CLINICAL REVIEW

Application Type	sNDA
Application Number	021999/Supplement 024
Priority or Standard	Priority
Submit Date	October 8, 2010
Received Date	October 8, 2010
PDUFA Goal Date	April 8, 2011
Division/Office	DPP/ODE1
Reviewer Name	Jenn Sellers, MD, Ph.D.
Review Completion Date	March 8, 2011
Established Name	Paliperidone ER
Trade Name	Invega
Therapeutic Class	Atypical Antipsychotic
Applicant	Johnson & Johnson
Formulations	Oral Extended-Release Tablets (1.5mg, 3mg, 6mg and 12mg)
Dosing Regimen	(b) (4) mg to 12mg Once Daily
Indication	Schizophrenia
Intended Population	Adolescents 12-17 Years Old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc. has submitted sufficient data to support the conclusion that paliperidone extended-release (ER) tablet is effective and safe in the treatment of schizophrenia in adolescents (aged 12-17 years). I recommend that this application be approved. However, we need to examine the report of site inspections from the Division of Scientific Investigation (DSI), which is pending at this moment, and we need to reach agreement on labeling with the sponsor before the approval action is taken.

1.2 Risk Benefit Assessment

The efficacy of paliperidone ER tablet in improving symptoms of schizophrenia in adolescents aged 12-17 years was demonstrated by the results on the primary Endpoint, the change from Baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score at Endpoint, from a 6-week, randomized, double-blind, placebo-controlled trial.

The safety evaluation demonstrated that the safety profile of paliperidone ER tablet in the adolescent population was similar to that obtained from adult population and that of risperidone, of which paliperidone is the major active metabolite, in adolescent population. Paliperidone ER tablet was generally safe and tolerated in the adolescent population.

1.3 Recommendations for Post-Market Risk Evaluation and Mitigation Strategies

No specific safety concerns have been identified from this submission. Risk Evaluation and Mitigation Strategies are not required at this time.

1.4 Recommendations for Post-Market Requirements and Commitments

A two year open label extension safety trial of paliperidone ER in adolescent population is ongoing. The completed trial will provide longer-term safety data in the target population. This submission included the safety data in this open label safety trial through the cutoff date: July 30, 2009.

A controlled relapse prevention trial in adolescent subjects with schizophrenia was not required according to Written Request (WR) Amendment #2 dated March 31, 2010.

2 Introduction and Regulatory Background

2.1 Product Information

Paliperidone belongs to atypical antipsychotic drugs. It is 9-hydroxy-risperidone, a major active metabolite of risperidone. It is a monoaminergic antagonist that has activities of dopamine type 2 and serotonin type 2A antagonism.

Invega (paliperidone) ER Tablets (1.5, 3, 6 and 9 mg), are currently approved for the treatment of schizophrenia in adults in the United States (US), the European Union and other countries.

According to the sponsor, there have been no withdrawals or restrictions of use of paliperidone ER tablets in any foreign market at this time; an application for pediatric use for the product has been filed in Canada and it is being reviewed.

2.2 Tables of Currently Available Treatments for Proposed Indications

At present, the atypical antipsychotics, risperidone (Risperdal®), olanzapine (Zyprexa®), quetiapine (Seroquel®), and aripiprazole (Abilify®) have been approved in US for the treatment of schizophrenia in adolescents.

2.3 Availability of Proposed Active Ingredient in the United States

Invega is an approved drug in US.

2.4 Important Safety Issues with Consideration to Related Drugs

Paliperidone is a metabolite of risperidone. Risperidone has a boxed warning for increased mortality in elderly patients with dementia related psychosis. Other warnings and precautions for risperidone use include cerebrovascular events (including stroke in the elderly with dementia), neuroleptic malignant syndrome (NMS), tardive dyskinesia, orthostatic hypotension, hyperglycemia/ diabetes mellitus, hyperprolactinemia, seizures, disruption of body temperature regulation, potential for cognitive/motor impairment and suicide, and agranulocytosis. Atypical antipsychotics may also be associated with an increased risk of sudden cardiac death.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In US, paliperidone ER tablet, marketed as Invega, was approved by FDA for the acute treatment of schizophrenia (NDA 21,999) on December 19, 2006; for the maintenance treatment of schizophrenia (NDA 22,043) on April 27, 2007 and for the treatment of schizoaffective disorder as monotherapy (NDA 21,999 S-013) and as an adjunct to mood stabilizers and/or anti-depressants (NDA 21,999 S014) on July 31, 2009.

Paliperidone ER tablet was developed for this indication under IND 65,850.

FDA issued an original Pediatric Written Request (WR) for paliperidone ER for adolescent schizophrenia dated November 2, 2006; subsequently, Amendment #1 dated August 29, 2007 and Amendment #2 dated March 31, 2010.

A pediatric pre-sNDA teleconference was held on April 13, 2010.

This sNDA was submitted to the Agency on October 8, 2010. It was classified as a priority review due to the WR. The Filing Meeting was held on November 16, 2010 and it was concluded that this supplement was fileable. The pediatric exclusivity determination meeting was held on January 4, 2010. A Mid-Cycle Meeting was held on January 11, 2011. The PeRC meeting will be held on March 16, 2011. The PDUFA goal date is April 8, 2011.

2.6 Other Relevant Background Information

The sponsor requested six months of pediatric exclusivity for Invega.

The Sponsor submitted this sNDA also to fulfill the WR for Invega. The Sponsor has conducted one non-clinical animal study and 3 clinical studies which included pediatric pharmacokinetic (PK) study, pediatric efficacy and safety trial and pediatric long-term open-label safety trial. The report of the animal study was submitted to NDA 21999 dated September 9, 2009. This submission included the final reports of the 3 clinical studies.

- **Nonclinical Toxicology Study**: “Paliperidone (R076477) 7 Week Toxicity Study in the Juvenile Rat by Oral (Gavage) Administration” (study no. JJB/0043, TOX 8691, February 13, 2009).

- **Pediatric PK Study (PALIOROS-PSZ-1001)**: Open-label study to evaluate the safety and PK of single- and multiple-dose paliperidone ER in pediatric subjects aged 10 to 17 years with schizophrenia, schizoaffective disorder or schizopheniform disorder.

- **Pediatric Efficacy and Safety Trial (R076477-PSZ-3001)**: A randomized, multicenter, double-blind, weight-based, fixed-dose (paliperidone ER Low, Medium and High group), placebo-controlled trial of the efficacy and safety of paliperidone ER for the treatment of schizophrenia in adolescent subjects aged 12 to 17 years.

- **Pediatric Safety Trial (R076477-PSZ-3002)**: A 2-year, open-label, single-arm safety trial of flexibly dosed paliperidone ER (1.5-12 mg/day) in the treatment of adolescents aged 12 to 17 years with schizophrenia.

The pediatric exclusivity was granted on January 4, 2011.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Adverse event (AE) safety data were audited for completeness and accuracy in a 5% sample (N=1) of submitted Case Report Forms (CRFs). The AEs from the CRF for the subject (601041) were compared to those in the Narrative Summary in the study report and those listed in dataset file kae.xpt. No deficiencies or discrepancies were noted by this reviewer.

The Division of Scientific Investigation (DSI) is inspecting 3 trial sites and the findings are pending at this time. The 3 sites being inspected and the reasons for inspections are listed below:

Site 001006 (US; Lowy, Adam; 6 subjects)
This domestic site was chosen to be inspected due to large observed improvements in the primary Endpoint in all treatment arms. For example, 2 subjects from this site had changes from Baseline of -62 (paliperidone ER High group) and -59 (placebo). DSI was informed of this observation and requested to investigate the integrity of the trial conduct at this site.

Site 091002 (India; Jhanwar, Gopal; 18 subjects)
The subjects in this site had large observed changes from Baseline in the primary Endpoint in both directions (ranged from -54 to +30) in all treatment arms. Again, DSI was informed. This site was chosen to be inspected also because of the enrollment of a relatively large number of study subjects.

Site 007012 (Russia; Yakhin, Kausar; 13 subjects)
This foreign site was chosen to be inspected due to enrollment of a relatively large number of study subjects.

3.2 Compliance with Good Clinical Practices

The sponsor claimed that the trial R076477-PSZ-3001 was conducted in accordance with International Conference on Harmonization (ICH) of Good Clinical Practice and local ethical and legal requirements, and with the Declaration of Helsinki.

3.3 Financial Disclosures

The Sponsor certified that they had no financial arrangements with any of the clinical investigators whereby the value of compensation to the investigators could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). None of the clinical investigators listed claimed holding any disclosable financial arrangements with Johnson and Johnson as defined in 21 CFR 54.2(a)(b)(c) and (f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new Chemistry Manufacturing and Control (CMC) information was provided in this submission.

4.2 Clinical Microbiology

No clinical microbiology study was conducted.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical toxicology study titled “Paliperidone (R076477) 7-Week Toxicity Study in the Juvenile Rat by Oral (Gavage) Administration” was conducted. The Pharmacology/ Toxicology team has reviewed the final report (review signature date: August 19, 2010) and concluded that this study was acceptable to fulfill the pediatric WR and to support the proposed treatment in adolescents aged 12 to 17 years with schizophrenia. The following is the brief summary of the review.

Paliperidone was generally well tolerated in juvenile rats. The treatment of paliperidone did not affect brain histopathology, motor activity, sexual maturity and reproductive performance.

In females, the dose of 2.5 mg/kg/day was considered the Maximum Tolerated Dose (MTD) because the AEs on learning and memory were demonstrated at this dose. The mid dose of 0.63 mg/kg/day was considered to be the No Observable Adverse Effect Level (NOAEL).

In male, no MTD was achieved. Therefore, the highest dose of 2.5 mg/kg/day was considered to be the NOAEL in males.

4.4 Clinical Pharmacology

Study PALIOROS-PSZ-1001 (PSZ-1001) titled “Open-Label Study to Evaluate the Safety and Pharmacokinetics of Single- and Multiple-Dose Extended Release OROS Paliperidone in Pediatric Subjects (≥10 to ≤17 Years of Age) with Schizophrenia, Schizoaffective Disorder or Schizopheniform Disorder” was conducted and the final report was submitted to this sNDA.

This study included 25 pediatric subjects (18 males, 7 females) aged 10 to 17 years diagnosed with schizophreniform disorder (n=8), schizoaffective disorder (n=7),

paranoid schizophrenia (n=6), undifferentiated schizophrenia (n=3), and disorganized schizophrenia (n=1). The study evaluated the doses ranged from 4 to 12 mg/day.

In summary, the plasma concentrations of paliperidone rose steadily to reach peak plasma concentration approximately 24 hours after single dosing. Steady-state drug concentrations were attained within 4–5 days of dosing. PK observations in pediatric subjects were consistent with those observed in adults following single- and multiple-dose administration of paliperidone ER.

Pediatric subjects (10 to17 years of age) tolerated paliperidone ER dosing from 4 - 12 mg/day well (corresponding to weight-based doses ranging 0.086 - 0.171 mg/kg) with no serious treatment-emergent AEs (TEAEs). The safety profile was similar to that seen in adults.

4.5 Statistics

In the pediatric efficacy and safety trial PSZ-3001, a total of 201 subjects were randomly assigned to 1 of 4 treatment groups: 54 to paliperidone Low [paliperidone ER 1.5 mg/day regardless of body weight (wt)], 48 to Medium (paliperidone ER 3 mg/day in 29 kg $\leq$ wt < 51kg and 6 mg/day in wt $\geq$ 51kg), 48 to High (paliperidone ER 6 mg/day in 29 kg $\leq$ wt < 51kg and 12 mg/day in wt $\geq$ 51kg) and 51 to placebo respectively. Based on the actual number of subjects randomly assigned to each treatment group, retrospective power calculation showed the trial had sufficient power (≥ 80.167%).

The primary efficacy measurement was the change in PANSS total score from Baseline to Endpoint. There was no prespecified key secondary Endpoint in this trial.

The hypothesis of the trial was: at least one paliperidone ER dose group (as randomized – paliperidone ER Low, Medium and High group) would be superior to placebo in improving the symptoms of schizophrenia as measured by the change in PANSS total score from Baseline to Endpoint (Week 6 LOCF).

It was prespecified that the efficacy result would be analyzed by weight-based fixed dose randomization groups: paliperidone ER Low, Medium and High group (**Table 4**).

The efficacy analysis showed that the paliperidone ER Medium group demonstrated statistical significance ($p = 0.006$) compared to placebo while the paliperidone ER High and Low group did not show statistical significance ($p = 0.086$ and $p = 0.508$ respectively).

The effect size at Endpoint was -2.1, -10.1 and -6.6 for paliperidone ER Low, Medium and High treatment group respectively.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Summary of the Pediatric PK Study (PSZ-1001)

Total Number of Subjects	25
Study Dates	March 17, 2006 to August 25, 2006
Study Design	Open label study to evaluate safety and PK of single dose and multiple doses of paliperidone ER in pediatric subjects (10 to 17 years of age) with schizophrenia, schizoaffective disorder or schizophreniform disorder
Study Drugs	Paliperidone ER
Gender	Male (72%), female (28%)
Age (years): Mean (Range)	14.6 (10-17)

Source: reviewer's summary

Table 2: Summary of 6-Week Efficacy and Safety Trial in Adolescents with Schizophrenia (PSZ-3001)

Study Country, # study sites, (% of Total Number of Subjects)	Russia, 12 sites, (41%), India, 7, (23%), Ukraine, 6, (17%), US, 9, (15%), and Romania, 1, (5%). Total study sites: 35.
Study Dates	August 8, 2007 to March 30, 2009
Study Design	6-week, randomized, double-blind, placebo-controlled, weight-based, fixed-dose trial to assess the efficacy, safety and tolerability of paliperidone ER treatment (Low, Medium and High dose) compared to placebo in an acute episode of schizophrenia (PANSS total score 60 - 120) in adolescents (12-17 years)
Study Drugs	Paliperidone ER and placebo
Randomized/Treated	201/201 (48 - 54 subjects in each treatment group)
Gender	Male (59%), female (41%)
Age (years): Mean (Range)	15.4 (12-17)
Endpoints Primary Secondary	 The change in PANSS total score from Baseline to Endpoint (Week 6-LOCF) No key secondary Endpoint

Source: reviewer's summary

Table 3: Summary of 2-Year Open-Label Safety Trial in Adolescents with Schizophrenia (PSZ-3002)

Total Number of Subjects	282
Study Start Date	June 29, 2007
Report Cutoff Date	July 30, 2009
Study Design	2-year, open-label, safety trial of flexibly dosed paliperidone ER (1.5 - 12 mg/day) in the treatment of adolescents with schizophrenia
Study Drug	Paliperidone ER
Gender	Male (59%), female (41%)
Age (years): Mean (Range)	15.4 (12-18)
Number of subjects who have completed $\geq$ 6 months at or above the minimum effective dose (3mg/day) at the report cut off date	148

Source: reviewer's summary

5.2 Review Strategy

This reviewer has reviewed the Clinical Study Report (CSR) of PSZ-3001 and R076477-PSZ-3002 (PSZ-3002 for short), clinical overview, summaries of efficacy and safety, proposed labeling, financial disclosure certification, debarment certification, list of investigators, audit certificate, the pediatric exclusivity request, correspondence regarding meetings, the original written request and its 2 amendments, case report forms, narratives, dataset file, 4-month safety update report, postmarketing report, literature search results. This reviewer has consulted Dr. George Kordzakhia for statistical analyses, Dr. Islam Younis for the review of pediatric PK study and Dr. Elzbieta Chalecka for juvenile rat data. Please refer their reviews for details.

5.3 Discussion of Individual Studies/Clinical Trials

PSZ-1001
It was an open label study to evaluate the safety and PK of single dose and multiple doses of Paliperidone ER in pediatric subjects with schizophrenia, schizoaffective disorder or schizophreniform disorder.

PSZ-3001
It was a 6 week, randomized, double-blind, placebo-controlled, fixed-dose trial to assess the efficacy and safety of paliperidone ER treatment in adolescents (aged 12-17 years) with schizophrenia.

PSZ-3002
It is an ongoing 2-year, open-label, single-arm safety trial of flexibly dosed paliperidone ER (1.5 - 12 mg/day) in the treatment of adolescents (aged 12 to 17 years) with schizophrenia.

6 Review of Efficacy

6.1 Rationale for Selection of Studies for Review

The following efficacy review focused on PSZ-3001 which was the only pediatric efficacy and safety trial in this adolescent schizophrenia development program.

6.2 Study Summary

6.2.1. Method/Study Design/Analysis Plan

PSZ-3001 was conducted from August 8, 2007 to March 30, 2009.

Overall Study Design

PSZ-3001 was a 6-week, phase 3, multicenter, randomized, double-blind, placebo-controlled, weight-based, fixed-dose, parallel-group trial designed to assess the efficacy, safety and tolerability of paliperidone in 201 adolescents (12-17 years of age) with a DSM-IV diagnosis of schizophrenia who were experiencing acute exacerbations.

This trial included the following 3 phases:

- A screening phase of up to 3 weeks to assess eligibility criteria, including a flexible washout phase during which any current disallowed psychotropic medications were tapered and discontinued, as appropriate;
- A 6-week double-blind treatment phase with an end-of-study or early-withdrawal visit;
- A 1-week follow-up visit for subjects who did not enter the open-label safety trial PSZ-3002. Subjects who completed PSZ-3001 or who completed at least 21 days of the double-blind treatment phase and dropped out due to lack of efficacy had the option to enter the open label trial: PSZ-3002.

Dose and Administration

All eligible subjects were randomized 1:1:1:1 to placebo, paliperidone ER Low, Medium or High dose group. Subjects weighing 29 kg - 51 kg at the Baseline visit were randomly assigned to receive placebo or 1.5, 3, or 6 mg of paliperidone ER daily, corresponding to the placebo, paliperidone ER Low, paliperidone ER Medium, or paliperidone ER High groups, respectively. Subjects weighing $\geq$ 51 kg at the Baseline visit were randomly assigned to receive placebo or 1.5, 6, or 12 mg of paliperidone ER daily, corresponding to the placebo, paliperidone ER Low, paliperidone ER Medium, or paliperidone ER High groups, respectively. **Table 4** shows the detailed weight-based fixed doses to be given.

Table 4: Weight-Based Fixed Dose Randomization Groups in PSZ-3001

	Randomization Group			
	Placebo	Paliperidone ER Low (0.0150-0.0517 mg/kg)	Paliperidone ER Medium (0.0589-0.1176 mg/kg)	Paliperidone ER High (0.1179-0.2353 mg/kg)
Body weight ≥29 to <51 kg	placebo	Paliperidone ER 1.5 mg (0.0295-0.0517 mg/kg)	Paliperidone ER 3 mg (0.0589-0.1034 mg/kg)	Paliperidone ER 6 mg (0.1179-0.2069 mg/kg)
Body weight ≥51 to ≤100 kg	placebo	Paliperidone ER 1.5 mg (0.0150-0.0294 mg/kg)	Paliperidone ER 6 mg (0.0600-0.1176 mg/kg)	Paliperidone ER 12 mg (0.1200-0.2353 mg/kg)
Analysis	placebo	Paliperidone ER 1.5 mg	Paliperidone ER 3 mg and paliperidone ER 6 mg combined	Paliperidone ER 6 mg and paliperidone ER 12 mg combined

ER= extended release
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 1, page 25

Study drug was administered once daily without regard to food intake in the morning (before 10 AM) beginning on Day 1. No dosage adjustment was permitted during this trial.

Selection of Study Population

Key Inclusion Criteria:

1. Male or female subjects who were 12 to 17 years of age, inclusive, with a body weight of at least 29 kg;

2. Subjects diagnosed with schizophrenia according to the DSM-IV at least 1 year before screening. The diagnosis was to have been established using the semi-structured K-SADS-PL questionnaire (including all supplements), and all subjects were to have had at least 1 adequate treatment course with an antipsychotic drug prior to study enrollment;

3. Subjects experiencing an acute exacerbation, with a PANSS total score between 60 and 120, inclusive, at screening and at Baseline;

4. Subjects who were not in a danger to themselves or others and had family support available to be maintained as outpatients. The K-SADS-PL diagnostic interview Item ‘a’, recurrent thoughts of death; Item ‘b’, suicidal thoughts; Item ‘c’, suicide attempts and their seriousness; Item ‘d’, suicide attempts and their lethality; and Item ‘e’ self-harming behavior must each have had a score of no more than 2.

Key Exclusion Criteria:

1. Subjects who, at screening, met the DSM-IV criteria for dissociative disorder, bipolar disorder, major depressive disorder, schizoaffective disorder, schizophreniform disorder, autistic disorder, or primary substance-induced

psychotic disorder; Other comorbid disorders such as attention-deficit hyperactivity disorder, were allowed as long as the diagnosis of schizophrenia was the primary diagnosis and the comorbid disorders did not require medications in the investigator's judgment;

2. History or conditions that could have increased the risk of the occurrence of torsade de pointes or sudden death in association with the use of drugs that prolong the QT interval corrected for heart rate (QTc); concomitant use of drugs that prolong the QTc interval;

3. Subjects with a known or suspected history of seizure disorder, neuroleptic malignant syndrome (NMS), encephalopathic syndrome, tardive dyskinesia, or insulin-dependent diabetes mellitus;

4. History of severe preexisting gastrointestinal narrowing (pathologic or iatrogenic) or an inability to swallow oral study drug with the aid of water. Subjects could not chew, divide, dissolve, or crush the study drug;

5. History of any prior surgical procedures such as gastric or bowel resection which could interfere with the absorption and release of paliperidone ER;

6. Subjects who, in the opinion of the investigator, were not to discontinue or participate in washout of prohibited concomitant psychotropic medications;

7. Subjects who received clozapine in the 2 months or a depot antipsychotic within 2 treatment cycles or electroconvulsive therapy in the 3 months before the Baseline visit;

8. Subjects experiencing their first psychotic episode.

The Primary and Secondary Efficacy Endpoints

The primary efficacy outcome measure was the mean change from Baseline to Endpoint in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score.

The PANSS is designed to measure the severity of symptoms in subjects with schizophrenia and other psychotic disorders and provides a total score (sum of the scores of all 30 items) and scores for 3 subscales, the positive subscale (7 items), the negative subscale (7 items), and the general psychopathology subscale (16 items). The severity of each item is rated on a scale of 1 (absent) to 7 (extreme), with higher scores representing greater symptom severity.

PANSS is a well-established rating scale that has been demonstrated to have strong psychometric characteristics, including good inter-rater reliability, internal consistency, and construct validity, in numerous studies in populations with schizophrenia, including

adolescents. Furthermore, the PANSS has been shown to be responsive to treatment interventions in clinical trials of adolescent subjects with schizophrenia.

The secondary efficacy outcome measures at Endpoint included Clinical Global Impressions - Severity Scale (CGI-S), Children's Global Assessment Scale (CGAS) and Sleep Visual analog scales (VAS). The sponsor did not identify any key secondary efficacy measures.

Statistical Methods

A closed testing procedure using Dunnett's test in testing each of the 3 paliperidone ER dose groups against placebo for the primary efficacy variable was used.

The primary efficacy measurement, the change in PANSS total score from Baseline to the Endpoint, was analyzed by a last observation carried forward (LOCF) ANCOVA. It was also analyzed separately for age, sex, race and geographic region. Treatment effects will be estimated based on differences between least-squares means.

A total of 49 subjects per each paliperidone treatment and placebo group were estimated to provide 80% power to detect a clinically relevant difference of 13.2 points between any paliperidone group compared with placebo in the change from Baseline in total PANSS score, applying Dunnett's adjustment for multiplicity (2-sided family wise α level of 0.05).

The intent-to-treat (ITT) analysis set was the primary analysis set for all efficacy analyses. It included all subjects who were randomly assigned to treatment and received at least 1 dose of study medication, and had efficacy assessments both at Baseline and post-Baseline.

6.2.1. Results

Demographics

Demographic and Baseline characteristics for the randomized sample are presented in **Table 5**.

The 4 weight-based fixed-dose groups were comparable with respect to race. A majority of the subjects were white (65% to 71% across the 4 treatment groups) and non-Hispanic (96% - 100%).

The distribution of age and gender appeared roughly comparable among the groups. Most subjects among all groups (69 – 82%) were older - aged 15 to 17 years which are consistent with the fact that the diagnosis of schizophrenia in pediatric population is most commonly made in late adolescence. More than half of subjects (56% - 70%) in all 3 paliperidone ER treatment groups were male which was consistent with that schizophrenia occurs more frequently in males than females. The placebo group had slightly less male (45%) than female which could be the result of small number of subjects (51).

The Baseline mean, median weight, and weight category (<51 kg or ≥51 kg) were comparable among all 4 treatment groups. Most subjects (65% - 73%) weighed ≥51 kg which was expected in adolescents aged 12 to 17 years. The Baseline mean and median BMI were also comparable among all 4 treatment groups.

The 4 treatment groups were generally comparable with respect to smoking history and parents' ages.

Baseline Disease Diagnosis and History Characteristics

The Baseline disease characteristics (schizophrenia type, age onset), psychiatric history and disease severity, which were demonstrated in PANSS total score, CGI-S, CGAS, and prior hospitalizations were summarized in **Table 6.**

The 4 treatment groups were generally comparable with respect to Baseline disease characteristics, psychiatric history, disease severity and prior hospitalizations.

A majority of the subjects had a diagnosis of paranoid schizophrenia with mean Baseline PANSS total score about 91 and had no prior hospitalizations.

The mean age at diagnosis was about 13 years. The age range at diagnosis was 3 to 16 years. Since schizophrenia is thought to be uncommon in children and the symptoms in childhood schizophrenia differ from those typically seen in adult schizophrenia, the diagnosis is difficult in younger age. This reviewer considers the diagnosis of schizophrenia at 3 years old questionable (**Table 6**).

Table 5: Demographic and Baseline Characteristics in PSZ-3001 (ITT Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)	Total (N=200)
Age (years)					
N	51	54	48	47	200
Category, n (%)					
12-14	9 (18)	16 (30)	15 (31)	13 (28)	53 (27)
15-17	42 (82)	38 (70)	33 (69)	34 (72)	147 (74)
Mean (SD)	15.7 (1.40)	15.1 (1.50)	15.3 (1.60)	15.5 (1.60)	15.4 (1.53)
Median	16.0	16.0	16.0	16.0	16.0
Range	(12;17)	(12;17)	(12;17)	(12;17)	(12;17)
Sex, n (%)					
N	51	54	48	47	200
Male	23 (45)	30 (56)	31 (65)	33 (70)	117 (59)
Female	28 (55)	24 (44)	17 (35)	14 (30)	83 (42)
Race, n (%)					
N	51	54	48	47	200
White	35 (69)	35 (65)	34 (71)	32 (68)	136 (68)
Black	4 (8)	5 (9)	3 (6)	5 (11)	17 (9)
Asian *	12 (24)	14 (26)	11 (23)	10 (21)	47 (24)
Ethnicity, n (%)					
N	51	54	48	47	200
Hispanic or Latino	0	1 (2)	2 (4)	1 (2)	4 (2)
Not hispanic or latino	51 (100)	53 (98)	46 (96)	46 (98)	196 (98)
Baseline weight (kg)					
N	51	54	48	47	200
Mean (SD)	59.5 (16.47)	60.4 (16.07)	57.7 (14.63)	61.5 (16.08)	59.8 (15.78)
Median	59.0	58.6	54.7	59.0	57.7
Range	(32;146)	(29;105)	(38;104)	(31;101)	(29;146)
Baseline body weight category, n (%)					
N	51	54	48	47	200
<51 kg	14 (27)	19 (35)	16 (33)	13 (28)	62 (31)
≥ 51 kg	37 (73)	35 (65)	32 (67)	34 (72)	138 (69)
Baseline height (cm)					
N	51	54	48	47	200
Mean (SD)	164.8 (10.27)	164.2 (9.93)	163.6 (10.50)	166.7 (12.20)	164.8 (10.70)
Median	165.0	162.8	165.0	170.0	165.0
Range	(136;184)	(142;185)	(143;184)	(135;186)	(135;186)

* Asian Indian and Asian Other (Taiwanese, Vietnamese and Chinese-Vietnamese) categories grouped as Asian,
Cross-reference: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 10 page 69
(Continued)

Table 5 (Continued): Demographic and Baseline Characteristics in PSZ-3001 (ITT Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)	Total (N=200)
Baseline body mass index (kg/m^2)					
N	51	54	48	47	200
Category, n (%)					
Normal <25	45 (88)	43 (80)	39 (81)	38 (81)	165 (83)
Overweight 25-<30	4 (8)	8 (15)	8 (17)	5 (11)	25 (13)
Obese ≥ 30	2 (4)	3 (6)	1 (2)	4 (9)	10 (5)
Mean (SD)	21.85 (5.578)	22.19 (4.861)	21.36 (3.964)	21.91 (4.315)	21.84 (4.714)
Median	21.10	20.80	20.90	20.90	20.95
Range	(14.0;53.4)	(13.9;39.6)	(15.2;34.9)	(14.4;34.6)	(13.9;53.4)
Baseline waist circumference (cm)					
N	51	54	48	47	200
Mean (SD)	75.5 (15.14)	76.5 (13.23)	73.2 (12.92)	76.1 (14.18)	75.3 (13.85)
Median	73.7	75.0	70.8	73.0	73.4
Range	(52;150)	(44;117)	(49;122)	(42;115)	(42;150)
Does subject currently smoke?, n (%)					
N	51	53	47	47	198
Yes	6 (12)	7 (13)	4 (9)	6 (13)	23 (12)
No	45 (88)	46 (87)	43 (91)	41 (87)	175 (88)
Mother's age (years)					
N	45	44	40	40	169
Mean (SD)	41.5 (5.96)	41.6 (4.88)	43.8 (6.40)	44.2 (6.03)	42.7 (5.90)
Median	40.0	41.0	44.5	45.0	42.0
Range	(31;54)	(33;52)	(31;56)	(32;58)	(31;58)
Father's age (years)					
N	41	41	39	39	160
Mean (SD)	44.0 (7.13)	44.9 (5.82)	45.3 (7.46)	46.2 (5.46)	45.1 (6.51)
Median	43.0	45.0	45.0	46.0	45.0
Range	(33;67)	(34;58)	(33;63)	(35;60)	(33;67)

Cross-reference: Mod 5.3.5.1, R076477-PSZ-3001, Table 10, page 70.
Asian Indian and Asian Other (Taiwanese, Vietnamese and Chinese-Vietnamese) categories grouped as Asian

Table 6: Diagnosis and Psychiatric History at Baseline in PSZ-3001 (ITT Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)	Total (N=200)
Schizophrenia type, n (%)					
N	51	54	48	47	200
Paranoid (295.30)	37 (73)	39 (72)	35 (73)	31 (66)	142 (71)
Disorganized (295.10)	3 (6)	3 (6)	6 (13)	7 (15)	19 (10)
Catatonic (295.20)	2 (4)	1 (2)	1 (2)	1 (2)	5 (3)
Undifferentiated (295.90)	9 (18)	9 (17)	5 (10)	8 (17)	31 (16)
Residual (295.60)	0	2 (4)	1 (2)	0	3 (2)
Age at diagnosis of schizophrenia (yr)					
N	51	54	48	47	200
Mean (SD)	13.4 (2.44)	12.5 (2.85)	13.0 (1.87)	12.8 (3.19)	12.9 (2.64)
Median	14.0	13.0	13.0	14.0	13.0
Range	(5;16)	(5;16)	(8;16)	(3;16)	(3;16)
Baseline PANSS total					
N	51	54	48	47	200
Mean (SD)	90.6 (12.13)	91.6 (12.54)	90.6 (14.01)	91.5 (13.86)	91.1 (13.03)
Median	88.0	89.5	88.0	90.0	89.0
Range	(65;118)	(70;118)	(69;119)	(63;119)	(63;119)
Baseline CGI-S, n (%)					
N	51	54	48	47	200
Very mild	0	1 (2)	0	0	1 (1)
Mild	3 (6)	3 (6)	3 (6)	2 (4)	11 (6)
Moderate	27 (53)	28 (52)	19 (40)	26 (55)	100 (50)
Marked	19 (37)	19 (35)	21 (44)	14 (30)	73 (37)
Severe	2 (4)	3 (6)	5 (10)	5 (11)	15 (8)
Baseline CGAS					
N	51	54	48	47	200
Mean (SD)	48.8 (11.23)	48.4 (11.82)	47.2 (11.36)	46.5 (11.96)	47.8 (11.54)
Median	46.0	47.5	48.0	45.0	47.0
Range	(30;76)	(30;75)	(25;75)	(24;73)	(24;76)
Prior hospitalization[a], n (%)					
N	51	54	48	47	200
None	18 (35)	26 (48)	19 (40)	18 (38)	81 (41)
Once	10 (20)	14 (26)	17 (35)	15 (32)	56 (28)
Twice	13 (25)	6 (11)	6 (13)	6 (13)	31 (16)
Three times	4 (8)	2 (4)	1 (2)	4 (9)	11 (6)
Four times or more	6 (12)	6 (11)	5 (10)	4 (9)	21 (11)

[a] Prior hospitalization for psychosis, excluding the current hospitalization.
Source: Mod 5.3.5.1, R076477-PSZ-3001, Clinical Study Report, Table 11, page 71.

Subject Disposition

A total of 201 subjects were enrolled and randomly assigned to double-blind treatment groups: placebo (n=51), or paliperidone ER (Low, n=54; Medium, n=48; or High, n=48). Refer to **Table 7**.

Table 7: Number of Subjects Randomly Assigned to Each Treatment Group in PSZ-3001 (All Randomized Subjects Analysis Set)

	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)	Total (N=201) n (%)
All randomized subjects	51 (100)	54 (100)	48 (100)	48 (100)	201 (100)
Safety	51 (100)	54 (100)	48 (100)	48 (100)	201 (100)
Intent-to-Treat	51 (100)	54 (100)	48 (100)	47 (98)	200 (>99)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 8, page 64.

One subject in the paliperidone ER High group did not have any post-Baseline efficacy assessments so that this subject was not included in the intent-to-treat (ITT) analysis set. Of the total 200 subjects in the ITT analysis set, 41% came from Russia, 23% from India, 17% from Ukraine, 15% from US, and 5% from Romania.

A total of 69% of the 200 subjects (=138 subjects) in the ITT analysis set completed the double-blind treatment. A higher percentage of subjects in the placebo (39%) and paliperidone ER Low (26%) group discontinued double-blind treatment due to lack of efficacy compared to the paliperidone ER Medium (4%) and High (9%) group, respectively. 2% of subjects in paliperidone ER Low, Medium and High group discontinued double-blind treatment due to AE (Refer to **Table 8**).

Table 8: Study Completion/Withdrawal Information in PSZ-3001 (All Randomized Subjects Analysis Set)

Subject Completed Treatment/trial Reason for Withdrawal/termination	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)	Total (N=201) n (%)
Completed	26 (51)	35 (65)	40 (83)	37 (77)	138 (69)
Withdrawn	25 (49)	19 (35)	8 (17)	11 (23)	63 (31)
Lack of efficacy	20 (39)	14 (26)	2 (4)	4 (8)	40 (20)
Subject choice (subject withdrew consent)	2 (4)	1 (2)	2 (4)	4 (8)	9 (4)
Lost to follow-up	3 (6)	0	2 (4)	1 (2)	6 (3)
Adverse event	0	1 (2)	1 (2)	1 (2)	3 (1)
Other	0	3 (6)	1 (2)	1 (2)	5 (2)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 9, page 66.

Concomitant Medication Use

The prohibited concomitant medications during PSZ-3001 included all antipsychotics other than the study drug, lithium, psychostimulants or other dopamine agonists, beta-adrenergic blockers (except propranolol which was permitted to treat emergent akathisia during the treatment period), and electroconvulsive therapy, antidepressants (for mood, anxiety, or sleep disorders, or for smoking cessation), anticonvulsants, sedatives hypnotics, or anxiolytics, other than those indicated in the protocol (described in the next paragraph), cholinesterase inhibitors, and other psychotropic drugs (including over-the-counter preparations such as St. John's Wort).

Benzodiazepines (up to 3 mg/day of oral lorazepam or the equivalent) could be administered as rescue medications for agitation, anxiety, or sleep difficulties during the screening/washout phase and first 3 weeks of the double-blind phase of PSZ-3001. Trihexyphenidyl and biperiden were allowed to use to relieve treatment-emergent extrapyramidal symptoms (EPS).

A listing of concomitant medications received during the double-blind phase for the ITT analysis set in the submission (Attachment 1.3.6) was reviewed. Prohibited medications used that might have confounded the evaluation of efficacy were listed below.

Table 9: Enumeration of Patients Using Prohibited Concomitant Medications during the Double-Blind Phase in PSZ-3001 (ITT Analysis Set)

Drug Name		Placebo (N=51) n (%)	Paliperidone ER		
			Low (N=54) n (%)	Medium (N=48) n (%)	High (N=47) n (%)
Antipsychotics	Zuclopenthixol			1 (2)	2 (4)
	Chlorpromazine		1 (2)		1 (2)
	Haloperidol	1 (2)	1 (2)		
	Aripiprazole	1 (2)			
	Antipsychotics*		1 (2)		
	Clozapine		1 (2)		
	Fluphenazine				1 (2)
	Levomepromazine	1 (2)			
	Olanzapine	1 (2)			
	Risperidone			1 (2)	
	Ziprasidone			1 (2)	
Total NO. Subjects with Prohibited Concomitant Antipsychotics		4 (8)	4 (8)	3 (6)	4 (8)
Antidepressant	Amitriptyline				1 (2)
Anticonvulsant	Barbiturates	1 (2)			
	Phenobarbital				1 (2)
Beta Blocker	Metoprolol				1 (2)
Sedative Hypnotics	Zolpidem		1 (2)		

*did not specify which antipsychotics.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Attachment 1.3.6, page 252-254

The use of the prohibited antipsychotics probably would affect the final efficacy results the most. The effects of use of the prohibited antipsychotics on the overall final efficacy outcome depended on the time of the usage: whether the prohibited concomitant antipsychotics were used at Baseline or in the early or late stage of the double-blind treatment phase. Interestingly, Paliperidone ER Medium group, the only group which demonstrated efficacy compared to placebo, had the fewest subjects who used prohibited antipsychotics. Therefore, this reviewer concluded that the use of prohibited concomitant medications probably has not affected the overall final efficacy outcome.

Protocol Deviations

Clinical major protocol deviations were identified during the trial and were summarized in **Table 10**.

A total of 42 subjects had protocol deviations. The paliperidone ER Medium treatment group had the most (27%) protocol deviations while the placebo group had the least (16%). The most frequent deviations included use of prohibited concomitant medications, investigator mistake, and safety assessment deviation. The use of prohibited concomitant medications occurred 6% - 8% across all of the groups. The paliperidone ER Medium and High groups had the highest percentage of investigator mistake (10% and 9% respectively) while the placebo only had 2%.

The effect of use of prohibited concomitant medications on overall efficacy outcome was discussed previously. This reviewer has examined the investigator mistakes in the JMP file: KPROTDEV.xpt, especially those mistakes in the paliperidone ER Medium group - the only group that was shown to be significantly efficacious compared to placebo.

The review found out that most investigator mistakes were prolonged duration of drug treatment. There were a total of 4 cases in paliperidone ER Medium group that had prolonged duration of treatment and had PANSS assessment at the end of the treatment: 3 cases were treated with paliperidone ER Medium dose for 46 days and 1 case was treated for 48 days.

The other investigator mistake was the shorter duration of treatment. One case in paliperidone ER Medium group received paliperidone ER for 40 days.

Since the total duration of the double-blind treatment was 6 week (42 days), an extra 4 to 6 days of treatment in a total of 6 week duration trial probably would not make the study drug appear more efficacious. Shorter duration of treatment would certainly not do so either. Therefore, this reviewer concluded that these protocol deviations would probably not have biased efficacy in favor of the study drug.

Table 10: Protocol Deviations in PSZ-3001 (ITT Analysis Set)

	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=47) n (%)	Total (N=200) n (%)
Total no. subjects with any protocol deviation	8 (16)	11 (20)	13 (27)	10 (21)	42 (21)
Excluded concomitant medication	3 (6)	4 (7)	4 (8)	3 (6)	14 (7)
Investigator mistake	1 (2)	3 (6)	5 (10)	4 (9)	13 (7)
Safety assessment deviation	3 (6)	4 (7)	2 (4)	4 (9)	13 (7)
Selection criteria not met	0	3 (6)	1 (2)	1 (2)	5 (3)
Efficacy assessment deviation	1 (2)	0	1 (2)	1 (2)	3 (2)
Treatment deviation	1 (2)	0	1 (2)	1 (2)	3 (2)
Subject not withdrawn as per protocol	0	0	1 (2)	0	1 (1)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 15, page 77.

Efficacy Findings

Primary Efficacy Endpoint

The primary efficacy measurement was the mean change from Baseline to Endpoint in the PANSS total score. As shown in **Table 11**, each treatment group showed decrease in the PANSS total score at Endpoint based on the protocol-specified analysis (LOCF). However, only the paliperidone ER Medium group demonstrated statistical significance ($p = 0.006$) compared to placebo while the paliperidone ER High and Low group did not show statistical significance ($p = 0.086$ and $p = 0.508$ respectively). A box plot for changes in PANSS total scores from Baseline to Endpoint is shown in **Figure 1**.

Results of the MMRM analysis of PANSS total score were consistent with the findings from the primary LOCF analysis. Only the paliperidone ER Medium group showed significant reduction in the PANSS total score ($p = 0.0034$).

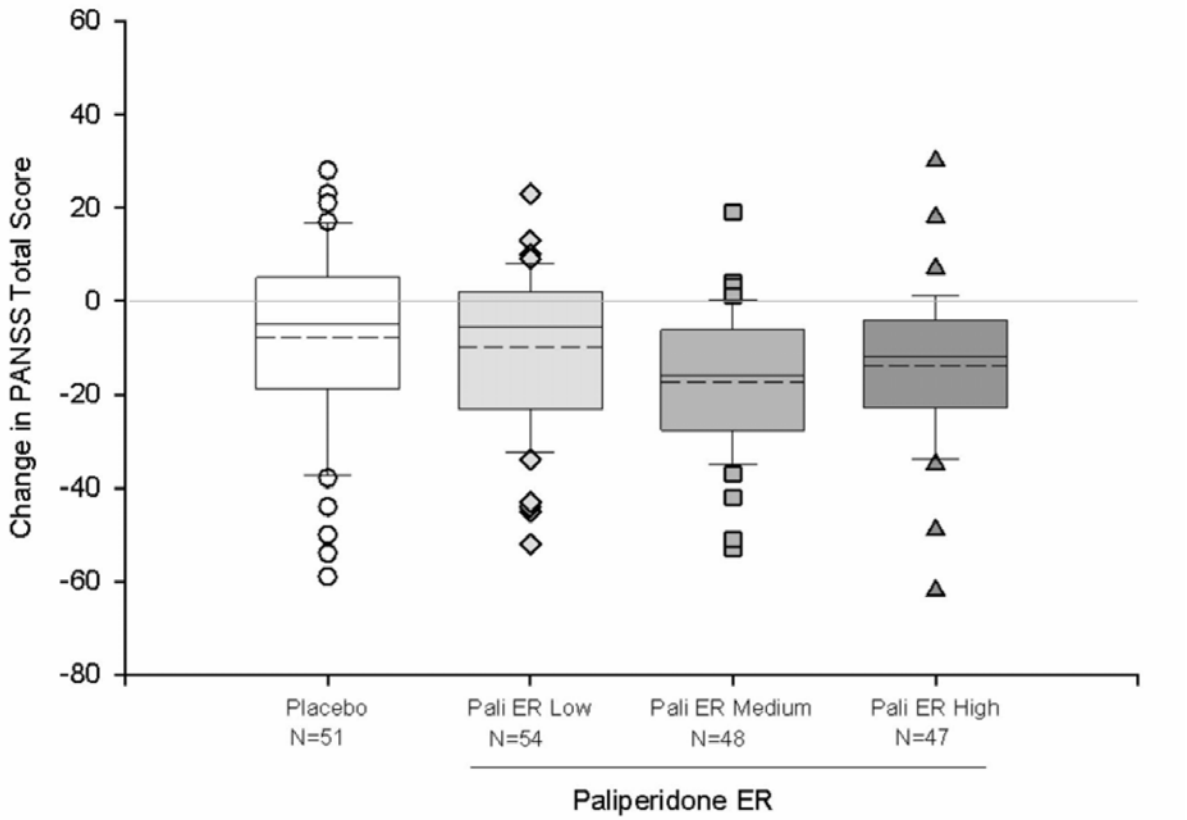
Table 11: PANSS Total Score - Change from Baseline to Endpoint (LOCF) Using Closed Testing Procedure with Dunnett's Test in PSZ-3001 (ITT Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)
Baseline				
N	51	54	48	47
Mean (SD)	90.6 (12.13)	91.6 (12.54)	90.6 (14.01)	91.5 (13.86)
Median (Range)	88.0 (65;118)	89.5 (70;118)	88.0 (69;119)	90.0 (63;119)
End Point				
N	51	54	48	47
Mean (SD)	82.7 (21.45)	81.9 (19.54)	73.3 (21.99)	77.7 (18.24)
Median (Range)	81.0 (36;129)	80.0 (45;121)	70.0 (33;126)	75.0 (49;135)
Change From Baseline				
N	51	54	48	47
Mean (SD)	-7.9 (20.15)	-9.8 (16.31)	-17.3 (14.33)	-13.8 (15.74)
Median (Range)	-5.0 (-59;28)	-5.5 (-52;23)	-16.0 (-53;19)	-12.0 (-62;30)
p value (minus Placebo)[a]		0.508	0.006	0.086
Diff. of LS Means (SE)		-2.1 (3.17)	-10.1 (3.27)	-6.6 (3.29)
95% CI[b]		(-8.36;4.16)	(-16.58;-3.67)	(-13.07;-0.09)

[a] Based on ANCOVA model with treatment (Placebo, Paliperidone ER Low, Paliperidone ER Medium, Paliperidone ER High) and country as factors, and baseline value as a covariate. The p values were associated with closed testing procedure using Dunnett's test.
[b] The 95% confidence intervals are unadjusted for multiplicity.
Note: Negative change in score indicates improvement.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 17, page 80

The sponsor also analyzed the change of PANSS total score from Baseline to Endpoint by actual paliperidone ER dose (1.5, 3, 6 and 12 mg) and by combing the paliperidone ER Medium and High groups against placebo. This reviewer found these approaches not acceptable because they were post hoc.

Figure 1: Box Plot for the Change from Baseline in PANSS Total Score at Endpoint (LOCF) in PSZ-3001 (ITT Analysis Set)



Note: the lower boundary of the box is the 25th percentile and the higher boundary is the 75th percentile. Whiskers above and below the box indicate the 90th and 10th percentile. The solid line within the box marks the median and the dash line marks the mean value. Outlying data points are extreme values.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Figure 3, page 81.

6.2.3. Conclusions

The treatment with paliperidone ER 3 mg/day in weight < 51kg and 6 mg/day in weight ≥ 51kg was efficacious in improving the symptoms of schizophrenia in adolescents aged 12 to 17 years, as demonstrated by the results on the primary efficacy measurement, the change from Baseline in PANSS total score at Endpoint.

The treatment with paliperidone ER High (6 mg/day in weight < 51kg and 12 mg/day in weight ≥ 51kg) and Low group (1.5 mg/day) did not demonstrate efficacy compared to placebo on the primary Endpoint.

6.3 Crosscutting Issues

6.3.1. Subgroup Analyses

Age
The least-squares (LS) mean differences (paliperidone ER group minus placebo) were similar in both age groups (12-14 years and 15-17 years) among the subjects randomly

assigned to the paliperidone ER Medium treatment group. The LS mean differences appeared larger in the subjects aged 15-17 years than that in the subjects aged 12-14 years among those randomly assigned to the paliperidone ER Low and High treatment groups (**Figure 2**).

Gender

The changes from Baseline in PANSS total score at Endpoint (LOCF) were also analyzed by gender (**Figure 2**). The LS Mean difference in females appeared more negative in paliperidone ER Medium and High groups especially in Medium group compared to that in males, which means, it appeared that females in paliperidone ER Medium and High groups may have greater clinical improvement than males, but this result could be caused by the small number of subjects.

Race

The LS Mean difference by race (Asian, White and Black) was also shown in **Figure 2**. The LS Mean Difference in paliperidone ER Medium group in Asian and White appeared to be similar. The LS Mean Difference in Black appeared to favor placebo treatment. However, each of the Black subgroup had less than 10 subjects; the results were hard to interpret due to small subject number.

Region

The changes from Baseline in PANSS total score at Endpoint (LOCF) were also analyzed by region (Asia, Eastern Europe and North America). It appeared that the LS mean differences in Asia and Eastern Europe were similar but not in North America (**Figure 2**). Again, the results were hard to interpret due to small subject number because there were less than 10 subjects in each subgroup of North America.

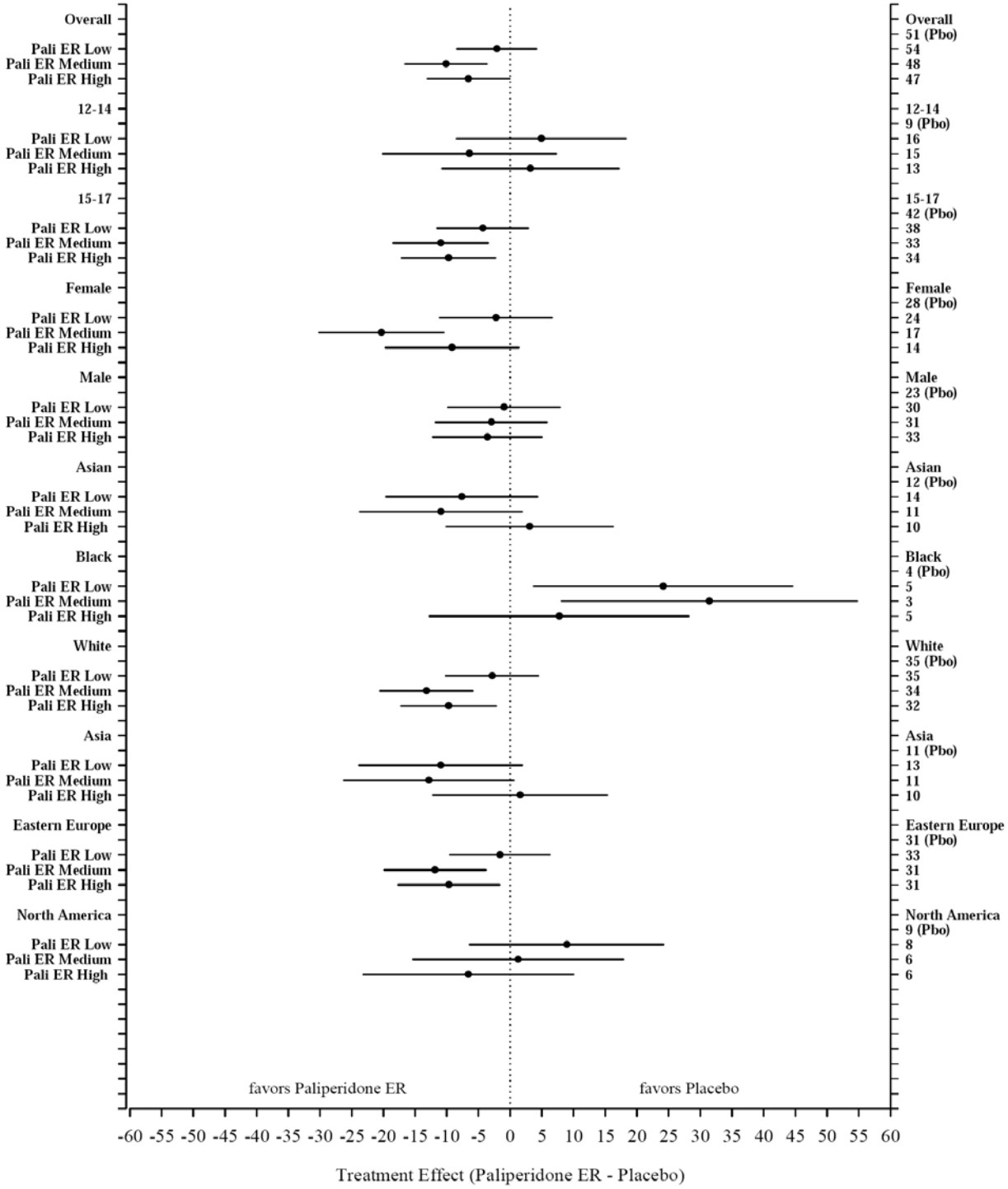
Country

Overall, no statistically significant interactions between treatment and country were found using the ANCOVA model ($p = 0.439$). Interestingly, in US, the mean decrease in the PANSS total score in the placebo was larger than that in paliperidone ER Low and Medium groups and also larger than those in placebo groups from other countries. In India, the paliperidone ER High treatment group had the least LS mean decrease in PANSS total score including the placebo group. Refer to **Figure 3.**

Baseline PANSS Total Score

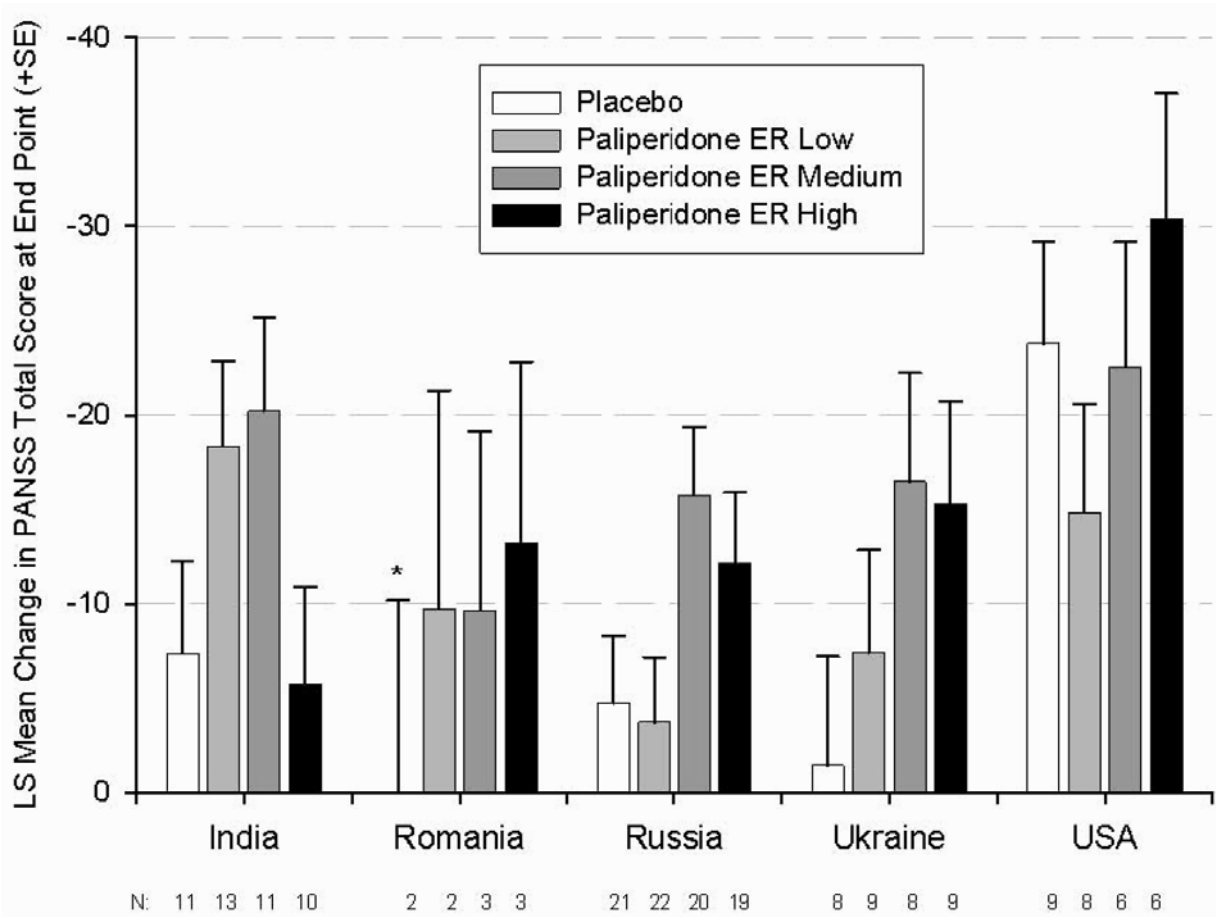
No statistically significant interactions between treatment and Baseline PANSS total score were found using the ANCOVA model ($p = 0.197$).

Figure 2: Subgroup Analyses of the Change from Baseline in PANSS Total Score at Endpoint (LOCF) - Unadjusted 95% Confident Intervals: LS Mean Difference (Paliperidone ER minus Placebo) in PSZ-3001 (ITT Analysis Set)



Source: original application 10/8/2010: 2.7.3. Summary of Clinical Efficacy: Figure 6, page 41.

Figure 3: Least-Squares Mean Change in PANSS Total Score at Endpoint by Country in PSZ-3001 (ITT Analysis Set)



* LS Mean (SE) for the 2 subjects in the placebo group in Romania is 1.3577 (11.55)
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Figure 4, page 84.

Weight

The primary efficacy variable by body weight category (< 51 kg and ≥ 51 kg) was analyzed and shown in **Table 12**. In the weight category of < 51 kg, the paliperidone ER High treatment group had the least mean change in PANSS total score from Baseline. Subjects with lower weight (< 51 kg) even did not respond to paliperidone ER High or Low dose treatment as well as to placebo. But, for wt ≥ 51 kg, both paliperidone ER Medium and High groups were superior to placebo. Luckily, the paliperidone ER Medium group beat the placebo for both weight categories.

Table 12: PANSS Total Score - Change From Baseline to Endpoint (LOCF) by Body Weight Categories (<51 kg and ≥51 kg) in PSZ-3001 (ITT Analysis Set)

Baseline Body Weight Category: <51 kg Parameter: PANSS Total Score	Placebo (N=14)	Paliperidone ER Low (N=19)	Paliperidone ER Medium (N=16)	Paliperidone ER High (N=13)
Baseline				
N	14	19	16	13
Mean (SD)	93.9 (13.98)	88.3 (12.67)	92.1 (16.88)	93.0 (16.37)
Median (Range)	91.0 (78;118)	89.0 (71;118)	91.0 (70;119)	90.0 (63;118)
End Point				
N	14	19	16	13
Mean (SD)	79.4 (23.66)	76.3 (21.24)	73.1 (26.55)	85.6 (20.67)
Median (Range)	78.5 (44;120)	79.0 (45;121)	70.0 (33;115)	79.0 (51;135)
Change From Baseline				
N	14	19	16	13
Mean (SD)	-14.4 (19.07)	-11.9 (17.49)	-19.0 (15.45)	-7.4 (15.32)
Median (Range)	-9.0 (-54;10)	-6.0 (-45;13)	-19.0 (-53;3)	-4.0 (-34;30)

Baseline Body Weight Category: ≥51 kg Parameter: PANSS Total Score	Placebo (N=37)	Paliperidone ER Low (N=35)	Paliperidone ER Medium (N=32)	Paliperidone ER High (N=34)
Baseline				
N	37	35	32	34
Mean (SD)	89.4 (11.32)	93.5 (12.27)	89.9 (12.57)	91.0 (13.00)
Median (Range)	88.0 (65;112)	93.0 (70;118)	85.5 (69;111)	89.0 (70;119)
End Point				
N	37	35	32	34
Mean (SD)	84.0 (20.76)	84.9 (18.16)	73.4 (19.80)	74.7 (16.57)
Median (Range)	82.0 (36;129)	86.0 (55;117)	70.0 (42;126)	73.0 (49;115)
Change From Baseline				
N	37	35	32	34
Mean (SD)	-5.4 (20.23)	-8.6 (15.77)	-16.5 (13.91)	-16.3 (15.41)
Median (Range)	-5.0 (-59;28)	-4.0 (-52;23)	-15.0 (-51;19)	-15.0 (-62;18)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 19, page 86.

6.3.2. Dose Response

It did not appear to have a clear dose-response relationship. The improvement in the paliperidone ER Medium group achieved statistical significance compared to the paliperidone ER Low group ($p = 0.014$). The differences between the paliperidone ER High and Medium group or High and Low group did not achieve statistical significance ($p = 0.289$ and $p = 0.170$, respectively).

6.3.3. Secondary Endpoints

No key secondary efficacy measure was pre-specified. There were 3 secondary efficacy measures used in this trial: CGI-S, CGAS and Sleep VAS.

The change from Baseline to Endpoint in the CGI-S score in both paliperidone ER Medium and High groups achieved statistically significant in comparison with placebo. The change from Baseline to Endpoint in the CGAS score in paliperidone ER Medium group achieved statistically significant in comparison with placebo ($p<0.001$). The changes from Baseline to Endpoint in Sleep VAS in the paliperidone ER Medium and High treatment groups achieved statistical significance in comparison with placebo.

6.3.4. Effect Size

The effect size of all paliperidone treatment groups at Endpoint is shown in **Table 11**. A negative difference in LS mean (paliperidone ER - placebo) indicated a positive effect of paliperidone ER treatment over placebo. It was -2.1, -10.1 and -6.6 for the paliperidone ER Low, Medium and High treatment group respectively.

6.3.5. Long-Term Efficacy

A controlled relapse prevention trial in adolescent subjects with schizophrenia was not required according to Written Request Amendment #2 dated March 31, 2010.

PSZ-3002, an open label, 2 year safety trial, is ongoing. But this open label uncontrolled trial cannot address long term efficacy.

6.3.6. Pediatric Development

The application has been taken to the Pediatric Exclusivity Board meeting. The Board agreed with the Division's assessment that the studies have fulfilled the WR and therefore, the pediatric exclusivity was granted.

6.4 Efficacy Conclusion

The treatment with paliperidone ER Medium (3 mg/day in weight < 51kg and 6 mg/day in weight $\geq$ 51kg) was efficacious compared to placebo. None of the treatment-by-subgroup interaction terms appeared to be significantly different.

The paliperidone ER Low (1.5 mg/day) and High (6 mg/day in weight < 51kg and 12 mg/day in weight ≥ 51kg) groups did not show statistical significance compared to placebo on the primary Endpoint.

No dose-response pattern was identified with respect to efficacy for the primary Endpoint.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review included the placebo-controlled adolescent schizophrenia trial (PSZ-3001) as the primary source of safety data. It also included the long-term safety trial (PSZ-3002) as of the cut off date July 30, 2009 and the PK study (PSZ-1001) for serious AEs.

7.1.2 Categorization of Adverse Events

An Adverse Events (AE) was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product.

A serious adverse events (SAE) was any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the subject or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a cancer
- Is a congenital anomaly/birth defect
- Results in the development of drug dependency or drug abuse
- Is an important medical event (including pregnancy or overdose)

The sponsor's coding of verbatim AE terms to MedDRA preferred terms was audited by this reviewer via examining the JMP file kae.xpt in the dataset. My comparison of the verbatim and preferred terms for all subjects in this file revealed no significant coding errors or deficiencies.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The data were not pooled due to different study designs.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 150 subjects received paliperidone ER in PSZ-3001.

An overall summary of drug exposure is presented in **Table 13**. The mean length of exposure was 37 days for subjects in paliperidone ER treatment groups.

Table 13: Duration (Days) of Exposure to Study Medication and Compliance in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=48)	Total Paliperidone (N=150)
Treatment duration, days (on drug)					
N	51	54	48	48	150
Category, n (%)					
≤ 14	2 (4)	4 (7)	2 (4)	3 (6)	9 (6)
15 - 28	17 (33)	13 (24)	2 (4)	7 (15)	22 (15)
29 - 42	22 (43)	28 (52)	29 (60)	22 (46)	79 (53)
≥ 43	10 (20)	9 (17)	15 (31)	16 (33)	40 (27)
Mean (SD)	33.0 (10.88)	34.9 (10.52)	39.2 (8.78)	37.3 (11.19)	37.0 (10.31)
Median	38.0	41.0	42.0	42.0	42.0
Range	(7;44)	(8;45)	(3;45)	(3;49)	(3;49)
Compliance (%)					
N	51	54	48	48	150
Mean (SD)	99.6 (1.91)	99.6 (1.36)	98.9 (4.87)	98.7 (5.99)	99.1 (4.43)
Median	100.0	100.0	100.0	100.0	100.0
Range	(88;100)	(93;100)	(68;100)	(60;100)	(60;100)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 16, page 78

The combined mean patient exposure year (PEY) for paliperidone ER in PSZ-3001 and PSZ-3002 was 180.3 days for 314 subjects according to the submission dated 12/15/2010 (the Global Submit eCTD sequence number 129).

7.2.2 Explorations for Dose Response

This reviewer has examined the summary of treatment-emergent AEs reported by >2% of subjects in any one treatment group by system organ class and preferred term in the

safety population in PSZ-3001 (submission dated 12/15/2010). The incidences of few common AEs such as somnolence, akathisia, dystonia and tachycardia appeared to be dose-related.

Somnolence
The proportion of subjects with somnolence was 5.6%, 14.6% and 20.8% in the paliperidone ER Low, Medium and High treatment groups, respectively, while only 2.0% subjects in placebo had somnolence.

Akathisia
The proportion of subjects with akathisia was 3.7%, 8.3% and 16.7% in the paliperidone ER Low, Medium and High treatment groups, respectively while no subjects in placebo reported akathisia.

Dystonia
The proportion of subjects with dystonia was 1.9%, 2.1% and 8.3% in the paliperidone ER Low, Medium and High treatment groups, respectively while no subjects in placebo reported dystonia.

Tachycardia
Tachycardia has demonstrated less clear evidence of dose response. The proportions of subjects with tachycardia was 4.2% and 8.3% in the paliperidone ER Medium and High treatment groups, respectively while no subjects in the paliperidone ER Low and placebo groups reported tachycardia.

7.2.3 Special Animal and/or In Vitro Testing

A juvenile rat study was conducted and reviewed by the Pharmacology/Toxicology team.

7.2.4 Routine Clinical Testing

Routine clinical testing includes monitoring for AEs, assessment of suicidality using C-CASA and C-SSRS, extrapyramidal symptom (EPS) evaluations, safety laboratory tests including hematology, clinical chemistry, glucose homeostasis assessment (fasting glucose, insulin, insulin-like growth factor (IGF), and IGF binding protein-3 concentrations), lipids profile (total cholesterol, triglycerides, high density lipoprotein, and low density lipoprotein), serum prolactin, urinalysis and serum beta HCG pregnancy test for females, vital signs, body weight, height, BMI, Tanner staging and EKG. These safety assessments were felt to be adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

A pediatric PK study (PSZ-1001) was conducted by the sponsor and reviewed by the Clinical Pharmacology team.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Atypical antipsychotics are associated with EPS, neuroleptic malignant syndrome (NMS), tardive dyskinesia, hyperglycemia and diabetes mellitus, weight gain and hyperprolactinemia. The evaluation and monitoring of these AEs in PSZ-3001 and PSZ-3002 were felt to be adequate.

7.3 Major Safety Results

7.3.1 Deaths

No death was reported during either the trial of PSZ-1001, PSZ-3001 or PSZ-3002.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

7.3.2.1 Nonfatal SAEs in PSZ-1001

There were no treatment-emergent SAEs in PSZ-1001.

7.3.2.2 Nonfatal SAEs in PSZ-3001

A total of 4 subjects in the controlled trial PSZ-3001 experienced treatment-emergent SAEs in the paliperidone ER groups (schizophrenia [2 subjects], agitation [1 subject], and Mallory-Weiss syndrome [1 subject]). Half of SAEs in paliperidone ER groups were felt to be due to the underlying disease – schizophrenia, which was expected. One SAE (psychotic disorder) occurred in the placebo group.

Table 14: Treatment-Emergent SAEs in PSZ-3001 (Safety Analysis Set)

Body System or Organ Class Dictionary-Derived Term	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)	Total Paliperidon (N=150) n (%)
Total no. subjects with serious AE	1 (2.0)	2 (3.7)	1 (2.1)	1 (2.1)	4 (2.7)
Psychiatric disorders	1 (2.0)	2 (3.7)	0	1 (2.1)	3 (2.0)
Schizophrenia	0	1 (1.9)	0	1 (2.1)	2 (1.3)
Agitation	0	1 (1.9)	0	0	1 (0.7)
Psychotic disorder	1 (2.0)	0	0	0	0
Gastrointestinal disorders	0	0	1 (2.1)	0	1 (0.7)
Mallory-Weiss syndrome	0	0	1 (2.1)	0	1 (0.7)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Adverse events are coded using MedDRA Version 11.0.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 35, page 115

The event of Mallory-Weiss syndrome occurred in a 17-year-old Indian male, in paliperidone ER Medium (3 mg) group, diagnosed with disorganized schizophrenia at age 15 without other relevant medical history.

At screening, physical exam and labs were normal. On the study visit Day 15, the subject did not report any AEs. On Day 16, the subject complained of abdominal pain and had 4 episodes of hematemesis. He was referred to a gastroenterologist for evaluation and was subsequently admitted to ICU.

On ICU admission (Day 16), physical exam showed tachycardia (135 bpm) and pallor. Hemoglobin was 10.8 g/dL. An endoscopy on Day 18 showed "Mallory-Weiss tear with fundal erosion". On Day 31, this event was determined to be resolved.

Paliperidone ER 3 mg was temporarily discontinued on Day 15 and resumed on Day 26 and then permanent discontinued on Day 31 due to the belief by the investigator that the event was probably related to paliperidone ER treatment.

This reviewer was not convinced that the event of Mallory-Weiss tear was caused by the treatment of paliperidone ER 3 mg x 15 days, because the subject did not experience another GI bleeding after paliperidone ER 3 mg had restarted on Day 26 and continued for another 5 days. Also, Mallory-Weiss tear was not reported in other paliperidone ER trials and is not an event previously thought to be possibly related to paliperidone ER or risperidone.

7.3.2.3 Nonfatal SAEs in PSZ-3002

The treatment-emergent SAEs that occurred in PSZ-3002 as of the cut-off date (July 30, 2009) are showed in **Table 15**. Thirty three (n=33, 11.7%) subjects had SAEs.

The most common SAE was schizophrenia (n=16, 5.7%). Most other common SAEs were also under psychiatric disorder category: suicidal ideation (n=3), anxiety (n=3), suicide attempt (n=2), schizophrenia, paranoid type (n=2), psychotic disorder (n=2), hallucination, auditory (n=2), delusion (n=2) and aggression (n=2). There were 2 SAEs of extrapyramidal disorder.

This reviewer believed that paranoid type schizophrenia, auditory hallucination and delusion should also be categorized under schizophrenia. Again, half of SAEs in paliperidone ER groups were felt to be due to the underlying disease - schizophrenia.

Table 15: Treatment-Emergent SAEs in PSZ-3002 (Open- Label Safety Analysis Set)

Body System or Organ Class Dictionary-Derived Term	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (No DB)/Pali (N=125) n (%)	Total (N=282) n (%)
Total no. subjects with serious AE	7 (17.9)	2 (1.7)	24 (19.2)	33 (11.7)
Psychiatric disorders	6 (15.4)	2 (1.7)	21 (16.8)	29 (10.3)
Schizophrenia	4 (10.3)	1 (0.8)	11 (8.8)	16 (5.7)
Anxiety	1 (2.6)	0	2 (1.6)	3 (1.1)
Suicidal ideation	0	0	3 (2.4)	3 (1.1)
Aggression	0	1 (0.8)	1 (0.8)	2 (0.7)
Delusion	0	0	2 (1.6)	2 (0.7)
Hallucination, auditory	0	0	2 (1.6)	2 (0.7)
Psychotic disorder	0	0	2 (1.6)	2 (0.7)
Schizophrenia, paranoid type	1 (2.6)	0	1 (0.8)	2 (0.7)
Suicide attempt	0	0	2 (1.6)	2 (0.7)
Agitation	0	1 (0.8)	0	1 (0.4)
Delusion of grandeur	0	0	1 (0.8)	1 (0.4)
Depression	0	0	1 (0.8)	1 (0.4)
Flight of ideas	0	0	1 (0.8)	1 (0.4)
Hallucination	0	0	1 (0.8)	1 (0.4)
Intentional self-injury	1 (2.6)	0	0	1 (0.4)
Mania	0	0	1 (0.8)	1 (0.4)
Paranoia	0	1 (0.8)	0	1 (0.4)
Self injurious behaviour	0	0	1 (0.8)	1 (0.4)
Nervous system disorders	0	0	2 (1.6)	2 (0.7)
Extrapyramidal disorder	0	0	2 (1.6)	2 (0.7)
Blood and lymphatic system disorders	1 (2.6)	0	0	1 (0.4)
Lymphadenitis	1 (2.6)	0	0	1 (0.4)
Cardiac disorders	0	0	1 (0.8)	1 (0.4)
Bradycardia	0	0	1 (0.8)	1 (0.4)
General disorders and administration site conditions	1 (2.6)	0	0	1 (0.4)
Irritability	1 (2.6)	0	0	1 (0.4)
Infections and infestations	1 (2.6)	0	0	1 (0.4)
Sinusitis	1 (2.6)	0	0	1 (0.4)
Injury, poisoning and procedural complications	0	0	1 (0.8)	1 (0.4)
Spinal compression fracture	0	0	1 (0.8)	1 (0.4)
Renal and urinary disorders	0	0	1 (0.8)	1 (0.4)
Nephrolithiasis	0	0	1 (0.8)	1 (0.4)

Source: Mod 5.3.5.2 Clinical Study Report R076477-PSZ-3002 - 6 month, Table 36, page 89.
Pali=paliperidone

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Dropouts and/or Discontinuations in PSZ-1001

There were no TEAEs leading to discontinuation in PSZ-1001.

7.3.3.2 Dropouts and/or Discontinuations in PSZ-3001

A total of 3 subjects discontinued the trial PSZ-3001 due to TEAEs. Dystonia was felt to be the only drug-related AE that led to a dropout in this trial. The case with Mallory-Weiss Syndrome was discussed in the previous SAE section and was not felt to be related to paliperidone ER treatment.

Table 16: TEAEs Leading to Study Discontinuation in PSZ-3001 (Safety Analysis Set)

Body System or Organ Class Dictionary-Derived Term	Placebo (N=51) n (%)	Pali ER 1.5 mg (N=54) n (%)	Pali ER 3 mg (N=16) n (%)	Pali ER 6 mg (N=45) n (%)	Pali ER 12 mg (N=35) n (%)	Total Paliperidone (N=150) n (%)
Total no. subjects who discontinued due to AE	0	1 (1.9)	1 (6.3)	0	1 (2.9)	3 (2.0)
Gastrointestinal disorders	0	0	1 (6.3)	0	0	1 (0.7)
Mallory-Weiss syndrome	0	0	1 (6.3)	0	0	1 (0.7)
Nervous system disorders	0	0	0	0	1 (2.9)	1 (0.7)
Dystonia	0	0	0	0	1 (2.9)	1 (0.7)
Skin and subcutaneous tissue disorders	0	1 (1.9)	0	0	0	1 (0.7)
Dermatitis allergic	0	1 (1.9)	0	0	0	1 (0.7)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 37, page 116

7.3.3.3 Dropouts and/or Discontinuations in PSZ-3002

A total of 9 subjects discontinued trial PSZ-3002 due to TEAEs (**Table 17**). The most common TEAEs leading to study discontinuation were psychiatric disorders followed by EPS-Related AEs.

One discontinuation was due to increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST). This case will be discussed in the following Section 7.3.4 Significant Adverse Events under PSZ-3002.

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Table 17: TEAEs Leading to Study Discontinuation in PSZ-3002 (Open-Label Safety Analysis Set)

Body System or Organ Class Dictionary-Derived Term	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (No DB)/Pali (N=125) n (%)	Total (N=282) n (%)
Total no. subjects who discontinued due to adverse event	1 (2.6)	0	8 (6.4)	9 (3.2)
Psychiatric disorders	0	0	4 (3.2)	4 (1.4)
Suicide attempt	0	0	2 (1.6)	2 (0.7)
Anxiety	0	0	1 (0.8)	1 (0.4)
Delusion	0	0	1 (0.8)	1 (0.4)
Hallucination	0	0	1 (0.8)	1 (0.4)
Suicidal ideation	0	0	1 (0.8)	1 (0.4)
Nervous system disorders	1 (2.6)	0	2 (1.6)	3 (1.1)
Akathisia	0	0	1 (0.8)	1 (0.4)
Burning sensation	1 (2.6)	0	0	1 (0.4)
Dystonia	0	0	1 (0.8)	1 (0.4)
Tremor	0	0	1 (0.8)	1 (0.4)
Gastrointestinal disorders	0	0	1 (0.8)	1 (0.4)
Vomiting	0	0	1 (0.8)	1 (0.4)
Investigations	0	0	1 (0.8)	1 (0.4)
Alanine aminotransferase increased	0	0	1 (0.8)	1 (0.4)
Aspartate aminotransferase increased	0	0	1 (0.8)	1 (0.4)
Reproductive system and breast disorders	1 (2.6)	0	0	1 (0.4)
Amenorrhoea	1 (2.6)	0	0	1 (0.4)

Source: Mod 5.3.5.2 Clinical Study Report R076477-PSZ-3002 - 6 month, Table 37, page 91.
Pali=paliperidone

7.3.4 Significant Adverse Events

PSZ-3001
One subject (Subject 604121, 17 year old male from Ukraine) had an AE of allergic dermatitis that was considered significant because it led to a discontinuation on Day 22.

PSZ-3002
Subject 609301, a 17 year old female from Russia, discontinued the PSZ-3002 at Day 42 due to elevated ALT/AST. Her chemistry results were shown in **Table 18**. She received paliperidone ER 6 mg from Day 1 - Day 35 and 1.5 mg from Day 36 - Day 41.

This subject was in the paliperidone ER Low (1.5 mg) group in the double-blind placebo controlled 6 week trial PSZ-3001 (Subject ID 603302). She was withdrawn from the trial due to lack of efficacy on Day 22. Her ALT/AST was normal at Baseline but found to be elevated on Day 22 (ALT 161 and AST 128 U/L). No other markedly abnormal laboratory values, abnormal vital signs, or clinically significant EKG findings were observed during the trial.

Table 18: Chemistry Results for Subject 609301 in PSZ-3002

Clinical Chemistry (Normal Range)	Baseline	Day 13	Day 42
ALT (6-34 U/L)	161	217	86
AST (10-40 U/L)	128	118	54
GGT (0-33 U/L)	41	57	45
Total Bilirubin (3-21 umol/L)	7	6	5
Alkaline Phosphatase (31-110 U/L)	96	119	111

Source: Clinical Study Report R076477-PSZ-3002 - 6 month, Attachment 3.2.4.1: Subject Narratives, page 702

7.3.5 Submission Specific Primary Safety Concerns

Submission specific primary safety concerns included suicidality, extrapyramidal symptom (EPS), glucose and potentially prolactin-related AEs and other AEs of special interest.

Suicidality

Suicidality in PSZ-3001

The incidence of potentially suicide-related events was based on Columbia Classification Algorithm of Suicide Assessment (C-CASA).

Table 19: Incidence of Potentially Suicide-Related Events: C-CASA in PSZ-3001 (Safety Analysis Set)

C-CASA	Placebo (N=51) n (%)	Paliperidone PR Low (N=54) n (%)	Paliperidone PR Medium (N=48) n (%)	Paliperidone PR High (N=48) n (%)	Total Paliperidone (N=150) n (%)
Suicidal Behavior (Codes 1-4)	0	0	0	0	0
Completed suicide	0	0	0	0	0
Suicide attempt	0	0	0	0	0
Preparatory acts toward imminent suicidal behavior	0	0	0	0	0
Suicidal ideation	0	0	0	0	0
Indeterminate (codes 5-6, 9)	0	0	1 (2.1)	0	1 (0.7)
Self-injurious behavior, intent unknown	0	0	0	0	0
Not enough information, fatal	0	0	0	0	0
Not enough information, nonfatal	0	0	1 (2.1)	0	1 (0.7)
Non-Suicidal (Codes 7-8)	1 (2.0)	0	0	0	0
Self-injurious behavior, no suicidal intent	0	0	0	0	0
Other, accident, psychiatric, medical	1 (2.0)	0	0	0	0

Note: The adverse events preferred term(s) assigned to the C-CASA codes were 'Wound' to the 'Indeterminate - Not enough information, nonfatal' code and 'Genital Injury' to the 'Non-Suicidal - Other, accident, psychiatric, medical' code. Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 39, page 118.

One subject (R076477-PSZ-3001-091009-601241) in the paliperidone ER Medium group reported a wound (reported term: "incisional wound on right arm"), which was

classified as “Indeterminate” due to not enough information and nonfatal incidence. The subject did not report a history of suicidality and has recovered without sequelae.

Suicidality in PSZ-3002
There were suicidal ideation in 4 (1.4%) subjects and suicide attempt in 2 (0.7%) subjects based on C-CASA.

Extrapyramidal Symptom (EPS)-Related AEs

EPS-Related AEs in PSZ-3001

Hyperkinesia (9.3%) and dystonia (7.3%) were the most common EPS groups in dictionary derived term. The incidences of akathisia, dystonia and Parkinsonism appeared to be dose related. The incidences of tremor were the same in the paliperidone ER Medium (8.3%) and High (8.3%) treatment groups and were higher than that in the Low treatment group (1.9%). The same pattern was seen in dyskinesia. No EPS-related TEAEs occurred in the placebo group.

Table 20: Treatment-Emergent EPS-Related AEs in PSZ-3001 (Safety Analysis Set)

EPS Group Dictionary-Derived Term	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)	Total Paliperidone (N=150) n (%)
Hyperkinesia	0	2 (3.7)	4 (8.3)	8 (16.7)	14 (9.3)
Akathisia	0	2 (3.7)	4 (8.3)	8 (16.7)	14 (9.3)
Dystonia	0	1 (1.9)	3 (6.3)	7 (14.6)	11 (7.3)
Dystonia	0	1 (1.9)	1 (2.1)	4 (8.3)	6 (4.0)
Oculogyric crisis	0	0	2 (4.2)	1 (2.1)	3 (2.0)
Muscle contracture	0	0	0	1 (2.1)	1 (0.7)
Tongue paralysis	0	0	0	1 (2.1)	1 (0.7)
Torticollis	0	0	0	1 (2.1)	1 (0.7)
Tremor	0	1 (1.9)	4 (8.3)	4 (8.3)	9 (6.0)
Tremor	0	1 (1.9)	4 (8.3)	4 (8.3)	9 (6.0)
Parkinsonism	0	0	2 (4.2)	5 (10.4)	7 (4.7)
Cogwheel rigidity	0	0	0	4 (8.3)	4 (2.7)
Muscle rigidity	0	0	1 (2.1)	1 (2.1)	2 (1.3)
Extrapyramidal disorder	0	0	1 (2.1)	0	1 (0.7)
Dyskinesia	0	1 (1.9)	2 (4.2)	2 (4.2)	5 (3.3)
Dyskinesia	0	1 (1.9)	2 (4.2)	1 (2.1)	4 (2.7)
Muscle contractions involuntary	0	0	0	1 (2.1)	1 (0.7)

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
Adverse events are coded using MedDRA Version 11.0.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 40, page 119

EPS-Related AEs in PSZ-3002

The most commonly occurring (>5%) EPS groups in dictionary-derived term were Parkinsonism (13.5%) and hyperkinesia (12.8%).

Table 21: Treatment-Emergent EPS-Related AEs in PSZ-3002 (Open-Label Safety Analysis Set)

EPS Group Dictionary-derived Term	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=125) n (%)	Total (N=282) n (%)
Parkinsonism	2 (5.1)	13 (11.0)	23 (18.4)	38 (13.5)
Muscle rigidity	1 (2.6)	5 (4.2)	5 (4.0)	11 (3.9)
Musculoskeletal stiffness	0	0	10 (8.0)	10 (3.5)
Extrapyramidal disorder	0	2 (1.7)	7 (5.6)	9 (3.2)
Bradykinesia	1 (2.6)	4 (3.4)	0	5 (1.8)
Cogwheel rigidity	1 (2.6)	2 (1.7)	0	3 (1.1)
Hypokinesia	0	1 (0.8)	2 (1.6)	3 (1.1)
Nuchal rigidity	0	0	2 (1.6)	2 (0.7)
Hypertonia	0	0	1 (0.8)	1 (0.4)
Parkinsonian gait	0	0	1 (0.8)	1 (0.4)
Parkinsonism	0	1 (0.8)	0	1 (0.4)
Hyperkinesia	1 (2.6)	9 (7.6)	26 (20.8)	36 (12.8)
Akathisia	0	8 (6.8)	25 (20.0)	33 (11.7)
Restlessness	1 (2.6)	1 (0.8)	1 (0.8)	3 (1.1)
Dystonia	3 (7.7)	5 (4.2)	9 (7.2)	17 (6.0)
Dystonia	1 (2.6)	3 (2.5)	5 (4.0)	9 (3.2)
Oculogyric crisis	1 (2.6)	1 (0.8)	2 (1.6)	4 (1.4)
Muscle spasms	0	1 (0.8)	0	1 (0.4)
Opisthotonus	0	0	1 (0.8)	1 (0.4)
Tongue paralysis	0	0	1 (0.8)	1 (0.4)
Trismus	1 (2.6)	0	0	1 (0.4)
Tremor	1 (2.6)	8 (6.8)	8 (6.4)	17 (6.0)
Tremor	1 (2.6)	8 (6.8)	8 (6.4)	17 (6.0)
Dyskinesia	1 (2.6)	1 (0.8)	4 (3.2)	6 (2.1)
Dyskinesia	1 (2.6)	1 (0.8)	4 (3.2)	6 (2.1)

Based on data up to 30 July 2009 cut-off date for subjects enrolled prior to that date.
Source: Mod 5.3.5.2 Clinical Study Report R076477-PSZ-3002 - 6 month, Table 38, page 92.

Glucose-Related AEs

Glucose-Related AEs in PSZ-3001

One subject in the paliperidone ER Low group had experienced ketonuria (**Table 22**), but this subject was not reported to have high fasting glucose level post-Baseline.

Table 22: Treatment-Emergent Glucose-Related AEs in PSZ-3001 (Safety Analysis Set)

Glucose Group Dictionary-Derived Term	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)	Total Paliperidone (N=150) n (%)
Glucose related	0	1 (1.9)	0	0	1 (0.7)
Ketonuria	0	1 (1.9)	0	0	1 (0.7)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 48, page 126.

Glucose-Related AEs in PSZ-3002

No glucose related AE was reported in the open-label trial PSZ-3002.

Prolactin-Related AEs

Prolactin-Related AEs in PSZ-3001

Both galactorrhea and amenorrhea occurred only in paliperidone Medium group. They did not seem to be dose-related because they were not seen in paliperidone High group.

Table 23: Treatment-Emergent Potentially Prolactin-Related AEs by Sex in PSZ-3001 (Safety Analysis Set)

Sex Dictionary-Derived Term	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)	Total Paliperidone (N=150) n (%)
Both	51	54	48	48	150
Galactorrhoea	0	0	2 (4.2)	0	2 (1.3)
Female	28	24	17	14	55
Amenorrhoea	0	0	1 (5.9)	0	1 (1.8)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 47, page 125.

Prolactin-Related AEs in PSZ-3002

Amenorrhea occurred in 4.3% of female subjects and galactorrhea occurred in 3.9% of both male and female subjects (**Table 24**).

Table 24: Treatment-Emergent Potentially Prolactin-Related AEs in PSZ-3002 (Open-Label Safety Analysis Set)

Sex Dictionary-derived Term	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=125) n (%)	Total (N=282) n (%)
Both	39	118	125	282
Galactorrhoea	2 (5.1)	3 (2.5)	6 (4.8)	11 (3.9)
Gynaecomastia	1 (2.6)	0	2 (1.6)	3 (1.1)
Breast discharge	0	0	1 (0.8)	1 (0.4)
Breast pain	1 (2.6)	0	0	1 (0.4)
Libido decreased	0	0	1 (0.8)	1 (0.4)
Female	21	44	50	115
Amenorrhoea	1 (4.8)	1 (2.3)	3 (6.0)	5 (4.3)
Menstruation irregular	0	0	1 (2.0)	1 (0.9)

Source: Mod 5.3.5.2 Clinical Study Report R076477-PSZ-3002 - 6 month, Table 46, page 99.

Other AEs of Interest in PSZ-3001 and PSZ-3002

No subjects in either trial had other AEs of interest such as seizure, cardiac arrhythmias, proarrhythmic potential, gastrointestinal perforations/ulcers, pancreatitis, rhabdomyolysis, and overdose and drug withdrawal.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Common AEs in PSZ-1001

The most common TEAEs (>10%) were sedation (n=4, 16.0%) and epistaxis (n=3, 12.0%). The incidence rate of epistaxis appeared to be high. However, this reviewer is not concerned because epistaxis is common in adolescents and there was no placebo control to compare to in this PK study.

7.4.1.2 Common AEs in PSZ-3001

Incidence of TEAEs occurred ≥5% in paliperidone treatment groups is shown in **Table 25**. The most common AEs were somnolence, akathisia, headache, tremor, dystonia, cogwheel rigidity, anxiety, weight increased and tachycardia (incidence ≥ 5% and at least twice that for placebo).

Somnolence, akathisia, dystonia and tachycardia also appeared to be dose-related. Tremor, cogwheel rigidity, weight increased were only seen in paliperidone ER treatment groups but they did not appear to be clearly dose-related.

Table 25: TEAEs in ≥ 5% of Subjects in any Paliperidone ER Treatment Group in PSZ-3001 (Safety Analysis Set)

Body System or Organ Class Dictionary-Derived Term	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)	Total Paliperidone (N=150) n (%)
Total no. subjects with adverse events	30 (58.8)	27 (50.0)	29 (60.4)	36 (75.0)	92 (61.3)
Nervous system disorders	6 (11.8)	14 (25.9)	17 (35.4)	29 (60.4)	60 (40.0)
Somnolence	1 (2.0)	3 (5.6)	7 (14.6)	10 (20.8)	20 (13.3)
Akathisia	0	2 (3.7)	4 (8.3)	8 (16.7)	14 (9.3)
Headache	2 (3.9)	5 (9.3)	3 (6.3)	5 (10.4)	13 (8.7)
Tremor	0	1 (1.9)	4 (8.3)	4 (8.3)	9 (6.0)
Dystonia	0	1 (1.9)	1 (2.1)	4 (8.3)	6 (4.0)
Cogwheel rigidity	0	0	0	4 (8.3)	4 (2.7)
Psychiatric disorders	18 (35.3)	12 (22.2)	5 (10.4)	11 (22.9)	28 (18.7)
Insomnia	11 (21.6)	5 (9.3)	3 (6.3)	6 (12.5)	14 (9.3)
Schizophrenia	4 (7.8)	6 (11.1)	0	3 (6.3)	9 (6.0)
Agitation	2 (3.9)	3 (5.6)	1 (2.1)	0	4 (2.7)
Anxiety	2 (3.9)	0	0	4 (8.3)	4 (2.7)
Gastrointestinal disorders	10 (19.6)	2 (3.7)	6 (12.5)	9 (18.8)	17 (11.3)
Vomiting	5 (9.8)	0	3 (6.3)	4 (8.3)	7 (4.7)
Nausea	6 (11.8)	0	0	4 (8.3)	4 (2.7)
Investigations	3 (5.9)	6 (11.1)	2 (4.2)	1 (2.1)	9 (6.0)
Weight increased	0	4 (7.4)	2 (4.2)	1 (2.1)	7 (4.7)
Cardiac disorders	0	0	3 (6.3)	4 (8.3)	7 (4.7)
Tachycardia	0	0	2 (4.2)	4 (8.3)	6 (4.0)
Metabolism and nutrition disorders	3 (5.9)	1 (1.9)	0	1 (2.1)	2 (1.3)
Decreased appetite	3 (5.9)	1 (1.9)	0	0	1 (0.7)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 33, page 110.

7.4.1.3 Common AEs in PSZ-3002

The most common (>10%) TEAEs reported in the total group were somnolence (14.5%), headache (12.4%) and akathisia (11.7%). See **Table 26**.

Table 26: TEAEs in ≥ 5% of Subjects in the Total Group in PSZ-3002 (Open-Label Safety Analysis Set)

Body System or Organ Class Dictionary-Derived Term	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (No DB)/Pali (N=125) n (%)	Total (N=282) n (%)
Total no. subjects with adverse events	28 (71.8)	79 (66.9)	97 (77.6)	204 (72.3)
Nervous system disorders	15 (38.5)	46 (39.0)	67 (53.6)	128 (45.4)
Somnolence	10 (25.6)	18 (15.3)	13 (10.4)	41 (14.5)
Headache	4 (10.3)	6 (5.1)	25 (20.0)	35 (12.4)
Akathisia	0	8 (6.8)	25 (20.0)	33 (11.7)
Dizziness	4 (10.3)	7 (5.9)	10 (8.0)	21 (7.4)
Tremor	1 (2.6)	8 (6.8)	8 (6.4)	17 (6.0)
Psychiatric disorders	12 (30.8)	27 (22.9)	41 (32.8)	80 (28.4)
Insomnia	6 (15.4)	9 (7.6)	9 (7.2)	24 (8.5)
Schizophrenia	4 (10.3)	8 (6.8)	11 (8.8)	23 (8.2)
Gastrointestinal disorders	4 (10.3)	19 (16.1)	37 (29.6)	60 (21.3)
Salivary hypersecretion	2 (5.1)	6 (5.1)	13 (10.4)	21 (7.4)
Nausea	1 (2.6)	3 (2.5)	12 (9.6)	16 (5.7)
Infections and infestations	9 (23.1)	22 (18.6)	19 (15.2)	50 (17.7)
Nasopharyngitis	2 (5.1)	15 (12.7)	10 (8.0)	27 (9.6)
Investigations	1 (2.6)	10 (8.5)	22 (17.6)	33 (11.7)
Weight increased	1 (2.6)	8 (6.8)	14 (11.2)	23 (8.2)

Based on data up to 30 July 2009 cut-off date for subjects enrolled prior to that date.
Source: Mod 5.3.5.2 Clinical Study Report R076477-PSZ-3002 - 6 month, Table 35, page 86.

7.4.2 Laboratory Findings

7.4.2.1 Extent of Laboratory Testing

Laboratory testing of hematology, serum chemistry including metabolic parameters, serum prolactin and urinalysis was conducted at Baseline and Endpoint.

7.4.2.2 Mean Change from Baseline to Endpoint in Laboratory Values

Between Baseline and Endpoint, most parameters including serum fasting glucose and lipids had small and similar mean changes among the 4 treatment groups except insulin and prolactin.

Insulin

The results of insulin mean changes in the paliperidone ER treatment groups were hard to interpret. There was a mean decrease in insulin in the paliperidone ER Medium (-6.6 pmol/L) treatment group while there was a mean increase in placebo (24 pmol/L), and even relatively larger mean increases in the paliperidone ER Low (45.5 pmol/L) and High (45.2 pmol/L) treatment group.

Despite the larger mean increases of insulin in the paliperidone ER Low and High treatment group compared to placebo, the treatment-emergent insulin changes from

normal Baseline to High (>161 pmol/L) at Endpoint in these two groups were comparable to that of placebo (refer to **Table 32)**. And the glucose level changes did not appear to differ substantially across paliperidone ER dose groups, as shown in the table below.

Table 27: Means and Mean Changes of Insulin and Glucose from Baseline to Endpoint in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=48)
Insulin (pmol/L)				
N	37	47	35	37
Mean baseline (SD)	102.8 (85.14)	84.7 (82.61)	91.4 (95.29)	95.2 (61.89)
Mean change (SD)	24.0 (200.68)	45.5 (338.90)	-6.6 (75.68)	45.2 (165.81)
Glucose (mmol/L)				
N	46	51	43	44
Mean baseline (SD)	5.1 (0.60)	5.2 (0.60)	5.4 (0.80)	5.1 (0.63)
Mean change (SD)	0.1 (1.12)	-0.1 (0.71)	-0.2 (0.86)	0.4 (1.00)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 49, page 130-131.
Insulin reference ranges: 13.3 – 161 pmol/L.

Prolactin

The paliperidone ER Medium and High treatment groups had much larger mean increases in prolactin level compared to the placebo and the paliperidone ER Low. The mean changes were similar for males and females in each treatment group.

Table 28: Prolactin Results by Sex: Means and Mean Changes in PSZ-3001 (Safety Analysis Set)

Sex: Male							Base	Change From Baseline					
	N	Mean	SD	Med	Min	Max	Mean (SD)	N	Mean	SE	SD	Med	Min	Max
Prolactin (ng/mL)														
Placebo														
Baseline	23	13.56	13.606	8.81	5.0	67.1								
End Point	21	14.73	15.371	9.91	1.6	73.4	14.18 (14.102)	21	0.55	2.052	9.403	-0.36	-29.8	19.1
Paliperidone ER Low														
Baseline	29	14.69	14.490	7.41	2.1	51.9								
End Point	29	18.40	10.736	14.19	3.8	44.4	15.06 (14.609)	28	3.60	3.607	19.085	4.49	-41.0	37.1
Paliperidone ER Medium														
Baseline	30	16.08	18.786	8.89	2.9	86.8								
End Point	28	38.95	24.777	35.42	3.4	110.1	16.13 (19.568)	27	22.82	5.794	30.109	22.34	-43.8	101.1
Paliperidone ER High														
Baseline	33	18.18	13.740	14.03	3.2	58.2								
End Point	31	39.81	26.675	36.77	4.4	120.2	19.26 (13.969)	30	21.32	5.677	31.092	24.09	-51.6	86.6

Table 28: Prolactin Results by Sex: Means and Mean Changes in PSZ-3001 (Safety Analysis Set), continued

Sex: Female

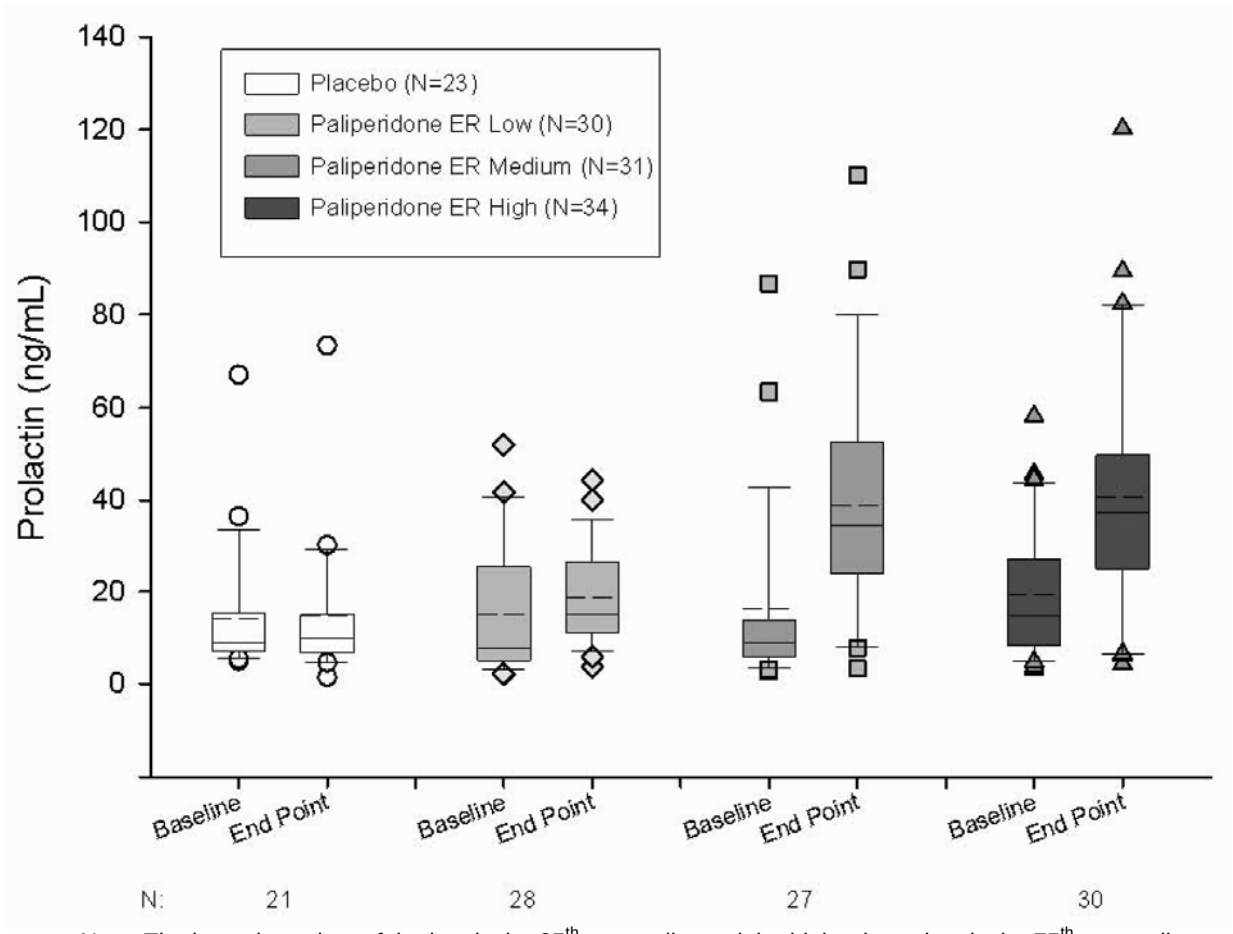
							Base		Change From Baseline					
	N	Mean	SD	Med	Min	Max	Mean (SD)	N	Mean	SE	SD	Med	Min	Max
Prolactin (ng/mL)														
Placebo														
Baseline	24	33.43	38.465	19.17	3.5	137.8								
End Point	24	22.54	20.951	12.18	3.3	70.0	18.78 (14.091)	20	4.37	4.082	18.254	3.17	-25.4	54.9
Paliperidone ER Low														
Baseline	24	38.02	45.507	13.62	5.5	149.8								
End Point	23	42.29	31.572	37.04	5.9	113.8	39.37 (46.038)	23	2.92	10.126	48.561	16.87	-92.1	108.3
Paliperidone ER Medium														
Baseline	16	45.67	71.004	18.49	1.0	280.3								
End Point	15	52.47	24.183	59.26	6.3	98.2	30.03 (34.747)	15	22.44	10.002	38.738	38.69	-47.3	89.8
Paliperidone ER High														
Baseline	13	26.88	33.860	11.24	3.8	122.0								
End Point	13	57.50	53.310	43.08	5.5	179.8	27.81 (35.193)	12	24.92	12.122	41.992	10.40	-13.7	139.6

Note: Normal ranges for prolactin were: Males (12-13 years): 3.27-16.08 ng/mL
Males (14-18 years): 3.34-17.24 ng/mL
Female (12-13 years): 3.75-19.12 ng/mL
Female (14-18 years): 3.44-22.5 ng/mL

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 50, page 137-138.

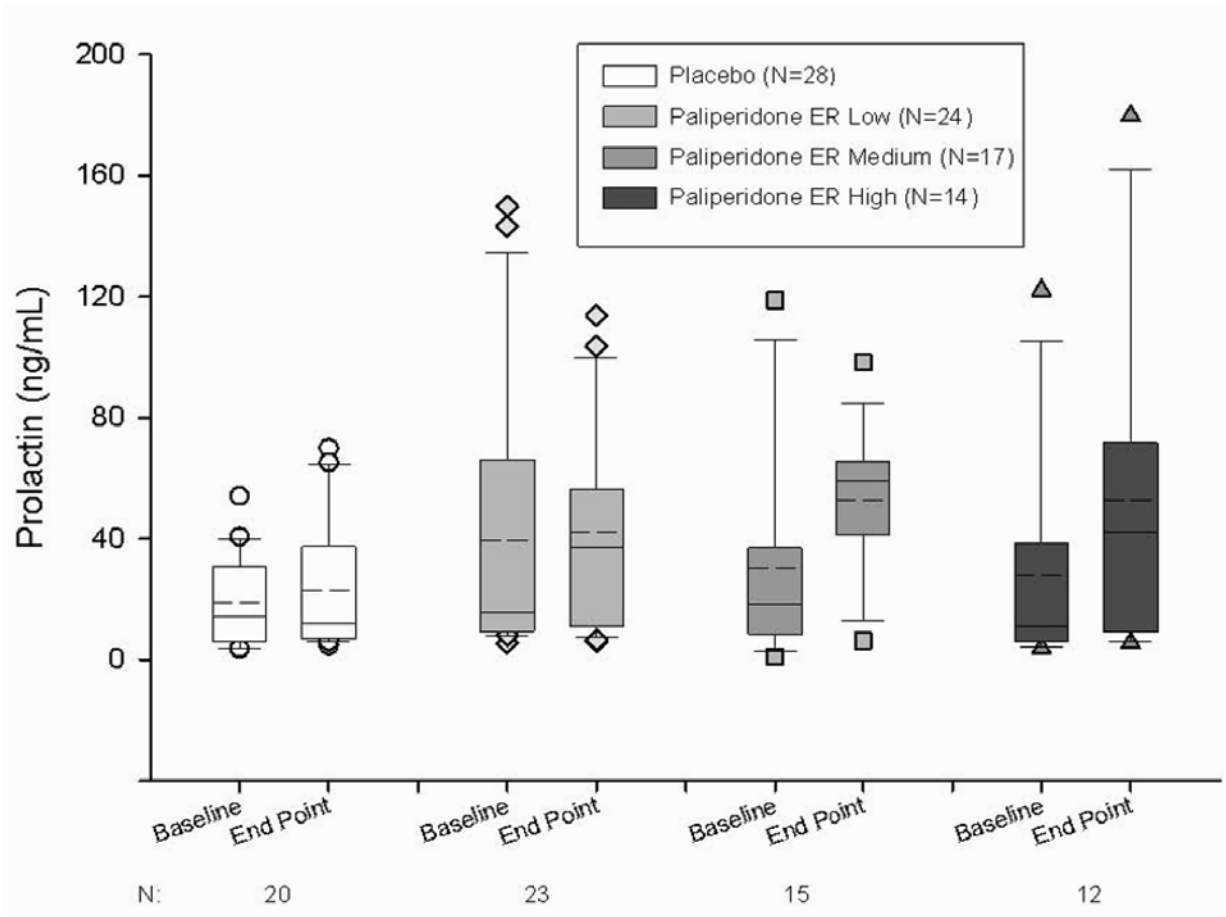
The distributions of prolactin values for males and females at Baseline and Endpoint were also illustrated in **Figure 4** and **Figure 5**.

Figure 4: Distribution of Prolactin Values for Males at Baseline and Endpoint in PSZ-3001 (Safety Analysis Set)



Note: The lower boundary of the box is the 25th percentile, and the higher boundary is the 75th percentile. Whiskers below and above the box indicate the 10th and 90th percentiles. The solid line within the box marks the medium, and the dash line marks the mean value. Outlying data points are extreme values.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Figure 13, page 139

Figure 5: Distribution of Prolactin Values for Females at Baseline and Endpoint in PSZ-3001 (Safety Analysis Set)



Note: The lower boundary of the box is the 25th percentile, and the higher boundary is the 75th percentile. Whiskers below and above the box indicate the 10th and 90th percentiles. The solid line within the box marks the medium, and the dash line marks the mean value. Outlying data points are extreme values.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Figure 14, page 140.

7.4.2.3 Potentially Clinically Significant Laboratory Changes

The sponsor has set criteria (please refer to **Appendix 1**) to identify treatment emergent potentially clinically significant (PCS) laboratory changes in subjects with normal Baseline values. My analyses focused on comparison of the paliperidone ER treatment groups and placebo in terms of the proportions of these subjects meeting those criteria during this adolescent schizophrenia trial PSZ-3001.

1) Serum Chemistry and Hematology

No subject in any treatment group had treatment-emergent abnormally high ALT or AST levels according to the criteria in **Appendix 1**; that is, ALT $\geq$ 200 or AST $\geq$ 250 U/L, respectively.

One subject in the paliperidone ER Low treatment group had ALT or AST levels above 3 times the upper limit of normal. This case was discussed previously in Section 7.3.4 Significant Adverse Events under PSZ-3002.

The following table listed all the abnormal chemistry and hematology labs according to the criteria shown in **Appendix 1**.

Table 29: Treatment-Emergent Markedly Abnormal Laboratory Results in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51) N (%)	Paliperidone ER Low (N=54) N (%)	Paliperidone ER Medium (N=48) N (%)	Paliperidone ER High (N=48) N (%)
Chemistry				
Potassium Abnormally high	46 1 (2)	52 1 (2)	42 0	45 0
TSH Abnormally low	45 1 (2)	52 1 (2)	44 0	44 0
Hematology				
Eosinophils (%) Abnormally high	44 1 (2)	48 1 (2)	41 1 (2)	43 0
Hemoglobin Abnormally low	44 0	48 1 (2)	41 0	43 0
Lymphocytes (%) Abnormally low	44 0	48 1 (2)	41 0	43 0
Neutrophils (%) Abnormally low	44 1 (2)	48 0	41 1 (2)	43 0
Platelets Abnormally low	43 2 (5)	47 0	41 0	41 0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 55, page 148-151.

2) Metabolic Parameters

Fasting Glucose

The sponsor concluded that there was no treatment-emergent markedly abnormally high fasting glucose. However, it is worth to point out that the upper limit of the criterion they used was 18 mmol/L (see **Appendix 1**), which is equivalent to 324 mg/dL.

This reviewer believes that fasting glucose ≥ 126 mg/dL is clinically significant. The following table shows the incidences of treatment-emergent fasting glucose shifting from normal (< 100 mg/dL) at Baseline to high (≥ 126 mg/dL) any time post-Baseline.

The paliperidone ER High treatment group had relatively higher incidence (8.6%) compared to paliperidone ER Low (0%), Medium (0%) group and placebo (2.4%).

This reviewer is not surprised by this finding because hyperglycemia and diabetes mellitus were seen in adults treated with Invega and are labeled under the Warnings and Precautions of the labeling.

Table 30: Fasting Glucose Treatment-Emergent Shifts from Baseline to any Post-Baseline Assessment in Study-PSZ 3001 (Safety Analysis Set)

	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)	Total Paliperidone (N=150) n (%)
Total no. subjects[a]	41 (80.4)	44 (81.5)	37 (77.1)	35 (72.9)	116 (77.3)
Normal to high	1 (2.4)	0	0	3 (8.6)	3 (2.6)
Impaired glucose tolerance to high	0	0	0	0	0
Normal/impaired glucose tolerance to high	1 (2.4)	0	0	3 (8.6)	3 (2.6)
<126 mg/dL to ≥ 140 mg/dL	1 (2.4)	0	0	1 (2.9)	1 (0.9)
<126 mg/dL to ≥ 200 mg/dL	0	0	0	0	0
<126 mg/dL to ≥ 300 mg/dL	0	0	0	0	0

[a] The number of subjects with paired fasting data (Baseline and any post Baseline assessment).
Normal: <100 mg/dL. Impaired: ≥ 100 mg/dL to < 126 mg/dL High: ≥ 126 mg/dL.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 53, page 144.

Insulin Sensitivity and Beta-Cell Function Estimated by Homeostasis Model Assessment

The sponsor used homeostatic model assessment (HOMA) to quantify insulin resistance (IR) and beta-cell function (%B). Insulin resistance (HOMA-IR) and beta-cell function (HOMA-%B) are calculated as follows:

HOMA-IR = (Glucose x Insulin) / 22.5 (mmol/L)

HOMA-%B =

$$\frac{(20 \times \text{Insulin})}{(\text{Glucose} - 3.5)} \%\ (\text{mmol/L}).$$

Table 31 shows the insulin resistance and beta-cell function at Baseline and Endpoint. The paliperidone ER High group had mean HOMA-IR 1.0 increase (3.27 – 2.27 = 1.0) from Baseline to Endpoint while placebo only had 0.1 increase (2.34 - 2.23 ≈ 0.1). The calculated mean HOMA-%B changes were about 1%, 15%, -16% and 4% in placebo, paliperidone ER Low, Medium and High group from Baseline to Endpoint.

Table 31: Insulin Sensitivity and Beta-Cell Function Over Time as Estimated by HOMA-IR and HOMA-%B Models Geometric Mean at Baseline and Endpoint in PSZ-3001 ((Safety Analysis Set)

Time Interval	Placebo (N=51) N	Placebo (N=51) Mean *	Paliperidone ER Low (N=54) N	Paliperidone ER Low (N=54) Mean *	Paliperidone ER Medium (N=48) N	Paliperidone ER Medium (N=48) Mean *	Paliperidone ER High (N=48) N	Paliperidone ER High (N=48) Mean *	Total Paliperidone (N=150) N	Total Paliperidone (N=150) Mean *
HOMA-IR										
Baseline	43	2.23 (0.98 - 5.05)	47	1.92 (0.75 - 4.88)	42	2.30 (1.09 - 4.85)	37	2.27 (1.05 - 4.92)	126	2.14 (0.94 - 4.89)
End Point	36	2.34 (0.88 - 6.23)	44	2.25 (0.82 - 6.16)	32	2.04 (0.91 - 4.54)	32	3.27 (1.35 - 7.95)	108	2.44 (0.96 - 6.17)
HOMA-%B										
Baseline	43	124.7(59.86- 259.7)	47	111.5(45.44- 273.8)	42	118.9(62.60- 225.7)	37	137.3(81.25- 232.1)	126	121.1(58.95- 248.8)
End Point	36	125.4(62.54- 251.3)	43	126.9(54.66- 294.4)	32	103.1(52.07- 204.1)	32	141.3(71.14- 280.6)	107	123.1(57.85- 262.1)

Insulin and Glucose levels collected only in a fasting state were included in the determination of HOMA-IR and HOMA-%B
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 54, Page: 146

Fasting Insulin

The incidences of fasting insulin changes from normal Baseline to high (> 161 pmol/l) at Endpoint were comparable among paliperidone ER High, Low and placebo. All insulin levels remained normal in paliperidone ER Medium group.

Table 32: Treatment-Emergent Fasting Insulin Changes from Normal Baseline to High (> 161 pmol/L) at Endpoint in PSZ-3001 (Safety Analysis Set)

Normal to High n (%)	Placebo	Paliperidone ER Low	Paliperidone ER Medium	Paliperidone ER High
N	26	34	27	23
Yes	4 (15)	4 (12)	0	3 (13)
No	22 (85)	30 (88)	27 (100)	20 (87)

Note: Only subjects with paired fasting data (Baseline and Endpoint assessment) are included in this summary.
Source: Submission dated 2/28/2011.

Fasting Lipid Profile

The sponsor did not find any markedly abnormal values for lipid profile except high-density lipoprotein (HDL) as shown in table below. 4%, 0% and 2% of subjects in paliperidone ER Low, Medium and High group had HDL < 0.6 mmol/L (see **Appendix 1)** (0.6 mmol/L x 38.67 = 23 mg/dL) while no subjects in placebo had markedly abnormally low HDL.

Table 33: Treatment-Emergent Markedly Abnormal Lipid Profile in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51) N (%)	Paliperidone ER Low (N=54) N (%)	Paliperidone ER Medium (N=48) N (%)	Paliperidone ER High (N=48) N (%)
HDL	45	50	43	43
Abnormally low	0	2 (4)	0	1 (2)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 55, page 149.

However, this reviewer has to point out that the upper bound of the markedly abnormal reference ranges used by the sponsor was much higher than the upper limit of normal range. For example, the upper bounds of the markedly abnormal ranges in the criteria (**Appendix 1**) were: total cholesterol 10.9 mmol/L (10.9 mmol/L x 38.67 = 421 mg/dL), low-density lipoprotein (LDL) 5.8 mmol/L (5.8 mmol/L x 38.67 = 224 mg/dL), and triglycerides 5 mmol/L (5 mmol/L x 88.57 = 443 mg/dL).

3) Prolactin

Prolactinemia is labeled under the Warning and Precaution of Invega labeling. It was also seen in this controlled adolescent schizophrenia trial. In males, the proportions of subjects with abnormally high values were greater in the paliperidone ER Medium (61%) and High (52%) treatment groups than in the paliperidone ER Low (34%) treatment group. In females, the proportions were similar in the paliperidone ER Low (43%) and ER Medium (47%) treatment groups and lower in the paliperidone ER High (31%) treatment group.

Table 34: Number of Subjects with Treatment-Emergent Abnormally High Prolactin Results by Sex in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51) N (%)	Paliperidone ER Low (N=54) N (%)	Paliperidone ER Medium (N=48) N (%)	Paliperidone ER High (N=48) N (%)
Male	21	29	28	31
High Prolactin	2 (10)	10 (34)	17 (61)	16 (52)
Female	24	23	15	13
High Prolactin	4 (17)	10 (43)	7 (47)	4 (31)

Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 51, page 141.

4) Urinalysis

The sponsor did not conduct a standard analysis of outlier results for urinalysis.

7.4.2.4 Dropouts due to Abnormal Laboratory Findings

There were no dropouts due to abnormal laboratory findings.

7.4.3 Vital Sign Data

7.4.3.1 Vital Sign Assessments

Systolic blood pressure (BP), diastolic BP and pulse rate were measured at screening, Baseline and each weekly visit during this 6 week double-blind adolescent schizophrenia trial and the follow up visit. Blood pressure and heart rate were measured while the subject was supine after 5 minutes rest, and again after the subject has been

standing for 2 minutes. The same arm with the same cuff and same location of pulse measurement was used.

7.4.3.2 Mean Change from Baseline in Vital Sign Measures

Between Baseline and Endpoint, there were no clinically meaningful mean changes in standing and supine pulse, SBP/DBP among all treatment groups. Also there were no clinically meaningful orthostatic changes in pulse, SBP/DBP from standing to supine position.

7.4.3.3 Potentially Clinically Significant Vital Sign Changes

The sponsor identified subjects who experienced a potentially clinically significant (PCS) vital sign changes by the criteria shown in the tables below. The sponsor has listed the numbers of subjects with abnormal vital sign values at any time post-Baseline during the double-blind phase by age group 12-14 years (**Table 35**) and 15-17 years (**Table 36**).

Among the subjects who were 12 to 14 years old, there were no dose-related trends for any parameter. It only appeared that the paliperidone ER High group had slightly high incidence of decreases in both standing and supine systolic BP compared to other groups (**Table 35**).

Among the subjects who were 15 to 17 years old, it appeared that there were dose-related increases in both standing and supine pulse rates. Also, all the paliperidone ER treatment groups had decreases in standing DBP (**Table 36**).

Table 37 showed the number of subjects with treatment-emergent orthostatic hypotension at any time during the double-blind phase. Only 1 subject, who received doses of 12 mg in the paliperidone ER High treatment group, met the criteria for orthostatic hypotension on Day 15 but did not meet the same criteria on Day 22. This reviewer is not concerned because orthostatic hypotension and syncope is also labeled under the Warnings and Precautions of the labeling.

7.4.3.4 Dropouts due to Vital Sign Abnormalities

There were no dropouts due to vital sign abnormalities.

Table 35: Number of Subjects with Abnormal Vital Sign Values at Any Time Post-Baseline during the Double-Blind Phase – 12 To 14 Years Old in PSZ-3001 (Safety Analysis Set)

	Placebo (N=9) n (%)	Paliperidone ER Low (N=16) n (%)	Paliperidone ER Medium (N=15) n (%)	Paliperidone ER High (N=14) n (%)
Standing pulse classification	9	16	15	12
Decrease ≥15 and value ≤60	0	0	0	0
Increase ≥15 and value ≥110	1 (11)	1 (6)	0	1 (8)
Supine pulse classification	9	16	15	13
Decrease ≥15 and value ≤60	1 (11)	0	2 (13)	0
Increase ≥15 and value ≥110	0	1 (6)	0	1 (8)
Standing SBP classification	9	16	15	12
Decrease ≥20 and value ≤105	1 (11)	3 (19)	0	3 (25)
Increase ≥20 and value ≥128	0	1 (6)	1 (7)	0
Supine SBP classification	9	16	15	13
Decrease ≥20 and value ≤105	1 (11)	1 (6)	1 (7)	3 (23)
Increase ≥20 and value ≥128	0	0	1 (7)	0
Standing DBP classification	9	16	15	12
Decrease ≥15 and value ≤62	2 (22)	1 (6)	0	2 (17)
Increase ≥15 and value ≥82	1 (11)	2 (13)	0	0
Supine DBP classification	9	16	15	13
Decrease ≥15 and value ≤62	1 (11)	3 (19)	2 (13)	1 (8)
Increase ≥15 and value ≥82	0	1 (6)	1 (7)	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 57, page 154.

Table 36: Number of Subjects with Abnormal Vital Sign Values at Any Time Post-Baseline during the Double-Blind Phase – 15 To 17 Years Old in PSZ-3001 (Safety Analysis Set)

	Placebo (N=42) n (%)	Paliperidone ER Low (N=38) n (%)	Paliperidone ER Medium (N=33) n (%)	Paliperidone ER High (N=34) n (%)
Standing pulse classification	42	38	33	34
Decrease ≥15 and value ≤50	0	0	0	0
Increase ≥15 and value ≥100	4 (10)	5 (13)	4 (12)	7 (21)
Supine pulse classification	42	38	33	34
Decrease ≥15 and value ≤50	0	0	0	0
Increase ≥15 and value ≥100	2 (5)	3 (8)	3 (9)	4 (12)
Standing SBP classification	42	38	33	34
Decrease ≥20 and value ≤110	5 (12)	2 (5)	3 (9)	2 (6)
Increase ≥20 and value ≥136	1 (2)	2 (5)	0	2 (6)
Supine SBP classification	42	38	33	34
Decrease ≥20 and value ≤110	3 (7)	2 (5)	1 (3)	0
Increase ≥20 and value ≥136	2 (5)	1 (3)	0	0
Standing DBP classification	42	38	33	34
Decrease ≥15 and value ≤64	0	2 (5)	2 (6)	2 (6)
Increase ≥15 and value ≥87	1 (2)	2 (5)	3 (9)	0
Supine DBP classification	42	38	33	34
Decrease ≥15 and value ≤64	3 (7)	1 (3)	0	4 (12)
Increase ≥15 and value ≥87	2 (5)	2 (5)	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 58, page 155.

Table 37: Number of Subjects with Treatment-Emergent Orthostatic Hypotension at Any Time during the Double-Blind Phase in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)
Total no. subjects with orthostatic Hypotension	0	0	0	1 (2)
Pulse (std-sup) >15 and DBP (std-sup) <-10	0	0	0	1 (2)

Note: Percentages calculated with the number of subjects per parameter as denominator.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 61, page 158.

7.4.4 Weight

7.4.4.1 Weight Assessments

Weight was measured at screening, Baseline and each weekly visit during this 6 week placebo controlled adolescent schizophrenia trial and the follow up visit.

7.4.4.2 Mean Weight Changes from Baseline

The mean weight increase was only seen in paliperidone treatment groups and appeared in a dose-related fashion, which was 0.3kg, 1.1kg and 1.4kg in paliperidone ER Low, Medium and High group. The mean weight change was 0 in placebo.

The mean BMI (kg/m^2) increase was relatively larger in paliperidone ER Medium (0.3) and High (0.4) group than that in paliperidone ER Low (0.1) and placebo group (0.1).

Table 38: Body Weight and BMI: Change from Baseline to Endpoint in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=48)
Weight (kg)				
N	51	54	48	47
Mean baseline (SD)	59.5 (16.47)	60.4 (16.07)	57.7 (14.63)	61.5 (16.08)
Mean change (SD)	0.0 (1.68)	0.3 (1.52)	1.1 (2.13)	1.4 (2.16)
Weight percent change (%)				
N	51	54	48	47
Mean baseline (SD)	59.5 (16.47)	60.4 (16.07)	57.7 (14.63)	61.5 (16.08)
Mean % change (SD)	0.1 (2.62)	0.5 (3.02)	1.9 (3.92)	2.2 (3.54)
Body mass index (kg/m^2)				
N	51	54	48	47
Mean baseline (SD)	21.8 (5.58)	22.2 (4.86)	21.4 (3.96)	21.9 (4.31)
Mean change (SD)	0.1 (1.16)	0.1 (0.58)	0.3 (0.83)	0.4 (0.77)

For the weight percent change, the mean Baseline represents the actual weight (in kg).
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 62, page 159.

7.4.4.3 Potentially Clinically Significant Weight Changes

The number of subjects with abnormal weight changes from Baseline at Endpoint is displayed in **Table 39**.

There was a dose-related trend in the percentage of subjects with weight increase of ≥ 7%. The percentage of subjects who had weight gain ≥ 7% was 6%, 13% and 13% in paliperidone ER Low, Medium and High group while it was 2% in placebo.

Significant weight gain was seen in adult Invega trials. The sponsor proposed to include weight gain in Warnings and Precautions section of the labeling. The Division is currently reviewing this labeling supplement.

Table 39: Number of Subjects with Abnormal Weight Change at Endpoint in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)
Weight classification	51	54	48	47
Decrease ≥7%	1 (2)	1 (2)	0	0
Increase ≥7%	1 (2)	3 (6)	6 (13)	6 (13)

Note: Percentages calculated with the number of subjects per parameter as denominator.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 63, page 159.

7.4.4.4 Dropouts due to Weight Changes

There were no dropouts due to weight changes.

7.4.5 Tanner Staging

A majority of both male and female subjects in each treatment group did not have Tanner stage rating changes at Endpoint from Baseline.

7.4.6 Electrocardiograms (EKGs)

7.4.6.1 EKG Assessments

Three EKGs were recorded before the first administration of the study drug: 2 were recorded during the screening period (at least 24 hours apart) and the third was recorded at the Baseline visit on Day 1. Additional EKGs were recorded at Visit 5 and Visit 8 or upon early withdrawal and at the follow-up visit for subjects not continuing into the open-label trial.

The Baseline corrected QT interval was the average of 3 QT intervals recorded before the drug treatment. The sponsor used the study specific linear-derived correction (QTcLD) as well as Fridericia (QTcF) and Bazett (QTcB) for the corrected QT.

7.4.6.2 Mean EKG Changes from Baseline to Endpoint

There were no clinically relevant mean changes in heart rate, PR, QRS, QT, RR intervals, QTcLD, QTcF or QTcB.

7.4.6.3 Potentially Clinically Significant EKG Changes

The sponsor identified subjects who experienced a treatment-emergent abnormal EKG value at any time during the double-blind phase using the criteria shown in the note under the **Table 40**.

The only potentially clinically significant abnormal EKG value according to the criteria was abnormally high heart rate (≥ 100 bpm), which occurred more often in the paliperidone ER treatment groups (14%, 13% and 16% in paliperidone ER Low, Medium and High treatment group and 4% in placebo) as shown in **Table 40**. There were no potentially clinically significant abnormal PR, QRS and QT interval.

Table 40: Number of Subjects with Treatment-Emergent Abnormal EKG at Any Time during the Double-Blind Phase in PSZ-3001 (Safety Analysis Set)

	Placebo (N=51) n (%)	Paliperidone ER Low (N=54) n (%)	Paliperidone ER Medium (N=48) n (%)	Paliperidone ER High (N=48) n (%)
Heart Rate	46	50	45	44
Abnormally high	2 (4)	7 (14)	6 (13)	7 (16)
Abnormally low	2 (4)	0	0	0
PR interval	46	50	45	44
Abnormally high	1 (2)	0	0	0
Abnormally low	0	0	0	0
QRS interval	46	50	45	44
Abnormally high	0	0	0	0
Abnormally low	0	0	0	0
QT interval	46	50	45	44
Abnormally high	0	0	0	0
Abnormally low	0	0	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: Heart rate: abnormally low: ≤50 bpm, abnormally high: ≥100 bpm. PR interval: abnormally high: ≥210 ms. QRS interval: abnormally low: ≤50 ms, abnormally high: ≥120 ms. QT interval: abnormally low: ≤200 ms, abnormally high: ≥500 ms.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 68, page 172.

The sponsor also analyzed the QTc increases from average pre-dose to maximum post-dose for all subjects.

No subject in any treatment group had a QTc increase ≥ 60 ms.

For QTcB, the percentages with increases of ≥ 30 to 60 ms were higher in the paliperidone ER Medium (9%) and High (14%) treatment groups than in placebo (2%) and paliperidone ER Low (2%) treatment group.

For QTcLD and QTcF, the percentages of subjects with increases of ≥ 30 to 60 ms were similar in all 4 treatment groups.

Table 41: Distribution of Changes from Average Pre-dose to Maximum Corrected QT Values in PSZ-3001 (Safety Analysis Set)

QTcLD	46	50	45	44
≤30 (ms)	44 (96)	50 (100)	42 (93)	43 (98)
>30-60 (ms)	2 (4)	0	3 (7)	1 (2)
>60 (ms)	0	0	0	0
QTcF	46	50	45	44
≤30 (ms)	44 (96)	50 (100)	43 (96)	43 (98)
>30-60 (ms)	2 (4)	0	2 (4)	1 (2)
>60 (ms)	0	0	0	0
QTcB	46	50	45	44
≤30 (ms)	45 (98)	49 (98)	41 (91)	38 (86)
>30-60 (ms)	1 (2)	1 (2)	4 (9)	6 (14)
>60 (ms)	0	0	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Source: Mod 5.3.5.1 Clinical Study Report R076477-PSZ-3001, Table 70, page 176.

7.4.6.4 Dropouts due to EKG Changes

There were no dropouts due to EKG Changes.

7.4.7 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this indication.

7.4.8 Immunogenicity

No immunogenicity study was conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to **Table 25**.

7.5.2 Time Dependency for Adverse Events

There were no additional analyses for the dose-related AEs in terms of the time to onset of AEs, duration of event, and the extent to which the AE resolved.

7.5.3 Drug-Demographic Interactions

This reviewer has examined the common and likely drug-related treatment-emergent AEs reported by gender, age and race in PSZ-3001. It only appeared that weight increased occurred more often in males than females in paliperidone ER treatment groups (**Table 42**), which could be the result of small number of subjects. The other AEs did not appear to be different by age, gender and race.

Table 42: Treatment-Emergent Weight Increased reported by Sex in PSZ-3001 (Safety Analysis Set)

	Weight Increased Sex n (%)	
	Male	Female
Placebo Total (N = 51)	0 Total (N = 23)	0 Total (N = 28)
Paliperidone ER Low Total (N = 54)	3 (10.0) Total (N = 30)	1 (4.2) Total (N = 24)
Paliperidone ER Medium Total (N = 48)	2 (6.5) Total (N = 31)	0 Total (N = 17)
Paliperidone ER High Total (N = 48)	1 (2.9) Total (N = 34)	0 Total (N = 14)
Total Paliperidone ER Total (N = 150)	6 (6.3) Total (N = 95)	1 (1.8) Total (N = 55)

Source: Submission dated 12/15/2010. The Global Submit eCTD sequence number: 129.

7.5.4 Drug-Disease Interactions

There were no analyses for the drug-disease interactions in this submission.

7.5.5 Drug-Drug Interactions

There were no analyses for the drug-drug interactions in this submission. Paliperidone is a marketed drug in the USA since 2006. Drug-drug interaction profile had been established and has been addressed in current approved Invega labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity study has been conducted.

7.6.2 Human Reproduction and Pregnancy Data

There were no human reproduction and pregnancy data in this trial.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Pediatric and Maternal Health Staff was consulted and the Pediatric Review Committee (PeRC) meeting will be held on March 16, 2011.

There was a pediatric waiver of studies in children younger than 12 years old.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose of paliperidone ER was found in this trial. There is no new information on abuse potential, withdrawal and rebound.

7.7 Additional Submissions / Safety Issues / 4-month Safety Update

A 4-month Safety Update report was submitted by the Sponsor on January 28, 2011 for this sNDA. This safety report included the safety data from 2 trials that were ongoing at the time of this sNDA submission.

- PSZ-3002 is an ongoing 2-year, open-label, single-arm safety trial of flexibly dosed paliperidone ER (1.5 - 12 mg/day) in the treatment of adolescents (12 to 17 years of age) with schizophrenia.

- PSZ-3003 is an ongoing, randomized, double-blind, active-controlled (not placebo controlled), parallel-group, multicenter, efficacy and safety trial of flexible doses of paliperidone ER (3 - 9 mg/day) or aripiprazole (5 - 15 mg/day) in the treatment of adolescents (12 to 17 years of age) with schizophrenia.

This 4-month safety update reported deaths, SAEs, and discontinuations due to AEs in the Sponsor's database as of cut off date September 8, 2010, plus CIOMS reports of deaths and SAEs received after that cut-off date through September 30, 2010 for both PSZ-3002 and PSZ-3003 and other safety data for PSZ-3002.

The following is a summary of findings.

7.7.1 Overall Extent of Exposure

In PSZ-3002, a total of 399 adolescent subjects with schizophrenia had received at least 1 dose paliperidone ER as of the cut-off date September 8, 2010. The mean

duration of exposure was 342.2 days. A total of 266 (67%) subjects had received paliperidone ER for 180 days.

392 subjects had received a mode dose of paliperidone ER that was ≥ 3 mg/day. Of these, 260 (66%) subjects had ≥ 6 months of exposure to paliperidone ER, 161 (41%) subjects had ≥ 1 year of exposure, and 27 (7%) subjects had ≥ 2 years of exposure.

In PSZ-3003, only 25 adolescent subjects had received ≥ 1 dose of blinded study drug as of the cut-off date for the Safety Update.

7.7.2 Deaths

There were no deaths reported in either trial as of September 30, 2010.

7.7.3 SAEs

PSZ-3002
A total of 13.3% of the subjects in the Safety Update had treatment-emergent SAEs compared to 11.7% of the subjects in the sNDA. Schizophrenia (6.5%), anxiety (1.0%), and suicidal ideation (1.0%) were the most common SAEs reported in this Safety Update. There were no unusual SAE's of concern, such as hepatitis or Stevens - Johnson syndrome reported.

PSZ-3003
Two of 25 subjects had experienced SAEs (psychotic disorder and schizophrenia) as of the cut-off date for the Safety Update.

7.7.4 Dropouts and/or Discontinuations

PSZ-3002
A total of 5.3% of the subjects had TEAEs leading to discontinuations compared to 3.2% of the subjects in the sNDA. Suicide attempt (n=3), akathisia (n=3), and suicidal ideation (n=2) were the most common.

PSZ-3003
No subjects had TEAEs leading to discontinuations in this trial.

7.7.5 Weight Gain

The weight gain in the open label trial PSZ-3002 is hard to characterize due to the lack of control. The following table shows that the mean change of BMI percentile varied from 1.1% to 4.4% from the open label Baseline to Endpoint.

Table 43: Standardized Growth Parameters for Height, Body Weight, and BMI – Mean and Mean Changes at Endpoint (OL) Relative to Baseline (OL) in PSZ-3002 (Safety Analysis Set)

	---------- Placebo/Pali ---------- (N=39)					--------- Pali (DB)/Pali --------- (N=118)					-------- Pali (NO DB)/Pali ------- (N=242)				
				Change from Baseline(open)					Change from Baseline(open)					Change from Baseline(open)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Height (cm)															
Actual	32	167.7	9.58	2.9	5.27	112	167.0	10.56	1.9	2.96	194	169.6	9.96	1.4	2.86
Z-score	32	-0.2	1.18	0.2	0.77	112	-0.3	1.17	-0.0	0.29	194	0.1	1.16	-0.0	0.24
Percentile	32	47.3	33.29	3.6	16.35	112	42.4	31.49	-1.0	8.68	194	54.2	31.06	-0.5	6.88
Weight (kg)															
Actual	39	63.4	11.94	5.0	7.04	116	64.7	16.13	3.9	5.98	224	67.2	16.81	4.1	7.20
Z-score	39	0.1	1.10	0.2	0.67	116	0.1	1.23	0.0	0.52	224	0.4	1.27	0.1	0.53
Percentile	39	52.7	31.20	5.4	16.97	116	53.7	32.72	0.5	14.43	224	61.6	30.94	2.9	14.37
BMI (kg/m^2)															
Actual	39	22.6	3.57	1.1	1.99	116	23.0	4.57	0.9	2.01	224	23.4	4.95	1.1	2.40
Z-score	39	0.1	1.01	0.2	0.55	116	0.3	1.12	0.1	0.58	224	0.4	1.16	0.2	0.63
Percentile	39	55.1	30.28	4.1	16.68	116	58.3	30.89	1.1	17.16	224	62.6	29.37	4.4	17.27

NOTES: The results are based on subjects with both Baseline and Endpoint data
The z-score indicates how many standard deviations an observed value is away from the expected weight, height, or BMI based on a subject's age (in months) and sex. Normative data (and SAS program) retrieved from website http://www.cdc.gov/nccdphp/dnpa/growthcharts/resources/sas.htm. The L (power in the Box-Cox transformation), M (median), and S (generalized coefficient of variation) parameters from the website were used to compute z-scores according to the following equation:
(((x/M)^L)-1)/(L*S) for |L|≥0.01, and log(X/M)/S for |L|<0.01.
The percentile, based on a standard normal distribution, ranks the position of an individual by indicating what percent of the reference population the individual would equal or exceed.
Reference: http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf
Based on data up to 8 September 2010 cutoff date for subjects enrolled prior to that date.
DB=double-blind; OL=open-label; Pali=paliperidone
Source: 4 month Safety Update: Submission dated on January 28, 2011: 2.7.4: summary of Clinical Safety, page 57.

8 Postmarket Experience

The sponsor submitted the Postmarket Experience with the Clinical Study Report (CSR) dated October 8, 2010. They summarized the postmarketing exposure and safety information for Invega ER tablets in patients < 18 years of age from drug approval through May 31, 2010. They identified 185 spontaneous case reports (3.81 cases/10,000 person years, <1%) for paliperidone involving patients < 18 years old. 42% of these cases had SAEs (Refer to **Table 44**).

Table 44: Postmarket Experience: Number of Serious Cases Reported from Drug Approval through May 31, 2010

Age Group	Number of Serious Cases	Total Number of Cases	% of Cases Coded as Serious
Less than 18 years of age	77	185	41.6
All other ages	879	2,406	36.5

Source: Original application 10/8/2010, 5.3.6, Reports of Post-marketing Experience, Page 19.

The AEs that was reported more in < 18 years compared to all other ages (≥ 18 years) included swollen tongue, chest pain, and accidental drug intake by child, increased appetite, drooling, dystonia, hypersomnia, abnormal behavior, aggression, and off label use (Refer to **Table 45**).

Table 45: Distribution of AEs Reported in ≥ 3 Cases with a Proportional Reporting Ratio ≥ 2 in Patients < 18 Years versus ≥ 18 Years Treated With Paliperidone Cumulatively Through 31 May 2010

MedDRA System Organ Class (SOC) MedDRA Preferred Term (PT)	Number of Spontaneous Cases[b,c]		Percentage of Spontaneous Cases Within Age Group		Proportional Reporting Ratio of Cases[a]
	Less Than 18 Years	All Other Ages	Less Than 18 Years	All Other Ages	
Gastrointestinal Disorders					
Swollen tongue	5	13	2.70	0.54	5.00
General Disorders and Administration Site Conditions					
Chest pain	6	19	3.24	0.79	4.10
Injury, Poisoning and Procedural Complications					
Accidental drug intake by child	6	0	3.24	0	N/A
Metabolism and Nutrition Disorders					
Increased appetite	5	15	2.70	0.62	4.35
Nervous System Disorders					
Drooling	8	19	4.32	0.79	5.47
Dystonia	21	61	11.35	2.54	4.47
Hypersomnia	4	6	2.16	0.25	8.64
Psychiatric Disorders					
Abnormal behaviour	4	10	2.16	0.42	5.14
Aggression	6	30	3.24	1.25	2.60
Surgical and Medical Procedures					
Off label use	4	12	2.16	0.50	4.32
Total Number of Cases	**185**	**2,406**			

Note: Only PTs (by SOC) that were shown to be disproportional in the cumulative reporting period are included in this table.
Key: MedDRA=Medical Dictionary for Regulatory Activities; N/A=not applicable (PRR=0); PT=Preferred Term; SOC=System Organ Class. a: Percentage of spontaneous cases in patients less than 18 years divided by the percentage of spontaneous cases in all

other ages (for PTs with ≥3 cases) b: Includes both serious and nonserious cases. c: One case may report more than 1 event.
Source: Original application 10/8/2010, 5.3.6. Post-marketing Experience, Page 20

This reviewer has looked all the reports of serious cases submitted. No death was reported. There were very few events of NMS and seizure but both are already labeled under Warnings and Precautions for Invega.

The sponsor also submitted Postmarket Experience in the Safety Update dated January 28, 2011 which covered the period from June 1, 2010 to September 8, 2010. A total of 15 pediatric cases with 42 AEs were reported in this period. Nine of 15 cases involved SAEs. One event of Torsade de pointes was reported at this time but not in the previous Postmarket Experience. Torsade de pointes is also labeled under Warnings and Precautions.

This reviewer agreed with the sponsor's conclusion that no new safety concerns, which specifically occurred in pediatric patients receiving paliperidone, were identified.

9 Appendices

9.1 Literature Review/References

The literature searches, performed by Johnson & Johnson, included published literatures containing paliperidone/9-hydroxyrisperidone from November 2008 to May 2010.

Johnson & Johnson has reviewed the literature search results and concluded that the published data were consistent with the safety data obtained from their clinical trials and supported their conclusion that paliperidone ER is generally safe and well tolerated.

9.2 Labeling Recommendations

The labeling review is still ongoing.

This reviewer proposed the following tentative labeling language that is different from what the sponsor proposed:

(b) (4)

9.3 Advisory Committee Meeting

No advisory committee meeting is currently planned for this submission.

Appendix 1: Reference Ranges and Markedly Abnormal Ranges for Clinical Laboratory Results in PSZ-3001

Analyte	Standard Unit	Reference Ranges in Standard Unit	Markedly Abnormal Reference Ranges in Standard Unit	Gender	Age Range
Category: CHEMISTRY					
ALBUMIN	g/l	29-47	24-60	FEMALE	12-15
				MALE	12-15
		33-47	24-60	FEMALE	16-17
				MALE	16-17
		33-49	24-60	FEMALE	18-18
				MALE	17-18
ALKALINE PHOSPHATASE	U/L	31-106	N/A-450	FEMALE	18-18
		31-110	N/A-450	FEMALE	15-17
		31-129	N/A-450	MALE	17-18
		50-250	N/A-450	MALE	15-17
		51-300	N/A-450	FEMALE	12-14
		95-385	N/A-450	MALE	12-14
ALT (SGPT)	U/L	6-34	N/A-200	FEMALE	12-18
		6-43	N/A-200	MALE	12-18
AST (SGOT)	U/L	10-40	N/A-250	FEMALE	12-17
				MALE	12-17
		11-36	N/A-250	MALE	17-18
		9-34	N/A-250	FEMALE	18-18
BICARBONATE	mmol/l	17-30.6	15.1-34.9	FEMALE	12-18
				MALE	12-18
BILIRUBIN	umol/l	3-21	N/A-51.3	FEMALE	12-18
				MALE	12-18
CALCIUM	mmol/l	2.07-2.64	1.5-3	FEMALE	18-18
				MALE	17-18
		2.1-2.57	1.5-3	FEMALE	12-17
				MALE	12-17
CHLORIDE	mmol/l	94-112	75.2-134.4	FEMALE	12-18
				MALE	12-18
CHOLESTEROL	mmol/l	2.95-5.12	N/A-10.9	MALE	15-18
		3.21-5.61	N/A-10.9	FEMALE	12-14
		3.23-5.48	N/A-10.9	FEMALE	15-18
		3.36-5.28	N/A-10.9	MALE	12-14
CREATININE	umol/l	23-66	N/A-265.2	FEMALE	12-12
				MALE	12-12
		23-83	N/A-265.2	MALE	13-15
		31-101	N/A-265.2	FEMALE	18-18
		31-75	N/A-265.2	FEMALE	13-15
		40-101	N/A-265.2	MALE	16-17
		40-110	N/A-265.2	MALE	17-18
		40-83	N/A-265.2	FEMALE	16-17
GGT	U/L	0-33	N/A-300	FEMALE	12-17
		0-51	N/A-300	MALE	12-17
		10-61	N/A-300	MALE	17-18
		4-49	N/A-300	FEMALE	18-18
GLUCOSE	mmol/l	3.9-6.4	2.4-18	FEMALE	12-18
				MALE	12-18
HDL	mmol/l	0.78-1.63	0.6-N/A	MALE	14-18
		0.91-1.91	0.6-N/A	FEMALE	14-18
		0.96-1.81	0.6-N/A	FEMALE	12-13
		0.96-1.91	0.6-N/A	MALE	12-13
IGF BINDING PROT 3	nmol/l	835-3778		FEMALE	18-18
				MALE	17-18
INSULIN	pmol/l	13.3-161		FEMALE	18-18
				MALE	17-18
INSULIN-LIKE GF-1	ng/ml	40-258		FEMALE	18-18
				MALE	17-18

Continue

Appendix 1: Criteria of Markedly Abnormal Laboratory Values in PSZ-3001, continued

Analyte	Standard Unit	Reference Ranges in Standard Unit	Markedly Abnormal Reference Ranges in Standard Unit	Gender	Age Range
Category: CHEMISTRY (CONTINUED)					
LDL	mmol/l	1.53-3.54	N/A-5.8	FEMALE	15-18
		1.6-3.36	N/A-5.8	MALE	15-18
		1.66-3.44	N/A-5.8	MALE	12-14
		1.76-3.52	N/A-5.8	FEMALE	12-14
MAGNESIUM	mmol/l	0.62-0.9	0.492-1.517	FEMALE	16-17
				MALE	16-17
		0.62-1.27	0.492-1.517	FEMALE	18-18
				MALE	17-18
		0.66-0.9	0.492-1.517	FEMALE	12-12
				MALE	12-12
		0.66-0.94	0.492-1.517	FEMALE	13-15
				MALE	13-15
POTASSIUM	mmol/l	3.4-5.4	3-5.8	FEMALE	12-18
				MALE	12-18
PROLACTIN	ng/ml	3.27-16.08		MALE	12-13
		3.34-17.24		MALE	14-18
		3.44-22.5		FEMALE	14-18
		3.75-19.12		FEMALE	12-13
PROTEIN	g/l	61-84	50-N/A	FEMALE	12-18
				MALE	12-18
SODIUM	mmol/l	132-147	125-155	FEMALE	12-18
				MALE	12-18
TRIGLYCERIDES	mmol/l	0.36-1.41	N/A-5	MALE	12-14
		0.42-1.48	N/A-5	FEMALE	12-14
		0.42-1.67	N/A-5	MALE	15-18
		0.44-1.4	N/A-5	FEMALE	15-18
TSH	U/L	0.0003-0.0056	0.0003-0.006	FEMALE	12-18
				MALE	12-18
UREA NITROGEN	mmol/l	1.4-8.6	N/A-18	FEMALE	12-18
				MALE	12-18
Category: HEMATOLOGY					
BASOPHILS	%		N/A-6	FEMALE	12-18
				MALE	12-18
	giga/l	0-0.2		FEMALE	12-18
				MALE	12-18
EOSINOPHILS	%		N/A-10	FEMALE	12-18
				MALE	12-18
	giga/l	0-0.2		FEMALE	12-17
		0-0.3		MALE	12-17
		0-0.57		FEMALE	18-18
				MALE	17-18
HEMATOCRIT	vol-%	34-48	28-50	FEMALE	12-18
		39-54	24-55	MALE	12-18
HEMOGLOBIN	g/l	116-164	80-190	FEMALE	12-18
		127-181	80-190	MALE	12-18
LYMPHOCYTES	%		10-60	FEMALE	12-18
				MALE	12-18
	giga/l	0.91-4.28		FEMALE	18-18
				MALE	17-18
		0.95-5.25		FEMALE	12-17
				MALE	12-17
MONOCYTES	%		N/A-20	FEMALE	12-18
				MALE	12-18
	giga/l	0.12-0.92		FEMALE	18-18
				MALE	17-18
		0.4-0.9		FEMALE	12-17
		0.4-1.3		MALE	12-17

Continue

Appendix 1: Criteria of Markedly Abnormal Laboratory Values in PSZ-3001, continued

Analyte	Standard Unit	Reference Ranges in Standard Unit	Markedly Abnormal Reference Ranges in Standard Unit	Gender	Age Range
Category: HEMATOLOGY (CONTINUED)					
NEUTROPHILS	%		30-90	FEMALE	12-18
				MALE	12-18
	giga/l	1.65-8.15		FEMALE	12-17
				MALE	12-17
		1.96-7.23		FEMALE	18-18
				MALE	17-18
PLATELETS	giga/l	140-400	100-600	FEMALE	12-18
				MALE	12-18
RBC	tera/l	4.1-5.6	3.1-6.6	FEMALE	12-18
		4.5-6.4	3.1-6.6	MALE	12-18
WBC	giga/l	3.8-10.7	2.5-15	FEMALE	18-18
				MALE	17-18
		4.35-13.15	2.5-15	FEMALE	12-17
				MALE	12-17
Category: URINALYSIS					
U EPITHELIAL CELLS	/HPF	0-3		FEMALE	12-17
				MALE	12-17
U SP GRAVITY		1.003-1.035		FEMALE	12-18
				MALE	12-18
URINE PH		5-8		FEMALE	12-18
				MALE	12-18
URINE RBC	/HPF	0-3		MALE	12-17
		0-8		FEMALE	12-17
URINE WBC		0-5		MALE	16-16
	/HPF	0-12		FEMALE	12-17
		0-5		MALE	12-17

Source: Mod 5.3.5.1, Clinical Study Report R076477-PSZ-3001, Attachment 4.1.3, page 684-688

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/s/

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03/09/2011

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03/09/2011