

The following summary table is copied from Module 2.7.4 of the submission.

**Table S2: Number of Subjects With Abnormal Weight Values at End Point**  
 (Pooled Open-Label Studies R376477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali -6 months (N=99) n (%)	Pla/Pali -6 months (N=157) 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>Weight classification</b>	73	100	158	360	80	105	311	565
Decrease $\geq$ 7%	4 (5)	10 (10)	5 (3)	26 (7)	4 (5)	7 (7)	13 (4)	45 (8)
Increase $\geq$ 7%	8 (11)	18 (18)	25 (16)	38 (24)	15 (18)	30 (29)	48 (15)	136 (24)
<b>Weight classification (OL)</b>	74	100	158	360	80	105	312	565
Decrease $\geq$ 7%	3 (4)	5 (5)	1 (1)	22 (6)	5 (6)	11 (10)	9 (3)	41 (7)
Increase $\geq$ 7%	6 (8)	17 (17)	11 (7)	37 (26)	3 (4)	17 (16)	20 (6)	91 (16)

Note: Percentages calculated with the number of subjects per parameter as denominator.  
 Weight classification: relative to baseline(DB)  
 Weight classification (OL): relative to base(OPEN)  
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#### 7.1.11 Immunogenicity

Not applicable to this efficacy supplemental NDA.

#### 7.1.12 Human Carcinogenicity

No new information on this topic can be found in NDA 22043.

#### 7.1.13 Special Safety Studies

Refer to the clinical review of NDA 21999 for this drug product for the schizophrenia indication and for results of a special QT prolongation study. The Agency QT Team was consulted on QT prolongation effects of Pal. Following input from the QT Team, NDA 21999 was approved by the Agency on 12/19/06 that includes a QT section under Warnings in approved labeling.

#### 7.1.14 Withdrawal Phenomena and/or Abuse Potential

This drug which was approved under NDA 21999 for schizophrenia is not classified as a controlled substance.

The submission does not include special safety trials on this topic.

#### 7.1.15 Human Reproduction and Pregnancy Data

The submission does not include special safety trials. The sponsor indicates that there were not pregnancies during any of the clinical trials described in the current NDA (as specified in Section 6.4 of Module 2.7.4).

#### 7.1.16 Assessment of Effect on Growth

The submission does not include special safety studies.

#### 7.1.17 Overdose Experience

Refer to the clinical review of NDA 21999 describing overdose cases during the sponsor's clinical trials and of results of a review for safety data in the literature. A description of any new or additional cases of overdose cannot be found except for one new case of "accidental overdose" (subject 500680 described below) during November 9-16, 2005 (either based on a review of literature using a more recent cut-off date of 3/31/06 since the NDA 21999 submission or based on cases in clinical trials, as described in Sections 4.10 of Module 2.5 or Section 6.5 of Module 2.7.4).

Subject 500680 was in OL Extension Study -705 was a 26 year old male who ingested an extra 15 mg dose nightly for 8 nights for sleep disturbance (he was receiving 15 mg daily as part of the protocol). He was hospitalized for exacerbation of schizophrenia thereafter (he was also having hallucinations and delusions that started prior to this "accidental overdose"). He became suicidal during hospitalization.

*Reviewer Comment of Subject 500680: This subject is not described as having any clinical sign or symptom associated with the overdose but is described as having AEs that appear to be consistent with signs and symptoms of worsening schizophrenia (based on a review of the in-text description of this subject in Section 6.5 of Module 2.7.4). The narrative failed to reveal any additional findings that would suggest a new clinically remarkable and unexpected adverse effect associated with overdose.*

#### 7.1.18 Postmarketing Experience

Pal (ER OROS) has not been marketed in any country. Refer to the review of NDA 21999 for the same drug product (for a schizophrenia indication) regarding postmarketing information on risperidone.

#### 7.1.19 7.1.18 Review of the Literature

See section 7.2.2.3 for a summary of the literature review.

## **7.2 Adequacy of Patient Exposure and Safety Assessments**

See sections 4 and previous subsections of 7. Section 7.1 describes each safety dataset that was reviewed and information on the safety assessments conducted. Section 7.1.4.1 of this review also provides more detailed information on exposure in subjects of the OL trial safety dataset. Section 6 provides details for the pivotal maintenance Study -301.

The sponsor has met ICH guidelines for 6 and 12 month exposure (as previously discussed in the original review of NDA 21999).

Limitations with the safety datasets and are also relevant to exposure were previously discussed under various subsections of Sections 4 and 7.1. Some potential limitations to the safety datasets are also discussed under corresponding subsections of Section 7, relevant to a given clinical parameter. See past clinical reviews of NDA21999 for additional limitations.

### **7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety**

**Description of Studies, Safety Datasets and other Aspects of Exposure and Safety Assessments.** To avoid redundancy, refer to Section 4 for a description of studies and overall enumeration of subjects and refer to Subsection 7.2.1.3 below and previous Sections 4, 6, 7.1, 7.1.4.1 of this review. Section 4 describes the contents of the submission, the review strategy and other aspects of the data. Potential limitations to the safety datasets are also discussed under various subsections of Section 7.

The sponsor has met ICH guidelines for 6 and 12 month exposure (as previously discussed in the original review of NDA 21999).

#### **7.2.1.1 Study type and design/patient enumeration**

See Sections 4 and 7.1 for this topic. The review of NDA 21999 also provides this information. The sponsor has provided updated information of OL extension trials in which more subjects are exposed to longer term treatment of 6-12 months.

#### **7.2.1.2 Demographics**

See Section 6 for demographic information on the pivotal Phase III trial and the review of NDA 21999 covered this topic for all trials that include those for NDA 22043. Demographic features for the Phase III trials of the current submission are generally similar to those of the schizophrenia patient population. The original clinical review of NDA21999 provides more details on demographic information of each Phase III safety dataset that includes safety datasets

described in the current review (in which updated results are provided since trials were ongoing and/or continue to be ongoing).

#### 7.2.1.3 Extent of exposure (dose/duration)

As previously discussed ICH guidelines on exposure were met (see original review of NDA 21999. See previous sections of this review and sections as specified under Section 7.2 above and Section 7.1.4.1 on the disposition of subjects and a summary of completers in the OL trials.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Literature review results and postmarketing information is addressed elsewhere in this review. Individual subject information that is described in this review came from either in-text descriptions, narratives or for more recently reported cases from CIOMS (safety alert report) forms, as specified elsewhere in this review.

#### 7.2.2.1 Other studies

Other studies are addressed in other sections of this review (refer to Section 7.1 and Section 4 of this review and section 7.1.12).

#### 7.2.2.2 Postmarketing experience

Paliperidone is not approved for the market in any country, as previously described, in subsection 7.1.17. Refer to this previous section for details relevant to this topic.

#### 7.2.2.3 Literature

Refer to section 8.6.

*Reviewer comments on search methods. Search methods generally appear to be acceptable.*

### 7.2.3 Adequacy of Overall Clinical Experience

*Reviewer Comments. This subsection focuses only on clinical experience relevant to safety. Some limitations of safety datasets were previously addressed in various section of this review.*

*The sponsor meets ICH guidelines for exposure which is a topic discussed primarily in the clinical review of NDA 21999 that is also relevant to the current NDA 22043.*

*The bulk of longterm safety data was previously provided under NDA 21999 and was previously reviewed. The current review of NDA 222043 provided updated results of OL trials in which more subjects had exposure of 6-12 months. The focus of the current review was an attempt to identify any clinical remarkable findings that were not previously found in NDA 21999 (as*

*described in the original and addendum clinical reviews of NDA 21999, as previously discussed under Section 4 of the current review).*

*The longterm safety data is limited due to the inherent nature of OL trials (e.g. no placebo group for comparisons, greater between subject, test-retest and other sources of variability, as well as the likelihood for existing confounding variables influencing outcome measures, in contrast to variance that would be expected in a more focused, controlled special safety study that incorporates methods to control for specific confounding variables relevant to a given clinical parameter). However, OL trials provide some information relevant to safety. Furthermore, logistical and ethical considerations limit how longterm trials may be conducted. Study -301 which included a DB phase had key limitations, as previously discussed in this review.*

*Additional limitations with interpreting study results as provided in NDA22043 are previously discussed in corresponding sections of this review (also see Section 7.2). Refer to the review of NDA 21999 for other limitations and on limitations with extrapolating results to the elderly population and other special populations.*

*Special longterm safety studies (e.g. studies designed to examine a specific potential adverse drug effect) could not be found in the submission.*

*Comments and recommendations for special safety studies that included longterm studies were previously provided in the original review of NDA 21999. Among these past recommendations were recommendations involving challenge studies to further explore potential longterm cardiovascular system effects of Pal. These recommendations also included comments about using an adequate dose-range. It was suggested that the use of a slightly higher than approved dose-level be used for some studies (under adequately safety study conditions), since plasma levels of the drug can fluctuate over time and vary across individuals due to a number of factors (e.g. due to food effects, accumulation, among other factors). OCPB input was also recommended, as well as input from other experts.*

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

*See the last section of this review for further comment and recommendations relevant to the current proposed claim for longer term use, as discussed under Section 9 of this review.*

#### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable to this NDA.

### 7.2.5 Adequacy of Routine Clinical Testing

*Concerns with the clinical data were previously discussed in appropriate sections in this review. Refer to the last section of this review for any additional comments or recommendations that may apply to this topic and that were not previously conveyed in reviews of NDA 21999 conducted by the undersigned reviewer of the current NDA 22043 review.*

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

*This topic is not applicable to this NDA, since this topic was previously reviewed for the schizophrenia indication under NDA 21999 which was approved on 12/19/06.*

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

*This topic was covered in reviews of NDA 21999 for the schizophrenia indication and this previous NDA of this same drug product was approved.*

*Refer to the last section of this review for any additional comments and recommendations that were not previously provided in reviews of NDA 21999 that were conducted by the undersigned reviewer of the current NDA 22043 review.*

### 7.2.8 Assessment of Quality and Completeness of Data

*Refer to Section 4 of this review. No additional concerns were found that differ from those previously conveyed for NDA 21999.*

### 7.2.9 Additional Submissions, Including Safety Update

#### 7.2.9.1 120-Day Safety Update Report

##### ***Reviewer Comments of SAEs and ADOs***

*The sponsor's summary tables and in-text sections of the 120-Day SUR fail to reveal any new, clinically remarkable findings that were not already described in this review (see sections 7.1.1-3) or described in past clinical reviews of NDA21999. Summary tables are shown below.*

*Few newly reported ADOs and SAEs occurred between the cut-off dates used for the original NDA22043 submission and for the current SUR submission. The following are reviewer comments about newly reported SAEs and ADOs that were found in the 120-Day SUR submission:*

- *Most of these newly reported SAEs and ADOs were not unexpected for the patient population or for the study drug (e.g. exacerbation of schizophrenia, among others).*
- *One newly reported ADO of “moderate-severe dermatitis was reported (subject 100837) during OL Pal treatment but the narrative did not indicate that the “dermatitis” had any signs of toxic erythematous necrotizing syndrome (TENS) or Steven’s Johnson syndrome (SJS). No other clinical abnormalities (other than obesity noted at baseline) were described in the narrative.*
- *No SAEs or ADOs of TENS or SJS were reported (refer to tables below) or were found in the in-text SUR sections of ADOs and SAEs (sections 2.1.2-4) or in the special AE search section (2.1.6 section of the SUR).*
- *Only 1 subject with NMS was described (100057).*
- *One ADO and SAE of dyspnea was reported (subject 500547). “No organic findings” were revealed by an emergency room evaluation that included an ECG assessment and other “tests.” The subject was treated for anxiety and the dyspnea resolved. At the next study visit 10 days later the subject had normal ECG and vital sign assessments, according to the narrative but a day later Pal treatment was discontinued. There were no other abnormalities found in the narrative and clinical data could not be found in the narrative.*

*The sponsor included narratives of subjects not reported to as ADOs or as having SAEs but who had elevations of ALT or AST increases of at least 3 times the ULN. Several newly reported subjects were found upon review of this section of the narratives:*

- *Several subjects were found to have abnormal baseline values, although their past medical histories generally did not include any pre-existing condition related to liver function abnormalities or risk factors.*
- *A few subjects had normal baseline values but had new onset elevations during Pal treatment. These subjects had no prior history suggesting that these subjects did not have a pre-existing condition. Therefore, these subjects appeared to have drug-related elevations of LFTs.*
- *At least one of the subjects (502015) had elevations of up to about 10 times the ULN (on ALT or AST) but values decreased (but remained abnormally elevated) at 2 additional time-points during OL treatment before completing the study.*
- *None of these subjects were described as having elevations in bilirubin, although bilirubin values were generally not found in the narrative*
- *None of the subjects were described as having liver failure, jaundice or other related AEs (in the narratives).*
- *None of these subjects were newly reported ADOs or SAEs (they were found in a separate section of narratives for subjects with ALT and AST elevations, as specified, but who were not reported to have ADOs or SAEs.*
- *Additional subjects are described later.*
- *Also refer to previous sections of this review under Section 7.1.8 that discuss outliers on LFTs.*
- *Similar cases such as the above cases with elevated LFTs were previously described in past reviews of NDA21999.*

*The above new cases (as found in the current SUR in Appendices 3.5.1-2) that appeared to have drug-related elevations in LFTs are not different from several previously described cases in reviews of NDA21999. Only a few new cases were reported. Therefore, the number of these cases (over 3 x ULN) would not appear to significantly alter the previously reported, overall incidence of LFT elevations in Study 701 and in the integrated OL trial dataset. Consequently, the results on the basis of the incidence of outliers on LFTs does not suggest a safety signal, as previously noted on past reviews of NDA21999 and as noted by Dr. Laughren in his Memo-to-the-File for NDA21999.*

*Yet, as previously discussed (in reviews of NDA21999) there were a greater number of ADOs due to LFT function related events in Pal subjects compared to placebo subjects in the 6-week Phase III schizophrenia trial safety dataset. Additional cases (that were not ADOs) that appeared to have drug-related LFT elevations were also previously described in which a non-drug-related etiology could not be identified (refer to past clinical reviews of NDA21999).*

*See additional cases described in a subsection below summarizing results on laboratory parameters, as provided in the SUR submission.*

*NDA21999 was approved on 12/16/06.*

**Serious Adverse Events in OL Trials**

The following are summary tables of SAEs as provided by the sponsor.

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Table 24: Serious Adverse Events Through 26 June 2006  
 (Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali	Pla/Pali	Pla/Pali	Pla/Pali	Pali/No DBV	Pali/No DBV
	≤6 months (N=10) n (%)	>6 months (N=70) n (%)	≤6 months (N=2) n (%)	>6 months (N=79) n (%)	Pali ≤6 months (N=25) n (%)	Pali >6 months (N=69) n (%)
<b>Total no. subjects with serious adverse events</b>	3 (20)	3 (4)	0	4 (5)	1 (4)	3 (5)
<b>Psychiatric disorders</b>	1 (10)	3 (4)	0	3 (4)	0	2 (3)
Schizophrenia	0	3 (4)	0	3 (4)	0	1 (2)
Delusion	0	0	0	0	0	1 (2)
Suicide attempt	1 (10)	0	0	0	0	0
<b>Injury, poisoning and procedural complications</b>	0	1 (1)	0	1 (1)	0	0
Alcohol poisoning	0	0	0	1 (1)	0	0
Tibia fracture	0	1 (1)	0	0	0	0
<b>Nervous system disorders</b>	1 (10)	0	0	0	0	1 (2)
Convulsion	0	0	0	0	0	1 (2)
Syncope	1 (10)	0	0	0	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>	0	0	0	0	0	1 (2)
Pulmonary embolism	0	0	0	0	0	1 (2)
<b>Reproductive system and breast disorders</b>	0	0	0	0	1 (4)	0
Vasovagal	0	0	0	0	1 (4)	0

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

(Continued)

Table 24: Serious Adverse Events Through 26 June 2006 (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=33) n (%)	>6 months (N=200) n (%)
<b>Total no. subjects with serious adverse events</b>	3 (9)	10 (5)
<b>Psychiatric disorders</b>	1 (3)	3 (4)
Schizophrenia	0	2 (4)
Delusion	0	1 (1)
Suicide attempt	1 (3)	0
<b>Injury, poisoning and procedural complications</b>	0	2 (1)
Alcohol poisoning	0	1 (1)
Tibia fracture	0	1 (1)
<b>Nervous system disorders</b>	1 (3)	1 (1)
Convulsion	0	1 (1)
Syncope	1 (3)	0
<b>Respiratory, thoracic and mediastinal disorders</b>	0	1 (1)
Pulmonary embolism	0	1 (1)
<b>Reproductive system and breast disorders</b>	1 (3)	0
Vasovagal	1 (3)	0

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

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Table 25: Serious Adverse Events Through 26 June 2006  
 (Pooled Open-Label Studies R006+77-SCM-702, -703, -704, -705; Safety Analysis Set)

Body System or Organ Class Dictionaries-derived Term	Plit/Pali	Plit/Pali	Pali/Pali	Pali/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	≤6 months (N=102) n (%)	>6 months (N=134) n (%)	≤6 months (N=213) n (%)	>6 months (N=473) n (%)	≤6 months (N=108) n (%)	>6 months (N=141) n (%)	≤6 months (N=423) n (%)	>6 months (N=748) n (%)
<b>Total no. subjects with serious adverse events</b>	17 (17)	34 (19)	46 (19)	57 (13)	33 (31)	34 (19)	90 (21)	55 (11)
<b>Psychiatric disorders</b>								
Psychotic disorder	12 (12)	30 (7)	35 (16)	45 (10)	30 (28)	31 (8)	77 (18)	66 (9)
Schizophrenia	7 (7)	2 (1)	14 (7)	21 (4)	12 (11)	3 (4)	33 (8)	28 (4)
Depressive	2 (2)	3 (3)	13 (7)	15 (3)	13 (12)	3 (2)	30 (7)	21 (3)
Suicidal ideation	0	2 (1)	1 (<1)	4 (1)	2 (2)	1 (1)	3 (1)	7 (1)
Agitation	2 (2)	1 (1)	3 (1)	5 (1)	0	0	5 (1)	6 (1)
Hallucination, auditory	0	0	0	4 (1)	0	0	0	4 (1)
Acute psychosis	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Anxiety	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Completed suicide	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Depressed mood	0	0	0	2 (<1)	0	0	0	2 (<1)
Suicide attempt	1 (1)	2 (1)	2 (1)	0	1 (1)	0	4 (1)	2 (<1)
Aggression	2 (2)	1 (1)	0	0	4 (4)	0	6 (1)	1 (<1)
Alcoholism	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Confusional state	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Delusion	0	0	2 (1)	1 (<1)	0	0	2 (<1)	1 (<1)
Insomnia	0	1 (1)	1 (<1)	0	2 (2)	0	3 (1)	1 (<1)
Dementia	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Dyslexia psychogenica	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia, paranoid type	0	0	0	1 (<1)	0	0	0	1 (<1)
Self-harmful ideation	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Infections and infestations</b>								
Nasopharyngitis	0	0	1 (<1)	3 (2)	1 (1)	1 (1)	2 (<1)	9 (1)
Bronchitis acute	0	0	0	2 (<1)	0	0	0	2 (<1)

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

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Table 25 Serious Adverse Events Through 26 June 2006 (Continued)  
 (Pooled Open-Label Studies R076477-SCH-702, -703, -704, -705; Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Flu/Pali	Flu/Pali	Pali/Pali	Pali/Pali	Olas/Pali	Olaz/Pali	Tanz/Pali	Total/Pali
	≤6 months (N=102) n (%)	>6 months (N=134) n (%)	≤6 months (N=213) n (%)	>6 months (N=475) n (%)	≤6 months (N=108) n (%)	>6 months (N=141) n (%)	≤6 months (N=423) n (%)	>6 months (N=748) n (%)
<b>Infectious and infestation (continued)</b>								
Cellulitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Meningitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Pericardial effusion	0	0	0	1 (<1)	0	0	0	1 (<1)
Pulmonary tuberculosis	0	0	0	0	0	1 (1)	0	1 (<1)
Scabies	0	0	0	1 (<1)	0	0	0	1 (<1)
Urinary tract infection	0	0	0	1 (<1)	0	0	0	1 (<1)
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	0	0	0	0	1 (1)	0	1 (<1)	0
<b>Nervous system disorders</b>								
Ataxia	1 (1)	2 (1)	4 (2)	5 (1)	1 (1)	0	6 (1)	7 (1)
Alcoholism	0	0	0	2 (<1)	1 (1)	0	1 (<1)	2 (<1)
Dizziness	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Dystonia	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Ischemic stroke	0	1 (1)	0	0	0	0	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Transient ischemic attack	1 (1)	0	0	0	0	0	1 (<1)	0
<b>General disorders and administration site conditions</b>								
Pyrexia	0	0	1 (<1)	4 (1)	1 (1)	0	2 (<1)	4 (1)
Cyst	0	0	0	2 (<1)	0	0	0	2 (<1)
Pruritus	0	0	0	1 (<1)	0	0	0	1 (<1)
Irritability	0	0	0	1 (<1)	0	0	0	1 (<1)
Chills	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0

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

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Table 15. Serious Adverse Events Through 26 June 2006 (Continued)  
 (Pooled Open-Label Studies B076477-SCH-702, -703, -704, -705; Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Plu/Pali	Plu/Pali	Pali/Pali	Pali/Pali	Olun/Pali	Olun/Pali	Total Pali	Total Pali
	≤6 months (N=102) n (%)	>6 months (N=134) n (%)	≤6 months (N=213) n (%)	>6 months (N=473) n (%)	≤6 months (N=108) n (%)	>6 months (N=141) n (%)	≤6 months (N=423) n (%)	>6 months (N=748) n (%)
<b>Injury, poisoning and procedural complications</b>	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	0	4 (1)	4 (1)
Alcohol poisoning	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Fall	0	0	0	1 (<1)	0	0	0	1 (<1)
Road traffic accident	0	1 (1)	0	0	0	0	0	1 (<1)
Traumatic haematomas	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Overdose	0	0	0	0	1 (1)	0	1 (<1)	0
<b>Respiratory, thoracic and mediastinal disorders</b>	0	1 (1)	1 (<1)	1 (<1)	0	1 (1)	1 (<1)	3 (<1)
Dyspnoea	0	1 (1)	1 (<1)	0	0	1 (1)	1 (<1)	2 (<1)
Asthma	0	0	0	0	0	1 (1)	0	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
<b>Metabolism and nutrition disorders</b>	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Diabetes mellitus	0	0	0	1 (<1)	0	0	0	1 (<1)
Hypoglycaemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Hypokalaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Benign neoplasm of skin	0	0	0	0	0	1 (1)	0	1 (<1)
Cervix neoplasm	0	0	0	1 (<1)	0	0	0	1 (<1)
<b>Blood and lymphatic system disorders</b>	0	0	0	1 (<1)	0	0	0	1 (<1)
Anaemia	0	0	0	1 (<1)	0	0	0	1 (<1)

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

(Continued)

Table 15. Serious Adverse Events Through 26 June 2006 (Continued)  
 (Pooled Open-Label Studies B076477-SCH-702, -703, -704, -705; Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Plu/Pali	Plu/Pali	Pali/Pali	Pali/Pali	Olun/Pali	Olun/Pali	Total Pali	Total Pali
	≤6 months (N=102) n (%)	>6 months (N=134) n (%)	≤6 months (N=213) n (%)	>6 months (N=473) n (%)	≤6 months (N=108) n (%)	>6 months (N=141) n (%)	≤6 months (N=423) n (%)	>6 months (N=748) n (%)
<b>Gastrointestinal disorders</b>	1 (1)	1 (1)	0	0	0	0	1 (<1)	1 (<1)
Cholera disease	0	1 (1)	0	0	0	0	0	1 (<1)
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
<b>Hepatobiliary disorders</b>	0	0	0	1 (<1)	0	0	0	1 (<1)
Cholelithiasis	0	0	0	1 (<1)	0	0	0	1 (<1)
<b>Investigations</b>	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
<b>Cardiac disorders</b>	1 (1)	0	2 (1)	0	2 (2)	0	3 (1)	0
Bundle branch block	1 (<1)	0	0	0	0	0	1 (<1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Supraventricular tachycardia	0	0	0	0	1 (1)	0	1 (<1)	0
Tachycardia	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
<b>Social circumstances</b>	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

Note: Percentages calculated with the number of subjects in each group as denominator  
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### Adverse Dropouts in OL Trials

The following are summary tables on ADOs provided by the sponsor.

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

Table 26: 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	Flu/Pali	Pli/Pali	Pali/Pali	Flu/Pali	Pali(N=187)	Pali(N=187)
	≤6 months (N=10) n(%)	>6 months (N=70) n(%)	≤6 months (N=2) n(%)	>6 months (N=70) n(%)	Pali ≤6 months (N=23) n(%)	Pali >6 months (N=60) n(%)
<b>Total no. subjects with adverse events</b>	3 (30)	5 (7)	0	5 (1)	3 (13)	0
<b>Investigations</b>	0	2 (3)	0	0	0	0
Electrocardiogram QT corrected interval prolonged	0	1 (1)	0	0	0	0
Electrocardiogram QT prolonged	0	1 (1)	0	0	0	0
<b>Psychiatric disorders</b>	1 (10)	1 (1)	0	1 (1)	1 (4)	0
Anxiety	0	1 (1)	0	0	0	0
Depressive	0	1 (1)	0	0	1 (4)	0
Suicidal ideation	0	0	0	1 (1)	0	0
Suicide attempt	1 (10)	0	0	0	0	0
<b>Nervous system disorders</b>	2 (20)	1 (1)	0	0	1 (4)	0
Dyskinesia	1 (10)	1 (1)	0	0	0	0
Dizziness	0	0	0	0	1 (4)	0
Syncope	1 (10)	0	0	0	0	0
Tremor	1 (10)	0	0	0	0	0
<b>Skin and subcutaneous tissue disorders</b>	0	1 (1)	0	0	0	0
Dermatitis	0	1 (1)	0	0	0	0
<b>Gastrointestinal disorders</b>	0	0	0	0	1 (4)	0
Vomiting	0	0	0	0	1 (4)	0
<b>Reproductive system and breast disorders</b>	0	0	0	0	1 (4)	0
Amenorrhea	0	0	0	0	1 (4)	0

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

(Continued)

Table 26: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)  
 (Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Total Pali ≤6 months (N=35) n(%)	Total Pali >6 months (N=200) n(%)
	<b>Total no. subjects with adverse events</b>	6 (17)
<b>Investigations</b>	0	2 (1)
Electrocardiogram QT corrected interval prolonged	0	1 (1)
Electrocardiogram QT prolonged	0	1 (1)
<b>Psychiatric disorders</b>	2 (6)	2 (1)
Anxiety	0	1 (1)
Depression	1 (3)	1 (1)
Suicidal ideation	0	1 (1)
Suicide attempt	1 (3)	0
<b>Nervous system disorders</b>	3 (9)	1 (1)
Dyskinesia	1 (3)	1 (1)
Dizziness	1 (3)	0
Syncope	1 (3)	0
Tremor	1 (3)	0
<b>Skin and subcutaneous tissue disorders</b>	0	1 (1)
Dermatitis	0	1 (1)
<b>Gastrointestinal disorders</b>	1 (3)	0
Vomiting	1 (3)	0
<b>Reproductive system and breast disorders</b>	1 (3)	0
Amenorrhea	1 (3)	0

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

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Table 17: 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 Dichotomized Term	FluPaM	FluPaM	FaE3PaM	FaE3PaM	OlanPaE	OlanPaE	Total PaM	Total PaM
	≤5 months (N=102) n (%)	>5 months (N=334) n (%)	≤5 months (N=213) n (%)	>5 months (N=473) n (%)	≤5 months (N=168) n (%)	>5 months (N=341) n (%)	≤5 months (N=423) n (%)	>5 months (N=748) n (%)
Total no. subjects with adverse events	10 (10)	7 (5)	29 (14)	13 (3)	16 (17)	6 (6)	57 (13)	28 (4)
<b>Psychiatric disorders</b>								
Depressive	4 (4)	5 (4)	16 (8)	5 (2)	10 (9)	5 (4)	32 (8)	16 (2)
Psychotic disorder	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	1 (1)	4 (1)	5 (1)
Agility	2 (2)	0	2 (1)	2 (<1)	3 (3)	2 (1)	7 (2)	4 (1)
Insomnia	0	1 (1)	0	0	1 (1)	1 (1)	2 (<1)	2 (<1)
Panic disorder	0	0	1 (1)	1 (<1)	1 (1)	1 (1)	4 (1)	2 (<1)
Suicidal ideation	0	2 (1)	1 (<1)	0	0	0	1 (<1)	2 (<1)
Acute psychosis	1 (1)	0	1 (<1)	2 (<1)	2 (2)	0	4 (1)	2 (<1)
Depression	0	0	0	0	0	1 (1)	0	1 (<1)
Depressed mood	0	1 (1)	2 (1)	0	2 (1)	0	3 (1)	1 (<1)
Depressive symptoms	0	0	0	0	0	1 (1)	0	1 (<1)
Polysomnia	0	1 (1)	0	0	0	0	0	1 (<1)
Polysomnia 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)
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	2 (<1)	0	0	0	2 (<1)	0
Suicide attempt	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Nervous system disorders</b>								
Ataxia	1 (1)	1 (1)	6 (3)	1 (<1)	2 (2)	3 (2)	9 (2)	5 (1)
Convulsion	0	0	2 (1)	0	0	2 (1)	2 (<1)	2 (<1)
Dyskinesia	0	0	0	1 (<1)	0	0	0	1 (<1)
Extrapyramidal disorder	0	1 (1)	0	0	0	0	0	1 (<1)
	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

(Continued)

Table 17: 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 Dichotomized Term	FluPaM	FluPaM	FaE3PaM	FaE3PaM	OlanPaE	OlanPaE	Total PaM	Total PaM
	≤5 months (N=102) n (%)	>5 months (N=334) n (%)	≤5 months (N=213) n (%)	>5 months (N=473) n (%)	≤5 months (N=168) n (%)	>5 months (N=341) n (%)	≤5 months (N=423) n (%)	>5 months (N=748) n (%)
<b>Nervous system disorders (continued)</b>								
Hypotonia	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)
Alanine aminotransferase increased	0	1 (1)	0	1 (<1)	0	0	0	2 (<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	2 (1)	0	0	0	0	0	2 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	0	1 (<1)
Gamma-glutamyltransferase increased	0	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Electrocardiogram T wave abnormal	0	0	0	1 (<1)	0	0	0	1 (<1)
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)
Gonadotropin	0	0	0	0	0	1 (1)	0	1 (<1)
Retropubic ejaculation	0	0	1 (<1)	0	0	0	1 (<1)	0

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

(Continued)

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Table 25. Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)  
 (Pooled Open-Label Studies R036477-SCH-702, -703, -704, -705; Safety Analysis Set)

Body System or Organ Class Distichemy-derived Term	Flu/Pali	Flu/Pali	Flu/Pali	Flu/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	≤5 months (N=502) n (%)	>5 months (N=134) n (%)	≤5 months (N=213) n (%)	>5 months (N=473) n (%)	≤5 months (N=108) n (%)	>5 months (N=141) n (%)	≤5 months (N=423) n (%)	>5 months (N=748) n (%)
<b>Respiratory, thoracic and mediastinal disorders</b>								
Dyspnea	0	1 (1)	1 (<1)	1 (<1)	0	0	1 (<1)	2 (<1)
Pneumonia aspiration	0	1 (1)	1 (<1)	0	0	0	1 (<1)	1 (<1)
<b>Injury, poisoning and procedural complications</b>								
Traumatic herniations	1 (1)	0	2 (1)	1 (<1)	0	0	3 (1)	1 (<1)
Accidental overdose	0	0	0	1 (<1)	0	0	0	1 (<1)
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Self-harmicide	1 (1)	0	0	0	0	0	1 (<1)	0
<b>Metabolic and nutrition disorders</b>								
Hypoglycemia	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Anorexia	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Cardiac disorders</b>								
Myocardial infarction	1 (1)	0	1 (1)	0	2 (2)	0	6 (1)	0
Myocardial ischemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Myocardial ischemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Palpitation	0	0	0	0	1 (1)	0	1 (<1)	0
Sinus tachycardia	1 (1)	0	0	0	1 (1)	0	2 (<1)	0
Tachycardia	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Eye disorders</b>								
Vision blurred	0	0	0	0	1 (1)	0	1 (<1)	0
<b>Gastrointestinal disorders</b>								
Constipation	1 (1)	0	1 (<1)	0	1 (1)	0	3 (1)	0
Dysphagia	0	0	0	0	1 (1)	0	1 (<1)	0
Nausea	0	0	1 (<1)	0	0	0	1 (<1)	0
Peritonitis	0	0	0	0	1 (1)	0	1 (<1)	0
Rectal ulcer	1 (1)	0	0	0	0	0	1 (<1)	0

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

(Continued)

Table 27. Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)  
 (Pooled Open-Label Studies R036477-SCH-702, -703, -704, -705; Safety Analysis Set)

Body System or Organ Class Distichemy-derived Term	Flu/Pali	Flu/Pali	Flu/Pali	Flu/Pali	Olan/Pali	Olan/Pali	Total Pali	Total Pali
	≤5 months (N=502) n (%)	>5 months (N=134) n (%)	≤5 months (N=213) n (%)	>5 months (N=473) n (%)	≤5 months (N=108) n (%)	>5 months (N=141) n (%)	≤5 months (N=423) n (%)	>5 months (N=748) n (%)
<b>Gastrointestinal disorders (continued)</b>								
Vomiting	0	0	0	0	2 (2)	0	2 (<1)	0
<b>General disorders and administration site conditions</b>								
Fatigue	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
<b>Infectious and infestations</b>								
Herpes simplex 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>								
Astria	0	0	1 (<1)	0	0	0	1 (<1)	0
<b>Social circumstances</b>								
Alcohol use	0	0	2 (1)	0	1 (1)	0	4 (1)	0
Drug abuse	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
<b>Yeast infections</b>								
Exasperation	0	0	0	0	1 (1)	0	1 (<1)	0

Note: Percentages calculated with the number of subjects in each group as denominator  
 Percentages not generated by reference

**Statistical Results on Clinical Parameters of the Integrated OL Trial Dataset (laboratory parameters, vital signs and ECG parameters)**  
 See the assessment schedules and outlier criteria employed in each safety dataset in Table Series 10.1 and 10.2 in the appendix of this review.

***Reviewer Comment on the Review Strategy of Clinical Parameter Results Provided in the SUR***  
***The Purpose of the Review of the SUR***

*The purpose of the review as described below is to determine if any clinically new and remarkable findings were revealed that differ from findings already described elsewhere in this review or that were previously described in past clinical reviews of NDA 21999 (for the schizophrenia indication that was recently approved).*

***Results that were Reviewed***

*Results of Study -701 were not reviewed, unless otherwise specified below, since the larger integrated safety dataset is considered to be more informative given the longer duration of treatment (up to 12 months) employed and the larger sample size of subjects.*

*The results of the integrated OL safety dataset were provided in the same manner as provided in the original NDA22043 submission and as in NDA 21999. Section 7 describes the subgroupings of subjects that were used for data analyses. As previously described, the subgroupings of subjects were according to their DB treatment assignment (in the 6-week, placebo controlled Phase III lead-in studies, -302, -303, -304 and -305 which included placebo, olanzapine or Pal treatment). These treatment groups were then further divided into subgroups on the basis of total duration of Pal treatment (over 6 months of Pal treatment or  $\leq 6$  months of Pal treatment which includes DB and OL exposure combined). Consequently, the clinical parameter results (descriptive statistical results and incidence of outliers) of DB/OL treatment groups that were not each subdivided into 2 additional subgroups on the basis of duration of Pal exposure could not be found.*

*For the purposes of this review of the 120Day SUR results, the following subgroup of the integrated OL safety dataset was reviewed since this was the subgroup with the longest continuous Pal exposure and was the largest subgroup among the DB/OL treatment subgroups:*

- *>6 month DB Pal/OL Pal subgroup*

*In-text sections of the SUR were primarily reviewed (results of -701 and integrated OL trial safety dataset), unless otherwise specified.*

***Limitations to the Safety Dataset Reviewed***

*The previous original clinical review of NDA21999 and previous sections of this review discuss limitations with the results from the OL Safety dataset. Among the limitations were the following:*

- *Some clinical parameter results could not be found or were limited (e.g. urinalyses RBC, ketones, among others, special glucose laboratory parameters and insulin levels either could not be found or were found in only a few subjects and only at a few time-points except for DB and OL baseline time-points, as examples).*
- *Other limitations were regarding the large within group variance and test-retest variance, among others.*

- *Additional limitations inherent with OL studies were also previously discussed (e.g. OL design, outpatient trials, among other aspects of these studies that introduce limitations with the interpretation of the results).*

***Reviewer Comments and Conclusions on Descriptive Statistical Results on Clinical Parameters (Laboratory, Vital Sign and ECG Parameters) Over Each Time-point in the Over 6-month DB Pal/OL Pal Subgroup of the Integrated Safety Dataset***

***Descriptive Statistical Results Found in Appendices 5.2.1, 6.2.1 and 7.2.1 of the SUR***

*Descriptive statistical results (of each laboratory, vital sign and ECG parameter) over each time-point in each treatment subgroup of the Integrated Safety Dataset could generally not be found in the in-text section of the SUR, but were instead found in appendices. The descriptive statistical results of the >6 month DB Pal/OL Pal subgroup (on mean $\pm$ SD and median results and mean change $\pm$ SD and median change for each assessment time-point) were found in Appendices 5.2.1, 6.2.1 and 7.2.1 of the SUR and were reviewed.*

*The results (of the subgroup specified) failed to reveal any new clinically remarkable findings (in mean and median change on any given clinical parameter) that differ from safety findings previously described in the current review or in the original and addendum clinical reviews of NDA 21999.*

***Review Comments and Conclusions on In-Text Results on Clinical Parameters for Study -701 and for the Integrated OL trial Safety Dataset***

*In-text Sections 3 and 4 were reviewed which summarized clinical parameter results for Study -701 and for the integrated OL trial dataset. These results included some selected descriptive statistical results or were provided on selected parameters (only included changes from baseline to treatment endpoint). Results on the incidence of outliers were also provided on selected parameters (as found in in-text sections of the SUR). These in-text results are described below.*

***Laboratory Parameter Results Found in In-text Section 3 of the SUR.*** *The results did not reveal any clinically new or remarkable findings that differ from previously described in this review or in the results of Phase III safety datasets summarized in the original and addendum clinical reviews of NDA 21999.*

*The following are additional comments of the results as found in Section 3 of the SUR:*

- *A 5% incidence of high eosinophil outliers was observed in Study 701 that was not previously described. However, the incidence of high outliers on this parameter was only 0-1% in each treatment subgroup of the integrated OL trial dataset (except for 2% observed in 1 of the subgroups).*
- *It is also notable that reticulocyte was also low in 14% of subjects in Study 701. Previous reviews of NDA21999 also described outliers on low reticulocyte count (incidence greater in Pal than placebo subjects and greater in the low than in the high outlier categories in OL datasets). However, the incidence previously observed was*

not as great as 14%. In the current updated integrated safety datasets, most subgroups had an incidence of 3-9% on low reticulocyte count. Consequently, observations on this larger OL dataset are generally similar to those previously described in the original review of NDA 21999.

- The sponsor specifies that 4 subjects (listed on page 146 of the SUR) had "markedly elevated" CPK levels in the integrated OL trials, but the sponsor does not specify any other clinically remarkable findings in these subjects.

The sponsor indicates that no ADOs or SAEs occurred due to "laboratory-related" AEs in Study 701.

The integrated OL trial dataset had the following subjects with laboratory related SAEs in the integrated OL trials:

- 200326 had anemia,
- 500108 had hyponatremia and
- 500526 had hypokalemia.

Laboratory related AEs did not result in an ADO in more than 1 subject on a given AE (refer to previous summary tables of SAEs and ADOs).

The sponsor notes the following outliers on ALT or AST:

- Only 1 subject in the integrated OL trials was noted by the sponsor to have AST or ALT exceeding 8 times the upper limit of normal (ULN) who had normal LFT values at baseline. This subject was 501558 and as previously described in the review of NDA21999 this subject had a history of viral hepatitis. A potential role of Pal is possible that may have exacerbated a pre-existing condition that at baseline appeared to be in remission.
- Other subjects were noted by the sponsor to have markedly high ALT and/or AST values. It is not clear if any of these subjects were newly identified subjects. The numbers of these subjects were not found in a spot check of past reviews of NDA21999. These subjects are listed below.

Subjects reported as having markedly high AST ( $\leq 250$  U/l) or ALT ( $\geq 200$  U/L) and that appear to be newly reported subjects were:

- 500809
- 200231
- 21434
- 201321
- 501558

No other information on the above subjects could be found.

Subjects in the integrated OL trials that were reported as having AST or ALT values of  $>3$  times the ULN and that appear to be newly reported subjects, unless otherwise specified (these subjects are reported to have narratives):

- 502208
- 501394

- 502015 and 502035 were previously reported but have updated narratives.

No other in-text information could be found on the above subjects (in Section 3.3.2 of the SUR).

Subject 500501 with an SAE related to elevated LFTs was also noted by the sponsor. Although this subject was previously described in reviews of NDA21999. The previous reviews of NDA 21999 described additional subjects (SAEs, ADOs and others) with elevated LFTs in which several subjects did not appear to have a non-drug-related etiology that could be identified or that was clearly identifiable, while others had abnormal values at baseline and/or had other potential non-drug-related etiologies.

A review of narratives of subjects identified as having >3 times ULN of ALT or AST was previously discussed, in which cases can be found in which a non-drug-related etiology for elevations could not be found in the narratives of some subjects and that appeared to be drug-related elevations. See Section 7.1.8.3.3. of this review for additional subjects.

Similar cases with elevated LFTs were previously described in past reviews of NDA21999, such that the few additional new cases do not alter overall comments and conclusions made in the past clinical reviews of NDA21999.

The overall incidence of outliers in AST or ALT when using prespecified criteria (as shown in Table series 10.2 in the appendix of this review) was:

- 1% or less among the integrated-OL trial treatment subgroups and
- The over 6 month Pal subgroup of Study 701 had an incidence that did not exceed 5 subjects in a given subgroup (the sponsor noted an incidence of 3% or greater for other analytes of which results did not differ remarkably from previous findings in Phase III trials in reviews of NDA21999). No subject in Study 701 was reported to have AST or ALT value of over 8 times the ULN.

See a subsection below (as part of Section 7.2.9.1 of this review) for prolactin level results (which were described elsewhere in the SUR) that showed sex differences for greater median increases in females than in males from pre-treatment to OL treatment endpoint values and for sex differences in potentially-related AEs. This observation was also previously described in this review.

Given the observation for trends for a mean increase in uric acid levels previously noted in OL treated subjects (this was described in more detail under 7.1.7.3.1 of this review, it is noted that the incidence of high outliers on this parameter ranged from 0-3% among subgroups of the integrated OL trial dataset.

Vital Sign and Weight Parameter Results Found in In-text Section 4 of the SUR.

The results did not reveal any new and clinically remarkable findings in Study -701 and in the integrated OL dataset that differ from previously described observations in the current review or in the Phase III trials that were summarized in past reviews of NDA21999.

*Descriptive statistical results were not found in in-text sections of the SUR but the sponsor refers to appendices and does not describe any new and clinically remarkable findings on the basis of their results. The sponsor shows the incidence of outliers in in-text summary tables in which results are similar to those previously reported. Finally, the sponsor does not describe any individual subject with clinically remarkable cardiovascular or weight related events.*

*ECG Parameter Results Found in In-text Section 4 of the SUR.*

*No new or clinically remarkable findings were found or described in in-text sections on ECG results presented in Section 4 of the SUR (that differ from previously described findings in the current review or in the Phase III trial datasets in past reviews of NDA21999).*

*The sponsor also provided the overall incidence of “abnormal” (versus “normal”) ECGs. However, it is difficult to interpret results on the basis of the incidence of “abnormal” ECGs since subjects were categorized by the type of ECG abnormality observed. The incidence of a given type of ECG abnormality could not be found except for the incidence of outliers on ECG parameters (QT, QTc, RR, ventricular rate, PR and QRS interval).*

*Only line listings of subjects categorized as having “abnormal ECGs” were provided in appendices but the sponsor does not describe any clinically remarkable ECG abnormalities in any subject except for subjects 201418 and 200214 who had SAEs and ADOs (both subjects) due to “ECG-related” AEs and had QTcLD values exceeding 500 msec as follows.*

- *Subject 201418 was previously described in the original review of NDA2199 but is also described in the current SUR submission of NDA22043. In case new information was provided on this subject the following describes this subject as found in the current SUR submission. The subject:*
  - *Was a 32 year old generally healthy female*
  - *Who had a QTcLD of 454 at baseline*
  - *Who received 41 days of 6 mg pal daily during the DB lead-in Study -303 and received approximately 6 months of 9 mg Pal daily during the OL extension trial, -704.*
  - *Her QTcLD reached 549 msec on Day 174 of treatment and the cardiologist recommended that Pal be terminated due to “risk of sudden death.”*
  - *It was noted that her potassium was on the low end of the normal range (3.4 with normal range being 3.4-5.4 in units of mmol/l).*
  - *QT prolongation was reported as a SAE and an AE leading to an ADO.*
  - *The QTcLD value normalized by the next day after treatment cessation and continued to be normal 6 days later.*

*The sponsor considers the timing of this event and a resolution of this event within 24 hours post-treatment cessation to indicate that this event is “unlikely” to be “causally related” to Pal.*

- *While a low normal potassium level (being female and having borderline QTcLD values at baseline) may have increased her risk for this event, a resolution of the event with 24 hours post-treatment does not preclude a role of Pal, based on*

- observations of QT prolongation in Study SCH-1009 (as previously described in past clinical reviews of NDA 21999).*
- *Other than being female, having a low normal potassium level and a borderline QTcLD value of 454 msec at baseline, the narrative does not describe any other potential risk factors or potential non-drug-related etiologies (e.g. no concomitant medications, or medical conditions, among others).*
  - *The timing of the event relative to “steady state” as suggested by the sponsor does not preclude a role of Pal based on findings of Study SCH-1009. Furthermore, fluctuations of Pal levels occur even when steady state levels are achieved and levels can be influence by other factors. There are a number of potential factors to consider before one can preclude a role of Pal.*
  - *Subject 200214 was a subject who died (had bronchopneumonia and other events), as previously described and as described in past reviews of NDA21999. Subject 201418 was previously described in the original review of NDA21999.*

*Examples of cases that were similar to subject 500608 (who were found to have increased QTc prolongation after longer term treatment but without any clear non-drug-related etiology), were previously identified and/or described in past reviews of NDA 21999. Other cases are previously described in this review.*

*Very few subjects among all Phase III trials, were reported to have QTcLD, QT or QTcF prolongation of greater than 500 msec. QT and QTc values fluctuate over repeated ECG assessments in Phase III trials, including placebo treated subjects and the between subject variance is also large in typical Phase III trials. Therefore, it can be difficult to interpret the results of a single, absolute QT or QTc value in a single subject. However, in the opinion of the undersigned a role of Pal on QTcLD prolongation is highly suspected in subject 500608 (see previous comments, above, regarding this subject). See additional cases described under Section 7.1.10 of this review that also included cases from an elderly OL Study -701 and cases from other OL trials.*

*As to the severity of the QTcLD prolongation in a given subject, such as 500608, it is difficult to assess the extent in which the absolute value of 549 msec reflects a true value (given the variance typically observed in determining QT and QTc interval values in a typical Phase III trial).*

*One concern is that QT prolongation may occur with prolonged exposure and may not be restricted to only short term use or to the first few doses before steady state levels are achieved (e.g. consider food effects, effects of increasing the daily dose-level, effects associated with accumulation, among other potential effects). Refer to the previous reviews of NDA21999 describing QT prolongation observed after longterm OL treatment. Also refer to past sections of the current review on ECG results for a description of similar findings during longterm OL treatment in Study 301 and in the updated results of the integrated OL trial safety dataset. Both datasets show results suggestive of a possibly greater QT prolongation effect with longer term exposure as previously discussed under Section 7.1.10 of this review.*

The above findings are similar to those previously described under NDA21999. The QT Team was consulted regarding a focused ECG study, Study -1009 and NDA21999 was approved that included a QT section under Warnings in labeling.

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

Given the above findings on QT and QTcLD interval during longterm treatment the following are updated results on outliers on QTcLD as found in the SUR (only results of QTcLD from the sponsor's summary table 61 are shown below.

Table 61: 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)

QTcLD	Treatment Group and Evaluation at Average Predose															
	Pia/Pali ≤6 months (N=102)			Pia/Pali >6 months (N=134)			Pali/Pali ≤6 months (N=213)			Pali/Pali >6 months (N=473)						
	Norm	≥450	≥480	Total	Norm	≥450	≥480	Total	Norm	≥450	≥480	Total	Norm	≥450	≥480	Total
Maximum value																
Normal	99	0	0	99	132	0	0	132	202	0	0	202	459	1	0	460
≥450 - <480	2	0	0	2	2	0	0	2	5	2	0	5	6	4	0	10
≥480	0	1	0	1	6	0	0	6	0	0	0	0	1	1	0	2
Total	101	1	0	102	134	0	0	134	207	2	0	207	466	6	0	472

Table 61: Classification of Maximum Corrected QT Intervals During Open-Label Treatment Versus Average Predose Value (Continued) (Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705: Safety Analysis Set)

QTcLD	Treatment Group and Evaluation at Average Predose															
	Olisa/Pali ≤6 months (N=105)			Olisa/Pali >6 months (N=141)			Total Pali ≤6 months (N=423)			Total Pali >6 months (N=745)						
	Norm	≥450	≥480	Total	Norm	≥450	≥480	Total	Norm	≥450	≥480	Total	Norm	≥450	≥480	Total
Maximum value																
Normal	107	0	0	107	140	0	0	140	408	0	0	408	731	1	0	732
≥450 - <480	0	0	0	0	1	0	0	1	5	2	0	7	9	4	0	13
≥480	0	0	0	0	6	0	0	6	0	1	0	1	1	1	0	2
Total	107	0	0	107	141	0	0	141	413	3	0	416	741	6	0	747

The following table on the incidence of QTc shifts, as specified, was also provided by the sponsor.

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**Table 62: 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 ≤6 months (N=162) n (%)	Pla/Pali >6 months (N=134) n (%)	Pali/Pali ≤6 months (N=213) n (%)	Pali/Pali >6 months (N=173) n (%)	Olan/Pali ≤6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali ≤6 months (N=423) n (%)	Total Pali >6 months (N=748) n (%)
<b>QTcD</b>	162	134	207	472	107	141	416	747
<30 (ms)	92 (90)	119 (89)	196 (95)	417 (88)	104 (97)	127 (90)	392 (94)	663 (89)
30-60 (ms)	9 (9)	11 (11)	11 (5)	34 (13)	3 (3)	14 (10)	23 (6)	33 (11)
>60 (ms)	1 (1)	0	0	1 (-1)	0	0	1 (-1)	1 (-1)
<b>QTcF</b>	162	134	207	472	107	141	416	747
<30 (ms)	91 (89)	115 (86)	197 (95)	412 (87)	102 (95)	126 (89)	392 (94)	653 (87)
30-60 (ms)	10 (10)	19 (14)	10 (5)	39 (13)	5 (5)	15 (11)	25 (6)	93 (12)
>60 (ms)	1 (1)	0	0	1 (-1)	0	0	1 (-1)	1 (-1)
<b>QTcE</b>	162	134	207	472	107	141	416	747
<30 (ms)	92 (90)	118 (88)	198 (96)	416 (88)	103 (96)	128 (91)	392 (94)	662 (89)
30-60 (ms)	9 (9)	16 (12)	9 (4)	33 (12)	4 (4)	13 (9)	22 (5)	34 (11)
>60 (ms)	1 (1)	0	0	1 (-1)	0	0	1 (-1)	1 (-1)
<b>QTcB</b>	162	134	207	472	107	141	416	747
<30 (ms)	73 (76)	95 (71)	169 (82)	362 (77)	83 (78)	104 (74)	330 (79)	551 (75)
30-60 (ms)	21 (21)	36 (27)	37 (18)	104 (22)	23 (21)	36 (26)	31 (8)	176 (24)
>60 (ms)	3 (3)	3 (2)	1 (-1)	6 (2)	1 (1)	1 (1)	2 (1)	3 (1)

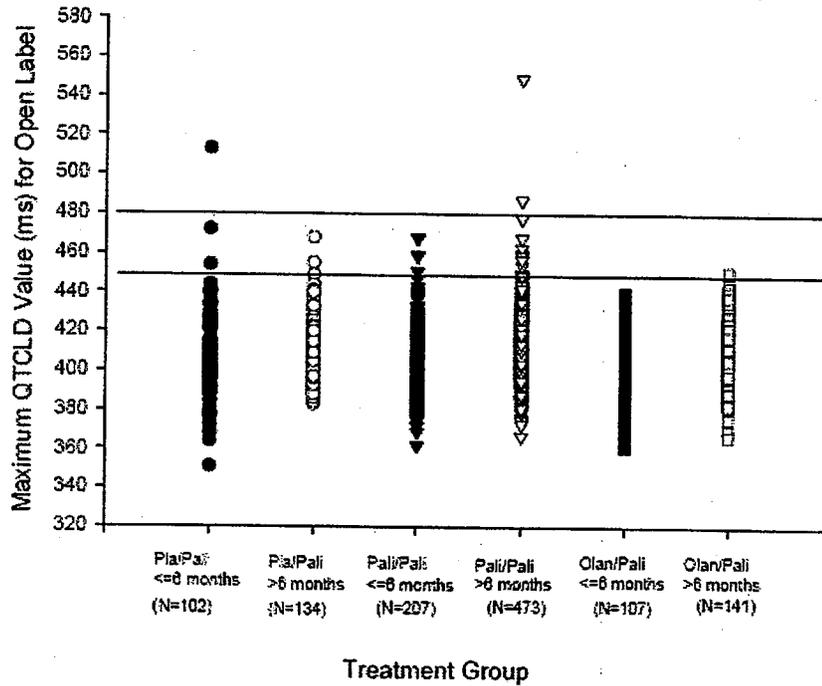
Note: Percentages calculated with the number of subjects per parameter as denominator.  
 IntegRx, Inc. generated by IntegRx, Inc.

The following are scatterplots provided by the sponsor for the integrated OL safety dataset.

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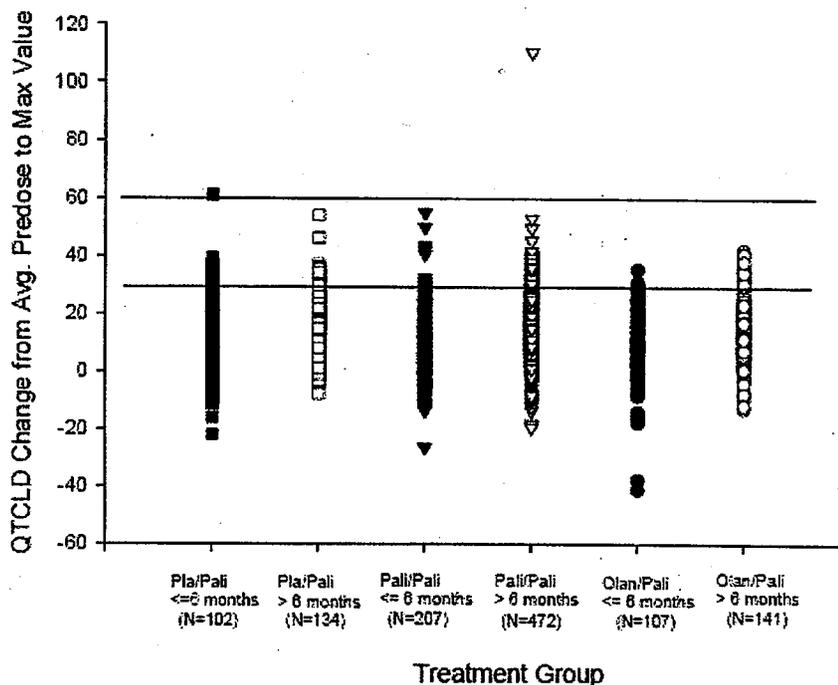
Figure 8: Scatterplot of Maximum QTcLD Values During Open-Label Treatment  
 (Pooled Open-Label Studies R076477-SCH-702, -703, -704, -705: Safety Analysis Set)



Note: The 2 subjects with maximum values greater than 500 ms were Subjects 201418 and 200214.

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Figure 9: Change in QTcLD From Average Predose Value to Maximum Value During Open-Label Treatment (Pooled Open-Label Studies: R076477-SCH-702, -703, -704, -705: Safety Analysis Set)



Note: The subject with a change of more than 100 ms, who also had a maximum value greater than 500 ms, was Subject 201418.

See the last section of this review for further comment and recommendations relevant to the above findings.

**Individual Subjects with Clinically Remarkable or Potentially Clinically Remarkable Events**

Individual Subjects with Clinically Remarkable or Potentially Clinically Remarkable Events Related to Clinical Parameter Abnormalities

Other than the individual subjects that were previously described above, the sponsor does not identify and describe any clinically remarkable subjects with clinical parameter abnormalities or related events in Sections 3 and 4 of the SUR, as well as in Sections 2.1.3 and 2.1.4 (on SAEs and ADOs in which summary tables are provided but the identification and a discussion of individual, clinically remarkable subjects cannot be found). See the next subsection on special search strategies conducted by the sponsor.

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 the SUR submission. Among the selected AEs were tachycardia, AEs “suggestive of proarrhythmic potential” (using a listing of AE search terms as specified in the SUR) and “ischemia-related” AEs (using a listing of AE search terms as specified in the SUR).*

*Very few new subjects were identified in Sections 2.1.5 and 2.1.6 (new subjects that were not previously reported in the original NDA 22043 submission) based on special AE search strategies for each of the following AEs (using search strategies and search terms as specified in the SUR):*

- *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*
- *EPS-related AEs*
- *Potential Prolactin-related AEs*

*Limitations and potential limitations with these results were previously discussed under section 7.1.5 of this review. One key limitation is that at least several of the AE searches appear to be searches of only dictionary derived terms, as previously discussed. Also refer to past reviews of NDA 21999 that include a discussion of limitations and potential limitations with the results of the sponsor’s special search strategies. The original review of NDA21999 also discusses potential concerns regarding the quality and completeness of these results.*

*In summary, the results of the incidence of subjects identified for a given search strategy in each treatment subgroup of Study 701 and the integrated OL dataset failed to reveal any clinically new and remarkable findings (as found in the in-text sections 2.1.5-6) that were not previously described in past reviews of NDA 21999 or in previous sections of the current review. However, sex differences on prolactin related AEs in the OL integrated dataset that were not generally discussed in past NDA 21999 clinical reviews are discussed below.*

*Among the few newly identified subjects that the sponsor described in in-text Sections 2.1.5-6 in the SUR submission the sponsor generally only specified the subject number (in some cases) and the AE term that was searched that identified the subject. These additional subjects did not lead to clinically remarkable alteration in the overall incidence of these events. Furthermore, a description of any clinically new and remarkable findings in these individual subjects could not be found (in the in-text sections 2.1.5-6) with a few possible exceptions as follows:*

- A prolactin related AE of amenorrhea that was also associated with dizziness led to an ADO in 1 subject (subject number not specified).
- Only 1 subject with Neuroleptic Malignant Syndrome (NMS) was identified by the sponsor: subject 100057 among OL datasets (Study 701 and the integrated OL dataset). This subject was previously described in the original review of NDA21999.
- Cases of Seizure or Syncope specified in Section 2.1.6.8 of the SUR:
  - Study 701: Subjects 100963 (death) and 100140 of Study 701 were previously described in this review or in past reviews of NDA21999. The original review of NDA21999 also described 2 subjects (1 syncope and 1 seizure) but the subject numbers could not be found and information on these subjects (as found in the in-text section where the subjects were mentioned) could not be found. The current SUR submission of the current NDA22043 indicates the following 5 total subjects with proarrhythmic-related AEs:
    - Integrated OL trial dataset:
      - Subjects 500108 and 200986: these subjects each had a seizure, were reported as SAEs and ADOs. They were previously described in the original review of NDA21999
      - 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).

*None of the above subjects are described as having QTcLD values of over 450 msec or an increase of QTcLD by more than 60 msec. No other information is described regarding the above subjects (no clinically remarkable findings other than the reported terms were found in the sponsor's summary of proarrhythmic related events in Section 2.1.6.8).*
  - The sponsor refers to appendices 3.6.1 and 3.6.2 regarding new subjects found for the reporting period for the SUR who had AEs "signifying potentially symptomatic vital sign values and heart rate abnormalities, including bradycardia, tachycardia, hypotension, orthostatic hypotension, or syncope. A summary of these results could not be found in Section 2.1.6.8.2. 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). Instead over approximately 100 pages in appendices of multiple line listings with the following information was found: listings of subjects numbers with AE terms, separate listings of subject numbers with vital sign results, and additional line listings (in which subject numbers are repeated within a given listing and across listings). This information was difficult to follow. It was also difficult to cull out meaningful observations. An outline of methodology for identifying these subjects was also provided which was difficult to follow or that was not clear in some respects. Narrative descriptions of potentially clinically remarkable subjects as requested could not be found.
- The information found in appendices 3.6.1-2 was not reviewed for reasons previously discussed in Section 7.1.4 of this review.

*Sex differences in Prolactin Related AEs and in Prolactin Levels*

*In a Section 2.1.6.7 of the SUR the sponsor discusses sex differences in prolactin levels and provides results of prolactin-related AEs that also show sex differences in the OL datasets.*

*Study 701 showed*

- *A greater median increase from baseline when using the pre-treatment run-in baseline value in prolactin levels in females (88.3 ng/ml) than observed in males (29.49 ng/ml) among the subjects with over 6 months of Pal treatment. However, this subgroup of subjects (the over 6 month Pal treated group) showed median decreases in prolactin levels as treatment was continued (from the OL phase to the DB phase, using the DB baseline phase value as the baseline value for comparison). The females showed the greatest mean decrease with continued treatment (-22.5 compared to -4.6 in females and males respectively, in units of ng/ml).*
- *The incidence of outliers on prolactin levels also showed sex differences (5% in males and 10% in females, compared to DB baseline values) but when compared to pre-treatment values (baseline of the run-in phase) the incidence was similar between males and females (68% and 71% respectively).*

*Similar sex differences were also observed in the integrated OL dataset as follows:*

- *Female and male median increases in prolactin levels (in units of ng/ml) from pre-treatment values (DB baseline value of the DB lead-in study) to OL phase endpoint values were 72.1 and 19.8, respectively for the  $\leq 6$  month Pal treated subgroup and 61.2 and 19.5, respectively, for the over 6 month Pal treated subgroup.*
- *However, males and females were similar on the incidence of high prolactin level outliers (63% and 60%, respectively) in the over 6 month treated Pal subgroup.*

*Sex differences in prolactin related AEs can also be observed and as shown in in-text summary tables in Section 2.1.6.7 of the SUR.*

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

These topics were previously discussed (in preceding sections and subsections in which they apply). Also see additional comments of data limitations in sections and subsections that follow. The original review of NDA 21999 also describes data limitations relevant to the current submission (since the current submission provides updated results from datasets of studies that were ongoing and/or previously described in NDA 21999). Also see Sections 4, subsections of 7 and section 7.2.3 of the current review.

### **7.4 General Methodology**

See previous sections regarding concerns or potential concerns with methodology.

## 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

### 7.4.1.1 Pooled data vs. individual study data

This topic was previously discussed.

*Reviewer Comment. See sections below. See Section 7.1 for pooled safety dataset methods. Specific limitations to safety datasets are discussed in detail in appropriate sections of this review that describe the results and the interpretation of results. Also see Section 4 of review strategy.*

### 7.4.1.2 Combining data

This topic was previously addressed.

## 7.4.2 Explorations for Predictive Factors

This was not systematically evaluated in Phase III trials.

*Reviewer Comments. The sponsor provides some results of analyses of safety data from Studies -301, -701 and the integrated OL extension trial safety databases on the basis of potential "intrinsic" (age, sex and "race") and/or potential "extrinsic" factors (geographical region) in Section 6 of Module 2.7.4. However for reasons described in subsections below, these safety databases are not considered by the undersigned to be adequate for examining these potential factors and others, specified below.*

*Refer to the clinical review of NDA 21999 for some additional information relevant to these topics which included results of placebo-controlled, short-term, schizophrenia trials.*

### 7.4.2.1 Explorations for dose dependency for adverse findings

Dose dependency of adverse effects was not systematically evaluated in Phase III trials.

**Reviewer Comments.**

*Refer to the original clinical review for NDA 21999 for results from placebo controlled trials that employed fixed doses over multiple daily dose levels using a parallel group design. Studies in NDA22043 did not employ this study design, such that dose-dependency of adverse effects was not systematically evaluated in these studies. In addition to the limitations inherent with an OL, flexible dose study design, Study -301 which included a DB, placebo controlled treatment phase employed a study design that presented limitations for exploring potential dose-dependent effects (e.g. used a flexible dose and was aborted early according to the protocol, among other limitations, as previously discussed).*

#### 7.4.2.2 Explorations for time dependency for adverse findings

*Reviewer Comments. Refer to the original clinical review for NDA 21999 for results over time from placebo controlled trial results. Study -301 results and OL trial results are generally not considered appropriate databases to explore potential time-dependent effects for several reasons, such as those described as follows. These trials were non-placebo controlled trials except for the DB phase of Study -301. The DB phase of Study -301 had fewer subjects over successive time-points with an insufficient sample size at later time-points, as previously described. OL studies also used a flexible dose-designs and Study -301 did not include parallel treatment groups at different daily dose-levels which can confound results presented over time.*

*Although limitations exist with the interpretation of results of OL studies, the integrated OL safety dataset involved a large sample size of subjects with many subjects receiving over 6 months of Pal treatment (and up to 12 months of treatment). Consequently, this dataset offers the opportunity to explore adverse effects over time for selected parameters (e.g. parameters in which floor effects were not revealed, parameters with a sufficient number of assessment time-points during the OL trials, among other methodological considerations). Previous corresponding subsections of Section 7 discuss potential time-dependent effects on clinical safety measures of the integrated OL safety dataset. Given observations of QT interval in this dataset, QT results over time for other individual OL trial datasets were also discussed in this review (Section 7.1.9.3).*

#### 7.4.2.3 Explorations for drug-demographic interactions

This was not systematically evaluated in Phase III trials.

*Reviewer Comments. Refer to the original clinical review for NDA 21999 for additional information on this topic for placebo controlled trial results. Study -301 results and OL trial results are not considered appropriate databases to explore potential demographic-drug interaction effects for several reasons, such as the reasons described in the previous subsection.*

#### 7.4.2.4 Explorations for drug-disease interactions

This was not systematically evaluated in Phase III trials.

*Reviewer Comments. Refer to the original clinical review for NDA 21999 for additional information on this topic for placebo controlled trial results.*

*Study -301 results and OL trial results are not considered appropriate databases to explore potential drug-disease interaction effects for several reasons, such as the reasons described in the previous subsections of this review (regarding limitations with OL safety data).*

#### 7.4.2.5 Explorations for drug-drug interactions

Drug-drug interactions were not systematically evaluated in Phase III trials.

*Reviewer Comments. Refer to the original clinical review for NDA 21999 for additional information on this topic for placebo controlled trial results. Study -301 results and OL trial results are not considered appropriate databases to explore potential drug-dependent effects for several reasons, such as the reasons described in the previous subsection. An exploratory analyses of these safety databases with respect to potential drug-drug interaction effects could not be found in Modules 2.7.4 and Module 2.5 of the submission.*

*The sponsor indicates the following in Section 6.3 of Module 2.7.4:*

- *In vitro and in vivo PK study results led to a prediction that the “probability of drug-drug interactions is low.”*
- *Potential drug-drug interaction effects are briefly discussed from a theoretical standpoint on the basis of potential or clearly established pharmacodynamic properties (e.g. alpha-1 antagonism, CNS effects and more specifically dopamine-related CNS effects).*

*New information on potential drug-drug interactions effects (that were not previously provided in NDA 21999) could not be found in the submission (on the basis of a review of selected clinical sections, as described in this review and in Section 4 of this review). An OCPB review was conducted for NDA 21999 and this NDA was approved on 12/19/06. Refer to approved labeling with respect to potential drug-drug interactions on the basis of results described in the OCPB review of relevant sections.*

#### 7.4.3 Causality Determination

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

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

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

### 8.2 Drug-Drug Interactions

No new information on drug-drug interactions could be found in Modules 2.5 or 2.7.4 of the submission that was not previously reviewed under NDA 21999. See the previous section

7.4.2.5 which also covers this topic. The past NDA21999 was also reviewed by OCPB. The current NDA22043 is also under review by OCPB in which input is recommended on this topic.

### 8.3 Special Populations

Results of special population studies were previously summarized in clinical and OCPB reviews of NDA21999 for the schizophrenia indication. Refer to reviews of NDA 21999 on special population studies that were conducted for the same drug product as described under NDA 21999.

The undersigned reviewer is not aware of any new special population studies provided in the current NDA 22043 submission. The focus of NDA22043 is in seeking an efficacy maintenance claim based on results of Study -301 with supportive safety data from this study and from longterm OL studies. No pregnancies occurred during the clinical trials (as described in Section 4.9 of Module 2.5).

### 8.4 Pediatrics

#### A Deferral for Conducting Adolescent Acute Schizophrenia Trials and a Waiver for Schizophrenia Trials of Younger Children

As described in the clinical review of NDA 21999 the sponsor was granted a waiver from performing short-term studies of acute schizophrenia patients  $\leq 12$  years old. A deferral for studies of 13-17 year old patients was also granted until their adult Phase III program is completed, as described in the section of the NDA submission entitled "Pediatric Use Information."

*Reviewer comment and conclusion: A pediatric waiver for the younger age-group is appropriate for the schizophrenia indication for several reasons, such as those described in a 11/2/06 Written Request Letter for Pediatric Studies for the IND of Pal for the schizophrenia indication (IND65850 which is the IND under which trials described in this submission were conducted). Schizophrenia is a disorder of the adult population with an age of onset that is generally in the young adult or adolescent. Psychoses in children under the age of 10 years old is difficult to diagnose and schizophrenia is considered to be uncommon if not rare in this age-group, as described in the 11/2/06 Written Request Letter. This 11/2/06 Letter requests submission of pediatric protocols relevant to a Pal development program for treatment of schizophrenia in adolescents as specified in the letter (the letter was issued in response to receipt of Proposed Pediatric Study Request submissions IND65850 N188 and IND73845 N020 of which the latter IND is for the Bipolar indication).*

#### Waiver from Conducting "Recurrence of Prevention" Trials in Children

The following was copied from the relevant section of the Division's pre-NDA meeting minutes submitted to DFS (meeting date was 2/16/06):

### **Pediatrics**

**Question 12.** In compliance with the requirements set forth in the Pediatric Research Equity Act (PREA) and agreements from the End of Phase 2/Pre-Phase 3 Meeting (April 25, 2003), J&JPRD will assess the efficacy and safety of short-term treatment with paliperidone extended release tablets in pediatric patient population with schizophrenia. At this time, we are requesting a waiver from conducting recurrence prevention trials in pediatric patients (<18 years of age). Does the Agency agree that such a waiver can be granted for the parallel NDA for prevention of recurrence of schizophrenia?

**Comment:** Yes.

*Reviewer comment: The above waiver was granted. Such a waiver is reasonable to the undersigned reviewer for reasons as follows. The sponsor will be studying efficacy of acute treatment in adolescent patients. The Division generally requires acute data from both adult and pediatric (adolescent) patients with schizophrenia, while longer term data is generally only required from the adult age-group. The longterm data from the adults can generally be extrapolated to the adolescent population, since the two age-groups are similar from an efficacy perspective. Consequently, the sponsor was granted a waiver from conducting a maintenance-treatment efficacy trial in adolescents.*

### **8.5 Advisory Committee Meeting**

To the knowledge of the undersigned an advisory committee will not be held on this NDA.

### **8.6 Literature Review**

Refer to the original review and the review of the response to the approvable action letter of NDA 21999. These reviews describe methods and results of a literature review using the most recent cut-off date of 3/31/06 that was employed for the current NDA 22043 submission. A literature review conducted from 4/1/06 through 7/31/06 cut-off dates was provided in the 120-Day SUR submission of NDA22043 (refer to past reviews of NDA21999 for search/review methods employed). This updated search yielded 3 articles on Pal that contained safety information. However, the information is not new, since the published results were extracted from CSRs of the short-term DB Phase III trials (-303, -305 and -302). The results of these studies were previously summarized in the clinical review of the original NDA 21999 submission.

### **8.7 Postmarketing Risk Management Plan**

A postmarketing risk plan cannot be found in the submission. Although, to the knowledge of the undersigned the sponsor has a postmarketing surveillance program for their approved formulations as required by CRF regulations. Postmarketing commitments are also specified in the Approval Letter of NDA21999.

## 8.8 Other Relevant Materials

The undersigned reviewer previously recommended a cardiology and a QT Team consult regarding NDA 21999 regarding cardiovascular and QT effects of Pal (that included results of short-term and OL trials, as well as results of an ECG study -1009). A QT Team consult was obtained by the DPP for input regarding an ECG Study -1009. The QT Team recommended a section in labeling describing QT results under Warnings (and provided input on specific text for this section).

## 9 OVERALL ASSESSMENT

A review of N000-N002 submission was conducted as described in Sections 4 and 7. The sponsor recently submitted N003. The undersigned reviewer was instructed to only review N000-002 (not N003). The undersigned reviewer was also instructed to review a more recent version of annotated labeling that was provided by the sponsor (that differs from the N000 submission and that followed the N003 submission). This more recent annotated version was forwarded to the review Team for review. Therefore, this review addresses key proposed revisions found in the most recent version of proposed labeling (rather than as found in the N000 version and as specified under Section 9.4, below).

All conclusions and recommendations in this review are provided from a clinical perspective.

### 9.1 Conclusions

#### Efficacy Related Conclusions

Study 301 is considered by the undersigned reviewer (and from a clinical perspective) as a positive study to support a maintenance treatment claim for treatment of schizophrenia (as specified in more detail in subsections below and pending input from the Biometrics Review Team).

Subsections below provide advice on specific aspects of the claim and language in labeling. As specified later, Study -301 is not adequately designed to systematically evaluate prevention of relapse (or recurrence) and does not evaluate the total duration of treatment that would be needed to prevent relapse. The study is also not designed to determine how long a patient should receive longterm treatment to maintain clinical stability. However, the study does provide adequate evidence that Pal is efficacious in stabilized patients for up to a period of treatment that was actually employed in the study, as follows. The duration of treatment in Study -301 included at least 8 weeks of treatment when patients were required to be stabilized on a fixed dose of OL Pal (that followed a period of OL flexible dosing in order to stabilize acute patients and achieve an optimal daily dose-level to be continued during the fixed dose OL phase). Stabilized subjects were then continued on DB Pal treatment. However, the treatment duration in the DB phase was variable across individual subjects while using a flexible-dose design. Therefore, recommendations are provided later in this review on describing the duration of

treatment for the purposed of labeling and relevant to the proposed treatment claims proposed in labeling.

Study -301 was the only pivotal efficacy study described in NDA22043. One positive adequately controlled study has generally been considered by Agency to be adequate for maintenance claim in patients with schizophrenia who are stabilized on the drug (refer to labeling of drugs that are approved for this claim). This approach is acceptable to the undersigned reviewer with respect to Pal and the use of positive results from Study -301 to support a maintenance treatment claim (as specified later) for the following reasons:

- Pal is already approved for acute treatment of schizophrenia under NDA21999.
- Other drugs in the same drug class as Pal are also found to be efficacious in maintenance treatment trials and are approved for maintenance treatment of schizophrenia (refer to labeling of approved drugs for details).
- Finally Pal is the major active metabolite of risperidone and this drug is approved for a maintenance claim in the same patient population (refer to approved labeling).

Consequently, these additional observations provide further support for efficacy of Pal in longer term/maintenance treatment of Pal in patients who are stabilized on Pal for a duration of treatment that was employed in Study -301 and as discussed in more detail in Sections 9.2 and 9.4 of this review.

#### Safety Related Conclusions

Safety results summarized in this review (as submitted to N000-002 under NDA22043) do not yield any new and clinically remarkable findings that alter overall conclusions and recommendations that were previously provided for this drug for this patient population under NDA21999 (as provided in the original clinical and addendum clinical reviews of NDA21999 for the schizophrenia indication).

NDA 21999 was approved on 12/19/06.

Pal is in the same drug class as several other previously approved drugs for the maintenance claim for treatment of schizophrenia. Pal is a major active metabolite of one of these approved drugs (risperidone). Consequently, there is extensive pre-marketing and postmarketing experience with drugs in the same drug class as Pal and with the precursor to Pal (risperidone).

In conclusion Pal is adequately safe, from a clinical perspective within the recommended dose range of up to 12 mg daily (as appears in approved labeling) and for longer-term treatment, as specified in recommendations for labeling (as discussed in detail in Section 9.4 of this review).

#### Input From other Disciplinary Teams

From a safety-related standpoint, OCPB input is recommended for NDA22043. The undersigned reviewer is not aware of any key issues that have been identified by the OCPB review team, at the time of this writing.

The undersigned reviewer is also not aware of any issues identified by the CMC or DSI-review Teams at the time of this writing.

The undersigned reviewer is not aware of any key statistical related issues identified by the Biometric. However, some Biometric-related issues with respect to proposed labeling for the efficacy claim are discussed below, as identified by the undersigned reviewer. Input from the Biometrics Team on these identified issues is recommended, as specified later.

See more specific recommendations, provided from a clinical perspective, below.

## **9.2 Recommendation on Regulatory Action**

It is recommended that an Approvable Action be granted on NDA22043, from a clinical perspective.

Recommendations in this Section 9.2 and in Section 9.4 are considered by the undersigned reviewer as issues that need to be resolved before considering a final approval action on the NDA.

### The following are efficacy-related recommendations:

1. The study provides adequate evidence that Pal is efficacious in stabilizing patients for up to a period of treatment that was actually employed in the study. However, as previously discussed (refer to Section 9.1 of this review) Study -301 is not adequately designed as a prevention relapse (recurrence) study or as a study to determine how long a patient should receive treatment to maintain clinical stability.

Therefore, it is recommended that precautionary statements be included in labeling to address these efficacy-related issues, using standard language provided for more recently approved drugs for a maintenance treatment claim in this patient population, as recommended under Section 9.4 of this review. Also see Item 2 below, which is relevant to this issue.

The duration of treatment in which efficacy was demonstrated and for recommending longer term treatment (under Indications and Usage and Dosage and Administration of labeling, respectively) should reflect the actual duration of treatment that was given to at least the majority of subjects stabilized on Pal in Study 301 as follows. Subjects were stabilized for at least 8-weeks in study -301 during the OL phase of Study -301.

The following discusses issues involved with including a period of DB treatment beyond the 8-weeks in which subjects were stabilized during the OL phase for the purposes of labeling. The duration of DB treatment was variable across subjects (and also used a flexible dose design). Therefore, it is potentially misleading to make an efficacy claim or to recommend longer term treatment for the maximum treatment duration given during the DB phase, as this would only reflect duration of treatment for only a few subjects in the study.

Consequently, consider the following ways to including the duration of DB treatment (combined with 8-weeks of OL treatment, as above) for making an efficacy claim and recommending treatment in labeling. The treatment duration during the DB phase may best be reflected by using the median duration of DB treatment before subjects had an event of recurrence (among subjects included in the efficacy analyses on time-to-relapse). Alternatively, consider the mean duration ( $\pm$ SD) if subjects were normally distributed on duration of DB treatment. Biometric input is also recommended. Also see section 9.4 of this review for key labeling recommendations.

2. Only the results on the primary efficacy variable should be described in labeling and should not include secondary efficacy results (to the knowledge of the undersigned reviewer, the sponsor did not have key secondary variables that were declared *a priori*). See section 9.4 of this review for key labeling recommendations.
3. Study -301 used a daily dose level of Pal that was generally comparable to that which is described in approved labeling for NDA21999 for treatment of acute patients with schizophrenia. See section 9.4 of this review for key labeling recommendations.
4. See additional recommendations in this section, below, and in sections that follow.

The following are safety-related recommendations:

1. Unclear QT Results after Longterm Pal Treatment: OL trial results may suggest QT prolongation with longer-term treatment at later assessment time-points (6 or 12 month time-points) that are generally not observed at earlier time-points during OL Pal treatment, as described in 7.1.10.3. This comment is based on descriptive statistical results provided over time and as observed by the undersigned reviewer within the specific treatment groups that were reviewed (as described in section 7.1.10). These numerical trends appear to be reproducible across independent OL trials (that were reviewed, as described in Section 7.1.10) and were generally observed in pooled and unpooled OL trial datasets (that were reviewed). Refer to Section 7.1.10 for details.

Results on the incidence of outliers are suggestive of an effect with chronic treatment. However, these results are more difficult to interpret since the chances of identifying an outlier increases with increased frequency/duration of monitoring subjects.

The OL results are difficult to interpret for a number of reasons related to the limitations with data obtained from trials of this nature (including the ECG monitoring methods). Some of the key limitations with the OL trial QT results are discussed in the above specified sections of this review (e.g. no placebo control group for comparisons, wide test-retest variance, wide between subject variance, among other key limitations).

Approved labeling under NDA21999 has a QT section under Warnings. OL trials generally show group mean and median increases in QT that are generally comparable to the degree of QT prolongation that is described in labeling and specifies conditions in Pal treatment should be avoided. OCPB input is recommended regarding accumulation of Pal that may in turn influence risk for QT prolongation.

2. Safety results from Study 301 and extension OL trials did not reveal any new and clinically remarkable safety signals that differ from findings that were previously described in past clinical reviews of NDA21999 (that would alter previously conclusions and recommendations by the undersigned reviewer). NDA 21999 was approved on 12/19/06. These safety results are limited by the difficulties with interpreting results from trials involving OL treatment and due to other key limitations as previously discussed in various sections of this review. Therefore, it is recommended that only newly reported AEs, ADOs and SAEs be incorporated into the "Other Events Observed During the Premarketing..." section of labeling (this applies to all new cases from all trials described in this review that were not included in approved labeling under NDA21999).
3. See additional recommendations below in this section and in sections that follow.

Additional Recommendations:

1. Input from other disciplinary review teams is recommended (as DSI, OCPB and Biometric reviews are pending at the time of this writing). The undersigned reviewer is not aware of any key issues from other disciplines at the time of this writing, except for excluding descriptions of secondary efficacy results in labeling. It is also the understanding of the undersigned that the Biometric Team agrees with the need to more accurately describe the duration of treatment for demonstrating efficacy (see Section 9.4 below).
2. N003 was not reviewed as previously discussed.
3. Also see sections below for additional recommendations.

### **9.3 Recommendation on Postmarketing Actions**

#### **9.3.1 Risk Management Activity**

The proposed Risk Management program cannot be found in the submission. The proposed Risk Management program cannot be found in the submission. Sponsors maintain a world-wide safety database and are required to submit annual reports or periodic safety reports, as specified in the regulations.

#### **9.3.2 Required Phase 4 Commitments**

Refer to the Pediatric section regarding pediatric adolescent trials (Section 8.4).

### 9.3.3 Other Phase 4 Requests

None (see the previous section).

## 9.4 Labeling Review

As previously discussed under the main heading of this Section 9 this review only addresses key revisions in the annotated proposed labeling provided by the sponsor that was forwarded to the review Team. Annotated proposed labeling was provided to reflect new changes (that differ from the approved version under NDA21999) and are provided on the basis of new efficacy and safety data included in N000-002 submissions.

All recommendations in this section are provided from a clinical perspective and are considered by the undersigned reviewer as issues that need to be resolved before considering a final approval action on the NDA.

### I. Efficacy Related Sections

The following are recommendations regarding key efficacy-related revisions found in proposed labeling (as found in the annotated version most recently provided by the sponsor and forwarded to the Review Team). Refer to Sections 9.1 and 9.2 of this review for the rationale for these recommendations for efficacy-related sections of labeling (under Indications and Usage, Dosage and Administration and under Clinical Trials). Also input from other disciplines is pending, at the time of this writing (refer to Section 9.2).

#### A. Clinical Trials Section:

See Section 9.1 and 9.2 for the rationale and for recommendations on approaches to more accurately describing the duration of treatment when patients were stabilized in Study 301.

The following is recommended text under Clinical Trials for labeling that incorporate some of the sponsor's proposed text but is modified to address key issues previously discussed under Sections 9.1 and 9.2 of this review. Bolded text within brackets is provided as recommended comments to the sponsor (preceding this section of labeling). Italicized text is new text for labeling (that differs from that found in approved labeling under NDDA 21999).

Input from Biometrics is pending at the time of this writing.

[A new paragraph describing the results of Study -301 appears in this section incorporating proposed text, except for the following changes:

- Only primary efficacy results and results on final analysis on the primary variable are described (all secondary results are deleted).
- The language is kept as concise as possible while generally using current standard language.
- It is important to accurately specify the duration of treatment in which subjects were stabilized on treatment in the OL phase (8 weeks) and may include a period

**of time during DB phase but should reflect treatment for at least the majority of subjects (among the subjects that were included in the efficacy analysis on the time-to-recurrence). This could be the median duration or mean±SD duration of DB treatment depending on whether or not subjects were normally distributed on this variable. Please insert a proposed duration of treatment that may also be used for other sections relevant to the efficacy claim and treatment recommendations, as specified by [xx's] below and in other relevant labeling sections. While it is reasonable to also include the range of DB treatment in the section below, other sections of labeling should avoid any suggestion that the study showed efficacy for a longer duration than the duration of treatment given to at least most patients who were stabilized on DB treatment (beyond the 8-weeks of OL treatment). This final comment also applies to making treatment recommendations under Dosage and Administration.]**

### **CLINICAL TRIALS**

The short-term efficacy of INVEGA™ (3 to 15 mg once daily) was established in three placebo-controlled and active-controlled (olanzapine), 6-week, fixed-dose trials in non-elderly adult subjects (mean age of 37) who met DSM-IV criteria for schizophrenia. Studies were carried out in North America, Eastern Europe, Western Europe, and Asia. The doses studied among these three trials included 3, 6, 9, 12, and 15 mg/day. Dosing was in the morning without regard to meals.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. Efficacy was also evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician-rated scale that measures personal and social functioning in the domains of socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors.

In all 3 studies (n = 1665), INVEGA™ was superior to placebo on the PANSS at all doses. Mean effects at all doses were fairly similar, although the higher doses in all studies were numerically superior. INVEGA™ was also superior to placebo on the PSP in these trials.

An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of gender, age (there were few patients over 65), or geographic region. There were insufficient data to explore differential effects based on race.

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**B. Indications and Usage Section:**

The following is recommended text under Clinical Trials for labeling that incorporate some of the sponsor's proposed text but is modified to address key issues previously discussed under Sections 9.1 and 9.2 of this review. Section 9.2 outlines specific issues relevant to labeling and the rationale to recommendations provided below.

Bolded text within brackets is provided as recommended comments to the sponsor (preceding this section of labeling). Italicized text is new text for labeling (that differs from that found in approved labeling under NDDA 21999).

Refer to Abilify™ and other more recently approved drugs for examples of precautionary language included for this section and for the Dosage and Administration section.

**INDICATIONS AND USAGE**

b(4)

The efficacy of TRADENAME in the acute treatment of schizophrenia was established in three 6-week, placebo-controlled, fixed-dose trials in subjects with schizophrenia.

[Note that the third paragraph under the Indications and Usage section has been deleted and replaced with the new text that appears below.

It is important to accurately specify the duration of treatment in which subjects were stabilized on treatment in the OL phase (8 weeks) and may include a period of time during DB phase but should reflect treatment for at least the majority of subjects. See previous bracketed comments about the duration to specify in place of the xx's below.

The text was also modified to enhance accuracy on describing the indication. Precautionary text was also included (as found in approved labeling for other drugs with this indication (refer to Abilify™ as an example).]

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### C. Dosage and Administration Section

The following is recommended text under Clinical Trials for labeling that incorporate some of the sponsor's proposed text but is modified to address key issues previously discussed under Sections 9.1 and 9.2 of this review.

Bolded text within brackets is provided as recommended comments to the sponsor (preceding this section of labeling). Italicized text is new text for labeling (that differs from that found in approved labeling under NDDA 21999).

OCPB input: since accumulation appears to exist with multiple ER dosing, OCPB input is recommended regarding the inclusion of a description of accumulation in labeling. Input from OCPB on the potential affect of accumulation with chronic treatment on safety is also recommended that in turn, may impact on labeling for the maintenance therapy section below and/or OCPB related sections of labeling.

One comment is that the below proposed section (Maintenance Therapy) does not specify a dose-range since this is provided in the first paragraph under the subheading of Schizophrenia. Consideration should be given for repeating the recommended dose range and maximum recommended dose level under the Maintenance Therapy subsection as well, for adequate emphasis. Although, this information is not necessarily provided in both of these labeling subsections for drugs approved for this indication.

[A section is inserted on "Maintenance Therapy" as used in current standard labeling for drugs in this drug class that are approved for longer term treatment of schizophrenia. See previous comments under Clinical Trials and Indications and Usage Sections pertaining to inserting duration of treatment where "xx's" appear below and the rationale for this change. Precautionary statements are also included according to current standard labeling for this drug class and indication.]

## DOSAGE AND ADMINISTRATION

b(4)

The recommended dose of INVEGA™ (paliperidone) Extended-Release Tablets is 6 mg once daily, administered in the morning. Initial dose titration is not required. Although it has not been systematically established that doses above 6 mg have additional benefit, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase in adverse effects. Thus, some patients may benefit from higher doses, up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, small increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.

INVEGA™ can be taken with or without food. Clinical trials establishing the safety and efficacy of INVEGA™ were carried out in patients without regard to food intake.

INVEGA™ must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Concomitant use of INVEGA™ with risperidone has not been studied. Since paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if risperidone is coadministered with INVEGA™.

b(4)

b(4)

## II. Key Safety Labeling Revision

The following are recommendations for the only labeling safety related changes to the approved NDA21999 version that the sponsor proposed (that could be found from the annotated version recently provided by the sponsor).

Bolded text within brackets is provided as recommended comments to the sponsor (preceding this section of labeling). Italicized text is new text for labeling (that differs from that found in approved labeling under NDDA 21999). Input from other Disciplines is pending (refer to Sections 9.1 and 9.2).

### The Sponsor's Proposed Text

The following paragraph was inserted in the Section of "Other Events Observed During ...Premarketing..." Section of labeling.

The safety of INVEGA™ was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA™ in adults with schizophrenia (see CLINICAL PHARMACOLOGY: Clinical Trials). In general, adverse event types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse events reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase, [

b(4)

### Reviewer Recommended Text

Pending input from other disciplines (as previously specified in Section 9.2 that includes input on OL Trial results on QT interval) the following bracketed comments are recommended for this section of labeling:

[Results on newly reported adverse events, serious adverse events and adverse dropouts from all Phase III clinical trials in NDA22043 (that are not already included in approved labeling the approval of NDA21999) should be

**incorporated into the listings of adverse event under this section of labeling. We cannot find newly reported events included in these listings. Please insert all newly reported events in this section of labeling.**

**The proposed description of safety results from Study 301 is not included in labeling as proposed due to the limitations with interpreting safety results given the study design of this trial. For example, this trial used an OL phase and only randomized a subgroup of patients to DB treatment. Furthermore, the duration of DB treatment was not held constant, among other limitations with the study design. Moreover, it is not considered valid to compare safety results between independent trials of trials using a different study design and safety results between OL and DB phases of Study 301, as proposed. ]**

#### **9.5 Comments to Applicant**

See the previous section for labeling. Any other comments for a letter to the sponsor will depend on the Action as deemed by the Agency and the Action Letter contents will be determined at the Division and Agency levels.

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

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- 1. Within 5 days prior to baseline.
- 2. Within 24 hours prior to first dose of ER OROS paliperidone.
- 3. For outpatient subjects, visits may have taken place  $\pm$  3 days around the indicated day when visits were  $\leq$  2 weeks apart and  $\pm$  7 days around the scheduled day when visits were 4 weeks apart.
- 4. Two weeks after each of the visits that were 4 weeks apart, subjects were to be contacted by telephone to assess safety, monitor for recurrence, and provide instructions.
- 5. Subjects who experienced a recurrence in the double-blind phase, discontinued study drug during the double-blind phase for other reasons, or withdrew from the study had the end-of-study/early withdrawal visit procedure performed (subjects exiting the run-in phase did not complete the SCL5 or PSP).
- 6. Subjects who discontinued study medication for any reason during the double-blind phase, including those who had a recurrence but elected not to continue into the open-label extension phase, had the end-of-study/early withdrawal visit procedure performed then remained in the study to be followed every 4 weeks for efficacy and safety until they either experienced a recurrence or withdrew from the study, or the study concluded. At each subsequent visit the following procedures were performed: PANSS, CGI-S, vital signs (BP and pulse rate, supine and standing), concomitant medication review, and adverse event monitoring. In addition, ECGs and fasting clinical laboratory tests were performed every 12 weeks.
- 7. Subjects who did not continue into the open-label phase completed the follow-up visit 1 week after their last dose.
- 8. Included diabetic history and smoking history.
- 9. DNA informed consent was obtained before collection of the pharmacogenomics blood sample, but the consent may have been obtained later in the study if the blood sample for genetic testing was not collected at baseline. The sample may have been collected at any subsequent visit at which blood was drawn, if not done at baseline.
- 10. Collected PE blood sample (5 mL) from subjects at the end-of-study/early withdrawal visit to verify compliance with study drug administration (to have been analyzed only if necessary).
- 11. In addition to the indicated visits, the PANSS and CGI-S scales were administered whenever the investigator suspected a subject may have been experiencing a recurrence event. NOTE: If any of the PANSS or CGI-S criteria for recurrence were exceeded on a given day, the PANSS and CGI-S assessments were repeated the following day.
- 12. Only weight was measured at the follow-up visit.
- 13. A total of 3 ECG tracings were obtained before administration of the first dose of study drug; 2 ECG tracings were obtained during the screening phase (Days -5 to -1) and the third ECG tracing was obtained at the baseline visit. The ECGs were recorded at approximately the same time each day (preferably in the morning) to minimize possible diurnal variation and food effects.
- 14. On Days 4 and 8, ECG recordings were obtained at 4, 10, and 22 hours postdose.
- 15. ECGs and clinical laboratory tests were performed every 12 weeks when visits were 4 weeks apart, starting 12 weeks after the Day 99 visit (Visit 12).
- 16. Vital signs: blood pressure and pulse rate were measured supine and standing.
- 17. Vital signs were also recorded on Days 1, 2, and 3.
- 18. Hematology: serum chemistry (including serum prolactin, fasting plasma glucose [FPG], insulin, and C-peptide), and urinalysis. All specimens for laboratory tests were collected from subjects who had fasted for a minimum of 6 hours.
- 19. The day before this visit, outpatient subjects were contacted by telephone to remind them to fast overnight (minimum of 6 hours) and return to the study center the next day for their visit.
- 20. Performed prior to administration of allowed concomitant medication for extrapyramidal symptoms.
- 21. Monitoring for adverse events began with the first study-related procedure after signing of the informed consent form and continued until the last study-related procedure was performed.
- 22. Subjects may have been hospitalized at any time during the screening period, as deemed necessary by the investigator. Subjects must have been hospitalized at baseline if they were not already inpatients. As early as Day 15, subjects may have been discharged from the hospital and followed as outpatients if the investigator believed they were not at significant risk for suicidal or violent behavior and if their CGI-S was 4 (moderately ill) or less.
- 23. For women of childbearing potential, serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test was performed at screening and at the follow-up visit; other pregnancy tests were urine pregnancy tests. After Visit 18, pregnancy tests were performed every 8 weeks.
- 24. Interactive Voice Response System (IVRS) guidelines for drug dispensation were followed.
- 25. The IVRS was contacted on Day 99 for the random assignment of the subject to treatment (ER OROS paliperidone or matching placebo) for the double-blind phase.

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**Study Schedule for an OL Trial (Study 704 as provided by the sponsor)**

**Table 3: Time and Events Schedule**  
 Open-Label Extension (Protocol R076477-SCH-704)

	Baseline <sup>a</sup>	Open-Label Treatment Phase																		Post-Study Visit	
		101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118 <sup>c</sup>		119
Visit				1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	53	
Week				1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52	53	
Day	1	4 <sup>d</sup>	8 <sup>e</sup>	15 <sup>f</sup>	22 <sup>f</sup>	29 <sup>f</sup>	57 <sup>f</sup>	85 <sup>f</sup>	113 <sup>f</sup>	141 <sup>f</sup>	169 <sup>f</sup>	197 <sup>f</sup>	225 <sup>f</sup>	253 <sup>f</sup>	281 <sup>f</sup>	309 <sup>f</sup>	337 <sup>f</sup>	365 <sup>f</sup>	372		
Informed consent	X																				
Inclusion/exclusion criteria	X																				
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X																				
Physical examination	X																				
Electrocardiogram (ECG)	X	X	X	X		X	X		X		X				X				X	X	X
Clinical laboratory tests (fasting) <sup>g</sup>	X												X						X	X	X
Pregnancy test in female <sup>h</sup>	X						X		X		X								X	X	X
Schizophrenia Quality of Life Scale, Revision 4 (SOLS-R4)	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Positive and Negative Syndrome Scale (PANSS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Global Impression Scale - Severity (CGI-S)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Personal and Social Performance Scale (PSP)	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Healthcare resource use questionnaire	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Barnes Akathisia Rating Scale (BARS) <sup>i</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Simpson-Angus Scale (SAS) <sup>j</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug <sup>k</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: footnotes are provided on the following page.

(Continued)

- <sup>a</sup> Scheduled baseline procedures that were previously completed at the final double-blind phase visit do not have to be repeated. If at all feasible, end-of-phase procedures (Visit 10) in the double-blind phase should be completed the same day as baseline (Visit 101) for the open-label extension; the first dose of open-label medication should be taken by 10:00 AM if possible.
- <sup>b</sup> Post-study visit will be scheduled for 1 week after the final dose of study drug.
- <sup>c</sup> Subjects who withdraw early from the study will have end-of-phase procedures performed on the day after their last dose.
- <sup>d</sup> This visit may NOT take place before Day 4 but may occur up to Day 6.
- <sup>e</sup> This visit may NOT take place before Day 8 but may occur up to Day 10.
- <sup>f</sup> This visit may take place ±7 days around the indicated day.
- <sup>g</sup> Hematology, serum chemistry, and urinalysis. All labs are drawn in the fasting state. The site should call subjects the day before Visits 101, 111, 118, and 119, to remind them to fast after dinner that evening.
- <sup>h</sup> Serum pregnancy test at end-of-phase (Visit 118) and post-study visits (Visit 119); urine pregnancy test at baseline (Visit 101) and Visits 107, 109, 111, 113, and 115.
- <sup>i</sup> To be performed prior to administration of allowed concomitant medication for extrapyramidal symptoms.
- <sup>j</sup> Drug will be dispensed according to Interactive Voice Response System guidelines.
- <sup>k</sup> Monitoring for adverse events begins after the Informed Consent Form for the open-label extension is signed and the first study-related procedure is performed, and continues until the last study-related procedure is performed.

Cross-reference: Appendix 1.1.

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**Table Series 10.2 Outlier Criteria for Clinical Parameters in Study 301 and in Open Label (OL) Trials**

Outlier Criteria for Laboratory Parameters for Study -301 Trial (as provided by the sponsor)

Laboratory Parameter	Markedly Abnormal Limits	
	Low	High
Albumin (g/dL)	2.4	6.0
Alkaline phosphatase (μ/L)	N/A	250
Alanine transaminase (SGPT) (μ/L)	N/A	200
Aspartate transaminase (SGOT) (μ/L)	N/A	250
Bicarbonate (mEq/L)	15.1	34.9
Blood urea nitrogen (mg/dL)	N/A	50
C Peptide (ng/mL)	1	4
Calcium (mg/dL)	6	12
Chloride (mEq/L)	94	112
Cholesterol (mg/dL)	N/A	300
Creatine kinase (μ/L)	N/A	990
Creatinine (mg/dL)	N/A	3
Gamma glutamyl transferase (μ/L)	N/A	300
Glucose (mg/dL)	40	300
HDL (mg/dL)	35	N/A
Insulin (mU/mL)	N/A	25
LDH (μ/L)	N/A	500
LDL (mg/dL)	89	160
Phosphorus (mg/dL)	2.2	3.1
Potassium (mEq/L)	3.0	5.8
Sodium (mEq/L)	125	155
Total bilirubin (mg/dL)	N/A	3.0
Total protein (g/dL)	5	N/A
Triglycerides (mg/dL)	N/A	500
Uric acid (mg/dL)	1.5	10
Hematocrit (%)-- female	28	50
-- male	24	55
Hemoglobin (g/dL)	8	19
Hemoglobin A1C (%)	4.3	6.1
Neutrophils (%)	30	90
Monocytes (%)	N/A	20
Eosinophils (%)	N/A	10
Basophils (%)	N/A	6
Lymphocytes (%)	10	60
Platelet count (x10 <sup>9</sup> /μL)	100	600
Red blood cell count (x10 <sup>6</sup> /μL) -- female	3.0	5.5
-- male	3.0	6.4
Reticulocytes (%) --female	0.9	4.4
--male	1.0	3.8
White blood cell count (x10 <sup>3</sup> /μL)	2.5	15.0

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

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

**Laboratory Outlier Criteria used in an OL Extension Trial -704 (as provided by the sponsor).**

APPENDIX B.4.1.  
 Criteria of Merckilly Abnormal Laboratory Values

Analyte	Units	Sex	Laboratory Values	
			Low	High
<b>Chemistry</b>				
Albumin	g/dL	Both	2.4	5
Alkaline phosphatase	U/L	Both	N/A	250
ALT (SGPT)	U/L	Both	N/A	200
Bicarbonate	mEq/L	Both	15.1	34.9
AST (SGOT)	U/L	Both	N/A	250
Bilirubin, direct	mg/dL	Both	N/A	0.400
Bilirubin	mg/dL	Both	N/A	3
BUN	mg/dL	Both	N/A	30
Calcium	mg/dL	Both	6	12
Chloride	mEq/L	Both	94	112
Cholesterol	mg/dL	Both	N/A	300
Creatinine kinase	U/L	Both	N/A	900
Creatinine	mg/dL	Both	N/A	3
GGT	U/L	Both	N/A	300
Glucose	mg/dL	Both	40	300
HDL	mg/dL	Both	35	N/A
LDH	U/L	Both	N/A	500
LDL	mg/dL	Both	60	160
Magnesium	mmol/L	Both	0.40	3.3
Phosphorus	mg/dL	Both	2.2	8.1
Potassium	mEq/L	Both	3.0	5.8
Protein	g/dL	Both	5.0	N/A
Sodium	mEq/L	Both	135	155
Triglycerides	mg/dL	Both	N/A	500
Uric acid	mg/dL	Both	4.5	10.0
<b>Hematology</b>				
Eosinophils	%	Both	N/A	6
Emiophils	%	Both	N/A	10
Lymphocytes	%	Both	40	60
Monocytes	%	Both	N/A	20
Neutrophils	%	Both	50	90

Note: The same limits apply to both men and women unless gender is indicated.  
 ALT (SGPT) = alanine transaminase (serum glutamate pyruvate), AST (SGOT) = aspartate transaminase (serum glutamic oxaloacetic transaminase), BUN = blood urea nitrogen, HDL = high-density lipoprotein, HbA1c = hemoglobin A1c, LDH = lactic dehydrogenase, LDL = low-density lipoprotein, N/A = not applicable, RBC = red blood cell, and WBC = white blood cell.

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**Vital Sign and ECG Outlier Criteria Used in Phase III Trials (as provided by the sponsor)**

**Table 73: Criteria for Treatment-Emergent Abnormal Vital Signs, Orthostatic Changes, and Body Mass Index**

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

**Table 84: Criteria for Abnormal Electrocardiographic Findings**

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

<sup>a</sup> Classification based on ICH E14 Guideline (reference 4).

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/s/

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