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Committee for Medicinal Products for Human Use (CHMP)

Invega

(paliperidone)

EMEA/H/C/000746/A45/010

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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I. INTRODUCTION

On 14 May 2009 the MAH submitted one completed paediatric study for Invega (paliperidone) prolonged-release tablet, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short expert overview has also been provided.

The MAH proposed that the submitted paediatric study does not influence the benefit risk for Invega and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Paliperidone is a monoaminergic antagonist that exhibits the dopamine type 2 and predominant serotonin antagonism of the newer, or second-generation, antipsychotic drugs. Paliperidone is the major active metabolite of risperidone. Paliperidone Prolonged Release (PR) 1.5-mg, 3-mg, 6-mg, 9-mg, and 12-mg tablets are approved for the treatment of schizophrenia in adults. The indication and some of the posology statements follow below:

Invega is indicated for the treatment of schizophrenia.

Adults
INVEGA is for oral administration. The recommended dose of INVEGA is 6 mg once daily, administered in the morning. The administration of INVEGA should be standardised in relation to food intake. The patient should be instructed to always take INVEGA in the fasting state or always take it together with breakfast and not to alternate between administration in the fasting state or in the fed state. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 5 days.

Paediatric population
Safety and efficacy of INVEGA in patients < 18 years of age have not been studied. There is no experience in children.

The Applicant is planning to seek approval under European Community Regulation 1901/2006 and amendments ("the paediatric regulation") for the use of paliperidone PR in adolescents (12 to 17 years of age, inclusive) with schizophrenia on the basis of a clinical research program according to an agreed Paediatric Investigation Plan (PIP, EMEA-000014-PIP01-07). The PIP was adopted on 31 March 2008 and includes a waiver for the investigation of paliperidone PR tablets in children less than 12 years of age.

The clinical research program consists of one Phase 1 study (PALIOROS-PSZ-1001) and three Phase 3 studies (R076477-PSZ-3001, R076477-PSZ-3002, and R076477-PSZ-3003) (Table 1).

Table 1: Summary of Paliperidone PR Pediatric and Adolescent Clinical Studies

Study	Type	Status	No. of Subjects	Age Range (years)	Dose Range (mg/d)	Duration[a]
PALIOROS-PSZ-1001	PK and tolerability	Completed	25	10-17	4-12	1+7 days
R076477-PSZ-3001	Efficacy and safety	Ongoing	200	12-17	1.5-12	6 weeks
R076477-PSZ-3002	Long-term safety	Ongoing	400	12-17	1.5-12	2 years
R076477-PSZ-3003	Efficacy and safety	Planned	228	12-17	3-6	26 weeks

[a]Treatment phase only

Study PALIOROS-PSZ-1001, a Phase 1 PK and tolerability study in 25 subjects aged 10 to 17 years, inclusive, with schizophrenia, schizoaffective disorder, or schizophreniform disorder, has been completed. The study included 3 dose groups (0.086, 0.129, and 0.171 mg/kg/day), which were studied in a sequential ascending design. Paliperidone PR was supplied as 1-mg, 3-mg, and 6-mg tablets. No paediatric formulation was used.

The Phase 3 studies are ongoing or in planning (see Section II.3 for additional details).

The data obtained from the 4 clinical studies above will provide information for inclusion in the SPC concerning the safety and efficacy of paliperidone in the paediatric and adolescent populations.

Paliperidone prolonged release (PR) (European Union) and extended release (ER) (United States) may be used interchangeably in the remainder of this assessment report.

II.2 Non-clinical aspects

The paliperidone PR Marketing Authorization Application for the treatment of schizophrenia in adults was submitted to the EMEA in May 2006. The MAH stated that this was supported by a full paliperidone nonclinical safety package. The nonclinical data included a full general toxicity package and a full reproduction toxicity package, but did not include a rat juvenile toxicity study conducted with paliperidone.

In the repeat-dose general toxicity studies in rats (which continued up to 6 months), dosing with paliperidone started at the age of 4 weeks. At 4 weeks rats are in early puberty, based on the development of the male and female reproductive systems. Brain development is still ongoing in rats at that age.

Thus, it appears that adolescent animals have been included in these studies although juvenile toxicity effects were not specifically addressed. A new pre- and postnatal development toxicity study with higher doses of paliperidone is part of the agreed PIP.

II.3 Clinical aspects

1. Introduction

The MAH submitted a report for:

- **PALIOROS-PSZ-1001**: Open-Label Study to Evaluate the Safety and Pharmacokinetics of Single- and Multiple-Dose Extended-Release OROS Paliperidone in Pediatric Subjects (to Years of Age) with Schizophrenia, Schizoaffective Disorder, or Schizophreniform Disorder

In addition, a post-marketing cumulative safety summary was submitted providing a review of post-marketing AEs reported to the MAH since the launch of the paliperidone PR tablets.

The MAH provided a brief description of the following three Phase 3 studies, which are ongoing or planned:

- R076477-PSZ-3001 (ongoing);
- R076477-PSZ-3002 (ongoing);
- R076477-PSZ-3003 (planned);

The ongoing safety and efficacy study PSZ-3001 is a 6-week, randomized, double-blind, weight-based fixed dose, parallel-group, placebo-controlled, multicentre study in approximately 200 adolescents aged 12 to 17 years, inclusive, with schizophrenia. Subjects are randomly assigned to 1 of 4 treatment groups (corresponding to non-overlapping milligram per kilogram groups) to explore the tolerated adult dose range (1.5-12 mg) of paliperidone PR in this population.

The ongoing long-term safety study PSZ-3002 is a 2-year, open-label, multicentre study in which approximately 400 subjects will be enrolled in order to have at least 100 evaluable adolescent subjects 12 to 17 years of age, inclusive, with schizophrenia. Subjects are flexibly dosed with 1.5 to 12 mg/day paliperidone PR.

Study PSZ-3003 is planned to be a 26-week, randomized, double-blind, active-controlled efficacy and safety study of paliperidone PR for the treatment of schizophrenia in adolescents (aged 12-17 years, inclusive), with assessment of positive and negative symptoms of schizophrenia at 8 weeks and maintenance of effect at 26 weeks.

2. Clinical study(ies)

PALIOROS-PSZ-1001
Open-Label Study to Evaluate the Safety and Pharmacokinetics of Single- and Multiple-Dose Extended-Release OROS Paliperidone in Pediatric Subjects (≥10 to ≤17 Years of Age) with Schizophrenia, Schizoaffective Disorder, or Schizophreniform Disorder

➢ Description

This was a multicenter, open-label study to evaluate the PK, safety, and tolerability of single- and multiple-dose paliperidone PR tablet administration in children and adolescent subjects, ≥10 to ≤17 years of age with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

➢ Methods

- Objective(s)
  To characterize the pharmacokinetics of paliperidone after single-dose administration and at steady state following multiple oral administrations of paliperidone ER in children and adolescent subjects (≥10 to ≤17 years of age) with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

  To evaluate the safety and tolerability of paliperidone PR in this subject population

- Study design
  This was a multicenter, open-label study. The study included 3 dosage groups (0.086, 0.129, and 0.171 mg/kg/day paliperidone PR), which were studied in a sequential ascending design. The dose groups approximated 6, 9, and 12 mg/day in adults. The maximum absolute dosage was not to exceed 12 mg/day.

For each dosage group, the study consisted of a screening phase; a 2-day single-dose PK and tolerability evaluation phase; a 7-day multiple-dose phase, with evaluation of PK and tolerability; and an end-of-study visit (upon completion or upon early withdrawal).

For each subject, safety and tolerability were evaluated after single-dose treatment before continuing with multiple-dose treatment beginning on Day 3. An interim safety evaluation was conducted after completion of the first 4 subjects in the 0.086 mg/kg/day dosage group and after completion of all subjects in a dosage group. Following the completion of all subjects in each dosage group, safety and tolerability were evaluated in order to determine whether to proceed to the next higher dosage level.

Within each dosage group, subjects were randomly assigned to 1 of 2 PK blood sampling schemes (Schedule A or B) in a 1:1 ratio. Safety and tolerability were assessed at several points during the study.

- Study population /Sample size
  The study enrolled children and adolescent subjects (≥10 to ≤17 years of age) with schizophrenia (of any subtype), schizoaffective disorder, or schizophreniform disorder according to DSM IV-TR and with Clinical Global Impression-Severity Scale (CGI-S) ≤3. Subjects were required to be healthy other than the DSM-IV-TR classification.
  Subjects who had taken any of the following medications were excluded:
  – Oral paliperidone or risperidone within 14 days before Day 1
  – Risperidone long-acting injectable (Risperdal CONSTA®) within 10 weeks before Day 1
  – Long-acting formulations of other neuroleptics within 1 treatment cycle before Day 1
  – Ziprasidone or thioridazine within 1 week before Day 1
  – Any hepatic enzyme inducer (e.g., rifampicin, carbamezepine, barbiturates, phenytoin, and St. John's Wort) within 14 days before Day 1
  – Clozapine therapy within 6 weeks before Day 1
  – Any anticonvulsant medication within 14 days before Day 1
  – Daily use of aspirin or any nonsteroidal anti-inflammatory medication

  The planned sample size was 24 subjects. The sample size was not chosen based on statistical considerations, but in order to limit the exposure in pediatric subjects while providing sufficient data to develop a population PK model.

- Treatments
  The study included 3 dosage groups (approximately 0.086, 0.129, and 0.171 mg/kg/day of paliperidone PR, corresponding to daily doses of 6, 9, and 12 mg, respectively, for a 70-kg adult on a milligram per kilogram basis) studied in a sequential ascending design. The dose was determined based on the dosage group and the subject's body weight and was rounded to the nearest whole milligram.

- Outcomes/endpoints
  PK parameters were estimated based on non-compartmental analysis. Safety was evaluated based on adverse events, clinical laboratory results, vital sign measurements, 12-lead ECGs, and physical examination results, including Tanner Staging. Subjects were also monitored for extrapyramidal symptoms, using the Simpson and Angus Rating Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS).

- Statistical Methods
  Descriptive statistics of the PK parameters were calculated for all completed subjects aged between 10–17 years (i.e., children and adolescents) and for subjects aged between 12–17 years (i.e., adolescents). Safety and tolerability data were tabulated and evaluated at the completion of the study using descriptive statistics.

- **Results**

  - Recruitment/ Number analysed
    A total of 25 subjects were enrolled (8, 9, and 8 in the respective dosage groups of 0.086, 0.129, and 0.171 mg/kg/d paliperidone PR) and 24 subjects (8, 9, and 7 subjects in the respective dosage groups) completed the study. One subject in the high-dose group withdrew consent prior to dosing on Day 3.

  - Baseline data
    There were 18 males and 7 females. Body weight ranged from 31 to 89 kg. There was a reasonable age distribution, with at least 6 completers in each stratum from 12 to 17 years of age (i.e., 7 subjects aged 12 to 13, 6 subjects aged 14 to 15, and 10 subjects aged 16 to 17, as well as 1 subject aged 10). Overall, 56% of the subjects were white, 24% were black, and 20% were Asian. Eight (32%) subjects had schizophreniform disorder, 7 (28%) had schizoaffective disorder, and 10 (40%) had schizophrenia.
    The total daily dose ranged from 4 mg to 12 mg/day. The number of subjects, weight, and total daily dose per age stratum are given in Table 2. The most common concomitant medications were olanzapine and quetiapine, which were taken by 8 subjects each.

Table 2: Body weight and total daily dose per age stratum

	---- 10–11 ----	---- 12–13 ---	---14–15 ---	----- 16–17 -----	----- Total -----
Weight (kg)					
N	1	8	6	10	25
Mean (SD)	30.8	53.7 (12.41)	66.5 (12.26)	72.2 (12.97)	63.2 (15.79)
Median	30.8	55.7	72.3	68.7	64.5
Range	(31;31)	(35;69)	(45;76)	(51;89)	(31;89)
Total dose (mg/day)					
N	1	8	6	10	25
Mean (SD)	4.0	6.8 (2.12)	8.7 (2.73)	8.3 (2.36)	7.7 (2.49)
Median	4.0	6.5	8.0	8.0	8.0
Range	(4;4)	(4;10)	(6;12)	(5;12)	(4;12)

One subject switched from 4 to 5 mg on Days 8 and 9: total daily dose of 4 mg is taken into account.
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  - Efficacy results

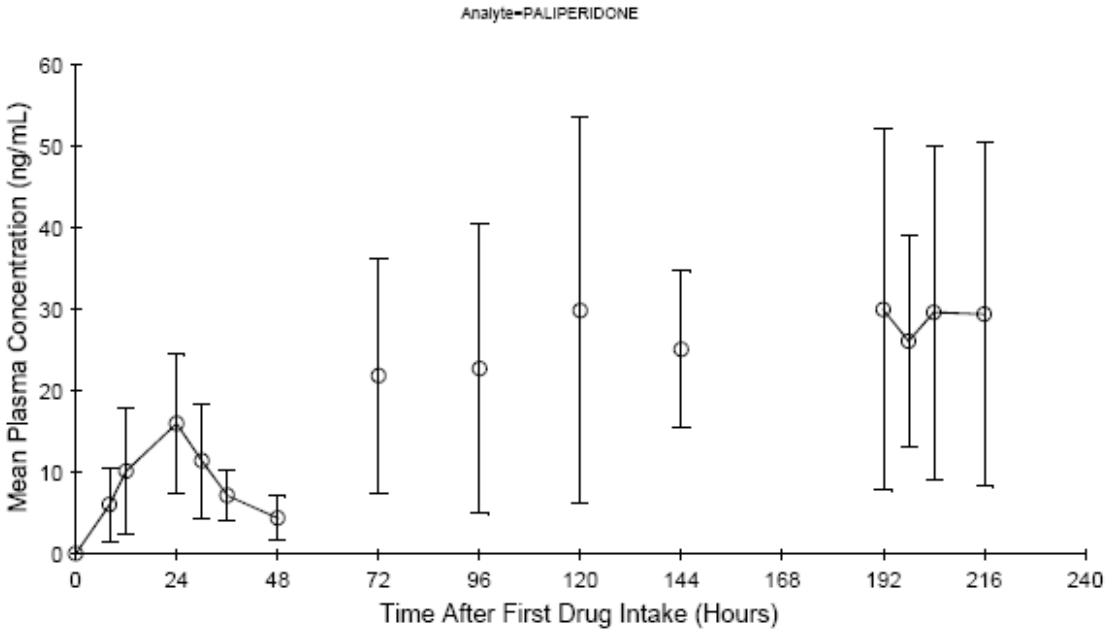
This was an open label study and no efficacy results were obtained. Blood sampling for PK analyses was performed, though. Pharmacokinetics and tolerability were evaluated during both treatment phases. Subjects were randomly assigned to 1 of 2 PK blood-sampling schemes in order to minimize blood sampling per subject. Frequent blood sampling was performed after the first dose of paliperidone (up to 36h), pre-dose samples were drawn during the multiple-dose phase and samples were drawn up to 24h after the last dose.

Pharmacokinetic data were analyzed from 25 subjects for the single-dose treatment phase and 24 subjects for the multiple-dose treatment phase. Plasma concentrations of the paliperidone enantiomers were determined using a validated liquid chromatography coupled to tandem mass spectroscopy method with a target limit of quantification of 0.20 ng/mL and 1 ng/mL for plasma and urine, respectively. Descriptive statistics were calculated for the actual and dose-normalized (to 6 mg/d and 0.086 mg/kg/d) plasma and urine concentrations of paliperidone and its enantiomers at each sampling time, and for the derived estimated actual and dose-normalized

plasma and urine steady-state PK parameters. Plasma and urine PK parameters at steady state (Day 9) were estimated for paliperidone and its enantiomers using noncompartmental analysis and were based on sparse blood sampling.

Pharmacokinetic results are presented in Figure 1 and Table 3 below. For comparison, a table with PK results from adults has been included as Table 4.

Figure 1: Paliperidone Plasma Concentration-Time Profile in Paediatric and Adolescent Subjects, Dose- Normalized to 6 mg/d (Mean±SD), PALIOROS-PSZ-1001 (PK Analysis Set)



n=23 observations
Source: CSR PALIOROS-PSZ-1001\Att2.7

Table 3: Steady-State Plasma and Urine PK Parameters of Paliperidone in Paediatric and Adolescent Subjects, Dose-Normalized to 6 mg, PALIOROS-PSZ-1001 (PK Analysis Set)

	Mean ± SD	%CV	Median	Min-Max
C_{max}, ng/mL	34.2 ± 22.3	65.3	23.2	9.62–89.3
AUC_{24h}, ng.h/mL	686 ± 448	65.4	486	215–1750
CL/F, mL/min	209 ± 117	56.3	206	57.1–465
CL_R, mL/min	42.4 + 17.4	41.0	37.8	8.01–68.5
% of the dose renally excreted	24.4 ± 12.7	51.8	23.1	7.88–60.8

n=23 observations

Plasma PK parameters were dose normalized to 6 mg/d.
Source: CSR PALIOROS-PSZ-1001\Att2.3, Att2.5

Table 4: Steady-State Plasma and Urine PK Parameters of Paliperidone in Adult Subjects, Dose- Normalized to 6 mg (Pooled PK dataset from Studies R076477-P01-1005, PAL-SCH-101, R076477-SCH-102, R076477- SCH-1011)

	Mean ± SD	%CV	Median	Min – Max
C_{max}, ng/mL[a]	23.7 ± 12.3	51.9	21.0	5.86–86.7
AUC_{24h}, ng.h/mL[a]	457 ± 235	51.5	396	115–1563
CL/F, mL/min[b]	268 ± 119	44.4	252	54.0–869
CL_R, mL/min[c]	36.2 ± 15.8	43.6	34.5	11.4–86.7

[a]Adult subjects: n=172; [b]n=173; [c]n=74

Source: CSR PALIOROS-PSZ-1001\Tab11, Tab13

The relationship between CL/F and body weight is shown in Figure 2 and the relationship between dose-normalized (to 6 mg) paliperidone AUC24h and age is shown in Figure 3, with dose-normalized paliperidone (to 6 mg/d) steady-state AUC0-24h in adults (≥18 years) included for comparison.

Figure 2: Relationship Between CL/F and Body Weight, PALIOROS-PSZ-1001 (PK Analysis Set)

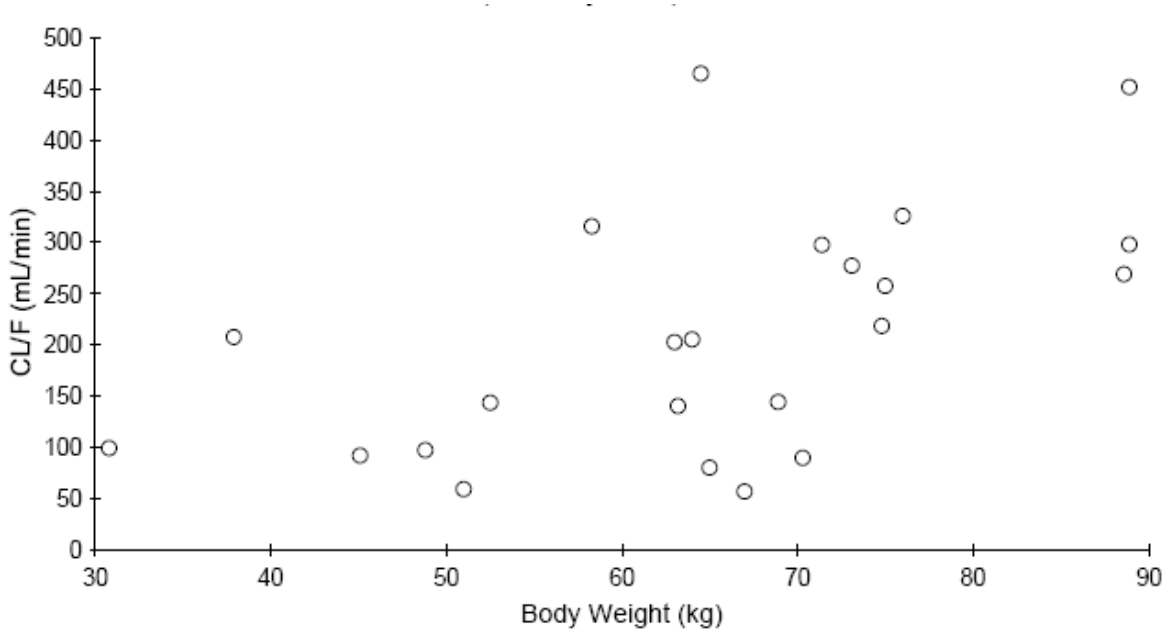
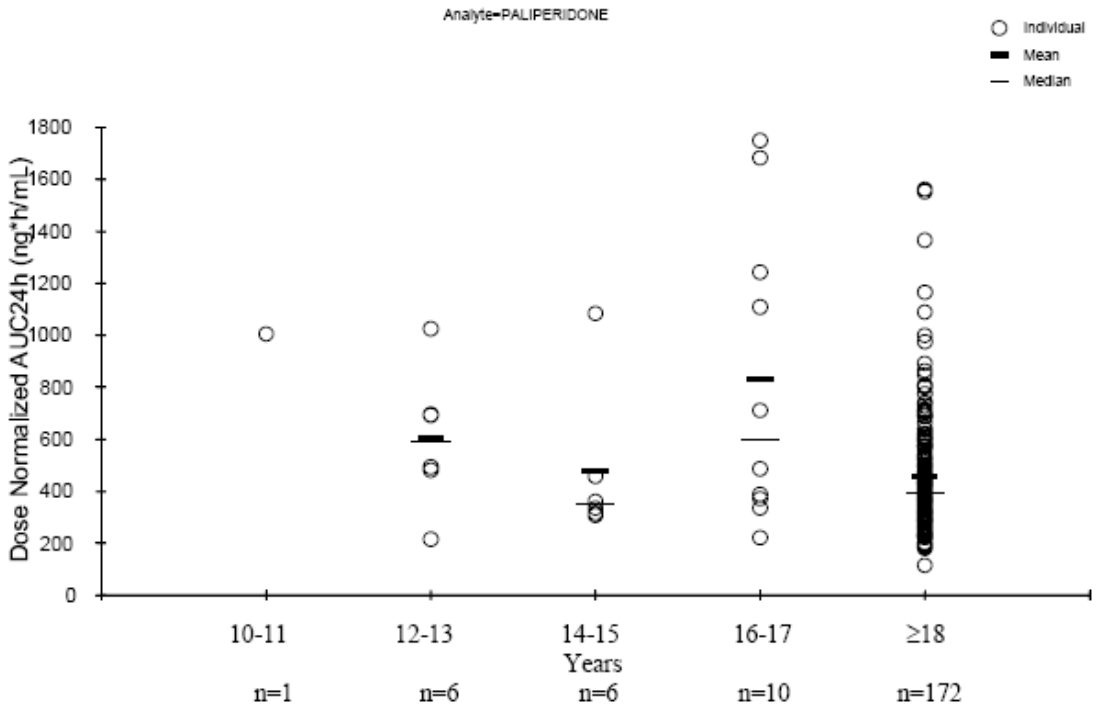


Figure 3: Paliperidone Steady-State AUC24h (Dose-Normalized to 6 mg/d) vs. Age, PALIOROS-PSZ-1001 (PK Analysis Set)



Comments on PK results:
After single-dose administration of paliperidone PR, the plasma concentrations of paliperidone reached peak plasma concentrations after approximately 24 hours. This was consistent with the release characteristics of paliperidone PR and the plasma concentration profile in adults. Steady-state drug concentrations were attained within 4 to 5 days of dosing, which was also consistent with observations in adults. Plasma exposure (Cmax and AUC) increased with increasing dose.

Following multiple-dose administration, dose-normalized median Cmax was similar between adolescents and adults (Tables 3 and 4). Mean Cmax was somewhat higher in adolescents vs. adults. Median AUC24h of paliperidone in adolescents was higher, and median CL/F was lower than in adults. The ranges (min-max) of plasma exposure observed in paediatric and adolescent subjects were similar to adults.

The applicant believes that differences in body weight may, at least partly, explain the differences in CL/F of paliperidone between adolescents and adult subjects. Figure 2 suggests that CL/F increased with increasing body weight in Study PSZ-1001. This observation is consistent with results from the population PK analysis of adult data, where paliperidone clearance was found to increase with increasing weight. According to Figure 3, there is no apparent relationship to the plasma exposure of paliperidone with age in the studied age range. It should be noted that the number of subjects in each age category is small and the range of exposures within each age category is wide.

- The steady-state plasma (+)/(-) enantiomer ratio, accumulation ratio,fraction unbound (fu) and renal clearance of paliperidone in adolescent subjects were similar to values obtained in adults. The reported renal clearance values and amount of the dose excreted in urine were lower compared with the figures reported in the Invega adult MAA

(approximately 53 ml/min and 50-60%, respectively), which could be due to a urine sampling time of only 24 hours in this study.

- Safety results

  All but 1 of the 25 subjects in the safety population received multiple dose administration of paliperidone. In total, 15 subjects (60%) experienced one or more treatment-emergent adverse events (AEs). The most common AEs were sedation (16%) and epistaxis (12%). Most events were reportedly mild or moderate in intensity. No serious AEs were reported and no subject discontinued from the study because of an AE.

  Five subjects (20%) reported extrapyramidal symptoms, which included extrapyramidal disorder (2), akathisia (1), dystonia (1), and tremor (1). A summary of treatment-emergent AEs is provided in Table 5.

Table 5: Treatment-emergent AEs by Body System or Organ Class (Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	GROUP A [0.086 mg/kg] (N=8) n (%)	GROUP B [0.129 mg/kg] (N=9) n (%)	GROUP C [0.171 mg/kg] (N=8) n (%)	Total (N=25) n (%)
Total no. subjects With Adverse Events	3 (37.5)	6 (66.7)	6 (75.0)	15 (60.0)
Nervous system disorders	3 (37.5)	5 (55.6)	3 (37.5)	11 (44.0)
Sedation	1 (12.5)	1 (11.1)	2 (25.0)	4 (16.0)
Extrapyramidal disorder	1 (12.5)	1 (11.1)	0	2 (8.0)
Headache	1 (12.5)	1 (11.1)	0	2 (8.0)
Akathisia	0	0	1 (12.5)	1 (4.0)
Dystonia	0	0	1 (12.5)	1 (4.0)
Somnolence	0	1 (11.1)	0	1 (4.0)
Tremor	0	1 (11.1)	0	1 (4.0)
Gastrointestinal disorders	1 (12.5)	1 (11.1)	2 (25.0)	4 (16.0)
Nausea	1 (12.5)	0	1 (12.5)	2 (8.0)
Vomiting	1 (12.5)	0	1 (12.5)	2 (8.0)
Salivary hypersecretion	0	1 (11.1)	0	1 (4.0)
Respiratory, thoracic and mediastinal disorders	1 (12.5)	2 (22.2)	1 (12.5)	4 (16.0)
Epistaxis	0	2 (22.2)	1 (12.5)	3 (12.0)
Pharyngolaryngeal pain	1 (12.5)	0	0	1 (4.0)
Psychiatric disorders	2 (25.0)	1 (11.1)	0	3 (12.0)
Anxiety	1 (12.5)	0	0	1 (4.0)
Depressed mood	1 (12.5)	0	0	1 (4.0)
Psychotic disorder	0	1 (11.1)	0	1 (4.0)
Investigations	1 (12.5)	1 (11.1)	0	2 (8.0)
Alanine aminotransferase increased	1 (12.5)	0	0	1 (4.0)
Aspartate aminotransferase increased	1 (12.5)	0	0	1 (4.0)
Blood creatine phosphokinase increased	1 (12.5)	0	0	1 (4.0)
Electrocardiogram qt corrected interval prolonged	0	1 (11.1)	0	1 (4.0)
Cardiac disorders	0	0	1 (12.5)	1 (4.0)
Tachycardia	0	0	1 (12.5)	1 (4.0)
General disorders and administration site conditions	1 (12.5)	0	0	1 (4.0)
Fatigue	1 (12.5)	0	0	1 (4.0)
Injury, poisoning and procedural complications	0	1 (11.1)	0	1 (4.0)
Joint injury	0	1 (11.1)	0	1 (4.0)
Metabolism and nutrition disorders	1 (12.5)	0	0	1 (4.0)
Increased appetite	1 (12.5)	0	0	1 (4.0)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Overall, there was an increased incidence of AEs with dose.

Regarding clinical laboratory results, mean increases for prolactin from screening to end-of-study approximated 44 ng/mL, 31 ng/mL, and 52 ng/mL in the 0.086 mg/kg/day, 0.129 mg/kg/day, and 0.171 mg/kg/day dosage groups. Changes from baseline ranged from -21.4 to 116.2 ng/mL.

One subject (male, 17 years of age) in the 0.086 mg/kg/day dosage group had treatment-emergent markedly abnormal values for alanine aminotransferase (ALT, up to 415 U/L), aspartate aminotransferase (AST, up to 192 U/L) and creatine kinase (up to 2890 U/L) at the end of the study. The values normalized at the follow-up visit 2 weeks later and were attributed to weight lifting.

One subject in the 0.086 mg/kg dose group, 3 subjects in the 0.129 mg/kg dose group, and 3 subjects in the 0.171 mg/kg dose group experienced a prolonged value for QTcB, defined as ≥450 ms at any time point during the study (Table 6).

No subject had an increase in QTcB or QTcF >60 ms from baseline. Two subjects (one in the 0.086 mg/kg dose group and one in the 0.129 mg/kg dose group) experienced in QTcF>30 ms from baseline.

Table 6: Individual QTcB abnormalities

Subject No.	Sex/Age	Screening	Day 1, predose	Day 2 (Change)	Day 3 (Change)	Day 9 (Change)	EOS/EW (Change)
Group A (0.086 mg/kg)							
100022	M/12 y	426	416	428 (+12)	430 (+14)	458 (+42)	455 (+39)
Group B (0.129 mg/kg)							
100001	M/10 y	434	432	466 (+34)	456 (+24)	457 (+25)	451 (+19)
100031	M/17 y	419	437	425 (–12)	430 (–7)	470 (+33)*	443 (+6)
100033	F/17 y	438	459	447 (–12)	460 (+1)	463 (+4)	450 (–9)
Group C (0.171 mg/kg)							
100035	F/17 y	443	439	459 (+20)	453 (+14)	438 (–1)	448 (+9)
100051	F/13 y	385	426	433 (+7)	432 (+6)	453 (+27)	447 (+21)
100082	M/14 y	463	468	460 (–8)	458 (–10)	471 (+3)	471 (+3)

EOS = end-of-study; EW = early withdrawal.
*: unscheduled visit; Cross reference: Appendix 3.8.4.2.

3. Discussion on clinical aspects

The safety profile of paliperidone based on the limited data from this Phase 1 study appeared to resemble that observed in adults. The results from the Phase 3 studies should provide a more comprehensive data set to evaluate safety, including clinical laboratory changes and cardiac safety.

The MAH also submitted a post-marketing evaluation of AEs reported in paediatric and adolescent subjects taking paliperidone PR. A search was conducted of the Benefit Risk Management worldwide safety database to identify all cases involving patients receiving paliperidone reported to the Sponsor cumulatively through 31 October 2008. Based on the 439,910.7 grams of paliperidone sold or distributed (from launch to 31 October 2008) the estimated exposure is 2,443,948 person-months. A breakdown of exposure in the paediatric and adolescent population is not available.

The search retrieved a total of 1768 cases associated with paliperidone. Of these, a total of 72 cases involved paediatric and adolescent patients (age <18 years old), including a total of 131 adverse events. Twenty-eight of the 72 cases were considered serious. None had a fatal outcome. The 44 remaining cases were considered non-serious. Fifty-five cases were medically confirmed by a health care professional while 17 cases were not

medically confirmed. Paediatric and adolescent patients who experienced adverse events associated with paliperidone ranged in age from neonate to 17 years old. Events reported more than once are presented in Table 7.

Table 7: Adverse events reported in paediatric and adolescent cases up to 31 Oct 2008

Preferred Term	Number of Cases (N=72)
Dystonia	11
Galactorrhoea	8
Weight increased	6
Accidental drug intake by child*	3
Aggression*	3
Blood prolactin increased	3
Dyskinesia	3
Headache	3
Increased appetite	3
Neuroleptic malignant syndrome	3
Rash	3
Tremor	3
Amenorrhoea	2
Drooling	2
Extrapyramidal disorder	2
Fatigue	2
Hypersomnia*	2
Palpitations	2
Restless legs syndrome*	2
Somnolence	2
Weight decreased*	2

* Events are not listed in the Company Core Data Sheet (CCDS).

Overall, the limited data available to date indicate a similar adverse event profile in adolescent patients compared with adults. However, this can only be evaluated more fully once the results from the larger studies become available.

RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The pharmacokinetic data indicated a similar PK profile of paliperidone PR in adolescents as in adults, with maximum plasma levels reached after approximately 24 hours and steady state reached after 4-5 days. A comparison with historical data in adults indicate a lower CL/F and higher exposure (Cmax and AUC0-24h) in adolescents compared with adults. The applicant´s proposed explanation for this finding is a lower weight in adolescents vs. adults.

Doses from 4 to 12 mg paliperidone PR (corresponding to weight-adjusted doses ranging between 0.086 and 0.171 mg/kg) were fairly well tolerated. No serious adverse events occurred.

- **Recommendation**

It is recommended to evaluate Phase 3 study results in adolescents prior to updating the Summary of Product Characteristics. No regulatory action is required at this time.

☒ **Fulfilled –**

No further action required.

☐ **Not fulfilled:**

III. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable.