in appendices) or in some cases urinalysis results appeared to reflect contaminated specimens (i.e. a number of RBCs were found in urine samples in most treatment groups in one of the Phase I/IIa datasets as described later). Fortunately, these problems did not exist for all datasets such that some useful information could be gleaned from some of the datasets to sufficiently assess safety. While urine ketone results would be helpful given that hyperglycemia is reported to occur with drugs in this drug-class, other safety information could be used to assess safety regarding potential effects on glucose regulation (e.g. glucose plasma levels, results of SAEs, ADOs and other safety data).*

*Most laboratory parameters had large standard deviations. CPK levels were most remarkably variable which is not unexpected given the study population in the Phase III trials. Since the variance on CPK was large, it is also not surprising that some treatment groups showed remarkable mean changes (increased or decreased) that were generally inconsistent. However, results of Phase I trials on this parameter could be examined.*

*Another problem with laboratory results found in the SCS is that for at least some of the safety datasets values could only be found for a subgroup of subjects (e.g. on 76 out of 138 subjects LD OROS Pal treated subjects had CPK results found in a summary table on the incidence of CPK outliers found on page 3637 in an appendix of the SCS).*

*The in-text tables of the SCS only showed results of selected parameters and showed sample sizes, mean baseline ±SD, mean change from baseline to endpoint±SD, but the range of values for selected datasets could not be found (the completed short-term Phase III trials and the ongoing OL Extension Trials as described below). However, these results could generally be found in appendices, unless otherwise specified in this review (e.g. incidence of outliers on some parameters could not be found and were later provided by the sponsor upon request). A description of Phase I/II results could generally not be found in the SCS but results could be found in tables provided in appendices of the SCS, as specified below.*

*Comments on Potential Limitations with the OL safety dataset*

*The OL safety dataset was limited by the number of subjects exposed to over 6 months of treatment, since these trials are ongoing. The majority of longterm safety data beyond 6 months was provided later in a 120-Day SUR which is covered in Section 7.2.9 of this review. Sample sizes at given time-point were further limited for several treatment subgroups in the N000 submission since subjects were not only subgrouped by their previous DB treatment assignment (placebo, Pal or olanzapine in the lead-in studies) but also by the duration of treatment (≤ 3 month and > 3 month exposure subgroups). Fortunately results of subjects from all treatment subgroups, combined ("Total" Pal group) were provided for these 2 exposure subgroups. The*

*results of the largest exposure subgroup (the > 3month Total Pal group) was the focus of review for the 24 week assessment time-point since this subgroup had 462 subjects at this time-point (the ≤ Total Pal subgroup had 131 or fewer subjects assessed at this time-point and at later time-points, and only 7 subjects were found to be assessed at week 52 for the largest subgroup). Consequently, the results of other subgroups and other time-points in the N000 submission are generally considered to be seriously limited. The sponsor used 5/31/05 as their cut-off date for their safety data analyses. See Section 7.2.9 of this review for updated OL results in which the number of subjects exposed to 12 months of Pal had met ICH guidelines and the number exposed to at least 6 months of treatment was larger for any given treatment subgroup.*

**Short-Term Phase III Safety Datasets (Trials -303, -304 and -305, combined and the elderly Trial -302).**

***Reviewer Comment.*** *Key findings are outlined below and are followed by data from the sponsor's summary tables:*

- *Inconsistent but remarkable CK results: Although mean increases in CK were observed among treatment groups in the 2 safety datasets, the observations were inconsistent. Given the following observations results on CK are difficult to interpret due to fluctuating levels over time during placebo treatment and elevations observed at baseline:*
  - *Treatment group mean increases in CK were inconsistent across dose-levels of Pal, and when compared to mean changes in the placebo group.*
  - *Results were also inconsistent across the 2 safety datasets.*
  - *Mean CK values at baseline were somewhat elevated in several treatment groups.*
  - *The within group variance (the SD) for a given treatment group was large (approximately 125 to over 400 U/l).*
  - *The placebo group also showed inconsistent mean increases in CPK over some time-points and high group mean values on some time-points (e.g. 573 U/l group mean value at Day 43), as revealed by a review of mean change of CPK over time (from baseline to each time-point of assessment) that was found in Appendix 2.7.4.4.11 of the SCS (data not shown below).*
  - *Finally, large fluctuations in CPK were also observed over time in some individual placebo subjects (e.g. from 172 U/l to 1208 U/l), as found in Appendix 2.7.4.4.2.1 for the 3 Phase III trial dataset.*
  - *Therefore, results on CPK are difficult to interpret.*
  - *While the above findings appear to reflect underlying elevations of CPK that are reported to occur with the schizophrenia-acute population, results from Phase I trials also show some elevations as described later that suggest the need for further explanation or exploration.*
- *Reproduceable Mean Decreases in Hemoglobin in Pal Groups with a Magnitude of Change that is Considered Clinically Unremarkable:*
  - *Group mean decreases in hemoglobin were observed Pal treatment groups that were not observed in placebo groups in both the non-elderly and elderly trial datasets, respectively (see data below).*

- *The magnitude of these mean changes was clinically unremarkable (a group mean change of up to 4.3±8.4, SD, in units of g/l was observed among the pal groups in the 2 safety datasets).*
- *Also mean changes generally did not show a trend for a greater mean change with increasing dose-levels.*

- *Reproduceable Pal Group Mean Decreases in Platelet Count of a Clinically Unremarkable Magnitude of Change:*
  - *Pal group mean decreases in platelet count of up to -15.6±58.5 (SD) units (units are in giga/l) were observed in both safety datasets (the pooled non-elderly trials and the single elderly trial, respectively).*
  - *The placebo groups in each safety dataset showed little change or a mean increase in this parameter (a mean increase of up to 22.6±57.8 units). However, the magnitude of the mean decrease in platelet count in each Pal group is not clinically remarkable.*

*Other laboratory parameter results on mean change from baseline on a given parameter were clinically unremarkable and failed to reveal any unexpected drug effect.*

The following are key results copied from sections of summary tables provided in the SCS:

Table 69: Selected Clinical Laboratory Analytes: Change From Baseline to End Point
(Pooled Double-Blind Studies R076477-303, 304, 305: Safety Analysis Set)

| | Placebo (N=355) | ER OROS PAL 3 mg (N=127) | ER OROS PAL 6 mg (N=335) | ER OROS PAL 9 mg (N=246) | ER OROS PAL 12 mg (N=243) | ER OROS PAL 15 mg (N=113) | Total Paliperidone (N=963) | Olanzapine 10 mg (N=364) |
|---|---|---|---|---|---|---|---|---|
| Creatine kinase (U/L) | | | | | | | | |
| N | 329 | 130 | 315 | 235 | 230 | 110 | 910 | 353 |
| Mean baseline (SD) | 149.8 (179.72) | 160.6 (220.83) | 171.7 (555.95) | 151.1 (239.82) | 172.4 (529.61) | 134.3 (149.40) | 160.6 (484.81) | 186.9 (385.42) |
| Mean change (SD) | 30.7 (455.40) | -6.9 (237.66) | 25.5 (617.14) | -9.1 (253.62) | -6.6 (521.95) | 5.4 (100.22) | 1.7 (427.83) | -18.1 (449.75) |
| Platelets (giga/l) | | | | | | | | |
| N | 325 | 119 | 313 | 227 | 225 | 108 | 892 | 341 |
| Mean baseline (SD) | 272.6 (72.51) | 297.5 (79.18) | 285.4 (77.59) | 283.5 (84.91) | 281.2 (73.65) | 301.2 (82.67) | 287.4 (78.54) | 279.1 (76.57) |
| Mean change (SD) | 6.0 (54.04) | -13.6 (57.59) | -6.6 (55.11) | -7.5 (55.61) | -11.2 (47.41) | -15.6 (58.50) | -10.0 (54.16) | -1.4 (51.89) |
| Reticulocytes (%) | | | | | | | | |
| N | 319 | 118 | 306 | 221 | 219 | 109 | 873 | 335 |
| Mean baseline (SD) | 1.8 (0.76) | 1.7 (0.88) | 2.0 (0.77) | 1.9 (0.82) | 1.9 (0.70) | 1.9 (1.24) | 1.9 (0.86) | 2.0 (1.07) |
| Mean change (SD) | -0.0 (0.55) | -0.1 (0.69) | -0.1 (0.47) | 0.0 (1.76) | -0.1 (0.53) | -0.1 (1.08) | -0.1 (1.05) | 0.1 (1.62) |
| Hemoglobin (g/L) | | | | | | | | |
| N | 328 | 120 | 314 | 228 | 227 | 110 | 899 | 344 |
| Mean baseline (SD) | 146.5 (16.28) | 145.9 (13.87) | 145.6 (16.13) | 144.6 (15.63) | 144.6 (16.04) | 143.5 (15.18) | 144.9 (15.56) | 147.6 (15.19) |
| Mean change (SD) | -0.1 (9.72) | -2.2 (8.51) | -4.3 (8.42) | -4.0 (8.49) | -3.0 (8.80) | -3.0 (7.71) | -3.5 (8.48) | -3.0 (9.20) |

Table 70: Selected Clinical Laboratory Analytes: Change From Baseline to End Point
(Study R076477-302: Safety Analysis Set)

| | Placebo (N=38) | ER OROS PAL (N=76) |
|---|---|---|
| Creatine kinase (U/L) | | |
| N | 36 | 75 |
| Mean baseline (SD) | 119.9 (194.15) | 75.7 (38.03) |
| Mean change (SD) | -3.9 (217.71) | 34.4 (113.12) |

| | | |
|---|---|---|
| Hemoglobin (g/L) | | |
| N | 37 | 74 |
| Mean baseline (SD) | 133.6 (13.33) | 132.1 (13.78) |
| Mean change (SD) | 1.3 (7.90) | -3.6 (9.05) |
| Platelets (giga/l) | | |
| N | 37 | 73 |
| Mean baseline (SD) | 347.4 (81.03) | 359.7 (86.88) |
| Mean change (SD) | 23.6 (57.77) | -8.0 (52.52) |

**Ongoing Phase III Trial -301.**
Results not provided. The study is blinded and ongoing.

**Ongoing Phase III Open Label Trials -703, -704, and -705.**
***Reviewer Comment.*** *Upon review of the >3month and ≥ 3 month "Total Pal" subgroups of the OL extension trials (see table below for each treatment subgroup analyzed by the sponsor), the results were generally found to be similar to previously described results of the two short-term, completed Phase III trial datasets. The following outlines key observations are noted (based on numerical comparisons of the sponsor's results, as provided in the submission):*

- *CK Mean Increase (from baseline to study endpoint) in the ≤ 3 month total Pal group:*
  - *The ≤3 month Pal group showed a mean increase in CK with little to no mean change in the > 3 month Pal group.*
  - *However, these results are difficult to interpret in the absence of a placebo group.*
  - *Furthermore, mean values at baseline were elevated in some subgroups and standard deviations for each subgroup were large.*
  - *Consequently, results are difficult to interpret.*
- *Group mean decreases in platelet count (from baseline to study endpoint in the >3 month and the ≤ 3 month subgroups) were observed (based on results found in-text summary tables in the SCS that are clinically unremarkable in magnitude were observed.*
  - *The >3 month subgroups generally showed numerically greater mean decreases than the ≤3 month subgroups, suggesting that a potential drug induced decrease in platelet count increases with duration of treatment.*
  - *Without a placebo group, these results are difficult to interpret and the magnitude of the observed decreases is clinically unremarkable for the duration of treatment examined.*

*The following results were copied out of the sponsor's in-text summary table.*

Table 71: Selected Clinical Laboratory Analytes: Change From Baseline to End Point
(Pooled Open-Label Studies R076477-702, 703, 704, 705: Safety Analysis Set)

| | Pla/Pali <=3 months (N=107) | Pla/Pali >3 months (N=128) | Pali/Pali <=3 months (N=178) | Pali/Pali >3 months (N=505) | Olan/Pali <=3 months (N=106) | Olan/Pali >3 months (N=143) | Total Pali <=3 months (N=391) | Total Pali >3 months (N=776) |
|---|---|---|---|---|---|---|---|---|
| Chemistry (continued) | | | | | | | | |
| Creatine kinase (U/L) | | | | | | | | |
| N | 43 | 93 | 63 | 324 | 42 | 94 | 147 | 511 |
| Mean baseline (SD) | 179.3 (237.60) | 115.5 (117.43) | 148.0 (197.71) | 144.8 (455.66) | 160.3 (153.07) | 152.2 (322.78) | 150.7 (198.30) | 140.8 (390.88) |
| Mean change (SD) | 6.1 (215.26) | 34.7 (118.26) | 91.5 (182.83) | -10.2 (454.02) | 82.4 (406.78) | 1.9 (358.73) | 63.9 (274.17) | 0.2 (396.02) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Hemoglobin (g/L) | | | | | | | | |
| N | 42 | 91 | 59 | 306 | 41 | 89 | 142 | 486 |
| Mean baseline (SD) | 144.9 (14.19) | 143.0 (15.38) | 144.9 (18.89) | 143.2 (15.37) | 146.1 (14.60) | 146.7 (13.03) | 145.2 (16.32) | 143.8 (15.01) |
| Mean change (SD) | -2.9 (9.29) | -2.7 (9.96) | -3.5 (10.88) | -2.1 (10.34) | -2.9 (8.99) | -2.1 (9.94) | -2.7 (9.84) | -2.3 (10.18) |
| Platelets (giga/l) | | | | | | | | |
| N | 42 | 89 | 59 | 303 | 40 | 87 | 141 | 479 |
| Mean baseline (SD) | 264.1 (74.45) | 260.0 (76.16) | 281.4 (77.33) | 276.2 (77.54) | 271.5 (65.48) | 293.6 (79.70) | 273.4 (73.13) | 276.4 (78.19) |
| Mean change (SD) | -9.6 (47.11) | -2.2 (54.80) | -0.6 (44.81) | -15.4 (62.85) | -6.4 (38.86) | -26.7 (61.63) | -4.9 (43.79) | -15.0 (61.54) |

*Since the sponsor's in-text summary table on showed mean changes from baseline to endpoint (after treatment cessation), on-treatment data that was found in Appendix 2.7.4.4.1.2 of the SCS was reviewed. The table in this appendix was too long to show in this review but it should descriptive statistical results for each assessment time-point. Upon review of this table, the following additional observations were made by the undersigned reviewer.*

*1. Additional Observations on Decreases in Group Mean Platelet count upon review of results that include on-treatment time-points*

- *At 6 Months of Treatment Mean and median Decreases in Platelet Count of approximately -15 to -17 giga/l, respectively were observed (insufficient data after 6 months) in the Total Pal group:*
  - *The > 3 month Total Pal group showed mean and median decreases of approximately -15 to -17giga/l after 6 months of treatment (at week 24 with insufficient data after 6 months). This subgroup was large, consisting of at least 450 subjects for 6 month and previous time-points which includes all subjects in the OL ongoing trials, as of the 5/31/05 cut-off date).*
- *At 6 months of treatment approximately -25 to -30 giga/l in the > 3 month subgroup that previously received DB Olanzapine treatment in the 6-week Short term Lead-in Trials was observed (upon review of On-Treatment Data found in Appendix 2.7.4.4.1.2 of the SCS):*
  - *The > 3 month DB Olanzapine/OL Pal subgroup (received DB olanzapine in the lead-in study) showed a mean or median decrease of up to -25 or -30 giga/l at the 6 months (week 24) and at study endpoint for the >3 month subgroup that previously received DB olanzapine treatment (DB Olanzapine/OL Pal subgroup). The sample size for this subgroup was 87 for these time-points.*
  - *The above results are compared to those of the DB Pal/OL Pal subgroup (received Pal treatment during the DB treatment phase of the lead-in study followed by OL Pal) showed a mean and median decrease of -17 giga/l at 6 months in which the sample size was over 280 subjects for this time-point. The sample sizes were insufficient for other OL on-treatment time-points which were the 12 week and 52 week time-points of this subgroup and for the ≤ 3 month subgroup of this DB Pal/OL Pal subgroup.*
  - *Other subgroups generally had insufficient sample sizes at any given on-treatment timepoint during OL treatment.*
  - *The following additional findings are noted as well as a more detailed description of results in the olanzapine/pal subgroup showing the largest numerical mean and median decreases. Mean or median decreases for any given time-point were generally less than -10 giga/l for any given treatment group except for the >3 month subgroup that previously received olanzapine treatment during the DB treatment phase of the lead in studies that preceded the OL extension trials. This*

*subgroup showed a mean and median decrease of approximately -25 to -30 giga/l at weeks 24 (n=87) and study endpoint (n=87, which occurred days after treatment). The only post-6 month OL treatment phase assessment time-point in the dataset was at week 52. Only 1 subject had data at week 52 in this subgroup who did not show a decrease in platelet count (and only 7 total subjects with data for all subgroups, combined). These observations can only be considered preliminary due to serious limitations with this dataset, as previously discussed.*

- *Since the standard deviations were generally large (e.g. approximately ±78 giga/l was observed in a given subgroup at any given time-point) the above observations would not reach statistical significance upon pairwise comparisons between treatment groups or between time-points in a given treatment group.*
- *The minimum within treatment group value for this parameter was approximately 61 giga/l among all the subgroups and among all time-points, but this value or a low within group value of approximately 90 were only observed for a few data points. Most values for any given time-point and any given subgroup were over 100 giga/l. Furthermore, low minimum within group values (as low as approximately 61) were also found on a few baseline or screening time-points (prior to treatment and before the DB phase). Therefore, these low minimum values were not consistent on or off treatment and do not alone provide evidence for a remarkable drug effect on hemoglobin levels.*
- *On-treatment Mean and Median Platelet Decreases Appear to be Greatest in Magnitude after Long term treatment (based on 6 month data, as described in the previous bulleted item) compared to Short-Term DB treatment Time-points (based on results in Appendix 2.7.4.4.1.2 of the SCS).*
  - *Mean and median decreases in the OL Pal subjects during the DB treatment phase were generally between approximately -1 to -10 giga/l per OL treatment subgroup, compared to the larger median and mean decreases observed in the described under the previous bulleted items describing OL Pal results.*
  - *It is also important to note that this pattern of smaller decreases during DB treatment compared to decreases observed with OL longer term treatment was observed for all treatment subgroups over almost all time-points during these DB and OL treatment phases.*
  - *The DB placebo/OL Pal subgroup which had the shortest total duration of Pal exposure over the lead-in and extension trials had an insufficient sample size during OL treatment time-points which still showed a trend for drug-induced decrease in platelet count (mean and median changes during placebo treatment were approximately 7 to 11 giga/l for any given time point compared to a mean decrease of -11 giga/l and a median decrease of -5 giga/l at 6 months.*
  - *These results are only considered preliminary given the serious limitations with this dataset, as previously discussed. See the final section of this review for more comments and recommendations.*

2. *Group mean decreases were observed at on-treatment time-points for hemoglobin that is clinically unremarkable in the observed magnitude of change. These observations were found upon review of data shown below (upon review of Appendix 2.7.4.4.1 for the mean change from baseline to 24 week time-point) as follow:*

- *The 6 month time-point showed a mean and median change of up to -3 or -4 g/l but generally -2 g/l or less in any given treatment subgroup either during the preceding DB treatment phase of lead in studies or during OL treatment up to 6 months (inadequate data past the 6 month time-point (results of he lead in studies that preceded OL extension trials were are also provided in Appendix 2.7.4.4.1).*
- *The standard deviation for each data point was generally at approximately ±15 g/l, such that the above observations would not be statistically significant upon pairwise group or time-point comparisons.*
- *The minimum within group values of hemoglobin approximately 80 or above observed on several time-points of several subgroups, but were not consistently low over time within a given subgroup and were also observed in several subgroups at baseline or screening.*

*No other clinically remarkable mean changes were observed in the 2 Total Pal ≤ 3 month and > 3 month exposure subgroups.*

**Phase I/IIa Studies.**

17 Healthy Subject Phase I Studies.

***Reviewer Comment.*** *Results described in this subsection are based on a review of results on the mean change from baseline to treatment endpoint (LOCF data) in the 17 Phase I dataset (healthy subject Phase I pooled results were found in Appendix 2.7.4.4.3.1 of the SCS). Treatment conditions in this pooled dataset included the following (results based on numerical comparisons between treatment conditions are described below): placebo, Low Dose OROS Pal (LD OROS Pal group), High Dose OROS Pal (HD OROS Pal group), IR Pal, and "Other" Pal groups. Refer to Section 7.1 of this review for details on the treatment conditions employed in these studies and refer to Section 4.2 of this review for the overall study design of each study in this pooled dataset.*

*Before describing the results of this pooled, Phase I, safety-dataset, it is important to note that results are generally difficult to interpret for a number of reasons. Most Phase I trials were SD, OL, cross-over studies that did not include a placebo group. Only 20 total subjects received placebo in this pooled dataset. Other treatment groups were also small, while between subject variance on most parameters was large. Given the large variance (large SDs) for each treatment condition numerical pairwise comparisons between treatment conditions would not generally reach statistical significance (e.g. differences were generally not greater than 2 SDs of the group mean).*

*See a previous discussion of other potential limitations in the dataset and on urinalysis results.*

*In some cases, data could not be found as follows. Data could not be found on a few laboratory parameters in the sponsor's tables (in the above mentioned appendix) for one or a few treatment conditions (e.g. results on CPK for placebo and a few active treatment conditions, as described later). The sponsor was asked about CPK results and a response was provided that is under review (the N005 submission was obtained late in the review cycle).*

*Given the potential limitations in interpreting pooled Phase I results minimal to no mean changes were observed in each treatment group on most laboratory parameters or results were clinically unremarkable or inconsistent. The following are key observations of unexpected findings, while noting that these results are generally difficult to interpret for reasons already provided and are considered preliminary observations:*

- *Mean Increase in CPK that is Greatest in the High-Dose OROS Pal Treatment Condition. The greatest mean increase in CPK were observed in the HD Pal OROS treatment condition (46.9±542.3 U/l) with little to no mean increases in the LD Pal OROS treatment conditions (3.3±189 U/l) and in the IR Pal treatment condition (9.0±97 U/l). Mean baseline CPK values for each treatment condition were within approximately 98 and 116 U/l.*
  - *Results of placebo subjects, the "Other" Pal and the risperidone treatment conditions could not be found in the sponsor's table in the above appendix of the SCS. It is difficult to interpret these results due to the large between subject variance (large SDs) and in the absence of data from a placebo treatment condition (the sponsor was asked about placebo results and a N005 response was recently received late in the review cycle).*
  - *Given the large standard deviations, observed numerical differences between treatment conditions would not generally be statistically significant upon pairwise comparisons (the differences were generally not greater than 2 SDs of the treatment condition means). The results suggest a possible mean increase in CPK with high dose OROS Pal in contrast to low dose OROS Pal and non-OROR or IR formulations.*
  - *Despite the difficulties in interpreting the above results, the findings appear to be reproduceable since similar group mean increases were observed in the HD OROS Pal group in the schizophrenia,-Phase I trial dataset as described later in a subsection below.*
- *Inconsistent Mean Changes in Platelets with a Magnitude of Change that is Clinically Unremarkable. While placebo subjects showed a mean change of -7.9 in platelet count (all values are in units of giga/l), the IR Pal and "other"Pal (non-OROS) Pal groups showed a mean change of approximately 12. However, the standard deviations were large (approximately ±30), such that group differences would not be statistically significant upon pair-wise comparisons (e.g. group differences were generally not greater than 2 standard deviations from the group mean). Furthermore, both OROS groups (LD and HD groups) failed to show a mean increase in platelet count (-6.8 and -1.7, respectively, with SDs of approximately 30). Due to the large SDs it is also difficult to interpret these results. Furthermore, the magnitude of group mean changes is clinically remarkable for all groups examined.*

Schizophrenia Phase I/IIa Trials.

***Reviewer Comments.*** *The following summarize key findings on mean change from baseline to treatment endpoint (LOCF) for laboratory parameters in treatment groups of the schizophrenia Phase I trial dataset (based on a review of Appendix 2.7.4.4.3.1 of the SCS that provided these*

*results in which numerical group comparisons were made by the undersigned reviewer, as with previously described results in this review).*

*The results described in this section are generally difficult to interpret due to major limitations with the dataset or study design of the Phase I trials, as described in the following. The Phase I/IIa Schizophrenia trials were generally OL, MD, non-placebo controlled trials. The exception was a MD DB study but only one group of subjects received a placebo treatment condition that was only given on Day 1 followed by Pal on subsequent treatment days in this MD trial. Sample sizes were generally small (e.g. only approximately 30 Pal IR subjects) while between subject variance was often large for a given parameter for a given treatment condition.*

*While, results were generally found for the IR Pal and HD OROS Pal treatment conditions (as well as a Risperidone condition) results on a few parameters for 1 or 2 of these treatment conditions could not be found in the above mentioned appendix (e.g. mean CPK values for the Pal IR treatment condition).*

*While considering the serious limitations with the dataset, the results generally failed to show evidence for a clinically remarkable drug effect (often little to no mean changes were observed on each parameter or observed mean changes were clinically unremarkable or mean changes were inconsistent across treatment conditions). The following key findings are possible exceptions to this overall conclusion:*

- *Mean Increase in CPK in the High-Dose OROS Pal Treatment Condition and in the Risperidone Treatment Condition. Similar to that observed in the Phase I dataset of healthy subjects, the schizophrenia-Phase I trial dataset also showed mean numerical increases in CPK in the HD OROS Pal condition of 105 U/l. A LD OROS Pal group was not included in these pooled schizophrenia trial. Results of the risperidone treatment condition were found that showed a small mean increase of 26 U/l. However, the within group variance (standard deviation) was large such that these results are difficult to interpret (SD of 798 for the HD OROS Pal condition). Results of the Pal IR treatment condition could not be found for this parameter in Appendix 2.7.4.3.2*
- *Platelet count mean changes were generally small increases that were clinically unremarkable and difficult to interpret (given the large SDs and other factors). The observed mean changes were 6.7, 11.1 and 16.9 giga/l for the IR Pal, HD OROS Pal and Risperidone treatment conditions, respectively while the standard deviation was approximately 40 in each treatment condition (in units of giga/l).*

**7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal**

Only the incidence of outliers was described in the SCS and in-text summary tables only showed results of selected parameters and could not find results anywhere in the SCS for all Phase III safety datasets (e.g. could not be found in other sections of the SCS or in an appendix to the SCS). However, this information was provided upon request and reviewed. No new or clinically remarkable findings were revealed upon review of parameters that were omitted from the in-text summary tables found in the SCS.

See the next subsection below on marked outliers regarding subjects identified as being remarkable outliers on LFT based on information provided by the sponsor upon request.

***Reveiwer comment.*** *The following describes results on the 3 safety datasets of Phase III trials. The 2 safety datasets for the completed, short-term Phase III trials are described (the pooled non-elderly trial dataset of Studies -303 through -305 and the elderly trial dataset, Study -302), as well as the results of the OL extension trial dataset (pooled data from OL Studies -702 through -705). The observations noted here, are based on a examination of the incidence of outliers as provided in summary tables in the SCS, as provided by the sponsor (with group numerical comparisons of treatment groups).*

*Data supporting key observations noted in the following paragraphs are provided in tables that follow the description of the results.*

*The incidence of outliers on any given parameter in the three Phase III trial datasets were generally 0-1 % with a few exceptions, as follows. A few parameters showed an incidence of 2% or greater but these parameters failed to show clinically remarkable groups differences between each Pal group and the placebo group (e.g. up to 6-13% incidence of outliers on low HDL values across treatment groups of which 10% of placebo subjects were outliers on this parameter). The few exceptions to this general observation are noted below with additional comments of relevant negative findings for a given signal (e.g. regarding CK outliers).*

*The following are potential key comments regarding results of the two completed Phase III trial datasets (also see actual results following this italicized section):*

- *A Potential Signal for a Greater Incidence of High LDL Outliers in Pal Groups compared to Placebo. The incidence of outliers for high LDL values was greater in Pal groups compared to placebo in the pooled short-term Phase III trial dataset, while Pal and placebo groups were similar on the incidence of outliers of low LDL values.*
- *The Potential Signal on High LDL Outliers was not Observed in the Elderly Trial. A Pal related signal for outliers on high LDL values that was observed in the non-elderly Phase III trial dataset (as above) was not observed in the elderly Phase III trial. However, this elderly trial was optimally designed for detecting a potential signal on potential group differences for a given parameter. The sample size of the treatment groups in this study were small and only one Pal group at a flexible dose design was examined, rather than employing multiple dose levels in a parallel group design. Furthermore, the detection of a signal may be more difficult in this older age-group, since LDL values are commonly elevated in elderly subjects and more likely to be further elevated in elderly patients with schizophrenia (consider for example a potential ceiling effect, as well as greater between individual variance on values). Consequently, it is difficult to make conclusions on the basis of the results of this study, alone and the results are only considered as preliminary.*
- *The Results on CK Outliers is Unremarkable. Results on the incidence of CK outliers by treatment group were unremarkable.*

- *Inconsistent and Clinically Unremarkable Observations on Low Reticulocyte Count Outliers. The incidence of outliers on low reticulocyte counts in any given group was higher than 1% (ranging form 2 to 8% in any given group).*
  - *However, the incidence in any given Pal group in the non-elderly Phase III trial dataset was not remarkably greater to the incidence observed in placebo groups.*
  - *Results across dose-levels of Pal in the pooled dataset failed to show consistent dose-dependent differences on the incidence of these outliers.*
  - *In the elderly trial 8% of Pal subjects were outliers (on low reticulocyte count) compared to 3% of placebo. It is not clear if this a drug-related signal or a false positive finding (e.g. due to multiple comparisons on multiple parameters).*

*The following are key observations in the pooled OL trial dataset. The incidence of 0-1% in the ≤ 3month and > 3 month total Pal groups except for the incidence of outliers on:*

- *The Pal subgroups showed an incidence of 4 or 7 % for high LDL outliers (for ≤3 month and > 3 month groups, respectively) and of 16 and 11%, respectively, for low LDL outliers. While the clinical significance of these findings is difficult to interpret it is notable that no subjects were outliers on high HDL but all groups except for one of them had an incidence within 7 to 9% in any given group for low HDL. This finding may have clinical relevance but without a placebo group this finding is only considered preliminary.*
- *The incidence of low reticulocyte count in contrast to that of high reticulocyte count suggests a possible drug-related signal for low reticulocyte count. Yet this observation is not consistent across groups and can only be considered preliminary since a placebo group is not included. Furthermore, the finding alone is not considered clinically remarkable.*

*No Outliers on Low Platelet Count or on Low values of Red Cell-related Parameters. Given previous observations for reproduceable mean decreases in platelet counts and hemoglobin in placebo controlled Phase III trial datasets, no Pal subject in any Phase III trial met outlier criteria for low platelet count, low hemoglobin, low red blood cell count or low hematocrit (in the non-elderly Studies -303 through -305, elderly trial -302 and OL extension trials -702 through -705).*

*Laboratory results from the ongoing, blinded "prevention of recurrence" Phase III trial (Study -301) and it's corresponding OL Extension Study -701 were not provided by the sponsor (since the trial is ongoing and blinded at this time).*

The following tables were copied from sections of summary tables found in the SCS (see above review comments).

Table 72: Treatment-Emergent Markedly Abnormal Laboratory Results
(Pooled Double-Blind Studies R076477-303, 304, 305: Safety Analysis Set)

| | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) n (%) | ER OROS PAL 6 mg (N=235) n (%) | ER OROS PAL 9 mg (N=346) n (%) | ER OROS PAL 12 mg (N=342) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Total Paliperidone (N=963) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|---|---|---|---|
| LDL (mmol/L) | 328 | 118 | 212 | 234 | 229 | 109 | 902 | 345 |
| Abnormally high | 20 ( 6) | 14 ( 12) | 29 ( 14) | 14 ( 6) | 19 ( 8) | 4 ( 4) | 80 ( 9) | 45 ( 13) |
| Abnormally low | 43 ( 13) | 19 ( 16) | 28 ( 13) | 42 ( 18) | 30 ( 13) | 20 ( 18) | 139 ( 15) | 24 ( 7) |
| Creatine kinase (U/L) | 330 | 121 | 215 | 236 | 231 | 110 | 913 | 353 |
| Abnormally high | 6 ( 2) | 0 | 4 ( 2) | 1 ( <1) | 4 ( 2) | 1 ( 1) | 10 ( 1) | 10 ( 3) |
| Abnormally low | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Reticulocytes (%) | 321 | 120 | 207 | 223 | 219 | 109 | 878 | 339 |
| Abnormally high | 3 ( 1) | 0 | 1 ( <1) | 3 ( 1) | 2 ( 1) | 1 ( 1) | 7 ( 1) | 9 ( 3) |
| Abnormally low | 11 ( 3) | 9 ( 8) | 7 ( 3) | 8 ( 4) | 4 ( 2) | 5 ( 5) | 33 ( 4) | 7 ( 2) |

It is noteworthy that none of the subjects in Study -302 met outlier criteria for high CPK, despite the previously shown markedly greater group mean elevation in CPK from baseline during treatment in Pal subjects that was not observed in the placebo group.

Table 73: Treatment-Emergent Markedly Abnormal Laboratory Results
(Study R076477-SCH-302: Safety Analysis Set)

| | Placebo (N=38) n (%) | ER OROS PAL (N=76) n (%) |
|---|---|---|
| LDL (mmol/L) | 37 | 73 |
| Abnormally high | 1 ( 3) | 0 |
| Abnormally low | 5 ( 14) | 9 ( 12) |
| HDL (mmol/L) | 37 | 75 |
| Abnormally high | 0 | 0 |
| Abnormally low | 1 ( 3) | 3 ( 4) |
| Reticulocytes (%) | 37 | 74 |
| Abnormally high | 1 ( 3) | 2 ( 3) |
| Abnormally low | 1 ( 3) | 6 ( 8) |

**Table 74:** Treatment-Emergent Markedly Abnormal Laboratory Results
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

| | 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 (%) |
|---|---|---|---|---|---|---|---|---|
| LDL (mmol/L) | 39 | 91 | 60 | 313 | 43 | 92 | 142 | 496 |
| Abnormally high | 2 ( 5) | 5 ( 5) | 4 ( 7) | 13 ( 4) | 4 ( 9) | 3 ( 3) | 10 ( 7) | 21 ( 4) |
| Abnormally low | 6 ( 15) | 11 ( 12) | 8 ( 13) | 31 ( 10) | 9 ( 21) | 14 ( 15) | 23 ( 16) | 56 ( 11) |
| HDL (mmol/L) | 42 | 93 | 63 | 321 | 43 | 93 | 148 | 507 |
| Abnormally high | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Abnormally low | 1 ( 2) | 8 ( 9) | 5 ( 8) | 28 ( 9) | 4 ( 9) | 7 ( 8) | 10 ( 7) | 43 ( 8) |
| Reticulocytes (%) | 41 | 88 | 59 | 304 | 42 | 87 | 142 | 479 |
| Abnormally high | 0 | 0 | 0 | 5 ( 2) | 0 | 1 ( 1) | 0 | 6 ( 1) |
| Abnormally low | 3 ( 7) | 7 ( 8) | 1 ( 2) | 12 ( 4) | 0 | 1 ( 1) | 4 ( 3) | 20 ( 4) |

The sponsor did not describe any observations from individual subject outliers.

**Phase I/IIa Studies.**
The incidence of outliers was found in Appendix 2.7.4.4.3.4 and results are described based on numerical observations or numerical comparisons between treatment conditions. Refer to the previous section of this review (7.1.7.3.1) for a discussion of serious limitations with interpreting results of the Phase I/II safety datasets described in the SCS that are also described in this review.

17 Healthy Subject Phase I/IIa Studies.
***Reviewer Comment.*** *See previous discussions on the serious limitations with interpreting laboratory results in Phase I/II Trials. The incidence of outliers were generally 0 to 1% in any given treatment condition on any given parameter with a few exceptions. The few exceptions were as follows:*

- *High CPK outliers among Subjects treated with OROS Pal but not in Placebo and non-OROS Pal Treatment Conditions.*
  - *No subjects had high outlier values for CPK in the placebo, IR Pal, "other' Pal or risperidone treatment conditions.*
  - *In contrast to these groups the incidence of high CPK outliers in the LD OROS Pal, HD OROS Pal and all OROS Pal treated subjects (LD and HD treated subject, combined) was 1% (1/76 subjects), 3% (1/127 subjects) and 3% (1/156 subjects), respectively.*
  - *No subjects had low outlier CPK values in any of the treatment conditions of this safety dataset.*
  - *These results are generally consistent with results on mean increases of CPK in the HD OROS Pal treatment condition and numerically smaller mean increases observed in other Pal treatment conditions observed in this Phase I/IIa dataset, as previously described.*

- *The incidence of each of outliers on each of the following parameters conditions were generally greater than 1% but were often no greater than 2% in any given Pal treatment condition (unless otherwise specified) compared to an incidence of 0 subjects in the placebo condition:*
  - *High LDH (up to 4% in the "Other" Pal condition and 3% in the HD OROS Pal Condition),*
  - *High eosinophil count,*
  - *Low platelet count,*
  - *Low neutrophil count, and*
  - *Low phosphorous.*

Schizophrenia Phase I/IIa Trials.
***Reviewer Comments.*** *Results of the Schizophrenia Phase I/IIa dataset were generally similar to those of the healthy subject Phase I/IIa dataset, previously described.*

*2% (12/103) subjects in the HD OROS Pal condition were high CPK outliers compared to no Pal IR subjects (0/33 subjects) and no risperidone subjects (0/53 subjects).*

**7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities**

See previous sections on ADOs and SAEs for clinically remarkable outliers. Also see section 7.1.3.3 for potentially clinically remarkable subjects, ADOs and/or SAEs.

**The Incidence of Outliers on LFTs (based on results in N005 submission, provided by the sponsor upon request)**

ALT or AST at 3 times greater than the ULN in Subjects with Normal Baseline Values:
The sponsor was asked to provide the incidence of LFT outliers in all Phase III trials that included a placebo-controlled DB phase (6-week Studies -301, -302, -303 through -305) using the following criterion. An outlier was defined as having 3 times greater than the upper limit of normal on ALT or AST values during treatment among subjects with normal baseline baseline values on these parameters and on bilirubin levels. The studies with small samples sizes of Pal and placebo treatment groups (Studies -301 and -302) failed to reveal any outliers using this criterion. The following table shows results of outliers, as provided by the sponsor (in a response submission, N005).

TLABHP: Number of Subjects with ALT or AST >3ULN During Double Blind Phase
(Study R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

| | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) n (%) | ER OROS PAL 6 mg (N=235) n (%) |
|---|---|---|---|
| **Normal baseline** | 260 | 104 | 176 |
| >3xuln | 2 ( 1) | 3 ( 3) | 1 ( 1) |

Note: Percentages calculated with the number of subjects who had normal AST, ALT, and bilirubin values at double-blind baseline as denominator.

Table continued on next pagexx?
LFT Table, continued

**TLABHP: Number of Subjects with ALT or AST >3ULN During Double Blind Phase**
**(Study R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)**

| | ER OROS PAL 9 mg (N=346) n (%) | ER OROS PAL 12 mg (N=142) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|
| **Normal baseline** | 198 | 185 | 88 | 290 |
| >3xuln | 0 | 0 | 2 ( 3) | 16 ( 6) |

Note: Percentages calculated with the number of subjects who had normal AST, ALT, and bilirubin values at double-blind baseline as denominator.

ALT or AST of greater than 8 times the ULN in Subjects with Normal Baseline Values:
Also upon request the sponsor identified any subjects with normal LFTs at baseline (ALT, AST and bilirubin) that later developed elevations in ALT and/or AST of greater than 8 times the ULN in the Phase III trials (the above listed Phase III trials, as well as for OL extension trials using the cut-off date of the more recent 120-Day Safety Update Report submission (submission was dated 2/1/06). There were no subjects meeting these criteria for the studies with small sample sizes for the Pal and placebo groups (Studies -301, -302) and for the OL Study -701 that also has a limited number of subjects relative to the larger OL trials, -702-705 (combined). Only 4 subjects met the outlier criteria among the Phase III trials.

The following is a line listing of LFT values for the 4 above subjects, as provided by the sponsor that in summary, showed transient, yet marked elevations in LFTs in the 3 subjects that continued on Pal treatment. The fourth subject was an ADO due to elevated LFTs on Day 22 of Olanzapine treatment. See reviewer comments below.

Study R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

OUTPUT sch2345 : Subjects Who had Normal ALT, AST, and Bilirubin at Baseline(DB) with AST or ALT of >8x Upper Limit of Normal Post Double Blind Baseline

Analysis Set: Safety

| Subject Number | Age (years) | Sex | Country | Time Interval | Actual Date of Sample | Relative Day | ALT (U/L) | ALT >8x ULN | AST (U/L) | AST >8x ULN | BILIRUBIN (umol/l) | DIRECT BILIRUBIN (umol/l) | GGT (U/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Id: R076477-SCH-303/703 Treatment Group: Olan/Pali | | | | | | | | | | | | | |
| 201609 | 23 | FEMALE | RUSSIA | SCREENING(DB) | 24JUN2004 | -5 | 13 | | 11 | | 9 | 2 | 31 |
| | 23 | FEMALE | RUSSIA | BASELINE(DB) | 24JUN2004 | -5 | | | | | | 2 | |
| | 23 | FEMALE | RUSSIA | BASELINE(DB) | 29JUN2004 | 1 | 11 | | 12 | | 11 | | 26 |
| | 23 | FEMALE | RUSSIA | DAY 15(DB) | 13JUL2004 | 15 | 22 | | 18 | | 5 | | 20 |
| | 23 | FEMALE | RUSSIA | DAY 43(DB) | 11AUG2004 | 44 | 423 | Yes | 149 | | 5 | 2 | 80 |
| | 23 | FEMALE | RUSSIA | BASE(OPEN) | 11AUG2004 | 1 | 423 | | 149 | | 5 | 2 | 80 |
| | 23 | FEMALE | RUSSIA | WEEK 24(OPEN) * | 18AUG2004 | 8 | 115 | | 36 | | 8 | 2 | 72 |
| | 23 | FEMALE | RUSSIA | WEEK 24(OPEN) | 08SEP2004 | 29 | | | | | | 2 | |
| | 23 | FEMALE | RUSSIA | WEEK 24(OPEN) * | 08SEP2004 | 29 | 23 | | 13 | | 6 | | 36 |
| | 23 | FEMALE | RUSSIA | WEEK 24(OPEN) | 26JAN2005 | 169 | 41 | | 24 | | 4 | | 23 |
| | 23 | FEMALE | RUSSIA | WEEK 52(OPEN) | 08AUG2005 | 363 | 30 | | 20 | | 10 | 3 | 15 |
| | 23 | FEMALE | RUSSIA | POST DAY 7(OPEN) | 15AUG2005 | 370 | 17 | | 16 | | 5 | 2 | 14 |
| Study Id: R076477-SCH-305/705 Treatment Group: Pali/Pali | | | | | | | | | | | | | |
| 502015 | 32 | MALE | UKRAINE | SCREENING(DB) | 24FEB2005 | -4 | 14 | | 16 | | 9 | 2 | 7 |
| | 32 | MALE | UKRAINE | BASELINE(DB) | 24FEB2005 | -4 | 14 | | 16 | | 9 | 2 | 7 |
| | 32 | MALE | UKRAINE | DAY 15(DB) * | 01MAR2005 | 2 | 24 | | 16 | | 6 | | 6 |
| | 32 | MALE | UKRAINE | DAY 15(DB) | 14MAR2005 | 15 | 46 | | 20 | | 4 | 2 | 9 |
| | 32 | MALE | UKRAINE | DAY 43(DB) | 12APR2005 | 44 | 428 | Yes | 200 | | 7 | 3 | 17 |
| | 32 | MALE | UKRAINE | BASE(OPEN) | 12APR2005 | 1 | 428 | | 200 | | 7 | 3 | 19 |
| | 32 | MALE | UKRAINE | WEEK 24(OPEN) | 27SEP2005 | 169 | 89 | | 43 | | 4 | | 17 |
| Study Id: R076477-SCH-305/705 Treatment Group: Olan/Pali | | | | | | | | | | | | | |
| 501368 | 24 | MALE | UNITED STATES OF AMERICA | SCREENING(DB) | 20AUG2004 | -4 | 12 | | 19 | | 9 | 2 | 17 |
| | 24 | MALE | UNITED STATES OF AMERICA | BASELINE(DB) | 24AUG2004 | 1 | 10 | | 16 | | 9 | 2 | 16 |
| | 24 | MALE | UNITED STATES OF AMERICA | DAY 15(DB) | 07SEP2004 | 15 | 385 | Yes | 119 | | | | 80 |
| | 24 | MALE | UNITED STATES OF AMERICA | DAY 15(DB) | 14SEP2004 | 22 | | | | | 7 | 2 | |
| | 24 | MALE | UNITED STATES OF AMERICA | DAY 15(DB) * | 14SEP2004 | 22 | 254 | | 74 | | | | 01 |
| | 24 | MALE | UNITED STATES OF AMERICA | POST DAY 7(DB) | 21SEP2004 | 29 | 45 | | 18 | | 7 | 2 | 59 |
| Study Id: R076477-SCH-305/705 Treatment Group: Pali/Pali | | | | | | | | | | | | | |
| 501558 | 48 | FEMALE | UKRAINE | SCREENING(DB) | 08NOV2004 | -5 | 20 | | 16 | | 6 | 2 | 18 |
| | 48 | FEMALE | UKRAINE | BASELINE(DB) | 08NOV2004 | -5 | | | | | | 2 | |
| | 48 | FEMALE | UKRAINE | BASELINE(DB) | 11NOV2004 | -2 | 25 | | 18 | | 5 | | 16 |
| | 48 | FEMALE | UKRAINE | DAY 15(DB) | 26NOV2004 | 14 | 19 | | 17 | | 7 | | 13 |
| | 48 | FEMALE | UKRAINE | DAY 43(DB) | 24DEC2004 | 42 | 25 | | 22 | | 7 | | 18 |
| | 48 | FEMALE | UKRAINE | BASE(OPEN) | 24DEC2004 | 1 | 25 | | 22 | | 7 | | 18 |
| | 48 | FEMALE | UKRAINE | WEEK 24(OPEN) | 07JUN2005 | 166 | 373 | Yes | 186 | | 11 | 2 | 15 |
| | 48 | FEMALE | UKRAINE | WEEK 24(OPEN) * | 15JUN2005 | 174 | 143 | | 72 | | 10 | 2 | 18 |
| | 48 | FEMALE | UKRAINE | WEEK 52(OPEN) | 20DEC2005 | 362 | 17 | | 19 | | 9 | 2 | 7 |
| | 48 | FEMALE | UKRAINE | POST DAY 7(OPEN) | 28DEC2005 | 370 | 17 | | 25 | | 15 | 2 | 7 |

Best Possible Copy

***Reviewer Comment***

*Elevations during Pal treatment were transient in the subjects revealed in the special search even in subjects that had Pal dose-levels increased, as LFT values declined or normalized (upon review of the narratives for the above subjects provided in the original NDA submission and in the SUR, as well as in the sponsor's response submission N005). One subject also had a history of viral hepatitis (501558).*

*An olanzapine subject was withdrawn on Day 22 (subject 501268) due to elevated LFTs in which values normalized at 7 days after the last dose. Since study drug was not continued in this subject it is not known if values would have eventually normalized with continued treatment, as observed among the Pal subjects described above. It is also noteworthy that olanzapine subjects showed the largest incidence of outliers on ALT or AST of greater than 3 times the ULN (in subjects with normal baseline values) which was 6% compared to only 1% of placebo subjects and 0-3% of subjects in Pal groups (as previously shown for the short-term Phase III trial, combined, dataset). Approved labeling for olanzapine describes transient elevations in LFTs under the Precautions section of labeling.*

*Also see previous sections on ADOs and SAEs in this review. One ADO due to elevated LFTs is described that appear to be drug-related transient and remarkable elevations of LFTs (of up to approximately 8 times the ULN) in Subject 503018. as previously described in this review. Pal*

*treatment was discontinued while LFTs were markedly elevated. Consequently, it is not clear if these elevations would have normalized spontaneously with continued Pal treatment. Despite this uncertainty, elevations to this degree are clinically remarkable and warrant cessation of treatment.*

*See Section 7.1.3.3 for additional potentially clinically remarkable subjects with abnormal LFT values.*

*See additional comments and recommendations in the last section of this review.*

**7.1.7.4 Additional analyses and explorations**

See the previous subsection.

**7.1.7.5 Special assessments**

**7.1.7.5.1 Results on Prolactin Levels**

***Reviewer Comments on Prolactin Results*** *Appendix 2.7.4.4.1.1 was found to contain some results on prolactin levels for some safety datasets. A drug class effect of increasing prolactin levels is well known. However, the following observations are notable findings:*

- *Dose dependent group mean increase was observed with OROS Pal in which little to no increase was revealed with a 3 mg daily dose of OROS Pal (similar to the placebo group), while a remarkable group mean increase was observed at the 6, 9, 12 and 15 mg daily dose-level groups in the 3-Phase III safety dataset. See results in the summary table below.*
- *The above results also revealed large group mean increases in Prolactin for each of the daily Pal dose levels of above the lowest dose level (in the 6, 9, 12 and 15 mg daily dose groups, but not in the placebo or 3 mg groups) that were remarkably greater than that observed for the olanzapine group (10 mg/daily). See results in the summary table below.*
- *Phase I/IIa results (schizophrenia trials) revealed similar mean Prolactin level increases in Pal groups (OROS and non-OROS groups compared) to Risperidone treatment (mean levels of 32.1 and 37.0 ng/ml were observed in the high dose OROS Pal and the risperidone groups, respectively.*
- *See section 7.1.4 for results showing a numerically greater incidence of potentially prolactin-related AEs in the 12 and 15 mg Pal groups compared to only a few to no reported AEs in the lower dose Pal groups, the Olanzapine group and the placebo group (revealed in the 3-Phase III trial dataset).*

Results on Prolactin Levels (copied from pages 3136-3138 of an appendix to the SCS)

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DLAB01: Laboratory Values: Means and Mean Changes Over Time - Double-Blind Phase (continued)

Analysis Set: Safety

| | | | | | | | Base | change from baseline | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | Med | Min | Max | Mean (SD) | N | Mean | SE | SD | Med | Min | Max |
| PROLACTIN (ng/ml) | | | | | | | | | | | | | | |
| Placebo | | | | | | | | | | | | | | |
| SCREENING | 352 | 35.73 | 42.452 | 19.00 | 2.1 | 279.3 | | | | | | | | |
| BASELINE | 355 | 20.69 | 30.564 | 11.43 | 1.1 | 257.1 | | | | | | | | |
| DAY 15 | 329 | 15.33 | 17.376 | 10.68 | 1.2 | 137.3 | 20.44 (30.537) | 329 | -5.11 | 1.567 | 28.421 | -0.96 | -243.8 | 81.8 |
| DAY 36 | 146 | 15.23 | 21.424 | 9.66 | 1.0 | 169.4 | 21.90 (36.105) | 146 | -6.67 | 3.037 | 36.694 | -1.16 | -227.2 | 149.5 |
| DAY 43 | 134 | 14.17 | 20.128 | 9.30 | 1.0 | 160.8 | 20.07 (29.976) | 134 | -5.90 | 2.647 | 30.641 | -1.21 | -226.4 | 144.9 |
| END POINT | 331 | 15.41 | 17.832 | 10.19 | 1.0 | 160.8 | 20.67 (30.840) | 331 | -5.26 | 1.632 | 29.685 | -1.15 | -226.4 | 144.9 |
| ER OROS PAL 3 mg | | | | | | | | | | | | | | |
| SCREENING | 124 | 46.65 | 66.731 | 24.95 | 3.4 | 385.3 | | | | | | | | |
| BASELINE | 126 | 27.65 | 57.413 | 12.23 | 0.9 | 446.4 | | | | | | | | |
| DAY 15 | 121 | 62.92 | 68.442 | 37.94 | 4.5 | 473.8 | 28.56 (58.689) | 120 | 34.66 | 5.979 | 65.492 | 23.37 | -260.0 | 436.9 |
| DAY 36 | 73 | 64.71 | 83.056 | 33.47 | 3.5 | 548.9 | 27.30 (66.439) | 72 | 37.95 | 9.435 | 80.062 | 22.14 | -174.5 | 512.1 |
| DAY 43 | 67 | 66.01 | 101.489 | 32.72 | 4.5 | 750.4 | 24.27 (54.746) | 66 | 42.30 | 13.011 | 105.704 | 19.61 | -248.0 | 713.6 |
| END POINT | 121 | 60.83 | 84.577 | 32.68 | 4.5 | 750.4 | 28.56 (58.689) | 120 | 32.54 | 8.154 | 89.322 | 19.51 | -248.0 | 713.6 |
| ER OROS PAL 6 mg | | | | | | | | | | | | | | |
| SCREENING | 234 | 37.70 | 48.124 | 19.25 | 1.1 | 330.1 | | | | | | | | |
| BASELINE | 234 | 22.62 | 34.649 | 12.04 | 1.2 | 381.8 | | | | | | | | |
| DAY 15 | 218 | 72.40 | 62.473 | 52.51 | 2.9 | 479.2 | 22.48 (34.723) | 217 | 50.24 | 3.552 | 52.326 | 37.82 | -48.0 | 279.6 |
| DAY 36 | 125 | 67.79 | 58.432 | 50.81 | 4.4 | 334.9 | 20.68 (28.174) | 125 | 47.11 | 4.561 | 50.992 | 30.71 | -83.3 | 285.1 |
| DAY 43 | 125 | 66.10 | 57.905 | 49.70 | 4.5 | 350.3 | 20.78 (28.429) | 125 | 45.32 | 4.553 | 50.904 | 31.96 | -90.7 | 286.1 |
| END POINT | 218 | 67.35 | 61.153 | 48.15 | 1.2 | 364.9 | 22.48 (34.723) | 217 | 45.18 | 3.421 | 50.401 | 31.57 | -90.7 | 286.1 |
| ER OROS PAL 9 mg | | | | | | | | | | | | | | |
| SCREENING | 239 | 43.14 | 55.038 | 23.17 | 1.8 | 455.2 | | | | | | | | |
| BASELINE | 245 | 25.15 | 43.343 | 11.18 | 1.4 | 426.1 | | | | | | | | |
| DAY 15 | 235 | 85.16 | 69.238 | 60.84 | 5.9 | 489.2 | 25.24 (43.624) | 234 | 60.12 | 4.006 | 61.277 | 40.82 | -68.2 | 300.3 |
| DAY 36 | 157 | 84.09 | 96.490 | 53.85 | 4.7 | 989.3 | 22.84 (35.918) | 157 | 61.25 | 7.413 | 92.885 | 39.78 | -37.7 | 973.5 |
| DAY 43 | 158 | 83.15 | 61.602 | 59.40 | 3.4 | 278.1 | 23.90 (37.766) | 158 | 59.25 | 4.979 | 62.584 | 40.49 | -57.5 | 255.4 |
| END POINT | 235 | 76.14 | 59.756 | 51.76 | 3.4 | 297.3 | 25.24 (43.624) | 234 | 51.06 | 3.823 | 58.473 | 35.79 | -128.8 | 255.4 |
| ER OROS PAL 12 mg | | | | | | | | | | | | | | |
| SCREENING | 239 | 38.72 | 49.554 | 20.57 | 2.0 | 300.2 | | | | | | | | |
| BASELINE | 241 | 23.28 | 35.466 | 12.43 | 1.6 | 261.6 | | | | | | | | |
| DAY 15 | 230 | 88.09 | 64.191 | 68.13 | 5.4 | 325.3 | 22.74 (33.378) | 230 | 65.35 | 3.820 | 57.933 | 48.85 | -77.9 | 293.6 |
| DAY 36 | 147 | 80.49 | 62.315 | 62.11 | 5.6 | 379.0 | 19.98 (28.584) | 147 | 60.51 | 4.438 | 53.814 | 39.85 | -39.5 | 218.7 |
| DAY 43 | 151 | 81.68 | 62.961 | 62.83 | 2.4 | 344.8 | 22.59 (35.515) | 150 | 58.93 | 4.473 | 54.789 | 42.30 | -52.6 | 253.6 |
| END POINT | 232 | 77.03 | 62.026 | 56.93 | 2.4 | 344.8 | 22.81 (33.326) | 231 | 54.09 | 3.662 | 55.664 | 39.42 | -77.9 | 253.6 |
| ER OROS PAL 15 mg | | | | | | | | | | | | | | |
| SCREENING | 112 | 33.98 | 37.665 | 22.07 | 2.4 | 269.3 | | | | | | | | |
| BASELINE | 113 | 19.36 | 21.898 | 12.22 | 1.1 | 136.1 | | | | | | | | |
| DAY 15 | 108 | 92.00 | 67.450 | 71.24 | 8.3 | 303.4 | 19.63 (22.219) | 108 | 72.37 | 6.110 | 63.500 | 59.53 | -31.4 | 284.8 |
| DAY 36 | 78 | 90.34 | 67.495 | 66.33 | 7.2 | 318.3 | 19.58 (23.205) | 78 | 70.75 | 7.117 | 62.854 | 50.63 | -8.9 | 256.2 |
| DAY 43 | 79 | 85.98 | 62.485 | 67.78 | 7.4 | 286.5 | 17.73 (18.636) | 79 | 68.25 | 6.905 | 60.485 | 52.30 | -29.9 | 253.8 |
| END POINT | 110 | 80.92 | 61.181 | 63.31 | 5.5 | 286.5 | 19.53 (22.072) | 110 | 61.39 | 5.568 | 58.399 | 44.33 | -31.4 | 253.8 |
| Total Paliperidone | | | | | | | | | | | | | | |
| SCREENING | 948 | 40.06 | 52.031 | 21.09 | 1.1 | 455.2 | | | | | | | | |
| BASELINE | 959 | 23.71 | 39.709 | 12.02 | 0.9 | 446.4 | | | | | | | | |
| DAY 15 | 912 | 80.71 | 66.639 | 58.45 | 2.9 | 489.2 | 23.72 (39.650) | 909 | 57.18 | 1.997 | 60.198 | 39.99 | -260.0 | 436.9 |
| DAY 36 | 580 | 78.07 | 75.891 | 53.68 | 3.5 | 989.3 | 21.76 (36.670) | 579 | 56.39 | 2.948 | 70.931 | 37.28 | -174.5 | 973.5 |
| DAY 43 | 580 | 77.50 | 67.383 | 56.65 | 2.4 | 750.4 | 22.08 (35.729) | 578 | 55.45 | 2.703 | 64.981 | 39.07 | -248.0 | 713.6 |
| END POINT | 916 | 72.83 | 64.782 | 51.34 | 1.2 | 750.4 | 23.72 (39.593) | 912 | 49.24 | 2.034 | 61.438 | 34.77 | -248.0 | 713.6 |
| Olanzapine 10 mg | | | | | | | | | | | | | | |
| SCREENING | 361 | 39.50 | 55.231 | 20.48 | 1.4 | 361.1 | | | | | | | | |
| BASELINE | 364 | 21.84 | 34.632 | 11.33 | 1.3 | 324.4 | | | | | | | | |
| DAY 15 | 344 | 23.41 | 30.496 | 16.14 | 1.9 | 290.4 | 22.04 (35.474) | 344 | 1.37 | 1.657 | 30.725 | 3.09 | -204.6 | 248.5 |
| DAY 36 | 226 | 21.67 | 30.228 | 14.06 | 2.0 | 359.0 | 24.75 (41.859) | 226 | -3.08 | 2.396 | 36.019 | 1.58 | -294.9 | 158.1 |
| DAY 43 | 216 | 19.93 | 25.124 | 14.33 | 2.8 | 290.6 | 24.36 (40.456) | 216 | -4.43 | 2.349 | 34.522 | 2.05 | -313.8 | 89.7 |
| END POINT | 352 | 19.39 | 21.860 | 14.21 | 2.0 | 290.6 | 21.98 (35.135) | 352 | -2.59 | 1.636 | 30.703 | 2.42 | -313.8 | 89.7 |

## 7.1.8 Vital Signs

***A Caveat on Group and Time-point Comparisons on a Given Clinical Parameter.*** *Results of statistical group or time-point comparisons or in-text description of statistical results on clinical parameters could not be found in the SCS. Therefore, group and time-point comparisons described in this review on any given clinical parameter are based on numerical comparisons, unless otherwise specified (results on clinical parameters that were found in the SCS and are described in this review did not include statistical comparisons).*

### 7.1.8.1 Overview of vital signs testing in the development program

The outlier criteria for vital signs is provided in the Table 10.2 in the appendix of this review, as provided by the sponsor.

Vital signs were obtained at multiple time-points during the Phase III and OL trials. Refer to the schedule of assessments in Table series 10.1 in the appendix of this review for the study schedules of Phase III trials.

***Reviewer Comments of Vital Sign Methods.*** *Vital signs were conducted daily from Days 1-6 and then on selected Days for the remainder of the DB trials and OL trials.*

### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See the previous subsection and sections below. Also refer to Section 7.1 for a description of integrated datasets analyzed and described in this review.

### 7.1.8.3 Standard analyses and explorations of vital signs data

See the next subsection below.

### 7.1.8.3.1. Analyses focused on measures of central tendencies

**Completed Phase III Non-Elderly Trials -303, -304 and -305.**
***Reviewer Comments.*** *Descriptive statistical results were found in Appendix 2.7.4.5.1.1 of the SCS (time-points examined were: baseline, days 2, 3, 4, 5, 6, 8, 15, 22, 29, 36, 43 and endpoint).*

***A Caveat:*** *one critical caveat to interpreting vital sign results is that the window of time shown below for each scheduled assessment (copied from the submission):*

| Variable | Scheduled Visit Number | Time Interval (Label on ouput) | Time Interval (Day)* | Target Time Point (Day) |
|---|---|---|---|---|
| | | | | |

| Vital Signs | 1,2 | Baseline | ≤ 1 | 1 |
|---|---|---|---|---|
| | 3 | Day 2 | 2 | 2 |
| | 3 | Day 3 | 3 | 3 |
| | 4 | Day 4 | 4 | 4 |
| | 4 | Day 5 | 5 | 5 |
| | 4 | Day 6 | 6 | 6 |
| | 5 | Day 8 | 7-11 | 8 |
| | 6 | Day 15 | 12-18 | 15 |
| | 7 | Day 22 | 19-25 | 22 |
| | 8 | Day 29 | 26-32 | 29 |
| | 9 | Day 36 | 33-39 | 36 |
| | 10 | Day 43 | 40-end of DB | 43 |
| | | | | |

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

*Subjects were inpatients for the first 2 weeks of DB treatment but could be discharged thereafter. Between subject variance on the timing of assessments and relative to dosing (between subject variance on timing of dosing) is likely to be greatest on outpatient assessments days. However, the days that examined PK (with multiple blood samples collected on a give study day) would be anticipated to have the timing of assessments more tightly controlled (in which subjects would have to be a the study site or inpatients during this procedure) than on study days that did not involve multiple blood sample collections on the given day.*

***Another Caveat on Group and Time-point Comparisons on a Given Clinical Parameter.*** *Results of statistical group or time-point comparisons or in-text description of statistical results on clinical parameters could not be found in the SCS. Therefore, group and time-point comparisons described in this review on any given clinical parameter are based on numerical comparisons, unless otherwise specified (results on clinical parameters that were found in the SCS and are described in this review did not include statistical comparisons).*

*A Summary of the Results*
*Due to the lengthiness of the summary table of vital sign results (37 pages long for the summary table, Appendix 2.7.4.5.1.1 of the SCS) this review summarizes the results of this table, rather than showing the results shown in the 37 page table.*

*The descriptive statistical results on vital sign parameters generally failed to show any new or clinically remarkable findings other than a few potential exceptions. Key observations are outlined below (the below items include potentially unexpected or new findings, whole noting some relevant negative findings for a clinically remarkable effect on a given parameter):*

- *A mean increase from baseline in supine tachycardia was observed that was time-dependent and dose-dependent with greatest effects generally observed in the HD group (15 mg). The maximum mean increase observed in this group was 6.8±12.9 bpm on Day 6 (ranging up to a maximum individual-subject increase of 128 bpm in this group at this time-point).*

- *The placebo group generally showed little to no change at each time point (mean change from baseline to Day 6 was 0.6±11bpm).*
- *The Olanzapine group showed little to no change in this parameter compared to all Pal groups. It is important to note the large variance (SD) from a statistical standpoint. See previous discussions regarding this observation of a drug-induced increase in supine heart rate.*
- *Refer to the last section of this review for additional comments and recommendations.*

- *Another potentially unexpected finding that could be considered a real dose-dependent effect or could be an isolated finding (e.g. a false positive) is a slight mean increase (from baseline to DB treatment time-points) in supine systolic blood pressure (sBP) that was only observed in the HD Pal group (15 mg) during the first week of treatment (a group mean increase of up to 4.± 12.9 mmHg on Day 5). The lower-dose Pal groups and the placebo group generally showed no mean change in sBP at any given time-point (mean changes were generally within -1 to 1 mmHg for any given group at any given time-point).*
- *Mean changes in standing to supine (standing-supine) blood pressure (systolic and diastolic) failed to show any clinically remarkable findings in which the greatest mean change from baseline at any given time-point for sBP was generally in the HD group (15 mg Pal) which only showed a mean change of -2.5±11.8 mmHg on Day 5.*
- *Standing-supine mean changes on heart rate failed to show any remarkable mean or median changes at any given time-point in any given treatment group. The HD (15 mg) group showed mean changes of 1.3 to -0.5 bpm (±9 to 13).*
- *Results on standing heart rate showed dose-dependent and time-dependent mean increases from baseline as follows:*
  - *The HD Pal group generally showed higher mean increases of up to 7 bpm (SD of ±14 or ±15) on Days 3 and 4 (a mean increase of 5 to 6 were observed on Days 2, 5, 6 and 8) that appeared to be greater in magnitude and longer in duration over treatment than the mean increases observed in lower dose Pal groups (based on numerical comparisons) with little to no change in the placebo group (mean change of 1.5 to -0.8 observed in the placebo group).*
  - *The magnitude of these peak mean increases observed on Days 3 and 4 in the HD group appeared to be become increasingly smaller with each subsequent time-point. That is, the peak effect observed early in treatment (Days 3 and 4) appeared to diminish over time over Days 5 though Day 36 of treatment with a mean change of only 0.5 observed on the final on-treatment assessment day (Day 43).*
  - *The placebo group showed no mean increases from baseline to each time-point on standing heart rate (mean changes were generally less than 1 bpm).*
  - *Surprisingly, the olanzapine group (10 mg/day) generally showed no to little mean changes at any given time-point (similar to the placebo group), whereas even the lowest Pal group (3 mg) consistently showed mean increases in standing heart rate for all time-points that appeared to persist up to approximately Day 22 (a mean change of up to 4.4 was observed on Day 2 in this low dose group).*

- *Mean increases were generally observed for all time-points during the first 2-3 weeks of treatment in all Pal groups.*

***Caveat on Phase III results on BP and Timing of Assessments Relative to Dose, PK and other Potential Time-dependent Confounding Variable and Relative to Fed Versus Fasted Conditions.***

*The sponsor was asked to provide data for vital sign results near Tmax ideally from a schizophrenia trial but the Phase III trials and the QT prolongation study, Trial –SCH-1009 did not include assessments at multiple time-points in order to enhance capturing Tmax or other time-dependent confounding variables. Study -1009 only included baseline and end-of-study vital sign assessments (this study is described under Section 7.1.12). The sponsor provided results of Study SCH-1009 in response to this inquiry which is described in Section 7.1.13 but had a limited number of subjects and used 3 and 6 mg dose-levels. Also vital signs were only conducted at pre-dose, 24 and 48 hour post-dose time-points on selected treatment days.*

*Therefore, the undersigned reviewer describes results of 2 food effect Phase I studies (P01-1008 found in the N000 submission and P01-1002 found in the 210-Day SUR submission). See Section 7.1.12 C for additional vital sign and related observations from these trials.*

*See section 7.1.3.3.E for a description of individual potentially clinically remarkable subjects.*

*Summary of Results on Temperature in Phase III Trials:*

***A Caveat:*** *Temperature results were found for a subgroup of subjects within any treatment group during the DB treatment phase with samples sizes being insufficient for most on-treatment time-points except for Day 43 in which the sample size for any given group was generally over 150 subjects. The study end-point assessments generally had larger samples sizes of over 200 subjects in most group. The 15 mg Pal group only had 79 subjects on Day 43 and 104 subjects at end-point for this vital sign parameter.*

*Given the small samples sizes for most time-points in each treatment group this review only describes temperature results for Day 43 and study end-point assessments relative to baseline values.*

*Given the above critical caveat on the limitations of the data, the temperature results were unremarkable including results of the HD Pal group which showed a mean change of only 0 to -0.02±0.5 degrees C from baseline on Day 43 and study end-point.*

*Results on Respiratory Rate in Phase III trials*
*These results were not generally found, yet, such results in a Phase III trial study are generally non-revealing (fail to show or reveal an effect). Refer to Sections on SAEs and ADOs and Section 7.1.3.3 of this review for potentially clinically remarkable events that involved the respiratory system.*

*Refer to the last section of this review for additional comments and for recommendations.*

**Results of the Completed Elderly Phase III Trial (-302)**

*Summary of Results as described in Section 6.5.1 of the CSR and based on a review of vital sign results found in a 10-page table in Attachment 9.1.1 of the CSR, that was hyperlinked from the SCS (rather than showing a 10-page table the results are summarized in this review):*

- *These results failed to reveal any new, clinically remarkable findings other than the following bulleted item.*
- *Greater effects on increased supine and standing HR appeared to exist in older subjects (70-75 year old) compared to younger subjects (64-69 year old) that persisted until treatment endpoint in the older group*

*Refer to the last section of this review for additional comments and recommendations.*

**Results of Ongoing Phase III Open-Label Extension Studies (-702 through -705)**
*Results of the following treatment groups were reviewed in the sponsor's summary table in Appendix 2.7.4.5.1.2 of the SCS which showed descriptive statistical results during the DB phase of the lead-in studies, as well as during the OL phase of the extension trials for the pooled dataset for each treatment subgroup.*

*Due to the lengthiness of the sponsor's summary table (69 pages) the results are summarized below rather than providing a lengthy summary table in this review.*

***Caveats***
*Each treatment subgroup had sample sizes for vital sign assessments that ranged from only a few subjects to generally less than 50 subjects at time-points beyond week 4 of OL treatment for the ≤ 3month subgroups and beyond week 24 for the > 3 month subgroups (the treatment subgroups were: DB-placebo/OL-Pal, DB-Olanz/OL-Pal, DB-Pal/OL-Pal treatment groups).*

- *The ≤ 3 month "total" Pal group (all subjects in the OL phase who participated in the OL study for > 3 months) had sample sizes of over 50 subjects for all time-points through Week 40.*
- *Only the time-points of these subgroups that had at least 50 subjects were reviewed and described below (since smaller samples sizes were generally considered insufficient for the purposes of this review).*

*Comments and description of observations below are based on numerical comparisons (statistical comparison results could not be found in the sponsor's summary table or in-text tables or descriptions in the SCS).*

*Summary of Results*
*The results of this safety dataset were generally unremarkable for revealing any new, clinical significant drug effects on vital sign parameters except for results described below that may provide some potentially new clinically relevant observations.*

*Similar to that observed for the short-term trial dataset, a mean increase (from baseline) in standing heart rate was observed during treatment. This positive result is not unexpected. However, observations on the timing of peak effects and the duration of this effect during longterm treatment are potentially new such that a discussion of these results is warranted.*

*Similar observations for a drug-induced increase in supine heart rate (which was observed in short term trials) also warrant some discussion with respect to timing of peak effects and the duration of this effect.*

*Key findings are noted, as follows:*

- *Peak mean increases in standing heart rate were generally observed within approximately one week of OL Pal treatment or DB olanzapine treatment. This known drug-class effect either persisted at a smaller magnitude on subsequent time-points during treatment or this effect appeared to resolve by approximately 4 weeks in most subgroups examined. See the paragraphs that follow these bulleted items for a more detailed description of these results.*
- *Subjects started on DB olanzapine treatment in the short-term lead-in studies also showed the expected drug-induced mean increase in standing heart rate that also appeared to resolve during DB olanzapine treatment.*
- *This known drug-class effect on standing heart rate appeared to return after switching subjects from Olanzapine to OL Pal in the OL extension trials following completion of the short-term DB lead-in studies. Perhaps this apparent recurrence of a drug-induced effect on standing heart rate reflects an interruption of treatment between the DB lead-in and OL extension trials. Yet this effect does not appear to exist for the DB Pal/OL Pal treatment group (examine ECG HR results provided in this review under Section 7.1.9 which shows this phenomenon). Consequently, this observation could be reflecting a differential drug or dose-level effect between olanzapine and Pal treatment. See the paragraphs that follow these bulleted items for a more detailed description of these results. Also see the final section of this review for additional comments and recommendations.*
- *Supine heart rate showed a peak mean increase from baseline of up to 5.5 bpm on Day 4 and 4.2 bpm on Day 4 in the DB-Placebo/OL-Pal ≤ 3month and > 3 month subgroups, respectively. This drug effect appeared to persist over time. However, the magnitude of this effect did not appear to increase over time. Similar results were observed for other treatment subgroups in this OL extension trial safety dataset.*
- *DB Olanzapine treatment showed similar effects on increasing supine heart rate (in the DB Olanzapine/OL Pal subgroups) that appeared to resolve within approximately 2 weeks. As observed with standing heart rate, the drug-induced increase in supine heart rate appeared to return upon switching these subjects to OL Pal. Again, these observations may reflect an interruption of antipsychotic treatment between the DB lead-in and OL extension trials. However, subjects were to have DB treatment abruptly*

*terminated before entering into the OL phase. Alternatively, this observation could be reflecting a differential drug or dose-level effect between olanzapine and Pal treatment.*

*While the interpretation of OL results is limited by the absence of a placebo control group, the above findings were observed in the direction of an expected drug-effect (e.g. increases in heart rate instead of decreases in heart rate), whereby the results are strongly suspicious of a read Pal induced effect.*

*See the final section of this review for further comment and recommendations.*

*The following outline provides more details on the above results on drug-induced mean increases in standing heart rate over time (during OL Pal and DB olanzapine treatment:*

- *A mean increase from baseline in standing heart rate of up to 5.9 bpm and 5.6 bpm in the ≤ 3 month and > 3 month subgroups, respectively, of the DB-placebo/OL-Pal treatment group was observed by week 1 of OL treatment (with little to no change during DB placebo treatment in these two subgroups).*
- *Other subgroups generally showed similar results, including results during DB olanzapine treatment during the lead-in phase followed by OL pal treatment.*
- *This mean increase generally appeared to persist, but with an apparent smaller magnitude of effect over subsequent OL time-points or the effect appeared to resolve by approximately 4 weeks of treatment (for time-points that had a sample size of at least 50 subjects).*

*The following is a more detailed discussion of standing heart rate increases when switching from DB Olanzapine to OL Pal treatment:*

- *DB olanzapine treatment (in the DB-Olanzapine/OL-Pal exposure subgroups) showed a peak mean increase of 2.7 bpm on Day 4 and Day 6 for each of the ≤ 3 month and > 3month exposure-subgroups, respectively.*
- *Little to no change (from baseline) in standing heart rate was observed after the first few weeks of DB Olanzapine treatment, such that Olanzapine induced increased heart rate appear to resolve over time.*
- *After being switched from DB Olanzapien to OL Pal, these subjects showed an apparent recurrence in antipsychotic-induced increased in heart rate. The peak mean increase observed during OL Pal treatment in these subjects was 5.2 bpm on Day 4 for the ≤ 3 month subgroup and 3.3 bpm on week 1 in the > 3 month group. This drug effect appeared to resolve by approximately 4 weeks or less.*
- *It is not clear why a recurrence of a drug class effect would occur when switching from one drug to another within the same drug class. Perhaps treatment was interrupted between the DB lead-in and OL extension trials or this observation could be reflecting a differential drug or dose-level effect between olanzapine and Pal treatment. Yet, this phenomenon was not observed in the DB pal/OL Pal subgroup (refer to heart rate data shown under section 7.1.9 on ECG results that shows the same pattern on this heart rate determined by ECG).*

## 7.1.8.3.2. Analyses focused on outliers or shifts from normal to abnormal

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

***Reviewer Comments.***

*An important positive finding in the pooled short-term Phase III trial dataset was a greater incidence of outliers for increased supine heart rate in paliperidone groups. While a consistent dose-dependent effect on the incidence of outliers was not observed in this safety dataset, the greatest incidence of outliers was in the highest dose group (22% in the 15 mg group compared to 10% in placebo subjects and 15 to 18% in each lower dose Pal group).*

*Evidence for orthostatic hypotension was revealed, which is an expected finding based on that which is known and described in labeling for Risperdal® and other approved drugs in this drug class. Refer to section 7.1.4 for reviewer comments and description of results that were found in a separate section of the SCS (section 2.1.6.5 in the SCS). Results are provided in this section of this review, for the convenience of the reader.*

### The Incidence of Outliers on Vital Sign Measures

**Table 76:** Number of Subjects With Abnormal Vital Sign Values During the Double-Blind Period (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

| | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) N (%) | ER OROS PAL 6 mg (N=235) n (%) | ER OROS PAL 9 mg (N=246) n (%) | ER OROS PAL 12 mg (N=242) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Total Paliperidone (N=963) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|---|---|---|---|
| **Standing pulse classification** | 353 | 126 | 234 | 245 | 240 | 113 | 958 | 363 |
| Decrease ≥15 and value ≤50 | 1 (<1) | 0 | 0 | 2 ( 1) | 2 ( 1) | 1 ( 1) | 5 ( 1) | 3 ( 1) |
| Increase ≥15 and value ≥100 | 77 ( 22) | 42 ( 33) | 61 ( 26) | 72 ( 29) | 75 ( 31) | 44 ( 39) | 294 ( 31) | 88 ( 24) |
| **Supine pulse classification** | 353 | 125 | 234 | 245 | 241 | 113 | 958 | 363 |
| Decrease ≥15 and value ≤50 | 6 ( 2) | 1 ( 1) | 1 (<1) | 6 ( 2) | 4 ( 2) | 3 ( 3) | 15 ( 2) | 5 ( 1) |
| Increase ≥15 and value ≥100 | 35 ( 10) | 23 ( 18) | 33 ( 14) | 45 ( 18) | 36 ( 15) | 25 ( 22) | 160 ( 17) | 42 ( 12) |
| **Standing SBP classification** | 353 | 126 | 234 | 245 | 241 | 113 | 959 | 363 |
| Decrease ≥20 and value ≤90 | 12 ( 3) | 8 ( 6) | 7 ( 3) | 16 ( 7) | 13 ( 5) | 7 ( 6) | 51 ( 5) | 13 ( 4) |
| Increase ≥20 and value ≥180 | 4 ( 1) | 0 | 3 ( 1) | 1 (<1) | 0 | 1 ( 1) | 5 ( 1) | 1 (<1) |
| **Supine SBP classification** | 352 | 125 | 234 | 245 | 241 | 113 | 958 | 363 |
| Decrease ≥20 and value ≤90 | 12 ( 3) | 6 ( 5) | 4 ( 2) | 16 ( 7) | 4 ( 2) | 6 ( 5) | 36 ( 4) | 12 ( 3) |
| Increase ≥20 and value ≥180 | 4 ( 1) | 0 | 3 ( 1) | 1 (<1) | 1 (<1) | 1 ( 1) | 6 ( 1) | 0 |
| **Standing DBP classification** | 353 | 126 | 234 | 245 | 241 | 113 | 959 | 363 |
| Decrease ≥15 and value ≤50 | 7 ( 2) | 3 ( 2) | 6 ( 3) | 1 (<1) | 5 ( 2) | 2 ( 2) | 17 ( 2) | 9 ( 2) |
| Increase ≥15 and value ≥105 | 13 ( 4) | 2 ( 2) | 6 ( 3) | 7 ( 3) | 4 ( 2) | 2 ( 2) | 21 ( 2) | 16 ( 4) |
| **Supine DBP classification** | 352 | 125 | 234 | 245 | 241 | 113 | 958 | 363 |
| Decrease ≥15 and value ≤50 | 6 ( 2) | 0 | 9 ( 4) | 3 ( 1) | 4 ( 2) | 2 ( 2) | 18 ( 2) | 11 ( 3) |
| Increase ≥15 and value ≥105 | 7 ( 2) | 0 | 2 ( 1) | 2 ( 1) | 4 ( 2) | 4 ( 4) | 12 ( 1) | 8 ( 2) |

Note: Percentages calculated with the number of subjects per parameter as denominator.

The sponsor notes that the above findings on increased heart rate are consistent with the incidence of AEs of tachycardia observed with this dataset (as previously described in Section 7.1.5) which was reported in 12% of Pal subjects compared to 7% of placebo subjects.

The sponsor also notes that 5 SAEs and 5 ADOs of tachycardia or sinus tachycardia were observed in this safety dataset. See Sections 7.1.3.1 and 7.1.3.2 on SAEs and ADOs and Section 7.1.3.3 of this review.

Upon review of the CSR for this study, Section 6.5.1 indicates no ADOs and SAEs due to orthostatic hypotension.

According to Section 6.5.1 of the CSR there also no SAEs or ADOs due to hypotension. However, a greater incidence of AEs of hypotension were reported in Pal compared to placebo subjects (5% and 0%, respectively) and subject 2007010 is described as having "severe" hypontesion on Day 40 after receiving her last Pal dose (9mg) on the previous day. This subject was hospitalized for pneumonia and pleural effusion. *In the opinion of the undersigned these events could at least in part be drug-related.* Three additional subjects had AEs of "moderate" hypotension of whom each received 6 mg, 9 mg and inadvertently 15 mg Pal, respectively, at the time of this AE (subjects 200309, 200702 and 200625, respectively).

*A description or notation of any other SAEs or ADOs due to abnormal vital sign parameters, could not be found in sections in the SCS related to this topic. However, potentially clinically remarkable subjects relevant to abnormal vital sign parameters (e.g. outliers for high blood pressure values) were found by the undersigned reviewer upon review of line listings, narratives or CSRs, as described under Section 7.1.3.3 of this review.*

**Table 52:** Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Any Time During the Double-Blind Period
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

| | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) n (%) | ER OROS PAL 6 mg (N=235) n (%) | ER OROS PAL 9 mg (N=246) n (%) | ER OROS PAL 12 mg (N=242) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Total Paliperidone (N=963) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|---|---|---|---|
| **Total no. subjects with orthostatic hypotension** | 14 ( 4) | 10 ( 8) | 13 ( 6) | 23 ( 9) | 9 ( 4) | 12 ( 11) | 67 ( 7) | 15 ( 4) |
| Pulse(std-sup) > 15 and SBP(std-sup) < -20 | 11 ( 3) | 8 ( 6) | 7 ( 3) | 18 ( 7) | 5 ( 2) | 8 ( 7) | 46 ( 5) | 11 ( 3) |
| Pulse(std-sup) > 15 and DBP(std-sup) < -10 | 10 ( 3) | 5 ( 4) | 12 ( 5) | 12 ( 5) | 7 ( 3) | 8 ( 7) | 44 ( 5) | 7 ( 2) |

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

Results on Outliers found in a Separate Section 2.1.6.5 of the SCS

Table 52: Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Any Time During the Double-Blind Period
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

| | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) n (%) | ER OROS PAL 6 mg (N=235) n (%) | ER OROS PAL 9 mg (N=246) n (%) | ER OROS PAL 12 mg (N=242) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Total Paliperidone (N=963) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|---|---|---|---|
| **Total no. subjects with orthostatic hypotension** | 14 ( 4) | 10 ( 8) | 13 ( 6) | 23 ( 9) | 9 ( 4) | 12 ( 11) | 67 ( 7) | 15 ( 4) |
| Pulse(std-sup) > 15 and SBP(std-sup) < -20 | 11 ( 3) | 8 ( 6) | 7 ( 3) | 18 ( 7) | 5 ( 2) | 8 ( 7) | 46 ( 5) | 11 ( 3) |
| Pulse(std-sup) > 15 and DBP(std-sup) < -10 | 10 ( 3) | 5 ( 4) | 12 ( 5) | 12 ( 5) | 7 ( 3) | 8 ( 7) | 44 ( 5) | 7 ( 2) |

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

**Results from Elderly Study -302.**

***Reviewer Comment.*** *Results of Study -302 were generally similar to those of the pooled short-term Phase III dataset of primarily non-elderly subjects (as previously described). However, one potentially new finding (not observed in the primarily non-elderly, short-term trials) was the following observations:*

- *A numerically greater incidence of outliers on increased supine systolic BP and decreased supine systolic BP were observed in Pal compared to placebo subjects. The outliers occurred in only 4 or 5 out of the 76 Pal subjects. Given the small sample size of this study (only 38 placebo subjects and 76 Pal subjects), these findings are considered preliminary.*

*Upon review of the CSR for Study -302, the following additional findings were noted in Section 6.3.2.4.3 of the CSR:*

- *One subject (200234) developed tachycardia on Day 5 of Pal treatment who later was found to have supraventricular tachycardia on Day 29. More information (e.g. ECG results) could not be found in the in-text CSR description or in in-text sections of the SCS.*
- *No ADOs or SAEs of tachycardia occurred in Pal subjects of this study.*
- *12 Subjects had an AE of tachycardia as follows:*
  - *9 out of 12 Pal subjects with the AE of tachycardia had this event reported within 2 weeks of treatment.*
  - *The other 3 subjects had this AE reported on Days 33, 36 or on both Days 9 and 42, respectively.*
  - *The lowest dose level of Pal among these 12 Pal subjects was 6 mg daily and the mean dose at the onset of the AE was 8.5 mg daily among these subjects.*

- *The incidence of preexisting medical conditions in these 12 subjects was 67% and 42% for cardiovascular or cerebrovascular disease, respectively compared to an incidence of 38% and 16% in Pal subjects who did not have the AE of tachycardia.*

*The findings on concomitant illness are considered preliminary, given the small sample size and post hoc analyses. It is also not known if the above observations are reproduceable.*

*See the final section of this review for comments and recommendations.*

*Results on the incidence of orthostatic hypotension outliers were previously described under Section 7.1.4 (found in a separate section in the SCS). Refer to section 7.1.4 for reviewer comments and description of results.*

*The sponsor's summary table found in a separate section 2.1.6.5 in the SCS is provided below for the convenience of the regulatory supervisor reading of this review.*

*Also refer to Sections 7.1.1-3 of this review for additional information (SAEs and ADOs and a description of potentially remarkable subjects with cardiovascular related events).*

The table below summarizes the vital sign results (as provided by the sponsor).

Table 77: Subjects With Abnormal Vital Sign Values During the Double-Blind Period
(Study R076477-SCH-302: Safety Analysis Set)

| | Placebo (N=38) n (%) | ER OROS PAL (N=76) n (%) |
|---|---|---|
| **Standing pulse classification** | 38 | 76 |
| Decrease ≥15 and value ≤50 | 0 | 0 |
| Increase ≥15 and value ≥100 | 2 ( 5) | 9 ( 12) |
| **Supine pulse classification** | 38 | 76 |
| Decrease ≥15 and value ≤50 | 0 | 0 |
| Increase ≥15 and value ≥100 | 0 | 5 ( 7) |
| **Standing SBP classification** | 38 | 76 |
| Decrease ≥20 and value ≤90 | 2 ( 5) | 7 ( 9) |
| Increase ≥20 and value ≥180 | 0 | 4 ( 5) |
| **Supine SBP classification** | 38 | 76 |
| Decrease ≥20 and value ≤90 | 1 ( 3) | 4 ( 5) |
| Increase ≥20 and value ≥180 | 0 | 3 ( 4) |
| **Standing DBP classification** | 38 | 76 |
| Decrease ≥15 and value ≤50 | 3 ( 8) | 4 ( 5) |
| Increase ≥15 and value ≥105 | 0 | 0 |
| **Supine DBP classification** | 38 | 76 |
| Decrease ≥15 and value ≤50 | 1 ( 3) | 1 ( 1) |
| Increase ≥15 and value ≥105 | 0 | 1 ( 1) |

Note: Percentages calculated with the number of subjects per parameter as denominator.
Cross-reference: Mod5.3.5.1/R076477-SCH-302/Sec6.5.1



Results on Orthostatic Hypotension Outliers found in a Separate Section 2.1.6.5 of the SCS

**Table 53: Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Any Time During the Double-Blind Phase (Study R076477-SCH-302: Safety Analysis Set)**

| | Placebo (N=38) n (%) | ER OROS PAL (N=76) n (%) |
|---|---|---|
| **Total no. subjects with orthostatic hypotension** | 0 | 3 ( 4) |
| Pulse (std-sup) > 15 and SBP (std-sup) < -20 | 0 | 2 ( 3) |
| Pulse (std-sup) > 15 and DBP (std-sup) < -10 | 0 | 1 ( 1) |

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: Mod5.3.5.1\R076477 SCH 302\Sec6.5.1.

**Results from Pooled Open Label Extension Trial Dataset (Studies -702 through -705).**
***Reviewer Comment.*** *Only 0-6% of subjects in the OL trial dataset (all subjects received Pal) met outlier criteria for supine or standing, diastolic or systolic BP changes, while 10 to 25% of subjects had increased standing or supine heart rates. These observations suggest that tachycardia or increased heart rate (supine or standing) can occur in some subjects, in the absence of clinically remarkable orthostatic decreases in blood pressure. However, this observation is not considered conclusive evidence for increased heart rate in the absence of a drug effect on blood pressure since comparisons on the incidence of outliers across parameters depends on the cut-off values selected.*

*SAEs and ADOs due abnormal vital signs that included tachycardia are previously discussed (see Sections 7.1.3.1 and 7.1.3.2 of this review).*

*Results on the incidence of orthostatic hypotension outliers was previously described under Section 7.1.4 and were also provided as a separate section in the SCS. Refer to section 7.1.4 for reviewer comments and description of results. The sponsor's summary table found in a separate section 2.1.6.5 in the SCS is provided below for the convenience of the regulatory supervisor reading of this review.*

The sponsor indicates that 3 ADOs and 3 SAEs of sinus tachycardia or tachycardia were reported, all of which occurred among subjects that received ≤ 3 months of Pal as of the May 31, 2005 cut-off date of these ongoing OL trials (out of 1167 total subjects who received ≤ 3 months of OL drug).

Results of Orthostatic Hypotension Outliers found in a separate Seciton 2.1.6.5 of the SCS

**Table 54:** Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Anytime During the Open-Label Period
(Pooled Open-label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

| | 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 orthostatic hypotension** | 3 ( 3) | 7 ( 5) | 6 ( 3) | 23 ( 5) | 3 ( 3) | 8 ( 6) | 12 ( 3) | 38 ( 5) |
| Pulse(std-sup) > 15 and DBP(std-sup) < -10 | 2 ( 2) | 5 ( 4) | 2 ( 1) | 16 ( 3) | 1 ( 1) | 6 ( 4) | 5 ( 1) | 27 ( 3) |
| Pulse(std-sup) > 15 and SBP(std-sup) < -20 | 1 ( 1) | 2 ( 2) | 4 ( 2) | 12 ( 2) | 2 ( 2) | 4 ( 3) | 7 ( 2) | 18 ( 2) |

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

**Table 99:** Number of Subjects With Abnormal Vitals Sign Values
(Phase 1/2a Studies in Healthy Adult Subjects Who Received PaliperidoneOROS Formulations: Safety Analysis Set)

| Parameter Indicator | PALI OROS LOW DOSE[a] (N=154) n (%) | PALI OROS HIGH DOSE[a] (N=200) n (%) | PALI OROS ALL (N=275) n (%) |
|---|---|---|---|
| **Standing pulse(bpm)** | 75 | 0 | 75 |
| Increase >=15 and value >=100 | 43 ( 57) | 0 | 43 ( 57) |
| **Supine pulse(bpm)** | 147 | 193 | 268 |
| Decrease >=15 and value <=50 | 25 ( 17) | 50 ( 26) | 63 ( 24) |
| Increase >=15 and value >=100 | 11 ( 7) | 51 ( 26) | 59 ( 22) |
| **Standing SBP(mmHg)** | 75 | 0 | 75 |
| Decrease >=20 and value <=90 | 26 ( 35) | 0 | 26 ( 35) |
| **Supine SBP(mmHg)** | 147 | 193 | 268 |
| Decrease >=20 and value <=90 | 47 ( 32) | 81 ( 42) | 102 ( 38) |
| Increase >=20 and value >=180 | 0 | 3 ( 2) | 3 ( 1) |
| **Standing DBP(mmHg)** | 75 | 0 | 75 |
| Decrease >=15 and value <=50 | 22 ( 29) | 0 | 22 ( 29) |
| Increase >=15 and value >=105 | 2 ( 3) | 0 | 2 ( 3) |
| **Supine DBP(mmHg)** | 147 | 193 | 268 |
| Decrease >=15 and value <=50 | 67 ( 46) | 141 ( 73) | 163 ( 61) |
| Increase >=15 and value >=105 | 0 | 3 ( 2) | 3 ( 1) |

Note: Percentages calculated with the number of subjects per parameter as denominator.
[a] Low dose = 3 to 6 mg, and high dose = 9 to 15 mg doses (Section 1.1.3.3.1).

**Table 97: Number of Subjects With Treatment-Emergent Orthostatic Hypotension (Phase 1/2a Studies in Healthy Adult Subjects Who Received Paliperidone OROS Formulations: Safety Analysis Set)**

| | PALI OROS LOW DOSE[a] (N=55) n (%) | PALI OROS HIGH DOSE[a] (N=1) n (%) | PALI OROS ALL (N=56) n (%) |
|---|---|---|---|
| **No. subjects with orthostatic hypotension** | 22 ( 40) | 0 | 22 ( 39) |
| Pulse(std-sup)>=15 and sbp(std-sup)<=-20 | 11 ( 20) | 0 | 11 ( 20) |
| Pulse(std-sup)>=15 and dbp(std-sup)<=-10 | 18 ( 33) | 0 | 18 ( 32) |

Note: Percentages calculated with the number of subjects in each group as denominator.
[a] Low dose = 3 to 6 mg, and high dose = 9 to 12 mg doses (Section 1.1.3.3.1).

**Table 100: Number of Subjects With Abnormal Vital Signs (Phase 1/2a Studies in Healthy Adult Subjects Who Did Not Receive ER OROS Paliperidone: Safety Analysis Set)**

| Parameter Indicator | PLACEBO (N=63) n (%) | PALI IR (N=174) n (%) | PALI OTHER (N=155) n (%) | PALI ALL (N=206) n (%) | RISPERIDONE (N=37) n (%) |
|---|---|---|---|---|---|
| **Standing pulse(bpm)** | 53 | 164 | 151 | 194 | 28 |
| Decrease >=15 and value <=50 | 5 ( 9) | 7 ( 4) | 13 ( 9) | 19 ( 10) | 1 ( 4) |
| Increase >=15 and value >=100 | 10 ( 19) | 114 ( 70) | 129 ( 85) | 150 ( 77) | 22 ( 79) |
| **Supine pulse(bpm)** | 63 | 173 | 154 | 205 | 37 |
| Decrease >=15 and value <=50 | 8 ( 13) | 13 ( 8) | 23 ( 15) | 28 ( 14) | 7 ( 19) |
| Increase >=15 and value >=100 | 1 ( 2) | 9 ( 5) | 13 ( 8) | 17 ( 8) | 3 ( 8) |
| **Standing SBP(mmHg)** | 62 | 174 | 152 | 204 | 36 |
| Decrease >=20 and value <=90 | 22 ( 35) | 93 ( 53) | 103 ( 68) | 129 ( 63) | 22 ( 61) |
| Increase >=20 and value >=180 | 0 | 1 ( 1) | 2 ( 1) | 3 ( 1) | 0 |
| **Supine SBP(mmHg)** | 63 | 174 | 155 | 206 | 37 |
| Decrease >=20 and value <=90 | 3 ( 5) | 33 ( 19) | 47 ( 30) | 61 ( 30) | 11 ( 30) |
| **Standing DBP(mmHg)** | 62 | 174 | 152 | 204 | 36 |
| Decrease >=15 and value <=50 | 10 ( 16) | 83 ( 48) | 98 ( 64) | 123 ( 60) | 14 ( 39) |
| Increase >=15 and value >=105 | 0 | 9 ( 5) | 21 ( 14) | 29 ( 14) | 1 ( 3) |
| **Supine DBP(mmHg)** | 63 | 174 | 155 | 206 | 37 |
| Decrease >=15 and value <=50 | 7 ( 11) | 44 ( 25) | 56 ( 36) | 66 ( 32) | 7 ( 19) |
| Increase >=15 and value >=105 | 1 ( 2) | 0 | 0 | 0 | 0 |

Note: Percentages calculated with the number of subjects per parameter as denominator. See Section 1.1.3.3.1 for a description of the treatment groups.

**Table 98: Number of Subjects With Treatment-Emergent Orthostatic Hypotension (Phase 1/2a Studies in Healthy Adult Subjects Who Did Not Receive PaliperidoneOROS Formulations: Safety Analysis Set)**

| | PLACEBO (N=62) n (%) | PALI IR (N=174) n (%) | PALI OTHER (N=152) n (%) | PALI ALL (N=204) n (%) | RISPERIDONE (N=36) n (%) |
|---|---|---|---|---|---|
| **No. subjects with orthostatic hypotension** | 11 ( 18) | 87 ( 50) | 107 ( 70) | 133 ( 65) | 18 ( 50) |
| Pulse(std-sup)>15 and sbp(std-sup)<-20 | 6 ( 10) | 57 ( 33) | 82 ( 54) | 103 ( 50) | 12 ( 33) |
| Pulse(std-sup)>15 and dbp(std-sup)<-10 | 9 ( 15) | 71 ( 41) | 85 ( 56) | 112 ( 55) | 18 ( 50) |

Note: Percentages calculated with the number of subjects in each group as denominator. See Section 1.1.3.3.1 for a description of treatment groups

**Table 106: Number of Subjects With Abnormal Vital Sign Values (Phase 1/2a Studies in Subjects With Schizophrenia)**

| Parameter Indicator | PALI IR (N=34) n (%) | PALI OROS HIGH DOSE[a] (N=111) n (%) | RISPERIDONE (N=55) n (%) |
|---|---|---|---|
| **Standing pulse(bpm)** | 34 | 111 | 55 |
| Decrease >=15 and value <=50 | 0 | 1 ( 1) | 0 |
| Increase >=15 and value >=100 | 24 ( 71) | 95 ( 86) | 52 ( 95) |
| **Supine pulse(bpm)** | 34 | 110 | 54 |
| Decrease >=15 and value <=50 | 0 | 1 ( 1) | 1 ( 2) |
| Increase >=15 and value >=100 | 10 ( 29) | 40 ( 36) | 17 ( 31) |
| **Standing SBP(mmHg)** | 34 | 111 | 55 |
| Decrease >=20 and value <=90 | 7 ( 21) | 11 ( 10) | 7 ( 13) |
| Increase >=20 and value >=180 | 1 ( 3) | 2 ( 2) | 2 ( 4) |
| **Supine SBP(mmHg)** | 34 | 110 | 54 |
| Decrease >=20 and value <=90 | 2 ( 6) | 6 ( 5) | 1 ( 2) |
| Increase >=20 and value >=180 | 0 | 1 ( 1) | 1 ( 2) |
| **Standing DBP(mmHg)** | 34 | 111 | 55 |
| Decrease >=15 and value <=50 | 3 ( 9) | 7 ( 6) | 4 ( 7) |
| Increase >=15 and value >=105 | 5 ( 15) | 8 ( 7) | 8 ( 15) |
| **Supine DBP(mmHg)** | 34 | 110 | 54 |
| Decrease >=15 and value <=50 | 2 ( 6) | 6 ( 5) | 2 ( 4) |
| Increase >=15 and value >=105 | 4 ( 12) | 1 ( 1) | 2 ( 4) |

Note: Percentages calculated with the number of subjects per parameter as denominator. See Section 1.1.3.3.1 for a description of the treatment groups.
[a] High dose = 9 to 15 mg doses

Table 105: Number of Subjects With Treatment-Emergent Orthostatic Hypotension (Phase 1/2a Studies in Subjects With Schizophrenia Safety Analysis Set)

| Indicator | PALI IR (N=34) n (%) | PALI OROS HIGH DOSE[a] (N=111) n (%) | RISPERIDONE (N=55) n (%) |
|---|---|---|---|
| **No. subjects with orthostatic hypotension** | 11 ( 32) | 44 ( 40) | 29 ( 53) |
| Pulse(std-sup)>15 and sbp(std-sup)<=-20 | 9 ( 26) | 29 ( 26) | 24 ( 44) |
| Pulse(std-sup)>15 and dbp(std-sup)<=-10 | 9 ( 26) | 32 ( 29) | 18 ( 33) |

Note: Percentages calculated with the number of subjects in each group as denominator. See Section 1.1.3.3.1 for a description of the treatment groups.
[a] High dose = 9 to 15 mg doses

### 7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

*A comprehensive description of marked outliers and dropouts could not be found in in-text sections of the SCS. Refer to sections 7.1.1-3 for SAEs and ADOs and Section 7.1.3.3. for some potentially clinically remarkable subjects found by the undersigned reviewer in various sections in the N000 submission or in the 120-Day SUR.*

*Also see Section 4 of this review regarding concerns (from the undersigned reviewer's perspective) in capturing potentially remarkable subjects.*

### 7.1.8.4 Additional analyses and explorations: Weight and Body Mass Index

#### 7.1.8.4.1 Analyses focused on central tendency

**Results from the 3 Non-Elderly Short-Term Phase III Trial Dataset (-303, -304 and -305).**
***Review Comments.*** *A dose-dependent Pal group mean change compared to placebo was observed for body weight and body mass index (BMI), as anticipated for this drug class. Results from the SCS from the submission are coped below.*

**Table 79:** Body Weight and BMI: Change From Baseline to End Point
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

| | Placebo (N=355) | ER OROS PAL 3 mg (N=127) | ER OROS PAL 6 mg (N=235) | ER OROS PAL 9 mg (N=246) | ER OROS PAL 12 mg (N=242) | ER OROS PAL 15 mg (N=113) | Total Paliperidone (N=963) | Olanzapine 10 mg (N=364) |
|---|---|---|---|---|---|---|---|---|
| **Weight (kg)** | | | | | | | | |
| N | 323 | 112 | 215 | 235 | 218 | 107 | 887 | 328 |
| Mean baseline (SD) | 78.6 (19.88) | 73.8 (20.41) | 78.6 (19.85) | 72.1 (16.46) | 78.5 (21.06) | 76.5 (23.41) | 76.0 (20.02) | 78.0 (22.14) |
| Mean change (SD) | -0.4 (3.49) | 0.6 (2.77) | 0.6 (3.18) | 1.0 (2.97) | 1.1 (3.07) | 1.9 (3.63) | 1.0 (3.12) | 2.0 (3.73) |
| Mean percent (%) change (SD) | -0.5 (4.75) | 1.1 (4.02) | 0.9 (4.08) | 1.5 (4.14) | 1.6 (4.01) | 2.6 (4.73) | 1.5 (4.18) | 2.9 (5.02) |
| **Body mass index (kg/m2)** | | | | | | | | |
| N | 323 | 112 | 215 | 235 | 218 | 107 | 887 | 326 |
| Mean baseline (SD) | 26.9 (6.19) | 25.7 (5.86) | 27.2 (6.50) | 25.0 (5.09) | 26.9 (6.30) | 26.6 (7.48) | 26.3 (6.21) | 26.7 (6.98) |
| Mean change (SD) | -0.2 (1.19) | 0.2 (0.95) | 0.2 (1.11) | 0.4 (1.02) | 0.4 (1.03) | 0.6 (1.25) | 0.3 (1.07) | 0.7 (1.24) |

## Results from Elderly Phase III Trial -302.

**Table 81:** Body Weight and BMI: Change From Baseline to End Point
(Study R076477-SCH-302: Safety Analysis Set)

| | Placebo (N=38) | ER OROS PAL (N=76) |
|---|---|---|
| **Weight (kg)** | | |
| N | 36 | 73 |
| Mean baseline (SD) | 67.2 (9.60) | 65.5 (13.14) |
| Mean change (SD) | -0.0 (2.34) | -0.0 (2.10) |
| Mean percent (%) (change (SD) | -0.0 (3.23) | -0.0 (3.31) |
| **Body mass index (kg/m2)** | | |
| N | 36 | 73 |
| Mean baseline (SD) | 25.5 (3.95) | 25.1 (5.14) |
| Mean change (SD) | -0.0 (0.91) | -0.0 (0.84) |

Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec6.5.2

## Results from the Open-Label Ongoing Extension Trials (-702, -703, -704, -705).

**Table 82:** Body Weight and BMI: Change From Baseline to End Point (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

| | Pla/Pali ≤3 months (N=107) | Pla/Pali >3 months (N=128) | Pali/Pali ≤3 months (N=178) | Pali/Pali >3 months (N=505) | Olan/Pali ≤3 months (N=106) | Olan/Pali >3 months (N=143) | Total Pali ≤3 months (N=391) | Total Pali >3 months (N=776) |
|---|---|---|---|---|---|---|---|---|
| **Weight (kg)** | | | | | | | | |
| N | 44 | 21 | 76 | 111 | 56 | 26 | 176 | 158 |
| Mean baseline (SD) | 79.9 (21.56) | 71.2 (20.85) | 77.9 (22.11) | 77.3 (24.67) | 82.5 (23.14) | 77.6 (21.86) | 79.9 (22.27) | 76.6 (23.71) |
| Mean change (SD) | 0.4 (4.98) | 1.4 (9.73) | 1.4 (3.90) | 2.9 (6.50) | 1.6 (4.41) | 1.4 (7.79) | 1.2 (4.35) | 2.5 (7.20) |
| Mean percent (%) change (SD) | 0.6 (6.23) | 3.4 (13.46) | 1.8 (5.02) | 4.1 (8.73) | 2.6 (6.46) | 1.8 (8.75) | 1.8 (5.84) | 3.6 (9.45) |
| **Body mass index (kg/m2)** | | | | | | | | |
| N | 44 | 21 | 76 | 111 | 56 | 26 | 176 | 158 |
| Mean baseline (SD) | 27.7 (6.97) | 24.9 (5.64) | 26.8 (6.88) | 26.7 (7.58) | 27.6 (6.65) | 26.4 (7.02) | 27.3 (6.81) | 26.4 (7.25) |
| Mean change (SD) | 0.2 (1.76) | 0.6 (3.39) | 0.5 (1.31) | 1.0 (2.31) | 0.5 (1.48) | 0.5 (2.42) | 0.4 (1.49) | 0.9 (2.49) |

Note: Results are changes from double-blind baseline to end point (i.e., last evaluation on or before the 31 May 2005 cut-off date).

## 7.1.8.4.2 Analyses focused on outliers or shifts from normal to abnormal

**Results from the 3 Non-Elderly Short-Term Phase III Trial Dataset (-303, -304 and -305).**

**Table 80:** Number of Subjects With Abnormal Weight Values at End Point (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

| | Placebo (N=355) n (%) | ER OROS PAL 3 mg (N=127) n (%) | ER OROS PAL 6 mg (N=235) n (%) | ER OROS PAL 9 mg (N=246) n (%) | ER OROS PAL 12 mg (N=242) n (%) | ER OROS PAL 15 mg (N=113) n (%) | Total Paliperidone (N=963) n (%) | Olanzapine 10 mg (N=364) n (%) |
|---|---|---|---|---|---|---|---|---|
| **Weight classification** | 323 | 112 | 215 | 235 | 218 | 107 | 887 | 328 |
| Decrease ≥ 7% | 22 ( 7) | 2 ( 2) | 6 ( 3) | 6 ( 3) | 3 ( 1) | 2 ( 2) | 19 ( 2) | 3 ( 1) |
| Increase ≥ 7% | 15 ( 5) | 8 ( 7) | 13 ( 6) | 21 ( 9) | 20 ( 9) | 19 ( 18) | 81 ( 9) | 60 ( 18) |

Note: Percentages calculated with the number of subjects per parameter as denominator.

***Reviewer Comments.***
*Results show dose-dependent effects of Pal on weight gain.*

*The sponsor notes the following geographical region differences on the magnitude of weight gain effects:*
"ER OROS paliperidone-treated subjects, the percentages of subjects with of the weight and BMI increases of ≥7% from baseline to end point also were higher in subjects from North America or Western Europe, who also had higher baseline body weight and BMI, compared to subjects from Eastern Europe or other regions."

**Results from the Elderly Phase III Study -302.**

Only 1 placebo subject in Study -302 met outlier criteria for increased weight (an increase exceeding 7% from baseline to endpoint, as predefined).

**Results from the Open-Label Ongoing Extension Trials (-702, -703, -704, -705).**
***Reviewer Comments.*** *As expected weight gain appears to be greater over time during OL Pal treatment as shown below. Yet the extent of Pal induced effects over time is difficult to determine, in the absence of a placebo group (using a DB study design).*

**Table 83:** Number of Subjects With Abnormal Weight Values at End Point (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

| | Pla/Pali ≤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 (%) |
|---|---|---|---|---|---|---|---|---|
| **Weight classification** | 45 | 21 | 76 | 111 | 56 | 26 | 177 | 158 |
| Decrease ≥ 7% | 3 ( 7) | 2 ( 10) | 1 ( 1) | 4 ( 4) | 1 ( 2) | 3 ( 12) | 5 ( 3) | 9 ( 6) |
| Increase ≥ 7% | 4 ( 9) | 6 ( 29) | 10 ( 13) | 29 ( 26) | 11 ( 20) | 6 ( 23) | 25 ( 14) | 41 ( 26) |

Note: Percentages calculated with the number of subjects per parameter as denominator. Results are based on changes from double-blind baseline to end point (i.e., last evaluation on or before the 31 May 2005 cut-off date).

*The sponsor notes the following geographical differences:*

"As noted previously, mean body weight and BMI values at baseline were highest for North American subjects, followed by Western European and Eastern European Subjects, and lowest among subjects in other regions. Regional trends in abnormal weight changes from baseline were difficult to interpret due to the small numbers of subjects in some of the region/exposure (≤3 months versus >3 months) groups. For subjects from 3 of the 4 regions (North America, Eastern Europe, and rest of world), higher percentages of subjects who received >3 months versus ≤3 months of ER OROS paliperidone had weight increases of ≥7% from baseline; an opposite trend was observed for Western European subjects."

## 7.1.9 Electrocardiograms (ECGs)

***A Caveat on Group and Time-point Comparisons on a Given Clinical Parameter.*** *Results of statistical group or time-point comparisons or in-text description of statistical results on clinical parameters could not be found in the SCS. Therefore, group and time-point comparisons described in this review on any given clinical parameter are based on numerical comparisons, unless otherwise specified (results on clinical parameters that were found in the SCS and are described in this review did not include statistical comparisons).*

**7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results**

See sections below for ECG results of primarily Phase III trials. See section 7.1.12 for results of a special safety study on QT interval effects. See section 3 of this review regarding a discussion of potential major issues conveyed by reviewers of other disciplines, which includes the Pharmacology Toxicology reviewer who is conducting a review of preclinical information provided in this NDA.

**7.1.9.2 Selection of studies and analyses for overall drug-control comparisons**

See sections below and Section 7.1 for a description of datasets analyzed and described in this review.

**7.1.9.3 Standard analyses and explorations of ECG data**

See previous subsections and subsections below.

**7.1.9.3.1 Analyses focused on measures of central tendency**

**Results of Non-Elderly Phase III Short Term Trials (-303, -304 and -305)**
***Reviewer Comments.*** *Due to the lengthiness of the 49 page summary table (Appendix 2.7.4.6.2.1.) results are summarized in this review and selected sections of the sponsor's summary tables are shown below.*

*The ECG parameter results found in the sponsor's summary table showed results from the following assessment time-points: screening, baseline, and the average value is provided for these 2 pre-dose time-points (referred to as average pre-dose), then 4, 10 and 22 hour post-dose time-points on Days 4 and 8 of DB treatment, in addition to pre-dose, 1-2 hours and 4 hours post-dose time-points on Days 15 and 36, then time-points of Day 29 and Day 43 and a final end-point assessment.*

*One critical caveat to interpreting vital sign results is that the window of time that could vary across subjects for each scheduled assessment. The following table was copied from the submission (as part of the statistical analysis plan):*

**Table 1a: Time Intervals for ECG, Lab, Vitals and EPS Scales Visits for R076477-SCH-303, 304, and 305**

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

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

*It is not clear how much subjects varied on the timing of a given assessment, but variance across individuals can impact on the interpretation of the results.*

*Statistical analyses results could not be found in the SCS. Comments below are based on numerical comparisons of the sponsor's results.*

***I. Time- and Dose-dependent Pal Effects on Increasing Heart Rate***

*As previously noted, the sponsor's summary tables, as shown later, do not provide results of statistical comparisons and the in-text sections of the SCS generally refer to the appendices for results (to the tables from which data below was obtained). Consequently, reviewer comments are based on numerical comparisons between treatment groups and assessment time-points.*

*Descriptive statistical ECG results are generally clinically unremarkable except for:*

- *Greater group mean increase (from the average pre-dose value) in heart rate that was observed during DB treatment of Pal compared to only small or no mean increases observed in the placebo group.*
- *Group mean increases in heart rate that were observed in the Olanzapine group were intermediate in magnitude compared to that observed in Pal and placebo groups (based on numerical comparisons).*

*Since ECG assessments are generally obtained in the supine position, then the ECG results on HR are reflecting changes that are not orthostatic HR changes.*

*The Pal-induced effect on increasing heart rate appeared to be dose-dependent and time-dependent, as described in the following:*

- *The largest treatment-group mean increases consistently occurred at 4 hours post-dose after the first assessment day of DB treatment (which occurred on Day 4 of treatment) in any given Pal group.*
  - *Smaller group mean increases (or little to no change of mean heart rate) were observed on other post-dose time-points of these assessment days (e.g. at 10 or 22 hour post-dose time-points on Days 4, 8, 15) and on other assessment days that did not include a 4-hour post-dose time-point (e.g. Days 29, 36 and 43, based on numerical comparisons of mean changes).*
- *The magnitude of this time-dependent effect appeared to increase with increasing dose-level as follows:*
  - *Group mean increases of approximately 6, 9, 9, 10 and 12 bpm were observed in the 3 mg, 6 mg, 9 mg, 12 mg and 15 mg groups, respectively at 4 hours post-dose on Day 4, compared to a 1.9 mean increase in the placebo group at this time-point on Day 4 (these results are shown in summary tables that follow reviewer comments).*

*The 4-hour post-dose time-dependent effect on increased heart rate appeared to attenuate over subsequent DB treatment days that included a 4 hour post-dose time-point (Days 8 and 15) in each Pal group, as follows:*

- *Smaller (secondary) peaks appeared to occur at the 4 hour post-dose time-point on subsequent assessment days that included this 4-hour post-dose time-point (which was on Days 8 and 15).*

*The placebo group appeared to show a similar but smaller trend for time-dependent mean increase in heart rate as described in the following:*

- *Peak mean increases of 1.9 bpm and 1.5 bpm were observed in the placebo group at 4 hours post-dose on Days 4 and 8, respectively, compared to little to no mean changes in heart rate observed on other time-points or other treatment days.*
- *Subsequent assessment days showed small to negligible mean increases as follows: the largest group placebo group mean increase observed on subsequent treatment days was on Treatment Day 29 (time-point not specified) and treatment Day 36 (at the 1-2 hour assessments) in which mean changes were small to negligible (only 1.2 and 0.3 bpm, respectively).*
- *As previously described, the magnitude of mean increases in the placebo group that were observed at 4 hours post-dose time-points on treatment days that included this time-point, were consistently smaller than that observed for Pal groups at these time-points (peak group mean increases as low as 5.8 bpm in the low-dose Pal group and as high as 12 bpm in the high-dose Pal group at the 4 hour post-dose time-point on the first assessment day during DB treatment which was on Day 4, as previously described and as shown in summary tables below).*

*The olanzapine group generally showed:*

- *A similar time-dependent group mean increase in heart rate that generally peaked at 4 hours post-dose (that attenuated over subsequent days), except for Day 4 in which the 10 hour post-dose assessment showed a slightly greater mean increase in heart rate than observed at the 4-hour post-dose time-point (as shown later).*
- *However, the 4-hour post-dose mean increases of this active control group (on assessment days that included this time-point) are numerically smaller than group mean increases observed in any given Pal group (including the lowest-dose Pal group at the 3 mg dose-level), but were numerically larger than placebo group mean increases in heart rate.*

*Potential Dynamic versus Static Drug Effects on the Cardiovascular System*

*The above observations provide evidence for a dose-dependent and time-dependent drug effect on increasing heart rate. Preliminarily, the results also suggest a drug-effect on heart rate that is more dynamic than static in its effect, whereby drug-induced increases in heart rate may be influenced by underlying non-drug-related changes in heart rate. For example, underlying increases of heart rate (as was observed in the placebo group at 4-hour post-dose time-points) may be exaggerated by Pal treatment. Consequently, one consideration is that greater drug-effects on heart rate may be unmasked by examining drug effects during an appropriate condition in which the cardiovascular system is perturbed. Further investigation is needed to examine this possible dynamic drug effect on heart rate. Refer to the final section of this review for additional comments and recommendations that includes recommendations for cardiovascular challenge studies to unmask a potential dynamic drug effect on the cardiovascular system.*

*The Data from which Reviewer Comments are Based*

*The following table shows sections of the sponsor's summary table (Appendix 2.7.4.6.2.1) in which the above-described time-dependent and dose-dependent effects on mean increase in heart rate can be observed.*

*Selected time-points are highlighted (by the undersigned reviewer) for demonstration purposes (to indicate time-points for peak and secondary peak mean increases, as previously described in this review).*

*Note that Pal groups (which follow the placebo group) are organized in the order of decreasing (not increasing) dose-level starting with the HD 15 mg group in the table below.*

*Results of the olanzapine group are shown last.*

Studies R076477-SCH-301, R076477-SCH-304, and R076477-SCH-305

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase

Analysis Set: Safety

| | N | Mean | SD | Med | Min | Max | Base Mean | change from average predose N | Mean | SE | SD | Med | Min | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HEART RATE (beats/min)** | | | | | | | | | | | | | | |
| Placebo | | | | | | | | | | | | | | |
| SCREENING | 354 | 76.8 | 12.92 | 76.0 | 47 | 126 | | | | | | | | |
| BASELINE | 355 | 75.1 | 12.72 | 75.0 | 43 | 114 | | | | | | | | |
| AVERAGE PREDOSE | 355 | 76.1 | 11.52 | 76.0 | 48 | 115 | | | | | | | | |
| DAY 4:4H PST-DS | 327 | 77.8 | 13.53 | 77.0 | 38 | 129 | 75.9 | 327 | 1.9 | 0.61 | 11.00 | 2.7 | -25 | 40 |
| DAY 4:10H PST-DS | 323 | 76.5 | 13.47 | 77.0 | 45 | 127 | 75.9 | 323 | 0.6 | 0.66 | 11.84 | 1.3 | -30 | 39 |
| DAY 4:22H PST-DS | 325 | 73.9 | 13.59 | 73.0 | 32 | 120 | 75.7 | 325 | -1.9 | 0.58 | 10.40 | -2.0 | -29 | 30 |
| DAY 8:4H PST-DS | 315 | 77.1 | 13.61 | 76.0 | 39 | 121 | 75.5 | 315 | 1.5 | 0.72 | 12.78 | 0.7 | -32 | 50 |
| DAY 8:10H PST-DS | 311 | 76.3 | 13.80 | 76.0 | 45 | 124 | 75.5 | 311 | 0.9 | 0.74 | 12.98 | 0.3 | -32 | 49 |
| DAY 8:22H PST-DS | 307 | 73.4 | 13.59 | 72.0 | 43 | 108 | 75.5 | 307 | -2.1 | 0.71 | 12.51 | -2.7 | -32 | 43 |
| DAY 15:PRE-DS | 280 | 72.8 | 15.12 | 70.0 | 36 | 132 | 75.2 | 280 | -2.4 | 0.77 | 12.82 | -3.7 | -42 | 55 |
| DAY 15:1-2H PST-DS | 281 | 75.8 | 14.82 | 73.0 | 40 | 120 | 75.2 | 281 | 0.5 | 0.82 | 13.78 | 0.0 | -41 | 48 |
| DAY 15:4H PST-DS | 279 | 76.2 | 14.74 | 75.0 | 40 | 129 | 75.2 | 279 | 0.9 | 0.82 | 13.67 | 1.0 | -50 | 40 |
| DAY 29 | 206 | 76.2 | 14.39 | 74.5 | 50 | 123 | 74.9 | 206 | 1.2 | 0.99 | 14.20 | 0.7 | -30 | 63 |
| DAY 36:PRE-DS | 136 | 73.0 | 14.52 | 73.0 | 47 | 105 | 74.7 | 136 | -1.7 | 1.15 | 13.44 | -2.7 | -45 | 43 |
| DAY 36:1-2H PST-DS | 136 | 74.9 | 14.30 | 74.0 | 48 | 119 | 74.7 | 136 | 0.3 | 1.14 | 13.27 | 0.3 | -33 | 44 |
| DAY 36:4H PST-DS | 136 | 74.8 | 13.81 | 76.0 | 45 | 111 | 74.6 | 136 | 0.2 | 1.22 | 14.23 | -0.2 | -37 | 41 |
| DAY 43 | 139 | 71.7 | 13.28 | 69.0 | 47 | 103 | 74.1 | 139 | -2.4 | 0.98 | 11.50 | -2.7 | -32 | 35 |
| END POINT | 350 | 75.8 | 14.82 | 76.0 | 47 | 120 | 76.0 | 350 | -0.2 | 0.74 | 13.91 | -1.0 | -34 | 63 |
| ER OROS PAL 15 mg | | | | | | | | | | | | | | |
| SCREENING | 112 | 76.9 | 13.27 | 76.0 | 47 | 117 | | | | | | | | |
| BASELINE | 113 | 75.7 | 12.77 | 75.0 | 50 | 123 | | | | | | | | |
| AVERAGE PREDOSE | 113 | 76.6 | 12.17 | 76.3 | 49 | 118 | | | | | | | | |
| DAY 4:4H PST-DS | 105 | 87.6 | 13.26 | 88.0 | 53 | 122 | 76.5 | 105 | 11.1 | 1.05 | 10.79 | 11.7 | -15 | 48 |
| DAY 4:10H PST-DS | 101 | 84.1 | 13.98 | 85.0 | 51 | 126 | 76.6 | 101 | 7.5 | 1.19 | 11.96 | 7.0 | -40 | 34 |
| DAY 4:22H PST-DS | 105 | 82.7 | 14.44 | 83.0 | 48 | 119 | 76.7 | 105 | 6.1 | 1.15 | 11.83 | 4.7 | -21 | 38 |
| DAY 8:4H PST-DS | 106 | 83.1 | 13.73 | 85.0 | 52 | 116 | 76.8 | 106 | 6.3 | 1.23 | 12.64 | 6.0 | -26 | 36 |
| DAY 8:10H PST-DS | 103 | 81.2 | 12.50 | 82.0 | 53 | 110 | 76.6 | 103 | 4.5 | 1.20 | 12.15 | 5.5 | -37 | 33 |
| DAY 8:22H PST-DS | 105 | 80.1 | 14.82 | 80.0 | 44 | 128 | 76.7 | 105 | 3.5 | 1.33 | 13.62 | 1.7 | -28 | 42 |
| DAY 15:PRE-DS | 101 | 77.9 | 14.84 | 76.0 | 49 | 116 | 76.8 | 101 | 1.1 | 1.29 | 12.95 | 1.3 | -39 | 43 |
| DAY 15:1-2H PST-DS | 99 | 80.5 | 12.60 | 82.0 | 50 | 109 | 76.4 | 99 | 4.0 | 1.45 | 14.46 | 5.3 | -43 | 39 |
| DAY 15:4H PST-DS | 101 | 83.1 | 13.72 | 82.0 | 52 | 137 | 76.9 | 101 | 6.2 | 1.32 | 13.25 | 6.7 | -26 | 41 |
| DAY 29 | 93 | 76.9 | 12.76 | 76.0 | 50 | 107 | 77.2 | 93 | -0.3 | 1.41 | 13.58 | 0.5 | -40 | 34 |
| DAY 36:PRE-DS | 76 | 74.0 | 11.92 | 73.0 | 52 | 105 | 77.0 | 76 | -3.0 | 1.76 | 15.35 | -1.8 | -51 | 32 |
| DAY 36:1-2H PST-DS | 80 | 77.1 | 13.76 | 76.0 | 51 | 122 | 77.1 | 80 | -0.0 | 1.73 | 15.49 | -1.3 | -42 | 53 |
| DAY 36:4H PST-DS | 78 | 77.6 | 12.64 | 76.0 | 52 | 111 | 77.0 | 78 | 0.7 | 1.69 | 14.96 | 1.7 | -37 | 42 |
| DAY 43 | 82 | 73.5 | 10.78 | 72.5 | 51 | 109 | 77.0 | 82 | -3.5 | 1.40 | 12.69 | -5.0 | -44 | 26 |
| END POINT | 113 | 74.8 | 11.80 | 73.0 | 48 | 109 | 76.6 | 113 | -1.8 | 1.20 | 12.74 | -2.3 | -44 | 26 |
| ER OROS PAL 12 mg | | | | | | | | | | | | | | |
| SCREENING | 240 | 78.1 | 13.70 | 77.5 | 50 | 119 | | | | | | | | |
| BASELINE | 242 | 77.0 | 13.75 | 77.5 | 44 | 149 | | | | | | | | |
| AVERAGE PREDOSE | 242 | 77.7 | 12.63 | 77.7 | 46 | 134 | | | | | | | | |
| DAY 4:4H PST-DS | 218 | 88.2 | 14.49 | 89.0 | 43 | 128 | 78.0 | 218 | 10.2 | 0.89 | 13.17 | 10.7 | -28 | 54 |
| DAY 4:10H PST-DS | 211 | 85.6 | 14.40 | 87.0 | 46 | 130 | 77.9 | 211 | 7.7 | 0.89 | 12.86 | 7.3 | -27 | 48 |
| DAY 4:22H PST-DS | 212 | 84.0 | 14.52 | 84.0 | 46 | 120 | 78.2 | 212 | 5.8 | 0.88 | 12.86 | 5.5 | -32 | 48 |
| DAY 8:4H PST-DS | 213 | 85.4 | 13.54 | 86.0 | 47 | 120 | 78.0 | 213 | 7.4 | 0.86 | 12.49 | 8.0 | -29 | 46 |
| DAY 8:10H PST-DS | 207 | 83.4 | 14.35 | 83.0 | 46 | 115 | 78.2 | 207 | 5.2 | 0.90 | 12.99 | 4.7 | -33 | 46 |
| DAY 8:22H PST-DS | 210 | 81.5 | 14.51 | 82.0 | 44 | 123 | 78.0 | 210 | 3.5 | 0.95 | 13.73 | 3.7 | -35 | 48 |
| DAY 15:PRE-DS | 198 | 81.1 | 14.94 | 81.0 | 47 | 123 | 78.4 | 198 | 2.7 | 0.89 | 12.53 | 3.3 | -35 | 51 |
| DAY 15:1-2H PST-DS | 194 | 83.8 | 14.81 | 84.5 | 40 | 140 | 78.4 | 194 | 5.4 | 1.04 | 14.52 | 4.8 | -52 | 61 |
| DAY 15:4H PST-DS | 194 | 85.7 | 16.09 | 85.0 | 42 | 144 | 78.7 | 194 | 7.0 | 1.19 | 16.64 | 5.0 | -40 | 66 |
| DAY 29 | 174 | 78.5 | 15.04 | 77.0 | 44 | 117 | 78.8 | 174 | -0.3 | 1.01 | 13.33 | 0.3 | -51 | 36 |
| DAY 36:PRE-DS | 150 | 76.9 | 14.94 | 75.0 | 44 | 138 | 78.1 | 150 | -1.2 | 1.01 | 12.31 | -1.2 | -30 | 30 |
| DAY 36:1-2H PST-DS | 148 | 77.9 | 13.66 | 77.0 | 47 | 109 | 78.0 | 148 | -0.2 | 1.05 | 12.83 | 1.7 | -46 | 29 |
| DAY 36:4H PST-DS | 146 | 79.4 | 13.29 | 79.0 | 50 | 114 | 78.2 | 146 | 1.2 | 1.09 | 13.11 | 1.5 | -52 | 32 |
| DAY 43 | 152 | 75.8 | 13.57 | 74.5 | 47 | 112 | 77.7 | 152 | -1.9 | 1.05 | 12.92 | -3.0 | -52 | 31 |
| END POINT | 238 | 78.7 | 14.73 | 78.0 | 47 | 117 | 77.7 | 238 | 1.0 | 0.89 | 13.76 | 0.2 | -52 | 43 |
| ER OROS PAL 9 mg | | | | | | | | | | | | | | |
| SCREENING | 243 | 76.1 | 12.79 | 75.0 | 48 | 112 | | | | | | | | |
| BASELINE | 245 | 75.7 | 12.71 | 75.0 | 42 | 116 | | | | | | | | |
| AVERAGE PREDOSE | 245 | 76.1 | 11.53 | 75.3 | 42 | 107 | | | | | | | | |
| DAY 4:4H PST-DS | 234 | 85.2 | 14.59 | 85.0 | 47 | 125 | 76.0 | 234 | 9.2 | 0.80 | 12.26 | 8.1 | -32 | 52 |
| DAY 4:10H PST-DS | 229 | 83.1 | 14.77 | 82.0 | 48 | 126 | 75.6 | 229 | 7.5 | 0.86 | 12.94 | 8.0 | -26 | 55 |
| DAY 4:22H PST-DS | 226 | 80.9 | 14.43 | 80.0 | 46 | 131 | 75.8 | 226 | 4.9 | 0.83 | 12.55 | 3.3 | -26 | 50 |
| DAY 8:4H PST-DS | 221 | 82.3 | 13.04 | 82.0 | 50 | 121 | 75.6 | 220 | 6.8 | 0.79 | 11.71 | 6.2 | -25 | 44 |
| DAY 8:10H PST-DS | 216 | 80.0 | 12.97 | 80.0 | 49 | 135 | 75.1 | 215 | 4.9 | 0.87 | 12.76 | 3.7 | -25 | 48 |
| DAY 8:22H PST-DS | 220 | 78.2 | 13.37 | 77.0 | 46 | 129 | 75.5 | 219 | 2.7 | 0.83 | 12.36 | 1.3 | -24 | 60 |
| DAY 15:PRE-DS | 211 | 76.0 | 14.23 | 75.0 | 48 | 123 | 75.5 | 210 | 0.5 | 0.86 | 12.44 | -0.2 | -27 | 52 |
| DAY 15:1-2H PST-DS | 211 | 79.5 | 14.34 | 79.0 | 46 | 128 | 75.6 | 210 | 4.0 | 0.92 | 13.32 | 3.8 | -29 | 41 |
| DAY 15:4H PST-DS | 210 | 81.5 | 13.87 | 81.0 | 47 | 118 | 75.7 | 209 | 5.8 | 0.84 | 12.13 | 5.3 | -21 | 45 |
| DAY 29 | 188 | 75.1 | 14.00 | 74.0 | 45 | 111 | 74.7 | 187 | 0.5 | 0.82 | 11.27 | 0.0 | -37 | 39 |
| DAY 36:PRE-DS | 157 | 72.6 | 14.32 | 70.0 | 43 | 108 | 74.6 | 156 | -2.0 | 1.03 | 12.85 | -2.2 | -33 | 30 |
| DAY 36:1-2H PST-DS | 156 | 74.7 | 13.91 | 73.5 | 46 | 113 | 74.6 | 155 | 0.1 | 1.01 | 12.63 | -1.0 | -28 | 38 |
| DAY 36:4H PST-DS | 153 | 75.0 | 12.19 | 74.0 | 47 | 108 | 74.2 | 152 | 0.8 | 0.92 | 11.38 | 1.7 | -31 | 45 |
| DAY 43 | 160 | 72.5 | 13.20 | 71.5 | 44 | 121 | 74.7 | 159 | -2.1 | 0.90 | 11.30 | -1.7 | -33 | 25 |
| END POINT | 243 | 75.7 | 14.51 | 74.0 | 44 | 121 | 76.0 | 242 | -0.3 | 0.79 | 12.27 | -1.2 | -33 | 43 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ER OROS PAL 6 mg | | | | | | | | | | | | | |
| SCREENING | 234 | 76.4 | 13.75 | 75.0 | 51 | 112 | | | | | | | |
| BASELINE | 235 | 75.4 | 14.27 | 77.0 | 46 | 122 | | | | | | | |
| AVERAGE PREDOSE | 235 | 75.9 | 12.63 | 75.7 | 51 | 112 | | | | | | | |
| DAY 4:4H PST-DS | 218 | 85.9 | 13.68 | 85.5 | 53 | 130 | 75.9 | 218 | 9.9 | 0.80 | 11.86 | 9.8 | -20 | 16 |
| DAY 4:10H PST-DS | 209 | 83.4 | 14.16 | 83.0 | 56 | 134 | 76.1 | 209 | 7.4 | 0.87 | 12.53 | 7.3 | -32 | 60 |
| DAY 4:22H PST-DS | 203 | 80.4 | 14.03 | 79.0 | 44 | 118 | 76.1 | 203 | 4.3 | 0.94 | 13.33 | 3.3 | -43 | 52 |
| DAY 8:4H PST-DS | 210 | 83.6 | 12.92 | 84.0 | 52 | 111 | 75.9 | 210 | 7.7 | 0.80 | 11.58 | 8.0 | -22 | 36 |
| DAY 8:10H PST-DS | 201 | 82.7 | 12.62 | 82.0 | 54 | 114 | 75.6 | 201 | 7.0 | 0.86 | 12.15 | 8.0 | -32 | 40 |
| DAY 8:22H PST-DS | 203 | 78.9 | 14.20 | 78.0 | 49 | 117 | 76.0 | 203 | 2.9 | 0.92 | 13.10 | 2.3 | -33 | 38 |
| DAY 15:PRE-DS | 187 | 76.4 | 14.08 | 76.0 | 39 | 124 | 75.8 | 187 | 0.6 | 0.88 | 11.99 | 1.0 | -37 | 40 |
| DAY 15:1-2H PST-DS | 184 | 79.2 | 13.72 | 79.0 | 44 | 115 | 75.6 | 184 | 3.6 | 0.96 | 13.00 | 3.7 | -44 | 37 |
| DAY 15:4H PST-DS | 176 | 81.6 | 13.86 | 81.0 | 49 | 119 | 75.7 | 178 | 5.9 | 0.99 | 13.21 | 4.8 | -38 | 38 |
| DAY 29 | 157 | 76.5 | 13.78 | 75.0 | 47 | 113 | 75.6 | 157 | 0.9 | 1.03 | 12.91 | 0.7 | -30 | 36 |
| DAY 36:PRE-DS | 125 | 74.9 | 16.54 | 73.0 | 47 | 163 | 76.2 | 125 | -1.3 | 1.26 | 14.14 | -2.7 | -34 | 75 |
| DAY 36:1-2H PST-DS | 123 | 75.7 | 13.85 | 75.0 | 44 | 139 | 76.0 | 123 | -0.3 | 1.11 | 12.28 | 0.0 | -31 | 51 |
| DAY 36:4H PST-DS | 122 | 77.1 | 14.04 | 76.0 | 39 | 135 | 76.1 | 122 | 1.1 | 1.26 | 13.88 | 0.0 | -36 | 47 |
| DAY 43 | 124 | 75.2 | 13.69 | 73.5 | 47 | 113 | 76.1 | 124 | -0.9 | 1.03 | 11.47 | -1.0 | -34 | 37 |
| END POINT | 232 | 77.8 | 14.13 | 77.0 | 47 | 118 | 75.8 | 232 | 2.1 | 0.85 | 12.94 | 1.0 | -34 | 37 |
| ER OROS PAL 3 mg | | | | | | | | | | | | | | |
| SCREENING | 127 | 77.3 | 14.28 | 76.0 | 43 | 132 | | | | | | | | |
| BASELINE | 127 | 75.9 | 14.99 | 75.0 | 47 | 130 | | | | | | | | |
| AVERAGE PREDOSE | 127 | 77.0 | 14.01 | 76.3 | 49 | 125 | | | | | | | | |
| DAY 4:4H PST-DS | 118 | 82.6 | 13.70 | 81.5 | 53 | 120 | 76.8 | 118 | 5.8 | 1.12 | 12.17 | 5.3 | -19 | 38 |
| DAY 4:10H PST-DS | 114 | 81.1 | 13.79 | 79.5 | 49 | 115 | 76.9 | 114 | 4.1 | 1.16 | 12.36 | 4.7 | -27 | 33 |
| DAY 4:22H PST-DS | 118 | 78.4 | 14.81 | 76.0 | 47 | 116 | 76.8 | 118 | 1.6 | 1.27 | 13.74 | 1.3 | -36 | 43 |
| DAY 8:4H PST-DS | 112 | 82.4 | 14.86 | 82.0 | 55 | 130 | 77.0 | 112 | 5.5 | 1.20 | 12.66 | 5.3 | -26 | 56 |
| DAY 8:10H PST-DS | 107 | 80.3 | 14.28 | 81.0 | 52 | 119 | 76.9 | 107 | 3.5 | 1.17 | 14.20 | 4.3 | -28 | 49 |
| DAY 8:22H PST-DS | 113 | 77.5 | 13.84 | 76.0 | 49 | 112 | 76.8 | 113 | 0.7 | 1.20 | 12.74 | 2.3 | -29 | 34 |
| DAY 15:PRE-DS | 104 | 75.5 | 14.30 | 74.5 | 52 | 115 | 76.5 | 104 | -1.0 | 1.21 | 12.35 | -1.2 | -32 | 28 |
| DAY 15:1-2H PST-DS | 103 | 79.8 | 14.66 | 79.0 | 53 | 121 | 76.5 | 103 | 3.4 | 1.31 | 13.26 | 3.3 | -38 | 44 |
| DAY 15:4H PST-DS | 104 | 81.3 | 15.03 | 80.0 | 50 | 118 | 76.9 | 104 | 4.4 | 1.36 | 13.88 | 4.5 | -34 | 43 |
| DAY 29 | 96 | 77.0 | 14.57 | 76.0 | 51 | 120 | 77.0 | 86 | -0.0 | 1.65 | 15.27 | 1.0 | -40 | 46 |
| DAY 36:PRE-DS | 66 | 74.8 | 14.28 | 73.0 | 49 | 109 | 76.8 | 66 | -2.0 | 1.63 | 13.22 | -2.8 | -34 | 30 |
| DAY 36:1-2H PST-DS | 69 | 75.3 | 12.37 | 73.0 | 53 | 109 | 76.5 | 69 | -1.2 | 1.67 | 13.89 | 0.3 | -34 | 25 |
| DAY 36:4H PST-DS | 68 | 76.8 | 12.55 | 77.0 | 50 | 102 | 76.9 | 68 | -0.2 | 1.63 | 13.42 | 2.6 | -32 | 24 |
| DAY 43 | 70 | 74.2 | 13.38 | 74.0 | 48 | 110 | 76.7 | 70 | -2.5 | 1.69 | 14.11 | -3.5 | -42 | 34 |
| END POINT | 124 | 76.9 | 14.24 | 76.0 | 48 | 114 | 77.2 | 124 | -0.3 | 1.36 | 15.11 | -0.8 | -42 | 37 |
| Olanzapine 10 mg | | | | | | | | | | | | | | |
| SCREENING | 364 | 77.4 | 13.50 | 77.0 | 45 | 119 | | | | | | | | |
| BASELINE | 364 | 76.0 | 13.65 | 74.5 | 48 | 117 | | | | | | | | |
| AVERAGE PREDOSE | 364 | 76.9 | 12.14 | 76.7 | 47 | 114 | | | | | | | | |
| DAY 4:4H PST-DS | 340 | 79.5 | 15.07 | 78.0 | 46 | 128 | 76.9 | 340 | 2.6 | 0.65 | 12.07 | 2.3 | -33 | 44 |
| DAY 4:10H PST-DS | 330 | 79.9 | 15.24 | 79.0 | 41 | 128 | 76.9 | 330 | 2.9 | 0.72 | 12.99 | 2.3 | -30 | 51 |
| DAY 4:22H PST-DS | 328 | 76.2 | 13.96 | 75.0 | 44 | 115 | 76.7 | 328 | -0.5 | 0.65 | 11.77 | -1.0 | -32 | 42 |
| DAY 8:4H PST-DS | 332 | 80.3 | 13.53 | 80.0 | 50 | 128 | 77.0 | 332 | 3.3 | 0.73 | 13.31 | 3.7 | -30 | 42 |
| DAY 8:10H PST-DS | 326 | 79.9 | 13.91 | 80.0 | 46 | 120 | 77.0 | 326 | 2.9 | 0.72 | 13.06 | 2.8 | -43 | 51 |
| DAY 8:22H PST-DS | 327 | 76.2 | 13.16 | 76.0 | 43 | 113 | 77.0 | 327 | -0.8 | 0.67 | 12.03 | -1.0 | -38 | 47 |
| DAY 15:PRE-DS | 321 | 76.4 | 12.96 | 76.0 | 46 | 117 | 77.0 | 321 | -0.6 | 0.68 | 12.12 | -1.0 | -35 | 39 |
| DAY 15:1-2H PST-DS | 310 | 80.8 | 14.44 | 80.0 | 48 | 117 | 77.1 | 310 | 3.8 | 0.80 | 14.01 | 3.2 | -36 | 48 |
| DAY 15:4H PST-DS | 307 | 81.9 | 14.66 | 82.0 | 52 | 120 | 77.0 | 307 | 4.9 | 0.80 | 14.02 | 3.7 | -34 | 44 |
| DAY 29 | 262 | 79.6 | 13.00 | 79.0 | 47 | 122 | 77.1 | 262 | 2.5 | 0.82 | 13.20 | 2.0 | -34 | 60 |
| DAY 36:PRE-DS | 221 | 75.1 | 13.29 | 73.0 | 50 | 117 | 76.7 | 221 | -1.6 | 0.85 | 12.61 | -2.3 | -35 | 33 |
| DAY 36:1-2H PST-DS | 224 | 76.4 | 13.46 | 75.0 | 43 | 118 | 76.7 | 224 | -0.3 | 0.83 | 12.37 | -0.3 | -39 | 31 |
| DAY 36:4H PST-DS | 217 | 77.9 | 14.96 | 77.0 | 44 | 129 | 76.7 | 217 | 1.2 | 0.90 | 13.31 | 1.3 | -39 | 43 |
| DAY 43 | 220 | 75.2 | 13.48 | 74.0 | 44 | 113 | 76.8 | 220 | -1.6 | 0.85 | 12.61 | -3.2 | -33 | 45 |
| END POINT | 357 | 77.7 | 13.68 | 77.0 | 44 | 115 | 76.9 | 357 | 0.9 | 0.69 | 13.08 | -0.7 | -33 | 45 |

## *II. Clinically Unremarkable Drug-related Effects on RR*

*Time and dose dependent effects on mean decreases in RR interval were observed that showed a similar time and dose-dependent pattern (maximal effects appeared to occur at the 4-hour post-dose time-points and increased with increasing dose-level) that was observed for mean increases in heart rate (described above). These observations are likely to be secondary to drug-induced effects on increasing heart rate.*

*See the results on this parameter below (taken from the sponsor's summary table, Appendix 2.7.4.6.2.1).*

*Note that selected time-points are highlighted by the undersigned reviewer for demonstration purposes (to denote peak and secondary peak mean decreases, that occurred generally at the*

*same time-points of pea and secondary peak mean increases observed for heart rate, as previously described in this review).*

*Also note that Pal groups are shown in order of decreasing dose-level.*

Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase (continued)

Analysis Set: Safety

| | | | | | | | Base | change from average predose | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | Med | Min | Max | Mean | N | Mean | SE | SD | Med | Min | Max |
| RR (ms) | | | | | | | | | | | | | | |
| Placebo | | | | | | | | | | | | | | |
| SCREENING | 354 | 803.9 | 138.95 | 789.0 | 476 | 1277 | | | | | | | | |
| BASELINE | 355 | 823.0 | 143.27 | 800.0 | 526 | 1395 | | | | | | | | |
| AVERAGE PREDOSE | 355 | 813.6 | 128.09 | 798.7 | 523 | 1269 | | | | | | | | |
| DAY 4:4H PST-DS | 327 | 795.7 | 146.11 | 779.0 | 465 | 1579 | 815.8 | 327 | -20.0 | 6.73 | 121.69 | -29.3 | -452 | 327 |
| DAY 4:10H PST-DS | 323 | 810.1 | 149.86 | 779.0 | 472 | 1333 | 815.6 | 323 | -5.5 | 7.26 | 130.39 | -13.0 | -474 | 460 |
| DAY 4:22H PST-DS | 325 | 841.2 | 164.43 | 822.0 | 500 | 1875 | 817.7 | 325 | 23.5 | 6.88 | 124.09 | 17.0 | -384 | 606 |
| DAY 8:4H PST-DS | 315 | 804.0 | 148.02 | 789.0 | 496 | 1538 | 819.5 | 315 | -15.5 | 7.70 | 136.72 | -11.0 | -549 | 404 |
| DAY 8:10H PST-DS | 311 | 812.2 | 150.09 | 789.0 | 484 | 1333 | 819.8 | 311 | -7.5 | 8.04 | 141.78 | -8.7 | -536 | 431 |
| DAY 8:22H PST-DS | 307 | 846.5 | 158.84 | 833.0 | 556 | 1395 | 820.6 | 307 | 25.9 | 8.16 | 143.00 | 23.3 | -539 | 499 |
| DAY 15:PRE-DS | 280 | 858.5 | 174.76 | 857.0 | 455 | 1667 | 823.3 | 280 | 35.2 | 8.94 | 149.61 | 36.2 | -569 | 749 |
| DAY 15:1-2H PST-DS | 281 | 822.6 | 162.93 | 822.0 | 500 | 1500 | 823.2 | 281 | -0.7 | 9.32 | 156.30 | -8.0 | -490 | 627 |
| DAY 15:4H PST-DS | 279 | 817.7 | 162.01 | 800.0 | 465 | 1500 | 822.5 | 279 | -4.8 | 9.27 | 154.85 | -16.0 | -430 | 638 |
| DAY 29 | 206 | 815.8 | 152.48 | 805.5 | 488 | 1200 | 826.7 | 206 | -11.0 | 10.72 | 153.88 | -10.3 | -693 | 453 |
| DAY 36:PRE-DS | 136 | 855.7 | 174.56 | 822.0 | 571 | 1277 | 829.3 | 136 | 26.4 | 13.75 | 160.33 | 28.3 | -500 | 520 |
| DAY 36:1-2H PST-DS | 136 | 831.0 | 163.06 | 811.0 | 504 | 1250 | 829.8 | 136 | 1.2 | 13.44 | 156.75 | -3.3 | -579 | 486 |
| DAY 36:4H PST-DS | 136 | 831.0 | 162.12 | 789.0 | 541 | 1333 | 830.2 | 136 | 0.8 | 14.37 | 167.62 | -3.5 | -557 | 414 |
| DAY 43 | 139 | 866.0 | 161.42 | 870.0 | 583 | 1277 | 835.3 | 139 | 30.7 | 11.52 | 135.83 | 30.3 | -320 | 350 |
| END POINT | 350 | 822.6 | 165.59 | 789.0 | 500 | 1277 | 813.9 | 350 | 8.7 | 8.17 | 152.91 | 5.0 | -693 | 453 |
| ER OROS PAL 3 mg | | | | | | | | | | | | | | |
| SCREENING | 127 | 803.1 | 153.69 | 789.0 | 455 | 1395 | | | | | | | | |
| BASELINE | 127 | 821.1 | 159.89 | 800.0 | 462 | 1277 | | | | | | | | |
| AVERAGE PREDOSE | 127 | 811.3 | 147.33 | 788.3 | 484 | 1220 | | | | | | | | |
| DAY 4:4H PST-DS | 118 | 746.8 | 126.80 | 736.5 | 500 | 1132 | 812.9 | 118 | -66.0 | 11.01 | 119.59 | -65.3 | -396 | 168 |
| DAY 4:10H PST-DS | 114 | 762.8 | 136.96 | 754.5 | 522 | 1224 | 810.8 | 114 | -48.0 | 12.18 | 130.02 | -55.9 | -442 | 245 |
| DAY 4:22H PST-DS | 118 | 792.7 | 150.72 | 789.0 | 517 | 1277 | 812.9 | 118 | -20.2 | 12.68 | 137.75 | -19.2 | -325 | 353 |
| DAY 8:4H PST-DS | 112 | 750.9 | 133.00 | 732.0 | 462 | 1091 | 812.1 | 112 | -61.3 | 11.65 | 123.26 | -53.8 | -378 | 210 |
| DAY 8:10H PST-DS | 107 | 770.5 | 137.21 | 741.0 | 504 | 1154 | 814.0 | 107 | -43.5 | 13.98 | 144.66 | -45.0 | -457 | 275 |
| DAY 8:22H PST-DS | 113 | 800.1 | 149.67 | 789.0 | 536 | 1224 | 813.1 | 113 | -13.0 | 12.55 | 133.41 | -23.7 | -385 | 383 |
| DAY 15:PRE-DS | 104 | 823.0 | 152.35 | 805.5 | 522 | 1154 | 817.0 | 104 | 6.0 | 12.28 | 125.25 | 10.0 | -285 | 283 |
| DAY 15:1-2H PST-DS | 103 | 777.5 | 145.98 | 769.0 | 496 | 1132 | 817.4 | 103 | -39.9 | 13.50 | 137.03 | -32.0 | -483 | 281 |
| DAY 15:4H PST-DS | 104 | 764.4 | 147.20 | 750.0 | 508 | 1200 | 814.3 | 104 | -49.8 | 13.61 | 138.83 | -36.3 | -432 | 283 |
| DAY 29 | 86 | 808.0 | 155.56 | 789.0 | 500 | 1176 | 812.8 | 86 | -4.8 | 15.60 | 144.68 | -14.7 | -442 | 357 |
| DAY 36:PRE-DS | 66 | 831.6 | 163.43 | 822.0 | 550 | 1224 | 811.5 | 66 | 20.1 | 17.09 | 138.81 | 22.2 | -356 | 398 |
| DAY 36:1-2H PST-DS | 69 | 817.5 | 130.47 | 822.0 | 550 | 1132 | 817.1 | 69 | 0.3 | 17.04 | 141.54 | -4.3 | -490 | 354 |
| DAY 36:4H PST-DS | 68 | 803.8 | 140.70 | 779.0 | 588 | 1200 | 811.8 | 68 | -8.1 | 16.73 | 137.94 | -27.7 | -268 | 412 |
| DAY 43 | 70 | 835.8 | 156.63 | 811.0 | 545 | 1250 | 813.7 | 70 | 22.1 | 18.46 | 154.45 | 29.2 | -360 | 376 |
| END POINT | 124 | 807.6 | 152.63 | 789.0 | 526 | 1250 | 809.3 | 124 | -1.7 | 13.92 | 154.97 | 7.0 | -376 | 376 |
| ER OROS PAL 6 mg | | | | | | | | | | | | | | |
| SCREENING | 234 | 810.3 | 144.46 | 800.0 | 536 | 1176 | | | | | | | | |
| BASELINE | 235 | 825.5 | 163.65 | 779.0 | 492 | 1304 | | | | | | | | |
| AVERAGE PREDOSE | 235 | 819.0 | 138.43 | 806.3 | 540 | 1197 | | | | | | | | |
| DAY 4:4H PST-DS | 218 | 717.7 | 119.65 | 702.0 | 462 | 1132 | 819.7 | 218 | -100.9 | 7.98 | 117.88 | -98.8 | -438 | 166 |
| DAY 4:10H PST-DS | 209 | 740.3 | 127.78 | 723.0 | 448 | 1071 | 817.1 | 209 | -76.8 | 8.50 | 122.93 | -69.3 | -436 | 339 |
| DAY 4:22H PST-DS | 203 | 770.3 | 141.79 | 759.0 | 508 | 1364 | 816.7 | 203 | -46.5 | 9.65 | 137.48 | -33.3 | -474 | 434 |
| DAY 8:4H PST-DS | 210 | 735.8 | 122.57 | 714.0 | 541 | 1154 | 819.0 | 210 | -83.1 | 8.22 | 119.12 | -84.2 | -395 | 224 |
| DAY 8:10H PST-DS | 201 | 743.4 | 117.98 | 732.0 | 526 | 1111 | 821.4 | 201 | -78.0 | 8.66 | 122.84 | -86.7 | -446 | 255 |
| DAY 8:22H PST-DS | 203 | 785.7 | 144.66 | 769.0 | 513 | 1224 | 817.8 | 203 | -32.1 | 9.64 | 137.32 | -30.3 | -491 | 381 |
| DAY 15:PRE-DS | 187 | 812.5 | 153.37 | 789.0 | 484 | 1538 | 820.0 | 187 | -7.5 | 9.98 | 136.45 | -17.7 | -454 | 608 |
| DAY 15:1-2H PST-DS | 184 | 781.6 | 142.62 | 759.0 | 522 | 1364 | 822.0 | 184 | -40.4 | 10.65 | 144.40 | -38.2 | -421 | 434 |
| DAY 15:4H PST-DS | 178 | 756.9 | 132.11 | 741.0 | 504 | 1224 | 820.3 | 178 | -63.4 | 10.35 | 138.15 | -53.7 | -419 | 442 |
| DAY 29 | 157 | 810.1 | 147.54 | 800.0 | 531 | 1277 | 821.4 | 157 | -11.3 | 11.16 | 139.86 | -14.7 | -324 | 331 |
| DAY 36:PRE-DS | 125 | 834.7 | 160.92 | 822.0 | 368 | 1277 | 813.7 | 125 | 21.1 | 11.93 | 133.37 | 22.0 | -315 | 368 |
| DAY 36:1-2H PST-DS | 123 | 817.8 | 147.20 | 800.0 | 432 | 1364 | 815.4 | 123 | 2.4 | 11.17 | 123.92 | -13.0 | -333 | 434 |
| DAY 36:4H PST-DS | 122 | 803.5 | 149.39 | 789.0 | 444 | 1538 | 814.8 | 122 | -11.3 | 13.62 | 150.46 | -3.3 | -319 | 608 |
| DAY 43 | 124 | 825.0 | 152.31 | 816.5 | 531 | 1277 | 815.6 | 124 | 9.4 | 11.43 | 127.26 | 2.7 | -341 | 368 |
| END POINT | 232 | 796.8 | 147.65 | 779.0 | 508 | 1277 | 820.3 | 232 | -23.5 | 8.98 | 136.72 | -19.7 | -341 | 368 |