Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Paliperidone

Proprietary Product Name: Invega

Sponsor: Janssen-Cilag Pty Ltd

Date of CER:
28 May 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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Contents

List of abbreviations

Abbreviation	Meaning
ADR	adverse drug reaction
AE	adverse event (or effect)
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	Area Under the plasma concentration time Curve
AV	atrioventricular
BARS	Barnes Akathisia Rating Scale
b.i.d.	twice a day
BMI	body mass index
bpm	beats per minute
BW	body weight
Cavg	average plasma concentration
CGAS	Children's Global Assessment Scale
CGI-S	Clinical Global Impression-Severity
CI	confidence interval
CL	clearance
Cmax	maximum plasma concentration
CMI	Consumer Medicine Information
CRF	case report form
CSR	Clinical Study Report
CV	coefficient of variation
DB	double-blind

Abbreviation	Meaning
DNA	deoxyribonucleic acid
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revised
ECG	electrocardiogram
EPS	extrapyramidal symptoms
ER	extended release
EU	European Union
F	bioavailability
fu	fraction unbound
HOMA	homeostasis model assessment
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IGF	insulin-like growth factor
IGFBP-3	insulin-like growth factor binding protein-3
IQ	intelligence quotient
IR	immediate-release
ITT	intention-to-treat
IVRS	interactive voice response system
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children Present and Lifetime version
LOCF	last observation carried forward
LS	least squares
MITT	modified intention-to-treat
ms	millisecond
NMS	neuroleptic malignant syndrome

Abbreviation	Meaning
NS	not statistically significant
OROS	Osmotic controlled Release Oral delivery System
OTC	over-the-counter
PANSS	Positive and Negative Syndrome Scal
PI	Product Information
PIP	paediatric investigation plan
PK	pharmacokinetics
Pop-PK	population pharmacokinetics
QTc	QT interval corrected for heart rate
QTcF	the QTC interval calculated using the Fridericia formula
QTcLD	the QTC interval calculated using the linear-derived formula
RMP	Risk Management Plan
SAE	serious adverse event
SAS	Simpson-Angus Rating Scale
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
TD	tardive dyskinesia
TEAE	treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TSH	thyroid-stimulating hormone
t½	half-life
US	United States
V	volume of distribution
VAS	Visual Analogue Scale

1. Clinical rationale

The following clinical rationale was provided in the Sponsor's Clinical Overview (in Module 2) and is considered to be acceptable:

Paliperidone is a monoaminergic antagonist with a high affinity for serotonergic (5-hydroxytryptamine Type 2A) and dopaminergic Type 2 receptors. Paliperidone binds also to α1-adrenergic receptors, and, with lower affinity to H1-histaminergic and α2-adrenergic receptors. Paliperidone has no affinity for cholinergic, muscarinic orβ1- or β2-adrenergic receptors.

Paliperidone is a chemical entity belonging to the atypical antipsychotic class of psychotropic drugs. It is the major active metabolite of risperidone that is registered worldwide for the treatment of schizophrenia. Paliperidone is a racemate comprised of the enantiomers R078533 (+) and R078544 (-). The pharmacological profiles of the racemate and the two enantiomers are similar in in vitro binding assays, *in vivo* occupancy studies, and *in vivo* functional interaction studies.

Schizophrenia is a complex and severe neurodevelopmental brain disorder with a chronic course resulting in significant long-term morbidity and functional impairment. The lifetime morbidity risk of schizophrenia was estimated to be 7.2 per 1000 individuals. An estimated 1 in 10,000 children and adolescents worldwide develop full (DSM-IV) criteria for the diagnosis of schizophrenia. Furthermore, many young people are thought to have sub-threshold symptomatology well before they meet the formal diagnostic criteria for the disorder.

The onset of schizophrenia often occurs in adolescence, with close to one-third of patients diagnosed with schizophrenia developing their first positive symptoms of psychosis during adolescence. These symptoms are generally similar to those in adults. Schizophrenia has also been described in children but is considered uncommon in patients less than 12 years of age. It has been estimated that only 0.1% to 1% of all schizophrenic disorders present before 10 years of age, with 4% occurring before 15 years of age.

Although the phenomenology and diagnostic criteria are similar in the adolescent and adult populations, an earlier age of onset is associated with a poorer prognosis and a more negative impact of the disease on personality and relationship development, cognitive functioning, educational and work attainment, and social functioning. There is also evidence to suggest a younger age of onset of schizophrenia is associated with a form of the illness that may be more resistant to treatment than adult-onset illness, especially with regard to treatment with typical antipsychotics. As in adults, adolescent-onset schizophrenia is a lifelong illness with no known cure.

1.1. Guidance

The application was preceded by a pre-submission briefing document and subsequent teleconference between a Delegate of the Therapeutic Goods Administration (TGA) and the Sponsor's representatives. The Delegate advised the Sponsor to submit a Risk Management Plan (RMP) pertinent to Australia. An appropriately modified RMP was submitted.

There are no TGA-adopted guidelines relating specifically to schizophrenia. However, there is a general adopted "Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia" (CPMP/EWP/559/95). The Sponsor complied with TGA guidance.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The clinical dossier documented a development program of PK, efficacy and safety studies relating to the proposed extension of indications. The submission was well presented and contained the following clinical information:

Module 1:

Application letter, table of contents, application form, draft Australian PI and CMI, information on experts (nonclinical and clinical), statement regarding individual patient data, overseas regulatory statement, RMP prepared for the European Union (EU). Dataset similarities statement, EU paediatric investigation plan (PIP), therapeutic goods and human embryo statement.

Module 2:

Introduction, nonclinical overview, clinical overview, summary of clinical pharmacology studies, summary of clinical efficacy (SCE), summary of clinical safety (SCS), literature references, synopses of individual studies, table of contents, summary of adverse drug reaction (ADR) determination.

Module 5

- 1 key PK study (PSZ-1001).
- 1 population PK (Pop-PK) analysis (based on 10 adult studies, PSZ-1001 and sparse PK data from PSZ-3001).
- 1 pivotal efficacy/safety study (PSZ-3001).
- 2 ongoing efficacy/safety studies (PSZ-3002* and PSZ-3003).
- Literature references provided for background information.
- No bioavailability or bioequivalence studies were submitted (Module 1.11.1).

  ***Comment:** The Sponsor nominated study PSZ-3002 as pivotal but this evaluator does not agree. In brief, the study does not qualify as pivotal because efficacy is only regarded as a secondary outcome variable, multiplicity is unadjusted for and the OL design, without a comparator or placebo group, may introduce significant bias.

2.2. Good clinical practice

The submitted studies were stated to have been conducted in compliance with Good Clinical Practice and according to appropriate ethical standards.

3. Pharmacokinetics and clinical trials

3.1. Studies providing pharmacokinetic data

The submission included PK data from one Phase I study (25 subjects) and one Pop-PK study, including pooled sampling data from a total of 137 subjects from one Phase III study in the target population and 153 subjects from three Phase I adult trials. Table 1 lists each study.

No PK study had deficiencies that excluded their results from consideration.

Table 1: Pharmacokinetic studies.

PK Topic	Sub-topic	Study ID	N	Primary Aims
PK in children with schizophrenia, schizoaffective disorder and schizophreniform disorder	General PK single-dose multi-dose	PALIOROS-PSZ-1001	25	Dose normalisation
Pop-PK Analysis	Healthy adult subjects/adults with schizophrenia/ Target population	Population PK	315	PK modelling

3.1.1. Study summary: PSZ-1001

This was a multicentre, multi-national, open-label, multiple-dose, Phase I study in children and adolescents (≥ 10 to ≤ 17 years of age) with schizophrenia, schizoaffective disorder or schizophreniform disorder. The clinical conduct of the study was undertaken in an outpatient setting by Johnson & Johnson Pharmaceutical Research between 17 March 2006 and 25 August 2006. This study aimed to characterise the PK of single- and multiple-dose (at steady state) paliperidone in a paediatric population, as well as evaluate its safety and tolerability.

Twenty-five subjects were enrolled into the study from 13 centres; 18 males, 7 females from six countries (Argentina,2; Belgium, 2; Finland, 2; Korea, 5; USA, 8). Their mean (SD) age was 14.6 years (±2.18) with range 10-17 years. Body weight ranged from 31-89kg (median weight 64.5kg). Racially, 56% of subjects were white, 24% black and 20% Asian. Twenty-four subjects completed the study (8, 9 and 7 subjects in groups A, B and C, respectively). PK data were analysed from 24 subjects for the single-dose treatment phase and 23 subjects for the multiple-dose treatment phase. The Sponsor cites four study deviations (16% subjects).

Enrolled subjects were randomised into: Group A, 8 subjects at 0.086mg/kg/day paliperidone equating to 6mg for a 70-kg adult on a mg/kg basis; Group B, 9 subjects at 0.129mg/kg/day paliperidone equating to 9mg; Group C, 8 subjects at 0.171mg/kg/day paliperidone equating to 12mg. Within each dosage group, subjects were randomised (computer-generated by Sponsor) on a 1:1 ratio into either Schedule A or Schedule B PK sampling schemes. Subjects were studied in sequential ascending group order so safety could be evaluated at a lower dosage before proceeding to the next highest dose. Each group entered a screening phase (maximum 21 days) followed by a 2-day single-dose PK and tolerability evaluation phase, followed by a 7-day multiple-dose phase with evaluation of PK and tolerability and finally an end-of-study visit.

3.1.2. Study summary: Population pharmacokinetic analysis

No detailed evaluation of the submitted data was undertaken as the PK data from PSZ-1001 did not support a dosage regimen of 3mg/day, the proposed recommended dosage regimen in adolescents with schizophrenia. Dose normalisation of adolescent data to 6mg/day has little relevance to the proposed clinical dose. See below for more detailed information on the Pop-PK analysis.

3.2. Summary of pharmacokinetics

3.2.1. Pharmacokinetic data in adults

Following a single dose, the plasma concentrations of paliperidone rose steadily to reach peak plasma concentration (Cmax) in approximately 24 hours after dosing. The PK of paliperidone following Invega administration are dose-proportional within the recommended clinical dose range (3 to 12mg).*The terminal elimination half-life (t½) of paliperidone is approximately 23 hours. Steady-state concentrations of paliperidone are attained within 4 to 5 days of dosing in most subjects and the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio approximately 1.6 at steady state. The absolute oral bioavailability of paliperidone following Invega administration is 28%. Based on a population analysis, the apparent volume of distribution (V) is 487 litres. The plasma protein binding is 74% and approximately 80% of radioactive paliperidone was recovered in urine and 11% in faeces. Elimination of paliperidone is reduced with decreasing creatinine clearance. Hence, renal impairment necessitates dosage reduction in all grades of impairment. One week following administration of a single oral dose of 1mg immediate-release 14C-paliperidone, 59% (range 51% - 67%) of the dose was excreted unchanged into urine, 32% (26% - 41%) was recovered as metabolites, and 6% - 12% was not recovered.

*The Sponsor cites study R076477-SCH-1015 in its PIP dated 27 September 2011, claiming dose-proportionality over the range 1.5 to 3mg paliperidone ER in adult men.

3.2.2. Pharmacokinetic data in children and adolescents

Following single-dose administration, paliperidone plasma concentrations rose steadily and peaked approximately 24 hours after dosing. No other single-dose PK results were provided. Steady state was achieved between 4 to 5 days, the paliperidone plasma (+) to (-) enantiomer ratio approximated 1.3 to 1.5 and the fraction of paliperidone in plasma unbound 25.6%. Plasma PK data was normalised to 6mg/day paliperidone. Comparison with adult data showed similar median values between adolescents and adults in terms of Cmax and AUC (23.2 v 21.0 ng/mL and 486 v 396 ng/h per mL, respectively). Furthermore, inter-subject variability of plasma PK parameters (expressed as % CV) ranged from 56 to 66% in adolescents compared to 44 to 52% in adults. The Sponsor reports no demonstrable relationship between plasma exposure and age. Comparison of urinary PK parameter results revealed the apparent clearance (CL/F) of paliperidone in children and adolescents was approximately 22% lower than observed in adults (209mL/min v 268mL/min, respectively). On average, 24.4% of administered dose was excreted unchanged compared with 13.8 to 17.7% in adults. The renal clearance of 42.4mL/min accounted for 20% of the apparent oral clearance of 209mL/min compared to 15% in adults. About 80% of paliperidone renal clearance was through excretion by passive glomerular filtration (33.7mL/min / 42.4mL/min) compared to 59 to 68% in adults. The remaining fraction was cleared by active secretion. The difference in glomerular filtration clearance between adolescents and adults is explained by a higher creatinine clearance (134mL/min median in children and adolescents compared to 116mL/min in adults).

3.3. Population based pharmacokinetic data

The primary objectives of the Pop-PK analysis were to:

- Evaluate the applicability of the originally developed adult model to describe the PK of paliperidone in adolescents;
- Model the PK of paliperidone after administration of the ER formulation to get estimates of typical PK parameters in adolescents (age 12 to ≤17 years) and their inter- and intra-individual variability;

- Evaluate the effects of subjects' demographic characteristics and other covariates on the PK of paliperidone;
- Derive information necessary to make a recommendation on paliperidone ER dosing in adolescents with schizophrenia.

Phase I of the population PK model utilised data obtained from PSZ-1001 (n=25; 18M/7F) and "sparse" PK data from a single Phase III efficacy trial (PSZ-3001; n=137; 87M/50F) in which PK samples were taken on Days 15 and 36 of the 6-week study [target population]. No separate PK data from study PSZ-3001 are presented in this report. A total of 315 subjects were used to develop the model, including 153 subjects from three Phase I adult trials (PALIOROS-SCH-1011, R076477-PO1-1010 and R076477-RE1-1001). These adult studies were specifically chosen to facilitate the evaluation of dose, age and renal function. Study R076477-P01-1010 did not include female subjects.

The PK model was developed through other phases to its final form, using data from nine Phase I and four Phase III trials (including those in the aforementioned paragraph and seven trials attached as part of this submission, namely, R076477-PO1-1005, R076477-SCH-302, R076477-SCH-102, PAL-SCH-101, R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305) making 1368 subjects in total.

After oral dosing, the PK of paliperidone in an adolescent population was best described by an open two-compartment disposition model with linear elimination from a central compartment. The apparent oral clearance (CL/F) was reported to correlate with creatinine clearance and body weight. Age was not reported as a significant covariate of oral clearance.

Estimated PK parameters from the final Pop-PK model for adolescents were reported as comparable to an adult model for paliperidone. However, the adolescent population weighing <51kg had 24% higher plasma exposure (using median Cavg) compared to adults. In an ad-hoc analysis, the Sponsor compared the low-weight adolescent group in the population PK model with those adults weighing less than 51kg (i.e. 58 subjects from 947 of the total population studied) and declared the groups comparable in terms of clearance, but no numerical values are provided. Furthermore, no comment on comparative plasma concentration/exposure was cited.

3.4. Evaluator's overall conclusions on pharmacokinetics

PK parameters for oral paliperidone ER in children and adolescents aged ≥ 10 to <18 years appear to be similar to those found in adults in the dose-range 6 to 12mg/day. Although the PK findings were similar to adults, adolescents had reduced apparent clearance as well as higher plasma exposure in low-weight subjects. Such findings may impact upon the tolerability and safety of paliperidone in an adolescent population.

The PK results do not support a dosage regimen below 6mg/day in children and adolescents. The weight-based dosing schedule employed in study PSZ-1001 appeared to assume older children and adolescents will require a 6mg/day clinical dose i.e. the recommended adult starting dose. This is reflected in the way PK parameters were dose-normalised to 6mg/day. From the CSR, older heavier subjects (80% ≥15 years & 80% ≥51kg) were recruited into the study. The actual dose range employed in this study was 4 to 12mg/day, with only five (20%) subjects (all weighing <51kg) receiving paliperidone <6mg/day. No subject received a 3mg/day dose, the recommended proposed starting paliperidone ER dosage regimen in adolescents. Given paliperidone ER dose-proportionality in adults for the range 3 to 12mg/day (with further evidence down to 1.5mg) and the similarity in PK parameters between adolescents and adults, extrapolation of the results to include a 3mg dosing regimen in adolescents in a clinical setting is proposed. A 3mg/day dosage regimen is not well supported based on the data provided in this report. There is no comparison of the PK of the proposed 3mg daily dose in adolescents

with the 6mg dose in adults. It appears 6mg daily leads to higher exposure and 3mg daily to lower exposure in children and adolescents compared with adults.

The paliperidone paediatric PK study, PSZ-1001, has many significant design flaws. Firstly, it has an ill-defined study base. The selection of 25 subjects from thirteen centres in six countries, only one of which was English-speaking, raises the issue of the standardisation of medical practices across these countries, and the investigators' experiences of schizophrenia and related disorders in a cultural context. Recruitment of subjects from such a wide study base has the potential to introduce significant selection bias into the study. Furthermore, subject numbers were too small to provide high statistical power in the PK parameters measured. Only descriptive statistics were reported. The Sponsor justified this action "in order to limit the exposure in paediatric subjects while providing sufficient data to develop a population PK model". The higher paliperidone dosages this study employed do not support this statement. From earlier statements, it appeared patients were at home during the steady state assessment phase. This raises the possibility of lack of strict adherence to the dosing schedule.

The results of this study need to be interpreted in terms of the dosage study participants received by a Push-Pill formulation (assumed equivalent to OROS). There is no marketed 1mg OROS preparation and patient dosages were rounded to the nearest 1mg, which raises concerns over the suitability of the 1mg tablet and the accuracy of dosing for each individual patient (16 subjects i.e. 64% received the 1mg tablet). The Sponsor provided dissolution data) in support of the use of a 1mg OROS-equivalent tablet formulation. However, examination of the dissolution data reveals a profile that suggests a quicker release of drug for the 1mg tablet compared to the 3mg and 6mg tablets. In the Paediatric Investigation plan (Parts B, C, D and E) dated 27 September 2011, the Sponsor states: "Current OROS technology does not allow reliable production of doses less than 1.5mg". Hence, the findings of PSZ-1001 need to be considered carefully in view of this fact.

The Sponsor did not report upon several key PK parameters in Study PSZ-1001 i.e. elimination half-life and volume of distribution. Furthermore, no single-dose PK parameter results are provided. Such omissions should be justified. These matters are addressed as Section 31 questions.

The proportion of study protocol violations was unreasonably high. Furthermore, eight subjects (equating to more than 30% of total participants) received olanzapine or quetiapine concomitantly. Although no drug interactions with paliperidone have been demonstrated, one cannot rule out the possibility of an effect on the PK and pharmacodynamic properties of paliperidone, as well as the reported AEs.

Despite an adult Pop-PK model that identified lean body mass as a significant predictor of apparent oral clearance of paliperidone, the Sponsor chose body weight (BW) instead. BW was considered a more practical covariate on clearance for dose adaptation in adolescents. The Sponsor cites Reigner and Welker (see References), yet these authors refer to a meta-analysis that showed a linear increase in volume of distribution over systemic availability with lean body weight not body weight *per se*. An accurate assessment of weight is particularly pertinent in paediatric populations. Using BW instead of lean body mass (or lean body weight) appears a crude measure, again questioning the validity and applicability of the study findings. This is the subject of a Section 31 question.

While the Sponsor investigated the higher plasma concentration and lower clearance of paliperidone found in low weight subjects (<51kg) compared with those ≥51kg, no specific analysis by gender was reported. This was despite the recognised effect of female gender on paliperidone pharmacokinetics as declared in the Invega PI: "The apparent clearance of paliperidone following INVEGA administration is approximately 19% lower in {adult} women than men". The latter may be explained largely by gender differences in lean body mass and creatinine clearance, again highlighting the need of applying lean body mass in PK modelling.

No separate PK data from Study PSZ-3001 were presented in this report.

3.4.1. Recommendation

The study objectives of characterising the single- and multiple-dose PK of paliperidone in a paediatric population were only partially met. No single PK data are presented in this report. Furthermore, the multiple dose PK data (at steady state) were only characterised for a 6mg daily dose, not a 3mg daily dose as proposed in the PI. Elimination half-life and volume of distribution data were omitted from this report making it difficult to fully evaluate the submitted data (subject of a S31 question). The 3mg/day dosage regimen in the proposed PI is not based on the submitted PK data or other paediatric dose-ranging paliperidone studies. The Sponsor justifies its proposed regimen based on PK data from risperidone in children and adolescents, as well as paliperidone dose-proportionality studies in adults. This evaluator suspects the AUC at the proposed 3mg/day dose will be substantially lower for most children and adolescents, depending most on their body weight. In addition, the mechanism for the apparent reduction in active secretion of paliperidone in children and adolescents has not been explored. Caution is required when extrapolating data from other sources.

This evaluator would recommend rejection of the proposed extension of indications for paliperidone use in adolescents with schizophrenia, if such indication relied solely on the submitted PK data. Even though the Sponsor failed to provide a dose-ranging study in adolescents or demonstrate similar PK to adults at doses below 6mg/day, the risk to the adolescent subject, provided they do not have renal impairment, is not regarded as high by this evaluator. Adult data clearly demonstrates consistency in PK parameters from 3-12mg/day. Furthermore, based on PK data from risperidone in children and adolescents, this evaluator is confident the risk of administering paliperidone ER to the 15-17-year age-group (representing 80% of the study population) is acceptable, especially given the lower expected toxicity for a 3mg/day dosing regimen.

4. Pharmacodynamics

No new pharmacodynamic data are included in this submission.

5. Dosage selection for the pivotal studies

The following justification for dosing in the pivotal efficacy study, PSZ-3001, was provided in the Sponsor's Paediatric Investigation Plan (Parts B, C, D and E; Module 1.12).

- Based upon Study PALIOROS-PSZ-1001 (Part D.1.5), the single- and multiple-dose pharmacokinetics of paliperidone in paediatric subjects (10-17 years of age, inclusive) are in the same range as adults. The study also showed that the safety profile of paliperidone ER in paediatric subjects was similar to that observed in adults: Paliperidone ER was well tolerated in doses up to 12 mg in both populations. Doses starting with paliperidone ER 3 mg administered once daily have been shown to be effective in adults with schizophrenia.
- Recently, a pharmacokinetic study (Study R076477-SCH-1015,) was completed to assess the dose proportionality of the 1.5- and 3-mg doses of paliperidone ER. Both doses were well tolerated by adult men. Dose proportionality was shown from paliperidone ER 1.5 to 3 mg for Cmax and area under the curve extrapolated from time zero to infinite time (AUC∞). In the previous Phase 1 Study R076477-P01-1010, dose proportionality was shown over the 3- to 15-mg dose range. Hence it can be concluded that all doses between 1.5 and 15 mg behave in a dose-proportional manner.
- Based upon the combined pharmacokinetic and tolerability dose range data from these studies and the efficacy and safety data from the Phase 3 studies in adults, the Applicant

intends to study paliperidone ER 1.5 to 12 mg daily for the efficacy and safety Study R076477-PSZ-3001 and the long-term safety Study R076477-PSZ-3002.

- The doses (1.5-12 mg/d) selected for the paediatric studies will allow exploration of the entire dose range and determination of the benefit-to-risk ratio at each dose level. Maximum exposure to paliperidone observed in Study PALIOROS-PSZ-1001 was comparable to exposure at the doses established to be safe in adults (Part D.1.5). In risperidone paediatric studies (Part B.2), the maximum dose (6 mg/d) of risperidone was equivalent to paliperidone ER 18 mg/d and was well tolerated. Thus, while the maximum possible doses (6 mg for a 29 kg subject [0.2069 mg/kg], and 12 mg for a 51kg subject [0.2353 mg/kg]) in Study R076477-PSZ-3001 slightly exceed the maximum dose (0.171 mg/kg) used in Study PALIOROS-PSZ-1001 on a milligram per kilogram basis, they are within the limits of safety established for paliperidone ER. Study results will include analysis of exposure based on weight that will allow us to maximize the risk-benefit ratio for dose recommendations.
- The Applicant considered lowering the dose to a maximum of 0.171 mg/kg for the low-weight paediatric group; however, on reviewing data in adults weighing between 30 and 50 kg, there was no difference in the incidence or severity of adverse events between subjects of low weight and high weight. While there was a dose-dependent increase in adverse events, it was not dependent on weight. Furthermore, paliperidone ER studies in adults included doses from 3 to 15 mg. The 15 mg dose did not have a significant therapeutic advantage over the 12 mg dose; however, there was an increase in adverse events at the higher dose. The maximum recommended dose of paliperidone ER in adults is 12 mg.
- Dosing on a milligram per kilogram basis is generally recommended for young paediatric patients or infants, using liquid preparations for improved accuracy. The Applicant is planning to recruit adolescents with a majority of patients in the adult weight range, where fixed dosing is preferable.

Study drug was taken in the morning, standardised in relation to food intake. That is, the patient was instructed to always take the study drug in the fasting state in the morning or always take it with breakfast. Invega must be swallowed whole, not chewed, divided or crushed.

> **Comment:** There are no formal dose-ranging studies for paliperidone in paediatric or adolescent subjects. Given a half-life approximating 24 hours, the dose-interval is appropriate for the pivotal study. The proposed PI cites 3mg/day as the recommended dose in adolescents (12-17 years of age). Dosage selection based on adolescent PK data only applies to the 6-12mg/day range (similar to adult PK data). This is discussed further in the section on benefit-risk analysis.
>
> Given "The Applicant is planning to recruit adolescents with a majority of patients in the adult weight range, where fixed dosing is preferable" this raises a question of selection bias at the screening phase of the pivotal study. The Sponsor did not provide further details on this aspect of subject recruitment.

6. Clinical efficacy

6.1. Schizophrenia in adolescents (12-17 years of age)

6.1.1. Pivotal efficacy study: study psz-3001

6.1.1.1. Study design, objectives, locations and dates

The study design was a 6-week Phase III, randomised, multicentre, multinational, double-blind, weight-based, fixed-dose, parallel-group, placebo-controlled trial conducted in an outpatient setting at 35 centres in five countries (see Table 2, below).

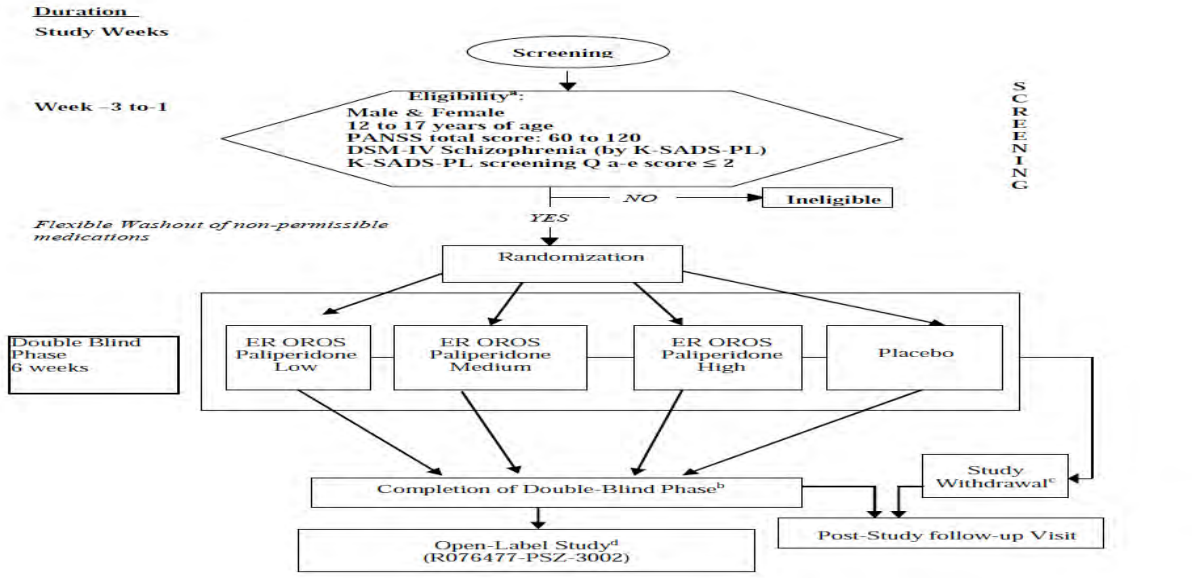
The primary objectives were to evaluate the efficacy, safety and tolerability of three weight-based, fixed-dose groups of extended-release paliperidone compared to placebo in adolescent subjects 12 to 17 years of age, inclusive, with schizophrenia.

Table 2: Subject Recruitment by Country and Centre

Country	Number of Centres	Number (%) of patients recruited
Russia	12	82 (41)
India	7	45 (23)
Ukraine	6	34 (17)
Romania	1	10 (5)
US	9	30 (15)
Total	35	201

The secondary objectives were to: assess the change in the global impression of severity of illness associated with the use of paliperidone compared to placebo as measured by the Clinical Global Impression-Severity Scale (CGI-S); assess the benefits in psychological, social and school functioning associated with treatment with paliperidone compared to placebo as measured by the Children's Global Assessment Scale (CGAS); assess the effect on sleep associated with treatment with paliperidone as measured by the sleep Visual Analog Scale (VAS); explore the PK of paliperidone; explore the relationships between its PK and results of efficacy parameters (e.g. Positive and Negative Syndrome Scale [PANSS]) and safety parameters (including extrapyramidal symptoms [EPS] and AEs) of interest.

Figure 1: Design for Study PSZ-3001



The study consisted of a screening phase (up to 21 days) followed by a double-blind (DB) post-randomisation phase (6-weeks duration) with an end-of-study or early-withdrawal visit and a one-week follow-up visit for subjects who did not enter an optional long-term OL study, PSZ-3002.

The study was sponsored by Johnson & Johnson Pharmaceutical Research & Development, LLC; the Sponsor's parent company. The coordinating investigator was located at the Children's National Medical Center, Washington DC, USA. The study was initiated on 8 August 2007 (first subject enrolled) and completed on 30 March 2009 [Document No.: EDMS-PSDB-9999235:3.0]. The study protocol and single amendment were reviewed by an independent ethics committee or institutional review board. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and undertaken in compliance with Good Clinical Practices (including the archival of essential documents) and applicable regulatory requirements. Subjects or their legally acceptable representatives provided written consent to participate in the study.

6.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included: male or female between 12 and 17 years of age, inclusive. (The subject could become 18 years of age during the study but should have been 17 years of age at the time of random assignment); weigh at least 29kg; diagnosed with schizophrenia according to the DSM-IV (295.10, 295.20, 295.30, 295.60 and 295.90) at least one year before screening. The diagnosis was established using the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL), including all supplements. Subjects should have had at least one adequate treatment with an antipsychotic before participation in this study; must have had a PANSS total score between 60 and 120, inclusive, at screening and baseline, and must not have been a danger to themselves or others, and must have 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 behaviour, must have had a score of no more than two for each item. The full inclusion and exclusion criteria are provided in the submission.

The exclusion criteria included: history or presence of circumstances that could have increased the risk of the occurrence of torsades de pointes or sudden death in association with the use of drugs that prolong QT interval corrected for heart rate (QTc); subjects with a known or suspected history of seizure disorder, neuroleptic malignant syndrome (NMS), encephalopathic

syndrome, tardive dyskinesia (TD), or insulin-dependent diabetes mellitus; presence of any significant or unstable cardiovascular, respiratory, renal, hepatic, haematologic, endocrine, immunologic, or other systemic disease; had active and clinically relevant hypothyroidism or hyperthyroidism unless stabilised on appropriate medications for three months; history of severe pre-existing gastrointestinal narrowing (pathologic or iatrogenic) or an inability to swallow oral study drug with the aid of water; evidence of clinically significant hepatic disease (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] more than two times the upper limit of normal) at screening and subjects experiencing their first psychotic episode.

6.1.1.3. Study treatments

ER Paliperidone was supplied as capsule-shaped longitudinal compressed tablets in 1.5, 3, 6 and 12mg dose strengths based on the proprietary osmotic pump technology (OROS). The Placebo capsules looked identical in size, colour and shape.

Eligible subjects were randomised into one of four treatment groups (Placebo, paliperidone ER Low, the "Low group", paliperidone ER Medium, the "Medium group" and paliperidone ER High, the "High group"). Dosing of paliperidone depended on baseline bodyweight. The Table below shows the weight-based, fixed-doses administered for each randomisation dose group. Paliperidone ER or Placebo was taken daily before 10 a.m.

Table 3: Weight-Based Fixed-Dose Treatment Groups for Study PSZ-3001

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

Prior and concomitant therapy

The use of any concurrent medication (prescription or over-the-counter, OTC) from screening through the treatment phase was recorded on the relevant case report form (CRF) along with the reason for treatment. Concurrent enrolment in another clinical investigational drug study was prohibited. For a concomitant medication given as a treatment for a new or worsening condition, the condition was documented on the adverse event form of the CRF. The Sponsor had to be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies were administered.

Permissible medications included: oral lorazepam 0.25 to 2mg (up to 3mg/day or an equivalent dosage regimen for an alternative benzodiazepine if lorazepam not available) could be used for agitation, anxiety or sleep difficulties that occurred during the screening or washout period and the first three weeks of the DB treatment period. None were allowed between Weeks 3 and 6. A sedating antihistamine could be used instead of a benzodiazepine but not during the 8 hours preceding any behavioural assessment. Beta-adrenergic blockers, with the exception of propranolol, were not allowed during the study. Propranolol was to be initiated during the DB treatment period only for treatment-emergent akathisia and recorded in the CRF. The Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) and the Simpson-

Angus Scale (SAS) had to be administered before the initiation or change in the dose of medication for akathisia. Antiparkinsonian drugs (e.g. anticholinergics or antihistamines) could only be initiated during the DB treatment period after treatment-emergent EPS occurred. Oral benztropine 1 to 2mg twice daily or biperiden 2mg three times a day was permitted for the treatment of EPS and this was recorded in the CRF. The AIMS, BARS and SAS had to be administered before the initiation or change in the dose of medication for EPS.

Permissible interventions: subjects could not receive insight-oriented (psychodynamic, psychoanalysis) or cognitive-behavioural therapies during this study. Those subjects treated on an inpatient basis could participate in the usual therapeutic activities of the ward. If a subject had ongoing therapy before entering the study, they could continue this therapy.

Prohibited medications included: anti-depressants (for mood disorder, anxiety disorders, sleep disorders or for smoking cessation); lithium; antipsychotics other than study drug; psychostimulants or other dopamine agonists such pramipexole and modafinil; anticonvulsants such as valproate, carbamazepine and lamotrigine; cholinesterase inhibitors, antiparkinsonian or antidyskinetic drugs other than those permitted; sedatives, hypnotics and anxiolytics other than permitted rescue medication (lorazepam or its equivalent) in the first 3 weeks of the DB phase; beta-adrenergic blockers other than those permitted and other psychotropic agents including OTC St. John's Wort, gingko biloba, kava kava, carnitine and coenzyme q10.

Pharmacokinetic sampling

No formal PK study was planned. The data collected from this study was used in a population PK model for adolescents. One venous blood sample was taken at baseline to determine plasma concentrations of paliperidone enantiomers and two samples (one pre- and post-dose) on visits four and seven. The Sponsor's pharmaceutical bioanalytical laboratory performed PK data analyses, whereas a central laboratory analysed serum chemistry, haematology and urinalysis.

6.1.1.4. Criteria for discontinuing from the study

A subject was discontinued from the study if: the subject was lost to follow-up; the subject's parent or legal guardian withdrew consent (or the subject withdrew assent); the investigator believed that for safety reasons (e.g. an adverse event occurred) it was in the best interest of the subject to stop treatment; the subject became pregnant; the subject did not comply with protocol requirements; the investigator broke the treatment blind for the subject, and lack of efficacy. The reason for withdrawal from the study was documented on the CRF. Subjects who withdrew were not replaced.

At the discretion of the investigator, a subject could be discontinued for lack of efficacy (recommended criterion: minimum increase from Day 1 [baseline] of 20% in PANSS total score). Subjects could be withdrawn from the study after 21 days of the DB period for lack of efficacy and enrolled in the optional OL safety study, PSZ-3002, if it was believed the subject could benefit from participation in this study.

6.1.1.5. Efficacy variables and outcomes

The primary efficacy endpoint was the change in the PANSS total score (sum of the scores of all 30 PANSS items) from baseline to the last post-randomisation assessment in the DB period (i.e. the endpoint is the last observation carried forward, LOCF), excluding the follow-up visit. The PANSS was administered as a semi-structured interview by an adequately trained clinician, qualified in PANSS by the Sponsor. Wherever possible, for each subject, the same person administered this scale at all visits.

Pre-specified subgroup analyses planned for the primary efficacy endpoint were: age (12-14, 15-17 years); sex (male, female); race (white, black, Asian) and geographic region [US, Eastern Europe, Asia].

The secondary efficacy and other endpoints were: the change from baseline to endpoint in the CGI-S score; CGAS score; sleep VAS score (quality of sleep and daytime drowsiness); PANSS Marder factors and subscales; onset of therapeutic effect* and responder rates.**

*The onset of therapeutic effect for a given dose regimen was defined as the first time point at which a given treatment group (each dose of paliperidone versus placebo) was different (at the 2-sided nominal 5% level of significance) and remained statistically significantly different thereafter until endpoint, based on the change from baseline in the PANSS total score.

**Responder rates were defined as those subjects who showed a 20% or more reduction from baseline to endpoint (Day 43 or LOCF) in the PANSS total score. The percent change of PANSS was defined as 100*[change/(baseline-30)], as 30 points is the lowest possible score for the PANSS total score. This variable was analysed using the Cochran-Mantel-Haenszel test, controlling for country. A separate analysis was performed that defined response as a 30% or greater reduction from baseline in the PANSS total score.

> **Comment:** The primary and secondary endpoints are satisfactory. These endpoints are considered reliable measures of clinical benefit in patients with schizophrenia. The efficacy endpoints meet the relevant TGA adopted guideline relating to the clinical assessment of schizophrenia [CPMP/EWP/559/95]. The other efficacy endpoints and subgroup analyses of the primary efficacy endpoint are considered exploratory. Possible lack of interviewer blinding to study treatment, use of a semi-structured interview and the possibility of using different interviewers for the same subject have the potential to introduce measurement bias.

6.1.1.6. Sample size

The study stated the sample size of 200 subjects (50 subjects in each of four blinded groups) calculation assumed the standard deviation (SD) of the change from baseline to endpoint in PANSS total score of 20 points, based on clinical study results with paliperidone in adult schizophrenia. Approximately 49 subjects per dose, who have a 6-week LOCF/endpoint PANSS total score assessment, were required to detect a clinically relevant difference of 13.2 points between any paliperidone ER dose group compared with Placebo in the change from baseline in PANSS total score, applying Dunnett's adjustment for multiplicity (2-sided familywise α level of 0.05 with approximately 80% power). The number of randomised subjects was adjusted to 50 in each of the four dose groups assuming approximately 2% of randomised subjects will discontinue before providing any post-baseline PANSS total assessment.

> **Comment:** The assumptions on which the calculation of sample size is based are acceptable.

6.1.1.7. Randomisation and blinding methods

The following justification for randomisation and blinding was provided in the Sponsor's CSR:

Random assignment was used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) were evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double blinding was used during the 6-week treatment period (i.e., subjects, parents, legal guardians, investigators, and the sponsor remained blinded to the study drug) to reduce potential bias during data collection and evaluation of clinical endpoints. Tablets containing different dose strengths of paliperidone ER and tablets containing placebo were identical in appearance.

Subjects were randomly assigned to 1 of 4 treatment groups (placebo, paliperidone ER Low, paliperidone ER Medium, and paliperidone ER High) based on a computer-generated randomization schedule (Appendix 2.1) prepared by the sponsor before the start of the study. The randomization was balanced by using permuted blocks of treatments and was stratified by study center.

Central randomization was implemented in conducting this study. The randomization code and treatment code were assigned using an interactive voice response system (IVRS). The investigator was not provided with randomization codes. The codes were maintained within the IVRS, which had the functionality to allow the investigator to break the blind for an individual subject.

Under normal circumstances, the blind was not to be broken until all subjects completed the study and the database was finalized. Otherwise, the blind was broken only if specific emergency treatment was dictated by knowing the treatment status of the subject. In such cases, the investigator had to contact the sponsor. If the investigator was unable to contact the sponsor, the investigator could in an emergency determine the identity of the treatment by telephoning the IVRS. Individual code breaks by the investigator resulted in withdrawal of the subject from the study. The sponsor had to be informed as soon as possible. The date, time, and reason for the unblinding had to be documented in the appropriate section of the CRF and in the source document.

> **Comment:** The randomisation was conducted by the Sponsor not by an independent statistician. This has the potential to introduce bias. The randomisation schedule does not appear truly random to this evaluator. Blocks of sequential subject numbers allocated to particular centres exhibit a consistent pattern whereby every group of four subjects allocated has one subject assigned to each of the treatment arms. A sub-optimal randomisation process may fail to achieve distribution of known and unknown confounders across treatment groups, thereby skewing the observed data away from a true effect of treatment. The validity of an interactive voice response system to assign randomisation and treatment codes has not been determined by the Sponsor.

6.1.1.8. Statistical methods

The intention-to-treat (ITT) population was used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics. The ITT population included the assigned randomised, weight-based, fixed-dose treatment group who received at least one dose of study medication during the DB treatment phase and had a baseline and at least one post-baseline assessment on any of the following scales: PANSS total score, CGAS, CGI-S or sleep VAS. The safety population included all subjects in the randomised population who received study medication.

The overall type I error rate for testing all paliperidone ER dose groups versus Placebo for the primary endpoint was controlled at the 2-sided 0.05 significance level. A closed testing procedure using Dunnett's test adjustment was used to identify effective dose groups while adjusting for multiplicity in testing the three paliperidone ER dose groups against Placebo for the primary efficacy variable (change in PANSS total score at endpoint). Treatment effects were estimated based on least-squares (LS) means of the difference using an ANCOVA model with treatment and country as factors, and baseline PANSS total score as a covariate. Unadjusted 95% confidence intervals (CI) are presented for the difference in LS mean change between each paliperidone ER dose group and Placebo.

At endpoint, possible interactions between treatment and country, and treatment and baseline PANSS total score included in the ANCOVA model were explored. Any observed interaction (significant at the 0.10 level) was further evaluated to assess and explain the nature of the interaction. In addition, interactions between region (US vs. Non-US) and treatment were further explored. Significant interactions were also examined using a two-sided Gail-Simon test, with a 0.10 significance level. This is a likelihood ratio test for the null hypothesis of no qualitative interaction (where qualitative interaction means the treatment effects in all subgroups are not in the same direction). An ANCOVA model was used to determine the consistency of treatment effect within each bodyweight category (<51kg, ≥ 51kg), without adjustment for multiplicity.

For each time point (both LOCF and observed case), descriptive statistics were produced on the PANSS total score and change from baseline. In addition, to explore the course of treatment effect over time, ANCOVA models on both LOCF and observed case data were performed for each time point using the same factors as mentioned above for the primary endpoint, without adjustment for multiplicity. For secondary and other endpoints (including exploratory post hoc analyses by actual dose taken and pair-wise comparison between the three active treatment groups), no adjustment for multiple testing was planned, and each comparison between treatment groups was carried out at a nominal alpha of 0.05.

To assess the sensitivity of the results, a repeated measures mixed effects model (MMRM) was carried out on the observed data. Change from baseline over time was modelled using a mixed effects model with time, country, treatment, and time-by-treatment interaction as factors and baseline PANSS total score as a covariate. An unstructured variance-covariance matrix was employed. Appropriate contrasts were used to determine the CI of the difference between paliperidone ER dose groups and Placebo at endpoint. In case of convergence problems, simpler variance-covariance structures were considered (e.g. Cholesky root parameterisation). The selection of any of these structures was determined after exploration of the observed correlation structure. To further assess the robustness of the results, a sandwich estimator of the standard error of the fixed effects parameters was used.

Subjects who discontinued early due to lack of efficacy had a worst rank analysis performed, for robust interpretation of the primary efficacy data. Such withdrawal indicates no improvement, or a worsening of condition thus leading to informatively missing data at the endpoint (Day 43). In the worst rank analysis, subjects who discontinue due to lack of efficacy were assigned a rank that represents a "worst-rank score" relative to those actually observed. These ranks reflect the relative inverse ordering of the actual times to discontinuation, so the earlier times of withdrawal can be assigned a worse ranking than the later points in time.

> **Comment:** The statistical methods and statistical analysis plan are considered to be satisfactory. The methods are conventional and appropriate. Apart from the primary efficacy variable, all over analyses performed did not adjust for multiplicity and therefore have limited usefulness in assessing efficacy. Similarly, post hoc and other exploratory analyses have limited usefulness in assessing efficacy. The Sponsor's ITT population represents a "modified ITT" (MITT) one as the results do not represent treatment-by-randomisation-alone. The MITT has the potential to strengthen any observed treatment-effect from study medication compared to an unmodified ITT analysis set.

6.1.1.9. Participant flow

The eligible population comprised 228 subjects. Twenty-seven subjects (12%) failed the screening phase (one from an AE but no further explanation is provided for the remaining 26 subjects). The study population included 201 subjects randomised to four treatment groups. One subject randomised to receive paliperidone ER High treatment was excluded from the ITT analysis set (no explanation provided). Hence, 200 subjects comprised the MITT analysis set. All randomised subjects received at least one dose of study medication and were included in the safety analysis set.

Thirty-one percent of the study population failed to complete the study (n=63). Most study withdrawals were due to lack of efficacy of study treatment (63% as per Sponsor review). Furthermore, most study withdrawals occurred in the Placebo and Low treatment groups (49% and 35%, respectively), lack of efficacy comprising 80% (n=20) and 74% (n=14) of these, respectively. The reasons for study withdrawal are provided in the submission data.

Protocol deviations

Major protocol deviations were reported in 21% (n=42) of all subjects in the MITT analysis set, ranging from 16% (n=8) in the Placebo group to 27% (n=13) in the Medium group. Use of

excluded medication, investigator mistakes (i.e. study duration > 43 days) and safety assessment accounted for most deviations (7% each total). Generally, protocol deviations were evenly distributed across treatment groups.

Treatment compliance

Drug logs of investigational tablets dispensed and returned were maintained throughout the study period. Qualified site personnel administered study drug when a subject was hospitalised, and dispensed study drug as capsules in blister cards for administration by a parent or legal guardian when a subject was an outpatient. A subject's parent or legal guardian was instructed to keep missed and unused study drug capsules on the blister card and to return all blister cards (used or unused) to the study centre. Compliance was assessed by the number of tablets taken by a subject compared with the number of tablets the subject should have taken. Across treatment groups, total mean compliance was 99.1% (range 98.7 to 99.6%) and median compliance in all groups was 100%. Treatment discontinuation because of dosing noncompliance did not occur.

> **Comment:** The differential withdrawal of approximately half the placebo (i.e. control) population and an overall withdrawal rate in excess of 30% may introduce significant bias into the results.
>
> Subject disposition over time revealed many study withdrawals occurred in the Placebo and Low treatment groups between Days 21 and 28 (inclusive) after DB commencement (n=14, 56% and n=9, 47%, respectively). The Sponsor has not provided further details of these withdrawals, in particular reason for withdrawal and those subjects who then entered the open label safety study, PSZ-3002 [Section 31 question]. Given a key entry criterion for study PSZ-3002 required completion of at least 21 days of the pivotal efficacy study, and the large number of withdrawals for the Placebo and Low treatment groups in the fourth study week, this evaluator is concerned investigator bias may have played a major factor in selecting patients out of the pivotal study. For example, review of the PANSS total scores over time by country revealed most study withdrawals from Days 22 to 29 (inclusive) occurred in Russian and Ukrainian centres (50% and 33% in the Placebo group, respectively; 44% and 33% in the Low group, respectively). Furthermore, subject withdrawals from these countries showed minor changes to subsequent mean PANSS total scores for those continuing in the DB phase, suggesting the most ill subjects were not necessarily being withdrawn from the study from lack of efficacy. Interestingly, a high percentage of Ukrainian subjects withdrew in Week 4, yet this group had the lowest baseline PANSS total score across all countries while Romanian subjects (albeit small numbers), had approximately a mean baseline PANSS total score 20 points greater than Ukrainian subjects yet had a minimal withdrawal rate across the entire study duration. This evaluator has requested (under Section 31 of the Act) further details to ascertain whether study investigators (and subjects) were blinded to the knowledge of the concurrent open-label study and its entry criterion of completion of at least 21 days of study PSZ-3001, to more fully determine the role of investigator/selection bias.
>
> Mean treatment compliance > 99% seems unreasonably high in view of this primarily outpatient-based study, in a challenging population. No other objective/pharmacokinetic measure was undertaken to monitor treatment adherence.

6.1.1.10. Baseline data

The baseline demographic characteristics of the treatment groups were well balanced in terms of mean (SD) age 15.4 years (1.53), race (61% white, 24% Asian), mean baseline (SD) weight 59.8kg (15.76), mean baseline (SD) height 164.8cm (10.70), mean baseline (SD) waist circumference 75.3cm (13.85), baseline smoking status (88% non-smokers), mother's and father's ages. Mean baseline BMI was similar across the groups except Placebo had less

overweight and obese subjects. The 12-14 year-olds accounted for 27% of the study population with the Placebo group under-represented (18%). Males accounted for 59% of the study population and were under-represented in the Placebo and Low treatment groups, the converse for female subjects. While overall body-weight (BW) category (<51kg or ≥51kg) was similar across all groups (31% and 69%, respectively), there were age and gender differences when stratified. The low BW category had similar mean age across treatment groups but there was a predominance of female subjects (58%). The Medium group (n=16) was over-represented in 12-14 year-olds (n=8) and the High group under-represented. This group all had a normal BMI. The high BW category had similar mean age across treatment groups but there was a predominance of male subjects (66%). This category represented 80% of 15-17 year-olds and 58% of 12-14 year-olds, a taller population (mean height 168.8cm compared to 156.0cm), a heavier population (BMI revealed 18% subjects overweight and 7% obese) and a lower proportion of Asian subjects (10%) than the low BW category (53%). There were markedly less 12-14 year-olds in the Placebo group (8%) compared to the other three treatment groups (range 22-26%). Furthermore, females were over-represented in the Placebo group (51%) compared to the other treatment groups.

The baseline disease characteristics of the treatment groups were well balanced in terms of schizophrenia diagnosis (71% paranoid type), except the Medium group had proportionately more disorganised and less undifferentiated types. Mean (SD) age at diagnosis of schizophrenia of 12.9 years (2.64) while being similar across all groups, this evaluator noted the age of diagnosis ranged from 3 to 16 years. This issue is the subject of a Section 31 question and will be discussed elsewhere in the report. Mean (SD) baseline PANSS total score 91.1 (13.03) was similar across groups as was the mean (SD) CGAS score of 47.8 (11.54). While the baseline CGI-S scores were similar across groups, the Medium group had fewer subjects with moderate illness than other groups and more subjects with marked and severe illness. The mean baseline CGI-S revealed a majority of subjects had moderate (50%) or marked (37%) scores indicative of active psychosis at study entry. In terms of previous hospitalisation rates for psychosis, 41% subjects had never been hospitalised (48% in the Low group) prior to study enrolment, implying diagnosis was made in an outpatient setting in many cases. The Sponsor did not present family history of schizophrenia data [Section 31 question].

> **Comment:** Generally the baseline demographic and disease characteristics were well balanced across the treatment groups. Of note, 12-14 year olds were under-represented (27% of study population). Given the study population of 201, it is doubtful whether the study was powered to demonstrate differences in efficacy between 12-14 year-olds and 15-17 year-olds. As such, the generalisability of the study findings in relation to Australian 12-14 year-olds is doubtful. Given the rise in childhood obesity and body mass index (BMI) in Australia, the study population in PSZ-3001 may not be representative of Australian adolescents.

6.1.1.11. Results for the primary efficacy outcome

The results for PANSS total score (the primary efficacy endpoint) in the MITT population are summarised below in Table 4 (as per Sponsor). The primary efficacy outcome was a statistically significant response in the Medium group (-17.3, p=0.006, CI -16.58 to -3.67) compared to Placebo (-7.9). A negative result means an improvement in function i.e. the more negative values represent greater improvement. Neither the Low nor High treatment groups achieved statistical separation at the 0.05 level versus Placebo, although the High group had borderline significance (-13.8, p=0.086, CI -13.07 to -0.09).

- In an exploratory pair-wise comparison, only the Medium group to Low group comparison demonstrated statistical separation (p=0.014).

- Sub-group analyses of the primary efficacy variable by age, gender, race and geographic region are presented in the dossier. These are descriptive analyses with unadjusted CIs. The subject numbers were too small to allow meaningful observations to be made.
- The Sponsor undertook a planned treatment-by-baseline category analysis and did not find an interaction at the pre-determined10% level (p=0.197), with no adjustment made for multiplicity.

Table 4: Results of Primary Efficacy Variable (PANSS total score) for Randomised Treatment Groups

	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. P values associated with closed testing procedure using Dunnett's test.
[b] The 95% confidence intervals are unadjusted for multiplicity.

- The Sponsor undertook a planned treatment-by-baseline bodyweight category analysis and found an interaction at the pre-determined10% level (p=0.0815). Information was provided on the descriptive statistical representation of change in PANSS total score from baseline to endpoint (LOCF) for those subjects weighing less than 51kg and those weighing at least 51kg. In those weighing < 51kg, the PANSS total score in the Placebo group had a greater reduction than those ≥51kg (-14.4 v -5.4, respectively). Furthermore, only the Medium group achieved a greater reduction than Placebo (-19.0 v -14.4) in the low BW category. In those weighing at least 51kg, all active groups achieved greater reductions than Placebo (-8.8 v -16.5 v -16.3 v -5.4 for Low, Medium, High and Placebo groups, respectively). All three paliperidone ER groups were further evaluated using a 2-sided Gail-Simon test. The Sponsor reported the latter analysis showed insufficient evidence to indicate a qualitative treatment-by-baseline weight category interaction.
- The Sponsor undertook a planned treatment-by-country category analysis. In non-US subjects (representing 85% of the study population), the mean change from baseline in PANSS total score was -4.4 in the Placebo group, -8.8 in the Low group, -16.5 in the Medium group and -11.3 in the High group. These reductions are less than that achieved in the US population across all treatment groups yet the Sponsor claims not to have found any treatment-by-country category interaction at the pre-determined 10% level (p=0.439, with no adjustment for multiplicity) and implies the US findings are an anomaly inherent in the US population with schizophrenia.

The distribution of PANSS total scores for each treatment group by country is shown in Table 5 below. Of note, the mean baseline PANSS total score was similar across individual countries, mean baseline PANSS total score ranged from 84.0 in Ukraine to 112.7 in Romania and there were a wide range of PANSS total scores at endpoint (LOCF) in each treatment arm too. There were few consistent findings between countries. In the US, only the High group achieved a

greater reduction in PANSS total score than Placebo, although the size of the reductions in the Low and Medium groups were considerable compared to those achieved in most of the corresponding groups from the other four countries.

Table 5: Distribution of PANSS Total Score for each Treatment Group from Mean Baseline (B) to End-Point (EP; LOCF) by Country

	Placebo			Low			Medium			High		
Country	**B**	**EP**	**Δ**	**B**	**EP**	**Δ**	**B**	**EP**	**Δ**	**B**	**EP**	**Δ**
India	91.1	83.7	-7.4	89.2	71.1	-18.2	88.8	68.8	-20	93.6	87.6	-6
Romania	105	105	0	104	93	-11	105	94	-11	112.7	97.3	-15.3
Russia	89.8	85.2	-4.6	92.5	88.6	-3.9	89.7	74.1	-15.6	87.8	76	-11.8
Ukraine	84	83.3	-0.8	85.8	78.9	-6.9	88.8	72.5	-16.3	87	72.1	-14.9
US	94.6	70.4	-24.1	96.9	81.5	-15.4	92.5	69.8	-22.7	96	65.2	-30.8

Δ - change

Comment: The study met its primary endpoint at the pre-specified level only in the Medium treatment group. The mean difference in PANSS total scores between the Medium and Placebo groups was 9.4 points. While statistical significance was achieved in the Medium treatment arm, the clinical significance of this finding is questionable given the pre-defined criterion of a difference of 13.2 points. This evaluator considers any dosage recommendations in the PI should be based on the Medium group sub-population i.e. 3mg/day for subjects <51kg and 6mg/day for subjects ≥51kg. This matter is discussed further in the Section on benefit-risk assessment.

Sub-group analyses by age-group, gender, race and geographic region failed to provide any meaningful findings. The stratification groups were too small and the study lacked sufficient power to draw meaningful associations between them. The Sponsor has not provided any convincing evidence of efficacy in the younger age-group, 12-14 years. Furthermore, treatment-by-baseline bodyweight category and treatment-by-country category interactions cannot be ruled out. These factors may give rise to study bias.

Given US subjects have similar demographic characteristics to the Australian population compared to other participating countries; this evaluator is concerned the US findings appear to have been regarded as a US anomaly for the study population rather than a true treatment effect (i.e. lack of efficacy in this study). This matter is discussed in Section on benefit-risk assessment.

6.1.1.12. Results for secondary and other efficacy outcomes

The results for secondary and other efficacy variables were summarised in the dossier. Note: The results are descriptive or exploratory in nature with no adjustment for multiplicity:

- CGI-S analysis revealed a median decrease of -1.0 (indicating clinical improvement) from baseline in the Medium ($p<0.0001$) and High groups ($p=0.021$) compared to Placebo. The higher median baseline in the Medium group indicates more severe subjects.
- CGAS analysis revealed a mean increase from baseline (indicating functional improvement) in all groups although only the Medium group achieved statistical separation against Placebo ($p<0.0001$), with the High group achieving borderline statistical significance ($p=0.067$).

- Sleep VAS analysis revealed improvement in sleep quality in the Medium and High groups versus Placebo ($p<0.001$ and $p=0.003$, respectively) with a tendency to significance in the Low group ($p=0.058$) and slight worsening in the Placebo group. In daytime drowsiness, there were no statistically significant effects of any paliperidone dose.
- Responder rate analysis: A reduction of at least 20% in the PANSS total score occurred in a significantly higher percentage of subjects in the Medium and the High groups than Placebo (64.6%, $p=0.001$ v 51.1%, $p=0.043$ v 33.3%, respectively). At the 30% level, only the Medium group achieved statistical separation compared with Placebo (45.8% v 27.5%, $p=0.031$).
- PANSS factors and subscale analysis revealed an improvement from baseline to endpoint (LOCF) in PANSS positive symptoms in the Medium and the High groups compared to Placebo ($p=0.003$ and $p=0.033$, respectively).While the Medium group achieved statistical separation against Placebo for negative symptoms ($p=0.048$) the High group did not ($p=0.586$, NS). The Medium and High groups achieved statistical separation in hostility/excitement ($p=0.004$ and $p=0.017$, respectively) but only the Medium group achieved this in disorganised thoughts ($p=0.002$) whereas the High group attained borderline significance ($p=0.060$). No groups achieved statistical separation in the anxiety/depression factor and the Low group achieved no statistically significant result in any PANSS factor subscales.
- The onset of effect in the Medium group was achieved on Day 22 whereas the High group achieved statistical separation ($p<0.05$) on Days 8, 15, 36 and at the endpoint but did not achieve statistical separation on Day 22 ($p=0.079$) and Day 29 (0.075). Hence, the Placebo, Low and High groups did not achieve therapeutic onset of effect.

  Comment: The secondary outcomes consistently showed similar findings to the primary outcome results in which the Medium group showed statistical separation and superiority over the other treatment groups, with the High group showing an overall tendency to borderline significance.

  The responder rate of 20% used is (the minimum) acceptable level in an efficacy study according to the TGA adopted European guideline CPMP/EWP/559/95. Both the Medium and High groups achieved statistical separation at this level, although only the Medium group achieved statistical separation at the 30% level. Responder rate provides useful information on the efficaciousness of a medicinal product in schizophrenia. The higher the response rate achieved the more confident we are the product will serve its intended purpose. In comparison, trials of Invega in adults for schizophrenia used the 30% level (see PI), risperidone in a similar population used the 50% level (see Risperdal PI) and Seroquel (quetiapine) in adolescents with schizophrenia achieved separation at the 30% level. Non-responder rates to treatment were not provided.

  The PANSS factor and subscale analyses need to be considered in context. The primary objective was to assess the efficacy of paliperidone in acute **positive** symptoms of psychosis not the negative symptoms. As the Sponsor indicated, the assessment of negative symptoms requires subjects not to be experiencing an acute psychotic episode and should be stable for greater than six months with predominant and persistent negative symptoms (supported by the CPMP/EWP/559/95: Note for Guidance on the Clinical Investigation of Medicinal products in the Treatment of Schizophrenia).

  While several time-points demonstrated statistical separation for the High group, onset of therapeutic effect was not demonstrated as per the definition used in the study protocol and therefore the dosage regimen employed for this group of subjects (i.e. 6mg for <51kg and 12mg ≥51kg) should not be used in the PI. This matter will be discussed in the Section on benefit-risk assessment.

The Sponsor provided many exploratory post-hoc analyses by actual dosage taken as well as collating all paliperidone treatment groups into one "Total" group, which showed statistical separation for the High group and/or 12mg dosage regimen. The findings of such analyses are not reported in the body of this report as their usefulness in efficacy studies is limited. Unlike efficacy studies, such analyses may provide useful safety-related data though.

6.1.2. Other efficacy study: PSZ-3002

This study only provided secondary efficacy outcome data and these outcomes are considered exploratory (only descriptive statistics are supplied with no adjustment for multiplicity). In view of the exploratory nature and the open-label design, which does not include an active comparator or placebo group, the usefulness of the study findings is limited. Furthermore, while this study forms a partial extension study from the pivotal study, PSZ-3001, the findings cannot be directly compared in view of the differences in subject populations, methodology, dosage and the study limitations. For these reasons, PSZ-3002 is not considered a pivotal study.

In summary, PSZ-3002 was an ongoing Phase III, two-year, open-label, multinational, multicentre, single-arm, safety study of flexibly-dosed extended-release paliperidone (1.5 to 12mg/day) in the treatment of adolescents (12 to 17 years of age) with schizophrenia. It was conducted in an outpatient setting between 29 June 2007 and the 30 July 2009 cut-off date (for all safety and efficacy data). The original 6-month protocol was amended to two years to investigate any study treatment effects on growth and maturation. Those enrolled into the 6-month study were considered to have completed the study at 6 months and offered the option of participating in the amended study.

The primary objective was to evaluate the long-term safety and tolerability of paliperidone in at least 100 adolescents (12 to 17 years, inclusive) with schizophrenia. This study was commenced before the pivotal efficacy study, PSZ-3001. Secondary objectives assessed the effect of paliperidone on the long-term symptoms of schizophrenia as measured by changes in: PANSS scores (total and subscales); CGI-S scores; CGAS scores; VAS scores (quality of sleep and daytime drowsiness) and modified measurements and treatment research to improve cognition in schizophrenia cognition assessment battery (MATRICS; This test examines the changes in multiple domains of cognitive functioning associated with paliperidone treatment).

Sixty centres from eleven countries recruited 282 subjects. US centres recruited around 3 subjects for each centre whereas most other countries had a greater subject recruitment rate (especially Romania, which recruited 12 subjects in one centre alone). This raises concerns over subject selection into this study from a diagnostic perspective. The study design is provided in the dossier. The inclusion and exclusion criteria were very similar to those used in study PSZ-3001 except eligible subjects did not have to have a PANSS total score between 60 and 120, inclusive, at either screening or baseline and subjects from PSZ-3001 could enter this OL study after completing the DB phase or withdrawing from lack of efficacy after 21 days, provided they were expected to benefit from paliperidone treatment. Participating study centres had to complete their enrolment requirement for study PSZ-3001 before they could directly enrol subjects in the OL study.

The ER formulation was based on the proprietary osmotic pump technology (OROS) in the following strengths: 1.5mg, 3mg and 6mg tablets. These tablets differed in their physical appearance. Treatment started with a 6mg once daily dose but could be titrated up or down in 3mg increments at least every five days if clinically indicated, within the dose range 1.5 to 12mg paliperidone once daily (taken in the morning without regard to food). The 6mg starting dose was to be reviewed when the PSZ-3001 results were known and the lowest effective dose determined. No details are provided when such analysis was undertaken, when these results were disseminated to the treatment centres and how many subjects required immediate dose modification. Hence, investigators were directed to dose subjects at a 6mg/day dose

irrespective of weight, age and previous assigned treatment until the lowest effective dose in PSZ-3001 had been identified.

The single-arm study comprised three treatment groups. These were investigated and reported upon singly and combined: Placebo/Pali (from Study PSZ-3001, who withdrew due to lack of efficacy after 21 days, n=39); Pali [DB]/Pali (from study PSZ-3001, who completed DB treatment and received one of the treatment doses, n=117);** Pali [No DB]/Pali (entered this study directly, n=122).

**The three active treatment groups (Low, Medium and High) were analysed together as one group(Protocol deviation without explanation).

Clinical chemistry analyses and urinalysis were undertaken by the Covance Central Laboratory Services. Unlike Study PSZ-3001, this study undertook additional testosterone testing in male subjects to assess long-term endocrine effects.

The "main" secondary efficacy variable was the change in PANSS total score from OL baseline to OL endpoint (observed and LOCF). Most other efficacy variables were explored from DB baseline and OL baseline to OL endpoint (observed and LOCF). Subgroup analyses, based on age (12-14, 15-17 years), sex (male, female), race (white, black, Asian) and geographic region (North America, Western Europe, Eastern Europe, Asia) were conducted on the change in PANSS total score from OL baseline to OL endpoint.

No formal sample size calculation was performed. Approximately 400 subjects were planned for enrolment in this 2-year study to obtain data on at least 100 subjects who completed 6-months' treatment at or above the lowest effective dose identified in Study PSZ-3001. This was an open-label, single-arm study so no randomisation or blinding was necessary.

At cut-off point, 282 subjects were enrolled and included in the safety analysis. Of these, 278 subjects entered into the OL (modified) ITT analysis set (i.e. subjects received at least one dose of study medication and had a baseline and at least one post-baseline efficacy assessment). Two baseline values were defined and used in the analyses of changes from baseline: open-label baseline - latest observation prior to administration of OL paliperidone, including first day of dosing [Day 1] in this study and DB baseline - observation at the last visit prior to administration of DB study drug in PSZ-3001 (including Day 1). The latter baseline was used in the calculation of change from baseline scores only for subjects in the Placebo/Pali and Pali (DB)/Pali groups.

The overall withdrawal rate was 22% with the highest proportion withdrawn from the Placebo/Pali group (33%). Lack of efficacy accounted for most withdrawals (9% total). Information on completion and withdrawal rates and protocol deviations is included in the dossier. Total deviations occurred in 12% of subjects (n=34), a greater proportion of these in the Pali (No DB)/Pali group (21%). Efficacy assessment deviations occurred in 9% (n=11) subjects in the Pali (No DB)/Pali group. Two Indian sites (accounting for 12 subjects) failed to use a stadiometer for height measurements as this was not in the original study protocol. These sites used tape-measures and recorded no changes in height over the study duration for its patients prior to 1 April 2010 protocol amendment. Ten subjects did not have a post-baseline height taken and so were omitted from the analyses. From the results presented it is unclear whether these Indian subjects comprise the majority of efficacy assessment deviations.

Baseline demographics were similar to those in study PSZ-3001 in terms of age and gender distribution but there were differences in race, OL bodyweight category and OL BMI. In particular, there were more Asian subjects in the OL study (30%) reflecting more recruitment from Asian countries. In terms of BW category, PSZ-3002 recruited heavier subjects (78% ≥51kg compared to 69% in PSZ-3001). The mean OL baseline normal BMI in PSZ-3002 was 77 compared to 83 at baseline in PSZ-3001 (as the direct recruits tended to be heavier than those from PSZ-3001). Baseline disease characteristics were similar to PSZ-3001 in terms of schizophrenia type (paranoid 75%) and age at diagnosis (of schizophrenia). The mean OL

baseline PANSS total score was less than PSZ-3001 (82.5 versus 91.1, respectively) with less severe symptoms in those from the DB treatment group in PSZ-3001 (76.6) and more severe symptoms from those directly entering the study (88.0). The latter is supported by the OL baseline CGI-S scores that show reduced symptoms in the Pali (DB)/Pali group than the other two groups, with the Pali (No DB)/Pali group having proportionately more ill subjects.

There was a mean decrease (improvement) in PANSS total score from OL baseline to OL endpoint (LOCF) in all three treatment groups. Placebo/Pali showed the greatest reduction then the Pali (No DB)/Pali group followed by the Pali (DB)/Pali group (-17.9 v -17.2 v -9.2, respectively). While the mean decreases in PANSS total score are comparable between the two groups, the distribution among the treatment groups is different. In particular, those subjects recently exposed to study medication [Placebo/Pali and Pali (No DB)/Pali groups] had greater reduction in PANSS total scores. The results of sub-group analyses (using the mean change in PANSS total score from OL baseline to OL endpoint) for age, gender, race and geographical region are provided in the dossier. In particular, the Sponsor claims comparable findings in terms of age group: -12.1 and -14.6 for 12-14 year-olds 15-17 year-olds, respectively, and gender (-13.4 and -14.7 for males and females, respectively).

Like study PSZ-3001, the distribution of PANSS total score from OL baseline to OL endpoint by country varied considerably from country to country. Other than the new centres in Bulgaria and Estonia, the overall reductions in PANSS total scores at 6-months' treatment were modest (range -11.1 to -18.5). There is no placebo/comparator group to place these changes in a clinically meaningful context. Of particular note is the US data, which indicates no overall benefit in 6-months' OL treatment for those who entered from the pivotal study. This finding may be reflected in the low OL baseline values (75.6 for the Placebo/Pali group and 65.1 for the Pali (DB)/Pali group, respectively) compared to those US subjects entering the study directly (89.1), a group with more severe symptoms.

The other secondary efficacy variables (PANSS subscale scores/Marder factor, CGI-S score, CGAS score, sleep VAS scores) were consistent with those found for the OL PANSS total score i.e. the Placebo/Pali and Pali (No DB)/Pali groups had similar decreases in values (signifying improvement) compared to the lesser reductions in the Pali (DB)/Pali group. When the mean change from DB baseline for these variables was taken into consideration, the overall changes were similar between the Placebo/Pali and Pali (DB)/Pali groups (suggesting a "catch-up response"). The mean changes in the MATRICS score from OL baseline to endpoint showed modest improvement for most cognitive domains.

> **Comment:** The open-label efficacy data from study PSZ-3002 are considered not to be directly relevant to the application for the proposed extension of indication. PSZ-3002 appears to have employed dosing assumptions in adolescents with schizophrenia that are based on empirical findings in adults taking paliperidone rather than dose-ranging studies in adolescents with this condition. In particular, the Sponsor appears to have assumed the starting dose of paliperidone in adolescents will be 6mg once daily irrespective of body-weight and age. The Sponsor appears to be reliant on the optimal dosage regimen to be identified from the pivotal study but actually commenced the OL study before the pivotal study commenced or the results of this study were known. Given the findings of PSZ-3001 that dosing at 3mg once daily was found effective in low body-weight (<51kg) adolescents, disproves the Sponsor's assumption of a 6mg/day dosage regimen, irrespectively. Effectively, the study population in PSZ-3002 was exposed to supra-optimal paliperidone dosing (see mode data) and hence placed its subjects at higher risk of toxicity. This will be explored in greater detail in Sections on safety discussions and benefit-risk assessment.
>
> It is noted that once centres had recruited their assigned allocation of subjects into the pivotal study then they could commence recruitment into the OL study. This again raises issues of investigator/selection bias in the pivotal study. Investigators did not appear to

be blinded to the OL study and hence would know the entry criterion of completion of 21 days of the DB phase before entry into PSZ-3002. As discussed previously, a significant proportion of subjects withdrew from the pivotal study in week 4 (particularly Ukraine and Russia), and presumably most entered the OL study. The role of investigator bias in subject selection out of the pivotal study and into the open-label study is the subject of a Section 31 question.

The 6-months' findings provide little support for paliperidone maintenance treatment in adolescents with schizophrenia. The Sponsor did not provide responder rate for this study (and conversely, non-responder rate), a relapse rate or data on relapse prevention. These parameters were not cited in the study objectives *per se*, but given the Sponsor claims Invega is indicated for the "treatment of schizophrenia in adolescents" this implies treatment in the acute and chronic stages of the condition. The evidence presented in this application does not support treatment beyond the acute phase (i.e. up to six-weeks' treatment). This is discussed further in the Section on benefit-risk assessment.

6.2. Analyses performed across trials

No efficacy analyses have been performed across trials.

6.3. Evaluator's conclusions on clinical efficacy for schizophrenia

It is considered that the submitted data have not satisfactorily established the efficacy of paliperidone extended-release tablets in the treatment of adolescents (12 to 17 years of age) with schizophrenia.

The submission included one 6-week pivotal Phase III efficacy and safety study (PSZ-3001). Analysis showed that PANSS total score (the primary efficacy endpoint) was statistically reduced in the Medium treatment arm compared with Placebo. This group (of 48 subjects) represents 3mg/day dosing for subjects <51kg (n=16) and 6mg/day for those ≥51kg (n=32). Treatment reduced PANSS total score by 17.3 points (p=0.006, CI -16.58 to -3.67) compared to 7.9 points for Placebo. Given the Sponsor's pre-determined level of a 13.2 point reduction compared to Placebo to show a clinically meaningful result, these results suggest borderline clinical significance in just the one treatment arm. The High treatment group (receiving 6mg/day for <51kg and 12mg/day for ≥51kg) achieved borderline statistical significance in terms of PANSS total score reduction (-13.8, p=0.086, CI -13.07 to -0.09) and onset of therapeutic effect.

Clinical dosing recommendations can only be made on the findings in relation to the Medium group. Hence, efficacy data supports 3mg/day as the minimum effective dose in adolescents with schizophrenia. The Sponsor has proposed a starting dose of 3mg/day. This is acceptable to this evaluator on efficacy grounds and will be discussed further below.

Failure of the High group to maintain therapeutic dosing throughout the 6-week study period or show statistical separation in the primary efficacy variable has not proven the 12mg/day dosage regimen to be an effective treatment option (for those weighing at least 51kg) in adolescents with schizophrenia. Furthermore, as no 9mg dosage regimen was employed in this study, the evidence presented here does not support such inclusion. While a dose-response relationship exists for paliperidone in adults, at least between 3 to 12mg/day, such a dose-response relationship has not been demonstrated in this submission for adolescents. Hence, the efficacy data does not support a dosage above 6mg/day. This is at odds with the pharmacokinetic data in children and adolescents, which does not support a dosage regimen below 6mg/day.

The dosing regimens employed in the efficacy trials conducted in adolescents (PSZ-3001 and PSZ-3003) appear to have been derived empirically from adult studies, rather than from adolescent PK studies. While the pivotal efficacy study attempted to individualise dose according to bodyweight (less than or greater than 51kg) this appears a crude measure and contrary to the way most paediatric doses are calculated. The longer-term open-label safety study based dosage on clinical response and tolerability to paliperidone, in preference to a bodyweight dosing schedule. Furthermore, the higher doses used in those entering Study PSZ-3002 (as well as the ongoing Phase III study PSZ-3003) reflect the Sponsor's assumption that the predicted minimum effective dose in adolescents for paliperidone would be 6mg/day irrespective of baseline bodyweight (BW), age, gender and race. This assumption appears to be partially correct only for those subjects weighing at least 51kg.

In PSZ-3001, the Sponsor attempted to investigate the effect of paliperidone on age by dividing the adolescent group into 12-14 year and 15-17 year age-groups. The study appeared to have insufficient power to detect meaningful differences in the parameters examined. The Medium group comprised just 15 subjects in the 12-14 year age-group, eight receiving the 3mg/day dosage. In view of the small numbers of subjects in this age-group, the difficulty diagnosing schizophrenia in very young children (this is the subject of a Section 31 question) and the lack of efficacy data, this evaluator does not recommend dosing in the 12-14 year age-group.

Analyses of the secondary efficacy endpoints and pre-specified "other" efficacy endpoints against Placebo supported the findings of the primary efficacy endpoint for the Medium group, although these analyses did not adjust for multiplicity effects. Exploratory post hoc analyses of efficacy endpoints versus Placebo also supported the primary efficacy findings for the Medium group and suggested statistical separation for the High treatment group across several parameters.

The submission included no supportive randomised, double-blind, placebo-controlled studies. It did include one ongoing 2-year Phase III, open-label, single-arm, partial-extension study in the target population (PSZ-3002). The results appeared to show some symptom and functional improvement over the 6-months' study period analysed, which are encouraging, but the data from this study are not considered relevant to the current application. The effect of paliperidone on efficacy has not been established beyond six weeks.

Overall, it is considered that the efficacy of paliperidone ER for the proposed extension of indication is not supported by the one confirmatory pivotal study. The TGA adopted "Points to Consider" guideline (CPMP/EWP/2330/00) discusses applications that include only one pivotal study. This guideline discusses the "general demand for replication of scientific results", but notes that "clinical drug development differs from the situation with strictly experimental studies". The guideline states that where confirmatory evidence is provided by only one pivotal study "this study will have to be exceptionally compelling", but goes on to state "there is no formal requirement to include two or more studies in the Phase III program".

The "Points to Discuss" document lists factors that should be considered when determining whether the confirmatory evidence from one pivotal study is "exceptionally compelling". Applying these factors to study PSZ-3001 leads to the following conclusions:

- *The internal validity* may be compromised from potential biases in subject selection (in and out of the study), lack of blinding of investigators, the quality of the randomisation process (generated by the Sponsor) and hence the potential to introduce confounding into the results, the use of a modified ITT population in preference to an "all randomised population" and the loss of almost 50% of the placebo (control) group. Study PSZ-3001 did not use any robust objective measure of compliance. Although the Sponsor took blood samples to assess PK variables, no information relating these values to study medication was provided. The study was undertaken primarily on an outpatient basis and medication supervised by family members. To achieve such high compliance rates in subjects purported to have acute

psychosis, which tend to be a problematic group in terms of medication adherence, raises concern over the measures the Sponsor used to ensure and assess compliance.

- *The external validity* is uncertain as the results of the efficacy study may not be extrapolated to the general population of adolescent Australians with schizophrenia. The BMI distribution in the study population may differ considerably from the heavier Australian population, which could give rise to dosing issues. The age of first diagnosis (as young as three years of age) is cause for concern as is how a definitive of schizophrenia diagnosis was established. The distribution for age at first diagnosis is the subject of a Section 31 question. A large proportion of participants had never been hospitalised for psychosis and hence diagnosis was made in an outpatient setting. This may be at odds with how diagnosis is made in Australia. Furthermore, it is unclear from the submitted data what non-pharmacological interventions occurred during the study. The approaches used may differ considerably from those used in Australia (Section 31 question). The findings in US subjects i.e. the population that most closely resembles the Australian population (of those countries participating) were inconclusive, and indeed, did not appear to show efficacy at any dosage regimen (albeit small numbers recruited), giving rise to generalisability concerns. Furthermore, no family history of mental illness, and schizophrenia in particular, was provided. This information has relevance to establishing the diagnosis of schizophrenia. In addition, numbers of hospitalisations for schizophrenia were not provided (both the latter issues are Section 31 questions).
- To be *clinically relevant* the estimated size of treatment benefit must be large enough to be clinically valuable. In the Medium group, the net reduction in PANSS total score was 9.4 points. This, according to the Sponsor's pre-determined level of a 13.2 point reduction compared to Placebo, is of doubtful clinical meaningfulness. The efficacy findings for the 12-14 year age-group (27% of the study population) were not clearly established and hence any extrapolation of study results to this population should be approached with caution.
- The *degree of statistical significance* achieved in the Medium group for PANSS total score reduction was p=0.006 (CI -16.58 to -3.67). While the statistical result for this group is reasonably strong the confidence intervals are not particularly narrow.
- The *data quality* was acceptable and quality assurance audits/study monitoring processes appeared to be completed satisfactorily.
- The study revealed a reasonable degree of *internal consistency* in that the secondary and other efficacy variables supported the primary efficacy analysis for the Medium treatment group (showing efficacy over Placebo). In terms of PANSS total score baseline by country there was wide variation and the endpoints by country also showed a marked degree of variance. In sub-group analyses, especially by age-group (12-14 years; 15-17 years), race and geographical location, results were inconsistent and the data had wide distribution (albeit from small numbers in sub-groups).
- In regards to *centre effects*, the Sponsor reports no treatment-by-country treatment effect. This evaluator is concerned by the numbers of centres and countries used in selecting its study subjects (especially the lack of involvement of Western European countries **[Information redacted]**). These numbers may reflect the difficulty in finding suitable subjects for the adolescent age-group. However, Romania for instance, in Study PSZ-3001, had one centre yet recruited ten subjects (all of much higher PANSS total score baselines than other participating countries) whereas the ratio was more like one centre for every three subjects in the US. Indeed, all countries recruited relatively more subjects than the US. This trend was also noted in Study PSZ-3002. This raises an issue over the selection of subjects in terms of assessment and diagnosis of schizophrenia *per se*. Heterogeneity in the population base is demonstrated by the wide distribution of baseline PANSS total scores among the participating constituent countries in both PSZ-3001 and PSZ-

3002. In PSZ-3001, a large decrease in PANSS total score for the Placebo group was evident in US subjects. The Sponsor claims this effect was not statistically significant as a baseline treatment-by-country category interaction and refers to a similar response in an olanzapine study. No further explanation or supporting data is provided, particularly for paliperidone in adults or risperidone in adolescents. Dismissing this finding as an anomaly of the US population effectively negates the generalisability of US research to the Australian environment. The apparent "lack of placebo effect" in many participating countries in PSZ-3001 is of grave concern and suggests inappropriate selection of subjects and/or errors in applying diagnostic assessment to subjects.

- The *plausibility of the hypothesis* that paliperidone ER improves schizophrenia symptoms in adolescents with established disease is medically plausible.

In conclusion, the submitted data does not provide exceptionally compelling evidence to support the application for the extension of indication.

7. Clinical safety

7.1. Overview

The submission included a copy of the European Union Risk Management Plan (EU-RMP) for Invega and an Addendum that was requested at the pre-submission meeting. The latter document places the RMP in context of Australian regulatory and prescribing practices. The RMP identifies risk as those considered "important identified risks" for which specific pharmacovigilance activities are proposed (hyperprolactinemia and potentially prolactin-related events, QT prolongation, orthostatic hypotension, extrapyramidal symptoms/tardive dyskinesia (TD), neuroleptic malignant syndrome (NMS), diabetes mellitus and hyperglycaemia-related adverse events, weight gain, seizures, somnolence, priapism, cerebrovascular accident, venous thromboembolism, leukopenia, agranulocytosis, thrombocytopenia, rhabdomyolysis, neonatal drug withdrawal syndrome, elevated plasma concentrations in patients with renal disease), "important potential risks" (carcinogenicity [pituitary adenomas; endocrine pancreas tumours; breast cancer], overall increased mortality in elderly patients with dementia, cerebrovascular AEs in elderly patients with dementia, cognitive and motor impairment, antiemetic effect, body temperature dysregulation, suicidality, depression in patients with affective disorders, increased sensitivity to antipsychotics in patients with Parkinson's disease and dementia with Lewy bodies, gastrointestinal obstruction) and "important missing information" (use in haemodialysis patients, use during pregnancy, use in nursing mothers, long-term safety in patients with schizoaffective disorder, long-term paediatric safety [specific to the Australian RMP]).

The risks identified in the RMP are generally considered a class effect of antipsychotic agents. In children, significant weight gain is associated with olanzapine, risperidone and quetiapine administration. The latter, combined with AEs on lipid parameters (cholesterol fractions and triglycerides) and glucose metabolism give rise to a metabolic syndrome, which in turn is associated with increased cardiovascular risk. AEs secondary to hyperprolactinemia are of particular concern in adolescents, as well as possible negative effects on sexual maturity and growth.

7.2. Studies providing evaluable safety data

The submission included a comprehensive SCS, which assessed the safety of 339 subjects from one completed 6-week, double-blind, placebo-controlled Phase III study (PSZ-3001), one completed Phase I pharmacokinetic study (PSZ-1001) and 6-month safety data from one ongoing, open-label, long-term extension study (PSZ-3002). For the ongoing Phase III

randomised, double-blind, active-controlled, parallel-group multicentre study (PSZ-3003), deaths and SAEs through a cut-off date of 8 July 2010 are included. Studies PSZ-3001 and PSZ-3002 assessed safety as a primary outcome although only descriptive statistics are provided for each of these studies.

In the pivotal efficacy study, PSZ-3001, general AEs were assessed by clinical laboratory tests (haematology, serum chemistry and urinalysis), investigation of weight gain and metabolic disturbances, prolactin, ECG, vital sign measurements, physical examinations, Tanner staging, pregnancy testing, urine drug screen, extrapyramidal symptom (EPS) rating scales (AIMS; BARS; SAS). AEs of particular interest included treatment-emergent adverse events (TEAEs) analysed by age category (12-14 years and 15-17 years); race category (White, Black, Asian, other); sex (male and female); baseline BW category (<51kg and ≥ 51kg); geographic region (North America, Eastern Europe, Western Europe, Asia) and site location (US or non-US). Serious TEAEs, TEAEs leading to permanent discontinuation, relationship of drug (including dose-relationship) to TEAEs that led to subject discontinuation or SAEs, special clinical interest AEs[1] and death.

Study PSZ-3002 provided data on TEAEs, serious TEAEs, TEAEs leading to permanent discontinuation, special clinical interest AEs and death using clinical laboratory tests (haematology, serum chemistry and urinalysis), investigation of weight gain and metabolic disturbances, electrocardiogram[2], vital sign measurements (temperature, pulse, blood pressure), physical examination and Tanner staging, extrapyramidal symptom scales (SAS, BARS, AIMS), Columbia Suicide Severity Rating Scale (C-SSRS) and Columbia Classification Algorithm of Suicide Assessment (C-CASA) of potentially suicide-related events. For those AEs that began prior to the start of the study but led to discontinuation during the study, were not counted in the summary of TEAEs but in the study completion/withdrawal summary instead.

Study PSZ-1001 provided data on AEs using clinical laboratory results (haematology, serum chemistry and urinalysis), EPS-related TEAEs using incidences of AIMS, BARS and SAS scores and use of anti-cholinergic medication, pregnancy testing, urine drug screen, 12-lead ECGs (including ECG parameters: HR, PR, RR, QRS, QTcB, QTcF, QT, QTlc and QTcLD), vital sign measurements (respiratory rate, blood pressure, pulse rate and body temperature), physical examination results, including Tanner staging and CGI-S score.

PSZ-3003 is an ongoing randomised, double-blind, active-controlled, parallel-group, multicentre Phase III study designed to evaluate the efficacy and safety of flexibly-dosed paliperidone ER in adolescent subjects (12-17 years of age, inclusive) with schizophrenia. The study consists of three phases: a screening phase (with a possible overlapping washout period) of up to 3 weeks, an 8-week double-blind acute phase and an 18-week double-blind maintenance phase. Subjects are randomised to the following active treatment groups: Paliperidone treatment group: 6mg/day on Days 1 to 7 (Week 1) then paliperidone at doses of 3, 6 or 9mg per day throughout the treatment period depending on efficacy and tolerability or Aripiprazole treatment group: 2mg/day on Days 1 & 2; 5mg/day on Days 3 & 4; 10mg/day on Days 5 to 7 (Week 1) then aripiprazole at daily doses of 5, 10 or 15mg throughout the treatment period, depending on efficacy and tolerability. In this submission, only deaths and SAEs that occurred through to the cut-off date of 8 July 2010 are included.

[1] Suicidality, homicidal ideation, depressed mood, worsening of psychosis, aggression and agitation, somnolence and sedation, seizures and convulsions, NMS, cardiac arrhythmias, orthostatic hypotension, AEs suggestive of pro-arrhythmic potential, ischaemia-related, gastrointestinal-related, pancreatitis-related, potential rhabdomyolysis-related, overdose-related, weight-gain related, glucose-related, drug-withdrawal related, tachycardia-related and EPS-related (e.g. akathisia and dyskinesia, assessed by rating scales and use of anticholinergic medication).
[2] 2Electrocardiograms were summarised as follows: baseline of OL study for all treatment groups; average pre-dose from PSZ-3001 for the Placebo/Pali and Pali (DB)/Pali groups.

7.3. Patient exposure

The integrated exposure data for the Phase III studies, PSZ-3001 and PSZ-3002 are summarised in Table 6 below. Of the 314 adolescent subjects with schizophrenia who received at least one dose of paliperidone ER (comprising 282 subjects in PSZ-3002 and 32 subjects in PSZ-3001, who did not enter the OL study), the mean duration of exposure was 209.7 days. One hundred and sixty nine subjects received paliperidone for 6 months (180 days) or more as of 30 July 2009.

Table 6: Extent of exposure – integrated safety population for studies PSZ-3001 and PSZ-3002

Duration Days	Placebo/Pali (N=39) n (%)	Pali (DB)/ Pali (N=118) n (%)	Pali (No DB)/ Pali (N=125) n (%)	Pali/No OL (N=32) n (%)	Total (N=314) n (%)
≥ 1 days	39 (100)	118 (100)	125 (100)	32 (100)	314 (100)
≥ 30 days	36 (92)	118 (100)	103 (82)	16 (50)	273 (87)
≥ 60 days	32 (82)	115 (97)	88 (70)	0	235 (75)
≥ 90 days	31 (79)	111 (94)	79 (63)	0	221 (70)
≥ 120 days	30 (77)	107 (91)	69 (55)	0	206 (66)
≥ 150 days	27 (69)	104 (88)	57 (46)	0	188 (60)
≥ 180 days	25 (64)	101 (86)	43 (34)	0	169 (54)
≥ 210 days	21 (54)	86 (73)	29 (23)	0	136 (43)
≥ 240 days	19 (49)	65 (55)	28 (22)	0	112 (36)
≥ 270 days	15 (38)	58 (49)	24 (19)	0	97 (31)
≥ 300 days	14 (36)	42 (36)	23 (18)	0	79 (25)
≥ 330 days	13 (33)	39 (33)	23 (18)	0	75 (24)
≥ 360 days	13 (33)	35 (30)	21 (17)	0	69 (22)
≥ 390 days	10 (26)	31 (26)	17 (14)	0	58 (18)
≥ 450 days	7 (18)	23 (19)	11 (9)	0	41 (13)
≥ 510 days	0	12 (10)	1 (1)	0	13 (4)

In the pivotal 6-week study, PSZ-3001, the mean duration of exposure to study medication was higher in the Medium and High groups (39.2 days and 37.3 days, respectively) than the Low and Placebo groups (34.9 days and 33.0 days, respectively), reflecting the higher study withdrawal rates in the latter groups.

In study PSZ-3002, exposure was also quantified in terms of the mode dose (i.e. the dose most frequently taken) during the OL phase for each subject. The highest mode dose was 6mg/day (43%), followed by 12mg (22%) then 9mg (22%) and then 3mg (11%). There were 148 (52%) subjects who had at least 6 months (180 days) of exposure at or above a paliperidone ER mode dose of 3 mg (the lowest effective dose identified in study PSZ-3001) in the OL study based on the data up to the cut-off date of 30 July 2009.

A further 25 subjects (aged 10-17 years) with schizophrenia, schizoaffective disorder or schizophreniform disorder received up to eight doses of paliperidone in study PSZ-1001. All but one subject received multiple-dose administration of paliperidone.

7.4. Adverse events

AEs were assessed by subject reports, physical examinations and laboratory evaluations. A treatment-emergent adverse event (TEAE) was defined as an AE that is new in onset or worse in severity after administration of the first dose of drug. In this clinical evaluation report, AEs are categorised as TEAEs unless otherwise stated. A serious TEAE (or serious adverse event, SAE) was defined by any event that is fatal or immediately life threatening, resulting in or prolonging an existing hospitalisation, is permanently or significantly disabling, is a congenital anomaly, or requires medical or surgical intervention to prevent permanent sequelae or any of the previously mentioned outcomes. AEs were classified using Medical Dictionary for

Regulatory Activities (MedDRA) Version 11.0 in study PSZ-3001 and Version 12.1 in study PSZ-3002.

The overall profile for the safety population is summarised below in Table 7 for study PSZ-3001 and Table 8 for study PSZ-3002.

Table 7: Overall Summary of Treatment-Emergent Adverse Events in the Pivotal Study PSZ-3001

	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 (%)
TEAE	30 (58.8)	27 (50.0)	29 (60.4)	36 (75.0)	92 (61.3)
Possibly related TEAE[a]	15 (29.4)	13 (24.1)	21 (43.8)	28 (58.3)	62 (41.3)
1 or more serious TEAE	1 (2.0)	2 (3.7)	1 (2.1)	1 (2.1)	4 (2.7)
TEAE leading to permanent stop	0	1 (1.9)	1 (2.1)	1 (2.1)	3 (2.0)

[a] Study drug relationships of possible, probable, and very likely are included in this category.
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: Safety Analysis Set.

Dose-related trends in the incidences of all TEAEs and drug-related TEAEs appeared across the three active treatment groups.

Table 8: Overall Summary of Treatment-Emergent Adverse Events – Open-Label Stud, PSZ-3002

	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=125) n (%)	Total (N=282) n (%)
TEAE	28 (71.8)	79 (66.9)	97 (77.6)	204 (72.3)
Possibly related TEAE[a]	22 (56.4)	58 (49.2)	82 (65.6)	162 (57.4)
1 or more serious TEAE	7 (17.9)	2 (1.7)	24 (19.2)	33 (11.7)
TEAE leading to permanent stop	1 (2.6)	0	8 (6.4)	9 (3.2)

[a] Study drug relationships of possible, probable, and very likely are included in this category.
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 12.1
Based on data up to 30 July 2009 cut-off date for subjects enrolled prior to that date.

The proportions of all types of TEAE appeared markedly less in the Pali (DB)/Pali group than the other two groups, suggesting an effect of prior exposure to study drug in PSZ-3001.

TEAEs occurred in an apparent dose-response relationship in study PSZ-1001: 37.5% (n=3) in Group A, 66.7% (n=6) in Group B and 75.0% (n=6) in Group C. No SAEs were recorded. One subject withdrew from the study voluntarily.

One SAE was reported in study PSZ-3003.

> **Comment:** Due to population and design differences, the overall safety findings of the 6-month OL study and the 6-week pivotal study are not directly comparable. However, given the dose-related trend in TEAEs identified in study PSZ-3001, the higher proportions of all TEAE sub-types found in PSZ-3002 are consistent with those expected from prolonged exposure to study drug. In the absence of prevalence data the presented results are of limited value.

7.4.1. All adverse events (irrespective of relationship to study treatment)

Comment: The Sponsor appears to have not provided tabulated data of the incidence of all adverse events irrespective of relationship to study treatment. This is the subject of a Section 31 question.

7.4.2. Treatment-related adverse events (adverse drug reactions)

In order to determine what events were ADRs, the Sponsor's clinicians conducted ADR analyses of all AEs from subjects treated with paliperidone in studies PSZ-1001, PSZ-3001 and PSZ-3002. The Sponsor applied ADR assessment criteria based on the Council for International Organizations of Medical Sciences (CIOMS) Working Groups and medical judgement to determine what terms were ADRs. The definition of ADR (taken from the Food and Drug Administration guidance document, CIOMS 1999) is: "... an undesirable effect, reasonably associated with the use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all Paliperidone ER adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."

The following is taken from the Paliperidone ER – Adverse Drug Reaction Determination Using the MedDRA Terminology document dated 17 August 2010:

> Adverse event data from the paediatric studies were evaluated for ADRs in the following order: Placebo-controlled study R076477-PSZ-3001; Open-label study R076477-PSZ-3002; Phase I study PALIOROS-PSZ-1001. This was an algorithmic approach in that, once deemed to be an ADR in Study R076477-PSZ-3001, a given event was accepted as an ADR in the other two studies; and if deemed to be an ADR in Study R076477-PSZ-3002, a given event was accepted as an ADR in the other studies. Analyses were not done sequentially by study. The ADRs identified in Study R076477-PSZ-3001 were based upon the actual dose groups (placebo and paliperidone ER 1.5, 3, 6, and 12 mg).

In study PSZ-3001, there were dose-related trends in the incidence of somnolence, akathisia, dystonia and tachycardia (and a trend towards a dose-relationship in tremor). The most frequently reported AEs (≥2%) in the paliperidone group (versus placebo group) were: somnolence (13.3% v 2.0%); akathisia (9.3% v 0%); headache (8.7% v 3.9%); tremor (6.0% v 0%); dystonia (4.0% v 0%); weight increase (4.7% v 0%); tachycardia (4.0% v 0%); cogwheel rigidity (2.7% v 0%); dizziness (2.7% v 0%); dyskinesia (2.7% v 0%); salivary hypersecretion (2.0% v 0%); fatigue (2.7% v 0%) and oculogyric crisis (2.0% v 0%).

In study PSZ-3002, the most frequently reported AEs (≥5%) in the total paliperidone group were: somnolence (14.5%); headache (12.4%); akathisia (11.7%); nasopharyngitis (9.6%); insomnia (8.5%); weight increase (8.2%); schizophrenia (8.2%); dizziness (7.4%); salivary hypersecretion (7.4%); tremor (6.0%) and nausea (5.7%). Akathisia was reported at a higher incidence in the Pali (No DB)/Pali group (20.0%) than the Pali (DB)/Pali group (6.8%) and did not occur in the Placebo/Pali group.

In study PSZ-1001, the most frequently reported AEs in those who received paliperidone were: sedation (16%), epistaxis (12%), extrapyramidal disorder (8%), headache (8%), nausea (8%) and vomiting (8%).

> **Comment:** Comparative incidence data for adults with schizophrenia (from three pooled 6-week controlled trials – see Invega PI) demonstrated higher incident rates in adolescents for somnolence, akathisia and headache. Weight increase (as an AE), dyskinesia and cogwheel rigidity were common adolescent AEs not reported in the adult data.
>
> No safety data exceeding 6-weeks is provided in the Invega PI for adults so no direct comparison can be made with the 6-month open-label study, PSZ-3002. Of note, the

incidence of somnolence, headache and akathisia in adolescents are consistently higher than those rates cited in adults (and higher than those seen in the 6-week pivotal study, PSZ-3001). AEs that occurred with higher incidence in PSZ-3002 compared to PSZ-3001 are increased weight (8.2% v 4.7%), salivary hypersecretion (7.4% v 2.0%), schizophrenia (8.2% v 6.0%) and galactorrhoea (3.9% v 1.3%). No prevalence data is available for the time course of specific AEs so they cannot be fully evaluated and placed in clinical context.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Deaths

No deaths were reported in studies PSZ-3001, PSZ-3002, PSZ-3003, and PSZ-1001 or in Invega post-marketing worldwide surveillance.

7.4.3.2. Other serious adverse events

Regarding the incidence of SAEs reported by treatment group in study PSZ-3001: Treatment-emergent SAEs occurred in five subjects in total (including one in the Placebo group). Eighty percent of cases were described under 'Psychiatric Disorders'. The only SAE that occurred in more than one subject was schizophrenia (n=2, 40%).

For the incidence of SAEs reported by treatment group in study PSZ-3002: SAEs occurred in 11.7% of subjects (n=33). The Pali (DB)/Pali group had markedly less SAEs compared with the Placebo/Pali and Pali (No DB)/Pali groups (1.7% v 17.9% v 19.2%, respectively). The most common (>5%) SAE was schizophrenia (n=16, 5.7%). SAEs that occurred in more than one subject were suicidal ideation (n=3), anxiety (n=-3), extrapyramidal disorder (n=2), suicide attempt (n=2), paranoid-type schizophrenia (n=2), psychotic disorder (n=2), auditory hallucination (n=2), delusion (n=2) and aggression (n=2).

No serious TEAEs were reported in study PSZ-1001.

In study PSZ-3003, only one treatment-emergent SAE was reported at the cut-off point. The subject experienced psychotic disorder, pyrexia and blood creatine phosphokinase increased.

7.4.4. Discontinuation due to adverse events

In study PSZ-3001, three subjects (<2%) withdrew from the study secondary to TEAEs. One subject in the Low group withdrew with allergic dermatitis, one subject in the Medium group withdrew with Mallory-Weiss syndrome and one subject in the High group withdrew with dystonia.

In study PSZ-3002, TEAEs that led to discontinuation occurred in 3.2% of the subjects (n=9). Of these, eight occurred in the Pali (No DB)/Pali group and one in the Placebo/Pali group. The only TEAE that led to discontinuation in more than one subject was suicide attempt (n=2) in the Pali (No DB)/Pali group. One subject in the Placebo/Pali group withdrew because of amenorrhoea. One subject withdrew in the Pali (No DB)/Pali group from raised liver enzymes (ALT and AST).

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

7.5. Laboratory tests

7.5.1. Overview

This section focuses on the laboratory results presented in the clinical safety report (CSR) from study PSZ-3001, the six-week pivotal efficacy/safety study. The findings are compared to those in the CSR from PSZ-3002, the open-label six-month safety study, looking for trends in laboratory abnormalities and possible treatment-related laboratory AEs. Brief findings from the 9-day PK study, PSZ-1001, are also reported.

7.5.2. Endocrine

The significance of a 2.4 nmol/L mean decrease from baseline for testosterone in male subjects in the Pali (No DB)/Pali group in PSZ-3002 is unknown.

7.5.3. Haematology

High eosinophils (n=5) relative to OL baseline and high eosinophils (n=7) relative to DB baseline (six of these in the Pali (DB)/Pali group) were recorded in PSZ-3002.

7.5.4. Liver function

In study PSZ-3002, two subjects had abnormally high serum transaminases (ALP and ALT, both less than twice the upper limit of normal), one each in the Pali (DB)/Pali and Pali (No DB)/Pali groups. Neither subject had raised serum total bilirubin or evidence of liver disease.

In study PSZ-1001, a 17 year-old male ([**Information redacted**]) received low dose paliperidone and acquired elevated ALT (up to 415U/L i.e. less than twice the upper limit of normal) and creatine kinase (up to 2890U/L). This subject did not have raised serum total bilirubin or evidence of liver disease. His blood levels returned to normal two weeks after study cessation, his levels attributed to weight-lifting. This seems a reasonable explanation to this evaluator.

7.5.5. Thyroid

Three abnormally high thyroid-stimulating hormone (TSH) levels were found in the Pali (DB)/Pali group and one in the Pali (No DB)/Pali group in the OL baseline to OL endpoint in study PSZ-3002. The Sponsor did not consider these findings clinically meaningful although raised TSH is considered to be a class effect of neuroleptic agents.

7.5.6. Serum prolactin

In study PSZ-3001, males and females showed a dose-response relationship of comparable magnitude. Some baseline prolactin levels exceeded the reference ranges, which may reflect prior exposure to neuroleptic treatment. No male had a potentially prolactin-related AE whereas two female subjects in the Medium group had galactorrhoea and one had amenorrhoea.

In the longer study, PSZ-3002, female serum prolactin levels tended to almost double at 6-months compared to 6-weeks, whereas males tended to remain constant. The relationship to dosing and gender are not provided, or prevalence data, but this effect may in part be explained by the apparent higher dosing in PSZ-3002. Males and females who received DB paliperidone in PSZ-3001 achieved very small rises in serum prolactin levels at OL endpoint (males 2.32 ng/mL and females 2.18 ng/mL, respectively). Again, the relationship to dosing and gender are not provided, or prevalence data, however these results may suggest a reduced study drug effect on serum prolactin levels with prolonged exposure. Overall, 7.4% subjects (n=21) experienced a prolactin-related TEAE (14.8% females and 2.4% males) with a higher proportion of subjects in the Placebo/Pali (12.8%) and in the Pali (No DB)/Pali (11.2%) groups compared to the Pali (DB)/Pali group (3.4%). Galactorrhoea and amenorrhoea were reported in each treatment group with higher incidences in the Placebo/Pali (7.7%) and the Pali (No DB)/Pali (7.2%) groups compared to the Pali (DB)/Pali group (3.4%).

No AEs were reported in the 9-day PK study, PSZ-1001 but study duration may not have been long enough to assess the occurrence of AEs frequently associated with high prolactin levels. Despite the short study duration, 52% subjects experienced baseline to post-baseline shifts in prolactin from the normal to high range, with males and females with similar incidence (50% males, 57% females) but females achieved larger mean changes from baseline (34 ng/mL for males, 66 ng/mL for females).

7.5.7. Electrocardiograph

The criteria for abnormal QTc values in PSZ-3001 and PSZ-3002 were based on the classification from the International Conference on Harmonisation (ICH) E14 Guideline whereas PSZ-1001 was based on criteria suggested for adults by the Committee for Propriety Medicinal Products of the European Agency for the Evaluation of Medicinal Products.

In study PSZ-3001, no abnormal ECG was regarded as clinically significant. Abnormally high values for heart rate occurred in a greater percentage of subjects in the paliperidone groups (14% in the Low group, 13% in the Medium group and 16% in the High group) than Placebo (4%). Most subjects had QTc value increases of no more than 30ms and no subject in any treatment group exceeded 60ms.

In study PSZ-3002, electrocardiogram interpretations and summary statistics for ECG parameters (including OL baseline and average predose DB over time) revealed no clinically relevant mean or median changes in heart rate, PR interval, QRS interval, QT interval, RR interval or corrected QT intervals for those subjects treated with paliperidone. All subjects in the three treatment groups had normal QTcLD, QTcF and QTlc at OL baseline and had normal maximum postdose values. No subject in any treatment group had a maximum postdose value greater than 480ms.

Most subjects in the OL study from OL baseline had QTc value increases of no more than 30ms (98%). One subject in the Pali (DB)/Pali group had an increase in QTcLD and QTcF greater than 60ms. For QTcB, increases of greater than 60ms were reported in one subject in the Placebo/Pali group and three subjects in the Pali (DB)/Pali group. For QTcLD and QTlc, the percentages of subjects with increases of greater than 30 to 60ms were similar in all three groups (ranging from 5 to 8% for QTcLD and 5 to 9% for QTlc, respectively). For QTcB and QTcF, the proportion of subjects with increases of greater than 30 to 60ms was similar in the Pali (DB)/Pali (15%) and Pali (No DB)/Pali (14%) groups and lower in the Placebo/Pali group (11%).

Most subjects in the average predose DB analysis had QTc value increases of no more than 30ms (93%). For QTcB, increases of greater than 60ms were reported in one subject in the Pali (DB)/Pali group. For QTcB, proportionately more subjects in the Pali (DB)/Pali group had increases of greater than 30 to 60ms than the Placebo/Pali group (19% v 1%, respectively), which may reflect longer duration of exposure to study drug.

In study PSZ-1001, no clinically relevant changes from baseline in mean values for heart rate or ECG intervals were reported. Twenty-eight percent of the study population experienced a prolonged value for QTcB (defined as ≥ 450ms at any time point during the study). No subject had an increase in QTcB or QTcF > 60ms from baseline. One 10 year-old, in Group B experienced mild QTc prolongation that resolved without intervention and a 12 year-old male ([**Information redacted**]) who received high dose paliperidone had a moderate intensity tachycardia from Day 2, which lasted for five days.

7.5.8. Vital signs

In study PSZ-3001, overall there were no significant differences in respiration rate or temperature between the paliperidone and Placebo groups over the course of the study. However, one subject in the High group met the criteria for orthostatic hypotension (on Day 15 of the DB phase but no subsequent values met the criteria). There was an apparent dose-response relationship in heart rate with tachycardia-related events occurring in 0% in the Placebo group, 0% in the Low group, 6.3% in the Medium group and 8.3% in the High group.

In study PSZ-3002, overall there were no significant differences in respiration rate or temperature between the three treatment groups. However, the proportion of subjects with treatment-emergent orthostatic hypotension was highest in the Pali (No DB)/Pali group (10%, n=12) compared to the Pali (DB)/Pali group (2%), with no subjects in the Placebo/Pali group

meeting the criteria. Six subjects in total (2.1%), which included four subjects in the Pali (No DB)/Pali group and one each in the other two treatment groups met the criteria for treatment-related tachycardia.

In study PSZ-1001, there was an apparent dose-related trend with regard to increases in standing and supine pulse rates. Twelve percent total met the criteria for potential treatment-emergent orthostatic hypotension.

7.5.9. Growth-tanner staging

Overall, there were no significant differences in sexual maturity of the subjects (male and female) from baseline to endpoint in all treatment groups for all submitted studies, other than those regarded as normal development as per calendar age.

> **Comment:** Overall, the mean change from baseline to endpoint was small and variable across the treatment groups in study PSZ-3001 in most laboratory variables examined. As expected from its pharmacology, paliperidone ER displayed dose-response relationships for serum prolactin and heart rate/tachycardia. Asymptomatic eosinophilia was noted too but this has been reported for many atypical antipsychotics including risperidone, olanzapine and quetiapine. No Hy's Law case was identified in any of the submitted data. Hyperprolactinemia and prolactin-related AEs (galactorrhoea, amenorrhoea, gynecomastia and impotence) are predictable AEs based on dopamine D2 receptor antagonism. The findings in this application are consistent with paliperidone in adults and other antipsychotic agents (typical and atypical). The Sponsor claims studies in risperidone have shown rises in prolactin levels in children for the first two months and then a decline to the normal range from 3 to 5 months. This phenomenon may be suggested from the data presented in this submission by the small increases in prolactin levels at OL endpoint from those who entered the study from the DB treatment group in PSZ-3001.
>
> In adults taking paliperidone, Invega was not shown to result in any clinically significant increase in QTc intervals from baseline compared to Placebo. Although neither PSZ-3001 nor PSZ-3002 was a specific QT study, the findings are consistent with those found in adults, with maybe a suggestion of prolonged QTcB intervals in adolescents, of unknown significance. As with other antipsychotics, caution should be exercised when Invega is prescribed in patients with known cardiovascular disease or family history of QT prolongation, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia and in concomitant use with other drugs known to increase the QTc interval.
>
> The overall findings are generally consistent with those found in adults taking paliperidone.

7.6. Other adverse events of interest

7.6.1. Overview

No subject in any treatment group in study PSZ-3001 had TEAEs related to any of the following special categories of interest: seizures and convulsions, NMS, cardiac arrhythmias, pro-arrhythmic potential, ischaemia, gastrointestinal perforations/ulcers, pancreatitis, rhabdomyolysis, overdose, drug withdrawal and homicidal ideation. In study PSZ-3002, no subject in any treatment group had TEAEs related to any of the following special categories of interest: seizures and convulsions, NMS, cardiac arrhythmias, pro-arrhythmic potential, gastrointestinal perforations/ulcers, pancreatitis, rhabdomyolysis, drug withdrawal and homicidal ideation. There was one potential TEAE related to ischemia in the Placebo/Pali group but this was not substantiated. Two subjects in the Pali (No DB)/Pali group had an overdose

event. In study PSZ-1001, in addition to EPS-related AEs, one female subject had persistent (10 days' duration) mild nausea after commencing high dose paliperidone.

7.6.2. Agitation and aggression

In study PSZ-3001, no association with study medication was found. In study PSZ-3002, four subjects in the Pali (DB)/Pali group and two subjects in the Pali (No DB)/Pali group met the criteria for agitation. One subject in each of the Pali (DB)/Pali and the Pali (No DB)/Pali groups met the criteria for aggression.

7.6.3. Somnolence and sedation

In study PSZ-3001, the incidences of these events were dose-related with 3.9% in the Placebo group, 9.3% in the Low group, 14.6% in the Medium group and 27.1% in the High group. In study PSZ-3002, somnolence was reported in 14.5% of subjects (Placebo/Pali group 25.6%, Pali (DB)/Pali group 15.3% and the Pali (No DB)/Pali group 10.4%) and sedation was reported in 3.9% of subjects (Placebo/Pali group 2.6%, no subjects in the Pali (DB)/Pali group and 8.0% in the Pali (No DB)/Pali group). In study PSZ-1001, sedation was the most common AE (16%).

7.6.4. Extrapyramidal symptoms (EPS)

In subjects who received paliperidone in study PSZ-3001, the most commonly occurring EPS-related events were those grouped as hyperkinesia (9.3%) and dystonia (7.3%). The incidence rates for hyperkinesia, dystonia and cogwheel rigidity (i.e. Parkinsonism) appeared dose-related and the subject incidences of events grouped as tremor and dyskinesia showed a trend towards dose-responsiveness. During the DB phase, combining EPS rating scales and anti-cholinergic medication usage revealed an apparent dose-related increase in the occurrence of treatment-emergent EPS based on anti-cholinergic medication used and there was a higher incidence of treatment-emergent EPS (akathisia) in the Medium and High groups than the Low and Placebo groups based on BARS global clinical rating scores. SAS results were inconclusive.

In study PSZ-3002, the most common EPS-related events were grouped as Parkinsonism (13.5%) and hyperkinesia (12.8%). The most common (>5%) occurring EPS-related events were akathisia (11.7%) and tremor (6.0%) with no cases of akathisia in the Placebo/Pali group. The incidence of EPS-related AEs grouped as Parkinsonism, hyperkinesia and dyskinesia was highest in the Pali (No DB)/Pali group. The Pali (No DB)/Pali group experienced an earlier time to first onset of akathisia compared to the other two treatment groups. Furthermore, more subjects in the Pali (No DB)/Pali group had a BARS total score of five or more early in the study, coinciding with reporting of the akathisia AEs. The Sponsor did not provide an explanation for this finding, but it may reflect a higher dosing regimen employed for those entering the study directly rather than clinical need *per se*.

In study PSZ-1001, five subjects (20%) reported EPS-related AEs. The end-of-study BARS scores increased with increasing paliperidone dosage. Only one subject had clinically reported akathisia. No overall clinical trends in global SAS scores were apparent but individual changes suggested a dose-related increase in changes from baseline for specific symptoms.

7.6.5. Suicidality

A blinded clinical review was conducted retrospectively for PSZ-3001 and PSZ-3002 using a C-CASA coding to each potentially suicide-related event and reported under three categories: suicidal, indeterminate and non-suicidal. Reviewers were blinded to double-blind treatment information and other dosing information. The C-SSRS was added to PSZ-3002 as a safety assessment via a protocol amendment dated 13 May 2009 but this submission only reports C-CASA findings.

In study PSZ-3001, one subject in the Placebo group (not self-injurious behaviour) and one subject in the Medium group (indeterminate incisional wound) met the criteria. Neither was believed to be related to study drug, or an indication of increased suicidal risk.

In study PSZ-3002, a total of 4.6% subjects (n=13) had possible suicide-related events. The highest incidence was in the Pali (No DB)/Pali group (8%), then the Placebo/Pali group (5.1%) and finally the Pali (DB)/Pali group (0.8%). "Suicidal behaviour" occurred in six subjects, all in the Pali (No DB)/Pali group (two suicide attempts, one preparatory act towards imminent suicidal behaviour and three subjects with suicidal ideation). There were seven cases classified as indeterminate (five in the Pali (No DB)/Pali group and one each in the other groups) and one case classified as non-suicidal in the Placebo/Pali group.

No potentially suicide-related events were reported in studies PSZ-1001 and PSZ-3003.

> **Comment:** In pooled Invega adult studies of 6-weeks' duration (see PI), the incidence of somnolence was up to 7% in treatment groups compared to 27.1% in the High group in PSZ-3001. Likewise sedation was up to 6% in adults and 16% in adolescents (study PSZ-1001). Hence, the effects on sedation but especially somnolence are far greater in adolescents. These have implications for dosing in adolescents as discussed in the Section on benefit-risk assessment.
>
> From the Invega PI, the Sponsor claims there is no dose-relationship for EPS in adults for doses 6mg and lower as well as no observed difference in the incident rate of EPS-related AEs between placebo and either 3mg or 6mg doses. While study PSZ-3001 only provided descriptive statistics, the Sponsor provided actual dose analyses that revealed much higher incidence in adolescents than adults for somnolence, tremor, dystonia and cogwheel rigidity in a dose-response manner. The 12-14 year age-group seemed particularly susceptible to akathisia at high dosage. The higher incident rates of EPS-related AEs (no prevalence data available for comment) have dosing implications (see Section on benefit-risk assessment for further discussion).

7.7. Specific safety issues of regulatory importance

7.7.1. Cardiovascular safety: Metabolic analysis

The information provided in this section was taken from the Clinical Safety Report. The rationale is that antipsychotics as a class are associated with the development of metabolic syndrome and enhanced cardiovascular risk.

7.7.1.1. Discontinuation/completion information

No subject in studies PSZ-3001, PSZ-3002 and PSZ-1001 withdrew due to metabolic TEAEs (including hyperglycaemia, new onset diabetes mellitus, dyslipidaemia, body mass index increased, increased appetite, obesity, overweight and weight increased).

7.7.1.2. Weight / Height / Body Mass Index / Waist Circumference

In study PSZ-3001, there were apparent dose-related increases in mean weight (0.0kg in the Placebo group, 0.3kg in the Low treatment group, 1.1kg in the Medium group and 1.4kg in the High group) and percent change in weight (0.1%, 0.5%, 1.9% and 2.2%, respectively). Tendencies to dose-related mean increases in BMI and waist circumference also occurred. When the data was presented as z-scores (adjusted for sex- and age-specific normative values in the US population) the Sponsor claimed there were no clinically significant mean changes in z-scores for weight, height or BMI from baseline to endpoint between Placebo and any active treatment group. Furthermore, the Sponsor claims there was no evidence of a dose-effect on z-score adjusted height, weight or BMI. There was an apparent dose-related trend in the percentage of subjects with increases in weight of at least 7% (2% in the Placebo group, 6% in the Low group, 13% in the Medium group and 13% in the High group). Increases in weight of at least 7% occurred as early as Day 15 for two subjects in the Medium group (one with normal BMI at baseline and one obese at baseline).

In study PSZ-3002, the mean changes in body weight, BMI and waist circumference from OL baseline to OL endpoint were less in the Pali (DB)/Pali group than the other two groups (which were similar in these parameters). The baseline body weight, BMI and waist circumference were greater in the Pali (No DB)/Pali group then the Pali (DB)/Pali group and then the Placebo/Pali group. The mean weight increase was 3.4kg (n=265). Based on comparative normative data the Sponsor reported no clinically significant changes in z-scores for height, weight and BMI. The percentage of subjects with increases in weight of at least 7% were 33% in the Placebo/Pali group, 28% in the Pali (DB)/Pali group and 38% in the Pali (No DB)/Pali group (Total group 33%). The values reported from DB baseline to OL endpoint were even greater, reflecting an accumulative effect in the measure of these parameters.

7.7.1.3. Lipids

In study PSZ-3001, the mean change in normal cholesterol (<170mg/dL) from baseline to maximum post-baseline value was -2.8mg/dL in the Placebo group and 12.6mg/dL in the paliperidone Total group. This represents an 8.3% increase in cholesterol in the active treatment compared with a 2.0% reduction for Placebo (p=0.013, unadjusted)). From the SCS, statistically separation occurred in two categories: increases in fasting triglycerides from normal (<150mg/dL) to borderline/high/very high (≥ 150mg/dL) occurred in 17% (n=17) of subjects in the paliperidone Total group and 3% (n=1) in the Placebo group (p=0.042) and increases of ≥ 50mg/dL in fasting triglycerides occurred in 23% of the Total group and 5% in Placebo (p=0.010).

In study PSZ-3002, the largest mean changes from OL baseline to the maximum or minimum post-baseline value by baseline lipid category for the paliperidone Total group revealed: the largest mean changes in lipid parameters occurred in subjects with normal baseline values and in the groups of subjects with borderline or high values, the mean changes were generally in the direction of normal i.e. mean decreases for cholesterol, LDL and triglycerides and mean increases in HDL. From the SCS, OL baseline to OL endpoint treatment-emergent significant changes occurred in at least 20% of the paliperidone Total group as follows: increases in fasting total cholesterol from normal to borderline, 22%; increases in fasting total cholesterol from borderline to high, 24%; increases in fasting LDL from borderline to high, 21%; increases in triglycerides of at least 50mg/dL, 26%. The percentages of subjects with treatment-emergent significant changes were similar in the subset with at least 12 weeks exposure compared to the subset with at least 24 weeks exposure in all the parameters. However, a majority of the values recorded in the at least 24 week exposure subset were numerically higher than the corresponding at least 12 week values, indicating a possible upward trend towards dyslipidaemia.

7.7.1.4. Fasting glucose / Insulin / IGF / IGFBP-3 / HOMA

Fasting insulin, insulin-like growth factor (IGF) and IGF binding protein-3 concentrations were determined in addition to the normal serum chemistry panel to better characterise the occurrence of metabolic syndrome, hyperglycaemia and diabetes mellitus. Homeostasis model assessment (HOMA, measuring insulin resistance and beta-cell function) and glucose abnormalities (changes from baseline to treatment-emergent abnormal values, evaluated according to American Diabetes Association guidelines) were performed retrospectively for PSZ-3001 and prospectively for PSZ-3002.

In study PSZ-3001, at baseline, 98% subjects did not have a diabetes-related history (hypertension, dyslipidaemia, cardiovascular disease, cerebrovascular disease, hepatitis or relatives with diabetes). Overall, there were no clinically significant changes in these parameters over the 6-week study period. One subject in the Placebo group and three subjects in the High group went from normal to high (≤ 200mg/dL) in fasting glucose levels and one subject in the Low group had ketonuria. All treatment groups had mean HOMA-IR values greater than one indicating pre-existing insulin resistance (lower insulin sensitivity) at baseline. There

were no consistent changes in mean HOMA-IR from baseline to endpoint in paliperidone groups. All mean baseline values for HOMA-%B exceeded 100 indicating an increased beta-cell function at baseline and HOMA-%B analysis showed small increase at endpoint in all groups other than a small mean decrease in the Medium group.

In study PSZ-3002, all groups experienced a shift from fasting glucose to high (6.5% in the Placebo/Pali group, 2.1% in the Pali (DB)/Pali group and 1.2% in the Pali (No DB)/Pali group). One subject in the Pali (DB)/Pali group experienced a shift from impaired fasting glucose to high fasting glucose. From the SCS, increases in glucose of at least 10mg/dL relative to baseline occurred in subjects who had: normal baseline glucose levels (30%), impaired fasting glucose (12%) and none of those who had diabetes mellitus (i.e. high levels). One subject in the OL study Total paliperidone group had glycosuria. At OL baseline, HOMA-%B geometric mean values across all three treatment groups indicated a mild to moderate degree of beta-cell dysfunction (range 126.6 to 134.0). No consistent pattern in the change from OL baseline was observed across all treatment groups in HOMA-IR. Only the Pali (No DB)/Pali group had a mean increase in insulin resistance (from 2.49 at baseline to 2.75 at endpoint). Decreases in the geometric means for beta-cell function across all treatment groups were noted in HOMA-%B from OL baseline to endpoint, although the change for the Pali (No DB)/Pali group was negligible (0.5 units).

> **Comment:** The adverse changes across all lipid parameters, the significant weight gain and a tendency to hyperglycaemia and increased insulin resistance and reduced beta-cell function suggest a significant metabolic risk for the adolescent population who receive paliperidone in the long-term. This appears to be a class effect of antipsychotics. The effect on weight gain and lipid parameters appears to be greater than that seen in adults taking paliperidone. Furthermore, the increase in weight is comparable to that observed in adolescents with schizophrenia taking olanzapine. While the Sponsor claims no clinically significant findings in relation to weight from the results of z-score analyses, it is unclear (in terms of growth-adjusted weight gain) how much gain (in kilograms) is expected over the study periods examined. Furthermore, the usefulness of US normative data in which up to 85% of the study population in PSZ-3001was not from the US is uncertain.
>
> The usefulness of HOMA analysis in the clinical settings of PSZ-3001 and PSZ-3002 is not established. The insulin-resistance noted at baseline among all groups may not be representative of the Australian situation in the target group.

7.8. Other safety issues: Safety in special groups and situations

7.8.1. Intrinsic factors

Subgroup analyses of TEAEs were performed for PSZ-3001 and PSZ-3002 in the Clinical Safety Report. The population of PSZ-3001 was too small to draw meaningful conclusions, especially in relation to the under-representation of 12-14 year-olds.

7.8.1.1. Age

In study PSZ-3001, there were no dose-related trends for any parameter among 12-14 year olds. The only noteworthy differences between paliperidone and Placebo were in the proportions of subjects with decreases in standing and supine systolic blood pressure and decreases in standing and supine diastolic blood pressure, which occurred at higher incidences in at least one of the paliperidone treatment groups than in the Placebo group. Among 15-17 year olds there were apparent dose-related effects on increases in standing and supine pulse rates. Increases and decreases in standing diastolic blood pressure and increases in standing systolic blood pressure occurred at higher incidences in at least one of the paliperidone treatment groups than the Placebo groups. Decreases in supine diastolic blood pressure

occurred at higher incidences in the paliperidone High treatment group than the Placebo group. In the High group, the percentage of subjects with TEAEs was higher in the 12-14 year group (100%) than in the 15-17 year group (64.7%) whereas the other groups varied in their findings but the overall incident rate was comparable between age-groups (62.2% in 12-14 year-olds and 61.0% in 15-17 year-olds). A dose-response relationship appeared for somnolence in both age-groups (28.6% incidence in the 12-14 year old High group compared to 17.6% in the corresponding 15-17 year old age-group). A dose-response relationship appeared for akathisia in both age-groups (28.6% incidence in the 12-14 year old High group compared to 11.8% in the corresponding 15-17 year old age-group).

In study PSZ-3002, the incidence of subjects with an increase in standing and supine pulse rate in the Total group was higher in 15-17 year olds compared to 12-14 year olds relative to OL baseline and, in 15-17 year olds, 25% had an increase in standing pulse rate and 11% had an increase in supine pulse rate (compared to 14% and 5% for 12-14 year olds, respectively). The incidence of subjects with an increase in standing pulse rate in the Total group was higher in subjects aged 15-17 years (21%) compared to 12-14 year olds (7%), relative to DB baseline. The percentage of subjects with TEAEs was higher in the 12-14 year group (78.9%) than in the 15-17 year group (69.9%) based on all subjects who received OL paliperidone. The incidence of TEAEs in the Pali (DB)/Pali by age-group was similar (63.9% for 12-14 year-olds and 68.3% for 15-17 year-olds). In the Placebo/Pali group, 12-14 year-olds had a much higher incidence of TEAEs than the 15-17 year-olds (85.7% v 68.8%, respectively). In the Pali (No DB)/Pali group, 12-14 year-olds had a much higher incidence of TEAEs than the 15-17 year-olds (93.9% v 71.7%, respectively). In those subjects with somnolence, 15-17 year-olds had a much greater incidence in the Placebo/Pali group than in the Pali (DB)/Pali and Pali (No DB)/Pali groups (28.1% v 13.4 v 12.0%, respectively). In those subjects with somnolence, the 12-14 year-olds in the Pali (No DB)/Pali group had the lowest incidence then the Placebo/Pali group then the Pali (DB)/Pali group (6.1% v 14.3% v 19.4%, respectively). The incidences of akathisia were higher in both age-groups in the Pali (No DB)/Pali group (15.2% in 12-14 year-olds and 21.7% in 15-17 year-olds) compared to the Pali (DB)/Pali group (5.6% for 12-14 year-olds and 7.3% for 15-17 year-olds). The incidences of headache were higher in both age-groups in the Pali (No DB)/Pali group (21.2% in 12-14 year-olds and 19.6% in 15-17 year-olds) compared to the Pali (DB)/Pali group (2.8% for 12-14 year-olds and 6.1% for 15-17 year-olds) and Placebo/Pali group (0% for 12-14 year-olds and 12.5% for 15-17 year-olds).

7.8.1.2. Sex

In study PSZ-3001, the percentage of subjects with TEAEs was similar among males (61.1%) and females (61.8%). The percentage of subjects with TEAEs was higher in females than males in the Placebo, Low and Medium groups (67.9% v 47.8%, 58.3% v 43.3% and 64.7% v 58.1%, respectively). The percentage of subjects with TEAEs was higher in males than females in the High group (79.4% v 64.3%, respectively). Males and females showed a dose-response relationship in somnolence, with females generally having higher incidences than males (except in the High dose group). Males and females showed a dose-response relationship in akathisia, with females generally having higher incidences than males (except in the Medium dose group when no females reported akathisia).

In study PSZ-3002, the percentage of subjects with TEAEs was similar among males (71.9%) and females (73.0%) who received OL paliperidone. Females had higher incidences of TEAEs than males in the Placebo/Pali and Pali (No DB)/Pali groups than the Pali (DB)/Pali group (81% v 82.9% v 59.1%, respectively). Males had a higher incidence of TEAEs than females in the Pali (DB)/Pali group compared to the Placebo/Pali and Pali (No DB)/Pali groups (71.6% v 61.1% v 74.7%, respectively). Females had a higher incidence of somnolence than males in all groups (33.3% v 16.7% in the Placebo/Pali group, 18.2% v 13.5% in the Pali (DB)/Pali group and 14.0% v 8.0% in the Pali (No DB)/Pali group). Females in the Pali (No DB)/Pali group had the highest incidence of akathisia (30.0%) followed by males in the Pali (No DB)/Pali group

(13.3%) then males in the Pali (DB)/Pali group (8.1%) then females in the Pali (DB)/Pali group (4.5%). Females in the Pali (No DB)/Pali group had the highest incidence of headache (28.1%) followed by males in the same group (14.7%) then females in the Placebo/Pali group (14.3%).

7.8.1.3. Race

In view of the under-representation of many racial groups, other than Caucasian, the study findings prevent meaningful comparisons between treatment groups.

7.8.1.4. Baseline body weight

In study PSZ-3001, the incidences of most common TEAEs (somnolence, akathisia, insomnia, headache, tremor and schizophrenia) in the total paliperidone group were higher in the heavier subjects. In those weighing <51kg only the High group had a markedly higher incident rate than the other groups. In those weighing at least 51kg, there appeared to be a dose-response relationship in paliperidone treatment groups.

In study PSZ-3002, the incidence of TEAES was higher (74.2% v 65.6%) in subjects who weighed at least 51kg at open-label baseline than in subjects who weighed less than 51kg in the Total treatment group. TEAEs occurred in more subjects weighing under 51kg in the Placebo/Pali group than those weighing at least 51kg (77.8% v 70.0%). TEAEs occurred in more subjects weighing at least 51kg in the Pali (DB)/Pali group than those weighing less than 51kg (70.7% v 58.3%). Higher incidences of akathisia were found in the low-weight subjects in the Pali (No DB)/Pali and Pali (DB)/Pali groups (25.0% and 8.3%, respectively). The second highest incidence of akathisia was found in the heavier subjects in the Pali (No DB)/Pali group (19.3%). Somnolence occurred with greatest frequency in the Placebo/Pali group (26.7% for those at least 51kg and 22.2% less than 51kg) whereas the lowest incidence occurred in the heavier subjects in the Pali (No DB)/Pali group. No cases of headache were reported in those low-weight subjects in the Placebo/Pali and Pali (DB)/Pali groups. The highest incidence of headache occurred in the heavier subjects in the Placebo/ Pali group (13.3%) then the low-weight Pali (No DB)/Pali group (12.5%).

7.8.2. Extrinsic factors: US v non-US sites

In study PSZ-3001, in the paliperidone Total group, TEAEs occurred in 90.5% subjects from US sites and 56.6% from non-US sites. TEAEs occurred with higher frequencies from US sites than non-US sites in all treatment groups (88.9% v 52.4% in the Placebo group, 100% v 41.3% in the Low group, 83.35 v 57.1% in the Medium group and 85.7% v 73.2% in the High group). No cases of akathisia were identified in any US subject. A dose-response relationship occurred with akathisia in non-US sites (0.0% in Placebo, 4.3% in the Low group, 9.5% in the Medium group and 19.5% in the High group).

In study PSZ-3002, TEAEs occurred in 89.4% subjects from US sites and 68.9% from non-US sites. TEAEs occurred with higher frequencies from US sites than non-US sites in all treatment groups (100% in the Placebo/Pali group, 78.6% in the Pali (DB)/Pali group and 92.9% in the Pali (No DB)/Pali group). No cases of akathisia were reported from US subjects. Akathisia occurred in non-US subjects in 7.7% of the Pali (DB)/Pali group and 25.8% of the Pali (No DB)/Pali group. Headache appeared to be more common in US subjects than non-US subjects in the Pali (DB)/Pali and the Pali (No DB)/Pali groups (14.3% v 3.8% and 35.7% v 15.5%, respectively) although no cases of headache were reported for the US Placebo/Pali group (compared to 11.8% in non-US subjects).

> **Comment:** Generally, the older heavier subjects showed dose-response relationships in TEAEs. In several instances, 12-14 year-olds appeared more prone to certain TEAEs (especially EPS-related TEAEs), which goes against the assumption that dosing of Invega should be made irrespective of age. Males and females showed similar trends in TEAEs, although in the main females seemed more prone to certain TEAEs. This may reflect the recognised reduction in clearance of paliperidone in female subjects. The stratification

of TEAEs by bodyweight category is less clear. The findings also suggest marked differences in the US population versus other participating countries in terms of diagnostic and treatment approaches.

7.9. Post-marketing experience

The Sponsor's Global Medical Safety division assessed the post-marketing exposure and safety information for its Invega products in patients less than 18 years of age in a cumulative review ending 31 May 2010. This review included assessment of all spontaneous reports received recorded in SPECTRE, part of the Benefit Risk Management worldwide safety database. The results are summarised below:

> A total of 185 cases involving paediatric patients (aged <18 years) were received during the cumulative review period, of which 42% were serious. The patterns of disproportionality reported preferred terms were generally consistent with those identified during adult clinical studies and post-marketing experience. The preferred terms that demonstrated disproportionality were swollen tongue, chest pain, accidental drug intake by child, increased appetite, drooling, dystonia, hypersomnia, abnormal behaviour, aggression and off-label use.
>
> No disproportionality of reporting was noted for paediatric patients when compared to other age groups with respect to any of the predefined areas of clinical interest, including the collective group of all EPS, weight gain, prolactin-related events, glucose metabolism disorders, cardiac events, suicidality or sedation. AEs were consistent with the known safety profile for paliperidone. EPS, including dystonia, are reflected in the current company core data sheet for paliperidone.
>
> There were no fatal cases reported in paediatric patients treated with paliperidone during the cumulative review period.
>
> The Sponsor concludes that uncommon (<1%) AEs have been reported in paediatric patients consistent with the company core data sheet. No new safety concerns specific to a paediatric population receiving paliperidone were identified during the review.

Furthermore, the following is taken from the Paliperidone ER – Adverse Drug Reaction Determination Using the MedDRA Terminology document dated 17 August 2010:

> The following ADRs were identified in paediatric subjects with schizophrenia but not in adult subjects with schizophrenia or schizoaffective disorder, in clinical studies of other indications, or during post-approval use of INVEGA (INVEGA USPI 20103): Bundle branch block right, eye movement disorder, alanine aminotransferase increased, aspartate aminotransferase increased, nuchal rigidity, muscle contractions involuntary, opisthotonus, speech disorder, tongue paralysis, insomnia, anxiety, epistaxis, and hypertension.

Comment: Two years have elapsed since the Sponsor conducted its cumulative review and so it is difficult to determine whether the AE picture has changed in any significant way. The ADR Determination document indicates other AEs associated with the paediatric population receiving paliperidone. The Sponsor has requested inclusion of these latter ADRs into the PI. This is acceptable to this evaluator.

While the AEs reported post-market are generally consistent with those found with paliperidone in adults, risperidone in adolescents and children, and other neuroleptic agents, there are differences too. The incidence of EPS-related TEAEs in the submitted trials (and changes in body weight indices and lipid fractions) appears much higher than those reported in post-market reports with adults taking paliperidone. A direct comparison between pre- and post-market data has limitations with a suggestion of higher reporting rates of SAEs in the latter setting.

7.10. Evaluator's overall conclusions on clinical safety

The results of the Phase III studies, PSZ-3001 and PSZ-3002, were not pooled because of differences in their design and duration. However, many findings were similar across the studies and generally consistent to those found in paliperidone use in adults with schizophrenia and similar conditions, as well as those with risperidone and quetiapine in adolescents. However, higher incidences of dystonia, hyperkinesia, tremor and Parkinsonism were found in adolescents compared to adults receiving paliperidone. Furthermore, the incident rate of EPS-related AEs appears to be related to duration of exposure to paliperidone. In PSZ-1001, subjects were exposed for up to 9 days and experienced 20% EPS (comparable to the rate found in adult populations receiving paliperidone in longer-term studies). In the 6-week efficacy study this rate rose to 31% (46/150) and in the 6-month safety study the rate rose to 40% (114/282). However, these rates are based on the number of subjects experiencing at least one AE NOT the number of events *per se*.

Study PSZ-3001 revealed an apparent dose-related trend in all categories of treatment-emergent adverse event. This study also revealed an apparent dose-relationship for the incidence of somnolence, akathisia, tremor, dystonia and tachycardia, as well as an apparent dose-related trend in the incidence of EPS (supported by increased use of anti-EPS medication). These have implications for dosing (see Section on benefit-risk assessment).

In study PSZ-3002, most of the serious TEAEs and those that led to study discontinuation occurred in the newly exposed groups to study medication i.e. Placebo/Pali and Pali (No DB)/Pali. Higher incidences of many TEAEs e.g. akathisia and potential-suicide-related adverse events occurred in the Pali (No DB)/Pali group (8%), which may reflect a more severe patient population (supported by baseline PANSS total scores and CGI-S scores).

Whereas laboratory findings for haematology, urinalysis, endocrine, renal, hepatic, thyroid and electrolytes were generally unaffected by paliperidone treatment, prolactin levels rose in every study, as predicted by its effect on dopamine D2 receptors. Study PSZ-3001 showed dose-related increases in prolactin levels in males and females. Only female subjects had potential prolactin-related adverse events. In the open-label safety study, PSZ-3002, the highest prolactin levels were achieved in the Placebo/Pali and Pali (No DB)/Pali groups i.e. those more recently exposed to study drug. Again, female subjects experienced much more potential prolactin-related adverse events (14.7%) than their male counterparts (2.4%), with 7.4% incidence overall. Prolactin levels for Seroquel (quetiapine) in adolescents with schizophrenia were greater than 10% overall and higher than levels seen in adults (see Seroquel PI). Hyperprolactinemia may have long-term effects on pubertal development and sexual maturation.

No effect on growth and sexual maturation was demonstrated in this submission based on Tanner staging. However, such an effect cannot be ruled out without more long-term data. The findings for reduced IGF and IGFBP-3 levels in these studies suggest a possible effect on growth hormone. Further study is required. The effect of paliperidone on testosterone levels in males has not yet been established.

No consistent effect on QT indices or vital sign parameters was demonstrated in these studies other than heart rate, which is predicted based on the pharmacology of paliperidone. Study PSZ-3001 showed dose-related increases in standing and supine pulse rate, particularly in 15-17 year olds. Study PSZ-3002 supports this finding in this age-group and the effects have been observed in adult studies as well as in olanzapine in adolescents (see Zyprexa PI).

Orthostatic hypotension occurred primarily in the Pali (No DB)/Pali group in study PSZ-3002 (10%) and 12% incidence in Study PSZ-1001. Hence, this needs to be monitored in patients receiving paliperidone especially with initial dose titration or when used concurrently with anti-hypertensive medication.

A relationship to baseline bodyweight category (<51 kg or ≥ 51kg) was demonstrated. Study PSZ-3001 revealed an apparent dose-response relationship in TEAE incidence for those weighing at least 51kg, which represented a majority of the study population. Incidence of TEAEs was generally higher in heavier subjects except for the High group in Study PSZ-3001 and the low-weight subjects in the Pali (No DB)/Pali group in study PSZ-3002 (high incidence of akathisia). No analysis of baseline bodyweight by gender or age-group was presented here so the effect of baseline bodyweight could not be fully ascertained.

No new unexpected serious treatment-emergent adverse event or death occurred in any study presented here but the effect of study medication on lipid parameters is of particular concern, as these appear more marked in adolescents than adults. The metabolic analysis was inconclusive and further study is required to quantify the magnitude of the risk of developing metabolic syndrome, and its sequelae. However, the findings in this submission support a trend towards developing metabolic syndrome (and increased cardiovascular risk). In particular:

1. Study PSZ-3001 demonstrated dose-related changes in weight, BMI and waist circumference. Such trends continued into the OL study, when weight gain of at least 7% occurred in 41% of the Placebo/Pali group and 38% of the Pali (DB)/Pali group from DB baseline (compared to 33% Total from the OL baseline). The biggest changes that occurred from the OL baseline were in the newly exposed Placebo/Pali and Pali (No DB)/Pali groups, as expected from new exposure to study medication at higher doses than recommended. These findings are comparable to quetiapine in adolescents in an OL 26-week study, which revealed 45% of subjects had at least a 7% weight gain (see Seroquel PI). No values of percent weight-gain at the 15% and 25% levels are presented in this submission for paliperidone in adolescents.

2. Whereas total cholesterol rose by 8.3% from baseline to endpoint in the 6-week study, PSZ-3001, with a tendency towards hypertriglyceridemia, the findings in the OL study at endpoint revealed in excess of 20% changes from normal baseline in many lipid parameters. This is consistent with risperidone in which “significant rises in triglycerides” were noted (Risperdal PI).

3. HOMA analysis revealed all groups in studies PSZ-3001 and PSZ-3002 had pre-existing glucose resistance at baseline with accompanying increased beta-cell function, but no consistent changes occurred between the groups from baseline to their respective endpoints. However, in Study PSZ-3002, all groups had a shift from baseline fasting glucose to high glucose at endpoint, suggesting the potential to develop hyperglycaemia.

Differences in incidences of TEAEs between 12-14 year-olds and 15-17 year-olds may be due to the small numbers of the younger age-group that participated in the Phase III studies. While both age-groups showed an apparent dose-response relationship for somnolence and akathisia in study PSZ-3001, the latter adverse event was especially high in 12-14 year-olds (28.6%). Indeed, younger subjects in the High group had 100% incidence of TEAEs. Furthermore, 12-14 year-olds in study PSZ-3002 had higher incidences of TEAEs in the new exposure to study medication, Placebo/Pali and Pali (No DB)/Pali groups, especially in regards to akathisia. No analysis of age by gender or baseline bodyweight was presented here so the effect of age could not be fully ascertained. Based on these findings, dosing in 12-14 year-olds cannot be recommended.

Females generally showed higher incidences of TEAEs (especially somnolence and akathisia) than males in study PSZ-3001 (except the High group) and in the Placebo/Pali and Pali (No DB)/Pali groups in study PSZ-3002. No analysis of gender by age-group or baseline bodyweight was presented here so the effect of gender could not be fully ascertained.

The information provided in this submission regarding an effect of racial origin on incidence of TEAEs was inconclusive. In terms of US versus non-US subjects, the percentage of TEAEs in all treatment groups, irrespective of the study, was much higher in US subjects. Furthermore, no US

subject was diagnosed with akathisia. This raises the question of whether there are inherent differences between those selected to participate in the studies from the US and those not in the US, or indeed, there are major cultural differences in the experience of and diagnosis of schizophrenia.

Study PSZ-3002 protocol amendment INT-2 in June 2008 i.e. one year after study commencement deleted the following phrase: "As there is specific interest in the long-term tolerability of the higher doses investigators will be encouraged to titrate the dose to the maximum tolerable level". The mode dose data provided appear to reflect this approach, whereby most subjects exceeded the recommended starting dose of 3mg. The high incidence of weight-gain, prolactin levels, lipid parameters and the higher incidence of EPS-related AEs compared with paliperidone in adults in the open-label study lend further support to a trend towards supra-maximal dosing in the clinical trials cited in this application.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The following benefits for administering paliperidone in an adolescent population with schizophrenia have been identified:

- Paliperidone appears to have some benefit in terms of efficacy for the 15-17 year age-group at a dose of 3mg for those weighing under 51kg and a daily dose of 6mg for those weighing at least 51kg.
- Currently there is no Australian approved product for 12-year-olds with schizophrenia to receive an atypical antipsychotic (Seroquel is approved for 13 to 17 years, inclusive).
- Approval of Invega allows medical practitioners another choice of atypical antipsychotic agent in an adolescent population with diagnosed schizophrenia.
- From the submitted studies (and adult studies in paliperidone), most treatment-emergent adverse events tended to occur at higher dosages (9 to 12mg/day). Restricting the dosage to a maximum of 6mg/day for the heavier subjects may help to minimise some observed adverse events (especially extrapyramidal adverse events).
- The Sponsor has recommended in its PI that all adolescents be commenced on a dose of 3mg/day. For the heavier patients, this dosage may be sub-optimal but it vies on the side of caution, which is to be commended.
- Dose titration of paliperidone appears less complex than dose titration with Seroquel (quetiapine).
- The effects of paliperidone on weight gain are significant but may appear more favourable than quetiapine in adolescents with schizophrenia.
- On page 19 of the Paediatric Investigation Plan, paliperidone 3mg/day in adults is comparable to a 1mg/day risperidone dose, which is not considered an effective dose in the treatment of schizophrenia. Hence, paliperidone may offer some benefit over risperidone.
- The open-label study is ongoing and hence two years' data are expected to be available in late 2013. There is a lack of long-term safety data for antipsychotics in adolescents and so this new information will assist in understanding the longer-term effects of paliperidone in relation to maturational, growth, behavioural and cognitive development and also greater understanding of the metabolic risk this agent poses.

- The results of the on-going Phase III study, PSZ-3003, which is a comparator study of paliperidone versus aripiprazole will be available in late 2013 too. It is hoped the study findings will help establish the role of paliperidone in the acute and maintenance phase of schizophrenia and help to further quantify the metabolic risk of paliperidone (especially as aripiprazole is claimed to have much less effect on weight-gain than most other approved atypical antipsychotic agents).
- No deaths were reported in all paliperidone Phase I and Phase III studies at cut-off point.

8.2. First round assessment of risks

The risks of administering paliperidone to adolescents (12-17 years, inclusive) with schizophrenia are considerable:

- Short-term efficacy (6-weeks) was only established in a small group of subjects in one treatment arm (Medium group in the pivotal efficacy study, representing 48 subjects). Most of these subjects were in the 15-17 year age-group.
- The US subjects (which more closely align with the Australian population) failed to show any significant effect in efficacy or much benefit after 6-months treatment with open-label paliperidone.
- There is no pharmacokinetic data in children and adolescents to support a 3mg dosage regimen (the recommended starting dose in the Invega PI).
- The effects of toxicity on age were much more apparent than efficacy, with those younger subjects having generally higher incidences of TEAEs than their older peers. Study PSZ-3001 demonstrated dose-response relationships with akathisia and somnolence that were markedly higher in the High dose group in 12-14 year-olds. In the open-label study, 12-14 year-olds newly exposed to study medication (i.e. those in groups Placebo/Pali and Pali (No DB)/Pali) had much higher incidences in TEAEs (especially akathisia in the latter group) than their older peers. On this basis, the younger age-group appear to be more sensitive to developing TEAEs (especially EPS-related adverse events) than the 15-17 year age-group.
- Dosage reductions are recommended in all forms of renal dysfunction in adults but there are no comparative data in children or adolescents taking paliperidone. It is expected that dosage reduction will be required in any patient with a creatinine clearance below 80mL/min.
- The long-term safety data is limited in regards to the effects of paliperidone upon growth, maturational, behavioural and cognitive development. Such effects cannot be ruled out without further study.
- The findings for reduced IGF and IGFBP-3 levels in these studies suggest a possible effect on growth hormone and its sequelae. Further study is required. Similarly, the effect of paliperidone on endocrine function, testosterone levels in males in particular, has not yet been established.
- In Study PSZ-3002, 7.4% of subjects demonstrated markedly raised serum prolactin levels (females much greater than males). While the effect of paliperidone is predicted from its pharmacological effects on dopamine D2 receptors, such raised levels in an adolescent population are of concern at a time of major maturational, behavioural and cognitive development.
- The raised cholesterol fractions and triglycerides in the Phase III studies are a concern in relation to the risk of developing metabolic syndrome. The lipid results found in adolescents taking paliperidone appear worse than in adults.

- The effects on weight gain and metabolism in adolescents, including the risk of developing metabolic syndrome have not been studied over a prolonged period. However, the findings in this submission are of concern. Weight gain of at least 7% from study baseline to endpoint in the open-label study of 33% is of particular concern, especially when this level rises to 39% if the results of the double-blind baseline are taken into consideration. These findings are similar to those found in quetiapine. The Sponsor does not think the findings in relation to weight gain are clinically significant. The Sponsor argues the changes relate to normal changes in growth and development by using standardised normative data derived from a US population. Given the findings in terms of efficacy and toxicity in the US subjects and the diverse range of subjects from other countries (particularly Asia), the use of US normative data seems an inappropriate measure and downplays the real effect/risk of paliperidone on weight gain.
- In terms of hyperglycaemia, all groups in study PSZ-3002 had a shift from baseline fasting glucose to high glucose at endpoint, suggesting the potential to develop hyperglycaemia. Given epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with atypical antipsychotics, monitoring is recommended.
- The Phase III studies demonstrated a treatment-emergent effects on raised pulse rate (supine and standing). This was particularly seen in the 15-17 year-age group (dose-response relationship) and is consistent with this finding in adults taking paliperidone and adolescents taking olanzapine. The significance of this effect has not been determined.
- Females tended to have higher incidences of TEAEs than their male counterparts, especially somnolence, headache, akathisia and prolactin levels. From the Invega PI, adult females are reported to have a 19% reduction in apparent clearance compared to males. The higher incidences in some observed TEAEs in the Phase III studies lend support to lower dosage regimens in females and hence greater risk to females should dose modification not ensue.
- Study PSZ-3002 dosed according to clinical response and tolerability of study medication rather than a weight-based dosing schedule (as used in Study PSZ-3001). The Sponsor asserts that as most TEAEs were found in heavier subjects, no weight-based dosage schedule is required. While most TEAEs were experienced in heavier subjects (which accounted for a majority of participants in the Phase III studies) there were exceptions. In particular, those weighing <51kg in the High group in Study PSZ-3001 had a markedly higher incident rate than the other groups. Furthermore, higher incidence rates of akathisia were found in the low-weight subjects in the Pali (No DB)/Pali and Pali (DB)/Pali groups in study PSZ-3002. Therefore, low-weight subjects may be more at risk should no weight-based dosing schedule be employed.
- The Phase III studies did not demonstrate appreciable changes of study drug on QT indices but such an effect cannot be discounted in the use of antipsychotics especially in subjects with a history of cardiac arrhythmias, congenital long QT syndrome or those subjects taking concomitant medications that prolong the QT interval.
- Six subjects in study PSZ-3002 were categorised under “suicidal behaviour”, which included two suicide attempts. All of these cases came from the treatment group, Pali (No DB)/Pali. Five additional indeterminate cases were also recorded from this group. This treatment group was recruited independently from the pivotal efficacy (double-blind) study and formed a more severely unwell population than those entering from the double-blind study (based on PANSS total score and CGI-S score). Both Phase III studies had similar entry criteria (including a K-SADS-PL diagnostic interview to assess suicidality and a requirement to have a score of ≤ 2 for each item). This finding highlights the need for vigilance for suicidal and self-harming behaviours in an adolescent population.

- Paliperidone has been demonstrated in the acute phase treatment of schizophrenia in adolescents only in one treatment arm and not in first episode presentations. Furthermore, maintenance of efficacy has not been demonstrated in the open-label study, or relapse prevention. Administering paliperidone beyond established acute episodes of schizophrenia potentially places subjects, many of whom are vulnerable, at risk of unwanted and unnecessary side-effects.
- Adolescents with schizophrenia taking paliperidone have higher rates of some adverse events than adults. This was particularly evident in relation to EPS-related adverse events (especially akathisia and Parkinsonism). No adolescent subject taking paliperidone had established tardive dyskinesia but, given a weak association between the development of Parkinsonism and developing tardive dyskinesia, as well as the propensity of antipsychotic agents to develop this condition the risk of administering paliperidone (especially at doses exceeding 6mg/day) need to be carefully weighed.
- Although effects on reduced thyroid function, blood dyscrasias (leukopenia, thrombocytopenia and agranulocytosis in particular), seizures, NMS, body temperature dysregulation and gastro-intestinal obstruction have not been identified with paliperidone in adolescents the risk remains in place for all antipsychotic agents and need to be factored into a risk-benefit assessment process.
- Unlike adult data that suggests no dose-response relationship in TEAEs below 6mg/day, PSZ-3001 has demonstrated this does occur in adolescents, suggesting a higher likelihood of toxicity in this population (particularly the younger, lighter subjects).
- A comparison of pre- and post-market AEs for paediatric paliperidone ER as of two years ago, suggests higher rates of EPS-related TEAEs, weight gain and dyslipidaemia in the Phase III clinical trials for the target population. Caution needs to be exercised in comparing post-marketing data to controlled trials.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of paliperidone ER, given the proposed extension of indication, is not favourable. Only one treatment arm (the Medium group), representing 48 subjects, demonstrated clinical efficacy over the 6-week study period. Only 16 of these subjects were in the 12-14 year age-group, with no demonstrated efficacy in this sub-population. Considering the net mean reduction in PANSS total score was only 9.4 points, this result translates into a modest clinical benefit.

Efficacy findings in the open-label study, PSZ-3002, have limited usefulness, given the study limitations. The findings did not provide convincing evidence of efficacy over the 6-months' study duration and therefore maintenance treatment with paliperidone ER cannot be recommended (this was not a study objective).

In contrast to efficacy, significant dose-related toxicity has been demonstrated particularly in relation to extrapyramidal-related treatment-emergent adverse events. The 12-14 year old age-group is at particular risk of developing akathisia. The incidence of many TEAEs appeared higher during the open-label study, even allowing for higher dosing than in the pivotal study. In the absence of TEAE-specific prevalence data it is difficult to determine the risk of developing a particular adverse event. However, most of the observed TEAEs were expected as a class effect of neuroleptic agents.

The risk of developing metabolic syndrome and cardiovascular disease (as evidenced by significant weight gain and adverse lipid fractions in studies PSZ-3001 and PSZ-3002) by giving paliperidone to adolescents is too great when balanced against a possible short-term reduction in symptoms.

When the results are available for the entire 2-year safety study, PSZ-3002, as well as the ongoing Phase III safety and efficacy comparative study, PSZ-3003, the risk to the patient will become much clearer. As the application currently stands, given the lack of demonstrable efficacy beyond 6mg/day and the higher adverse event profile for doses exceeding 6mg/day (especially EPS-related and metabolic-related AEs) this evaluator cannot recommend this product for the proposed indication. Invega currently poses too great a risk to adolescents with schizophrenia for the expected benefit.

This evaluator would recommend rejection of the proposed extension of indications for paliperidone use in adolescents with schizophrenia, if such indication relied solely on the submitted PK data. Even though the Sponsor failed to provide a dose-ranging study in adolescents or demonstrate similar PK to adults at doses below 6mg/day, the risk to the adolescent subject, provided they do not have renal impairment, is not regarded as high by this evaluator. Adult data clearly demonstrates consistency in PK parameters from 3-12mg/day. Furthermore, based on PK data from risperidone in children and adolescents, this evaluator is confident the risk of administering paliperidone ER to the 15-17-year age-group (representing 80% of the study population) is acceptable, especially given the lower expected toxicity for a 3mg/day dosing regimen in this age-group.

The benefit-risk balance of paliperidone ER is unfavourable given the proposed usage, but would become favourable if the changes recommended under *First round recommendation regarding authorisation* are adopted.

9. First round recommendation regarding authorisation

This evaluator believes the clinical data provided in this submission does not support the safe and effective use of paliperidone in an adolescent population. On this basis, rejection of the proposed extension of indication of paliperidone to adolescents (12-17 years, inclusive) in schizophrenia is recommended.

Furthermore, should the application for extension of indications not continue to the next Milestone, this evaluator recommends the submitted safety-related data in relation to children and adolescents is still included in the Product Information.

The benefit-risk balance of paliperidone ER is unfavourable given the proposed usage, but would become favourable if the following recommended changes are adopted:

I Approval is restricted to acute treatment only (in established schizophrenia);

II Approval is restricted to the 15-17 year age-group (as currently licensed for risperidone, of which paliperidone is the major metabolite);

III The dosage range is restricted to 3 to 6mg once daily i.e. a maximum daily dose of 6mg. If higher doses are approved then this evaluator recommends a dosing-based schedule based on bodyweight as per the pivotal study i.e. those weighing less than 51kg should be given a lower dose than those weighing at least 51kg.

10. Clinical questions

10.1. Pharmacology (Pharmacokinetics)

1. What is the volume of distribution, elimination half-life and single-dose pharmacokinetic (PK) parameters for paliperidone in study PSZ-1001?

2. In the population PK analysis, why was body-weight used as a covariate on clearance when the adult model used for paliperidone identified lean body mass as a significant predictor of apparent oral clearance of paliperidone? The supporting reference by Reigner BG and Welker HA cites lean body weight not body-weight *per se*.

3. In the efficacy study, PSZ-3001, secondary objectives included an exploration of the PK of paliperidone and relationships between its PK and results of efficacy parameters (PANSS scores) as well as safety parameters of interest. PK data from Study PSZ-3001 were used in the PK modelling for paliperidone use in adolescents but no PK information is provided. Where are the PK data for Study PSZ-3001 located in this submission?

10.2. Efficacy

Pivotal Study PSZ-3001:

1. What proportion of subjects in each treatment group had a first diagnosis of schizophrenia aged less than 12 years?

2. What proportion of subjects had a family history of schizophrenia?

3. How was the initial diagnosis of schizophrenia established for subjects accepted into this study?

4. What community supports and non-pharmacological interventions did subjects receive during this study?

5. What are the mean, median and range of pre-study hospital admissions for psychosis (by treatment group) for subjects enrolled into this study?

Open-Label Extension Study PSZ-3002:

1. Were subjects who entered the open-label study from double-blind treatment all commenced on 6mg paliperidone, irrespective of their final dose of double-blind active treatment (and body-weight category)?

2. What proportion of subjects enrolled in the 6-month open-label study withdrew from the double-blind study (by double-blind treatment group)?

3. To evaluate study biases, were the investigators and/or subjects in this study aware of the concurrent open-label safety study, PSZ-3002, during the conduct of PSZ-3001? In particular, were investigators and/or subjects aware of the inclusion criterion of at least 21 days participation in Study PSZ-3001 prior to entry into PSZ-3002?

4. Subjects who entered the open-label study after receiving active treatment in the efficacy study were analysed as a single group. This is a protocol deviation but no further information is provided. What proportion of subjects from the Low, Medium and High groups in PSZ-3001 entered the open-label study and what are their baseline characteristics and PANSS total scores at open-label end-point?

10.3. Safety

The Module 2 Clinical Overview does not include the incidence rates for individual adverse events. What are the individual incidence rates (presented in tabulated format) for the adverse events displayed in the relevant Table?

11. Evaluation of responses to clinical questions

11.1. Questions on pharmacokinetics

Question 1

Sponsor's response

The Sponsor confirmed that a sparse sampling approach was used in study PSZ-1001, and so single-dose PK parameters were not estimated through non-compartmental analysis. The basis of this approach was to minimise blood sampling of participating subjects. Furthermore, because of the limited sample size and sparse sampling approach, the PSZ-1001 PK data alone were not considered sufficient to precisely estimate the volume of distribution (V/F) and elimination half-life. Instead, the Sponsor applied population-PK modelling and simulation techniques to the combined sparse paliperidone plasma concentration data from PSZ-1001 and the pivotal efficacy study PSZ-3001. Using this approach, the Sponsor showed the primary PK parameters (apparent clearance [Cl/F] and V/F), which are independent of the dosing regimen (single versus multiple dose), in adolescents were comparable to adults.

Detailed information was presented in the population-PK report. A total apparent V/F of 442 L was estimated (i.e., the sum of central and peripheral volumes of distribution [V2+V3, 198 L+244 L]) and was found to be similar to the estimate reported for adults (487 L). Because the adolescent pop-PK model was based on adolescent and adult data, individual estimates for V2 and V3 confirm they are similar for the presented subgroups. Similarly, the Cl/F was estimated for adolescents as 12.5 L/h, similar to that reported for adults (13.8 L/h). Given that Cl/F and V/F are similar in adolescents and adults, the terminal half-life is also similar, i.e. approximately one day (i.e. 24 hours).

Clinical comment on response

The Sponsor's response to the S31 question is satisfactory. Given one of the study objectives of PSZ-1001 was to characterise the pharmacokinetics of paliperidone after single-dose administration in adolescents, and in particular, determine the volume of distribution and elimination half-life, this study failed to achieve these outcomes in a stand-alone Phase I pharmacokinetic study. It would appear the study design, particularly employing a sparse sampling method, was unlikely to achieve the study objectives. The PK results in adolescents appear more reliant on the pop-PK analysis than a specific PK study, and are therefore only an approximation to the adolescent population.

The PK findings between adolescents and adults appear comparable using the Pop-PK analysis, and when the multiple-dose data in PSZ-1001 was normalised to 6mg/day. Given 80% of PSZ-1001 subjects were over 15 years of age and over 51kg in baseline bodyweight i.e. approximating an adult population, the comparative PK data between adolescents and adults is not unexpected. However, in context of the Product Information recommendation of a 3mg once daily paliperidone dose, the submitted data do not support such a dosage regimen. There is no comparison of the PK of the proposed 3mg daily dose in adolescents with the 6mg dose in adults. While extrapolation of the PK data to the proposed dosage regimen, based on adult paliperidone dose-proportionality studies and adolescent studies in risperidone, has some merit, this needs to be weighed up against the potential risk in dosing subjects. For instance, it appears 6mg daily paliperidone leads to higher exposure, and 3mg daily to lower exposure, in children and adolescents compared with adults.

Question 2

Sponsor's response

The Sponsor provided an explanation why the Pop-PK model developed for adolescents used bodyweight as a covariate instead of lean body mass, as used in the adult Pop-PK model. The

Sponsor used bodyweight as subjects' dose adjustments were made on bodyweight recommendations. Furthermore, the Sponsor substantiated its claim that lean body mass and bodyweight were well correlated and therefore equally useful as covariates (see section on the Pop-PK report).

Clinical comment on response

The Sponsor's response is satisfactory.

Question 3

Sponsor's response

The Sponsor confirmed the PK data for the pivotal efficacy study PSZ-3001 were not submitted in its application. Similar to study PSZ-1001, the efficacy study used a sparse sampling approach to PK analysis. The study design did not allow performance of a non-compartmental analysis. The Sponsor provided individual data as part of this response for evaluation, and made reference to the Pop-PK analysis report included in Module 5.3.3.5 of this submission, for the results (discussed above in question 1).

Clinical comment on response

The Sponsor's response is satisfactory and confirms the absence of non-compartmental PK data analysis in this submission.

11.2. Questions on efficacy

Study PSZ-3001

Question 1

Sponsor's response

The proportion of subjects with a first diagnosis of schizophrenia before the age of 12 years in the pivotal efficacy study PSZ-3001 is shown in Table 9. Overall, 22% (n=44) of subjects had a first diagnosis before the age of 12 years, ranging from 14% in the Placebo group to 28% in the High group.

Table 9. Proportion of subjects with first diagnosis of schizophrenia at age less than 12 years (Study R076477-PSZ-3001: Intent-to-treat Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)
First diagnosis of schizophrenia age <12 years, n (%)				
Yes	7 (14)	14 (26)	10 (21)	13 (28)
No	44 (86)	40 (74)	38 (79)	34 (72)

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The distribution by age of first diagnosis of schizophrenia is summarised in Table 10. The youngest age of first diagnosis was three years old (one subject in the High treatment group).

Table 10. First diagnosis of schizophrenia by age (Study R076477-PSZ-3001: Intent-to-treat Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)
Age at diagnosis of schizophrenia (yr), n (%)				
3	0	0	0	1 (2)
4	0	0	0	1 (2)
5	1 (2)	1 (2)	0	0
6	1 (2)	4 (7)	0	0
7	0	0	0	2 (4)
8	1 (2)	1 (2)	1 (2)	2 (4)
9	1 (2)	0	0	0
10	2 (4)	3 (6)	4 (8)	3 (6)
11	1 (2)	5 (9)	5 (10)	4 (9)
12	3 (6)	8 (15)	8 (17)	4 (9)
13	14 (27)	11 (20)	9 (19)	6 (13)
14	5 (10)	6 (11)	8 (17)	5 (11)
15	15 (29)	8 (15)	10 (21)	11 (23)
16	7 (14)	7 (13)	3 (6)	8 (17)

Clinical comment on response

The Sponsor's data is satisfactory. Given the difficulty in establishing a diagnosis of schizophrenia in children, especially under 12 years of age, this evaluator has concerns over the appropriate diagnosis of (and recruitment of) children given a definitive diagnosis of schizophrenia from as young as three years of age. No data on recruitment by age and country was submitted in this application (or requested as a S31 question) so no comment can be made as to where younger subjects were recruited.

While accepting the Sponsor recruited subjects who satisfied the DSM-IV criteria and had confirmed the diagnosis using the Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children Present and Lifetime Version, these measures are not without limitations. Diagnosis is made on the basis of a set of subjective behaviours and perceptions rather than rigorous scientific objective measures.

Question 2

Sponsor's response

The Sponsor confirmed data on family history of schizophrenia was not collected on its participating subjects in the pivotal efficacy study and is therefore not available for evaluation. The Sponsor stated "While early-onset patients are more likely to have a family history of the disease [schizophrenia], there is no clear evidence that family history affects response to medication".

Clinical comment on response

While accepting the explanation the Sponsor provided, family history of schizophrenia (and mental illness *per se*) in first degree relatives, may have provided more confidence in the correct diagnosis of this very young population.

Question 3

Sponsor's response

The Sponsor referred to the study's inclusion criteria. The treating psychiatrist established a diagnosis of schizophrenia based on DSM-IV criteria over one year prior to study entry, based

on medical histories obtained from the subject and family. Diagnosis was confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children Present and Lifetime Version.

Clinical comment on response

The Sponsor did not specifically address the question "How was the initial diagnosis of schizophrenia established for subjects accepted into this study?" This question may appear ambiguous. Given over 40% of participants (see Question 5) with an established first diagnosis of schizophrenia had never been hospitalised, this evaluator wanted to establish how participants had been diagnosed in the community and by whom. A large proportion of subjects diagnosed in an outpatient setting may be unreasonably high, at least compared to the Australian environment, which again challenges the accuracy of diagnosis of study participants, and generalisability.

Given the Sponsor's information, the diagnosis of schizophrenia based on histories taken from family and subjects over the preceding year again challenges the accuracy of diagnosis of study participants. One would have more confidence if a subject's case manager and other psychiatric reports were used in the establishment of a diagnosis. Of course, this information may have been known to the treating psychiatrist but it is unclear from the answer provided.

Question 4

Sponsor's response

The Sponsor confirmed the subject could not receive insight-oriented psychotherapy or cognitive behavioural therapy during the course of the pivotal efficacy study. However, subjects could receive other non-pharmacological treatment (inpatient or outpatient) or community support during the course of the study. The preference was that any treatment of this kind continued unchanged from prior to study entry through the screening and treatment period of the study.

Clinical comment on response

The Sponsor's response is satisfactory.

Question 5

Sponsor's response

The Sponsor provided tabulated data on the number of prior hospitalisations for psychosis for subjects in each treatment group (Table 11 below). Forty-one percent of all subjects had never had a previous admission for psychosis and 28% had only had one admission.

Table 11. Diagnosis and psychiatric history at baseline (Study R076477-PSZ-3001: Intent-to-treat Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)	Total (N=200)
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: Module 5.3.5.1/PSZ-3001 Clinical Study Report (Table 11)

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The Sponsor also provided tabulated data for the duration of the most recent hospitalisation prior to the double-blind treatment phase and the time since last acute psychotic symptom.

Clinical comment on response

The Sponsor's response is satisfactory. All treatment groups in the pivotal efficacy study appeared well balanced in terms of prior hospitalisations, duration of the most recent hospitalisation prior to the double-blind treatment phase and the time since last acute psychotic symptom. Of note, 67% of subjects had had one or no previous admissions for psychosis.

Study PSZ-3002

Question 1

Sponsor's response

The Sponsor confirmed all subjects who entered study PSZ-3002 after PSZ-3001 initially received paliperidone ER 6mg once daily, irrespective of their final dose in PSZ-3001. The treatment blind was continued until PSZ-3001 was completed, even after subjects entered the open-label study. In PSZ-3002, the starting paliperidone ER dose of 6mg could be changed after five days, depending on clinical symptoms or side effects.

Clinical comment on response

The Sponsor's response is satisfactory. It was unclear from the submission whether every subject entering PSZ-3002 from PSZ-3001 was dosed at 6mg once daily. The Sponsor has clarified this to my satisfaction. There is no information in this submission on when the study blind/analysis for PSZ-3002 was undertaken, and when the results of the least effective dose (i.e. 3mg/day) were disseminated to the participating centres. None of the latter was addressed as S31 questions. This has safety implications, as the mode dose data indicates supra-maximal dosing of subjects as evidenced by the few numbers of subjects who received 3mg/day, as well as some AE high rates.

Question 2

Sponsor's response

The Sponsor provided tabulated data (see Table 12 below) of the study completion/withdrawal information of subjects who enrolled in the 6-month open-label study, PSZ-3002, from PSZ-3001. Subjects could enrol after participating in at least 21 days of PSZ-3001. The only reason subjects who withdrew early from PSZ-3001 could enter PSZ-3002 was lack of efficacy in the double-blind study.

The 34 subjects who withdrew from PSZ-3001 from lack of efficacy represent 85% of the total number of subjects who withdrew from lack of efficacy in this study. Hence, a majority of subjects withdrawing from lack of efficacy in PSZ-3001 entered the open-label study. From Table 12, the Placebo and Low treatment groups accounted for 85% of total withdrawals from lack of efficacy who entered the open-label study.

Clinical comment on response

The Sponsor's response is satisfactory. It is evident that a high proportion of subjects who withdrew from PSZ-3001 entered the open-label study from lack of efficacy. It is also evident these withdrawals occurred after 21 days of double-blind treatment. No specific details are provided by number of subject withdrawals from lack of efficacy per treatment week and by country (not requested as S31 questions). The body of this report indicated most withdrawals from PSZ-3001 occurred in Ukrainian and Russian centres. The large proportion of study withdrawals in Week 4 (Days 22-29) and the high proportion of uptake of withdrawals into PSZ-3002 suggests investigator/selection bias has occurred (see Question 3).

Question 3

Sponsor's response

Investigators were aware of the need for at least 21 days treatment in PSZ-3001 before entry into PSZ-3002. The informed consent form for parents and guardians stated that there was an option of another study at the end of PSZ-3001. The wording of the consent form was as follows: "There is an extension (follow-up) study for you to continue to receive treatment with this study drug after your participation has ended." The consent form for parents and guardians did not mention the 21-day time period. The assent form for minor subjects did not mention the follow-up study.

Clinical comment on response

The Sponsor's response is satisfactory. Although the effect cannot be quantified here, the role of investigator bias in selecting patients out of the pivotal efficacy study may have had a major influence on the final outcomes, in particular the lack of efficacy in the Low and High treatment arms. This is based on the fact investigators were fully aware of the open-label study running concurrently to the pivotal efficacy study, the criterion for at least 21 days completion of the pivotal study before recruitment into the open-label study and such a high proportion of study withdrawals (from lack of efficacy) in the pivotal study from Placebo and Low treatment groups into the open-label study. Subjects' parents and guardians were aware of the extension study and this too may have played a part in subjects possibly selecting themselves out of the pivotal study. For such a high proportion of subjects to withdraw from PSZ-3001 for lack of efficacy, and agree to paliperidone treatment seems unreasonably high to this evaluator.

Question 4

Sponsor's response

The Sponsor provided tabulated data of the proportion of subjects in PSZ-3001 who entered the open-label study by double-blind treatment group (Table 12). Overall, 78% (n=156) of the double-blind subjects entered the OL study and study treatment groups ranged from 76% to 80%.

Table 12. Proportion of subjects from double-blind study entering open-label study (Study R076477-PSZ-3002: Double-blind Intent-to-treat Analysis Set)

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)
Subjects entered OL from DB study, n (%)				
Yes	39 (76)	43 (80)	38 (79)	36 (77)
No	12 (24)	11 (20)	10 (21)	11 (23)

DB=double-blind, OL=open-label
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Tabulated data on demographic and baseline characteristics of each treatment, as well as diagnosis and psychiatric history of those entering the OL study were provided. Generally, the groups were well balanced and similar in all parameters compared to the entire PSZ-3001 study population.

Tabulated data (see Table 13) provides PANSS total scores at OL baseline and OL end-point by double-blind treatment group. The Medium group had a much lower mean baseline PANSS total score compared to the Low and High groups (consistent with the greater efficacy demonstrated in the Medium group in the pivotal efficacy study). At OL endpoint, the Medium group achieved far less reduction in mean PANSS total scores than those from the Low and High groups, reportedly due to the lower score at baseline in the Medium group.

Clinical comment on response

The Sponsor's data is satisfactory. The Sponsor did not clarify why the three active treatment arms in the double-blind pivotal efficacy study, PSZ-3001, were combined and analysed as a single group in the OL study. Examination of Table 13 and the 4.3 points mean reduction in PANSS total score at 6-months in the Medium group may explain this approach. While the baseline score for the Medium group was in the order of 10 points less than the other treatment arms and therefore represented less ill subjects, it was the only group in the pivotal efficacy study that demonstrated statistical separation compared to Placebo. Taken at face value, this reduction of 4.3 points does not demonstrate continued efficacy of paliperidone. For reasons cited above, this evaluator does not consider study PSZ-3002 as pivotal and therefore these findings have limited usefulness in efficacy assessments.

Table 13. PANSS Total Score – Change from baseline (OL) to end point (OL) – LOCF – Subjects entering Open-label by Double-blind Treatment Group (Study R076477-PSZ-3002: OL Intent-to-treat Analysis Set)

	Placebo (N=39)	Paliperidone ER Low (N=43)	Paliperidone ER Medium (N=38)	Paliperidone ER High (N=36)
Baseline (OL)				
N	39	43	38	36
Mean (SD)	82.7 (22.11)	80.4 (19.95)	70.4 (20.64)	78.6 (19.98)
Median (Range)	80.0 (36;129)	80.0 (45;121)	68.5 (33;112)	75.0 (49;135)
End Point (OL)				
N	39	43	38	36
Mean (SD)	64.8 (20.69)	67.5 (18.39)	66.2 (23.69)	68.6 (20.30)
Median (Range)	67.0 (30;110)	69.0 (32;108)	64.0 (30;140)	67.5 (35;130)
Change from Baseline				
N	39	43	38	36
Mean (SD)	-17.9 (21.87)	-12.9 (17.86)	-4.3 (14.54)	-10.0 (20.85)
Median (Range)	-19.0 (-65;50)	-9.0 (-63;37)	-7.0 (-24;46)	-7.5 (-67;44)

Note: Negative change in score indicates improvement.
Based on data up to 30 July 2009 cutoff date for subjects enrolled prior to that date.
LOCF=last observation carried forward, OL=open-label
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11.3. Question on safety

Sponsor's response

The Sponsor provided tabulated data (Table 14) for the incidence of adverse drug reactions reported by paliperidone ER-treated subjects in studies PSZ-3001 and PSZ-3002. This data relates to 314 subjects exposed to paliperidone. This Table does not include data from PSZ-1001, the adolescent PK study.

Clinical comment on response

The Sponsor's response is unsatisfactory. This question relates to the safety parts of this report in which the incidence of all adverse events, irrespective of relationship to study treatment were requested. The S31 question may appear ambiguous. The basis of this request was to assist in the comparison of paliperidone in adolescents against paliperidone in adults, as well as competitor products. Such comparison has been partially made above.

Table 14. Adverse Drug Reactions as reported by Paliperidone ER-treated subjects in 2 clinical studies in adolescent subjects with schizophrenia (PSZ-3001 and PSZ-3002), sorted by System Organ Class and Frequency Category

(Studies R076477-PSZ-3001, -PSZ-3002)

Frequency Category	Dictionary-derived Term	No. of Subjects with Event	Total N	%
Body System or Organ Class: Cardiac disorders				
Common	Tachycardia	12	314	3.822
Uncommon	Atrioventricular block first degree	2	314	0.637
	Bundle branch block right	1	314	0.318
Body System or Organ Class: Eye disorders				
Common	Oculogyric crisis	7	314	2.229
	Vision blurred	6	314	1.911
Uncommon	Eye movement disorder	1	314	0.318
Body System or Organ Class: Gastrointestinal disorders				
Common	Abdominal pain upper	11	314	3.503
	Dry mouth	7	314	2.229
	Dyspepsia	6	314	1.911
	Nausea	20	314	6.369
	Salivary hypersecretion	22	314	7.006
	Vomiting	20	314	6.369
Uncommon	Swollen tongue	1	314	0.318
Body System or Organ Class: General disorders and administration site conditions				
Common	Asthenia	10	314	3.185
	Fatigue	11	314	3.503
Body System or Organ Class: Infections and infestations				
Common	Nasopharyngitis	31	314	9.873
Body System or Organ Class: Investigations				
Common	Alanine aminotransferase increased	4	314	1.274
	Weight increased	30	314	9.554
Uncommon	Aspartate aminotransferase increased	2	314	0.637
Body System or Organ Class: Metabolism and nutrition disorders				
Common	Decreased appetite	10	314	3.185
	Increased appetite	8	314	2.548
Body System or Organ Class: Musculoskeletal and connective tissue disorders				
Common	Muscle rigidity	13	314	4.140
	Musculoskeletal stiffness	10	314	3.185
Uncommon	Nuchal rigidity	2	314	0.637
	Torticollis	1	314	0.318
	Trismus	1	314	0.318
Body System or Organ Class: Nervous system disorders				
Very Common	Akathisia	45	314	14.331
	Headache	45	314	14.331

12. Final benefit-risk assessment

12.1. Final assessment of benefits

The clinical information submitted in the Sponsor's S31 Response does not change the assessment of benefits in the original clinical evaluation report (see Section on *First round benefit-risk assessment* above).

12.2. Final assessment of risks

The clinical information submitted in the Sponsor's S31 Response does not change the assessment of risks in the original clinical evaluation report (see Section on *First round benefit-risk assessment* above).

12.3. Final assessment of benefit-risk balance

The benefit-risk balance for paliperidone ER, given the proposed usage, is unfavourable. The clinical information submitted in the Sponsor's S31 Response does not change the unfavourable assessment of the benefit-risk balance provided in the original clinical evaluation report (see Section on *First round benefit-risk assessment* above).

13. Final recommendation regarding authorisation

It is recommended that the submission not be approved. The clinical information submitted in the Sponsor's S31 Response does not change the recommendation that the submission be rejected provided in the original clinical evaluation report. Unless conditions are met as in the clinical evaluation report section on *First round recommendation regarding authorisation*, above.

14. References

14.1. Submitted studies

PALIOROS-PSZ-1001: Open-label study to evaluate the safety and pharmacokinetics of single- and multiple-dose extended-release OROS paliperidone in paediatric subjects (≥10 to ≤17 years of age) with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

R076477-PSZ-3001: A randomized, multicenter, double-blind, weight-based, fixed-dose, parallel-group, placebo-controlled study of the efficacy and safety of extended release paliperidone for the treatment of schizophrenia in adolescent subjects, 12 to 17 years of age.

R076477-PSZ-3002: A 2-year, open-label, single-arm safety study of flexibly dosed paliperidone extended release (1.5-12mg/day) in the treatment of adolescents (12 to 17 years of age) with schizophrenia – safety and efficacy data from all subjects to a cut-off date of 30 July 2009.

R076477-P01-1010: Dose-proportionality study of the five ER OROS paliperidone to-be-marketed tablet strengths (3, 6,9,12 and 15mg) in healthy male subjects.

PALIOROS-SCH-1011: An open-label, single- and multiple-dose study to evaluate the pharmacokinetics of ER OROS paliperidone in healthy elderly and young subjects.

R076477-SCH-102: Comparison of steady-state pharmacokinetics of paliperidone after extended-release OROS paliperidone 15mg and immediate-release oral risperidone 8mg b.i.d. in subjects with schizophrenia or schizoaffective disorder.

PAL-SCH-101: A randomized, double-blind, placebo- and active-controlled, parallel-group, Phase 1 study to compare the tolerability of OROS paliperidone (extended-release) with immediate-release risperidone in subjects with schizophrenia.

R076477-P01-1005: A randomized, double-blind, placebo-controlled, single and multiple dose study to evaluate and compare the pharmacokinetics of ER OROS paliperidone in healthy Japanese and Caucasian subjects.

R076477-SCH-302: A randomized, 6-week, double-blind, placebo-controlled study with an optional 24-week open-label extension to evaluate the safety and tolerability of flexible doses of extended release OROS paliperidone in the treatment of geriatric subjects with schizophrenia.

R076477-SCH-303: A randomized, double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of extended release OROS paliperidone (6, 9 and 12mg/day) and olanzapine (10mg/day), with open-label extension, in the treatment of subjects with schizophrenia.

R076477-SCH-304: A randomized, double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 2 fixed dosages of extended release OROS paliperidone (6 and 12mg/day) and olanzapine (10mg/day), with open-label extension, in the treatment of subjects with schizophrenia.

R076477-SCH-305: A randomized, double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of extended release OROS paliperidone (3, 9 and 15mg/day) and olanzapine (10mg/day), with open-label extension, in the treatment of subjects with schizophrenia.

PSZ-3003: Randomised, double-blind, active-controlled, parallel-group, multicentre Phase 3 study designed to evaluate the efficacy and safety of flexibly-dosed paliperidone ER in adolescent subjects (12-17 years of age, inclusive) with schizophrenia.

14.2. Additional references

CPMP/EWP/559/95 Note for Guidance on the Clinical Investigation of Medicinal products in the Treatment of Schizophrenia.

Directive 75/318/EEC (amended 1988) Pharmacokinetic Studies in Man.

CPMP/EWP/2330/99 Points to consider on application with 1.meta-analyses; 2. One pivotal study (May 2001).

Reigner BG and Welker HA Factors influencing elimination and distribution of fleroxacin: Meta-analysis of individual data from 10 pharmacokinetic studies. Antimicrobial Agents and Chemotherapy 1996; 40 (3); pp575-580.

Seroquel (quetiapine) Australian approved Product Information.

Risperdal (risperidone) Australian approved Product Information.

Zyprexa (olanzapine) Australian approved Product Information.

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