25 April 2014
EMA/339041/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invega

International non-proprietary name: PALIPERIDONE

Procedure No. EMEA/H/C/000746/II/0037

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse Drug Reactions
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	Analysis of Covariance
AUC	Area Under Curve
BMI	Body Mass Index
BW	Body Weight
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CCDS	Company Core Data Sheet
CGA-S	Children's Global Assessment Scale
CGI-S	Clinical Global Impression Scale
CHMP	Committee for Human Medicinal Products
CI	Confidence Interval
Cl/F	Total apparent clearance
Cl/r	Renal clearance of drug
ClCr	Creatinine clearance
Cmax	Maximum Plasma Concentration
CNS	Central Nervous System
CONai	Estimated Consumption Of Active Substance In Geographic Region Per Year
Css	Steady State Concentration
C-SSRS	Columbia–Suicide Severity Rating Scale
DB	Double Blind
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EC	European Commission
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	End of Study
EPS	Extrapyramidal Symptoms
ER	Extended Release
ERA	Environmental Risk Assessment
EU	European Union
Fpen	Fraction of a Population receiving drug substance during a given time
Fu	Unbound Fraction
GLP	Good Laboratory Practices
GOF	Godness of Fit
HOMA	Homeostatic Model Assessment
IM	Intramuscular
ITT	Intention to Treat
K-SADS-PL	Kiddie-Sads-Present and Lifetime Version
LBM	Lean body mass
LOCF	Last Observation Carried Forward
LS	Least Squares
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MATRICS	Measurements and Treatment Research to Improve Cognition in Schizophrenia
MMRM	Mixed-effects Model for Repeated Measures
MO	Major Objection
NMS	Neuroleptic Malignant Syndrome
NO DB	No Double Blind
NOAEL	No Observed Adverse Effect Level
NONMEM	Non linear mixed effects modeling
OL	Open Label
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
PD	Pharmacodynamics
PDCO	Paediatric

PECsw	Predicted Environmental Concentration in Surface Water
PI	Product Information
PK	Pharmacokinetic
PL	Package Leaflet
PopK	Population Pharmacokinetic
PP	Per Protocol
PR	Prolonged Release
PRAC	Pharmacovigilance Risk Assessment Committee
PSP	Personal and Social Performance
PSRE	Potentially Suicide related events
PTs	Preferred Terms
QRD	Quality Review Document
QTc	Corrected QT
QTcB	QT interval corrected Bazett
QTcF	QT interval corrected Fridericia
QTcLD	QTc linear derived correction
QTlc	Linear corrected QT
RMP	Risk Management Plan
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
US	United States
VAS	Visual Analog Scale
VPC	Visual Predictive Check

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 8 March 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Invega	PALIPERIDONE	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed an extension of indication to add the treatment of schizophrenia in adolescents 12 years and older.

Consequently, the MAH proposed the update of sections 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC. Sections 1, 2, 3 and 4 of the Package Leaflet was proposed to be updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Filip Josephson

CoRapporteur: Martina Weise

1.2. Steps taken for the assessment

Submission date:	8 March 2013
Start of procedure:	29 March 2013
Rapporteur's preliminary assessment report circulated on:	23 May 2013
CoRapporteur's preliminary assessment report circulated on:	17 May 2013
Rapporteur's RMP assessment report adopted by PRAC on :	13 June 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	27 June 2013
MAH's responses submitted to the CHMP on:	18 October 2013
Rapporteurs' joint preliminary assessment report circulated on:	3 December 2013
Rapporteurs' joint updated assessment report on the MAH's responses circulated on:	13 December 2013
Follow on Request for supplementary information and extension of timetable adopted by the CHMP on:	19 December 2013
MAH's responses submitted to the CHMP on:	21 February 2014
Rapporteurs' joint preliminary assessment report on the MAH's responses circulated on:	8 April 2014
Rapporteurs' joint updated assessment report on the MAH's responses circulated on:	15 April 2014
CHMP opinion on:	25 April 2014

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/154/2011 on the agreement of a paediatric investigation plan (PIP).

The PDCO issued an opinion on compliance for the PIP P/154/2011 eligible for the reward.

2. Scientific discussion

2.1. Introduction

Invega (paliperidone) is a monoaminergic antagonist with a high affinity for serotoninergic (5-hydroxytryptamine Type 2A) and dopaminergic Type 2 receptors. It belongs to the atypical, antipsychotic class of psychotropic drugs. It is the major active metabolite of risperidone which is authorised for the treatment of schizophrenia. Paliperidone have been developed as an oral prolonged-release formulation (paliperidone ER or PR tablets) and a long-acting IM injectable formulation (paliperidone palmitate). Paliperidone palmitate (Xeplion) is subject to a separate marketing authorisation (MA).

Invega tablets (1.5, 3, 6, 9, and 12 mg) are currently approved in the European Union (EU) for the treatment of schizophrenia and schizoaffective disorder (psychotic or manic symptoms) in adults with recommended dose of 6 mg once daily. Dosage adjustment may be required within the recommended range of 3-12 mg once daily in patients with schizophrenia and 6-12 mg once daily in patients with schizoaffective disorder.

In December 2009, the MAH submitted one completed paediatric study, **R076477-PSZ-3001,** for Invega (paliperidone) in accordance with Article 46 of the Paediatric Regulation (EC) No1901/2006, as amended (EMEA/H/C/746/P46/011). No further actions were required by the CHMP awaiting for the completion of the phase III study **R076477-PSZ-3003** to consider an update of the Product Information (PI). The procedure was concluded in March 2010.

In December 2010, the MAH submitted two other completed paediatric studies, **R076477-PSZ-3002 and R076477-PSZ-3003,** for Invega (paliperidone) in accordance with Article 46 of the Paediatric Regulation (EC) No1901/2006, as amended (EMEA/H/C/746/P46/017). The CHMP agreed in February 2013 to assess these data within the planned submission for an extension of indication in March 2013.

Subsequently, the MAH submitted the present application. Within this procedure (EMEA/H/C/746/II/37), the MAH initially applied for an extension of indication of Invega (new indication is underlined) as follows:

"INVEGA is indicated for the treatment of schizophrenia in adults **and in adolescents 12 years and older."**

For the extension of indication applied for, the MAH initially proposed the following posology for Invega:

"The recommended starting dose is 3 mg once daily, administered in the morning. Some patients may benefit from a higher dose of 6 mg to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment based on the individual need of the patient. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of 5 days or more."

This application is based on the previously mentioned clinical studies (**R076477-PSZ-3001, R076477-PSZ-3002 and R076477-PSZ-3003)** which are part of the agreed Paediatric Investigation

Plan (PIP) for paliperidone ER. An open-label single and multiple dose Phase 1 study **(PALIOROS-PSZ-1001)** was also conducted to investigate the pharmacokinetics (PK) properties of paliperidone ER and its safety profile in paediatric subjects (aged 10 to 17 years) and is also referred in this application. This study was previously submitted in accordance with article 45 of the Paediatric Regulation (FUM 10). Additionally, 2 non-clinical studies (**TOX8691, TOX8145**) were submitted in this application, TOX8691 being part of the PIP.

During the evaluation, the MAH proposed to restrict the proposed indication to treatment of schizophrenia in adolescents **15 years and older.** The posology was also revised and is further discussed below.

2.2. Non-clinical aspects

The MAH provided one toxicity study with repeated oral administration of paliperidone for seven weeks in juvenile rats. Furthermore, another toxicity study with oral treatment of risperidone for 40 weeks in juvenile dogs was submitted. Both juvenile toxicities studies were conducted in compliance with Good Laboratory Practices (GLP).

2.2.1. Toxicology

These data are summarised in Table 1. Tables 2 and 3 present the toxicokinetic results.

Table 1: Summary of the toxicity studies performed with paliperidone and risperidone in juvenile rats and dogs.

Study number (tested drug)	**Species/ Strain** **Number/ Sex/Group**	**Route/Dose/Duration (mg/kg)**	**Major Findings**
TOX8691 (paliperidone)	Rats, 24 days of age at Day 1 32 female and males	Oral gavage 0.16, 0.63 or 2.5 mg/kg/day Controls: vehicle, tartaric acid and NaOH Seven weeks from Day 24 to Day 73 of age (12 males, 12 females) 4 extra weeks for recovery/repro phase (20 males, 20 females)	No treatment related deaths. Apart from below, all other parameters were unaffected by treatment. Clinical observations: Pharmacological effects, such as ptosis, underactivity, piloerection and reddening of the skin at 0.63 or 2.5 mg/kg, throughout the treatment period. Food consumption and body weight gain: Slightly increased in females. Morris Maze: Impaired learning and memory in females at 2.5 mg/kg from days 67 to 69 of age,but no effects in males or at lower dosages. Performance of the females was similar to controls after three weeks of recovery. Prolactin: Higher than controls in all treated groups of males and females, no dose response. In males at 2.5 mg/kg/day increase statistical significant. Oestrous cycles: Reduced cycle activity in all treated groups, 2.5 mg/kg group least affected. Normal after cessation of treatment. Histopathology: Glandular development and persistent corpora lutea in females.
TOX8145 (risperidone)	Beagle dogs, 10 weeks of age at Day 1	Oral gavage 0.31, 1.25 or 5 mg/kg/day	No treatment related deaths. Apart from below, all other parameters were unaffected by treatment. Clinical observations: Dose dependent reduced activity,

Study number (tested drug)	**Species / Strain** **Number / Sex / Group**	**Route / Dose / Duration (mg/kg)**	**Major Findings**
	8 females and males/group, 4 females and males were for recovery	Controls: vehicle, tartaric acid and NaOH 40 weeks Recovery: 12 weeks	pupil constriction, visible third eyelid, reddening of the sclera and loose or liquid faeces. Body weight gain: Reduced at 0.31 and 1.25 mg/kg, reversible. Femur growth: Reduced in females at 5 mg/kg, lower mineral density in femur and femoral diaphysis in females at 1.25 and 5 mg/kg, trend to reversibility during recovery period. Shoulder height: Reduced in females at 1.25 and 5 mg/kg and in males at 5 mg/kg; reversible in males but not in females during recovery. Serum chemistry: Increased prolactin at all dose levels in both males and females, reversible. Reduced testosterone levels in males at all dose levels, reversible. After 8 weeks of recovery, females at 0.31 and 1.25 mg/kg/day showed increased progesterone concentrations for the first time. Females at 5 mg/kg/day showed no detectable progesterone after up to 12 weeks of recovery. Oestrous cycles: Oestrus in majority of controls W32 to W40, only in one female at 0.31 mg/kg/day and in no females at 1.25 or 5 mg/kg/day. During the recovery in one female at 0.31 and in one at 1.25 mg/kg/day, not seen for any females at 5 mg/kg/day. Organ weights: Low epididymides and testes weights and reduction of total sperm counts at 1.25 and 5 mg/kg/day, low prostate weights at 5 mg/kg/day, no definite reversibility. Low ovary, uterus and cervix weights at all dose levels, no definite reversibility. Histopathology: Low colloid amount/atrophy in the prostate at 5 mg/kg/day, reversible. Active glandular development in the mammary, prominent luteal cells and endometrial gland hyperplasia in controls but not in any treated females.

Table 2: The mean C_{max} and AUC values of paliperidone after repeated oral dosing at 0.16, 0.63 and 2.5 mg/kg/day in male and female juvenile rats.

Day 31							
		Male			Female		
Dose	**(mg/kg/day)**	**0.16**	**0.63**	**2.5**	**0.16**	**0.63**	**2.5**
C_{max}	(ng/ml)	16.8	94.1	426	23.7	90.7	428
AUC_{0-24h}	(ng.h/ml)	76.7	385	1543	131	525	2056[a]

[a] $_1AUC_{0-8h}$

Table 3: The mean C_{max} and AUC values of risperidone+9-hydroxy-risperidone (active moieties) after repeated oral dosing at 0.31, 1.25 and 5 mg/kg/day in male and female juvenile dogs.

	Male			Female		
	Day 1					
Dose (mg/kg/day)	0.31	1.25	5	0.31	1.25	5
C_{max} (ng/ml)	126	351	2010	116	418	2505
$AUC_{0\text{-}inf}$ (ng.h/ml)	918	3024	17327	797	4572	22047
	Day 106					
Dose (mg/kg/day)	0.31	1.25	5	0.31	1.25	5
C_{max} (ng/ml)	123	500	1257	214	377	1445
$AUC_{0\text{-}24\,h}$ (ng.h/ml)	1345	4623	15000	1466	4472	17032
	Day 208					
Dose (mg/kg/day)	0.31	1.25	5	0.31	1.25	5
C_{max} (ng/ml)	154	531	1398	144	648	1637
$AUC_{0\text{-}24\,h}$ (ng.h/ml)	1405	5351	16492	1317	6333	16951

2.2.2. Ecotoxicity/environmental risk assessment

No new ERA data were initially submitted by the MAH. However, considering this application is to extend the use in the paediatric population with schizophrenia, the CHMP requested the MAH to provide an updated medical statistical data for the new estimated market penetration and the calculation of the refined Predicted Environmental Concentration in the surface water (PECsw) in Phase II tier A. Using an estimated consumption of active substance in geographic region per year (CON_{ai}) of 289 kg (the highest predicted usage of paliperidone from 2013-2019), the F_{pen} was found lower than previous calculation based on a predicted CON_{ai} of 775 kg for 2014. Consequently the PEC of paliperidone in surface water was 0.0001 μg/L (compared with 0.003 μg/L calculated in previous ERA). Therefore, the CHMP concluded that no further ERA data were required with the proposed extension of indication and agreed that adding a patient population of 12-17 year old would not significantly alter the exposure of paliperidone to the environment, also taking into account that schizophrenia only exists very rarely in children and adolescents (estimated 1 in 10,000) compared with a lifetime prevalence of 0.5 to 1 in 100 in adults.

2.2.3. Discussion on non-clinical aspects

In juvenile rats, dosing by oral gavage at 0.16, 0.63 and 2.5 mg/kg/day, no new findings were observed, compared to what is already known for paliperidone. The findings observed were expected pharmacological effects. A possibly treatment-related effect on learning and memory was seen in females only and the CHMP considered necessary to include this effect in the SmPC of paliperidone, although the clinical significance of this finding was unclear. Whilst learning and memory was not compromised in males in this study, the CHMP noted that slight effects on learning and memory were previously evident in juvenile rats of both genders administered with 1.25 mg/kg risperidone. Based on these results, the No Observed Adverse Effect Level (NOAEL) for males and females was 2.5 mg/kg/day and 0.63 mg/kg/day, respectively.

In juvenile dogs, dosed by oral gavage at 0.31, 1.25 or 5 mg/kg risperidone /day, no new findings were observed, compared to what is already known for risperidone/paliperidone. Testosterone and progesterone levels together with histopathological findings in the prostate, mammary gland, ovaries

and uterus indicated that sexual maturity was delayed in dogs at all dose levels. A trend to reversibility was seen during the recovery period for males and the low and mid dose females, whereas recovery was not seen in females administered 5 mg/kg/day.

In dogs, overall femur growth was reduced during treatment for females at 5 mg/kg/day and the overall change in shoulder height was also less for males and females at this dose level. Furthermore, at 40 weeks, the femurs of females at 5 mg/kg/day had lower mineral density for the proximal femur and the femoral diaphysis. These findings on bone development are expected effects of atypical antipsychotics such as paliperidone and likely due to increased levels of prolactin.

All the effects seen in dog were reversible during the recovery period. Based on these results the NOAEL for males and females was 0.31 mg/kg/day.

In previous studies conducted in adult animals, effects were seen at or below clinical exposure. In adolescents, the C_{max} was 23.2 (9.62-89.3) ng/mL and the AUC_{0-24} was 486 (215-1750) ng*h/mL. Comparing the clinical exposure with the exposures reached in the rat study, no margin to human exposure was reached at NOAEL in female rats, whereas a margin of 3 was reached in males (NOAEL was the highest dose tested). In dogs, at NOAEL, the margin to clinical exposure was approximately 3.

The nervous and reproductive systems are the main organ systems which are under development between 12-18 years. The rats were 3.5 weeks at the beginning of the study and the study lasted for 7 weeks, thus the critical maturation period regarding nervous and reproductive systems in the rats is considered covered. In the dog study, the critical period for skeletal and reproductive system development was covered.

Overall, available non-clinical data obtained in juvenile rats with paliperidone are consistent with previous results from treatment of juvenile rats and dogs with the parent compound risperidone. For this reason, these data are regarded sufficient to support the proposed therapy of schizophrenia in adolescents of 12 years and older initially applied for. It should be noted, however, that effects in juvenile animals already occurred at exposures (based on AUC), which are either close (delay of physical development and sexual maturation in risperidone-treated dogs) or equal (learning and memory deficits in rats administered either paliperidone or risperidone) to the level achieved at the maximum recommended dose in adolescents. The CHMP therefore considered necessary to include a description of the findings from the juvenile toxicity studies in the SmPC. In addition, SmPC warnings related to hyperprolactinaemia- and sedation-related side effects were added in view of the non-clinical findings that were further supported by clinical data (see 2.5).

2.2.4. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of Invega have been adequately documented and meet the requirements to support this application.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 4: Tabular overview of clinical studies in paediatric population with schizophrenia

Protocol Number	Study Design and Objective	Study Treatments	No. of Subjects (N)
R076477-PSZ-3001	6-week, randomized, double-blind, parallel-group, placebo-controlled multicenter efficacy and safety study in adolescents (12-17 years) with schizophrenia	Placebo or fixed doses of paliperidone ER (1.5, 3, 6, or 12 mg/day). Randomization to paliperidone ER Low, Medium, or High based on non-overlapping mg/kg groups.	Placebo, N=51 Paliperidone ER Low (1.5 mg) , N=54 Paliperidone ER Medium (3 or 6 mg), N=48 Paliperidone ER High (6 or 12 mg), N=48 Total N=201
R076477-PSZ-3003	26-week, randomized, double-blind, active-controlled, parallel-group, multicenter, efficacy and safety study in adolescents (12-17 years) with schizophrenia	Flexible doses of paliperidone ER (range, 3 to 9 mg/day) or aripiprazole (range, 5 to 15 mg/day)	Paliperidone ER, N=113 Aripiprazole, N=114 Total N=227
R076477-PSZ-3002[a]	2-year, long-term, open-label study of safety and tolerability of paliperidone ER in adolescents (12-17 years) with schizophrenia	Flexible doses of paliperidone ER titrated to maximum tolerated dose (range, 1.5 to 12 mg/day)	Paliperidone ER, Total N=400
PALIOROS-PSZ-1001	Open-Label, Safety and Pharmacokinetics of Single- and Multiple-Dose in children and adolescents (10-17 years) with schizophrenia, schizoaffective disorder, or schizophreniform disorder	0.086, 0.129, and 0.171 mg/kg/day paliperidone ER, corresponding to approximately 6, 9, and 12 mg/day in adults	Paliperidone ER (0.086 mg/kg), N=8 Paliperidone ER (0.129 mg/kg), N=9 Paliperidone ER (0.171 mg/kg), N=8

2.3.2. Pharmacokinetics

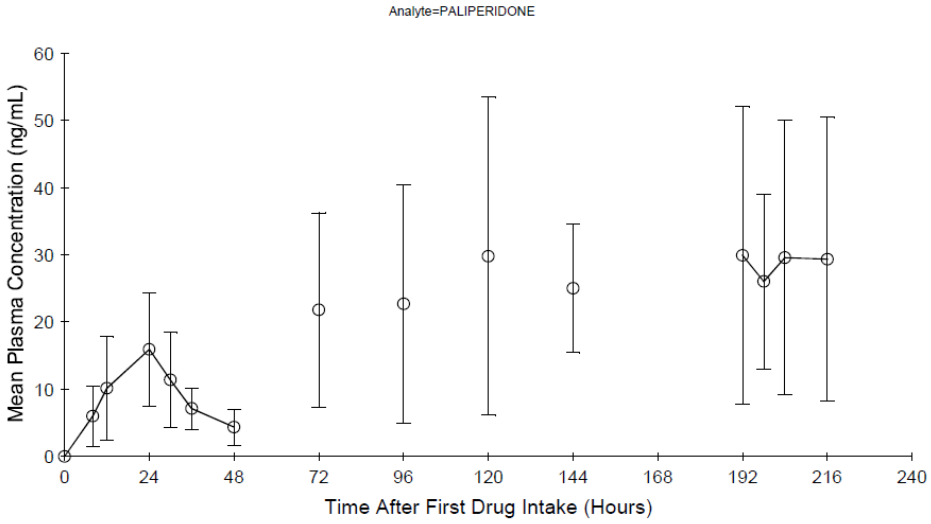
The pharmacokinetics of paliperidone in children and adolescents (10 to 17 years of age inclusive) was investigated in study PALIOROS-PSZ-1001 and R076477-PSZ-3001. The data were analysed both using non-compartmental analysis and population pharmacokinetic (popPK) modeling in NONMEM. In study PALIOROS-PSZ-1001, only one subject was below 12 years, hence the CHMP considered that the presented data characterised the PK in adolescents (12-17 years inclusive) and the term “adolescents” is used throughout the report as a reference to the studied population.

Absorption

The absolute bioavailability of paliperidone ER in adolescents has not been investigated.

Following single-dose administration, peak plasma concentration was reached after approximately 24 hours (Figure 1). Based on a popPK analysis the intra-individual variability in relative bioavailability (F1) is 46.4%.

Figure 1: Mean (±SD) Paliperidone Plasma Concentration-Time Profile (Dose-Normalized to 6 mg/day) in Adolescents (Study PSZ-1001)



Based on observed data, steady-state plasma exposure (dose-normalized to 6 mg/day) was on average 50% higher in adolescents compared to adults (see Table 5).

Table 5: Steady-State Plasma (Dose-Normalized to 6 mg/day) and Urine PK Parameters of Paliperidone in Pediatric (Adolescent) and Adult Subjects

PK parameter	N	Mean ± SD	Median	Min-Max
Pediatric Subjects (Study PSZ-1001)				
C_{max}, ng/mL	23	34.2 ± 22.3	23.2	9.62–89.3
AUC_{24h}, ng.h/mL	23	686 ± 448	486	215–1750
CL/F, mL/min	23	209 ± 117	206	57.1–465
CL_R, mL/min	23	42.4 + 17.4	37.8	8.01–68.5
Adult Subjects[a]				
C_{max}, ng/mL	172	23.7 ± 12.3	21.0	5.86–86.7
AUC_{24h}, ng.h/mL	172	457 ± 235	396	115–1563
CL/F, mL/min	173	268 ± 119	252	54.0–869
CL_R, mL/min[b]	74	36.2 ± 15.8	34.5	11.4–86.7

[a] Pooled PK dataset from Studies R076477-P01-1005, PAL-SCH-101, R076477-SCH-102, PALIOROS-SCH-1011.
[b] pooled data from Studies R076477-P01-1005 and PALIOROS-SCH-1011
Source: Mod5.3.3.2\PALIOROS-PSZ-1001\Att2.3, Att2.5, Table11, Table13

Distribution

The volume of distribution in adolescents was found to be large; Vss (sum of central and peripheral volume in the popPK model) is approximately 440 L. The corresponding figure for adults is approximately 490 L.

The steady-state AUC24h (+)/(–) enantiomer ratio and fraction unbound (fu) of paliperidone in adolescents were similar to values obtained in adults. The enantiomer ratio was approximately 1.4,

compared to 1.6 in adults. The mean fu of paliperidone was approximately 26% in both adolescents and adults.

Elimination

In adolescents, the observed average CL/F in study PSZ-1001 was 12.5 L/h (209 mL/min). The fraction excreted, fe, was approximately 20%.

Dose proportionality and time dependencies

In study PSZ-1001, steady-state drug concentrations were attained within 4 to 5 days of dosing as seen in Figure 1. Plasma exposure (Cmax and AUC24h) increased with increasing dose. The accumulation ratio, based on visual inspection of the peak plasma concentrations following single vs. multiple dosing, was approximately 3.7. The popPK model indicated linear, dose-proportional pharmacokinetics.

Special populations

The effect of renal or hepatic impairment has not been studied in adolescents.

According to the MAH, given that maturation of renal function is completed by early childhood and the PK and plasma protein binding of paliperidone are similar in adolescents and adults, it is expected that the impact of renal or hepatic impairment on the PK of paliperidone in adolescents will be similar to that in the adult population. In the popPK modeling the effects of body weight, age and creatinine clearance were investigated (see 2.3.3).

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies have been performed in adolescents. This was considered acceptable by the CHMP, given the available interaction data in adults (paroxetine, trimethoprim, carbamazepine and divalproex sodium).

2.3.3. PK/PD Modelling

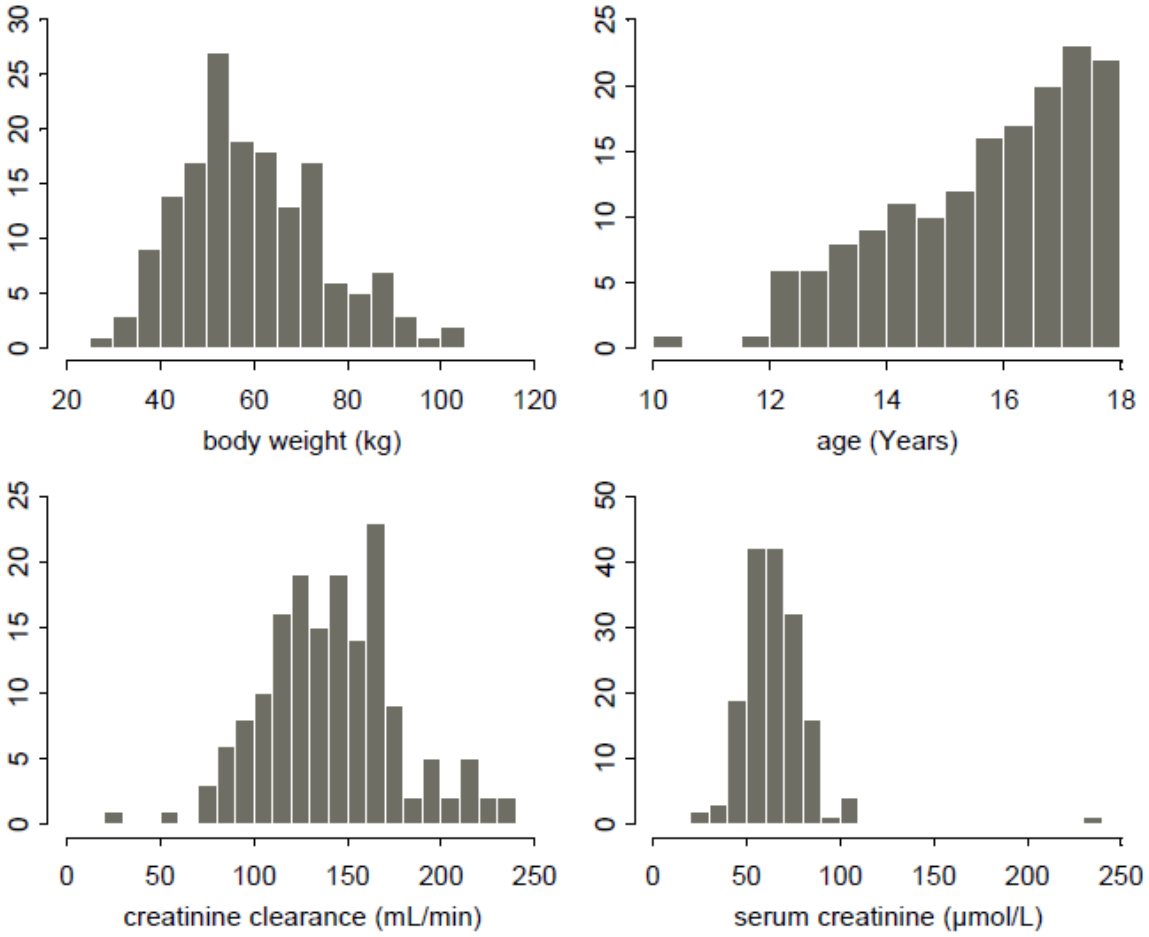
PK modeling

Exploratory popPK modeling was carried out using data from PSZ-1001 and PSZ-3001. An adult popPK model developed on Phase 3 data was used as a starting point. The final PK model was further validated taking into account the observed data from study PSZ-3003.

A total of 105 male and 57 female adolescent subjects were included in the PK dataset which also included adult data (110 male and 43 female subjects). The racial composition of the adolescent population was about 66.0% White, 10.5% Black (including African-American), 1.2% Hispanic-Latinos and 22.2% Asian. The median age was 16.1 years and ranged from 10.3 to 17.9 years. Only one subject in the dataset was < 12 years of age. The median BMI was 21 kg/m2 and ranged from 13.5 to 35.1 kg/m2. The median BW was 58.1 kg (range: 29.0 to 104.6 kg). The median CrCLc was 141 mL/min and ranged from 29.8 to 231 mL/min.

The distribution of continuous covariates for Adolescents is shown in Figure 2.

Figure 2: Distribution of Continuous Covariates From the Adolescents in the popPK Dataset



The available adult PK model was first used to simulate the adolescent data under the observed covariate values and design but with fixed model parameters. The model was found applicable since the prediction error (precision) and absolute prediction error (bias) were within the defined criteria.

The model was then executed on adolescent data only but the run was terminated. Body weight was used as covariate on CL/F instead of lean body mass. To improve stability adult data was included and the model was reduced in terms of random effects on structural parameters. After successful termination, the effect of age alone was tested n CL/F but was not found to be statistically significant.

The final model included body weight (BW) and calculated creatinine clearance (CLCr, Schwartz formula) as covariates on CL/F according to the equation below:

$$CL/F = 10.9 \cdot \left(\frac{BW}{74.4}\right)^{0.727} + 0.0240 \cdot CrCLc$$

The parameters estimates from the final model, relative standard error (RSE%) and calculated shrinkage are shown in Table 6.

Table 6: Parameter Estimates of the Model 3 (Final Model)

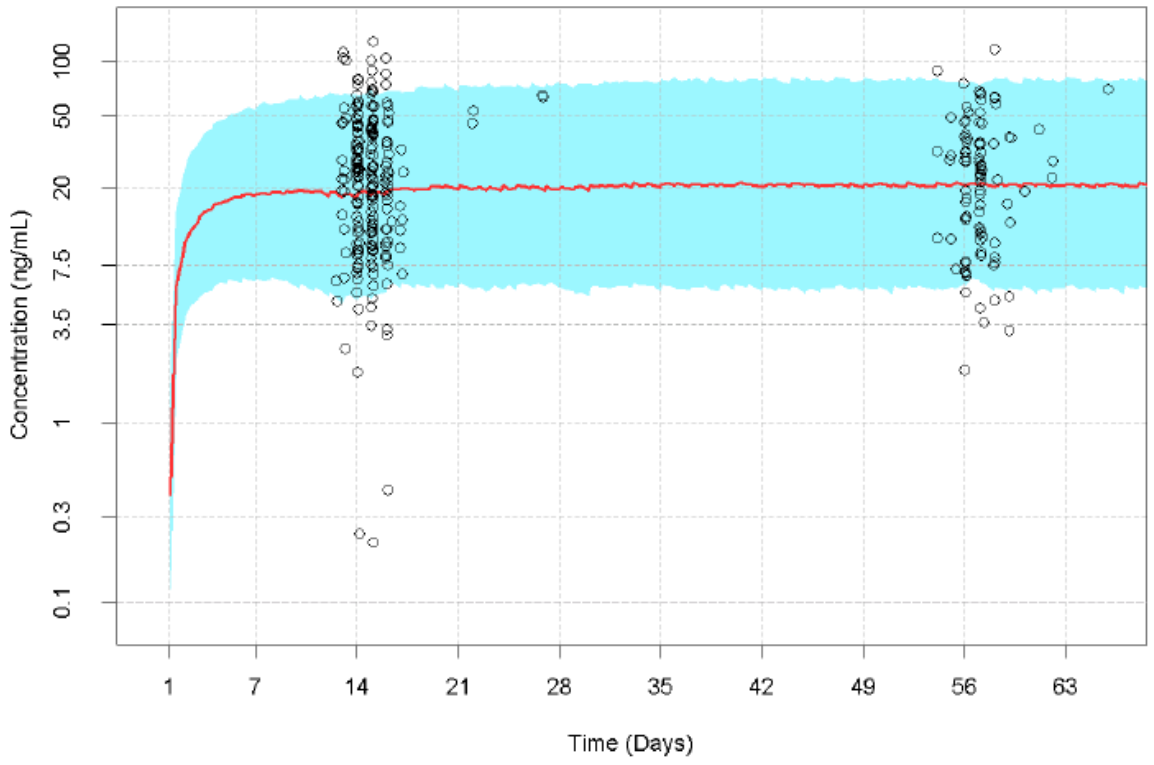
Parameter	Estimate	RSE %	IIV %CV	IIV RSE %	η-Shrinkage %
CL/F (L/hr) intercept	10.9	11.5	44.4	18.1	13.8
Power on CL/F for BW	0.727	21.7			
Linear Slope on CL/F for $CrCL_c$	0.024	46.3			
V2 (L)	198	6.67	34.5	31.3	52.1
V3 (L)	244	6.84	28.6	24.5	47.6
KA	0.63	12.0	59.9	20.3	41.0
Q (L/hr)	22	10.0			
D1	25.4	0.728	IOV		
ALAG1	0.761	8.66	Estimate	RSE %	
F1	NE		46.4	14.1	

Residual Variability %	20.5	4.58
Minimum Value Objective Function = -12670		

NE = not estimated, set equal to 1

The final PK model was further validated taking into consideration the observed data from study PSZ-3003 (Figure 3).

Figure 3: Comparisons of Population PK Simulation vs. Actual Plasma Concentration Data from Study PSZ-3003

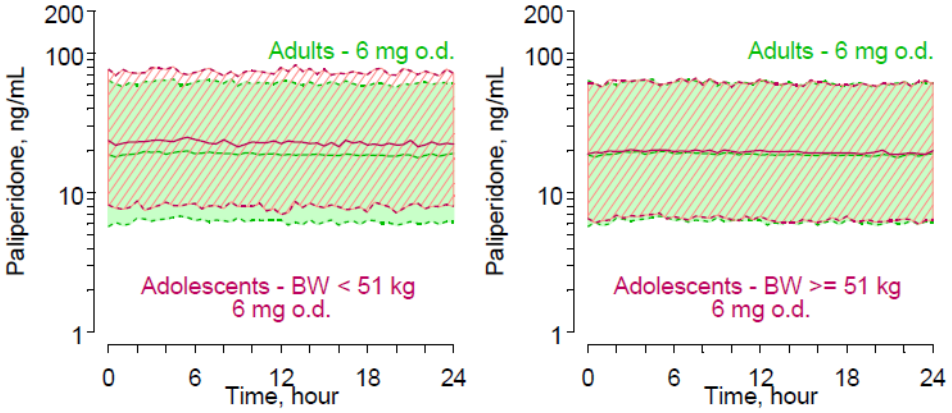


The x-axis represents time (days) and the y-axis represents plasma concentrations of paliperidone (ng/mL). The solid red line and the shaded area represent the median and the 90% prediction interval based on the population PK simulations. Open symbols represent actual plasma concentration data from clinical trial subjects in study PSZ-3003.

The final population PK model was used to simulate the exposure in the adult and adolescent populations.

Simulation of a once-daily dose of 6 mg in adults and in adolescents weighing at least 51 kg resulted in comparable plasma exposure to paliperidone. Similarly, paliperidone plasma exposure following once-daily dose of 6 mg in adults and adolescents weighing <51 kg was comparable. In adolescents weighing <51 kg, a 23% higher mean average plasma concentration was observed than in adolescents weighing ≥51 kg. Based on these results, no PK-based dose adjustments were proposed by the MAH in adolescents (12 to 17 years). See Figures 4 and 5.

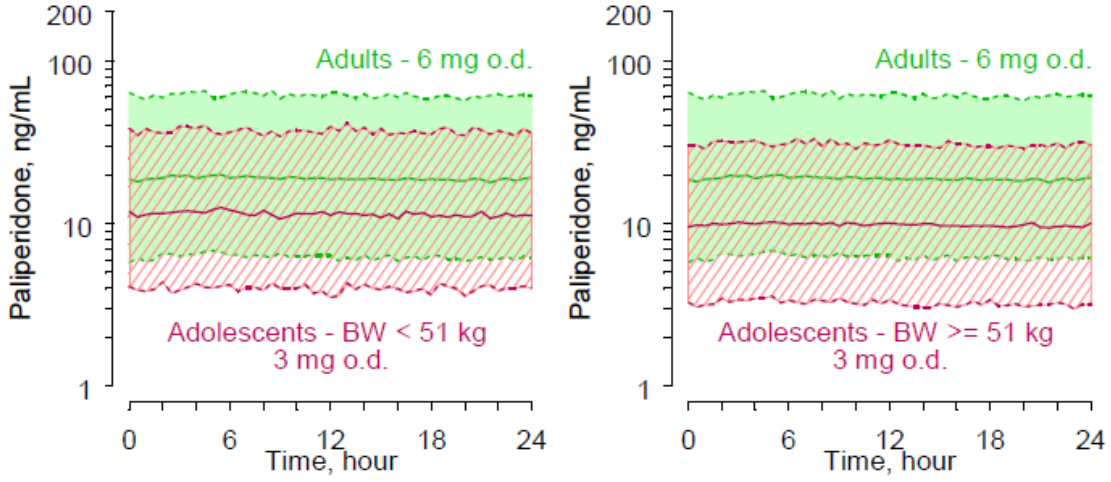
Figures 4 and 5: Simulations with Final Model with Phase 3 Adult and Adolescent Data of a once daily dose of 6 mg



The shaded area depicts the prediction interval (5th and 95th percentiles and median shown) (solid for adults and hatched for adolescents)

Simulation of a once-daily dose of 6 mg in adults and 3 mg in adolescents resulted in lower plasma exposure to paliperidone in adolescents, even in the lower-weight group, indicating that the lower clearance in adolescents < 51 kg is overcompensated by dividing dose in half. See Figures 6 and 7.

Figures 6 and 7: Simulations with Final Model with Phase 3 Data of a once daily dose of 6 mg for adults and once daily dose of 3 mg for adolescents



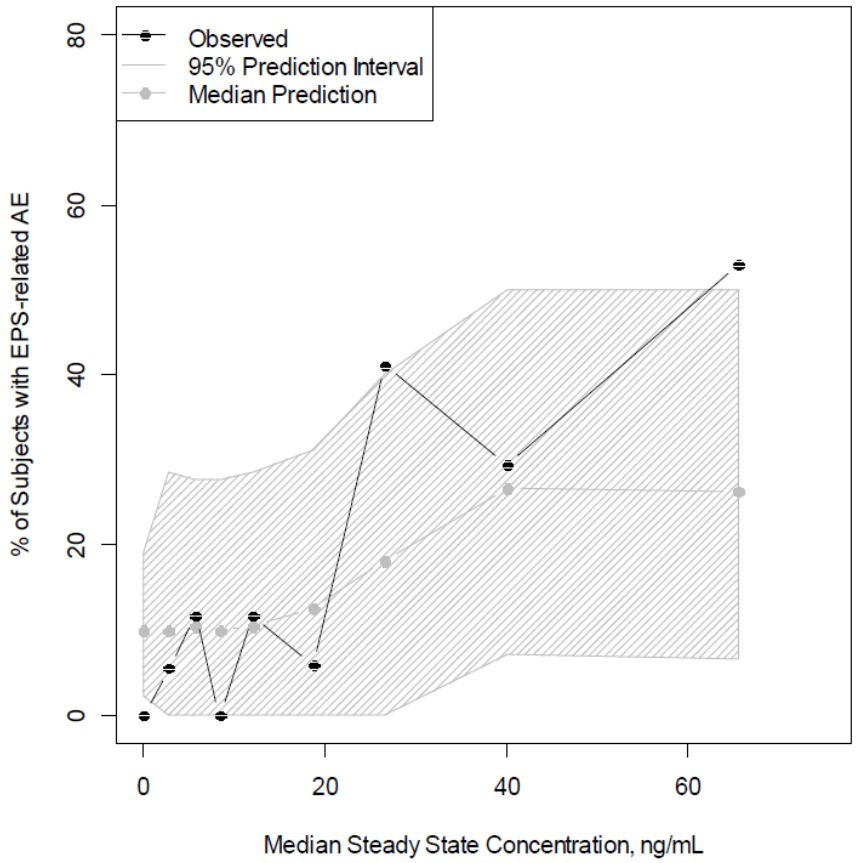
PKPD modeling

Safety - Incidence of Extrapyramidal Symptoms

Data from study PSZ-3001 were used to explore the PK/PD-relationship between the risk of having EPS-related treatment emergent adverse events and paliperidone exposure. To assess the similarity of the PK/PD-relationship in adolescents and adults, the percentage of subjects with EPS-related AEs in the PSZ-3001 study was simulated using the model that was previously developed for adults. The individual predicted average steady state concentration (Css) was calculated using empirical Bayes estimates derived from the popPK model (previous section).

There were no EPS-related AEs observed in the placebo group. The incidence of EPS-related AEs was low in the exposure groups with a median Css < 20 ng/mL. The EPS incidence was higher in exposure groups with a median Css > 20 ng/mL . Overall, 41% of subjects had a Css > 20 ng/mL, but there was a major difference in the distribution of Css between treatment groups: 0% in the low dose group had a Css > 20 ng/mL, while 49% in the medium dose group and 77% in the high dose group had a Css > 20 ng/mL. See Figure 8.

Figure 8: Observed incidence of EPS-related AEs by exposure group overlaying the 95% prediction interval (and median) of the EPS-incidence obtained by simulation of PSZ-3001 using the adult PK/PD-model



2.3.4. Additional analyses

During the evaluation, the MAH provided a revised popPK model using only the data in adolescents ie excluding the adult data and the data in renal impaired subjects (Studies PSZ-1001, PSZ-3001 and

PSZ-3003) to address the CHMP concern over the validity of the model for the purpose of simulation. An adapted covariate model was developed (see Table 7).

Table 7. Modeling of adolescent population PK with different covariates

Description	RunNo	Reference Run	Objective Function	Delta Objective Function
Base model without covariates	**8**		219.114	
Base model with BW on CL	**9**	8	207.876	-11.238
Base model with AGE on CL	10	8	218.82	-0.294
Base model with CrCL on CL	11	8	212.848	-6.266
Base model with BW and AGE on CL	12	9	207.877	0.001
Base model with BW and CrCL on CL	**13**	9	206.854	-1.022
Base model with BW and CrCL and AGEon CL	14	13	206.854	0

When testing BW, age and CrCL independently as covariates on CL/F in the adolescent dataset, only BW was statistically significant as a covariate. Including BW, and testing age and CrCL in addition to BW did not result in further statistical improvements of the model fit. However, as more than 60% of paliperidone is eliminated unchanged through the kidney, CrCL was included as a prior covariate on CL/F, and BW and age in addition to CrCL were tested. BW in addition to CrCL was found to be statistically significant, but age was not. Therefore, the final covariate model that had been developed using the adolescent data only, remained the same as presented in the original submission.

According to the MAH, the population PK parameter values derived from the adolescent dataset only are well in line with those of the original analysis, in which both adolescents and adult data were included (see Table 8).

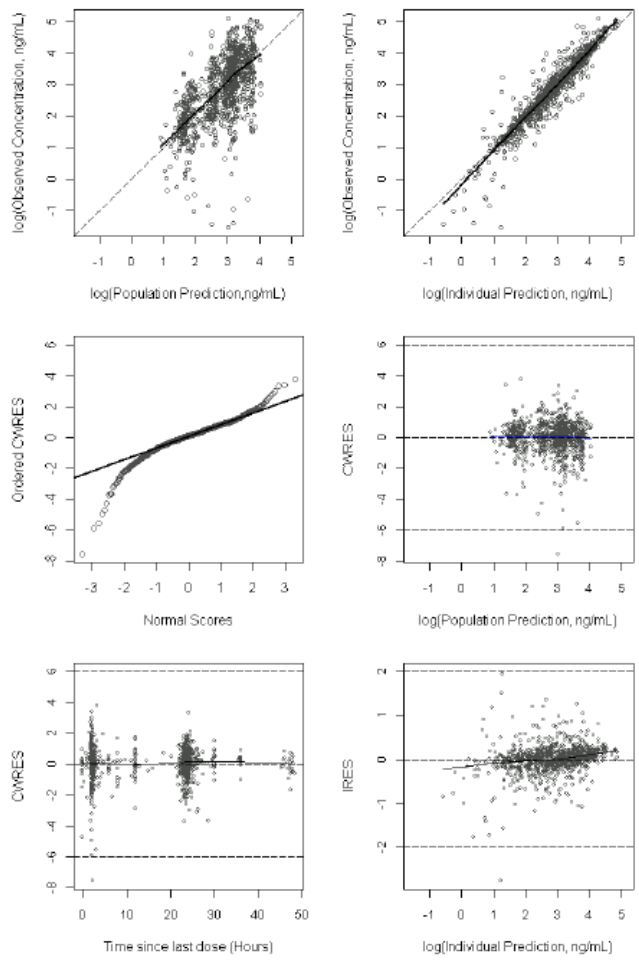
Table 8 Population PK parameters based on data from adolescent studies PSZ-1001, PSZ-3001 and PSZ-3003

Parameter	Estimate	RSE %	IIV %CV	RSE %
CL/F (L/hr) intercept	9.29	63.9		
Power on CL/F for BW	0.681	32.7	57.4	19.3
Linear Slope on CL/F for $CrCL_c$	0.0236	171.6		
V2 (L)	208	27.2	19.7	403
V3 (L)	337	46.3	-	
KA	0.63 fixed	-	-	
Q (L/hr)	12	36.6		
D1	23.6	14.1	IOV	
ALAG1	0.142	3401	Estimate	RSE %
F1	NE		47.5	22.5
Residual Variability %	43.2	19.0		

NE = not estimated, set equal to 1 for F1

The Goodness of Fit (GOF) plots (Figure 9 also indicates that the model describes the data well. For the MAH, this confirms that the developed population PK model describes the adolescent data effectively, and can be used for simulation purposes.

Figure 9 Goodness of Fit Plots Using Data from adolescent studies PSZ-1001, PSZ-3001 and PSZ-3003



2.3.5. Discussion on clinical pharmacology

In study PSZ-1001, 3 dosage groups were included (approximately 0.086, 0.129, and 0.171 mg/kg/day paliperidone ER) corresponding to daily doses of 6, 9, and 12 mg, respectively, for a 70-kg adult on a milligram per kilogram basis. Consistent findings between adolescents and adults were observed in relation to the plasma concentration-time profile and time to reach the steady-state drug concentrations (within 4-5 days). However, the mean CL/F was lower in paediatric subjects compared to healthy adults over the dose range 4 to 12 mg daily, resulting in 44% higher mean steady-state Cmax of paliperidone and 50% higher AUC24h.The range of plasma exposures for Cmax was similar whereas the upper threshold of the AUC range was higher in adolescents in comparison to adults (1750 versus 1563 ng.h/mL). The overall findings led the MAH to a weight-based dosing for the phase 3 study PSZ-3001 with a threshold of 51 kg to ensure that lower-weight subjects were not given too high a dose. Because the substantial inter-individual PK variability was only partly explained by differences in body weight in the phase 3 study PSZ-3001, a weight–based dosing approach was not used in the other phase III study PSZ-3003. In addition, the effect of body weight on CL/F was found to be relatively small in the combined PSZ-1001/PSZ-3001 dataset as compared to the PSZ-1001 alone.

Overall, the mean age of adolescents included in study PSZ-1001 was 14 years. Sixteen patients were 14 years and older in comparison to 8 patients aged 12 and 13 years old. Only 5 patients were both younger than 14 years and had a body weight less than 51 kg. However, patients younger than 14 years were included in the phase 3 study PSZ-3001. Taking into account the combined PSZ-1001/PSZ-3001 dataset, the CHMP considered that sufficient information was available to characterise the influence of body weight and age on the pharmacokinetics in the full population from 12-17 years inclusive.

In the popK analysis, the final model initially presented for adolescents was actually a model combining adult and adolescent data. The estimated parameters did not represent the PK in adolescents and were rather representative of the PK in the broader population. The effect of renal function on total clearance was incorporated in the model. The estimated slope for the relation between CL/F and CLCr did not seem to be in line with the reduction in CL/F observed in subjects with varying degree of renal impairment. The observed decrease in CL/F was 32% in mild (CLCr = 50 to < 80 mL/min), 64% in moderate (CLCr = 30 to < 50 mL/min), and 71% in severe (CLCr = < 30 mL/min) renal impairment. The estimate of the slope in the adult model was 0.0512. Assuming a CLCr of 120 mL/min as the reference, the model predicted decrease in CL/F was approximately 20%, 30% and 40% for adults. For the combined adult and adolescent data the slope was 0.0240, predicting an even lower decrease in CL/F due to renal impairment. Furthermore, the model did not account for the effect of body weight on volume of distribution. From the CHMP viewpoint, the initial model was not sufficiently qualified for purpose of simulation unless it could give a correct description of the pharmacokinetic properties of paliperidone. To address this concern, the MAH provided a revised model using only the data in adolescents ie excluding the adult data and the data in renal impaired subjects (Studies PSZ-1001, PSZ-3001 and PSZ-3003). To this extent, an adapted covariate model was developed and resulted in a final covariate model that remained the same as presented in the original submission (see Tables 7-8, Figure 9). As more than 60% of paliperidone is eliminated unchanged through the kidney, CrCL was included as a prior covariate on CL/F, and BW and age in addition to CrCL were tested. However, the CHMP remained concerned that the proposed model including CrCL on CL/F was misleading because the relation between Cl/F and renal elimination capacity (expressed as creatinine clearance) that had been established in adults could not be confirmed in adolescents due to lack of data. The CHMP therefore concluded that the presented model could be used for simulations of exposure in adolescents with normal renal function only. In this model, it was sufficiently well demonstrated that the clearance of paliperidone is related to body size (weight). The exponent describing relation between body weight and CL/F is 0.68, a value close to the theoretical allometric relation (0.75). However, due to the substantial inter-individual variability in CL/F (CV% 57.4), the explanatory value of weight on CL/F was reduced although it was still a valid factor on the population level. The MAH illustrated the variability with simulations showing that there was a large overlap in exposure comparing adolescents to adults as well as when comparing adolescents <51 kg to adolescents ≥51 kg. Thus, individual dose titration was considered by the CHMP sufficiently motivated from a pharmacokinetic viewpoint.

When investigating independently the effect of age and body weight on the clearance of paliperidone to accurately characterise the dose-response, body weight, and not age, was a significant predictor of clearance. In the study samples there was evidence that age and body weight was not as correlated as might be expected from the healthy population. There were no signs that patients below 14 years of age deviate from the relation between CL/F and body weight. Therefore, the PK of paliperidone could be considered to have been sufficiently characterized in patients down to 12 years of age.

Following the restriction of the proposed indication to the paediatric age range of 15 years and older (see 2.4.6), the MAH proposed that same dosing adjustments in case of renal impairment should be recommended for adolescent and adults patients, because the maturation of the renal function is

considered completed by early childhood and the pharmacokinetic and plasma protein binding of paliperidone were found similar in these populations. This proposal was accepted by the CHMP.

In addition, the time course of PANSS score and the influence of exposure to paliperidone and other covariates had not been evaluated by modelling as compared to the presented popPK analysis. This made it difficult to draw any conclusion about the relation between paliperidone exposure and clinical effect. In adults, a continuous relation between plasma exposure to paliperidone and the risk of developing EPS has been previously established. For adolescents, a similar pattern was seen but with the risk of EPS sharply increasing at exposure levels > 20 ng/mL. In addition, there was a slight trend towards adolescents having a higher risk of EPS compared to adults at exposure levels > 20 ng/mL. A higher frequency of EPS was reported more often in adolescents than in adults based on a pooled safety analysis. This is further discussed in 2.5.7.

2.3.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of Invega has been adequately documented and meet the requirements to support this application.

2.4. Clinical efficacy

The development program completed to support the proposed extension of indication consisted of:

- a Phase I, multicenter and open-label study (**PALIOROS-PSZ-1001**) to investigate the pharmacokinetic profile, safety and tolerability of paliperidone ER in children and adolescent patients (10-17 years) with schizophrenia, schizoaffective disorder, or schizophreniform disorder.
- a phase III, multicenter, randomised, double-blind, placebo-controlled, 6 week study (**R076477-PSZ3001**) evaluating 3 fixed oral doses of paliperidone ER (low: 1.5 mg; medium: 3 mg or 6 mg; high: 6 mg or 12 mg) in the treatment of children and adolescent patients, aged 12-17 years, with schizophrenia;
- a phase III, multicenter, randomised, double-blind, active-controlled, 26 week study (**R076477-PSZ3003**) evaluating flexible oral doses of paliperidone ER (3-9mg) versus aripiprazole (5-15mg) in the treatment of children and adolescent patients, aged 12-17 yearswith schizophrenia
- a phase III, multicenter, open-label, 2 year study (**R076477-PSZ-3002)**, designed to provide additional long term safety data of paliperidone ER in the paediatric population. Patients who had completed study **R076477-PSZ3001** were offered to continue in this study.

2.4.1. Dose response study

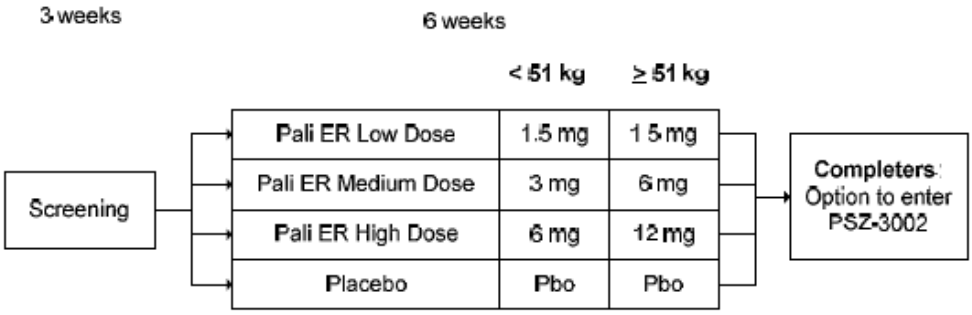
No specific dose response study was performed in the intended paediatric population. Dosing recommendation is derived from the combined clinical data (PSZ-3001, PSZ-3003 and PSZ-3002) and the population PK simulations previously presented (see 2.3.2). This approach was considered in principle acceptable by the CHMP, provided the presented data adequately support the proposed dosing recommendation in the intended paediatric population. This is further discussed in 2.4.6.

2.4.2. Main studies

STUDY PSZ3001

The study design is presented in Figure 10.

Figure 10



This study was conducted at 12 study sites in Russia, 9 sites in the United States, 7 sites in India, 6 sites in the Ukraine, and 1 site in Romania.

2.4.2.1. Methods

Study participants

Subjects were to be male or female aged 12-17 years inclusive with a diagnosis of schizophrenia according to DSM-IV at least one year prior to screening. Diagnosis had to be established using the semi structured K-SADS-PL questionnaire and the subject should have had at least one adequate treatment course with antipsychotic drug prior to enrolment. There should be an acute exacerbation of schizophrenia with PANSS score total between 60-120 inclusive at the time of enrolment (screening) and at the time of randomisation (baseline).

Treatments

The subjects were randomised to receive paliperidone ER 1.5 mg, 3 mg, 6 mg or 12 mg as tablets or placebo. During screening and washout the subjects were outpatients or hospitalized if judged necessary by the investigator. The study consisted of three phases; a screening phase of up to 3 weeks to assess eligibility criteria, a six week double blind treatment phase with an end of study or early withdrawal visit and finally a 1 week follow up visit for subjects who did not enter the open label safety study PSZ -3002. Subjects were able to enrol into the long term study PSZ-3002 after completing at least 21 days of treatment in study PSZ-3001.

No dosage adjustment was permitted during the study. The study allowed early rescue. Subjects who did not have any response to treatment or whose symptoms worsened could drop out after at least 21 days of the double-blind phase and were eligible to participate in open-label safety study PSZ-3002. Subjects who did not respond to treatment or whose symptoms worsened before 21 days of the double-blind phase discontinued the study at any time and were treated by their physicians as clinically appropriate. In addition, the protocol allowed the use of rescue medications including benzodiazepines for insomnia and anticholinergic medications for EPS.

Objectives

The primary objective was to assess the efficacy, safety and tolerability of 3 weight based fixed –dose groups of paliperidone ER (to fully explore tolerability); 1.5mg, 3mg, 6mg and 12 mg compared to placebo in adolescents 12-17 years with DSM-IV based diagnosis of schizophrenia who were currently experiencing an acute exacerbation.

Outcomes/endpoints

These are presented in Table 9.

Table 9:

Variable	Description	Endpoint
PANSS	• **Change from baseline in total score at endpoint (LOCF)**	**Primary**
	• Change from baseline in total score at each post-baseline visit (LOCF and observed case)	Other
	• Change from baseline in subscales and Marder factor scores at endpoint and at each post-baseline visit (LOCF and observed case)	Other
	• Number and percentage of subjects with ≥20% or ≥30% reduction from baseline in PANSS total score at endpoint (LOCF)	Other
	• Onset of therapeutic effect (LOCF)	Other
CGI-S	• **Change from baseline in overall score at endpoint and each postbaseline visit (LOCF)**	**Secondary**
	• Change from baseline in overall score at each post-baseline study visit (LOCF and observed case)	Other
	• Frequency distribution of overall score at endpoint and at each post-baseline visit (LOCF and observed case)	Other
CGAS	• **Change from baseline in overall score at endpoint and each post-baseline visit (LOCF)**	**Secondary**
	• Change from baseline in overall score at each post-baseline visit (observed case)	Other
	• Change from baseline in 10-point categories at endpoint and at each post-baseline visit (LOCF)	Other
	• Frequency distribution of overall scores (≥70 or <70) at endpoint and at each post-baseline visit (LOCF and observed case)	Other
	• Frequency distribution of	Other

	overall scores by 10-point categories at endpoint and at each post-baseline visit (LOCF and observed case)	
VAS	• **Change from baseline in Quality of Sleep and Daytime Drowsiness total scores at endpoint (LOCF)** • Change from baseline in Quality of Sleep and Daytime Drowsiness total scores at each post-baseline visit (LOCF and observed case)	**Secondary** Other

Sample size

The estimated sample size of 200 subjects (approximately 50 in each blinded group) assumed that the standard deviation (SD) of the change from baseline to endpoint in PANSS total score would be 20 points. If there were approximately 49 subjects per treatment group who had Week 6 (LOCF or endpoint) PANSS total measurements, the study was expected to have approximately 80% power to detect a clinically relevant difference of 13.2 points between any paliperidone ER group compared with placebo in the change from baseline in PANSS total score, applying Dunnett's adjustment for multiplicity (2-sided family wise α level of 0.05).

Randomisation

The randomisation was centralised, balanced by using permuted blocks of treatment and was stratified by study centre.

Blinding (masking)

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). Tablets containing different dose strengths of paliperidone ER and tablets containing placebo were identical in appearance.

Statistical methods

Efficacy and safety analyses were performed using the randomly assigned, weight-based, fixed-dose treatment groups. Additional analyses were performed using the actual paliperidone ER dose received.

The ITT analysis set was the analysis set for the efficacy analyses. This analysis set included all randomized subjects who received at least one dose of double-blind study drug and had both a baseline and at least one post-baseline assessment in the double-blind phase on any of the following scales: PANSS, CGAS, CGI-S or sleep VAS.

Efficacy analysis involving changes from baseline to the final double-blind phase visit (Day 43) used the last observation carried forward (LOCF) approach.

The primary variable was the change in PANSS total score from baseline to the end of the double-blind phase (Day 43 or the last post-baseline assessment). Treatment effects were estimated based on least-squares (LS) means using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline PANSS total score as a covariate. A closed testing procedure using Dunnett's

test was used to adjust for multiple comparisons in testing the 3 paliperidone ER treatment groups against placebo for the primary efficacy variable.

Responders are defined as those who achieved a 20% or higher reduction from baseline in the PANSS total score at the last post-baseline assessment in the double-blind phase. The percent change of PANSS was defined as [100*CHANGE / (BASELINE-30)], as 30 is the lowest possible value for PANSS.Differences at endpoint in percentage of responders between each active treatment group and placebo were evaluated using a Cochran-Mantel-Haenszel test controlling for country.

A worst-rank analysis was also performed where subjects who discontinued due to lack of efficacy were assigned a rank that represented a “worst-rank score” relative to those actually observed. These ranks reflected the relative inverse ordering of the actual times to discontinuation, so that the earlier times of withdrawal were assigned a worse ranking than the later points in time. In addition, a Kaplan-Meier plot of the time to discontinuation for those who discontinued due to lack of efficacy was generated by treatment group.

To assess the sensitivity of the results, a repeated measures mixed effects model was carried out on the observed data. Changes from baseline over time (observed case) were modelled using a mixed effects model with time, country, and treatment as factors and baseline PANSS total score as a covariate. In addition, a treatment-by-time interaction term was added to evaluate the changes in treatment effect over time. An unstructured variance-covariance matrix was employed.

2.4.2.2. Results

Participant flow

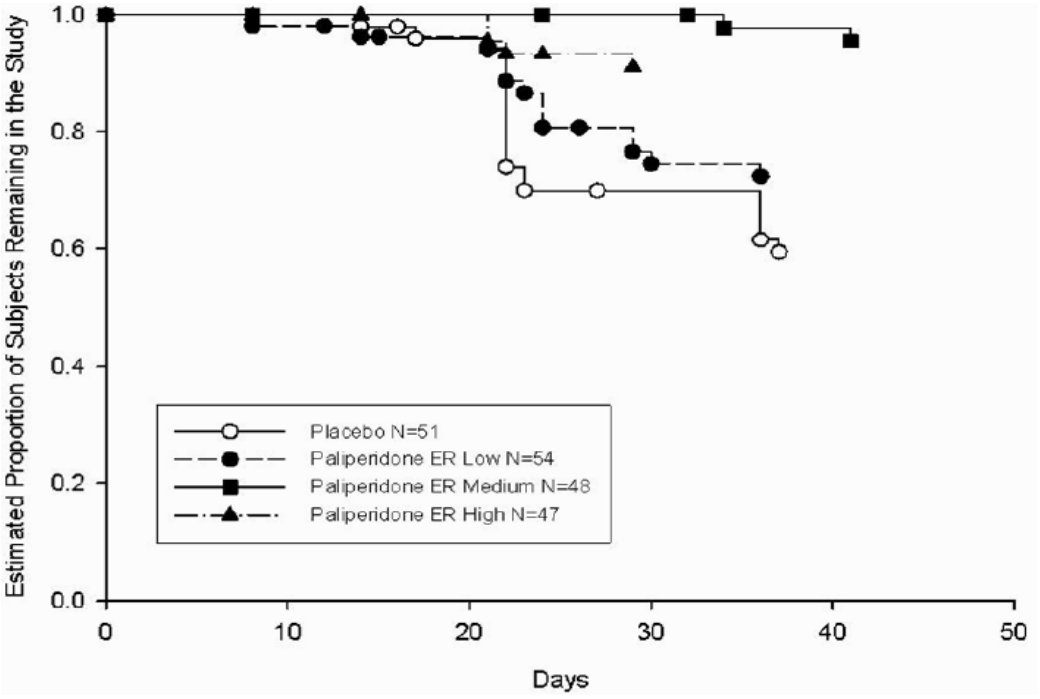
A total of 201 subjects met the eligibility criteria and were enrolled and randomly assigned to double blind treatment with placebo or paliperidone ER. A total of 200 subjects were randomised into the study. All but one subject (from the paliperidone ER high group) received at least one dose of study medication, provided both baseline and at least one post-baseline efficacy assessments and were included in the ITT analysis set.

Information on number of subjects who completed or withdrew the study and reasons for withdrawal is provided in Table 10. Time to withdrawal is presented in Figure 11.

Table 10: Study completion / withdrawal information for PSZ-3001 (All randomised subjects analysis set)

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

Figure 11: Time to withdrawal in study PSZ-3001



Recruitment

The study was conducted between 8 August 2007 and 30 March 2009.

Conduct of the study

There was one major protocol amendment prior study enrolment. This was related to the study design with the objective of testing the entire range of effective doses of paliperidone ER in adults (3-12mg) as well as a lower dose (1.5mg) to determine the least effective dose. Weight based doses were chosen to minimize the risk of exposing lower weight adolescents (≥ 29 kg and < 51 kg) to high doses of paliperidone ER and higher weight adolescents (≥ 51 kg) to too low of a dose, considering that lower-weight subjects could have nearly double the drug exposure of higher-weight subjects on the basis of available PK data from PSZ-1001.

Baseline data

These are presented in Tables 11 and 12.

Table 11: Baseline characteristics

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)	Total (N=200)
Age (years)					
Category, n (%)					
12-14	9 (18)	16 (30)	15 (31)	13 (28)	53 (27)
15-17	42 (82)	38 (70)	33 (69)	34 (72)	147 (74)
Mean (SD)	15.7 (1.40)	15.1 (1.50)	15.3 (1.60)	15.5 (1.60)	15.4 (1.53)
Median	16.0	16.0	16.0	16.0	16.0
Range	(12;17)	(12;17)	(12;17)	(12;17)	(12;17)
Sex, n (%)					
Male	23 (45)	30 (56)	31 (65)	33 (70)	117 (59)
Female	28 (55)	24 (44)	17 (35)	14 (30)	83 (42)
Country, n (%)					
India	11 (22)	13 (24)	11 (23)	10 (21)	45 (23)
Romania	2 (4)	2 (4)	3 (6)	3 (6)	10 (5)
Russia	21 (41)	22 (41)	20 (42)	19 (40)	82 (41)
Ukraine	8 (16)	9 (17)	8 (17)	9 (19)	34 (17)
United States	9 (18)	8 (15)	6 (13)	6 (13)	29 (15)
Race, n (%)					
White	35 (69)	35 (65)	34 (71)	32 (68)	136 (68)
Black	4 (8)	5 (9)	3 (6)	5 (11)	17 (9)
Asian [a]	12 (24)	14 (26)	11 (23)	10 (21)	47 (24)
Baseline body weight category, n (%)					
<51 kg	14 (27)	19 (35)	16 (33)	13 (28)	62 (31)
≥51 kg	37 (73)	35 (65)	32 (67)	34 (72)	138 (69)
Baseline body mass index (kg/m^2)					
Category, n (%)					
Normal <25	45 (88)	43 (80)	39 (81)	38 (81)	165 (83)
Overweight 25-<30	4 (8)	8 (15)	8 (17)	5 (11)	25 (13)
Obese ≥30	2 (4)	3 (6)	1 (2)	4 (9)	10 (5)
Mean (SD)	21.85 (5.578)	22.19 (4.861)	21.36 (3.964)	21.91 (4.315)	21.84 (4.714)
Median	21.10	20.80	20.90	20.90	20.95
Range	(14.0;53.4)	(13.9;39.6)	(15.2;34.9)	(14.4;34.6)	(13.9;53.4)
Schizophrenia type, n (%)					
Paranoid (295.30)	37 (73)	39 (72)	35 (73)	31 (66)	142 (71)
Disorganized (295.10)	3 (6)	3 (6)	6 (13)	7 (15)	19 (10)
Catatonic (295.20)	2 (4)	1 (2)	1 (2)	1 (2)	5 (3)
Undifferentiated (295.90)	9 (18)	9 (17)	5 (10)	8 (17)	31 (16)
Residual (295.60)	0	2 (4)	1 (2)	0	3 (2)
Age at diagnosis of schizophrenia (yr)					
Mean (SD)	13.4 (2.44)	12.5 (2.85)	13.0 (1.87)	12.8 (3.19)	12.9 (2.64)
Median	14.0	13.0	13.0	14.0	13.0
Range	(5;16)	(5;16)	(8;16)	(3;16)	(3;16)

[a] Asian Indian and Asian Other (Taiwanese, Vietnamese and Chinese-Vietnamese) categories grouped as Asian.

Table 12: Baseline disease severity in the different treatment groups

	Placebo (N=51)	Paliperidone ER Low (N=54)	Paliperidone ER Medium (N=48)	Paliperidone ER High (N=47)	Total (N=200)
Baseline PANSS total score					
Mean (SD)	90.6 (12.13)	91.6 (12.54)	90.6 (14.01)	91.5 (13.86)	91.1 (13.03)
Median	88.0	89.5	88.0	90.0	89.0
Range	(65;118)	(70;118)	(69;119)	(63;119)	(63;119)
Baseline CGI-S, n (%)					
Very mild	0	1 (2)	0	0	1 (1)
Mild	3 (6)	3 (6)	3 (6)	2 (4)	11 (6)
Moderate	27 (53)	28 (52)	19 (40)	26 (55)	100 (50)
Marked	19 (37)	19 (35)	21 (44)	14 (30)	73 (37)
Severe	2 (4)	3 (6)	5 (10)	5 (11)	15 (8)

Cross-reference: Mod5.3.5.1\PSZ-3001\Tabs10 and 11

Outcomes and estimation

PANSS Total Score related endpoints

Results on the primary endpoint are presented in Table 13.

Table 13: PANSS Total score –change from baseline to End Point (LOCF) used closed testing procedure with Dunnett´s test (study PSZ-3001 ITT analysis set)

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

[a] Based on ANCOVA model with treatment (Placebo, Paliperidone ER Low, Paliperidone ER Medium, Paliperidone ER High) and country as factors, and baseline value as a covariate. P values associated with closed testing procedure using Dunnett's test.
[b] The 95% confidence intervals are unadjusted for multiplicity.
Note: Negative change in score indicates improvement.

Source: CSr psz-3001

Table 14 presents data for the primary endpoint by actual dose group.

Table 14: PANSS Total Score- Change from baseline to endpoint (LOCF) by actual dosing, ANCOVA model (ITT)

	Placebo (N=51)	Paliperidone ER 1.5 mg (N=54)	Paliperidone ER 3 mg (N=16)	Paliperidone ER 6 mg (N=45)	Paliperidone ER 12 mg (N=34)
Baseline					
N	51	54	16	45	34
Mean (SD)	90.6 (12.13)	91.6 (12.54)	92.1 (16.88)	90.8 (13.66)	91.0 (13.00)
Median (Range)	88.0 (65;118)	89.5 (70;118)	91.0 (70;119)	90.0 (63;118)	89.0 (70;119)
End Point					
N	51	54	16	45	34
Mean (SD)	82.7 (21.45)	81.9 (19.54)	73.1 (26.55)	77.0 (20.59)	74.7 (16.57)
Median (Range)	81.0 (36;129)	80.0 (45;121)	70.0 (33;115)	75.0 (42;135)	73.0 (49;115)
Change From Baseline					
N	51	54	16	45	34
Mean (SD)	-7.9 (20.15)	-9.8 (16.31)	-19.0 (15.45)	-13.8 (14.75)	-16.3 (15.41)
Median (Range)	-5.0 (-59;28)	-5.5 (-52;23)	-19.0 (-53;3)	-12.0 (-51;30)	-15.0 (-62;18)
p value (minus Placebo)[a]		0.507	0.016	0.044	0.014
Diff. of LS Means (SE)		-2.1 (3.18)	-11.5 (4.75)	-6.8 (3.34)	-9.0 (3.64)
95% CI[b]		(-8.39;4.16)	(-20.85;-2.13)	(-13.35;-0.19)	(-16.23;-1.86)

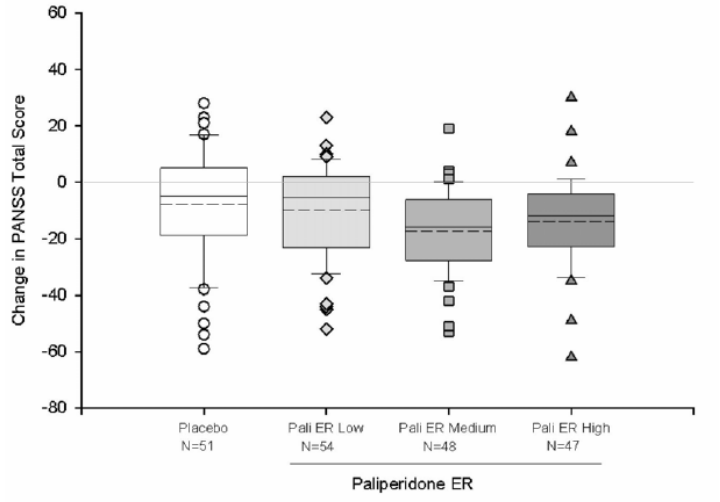
[a] Test for no difference between treatments (Placebo, Paliperidone ER 1.5 mg, Paliperidone ER 3 mg, Paliperidone ER 6 mg, Paliperidone ER 12 mg) from ANCOVA model with factors for treatment and country, and with baseline value as a covariate.

[b] Comparison with placebo without multiplicity adjustment.

Note: Negative change in score indicates improvement

Figure 12 shows the estimated LS mean changes (LOCF) from baseline in PANSS total scores over time by actual dose.

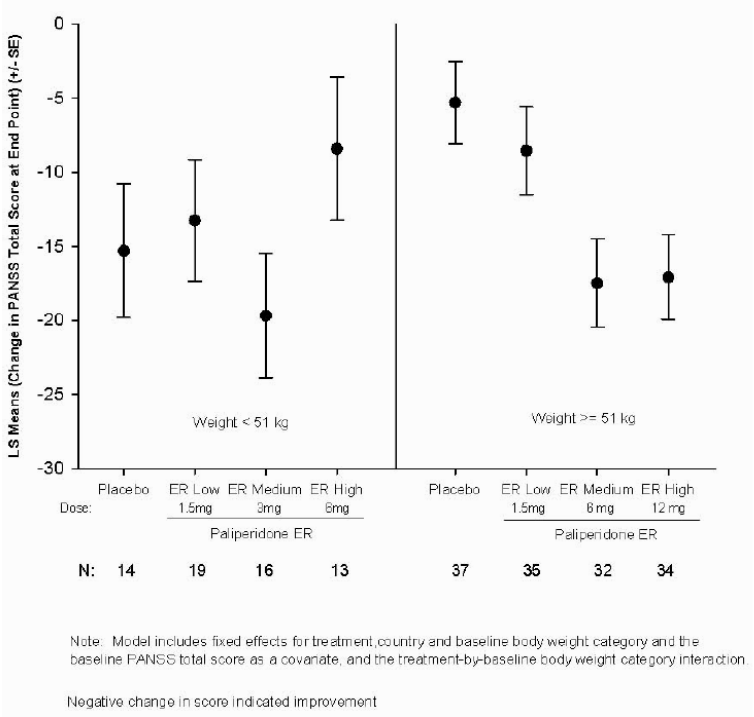
Figure 12: Estimated LS mean changes (LOCF) from baseline in PANSS total scores



NOTE: The lower boundary of the box is the 25th percentile and the higher boundary is the 75th percentile. Whiskers above and below the box indicate the 90th and 10th percentiles. The solid line within the box marks the median and the dash line marks the mean value. Outlying data points are extreme values.

Figure 13 shows the estimated LS means changes from baseline in PANSS total scores by baseline body weight.

Figure 13: Least square means changes in PANSS total score at endpoint by baseline body weight (ITT analysis)



Regarding the onset of therapeutic effect, a statistically significant improvement ($p<0.05$, LOCF) over placebo was first noted on Day 22 for the paliperidone ER Medium group and at the first assessment time point (Day 8) for the paliperidone ER High group. The statistically significant between-group differences were maintained from Day 22 to the Day 43 endpoint for the paliperidone ER Medium group but were not maintained from Day 8 for the paliperidone ER High group ($p=0.079$ on Day 22 and $p=0.075$ on Day 29, LOCF).

Regarding the responder rate, 64.4% of subjects in the paliperidone ER Medium group and 51.1% of those in the paliperidone ER High group had achieved a treatment response. This compared with 38.9% of subjects in the paliperidone ER Low group and and 33.3% of the placebo subjects.

Other endpoints

Results are presented in Table 15.

Table 15: Overview of key secondary and other efficacy results for study R076477-PSZ-3001 (ITT Analysis Set)

		Paliperidone ER			
	Placebo (N=51)	Low (N=54)	Medium (N=48)	High (N=47)	3-12 mg[a] (N=95)
Secondary Efficacy Variables					
CGI-S Score, n	51	54	48	47	95
Median (range) baseline	4.0 (3;6)	4.0 (2;6)	5.0 (3;6)	4.0 (3;6)	4.0 (3;6)
Median (range) change at End Point (LOCF)[b]	0.0 (-3;1)	0.0 (-3;1)	-1.0 (-3;0)	-1.0 (-3;1)	-1.0 (-3;1)
p value (vs placebo)[c]		0.968	< 0.001	0.021	<0.001
CGAS Score	51	54	48	47	95
Mean (SD) baseline	48.8 (11.23)	48.4 (11.82)	47.2 (11.36)	46.5 (11.96)	46.8 (11.60)
Mean (SD) change at End Point (LOCF)[d]	5.0 (13.82)	4.4 (10.72)	13.1 (12.07)	8.6 (11.18)	10.9 (11.79)
p value (vs placebo)[e]		0.846	< 0.001	0.067	<0.001
Sleep VAS Score					
Quality of Sleep, n	50	54	48	47	95
Mean (SD) baseline	64.9 (27.30)	66.8 (25.07)	65.5 (25.55)	63.3 (26.69)	64.4 (26.01)
Mean (SD) change at End Point (LOCF)[d]	-0.3 (34.21)	6.6 (24.57)	16.0 (27.06)	14.4 (22.72)	15.2 (24.89)
p value (vs placebo)[e]		0.058	< 0.001	0.003	<0.001
Daytime Drowsiness, n	50	54	48	47	95
Mean (SD) baseline	29.7 (25.84)	27.6 (26.10)	26.1 (22.92)	21.1 (21.21)	23.6 (22.12)
Mean (SD) change at End Point (LOCF)[b]	-2.8 (30.27)	-6.2 (24.69)	-7.2 (25.22)	1.0 (29.55)	-3.1 (27.61)
p value (vs placebo)[e]		0.237	0.119	0.574	0.214
Other Efficacy Variables					
Responder Rate[f]					
n (%)	17 (33.3%)	21 (38.9%)	31 (64.6%)	24 (51.1%)	55 (57.9%)
p value (vs placebo)[g]		0.479	0.001	0.043	0.003
PANSS Factor – Positive symptoms					
Mean (SD) baseline	25.4 (4.89)	25.0 (4.86)	24.6 (4.50)	24.5 (4.33)	24.6 (4.39)
Mean (SD) change at End Point (LOCF)[b]	-3.3 (7.00)	-3.1 (6.53)	-6.0 (5.39)	-5.0 (5.30)	-5.5 (5.34)
p value (minus Placebo)[e]		0.960	0.003	0.033	0.003
PANSS Factor – Negative symptoms					
Mean (SD) baseline	22.8 (5.16)	22.9 (5.32)	23.9 (5.26)	24.0 (5.10)	23.9 (5.15)
Mean (SD) change at End Point (LOCF)[b]	-1.8 (5.30)	-2.4 (4.31)	-3.7 (3.85)	-2.4 (5.56)	-3.1 (4.79)
p value (minus Placebo)[e]		0.430	0.048	0.586	0.142
PANSS Factor – Hostility/excitement					
Mean (SD) baseline	11.8 (3.45)	12.0 (3.81)	10.9 (2.69)	11.4 (3.72)	11.1 (3.23)
Mean (SD) change at End Point (LOCF)[b]	-0.6 (4.49)	-1.0 (3.44)	-2.2 (2.63)	-2.0 (3.76)	-2.1 (3.22)
p value (minus Placebo)[e]		0.595	0.004	0.017	0.002
PANSS Factor – Anxiety/depression					
Mean (SD) baseline	9.7 (3.32)	9.5 (2.41)	9.7 (2.98)	9.8 (3.38)	9.8 (3.17)
Mean (SD) change at End Point (LOCF)[b]	-1.1 (2.69)	-1.4 (2.22)	-1.9 (3.25)	-1.8 (3.19)	-1.9 (3.20)
p value (minus Placebo)[e]		0.348	0.074	0.134	0.056
PANSS Factor – Disorganized thoughts					
Mean (SD) baseline	20.9 (4.23)	22.3 (4.64)	21.6 (5.23)	21.8 (5.68)	21.7 (5.43)
Mean (SD) change at End Point (LOCF)[b]	-1.1 (4.65)	-1.8 (3.58)	-3.5 (3.26)	-2.6 (3.73)	-3.0 (3.51)
p value (minus Placebo)[e]		0.510	0.002	0.060	0.004

[a] Paliperidone ER Medium and High groups combined.
[b] Negative change in score indicates improvement.
[c] p values for between-treatment group comparisons are from an ANCOVA model on ranks with treatment and country as factors, and baseline value as a covariate; no adjustment for multiplicity.
[d] Positive change in score indicates improvement.
[e] p values for between-treatment group comparisons are from an ANCOVA model with fixed effects for treatment and country, and baseline value as a covariate; no adjustment for multiplicity.
[f] Responder defined as those who achieved a 20% or higher reduction from baseline in the PANSS total score at end point.
[g] p values for pairwise comparisons with placebo using a generalized CMH test for row mean score differences controlling for country.

Ancillary analyses

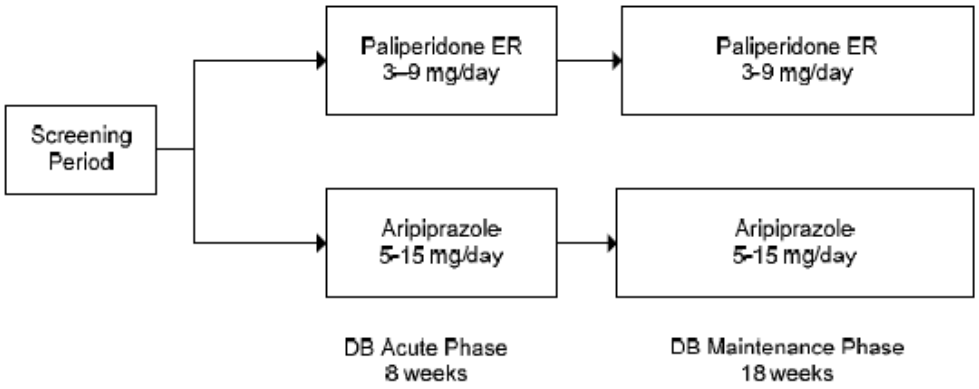
Worst rank analysis showed that the paliperidone ER Medium and High treatment groups were statistically significantly different from the placebo group. The magnitude of the median change was larger in both the paliperidone ER Medium and High treatment groups than the placebo group, and the difference from placebo was statistically significant for each group. The largest mean change occurred in the paliperidone ER Medium treatment group (-16 on PANSS).

Results from the longitudinal linear models (MMRM) corroborated the findings from the LOCF analysis of the primary efficacy endpoint (paliperidone ER Low, p=0.4039; paliperidone ER Medium, p=0.0034; paliperidone ER High, p=0.065).

STUDY PSZ3003

The study design is presented in Figure 14.

Figure 14:



A total of 41 sites in 7 countries participated in the study including 6 sites in India, 1 site in Romania, 16 sites in Russian Federation, 1 site in Slovakia, 3 sites in Spain, 8 sites in Ukraine, and 6 sites in the United States.

2.4.2.3. Methods

Study participants

Subjects were to be male or female aged 12-17 years inclusive with a diagnosis of schizophrenia according to DSM-IV at least one year prior to screening. Diagnosis had to be established using the semi structured K-SADS-PL questionnaire and the subject should have had at least one adequate treatment course with antipsychotic drug prior to enrolment. There should be an acute exacerbation of schizophrenia with PANSS score total between 60-120 inclusive at the time of enrolment (screening).

Treatments

The study design consisted of 3 phases: a screening phase up to 3 weeks (with a possible overlapping washout period), a double-blind acute phase of 8 weeks, and a double-blind maintenance phase of 18 weeks. The total duration of the study was approximately 29 weeks. The subjects in the paliperidone ER treatment group received 6 mg/day on Days 1 through 7 (Week 1), and subjects in the aripiprazole treatment group received 2 mg/day on Days 1 and 2, 5 mg/day on Days 3 and 4, and 10 mg/day on Days 5, 6, and 7.

Beginning at Week 2 and throughout the treatment period, paliperidone ER could be given at doses of 3, 6, or 9 mg/day, and aripiprazole may be given at doses of 5, 10, or 15 mg/day.

Objectives

The primary objective was to assess the efficacy of paliperidone ER relative to aripiprazole in the treatment of symptoms of schizophrenia in adolescent subjects (from 12 to 17 years of age, inclusive, ie, from 12 to less than 18 years of age) at the Week 8 (Day 56) endpoint as measured by the change from baseline in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score.

Outcomes/endpoints

These are presented in Table 16.

Table 16: Overview Efficacy Variables in PSZ-3003

Variable	Description	End Point
PANSS	• **Change from baseline in total score at endpoint acute (Day 56)** • **Change from baseline in total score at endpoint (Day 182)** • Change from baseline in total score at all other time points • Responders (reduction from baseline in total score ≥20% and ≥30%) • Change from baseline in Marder factor negative symptoms score at endpoint acute (Day 56) and endpoint (Day 182) • Change from baseline in other Marder factor scores (positive symptoms, disorganised thought, uncontrolled hostility/excitement, anxiety/depression) • Change from baseline in positive negative and psychopathology subscale scores	**Primary** **Secondary**
Clinical Stability	• **PANSS 20% responder and CGI-S ≤4 at Days 56 and 182, with no psychiatric hospitalization or clinically significant suicidal/homicidal ideation during the maintenance period**	**Secondary**
CGI-S	• **Change from baseline in overall score at endpoint acute (Day 56) and**	**Secondary**

	endpoint (Day 182) • Change from baseline at all other time points • Frequency distribution of overall score at endpoint and at each postbaseline visit (LOCF and observed case)	
PSP	• **Change from baseline in overall score at endpoint acute (Day 56) and endpoint (Day 182)** • Change from baseline in score at all other time points • Responders (PSP score≥71) • Change from baseline in 10 point categories	**Secondary**

Sample size

The estimated sample size of 228 subjects (114 subjects in each of 2 blinded groups) assumed that the standard deviation (SD) of the change from baseline to endpoint acute (Day 56) LOCF in the PANSS total score would be 20 points. With approximately 100 subjects per treatment group who had an endpoint acute (Day 56) PANSS total score, the study was expected to have at least 80% power to detect a clinically relevant difference of 8 points between paliperidone ER and aripiprazole in the change from baseline in PANSS total score, with a 2-sided α-level of 0.05.

With an estimate of approximately 12% of randomized subjects who could discontinue before providing post-baseline PANSS total score measurements, the number of randomly assigned subjects was adjusted from 100 to 114 in each treatment group.

Randomisation

The randomisation was centralised, balanced by using permuted blocks of treatment and was stratified by study centre.

Blinding (masking)

Double blinding was used during the 26-week treatment period (i.e., subjects, parents, legal guardians, investigators, and the sponsor remained blinded to the study drug). Study medication was packaged in blister cards containing over-encapsulated tablets.

Statistical methods

The primary and secondary efficacy analyses were performed based on the ITT analysis set, including all randomized subjects who received at least one dose of double-blind study drug and had both a baseline and at least one post-baseline assessment in the double-blind phase on any of the following scales: PANSS, CGI-S, or PSP. Endpoint (Day 182) was defined as the last post-baseline observation during the double-blind treatment phase. Endpoint acute (Day 56) was defined as the last post-baseline assessment in the acute double-blind phase, ie, up to the Day 56 Visit.

The primary efficacy endpoint was the change in the PANSS total score from baseline to the Week 8 (Day 56) endpoint. The changes from baseline in PANSS total score at both endpoint acute (Day 56) and endpoint (Day 182) were analysed using an ANCOVA model with treatment group and country as fixed factors and baseline PANSS total score as a covariate. Treatment effect was estimated based on the difference between LS means with the 95% confidence interval.

To assess the sensitivity of the results, a repeated measures mixed effects model was carried out using the observed data collected through the Day 56 visit. Changes from baseline over time (observed case) were modelled using a mixed effects model with time, country, and treatment as factors and baseline PANSS total score as a covariate. In addition, a treatment-by-time interaction term was included to evaluate the changes in treatment effect over time. An unstructured variance-covariance matrix was employed.

A worst-rank analysis was also performed, where subjects who discontinued due to lack of efficacy prior to the Day 56 visit were assigned a rank that represented a "worst-rank score" relative to those actually observed. These ranks reflected the relative inverse ordering of the actual times to discontinuation, so that the earlier times of withdrawal were assigned a worse ranking than the later points in time.

The proportion of subjects maintaining clinical stability at Week 26 (as measured from Week 8) as well as the proportion of symptom responders (defined as subjects with ≥20% (or ≥30%) reduction from baseline in PANSS total score at Week 8 and Week 26) was analysed using the Cochran-Mantel-Haenszel test, controlling for country.

2.4.2.4. Results

Participant flow

A total of 228 subjects were included in the all randomised analysis set; 113 subjects in the paliperidone ER group and 115 subjects in the aripiprazole group. Of the subjects recruited 9 were from Romania, 5 from Spain and 1 Slovakia. See table 17.

Table 17: Country of origin and percentage of participants in each dose group

Country	PaliER(N=113)	Ari (N=115)	TOTAL (N=228)
India	20 (18%)	19(17%)	39 (17%)
Spain	3(3%)	2 (2%)	5(2%)
Russia	56(50%)	58(50%)	114 (50%)
Ukraine	17(15%)	20 (17%)	37(16%)
US	12 (11%)	11(10%)	23 (10%)
Slovakia	1(1%)	0	1(<1%)
Romania	4(4%)	5(4%)	9(4%)

Information on number of subjects who completed or withdrew the study and reasons for withdrawal is provided in Table 18.

Table 18: Study completion / withdrawal information for PSZ-3003

(Study R076477-PSZ-3003: All Randomized Subjects)

Subject Completed Trial Reason For Withdrawal/Termination	Paliperidone ER (N=113) n (%)	Aripiprazole (N=115) n (%)	Total (N=228) n (%)
Completed	85 (75)	89 (77)	174 (76)
Withdrawn	28 (25)	26 (23)	54 (24)
Adverse event	5 (4)	0	5 (2)
Lack of efficacy	4 (4)	11 (10)	15 (7)
Lost to follow-up	0	2 (2)	2 (1)
Withdrawal of consent	16 (14)	11 (10)	27 (12)
Other	3 (3)	2 (2)	5 (2)

In the paliperidone ER group, a higher proportion of subjects (47%) receiving the 3 mg mode dose withdrew from the study compared with those receiving the mode dose of 6 mg (21%) or 9 mg (20%). In the aripiprazole group, approximately 25% of subjects withdrew from the study at the mode dose of 10 mg or 15 mg, whereas no subject withdrew at the 5 mg mode dose. The proportion of subjects withdrew from the study due to lack of efficacy was slightly higher at the paliperidone ER mode dose of 3 mg (7%) compared to those at the mode dose of 6 mg (2%) or 9 mg (4%). In contrast, a higher withdrawal rate was observed for subjects receiving the aripiprazole mode dose of 10 mg (12%) or 15 mg (10%) compared to those receiving the 5 mg mode dose (0%).

Recruitment

The study was conducted between 19 November 2009 and 11 June 2012.

Conduct of the study

Baseline data

These are presented in Tables 19 and 20.

Table 19: Baseline characteristics

	Paliperidone ER (N=112)	Aripiprazole (N=114)	Total (N=226)
Age			
Category, n (%)			
12-14	33 (29)	30 (26)	63 (28)
15-17	79 (71)	84 (74)	163 (72)
Mean (SD)	15.3 (1.46)	15.4 (1.45)	15.3 (1.46)
Median	16.0	16.0	16.0
Range	(12; 17)	(12; 17)	(12; 17)
Sex, n (%)			
Male	73 (65)	76 (67)	149 (66)
Female	39 (35)	38 (33)	77 (34)
Race, n (%)			
White	84 (75)	88 (77)	172 (76)
Black or African American	6 (5)	7 (6)	13 (6)
Asian	20 (18)	19 (17)	39 (17)
Other	1 (1)	0	1 (<1)
Multiple	1 (1)	0	1 (<1)
Ethnicity, n (%)			
Hispanic or Latino	4 (4)	3 (3)	7 (3)
Not Hispanic or Latino	108 (96)	111 (97)	219 (97)
Country, n (%)			
India	20 (18)	19 (17)	39 (17)
Romania	4 (4)	5 (4)	9 (4)
Russian Federation	56 (50)	58 (51)	114 (50)
Slovakia	1 (1)	0	1 (<1)
Spain	3 (3)	2 (2)	5 (2)
Ukraine	16 (14)	20 (18)	36 (16)
United States of America	12 (11)	10 (9)	22 (10)
Baseline body weight category, n (%)			
<51 kg	37 (33)	29 (25)	66 (29)
≥51 kg	75 (67)	85 (75)	160 (71)
Baseline BMI (kg/m^2)			
Category, n (%)			
Normal <25	95 (85)	95 (83)	190 (84)
Overweight 25-<30	11 (10)	15 (13)	26 (12)
Obese ≥30	6 (5)	4 (4)	10 (4)
Mean (SD)	21.23 (3.910)	21.40 (4.462)	21.32 (4.189)
Median	20.15	20.60	20.30
Range	(14.2; 35.0)	(14.7; 47.6)	(14.2; 47.6)
Schizophrenia type, n (%)			
Paranoid (295.30)	82 (73)	76 (67)	158 (70)
Disorganized (295.10)	4 (4)	8 (7)	12 (5)
Catatonic (295.20)	2 (2)	1 (1)	3 (1)
Undifferentiated (295.90)	21 (19)	27 (24)	48 (21)
Residual (295.60)	3 (3)	2 (2)	5 (2)

Table 20: Baseline disease severity in the different treatment groups

	Paliperidone ER (N=112)	Aripiprazole (N=114)	Total (N=226)
Age at diagnosis of schizophrenia (years)			
Mean (SD)	13.2 (2.06)	12.6 (2.76)	12.9 (2.45)
Median	14.0	13.0	13.0
Range	(6; 17)	(4; 17)	(4; 17)
Baseline PANSS total			
Mean (SD)	89.6 (12.22)	92.0 (12.09)	90.8 (12.19)
Median	89.0	93.0	91.0
Range	(63;122)	(65;116)	(63;122)
Prior hospitalization, n (%)			
None	42 (38)	47 (41)	89 (39)
Once	43 (38)	32 (28)	75 (33)
Twice	14 (13)	13 (11)	27 (12)
Three times	3 (3)	5 (4)	8 (4)
Four times or more	10 (9)	17 (15)	27 (12)
Baseline CGI-S, n (%)			
Mild	3 (3)	3 (3)	6 (3)
Moderate	67 (60)	70 (61)	137 (61)
Marked	39 (35)	34 (30)	73 (32)
Severe	3 (3)	7 (6)	10 (4)
India	20 (18)	19 (17)	39 (17)
Romania	4 (4)	5 (4)	9 (4)
Russian Federation	56 (50)	58 (51)	114 (50)
Slovakia	1 (1)	0	1 (<1)
Spain	3 (3)	2 (2)	5 (2)
Ukraine	16 (14)	20 (18)	36 (16)
United States of America	12 (11)	10 (9)	22 (10)
Baseline body weight category, n (%)			
<51 kg	37 (33)	29 (25)	66 (29)

Outcomes and estimation

PANSS Total Score related endpoints

Results on the primary endpoint are presented in Table 21.

Table 21: PANSS total score–Change from baseline to endpoint acute (Day 56) ITT-LOCF analysis

	Paliperidone ER (N=112)	Aripiprazole (N=114)
Baseline		
N	112	114
Mean (SD)	89.6 (12.22)	92.0 (12.09)
Median (Range)	89.0 (63; 122)	93.0 (65; 116)
End Point Acute (Day 56)		
N	112	114
Mean (SD)	70.3 (16.93)	72.2 (16.76)
Median (Range)	70.0 (35; 106)	70.5 (30; 128)
Change from Baseline		
N	112	114
Mean (SD)	-19.3 (13.80)	-19.8 (14.56)
Median (Range)	-18.0 (-79; 5)	-18.0 (-53; 26)
P-value(minus Aripiprazole)[a]	0.935	
Diff. of LS Means (SE)	0.1 (1.83)	
95% CI	(-3.46; 3.76)	

[a] Based on analysis of covariance (ANCOVA) model with treatment (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate.
Note: Negative change in score indicates improvement.

Source: Summary of Clinical efficacy

When using the mode dose (ie the dose that was most frequently taken), the changes from baseline were very similar across all mode doses for both treatment groups (see Table 21). This indicates that the approach of flexible dosing worked. It is noted that the most frequent mode dose for paliperidone ER is 6 mg.

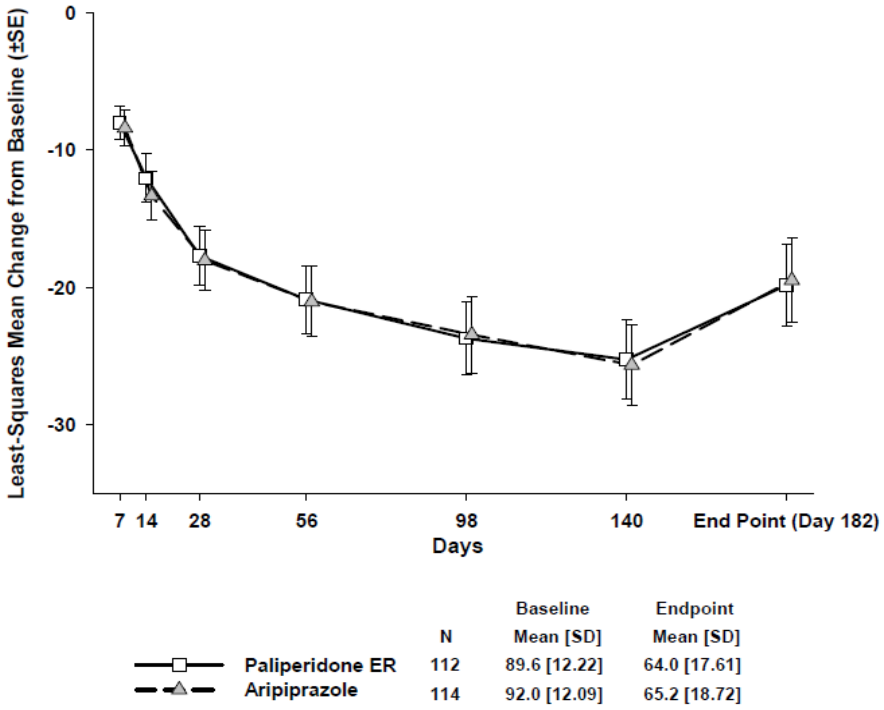
Table 22: PANSS total score change from baseline to endpoint acute by mode dose

Mode dose*	**Paliperidone 3mg (N=20)**	**Ari 5 mg (N=13)**	**Paliperidone 6 mg (N=54)**	**Ari 10mg (N=49)**	**Paliperidone 9mg (N=38)**	**Ari 15 mg (N=52)**
Baseline mean	88.2	87.1	90.3	90.3	89.2	94.8
Endpoint Acute mean	71.1	66.2	70.3	70.9	69.8	74.9
Change from baseline mean	-17.2	-20.9	-20.0	-19.4	-19.4	-19.9

When conducting a subgroup analysis of the primary efficacy variable there was a greater improvement in the younger subjects (12-14 yrs) in the aripiprazole group (-23.7) than in the paliperidone ER group (-17.5). In older subjects (15-17 yrs) there was a greater improvement in mean PANSS total score in the paliperidone ER group than in the aripiprazole group (-20.1 vs -18.5). in both weight groups (<51kg and ≥51 kg) improvement was similar in the mean PANSS total score at day 56 (around -20).

Figure 15 shows the estimated LS mean changes (LOCF) from baseline in PANSS total scores over time.

Figure 15: Estimated LS mean changes (LOCF) from baseline to endpoint (Day 182) in PANSS total scores



No statistically significant differences between treatment groups were observed at the two-sided 0.05 level.

Other endpoints

These are presented in Table 23.

Table 23: Key secondary Variables at Day 182 (ITT analysis set)

	Paliperidone ER (N=112)	Aripiprazole (N=114)
PANSS total score at End Point (Day 182)		
Mean baseline (SD)	89.6 (12.22)	92.0 (12.09)
Mean change (SD)	-25.6 (16.88)	-26.8 (18.82)
p value (minus Aripiprazole)[a]	0.877	
PANSS Marder Factors		
Positive symptoms		
Mean baseline (SD)	24.6 (4.08)	24.9 (4.32)
Mean change (SD)	-7.8 (5.82)	-7.8 (6.03)
p value(minus Aripiprazole)[a]	0.691	
Negative symptoms		
Mean baseline (SD)	23.2 (4.92)	23.3 (4.54)
Mean change (SD)	-6.0 (5.51)	-6.2 (5.84)
p value (minus Aripiprazole)[a]	0.723	
Disorganized thoughts		
Mean baseline (SD)	21.4 (4.40)	22.1 (3.86)
Mean change (SD)	-5.5 (4.18)	-5.7 (4.46)
p value (minus Aripiprazole)[a]	0.766	
Uncontrolled hostility/excitement		
Mean baseline (SD)	10.7 (3.19)	11.7 (3.48)
Mean change (SD)	-3.2 (3.11)	-3.8 (3.97)
p value (minus Aripiprazole)[a]	0.985	
Anxiety/depression		
Mean baseline (SD)	9.7 (3.17)	10.0 (3.26)
Mean change (SD)	-3.0 (3.29)	-3.2 (3.17)
p value (minus Aripiprazole)[a]	0.745	
Clinical Stability at Days 56 and 182[b]		
Yes: n (%)	58 (51.8%)	68 (59.6%)
No: n (%)	54 (48.2%)	46 (40.4%)
p value (vs Aripiprazole)[c]	0.296	
CGI-S Score		
Baseline Median (Range)	4.0 (3; 6)	4.0 (3; 6)
Change from Baseline		
Median (Range)	-1.0 (-4; 1)	-1.0 (-4; 1)
p value (minus aripiprazole)[d]	0.914	
PSP		
Mean Baseline(SD)	49.8 (10.32)	49.2 (10.21)
Mean Change (SD)	17.1 (14.46)	17.1 (14.03)
p value (minus Aripiprazole)[e]	0.705	
Responder Rate[f]		
n (%)	86 (76.8%)	93 (81.6%)
p value (vs Aripiprazole)[c]	0.444	

a Based on analysis of covariance (ANCOVA) model with treatment (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate.
Negative change in score indicates improvement. Factors derived from Marder Criteria.
b Clinical stability is defined as a decrease of 20% or more from baseline PANSS total score and a CGI-S score ≤4 at Day 56 and Day 182, and no hospitalizations due to psychiatric illness and no emergence of clinically significant suicidal or homicidal ideation during the maintenance phase. ITT subjects who do not meet these criteria are classified as not achieving clinical stability.
c Generalized Cochran-Mantel-Haenszel test for row mean score differences controlling for country.
d Based on analysis of covariance (ANCOVA) model on ranks with treatment (paliperidone ER, aripiprazole) and country as factors, and baseline value (unranked) as a covariate.
Negative change in score indicates improvement.
e Based on analysis of covariance (ANCOVA) model with treatment (paliperidone ER, aripiprazole) and country as factors, and baseline value as a covariate. Positive change in score indicates improvement.
f Responder defined as those who achieved a 20% or higher reduction from baseline in the PANSS total score at endpoint (Day 182).

Ancillary analyses

There was no statistically significant difference in the change from baseline to endpoint acute (Day 56) in the PANSS total score based on the worst rank analysis between the paliperidone ER and aripiprazole groups (p=0.465), which is consistent with the primary analysis.

Results from the MMRM analysis corroborated the findings from the LOCF analysis of the primary efficacy endpoint. Using an unstructured variance-covariance matrix for the MMRM analysis, the estimated LS mean change in PANSS total score at Day 56 was -22.4 for paliperidone ER and -24.2 for aripiprazole (p=0.313) which is consistent with the primary analysis result.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24: Summary of Efficacy for trial PSZ-3001

Title: 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			
Study identifier	PSZ-3001		
Design	6 week, randomized, double-blind, parallel-group, placebo-controlled multicentre efficacy and safety study		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		6 weeks 3 weeks screening phase See PSZ-3002, for patients who did not enter the open-label safety study there was a one-week follow-up visit
Hypothesis	Superiority of PAL over Placebo		
Treatment groups	Placebo		n = 51
	Paliperidone ER low (1.5 mg)		n = 54
	Paliperidone ER medium (3 or 6 mg)		n = 48
	Paliperidone ER high (6 or 12 mg)		n = 47
Endpoints and definitions	Primary endpoint	ΔPANSS total score	Change from baseline to the acute endpoint in the double-blind period
	Secondary	ΔCGI-S score	Change from baseline to endpoint in the CGI-S score
		ΔCGAS score	Change from baseline to endpoint in the CGAS score
	Exploratory endpoint	ΔVAS sleep	Change from baseline to endpoint

		Responder Rate	20% reduction from baseline in PANSS total score

Results and analysis					
Analysis description	**Primary analysis**				
Analysis population and time point description	Intent to treat (ITT) population which included all subjects who received at least 1 dose of double-blind study drug and had both a baseline and at least 1 post-baseline assessment in the double-blind phase on any of the following scales: PANSS, CGI-S, CGAS, or sleep VAS. Week 6 primary efficacy endpoint				
Descriptive statistics and estimate variability	Treatment group	PBO	PAL low (1.5 mg)	PAL medium (3 or 6 mg)*	PAL high (6 or 12 mg)**
	Number of subjects	51	54	48	47
	ΔPANSS total score; mean (LOCF)	-7.9	-9.8	-17.3	-13.8
	SD	20.15	16.31	14.33	15.74
	ΔCGI-S score Median (LOCF)	0.0	0.0	-1.0	-1.0
	range	-3.1	-3.1	-3.0	-3.1
	ΔCGAS score; mean (LOCF)	5.0	4.4	13.1	8.6
	SD	13.82	10.72	12.07	11.18
	Δ Sleep VAS Mean (LOCF)	-0.3	6.6	16.0	14.4
	SD	34.21	24.57	27.06	22.72
	Responder Rate (20% reduction from baseline in PANSS total); n(%)	17 (33.3%)	21 (38.9%)	31 (64.6%)	24 (51.1%)
Effect estimate per comparison	Primary endpoint	Comparison groups	PAL low	PAL medium	PAL high
	ΔPANSS total score	Diff. of LS means to PBO (95% CI) LOCF	-2.1 (-8.36; 4.16)	-10.1 (-16.58;-3.67)	-6.6 (-13.07;-0.09)
		SE	±3.17	±3.27	±3.29

		P-value	0.508	0.006	0.086
	Secondary endpoint ΔCGI-S score Median	Diff. to PBO (95% CI), median LOCF	0.0	-1.0	-1.0
		range	-3.1	-3.0	-3.1
		P-value	0.968	<0.001	0.021
	Secondary endpoint ΔCGAS score	Diff. of LS means to PBO (95% CI) LOCF	-0.4 (-4.54;3.73)	8.6 (4.28;12.82)	4.0 (-0.28;8.33)
		SE	±2.10	±2.17	±2.18
		P-value	0.846	<0.001	0.067
	Exploratory endpoint Sleep VAS	Diff. of LS means to PBO (95% CI) LOCF	8.1 (-0.29;16.56)	16.8 (8.08;25.43)	13.6 (4.76;22.23)
		SE	±4.27	±4.40	±4.43
		p-value	0.058	<0.001	<0.003
	Responder Rate (20% reduction from baseline in PANSS total)	Diff to PBO in %	5.6%	31.3%	17.8%
		p-value	0.479	0.001	0.043
Notes		Additional analyses by actual dose revealed that the improvement in the 3, 6 and 12 mg dose groups achieved statistical significance.			
Analysis description		The primary efficacy analysis was ANCOVA/LOCF. As additional sensitivity analysis MMRM and Worst Rank analysis were undertaken.			
* Medium dose group: 3 mg for subjects < 51 kg, 6mg for subjects ≥51 kg ** High dose group: 6 mg for subjects < 51 kg, 12 mg for subjects ≥51 kg					

Δ: change from baseline to endpoint, PAL: paliperidone, PBO: placebo, SE: standard error

Table 25: Summary of Efficacy for trial PSZ-3003

Title: A Randomized, Multicenter, Double-Blind, Active-Controlled, Flexible-Dose, Parallel-Group Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Symptoms of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age			
Study identifier	PSZ-3003		
Design	A randomized, double blind, active controlled, parallel group, flexible dose, multicenter efficacy and safety. The study consisted of three phases: an up to 3 weeks screening phase (with a possible overlapping washout period), an 8 Week double-blind acute phase, and an 18 Week double-blind maintenance phase.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		8 weeks double blind acute and 18 weeks double blind maintenance phase. 3 week screening phase NA
Hypothesis	Superiority versus Aripiprazole		
Treatment groups	Paliperidone 3, 6 or 9 mg		Paliperidone ER was administered at a fixed dose of 6 mg/day during the first week followed by flexible dosing (3, 6, or 9 mg/day) thereafter, n=113
	Aripiprazole 5, 10 or 15 mg		Aripiprazole was titrated from 2 mg/day to 10 mg/day during the first week, followed by flexible dosing (5, 10, or 15 mg/day) thereafter, n=115
Endpoints and definitions	Primary endpoint	ΔPANSS total score	Change from baseline to week 8
	Secondary endpoint	Proportion of subjects maintaining stability[1]	Maintenance of effect (as measured from Week 8) at Week 26
		ΔPANSS negative symptom factor score	Change from baseline at Week 8 and Week 26
		ΔPANSS total score	Change from baseline to week 26
		ΔCGI-S score	Change from baseline at Week 8 and Week 26
		Δ PSP score	Change from baseline at Week 8 and Week 26
	Exploratory endpoint	Responder rate	20% reduction from baseline in PANSS total score

[1] Defined as decrease of 20% or more from baseline PANSS total, CGI score ≤ 4 at Day 56 and 182, no hospitalisation or emergence of clinically significant suicidal or homicidal ideation

Database lock	10 July 2012		
Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat (ITT)		
Descriptive statistics and estimate variability	Treatment group	Paliperidone 3-9 mg	Aripiprazole 5-15 mg
	Number of subjects	112	114
	ΔPANSS total score; mean (LOCF)	-19.3	-19.8
	SD	13.80	14.56
	Proportion of subjects maintaining stability at Days 56 and 182; n (%)	58 (51.8)	68 (59.6)
	variability statistic	NA	NA
	ΔPANSS negative symptom factor score; mean change from baseline (LOCF) Day 56	-4.3	-4.7
	SD	4.56	4.61
	ΔPANSS total score at week 26; mean (LOCF)	-25.6	-26.8
	SD	16.88	18.82
	ΔCGI-S score, median (LOCF)	-1.0	-1.0
	range	(-4;1)	(-4;1)
	Δ PSP score; mean (LOCF)	17.1	17.1
	SD	(14.46)	(14.03)

	Responder rate; n (%)	86 (76.8%)	93 (81.6%)
	variability statistic	NA	NA
Effect estimate per comparison	Primary endpoint ΔPANSS total score	Comparison groups	PAL minus ARI
		Diff of LS means to ARI (95% CI)	0.1 (-3.46; 3.76)
		SE	1.83
		P-value	0.935
	Secondary endpoint, Proportion of subjects maintaining stability at Days 56 and 182	Comparison groups	PAL minus ARI
		P-value	0.296
	ΔPANSS negative symptom factor score; Day 56	Comparison groups	PAL minus ARI
		P-value	0.341
	ΔPANSS total score at week 26	Comparison groups	PAL minus ARI
		p-value	0.877
	ΔCGI-S score	Comparison groups	PAL minus ARI
		p-value	0.914
	Δ PSP score	Comparison groups	PAL minus ARI
		p-value	0.705
	Responder Rate	Comparison groups	PAL minus ARI
		p-value	0.444
Notes	Negative change in score indicates improvement.		
Analysis description	**LOCF**		

2.4.3. Analysis performed across trials (pooled analyses and meta-analysis)

Comparison on the change in the PANSS total score

A meta-analysis based on studies: PSZ-3001, PSZ-3003 and the only published aripiprazole placebo-controlled study of adolescent schizophrenia (Findling RL et al (2008)) was presented. However, the CHMP was in disagreement with the MAH consideration that the designs of the pooled studies were similar: study PSZ-3001 and the aripiprazole placebo-controlled study were 6 week studies with fixed doses while PSZ-3003 was an 8 week study with flexible dosing; fixed dose groups were pooled post-hoc within studies PSZ-3001 and the aripiprazole placebo-controlled study. Furthermore, the approach

to perform a pooled analysis of subject level data based on simulated data as if these were observed data is generally not considered valid. For the indirect comparison of paliperidone with aripiprazole using the data from their respective placebo-controlled trials, the assumption has also to be made that the treatment effects of paliperidone and aripiprazole would have been the same in the trial where the respective treatment was not included as observed in the placebo controlled trial where it was included, which is not verifiable.Hence, taking into account the different study designs and the additional assumptions that have to be made to conduct the meta-analysis, the CHMP considered highly questionable whether the meta-analysis of these studies was valid and meaningful, and whether it provides valid information beyond the single studies.

Comparison on the baseline data for EU/US versus non EU/US population

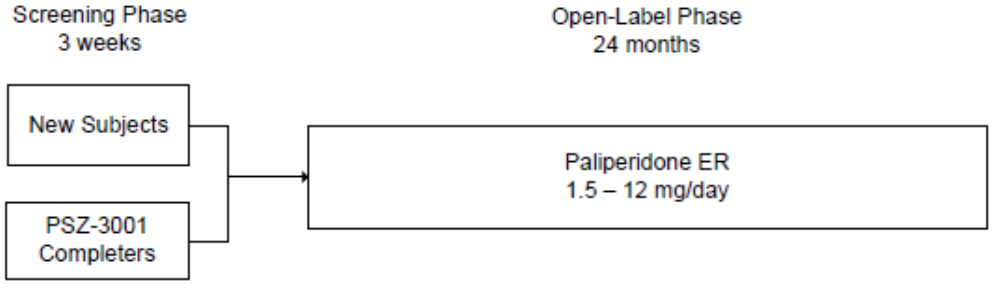
When the number of subjects from the EU was combined with that from the US, the percentages of subjects from the 2 combined subpopulations were 19.5%, 34.9%, and 16.4% in PSZ-3001, PSZ-3002, and PSZ-3003, respectively. The overall proportion of subjects from combined EU and US in all 3 studies was 27.8%. The demographic and psychiatric baseline characteristics of subjects from EU/US were similar to those of subjects from the non-EU/non-US in Studies PSZ-3001, PSZ-3002 and PSZ-3003. At least 90% of subjects received prior psychotropic medications across different country/regions. The percentage of subjects receiving atypical antipsychotic medications was higher for subjects from the EU/US than those non-EU/non-US countries. Additionally, subject baseline characteristics in Studies PSZ-3001, PSZ-3002, and PSZ-3003 were consistent with those of subjects from published reports in adolescents with schizophrenia. Of note, the Hass study enrolled subjects from EU and US only. Since the characteristics of subjects from the EU are similar to those from the US and the combined EU/US subpopulation for the 3 Phase 3 studies was over 25%, data from these studies were considered by the MAH relevant to the EU subject population.

2.4.4. Supportive study

STUDY PSZ3002

The study design is presented in Figure 16.

Figure 16:



This study was conducted at 1 site in Bulgaria, 2 sites in Estonia,1 site in Finland, 5 sites in India, 6 sites in Korea, 6 sites in Poland, 1 site in Romania, 12 sites in Russia, 6 sites in Ukraine, and the 15 sites in the US.

2.4.4.1. Methods

Study participants

This long-term study included subjects who had: a) completed double-blind treatment in PSZ-3001; b) discontinued PSZ-3001 due to lack of efficacy after completing at least 21 days of double-blind

treatment and who were expected to benefit from a continuation of paliperidone ER; or c) were aged between 12 and 17 years, inclusive, with K-SADS-PL confirmed DSM-IV diagnosis of schizophrenia and who were directly enrolled in the study.

Treatments

All enrolled subjects received a starting dose of paliperidone ER 6 mg daily, which could have been increased in increments of 3 mg once every 5 days until the maximum dose of 12 mg/day was reached. Alternatively, if the 6 mg dose was not tolerated, the dose could have been decreased to 3 or 1.5 mg/day

The washout period for current psychotropic medications (if necessary) was required only for subjects enrolling in this study directly. For subjects who enrolled from PSZ-3001, the end-of-study or early withdrawal visit of the double-blind study coincided with Day 1 of PSZ-3002.

Subjects entering the long-term study from PSZ-3001 were required to complete the Measurements and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) cognitive battery of tests, 23 the K-SADS-PL screening Items 'a' to 'e' for suicide, and an ECG.

End of study (EOS) laboratory assessments for PSZ-3001 counted as baseline assessments for PSZ-3002. The last study day for PSZ-3001 was the same day as the baseline visit (Day 1) for PSZ-3002.

Objectives

All efficacy analyses performed for this study were exploratory because this study did not have a control group for comparison and the primary objective of the study was to assess the safety and tolerability of paliperidone ER.

Outcomes/endpoints

The primary efficacy variable was the change from baseline in the PANSS total score at the end of the open-label phase (Week 104 or the last post-baseline assessment). Other measures of efficacy included the CGI-S, CGAS, the modified MATRICS cognition assessment battery, sleep VAS, and the PANSS negative symptom scale based on Marder factors.

Sample size

No formal sample size calculation was performed for this study. Based on the discontinuation rate seen in a similar study evaluating risperidone in adolescents, approximately 400 subjects were to be enrolled into this open-label study so that at least 100 subjects completed the 2-year open-label study at or above the lowest effective dose (≤3 mg) that was identified in Study R076477-PSZ-3001.

Randomisation

As this was an open-label, single-arm study, randomization was not applicable.

Blinding (masking)

As this was an open-label, single-arm study, blinding was not applicable. The treatment assignment in study PSZ-3001 continued to be blinded after subjects entered study PSZ-3002.

Statistical methods

Descriptive methods were used to present efficacy data in this open label, uncontrolled study.

The following treatment groups were analysed: subjects previously randomly assigned to 1) placebo in PSZ-3001 (placebo/paliperidone); 2) to any 1 of the paliperidone ER dose groups (low, medium, or

high) in PSZ-3001 (paliperidone (DB)/paliperidone) and new subjects who enrolled in the study (paliperidone (NO DB)/paliperidone).

For all efficacy variables except for the cognitive assessment battery, 2 baseline values were defined and used in the analyses of changes from baseline as follows: Open-label (OL) baseline (latest observation prior to administration of open-label paliperidone ER in PSZ-3002 (including first day of dosing [Day 1] in this study); Double-blind (DB) baseline (observation at the last visit prior to administration of double-blind study drug administration in PSZ-3001 (including Day 1).

2.4.4.2. Results

Participant flow

A total of 393 subjects were enrolled into PSZ-3002 receiving at least 1 dose of study medication, had a baseline and at least 1 post-baseline efficacy assessment. A total of 237 subjects entered the study directly and 156 subjects who were enrolled from PSZ-3001. See Table 26.

Table 26: Number of subjects assigned to each treatment group

	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=243) n (%)	Total (N=400) n (%)
Open-Label Safety	39 (100)	118 (100)	243 (100)	400 (100)
Open-Label Intent-To-Treat	39 (100)	117 (99)	237 (98)	393 (98)

Information on number of subjects who completed or withdrew the study and reasons for withdrawal is provided in Table 27. Time to withdrawal is presented in Figure 17.

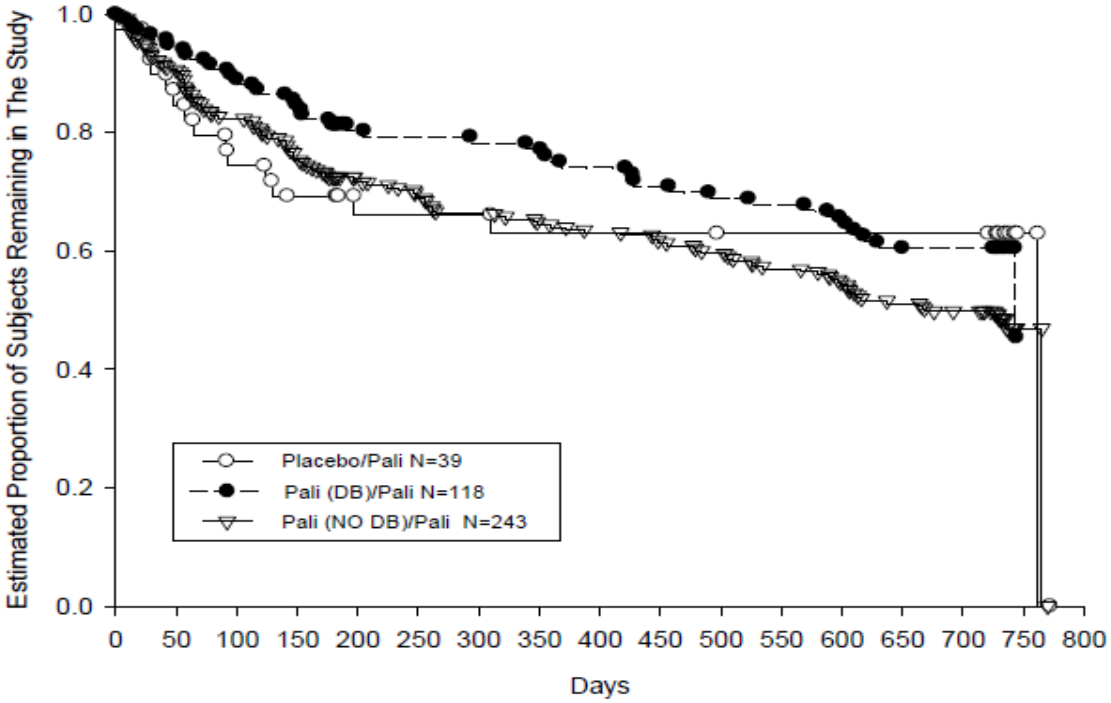
Table 27: Study Completion / Withdrawal information

	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=243) n (%)	Total (N=400) n (%)
Completed	24 (62)	75 (64)	121 (50)	220 (55)
Withdrawn	15 (38)	43 (36)	122 (50)	180 (45)
Subject choice (subject withdrew consent)	5 (13)	20 (17)	44 (18)	69 (17)
Lack of efficacy	6 (15)	12 (10)	27 (11)	45 (11)
Adverse event	1 (3)	2 (2)	23 (9)	26 (7)
Lost to follow-up	3 (8)	5 (4)	16 (7)	24 (6)
Other	0	4 (3)	12 (5)	16 (4)

Completed: Denotes the number of subjects who completed the study based on either the original protocol (6-month study) or the amended protocol (2-year study) period.

Withdrawn: Denotes the number of subjects who withdrew from the study based on either the original protocol or the amended protocol period.

Figure 17: Time to discontinuation for any reason



Only 2% of subjects had a mode dose of 1.5 mg, while 38% of subjects had a mode dose of 6 mg and 11% had a mode dose of 3 mg. Approximately 30% of subjects had their dose increased to the maximum daily dose of 12 mg. A total of 109 evaluable subjects had exposure to paliperidone ER for the study duration of 2 years and 18% (n=73) had exposure to paliperidone for ≥ 2 years.

Outcomes and estimation

PANSS Total Score related endpoints

Results on the primary endpoint are presented in Table 28.

Table 28: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score – Change from Baseline (OL) to End Point (OL) LOCF

	Placebo/Pali (N=39)	Pali (DB)/Pali (N=117)	Pali (NO DB)/Pali (N=237)	Total (N=393)
Baseline				
N	39	117	237	393
Mean (SD)	82.7 (22.11)	76.6 (20.48)	87.7 (18.89)	83.9 (20.27)
Median (Range)	80.0 (36;129)	76.0 (33;135)	87.0 (44;149)	84.0 (33;149)
End point(OL)				
N	39	117	237	393
Mean (SD)	63.8 (19.51)	64.0 (20.77)	65.3 (22.27)	64.8 (21.53)
Median (Range)	63.0 (33;110)	61.0 (32;140)	65.0 (31;134)	63.0 (31;140)
Change from Baseline				
N	39	117	237	393
Mean (SD)	-18.9 (21.47)	-12.6 (19.92)	-22.4 (22.25)	-19.1 (21.89)
Median (Range)	-18.0 (-62;50)	-11.0 (-67;46)	-23.0 (-82;48)	-17.0 (-82;50)

Note: Negative change in score indicates improvement.
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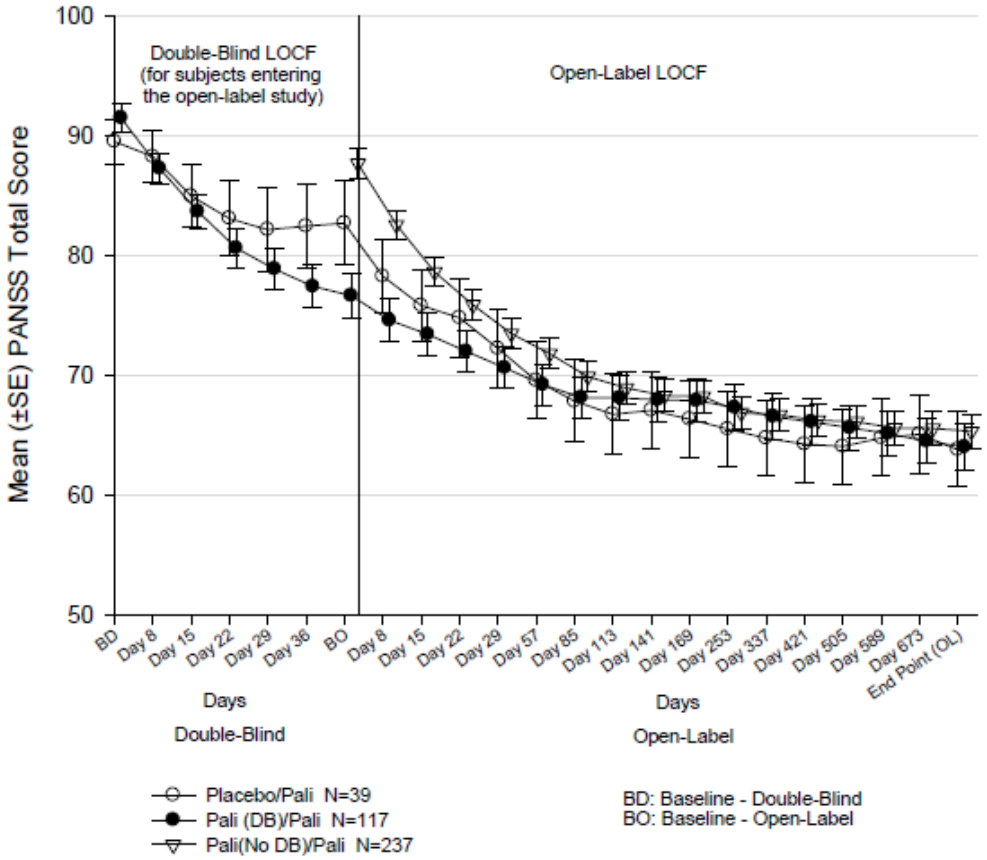
Figure 18 shows the mean changes from baseline in PANSS total scores over time.

Figure 18: Mean (+/- SE) Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score – LOCF (OL ITT Analysis Set)



Other endpoints

Results are presented in Table 29.

Table 29: Overview of key secondary variables

	Placebo/Pali (N=39)	Pali (DB)/Pali (N=117)	Pali (NO DB)/Pali (N=237)	Total (N=393)
PANSS Factors[a]				
Positive symptoms				
Mean baseline (SD)	22.3 (6.66)	19.8 (5.79)	24.8 (6.25)	23.0 (6.54)
Mean change (SD)[b]	-5.1 (6.45)	-3.4 (6.11)	-7.0 (7.12)	-5.7 (6.94)
Negative symptoms				
Mean baseline (SD)	20.6 (6.42)	20.6 (6.20)	22.3 (6.09)	21.6 (6.19)
Mean change (SD)[b]	-4.3 (6.30)	-3.8 (4.80)	-5.7 (6.68)	-5.0 (6.18)
Disorganized thoughts				
Mean baseline (SD)	19.8 (5.78)	19.1 (5.89)	20.1 (5.54)	19.8 (5.68)
Mean change (SD)[b]	-4.8 (5.57)	-3.3 (4.41)	-4.9 (5.52)	-4.4 (5.25)
Uncontrolled hostility/excitement				
Mean baseline (SD)	11.0 (4.63)	9.4 (3.89)	10.1 (4.08)	10.0 (4.09)
Mean change (SD)[b]	-2.6 (4.17)	-1.2 (4.41)	-2.1 (4.68)	-1.9 (4.56)
Anxiety/depression				
Mean baseline (SD)	9.1 (3.08)	7.7 (2.73)	10.4 (3.43)	9.5 (3.42)
Mean change (SD)[b]	-2.1 (3.35)	-0.9 (3.41)	-2.8 (3.61)	-2.2 (3.62)
20% Responder Rate[c]				
n (%)	27 (69.2%)	68 (58.1)	167(70.5%)	262 (66.7%)
CGI-S Score				
Median (Range) Baseline	4.0 (1;6)	4.0 (1;6)	4.0 (2;7)	4.0 (1;7)
Median (Range) Change at end point[b]	-1.0 (-3;2)	-1.0 (-3;3)	-1.0 (-5;3)	-1.0 (-5;3)
CGAS Score				
Mean (SD) Baseline	54.9 (15.84)	57.1 (15.36)	46.7 (11.84)	50.6 (14.23)
Mean (SD) Change from Baseline[d]	11.3 (16.65)	8.7 (16.02)	15.6 (17.77)	13.1 (17.39)
Sleep VAS Score[e]				
Quality of Sleep, N	36	116	223	375
Mean (SD) Baseline	69.3 (24.79)	79.5 (20.21)	60.7 (27.54)	67.3 (26.57)
Mean (SD) Change from Baseline[d]	8.2 (30.51)	2.7 (18.48)	9.8 (32.47)	7.4 (28.78)
Daytime Drowsiness[f]				
Mean (SD) Baseline	26.4 (23.72)	20.9 (21.57)	32.9 (26.77)	28.5 (25.52)
Mean (SD) Change from Baseline[b]	-7.4 (18.83)	-5.1 (22.39)	-3.9 (32.30)	-4.6 (28.42)

[a] Factors derived from Marder criteria
[b] Negative change in score indicates improvement.
[c] Responder defined as those who achieved a 20% or higher reduction from baseline in the PANSS total score at end point.
[d] Positive change in score indicates improvement.
[e] Based on answer to the question "How well have you slept in the past 7 nights?" 0 for very badly, 100 for very well.
[f] Based on answer to the question How often have you felt drowsy in the past 7 days? 0 for not at all, 100 for all the time.

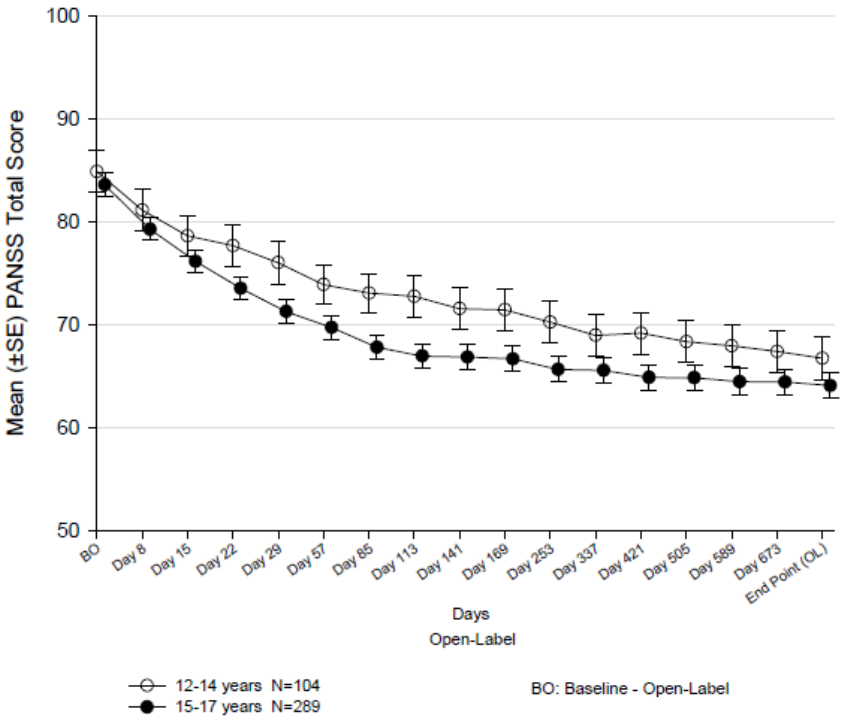
Similar mean changes in PANSS total score from double-blind baseline to open-label endpoint were observed for subjects from EU (-30.9, n=10), US (-27.1, n=19), EU/US (-28.4, n=29), and non-EU/non-US countries (-26.7, n=127). Mean change in PANSS total score from open-label baseline to open-label endpoint was slightly larger in subjects from non-EU/non-US countries (-21, n=256) than those from EU (-17.1, n=78), US (-13.6, n=59), and EU/US (-15.6, n=137). Reduction (ie, improvement) in PANSS total scores was observed from open-label baseline to open-label endpoint in both age groups of 12 to 14 and 15 to 17 years old with numerically greater decreases noted for the older group. In the total group, the magnitude of the mean decrease (improvement) from open-label baseline to endpoint in PANSS total score was higher for non-US subjects than the US subjects, and was numerically slightly greater for the non-EU subjects (-19.6, N=315) than the EU subjects (-17.1, N=78).

Across different regions, over 55% of subjects achieved a 20% or higher reduction in PANSS total score from open-label baseline to endpoint. A slightly higher proportion of subjects from non-EU/non-

US countries (69.9%) than those from EU (61.5%), US (59.3%), or EU/US (60.6%) achieved the 20% or higher reduction in PANSS total score. Similarly, a higher percentage of subjects from non-EU/non-US (60.9%) than those from EU (48.7%), US (54.2%), or EU/US (51.1%) achieved a 30% or higher reduction in PANSS total score from open-label baseline to open-label endpoint.

Figure 19 shows the mean (+/-SE) PANSS total scores over time for the 2 age groups (12 to 14 and 15 to17 years). Decrease (ie, improvement) in the PANSS total scores was observed from open-label baseline to open-label endpoint in both age groups, although the improvement was numerically better for the older group.

Figure 19: Mean (±SE) positive and negative syndrome scale for PANSS total Score by age



2.4.5. Additional analyses

At the CHMP request, additional analyses were presented by the MAH including efficacy data by age and weight groups. Analyses for the primary efficacy endpoint, change from baseline to endpoint on the total PANSS total score, are presented below.

Table 30: PANSS total score – Change from baseline to endpoint (LOCF) by age –PSZ-3001-ITT set

Age Group: 12-14 Parameter: Total PANSS	Placebo (N=9)	Paliperidone ER Low (N=16)	Paliperidone ER Medium (N=15)	Paliperidone ER High (N=13)
Baseline				
N	9	16	15	13
Mean (SD)	89.4 (12.93)	89.6 (11.47)	93.5 (13.77)	93.0 (15.92)
Median (Range)	83.0 (78;114)	89.5 (71;111)	94.0 (71;119)	90.0 (70;119)
End Point				
N	9	16	15	13
Mean (SD)	77.9 (7.46)	83.0 (20.46)	77.9 (23.43)	86.1 (20.82)
Median (Range)	80.0 (61;87)	84.0 (45;111)	84.0 (43;112)	78.0 (62;135)
Change from Baseline				
N	9	16	15	13
Mean (SD)	-11.6 (12.30)	-6.6 (18.28)	-15.5 (12.66)	-6.9 (19.73)
Median (Range)	-8.0 (-33;2)	-4.0 (-52;23)	-16.0 (-35;4)	-5.0 (-49;30)
Age Group: 15-17 Parameter: Total PANSS	Placebo (N=42)	Paliperidone ER Low (N=38)	Paliperidone ER Medium (N=33)	Paliperidone ER High (N=34)
Baseline				
N	42	38	33	34
Mean (SD)	90.9 (12.10)	92.5 (13.02)	89.4 (14.14)	91.0 (13.21)
Median (Range)	89.0 (65;118)	92.0 (70;118)	85.0 (69;116)	89.5 (63;117)
End Point				
N	42	38	33	34
Mean (SD)	83.8 (23.32)	81.4 (19.40)	71.2 (21.35)	74.5 (16.37)
Median (Range)	82.0 (36;129)	79.0 (45;121)	69.0 (33;126)	75.0 (49;114)
Change from Baseline				
N	42	38	33	34
Mean (SD)	-7.1 (21.49)	-11.1 (15.47)	-18.1 (15.14)	-16.5 (13.34)
Median (Range)	-4.0 (-59;28)	-6.5 (-45;10)	-17.0 (-53;19)	-13.5 (-62;1)

Note: Negative change in score indicates improvement.
LOCF=last observation carried forward, SD=standard deviation

Table 31: PANSS total score – Change from baseline to endpoint (LOCF): weight based treatment groups- by weight–PSZ-3001- ITT set

Baseline Body Weight Category: <51 kg
Parameter: Total PANSS

	Placebo (N=14)	Paliperidone ER Low (1.5 mg) (N=19)	Paliperidone ER Medium (3 mg) (N=16)	Paliperidone ER High (6 mg) (N=13)
Baseline				
N	14	19	16	13
Mean (SD)	93.9 (13.98)	88.3 (12.67)	92.1 (16.88)	93.0 (16.37)
Median (Range)	91.0 (78;118)	89.0 (71;118)	91.0 (70;119)	90.0 (63;118)
End Point				
N	14	19	16	13
Mean (SD)	79.4 (23.66)	76.3 (21.24)	73.1 (26.55)	85.6 (20.67)
Median (Range)	78.5 (44;120)	79.0 (45;121)	70.0 (33;115)	79.0 (51;135)
Change from Baseline				
N	14	19	16	13
Mean (SD)	-14.4 (19.07)	-11.9 (17.49)	-19.0 (15.45)	-7.4 (15.32)
Median (Range)	-9.0 (-54;10)	-6.0 (-45;13)	-19.0 (-53;3)	-4.0 (-34;30)

Baseline Body Weight Category: >=51 kg
Parameter: Total PANSS

	Placebo (N=37)	Paliperidone ER Low (1.5 mg) (N=35)	Paliperidone ER Medium (6 mg) (N=32)	Paliperidone ER High (12 mg) (N=34)
Baseline				
N	37	35	32	34
Mean (SD)	89.4 (11.32)	93.5 (12.27)	89.9 (12.57)	91.0 (13.00)
Median (Range)	88.0 (65;112)	93.0 (70;118)	85.5 (69;111)	89.0 (70;119)
End Point				
N	37	35	32	34
Mean (SD)	84.0 (20.76)	84.9 (18.16)	73.4 (19.80)	74.7 (16.57)
Median (Range)	82.0 (36;129)	86.0 (55;117)	70.0 (42;126)	73.0 (49;115)
Change from Baseline				
N	37	35	32	34
Mean (SD)	-5.4 (20.23)	-8.6 (15.77)	-16.5 (13.91)	-16.3 (15.41)
Median (Range)	-5.0 (-59;28)	-4.0 (-52;23)	-15.0 (-51;19)	-15.0 (-62;18)

Note: Negative change in score indicates improvement.
LOCF=last observation carried forward, SD=standard deviation

Table 32: PANSS total score – Change from baseline to endpoint (LOCF) by age and weight group - –PSZ-3001- ITT set

Age and Weight Group: <15 yrs / <51kg	Placebo (N=6)	Paliperidone ER Low (N=8)	Paliperidone ER Medium (N=8)	Paliperidone ER High (N=4)
Baseline				
N	6	8	8	4
Mean (SD)	91.5 (15.25)	82.8 (9.53)	89.1 (16.23)	97.8 (17.44)
Median (Range)	82.5 (80;114)	83.0 (71;98)	86.0 (71;119)	97.5 (78;118)
End Point				
N	6	8	8	4
Mean (SD)	76.2 (8.23)	76.4 (21.01)	73.0 (28.53)	97.0 (26.62)
Median (Range)	78.5 (61;83)	80.0 (45;102)	70.0 (43;112)	89.5 (74;135)
Change from Baseline				
N	6	8	8	4
Mean (SD)	-15.3 (13.35)	-6.4 (13.53)	-16.1 (14.14)	-0.8 (22.47)
Median (Range)	-15.0 (-33;2)	-5.0 (-26;13)	-16.0 (-35;3)	-4.5 (-24;30)
Age and Weight Group: <15 yrs/ ≥ 51 kg	Placebo (N=3)	Paliperidone ER Low (N=8)	Paliperidone ER Medium (N=7)	Paliperidone ER High (N=9)
Baseline				
N	3	8	7	9
Mean (SD)	85.3 (7.02)	96.4 (9.23)	98.4 (9.02)	90.9 (15.80)
Median (Range)	86.0 (78;92)	93.0 (86;111)	96.0 (84;109)	85.0 (70;119)
End Point				
N	3	8	7	9
Mean (SD)	81.3 (5.13)	89.6 (18.86)	83.6 (16.20)	81.2 (17.28)
Median (Range)	80.0 (77;87)	88.5 (56;111)	88.0 (56;98)	75.0 (62;115)
Change from Baseline				
N	3	8	7	9
Mean (SD)	-4.0 (5.57)	-6.8 (23.09)	-14.9 (11.82)	-9.7 (19.16)
Median (Range)	-5.0 (-9;2)	-3.0 (-52;23)	-11.0 (-29;4)	-9.0 (-49;18)

Table 33: PANSS total score – Change from baseline to endpoint (LOCF) by age and weight group - –PSZ-3001- ITT set

Age and Weight Group: ≥ 15 years/ <51 kg	Placebo (N=8)	Paliperidone ER Low (N=11)	Paliperidone ER Medium (N=8)	Paliperidone ER High (N=9)
Baseline				
N	8	11	8	9
Mean (SD)	95.6 (13.73)	92.3 (13.54)	95.1 (18.06)	90.9 (16.48)
Median (Range)	98.0 (78;118)	89.0 (73;118)	98.0 (70;116)	90.0 (63;116)
End Point				
N	8	11	8	9
Mean (SD)	81.9 (31.23)	76.3 (22.42)	73.3 (26.40)	80.6 (16.77)
Median (Range)	86.5 (44;120)	75.0 (45;121)	74.0 (33;115)	78.0 (51;114)
Change from Baseline				
N	8	11	8	9
Mean (SD)	-13.8 (23.38)	-16.0 (19.49)	-21.9 (17.11)	-10.3 (11.43)
Median (Range)	-4.0 (-54;10)	-23.0 (-45;10)	-20.5 (-53;-1)	-4.0 (-34;1)
Age and Weight Group: ≥ 15 years/ ≥ 51 kg	Placebo (N=34)	Paliperidone ER Low (N=27)	Paliperidone ER Medium (N=25)	Paliperidone ER High (N=25)
Baseline				
N	34	27	25	25
Mean (SD)	89.7 (11.62)	92.6 (13.06)	87.5 (12.52)	91.0 (12.22)
Median (Range)	88.5 (65;112)	95.0 (70;118)	84.0 (69;111)	89.0 (72;117)
End Point				
N	34	27	25	25
Mean (SD)	84.2 (21.63)	83.5 (18.08)	70.6 (20.06)	72.3 (16.00)
Median (Range)	82.0 (36;129)	79.0 (55;117)	69.0 (42;126)	72.0 (49;102)
Change from Baseline				
N	34	27	25	25
Mean (SD)	-5.5 (21.08)	-9.1 (13.43)	-16.9 (14.63)	-18.7 (13.48)
Median (Range)	-4.0 (-59;28)	-6.0 (-43;9)	-15.0 (-51;19)	-18.0 (-62;1)

Negative change indicates improvement.

Table 34: PANSS total score – Change from baseline to endpoint acute (day 56) (LOCF) by age group- PSZ-3003- ITT set

Age Group: 12-14	Paliperidone ER (N=33)	Aripiprazole (N=30)
Baseline		
N	33	30
Mean (SD)	94.2 (10.56)	96.7 (12.35)
Median (Range)	94.0 (69;112)	96.0 (77;116)
End Point Acute (Day 56)		
N	33	30
Mean (SD)	76.8 (15.07)	73.0 (15.02)
Median (Range)	79.0 (48;101)	72.0 (36;98)
Change from Baseline		
N	33	30
Mean (SD)	-17.5 (10.31)	-23.7 (10.53)
Median (Range)	-18.0 (-41;3)	-22.0 (-53;-11)
Age Group: 15-17	Paliperidone ER (N=79)	Aripiprazole (N=84)
Baseline		
N	79	84
Mean (SD)	87.6 (12.39)	90.3 (11.62)
Median (Range)	87.0 (63;122)	92.0 (65;113)
End Point Acute (Day 56)		
N	79	84
Mean (SD)	67.5 (17.02)	71.9 (17.42)
Median (Range)	68.0 (35;106)	69.5 (30;128)
Change from Baseline		
N	79	84
Mean (SD)	-20.1 (15.01)	-18.5 (15.57)
Median (Range)	-19.0 (-79;5)	-17.5 (-49;26)

Note: Negative change in score indicates improvement.
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Source: PSZ-3003/Table 32.

Table 35: PANSS total score – Change from baseline to endpoint acute (day 56) (LOCF) by baseline body weight group- PSZ-3003- ITT set

Baseline Body Weight Category: <51 kg	Paliperidone ER (N=37)	Aripiprazole (N=29)
Baseline		
N	37	29
Mean (SD)	89.4 (12.71)	87.3 (12.93)
Median (Range)	89.0 (63;112)	86.0 (65;113)
End Point Acute (Day 56)		
N	37	29
Mean (SD)	69.4 (16.82)	68.4 (17.77)
Median (Range)	67.0 (40;103)	70.0 (36;115)
Change from Baseline		
N	37	29
Mean (SD)	-20.1 (13.24)	-18.9 (15.89)
Median (Range)	-19.0 (-48;3)	-17.0 (-53;17)
Baseline Body Weight Category: ≥ 51 kg	Paliperidone ER (N=75)	Aripiprazole (N=85)
Baseline		
N	75	85
Mean (SD)	89.6 (12.05)	93.6 (11.43)
Median (Range)	89.0 (65;122)	93.0 (67;116)
End Point Acute (Day 56)		
N	75	85
Mean (SD)	70.7 (17.08)	73.5 (16.32)
Median (Range)	71.0 (35;106)	72.0 (30;128)
Change from Baseline		
N	75	85
Mean (SD)	-18.9 (14.14)	-20.2 (14.16)
Median (Range)	-18.0 (-79;5)	-18.0 (-49;26)

Note: Negative change in score indicates improvement.
tefpant26_t1.rtf generated by tefpant26.sas, 12JUL2012 15:01
Source: PSZ-3003/Table 33.

Figure 20 : Mean (+/-) PANSS Total Score by age- LOCF- study PSZ-3002: Open Label ITT set

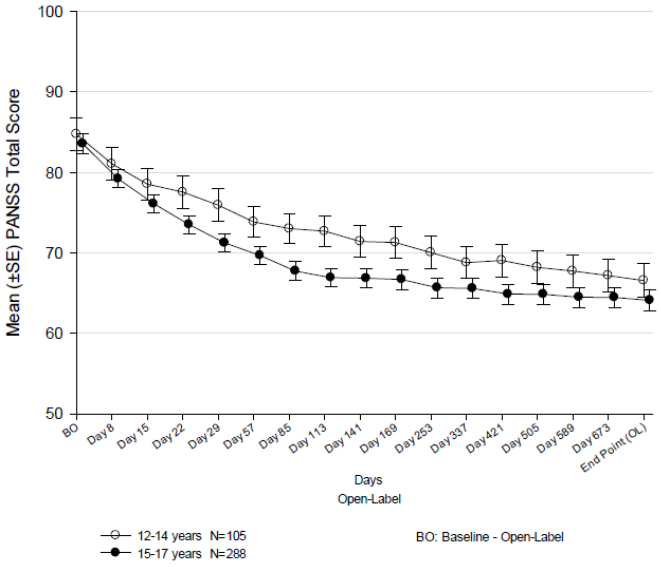


Figure 21 : Mean (+/-) PANSS Total Score by body weight- LOCF- study PSZ-3002: Open Label ITT set

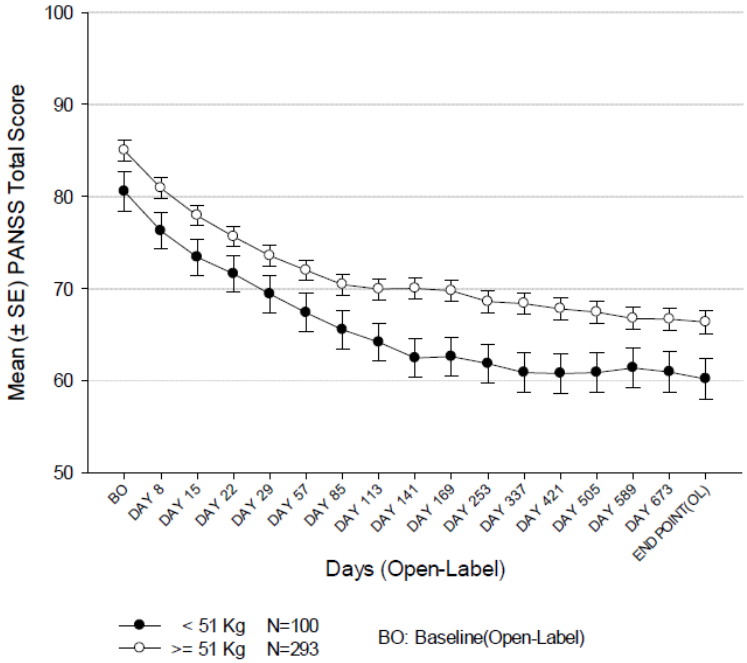
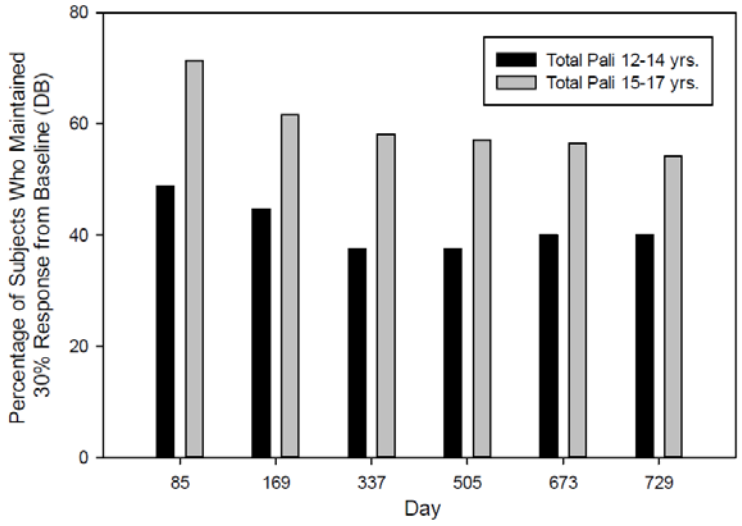


Figure 22: Percentage of subjects who maintained response from baseline (DB) based on PANSS 30% criteria by age – PSZ-3002- Open Label ITT set

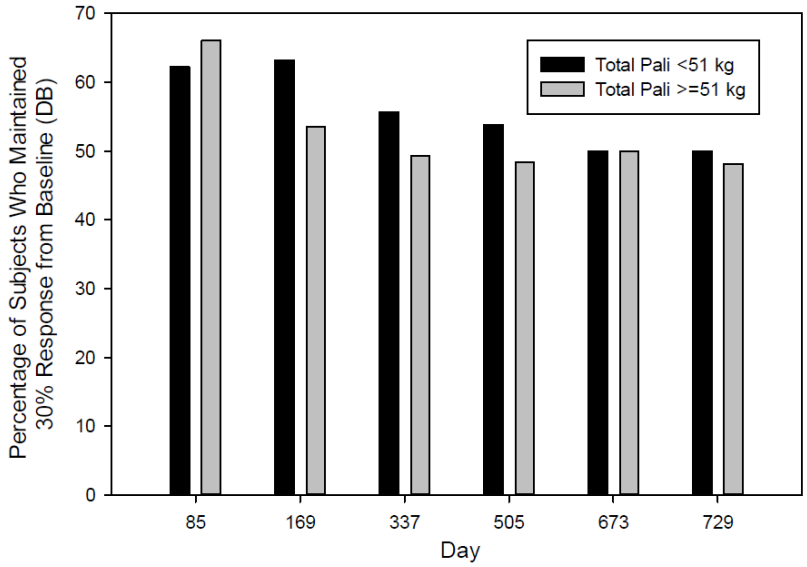


Number of Subjects

Day	85	169	337	505	673	729
12-14 yrs	41	38	32	32	30	30
15-17 yrs.	98	86	62	56	46	48

The denominator for each timepoint includes subjects with data for both Day 85 (OPEN) and the specified timepoint. A subject who maintains >= 30% improvement from Day 85 (OPEN) to the specified time point is considered a maintained responder. Improvement is determined based on DB Baseline value. The Age group is based on the subject's age at baseline (DB) for those subjects enrolled from PSZ-3001. Subjects who are 18 at the start of the open-label study are considered in the 15-17 group.

Figure 23: Percentage of subjects who maintained response from baseline (DB) based on PANSS 30% criteria by weight group – PSZ-3002- Open Label ITT set



Number of Subjects

Day	85	169	337	505	673	729
<51 kg	45	38	27	26	24	24
>=51 kg	94	86	67	62	52	54

The denominator for each timepoint includes subjects with data for both Day 85 (OPEN) and the specified timepoint. A subject who maintains >= 30% improvement from Day 85 (OPEN) to the specified time point is considered a maintained responder. Improvement is determined based on DB Baseline value The weight group is based on the subject's weight at baseline (DB) for those subjects enrolled from PSZ-3001.

2.4.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The presented data (study PSZ-3001, PSZ-3003 and PSZ-3002) are part of an agreed PIP. The studies were conducted in line with the Guideline on clinical investigation of medicinal products in the treatment of schizophrenia (EMA/CHMP/40072/2010 Rev.1). Studies in subjects younger than 12 years of age were not conducted given the low incidence of schizophrenia and the difficulty of establishing a diagnosis in this age group. All three phase 3 studies used similar entry criteria, restrictions to concomitant medications, rating scales and endpoints. The studies however differed with regard to duration of treatment and assessment time points, blinding (double-blind [PSZ-3001 and 3003] or open-label [PSZ-3002]), control (placebo [PSZ-3001] or active [PSZ-3003]) and dosing regimen (fixed [PSZ-3001] or flexible dose of paliperidone ER [PSZ-3003 and 3002]). Diagnosis of schizophrenia was made according to the DSM-IV at least 1 year before screening.

Given the study designs were not the same and considering the additional assumptions that have to be made to conduct a meta-analysis, the CHMP considered highly questionable whether the meta-analysis of these studies was valid and meaningful and whether it provided valid information beyond the single studies.

The change from baseline in the PANSS total score at endpoint was the primary efficacy variable in studies PSZ-3001, PSZ-3003 and PSZ-3002 (exploratory only). Secondary endpoints included changes from baseline to endpoint in CGI-S score, CGAS score and Sleep VAS (only PSZ-3001) and PSP score (only PSZ-3003). The choice of primary and secondary endpoints was considered adequate by the CHMP. No cognitive endpoint was included with the exception of the Cognitive Assessment Battery of Tests which was performed on an exploratory basis in the open-label study PSZ-3002. Additional analyses such as responder rate, change from baseline in PANSS Factor and Subscale Scores were undertaken and underline the clinical meaningfulness of these endpoints.

Studies PSZ-3001 and PSZ-3003 included a total of 18 European patients.

Study PSZ-3001

There was one major protocol amendment prior study enrolment. This was related to the study design with the objective of testing the entire range of effective doses of paliperidone ER in adults (3-12mg) as well as a lower dose (1.5mg) to determine the least effective dose. Weight based doses were chosen to minimize the risk of exposing lower weight adolescents (≥ 29 kg and < 51 kg) to high doses of paliperidone ER and higher weight adolescents (≥ 51 kg) to too low of a dose, considering that lower-weight subjects could have nearly double the drug exposure of higher-weight subjects on the basis of available PK data from PSZ-1001. However with this approach, efficacy data are missing for the 3 mg dose in patients weighing ≥51 kg and for the 12 mg dose in patients weighing < 51 kg.

The time pattern for total number of withdrawals was similar for all groups up to day 21 when higher withdrawal rate in the placebo group and to a lower extent in the paliperidone ER Low group became apparent. This is the time point where subjects could enter the open label phase study (PSZ-3002) and thus this finding may be expected.The rate of withdrawals in the paliperidone ER low group had a higher number of withdrawals due to Lack of Efficacy (26%) than the other dose groups. A total of 29% withdrew from the study and of those 17% from the paliperidone ER medium treatment group withdrew. The study duration was short and the withdrawal rate was high. The study was conducted all over the world with a very limited number of patients from the EU. Only 10 patients (5%) from Romania were included. Overall baseline disease severity as measured by PANSS total score and CGI-S

score was comparable across all arms but the paliperidone ER group Medium had fewer subjects with moderate CGI-S score(n=19, 40%) and more subjects with high CGI-S scores than the other groups.

Taking the improvements over time observed in the placebo completers and the high drop-out rate in the placebo group into account, the LOCF analysis was not necessarily conservative. The pre-specified sensitivity analyses are acknowledged; in particular, the MMRM analysis is considered relevant. However, the clinical interpretation of the worst-rank analysis is difficult as this analysis "mixes" effects on the variables 'change in PANSS total score' and 'time to treatment discontinuation due to lack of efficacy', whereby the clinical relevance of the latter is questionable, particularly since no clear criteria to determine lack of efficacy seemed to have been applied. It is generally recommended to minimize the occurrence of missing data in a clinical trial; therefore allowing discontinuation of study for lack of efficacy in the protocol may be considered as an issue. The CHMP noted that the recommended criterion for lack of efficacy in the study protocol was an increase of 20% in PANSS total score; however, the mean increase for the drop-outs in the placebo group was actually lower (9%). The pattern of PANSS total scores for patients who dropped out due to lack of efficacy was found to be different from those who completed the study, supporting that lower efficacy was indeed observed at drop-out time . Consequently, the CHMP considered the worst-case analysis as conservative. The patterns of PANSS total scores for patients who dropped out due to lack of efficacy suggested that the PANSS total scores were not temporarily but continuously increased for most of these patients, meaning that the imputation of the best value leads to an overestimation of the placebo effect. In the best observation carried forward analysis, the treatment effects were generally lower compared to the primary analysis, which is explained by a higher drop-out rate in the placebo group, leading to a conservative analysis. A significant treatment effect was however found for the medium dose group (<51 Kg: 3 mg/day; ≥51 Kg:6 mg/day) but not for the high (<51 Kg:6 mg/day; ≥51 Kg:12 mg/day) and the low (1.5 mg/day) dose group, which was consistent with the primary analysis.

Studies PSZ-3003 and PSZ-3002

In study PSZ-3003, the age distribution was not homogenous as across the treatment groups 12-14 year olds were only accounted for about 1/3 of the study population. Baseline disease severity was similar across the groups.. The LS Mean Change from baseline on PANSS total score decreases up to day 140 and then increases in both treatment groups at day 182. According to the MAH, this finding was due to the only subject enrolled in Slovakia and an analysis excluding this subject was performed showing continuous decrease through day 182 in both treatment groups. Since consistent findings were observed when including this patient and the region as a factor (instead of country) in the ANCOVA analysis, this explanation was considered plausible by the CHMP. A total of 15 European patients were recruited.

In study PSZ-3002, the design was open label without any comparator or placebo thus making difficult the assessment of the magnitude of treatment effect. The efficacy data for this study were considered exploratory only.Although the withdrawal rate was high with a total of 55% completing study of which 184 completed the two years which means a total of 46% completed the total two year study. This is however not unexpected in this population as the study had a long duration. Seventy-three (73%) of subjects were 15 years and older. Only 10 European patients were included.

Efficacy data and additional analyses

Study PSZ-3001

Results indicated that the study achieved its primary objective by demonstrating that at least one paliperidone ER weight-based group was statistically superior to placebo in improving the symptoms of schizophrenia as measured by the change in PANSS total score from baseline to endpoint (LOCF analysis).

Only the medium paliperidone ER weight-based group (<51 Kg: 3 mg/day; ≥51 Kg: 6 mg/day) was statistically superior to placebo in improving the symptoms of schizophrenia as measured by the change in PANSS total score from baseline to endpoint (p=0.006). The paliperidone ER Low (1.5mg/day) and High (<51 Kg: 6 mg/day; ≥51 Kg: 12 mg/day) groups did not show statistical significance in comparison to placebo on the primary endpoint (p= 0.508 and 0.086, respectively).

The analysis across weight categories indicated that for adolescents < 51 kg, only the medium dose group (3 mg) separated from placebo whereas for adolescent ≥ 51 kg , the medium (6mg) and high dose groups (12 mg) separated from placebo.

The consistency of the treatment effect across the body weight categories was explored by including the treatment-by-baseline body weight interaction in the model used for primary analysis. This interaction was significant at the pre-specified 10% level (p=0.08), possibly indicating inconsistent treatment effects across body weight categories.

These findings further supported the need for weight based dosing recommendation (see below justification for the dose).

Efficacy analyses of the secondary endpoints including CGI-S, CGAS, sleep VAS and PANSS factor scores were consistent with the findings of the primary efficacy analysis. The results for the responder rates (≥20 and 30 %) support the clinical relevance of the primary endpoint. As with the primary efficacy endpoint the medium dose treatment group performed the best. The CHMP noted that this completion rate was higher than the rates in the 6-week studies in adults (range 43 to 66%).The proportion of subjects who completed the study was higher in the 3 mg (81%), 6 mg (82%), and 12 mg (77%) dose groups than in the 1.5 mg dose group (65%) and the placebo group (51%). The proportion of subjects who were withdrawn due to lack of efficacy was higher in the placebo group (39%) and 1.5 mg dose group (26%) than in the other paliperidone ER dose groups (ranging from 0% in the 3 mg dose group to 9% in the 6 mg dose group).

Post-hoc analyses by actual dose received by the subjects showed statistically significant improvement relative to placebo in the PANSS total scores at endpoint (LOCF) for the paliperidone ER 3, 6, and 12 mg dose groups. However, no clear dose response pattern was observed, which might be due to the low number of patients in the 3 mg dose group (n=16). The difference of LS mean changes from baseline to endpoint was -11.5, -6.8, and -9.0, respectively; nominal p values of 0.016, 0.044, and 0.014, respectively, with no multiplicity adjustment. Results in the 1.5 mg dose group were not statistically significant (difference of LS means of -2.1; p=0.507). The changes in mean PANSS total score from baseline to endpoint for the 3 mg actual dose groups were comparable to those observed in studies in the adult population (-11.1 for the 3mg dose for the pooled data of the three 6 week placebo-controlled studies [R076477-SCH-303, 304 and 305] in adults). However, the effect sizes of the 6mg and the 12 mg actual dose groups were less comparable (-11.0 for the 6 mg and -14.5 for the 12 mg dose groups in the pooled adult studies). The higher placebo response in adolescents(-7.9 versus -4.8) that has been also described in the literature may be associated with such findings. The improvement in the paliperidone ER Medium group achieved statistical significance compared to the paliperidone ER Low group (p = 0.014). The differences between the paliperidone ER High and Medium group or High and Low group did not achieve statistical significance (p = 0.289 and p = 0.170, respectively).

Similarly to the overall study results, the medium dose group showed better improvement in PANSS total score in all analysed subgroups : (a) <15 yrs/<51kg, (b) <15 yrs/≥ 51 kg, (c) ≥ 15 yrs/<51 kg, and (d) ≥15 yrs/≥51 kg (see Tables 32-33). Among patients between 12-14 years and patients <51 kg, a better improvement in PANSS total score compared to placebo was observed only in the medium (3 mg) dose group, while a better dose-improvement trend was observed in patients 15-17 years old

or patients ≥51kg (See Tables 30-31). However the relatively small proportion of patients aged 12-14 years is of concern to conclude on these efficacy findings. In addition, the effect on the PANSS total score was considered weaker in this population, in the medium dose group, the difference of LS mean changes from baseline to endpoint was -15.5 in patients aged 12-14 years and -18.1 in patients aged 15-17 years, respectively.

Based on additional ANCOVA and regression analyses, the treatment response was claimed to be independent of age when body weight was taken into account. However, as the sample sizes are even smaller in these subgroups, these comparisons should be only taken into account as exploratory findings.

Study PSZ-3003

This study provided maintenance data over 26 weeks. However, it did not meet its primary objective, i.e. paliperidone ER did not demonstrate superior efficacy compared to aripiprazole. Nevertheless, robust and clinically meaningful reductions (ie, improvements) in mean PANSS total score from baseline to endpoint acute (Day 56, LOCF) in the paliperidone ER (-19.3) and aripiprazole (-19.8) groups were observed. The confidence interval of the difference between the two groups excluded larger changes than 3.8 to the advantage of aripiprazole. This finding cannot be considered a clinically relevant difference between the two treatments and therefore the study could only be interpreted as showing non inferiority. The changes from baseline for aripiprazole are of a similar magnitude as in previous studies in a paediatric population, and for paliperidone ER in the same magnitude as in study 3001. A PP analysis was provided and was found consistent with the ITT analysis, with a larger upper bound of the 95% CI (4.38 versus 3.76). In the absence of adequate justification for the assay sensitivity in study PSZ-3003, the CHMP considered that non inferiority conclusions could not be fully claimed based on this study.

The analyses of the secondary efficacy endpoints were consistent with the findings from the primary efficacy analyses. The results indicated that paliperidone ER and aripiprazole had similar treatment effects with regard to decreasing the PANSS total scores over the 26-week period. The mean (SD) decrease in PANSS total score from baseline to endpoint (Day 182) was -25.6 (16.88) for paliperidone ER and -26.8 (18.82) for aripiprazole. From endpoint acute (Day 56) to endpoint (Day 182), over 50% of the subjects in both treatment groups remained clinically stable. Comparable long-term improvements by Day 182 for paliperidone ER and aripiprazole treatments were noted with regard to the change from baseline to endpoint (Day 182) for the CGI-S score and in the PSP scale. In addition, there was no statistical significant differences in responder rates (paliperidone: 76%, aripiprazole: 81.6%, p=0.444). However it is difficult to draw any conclusions on the magnitude of difference since no confidence intervals have been presented. Furthermore, at least 75% of subjects completed the 26-week study in both groups and the withdrawal rates due to lack of efficacy were low (4% for paliperidone and 10% for aripiprazole). The longitudinal analysis using MMRM performed on the observed-case data and the worst-rank analysis corroborated the findings from the LOCF analysis. An analysis using the per-protocol analysis set (excluding subjects who had major protocol deviations from the ITT analysis set) was also conducted as a sensitivity analysis for the primary analysis. Results from this analysis were consistent with the ITT analysis.

In subgroup analyses, concerning the primary study endpoint related to change in PANSS total score, similar results were obtained in age and weight groups, at day 56 comparing aripiprazole and paliperidone treated patients. Similarly to the short term efficacy, the maintenance of the effect on the PANSS total score was considered weaker in this population in the paliperidone ER group, the difference of LS mean changes from baseline to endpoint was -17.5 in patients aged 12-14 years and -20.1 in patients aged 15-17 years, respectively. However, slightly better results for aripiprazole treatment compared to paliperidone in subjects aged between 12-14 years, 15-17 years and subjects≥51 kg were observed in maintaining clinical stability over 26 weeks (see Tables 34-35).

Study PSZ-3002

Improvement in the PANSS total scores were observed during the first 3 months of the open-label treatment in all 3 treatment groups. The improvements in PANSS total scores observed during the first 3 months were maintained during the remaining portion of the study. The subjects who entered the open label study directly without prior participation in PSZ-3001 and those who rolled over from the placebo arm in study PSZ-3001 showed a greater decrease from baseline in PANSS total score compared to those rolling over from the active treatment arms. This is probably due to a higher open label baseline PANSS total score, and therefore expected. All groups seem to converge towards similar levels in PANSS total score over time. The primary efficacy variable for the exploratory secondary objective was the change from open-label baseline to open-label endpoint in the PANSS total score. The efficacy analysis was based on the ITT analysis set which comprised of 393 subjects. There were mean decreases in PANSS total scores (indicating improvement) after administration of paliperidone ER from open-label baseline to open-label endpoint, the highest means (SD) change (-22.4 [22.25]) was noted in the Paliperidone (NO DB)/Paliperidone treatment group and the lowest change (-12.6 [19.92]) was noted in the Paliperidone (DB)/Paliperidone treatment group. The mean (SD) change in PANSS total score from double-blind baseline to open-label endpoint was slightly higher in the Paliperidone (DB)/Paliperidone treatment group (-27.5 [19.09]) than in the Placebo/Paliperidone treatment group (-25.7 [16.01]).Other efficacy analyses including the CGI-S, CGAS, sleep VAS, and PANSS factor scores corroborated the findings of the primary efficacy variable. Small improvements in performance on tests of cognitive function were observed in all groups from open-label baseline to the 6-month time point for most domains. These data are supportive that the clinical efficacy of paliperidone ER continues beyond 6 weeks and is maintained with long-term therapy up to two years.

According to the Schizophrenia Guideline (EMA/CHMP/40072/2010 Rev.1), data on maintenance of effect may be extrapolated from adults to adolescents as of the age of 15 years. The overall data to support extrapolation of long-term efficacy from 12 years onwards were not considered to be sufficient. Subgroup analyses based on age and weight did not reveal any significant difference in improvement in PANSS during the course of 2 year treatment. However, among younger adolescents a lower percentage of subjects who maintained a 30% PANSS response over time was observed compared to patients in 15-17 years. No difference was observed between weight groups (See Figures 20-23).Hence the CHMP maintains its previous conclusion that the maintenance of the efficacy in patients younger than 15 years remains to be established.

Overall discussion on efficacy

Following the CHMP concerns over the lack of sufficient evidence of short term and long term efficacy in subjects aged between 12-14 years, the MAH proposed to restrict the proposed indication to treatment of schizophrenia in adolescents 15 years and older. As discussed above, better dose-improvement trend in PANSS total score was observed in patients 15-17 years old. In addition, consistent efficacy findings were observed for the subgroup analyses (≥15 years, ≥51 kg and <51 kg) provided at the CHMP request on the secondary efficacy endpoints of particular clinical relevance. To provide further supporting evidence for the short term efficacy in the 15 to 17 year age range, the MAH repeated the ANCOVA analysis for the primary and secondary efficacy variables in the placebo controlled study (PSZ-3001) in the 15 to 17 year subgroup. Statistically significant differences versus placebo were observed in both the Medium (<51 Kg: 3 mg/day; ≥51 Kg: 6 mg/day, p=0.005) and High (<51 Kg: 6 mg/day; ≥51 Kg: 12 mg/day, p=0.012) dose groups of paliperidone ER for the primary endpoint (change from baseline to endpoint in PANSS total score). According to the MAH, these results are more robust than those observed for the total population (12 to 17 years), which only

showed a statistically significant difference versus placebo for the Medium dose level (<51 Kg: 3 mg/day; ≥51 Kg: 6 mg/day,).

Taking into account the overall short term and long term efficacy data (as discussed above) and additional subgroup analyses provided for the 15 to 17 year subgroup, the CHMP considered there was sufficient evidence to support the efficacy of paliperidone ER in the treatment of schizophrenia in patients 15 years and older.

Justification of the dose

According to the MAH, results from the double-blind placebo-controlled study PSZ-3001 established the efficacy of paliperidone ER in improving the symptoms and severity of schizophrenia compared to placebo based on the primary analysis of weight-based dose groups. Analyses by actual dose received indicated efficacy across the dose range of 3 to 12 mg/day, with 3 mg/day being the minimum effective dose; whereas no statistical separation from placebo was demonstrated for the 1.5 mg for any of the efficacy variables. Only the medium dose group comprising the doses of 3 mg and 6 mg (for adolescents < 51 kg and ≥ 51 kg, respectively) was efficacious from a strict interpretation viewpoint, as the high dose group (<51 Kg: 6 mg/day; ≥51 Kg: 12 mg/day) was not statistically significantly different from placebo (p=0.086). Post-hoc analysis by actual dose group indicated that there is a treatment effect of paliperidone ER in the dose range of 3 mg to 12 mg/day.

From the CHMP viewpoint, no clear dose-response pattern was identified with respect to efficacy for the primary endpoint for the paliperidone ER 3, 6 and 12 mg dose groups (difference of LS mean changes from baseline to endpoint of -11.5, -6.8, and -9.0, respectively; nominal p values of 0.016, 0.044, and 0.014, respectively). This might be due to the low number of patients in the 3 mg dose group (n=16). The improvement in the paliperidone ER Medium group achieved statistical significance compared to the paliperidone ER Low group (p = 0.014). The differences between the paliperidone ER High and Medium group or High and Low group did not achieve statistical significance (p = 0.289 and p = 0.170, respectively). A statistically significant dose-response relationship was found using a linear trend test and the non-parametric Jonckhere-Terpstra trend test (post-hoc analyses). However, considering the observed responses for the actual dose groups, a (linear) trend in the dose-response relationship appears unlikely, i.e. the fit of the linear model to describe the dose-response relationship is probably poor. The statistical significance of the trend tests is most likely driven by the differences between the placebo group/low dose group and the higher dose groups, but there is no clear evidence of a dose-response relationship for the higher doses 3, 6 and 12mg. Overall, the number of patients in the lower age group (the only one that received the 3 mg) was only around one quarter of the whole study population and data in this subpopulation are very limited. On this basis and considering the PK findings suggesting a dependence of paliperidone clearance on the patient's body weight (see 2.3.4), the CHMP considered that the proposed dose ranging (3 to 12 mg/day) was not adequate for the lower-weight patients, although the efficacy results were overall consistent with the adult data. This is not only due to the efficacy data but also due to the safety data where a clear dose-response pattern was observed for several safety parameters including common adverse events (somnolence, akathisia, tremor, and dystonia); EPS related adverse events (hyperkinesia, dystonia, and tremor) and associated use of anticholinergic medications; and mean increases in body weight and BMI (see 2.5.7). Regarding patients older than 15 years and ≥ 51 kg, the CHMP was of the opinion that the proposed dose range (3 to 12 mg/day) could be considered since these patients are more likely to have similar PK profile than in adults. To address the dosing concern over the lower weight patients, the MAH proposed to revise the initial dosing recommendation by setting a lower maximum recommended dose of 6 mg for children weighing <51 kg instead of 12 mg. The maximum recommended dose for children weighing ≥ 51 kg was proposed to be maintained at 12 mg, similarly to the adult population. Given an individual dose titration strategy was supported by PK/PD data, the CHMP agreed with the proposed

revised posology. Taking into account the pharmacokinetic profile of the product (prolonged release formulation) and the available efficacy data on the 1.5 mg dose of paliperidone ER, a lower increasing increment of 1.5 mg was not considered beneficial in the intended population.

Relevance of the data in the EU population

According to the MAH, difficulties were encountered in enrolling subjects from the EU in Study PSZ-3001 due to the use of a placebo control. Enrolment of subjects into Study PSZ-3003 from the EU was also difficult as the active control (aripiprazole) was already approved for use in adolescents within the EU and is often used as a first line treatment. This accounted for the relatively low proportion of subjects from the EU in the Phase 3 studies. There were only 5% and 6.6% of subjects enrolled from EU countries in PSZ-3001 and PSZ-3003, respectively. In the long-term, open-label safety and tolerability study PSZ-3002, 19.8% of subjects were from the EU countries.

On the other hand comparative data with respect to baseline characteristics and pre-treatment patterns in US/EU versus non-EU/non-US were presented. Overall, it can be concluded that subject population in paliperidone ER studies could be considered to be representative of the adolescent schizophrenia population in Europe. Subjects in the US were generally heavier in comparison with subjects from Asia and Eastern Europe but subjects with heavier body weight (≥51 kg) showed similar or slightly better efficacy compared to those with lighter body weight (<51 kg) and there were no apparent differences with regard to safety findings between the 2 weight subgroups. Even though a higher proportion of subjects from EU/US than those from non-EU/non-US received atypical antipsychotics, the most frequently used atypical or typical antipsychotics were similar. Overall, it can be accepted that the data from the 3 paliperidone ER studies are applicable to the adolescent patients in Europe.

2.4.7. Conclusions on the clinical efficacy

Overall, the CHMP concluded that the efficacy (short term and maintenance of the effect) of Invega for the treatment of schizophrenia in 15 years and older has been sufficiently demonstrated.

2.5. Clinical safety

The safety of paliperidone ER in the treatment of schizophrenia in children and adolescents was evaluated in the clinical studies that were already discussed in the clinical efficacy: PSZ-3001, PSZ-3002, PSZ-3003 and PSZ-1001. No pooled data have been provided due to a different study design for these studies.

Known safety issues with paliperidone are extrapyramidal side effects (EPS), glucose related adverse events, potentially prolactin levels as well as other adverse events of special interest such as suicidality, aggression, agitation, somnolence, sedation, seizures, convulsions, neuroleptic malignant syndrome (NMS), sexual maturation, weight gain and cardiac events.

Subjects with a history or presence of significant cardiac events/diseases and endocrine diseases were excluded from the studies.

2.5.1. Patient exposure

In total, 545 adolescent subjects with schizophrenia received at least 1 dose of paliperidone ER during the three Phase III studies. The mean duration of exposure to paliperidone ER for these subjects was 379.4 days. Data are presented in Tables 36 and 37.

Table 36: Cumulative Frequency Distribution of Duration (Days) of Exposure to Study Drug (PSZ-3003).

Duration Days	Paliperidone ER (N=113) n (%)	Aripiprazole (N=114) n (%)
≥1 day	113 (100)	114 (100)
≥15 days	111 (98)	112 (98)
≥29 days	109 (96)	107 (94)
≥57 days	99 (88)	98 (86)
≥99 days	93 (82)	95 (83)
≥141 days	87 (77)	90 (79)
≥180 days	75 (66)	80 (70)

Exposure days on drug only.

Table 37: Cumulative Frequency Distribution of Duration (Days) of Paliperidone ER Exposure – Double - Blind and Open-Label Studies (PSZ-3001/PSZ-3002).

Duration Days	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=243) n (%)	Pali/NO OL (N=32) n (%)	Total (N=432) n (%)
≥ 1 days	39 (100)	118 (100)	243 (100)	32 (100)	432 (100)
≥ 31 days	35 (90)	118 (100)	220 (91)	16 (50)	389 (90)
≥ 61 days	32 (82)	115 (97)	205 (84)	0	352 (81)
≥ 91 days	31 (79)	111 (94)	198 (81)	0	340 (79)
≥ 121 days	30 (77)	107 (91)	192 (79)	0	329 (76)
≥ 151 days	27 (69)	104 (88)	180 (74)	0	311 (72)
≥ 181 days	27 (69)	101 (86)	170 (70)	0	298 (69)
≥ 211 days	22 (56)	95 (81)	159 (65)	0	276 (64)
≥ 241 days	22 (56)	77 (65)	156 (64)	0	255 (59)
≥ 271 days	21 (54)	77 (65)	147 (60)	0	245 (57)
≥ 301 days	21 (54)	76 (64)	147 (60)	0	244 (56)
≥ 331 days	21 (54)	76 (64)	146 (60)	0	243 (56)
≥ 361 days	21 (54)	76 (64)	142 (58)	0	239 (55)
≥ 391 days	21 (54)	73 (62)	142 (58)	0	236 (55)
≥ 451 days	21 (54)	72 (61)	134 (55)	0	227 (53)
≥ 511 days	20 (51)	68 (58)	128 (53)	0	216 (50)
≥ 571 days	20 (51)	66 (56)	124 (51)	0	210 (49)
≥ 631 days	20 (51)	64 (54)	115 (47)	0	199 (46)
≥ 691 days	19 (49)	59 (50)	108 (44)	0	186 (43)
≥ 731 days	11 (28)	58 (49)	40 (16)	0	109 (25)

Table includes subjects who were exposed to the drug in PSZ-3001 but not in PSZ-3002

2.5.2. Adverse events

Data are presented in Tables 38 -40.

Table 38: PSZ-3001- Treatment emergent adverse events (TEAEs) in at least 5 % of Subjects in any dose group

Body System or Organ Class Dictionary-Derived Term	Placebo (N=51) n (%)	Pali ER 1.5 mg (N=54) n (%)	Pali ER 3 mg (N=16) n (%)	Pali ER 6 mg (N=45) n (%)	Pali ER 12 mg (N=35) n (%)	Total Paliperidone (N=150) n (%)
Total no. subjects with adverse events	30 (58.8)	27 (50.0)	8 (50.0)	30 (66.7)	27 (77.1)	92 (61.3)
Nervous system disorders	6 (11.8)	14 (25.9)	7 (43.8)	16 (35.6)	23 (65.7)	60 (40.0)
Somnolence	1 (2.0)	3 (5.6)	2 (12.5)	6 (13.3)	9 (25.7)	20 (13.3)
Akathisia	0	2 (3.7)	1 (6.3)	5 (11.1)	6 (17.1)	14 (9.3)
Headache	2 (3.9)	5 (9.3)	1 (6.3)	2 (4.4)	5 (14.3)	13 (8.7)
Tremor	0	1 (1.9)	1 (6.3)	3 (6.7)	4 (11.4)	9 (6.0)
Dystonia	0	1 (1.9)	0	2 (4.4)	3 (8.6)	6 (4.0)
Cogwheel rigidity	0	0	0	0	4 (11.4)	4 (2.7)
Dizziness	0	1 (1.9)	1 (6.3)	1 (2.2)	1 (2.9)	4 (2.7)
Dyskinesia	0	1 (1.9)	1 (6.3)	1 (2.2)	1 (2.9)	4 (2.7)
Extrapyramidal disorder	0	0	1 (6.3)	0	0	1 (0.7)
Psychiatric disorders	18 (35.3)	12 (22.2)	1 (6.3)	6 (13.3)	9 (25.7)	28 (18.7)
Insomnia	11 (21.6)	5 (9.3)	1 (6.3)	3 (6.7)	5 (14.3)	14 (9.3)
Schizophrenia	4 (7.8)	6 (11.1)	0	1 (2.2)	2 (5.7)	9 (6.0)
Agitation	2 (3.9)	3 (5.6)	0	1 (2.2)	0	4 (2.7)
Anxiety	2 (3.9)	0	0	1 (2.2)	3 (8.6)	4 (2.7)
Gastrointestinal disorders	10 (19.6)	2 (3.7)	3 (18.8)	7 (15.6)	5 (14.3)	17 (11.3)
Vomiting	5 (9.8)	0	1 (6.3)	5 (11.1)	1 (2.9)	7 (4.7)
Nausea	6 (11.8)	0	0	1 (2.2)	3 (8.6)	4 (2.7)
Salivary hypersecretion	0	1 (1.9)	1 (6.3)	1 (2.2)	0	3 (2.0)
Gastritis	0	0	1 (6.3)	0	0	1 (0.7)
Mallory-Weiss syndrome	0	0	1 (6.3)	0	0	1 (0.7)
Infections and infestations	4 (7.8)	5 (9.3)	1 (6.3)	4 (8.9)	1 (2.9)	11 (7.3)
Pharyngitis	0	0	1 (6.3)	0	0	1 (0.7)
Investigations	3 (5.9)	6 (11.1)	1 (6.3)	1 (2.2)	1 (2.9)	9 (6.0)
Weight increased	0	4 (7.4)	1 (6.3)	1 (2.2)	1 (2.9)	7 (4.7)
Cardiac disorders	0	0	1 (6.3)	4 (8.9)	2 (5.7)	7 (4.7)
Tachycardia	0	0	1 (6.3)	3 (6.7)	2 (5.7)	6 (4.0)
Reproductive system and breast disorders	0	0	1 (6.3)	2 (4.4)	1 (2.9)	4 (2.7)
Amenorrhoea	0	0	1 (6.3)	0	0	1 (0.7)
Dysmenorrhoea	0	0	1 (6.3)	0	0	1 (0.7)
Metabolism and nutrition disorders	3 (5.9)	1 (1.9)	0	0	1 (2.9)	2 (1.3)
Decreased appetite	3 (5.9)	1 (1.9)	0	0	0	1 (0.7)
Injury, poisoning and procedural complications	1 (2.0)	0	1 (6.3)	0	0	1 (0.7)
Wound	0	0	1 (6.3)	0	0	1 (0.7)

Source: Mod5.3.5.1\PSZ-3001\Table 34
Note: Incidence is based on the number of subjects experiencing at least one AE, not the number of events.
Adverse events are coded using MedDRA Version 11.0.
Pali=paliperidone

Table 39: PSZ-3002- TEAEs in at least 5% of Subjects in any dose group

Body System or Organ Class Dictionary-derived Term	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=243) n (%)	Total (N=400) n (%)
Total no. subjects with adverse events	32 (82.1)	88 (74.6)	221 (90.9)	341 (85.3)
Nervous system disorders	15 (38.5)	52 (44.1)	161 (66.3)	228 (57.0)
Somnolence	10 (25.6)	18 (15.3)	45 (18.5)	73 (18.3)
Headache	4 (10.3)	9 (7.6)	46 (18.9)	59 (14.8)
Akathisia	0	10 (8.5)	42 (17.3)	52 (13.0)
Tremor	1 (2.6)	12 (10.2)	31 (12.8)	44 (11.0)
Dizziness	4 (10.3)	8 (6.8)	13 (5.3)	25 (6.3)
Dystonia	1 (2.6)	6 (5.1)	14 (5.8)	21 (5.3)
Psychiatric disorders	14 (35.9)	35 (29.7)	120 (49.4)	169 (42.3)
Insomnia	7 (17.9)	11 (9.3)	40 (16.5)	58 (14.5)
Schizophrenia	7 (17.9)	12 (10.2)	31 (12.8)	50 (12.5)
Suicidal ideation	0	0	34 (14.0)	34 (8.5)
Anxiety	4 (10.3)	7 (5.9)	15 (6.2)	26 (6.5)
Infections and infestations	11 (28.2)	28 (23.7)	77 (31.7)	116 (29.0)
Nasopharyngitis	3 (7.7)	18 (15.3)	32 (13.2)	53 (13.3)
Gastrointestinal disorders	4 (10.3)	20 (16.9)	83 (34.2)	107 (26.8)
Salivary hypersecretion	2 (5.1)	9 (7.6)	22 (9.1)	33 (8.3)
Nausea	1 (2.6)	3 (2.5)	27 (11.1)	31 (7.8)
Vomiting	0	3 (2.5)	23 (9.5)	26 (6.5)
Investigations	3 (7.7)	15 (12.7)	77 (31.7)	95 (23.8)
Weight increased	2 (5.1)	12 (10.2)	59 (24.3)	73 (18.3)
Musculoskeletal and connective tissue disorders	2 (5.1)	10 (8.5)	56 (23.0)	68 (17.0)
Muscle rigidity	1 (2.6)	6 (5.1)	19 (7.8)	26 (6.5)

Note: Incidence is based on the number of subjects experiencing at least one AE, not the number of events.
Adverse events are coded using MedDRA version 15.0
tae01a_tsfae01a.rtf generated by tsfae01a.sas, 17AUG2012 17:26
Source: Mod5.3.5.2\PSZ-3002\Table 48

Table 40: PSZ-3003- TEAEs in at least 5% of Subjects in any dose group

Body System or Organ Class Dictionary-Derived Term	Paliperidone ER (N=113) n (%)	Aripiprazole (N=114) n (%)
Total no. subjects with adverse events	87 (77.0)	76 (66.7)
Nervous system disorders	55 (48.7)	41 (36.0)
Akathisia	13 (11.5)	9 (7.9)
Headache	12 (10.6)	5 (4.4)
Somnolence	12 (10.6)	12 (10.5)
Tremor	12 (10.6)	11 (9.6)
Sedation	6 (5.3)	3 (2.6)
Psychiatric disorders	23 (20.4)	28 (24.6)
Anxiety	6 (5.3)	3 (2.6)
Insomnia	6 (5.3)	9 (7.9)
Schizophrenia	4 (3.5)	13 (11.4)
Gastrointestinal disorders	19 (16.8)	13 (11.4)
Vomiting	8 (7.1)	1 (0.9)
Nausea	4 (3.5)	7 (6.1)
Investigations	17 (15.0)	14 (12.3)
Weight increased	12 (10.6)	7 (6.1)
General disorders and administration site conditions	13 (11.5)	5 (4.4)
Asthenia	6 (5.3)	1 (0.9)
Musculoskeletal and connective tissue disorders	13 (11.5)	5 (4.4)
Muscle rigidity	7 (6.2)	3 (2.6)
Metabolism and nutrition disorders	8 (7.1)	9 (7.9)
Decreased appetite	2 (1.8)	6 (5.3)

Note: Incidence is based on the number of subjects experiencing at least one AE, not the number of events.
Adverse events are coded using MedDRA version 15.0
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Extrapyramidal Syndrome (EPS) related symptoms

PSZ-3001

EPS related TEAEs have not been reported for placebo but for all other paliperidone ER dosing groups (1.5mg, 3mg, 6mg, and 12mg). A dose-related trend could be shown for Akathisia (3.7%, 6.3%, 11.1%, and 17.1%), Dystonia (1.9%, 0%, 4.4%, and 8.6%), Tremor (1.9%, 6.3%, 6.7%, 11.4%), and Muscle rigidity (0%, 0%, 2.2%, and 2.9%).

Treatment-emergent EPS assessed by rating scale (Barnes for Akathisia) revealed 0% for placebo and paliperidone ER 1.5mg and higher incidences for paliperidone ER 3mg, 6mg, and 12mg (6%, 9%, and 6%). Parkinsonism as per Simpson-Angus Scale was highest in the paliperidone ER 1.5mg group.

A dose-related use of anticholinergic medication was found (4%, 13%, 18%, and 31% in the paliperidone ER 1.5mg, 3mg, 6mg, 12mg group) with no anticholinergic medication in the placebo group.

Incidences of parkinsonism and akathisia and use of anticholinergic medications were higher in subjects <15 years old and <51 kg than those ≥15 years old and ≥51 kg, respectively.

PSZ-3003

EPS related TEAEs were (slightly) higher for paliperidone ER compared to aripiprazole for all EPS categories except for Dyskinesia. No cases of tardive dyskinesia were reported. The rates of dyskinesia (based on AIMS score) and anticholinergic medication use were slightly higher in the paliperidone ER group than in the aripiprazole group (3% vs. 0%, and 25% vs. 22%). Parkinsonism and Akathisia were similar between treatment groups based on rating scale results. However, in the <15 years old subgroup, the incidences of parkinsonism and akathisia were higher in subjects receiving paliperidone ER (6%) than those receiving aripiprazole (3%).

PSZ-3002

EPS-related TEAEs within the categories of Parkinsonism and Hyperkinesia were most frequently reported and highest in the paliperidone (NO DB)/paliperidone group . The most commonly occurring (>5%) EPS-related event was akathisia (13.0%), followed by tremor (11.0%), muscle rigidity (6.5%), and dystonia (5.3%). These TEAEs were mostly mild to moderate in severity. No case of tardive dyskinesia was reported. Further analysis was conducted regarding the time course of EPS-related TEAEs. Overall, treatment-emergent EPS occurred more frequently in the first 3 months than in subsequent months (See Table 41).

Table 41: Treatment-Emergent EPS Assessed by Rating Scale Incidence and Use of Anticholinergics – Open-Label Study (PSZ-3002).

Scale	Placebo/Pali (N=39) n (%)	Pali (DB)/Pali (N=118) n (%)	Pali (NO DB)/Pali (N=243) n (%)	Total (N=400) n (%)
Use of Anticholinergic Medications[a]	5 (13)	27 (23)	69 (28)	101 (25)
Parkinsonism[b]	0	2 (2)	17 (7)	19 (5)
Akathisia[c]	0	3 (3)	6 (2)	9 (2)
Dyskinesia[d]	0	0	2 (1)	2 (1)

[a] Use of Anti-EPS Medication during open-label study.
[b] Percent of subjects with Simpson-Angus Scale Global Score > 0.3 at End Point(OL) (Global Score defined as total sum of items score divided by the number of items).
[c] Percent of subjects with Barnes Akathisia Rating Scale Global Clinical Rating Score ≥2 at End Point (OL).
[d] Percent of subjects with a score ≥3 on any of the first seven items or a score ≥2 on two or more of any of the first seven items of the Abnormal Involuntary Movement Scale at End Point(OL)
Note: Percentages are calculated based on number of subjects in the OL safety analysis set per treatment group.

Thirty-five (35)% of the subjects received anti-EPS medication and antihistamines drug/therapy prior to the open-label study compared to 25.0% of subjects during the open-label study.

Suicide related events

PSZ-3001

No suicidality-related TEAEs were reported in this study. Evaluation of the Columbia Classification Algorithm of Suicide Assessment (C-CASA, retrospective assessment) revealed two patients who were suspect of potentially suicidality-related AEs, one in the placebo group and one in the paliperidone ER medium group. However, these events turned out to be not related after review. There was no indication of an increased suicidality risk in subjects receiving paliperidone ER compared with those receiving placebo.

PSZ-3003

Suicidality-related TEAEs occurred in 3 subjects, all in the paliperidone ER treatment group. The TEAEs were suicidal ideation in 2 subjects (1.8%) and suicide attempt in 2 subjects (1.8%). The C-SSRS assessment based on C-CASA classification confirmed the majority of subjects from the paliperidone ER group with no suicidal event at baseline remained non suicidal post-baseline (96.4%). The same was true for aripiprazole (98.2%).

PSZ-3002

Suicidality-related TEAEs occurred in 37 subjects in the Total group (9.3% overall). These were suicidal ideation in 34 (8.5%) subjects, suicide attempt in 3 (0.8%) subjects, and suicidal behaviour in 1 (0.3%) subject. TEAEs in this category were reported only in the paliperidone (NO DB)/ paliperidone treatment group.

Further data on suicidality assessment are presented in Tables 42 and 43.

Table 42: Treatment-Emergent Potentially Suicide-Related Events (PSREs) – Retrospective Columbia Classification Algorithm of Suicide Assessment (C-CASA) for Subjects Who Completed the Study Prior to the Initiation of C-SSRS – Open-Label Study (PSZ-3002).

C-CASA	Placebo/Pali (N=14) n (%)	Pali (DB)/Pali (N=46) n (%)	Pali (NO DB)/Pali (N=51) n (%)	Total (N=111) n (%)
Total no. subjects with PSRE	2 (14.3)	1 (2.2)	13 (25.5)	16 (14.4)
Suicidal Behavior (Codes 1-4)	0	0	5 (9.8)	5 (4.5)
Completed suicide	0	0	0	0
Suicide attempt	0	0	2 (3.9)	2 (1.8)
Preparatory acts toward imminent suicidal behavior	0	0	0	0
Suicidal ideation	0	0	3 (5.9)	3 (2.7)
Indeterminate (Codes 5-6, 9)	1 (7.1)	1 (2.2)	4 (7.8)	6 (5.4)
Self-injurious behavior, intent unknown	1 (7.1)	0	2 (3.9)	3 (2.7)
Not enough information, fatal	0	0	0	0
Not enough information, nonfatal	0	1 (2.2)	2 (3.9)	3 (2.7)
Non-Suicidal (Codes 7-8)	1 (7.1)	0	5 (9.8)	6 (5.4)
Self-injurious behavior, no suicidal intent	0	0	1 (2.0)	1 (0.9)
Other: accident, psychiatric, medical	1 (7.1)	0	4 (7.8)	5 (4.5)

Table 43: Incidence of Any Post Baseline (OL) PSREs - Columbia Classification Algorithm of Suicide Assessment (C-CASA) Based on C-SSRS - for Subjects Who Completed the Study After Initiation of C-SSRS – Open-Label Study (PSZ-3002).

Cssrs Score	Placebo/Pali (N=25) n (%)	Pali (DB)/Pali (N=72) n (%)	Pali (NO DB)/Pali (N=192) n (%)	Total (N=289) n (%)
Total no. subjects with PSRE	1 (4.0)	0	36 (18.8)	37 (12.8)
Suicidal Behavior (Codes 1-4)	1 (4.0)	0	30 (15.6)	31 (10.7)
Completed suicide	0	0	0	0
Suicide attempt	0	0	0	0
Preparatory acts toward imminent suicidal behaviour	0	0	3 (1.6)	3 (1.0)
Suicidal ideation	1 (4.0)	0	27 (14.1)	28 (9.7)
Indeterminate (Codes 5-6, 9)	0	0	1 (0.5)	1 (0.3)
Self-injurious behaviour, intent unknown	0	0	1 (0.5)	1 (0.3)
Not enough information, fatal	0	0	0	0
Not enough information, nonfatal	0	0	0	0
Non-Suicidal (Codes 7-8)	0	0	5 (2.6)	5 (1.7)
Self-injurious behaviour, no suicidal intent	0	0	3 (1.6)	3 (1.0)
Other: accident, psychiatric, medical	0	0	2 (1.0)	2 (0.7)

Only subjects with CSSRS data during open label are included in this summary.
For subjects with multiple post baseline(OL) events, the worst score was selected. A score of 9 was considered more severe than a score of 7 or 8.

Other psychiatric adverse events

PSZ-3001

TEAEs related to worsening of psychosis occurred at a lower incidence with paliperidone ER (6.7%) than with placebo (11.8%). Agitation occurred in a higher rate in placebo compared to paliperidone ER (7.8% vs. 4.7%). Aggression was only reported for placebo-treated patients. No TEAEs of seizure or convulsion were reported. Somnolence (including sedation) was highest and dose-related in the total paliperidone ER group compared to placebo (16.7% vs. 3.9%).

PSZ-3003

TEAEs related to worsening of psychosis occurred at a lower incidence with paliperidone ER (4.4%) than with aripiprazole (12.3%). Similarly, schizophrenia was reported more frequently with aripiprazole compared to paliperidone ER (11.4% vs. 3.5%). Depressed mood was slightly higher in paliperidone ER-treated patients compared to aripiprazole (2.7% vs. 1.8%). There were only isolated reports of agitation and aggression for both treatment options. No reports of NMS, seizure or convulsion. Somnolence was similar for paliperidone ER and aripiprazole (10.6% vs. 10.5%). The percentage of subjects with TEAEs of sedation was higher in paliperidone ER group (5.3%) than in the aripiprazole group (2.6%). Most of the TEAEs were mild to moderate in severity. None of these events were serious.

PSZ-3002

The incidence of psychosis TEAEs and schizophrenia was higher compared to the other studies. A total 55 subjects (13.8%) had a TEAE related to worsening of psychosis. In the Total group, 50 subjects (12.5%) had a TEAE of schizophrenia. Depressed mood happened in 5.5% of subjects. A total of 17 subjects (4.3%) had a TEAE related to agitation, and 6 subjects (1.5%) had a TEAE related to aggression. Most of these events were mild to moderate in severity. Two subjects (0.8% overall) had

TEAEs related to seizures and convulsions (one case of petit mal epilepsy and one case of tonic convulsion). Somnolence was reported for 23% of subjects.

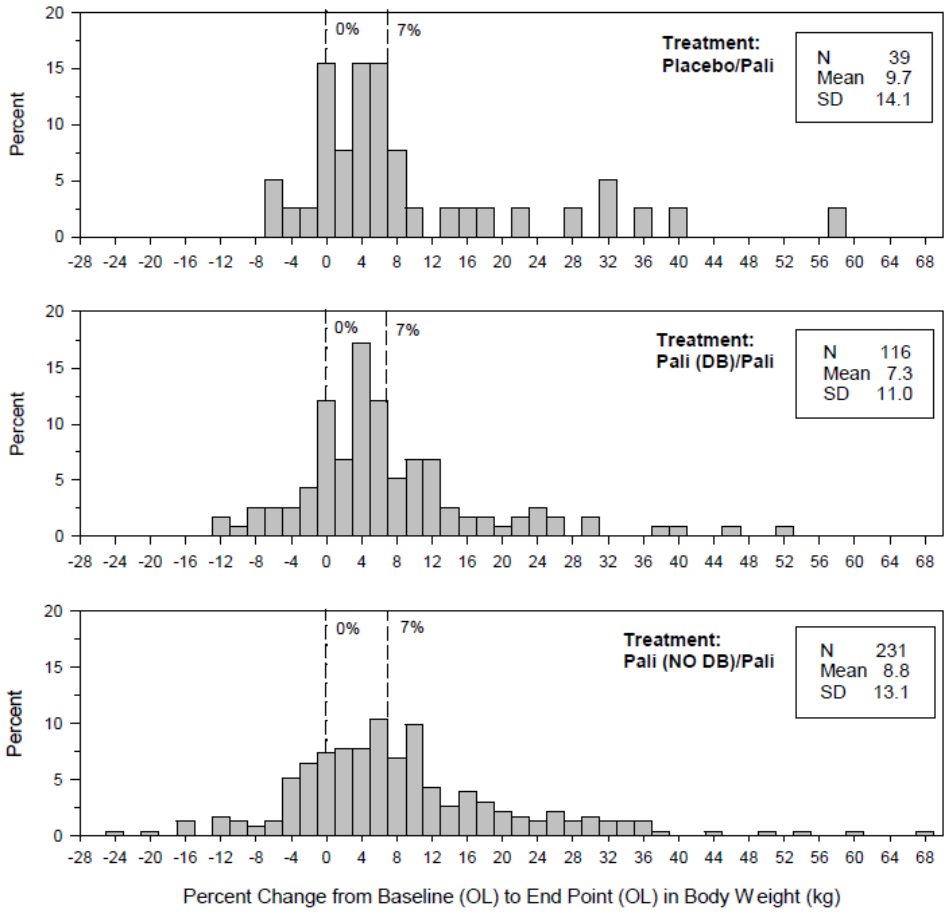
Weight gain related adverse events

Potentially clinically significant weight gain of 7% and more was reported for 26% of patients in study PSZ-3003 and for 47% in study PSZ-3002, reflecting a high risk of weight gain associated with various comorbidities, particularly in a schizophrenic population. This risk is clearly more pronounced with higher doses. However, post-marketing data from adolescents in the US did not indicate a difference in weight increase reporting compared to adults.

In the 26-week active-controlled study PSZ-3003, although there were 26% of patients with weight gain of ≥7%, the changes from baseline in z-score for weight and BMI were 0.09 and 0.13, respectively, indicating the change in weight was clinically insignificant (changes from baseline in z-score exceeding 0.5 would be judged a significant observation). In the 2-year long-term safety study PSZ-3002, the mean weight increase from open-label baseline to open-label endpoint was 4.7 kg (n = 400). Overall, 47.0% (73/157) of subjects experienced weight gain of at least 7.0% at open-label endpoint relative to double-blind baseline. The mean change in z-score was 0.1 for both weight and BMI from open-label baseline to endpoint.

The percentage change in body weight at endpoint relative to open-label baseline in Study PSZ-3002 is displayed in Figure 24.

Figure 24 Histogram of percentage change in body weight (kg) from open label baseline to endpoint (study PS-3002)



2.5.3. Serious adverse event / deaths / other significant events

No death cases have been reported in studies with adolescents.

PSZ-3001

There were 5 treatment emergent SAEs that occurred ; 1 from the placebo group (psychotic disorder), 2 from the paliperidone ER 1.5 mg group (schizophrenia and agitation), 1 from the paliperidone ER 3mg group (Mallory Weiss syndrome) and 1 from the paliperidone ER 6mg group (schizophrenia).

PSZ-3002

SAEs occurred in 59 subjects (14.8%). Most of these were in the SOC psychiatric disorders with the most common being schizophrenia (n=30) indicating worsening of illness. Other SAEs that occurred in more than 1 subject were suicidal ideation (n=7) and agression and anxiety (in 4 subjects each). There were 3 suicide attempts; all in the paliperidone(NO/DB)paliperidone group.

PSZ-3003

There were 6.2% of Treatment Emergent SAEs in the paliperidone ER group and 6.1% in the aripiprazole group. The most common was the SOC Psychiatric Disorders for both groups (5.3% each).

2.5.4. Laboratory, ECG and other findings

No clinically significant laboratory abnormalities other than prolactin levels have been noted. Measurement of testosterone for assessing a potential long-term endocrine effect of elevated prolactin levels did not point towards a significant change in testosterone levels in male adolescents with schizophrenia. Fasting glucose abnormalities and glucose-related TEAEs occasionally occurred with paliperidone ER; Homeostatic Model Assessment (HOMA) assessment revealed a pre-existing insulin resistance at baseline in all studies and all treatment groups and beta cell function was similarly increased at baseline. During treatment with paliperidone ER, the insulin resistance slightly increased and beta cell function slightly decreased, but not dose-related.

Prolactin levels

PSZ-3001

Abnormally high prolactin values were found more frequently in the paliperidone ER groups compared to placebo and for more than half of the male patients and almost half of the female patients with no clear relation to dose (placebo: 10% male and 17% female). A clear dose effect could be established for females with mean increases of 10.39 ng/ml, 26.93 ng/ml, and 29.96 ng/ml for the 3mg, 6mg, and 12mg dose group. These laboratory abnormalities did not generally translate into prolactin-related adverse events: two patients from the paliperidone ER 6mg dose group were reported with galactorrhoea and one female patient from the paliperidone ER 3mg group with amenorrhoea.

Higher incidences of treatment-emergent abnormal high prolactin results were observed in <15 years old subgroup than in ≥15 years old subgroup. It did not appear there was a dose-related trend in both age subgroups.

PSZ-3003

Abnormally high prolactin values could be shown for paliperidone ER: 59% of males and 57% of females. In contrast, aripiprazole-treated patients were affected to a smaller extend by high values due to its pharmacological properties (3% for males and 9% for females) but did show more decreases in prolactin (males: 52% and females: 29%).

Again, there was no significant increase in TEAEs related to high prolactin values and only single cases were reported regarding galactorrhoea, gynaecomastia, libido decreased, erectile dysfunction, amenorrhoea, menstruation irregular. Except for one case of galactorrhoea, no TEAE showed up in the aripiprazole group.

Higher incidences of treatment-emergent abnormal high prolactin results were observed in <15 years old than in ≥15 years old subgroup in paliperidone ER group, whereas higher incidences of treatment-emergent abnormal low prolactin results were observed in <15 years old than in ≥15 years old subgroup in aripiprazole group.

PSZ-3002

Incidences of treatment-emergent abnormal prolactin results by sex relative to baseline (open-label and double-blind) were shown to be higher for males through all treatment groups.

The mean prolactin levels for both males and females increased and reached a peak within the first 6 months of treatment, and then either stabilized or gradually declined over time. 60% of male subjects and 48% of female subjects had elevated prolactin levels from open-label baseline to endpoint during this study. 9.3% subjects experienced a prolactin-related TEAE (18.5% in females and 3.3% in males).

Higher incidences of treatment-emergent abnormal high prolactin results were observed in the <15 years old than the ≥15 years old subgroup from double-blind baseline to endpoint.

From open-label baseline to endpoint, similar incidences of treatment-emergent abnormal high prolactin results were observed for male subjects regardless of age, whereas higher incidences were observed for female subjects who were <15 years old compared ≥15 years old.

Electrocardiograms

PSZ-3001

Abnormally high heart rates occurred in greater percentages of subjects in the paliperidone ER dose groups than in the placebo group (1.5mg: 14%, 3mg: 33%, 6mg: 5%, 12mg: 18% vs. placebo: 4%). Tachycardia-related events occurred in 4.7% of the total paliperidone group and in no patient from placebo.

All subjects in each dose group had normal average pre-dose and maximum post-dose values for QTcF. No subject had a maximum post-dose value >480msec. Most subjects had increases in QTc values from average pre-dose to maximum post-dose of <30 ms. No subject in any dose group had an increase that was greater than 60 msec.

PSZ-3003

Abnormally high heart rate was observed in more subjects in the paliperidone ER group (8 subjects, 8%) compared to the aripiprazole group (6 subjects, 6%). There were no clinically relevant mean or median changes in heart rate, PR interval, QRS interval, QT interval, RR interval, QTcB, QTcF, QTlc, or QTcLD. TEAEs of tachycardia were reported with a higher incidence in the paliperidone ER group compared to aripiprazole (2.7% vs. 1.8%). One TEAE of sinus tachycardia was reported from the paliperidone ER group only. Most subjects in the paliperidone ER and aripiprazole group had a maximum increase of QTcF of 30msec and less (94% and 97%). 6% of subjects from the paliperidone ER group and 2% of subjects from the aripiprazole group had QTcF changes of 30 to 60msec. One subject on aripiprazole had a QTcF change of more than 60msec.

PSZ-3002

Abnormally high heart rate was reported for 13% of total paliperidone ER-treated subjects. One subject had a TEAE related to cardiac arrhythmias (sinus bradycardia). Two subjects had TEAEs related to proarrhythmic potential; one subject each had a TEAE of seizure and syncope.

With respect to QTcF changes from open-label baseline to endpoint, 88% of the total paliperidone ER group had changes of 30msec or less. 5% of subjects from the placebo/ paliperidone group, 8% from the paliperidone (DB)/ paliperidone group, and 14% from the paliperidone (No DB)/ paliperidone group had QTcF changes of >30 to 60msec. A total of three patients had QTcF changes of more than 60msec.

Tanner staging

PSZ-3001

Most male and female subjects had the same Tanner ratings at endpoint as at baseline in each treatment group. No significant differences have been found between paliperidone ER groups and placebo.

PSZ-3002

Most male and female subjects had the same Tanner ratings at endpoint as at open-label baseline (ratings were predominantly 4 and 5 indicating a mostly post-pubertal population). Adolescents aged 12 to 13 years showed an expected shift from lower to higher Tanner ratings during the 2-year study.

2.5.5. Discontinuation due to adverse events

The most common adverse events leading to discontinuation across the 3 Phase III studies were adverse events coded to the Nervous System Disorders and Psychiatric Disorders SOCs. Other events led to withdrawal infrequently and showed no pattern related to treatment or to the dose of paliperidone ER.

Treatment discontinuations due to TEAEs occurred at low rates in subjects treated with paliperidone ER in all Phase 3 studies (in study PSZ-3001, 2%; in study PSZ-3003, 4.4%; in the 2-year study PSZ-3002, 6.3%).The incidences of TEAEs that resulted in discontinuation of treatment were also low in adults who received paliperidone ER (≤7% in double-blind and open-label studies) and adolescents who received risperidone (≤9% in double-blind and open-label studies).

PSZ-3001

One patient each discontinued due to an adverse event from the paliperidone ER 1.5 mg (dermatitis allergic), 3mg (Mallory-Weiss Syndrome) and 12mg group (Dystonia), no patient from the placebo and the paliperidone ER 6 mg group.

PSZ-3003

Five patients from the paliperidone ER group and no patient from the aripiprazole treatment had a TEAE leading to treatment discontinuation. Four of these patients (3.5%) discontinued during the acute phase (through Day 56) of the study. The respective adverse events did not reveal a specific pattern (Oculogyric crisis, Lethargy, Anxiety, Galactorrhoea, and Rash).

PSZ-3002

Twenty-five patients (6.3%) discontinued due to TEAEs with the highest number in the paliperidone (No DB)/paliperidone group amounting to 23 patients. Three of these 23 patients discontinued subsequently to a suicide attempt and two due to suicidal ideation. Three patients discontinued due to Akathisia. All other TEAE-related treatment discontinuations happened in single subjects only.

2.5.6. Post marketing experience

A cumulative review was performed by the MAH (cut-off date: 11 September 2012) to provide an overall safety information about paliperidone in this patient population. All spontaneous cases reported with paliperidone or paliperidone palmitate, were compared by age group (<18 years versus all other age groups, ie, those patients ≥18 years of age) using a measure of disproportionality. Preferred terms (PTs) of interest were identified if disproportionality (ie, higher proportion of total events among paediatric patients than all other age groups) was present in the cumulative data.

There were 360 cases involving paediatric patients (<18 years) received during the cumulative review period, of which 40% were serious. The patterns of disproportionately reported ADRs with Preferred Terms (PTs) observed were generally consistent with adult clinical trials and post-marketing experience or were specific to the paediatric population.

The PTs that demonstrated disproportionality vs adults were as follows: Accidental overdose; Breast discharge; Dystonia; Gynaecomastia; Increased appetite; Oculogyric crisis; Somnolence; Suicidal ideation; Lethargy; Increased appetite; Trismus; Breast enlargement; Swollen tongue; Chest pain; Irritability; Medication residue; Sluggishness; Therapeutic response unexpected; Muscle twitching; Convulsion; Disturbance in attention; Drooling; Hypersomnia; Restless legs syndrome; Tic; Abnormal behaviour; Aggression; Anger; Catatonia; Priapism; Swelling face; and Urticaria.

There were no fatal cases reported in paediatric patients treated with paliperidone during the cumulative review period. No disproportionality of reporting was noted for paediatric patients when compared to all other age groups during this review with respect to any of the predefined areas of clinical interest, including the collective group of all extrapyramidal symptoms, weight gain, prolactin-related events, glucose metabolism disorders, cardiac events, suicidality, or sedation.

Adverse events reported in association with the predefined areas of clinical interest were consistent with the known safety profile for paliperidone ER and paliperidone palmitate and included EPS-related events, isolated cases of excessive weight gain, and prolactin-related events. PTs such as Accidental drug intake by child and Drug administered to patient of inappropriate age would not be reported in the adult population.

The disproportionate reporting of off-label use may be reflective of the limited indicated age range of paliperidone ER (schizophrenia in adolescents aged 12 to 17 years) and paliperidone palmitate (not indicated in children or adolescents) per the CCDS and the off label use for disorders found mostly in children (eg, attention deficit hyperactivity disorder and autism).

2.5.7. Discussion on clinical safety

The clinical development program for Paliperidone ER in adolescents included 3 phase III studies and one phase one study which included 653 subjects exposed to paliperidone ER. The number of patients for whom safety data is available seems adequate. No particular safety issues have been identified during the clinical development program. The type of adverse events reported in 545 adolescent subjects with schizophrenia receiving once-daily treatment with paliperidone ER in the 3 studies included in this submission were generally consistent with those reported for paliperidone ER in adult subjects and those known to be associated with risperidone treatment in adolescent subjects.

However, patients aged 12 to 14 years represented a minority across the three phase 3 studies 3001, 3003, and 3002. For example, dose range evaluation of TEAEs in study 3001 relied on a maximum of 16 patients aged 12 to 14 years in each treatment group. Similarly and with regard to clinical efficacy data, there are few safety data for patients weighing less than 51 kg compared to those weighing more than 51 kg. Whist further data were provided to support an individual dose titration depending on body

weight, the CHMP was still of the opinion that a positive benefit-risk in the younger age group 12 to 14 years was insufficiently demonstrated due to the lack of data.

Following ADR analyses on all data from the adolescent studies, the MAH identified the following new ADRs that had previously not been identified in the use in adults: 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. These have been added to the current paliperidone ER CCDS. In addition, "weight circumference increased" was also identified and is considered related to "weight increase" which is already listed in the SmPC. Similarly to the adult population, the highest incidence of TEAEs emerged from the Nervous System Disorders SOC. Dose-related trends were observed for Somnolence, Akathisia, Tremor, Dystonia, and Cogwheel rigidity.

Compared to paliperidone ER in adults, the frequency of EPS-related adverse events was clearly higher for adolescents in studies PSZ-3001, -3003, and -3002 (around 36.5% of subjects affected during open-label treatment). This finding is confirmed by the high concomitant use of anticholinergics (up to one-third of patients). EPS symptoms were highest during the first three months of treatment and reaching a plateau from six months of treatment up to 24 months. The CHMP however noted that the incidences of EPS related events observed in the open label study were in the range of that reported for other antipsychotics. In addition, there was no evidence of a dose effect with regard to either the incidences of treatment-emergent EPS as assessed by the results of the EPS scales or in the rate of anticholinergic medication use in the Paliperidone ER Total group. There were also no apparent differences in treatment-emergent EPS-related AEs by rating scales and use of anticholinergic medications with regard to age or weight. The CHMP concluded that a general SmPC warning related to regular examination of EPS symptoms for the paediatric population should be included.

Potentially clinically significant weight gain of 7% and more was reported for 26% of patients in study PSZ-3003 and for 47% in study PSZ-3002, reflecting a high risk of weight gain associated with various comorbidities, particularly in a schizophrenic population. This risk is clearly more pronounced with higher doses. Post-marketing data from adolescents in the US did not indicate a difference in weight increase reporting compared to adults. During the course of treatment in Phase 3 studies, there were no clinically significant mean changes in z-scores (adjusted for sex- and age-specific normative values) for weight or BMI. In the 2-year long-term study, the majority of subjects had z-scores below the clinically significant threshold of 0.5 in all categories. Subgroup analyses did not reveal apparent trends of weight gain related AEs with regard to age or body weight. The CHMP however recommended to include information related to weight gain as warning in the SmPC.

No clinically relevant changes in laboratory parameters were noted during short and long-term treatment with paliperidone ER in adolescents with schizophrenia except for serum prolactin. In addition, pre-existing insulin resistance was found in all treatment groups and slightly increased over time, whereas the compensatory increase in beta cell functioning slightly decreased.

Elevation in serum prolactin has been noted across all paliperidone ER treatment groups clearly increased by dose, whereas females were more affected than males. However, abnormalities did not simultaneously lead to TEAEs with regard to prolactin. The highest rate was observed in study 3002 with near 10% of all paliperidone ER-treated subjects. Serum prolactin was highest during the first six months of treatment and remained stable thereafter.Higher incidences of treatment-emergent abnormal prolactin results were observed in younger (<15 years) subjects than in older (≥15 years) subjects across all studies with adolescents. There were no corresponding increased incidences in AEs in the subgroups with younger subjects.Prolactin increases appeared to be in line with those from paliperidone ER in adults and with risperidone in adolescents. Because of the potential effects of

prolonged hyperprolactinemia on growth and sexual maturation, a SmPC warning related to regular clinical evaluation of endocrinological status for the paediatric population was recommended by the CHMP.

Increase in blood triglycerides was common in open label study 3002 and the frequency was more commonly observed in adolescents than in adults. However, treatment with paliperidone ER did not appear to alter blood triglyceride profile and triglyceride related AEs are not common. The increase in mean triglyceride levels in PSZ-3003 was not replicated in the longer and larger study PSZ-3002. The ADR rate of hypertriglyceridemia is higher in the pediatric population than the adult population.

A dose relationship was observed for somnolence, subgroup analyses by age and weight groups did not reveal a higher incidence of somnolence related AEs in the younger and lighter patients (<15 years and <51 kg). However, somnolence was found to be higher in adolescents compared to adults, dose-related (6 to 26%) and higher compared to placebo and also detected in 23% of patients during long-term treatment. Consequently, a SmPC warning related to close monitoring for sedative effect of paliperidone ER for the paediatric population was recommended by the CHMP.

No death cases have been reported during studies with adolescents. The overall number of serious adverse events was low, similar for paliperidone ER, placebo and active comparator, and most of all related to the underlying psychiatric illness.

ECG changes in adolescents were found to be in line with those in adults, e.g. the potential of paliperidone ER to increase heart rate (≥ 100 bpm). There were no clinically relevant mean or median changes in PR interval, QRS interval, QT interval, RR interval, or corrected QT intervals in subjects treated with paliperidone ER in any of the Phase 3 studies.

No retardation in growth as represented by changes in height, weight, and BMI based on Z-score analyses, as well as in sexual maturation (Tanner staging) was noted, which would indicate an abnormal adolescent maturation.

Based on post-marketing data, there were 360 cases involving paediatric patients (<18 years) during the cumulative review period, of which 40% were serious. The patterns of disproportionately reported ADRs with Preferred Terms (PTs) observed were generally consistent with adult clinical trials and post-marketing experience or were specific to the paediatric population.

2.5.8. Conclusions on clinical safety

Overall, the CHMP concluded that the safety of Invega for the treatment of schizophrenia in 15 years and older has been sufficiently characterised. From the safety database all the adverse reactions reported in paediatric clinical trials have been included in the SmPC.

2.5.9. PSUR cycle

Having considered the data submitted in the application and following the MAH proposal to restrict the proposed indication to treatment of schizophrenia in adolescents 15 years and older, the CHMP was of the opinion that the PSUR cycle for paliperidone should remain unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

The MAH has submitted an updated RMP (version 4.0) in which the results from studies including adolescent patient with schizophrenia have been added. However, no new safety issues have been proposed and therefore the pharmacovigilance and risk minimisation plans are unchanged. This is acceptable.

Additionally, the MAH has removed the safety issue “Neonatal withdrawal Syndrome” and “Antiemetic Effect” in accordance with the PRAC opinion during the recent PSUR assessment.

The CHMP endorsed this advice without changes.

Following the MAH proposal to restrict the proposed indication to treatment of schizophrenia in adolescents 15 years and older, updates of the RMP were proposed with regard to module SIII.2 and SVII.3. In addition, changes in line with the latest PRAC recommendation on the PSUR (January 2014) were made. These changes were agreed by the CHMP and RMP (version 5.1) was considered acceptable.

2.7. Update of the product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated to include efficacy and safety information resulting from the submitted paediatric studies. The Package Leaflet has been updated accordingly. The SmPC changes are summarised below:

Final recommended indication, posology and warnings are as follows:

Section 4.1

INVEGA is indicated for the treatment of schizophrenia in adolescents 15 years and older.

Section 4.2

Paediatric population

Schizophrenia: The recommended starting dose of INVEGA for the treatment of schizophrenia in adolescents 15 years and older is 3 mg once daily, administered in the morning.

Adolescents weighing < 51 kg*:* the maximum recommended daily dose of INVEGA is 6 mg.

Adolescents weighing ≥ 51 kg**:** the maximum recommended daily dose of INVEGA is 12 mg.

Dosage adjustment, if indicated, should occur only after clinical reassessment based on the individual need of the patient. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of 5 days or more. The safety and efficacy of INVEGA in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made. There is no relevant use of INVEGA in children aged less than 12 years.

Section 4.4

Paediatric population

The sedative effect of INVEGA should be closely monitored in this population. A change in the time of administration of INVEGA may improve the impact of sedation on the patient.

Because of the potential effects of prolonged hyperprolactinemia on growth and sexual maturation in adolescents, regular clinical evaluation of endocrinological status should be considered, including

measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

During treatment with INVEGA regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in the paediatric population see section 4.2.

In addition:

- A summary of safety profile related to the paediatric population was also added to section 4.8, listing ADRs that were reported more frequently in adolescents than in adults receiving Invega (and more frequently than placebo). Furthermore, the list of adult ADRs in the "Summary of safety profile" subsection of SmPC section 4.8 has been updated as a result of changes in frequency calculations resulting from the removal of the paediatric study PSZ-3001 when calculating ADR reporting frequency. In this subsection, the identification of those ADRs that are 'most frequently reported' were based on a cut-off of > 2% from the original analysis and led to the addition of cough (a common ADR). In addition, the tabulated list of adverse reactions considered all ADRs reported in clinical trials and post-marketing experience with paliperidone with a frequency category estimated from the adult trials and thus resulted in change in frequencies for some of the listed adverse reactions (e.g white blodd cell count decreased, thrombocytopenia, hyperprolactinemia, tardive dyskinesia, atrioventricular block, eczema);

- Sections 5.1 and 5.3 were updated to add the main results from the paediatric clinical studies and juvenile toxicity studies, respectively;

- Section 5.2 was updated to reflect the main findings from the pharmacokinetic modelling analyses.;

- Section 4.5 was updated to include a statement that "interaction studies have only been performed in adults".

No full user consultation with target patient groups on the package leaflet been performed and no bridging report was submitted making reference to the assessment of the initial patient leaflet for INVEGA prolonged release tablets, that was approved on 25 June 2007. The MAH states that since no additional safety issues have been identified and no new route of administration is proposed, there is no need for a user testing. The justification submitted by the MAH has been found acceptable.

In addition, the list of local representatives in the Package Leaflet has been revised to amend contact details for the representatives of Luxembourg and Belgium.

3. Benefit-risk balance

Beneficial effects

In study PSZ-3001, results indicated that the study achieved its primary objective by demonstrating that at least one paliperidone ER weight-based group (<51 Kg: 3 mg/day; ≥51 Kg: 6 mg/day) was statistically superior to placebo in improving the symptoms of schizophrenia as measured by the change in PANSS total score from baseline to endpoint (week 6, difference of LS means: -10.1; p=0.006). Efficacy analyses of the secondary endpoints including CGI-S, CGAS, sleep VAS and PANSS factor scores were consistent with the findings of the primary efficacy analysis.

Similarly to the overall study results for this short term trial, the medium dose group (<51 Kg: 3 mg/day; ≥51 Kg: 6 mg/day) showed better improvement in PANSS total score in all analysed

subgroups based on age and/or weight. In patients aged 15-17 years old, statistically significant differences versus placebo were observed in both the Medium (<51 Kg: 3 mg/day; ≥51 Kg: 6 mg/day, p=0.005) and High (<51 Kg: 6 mg/day; ≥51 Kg: 12 mg/day, p=0.012) dose groups of paliperidone ER for the primary endpoint (change from baseline to endpoint in PANSS total score). In addition, consistent efficacy findings were observed for the subgroup analyses on the secondary efficacy endpoints

In study PSZ-3003, maintenance data was provided over 26 weeks. The primary objective was not met i.e. paliperidone ER did not demonstrate superior efficacy compared to aripiprazole. However, robust and clinically meaningful reductions in mean PANSS total score from baseline to endpoint acute (Day 56, LOCF) in the paliperidone ER (-19.3) and aripiprazole (-19.8) groups were observed. Similar treatment effects with regard to decreasing the PANSS total scores over the 26-week period for paliperidone ER and aripiprazole were also noted.

In study PSZ-3002, improvement in the PANSS total scores in patients treated with paliperidone ER were observed during the first 3 months of the open-label treatment. The improvements in PANSS total scores observed during the first 3 months were maintained during the remaining portion of this 2 year study. Subgroup analyses based on age and weight did not reveal any significant difference in improvement in PANSS during the course of 2 year treatment.

Uncertainty in the knowledge about the beneficial effects

The time course of PANSS score and the influence of exposure to paliperidone and other covariates has not been evaluated by modelling as compared to the presented popPK analysis. This makes it difficult to draw any conclusion about the relation between paliperidone exposure and clinical effect.

Although post-hoc analyses by actual dose received by the subjects showed statistically significant improvement relative to placebo in the PANSS total scores at endpoint for the paliperidone ER 3, 6, and 12 mg dose groups, no clear dose response pattern was observed for the efficacy parameters.

The proportion of patients aged 12-14 years was relatively small to conclude on the efficacy (short term and maintenance of the effect) in this population. In both short term and long term studies, the effect on the PANSS total score was also considered weaker in this age group as compared to patients aged 15-17 years. In study PSZ-3001, the difference of LS mean changes from baseline to endpoint was -15.5 in patients aged 12-14 years and -18.1 in patients aged 15-17 years, respectively. In study PSZ-3003, the difference of LS mean changes from baseline to endpoint was -17.5 in patients aged 12-14 years and -20.1 in patients aged 15-17 years, respectively. In study PSZ-3002 (open label), among younger adolescents a lower percentage of subjects who maintained a 30% PANSS response over time was observed compared to patients in 15-17 years.

Risks

Unfavourable effects

Identified risks did not differ by nature between the adult and adolescent population but in terms of frequencies of EPS symptoms, weight gain, somnolence/sedation, triglycerides level and a slightly higher rate of suicidality-related events.

Weight increases have occurred at higher incidence in younger adolescents compared to older adolescents.

Somnolence was found to be higher in adolescents compared to adults, dose-related (6 to 26%) and higher compared to placebo (4%) and also detected in 23% of patients during long-term treatment.

A clear dose-response pattern was observed for several safety parameters including common adverse events (somnolence, akathisia, tremor, and dystonia), EPS related adverse events (hyperkinesia, dystonia, and tremor) and associated use of anticholinergic medications, and mean increases in body weight and BMI. In addition, elevation in serum prolactin has been noted across all paliperidone ER treatment groups and was clearly increased by dose.

Uncertainty in the knowledge about the unfavourable effects

There are limited data on the long term safety of paliperidone in the paediatric population, especially in patients aged 12-14 years.

Importance of favourable and unfavourable effects

Paliperidone (Invega) is an oral prolonged-release formulation, and do not require dose titration at initiation treatment. The clinical programme was part of an agreed PIP. Currently, authorised antipsychotics are limited for the treatment of schizophrenia in the paediatric population. There is therefore a need for evidence-based therapeutic options in this patient population. The efficacy of paliperidone ER was demonstrated over placebo in adolescent patients with schizophrenia at week 6, for the medium dose group only. The proportion of patients aged 12-14 years was relatively small to conclude on the efficacy (short term and maintenance of effect) in this population. In patients aged 15-17 years old, statistically significant differences versus placebo were observed in both the Medium ($p=0.005$) and High ($p=0.012$) dose groups of paliperidone ER for the primary endpoint at week 6. In addition, consistent efficacy findings were observed for the subgroup analyses on the secondary efficacy endpoints. Although the maintenance study did not meet its primary objective ie paliperidone ER did not demonstrate superior efficacy compared to aripiprazole, robust and clinically meaningful reductions in mean PANSS total score were observed for both paliperidone ER and aripiprazole and were numerically similar.

In the studied paediatric population, the overall safety profile appeared similar to that seen in adults..

Following the CHMP concerns over the lack of sufficient evidence of short term and long term efficacy in subjects aged between 12-14 years, the MAH proposed to restrict the proposed indication to treatment of schizophrenia in adolescents 15 years and older. According to the Schizophrenia Guideline (EMA/CHMP/40072/2010 Rev.1), data on maintenance of effect may be extrapolated from adults to adolescents as of the age of 15 years. Furthermore, considering individual dose strategy was supported by PK/PD data (including weight based dosing recommendation) and that the pharmacokinetic profile is expected to be similar between adolescents (15 years and older) and adults, the CHMP considered that the efficacy was established in patients over 15 years and older at a recommended starting dose of 3 mg.

Benefit-risk balance

Considering the efficacy and safety data across paediatric age groups from 12-17 years, the CHMP considered that limited data were available to conclude on a positive benefit-risk balance of paliperidone ER in the treatment of schizophrenia in patients aged 12-14 years old. In contrast, the efficacy and safety in the older paediatric population (15-17 years) have been sufficiently established. Therefore, in agreement with the MAH, the CHMP concluded on a positive benefit-risk balance in the following indication:

“INVEGA is indicated for the treatment of schizophrenia in adolescents 15 years and older.”

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to add the treatment of schizophrenia in adolescents 15 years and older. Consequential changes were made in sections 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 to include efficacy and safety information resulting from the submitted paediatric studies. The Package Leaflet has been amended accordingly. In addition, the list of local representatives in the Package Leaflet has been revised to amend contact details for the representatives of Luxembourg and Belgium.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/154/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.