

One of the 3 subjects is subject 10096 who died (a 24 year old female with an unremarkable PMH who developed agitation, coma, convulsion and dyspnea and died during OL 12 mg daily Pal treatment). This subject was previously described under the section on deaths.

The other 2 subjects had SAEs of "exacerbation of schizophrenia" and "psychotic disorder and suicidal ideation," respectively. The in-text section of module 2.7.4 of NDA22043 provides no other description of these subjects.

Additional SAEs are described below.

***Reviewer Comment.***

*No new clinically remarkable findings were revealed that change conclusions and recommendations that were previously described in the reviews of NDA 21999. The following are additional reviewer comments. The text below is similar to that provided in the review of RAAL submission under NDA21999 and do not contain new information since that review.*

***OL Safety Dataset (Studies -701, through -705).***

*Results shown above are generally similar to results of the 120-Day SUR of NDA 21999 that were previously shown in the review of NDA 21999.*

*Newly reported SAEs (between November 1, 2005 in February 1, 2006), since the time of the four month safety update report of NDA21999 were provided in the 210-Day safety update report of NDA 21999 (in the SCS section and line listing found in the appendix on page 1710 of this section). These results are identical to those provided in the current NDA 22043 (the SCS of the current submission is identical to the SCS of the 210-Day SUR submission under NDA 21999, as specified on page 3 of the "Reviewer's Guide for NDA 22-043). The line listing that was reviewed started on page 1710 of the 210-Day safety update report under NDA 21-999.*

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

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

*Psychiatric-related symptoms reported as SAE's and/or ADOs are expected for this patient population. However, it is theoretically possible to have exacerbation of symptoms secondary to underlying drug-related adverse effects (that could theoretically include non-psychiatric related adverse effects that may not be clearly expressed by an acutely psychotic or agitated patient). A description of such patients (i.e. patients of SAE's that could be reflecting a drug-related adverse*

effect) could not be found in in-text sections of the SCS section of this submission. The line listing that was found in the 210-Day safety update report under NDA 21999 (starting on page 1710) specified preferred and verbatim terms for each ADO and SAE in a given subject. This line listing was reviewed. Subjects were found in this line listing that had a psychiatric-related SAE or ADO that had non-psychiatric-related verbatim terms reported either as an ADO or SAE term. The following subjects are noted:

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

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

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

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

*The following are additional comments regarding SAEs of Study -702 since this was the OL extension trial of elderly patients with schizophrenia (the study followed the elderly Phase III 6-week efficacy DB, placebo controlled trial, Study -302). Efficacy and safety results of Study -302 were previously described in the review of NDA 21999. However, Study -702 was ongoing at that time and the current NDA 22043 provides the CSR for this OL elderly trial. A key difference on methodology of Study -702 (aside from the elderly age-group selected for the study) in contrast to the other OL extension trials (-703, -704, and -705) is that Study -702 involved 6 months of OL Pal treatment rather than a 12 month treatment phase.*

*Reviewer Comment and Results of a Completed Elderly OL Extension Trial*

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

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

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

#### 7.1.4 Dropouts and Other Significant Adverse Events

##### **Results of Study -301**

The following are summary tables for Study -301 were found in the current submission (these tables were also provided in the original review of NDA21999 (that included a 4-month SUR that had the same info

**Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation by MedDRA Preferred Term - Double-Blind Phase (Study R076477-SCH-301: Safety Analysis Set)**

Body System or Organ Class Dictionary-derived Term	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	Total (N=206) n (%)
<b>Total no. subjects who discontinued due to AE</b>	1 ( 1)	3 ( 3)	4 ( 2)
<b>Vascular disorders</b>	0	2 ( 2)	2 ( 1)
Hypertension	0	1 ( 1)	1 (<1)
Venous thrombosis	0	1 ( 1)	1 (<1)
<b>Cardiac disorders</b>	0	1 ( 1)	1 (<1)
Tachycardia	0	1 ( 1)	1 (<1)
<b>Eye disorders</b>	0	1 ( 1)	1 (<1)
Visual disturbance	0	1 ( 1)	1 (<1)
<b>Gastrointestinal disorders</b>	1 ( 1)	0	1 (<1)
Nausea	1 ( 1)	0	1 (<1)
<b>Musculoskeletal and connective tissue disorders</b>	0	1 ( 1)	1 (<1)
Musculoskeletal chest pain	0	1 ( 1)	1 (<1)
<b>Nervous system disorders</b>	0	1 ( 1)	1 (<1)
Sedation	0	1 ( 1)	1 (<1)

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**Results from Pooled and Unpooled OL Extension Trial Datasets**

The following summary tables of OL trials copied from the current submission provide updated information since the 120-Day SUR NDA 21999 submission (some trials continue to be ongoing studies as previously discussed in this review).

Safety results in summary tables in this subsection on OL trial results are identical to summary table results provided in the review of the RAAL of NDA21999, as previously discussed. Text descriptions of these results are also almost identical to the text descriptions that appear in the review of the RAAL of NDA 21999 for these same results.

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**Results of Study -701**

The following table summarizes results.

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Pali(NO	Pali(NO
	<=6 months (N=11) n (%)	>6 months (N=49) n (%)	<=6 months (N=2) n (%)	>6 months (N=70) n (%)	DB)/Pali <=6 months (N=23) n (%)	DB)/Pali >6 months (N=80) n (%)
<b>Total no. subjects with adverse events</b>	3 (27)	5 (7)	0	1 (1)	1 (13)	0
<b>Psychiatric disorders</b>						
Anxiety	1 (9)	2 (3)	0	1 (1)	1 (4)	0
Depression	0	1 (1)	0	0	0	0
Schizophrenia	0	1 (1)	0	0	1 (4)	0
Suicidal ideation	0	1 (1)	0	0	0	0
Suicide attempt	1 (9)	0	0	1 (1)	0	0
<b>Investigations</b>						
Electrocardiogram QT corrected interval prolonged	0	2 (3)	0	0	0	0
Electrocardiogram QT prolonged	0	1 (1)	0	0	0	0
<b>Nervous system disorders</b>						
Dyskinesia	2 (18)	1 (1)	0	0	1 (4)	0
Dizziness	1 (9)	1 (1)	0	0	0	0
Syncope	0	0	0	0	1 (4)	0
Tremor	1 (9)	0	0	0	0	0
<b>Gastrointestinal disorders</b>						
Vomiting	0	0	0	0	1 (4)	0
<b>Reproductive system and breast disorders</b>						
Amenorrhoea	0	0	0	0	1 (4)	0

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

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

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

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Results of Study -702

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

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

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

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**Results from the Integrated OL Extension Trial Dataset**  
 The following are summary tables of results.

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	≤6 months (N=99) n (%)	>6 months (N=137) n (%)	≤6 months (N=209) n (%)	>6 months (N=477) n (%)	≤6 months (N=103) n (%)	>6 months (N=141) n (%)	≤6 months (N=416) n (%)	>6 months (N=755) n (%)
Total no. subjects with adverse events	10 (10)	6 (4)	29 (14)	12 (3)	13 (17)	8 (6)	57 (14)	26 (3)
<b>Psychiatric disorders</b>	4 (4)	5 (4)	13 (9)	7 (1)	10 (9)	5 (4)	32 (8)	17 (2)
Depression	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	1 (1)	4 (1)	5 (1)
Psychotic disorder	2 (2)	0	2 (1)	1 (<1)	3 (3)	2 (1)	7 (2)	3 (<1)
Anxiety	0	1 (1)	0	0	1 (1)	1 (1)	1 (<1)	2 (<1)
Insomnia	0	0	3 (3)	1 (<1)	1 (1)	1 (1)	4 (1)	2 (<1)
Paranoia	0	2 (1)	1 (<1)	0	0	0	1 (<1)	2 (<1)
Acute psychosis	0	0	0	0	0	1 (1)	0	1 (<1)
Delusion	0	1 (1)	2 (1)	0	1 (1)	0	3 (1)	1 (<1)
Depressed mood	0	0	0	0	0	1 (1)	0	1 (<1)
Depressive symptom	0	1 (1)	0	0	0	0	0	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia	0	0	2 (1)	1 (<1)	3 (3)	0	5 (1)	1 (<1)
Sticidal ideation	1 (1)	0	1 (<1)	1 (<1)	2 (2)	0	4 (1)	1 (<1)
Aggression	0	0	0	0	1 (1)	0	1 (<1)	0
Agitation	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Alcoholism	0	0	0	0	1 (1)	0	1 (<1)	0
Confusional state	0	0	3 (1)	0	0	0	3 (1)	0
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Hallucination, auditory	0	0	1 (<1)	0	0	0	1 (<1)	0
Homicidal ideation	0	0	1 (<1)	0	0	0	1 (<1)	0
Hostility	0	0	1 (<1)	0	0	0	1 (<1)	0
Sticide attempt	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Nervous system disorders</b>	1 (1)	1 (1)	6 (3)	1 (<1)	2 (2)	3 (2)	9 (2)	5 (1)
Akathisia	0	0	3 (1)	0	0	2 (1)	2 (<1)	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyskinesia	0	1 (1)	0	0	0	0	0	1 (<1)
Extrapyramidal disorder	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)

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

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	<=6 months (N=99) n (%)	>6 months (N=157) n (%)	<=6 months (N=209) n (%)	>6 months (N=477) n (%)	<=6 months (N=168) n (%)	>6 months (N=141) n (%)	<=6 months (N=456) n (%)	>6 months (N=755) n (%)
<b>Nervous system disorders (continued)</b>								
Hypertonia	0	0	0	0	0	1 (<1)	0	1 (<1)
Mental impairment	0	0	0	0	0	1 (<1)	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dizziness	0	0	0	0	2 (2)	0	2 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Dystonia	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Tremor	1 (1)	0	0	0	0	0	1 (<1)	0
<b>Investigations</b>								
Weight increased	1 (1)	1 (1)	1 (<1)	3 (1)	2 (2)	0	4 (1)	4 (1)
Alkaline aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood prolactin increased	0	1 (1)	0	0	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Gamma-gutamyltransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram T wave abnormal	0	0	0	0	1 (1)	0	1 (<1)	0
Hepatic enzyme increased	0	0	0	0	1 (1)	0	1 (<1)	0
Weight decreased	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Reproductive system and breast disorders</b>								
Erectile dysfunction	0	0	2 (1)	1 (<1)	0	1 (1)	2 (<1)	2 (<1)
Galactorrhea	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Gynaecomastia	0	0	0	0	0	1 (1)	0	1 (<1)
Retrograde ejaculation	0	0	1 (<1)	0	0	0	1 (<1)	0

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 Supplemental NDA 22-043 N000-N002  
 Paliperidone OROS oral

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali (N=89)		Pali/Pali (N=209)		Olan/Pali (N=141)		Total Pali (N=416)	
	<=6 months n (%)	>6 months n (%)	<=6 months n (%)	>6 months n (%)	<=6 months n (%)	>6 months n (%)	<=6 months n (%)	>6 months n (%)
<b>Injury, poisoning and procedural complications</b>								
Traumatic haematoma	1 (1)	0	2 (1)	1 (<1)	0	0	3 (1)	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Self mutilation	1 (1)	0	0	0	0	0	1 (<1)	0
<b>Metabolism and nutrition disorders</b>								
Hyponatremia	0	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Anorexia	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Respiratory, thoracic and mediastinal disorders</b>								
Pneumonia aspiration	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Dyspnoea	0	0	0	1 (<1)	0	0	0	1 (<1)
<b>Cardiac disorders</b>								
Myocardial infarction	1 (1)	0	3 (1)	0	2 (2)	0	6 (1)	0
Myocardial ischaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Palpitations	0	0	1 (<1)	0	0	0	1 (<1)	0
Sinus tachycardia	1 (1)	0	0	0	1 (1)	0	1 (<1)	0
Tachycardia	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Eye disorders</b>								
Vision blurred	0	0	0	0	1 (1)	0	1 (<1)	0
<b>Gastrointestinal disorders</b>								
Ceasation	1 (1)	0	1 (<1)	0	3 (3)	0	5 (1)	0
Dysphagia	0	0	0	0	1 (1)	0	1 (<1)	0
Nausea	0	0	1 (<1)	0	0	0	1 (<1)	0
Peptic ulcer	1 (1)	0	0	0	1 (1)	0	1 (<1)	0
Vomiting	0	0	0	0	2 (2)	0	2 (<1)	0

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

Body System or Organ Class Dictionary-derived Term	Pla/Pali (N=89)		Pali/Pali (N=209)		Olan/Pali (N=141)		Total Pali (N=416)	
	<=6 months n (%)	>6 months n (%)	<=6 months n (%)	>6 months n (%)	<=6 months n (%)	>6 months n (%)	<=6 months n (%)	>6 months n (%)
<b>General disorders and administration site conditions</b>								
Fatigue	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Oedema	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Infections and infestations</b>								
Hepatitis A	1 (1)	0	1 (<1)	0	0	0	2 (<1)	0
Pneumonia	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Musculoskeletal and connective tissue disorders</b>								
Arthralgia	1 (1)	0	1 (<1)	0	2 (2)	0	4 (1)	0
Joint stiffness	0	0	0	0	1 (1)	0	1 (<1)	0
Muscle rigidity	1 (1)	0	0	0	0	0	1 (<1)	0
Muscle twitching	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Skin and subcutaneous tissue disorders</b>								
Acne	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Social circumstances</b>								
Alcohol use	0	0	2 (1)	0	2 (2)	0	4 (1)	0
Drug abuser	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Vascular disorders</b>								
Hypertension	0	0	0	0	1 (1)	0	1 (<1)	0

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***Reviewer Comments on Results from Pooled and Unpooled Safety Datasets.***

*The following are additional reviewer comments. The text below is similar to that provided in the review of RAAL submission under NDA219999 and does not contain new information since that review.*

**Study -301**

*Since, this study was completed in time for the 4-month safety update report under NDA 21999 the line listing for ADOs for this study found in the SCS in this previous submission is identical to the line listing in the current NDA 22043 submission (in appendix 3.4.3). Therefore no new ADOs were found that were not previously described in the review of the 4-month safety update report of NDA 21999.*

**Study -701**

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

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

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

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

**Pooled OL Trials (-702,-703,-704,-705)**

*No new clinically remarkable findings were revealed that differ from results previously described in the review and addendum review of NDA 21999.*

*Newly reported ADOs since the time of the four month safety update report were provided in the 210-Day safety update report of NDA 21999 (in the SCS section and line listing found in the appendix of this section, starting on page 1710). The 210-Day SUR is identical to Module 2.7.4 in NDA 22043, as previously discussed.*

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

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

1) Subjects with elevations in LFTs who were ADOs, as described:

- *Subject 501535 had increased hepatic enzymes reported as an AE leading to an ADO who had abnormal values at baseline. However, the subject showed more marked elevations in GGT during DB olanzapine and OL pal treatment and had treatment discontinued on Day 5 of OL Pal (9 mg/day). Levels remained elevated on Day 6. No other information could be found in the narrative regarding any subsequent levels, non-drug-related etiologies or risk factors. Additional cases of subjects with elevated LFTs and ADOs due to elevated LFTs were previously described in the previous clinical reviews of NDA 21999.*
- *Subject 500507 had elevations in liver function tests, but these elevations are also observed at baseline with no further increase observed during olanzapine and paliperidone treatment (this subject received double-blind olanzapine during Study-305 followed by open label paliperidone during Study-705). Since the LFT elevations persisted, the subject was withdrawn prematurely due to AEs of elevated LFTs (an ADO). His LFTs declined upon dechallenge. This subject was not previously described in the original clinical review of NDA 21999. However, similar cases were previously described.*
- *Subject 501535 had hepatic enzymes increased (ALT, AST, and GGT) reported as an ADO who had abnormal levels at baseline but had markedly greater elevations in gamma-glutamyltransferase levels during double-blind olanzapine treatment (on Day 21 of the double-blind lead-in Study-305). The subject continued to show elevations after five days of open label treatment with 9 mg, daily of paliperidone in Study-705 and was therefore discontinued from the study on Day 6.*

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

- *Subject 500501 had SAE's involving elevated liver function tests and elevated CPK that led to an ADO of this subject. This subject was previously described under the above section on SAE's and was also previously described in past clinical reviews of NDA 21999.*

2) ADOs due to QTc Prolongation or ECG abnormality:

*Subject 100921 (previously received placebo in the lead-in study) had QTc prolongation leading to an ADO that did not appear to be drug-related since similar QTc values were observed during placebo treatment in the lead-in study.*

- *Subject 100943 had junction nodal rhythm that led to an ADO that was first noted on Day 42 of 9 mg Pal daily (during the run-in phase) that was not reported at baseline or upon treatment cessation ("resolved" post-treatment-cessation). A cardiologist in the central laboratory read the same ECG and reported it as normal. Paliperidone treatment was discontinued after two days of 12 mg of daily paliperidone during the open-label these study-701 due to "nodal rhythm" that was reported "as persisting." Incomplete right bundle branch block was reported at baseline and at post treatment cessation. Ranitidine was given on Day 42 for dyspepsia. This subject was a 30 year old healthy female with a past medical history of anemia and respiratory infection. The role of Pal is considered probable in the absence of more information. Despite a normal reading by the cardiologist on Day 42, the event was considered persisting several days later, in which EKG results that led to this conclusion could not be found in the narrative description. The description of a cardiology work-up of the patient during or following the study or any mention of holter monitoring (which would have been helpful at least following treatment cessation) could not be found in the narrative description of this subject. It is noted that right bundle branch block and junctional rhythm are not uncommon events in the general population.*

*Upon further inquiry about the above subject additional information on this subject was provided in an 12/21/06 response submission. The sponsor consulted recently with their J&JPRD cardiologist. The following observations are noted based on the information found in their response submission:*

- *A Day 43 ECG (during the run-in phase) revealed "junctional rhythm." According to the cardiologist (who was recently consulted by the sponsor), the ECG could be read as either a junctional rhythm or an "ectopic atrial rhythm."*
- *The cardiologist also noted that the "P wave axis was not consistent with sinus rhythm on one ECG during screening and on one ECG on Day 8."*
- *Pal treatment was stopped on Day 45 (after 2 days on 12 mg Pal/day as above) and a Day 48 ECG showed an incomplete right bundle branch block.*
- *The ECG abnormalities in this subject are "commonly encountered in the normal population."*

*A higher incidence of first degree AV block compared to placebo was previously observed in placebo controlled Phase III trials as follows:*

- *A greater incidence of adverse events (AEs) of ° AV block in the 15 mg (highest-dose) Pal group compared to placebo (4.4%, 1.4%, respectively), in the 6-week Phase III integrated safety dataset (Trials 303, 304 and 305).*
- *Similar findings were observed in the small elderly Phase III trial -302 (3% and 0% in the Pal and placebo groups, respectively) that used a flexible dose design (3-12 mg/day),*
- *A small group-mean increase in PR interval in Pal compared to placebo groups in Phase III trials (the magnitude of this increase was clinically unremarkable).*

- *A few individual subjects with AV node-related events were previously described in the review of NDA 21999 (e.g. refer to a summary of an ADO due dizziness in subject 201526 who also had AEs of epigastric abdominal pain starting on day 15 of 12 mg daily of Pal and was also reported to have AEs of "first degree AV block" and "blurred vision."*

*The above subject was receiving 9-12 mg daily of Pal and had treatment stopped at the 12 mg daily dose-level. The role of Pal is suspicious but one cannot be certain that this event was Pal-related on the basis of the information found in the narrative and in the 12/21/06 response submission. This single additional subject does not alter past conclusions and recommendations previously provided for NDA21999 by the undersigned reviewer. NDA21999 was approved on 12/19/06.*

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

*Results and Reviewer Comments of Elderly OL Trial -702*

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

*Due to the unexpected ADOs of confusion in 2 subjects (200321 and 200719), a review of the narratives of these subjects was conducted. It appears these subjects had a pre-existing condition that was likely to at least play a role in the development of confusion. However, a clear diagnosis of dementia (e.g. with supporting diagnostic testing) could not be found in the narratives. These subjects are described in more detail later. One consideration is a possible role of Pal exacerbating underlying dementia-like conditions in these elderly subjects. Pal is not indicated for dementia and the sponsor is only seeking a schizophrenia indication. Furthermore, proposed labeling includes a drug class section on risk of mortality with patients with dementia.*

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

*The sponsor's in-text description of the ADO due to anorexia (subject 200309 as found in the CSR) did not describe any other abnormalities in this subject other than anorexia and weight loss. This subject was not reported to have any pre-existing condition. Although acute*

*psychosis, as well as the patient's age could be factors involved with this AE, a role of Pal is suggested since a non-drug-related etiology cannot be clearly identified.*

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

**DB-Placebo/OL-Pal Treated Subjects with ADOs in Study -702.**

These subjects previously received DB Placebo in the 6-week Phase III lead-in study to the OL Pal Extension Study -702:

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

**DB-Pal/OL-Pal Treated Subjects with ADOs in Study -702**

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

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

7.1.4.1 Overall profile of dropouts

According to the clinical review MAPP, the over disposition of subjects in clinical trials is to be summarized in this subsection.

The disposition of subjects in the pivotal Phase III maintenance treatment Study -301 was previously discussed under Section 6 of this review.

The following table is copied from the submission for the integrated OL safety dataset which provided the bulk of longer-term safety data.

**Table 4: Study Completion/ Withdrawal Information Through 1 February 2006**  
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	----- Pla/Pali -----		----- Pali/Pali -----		----- Olan/Pali -----		-- Total Paliperidone --	
	Pali Duration, n (%)		Pali Duration, n (%)		Pali Duration, n (%)		Pali Duration, n (%)	
	≤6 months	>6 months	≤6 months	>6 months	≤6 months	>6 months	≤6 months	>6 months
	(N=99)	(N=137)	(N=209)	(N=477)	(N=108)	(N=141)	(N=416)	(N=755)
Completed	10 (10)	83 (61)	0	271 (57)	0	82 (58)	10 (2)	436 (58)
Ongoing <sup>a</sup>	0	24 (18)	0	80 (17)	0	26 (18)	0	130 (17)
Withdrawn	89 (90)	30 (22)	209 (100)	126 (26)	108 (100)	33 (23)	406 (98)	189 (25)
Subject choice (subject withdrew consent)	38 (38)	9 (7)	87 (42)	53 (11)	39 (36)	9 (6)	164 (39)	71 (9)
Lost to follow-up	11 (11)	10 (7)	29 (14)	19 (4)	12 (11)	6 (4)	52 (13)	35 (5)
Adverse event	10 (10)	6 (4)	29 (14)	12 (3)	20 (19)	8 (6)	59 (14)	26 (3)
Death	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Other	30 (30)	5 (4)	64 (31)	41 (9)	37 (34)	9 (6)	131 (31)	55 (7)

<sup>a</sup> As of 01FEB2006

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**Completers and Exposure**

The following summary table on exposure was found in Module 2.7.4 regarding the integrated OL trial safety dataset.

Appears This Way  
 On Original

**Table 10: Extent of Exposure to Open-Label ER OROS Paliperidone Through 1 February  
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)**

	--- Pla/Pali --- (N=236)	-- Pali/Pali -- (N=686)	-- Olan/Pali -- (N=249)
<b>Total duration, days</b>			
N	236	686	249
<b>Category, n (%)</b>			
Week 1-4	35 (15)	73 (11)	44 (18)
Week 5-8	17 (7)	50 (7)	18 (7)
Week 9-12	17 (7)	42 (6)	16 (6)
Week 13-16	5 (2)	34 (5)	13 (5)
Week 17-20	5 (2)	16 (2)	6 (2)
Week 21-24	20 (8)	32 (5)	11 (4)
Week 25-28	18 (8)	51 (7)	11 (4)
Week 29-32	4 (2)	11 (2)	5 (2)
Week 33-36	5 (2)	18 (3)	3 (1)
Week 37-40	9 (4)	53 (8)	12 (5)
Week 41-44	18 (8)	33 (5)	15 (6)
Week 45-48	4 (2)	27 (4)	9 (4)
Week 49-52	43 (18)	147 (21)	53 (21)
> week 52	36 (15)	99 (14)	33 (13)
Mean (SD)	211.5 (136.79)	225.0 (133.32)	207.8 (144.02)
Median	202.0	260.0	238.0
Range	(1;391)	(1;393)	(2;392)

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#### 7.1.4.2 Adverse events associated with dropouts

This topic was previously covered.

#### 7.1.4.3 Other significant adverse events

The clinical reviews of NDA 21999 covered this topic in depth that included the majority of safety data described in the current review (results of OL extension trials, results of Study -301 and elderly trials -302 and -702). Some of the OL trials were ongoing at the time of the NDA 21999 submission. Some of these trials were since completed. Therefore, previous sections also describe selected ADOs and SAEs that either may be new cases or were not previously described in the reviews of NDA 21999. Sections on clinical parameter results that summarize the incidence of outliers (using cut-off criteria) also provide additional information related to the topic of "other significant AEs." Additional information on this topic is provided in section 7.1.4 which summarizes results of the sponsor's special search strategies.

#### 7.1.5 Other Search Strategies

*Special Search Strategy for Subjects with Clinically Remarkable or Potentially Clinically Remarkable Events*

*The sponsor conducted special search strategies for selected AEs as described in Sections 2.1.5 and 2.1.6 of Module 2.7.4 of AEs. This search was conducted for short-term DB and long-term OL Phase III trials conducted for the schizophrenia indication under NDA 21999 and results were previously reviewed (in the original review of NDA 21999). Since some of the OL trials were recently completed and others remain ongoing, updated results from the sponsor's special search strategy of AEs they selected for this purpose, was provided in NDA22043 and results are summarized below.*

*The following were the AEs selected using AE search strategies and related search AE terms, as described in Sections 2.1.5 and 2.1.6:*

- *Suicidality*
- *Tachycardia*
- *Orthostatic Hypotension*
- *Aggression or Agitation*
- *Ischemia-related AEs*
- *AEs Suggestive of Proarrhythmic Potential (seizures, syncope, ventricular fibrillation and flutter, ventricular tachycardia, torsade de pointes, AEs "consistent with sudden death")*
- *Somnolence*
- *Glucose-related AEs*
- *Gastrointestinal Obstruction*
- *Potentially Prolactin-related AEs: this topic is covered under 7.1.8.5 on special clinical assessments since it includes results on prolactin levels as well as results on potentially prolactin related AEs.*
- *Extrapyramidal Symptoms (EPS)-related AEs*

*Sections 2.1.5 and 2.1.6 provided the following information for all safety datasets; Study 301, Study 701 and for the integrated OL trial safety dataset (-702, 703, -704 and -705):*

- *Results of the incidence and number of subjects identified with a each AE term that was searched under the above categories.*
- *Brief descriptions of a few selected subjects that were among the total number of subjects that were captured by each special search strategy.*

*The results of the above special searches were reviewed to determine if any remarkable findings were found that were new or unexpected in comparison to previously described safety findings in past NDA 219999 clinical reviews (in-text information in Sections 2.1.5 and 2.1.6 of module 2.7.4 were reviewed unless otherwise specified below).*

Limitations or Potential Limitations with the Results

Most subject descriptions were brief (a few sentences or less) and generally provided the following information for a given subject, as specified:

- Sometimes subject numbers were provided.
- The AE terms for a given subject that had been captured by the search were generally specified.
- Sometimes the given subject was also specified as having an ADO or SAE due to a captured AE term. Deaths, SAEs and ADO were previously covered in this review in sections of 7.1.1-3.

Also refer to the original review of NDA 21999 for a discussion of limitations and potential limitations with the sponsor's results from their special search strategies. Potential concerns regarding the quality and completeness of these results were also discussed on this past review.

Additional limitations with the results are also discussed below.

One key limitation that is not discussed elsewhere is that it appears that dictionary-derived (DD) terms were search. It appears that a search of verbatim terms was not conducted. Consequently, additional cases may have been missed (not captured by the search) by the DD-term search. Other cases that were captured by the DD-term may not be an accurate reflection for a given AE category based on the associated verbatim term(s) that were reported (e.g. the DD term of syncope may actually have an associated verbatim term of dizziness). Consequently, the interpretation of results of the incidence of events within a given category is limited by the methods of the search employed and is limited if a further examination of verbatim terms was not conducted.

Another consideration with interpreting some of the results below that has not been previously discussed is regarding treatment methods between the lead-in study and OL extension study for a given subject. The sponsor notes (in the section on EPS-related AE-searched categories) that treatment between the DB lead-in study and the OL extension trial was not always continuous. Depending on the previous DB treatment group assignment, some subjects were abruptly switched from one placebo or olanzapine to 9 mg of daily Pal in the OL trial. Subjects who received DB Pal treatment could also be switched from a different daily dose-level (3 mg, 6 mg, 12 mg or 15 mg) to the required starting daily dose of 9 mg of OL Pal. Therefore the sponsor suggests that this potential confounding variable may have influenced results of AEs that are known to occur with acute treatment, but would generally not be expected with chronic treatment. This potential confounding variable may have also influenced results of AEs known to be associated with chronic treatment, since some subjects were abruptly switched to Pal from a different drug or dose-level. Note that the majority of DB-Pal subjects were receiving 9mg or higher daily dose-levels (12 and 15 mg) in the lead-in studies, while only a small subset of the DB-Pal subjects received a lower daily dose level of under 6 mg in the lead-in study (a small sample size were receiving the next lowest daily dose level of 3 mg which was the lowest daily dose-level employed). Consequently, the appearance of acute-treatment-related AEs in the DB-Pal/OL Pal subjects that were reported during OL extension trial would generally not be expected. Yet, another confounding variable is that OL treatment was flexible. A re-examination

*of the data to determine if acute AEs were reported in subjects after chronic treatment in the absence of these potentially confounding variables cannot be found by the undersigned. Also consider that Pal is an ER formulation in which acute reactions would not be expected to occur as often as they are observed with an IR formulation and that a larger increase in the dose would be required to potentially elicit an acute reaction than would be required of an IR formulation. Any additional analyses to explore possible explanations for observing acute-related AEs during the OL trials, as discussed later in this review, could not be the undersigned reviewer.*

*Aside from reports of acute AEs that may have occurred after longterm treatment in some of the OL trial subjects, the special search results as found in Sections 2.1.5-6 did not reveal any new and clinically remarkable safety signals that differed from safety results previously described in clinical review of NDA21999 (as described in Section 7 of the original clinical review of NDA21999 or in the addendum clinical review to NDA21999). A greater incidence of the following AEs were reported in subgroups receiving over 6 months Pal compared to subgroups receiving  $\leq 6$  months of Pal, as specified in more detail later:*

- *Tachycardia,*
- *Orthostatic hypotension,*
- *Glucose-related AEs*
- *EPS-related AEs, as discussed later that include EPS known to be more common with acute treatment (dystonia).*

*It is not clear how to interpret these results since an OL study flexible-dose design was employed and given other considerations and limitations with the results, as previously discussed. Furthermore, comparisons between  $> 6$  month and  $\geq 6$  month subgroups can be misleading with respect to potential effects over duration of treatment. Given this key limitation it is not clear why the sponsor presented the results in this manner (by subdividing subjects into these two subgroups).*

*The following subsections provide more details on the results for each special-search AE category based on the in-text information found in Sections 2.1.5 and 2.1.6. Some of these findings may reflect an observation that was not previously described in past reviews of NDA21999 or are results that may be notable, as specified.*

#### *Tachycardia*

*Tachycardia is not a new finding, but results show possible evidence for an effect of duration of treatment on the incidence of tachycardia with a greater incidence associated with a greater duration of treatment as follows:*

- *Treatment groups of the integrated OL safety dataset were subdivided on the basis of duration of treatment; into  $\leq 6$  month and  $> 6$  month Pal subgroups, as previously described in this review. The incidence of tachycardia-related AEs was:
  - *6-8% among the  $< 6$  month Pal subgroups compared to*
  - *10-14% among the  $> 6$  month Pal subgroups.**

*This finding could be reflecting a real effect of duration of exposure on the incidence of tachycardia. However, the results are limited by the OL trial design (no placebo group) and by the manner in which they were presented by the sponsor. For example, the results may have*

*been influenced by the chances of finding a given event in a given subject who is monitored more times than subjects who were on treatment for a shorter duration. The sponsor subdivided treatment groups by duration of exposure. Results or a discussion of results for all subjects of a treatment group over time (without categorizing the groups by duration of exposure) could not be found in Section 2.1.5.*

*A reference to another in-text section of Module 2.7.4 describing results of tachycardia related AEs over time could not be found in Section 2.1.5. However, the sponsor refers to "life-tables" in appendices 3.1.6 and 3.2.7. The sponsor concludes on the basis of these "life-tables" that "there was no relationship between duration of exposure and the time of first occurrence of tachycardia." The sponsor also concludes based on "life-tables" in appendices that AEs were "more likely to have their onset during the first month of OL treatment versus later time points." Yet a discussion and an explanation for any AEs of tachycardia that may have recurred in subjects with a "first occurrence of tachycardia" or had an initial onset with chronic treatment (at later time-points) cannot be found.*

*Interpreting results in "life-tables" requires a number of assumptions (as part of this statistical approach that the sponsor selected). It may be more revealing to simply examine the incidence over time intervals (e.g. of perhaps 1 month intervals, initially) within each treatment group without categorizing subjects on the basis of duration of treatment. Consideration should also be given to examining AEs that may have recurred at later time-points. Finally, other statistical approaches should be considered. Potential confounding variables should also be considered (PK related for example). Also consider that upon examination of individual cases that non-drug-related etiologies may be ruled out and that key drug-related factors should be considered (e.g. food effects, fluctuation levels over time or between dosing among other potential factors). As previously discussed, an analyses of results taking into account potential changes relevant to the treatment (change in dose or other related factors) or an examination of results for potential dose-dependent effects on the given parameter could not be found.*

*Other AEs as described below showed a similar pattern for a greater incidence in the over 6 month subgroups compared to the  $\leq 6$  month subgroups in which an examination of results over time, could not be found (or reference to life tables could not be found) in the section (Section 2.1.6) where these additional AEs were described.*

#### Orthostatic Hypotension

*Orthostatic hypotension is a known AE associated with the drug class and is described in approved labeling for Pal. Approved labeling also includes the incidence of this AE in the short-term trials. However, the following results outlined below suggest an effect of duration of treatment on increasing the incidence of this type of AE when it's either reported as an AE or reported as a subject meeting outlier criteria on orthostatic vital sign assessments. Yet these results are limited by the manner in which the results are presented such that the following observations may not be reflecting a real effect over time but rather may only be reflecting the effect the duration and/or frequency in which subjects were being monitored:*

- Results of DB, placebo controlled short-term trials compared to results of the DB, placebo controlled phase of the Maintenance treatment Study 301: The incidence and treatment group differences are greater in the longterm OL Study 301 than was observed in the 6-week short-term Phase III trials as follows:
  - Short-term Trial Incidence of <1%: As described in approved labeling, the incidence in the short-term trials (6-week DB Phase III trials) is <1% for placebo and Pal groups.
  - A greater incidence and treatment group difference was observed on the incidence in the Maintenance Study 301: In study 301 the following incidence was observed in Pal and placebo groups, respectively, during the DB phase, while noting that this phase followed 14 weeks of OL treatment:
    - 2% and 1%, in Pal and placebo groups, respectively, when the event was reported as an AE
    - 5% and 2%, respectively, when reporting the event on the basis of meeting outlier criteria on orthostatic vital sign measures (as shown in Table 55 of Section 2.1.6.5.1 of Module 2.7.4).

No SAEs or ADOs due to this event were reported in Study 301.

- Results of OL Study 701: The incidence in Study 701 shows a greater incidence in subjects with:
  - Over 6 months of treatment (7-10% for any treatment subgroup) compared to
  - Subjects with  $\leq$  6 months of Pal treatment (0%)These subjects were identified on the basis of meeting outlier criteria on orthostatic vital sign measures).

No SAEs or ADOs were reported.

- Results of the Integrated OL trial Dataset:  
The above results are supported by results of the integrated OL trial dataset as follows:
  - Orthostatic hypotension was reported as an AE in:
    - 2% of subjects receiving 6 months or less of Pal treatment compared to
    - 4% of subjects with over 6 months of treatment.
  - Orthostatic hypotension was reported (on the basis of meeting outlier criteria on orthostatic vital signs) in:
    - 4% of subjects receiving 6 months or less of Pal treatment compared to
    - 6% of subjects with over 6 months of treatment.
  - Similar results were observed within the subgroup that had previously received DB Pal (in the short-term Phase III lead-in studies). In the group of subjects who previously received DB Pal prior to the OL Pal extension trial, the incidence of orthostatic hypotension (reported on the basis of meeting outlier criteria on orthostatic vital signs) was:
    - 3% in the subgroup receiving 6 months or less of Pal treatment compared to
    - 6% of subjects with over 6 months of treatment.

See previous comments on the limitations with the above results. A discussion of results over time or in-text tables or figures showing the results over time could not be found in Section 2.1.6

of Module 2.7.4. A reference to another section of Module 2.7.4 covering this topic could also not be found in Section 2.1.6.

#### Ischemia-Related Adverse Events

The sponsor conducted a special search for ischemia related events (using MedDRA terms listed in Appendix 3.7 of Module 2.7.4) for studies included in the current NDA 22043.

Study-301: two (< 1%) subjects are reported to have angina pectoris while receiving open label paliperidone, while no subjects were reported to have ischemia related events during the double-blind phase of the study. The in-text section describes this AE in these two subjects as being "mild" in severity. More information and subject numbers could not be found. The sponsor refers to appendix 3.1.1 of Module 2.7.4 which shows incidence of these AEs and does not provide other information (e.g. subject numbers or relevant clinical information).

Study-701: the sponsor indicates that no subjects in this study had ischemia-related AE's.

Open-Label Extension Trial Dataset (-702,-703,-704, and-705): < 1% of subjects in these studies had ischemia related AE's. Several subjects are listed by subject number with a brief description in Section 2.1.6.9.2.2 which covers this topic in Module 2.7.4 as follows:

- Subjects 200214, 201452, 201139, 300166, and 501572; the subjects are briefly described and were also described in the review of the original NDA 2199 submission.
- Subject 300386: was a 47-year-old male who had "coronary artery disease" as an adverse event. He is summarized to have had a history of smoking, hypertension, EKG abnormalities of T-wave inversion and T-wave abnormality, obesity, hyperlipidemia and non-insulin dependent diabetes mellitus.
- Subject 501104: the subject was a 42-year-old female who is reported to have had "coronary artery insufficiency." This subject has an unremarkable past medical history.

*Reviewer Comments: refer to the review and addendum review of NDA 21999 which described subjects with cardiovascular system related events. While a pre-existing medical condition, such as coronary artery disease, can induce AEs, a potential role of Pal in AEs that develop still needs to be considered. For example, drug-related induced tachycardia or other cardiovascular system related adverse drug effects could alter cardiac output in a subject with an already compromised cardiovascular system. In turn, a serious complication could then develop, such as an episode of angina or EKG changes consistent with ischemia or a more serious event may occur. Additionally, the method for diagnosing coronary artery disease or coronary artery insufficiency is not clear to the undersigned reviewer. In the absence of other information such as with the above subjects, a role of paliperidone needs to be considered as previously discussed in the reviews of the original NDA 21999. Based on the information found in the in-text section covering the topic of ischemia related AE's the sponsor does not provide any new, remarkable clinical findings that differ from safety findings described in the reviews of the original NDA 21999.*

#### AEs "Suggestive of Proarrhythmic Potential"

*Results of AEs “Suggestive of Proarrhythmic Potential (PP AEs) failed to reveal any clinically remarkable new finding that was not discussed in previous NDA21999 clinical reviews. However, given the potential serious nature of these events the following results are noted:*

- Study 301:
  - 2 subjects in the OL phase had syncope and were the only subjects identified as having a PP AE.
  - No SAEs or ADOs due to PP AEs were reported in the OL phase.
- Study 701:
  - Subject 100140 was the only subject with a PP AE. This subject was in the  $\leq 6$  month Pal treated subgroup. The AE was syncope and was reported as an SAE (did not require hospitalization) and resulted in an ADO. This subject is described as having no abnormal vital sign values or orthostatic hypotension. No other clinical abnormalities were described and no potential non-drug-related etiologies were mentioned (in-text) in Section 2.1.6.8.2. This subject was described in previous reviews of NDA 21999.
  - The SUR as described in Section 7.2.9.1 of this review describes an additional subject 100963. This subject is only briefly described in Section 7.2.9.1. A description of this subject was previously provided in this review and is based on information found in the narrative of this subject. In summary, this 24 year old generally healthy female was in an OL Phase III trial who had no known risk factors, conditions or medications to account for the events she experienced that culminated in her death. She initially became “very anxious, agitated and complained of breathlessness,” before having a seizure with vomiting followed by cardiorespiratory arrest. The differential included bronchospasm, arrhythmia, and pulmonary embolism, among other diagnoses and possible causes of death (she was not known to abuse substances and was only 24 years old and received trihexyphenidyl PRN). Most recently the investigator changed the SAE term to “pulmonary embolism.” This subject was described in more detail in past NDA21999 reviews.
- Integrated OL Trial Dataset:
  - Subjects 500108 and 200986: these subjects each had a seizure and were reported as SAEs and ADOs. They were previously described in the original review of NDA21999 and were also included in the SUR (see Section 7.2.9.1 of this review).
  - 3 subjects are specified as having syncope (preferred terms of circulatory collapse in 1 subject, syncope in 1 subject, syncope and loss of consciousness in 1 subject). This same number of subjects was also specified as having this AE in the SUR of which results are summarized in section 7.2.9.1. Information on these 3 subjects is limited (subject numbers could not be found). See Section 7.2.9.1 where 3 syncope subjects are mentioned by the sponsor in a corresponding section (of special search strategy AE results) of the 120-Day SUR of this NDA.

Subjects Identified with Potentially Symptomatic Vital Sign Values and other Related Events  
The sponsor identified subjects as having potentially symptomatic vital sign values and heart rate abnormalities, including bradycardia, tachycardia, hypotension, orthostatic hypotension, or

*syncope. The sponsor briefly refers to Appendices 3.8.1-2 regarding these subjects but a summary of the results and a description of potentially clinically remarkable subjects cannot be found. The results found in Appendices 3.8.1-2 were difficult to review and to interpret (given that manner in which the results were found).*

*The rationale for not reviewing the above results (Appendices 3.8.1-2) is described in more detail in the following paragraphs.*

*In the section on PP AEs (Section 2.1.6.8) and as previously mentioned, the sponsor refers to appendices 3.8.1-2 regarding new subjects found for the reporting period for the submission who had the following AEs: AEs "signifying potentially symptomatic vital sign values and heart rate abnormalities, including bradycardia, tachycardia, hypotension, orthostatic hypotension, or syncope. These subjects (in appendix 3.8.1-2) and results are not summarized in Section 2.1.6.8.2 (where the appendices are referenced). Individual potentially clinically remarkable subjects are also not described (in the in-text section 2.1.6.8.2) and narrative information on these subjects cannot be found (in the referenced appendices or in Section 2.1.6.8.2).*

*The above appendices 3.8.1-2 that are referenced for the information were over approximately 100 pages of multiple line listings of subjects numbers, AE terms, with additional and separate listings of subject numbers and vital sign results, as well as additional line listings (the listings had some subject numbers that were repeated within a given listing, as well as across listings). This information, as presented, was difficult to follow and it was difficult to cull out meaningful findings. An outline of the methodology that the sponsor used for identifying these subjects was also provided that was also difficult to follow or was not clear in some respects.*

*Similar information was previously provided under NDA 21999. This information was provided in response to a request that the sponsor identify and describe any potentially clinically remarkable subjects regarding development of potentially symptomatic vital sign abnormalities with respect to bradycardia, tachycardia, hypotension, orthostatic hypotension, or syncope (in reference to the original NDA 21999 submission). Their response included a summary of their results (that was difficult to interpret) along with multiple line listings in appendices in a manner that was similar to the appendices found under NDA22043 (similar to the information provided in appendices 3.8.1-2 that are referenced in Section 2.1.6.8.2 of NDA22043).*

*As above, the sponsor was previously asked under NDA21999 to identify any potentially clinically remarkable subjects regarding development of potentially symptomatic vital sign abnormalities with respect to bradycardia, tachycardia, hypotension, orthostatic hypotension, or syncope. The reason for this request was because the undersigned reviewer found several clinically remarkable subjects with events such as sinus pauses, events of apparent drug-related tachycardia that were associated with clinically remarkable AEs or other events in the NDA 21999 submission that were generally found in appendices or in a section of a clinical study report. However, an in-text description of these subjects was generally not found in key and relevant sections of Module 2.7.4 of NDA21999. While summary tables were generally provided that showed the incidence of SAEs and ADOs by Preferred Terms, descriptions of*

*individual subjects were often not described in in-text sections. Also the summary tables generally did not include tables with verbatim terms. Sections on SAEs, ADOs, or sections on outliers on clinical parameters generally did not include a description of clinically remarkable subjects. For example, subjects that had SAEs and ADOs that could be related to abnormal vital signs were generally not found described in in-text key sections of Module 2.7.4.*

*Due to difficulties with the nature of the information, as provided by the sponsor, this information was shown to Team Leader and Deputy Director Dr. Mitch Mathis and a review strategy regarding this information was discussed. The undersigned reviewer and Dr Mathis concurred on the following conclusions and on the following review strategy:*

- The information provided is difficult to interpret (Appendix 3.8.1-2), as presented and following consultation with the sponsor (Dr. Mathis and the undersigned reviewer asked the sponsor to explain their methods and the information as provided and they suggested that Line listings 4A and 4B be reviewed for each dataset).*
- Consequently, the focus of the current review is on SAEs and ADOs, the incidence of outliers on clinical parameters, statistical descriptive results and other information, as summarized in this review (and as described in previous sections that address review strategies that were employed).*

*As a final note, a description of several remarkable and some potentially remarkable subjects were previously provided, as found by the undersigned reviewer in past reviews of NDA21999 (in Section 7 of the original NDA 21999 review and of subsequent NDA2199 reviews). Section 7.1.3.3 of the original NDA21999 review describes a number of individual subjects with clinically remarkable or potentially remarkable events that included those that would fall under several different categories with respect to the potential organ system involved with the event or with respect to the nature of the event. As noted in these previous reviews the selection and descriptions of subjects with clinically remarkable or potentially remarkable events are not to be considered comprehensive (e.g. does not include all subjects with a given type of event). Instead subjects described were provided as some examples of clinically remarkable subjects that were found (e.g. upon review of narratives, primarily or that were found in the review of selected in-text sections of CSRs that were provided at that time).*

#### Ischemia-related AEs

*Ischemia-related AE results failed to reveal any new, clinically remarkable findings that differ from observations in various Phase III safety datasets (as previously described in the past clinical reviews of NDA21999).*

#### Gastrointestinal Obstruction-related AEs

*Gastrointestinal obstruction-related AEs: the sponsor did not describe any individual subjects having this type of AE, but mentions "isolated" AEs of "duodenal perforation and peptic ulcer." Subject numbers and descriptions of these isolated cases were not found in the section of Module 2.7.4 that covers on this topic (in-text Section 2.1.6.10) However, cases (2 subjects) with these*

events (duodenal perforation and peptic ulcer) that were reported as SAEs and/or ADOs were found by the undersigned reviewer (in appendices of line listings or narratives) and were described in Section 7.1.3.3. of the original review of NDA 21999.

#### Somnolence AEs

Somnolence AEs: these results did not reveal any new and clinically remarkable results that differ from previous results described in past reviews of NDA21999. Among all subjects in the safety datasets of the current NDA22043, only a few ADOs and/or SAEs were mentioned but these subjects were not described as having any new and clinically remarkable events associated with somnolence (in-text Section 2.1.6.11 of Module 2.7.4).

#### Suicidality

The results on the incidence of suicidality and of individually described subjects included in the discussion of the results did not reveal any new, remarkable or unexpected findings. The integrated OL extension trial dataset showed an incidence of suicidality of 1-2% for a given treatment group, except for the under 6 month Placebo/Pal and  $\leq 6$  month Olanzapine/Pal subgroups (4 and 5%, respectively). A total of 3 completed suicides were reported among the 1171 OL Pal subjects.

#### Glucose-related AEs

Glucose-related AE results generally do not reveal any new, unexpected findings but the following observations are notable:

- Greater incidence in over 6 month Pal treated subgroups and subgroups treated for 6 months or less (2% and 1% respectively for the DB Placebo/OL Pal subgroups, and 1% and 0%, respectively for the other treatment subgroups).
- The sponsor briefly described a few subjects in Section 2.1.6.6 but did not describe any new and clinically remarkable findings associated with elevations in glucose (e.g. no cases of diabetic ketoacidosis or clinical signs suggestive of this condition were found). One of these subjects had the AE reported as an SAE (subject 501160 who was receiving an anti-diabetic medication that was started prior to the study) and no ADOs were found in this section.

#### Neuroleptic Malignant Syndrome (NMS)

No new cases of NMS were reported (only subject 100057, previously identified and included in the clinical review of NDA21999).

#### Prolactin-related AEs

Prolactin related AEs are covered elsewhere in this review, as previously specified.

#### EPS-related AEs.

The following are selected summary tables on these AEs for the integrated OL safety dataset that were provided by the sponsor.

**Table 52: Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events  
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)**

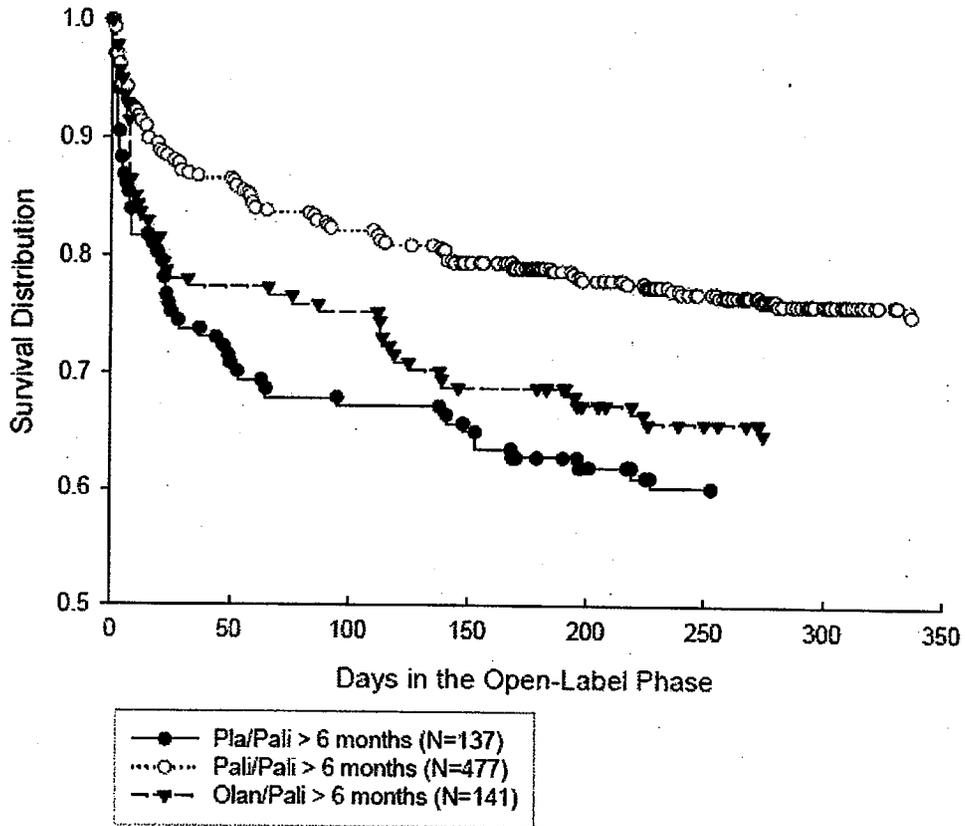
Eps Group Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali
	≤6 months (N=99) n (%)	>6 months (N=137) n (%)	≤6 months (N=209) n (%)	>6 months (N=477) n (%)	≤6 months (N=108) n (%)	>6 months (N=141) n (%)
<b>Total no. subjects with EPS related AE</b>	14 (14)	54 (39)	35 (17)	113 (24)	14 (13)	49 (35)
<b>DYSKINESIA</b>	8 (8)	20 (15)	10 (5)	39 (8)	5 (5)	11 (8)
Chorea	0	0	0	1 (<1)	0	0
Dyskinesia	1 (1)	3 (2)	1 (<1)	8 (2)	0	3 (2)
Extrapyramidal disorder	7 (7)	17 (12)	9 (4)	29 (6)	4 (4)	8 (6)
Muscle twitching	0	0	0	2 (<1)	1 (1)	0
Myoclonus	0	0	0	1 (<1)	0	0
Tardive dyskinesia	0	0	0	1 (<1)	0	0
<b>DYSTONIA</b>	3 (3)	9 (7)	1 (<1)	11 (2)	1 (1)	4 (3)
Dystonia	3 (3)	8 (6)	1 (<1)	6 (1)	1 (1)	4 (3)
Muscle spasms	0	1 (1)	0	2 (<1)	0	0
Oculogyration	0	0	0	3 (1)	0	0
Trismus	0	1 (1)	0	0	0	0
<b>HYPERKINESIA</b>	4 (4)	23 (17)	18 (9)	49 (10)	6 (6)	21 (15)
Akathisia	4 (4)	23 (17)	18 (9)	48 (10)	6 (6)	21 (15)
Restless legs syndrome	0	0	0	1 (<1)	0	0
<b>PARKINSONISM</b>	1 (1)	12 (9)	6 (3)	32 (7)	2 (2)	20 (14)
Akinesia	0	0	0	1 (<1)	0	0
Bradykinesia	0	1 (1)	0	1 (<1)	0	1 (1)
Drooling	0	0	2 (1)	7 (1)	0	1 (1)
Glabellar reflex abnormal	0	0	0	2 (<1)	0	0
Hypertonia	1 (1)	7 (5)	3 (1)	17 (4)	2 (2)	13 (9)
Hypokinesia	0	0	1 (<1)	0	0	1 (1)
Muscle rigidity	0	0	1 (<1)	0	0	2 (1)
Musculoskeletal stiffness	0	2 (1)	0	1 (<1)	0	2 (1)
Parkinsonism	0	4 (3)	0	5 (1)	0	4 (3)
<b>TREMOR</b>	2 (2)	9 (7)	6 (3)	18 (4)	2 (2)	10 (7)
Tremor	2 (2)	9 (7)	6 (3)	18 (4)	2 (2)	10 (7)

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

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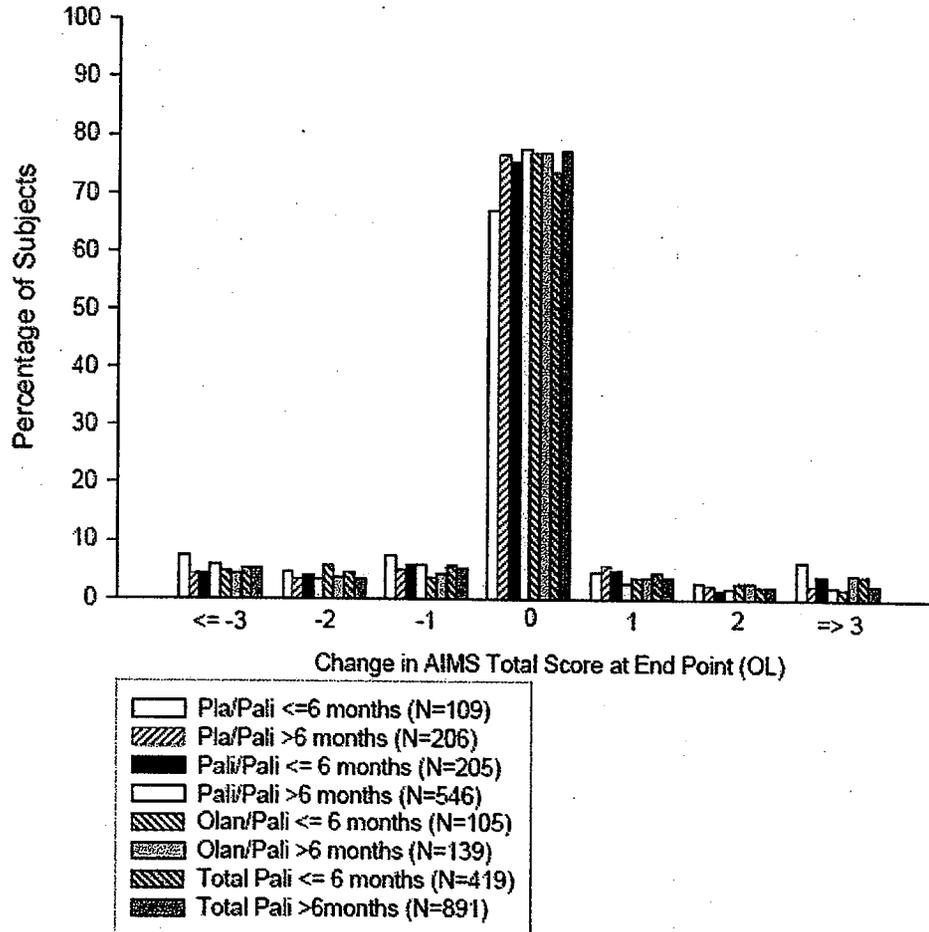
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Figure 3: Time to First Onset of EPS-Related Adverse Events During Open-Label Treatment  
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)



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**Figure 5: Abnormal Involuntary Movement Scale (AIMS): Change From Baseline to End Point**  
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)



**Reviewer Comments on Results of EPS-related AEs:**

Approved Pal labeling to date, includes TD (under Warnings), dyskinesia (mentioned under the TD section in warnings and included under the Adverse Reactions section) and provides an overview of EPS AEs (under Adverse reactions). The following observations regarding the sponsor's special search results are noted by the undersigned reviewer:

- Each major category of EPS-related AEs were commonly reported (generally  $\ge 5\%$  incidence for most subgroups) among treatment subgroups in the OL integrated safety database (including dyskinesias and dystonia, among others).
- It is surprising that most EPS related AEs showed a greater incidence in the over 6-month treated subgroups including the DB pal/OL Pal subgroups in which this particular subgroup would have been continued on Pal treatment when entering into the OL extension trial. Dystonia (the main category) is among the AEs showing this pattern. Dystonia (the main category) showed an incidence of only 1 subject (<math>< 1\%</math>) of

*the  $\leq 6$  month Pal/Pal group compared to 11 subjects (2%) in the  $> 6$  month Pal/Pal group. The timing of these events among these subjects is not clear and a description of the timing of these events could not be found in this in-text section. Oculogyration was also noted by the sponsor in which this event was reported in 3 subjects. All 3 were in the over 6 month Pal treated subgroup. The sponsor only noted the dose but not the timing of these events relative to treatment (the dose in these subjects was 15 mg for 2 of the subjects and 9 mg for the third subject). A few additional cases of oculogyration were observed in the other safety datasets (other trials). See previous discussions of the limitations with interpreting the sponsor's results, as they presented them and additional limitations discussed below.*

*While the timing of the above events relative to treatment is unclear, the following case of dystonia is notable since the sponsor included some information about when the event occurred relative to treatment. 1 subject was reported to have dystonia in the DB phase of Study 301 after completing the 14 week of OL pal phase in this maintenance treatment study. The daily dose level given to subjects entering the DB phase was to be the same daily dose level given over the last several weeks of the OL stabilization phase. Consequently, the appearance of dystonia during the DB phase of this study, as in the above mentioned subject would not be expected since the subject was receiving chronic treatment in which the daily dose level was to be held constant.*

#### Limitations and Potential Limitations with the Above Results

*A major caveat to the above results is that a number of limitations exist with the sponsor's results and in the manner in which the results are presented. For example, a presentation of results when considering such factors as a change in dose or dose-level, among other confounding variables could not be found in this in-text section of the submission.*

*One key limitation is that comparisons between the over 6 month treated group to the  $\leq 6$  month treated group may not be reflecting a real effect but rather an effect of observing subjects over a longer period of time. A discussion of potential Pal effects over time (based on an examination of appropriate dependent variables over time, without subdividing subjects into the  $> 6$  month and  $\leq 6$  month groups) cannot be found in this in-text section of Module 2.7.4 that covers this topic.*

*Additional limitations were previously discussed in this review and/or in the review of the original NDA 21999 submission (with results provided for the OL safety datasets and the sponsor's special search results that used the same methods employed for the special search results described in NDA 22043, and as discussed in the current section 7.1.4 of this review).*

*The subsection below describes results on TD and dyskinesias in more detail.*

#### Results of TD and Dyskinesia Reported as a Dictionary-derived Term

*The following observations are noted since TD is generally known to be an irreversible condition that can lead to debilitating and sometimes clinically significant complications (although, TD can wax and wane due to changes in antipsychotic dose and potentially from other factors). Furthermore, the true incidence of TD in the OL trials is not clear, due to limitations with the*

results and the nature of OL trials. It is also not clear to the undersigned reviewer how dyskinesias were distinguished from TD in the clinical trials (e.g. why cases of dyskinesias were not reported as TD). The following bulleted items outline some additional notable findings relevant to dyskinesias and TD reported AEs (dictionary-derived) by each safety dataset.

- In study 301:
  - The incidence of “dyskinesia” was similar in the placebo and Pal groups in the DB phase was 2% (2/102 subjects) and 1% (1/104 subjects).
  - SAE (100717) of dyskinesia, akathisia and tremor was reported that led to an ADO due to akathisia that were judged to be probably drug-related.
  - 3 Pal group subjects had “persisting” dyskinesia involving “orofacial movements” “at the end” of the DB phase “including 1 subject with a history of TD.”

It appears that perhaps these 3 subjects were not included in the summary Tables 48 and 49 for the OL and DB phases since the total number of Pal subjects with “dyskinesia” in each summary table was less than 3 subjects. If the dyskinesia was persisting since baseline and had not worsened (qualitatively or quantitatively) then they would have not been reported as an AE during treatment and would have not been included in the summary tables. However, it is not clear if the term “persisting” regarding these 3 subjects is relative to baseline or relative to the OL phase (it is not clearly specified).

Study 701:

- Subjects 100757 and 100098 were ADOs due to dyskinesia (and tremor in the former subject).
- Given the small sample sizes in most  $\leq 6$  month and  $> 6$  month treatment subgroups, it is difficult to interpret results of any comparisons between these subgroups on the incidence of dyskinesia.
- The incidence dyskinesia in subgroups was previously summarized and was unrevealing for a new, clinically remarkable finding.

Integrated OL Trial Dataset:

- One subject was reported to have TD. This was subject 300520 who was a 29 year old female who had “mild” on Day 157 in the Pal/Pal group in the integrated OL dataset. The TD did not resolve at completion of the 1 year OL extension trial. The subject is not described as having a past history of TD and more commonly TD occurs in older subjects and occurs in subjects who have received a number of years of typical neuroleptic agents. TD can fluctuate over time with changes in dose-level and when switching from one treatment to another. This particular case of TD appears to likely be Pal-related. The undersigned reviewer is only aware of one other subject reported to have TD in short-term 6-week DB Phase III schizophrenia trials (described in the original review of IND 21999).
- The incidence of dyskinesia was 2% in  $> 6$  month Pal treated subgroups compared to 0-1% in the  $\leq 6$  month Pal treated subgroups. It is difficult to interpret results by comparing subgroups in contrast to results among all Pal subjects over time. In any case the incidence remains low and comparable to the incidence in short-term trials.

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### 7.1.6 Common Adverse Events

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

AEs described in this section are spontaneously reported (unless otherwise specified, below).

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

Categorization and preferred terminology is generally 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).*

#### 7.1.6.3 Incidence of common adverse events

In accordance with the clinical review MAPP summary tables of the incidence of common AEs are provided in the next subsection (the sponsor provided in-text tables for AE with an incidence of at least 5%). Therefore this section provides some reviewer comments about the results shown later in Section 7.1.6.9, unless otherwise specified.

### Study -301 Adverse Events

#### The Double-blind Phase of Study 301

A complete listing of adverse events for Study-301 was found in the CSR but provided the results using the WHO coding system. The following are Preferred Term AE's (unless otherwise specified) with an incidence of at least 2% in the paliperidone group (N= 104) that was also at least twice the incidence observed in the placebo group (N = 102):

- Anxiety (4%, 2% in paliperidone and placebo groups, respectively)
- Somnolence (2%, 0%)
- Akathisia (Included Term; 3%, 0%)
- Headache (2%, 0%)
- Toothache (3%, 0%)
- Back Pain (3%, 0%)
- Postural Hypotension (2%, 0%)

- Tachycardia (3%, 0%)
- Amenorrhea (2%, 0%)
- Respiratory System Disorders (4%, 2%)
- Musculoskeletal System Disorders (2%, 1%)

#### **Reviewer Comments**

*The above results are generally similar to that found in the short-term, double blind, six-week, Phase III trials of patients with schizophrenia (as described are shown in the review of NDA 21999) with the exception of a greater incidence of toothache and anxiety in the paliperidone treated subjects compared placebo subjects. It is not clear if the results on anxiety and toothache during longer term treatment are reproducible. Therefore the results are considered preliminary while noting the following. Anxiety was a common AE in the short-term Phase III schizophrenia trials that generally did not show a greater incidence in paliperidone treated subjects comparative placebo subjects. Anxiety is common in this population. Yet, anxiety could be reflecting in some patients the development of another side effect of paliperidone, since anxiety is typically reported in patients who experience other known adverse effects of drugs in the drug-class (e.g. akathisia or extrapyramidal side effects). A greater incidence of toothache may not be a real effect and is an AE that would generally be expected of this patient population (e.g. due to poor hygiene that is common in these patients).*

#### **Run-in and Stabilization Phases of Study -301**

**Results and Reviewer Comments.** *Common AE's during these open-label paliperidone treatment phases of Study-301 (AE's with an incidence of at least 5%) did not reveal any new clinically remarkable findings that differ from safety results previously described in the original and addendum review of NDA 21999. However, the following AE's are worth noting:*

- *Hypersalivation occurred in 8% of subjects (all subjects in these phases received open-label paliperidone)*
- *A total of eight subjects had fever reported as an AE (2%)*
- *Two subjects had syncope reported as an AE. This AE was not common. Refer to Sections 7.1.3.3 and 7.4 for AEs of syncope.*

*These AE's are noted for the following reasons. It is not clear why there is an incidence of 8% of hypersalivation which could be reflecting extrapyramidal side effects or could be reflecting a drug-related adverse effect, such as direct or indirect effect on the parasympathetic nervous system. Under NDA21999 salivary hypersecretion was reported as an AE in the 6-week, Phase III efficacy trials as follows: 4% of paliperidone subjects in the 15 mg daily treatment group compared to only 0-1% of paliperidone groups at lower dose-levels (daily dose levels of 3 mg, 6 mg, 9 mg and 12 mg) and compared to the placebo group (refer to the review of NDA 21999).*

*The above subjects with AE's of syncope or fever are noted since these AE's could be representing a more serious type of adverse effect. With regards to fever, neuroleptic malignant syndrome (NMS) is a potential concern. However, this event was not reported (e.g. as an SAE or as an adverse dropout in this trial) and other potentially clinically remarkable events involving*

*fever would be expected to be captured as a reported SAE or adverse dropout (perhaps using another AE term such as pneumonia for a subject that also had fever, as an example).*

#### **Results from OL Extension Trials**

*Reviewer Comments. The results as shown in the next subsection do not reveal any new and clinically remarkable findings that were not previously described in the review and addendum review of NDA 21999. See the next subsection for reviewer comments on the elderly Study 702 on the basis of results provided in the summary table, as shown in the next subsection. Additional reviewer comments are also provided later with the results from the integrated OL extension trial safety dataset, as well.*

#### **Results of Study 701:**

See the above reviewer comments and see the next subsection for a summary table of the results.

#### **Results of Study 702:**

See the next subsection for results and reviewer comments.

#### **Results from the Pooled OL Extension Trial Safety Dataset (-702, -703, -704 and -705)**

See the next subsection for results and for additional reviewer comments.

#### **7.1.6.4 Common adverse event tables**

This section shows results of common AEs in summary tables, as found in the submission as specified.

#### **Study -301.**

The following summary tables were found in the CSR for Study -301.

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**Table 43: Treatment-Emergent Adverse Events in  $\geq 5\%$  of Subjects in ER OROS PAL (RI/ST) Treatment Group by Preferred Term - Run-In and Stabilization Phases (Study R076477-SCH-301: All Treated Analysis Set)**

Body System Who Preferred Term	ER OROS PAL (RI/ST) (N=530) n (%)
<b>Total no. subjects With Adverse Events</b>	<b>385 (73)</b>
<b>Centr &amp; periph nervous system disorders</b>	<b>222 (42)</b>
Tremor	86 (16)
Headache	73 (14)
Hyperkinesia	61 (12)
Extrapyramidal disorder	49 (9)
Hypertonia	39 (7)
<b>Gastro-intestinal system disorders</b>	<b>159 (30)</b>
Saliva increased	43 (8)
Constipation	25 (5)
<b>Psychiatric disorders</b>	<b>142 (27)</b>
Insomnia	51 (10)
Anxiety	37 (7)
Somnolence	33 (6)
Psychosis	30 (6)
Agitation	28 (5)
<b>Heart rate and rhythm disorders</b>	<b>49 (9)</b>
Tachycardia	35 (7)

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Table 44: Treatment-Emergent Adverse Events in  $\geq 2\%$  of Subjects in Any Treatment Group by Preferred Term - Double-Blind Phase  
 (Study R076477-SCH-301: Safety Analysis Set)

Body System Who Preferred Term	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)
Total no. subjects With Adverse Events	41 (40)	36 (35)
<b>Psychiatric disorders</b>	31 (30)	15 (14)
Psychosis	23 (23)	7 (7)
Insomnia	6 (6)	5 (5)
Anxiety	2 (2)	4 (4)
Somnolence	0	2 (2)
Aggressive reaction	6 (6)	1 (1)
Agitation	3 (3)	1 (1)
Anorexia	2 (2)	1 (1)
Suicide attempt	4 (4)	1 (1)
<b>Centr &amp; periph nervous system disorders</b>	4 (4)	10 (10)
Hyperkinesia	0	3 (3)
Headache	0	2 (2)
Dizziness	2 (2)	1 (1)
Dyskinesia	2 (2)	1 (1)
<b>Gastro-intestinal system disorders</b>	6 (6)	6 (6)
Tooth ache	0	3 (3)
Dyspepsia	2 (2)	1 (1)
Nausea	2 (2)	1 (1)
<b>Body as a whole - general disorders</b>	5 (5)	5 (5)
Back pain	0	3 (3)
Injury	2 (2)	0
<b>Cardiovascular disorders, general</b>	1 (1)	4 (4)
Hypotension postural	1 (1)	2 (2)
<b>Heart rate and rhythm disorders</b>	3 (3)	4 (4)
Tachycardia	3 (3)	3 (3)
<b>Reproductive disorders, female</b>	1 (1)	4 (4)
Amenorrhoea	0	2 (2)
<b>Metabolic and nutritional disorders</b>	3 (3)	2 (2)
Weight increase	2 (2)	2 (2)

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**Results of OL Extension Trials  
 Study 701.**

Results of Study 701 are shown below.

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 Supplemental NDA 22-043 N000-N002  
 Paliperidone OROS oral

Table 29: Treatment-Emergent Adverse Events in 5% or More of Subjects in Any Treatment Group by MedDRA Preferred Term  
 (Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Pali(NO
	<=6 months (N=11) n (%)	>6 months (N=69) n (%)	<=6 months (N=2) n (%)	>6 months (N=70) n (%)	DB)/Pali <=6 months (N=23) n (%)
Total no. subjects with adverse events	5 (45)	43 (61)	2 (100)	37 (53)	15 (65)
<b>Nervous system disorders</b>					
Tremor	3 (27)	21 (30)	1 (50)	18 (26)	6 (26)
Akathisia	1 (9)	4 (6)	0	7 (10)	2 (9)
Headache	0	7 (10)	0	4 (6)	1 (4)
Cogwheel rigidity	0	5 (7)	1 (50)	3 (4)	1 (4)
Dizziness	0	1 (1)	0	4 (6)	1 (4)
Drooling	0	5 (7)	0	1 (1)	3 (13)
Parkinsonian gait	0	1 (1)	0	2 (3)	2 (9)
Dyskinesia	0	1 (1)	0	3 (4)	2 (9)
Somnolence	2 (18)	2 (3)	0	2 (3)	0
Syncope	0	2 (3)	0	0	0
	1 (9)	0	0	0	0
<b>Psychiatric disorders</b>					
Insomnia	3 (27)	11 (16)	1 (50)	13 (19)	6 (26)
Schizophrenia	0	4 (6)	0	1 (1)	1 (4)
Anxiety	1 (9)	5 (7)	0	5 (7)	1 (4)
Agitation	1 (9)	4 (6)	1 (50)	4 (6)	1 (4)
Psychotic disorder	1 (9)	1 (1)	0	0	0
Aggression	0	2 (3)	0	0	2 (9)
Suicide attempt	1 (9)	1 (1)	0	0	0
	1 (9)	0	0	0	0
<b>Gastrointestinal disorders</b>					
Salivary hypersecretion	1 (9)	7 (10)	0	7 (10)	4 (17)
Vomiting	0	1 (1)	0	2 (3)	1 (4)
	1 (9)	1 (1)	0	3 (4)	1 (4)

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

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Table 29: Treatment-Emergent Adverse Events in 5% or More of Subjects in Any Treatment Group by MedDRA Preferred Term (Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pali(NO DB)/Pali >6 months (N=60) n (%)	Total Pali <=6 months (N=36) n (%)	Total Pali >6 months (N=199) n (%)
	<b>Total no. subjects with adverse events</b>	42 (70)	22 (61)
<b>Nervous system disorders</b>	28 (47)	10 (28)	67 (34)
Tremor	11 (18)	3 (8)	22 (11)
Akathisia	10 (17)	1 (3)	21 (11)
Headache	7 (12)	2 (6)	15 (8)
Cogwheel rigidity	6 (10)	1 (3)	11 (6)
Dizziness	4 (7)	3 (8)	10 (5)
Drooling	4 (7)	2 (6)	7 (4)
Parkinsonian gait	3 (5)	2 (6)	7 (4)
Dyskinesia	1 (2)	2 (6)	5 (3)
Somnolence	3 (5)	0	5 (3)
Syncope	0	1 (3)	0
<b>Psychiatric disorders</b>	12 (20)	10 (28)	36 (18)
Insomnia	7 (12)	1 (3)	12 (6)
Schizophrenia	2 (3)	2 (6)	12 (6)
Anxiety	3 (5)	3 (8)	11 (6)
Agitation	2 (3)	1 (3)	3 (2)
Psychotic disorder	0	2 (6)	2 (1)
Aggression	0	1 (3)	1 (1)
Suicide attempt	0	1 (3)	0
<b>Gastrointestinal disorders</b>	9 (15)	5 (14)	23 (12)
Salivary hypersecretion	4 (7)	1 (3)	7 (4)
Vomiting	1 (2)	2 (6)	5 (3)

See footnotes on the first page of the table.

Table 29: Treatment-Emergent Adverse Events in 5% or More of Subjects in Any Treatment Group by MedDRA Preferred Term (Continued) (Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=11) n (%)	Pla/Pali >6 months (N=69) n (%)	Pali/Pali <=6 months (N=2) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali(NO DB)/Pali <=6 months (N=23) n (%)
	<b>General disorders and administration site conditions</b>	0	6 (9)	0	5 (7)
Fyrexia	0	3 (4)	0	2 (3)	0
<b>Infections and infestations</b>	0	9 (13)	0	4 (6)	0
Nasopharyngitis	0	1 (1)	0	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>	0	6 (9)	0	2 (3)	0
Cough	0	5 (7)	0	0	0
<b>Reproductive system and breast disorders</b>	0	3 (4)	0	4 (6)	2 (9)
Amenorrhoea	0	3 (4)	0	4 (6)	1 (4)
<b>Skin and subcutaneous tissue disorders</b>	0	2 (3)	1 (50)	1 (1)	0
Swelling face	0	0	1 (50)	0	0

See footnotes on the first page of the table.

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 Supplemental NDA 22-043 N000-N002  
 Paliperidone OROS oral

Table 29: Treatment-Emergent Adverse Events in 5% or More of Subjects in Any Treatment Group by MedDRA Preferred Term (Continued)  
 (Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pali(NO DB) Pali >=6 months (N=60) n (%)	Total Pali <=6 months (N=36) n (%)	Total Pali >6 months (N=199) n (%)
General disorders and administration site conditions	7 (12)	1 (3)	18 (9)
Pyrexia	5 (8)	0	10 (5)
Infections and infestations	4 (7)	0	17 (9)
Nasopharyngitis	3 (5)	0	4 (2)
Respiratory, thoracic and mediastinal disorders	3 (5)	0	11 (6)
Cough	0	0	5 (3)
Reproductive system and breast disorders	1 (2)	2 (6)	8 (4)
Amenorrhoea	1 (2)	1 (3)	8 (4)
Skin and subcutaneous tissue disorders	1 (2)	1 (3)	4 (2)
Swelling face	0	1 (3)	0

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Study 702.

The following common AE summary table was found in the CSR of Study -702.

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Table 20: Treatment-Emergent Adverse Events in at Least 5% of Subjects in Any Treatment Group by MedDRA Preferred Term During the Open-Label Phase (Study R076477-SCH-702: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali (N=30) N (%)	Pali/Pali (N=58) N (%)	Total (N=88) n (%)
Total no. of subjects with adverse events	24 ( 80)	43 ( 74)	67 ( 76)
Cardiac disorders	8 ( 27)	11 ( 19)	19 ( 22)
Sinus tachycardia	4 ( 13)	6 ( 10)	10 ( 11)
General disorders and administration site conditions	5 ( 17)	10 ( 17)	15 ( 17)
Asthenia	4 ( 13)	8 ( 14)	12 ( 14)
Fatigue	0	3 ( 5)	3 ( 3)
Infections and infestations	5 ( 17)	7 ( 12)	12 ( 14)
Nasopharyngitis	2 ( 7)	3 ( 5)	5 ( 6)
Pneumonia	2 ( 7)	0	2 ( 2)
Investigations	5 ( 17)	12 ( 21)	17 ( 19)
Electrocardiogram QTc interval prolonged	3 ( 10)	2 ( 3)	5 ( 6)
Nervous system disorders	8 ( 27)	14 ( 24)	22 ( 25)
Dizziness	1 ( 3)	6 ( 10)	7 ( 8)
Extrapyramidal disorder	2 ( 7)	3 ( 5)	5 ( 6)
Headache	3 ( 10)	5 ( 9)	8 ( 9)
Somnolence	2 ( 7)	0	2 ( 2)
Psychiatric disorders	3 ( 10)	14 ( 24)	17 ( 19)
Anxiety	0	3 ( 5)	3 ( 3)
Insomnia	1 ( 3)	9 ( 16)	10 ( 11)

Cross-reference: Attachment 6.1.1.2.

**Reviewer Comments.** The AE profile for the elderly OL trial, as shown above, reveals some common AEs that were not common among subjects in the pooled OL trial dataset (compare the above table to the table of the pooled OL trial dataset shown below). For example pneumonia and asthenia are among common AEs in Study -702 that were not commonly reported in the combined OL trial dataset which consisted of mostly non-elderly subjects but also included subjects of the elderly Study -702. Although, the elderly study revealed some common AEs not observed in the combined dataset, some of these AEs may be reflecting events associated with the population (e.g. with elderly patients). However, in the absence of a placebo group a potential direct or indirect role of Pal cannot be ruled out. It is notable that respiratory system-related AEs showed a greater incidence in Pal compared to placebo subjects in the integrated short-term controlled phase III (6-week) trial dataset of primarily non-elderly Phase III patients as shown in the following (note that an incidence of approximately 3% for each AE occurred within at least the high-dose 15 mg/day Pal group compared to 0-1% of placebo subjects):

- Upper respiratory tract infection
- Cough

- *Nasal congestion.*

*Results from the integrated dataset of the short-term, placebo-controlled Phase III trials were previously reviewed and summarized in the original and addendum reviews of NDA 21999.*

*Another important consideration regarding the results of Study 702, are differences between treatment groups on some AEs as shown in the above table such as QTc prolongation. This AE was reported with a greater incidence in the group that was switched from DB placebo (in the 6-week, lead-in Phase III trial -302) to OL Pal (in the OL extension study -702) compared to the group that was continued on Pal (subjects who received DB Pal in the lead-in study). As noted by the sponsor the sample size of the former group was small (N=30) such that results are difficult to interpret. Yet QT prolongation effects were revealed in study of Pal in the schizophrenia patient population as described in the review of the original NDA 21999. Furthermore, the above QTc prolongation AE results appear to be potentially reproducible (e.g. in showing a potential drug-related signal for this AE) since the lead-in placebo controlled study showed a greater incidence of QTc prolongation of 7% in the Pal group compared to 3% (1/30 subjects) in the placebo group. Sinus tachycardia was reported in 9% of Pal subjects and 0% of placebo subjects in the lead-in study and was also a common AE during OL Pal treatment in the extension trial -702. It is not clear if AEs of QTc were associated with alterations in heart rate. See the more objective QT and QTc results from ECG assessments summarized later in this review.*

Results from Pooled OL Trials

The following common AE summary table was found in Module 2.7.4 for the combined OL extension trial dataset.

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Table 31: Treatment-Emergent Adverse Events in 5% or More of Subjects in Any Treatment Group by MedDRA Preferred Term (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	<=6 months (N=99) n (%)	>6 months (N=137) n (%)	<=6 months (N=209) n (%)	>6 months (N=477) n (%)	<=6 months (N=108) n (%)	>6 months (N=141) n (%)	<=6 months (N=416) n (%)	>6 months (N=755) n (%)
Total no. subjects with adverse events	66 (67)	121 (88)	138 (66)	373 (78)	76 (70)	116 (82)	280 (67)	610 (81)
<b>Nervous system disorders</b>	26 (26)	75 (55)	60 (29)	186 (41)	24 (22)	74 (52)	110 (26)	345 (46)
Headache	6 (6)	16 (12)	17 (8)	70 (15)	8 (7)	22 (16)	31 (7)	108 (14)
Akathisia	4 (4)	23 (17)	18 (9)	48 (10)	6 (6)	21 (15)	28 (7)	92 (12)
Somnolence	3 (3)	12 (9)	8 (4)	37 (8)	1 (1)	26 (14)	12 (3)	69 (9)
Extrapyramidal disorder	7 (7)	17 (12)	9 (4)	29 (6)	4 (4)	8 (6)	20 (5)	54 (7)
Hypertonia	1 (1)	7 (5)	3 (1)	17 (4)	2 (2)	13 (9)	6 (1)	37 (5)
Tremor	2 (2)	9 (7)	6 (3)	18 (4)	2 (2)	10 (7)	10 (2)	37 (5)
Dizziness	4 (4)	7 (5)	9 (4)	24 (5)	6 (6)	5 (4)	18 (4)	36 (5)
Dystonia	3 (3)	8 (6)	1 (<1)	6 (1)	1 (1)	4 (3)	5 (1)	18 (2)
<b>Psychiatric disorders</b>	31 (31)	51 (37)	82 (39)	177 (37)	50 (46)	56 (40)	163 (39)	284 (38)
Insomnia	11 (11)	22 (16)	17 (13)	66 (14)	15 (14)	20 (14)	53 (13)	108 (14)
Anxiety	5 (6)	10 (7)	18 (9)	42 (9)	9 (8)	12 (9)	33 (8)	64 (8)
Depression	4 (4)	14 (10)	6 (3)	34 (7)	5 (5)	11 (8)	15 (4)	58 (8)
Psychotic disorder	9 (9)	4 (3)	23 (11)	34 (7)	19 (18)	8 (6)	50 (12)	46 (6)
Schizophrenia	3 (3)	7 (5)	21 (10)	26 (5)	14 (13)	6 (4)	38 (9)	39 (5)
Agitation	5 (5)	4 (3)	10 (5)	18 (4)	10 (9)	7 (5)	25 (6)	29 (4)
<b>Infections and infestations</b>	8 (8)	28 (20)	18 (9)	166 (22)	14 (13)	34 (24)	40 (10)	168 (22)
Nasopharyngitis	1 (1)	9 (7)	2 (1)	37 (8)	4 (4)	13 (9)	7 (2)	59 (8)

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

Table 31: Treatment-Emergent Adverse Events in 5% or More of Subjects in Any Treatment Group by MedDRA Preferred Term (Continued) (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	<=6 months (N=99) n (%)	>6 months (N=137) n (%)	<=6 months (N=209) n (%)	>6 months (N=477) n (%)	<=6 months (N=108) n (%)	>6 months (N=141) n (%)	<=6 months (N=416) n (%)	>6 months (N=755) n (%)
<b>Cardiac disorders</b>	16 (16)	32 (23)	21 (10)	78 (16)	12 (11)	31 (22)	49 (12)	141 (19)
Tachycardia	1 (1)	12 (9)	10 (5)	27 (6)	3 (3)	12 (9)	14 (3)	51 (7)
Sinus tachycardia	8 (8)	11 (8)	2 (1)	25 (5)	5 (5)	7 (5)	15 (4)	43 (6)
Bundle branch block	3 (3)	6 (4)	2 (1)	10 (2)	2 (2)	7 (5)	7 (2)	23 (3)
<b>Investigations</b>	21 (12)	24 (18)	18 (9)	84 (18)	12 (11)	28 (20)	41 (10)	136 (18)
Weight increased	2 (2)	8 (6)	7 (3)	23 (5)	2 (2)	7 (5)	11 (3)	38 (5)
<b>Gastrointestinal disorders</b>	13 (13)	19 (14)	26 (12)	77 (16)	15 (14)	26 (18)	54 (13)	122 (16)
Nausea	1 (1)	3 (2)	7 (3)	22 (5)	4 (4)	4 (3)	12 (3)	29 (4)
<b>Vascular disorders</b>	1 (1)	9 (7)	9 (4)	25 (5)	6 (6)	9 (6)	16 (4)	43 (6)
Orthostatic hypotension	1 (1)	8 (6)	4 (2)	14 (3)	2 (2)	7 (5)	7 (2)	29 (4)

See footnotes on the first page of the table.  
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 Cross-reference: Appendix 3.3.1.

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**Reviewer Comments.** The above AE results are similar to those described in the past original and addendum reviews of NDA 21999 (the results shown for this combined-OL Trial Safety dataset in past reviews were since updated using a more recent cut-off date, as shown in the above table).

CPK elevations would generally not be expected in patients during the OL extension trial since theoretically they should no longer be acutely psychotic or agitated. Perhaps the CPK elevations observed in the OL extension trial dataset is reflecting another underlying etiology.

*Note that akathisia, hypertonia, dystonia, tremor, and extrapyramidal disorder are among common AEs that may theoretically contribute to CPK elevations observed in subjects of OL trials. See laboratory results later in this review regarding CPK results. Additional comments about CPK elevations and potential underlying etiologies were previously discussed in the original clinical review of NDA 219999.*

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

See previous sections and sections below where this topic is covered.

#### 7.1.6.6 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.

#### 7.1.7 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. Some of these sections describe or show results on some less common AEs (e.g. less common AEs reported as SAEs or ADOs, AEs of special interest).

#### 7.1.8 Laboratory Findings

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

Table series 10.2 in the appendix of this review shows the outlier criteria employed for determining the incidence of outliers on each parameter for each safety dataset.

*See previously comments in this review about key limitations with results. The clinical review of the original NDA 21999 also discusses key limitations.*

*The following outlines additional key limitations to the safety dataset from the pivotal efficacy Study -301 (results found in in-text safety sections of the CSR):*

- *Summary tables of descriptive statistical results generally showed mean changes (which did not include median values or changes or the range of values and changes). Mean changes that were shown for the DB phase showed changes from the DB baseline to endpoint. Therefore these results do not reflect mean change from pre-dose (baseline of the study) to endpoint. Upon request, the sponsor provided results on mean changes from baseline using a pre-dose (pre-run-in phase) value to DB treatment endpoint in a 12/21/06 response submission. However, the results were only provided for the DB treatment endpoint and not over time. Consequently, the DB results provided in the 12/21/06 response*

*submission are limited since most subjects only completed about 6 weeks of DB treatment (high drop out rate and the study was aborted, according to the protocol).*

- *Only 19 subjects and 7 subjects in the Pal group had assessments conducted at weeks 24 and 36 of the DB phase. The majority of subjects generally only had assessments out to week 6 (and fewer at week 12 for assessments conducted at week 12) of the DB treatment phase.*
- *In conclusion, the study provides limited longterm double-blind, placebo-controlled, safety information.*

*Additional key limitations of a given dataset are also provided in corresponding sections below.*

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

See Section 4.3 of this review describing the review strategy. Section 4 of this review also has subsections describing various trials that provided safety data. Section 7.1 of this review summarizes methods and the safety datasets in this review.

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

Standard analyses and explorations of laboratory data are covered in sections below.

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

Sections below first provide reviewer comments that are then followed by the sponsor's summary tables showing their results.

#### **Results of Study -301**

*Reviewer Comments. The sponsor only shows results of selected parameters in the in-text summary table in the CSR (these tables are copied below). Therefore a review of attachments found in the CSR that had results by each time-point for all parameters was conducted and as described in subsections below.*

#### **Results of Run-in and Stabilization Phases of Study -301**

##### **Reviewer Comment**

*The sponsor shows results of selected parameters in their summary tables. The results generally failed to reveal any new findings that are not already described in the review of NDA 21999. The only clinically remarkable findings were of increases in mean CPK levels, similar to elevations or in some subgroups mean decreases in CPK levels, as previously observed and described in the review of the original review of NDA 21999.*

*Section 7.1.7.3.3 of this review discusses the sponsor's explanations for elevations in CPK.*

*See the next section on results of outliers. Section 7.1.7.3.3 includes the sponsor's comment that elevations in CPK were not associated with AEs.*

The following summary tables show results on selected parameters (copied from the in-text section on laboratory results found in the CSR).

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Table 56: Selected Clinical Laboratory Analytes: Change From Baseline (RI) to End Point (Stab.) - Run-In and Stabilization Phases  
 (Study R076477-SCH-301: All Treated Analysis Set)

	ER OROS PAL (RI/ST) (N=530)
<b>Chemistry</b>	
Sodium (mmol/L)	
N	278
Mean baseline (SD)	140.4 (2.75)
Mean change (SD)	0.4 (3.13)
Potassium (mmol/L)	
N	278
Mean baseline (SD)	4.3 (0.35)
Mean change (SD)	0.0 (0.45)
Chloride (mmol/L)	
N	278
Mean baseline (SD)	103.0 (2.77)
Mean change (SD)	0.6 (2.68)
Bicarbonate (mmol/L)	
N	277
Mean baseline (SD)	24.0 (2.79)
Mean change (SD)	-0.1 (2.86)
Glucose (mmol/L)	
N	273
Mean baseline (SD)	5.4 (0.94)
Mean change (SD)	0.1 (1.35)
C-peptide (nmol/l)	
N	251
Mean baseline (SD)	1.0 (0.99)
Mean change (SD)	-0.0 (0.90)
Insulin (uU/ml)	
N	259
Mean baseline (SD)	9.9 (10.95)
Mean change (SD)	0.4 (14.18)
AST (SGOT) (U/L)	
N	276
Mean baseline (SD)	23.3 (8.49)
Mean change (SD)	-1.9 (9.41)
ALT (SGPT) (U/L)	
N	277
Mean baseline (SD)	25.1 (13.93)
Mean change (SD)	-2.4 (12.54)
Urea nitrogen (mmol/L)	
N	276
Mean baseline (SD)	4.1 (1.32)
Mean change (SD)	-0.0 (1.38)

(Continued)

Table 56: Selected Clinical Laboratory Analytes: Change From Baseline (BL) to End Point (Stab.) - Run-In and Stabilization Phases (Continued)  
 (Study R076477-SCH-301: All Treated Analysis Set)

	ER OROS PAL (R3/ST) (N=530)
<b>Chemistry</b>	
Creatinine (µmol/L)	
N	278
Mean baseline (SD)	73.2 (14.35)
Mean change (SD)	0.8 (10.52)
LDL (mmol/L)	
N	272
Mean baseline (SD)	3.0 (1.07)
Mean change (SD)	-0.1 (0.76)
HDL (mmol/L)	
N	277
Mean baseline (SD)	1.1 (0.30)
Mean change (SD)	0.0 (0.23)
Cholesterol (mmol/L)	
N	278
Mean baseline (SD)	4.8 (1.33)
Mean change (SD)	-0.2 (0.86)
Triglycerides (mmol/L)	
N	278
Mean baseline (SD)	1.6 (1.15)
Mean change (SD)	-0.1 (0.92)
Creatine kinase (U/L)	
N	277
Mean baseline (SD)	137.5 (188.28)
Mean change (SD)	2.7 (249.16)
<b>Hematology</b>	
WBC (giga/L)	
N	273
Mean baseline (SD)	7.6 (2.25)
Mean change (SD)	-0.5 (2.01)
RBC (tera/L)	
N	273
Mean baseline (SD)	4.9 (0.61)
Mean change (SD)	0.0 (0.38)
Hemoglobin (g/L)	
N	273
Mean baseline (SD)	143.8 (16.34)
Mean change (SD)	-1.3 (9.56)
Hematocrit (%)	
N	272
Mean baseline (SD)	0.4 (0.05)
Mean change (SD)	-0.0 (0.03)

(Continued)

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Table 56: Selected Clinical Laboratory Analytes: Change From Baseline (R3) to End Point (Stab.) - Run-In and Stabilization Phases (Continued)  
 (Study R076477-SCH-301: All Treated Analysis Set)

ER OROS PAL (R3/ST) (N=510)	
<b>Hematology</b>	
<b>Platelets (plate)</b>	
N	271
Mean baseline (SD)	278.8 (73.60)
Mean change (SD)	-10.6 (56.16)
<b>Reticulocytes (%)</b>	
N	268
Mean baseline (SD)	1.7 (0.76)
Mean change (SD)	-0.2 (0.43)
<b>Neutrophils (%)</b>	
N	273
Mean baseline (SD)	60.7 (9.16)
Mean change (SD)	1.1 (10.09)
<b>Lymphocytes (%)</b>	
N	273
Mean baseline (SD)	29.9 (8.70)
Mean change (SD)	-1.2 (8.93)
<b>Monocytes (%)</b>	
N	273
Mean baseline (SD)	5.5 (2.05)
Mean change (SD)	-0.3 (2.19)
<b>Eosinophils (%)</b>	
N	273
Mean baseline (SD)	3.3 (3.59)
Mean change (SD)	0.3 (2.76)
<b>Basophils (%)</b>	
N	273
Mean baseline (SD)	0.6 (0.41)
Mean change (SD)	0.0 (0.52)

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### DB Phase of Study -301

#### Reviewer Comments.

Since the mean/median changes were only found for changes from the DB baseline to endpoint, the values do not reflect mean change from pre-dose (baseline of the study) to DB treatment endpoint. Results on mean changes using the pre-treatment baseline value of the run-in phase were provided upon request in a 12/21/06 submission. However, as previously discussed results were only provided from OL pre-dose baseline to DB treatment endpoint, rather than for each DB assessment time-point. Dropout occurred and the study was aborted (according to protocol) such that most subjects had only 6-12 weeks of DB treatment. Consequently, the treatment endpoint results are limited, as previously discussed.

*Results that were presented over time (found in Attachment 8.2 of Module 2.7.4) were reviewed for time-points of up to week 12 of DB treatment, since subsequent time-points had an insufficient number of subjects.*

*The above, reviewed results failed to show any new clinically remarkable findings that differ from results previous described in reviews of NDA 21999.*

The following are the sponsor's summary tables.

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Table 57: Selected Clinical Laboratory Analytes: Change From Baseline (DB) to End Point (DB) - Double-Blind Phase  
 (Study R076477-SCH-301: Safety Analysis Set)

	Placebo (N=102)	ER OROS PAL (N=104)
<b>Chemistry</b>		
<b>Sodium (mmol/L)</b>		
N	85	87
Mean baseline (SD)	140.8 (2.73)	140.7 (2.89)
Mean change (SD)	0.7 (3.24)	-0.4 (3.08)
<b>Potassium (mmol/L)</b>		
N	85	86
Mean baseline (SD)	4.3 (0.38)	4.4 (0.34)
Mean change (SD)	0.0 (0.41)	-0.0 (0.41)
<b>Chloride (mmol/L)</b>		
N	85	87
Mean baseline (SD)	104.0 (2.38)	103.7 (2.64)
Mean change (SD)	0.3 (2.84)	-0.1 (2.55)
<b>Bicarbonate (mmol/L)</b>		
N	82	87
Mean baseline (SD)	23.9 (2.13)	23.5 (2.50)
Mean change (SD)	0.2 (2.92)	-0.2 (2.43)
<b>Glucose (mmol/L)</b>		
N	81	85
Mean baseline (SD)	5.4 (0.75)	5.5 (1.08)
Mean change (SD)	-0.1 (0.91)	-0.1 (0.66)
<b>C-peptide (nmol/L)</b>		
N	78	82
Mean baseline (SD)	1.0 (0.58)	1.0 (0.54)
Mean change (SD)	-0.0 (0.64)	0.1 (0.48)
<b>Insulin (uu/mL)</b>		
N	79	81
Mean baseline (SD)	9.0 (7.83)	10.2 (8.20)
Mean change (SD)	-0.2 (10.76)	-0.1 (8.84)
<b>AST (SGOT) (U/L)</b>		
N	81	86
Mean baseline (SD)	21.1 (7.29)	23.0 (12.41)
Mean change (SD)	-0.4 (9.38)	-0.3 (9.66)
<b>ALT (SGPT) (U/L)</b>		
N	84	86
Mean baseline (SD)	22.3 (11.70)	24.8 (16.98)
Mean change (SD)	-0.8 (11.49)	-1.6 (15.59)
<b>Urea nitrogen (mmol/L)</b>		
N	84	86
Mean baseline (SD)	4.2 (1.54)	4.1 (1.48)
Mean change (SD)	-0.1 (1.35)	-0.1 (1.16)

(Continued)

Table 57: Selected Clinical Laboratory Analytes: Change From Baseline (DB) to End Point (DB) -  
 Double-Blind Phase (Continued)  
 (Study R076477-SCH-301: Safety Analysis Set)

	Placebo (N=102)	ER OROS PAL (N=104)
<b>Chemistry</b>		
<b>Creatinine (umol/L)</b>		
N	85	87
Mean baseline (SD)	73.0 (12.46)	72.8 (16.85)
Mean change (SD)	4.8 (10.06)	1.0 (9.27)
<b>LDL (mmol/L)</b>		
N	82	84
Mean baseline (SD)	3.0 (1.02)	3.0 (1.09)
Mean change (SD)	-0.1 (0.67)	-0.0 (0.64)
<b>HDL (mmol/L)</b>		
N	85	86
Mean baseline (SD)	1.1 (0.30)	1.2 (0.35)
Mean change (SD)	-0.0 (0.20)	0.0 (0.21)
<b>Cholesterol (mmol/L)</b>		
N	86	87
Mean baseline (SD)	4.8 (1.19)	5.0 (1.31)
Mean change (SD)	-0.2 (0.77)	-0.0 (0.72)
<b>Triglycerides (mmol/L)</b>		
N	86	87
Mean baseline (SD)	1.6 (0.87)	1.7 (1.24)
Mean change (SD)	-0.1 (0.74)	-0.0 (0.87)
<b>Creatine kinase (U/L)</b>		
N	84	87
Mean baseline (SD)	132.4 (106.95)	155.2 (291.10)
Mean change (SD)	3.8 (115.91)	15.6 (492.41)
<b>Hematology</b>		
<b>WBC (giga/l)</b>		
N	83	86
Mean baseline (SD)	7.1 (1.97)	7.1 (2.33)
Mean change (SD)	0.5 (2.02)	-0.1 (1.70)
<b>RBC (tera/l)</b>		
N	83	86
Mean baseline (SD)	4.9 (0.48)	4.9 (0.50)
Mean change (SD)	0.1 (0.32)	-0.0 (0.30)
<b>Hemoglobin (g/L)</b>		
N	83	86
Mean baseline (SD)	143.9 (13.13)	141.1 (14.48)
Mean change (SD)	1.6 (9.30)	-0.8 (9.28)
<b>Hematocrit (l)</b>		
N	82	85
Mean baseline (SD)	0.4 (0.04)	0.4 (0.05)
Mean change (SD)	0.0 (0.03)	0.0 (0.03)

(Continued)

Table 57: Selected Clinical Laboratory Analytes: Change From Baseline (DB) to End Point (DB) -  
 Double-Blind Phase (Continued)  
 (Study R076477-SCH-301: Safety Analysis Set)

	Placebo (N=102)	ER OROS PAL (N=104)
<b>Hematology</b>		
<b>Platelets (giga/l)</b>		
N	81	83
Mean baseline (SD)	267.3 (69.50)	264.4 (59.80)
Mean change (SD)	11.3 (52.84)	12.4 (57.09)
<b>Reticulocytes (%)</b>		
N	81	84
Mean baseline (SD)	1.5 (0.61)	1.5 (0.67)
Mean change (SD)	0.0 (0.46)	0.0 (0.51)
<b>Neutrophils (%)</b>		
N	83	86
Mean baseline (SD)	62.0 (10.08)	62.0 (9.67)
Mean change (SD)	1.6 (9.82)	0.2 (8.84)
<b>Lymphocytes (%)</b>		
N	83	86
Mean baseline (SD)	29.1 (9.60)	29.0 (8.38)
Mean change (SD)	-2.0 (8.66)	-0.2 (7.31)
<b>Monocytes (%)</b>		
N	83	86
Mean baseline (SD)	5.2 (1.79)	4.9 (1.72)
Mean change (SD)	0.4 (2.13)	0.2 (1.93)
<b>Eosinophils (%)</b>		
N	83	86
Mean baseline (SD)	3.2 (4.07)	3.4 (4.73)
Mean change (SD)	-0.1 (2.00)	-0.3 (1.90)
<b>Basophils (%)</b>		
N	83	86
Mean baseline (SD)	0.6 (0.42)	0.6 (0.41)
Mean change (SD)	0.0 (0.61)	0.0 (0.51)

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## Results of OL Extension Trials

### Results of Study -702

*Reviewer Comments on Results of Elderly OL Trial -702*  
 Laboratory descriptive statistical results found in in-text summary table (Table 28) of selected parameters found in the CSR failed to reveal any clinically remarkable, new findings that differ from observations previously described in past clinical reviews of NDA 21999.

Results from the Integrated OL Extension Trial Dataset

*Reviewer Comments on Results of the Combined OL Extension Trial Dataset (-702, -703, -704 and -705)*

Elevations in CPK

The following results are noted:

- Mean CPK was increased to a greater extent in the 256 subjects receiving 6 months or less of Pal (50.8 U/l) compared to the 733 subjects receiving over 6 months of Pal (18.0U/l). However, note that the standard deviation in each of these 2 subgroups was large (over  $\pm 360$  U/l).
- Mean baseline values (at OL phase baseline) on CPK were generally similar across treatment subgroups in the OL extension trials (all subjects received OL Pal during the extension trials but safety results were presented for subjects categorized into subgroups on the basis of their assigned DB treatment in the lead-in 6-week Phase III trials which was either placebo, olanzapine or Pal).
- Theoretically subjects in an OL extension trial should be stabilized, such that it is not clear why CPK values would increase. It is notable that standard deviations are large within a given subgroup (up to  $\pm 1170$  U/l).
- Results on the incidence of outliers on CPK, described later in this review show that few subjects met outlier criteria in this longer term OL trial dataset, such that the results on group mean changes may in part be skewed by these few outliers.

See previous comments about CPK elevations. Additional comments and recommendations relevant to observations on CPK were provided in the original review of NDA21999.

Potentially New Safety Findings in the Update Integrated OL Trial Dataset

Other observations on mean change from baseline on selected clinical parameters shown in Table 70 of Module 2.7.4 of the submission were generally similar to those previously described in the review of NDA 21999. However, some potentially new findings are noted below that may suggest a potential signal with longterm treatment that was not previously described in reviews of NDA 21999. Yet the observed changes or trends were generally:

- of a magnitude that was clinically unremarkable and
- in some cases were not consistent across treatment groups or
- were not consistent with results on the incidence of outliers (described later in this review).

The results below are from the more recent updated results from the integrated OL trial dataset (as trials were ongoing under NDA21999 and still include a few ongoing trials but has more subjects with exposures of 6-12 months than were previously exposed in datasets previously reviewed under NDA 21999).

Elevations in LFTs

The following observations are based on a review of results (115 page Appendix 5.2.1 of Module 2.7.4) of mean changes of each clinical parameter at each time-point (during DB treatment in the 6-week lead-in phase and during OL extension trial treatment) in each treatment subgroup

*(subjects subdivided on the basis of prior DB treatment assignment; olanzapine, placebo or Pal and further subdivided by duration of Pal treatment; 6 months and under or 6-12 months Pal exposure):*

- *LFT parameters (ALT, AST, GGT, LDH and to a lesser extent direct bilirubin showed numerical trends for small and clinically unremarkable increases from pre-dose values (prior to DB treatment in the 6-week lead-in Phase III trials).*
- *These observations were not generally consistent with each time-point or across treatment groups.*
- *The DB olanzapine/OL Pal group appeared to show trends for the greatest numerical increases on some LFT parameters that did not appear to continue during OL Pal treatment (e.g. ALT).*
- *Yet, results on the incidence of LFT outliers described later fails to show consistent results for a potential LFT signal (the incidence for high values on a given parameter were generally 0-1% for each subgroup with some exceptions as described later and with respect to outliers on bilirubin levels).*
- *The incidence of outliers on high direct bilirubin levels reached 3-4% in a few subgroups but a consistent pattern across treatment groups could not be found (e.g. across subgroups of subjects categorized on the basis of previous DB treatment assignment and duration of Pal treatment in which the incidence in most subgroups was 0-1%).*
- *Section 7.1.7.3.3 of this review describes potentially remarkable subjects with elevations in LFTs.*
- *Observations relevant to elevations in LFTs were also discussed in the review and addendum review of NDA 21999.*
- *Finally it is important to keep in mind the inherent limitations of interpreting non-placebo data of ongoing trials with samples sizes that vary drastically one time-point to another among other limitations. Large standard deviations also exist on a given parameter suggesting a large noise: signal ratio.*

#### Comments on Results of Other Parameters

- Results on Insulin
  - *Numerical trends for clinically unremarkable increases in insulin levels are observed in the subgroups with more subjects exposed to longer term treatment (the DB pal/OL Pal over 6 month subgroup) and in the subgroups that received DB Olanzapine in the 6-week Phase III lead-in study.*
  - *Results on outliers of insulin cannot be found in the submission.*
  - *Treatment subgroup mean changes on glucose levels were generally under 0.50 mmol/l (although one needs to consider the variable timing of these levels relative to food intake).*

*The same caveats as discussed for the above LFT parameters also apply to results of insulin, as well as apply to most of the results of other clinical parameters described in this review for this dataset.*

- Results on Creatinine

*Numerical trends for clinically unremarkable increases in creatinine were observed in the over 6 month treatment subgroups.*

- *Results on Uric Acid*

*Numerical trends for clinically unremarkable increases in uric acid were observed in all treatment subgroups.*

- *Other Parameters*

*Other numerical trends for clinically unremarkable group mean changes were observed on other parameters, as previously described in the review of the original NDA 219999 (e.g. group mean decreases in hemoglobin, changes in platelet count, among others).*

*See results on outliers on clinical parameters in the next section, below.*

*Section 7.2.9 of this review summarizes updated results from the integrated OL safety dataset which includes trials that remain to be ongoing.*

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

#### **Results of Study -301**

*Reviewer Comments on the Results of -301. Results are generally similar to those previously described in the review of NDA 21999, except that the incidence for low reticulocyte count was high in the OL phase of Study 301. Yet results during OL treatment are generally difficult to interpret and generally yield higher reporting rates than in studies with a shorter duration and/or using a DB study design. It is also difficult to compare absolute values on a given parameter across independent trials.*

#### *The Incidence of Low Reticulocyte Count Outliers*

*The following outlines the results on low reticulocyte outliers:*

- *The incidence of low reticulocyte count outliers was:*
  - *Generally higher (11%) in the OL phases of Study-301 (run-in and stabilization phases)*
  - *Compared to subjects in the longer-term OL extension trials (combined) that generally received 6-12 months of treatment. The incidence in this integrated OL dataset was 3-6% per group except for 10% in one group (as described in the original review of NDA 21999).*
- *The DB phase of Study-301 showed an incidence for low reticulocyte count of only*
  - *3% in the paliperidone treated subjects compared to*
  - *6% in the placebo group.*

*It is important to note that one critical limitation regarding DB treatment results is that the sample size of subjects beyond the week 12 assessment time-point was generally small for each treatment group. Therefore, the results of the incidence of outliers in the DB phase primarily reflect the incidence over 12 weeks of DB treatment duration in the majority of subjects.*

*Results from the combined-OL trial dataset (as described in the previous review of NDA 21999) also showed a greater incidence of outliers on low reticulocyte count in the subgroup of the subjects exposed to over 6 months and up to 12 months of Pal compared to subjects exposed to less than 6 months of Pal treatment (using similar flexible dose treatment range as employed in Study 301).*

*In light of the above results on the incidence of outliers on reticulocyte count, the following results on hemoglobin previously described in the review of NDA 21999 are noted. The Phase III short-term DB trials and OL trial safety datasets described in the review of NDA 21999 showed small clinically unremarkable group mean decreases in HgB suggestive of a Pal related safety signal but the magnitude of the change was clinically unremarkable.*

*The subsection below shows results from the integrated OL extension trials that have been updated since the time of the original NDA21999 submission. These updated results did not reveal any clinically remarkable, new findings that differed from findings previously described in reviews of NDA21999 (either in this review or in the review and the addendum review of the original NDA 21999).*

#### **Results of Run-in and Stabilization Phases of Study -301**

The in-text section of the CSR indicates that the incidence of outliers on most parameters was 2% or less in the all-treated-analyses dataset.

The sponsor noted the incidence of outliers on the following parameters:

- High LDL levels: 5%
- Low LDL: 13%
- Low HDL: 10%
- High cholesterol: 2%
- High triglycerides: 2%
- High eosinophil count: 3%
- Low reticulocyte count: 11%.

#### **Results of the DB Phase of Study -301**

Most clinical parameters showed an incidence of 0% in any given group with some exceptions of which the following results are noted by the sponsor (based on results from Table 68 that was found in the CSR):

- Low LDL (placebo, 13%; ER OROS paliperidone, 12%),
- High LDL (1%, 8%, respectively)
- High cholesterol (placebo, 1%; ER OROS paliperidone, 0%),
- High triglycerides (placebo, 0%; ER OROS paliperidone, 2%).
- Low HDL (16%, 5%, respectively)
- Low reticulocytes (6%, 3%, respectively)

The following are the sponsor's summary tables.

Table 58: Treatment-Emergent Markedly Abnormal Clinical Laboratory Values - Double-Blind Phase  
 (Study R076477-SCH-301: Safety Analysis Set)

	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)
<b>Chemistry</b>	85	89
Sodium (mmol/L)	85	89
Abnormally high	0	0
Abnormally low	0	0
Potassium (mmol/L)	85	88
Abnormally high	0	0
Abnormally low	0	0
Chloride (mmol/L)	85	89
Abnormally high	0	0
Abnormally low	0	0
Bicarbonate (mmol/L)	82	89
Abnormally high	0	0
Abnormally low	1 ( 1)	0
Glucose (mmol/L)	82	87
Abnormally high	0	0
Abnormally low	0	0
AST (SGOT) (U/L)	82	88
Abnormally high	0	0
Abnormally low	0	0
ALT (SGPT) (U/L)	84	88
Abnormally high	0	0
Abnormally low	0	0
Urea nitrogen (mmol/L)	85	88
Abnormally high	0	0
Abnormally low	0	0
Creatinine (umol/l)	85	89
Abnormally high	0	0
Abnormally low	0	0
LDL (mmol/L)	82	86
Abnormally high	1 ( 1)	7 ( 8)
Abnormally low	11 ( 13)	10 ( 12)
HDL (mmol/L)	85	88
Abnormally high	0	0
Abnormally low	14 ( 16)	4 ( 5)
Cholesterol (mmol/L)	86	89
Abnormally high	1 ( 1)	0

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

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Table 58: Treatment-Emergent Markedly Abnormal Clinical Laboratory Values -  
 Double-Blind Phase (Continued)  
 (Study R076477-SCH-301: Safety Analysis Set)

	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)
<b>Chemistry (continued)</b>		
<b>Cholesterol (mmol/L) (continued)</b>		
Abnormally low	0	0
<b>Triglycerides (mmol/L)</b>		
Abnormally high	36	39
Abnormally low	0	2 ( 2)
<b>Creatine kinase (U/L)</b>		
Abnormally high	0	39
Abnormally low	0	3 ( 3)
<b>Hematology</b>		
<b>WBC (giga/l)</b>		
Abnormally high	34	39
Abnormally low	0	0
<b>RBC (tera/l)</b>		
Abnormally high	34	39
Abnormally low	0	0
<b>Hemoglobin (g/L)</b>		
Abnormally high	34	39
Abnormally low	0	0
<b>Hematocrit (l)</b>		
Abnormally high	33	39
Abnormally low	1 ( 1)	1 ( 1)
<b>Platelets (giga/l)</b>		
Abnormally high	33	36
Abnormally low	1 ( 1)	1 ( 1)
<b>Reticulocytes (%)</b>		
Abnormally high	33	39
Abnormally low	0	1 ( 1)
	5 ( 6)	3 ( 3)
<b>Neutrophils (%)</b>		
Abnormally high	34	39
Abnormally low	0	0
	0	1 ( 1)
<b>Lymphocytes (%)</b>		
Abnormally high	34	39
Abnormally low	0	1 ( 1)
	0	1 ( 1)
<b>Monocytes (%)</b>		
Abnormally high	34	39
	0	0

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Table 58: Treatment-Emergent Markedly Abnormal Clinical Laboratory Values -  
 Double-Blind Phase (Continued)  
 (Study R076477-SCH-301: Safety Analysis Set)

	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)
<b>Hematology (continued)</b>		
<b>Monocytes (%) (continued)</b>		
Abnormally low	0	0
<b>Eosinophils (%)</b>		
Abnormally high	84	89
Abnormally low	0	0
<b>Basophils (%)</b>		
Abnormally high	84	89
Abnormally low	0	0

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**Results of OL Extension Trials**  
**Results of Study -702**

**Reviewer Comments on Results of Elderly OL Trial -702**

Laboratory results on the incidence of outliers found in in-text summary table (Table 29) of selected parameters found in the CSR failed to reveal any clinically remarkable and new findings that differed from observations previously described above or in the reviews of NDA 21999.

**Results from the Integrated OL Extension Trial Dataset**

**Reviewer Comments on Results of the Combined OL Extension Phase Dataset (-702, -703, -704, and -705)**

Results shown for selected clinical laboratory parameters found in Table 72 of Module 2.7.4 of the submission failed to reveal any new remarkable findings that differ from results already described under NDA 21999.

Since the sponsor's summary tables on mean changes and incidence of outliers on laboratory parameters only included results of selected parameters, then Appendices 5.2.1-2 starting on page 4658 of Module 2.7.4 were reviewed. Results of the incidence of outliers (in Appendix 5.2.2) revealed the following findings (some of which are noted due to previously described observations for mean changes on a given parameter):

- LFT outliers were generally
  - 0-1% for high levels with few exceptions (2% high ALT outliers observed in the ≤6 month DB Placebo/OL Pal subgroup).
- The incidence on high direct bilirubin outliers was as follows in the over 6 month Pal subgroups:
  - 4% in the > 6 month DB placebo/OL pal subgroup
  - 3% in the > 6month DB Olanzapine/OL Pal subgroup
  - 1% in the > 6 month DB Pal/OL Pal subgroup
  - 2% in each of these > 6 month Pal subgroups, combined

- Yet all of the above subgroups had an incidence of 0% for low bilirubin outliers, and all ≤6 month treated subgroups had 0% incidence for high bilirubin outliers.*
- *Lipid profile parameters generally showed results expected of this drug class (on the incidence of outliers for high cholesterol levels, high triglycerides, low HDL levels and high LDL level). The incidence of outliers for:*
    - *Low HDL levels and high LDL levels was generally approximately 5%-13% and 5-8% for each parameter respectively.*
    - *The incidence of outliers with low LDL was approximately 12-20% for each subgroup.*
  - *An incidence on other clinical parameters were:*
    - *0-1% for most parameters (with a few subgroups showing an incidence of 2%)*
    - *Any group differences on parameters were generally small (e.g. did not differ by 1-2%) and were generally not consistent across subgroups (on the basis of comparisons between groups with different DB treatment assignments and duration of Pal exposure within each DB/Pal treatment subgroup).*
  - *Refer to the review of the original NDA 21999 for other observations.*

*It is difficult to interpret the results on bilirubin, but they suggest that with longer-term treatment the greater the incidence in outliers with high bilirubin. However, these results alone can only be considered preliminary since there is no placebo group and they could be simply reflecting a non-drug-related effect of duration of monitoring (in which the chance for abnormal findings is greater as monitoring duration or frequency increases).*

*Refer to the previous section, 7.1.7.3.1 on observations on mean changes of LFTs that showed small clinically unremarkable trends for increases. Also see the next section of this review, Section 7.1.7.3.3 for a description of individual subjects with elevated LFTs. Refer to the review of the original NDA21999, as well.*

*See previous sections on ADOs and SAEs for subjects with laboratory related events reported as an ADO or SAE. See the next section, as well.*

*Finally, updated results from the integrated OL safety dataset are discussed in section 7.2.9.1 of this review (since some of the OL trials remain ongoing).*

#### *7.1.8.3.3 Marked outliers and dropouts for laboratory abnormalities*

See previous sections including sections on SAEs and ADOs. The sponsor generally did not describe individual subjects meeting outlier criteria on laboratory parameters (e.g. in the in-text sections of the CSR for Study -301 or in module 2.7.4 of the submission with the exception of subjects from the combined OL extension trial dataset of which selected individuals are described in the previous section of this review). The following are additional comments relevant to the topics of previously described outliers on CPK and on outliers on LFTs. Outliers on LFTs are described in this review for reasons discussed later.

### **Results of Study -301**

The sponsor provided the following comments regarding CPK outliers on clinical parameters in Study-301:

“Throughout the study, there were no reports of adverse events associated with increased CK levels, suggesting that the observed increases in the ER OROS paliperidone-treated subjects were overall benign and asymptomatic.

It is notable that there were no serious adverse events associated with CK elevations, such as reports of EPS and symptoms associated with neuroleptic malignant syndrome (muscle rigidity, autonomic instability, or fever). There were no cases of rhabdomyolysis. It is not clear if muscle trauma or hyperactivity contributed to the release of CK from skeletal muscle in any of the cases.”

“Throughout the study, there were no reports of adverse events associated with increased CK levels, suggesting that the observed increases in the ER OROS paliperidone-treated subjects were overall benign and asymptomatic.

It is notable that there were no serious adverse events associated with CK elevations, such as reports of EPS and symptoms associated with neuroleptic malignant syndrome (muscle rigidity, autonomic instability, or fever). There were no cases of rhabdomyolysis. It is not clear if muscle trauma or hyperactivity contributed to the release of CK from skeletal muscle in any of the cases.”

### ***Reviewer Comments***

*Results described in this section do not reveal any clinically new and remarkable findings that were not already described under NDA21999. It is noted that updated safety data provided under NDA22043 is of OL extension trial data, such that in the absence of a placebo control group results are generally difficult to interpret.*

*Refer to the reviews of the original NDA 21999 and of responses to inquiries (an addendum review of NDA 21999) describing a potential safety signal of paliperidone adverse effects on elevations in liver function tests that were sometimes also associated with elevations in CPK.*

*The following paragraphs summarize some of the findings on elevated LFTs previously described in the review of NDA 21999.*

*Results Phase III 6-week, double-blind, placebo-controlled, trials (integrated safety dataset) revealed the following regarding ADOs due to elevations in LFTs:*

- *A total of 5 out of 963 paliperidone subjects required early discontinuation of treatment due to elevations in liver function tests,*

- *None of 355 placebo treated subjects had to discontinue treatment early for this reason.*
- *Among the 5 ADOs among the Pal treated subjects:*
  - *4 subjects did not have a prior history of related events.*
  - *3 subjects had abnormal baseline values of which 1 subject was previously receiving risperidone (not clear what the other subjects were previously receiving). Despite the baseline abnormalities the potential role of exacerbating an underlying abnormality cannot be ruled out (e.g. one subject had at least 10 times the ULN of a given LFT parameter that was only mildly elevated at baseline). Also, consider treatment prior to study entry that could have played a role (e.g. at least 1 subject with abnormal baseline values was previously receiving risperidone).*
  - *A non-drug-related etiology could not be identified in 4 out of these 5 subjects (the fifth subject was diagnosed with amebic dysentery).*
  - *Elevations in liver transaminases and in several cases elevations of gamma-glutamyltransferase were observed.*
  - *One subject also showed an elevation in bilirubin.*
  - *LFT elevations during DB treatment were observed as early as the first assessment time-point (Day 14) in the trials and at daily dose-levels as low as 3 mg.*

*The following observations relevant to LFT results from Phase III 6-week, double-blind, placebo-controlled, trials (integrated safety dataset) are also noted:*

- *Another subject had elevations of transaminases and gamma-glutamyltransferase levels showed elevations of up to 8 times the upper limit of normal at the first assessment time-point in the trial (Day 14). This subject had no prior history of liver disease. A non-drug-related etiology was not identified in this subject who was withdrawn from the study on Day 24 due to noncompliance for unspecified reasons.*
- *The placebo-controlled 6-week, Phase III trials did not reveal treatment group differences on mean changes in liver function tests or in the incidence of subjects meeting criteria for high liver function tests (defined as  $\geq 3$  times the upper limit of normal for transaminases).*

*4 out of 1167 subjects in 6-12 month open-label Pal trials were previously reported under NDA21999 as ADOs due to elevated liver function tests.*

*Some of the above Phase III subjects (of 6-week trials) also showed marked or abnormally high levels in CPK.*

*Refer to the past reviews of NDA21999 for more details.*

Subject 501245 (an SAE due to elevated LFTs) in OL Trials) and comments in Dr. Laughren's Memo-to-the File under NDA21999 Relevant to this Subject and Related Reviewer

Recommendations:

Refer to Dr. Thomas Laughren's memo-to-the file regarding cases of increased "transaminases" that includes the following comment about subject 501245:

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

Please note that the following information regarding 501245 in the undersigned reviewer's NDA21999 review which notes that subject 501245 was listed as an SAE with cholelithiasis:

- 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 subsection).

The review also included a copy of the narrative on this subject (as found in an appendix or attachment to Module 2.7.4 of NDA21999). The narrative specified that ultrasound results were unknown. A potential role of Pal in exacerbating an underlying condition still requires consideration even with subjects who may have a pre-existing condition (in the opinion of the undersigned reviewer). Additional cases (ADOs) were also listed but are not shown above since the intent in showing the above is to clarify reviewer comments about subject 501245 and recommendations, as provided in the review of NDA21999. The above appeared in a prominent section of the clinical review of NDA 21999 focusing on cases with elevated LFTs.

Dr. Laughren's memo-to the file for NDA21999 also noted the following:

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

The following was recommended for labeling in the review of NDA21999 with respect to LFT elevations and appears in the labeling recommendations section of the review (Section 9.4):

1. It is recommended that elevations in LFTs (and elevations leading early withdrawal) be described under Precautions. Current approved olanzapine labeling describes transient elevations reported in some subjects in clinical trials in this section of labeling. Some subjects with elevations in Pal trials were withdrawn prematurely and the outcome of these elevations if treatment had been continued in these subjects remains unclear (e.g.

whether or not elevations would progress). The number of SAEs and ADOs due to elevated LFTs should be included.

*Other labeling recommendations regarding elevated LFTs were only provided as draft recommendations in an e-mail to assist the Team Leader, Dr. Ni Khin for preparing labeling recommendations for Dr. Laughren. It is the understanding of the undersigned reviewer that reviewers are expected by the Division to provide labeling recommendations by e-mail and that these recommendations are to be provided as draft labeling in order to assist the Team Leader (and ultimately the Director). It is also the understanding of the undersigned reviewer that the clinical review which includes a section on labeling is submitted to the Agency's official electronic system and is intended to serve as an official and final document.*

*Dr. Laughren's memo to the file clearly provides a rationale (from his perspective) for not agreeing with the above reviewer recommendations. One key rationale, among others that he specifies is that the overall incidence of outliers does not show evidence for a signal.*

*The comments regarding Dr. Laughren's memo-to-the-file are being provided in this review only to clarify the above, since the safety dataset under review for NDA22043 is generally updated results from the previously reviewed safety datasets described in reviews of NDA21999.*

*As indicated in this review, there are no new, clinically remarkable findings that differ from those previously described in NDA12999. As previously discussed, the results of OL datasets are generally difficult to interpret for several reasons that include the absence of a placebo control group.*

*NDA21999 was approved on 12/19/06.*

*Newly identified cases found in the current NDA 22043 are described later in a subsection below. These newly identified cases do not alter previous conclusions provided in past clinical review of NDA21999.*

*The following is a more detailed outline of the cases of SAEs and ADOs due to elevated LFTs and is copied from the review of the original NDA 21999:*

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 subsection).
  - ADOs of
    - 1 subject with increased AST, ALT, GGT (GGT was elevated to greater extent than AST and ALT with values of up 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  $\leq 6$  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 led 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 led 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 led 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 cholelithiasis. Therefore, it is unlikely that this event was drug-related.

***Newly Identified Subjects with Elevated Liver Function Tests***

*The previous review of NDA 21999 described or summarized results of individual subjects who were ADOs or had SAE's, and also provided results of outliers on LFTs for studies -301 and the OL extension trials.*

*Since some of the trials were ongoing under NDA21999 the following describes newly identified outliers on LFTs found in narratives that the sponsor provided of subjects identified with  $\geq 3$  times the ULN on transaminases. See previous section on SAEs and ADOs that include those due to elevations in LFTs.*

*The following newly identified subjects do not change comments and conclusions previously provided in the past clinical reviews of NDA 21999 that were conducted by the undersigned reviewer.*

***Newly Identified Subjects in Study -301***

*The following additional information from Study -301 was found in the CSR (that is not described in the review of NDA 21999).*

*Only one subject was identified as an outlier on ALT or AST (defined as of  $\geq 3$  times the upper limit) who was not reported as an SAE or ADO as follows:*

- *This subject had transient and intermittent elevations of up to 122 and 68 of ALT and AST, respectively, compared to normal baseline values.*
- *The elevations were observed despite the following:*
  - *An unremarkable past medical history*
  - *No history of substance or alcohol abuse*
  - *A non-drug-related etiology could be clearly identified.*
- *This subject continued Pal treatment (OL) and in the DB phase through Day 81 of the DB phase with peak AST, ALT elevations occurring on Day 82 ("no further laboratory data was provided").*

*In the absence of identifying non-drug-related etiology, transient intermittent elevations in the subject may be drug-related but it is not clear why levels would fluctuate over time during*

*treatment, unless the dose was changed or drug levels fluctuated, among other possibilities (OL trials used a flexible dose design).*

#### Newly Reported Subjects in OL Trials

*Refer to past sections on ADOs and SAEs. A review of the narratives of newly reported subjects in open-labeled trials (-701 through -705) with ALT/AST elevations was conducted (narratives were provided for subjects with elevations of over 3 times the upper limit of normal who were not reported as SAEs or ADOs). The following outlines potentially notable subjects that were found. In many of these cases information on the subject was limited, such that in the absence of identifying a non-drug-related etiology, the role of Pal is strongly suspected unless otherwise specified below:*

- *In the absence of additional information, the role of Pal with elevations in LFTs in the following subject is highly suspected.*
  - Subject 300148 received double-blind placebo treatment during the lead-in study during which LFTs were consistently normal over multiple time-points. However, elevations in ALT, AST and GGT were observed during open-labeled paliperidone treatment during the open-label Study-704 as follows:*
    - *Elevations were first noted on Day 169 of open-labeled treatment after almost three months of receiving the highest daily dose-level employed in most of the OL trials which was 12 mg of daily paliperidone.*
    - *The subject previously received lower daily dose levels ranging from 3 mg to 9 mg during the OL trial.*
    - *Despite the observed elevation the next assessment time-point for determining LFTs did not appear to occur until Day 373. It appears that this assessment time-point was also not conducted during treatment but rather occurred seven days after completing the open label study. Elevations were greater at this time-point (with up to approximately 4 times the upper limit of normal) compared to the previous Day 169 assessment time-point. It is not surprising that elevations in the above subject continued several days following cessation of treatment for the following reasons. Pal has a long half-life. Some drugs that are believed to induce elevations in LFTs show an apparent delay in LFT elevations or a further increase in LFTs days after treatment cessation.*
    - *This 28-year-old male subject had an unremarkable past medical history and a non-drug-related etiology could not be found in the narrative.*
    - *The outcome of the elevations of LFTs in the above subject, or information on a diagnostic work-up could not be found in the narrative.*

*Similar cases to the above subject were previously described in reviews of NDA 2199.*

*The above subject had missed days of treatment during the OL phase. The narrative of the above subject indicates that open-labeled paliperidone was withheld on Days 58, 68, 72, 106, 111-112, and 316-31). The reason for withholding treatment on these days could not be found in a 12/21/06 submission that provided responses to questions that included questions about this subject (the sponsor indicated that the information was not found in the CRF of the subject and a review of AEs failed to show a consistent AE related reason). The following AEs are noted by the undersigned reviewer.*

*AEs of cough, headache and scratchy throat were reported on 2 days that coincided with Pal-free days (Days 111-112). Nausea was a potentially related AE but it was reported on Days 23 and 84 which did not coincide with any of the Pal-free days. The sponsor speculated that 8 missed doses over a 1 year period may have represented a "simple lapse in compliance on the part of the subject," which appears to be a plausible explanation.*

- *Subject 300668 appeared to have olanzapine induced elevations (observed during DB Olanzapine treatment in the lead-in study to the OL extension trial, -704). It is not clear if these elevations continued during OL Pal.*

*This subject:*

- *Was a 25-year-old male subject*
- *Had an unremarkable past medical history other than insomnia*
- *Had normal LFTs at multiple time-points prior to DB olanzapine treatment in a lead-in Study-704.*
- *Elevations of LFTs were first noted in the narrative to occur on Day 15 (of AST and ALT).*
- *Greater elevations of AST and ALT (approximately 2-3 times the upper limit of normal) were observed at baseline of the open-label extension Trial-704, but also included an elevation of GGT.*
- *No other LFTs values could be found in the narrative in the patient was "loss to follow up" on Day 21 of the open-label study.*

*Olanzapine is reported to be associated with transient elevations of LFTs, as described in approved labeling. It is not clear if elevations in LFTs continued during paliperidone treatment based on the limited information found in the narrative. Non-drug-related etiologies or potential etiologies were not found in the narrative.*

- *The following additional subjects with elevated LFTs were found in Section 3.3.2.2 of Module 2.7.4:*
  - *The role of Pal in the development of transient elevations of LFTs and possibly CPK in the following subject is strongly suspected, in the absence of additional information. Subject 500809:*
    - *Was a 28 year old male*
    - *Had an unremarkable PMH and*
    - *Had no concomitant medications during the OL Study -705*
    - *He developed transient elevations in AST and ALT and fluctuating elevated CPK levels during OL treatment (no mention of related events during DB Pal but he was only receiving 3 mg/day).*
    - *Abnormalities on other LFT parameters are not described.*
    - *The daily dose of Pal was changed during the OL phase in this subject but elevations at the 12 mg daily dose-level eventually normalized while receiving the same dose-level.*
    - *The patient was reported to be continuing the daily dose-level during the ongoing trial and no other related abnormalities were described in this subject.*
  - *Subject 200231:*

- *Was a 69 year old female with history of ischemic heart disease and chronic colitis*
- *Was not receiving concomitant medications.*
- *She began showing LFT elevations on Day 15 of DB Pal treatment in Study -302 (GGT of 200 U/l) that were also revealed at OL baseline (GGT of 278, as well as ALT of 84 U/l).*
- *On Day 28 of OL 12 mg/day of Pal LFT values continued to be elevated but somewhat less in value from the baseline value (GGT was 161 U/l on Day 28 of OL Pal), yet AST also became slightly elevated at this time-point.*
- *However, treatment was stopped “due to lack of efficacy” on this study day and 7 days later LFT values generally decreased (except AST increased from 39 to 48 U/l).*
- *No other post-treatment values or any other associated abnormalities are described for this subject.*

*It appears that Pal at least played a role in these elevations.*

- *Subject 201321:*
  - *Was a 22 year old white male with an unremarkable PMH and*
  - *Had no concomitant medications during the study (except for the last day when he was having pernazinum started for relapse of schizophrenia).*
  - *This subject had LFT abnormalities at baseline but had much greater LFT values after chronic OL Pal treatment in which Pal may have exacerbated an underlying liver condition.*
  - *8 days after treatment cessation while apparently receiving pernazinum LFT values remained elevated.*
  - *It is difficult to assess the etiology and role of Pal and pernazinum but these drugs could have exacerbated an underlying condition.*
- *Other subjects described in this section of the module 2.7.4 were either previously described in the review and addendum review of NDA21999 or occurred in a subject who reported using alcohol.*

#### 7.1.8.4 Additional analyses and explorations

See the previous section and Section 7.1.5. The previous original review and addendum review of NDA21999 also examined this topic in various sections of the reviews.

#### 7.1.8.5 Special assessments

##### ***Reviewer Comments on Results of Selected Special Assessments***

##### ***Results of Study -301 on Prolactin Levels and Potentially-Related AEs***

*Results on prolactin levels and the incidence of potentially related (PPR) AEs were found in Section 6.2.3.4.5 of the CSR of Study -301. These results generally did not reveal any clinically remarkable new findings, except for sex differences on PPR AEs that are consistent with observed sex differences on prolactin levels. Median or mean increases of prolactin levels (from baseline to on-treatment time-points) were previously described in short-term DB trials (under*

NDA21999). These differences were also observed in Study -301 and OL trials summarized in the current NDA22043 submission (between pretreatment and on-treatment values).

Consistent with sex differences observed with prolactin levels, a greater incidence of PPR AEs occurred in women compared to men, as shown in the sponsor's summary table below.

**Table 55: Treatment-Emergent Potentially Prolactin Related Adverse Events by Sex (Study R076477-SCH-301: All Treated and Safety Analysis Sets)**

	All Treated		DB Safety	
	ER OROS PAL RJ/ST (N=530) n (%)	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	
<b>Male, No. of subjects<sup>2</sup></b>	<b>362</b>			
Impotence	3 (1)			
<b>Female, No. of subjects<sup>2</sup></b>	<b>168</b>	<b>38</b>	<b>46</b>	
Amenorrhoea	11 (7)	0	2 (4)	
Lactation nonpuerperal	6 (4)	0	1 (2)	
Breast pain female	1 (1)			
<b>Both, No. of subjects<sup>2</sup></b>		<b>102</b>	<b>104</b>	
Libido decreased		0	1 (1)	

Note: Only adverse events that either newly appeared or worsened in severity after the initiation of double-blind medication were considered as treatment-emergent adverse events in the double-blind phase.

<sup>2</sup> Percentages calculated with the number of subjects per sex as denominator.

Results of the Integrated OL trial Dataset on Prolactin Levels and Potentially-Related AEs

The incidence of most of the PPR AEs in the updated OL trial dataset was generally greater than the incidence of these AEs in shorter-term DB trials (the clinical review of NDA21999 provides short-term trial results). The higher incidence in the OL trials is difficult to interpret since results could be explained by the longer period of monitoring in these longer term trial compared to shorter term DB trials. Also OL trials generally yield a higher incidence compared to DB trials.

Results of the integrated OL trials, as found in the 120-Day SUR submission showed similar results for these OL trials. Section 7.2.9.1 of this review summarizes results found in the 120-Day SUR submission.

ADOs and SAEs of PPR AEs

Several ADOs due to potentially prolactin related AEs were briefly described in Section 2.1.6.7 of Module 2.7.4 of NDA22043 submission that involved AEs of:

- *Amenorrhea (2 subjects of which 1 subject also had dizziness as described in Section 7.2.9.1 summarizing SUR results),*
- *Galactorrhea (1 subject),*
- *Erectile dysfunction (2 subjects).*

*No SAEs of potentially prolactin related AEs could be found in Section 2.1.6.7.*

*Current approved labeling has a drug class section on hyperprolactinemia under Precautions. PPR AEs are also included under Adverse Reactions (in the "Other Findings Observed..." section)*

## 7.1.9 Vital Signs

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

Refer to Table Series 10.1 and 10.2 in the appendix of this review for outlier criteria and for the Schedule of safety assessments in various trials.

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

See Section 4.3 of this review describing the review strategy. Section 4 of this review also has subsections describing various trials that provided safety data. Section 7.1 of this review summarizes methods and the safety datasets in this review.

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

See subsections below.

#### 7.1.9.3.1 Analyses focused on measures of central tendencies

### **Results of Study 301**

#### ***Reviewer Comments of Results from Study -301***

#### **Key Caveats Regarding Study -301 Results of the DB Phase**

*It is important to note that only a few subjects continued beyond the week 6 assessment time-point for vital signs during the DB treatment phase of Study-301 (due to early dropouts and early termination of the study for the interim analyses, according to protocol). Consequently, only the data obtained over the first six weeks of the DB phase of the trial were generally reviewed.*

*The sponsor used baseline values of the DB phase (rather than a pre-OL Pal treatment baseline value) to determine the mean change and median change from baseline to each time-point (shown in attachments to the CSR and includes mean changes from baseline to study endpoint). Consequently, subjects were already receiving study drug at the DB phase baseline assessment,*

*such that any change observed in each treatment group does not reflect the change from a pre-treatment value to an on-treatment value.*

*Upon request the sponsor provided results using a pre-dose baseline value of the OL phase as the baseline value for determining mean changes of each parameter during DB treatment (in an N002 submission). However, only the results on changes from this pre-dose time-point to the DB treatment endpoint could be found, while results over time (changes from pre-dose to each assessment time-point during the DB treatment phase) could not be found. Furthermore, it appears that results are based on LOCF data. Consequently, a potential signal that may only appear with acute treatment but resolves over time may not be captured by this approach in presenting the results. Refer to the review of NDA21999 N000 describing results over time in short-term, 6-week, DB trials and regarding potential time-dependent effects of Pal on vital sign parameters (and other parameters, as previously discussed).*

*Reviewer Conclusion of the Results, as Shown Later in this Subsection*

*No new and clinically remarkable findings were revealed by results of Study -301 that differ from results of trials previously described in past reviews of NDA 21999 (refer to the original clinical and addendum reviews of the original NDA 21999 submission). However, the sponsor provided results of subgroups of subjects in Study 301 who were subcategorized into subgroups on the basis of whether or not they continued into the DB phase of the study. Possible subgroup differences are noted below that were not previously described in the review of NDA21999 (Study 301 was ongoing at the time of the N000 NDA21999 submission). These differences were not clinically remarkable.*

*The sponsor's conclusions on positive findings in Study -301 are summarized later in this subsection of this review.*

*A Comparison of Results of Subgroups, categorized on the Basis of whether or not Subjects Entered the DB Phase of Study -301*

*The vital sign results from the subgroup of subjects who were randomized to DB treatment in Study 301 was numerically compared to results from the subgroup of subjects who were not randomized to DB treatment in Study 301 (based on a review of results found in Attachments 9.1.1.1-3 of the CSR of -301). The following outlines key observations based on numerical comparisons between these two subgroups on vital sign results:*

- The subgroup that was not randomized to DB treatment showed numerical trends for decreased orthostatic systolic and diastolic blood pressure (BP) values (compared to baseline values), while the subgroup that was randomized to DB showed little to no group mean decreases on these parameters.*
- These numerical changes were only by a few mmHg and this observation alone is not considered clinically remarkable.*
- The two subgroups did not appear to show numerical differences on other vital sign parameters.*

*The incidence of outliers on a given parameter in each of the above two subgroups could not be found in this submission.*

Positive Vital Sign Results of Study 301, as Noted by the Sponsor

**Run-in and Stabilization OL Phases of Study -301**

The following are positive findings that the sponsor described for the OL study phase of Trial -301:

- “Both standing and supine pulse rates showed mean increases at all evaluations in the beginning of the run-in phase.”
- “There were no clinically relevant changes from baseline to end point in mean blood pressure values.”

**DB Phase of Study -301**

The following summarizes positive findings during the DB phase that the sponsor noted:

- “Throughout the double-blind phase, mean standing pulse rates showed elevations at most evaluations in the ER OROS paliperidone group, compared to decreases in the placebo group. These treatment group differences were statistically significant at multiple time points during the double-blind phase.”

See the sponsor’s summary tables below that were found in the CSR of Study -301 in the submission.

Appears This Way  
On Original

Table 59: Vital Signs: Means and Mean Changes From Baseline (DB) to End Point (DB) -  
 Double-Blind Phase  
 (Study R076477-SCH-301: Safety Analysis Set)

	Placebo (N=102)	ER OROS PAL (N=104)
<b>Standing pulse rate (bpm)</b>		
N	101	104
Mean baseline (SD)	83.7 (9.72)	83.6 (11.75)
Mean change (SD)	-0.5 (11.29)	-0.1 (9.88)
<b>Supine pulse rate (bpm)</b>		
N	101	104
Mean baseline (SD)	75.7 (9.52)	76.7 (11.36)
Mean change (SD)	-0.4 (9.63)	-0.3 (9.83)
<b>Standing SBP (mmHg)</b>		
N	101	104
Mean baseline (SD)	117.5 (11.61)	119.5 (14.65)
Mean change (SD)	0.3 (11.19)	-0.7 (9.62)
<b>Supine SBP (mmHg)</b>		
N	101	104
Mean baseline (SD)	117.3 (10.18)	118.6 (14.01)
Mean change (SD)	0.1 (10.81)	0.5 (8.67)
<b>Standing DBP (mmHg)</b>		
N	101	104
Mean baseline (SD)	75.5 (8.42)	76.9 (9.82)
Mean change (SD)	0.8 (10.11)	1.1 (7.13)
<b>Supine DBP (mmHg)</b>		
N	101	104
Mean baseline (SD)	73.6 (7.98)	75.7 (9.95)
Mean change (SD)	0.7 (9.13)	-0.1 (8.81)
<b>Pulse (standing-supine) (bpm)</b>		
N	101	104
Mean baseline (SD)	8.1 (7.51)	6.9 (6.60)
Mean change (SD)	-0.2 (8.70)	0.7 (6.95)
<b>SBP (standing-supine) (mmHg)</b>		
N	101	104
Mean baseline (SD)	0.2 (8.68)	0.9 (8.03)
Mean change (SD)	0.2 (8.27)	-1.2 (8.35)
<b>DBP (standing-supine) (mmHg)</b>		
N	101	104
Mean baseline (SD)	2.0 (7.42)	1.2 (7.93)
Mean change (SD)	0.1 (7.44)	1.2 (6.66)

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## Results of OL Extension Trials

### Results of Study 702

#### *Reviewer Comments on Results of Elderly OL Trial -702*

*Descriptive statistical results found in an in-text summary table (Table 30) in the CSR of Study 702, failed to reveal any clinically remarkable and new findings that differed from observations previously described above or in the reviews of NDA 21999.*

#### Key Limitations with the Results

*Aside from limitations inherent in a longterm OL extension trial, the following are some additional key limitations impacting on the interpretation of the sponsor's results in Table 30:*

- *The results only show OL phase baseline mean values and mean changes from OL-phase baseline to OL-treatment endpoint (not median values, changes or range of values).*
- *Furthermore results do not reflect a mean change in value prior to Pal treatment (prior to the onset of the DB treatment phase of the 6-week lead-in study -302) except for the small group of 30 subjects that were previously assigned to DB placebo treatment (the remainder subjects were 70 subjects previously assigned to DB Pal).*
- *The sample size of each treatment group is small (particularly the placebo group).*
- *Consider the variance across subjects and over time on vital sign measures in the elderly population. This in turn could adversely impact on the ability to detect a safety signal in the trial.*

*Given the various key limitations with results of Study -702, it is difficult to interpret the results. Failure to show a remarkable drug effect may not be reflecting a true negative study but rather may be indicative of a failed study. Refer to comments and recommendations in previous reviews of the original NDA 21999 regarding the elderly patient population.*

#### Results from the Integrated OL Extension Trial Dataset

##### ***Combined OL Extension Trial Safety Dataset Results (-702, -703, -704 and -705)***

*Descriptive statistical results could not be found in in-text sections of Module 2.7.4. However, results (on the mean change  $\pm$  SD and median change on a given parameter) were found in a 69 page Appendix 6.2.1 (starting on page 5871) of Module 2.7.4. This appendix provided the results for each assessment time-point during the double-blind lead-in studies (the combined safety dataset) and during the open label extension trials (for the combined safety data set). The baseline/pre-dose value of the DB-treatment phase was used as the baseline value for determining the mean change and median change from baseline to each assessment time point (results were provided for the same treatment subgroups as were provided for laboratory parameters as previously described in this review).*

*No new, clinically remarkable findings were revealed that differed from results previously described in the review of the original NDA 21999 submission. It is important to note that only the results of those data points having at least approximately 50 subjects in Appendix 6.2.1 were reviewed (since smaller sample sizes are generally not considered sufficient for the purposes of this review).*

*Updated results found in the 120-Day SUR submission are summarized in section 7.2.9.1 of this review.*

##### ***7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal***

##### **Results of Study 301**

##### ***Reviewer Comment on Results of Study -301.***

*Only data through week 6 of the DB phase of the study were reviewed, due to the small number of subjects in a given treatment group beyond this time point, as previously noted.*

*The incidence of outliers during the run-in/stabilization OL phase of Study -301 were generally similar to results of the integrated-OL extension trial safety dataset (Studies -702, -703, -704, -705, combined). The incidence of outliers on some of the parameters was either similar to or generally greater than the incidence observed in the integrated safety dataset. One would expect that the incidence would be less in most cases in the OL phase of Study 301 that only used a few months of treatment compared to the incidence in OL extension trials that used up to 12 months of treatment. However, it is difficult to make comparisons on the incidence of outliers between independent studies.*

*It is also important to note that in the OL extension trials a number of subjects were being continued on active treatment instead of being initiated on treatment as in the case of Study -301, since the extension trials were preceded by 6-week DB lead-in studies. In light of this difference in treatment methods (between the OL extension trial and the OL phase of Study 301) the following observation is noted. The greatest incidence on increased standing and supine HRs (11% and 5%) occurred on Day 5 and Day 3, respectively during OL treatment of Study 301 (as treatment was being initiated). However, over approximately 5% incidence was observed on each parameter on additional assessment days during OL treatment in Study 301 (as shown in Attachment 9.3.1 of the CSR). These results suggest that increased HR may be more common following the acute phase of treatment. Yet, the interpretation of the results is limited by the OL study design and other limitations, as previously discussed.*

*Subsections below provide copies of the sponsor's summary tables and summarize positive findings, as noted by the sponsor.*

#### **Run-in and Stabilization OL Phases of Study -301**

The sponsor notes the following positive findings on the incidence of outliers reported during the OL phases of the study (summary tables are provided later):

- “Abnormally high pulse increases” were observed in which the incidence was higher during early stages than in the later stages of OL treatment.
- “Changes from baseline in blood pressure values were reported infrequent, i.e., at incidences not exceeding 2%.”
- “The percentages of subjects with abnormal standing pulse increases ranged from 6.2% to 11.3% in Weeks 1 through 3 versus 2.1% to 6.7% in Weeks 4 through 14.
- The incidence of outliers for increased standing and supine heart rate was 35% and 21%, respectively. “These results are consistent with the adverse event reports of tachycardia during the run-in and stabilization phases.”
- “Markedly abnormal decreases in blood pressure at any evaluation were noted more commonly than increases for both standing and supine systolic measurements (decreases, 6% vs. increases, 1%).”
- “Markedly abnormal changes in both standing and supine diastolic blood pressure were reported at the rates of 3% or less.”

The sponsor notes that “no vital sign abnormalities were reported as serious adverse events” during the OL phases, but noted the following ADO:

- Subject 100121: had “mild hypertension” that was reported on Day 1 of the run-in phase (9 mg/day).

The sponsor also notes the following incidence of vital sign-related AEs:

- Most vital sign related AEs were reported in only 1% or less of the subjects.
- Tachycardia was reported in 7% of subjects.
- Hypertension was reported in 3%.
- “Severe hypertension was reported only for 2 subjects during the run-in and stabilization phases. Both subjects had normal vital sign readings at baseline, and experienced multiple instances of transient mild or moderate hypertension during the first weeks of treatment. These events were judged by the investigators as possibly or probably related to study treatment.

*Reviewer Comment: Subject numbers and additional information on the above subjects identified as having VS-related AEs, could not be found in the sponsor’s description of the above subjects (e.g. narrative descriptions other than brief comments, as above could not be found in the section of Module 2.7.4 in which the above comments were provided in subsections of Section 6.4).*

The following subjects with “severe hypertension” were also noted by the sponsor in which subjects numbers were found:

- “Severe hypertension was reported on Day 4 for Subject 100760, a 64-year-old woman (standing systolic blood pressure of 180 mmHg);
- “Severe hypertension” was also reported “on Day 29 for Subject 101222, a 37-year-old man, (standing diastolic blood pressure of 112 mmHg, supine diastolic blood pressure of 118 mmHg), who also had multiple instances of elevated pulse rates early in treatment.”

*Reviewer Comment. As previously noted in the review of NDA 21999, Pal may induce hemodynamic fluctuations in blood pressure (e.g. secondary to an initial tachycardia and/or orthostatic hypotension) in subjects who may exhibit reduced cardiac output secondary to a cardiovascular challenge. Several examples of this potential Pal effect (of clinically remarkable subjects) were previously described in the review of NDA21999. Several of the above subjects may also be additional examples of a potential role of Pal. The above findings are similar to findings of Phase III trials described in reviews of NDA21999 and led to similar conclusions, as previously conveyed by the undersigned reviewer (refer to past clinical reviews of NDA21999 for details).*

#### **DB Phase of Study -301**

The criteria employed for identifying outliers on vital sign parameters are shown in the sponsor’s summary tables that are copied later in this subsection of this review. The sponsor notes the following positive findings on the incidence of outliers reported during the OL phases of the study:

- The incidence of increases in standing HR was greater in the Pal group compared to the placebo group (15% and 8%, respectively).

The following vital sign-related SAEs were noted in 1 subject:

- “1 subject in the ER OROS paliperidone group (Subject 100067, a 35-year-old woman with a history of controlled hypertension) experienced serious adverse events related to vital sign abnormalities (tachycardia and hypertension [reported term: “hypertensive urgency”]). Both events were reported on Day 120 concurrently with severe chest pain. The subject was receiving ER OROS paliperidone 9 mg/day; these 3 events, which resolved in 2 days without hospitalization, led to discontinuation of treatment”

The sponsor notes that no ADOs due to vital-sign-related AEs occurred during the DB phase.

The sponsor notes that the incidence of vital sign-related AEs during the DB phase was reported in only 1% or less of subjects except that tachycardia was reported in 3% of subjects in each treatment group.

Subject 100067 is also noted as having AEs of tachycardia and hypertension.

Table 60: Number of Subjects With Treatment-Emergent Abnormal Vital Sign Values (Study R076477-SCH-301: Safety and All Treated Analysis Sets)

	Run-in/Stabilization		Double-Blind	
	ER OROS PAL (REST) (N=104) n (%)	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	
<b>Standing pulse classification</b>				
Decrease $\geq$ 15 and value $\leq$ 50	1 (<1)	0	0	
Increase $\geq$ 15 and value $\geq$ 100	183 (35)	8 (8)	16 (15)	
<b>Supine pulse classification</b>				
Decrease $\geq$ 15 and value $\leq$ 50	9 (2)	0	0	
Increase $\geq$ 15 and value $\geq$ 100	111 (21)	4 (4)	5 (5)	
<b>Standing SBP classification</b>				
Decrease $\geq$ 20 and value $\leq$ 90	34 (8)	4 (4)	4 (4)	
Increase $\geq$ 20 and value $\geq$ 180	4 (1)	0	0	
<b>Supine SBP classification</b>				
Decrease $\geq$ 20 and value $\leq$ 90	32 (8)	2 (2)	2 (2)	
Increase $\geq$ 20 and value $\geq$ 180	3 (3)	0	0	
<b>Standing DBP classification</b>				
Decrease $\geq$ 15 and value $\leq$ 50	14 (3)	2 (2)	0	
Increase $\geq$ 15 and value $\geq$ 105	14 (3)	2 (2)	1 (1)	
<b>Supine DBP classification</b>				
Decrease $\geq$ 15 and value $\leq$ 50	18 (3)	1 (1)	1 (1)	
Increase $\geq$ 15 and value $\geq$ 105	9 (2)	0	0	

Note: Percentages calculated with the number of subjects per parameter as denominator.  
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The sponsor has a separated section on orthostatic hypotension and provides the incidence of standing-supine “orthostatic hypotension” vital sign outliers as shown below.

**Table 54: Number of Subjects With Treatment-Emergent Orthostatic Hypotension Anytime During the Run-in/Stabilization and Double-Blind Phases (Study R076477-SCH-301: All Treated and Safety Analysis Sets)**

	<u>All Treated</u>		<u>DB Safety</u>	
	ER OROS PAL RI/ST (N=530) n (%)	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	
<b>Total No. Subjects with Orthostatic Hypotension</b>	30 ( 6)	2 ( 2)	5 ( 5)	
Pulse(std-sup)>15 and sbp(std-sup)<-20	17 ( 3)	2 ( 2)	4 ( 4)	
Pulse(std-sup)>15 and dbp(std-sup)<-10	18 ( 3)	2 ( 2)	2 ( 2)	

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

The sponsor also notes that no ADOs or SAEs of orthostatic hypotension were reported in the study.

### **Results of OL Extension Trials**

#### Results of Study 702

##### **Reviewer Comments on Results of Elderly OL Trial -702**

*Results of outliers on vital sign parameters (diastolic, systolic or heart rate outliers in standing or supine positions and orthostatic hypotension outliers) were found in in-text summary tables (Tables 31 and 32) in the CSR. These results failed to reveal any clinically remarkable and new findings that differed from observations previously described above or in the reviews of NDA 21999. See the previous section for limitations with results of this study. Refer to the review of NDA 21999 for further comment and recommendations.*

#### Results from the Integrated OL Extension Trial Dataset

##### **Reviewer Comments on Results of the Combined Open Label Extension Trial Dataset (-702,-703,-704, and-705)**

*No clinically new and remarkable observations could be found that differ from results previously described in the clinical review of the original NDA21999.*

##### **7.1.9.3.3 Marked outliers and dropouts for vital sign abnormalities**

See previous sections of this review on SAEs and ADOs. An in-text description of individual subjects that were identified as remarkable vital sign outliers could not be found in 4.1 of Module 2.7.4, except that occasionally an ADO or SAE due to vital sign parameter is mentioned in which the SAE or ADO is specified and in some cases a subject number is provided (Section 4.1 covers the results of vital sign parameters). See sections 7.1.3.3 and 7.4 of this review that describes results of special AE term searches that included some terms related to vital sign parameters and in which a few individual subjects are described.

**Reviewer Comments.** *While treatment group differences on mean changes in a given parameter may not be clinically remarkable, a similar change in vital sign parameters may be considered clinically remarkable in a subject with pre-existing cardiovascular disease. For example, a small drug effect on vital signs (such as increased heart rate) could potentially be clinically remarkable in a subject with a pre-existing cardiovascular condition, such as hypertension. Hypertension developed in some patients and was reported as an SAE, ADO or as an AE of severe intensity in a few subjects in Study -301. Although antipsychotic drugs are not believed to induce an increase in blood pressure, hypertension in a subject at risk could be reflecting an indirect drug adverse effect. For example, a Pal induced tachycardia could potentially lead to a compensatory increase in BP to maintain cardiac output. Consequently, Pal treatment could exacerbate a pre-existing cardiovascular condition due to Pal-induced changes on vital signs. While in some cases it is possible that hypertension was pre-existing but undiagnosed, consider subjects that develop an exacerbation of hypertension during Pal treatment, as previously described under NDA21999.*

*The group difference on mean change in supine HR was up to approximately 8 bpm during DB treatment in Study 301 (as shown in Attachment. 9.1.2). This group difference occurred on the Week 6 assessment (-5.3 bpm and +3.0 bpm changes in placebo and Pal groups, respectively). Yet these results are potentially limited by the use of the DB baseline value rather than the pre-dose, OL phase baseline value. Therefore, the values do not reflect a pre-dose to on-treatment value, such that greater group and individual subject changes and group differences may be observed if using a pre-dose value for the baseline value.*

*Upon request the sponsor provided results on the mean change from pre-dose OL phase to DB treatment endpoint values on vital sign measures in a 12/21/06 response submission. However, the mean and median changes over each assessment time-point during treatment could not be found. Consequently, results as provided are difficult to interpret since treatment endpoint results appear to be based on an LOCF approach, such that results may not reveal potential effects that may be more prominent during the early phase of treatment. Furthermore, results of Study 301 are limited by the small sample sizes after only approximately 6 weeks of treatment during the DB phase.*

*Refer to the review of the original NDA 219999 submission for examples of additional subjects with cardiovascular-related events.*

*Also refer to other sections of this review, as previously specified for additional subjects.*

**Reviewer Comments on Results of Elderly OL Trial -702**

*Section 6.4.1 of the CSR for this study summarizes vital sign results that are also summarized in previous sections of this review. This section of the CSR does not include a description of any potentially clinically remarkable subjects as follows. A description of any of subject with the following observations could not be found in this section of the CSR:*

- *Subjects with remarkable vital sign values*
- *Subjects with vital sign related adverse events that were associated with abnormal vital sign values or*

- *Subjects with potentially associated AEs (such as chest pain, dyspnea). Individual descriptions of ADOs or SAEs with vital sign related events also cannot be found (in some cases the sponsor reports that none occurred). Instead this section of the CSR generally enumerates subjects with AEs due to selected vital sign events (e.g. tachycardia, orthostatic hypotension). A given reported adverse event may also be described with respect to the degree of severity or the likelihood that the event was drug-related (as judged by the investigator).*

#### 7.1.9.4 Additional analyses and explorations

See the previous section and Section 7.1.5. The review of NDA21999 provided results of a search for clinically remarkable subjects.

#### 7.1.10 Electrocardiograms (ECGs)

See subsections below.

##### 7.1.10.1 Overview of ECG testing in the development program, including brief review of preclinical results

Refer to Table Series 10.1 and 10.2 in the appendix of this review for the outlier criteria and Schedule of safety assessments for each safety dataset. See previous comments on limitations and potential limitations with the results.

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

See Section 4.3 of this review describing the review strategy. Section 4 of this review also has subsections describing various trials that provided safety data. Section 7.1 of this review summarizes methods and the safety datasets in this review.

##### 7.1.10.3 Standard analyses and explorations of ECG data

See subsections below.

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

###### **Results of Study 301**

*Reviewer Comment of Results from Study -301. Summary tables showing descriptive statistical results could not be found in the in-text sections of the CSR, but the sponsor refers to a number of attachments for results. The sponsor's description of EKG results focuses on the incidence of outliers, as discussed in the next section of this review. A description of mean or median change in EKG parameters cannot be found in the in-text sections of the CSR.*

*A review of Attachments 11.1.1.1-3, 11.1.2 and 11.2 was conducted by the undersigned reviewer. These results failed to show any new and clinically remarkable findings that differ from results previously described in the review and addendum review of the original NDA 21999.*

*An Overall Trend for a Numerically Greater QT value at Later OL time-points compared to Earlier OL time-points*

*One potentially important observation that was also previously observed and described in reviews of NDA 21999 is an overall trend for greater QT interval values at later OL time-points compared to earlier OL time-points (based on results provide over time during the study for the integrated OL safety dataset). This trend was observed while heart rate showed little to no change at these later time-points. All of these OL extension trials involved 12 months OL treatment except for the smaller elderly study -702 in which OL treatment was for 6 months. Study 301 only had a few months of OL treatment before subjects entered the DB phase. Attachment 11.1.12 shows a group mean increase from the averaged pre-dose value (the mean value of multiple ECG assessments prior to OL treatment) in QT raw as follows during OL phases of Study -301 (results were provided over time):*

- 12.3 msec on the last week of the run-in phase and*
- 11.1 msec at week 14 of the stabilization phase*

*These observations were found in the ITT safety population for these OL phases of Study -301. Additional observations during the OL phase of Study -301 that are relevant to the above findings are noted below:*

- Group mean heart rate changes from the pre-dose average value was -4.8 and -4.6 at each of the above respective time-points (with a similar group median decrease).*
- The absolute group-mean and group-median heart rate values at each of the above time-points were within normal limits (72-74 bpm for each time-point).*
- Standard deviations of QT were large ( $\pm 12-13$  msec).*

*Although, there was a trend for small mean and median decreases in heart rate during OL treatment, as outlined above, QTraw results rather than QTcB results were chosen for describing QT results of the OL phase of Study 301 in this review for the following reasons. QTcB is applicable to the case when heart rate decreases but it is considered to be more valid when heart rate is abnormally low. Mean and median heart rate at the above OL assessment time-points were within normal limits. Consequently, QT raw values may be most accurate among the QTc methods employed by the sponsor for time-points corresponding to chronic rather than acute treatment of Pal (at time-points when absolute values for mean and median heart rate are generally clinically unremarkable or are within normal limits).*

*As previously noted the standard deviations (at each assessment time-point) were large. A number of limitations with interpreting the OL phase results of study -301 exist, as previously discussed in previous clinical parameter sections of this review. The subsection below on the integrated OL trial safety dataset results discusses key limitations with OL trial results that also apply to results of the OL phase of Study -301.*

#### QT Interval in the DB Phase of Study -301

The results of the DB phase of Study -301 failed to show clear treatment group differences on mean change in QT values from the average pre-dose value. However, these results are limited by the small sample sizes of the treatment groups during the DB phase, as previously discussed under subsections on results of other clinical parameters. In contrast to the sample size of the DB phase of Study -301 the sample size of the OL phase was larger (includes the ITT population such that subjects that were not randomized to DB treatment were also included in this OL safety dataset). Furthermore, the sample sizes in each DB treatment group decreased dramatically to less than 50 subjects by week 8 which was only the second ECG assessment time-point during the DB phase. Consequently, DB phase results of study -301 are generally difficult to interpret. Another key limitation with the DB phase results is that subjects of the placebo group previously received Pal during the preceding OL phase, such that a potential effect on stopping Pal treatment on ECG parameters may need to be considered. Moreover, the pre-dose value used to examine mean and median changes during DB treatment was based on a value obtained several months prior to the onset of the DB phase (since the pre-dose value was obtained at baseline of the OL phase).

It is also important to be aware of the multiple limitations of the data from OL studies and from studies such as Study-301 that are inherent in trials with these study designs.

Descriptive statistical results on QTc prolongation could not be found in the CSR. However, results of the incidence of outliers of prolonged QTc were found as described in the next section of this review.

#### **Results of OL Extension Trials**

##### Results of Study 702

##### **Reviewer Comments on Results of Elderly OL Trial -702**

Descriptive statistical results found in Attachments 11.1.1-2 did not reveal any clinically remarkable and new findings that differ from observations previously described above or in the reviews of NDA 21999.

##### Results from the Integrated OL Extension Trial Safety Dataset

##### **Reviewer Comments of the Results of the Integrated OL trial Safety Dataset**

As previously described in the clinical review of the original NDA21999 submission mean and median change in QT interval was greater in later OL time-points compared to earlier OL time-points (the observations apply to results of QTraw, since heart rate showed little to no change and results of QTcLD). The following numerical trends are noted based on results shown over time as found in Attachment 11.1.1 of the Module 2.7.4:

- The over 6 month treatment subgroups generally had the greatest mean increase in QT interval at later assessment time-points than their corresponding treatment groups with  $\leq 6$  months Pal treatment.
- The DB placebo/OL Pal subgroups showed the smallest group mean increases with OL longterm treatment, while the DB Pal/OL Pal (over 6 month group) and the DB

*Olanzapine/OL Pal (over 6 month group) showed the greatest group mean increase in QT interval at the later OL time-points (time-points of 6 months or later).*

- *The group maximum group-mean and group-median increases did not exceed approximately 6 msec.*

*The interpretation of the above results (as are the results of Study 301 and 702) are limited not only due to the absence of a placebo group but also for the following reasons:*

- *The standard deviations were large and*
- *Values showed fluctuations over each assessment time-points*
- *Test-retest reliability of assessments was likely to be compromised.*
- *Among other limitations with the results or study design.*

*Yet the above findings of statistical results over time during OL treatment:*

- *Appear to be reproducible*
- *Appear to show a trend for greater mean and median increases in the treatment subgroups with the longest treatment duration (at time-points of at least 6 months of treatment or longer within the over 6 month treated subgroups).*

*Also see results on the incidence of outliers suggesting a greater number of outliers or shifts towards greater QT intervals in the over 6 month treated subgroups compared to  $\leq 6$  month treated subgroups. Yet it is difficult to interpret results of these 2 subgroups (in the absence of a placebo group) since they may not reflect a true effect of treatment duration on QT interval.*

#### *Potential QT Prolongation Observed in with Longterm OL Treatment in Study -704*

*Because of the above observations, a review of QT interval results of one of the OL studies, Trial -704, was conducted. Trial -704 was selected because the study is completed and a CSR was provided. The results of mean and median changes of QT and QTcLD interval over time were reviewed, as found in the CSR. This review revealed similar observations to those of the integrated OL safety dataset. A numerical trend for greater QT prolongation at treatment time-points of 6 months and over compared to earlier OL time-points were observed. Mean and median values over time were generally numerically greatest in the over 6 month Pal/Pal and Olanzapine/Pal subgroups at the later time-points (generally near or at 6 or 12 month assessment time-points). The mean QT interval values exceeded 9 msec and reached up to 14.5 msec in the over 6 month treated Olanzapine/Pal subgroup on the week 52 assessment time-point. However, these higher values were generally observed with sample sizes of less than approximately 20 subjects at this later time-point.*

*It is important to note that Study -704 results were also part of the integrated OL safety dataset. This is the only study with a CSR provided among the OL safety dataset, except for Study 702. Study 702 was very small since it was conducted on only elderly subjects and was only conducted for 6 months rather than for the 12 month OL period for the other OL extension trials of the integrated safety dataset.*

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

**Reviewer Comments of Results from Study -301.** *The results found in Section 6.4.3 of the CSR failed to show any new and clinically remarkable findings that differ from results that were previously described in the review and addendum review of the original NDA 21999. It is noted that the incidence of subjects with high PR interval was greater in the paliperidone group compared to the placebo group of the double-blind phase (2%, 0%, respectively). This finding is noted since it is an unexpected finding for the drug class, but is similar to results for a potential paliperidone-related effect on PR interval was previously described in the review of the original NDA 21999 (refer to this review for details). The review and addendum review of the original NDA 21999 describes other positive findings that were also observed in Study-301.*

*NDA 21999 was subsequently reviewed. Approved labeling includes the incidence of AEs of "atrioventricular block first degree" in a summary table (Table 1 under Adverse Reactions) for treatment groups receiving daily doses of up to 12 mg (Dosage and Administration recommends a maximum daily dose level of 12 mg).*

*Note the limitations with the data from Study -301, as previously discussed, that include small sample sizes during time points beyond the week 6 or 12 assessment time-points of the DB phase.*

*Results are summarized below.*

**Results of Study-301.**

The following paragraphs summarize results, according to the sponsor. Summary tables that were found in Section 6.4.3 of the CSR are also provided below. Note that the sponsor focuses primarily on QTc results and on describing individual subjects reported to have prolonged QTc interval, as described later.

Results of the Open-Label Phase of Study-301

The sponsor notes that events of "clinically significant QTc interval prolongation" were reported as AE's of "ECG abnormal specific" or "QT prolonged," as the Preferred Terms. These AE's were reported in less than 1% of subjects during the open-label phase (4 subjects with "EKG abnormal specific" and 2 subjects with "QT prolonged"). "None of the other events associated with ECG abnormalities was reported at the incidence of more than 1%." None of the events "were considered severe or serious by the investigators."

The sponsor notes 5 ADOs due to AE's "that reflected recorded ECG abnormalities" during the open-label phase of the study, of which four of these events occurred within 2.5 weeks of treatment. These ADOs occurred in subjects receiving 9 or 12 mg of Pal daily and are summarized by the sponsor as follows:

- Subject 100123 was a 30-year-old man with "ECG abnormal of mild severity (reported term, "non-specific T-wave abnormalities possibly secondary to heart disease")"
- Subject 100320 was a 53-year-old man with "T-wave inversion of moderate severity"
- Subject 100336 was a 50-year-old woman with "bundle branch block of mild severity"

- Subject 100767 was a 31-year-old man with “ECG abnormal specific of moderate severity”
- Subject 100232 was a 56-year-old man with “QT prolonged of mild severity” reported on Day 57 of treatment.

**Reviewer Comments of Potentially Remarkable Subjects with Cardiovascular System Related Event.**

*The review and addendum review of the original NDA 21999 submission describe individual subjects that appeared to develop cardiovascular-system (CVS) related complications associated with Pal adverse effects on the CVS or appeared to show an exacerbation or complications related to a pre-existing CVS condition that appear to be in part, Pal-related. See the reviews of NDA 21999 for more details. See recommendations related to these observations in the first and last sections of these past reviews. See the last section of this review for additional comments and recommendations.*

The following summary table shows the incidence of outliers, as provided by the sponsor.

Table 62: Number of Subjects With Treatment-Emergent Abnormal ECG Values During the Run-In and Stabilization Phases  
 (Study R076477-SCH-301: All Treated Analysis Set)

	ER OROS PAL (RI/ST) (N=530) n (%)
<b>Heart rate</b>	526
Abnormally high	166 (32)
Abnormally low	29 (6)
<b>PR interval</b>	526
Abnormally high	7 (1)
Abnormally low	0
<b>QRS interval</b>	526
Abnormally high	1 (<1)
Abnormally low	0
<b>QT interval</b>	526
Abnormally high	0
Abnormally low	0

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Note: Percentages calculated with the number of subjects per parameter as denominator.  
 Heart rate: abnormally low:  $\leq 50$  bpm, abnormally high:  $\geq 100$  bpm.  
 PR interval: abnormally high:  $\geq 110$  ms.  
 QRS interval: abnormally low:  $\leq 50$  ms, abnormally high:  $\geq 120$  ms.  
 QT interval: abnormally low:  $\leq 200$  ms, abnormally high:  $\geq 300$  ms.  
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**Results of the Double-Blind Phase of Study -301**

The sponsor notes positive findings relevant to increased heart rate and that “one subject” in the Pal group had “mild arrhythmia” reported. No other information on the subject could be found by the undersigned reviewer.

The sponsor noted that none of the AE's "associated with EKG abnormalities" that were reported during double-blind treatment were considered "severe" with the one exception of Subject 100067 who had tachycardia reported as an SAE.

The following table summarizes the results, as provided by the sponsor.

**Table 63: Number of Subjects With Treatment-Emergent Abnormal ECG Values During the Double-Blind Phase (Study R076477-SCH-301: Safety Analysis Set)**

	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)
<b>Heart rate</b>	94	92
Abnormally high	2 ( 2)	6 ( 7)
Abnormally low	5 ( 5)	5 ( 5)
<b>PR interval</b>	94	92
Abnormally high	0	2 ( 2)
Abnormally low	0	0
<b>QRS interval</b>	94	92
Abnormally high	1 ( 1)	0
Abnormally low	0	0
<b>QT interval</b>	94	91
Abnormally high	0	0
Abnormally low	0	0

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

Heart rate: abnormally low:  $\leq 50$  bpm, abnormally high:  $\geq 100$  bpm.

PR interval: abnormally high:  $\geq 210$  ms.

QRS interval: abnormally low:  $\leq 50$  ms, abnormally high:  $\geq 120$  ms.

QT interval: abnormally low:  $\leq 200$  ms, abnormally high:  $\geq 500$  ms.

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#### Results of Outliers of Prolonged QTc Interval

The sponsor's descriptions of ECG results generally focused on QT or QTc results. In addition to the previously described results in this review that included AE's of QTc prolongation as noted by the sponsor, the following are additional positive findings found in a section on QTc results (as found in Section 6.4.3.2 of the CSR).

The following scatterplots were provided by the sponsor.

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Figure 12: Scatterplot of Maximum Post-Baseline QTcLD Values Across Run-In, Stabilization, and Double-Blind Phases (Study R0764770-SCH-301)

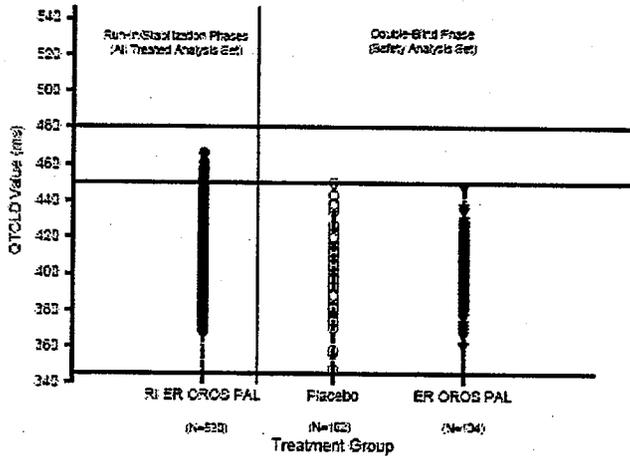
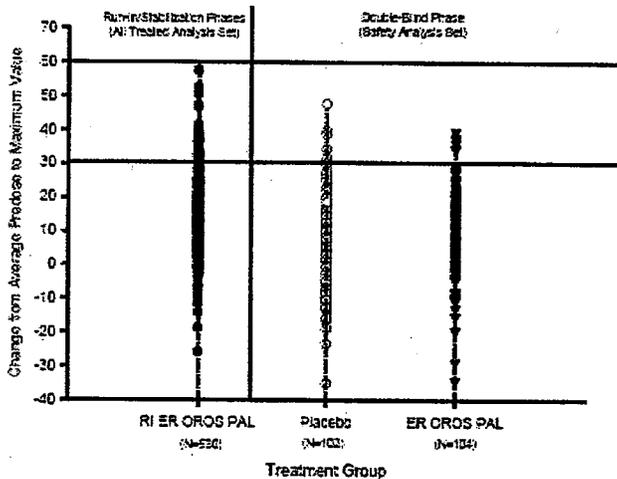


Figure 13: Change in QTcLD From Average Predose Value to Maximum Value in Individual Subjects Across Run-In, Stabilization, and Double-Blind Phases (Study R0764770-SCH-301)



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**Reviewer Comments on the Above Scatterplots**

Note that there appears to be an overall upward shift of the scatterplots of open label treated subjects towards greater QTc intervals than are observed in the subgroup of these subjects who entered the double-blind phase (subjects that were then randomized either to continue Pal treatment or to be switched to placebo treatment). These results suggest the possibility of greater QTc prolongation effects observed with initiating Pal treatment than when continuing Pal treatment. But, this observation is only speculative and is only based on results provided in the above scatterplots. Also consider the possible effect of an increase in the dose of Pal or

*other factors that may influence ADME or PK that were not examined (e.g. consider potential effects of accumulation with longer term treatment), as previously discussed in the clinical review of NDA21999. The clinical review and addendum clinical review of the original NDA 21999 discusses QT prolongation effects and includes results of scatterplots for the OL trial safety dataset.*

**Results of QTc Interval changes in the OL Phase:**

The sponsor used the same QTc calculation methods as employed for NDA 21999. The calculation methods are described in the review of the original submission (refer to the review for details).

The sponsor summarized results of Attachment 12.1.3 (of the CSR) on QTc outlier results for the OL phase of Study -301 as follows:

- An incidence of 91% of subjects had a maximum increase of less than 30 milliseconds from baseline in QTcLD during OL treatment
- A maximum increase of 30 to 60 milliseconds on QTcLD (from baseline) occurred in 9% of subjects during OL treatment (11% for QTcF will and 10% for QTlc).
- None of the subjects showed increases above 60 milliseconds in QTc (for -LD and lc)
- 2 subjects showed increases of QTcF of greater than 60 milliseconds (subjects 100177 and 100833; a description of these subjects could not be found in the submission).

See summary tables of results later in this subsection of this review (as provided by the sponsor).

The Sponsor's Descriptions of Individual Subjects with Prolonged QTc.

*Reviewer Comments. The sponsor noted individual subjects with events involving QTc interval prolongation as outlined below. QTcB values and observations on QTcB changes were also noted by the sponsor but these findings are generally excluded from descriptions below for the following reasons. Heart rate either increased or showed no change. Therefore, QTcB values which tended to yield the greatest values of QTc are not considered by the undersigned reviewer as appropriate or valid estimations of QT interval during the OL phase of Study -301. Note that the sponsor generally did not describe results of QTraw interval when describing results of individual subjects or in narratives found in attachments or appendices of Module 2.7.4 and in the CSR of Study -301.*

Subjects with Prolonged QTcLD During OL Treatment who had Normal Baseline QTcLD Values (see reviewer comments above):

- **Subject 100232 is an ADO due to QT prolonged, as previously mentioned.** This subject was a 56-year-old man with normal average predose QTcF, -lc and LD interval values except for a borderline QTcF value of 435 msec at baseline. He received 9 mg Pal daily during the study and developed QTc prolongation of up to 453 msec and values of 429-431 on Day 15 and values of 461 msec on Day 57 that was reported as an AE (QT prolonged). Treatment was discontinued due to this AE on Day 60 and the event resolved 22 days later.

- **Subject 100053** was a 54-year-old man who had a history of a coronary artery bypass graft and normal average predose QTc interval values. He developed QTc LD, F, lc values that ranged from 453-457 msec (increased from baseline values by 30-60 msec) on Day 4 (at 10 hours post-dose). QTc prolongation resolved on Day 5 and he completed the study-drug treatment on Day 114 (he was assigned to DB Pal and treated with 9 mg/day on week 1, then 12 mg daily for 15 days, then 15 mg daily for the remainder of the DB phase).

Subjects with Prolonged QTcLD During OL Treatment who had Normal Baseline QTcLD Values

**Subject 100105** and **Subject 100228** were middle-aged men with unremarkable past medical histories (except the former subject was overweight) who shifted from borderline QTc values at baseline to prolonged values (over 450 msec but values remained less than 470 msec).

**Subject 100091** was also described but only showed QTcB interval prolongation during treatment.

**Two ADOs due to QTc interval prolongation** that included the previously described Subject 100232 and Subject 100767, who was previously listed as having “ECG abnormal specific of moderate severity”. **Subject 100767:**

- Was a 31-year-old man
- Had an unremarkable past medical history
- Had a normal average predose QTc interval values (LD, lc and F).
- Had increased standing pulse rate of up to 119 bpm and borderline QTc interval values during treatment.
- Received 9 mg daily Pal over the first week of OL treatment followed by a daily dose of 12 mg.
- The last dose of Pal (12 mg) was given on Day 16 in which QTcB prolongation was reported as “moderately severe adverse event (ECG abnormal specific).” This AE led to early treatment cessation (an ADO).

**4 additional subjects with AEs of QTc prolongation during OL treatment** are described by the sponsor that included the following subjects:

- Subject 100095 who only had QTcB prolongation reported, but also had increased heart rate.
- Subjects 100312, 100739, and 100776 had borderline increases in QTc (-LD, lc and/or F) that were generally first noted on Days 4 or 5 of treatment. These subjects were also reported to have increased heart rates at various time-points in the study.

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Table 64: Classification of Maximum Corrected QT Intervals at End Point(Stab.) Versus Average Pre-Dose - Run-In and Stabilization Phases (Study R076477-SCH-301: All Treated Analysis Set)

	ER OROS PAL (R1/S1) (N=530)			Total
	Normal	Borderline	Prolonged	
<b>QTcD</b>				
Maximum value(R1/S1)				
Normal	494	0	0	494
Borderline	26	1	0	27
Prolonged	2	2	0	4
-----				
Total	522	3	0	525
<b>QTcF</b>				
Maximum value(R1/S1)				
Normal	491	0	0	491
Borderline	26	1	0	27
Prolonged	5	2	0	7
-----				
Total	522	3	0	525
<b>QTc</b>				
Maximum value(R1/S1)				
Normal	494	0	0	494
Borderline	26	1	0	27
Prolonged	2	2	0	4
-----				
Total	522	3	0	525
<b>QTcB</b>				
Maximum value(R1/S1)				
Normal	314	4	0	318
Borderline	140	19	3	162
Prolonged	27	15	3	45
-----				
Total	481	38	6	525

Note: Normal(Norm)(M: <=430 ms; F: <=450 ms); Borderline(Bord)(M: >430 ms to <=450 ms; F: >450 ms to <=470 ms); Prolonged(Prolo)(M: >450 ms; F: >470 ms)  
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**Double-blind Phase of Study -301**

The sponsor notes in Module 2.7.4 that:

- “No cases of QTc interval prolongation were reported as adverse events during the double-blind phase of the study.”

In-text descriptions of individual subjects could not be found (on pages 244-246 in Module 2.7.4).

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Clinical Review  
 Karen Brugge  
 Supplemental NDA 22-043 N000-N002  
 Paliperidone OROS oral

Table 65: Classification of Maximum Corrected QT Intervals at End Point (DB) Versus Average Pre-treatment Value - Double-Blind Phase (Study R076477-SCH-301: Safety Analysis Set)

	Treatment Group and Evaluation at Average Predose							
	Placebo (N=102)				ER OROS PAL (N=104)			
	Norm	Bord	Prolo	Total	Norm	Bord	Prolo	Total
<b>QTcLD</b>								
Maximum value								
Normal	91	0	0	91	90	0	0	90
Borderline	3	0	0	3	1	0	0	1
Prolonged	0	0	0	0	0	0	0	0
Total	94	0	0	94	91	0	0	91
<b>QTcF</b>								
Maximum value								
Normal	91	0	0	91	90	0	0	90
Borderline	2	0	0	2	1	0	0	1
Prolonged	1	0	0	1	0	0	0	0
Total	94	0	0	94	91	0	0	91
<b>QTcIc</b>								
Maximum value								
Normal	91	0	0	91	90	0	0	90
Borderline	3	0	0	3	1	0	0	1
Prolonged	0	0	0	0	0	0	0	0
Total	94	0	0	94	91	0	0	91
<b>QTcB</b>								
Maximum value								
Normal	79	1	0	80	74	5	0	79
Borderline	10	4	0	14	12	0	0	12
Prolonged	0	0	0	0	0	0	0	0
Total	89	5	0	94	86	5	0	91

Note: Normal(Norm)(M: <=430 ms; F: <=450 ms); Borderline(Bord)(M: >430 ms to <=450 ms; F: >450 ms to <=470 ms) Prolonged(Prolo)(M: >450 ms; F: >470 ms)  
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Table 66: Distribution of Changes From Average Pre-treatment Value to End Point in Maximum Corrected QT Values - Double-Blind Phase (Study R076477-SCH-303: Safety Analysis Set)

	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)
<b>QTcLD</b>	94	91
<30 (ms)	86 (91)	85 (93)
30-60 (ms)	8 (9)	6 (7)
>60 (ms)	0	0
<b>QTcF</b>	94	91
<30 (ms)	87 (93)	83 (91)
30-60 (ms)	7 (7)	8 (9)
>60 (ms)	0	0
<b>QTc</b>	94	91
<30 (ms)	88 (94)	85 (93)
30-60 (ms)	6 (6)	6 (7)
>60 (ms)	0	0
<b>QTcB</b>	94	91
<30 (ms)	89 (95)	83 (91)
30-60 (ms)	5 (5)	8 (9)
>60 (ms)	0	0

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

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**Reviewer Comments on Results of Elderly OL Trial -702**

Results found in in-text summary tables failed to reveal any clinically remarkable and new findings that differed from observations previously described above or in the reviews of NDA 21999. Based on the in-text summary tables, the following observations are noted. The incidence of outliers on the QTc parameters was:

- Numerically higher primarily for the intermediate prolongation category ( $\geq 450$  to  $< 480$  msec) than for the  $\geq 480$  msec category
- Generally numerically higher than observed for the integrated OL phase III trial safety dataset described in the review of NDA 21999 (of Studies -702, -703, -704, and -705 combined).

Without placebo control groups in these trials and given that comparisons are generally across studies, the above observations can only be considered preliminary. Furthermore, other QT results revealed by -702 were generally similar to those for the combined OL dataset (based on the results of the sponsor's summary tables found in the CSR for -702 and as shown in this review).

Individual subject descriptions of selected subjects were found in Section 6.4.3 (the section on ECG results) in the CSR. Overall the observations as described for each of these subjects in this section did not reveal any clinically remarkable observations that were not previously described in the review and addendum reviews of NDA 21999. The following subjects are described by the sponsor as follows:

- Subject 200214: this subject is described as an ADO due to the SAE of prolonged QTc interval. This subject is described in the review of NDA 21999 as subject who died from bronchopneumonia who also developed QTc prolongation.

- *Subjects 200720 and 200723 each had a history of coronary artery disease and hypertension. These subjects developed QTcLD prolongation (that were not reported as ADOs or SAE's) of:*
  - *Less than 480 milliseconds in subject 200720. QTc the prolongation was reported to occur at all assessment time-points during OL treatment in this subject.*
  - *Of greater than 500 milliseconds in subject 200723. QTc prolongation was only at baseline of the open label treatment phase in subject 200723. It is not clear to the undersigned reviewer is this baseline value was while on Pal, since it is not clear if this subject was in the placebo or Pal group in the DB phase of the lead-in Study -302 that preceded the OL extension trial, -702). QTc values were less than 450 milliseconds on other assessment time points during the OL trial.*

*Other clinically related abnormalities or adverse events could not be found in the sponsor's description of the above subjects.*

- Subject 200201:
  - *Was a 78-year-old female*
  - *Had completed double-blind paliperidone treatment before receiving open label paliperidone.*
  - *Had a history of hypertension, coronary artery disease and QTc prolongation.*

*The following QTc related observations on this subject are noted:*

- *It is not clear if QTc prolongation observed in the past in this subject was related to treatment with the medications such as an antipsychotic drug.*
- *The average predose value of QTc LD was 452.7 milliseconds (prior to double-blind treatment).*
- *She developed QTc LD that reached a maximum value of 487 milliseconds on week 24 (the last study visit) that corresponded with an increase of 30 to 60 milliseconds from baseline.*
- *One week later (corresponded to one week after her last dose) the QTc LD value was 466 milliseconds.*

*This subject also had multiple AE's of falls as follows:*

- *The subject was reported to have "falls that were not [reported] at times with other events."*
- *The sponsor also does not describe any other clinically related abnormalities that can explain these falls.*
- *The sponsor does not include falls as an event that occurred in this patient's past medical history.*

*Other AEs were:*

- *Multiple events of hypertension that required treatment with concomitant medication,*
- *AE's of dizziness,*
- *Increased blood pressure,*
- *Asthenia,*
- *Fatigue,*
- *Headache and*
- *Insomnia.*

*Reviewer comments on the reported events in the above subject 200201:*

- *A role of paliperidone in potentiating her pre-existing condition of borderline QTc prolongation. This potential effect of paliperidone occurred during chronic treatment with the drug.*
- *This subject had additional AE's that include falls and dizziness that are suspicious of at least a role of paliperidone, since this subject is not described as having these symptoms prior to treatment.*
- *Although the subject had a history of hypertension, a role of paliperidone in exacerbating her hypertension should also be considered.*

*Reviewer comments on difficulties with interpreting the observations reported in the above subject 200201:*

- *It is difficult to interpret the results as provided by the sponsor since it is not clear if the subject's heart rate also changed or became abnormal. Alterations in heart rate can influence the interpretation of QTc results.*
- *The sponsor also does not describe the timing of the EKG assessments relative to the timing of her daily treatment.*
- *The information provided in the sponsor's summary is limited (e.g. diagnostic testing and results of clinical assessments to determine potential underlying etiologies cannot be found).*
- *It is difficult to determine the role of paliperidone in the events reported in this elderly subject in light of her multiple medical conditions and in the absence of a diagnostic work-up for each of the events that were reported (e.g. diagnostic evaluations with test results for ruling out non-drug related etiologies for each of the above events).*

*Refer to a discussion and description of potentially clinically remarkable subjects in Section 7.1.3.3 in the review of the original NDA 21999, as well as the addendum review of this previous NDA.*

*In addition to the above the subjects, the sponsor briefly enumerates and describes subjects reported with AE's of QTc or QT interval prolongation. Yet, the sponsor indicates that EKG reading results of only QTcF and QTcB were available to investigators. A total of seven subjects were reported to have an AE of QTc or QT interval prolongation as follows:*

- *Two subjects were previously described (200214 and 200720).*
- *The sponsor does not describe any additional clinically related abnormalities or AEs in any of the 7 subjects.*
- *QTc LD values were normal in all but one of the subjects, which was subject 200214 who eventually died with bronchopneumonia, as previously mentioned in this review and as previously described in detail in the original review of NDA 21999.*

*It is difficult to interpret the limited information found on the above subjects with AEs of QTc prolongation for a number of reasons. For example, the sponsor does not include heart rate results in the brief descriptions of these subjects, which in turn, influences QT and QTc values. Other clinically related information could also not be found in the sponsor's descriptions.*

*Subjects meeting the prespecified outlier criteria (including the above subjects meeting these criteria) should have been captured in the database used to generate the results on the incidence of outliers on this EKG parameter.*

**Results of the Integrated OL Safety Dataset**

The following summary tables were copied from Module 2.7.4 which the sponsor provided to summarize the results.

**Table 87: Number of Subjects With Treatment-Emergent Abnormal ECG Values During the Open-Label Period**  
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali ≤6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali ≤6 months (N=209) n (%)	Pali/Pali >6 months (N=477) n (%)	Olan/Pali ≤6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali ≤6 months (N=416) n (%)	Total Pali >6 months (N=755) n (%)
<b>Heart rate</b>	99	137	203	477	107	141	409	755
Abnormally high	30 (30)	39 (28)	32 (16)	98 (21)	32 (30)	38 (27)	94 (23)	175 (23)
Abnormally low	2 (2)	14 (10)	7 (3)	36 (8)	4 (4)	7 (5)	13 (3)	57 (8)
<b>PR interval</b>	98	137	202	477	107	141	407	755
Abnormally high	0	4 (3)	1 (<1)	13 (3)	1 (1)	4 (3)	2 (<1)	21 (3)
Abnormally low	0	0	0	0	0	0	0	0
<b>QRS interval</b>	99	137	203	477	107	141	409	755
Abnormally high	2 (2)	1 (1)	1 (<1)	2 (<1)	1 (1)	0	4 (1)	3 (<1)
Abnormally low	0	0	0	0	0	0	0	0
<b>QT interval</b>	99	137	203	477	107	141	409	755
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	0	0	0	0	0	0	0	0

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

Note: Heart rate: abnormally low: ≤50 bpm, abnormally high: ≥100 bpm.

PR interval: abnormally high: ≥210 msec.

QRS interval: abnormally low: ≤50 msec, abnormally high: ≥120 msec.

QT interval: abnormally low: ≤260 msec, abnormally high: ≥500 msec.

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Table 94: Distribution of Maximum Changes From Average Predose Value in Corrected QT Values  
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali	Pla/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	<=6 months (N=99) n (%)	>6 months (N=137) n (%)	<=6 months (N=209) n (%)	>6 months (N=477) n (%)	<=6 months (N=108) n (%)	>6 months (N=141) n (%)	<=6 months (N=416) n (%)	>6 months (N=755) n (%)
<b>QTcLD</b>								
<30 (ms)	99 (91)	137 (88)	203 (95)	476 (89)	107 (97)	141 (96)	409 (94)	754 (89)
30-60 (ms)	3 (3)	18 (12)	11 (5)	33 (22)	3 (3)	14 (10)	22 (5)	33 (22)
>60 (ms)	1 (1)	0	0	1 (-1)	0	0	1 (-1)	1 (-1)
<b>QTcF</b>								
<30 (ms)	99 (89)	137 (86)	203 (95)	476 (88)	102 (95)	126 (89)	383 (94)	661 (88)
30-60 (ms)	10 (10)	19 (14)	10 (5)	38 (22)	5 (5)	15 (11)	25 (6)	92 (12)
>60 (ms)	1 (1)	0	0	1 (-1)	0	0	1 (-1)	1 (-1)
<b>QTcE</b>								
<30 (ms)	99 (91)	137 (88)	203 (95)	476 (88)	103 (96)	128 (91)	387 (95)	662 (89)
30-60 (ms)	3 (3)	17 (12)	9 (4)	54 (21)	4 (4)	13 (9)	21 (5)	34 (21)
>60 (ms)	1 (1)	0	0	1 (-1)	0	0	1 (-1)	1 (-1)
<b>QTcB</b>								
<30 (ms)	99 (77)	137 (72)	203 (82)	365 (77)	83 (78)	104 (74)	326 (80)	567 (75)
30-60 (ms)	20 (20)	36 (26)	35 (17)	105 (22)	15 (21)	36 (26)	78 (20)	177 (23)
>60 (ms)	3 (3)	3 (2)	1 (-1)	6 (3)	1 (1)	1 (1)	3 (1)	10 (3)

Note: Percentages calculated with the number of subjects per parameter as denominator.  
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Only the QTcLD results from Table 93 are shown below.

Table 93: Classification of Maximum Corrected QT Intervals During Open-Label Treatment Versus Average Predose Value  
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Treatment Group and Evaluation at Average Predose	Pla/Pali <=6 months (N=99)			Pla/Pali >6 months (N=137)			Pali/Pali <=6 months (N=209)			Pali/Pali >6 months (N=477)		
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
<b>QTcLD</b>												
Maximum value												
Normal	96	0	0	96	135	0	0	135	198	0	0	198
>=450 - <480	2	0	0	2	2	0	0	2	3	2	0	5
>=480	0	1	0	1	0	0	0	0	0	0	0	0
Total	98	1	0	99	137	0	0	137	201	2	0	203

Table 93: Classification of Maximum Corrected QT Intervals During Open-Label Treatment Versus Average Predose Value (Continued)  
 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Treatment Group and Evaluation at Average Predose	Olan/Pali <=6 months (N=108)			Olan/Pali >6 months (N=141)			Total Pali <=6 months (N=416)			Total Pali >6 months (N=755)		
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
<b>QTcLD</b>												
Maximum value												
Normal	107	0	0	107	140	0	0	140	401	0	0	401
>=450 - <480	0	0	0	0	1	0	0	1	5	2	0	7
>=480	0	0	0	0	0	0	0	0	1	0	1	2
Total	107	0	0	107	141	0	0	141	406	2	1	409

**Reviewer Comments**

Table 93 above, shows a larger incidence of subjects with increased QTcLD intervals in the DB Pal/OL Pal subgroup compared to other treatment subgroups and that the greatest incidence was observed in the over 6 month treatment DB Pal/OL Pal subgroup.

Table 94 shows a larger incidence of increased QTcLD interval shifts in the over 6 month treated subgroups compared to the ≤ 6 month subgroup within each DB/OL treatment group.

It is difficult to interpret whether or not the above numerical trends were due to real effects of Pal treatment over time or if they are reflecting differences due to a longer observational period or due to other confounding variables. Yet, the previous section on descriptive statistical results over time suggest a possible real effect when comparing assessment time-points of 6 months or later compared to earlier OL assessment time-points in primarily the DB Pal/OL Pal and DB Olanzapine/OL Pal treatment groups (and compared to the DB Placebo/OL Pal subgroups).

In text descriptions and subject numbers of clinically remarkable subjects with QT or QTc prolongation could not be found in Section 4.2 3.2.2 of Module 2.7.4 (where results on QT and QTc are described). Only 2 subjects are described since they had QTcLD of over 500 msec. These 2 subjects are 201418 and 220214 and were previously described in past reviews of NDA 21999.

**7.1.10.3.3 Marked outliers and dropouts for ECG abnormalities**

See the previous section. Also see sections 7.1.2-5 and 7.2.9.1 for additional clinically remarkable subjects and updated results in the SUR.

**7.1.10.4 Additional analyses and explorations**

**Body Weight Changes in Study -301**

The following table summarizes body weight changes in the DB phase of Study -301 (as provided by the sponsor).

**Table 61: Number of Subjects With Abnormal Weight Change At End Point (DB) - Double-Blind Phase (Study R076477-SCH-301: Safety Analysis Set)**

	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)
Weight classification (RI)	94	97
Decrease ≥ 7%	10 (11)	4 (4)
Increase ≥ 7%	11 (12)	19 (20)

Note: Percentages calculated with the number of subjects per parameter as denominator.  
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**Body Weight Results in the Integrated OL Trial Safety Dataset.**

The sponsor indicates that group mean increases of 1.1 kg and 2.2 kg were observed in the ≤ 6 month and over 6 month total Pal subgroups, respectively, of the integrated OL trial dataset.