Clinical Pharmacology Review

NDA Number:	21999
Submission Type; Code:	Pediatric Supplement, S-024
Applicant Name:	Johnson & Johnson
Submission Dates:	10/08/2010
Brand Name:	Invega®
Generic Name	Paliperidone
Dosage Form/Strenght:	ER Tablet/1.5, 3, 6, and 9 mg
Proposed Indication:	(b) (4) treatment of schizophrenia in adolescents 12-17 year old
OCP Review Team:	Islam R.Younis, Ph.D., Yaning Wang, Ph.D., Jogarao V. Gobburu, Ph.D.

Required Office Level Briefing held on 01/20/2011

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1 EXECUTIVE SUMMARY

The sponsor is seeking approval for paliperidone ER for the (b) (4) treatment of schizophrenia in adolescents 12-17 years of age. This supplement is submitted to satisfy the pediatric written request issued on 11/2/2006 and amended on 8/29/2007 and 3/31/2010. The submission contains a one phase I single and multiple dose PK study, one pivotal efficacy clinical trial in which sparse PK samples were collected, a population PK analysis using data form the above two studies and phase I adult data, and long-term safety study.

In the efficacy trial, paliperidone ER was administered to adolescents 12-17 years old on weight based dosing at three dose levels; low, medium, and high. The three dose levels were 1.5, 3, and 6 mg for subjects < 51 Kg and 1.5, 6, and 12 mg for subjects ≥ 51 Kg. A placebo group was included and the primary endpoint was change from baseline in the total PANSS score (LOCF) at end point. Pooled analysis indicated that only the medium dose was statistically significant relative to placebo. Subgroup analysis showed that the high dose for < 51 Kg group performed worse than placebo.

The following conclusions were reached upon reviewing the application:

1. Dose, exposure response analysis provides substantial evidences to support the efficacy paliperidone for the treatment of schizophrenia in adolescents 12-17 year of age.
2. The diminished efficacy of the high dose group in the < 51 Kg group can not be explained by exposure, dropouts, PANSS subscales, baseline characteristics, or time course of effect.
3. Population PK analysis indicated similar PK properties of paliperidone in adolescents ≥ 51 Kg and adults, and a 23% higher exposure for the < 51 Kg adolescents.

1.1 Recommendations

The Office of Clinical Pharmacology recommends the approval paliperidone for the treatment of schizophrenia in adolescents 12-17 years of age.

Acceptability of specific drug information is provided below:

Decision	Acceptable to OCP?	Comment
Overall	Yes	Pending satisfactory labeling agreement with sponsor
Evidence of Effectiveness	Yes	1 positive registration trial; dose-response.
Proposed Dosing	No	Starting dose should be 3 mg in adolescents < 51 Kg and 6 mg in adolescents ≥ 51 Kg. The maximum dose is 6 mg in adolescents < 51 kg and 12 mg in adolescents ≥ 51 Kg.
Proposed Labeling	No	Pending satisfactory agreement with sponsor

1.2 Labeling Recommendations

Strikethrough text is recommended to be deleted and underlined text is recommended to be added.

(b) (4)

2 QUESTION BASED REVIEW

2.1 Specific Questions

2.1.1 Does dose, exposure-response support effectiveness of paliperidone in adolescents?

Yes, over all dose- and exposure-PANSS relationship is significant. Figure 1 shows the dose-response relationship for paliperidone ER in adult and adolescents, and for risperidone (whose metabolite is paliperidone). In the subjects weighing ≥ 51 kg, there was a clear dose-response with 6 mg and 12 mg providing similar effects. In subjects weighing < 51 kg, the high dose of 6 mg resulted in a PANSS change of -7.4 units while that for placebo was -14.4 units. This anomalous result could not be explained by exposure, baseline and/or drop-out differences in the high dose group. As overall there is no clear additional benefit for the higher doses, the medium doses are recommended as starting doses. Mean placebo-corrected decrease in PANSS for paliperidone adolescents is similar to that for adults, and risperidone in adolescents. Higher doses for risperidone did not show added benefit.

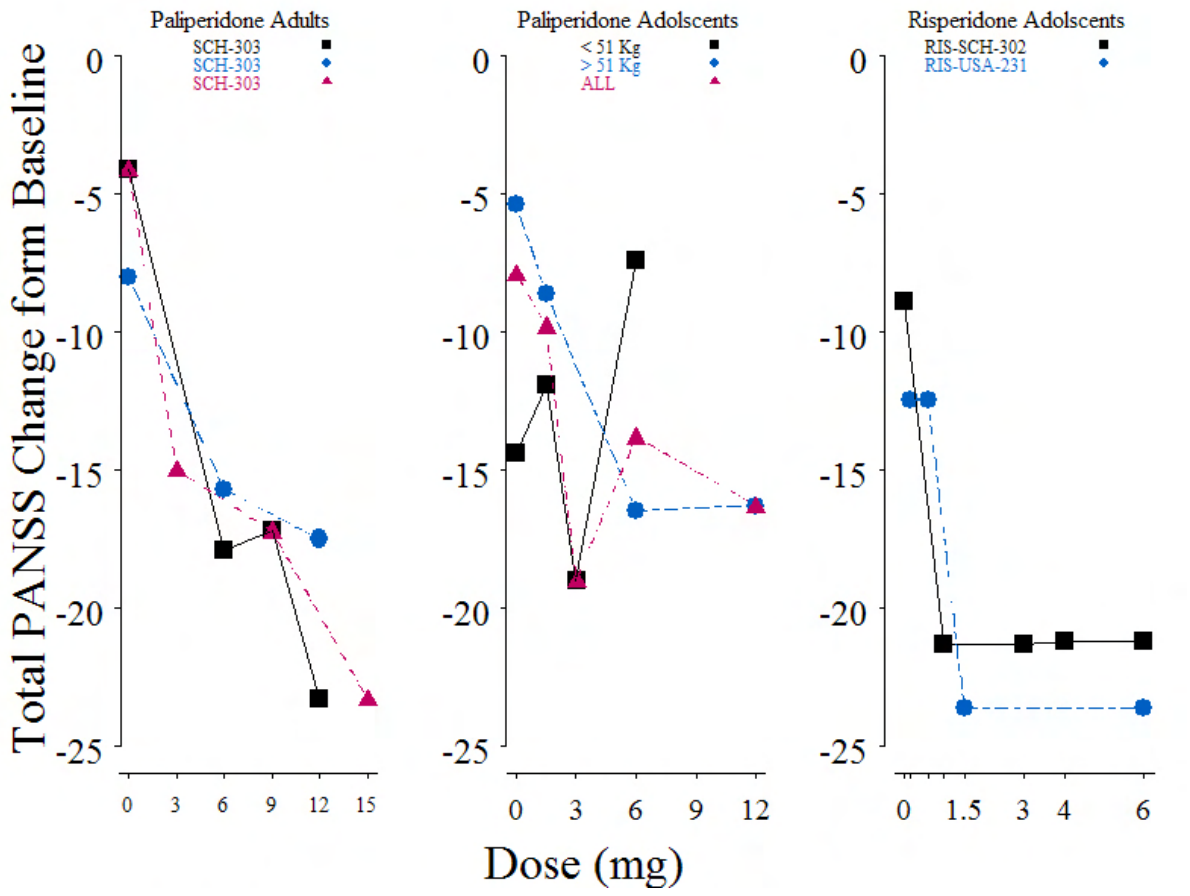

Figure 1. Dose-response of paliperidone ER in adults and adolescents and risperidone in adolescents.

2.1.2 Is the proposed dosing by weight category appropriate?

Dosing by weight provides a similar exposure in the two weight groups at all dose levels (Figure 2). The exposures in subjects weighing ≥ 51 kg are similar to those in adults. The exposures in subjects weighing < 51 kg are 23% more than those for adults.

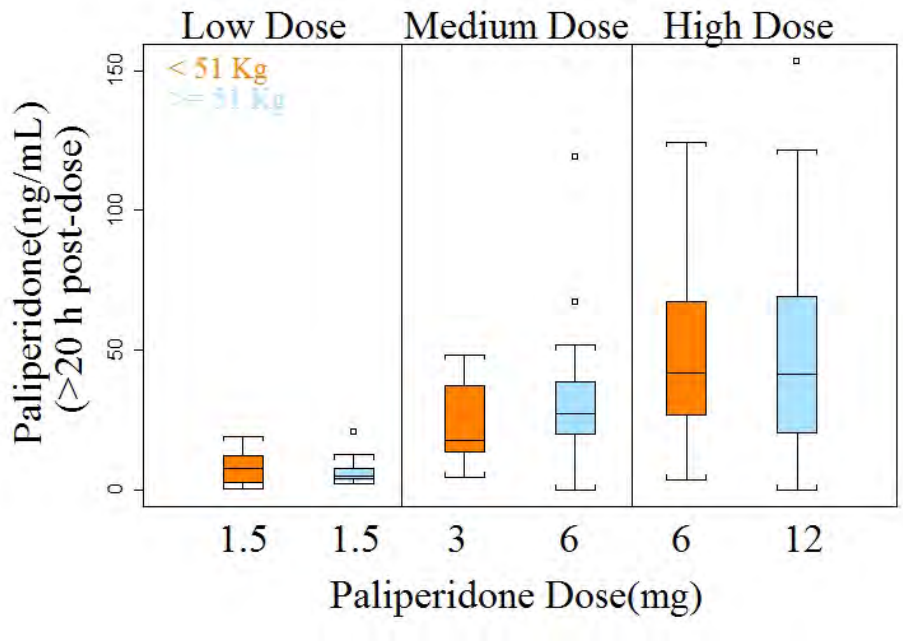

Figure 2. Paliperidone plasma concentration by dose level and weight group.

3 INDIVIDUAL STUDY REVIEWS

3.1 Pharmacokinetics

<table>
<tr><td>Report # EDMS-PSDB-6209922:3.0</td><td>EDR Link</td></tr>
<tr><td>Investigator: Vasile Chirita, M.D</td><td>Study Period: 03/17/2006 – 08/20/2006</td></tr>
<tr><td colspan="2">Title: Open-label study to evaluate the safety and pharmacokinetics of a single- and multiple-dose extended-release OROS paliperidone in pediatric subjects (≥10 to ≤17 years of age) with schizophrenia, schizophrenic disorder, or schizophreniform disorder.</td></tr>
<tr><td colspan="2">Objectives: Characterize PK, safety and tolerability of paliperidone in adolescents 10 – 17 years old following a single and multiple doses.</td></tr>
<tr><td colspan="2">Study Design:
- This was a multi-center, open-label, sequential ascending design study.
- Doses: 0.086, 0.129, and 0.171 mg/kg/day.
- Safety was evaluated before moving to the multiple doses phase for every subject and before incorporating the higher dose cohort.
- Study Phases: 1.Screening: Day -21 - Day 0/2. Single Dose PK: Day 1/3. Multiple Dose PK: Day 3-Day 9
- PK plasma sampling: within each dosage group, subjects were randomly assigned to 1 of 2 PK blood sampling schemes shown in the table below; p corresponds to pre-dose, time is in h post-dose.
<table>
<tr><td>Day</td><td>1</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td>Schedule A</td><td>P, 12,30</td><td>P</td><td>P</td><td></td><td>P</td><td></td><td></td><td>P,12,24</td></tr>
<tr><td>Schedule B</td><td>P, 8, 14, 36</td><td>P</td><td></td><td>P</td><td></td><td>P</td><td></td><td>P, 6,24</td></tr>
</table>
- Urine PK samples were collected during the following intervals: 0 - 6 hours, 6 - 12 hours, and 12 - 24 hours after dosing on Day 9.
- Plasma protein binding was assessed using pre-dose Day 1 samples ex vivo, and using subjects samples obtained on Day 9.
- PK parameters were calculated using non-compartmental methods.</td></tr>
<tr><td colspan="2">Results:

<u>Analytical Method:</u> A validated LC-MS/MS method with an LOQ of 0.2 ng/mL abd dynamic range of 0.2 – 100 ng/mL was used for the determination of paliperidone enantiomers in human plasma. The performance of the analytical method during study samples analysis, in terms of accuracy and precession, is acceptable. The validation of the method is acceptable.

<u>Study Population:</u>
<table>
<tr><td>Randomized/Completed/ Discontinued Due to AE</td><td>25/24/0</td></tr>
<tr><td>Age [Median (range)]</td><td>14 (10 – 17)</td></tr>
<tr><td>Male/Female</td><td>18/7</td></tr>
<tr><td>Race (Caucasian/Black/Asian/other)</td><td>14/6/5/0</td></tr>
<tr><td>Body Weight (Kg) [Median (range)]</td><td>64.5 (31-89)</td></tr>
</table></td></tr>
</table>

PK:

1. Single dose: Single dose PK parameters were not reported. Figure 3 shows the mean plasma concentration vs. time profile at the three dose levels. Note that the mean weight was 73.3, 58.8, and 58.1 Kg in the 0.086, 0.129, and 0.171 mg/kg/day groups, respectively.

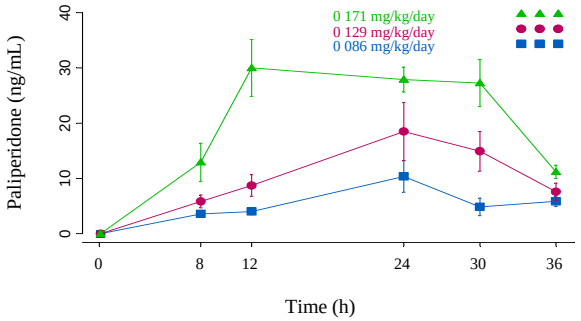

Figure 3. Paliperidone mean plasma concentration ± SE vs. time profile following a single dose.

2. Multiple Doses:

- Steady state was attained within 4-5 days of dosing (Figure 2, page 53 of sponsor report)

- Steady state PK parameters were estimated using Day 9 plasma levels and are displayed in the table 1 . Note that the table contain sponsor provided adult paliperidone steady state PK parameters previously obtained for comparison.

Table 1. Paliperidone steady state PK parameters in adolescents and adults.

	Adolescents (current study)		**Adult (previous studies)**	
Parameter	Mean	%CV	Mean	%CV
fu, %	25.6	20.1	26.1	16.9
$Cmax_{,0-24}$, ng/mL	34.2	65.3	23.7	51.9
AUC_{0-24}, ng·h/mL	686	65.4	457	51.5
CL/F, mL/min	209	56.3	268	44.4

- Paliperidone (+)/(-) enantiomer ratio were 1.3-1.5.
- Urine PK parameters are displayed in Table 2.

Table 2. Paliperidone urine PK parmeters.

Parameter	Mean	%CV
% of the dose renally excreted	24.4	51.8
CL_R, mL/min	42.4	41.0
CL_R, mL/min (Adult)	36.2	43.6

Safety

- There was no death or serious treatment-emergent adverse events (TEAE).
- 15 subjects experienced at least one TEAE. The most common adverse events (>10%) were sedation (n=4) and epistaxis (n=3).
- One subject in the 0.171 mg/kg/day group (12 year old and 37.9 Kg) had tachycardia.
- In general the incidence of TEAE increased with increasing the dose.

Conclusion

- Plasma steady-state PK parameters of paliperidone in adolescents are in the same range as those observed in adults.
- Paliperidone is well-tolerated in adolescents 10 – 17 years old.

3.2 Pharmacometrics Review

3.2.1 Population PK

1 Results of Sponsor's Analysis

1.1 Data sets used for model development

Plasma samples from the following two studies were used in the analysis:

I. PSZ-1001: A phase I single and multiple dose PK study in children and adolescents 10 – 17 years old.
II. PSZ-3001: The pivotal paliperidone ER efficacy clinical trial in children and adolescents 12 -17 years old.

A total of 162 (105 males and 57 females) were included in the PK dataset, of which 66.6% were White, 10.5% Black, 1.2% Hispanic, and 22% Asian with median body weight of 58.1 Kg (range = 29.0 – 104.6 Kg).

III. (CSR PALIOROS-SCH-1011 (2005): An open-label, single- and multiple-dose study to evaluate the PK of paliperidone ER in healthy elderly and young subjects.
IV. CSR R076477-P01-1010 (2005): Dose-proportionality study of the five paliperidone ER (3, 6, 9, 12, and 15 mg) in healthy male subjects
V. CSR R076477-REI-1001 (2005): The PK of paliperidone ER in subjects with impaired renal function.

A total of 153 (110 males and 43 females) were included in the PK dataset, of which 90.2% were White, 5.9% Black, 3.3% Asian, and <0.7% other, with median body weight of 75.1 Kg (range: 46.2 – 112 Kg), and median age of 44 years (range: 46.2 – 122 Kg).

1.2 Model Development

1. Model 1: run adult pop PK model using adolescent's data.
2. Model 2: same as model 1 except body weight (BW) rather than lean body mass (LBM) was used as covariate on clearance, since both LBM and BW were highly correlated. Minimization was terminated.
3. Model 3: Data from three adult studies were added to the dataset. IIV included on V2 and D1. IOV was implemented on F and not on KA. Minimization was successful.
4. Model 4: A total of 11 identified outliers were removed in order to reduce η-shrinkage. This resulted in a minor improvement.
5. Model 5: Age was added as a covariate to model 3 and resulted in 1 point increase in OFV.

1.3 Paliperidone Final Population PK model

- Model Structure: An open two compartment model with sequential zero- and first-order absorption
- Covariates: Body weight and creatinine clearance on clearance (CL/F). For a covariate to be included, the drop in value of objective function should exceed 6.63 ($P<0.01$, χ^2, 1 df).
- Data: Log transformed data were used.
- Within-subject variability:
    1. Additive error model.
    2. Inter-occasion variability (IOV): exponential error model on F1.
- Inter-individual variability: Exponential error model on CL/F, V3, ALAG, V2, KA, D1, and Q.
- Estimation Method: FOCE
- Visual predictive check: model was considered acceptable if the median percent prediction error (PE%)and the median |PE|% were ≤ |15|% and 30%, respectively
- Model parameters are displayed in the Table 3. Figure 4 shows goodness of fit plot.

Table 3. Paliperidone final population PK model parameters.

Parameter	Estimate (RSE%)
CL/F (L/h)	10.9 (11.5)
V2 (L)	198 (6.7)
Q(L/h)	22 (10.0)
V3 (L)	244 (6.8)
D1	25.4 (0.7)
ALAG1	0.76 (8.7)
KA	0.63 (12.0)
BW on CL/F	0.727 (21.7)
CLcr on CL/F	0.024 (46.3)

- Simulated C_{avg} with phase 3 adult and adolescent data are displayed in the Table 4:

Table 4. Paliperidone simulated average plasma concentration.

Subgroup (dose)	**n**	**mean C_{avg} ± SD**	**median C_{avg} (min-max)**
Adults (6 mg)	947	24.3 ± 17.9	19.2 (3.03-136)
≥51 kg (6 mg)	889	23.7 ± 17.3	18.7 (3.03-131)
< 51 kg (6 mg)	58	33.5 ± 24.6	29.9 (7.14-136)
Adolescents ≥51 kg (3 mg)	730	12.2 ± 8.57	10.2 (1.60-71.2)
Adolescents ≥51 kg (6 mg)	730	24.5 ± 17.1	20.4 (3.20-142)
Adolescents < 51 kg (3 mg)	270	15.0 ± 10.7	11.3 (1.85-76.1)
Adolescents < 51 kg (6 mg)	270	30.1 ± 21.5	22.7 (3.70-152)

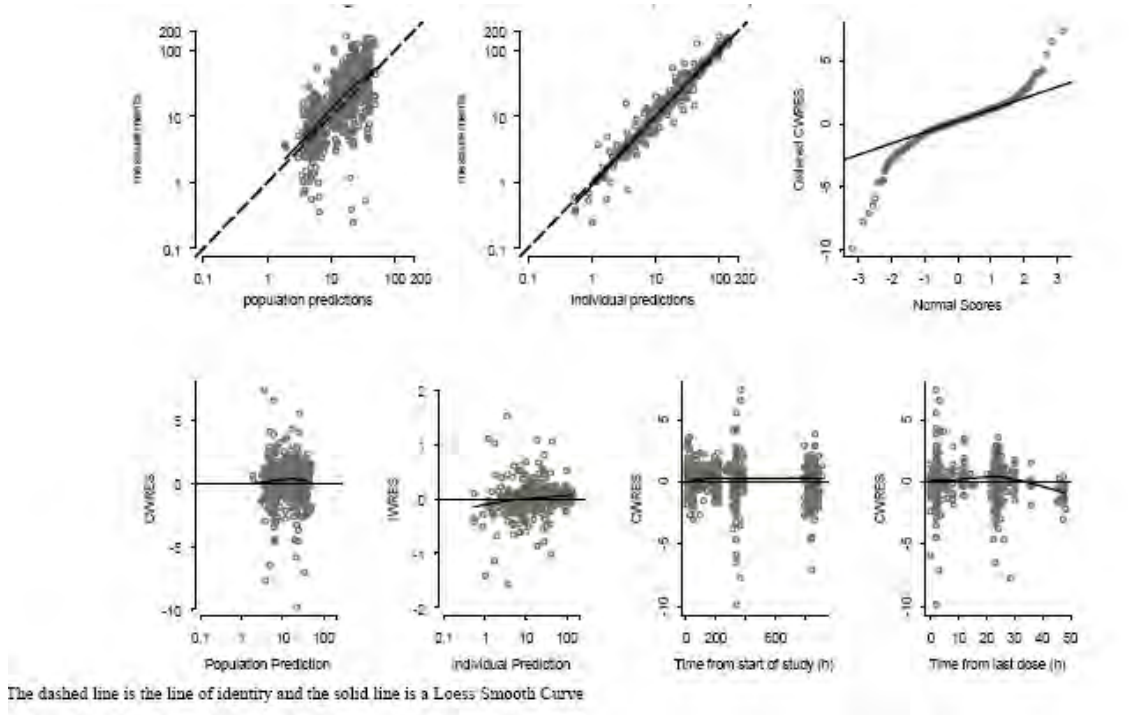

Figure 4. Paliperidone final model goodness-of-fit plots.

3.2.2 Exposure-Response

1 RESULTS OF SPONSOR'S ANALYSIS

1.1 Study

The sponsor conducted a randomized, multicenter, double-blind, 3 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. The study consisted of 3 phases: a screening phase (with a possible overlapping washout period), a 6-week double-blind treatment phase with an end-of-study or early-withdrawal visit, and a 1-week follow-up visit for subjects who did not enter an optional, long-term, open-label safety study. A total if 200 subjects were randomly assigned to receive placebo (N=51), paliperidone ER low dose treatment (N=54), paliperidone ER medium dose treatment (N=48), or paliperidone ER high dose treatment (N=48).

The primary efficacy variable was the change in the PANSS total score from baseline to the last post-randomization assessment in the double-blind period of the study (end point).

1.2 Results

The mean change from baseline to end point in the PANSS total score is shown in the Table 5. There were no significant treatment-by-country or treatment-by-baseline PANSS interactions, but there was a significant treatment-by-baseline weight category interaction. There was a lower treatment effect among subjects in the paliperidone ER high dose treatment group who weighed <51 kg than in the other paliperidone ER treatment groups and the placebo group.

Table 5. Mean change from baseline in PANSS by pooled dose groups.

Dose	Placebo	Paliperidone		
		Low	Medium	High
Mean change in PANSS	-7.9	-9.8	-17.3	-13.8
p-value		0.508	0.006	0.086

2 REVIEWER'S ANALYSIS

2.1 Objectives

Analysis objectives are:

1. Explore if the dose, exposure-response support effectiveness of paliperidone in adolescents
2. Explain the diminished paliperidone efficacy in the high dose < 51 Kg group
3. Provide recommendations for approval

2.2 Software

Analysis was performed using JMP (version 7) and plotting was done using S-plus (version 8.1) and Excel.

2.3 Dose, Exposure-Efficacy Analysis

A placebo anchored linear regression of paliperidone dose vs. total PANSS (LOCF) at end point produced a significant slope. The p-value for the slope was 0.0321 for the weight normalized dose (mg/kg) and 0.0193 for the absolute dose in mg. This provides additional evidence for the efficacy of paliperidone ER for the treatment of schizophrenia in adolescents 12 – 17 years old.

A similar analysis was performed between paliperidone plasma concentrations (>20 hours post-dose) collected on Day 36 (week 6) and total PANSS at end point (LOCF), which also produced a significant slope (p-value = 0.0111, n=153). It should be noted that performing this analysis using Day 36 observed total PANSS (n=133) did not produce a significant slope due to dropout being mainly in the placebo and low dose group.

2.4 Paliperidone's diminished efficacy after high dose for subjects < 51 Kg group

The below factors were explored in an attempt to explain the diminished paliperidone efficacy in the high dose < 51 Kg group:

1. **Exposure**: Paliperidone exposure can not explain the diminished efficacy in the high dose < 51 Kg group. As shown in Figure 2, paliperidone exposure increased with increasing doses within each weight group, and was similar at each dose level across the two weight groups.
2. **Dropouts**: As shown in Figure 5, the percentage of dropouts is slightly higher in the high dose group compared to the medium dose group in both weight groups. However, the difference is minimal. It should be noted that most of the dropouts were in the placebo and low dose groups due to lack of efficacy (64.5%). This conclusion is ensured when the average change from baseline in total PANSS was compared in the dropout's patients and patients remaining in the study at each visit as shown in the

Table 6. Only two patients withdrew due to adverse event; one was in the high dose < 51 Kg group and the other was in the low dose ≥ 51 Kg group. The total number of dropouts in the high < 51 Kg group was three; one due to adverse events, one due to lack of efficacy, and one due to consent withdrawal. Moreover, when the mean change from baseline in PANNS at each dose level and within each weight group using the observed data instead of the LOCF data was plotted, the same trend of diminished activity in the < 51 Kg group was still present, Figure 6.

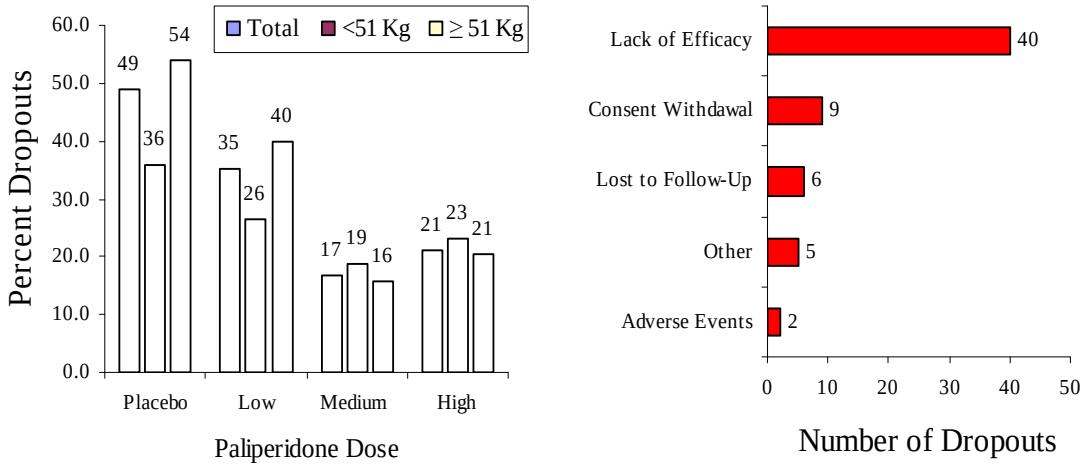

Figure 5. Percent of dropout per treatment arm and weight group(Left Panel), and distribution of dropout reasons (Right Panel).

Table 6. Mean change from baseline in PANSS in patients who remained and dropped out from the study.

Time Interval(Days)	1-8	8-15	15-22	22-29	29-36	36-43
N Remaining	200	194	186	158	149	140
Mean Δ PANSS	-4.14	-7.2	-10.1	-14.6	-16.3	-17.9
N Drops	0	6	8	28	9	9
% Drops		3%	4.1%	15%	5.7%	6.0%
Mean Δ PANSS		-3.7	-2.5	2.7	2.8	7.1

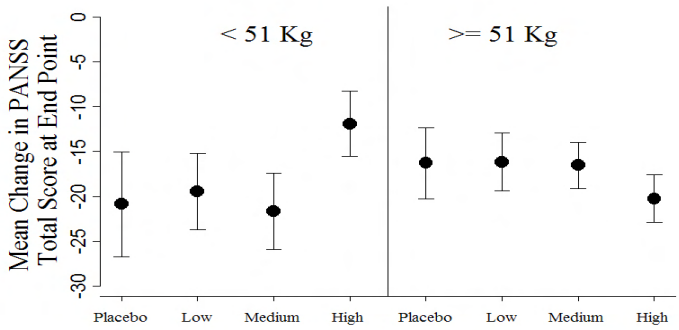

Figure 6. Mean change form baseline in total PANSS (± SE) using data from patients who remained in the study, no LOCF.

3. **Subscales of the primary end point**: The primary endpoint, total PANSS, is composed of three major components: positive subscale, negative subscale, and general psychopathology subscale. It is possible that one of these components is driving the observed diminished efficacy. Figure 7 depicts total PANSS and the three components for each dose level within each weight group. The change from baseline in each component is lower at the high dose group compared to the medium dose group, although the difference is more pronounced at the general psychopathology subscale. As a result, the diminished activity in the high dose < 51 group can not be explained in terms of any of the PANSS subscales.

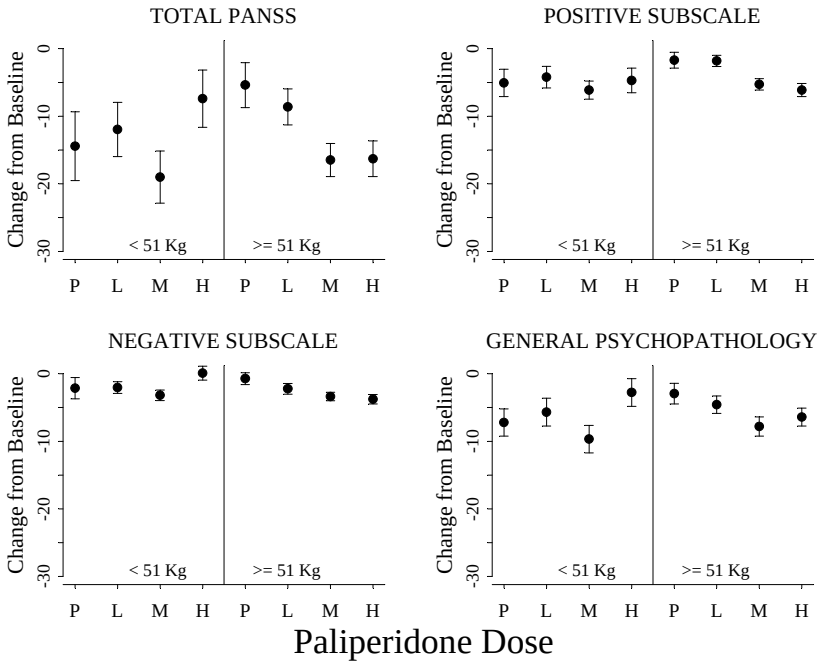

Figure 7. Change from baseline at end point (LOCF) in total PANSS and its subscales at different paliperidone dose levels within each weight group. P, placebo; L, low dose; M, medium dose; H, high dose.

4. **Baseline**: There is major difference in the subtypes of schizophrenia at baseline between the treatment arms. The high dose in the < 51 Kg group has a clear different distribution, with a much lower percentage of the paranoid subtype and a much higher percentage of undifferentiated subtype, Figure 8. This provides a potential explanation of the large placebo effect and diminished efficacy in the high dose arm of the < 51 Kg group. The unbalanced distribution of the schizophrenia subtype in the ≥ 51 Kg group may explain the flat dose-response due to the overestimation of the effect size for the medium dose arm because of the much lower percentage of undifferentiated subtype and the slightly higher percentage of paranoid subtype. Based on the above observations we can hypothesize that the paranoid subtype patients constitutes the responder group and undifferentiated subtype patients constitutes the non-responder group, Figure 9. This hypothesis needs furthers evaluation by comparing the response magnitude among subtype in other schizophrenia medications. There are no apparent differences in other baseline characteristics that can explain the difference in efficacy, as shown in Figure 10 and the Table 7

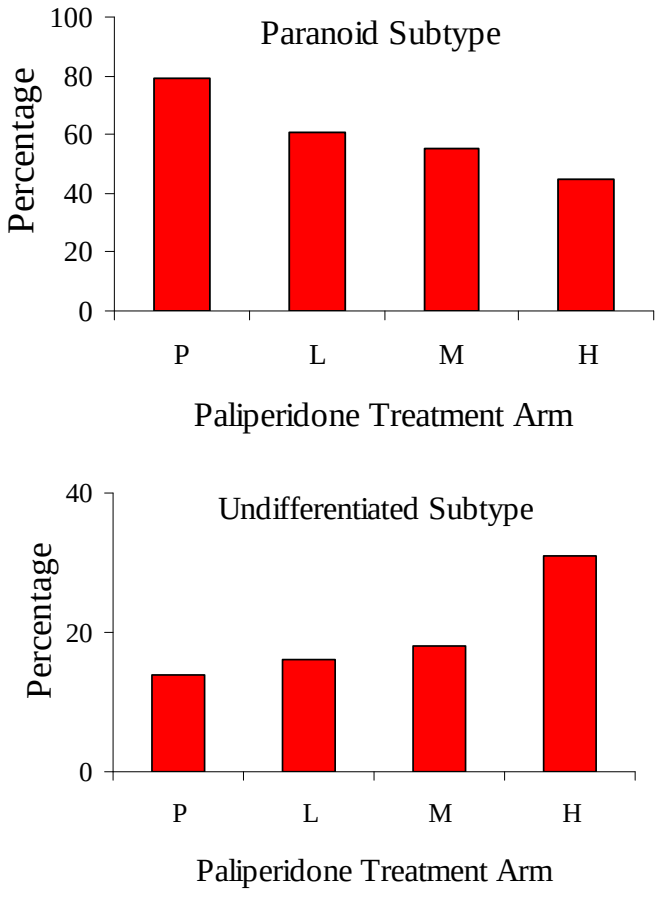

Figure 8. Schizophrenia subtype distribution in the < 51 Kg group; upper panel paranoid subtype; lower panel undifferentiated subtype.

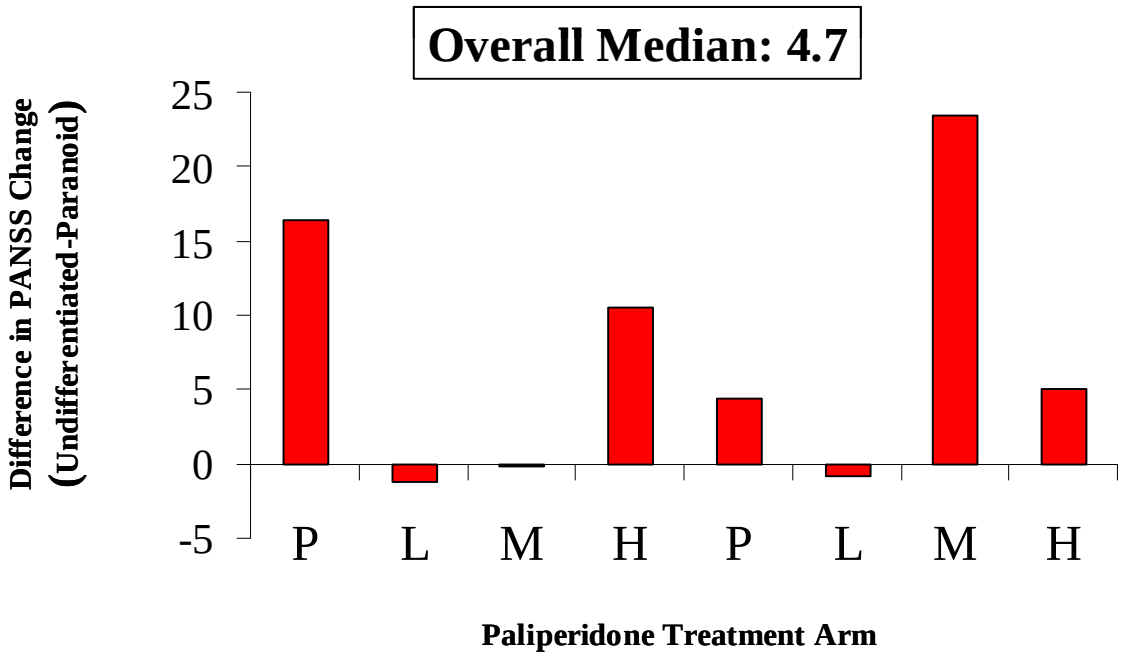

Figure 9. Difference in change from baseline in PANSS between undifferentiated and paranoid subtype of schizophrenia.

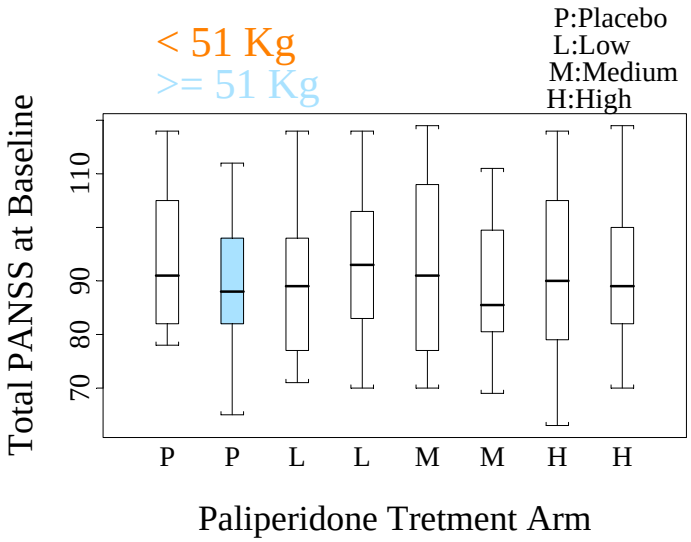

Figure 10. Total PANSS at baseline by treatment group.

Table 7. Baseline characteristics by weight group and treatment arm.

		Percent of subject							
		< 51 Kg				≥ 51 Kg			
		Placebo	Low	Medium	High	Placebo	Low	Medium	High
Country	India	35.7	63.2	50.0	61.5	16.2	2.9	9.4	5.9
	Romania	0.0	0.0	6.3	0.0	5.4	5.7	6.3	8.8
	Russia	35.7	21.1	25.0	30.8	43.2	51.4	50.0	44.1
	Ukraine	21.4	15.8	12.5	7.7	13.5	17.1	18.8	23.5
	USA	7.1	0.0	6.3	0.0	21.6	22.9	15.6	17.6
	Total	100	100	100	100	100	100	100	100
Race	Asian	35.7	63.2	50.0	61.5	18.9	5.7	9.4	5.9
	Black	7.1	0.0	0.0	0.0	8.1	14.3	9.4	14.7
	White	57.1	36.8	50.0	38.5	73.0	80.0	81.3	79.4
	Total	100	100	100	100	100	100	100	100
Gender	Female	64.3	73.7	43.8	46.2	51.4	28.6	31.3	23.5
	Male	35.7	26.3	56.3	53.8	48.6	71.4	68.8	76.5
	Total	100	100	100	100	100	100	100	100

5. **Adverse Events**: There are no apparent difference in the rate or type of adverse events (AE) that can explain the difference in efficacy as shown in Table 8. The rational was that some AE may negatively influence the outcome without causing the patient to dropout from the study.

Table 8. Adverse events by weight group and treatment arm.

	<51 Kg				>=51 Kg				Total
	Placebo	Low	Medium	High	Placebo	Low	Medium	High	
Number of Subjects per Treatment Arm	14	14	16	13	37	35	32	34	195
Number of Subjects with Adverse Events	10	10	8	9	20	17	21	26	121
% of Subjects with Adverse Events	71	71	50	69	54	49	66	76	62
Number of Subject with Severe Adverse Events	0	0	2	0	2	3	0	1	8
Number of Adverse Events (>10%) by Body System									
Gastrointestinal disorders	1	3	4	7	17	1	4	17	54
Nervous system disorders	3	7	9	7	4	14	22	46	112
Psychiatric disorders	4	5	1	3	25	17	5	13	73

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ISLAM R YOUNIS
03/08/2011

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