Table 41 ative Bioavailability of Paliperidone administered in Multiple Di\ .l Doses Compared to Administration as an Oral Solution– Stud .ZA-039

Arm	Profile Name	Total dose	Treatment Day 1	Treatment Day 2	Day	N	Cmax (ng/ml)	Tmax (hrs)	AUC(0-48) (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	t½ (hrs)
A	Ascend Profile	5.5 mg	3.5 mg solution in divided doses over 20.25 hrs	SD 2 mg solution	1	26	17.1 ± 5.4 (31.8) 10.5 - 32.1 [15.9]	22.6 ± 1.5 (6.6) 21.0 - 24.0 [23.9]			
					2	26	31.05 ± 10.64 (34.28) 15.5 - 59.3 [28.10]	2.29 ± 1.08 (47.26) 1.00 - 5.75 [2.0]			20.8 ± 6.3 (30.4) 13 - 44 [19.5]
					1&2	26	31.0 ± 10.6 (34.3) 15.5 - 59.3 [28.1]	25.9 ± 0.77 (3.0) 24.5 - 28.0 [26.0]	705.3 ± 263.8 (37.4) 296 - 1502 [666.0]	1171.0 ± 626.9 (53.5) 621 - 3305 [1004.3]	
B	Flat Profile	4.5 mg	2.5 mg solution in divided doses over 20.25 hrs	SD 2 mg solution	1	25	10.7 ± 3.7 (34.3) 6.5 - 24.3 [10.3]	19.2 ± 6.5 (34.0) 1.0 - 24.0 [21.0]			
					2	25	26.82 ± 7.31 (27.24) 16.0 - 48.5 [26.40]	2.0 ± 0.7 (34.62) 1.0 - 4.0 [2.0]			20.2 ± 4.1 (20.5) 13 - 29 [20.5]
					1&2	25	26.8 ± 7.3 (27.2) 16.0 - 48.5 [26.4]	26.0 ± 0.7 (2.7) 25.0 - 28.0 [26.0]	626.7 ± 177.8 (28.4) 383 - 1229 [617.5]	970.8 ± 309.9 (31.9) 492 - 1921 [945.2]	
C	IR Profile	4 mg	2 mg SD Soln	SD 2 mg Soln	1	27	18.2 ± 5.9 (32.25) 8.4 - 34.2 [17.3]	1.7 ± 0.94 (54.7) 1.0 - 4.0 [1.9]			
					2	27	22.89 ± 7.54 (32.95) 5.8 - 44.7 [22.40]	2.42 ± 1.83 (75.9) 1.0 - 8.0 [2.0]			21.3 ± 6.7 (31.5) 13 - 38 [18.7]
					1&2	27	23.2 ± 7.0 (30.3) 11.5 - 44.7 [22.4]	25.4 ± 5.2 (20.5) 1.0 - 32.0 [26.0]	582.1 ± 195.7 (33.6) 291 - 1218 [580.7]	892.2 ± 349.1 (39.1) 415 - 1974 [849.1]	

	Contrast	LN(Cmax) Day 1	LN(Cmax) Day 2	LN(AUCinf) (Dose Normalized to 4 mg)
Ratio 90% CI	Trt A/ Trt C	96.9 91.2 - 103.0	145.8 131.1 - 162.2	98.4 89.2 - 108.6
	Trt B/ Trt C	60.7 57.1 - 64.5	121.9 109.6 - 135.6	102.9 93.2 - 113.6
	Trt A / Trt B	159.7 150.3 - 169.8	119.6 107.5 - 133.0	95.6 86.6 - 105.6

Table 42 Prolactin Response to Paliperidone Administered in Multiple Divid Doses and as an Oral Solution – Study ALZA-039

Arm	Profile Name	Total dose	Day 1	Day 2	Day	N	Cmax (ng/ml)	Tmax (hrs)	AUC(0-48) (ng/ml x hr^{-1})
A	Ascend Profile	5.5 mg	3.5 mg solution in divided doses over 20.25 h	SD 2 mg Soln	1		1632.0 ± 1202.6 (73.7) 613 - 5938 [1235.0]	3.6 ± 1.6 (45.3) 1.0 - 7.0 [4.0]	
					2		898.5 ± 471.9 (52.5) 299 - 1921 [734.5]	15.4 ± 8.25 (53.4) 2.0 - 24.3 [12.0]	
					1 & 2	26	1632.0 ± 1202.6 (73.7) 613 - 5938 [1235.0]	3.6 ± 1.6 (45.3) 1.0 - 7.0 [4.0]	42531.5 ± 25074.6 (59.0 14846 - 106715 [32545.8]
B	Flat Profile	4.5 mg	2.5 mg solution in divided doses over 20.25 h	SD 2 mg Soln	1		2625.9 ± 2472.5 (94.2) 704 - 12086 [1869.0]	1.26 ± 0.4 (33.4) 1.0 - 1.9 [1.0]	
					2		999.0 ± 625.0 (62.6) 416 - 2861 [758.0]	10.3 ± 9.3 (90.2) 1.0 - 24.0 [8.0]	
					1 & 2	25	2625.9 ± 2472.5 (94.2) 704 - 12086 [1869.0]	1.26 ± 0.4 (33.4) 1.0 - 1.9 [1.0]	46626.2 ± 32524.2 (69.8 18520 - 157917 [35410.3]
C	IR Profile	4 mg	SD 2 mg Soln	SD 2 mg Soln	1		2996.0 ± 2752.6 (91.9) 831 - 13441 [1993.0]	1.1 ± 0.24 (22.9) 1.0 - 1.9 [1.0]	
					2		1068.9 ± 834.2 (78.0) 454 - 4461 [745.0]	8.8 ± 9.5 (108.0) 1.0 - 24.2 [4.0]	
					1 & 2	27	2996.0 ± 2752.6 (91.9) 831 - 13441 [1993.0]	1.1 ± 0.24 (22.9) 1.0 - 1.9 [1.0]	46228.6 ± 32375.5 (70.0 18053 - 162422 [32671.4]
D	PBO		PBO Soln SD	PBO Soln SD	1		442.0 ± 193.7 (43.8) 213 - 1110 [390.0]	16.9 ± 5.2 (30.8) 0.5 - 21.0 [18.0]	
					2		330.7 ± 114.4 (34.6) 184 - 589 [302.0]	10.7 ± 5.4 (50.) 4.3 - 24.0 [8.0]	
					1 & 2	25	454.4 ± 191.2 (42.1) 214 - 1110 [398.0]	19.6 ± 8.0 (40.6) 0.5 - 32.0 [18.0]	12206.8 ± 4294.5 (35.2 7098 - 27801 [10974.4]

Table 43 Bioavailability of Paliperidone and Risperidone Administered in Multiple Divided Doses Compared to Administration of Risperidone as an Oral Solution Study ALZA-019

Rx Arm	Rx	Day 1	Day 2	Total (mg)	Day(s)	Analyte	N	Cmax (ng/ml)	Tmax (hr)	AUCτ (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	t½ (hrs)
A	Ris	4 mg in 15 dd over 21 hr	2 mg IR	6 mg	1	Ris	24	8.45 ± 7.49 (88.59) 0.7 - 30.6 [6.09]	21.3 ± 4.5 (21.3 1.0 - 24.5 [22.0]			
						Pal	24	11.22 ± 5.73 (51.04) 1.6 - 21.4 [12.00]	23.1 ± 1.0 (4.4) 22.0 - 24.5 [23.9]			
						Comb		[illegible] [illegible] [illegible]	22.4 ± 0.9 (3.9) 22.0 - 24.5 [22.0]			
					2	Ris		18.75 ± 14.22 (75.84) 1.2 - 61.9 [13.60]	1.3 ± 0.6 (44.5) 0.5 - 2.0 [1.0]			
						Pal		17.22 ± 8.31 (48.25) 3.0 - 29.9 [19.50]	5.5 ± 7.6 (136.7) 1.0 - 24.0 [2.0]			
						Comb		[illegible] [illegible] [illegible]	1.6 ± 1.1 (68.1) 0.5 - 6.0 [1.0]			
					1 & 2	Ris	24	18.75 ± 14.22 (75.84) 1.2 - 61.9 [13.60]	25.3 ± 0.6 (2.30) 24.5 - 26.0 [25.0]	285.7 ± 305.0 (106.8) 18 - 1210 [158.4]	357.8 ± 454.0 (126.9) 18 - 1792 [160.2]	**6.3 ± 6.0** **(94.6)** **2 - 24** **[3.9]**
						Pal	24	17.22 ± 8.31 (48.25) 3.0 - 29.9 [19.50]	29.5 ± 7.6 (25.6) 25.0 - 48.0 [26.0]	425.3 ± 195.7 (46.0) 80 - 752 [468.3]	775.3 ± 415.7 (53.6) 173 - 1620 [710.0]	**26.2 ± 15.2** **(57.9)** **13 - 76** **[19.9]**
						Comb		[illegible] [illegible] [illegible]	25.6 ± 1.01 (4.2) 24.5 - 30.0 [25.0]	711.0 ± 222.1 (31.2) 281 - 1343 [696.2]	[illegible] [illegible] [illegible]	
					Ratio Risperidone AUCinf / Paliperidone AUCinf						1.135 ± 2.061 (181.62) 0.05 - 6.81 [0.170]	
B	Pal	4 mg in 15 dd over 21 hr	2 mg IR	6 mg	1			[illegible] [illegible] [illegible]	22.2 ± 4.2 (19.1 3.0 - 24.0 [23.0]			
					2			[illegible] [illegible] [illegible]	2.4 ± 4.5 (187.2) 0.6 - 24.6 [2.0]			
					1 & 2	Pal	26	31.35 ± 10.66 (34.01) 3.1 - 55.9 [29.95]	24.6 ± 4.6 (18.8) 2.0 - 26.0 [26.0]	677.9 ± 216.0 (31.9) 64 - 1114 [652.6]	[illegible] [illegible] [illegible]	**21.1 ± 5.6** **(26.4)** **9 - 30** **[20.5]**
C	Pal	2 mg in 15 dd over 21 hr	2 mg IR	4 mg	1			9.83 ± 2.96 (30.09) 4.6 - 16.5 [9.47]	22.5 ± 3.1 (13.8) 8.0 - 24.3 [23.1]			
					2			23.49 ± 6.62 (28.17) 12.1 - 39.5 [23.35]	1.5 ± 0.6 (38.2) 0.5 - 2.1 [2.0]			
					1 & 2	Pal	26	23.49 ± 6.62 (28.17) 12.1 - 39.5 [23.35]	25.5 ± 0.6 (2.3) 24.5 - 26.1 [25.5]	460.1 ± 120.1 (26.1) 228 - 708 [459.8]	758.0 ± 246.5 (32.5) 349 - 1260 [747.9]	**20.8 ± 5.2** **(24.8)** **11 - 32** **[20.8]**
D	Ris	2 mg IR	2 mg IR	[illegible]	1	Ris	16	16.08 ± 8.97 (55.81) 2.7 - 38.8 [17.10]	1.0 ± 0.4 (36.8) 0.5 - 1.9 [1.0]			
						Pal		7.29 ± 3.72 (51.01) 1.5 - 14.0 [8.48]	8.9 ± 9.0 (100.2) 1.0 - 24.0 [8.0]			
						Comb		22.0 ± 7.9 (35.8) 8.7 - 39.5 [21.7]	1.0 ± 0.4 (40.6) 0.5 - 1.9 [1.0]			
					2	Ris	26	16.62 ± 12.66 (76.150 1.7 - 52.9 [12.70]	1.2 ± 0.4 (38.6) 0.5 - 2.0 [1.0]			
						Pal		10.6 ± 5.2 (49.3) 2.3 - 18.0 [11.45]	6.1 ± 7.8 (127.6) 0.50 - 24.0 [2.0]			
						Comb		26.4 ± 10.6 (40.1) 9.7 - 56.6 [25.1]	1.4 ± 0.5 (36.4) 1.0 - 2.1 [1.0]			
					1 & 2	Ris	24	18.08 ± 12.34 (68.28) 2.7 - 52.9 [17.80]	12.1 ± 12.4 (102.7) 0.5 - 26. [1.0]	290.2 ± 339.6 (117.0) 18 - 1388 [158.6]	364.6 ± 525.6 (144.1) 18 - 2248 [160.7]	**6.6 ± 6.5** **(97.7)** **1 - 25** **[4.3]**
						Pal	17	10.55 ± 5.20 (49.26) 2.3 - 18.0 [11.45]	29.9 ± 7.7 (25.8) 24.5 - 48.0 [26.0]	287.2 ± 132.4 (46.1) 63 - 497 [315.1]	497.5 ± 270.3 (54.3) 130 - 1212 [509.3]	**25.4 ± 12.0** **(47.0)** **13 - 63** **[22.3]**
						Comb		26.5 ± 10.6 (39.9) 9.7 - 56.6 [25.5]	21.6 ± 9.1 (42.0) 0.5 - 26.1 [25.0]	577.3 ± 279.3 (48.4) 220 - 1519 [536.2]	862.1 ± 467.0 (56.5) 333 - 2514 [731.6]	
					Ratio Risperidone AUCin / Paliperidone AUCinf						1.430 ± 2.263 (158.26) 0.06 - 8.42 [0.211]	

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3.10.4 Absolute and Relative Bioavailability, Enantiomer Pharmacokinetics and Interconversion - Study P01-0007

Study P01-0007 was a randomized, open-label, single-dose, 5-way crossover study in healthy adults to evaluate the absolute and relative bioavailability of paliperidone, and enantiomer pharmacokinetics and interconversion.

Treatments consisted of:

A Paliperidone Oral Solution 1 mg
B Paliperidone OROS 3 mg
C Paliperidone 1 mg IV over 30 minutes
D (+)-Paliperidone Oral Solution 1 mg
E (-)-Paliperidone Oral Solution 1 mg

With a 7 – 14 days inter-period washout phase.

3.10.4.1 Absolute and Relative Bioavailability

For immediate release paliperidone tablets the absolute oral bioavailability was 106% and for paliperidone OROS the absolute oral bioavailability was 28%. The relative bioavailability or paliperidone OROS relative to an oral solution was 26% (see Table 48).

Table 48 Absolute Bioavailability of IR Paliperidone Oral Solution and ER OROS Paliperidone Versus Paliperidone IV Infusion, Based Upon AUC∞ of Total Paliperidone - Study P01-1007

Treatment	N	AUC∞ Dose Normalized LS Mean[a]	MSE	Fabs Absolute Bioavailability (90% CI)	Frel Relative Bioavailability
PAL IV (1 mg)	20	216.37	—	—	—
PAL solution (1 mg)	20	229.59	—	106. 1 (189.6 - 125.7)	—
PAL ER OROS (3 mg)	20	59.91	0.317	27.7 (23.4 - 32.8)	26.1

a The AUC∞ of the 3 mg ER OROS paliperidone treatment was dose-normalized to 1 mg. Data are analyzed on log scale, but results are back-transformed to the original scale.

The overall exposures, (AUC_∞), after orally administered IR paliperidone po (1 mg) [mean, range; 241, 118 - 36] and ER OROS po (3 mg) [210, 32- 357] are comparable to exposures after i.v. treatment (1 mg) [233, 105-411], (see Table 50).

The maximal plasma concentration after ER OROS paliperidone (3 mg) administration was approximately 1/2 of the IR paliperidone oral administration (1 mg) Cmax, and ~ ¼ of the post i.v. administration (1 mg) Cmax.

3.10.4.2 Enantiomer Pharmacokinetics and Interconversion

The plasma-protein binding differs between the 2 paliperidone enantiomers and was 82% for (+)-paliperidone (R76543), 65% for (−)-paliperidone (R078544), and 76% for racemic paliperidone (R078547).

There is preferential conversion from the (-) to the (+) enantiomer *in vivo*. Specifically, after administration of the (+) R078543 enantiomer there is about 28% *in vivo* interconversion from the (+) R078543 to the (−) R078544 enantiomer, whereas after administration of the (-) R078544enantiomer there is about 55% *in vivo* interconversion from the R078544 (−) to the enantiomer R078543 (+). After administration of paliperidone as a racemate, the (+):(−) paliperidone AUC_∞ ratio is about 1.6, irrespective of the route of administration and type of formulation, Although when unbound drug is examined the AUC for (-)-paliperidone is higher. Cmax +:- ratios are 1.9 after administration of the racemate, 8:1 after administration of (+)-paliperidone and 0.5 after administration of (-)-paliperidone, (see Table 49, Table 50, Figure 35, and Figure 40). No differences were noted by CYP2D6 phenotype, (see Figure 36).

Table 49 Summary of Paliperidone Exposures and Enantiomer Ratios after Administration of Individual Enantiomers and Racemic Formulations – Study P01-1007

Drug		(+)-Paliperidone	(-)-Paliperidone	Racemic Paliperidone		
Route		PO	PO	PO	IV	PO
Formulation		Solution	Solution	Solution	Solution	OROS
Dose		1 mg	1 mg	1 mg	1 mg	3 mg
Rx Arm		D	E	A	C	B
AUCinf (ng/ml x hr^{-1})	(+/-)-Paliperidone	275 ± 109 (39.6) 112 - 554 [259]	219 ± 77.9 (35.6) 87.0 - 418 [206]	241 ± 73.1 (30.4) 118 - 366 [227]	233 ± 89.0 (38.3) 105 - 411 [215]	210 ± 100 (47.7) 31.7 - 357 [194]
	(+)-Paliperidone	205 ± 84.0 (40.9) 73.6 - 420 [193]	118 ± 43.5 (37.0) 49.4 - 234 [107]	153 ± 48.5 (31.7) 68.2 - 243 [145]	148 ± 60.5 (41.0) 58.4 - 274 [133]	133 ± 64.7 (48.5) 21.2 - 237 [128]
	(-)-Paliperidone	79.2 ± 23.3 (29.4) 49.8 - 137 [73.7]	110 ± 32.8 (29.8) 48.9 - 186 [110]	91.3 ± 23.3 (25.5) 50.0 - 128 [89.9]	89.4 ± 26.7 (29.8) 47.0 - 141 [87.6]	85.3 ± 29.0 (33.9) 27.4 - 136 [81.3]
	Ratio for Racemate (+:-)	—	—	1.7 (63% : 37%)	1.7 (63% : 37%)	1.6 (61% : 29%)
	Ratio for Admin Enantiomer (Administered : Converted)	2.6 (72% : 28%)	1.1 (45% : 55%)	—	—	—
Cmax (ng/ml)	(+/-)-Paliperidone	13.1 ± 5.3 (40.6) 5.4 - 25.2 [12.7]	6.1 ± 1.9 (30.7) 2.8 - 9.9 [6.0]	9.4 ± 2.3 (24.8) 3.6 - 12.9 [9.4]	17.8 ± 4.5 (25.0) 9.45 - 25.7 [19.0]	4.9 ± 2.1 (43.7) 1.2 - 9.0 [4.9]
	(+)-Paliperidone	12.2 ± 4.98 (40.7) 4.88 - 23.6 [11.9]	2.35 ± 1.64 (70.0) 0.807 - 8.27 [1.98]	6.5 ± 1.8 (26.9) 2.5 - 9.2 [6.8]	11.5 ± 2.94 (25.6) 6.02 - 16.3 [12.2]	3.2 ± 1.45 (45.7) 0.7 - 6.1 [3.2]
	(-)-Paliperidone	1.5 ± 0.5 (33.5) 0.8 - 2.7 [1.4]	4.9 ± 1.3 (27.1) 2.3 - 7.4 [4.8]	3.1 ± 0.7 (23.0) 1.3 - 4.1 [3.2]	6.3 ± 1.6 (24.7) 3.4 - 9.4 [6.5]	1.7 ± 0.7 (41.0) 0.5 - 30 [1.8]
	Ratio for Racemate (+:-)	—	—	2.1 (68% : 33%)	1.8 (64% : 35%)	1.9 (64% : 35%)
	Ratio for Admin Enantiomer (Administered : Converted)	8.1 (89% : 11%)	0.5 (32% : 64%)	—	—	—
Tmax (hr)	(+/-)-Paliperidone	1.8 ± 1.5 (85.2) 1.0 - 8.0 [1.5]	3.3 ± 1.9 (57.8) 1.5 - 8.0 [2.0]	1.8 ± 0.9 (50.5) 1.0 - 4.0 [1.5]	0.5	23.5 ± 4.9 (20.9) 6.0 - 28.0 [24.0]
	(+)-Paliperidone	1.5 ± 0.6 (37.6) 1.0 - 3.0 [1.5]	10.0 ± 5.2 (51.9) 6.0 - 24.0 [8.0]	1.5 ± 0.8 (53.7) 0.5 - 4.0 [1.5]	0.5	23.6 ± 4.9 (20.7) 6.0 - 28.0 [24.0]
	(-)-Paliperidone	9.4 ± 5.3 (56.2) 6.0 - 24.0 [8.0]	1.9 ± 0.5 (25.8) 1.0 - 3.0 [2.0]	2.4 ± 1.6 (66.9) 1.0 - 8.0 [2.0]	0.5	23.6 ± 5.0 (21.1) 6.0 - 28.0 [24.0]
	Difference	-6.5	-6.0	0.5	0.0	0.0

Table 50 Pharmacokinetics of Paliperidone and its' Enantiomers by CYP2D6 Phenotype when Administered as Paliperidone OROS, IV, or as Solutions of Paliperidone or its' Enantiomers - Study P01-1007

Treatment	Analyte	Subj	N	Tmax, h	Cmax, ng/ml	AUClast, ng/ml x hr^{-1}	AUC∞, ng/ml x hr^{-1}	t1/2, h	AUC∞, Ratio+/-	CL/F, ml/min	Fabs	CL, ml/min	AUCu,∞, ng/ml x hr^{-1}	fu	CLu/F, ml/min	CLu, ml/min
Treatment A: paliperidone, oral solution 1 mg	Pali	All Subjs	20	1.80 ± 0.91 (50.5) 1.00 - 4.00 [1.50]	9.38 ± 2.32 (24.8) 3.64 - 12.9 [9.44]	222 ± 65.3 (29.4) 101 - 338 [217]	241 ± 73.1 (30.4) 118 - 366 [227]	25.2 ± 4.3 (17.2) 18.8 - 33.3 [24.0]	1.66 ± 0.194 (11.7) 1.31 - 1.98 [1.67]	76.5 ± 26.8 (35.0) 45.5 - 141 [73.6]	108 ± 21.1 (19.5) 65.0 - 157 [106]	83.2 ± 34.7 (41.7) 40.6 - 159 [77.9]	58.1 ± 12.5 (21.5) 36.5 - 84.3 [57.9]	0.245 ± 0.0313 (12.8) 0.188 - 0.309 0.244	301 ± 70.5 (23.5) 198 - 457 288	326 ± 102 (31.2) 157 - 530 310
		PM	10	1.75 ± 0.89 (50.8) 1.00 - 4.00 [1.50]	9.62 ± 2.17 (22.5) 7.29 - 12.9 [9.21]	239 ± 64.8 (27.1) 152 - 338 [225]	257 ± 72.6 (28.3) 161 - 366 [244]	24.9 ± 4.0 (16.1) 18.8 - 32.2 [24.5]	1.80 ± 0.111 (6.2) 1.62 - 1.98 [1.80]	69.8 ± 19.6 (28.1) 45.5 - 104 [69.1]	97.7 ± 17.0 (17.4) 65.0 - 125 [99.8]	68.8 ± 25.1 (36.5) 40.6 - 104 [62.9]	59.3 ± 10.1 (17.0) 45.6 - 70.1 [61.0]	0.233 ± 0.0323 13.8 0.188 - 0.287 [0.234]	289 ± 51.9 18.0 238 - 365 [275]	285 ± 82.7 29.0 157 - 447 [263]
		EM	10	1.85 ± 0.97 (52.6) 1.00 - 4.00 [1.50]	9.13 ± 2.57 (28.1) 3.64 - 12.6 [9.75]	205 ± 64.5 (31.4) 101 - 299 [217]	225 ± 73.8 (32.8) 118 - 341 [226]	25.5 ± 4.9 (19.1) 19.7 - 33.3 [23.7]	1.51 ± 0.136 (9.0) 1.31 - 1.74 [1.48]	83.1 ± 32.1 (38.6) 48.9 - 141 [73.8]	118 ± 20.4 (17.2) 97.8 - 157 [113]	97.6 ± 38.0 (39.0) 52.7 - 159 [82.5]	56.9 ± 14.9 (26.3) 36.5 - 84.3 [57.9]	0.256 ± 0.0272 10.6 0.217 - 0.309 [0.255]	313 ± 86.6 27.7 198 - 457 [288]	367 ± 106 28.9 244 - 530 [323]
	R078543 (+)	All Subjs	20	1.53 ± 0.82 (53.7) 0.50 - 4.00 [1.50]	6.51 ± 1.75 (26.9) 2.54 - 9.20 [6.81]	140 ± 44.7 (31.9) 59.1 - 225 [135]	153 ± 48.5 (31.7) 68.2 - 243 [145]	25.7 ± 4.1 (16.1) 18.4 - 33.4 [25.0]		60.9 ± 23.3 (38.3) 34.3 - 122 [57.7]			26.7 ± 6.16 (23.1) 14.9 - 35.6 [26.1]	0.180 ± 0.0241 (13.4) 0.136 - 0.234 [0.181]	332 ± 90.0 (27.2) 234 - 560 [320]	
		PM	10	1.25 ± 0.42 (34.0) 0.50 - 2.00 [1.25]	6.78 ± 1.65 (24.3) 4.88 - 9.20 [6.34]	156 ± 44.2 (28.4) 97.2 - 225 [146]	169 ± 47.6 (28.3) 106 - 243 [160]	25.4 ± 4.0 (15.9) 18.4 - 32.4 [26.6]		53.2 ± 14.9 (28.1) 34.3 - 78.6 [52.6]			28.3 ± 4.84 (17.1) 21.6 - 33.0 [29.4]	0.174 ± 0.0260 (15.0) 0.136 - 0.215 [0.174]	303 ± 54.2 (17.9) 252 - 385 [286]	
		EM	10	1.80 ± 1.03 (57.4) 0.50 - 4.00 [1.50]	6.24 ± 1.89 (30.3) 2.54 - 8.90 [6.91]	125 ± 41.7 (33.4) 59.1 - 188 [130]	138 ± 46.7 (33.9) 68.2 - 213 [138]	25.9 ± 4.4 (17.0) 19.2 - 33.4 [24.8]		68.7 ± 28.1 (40.9) 39.1 - 122 [60.4]			25.0 ± 7.13 (28.5) 14.9 - 35.6 [24.8]	0.187 ± 0.0213 (11.4) 0.158 - 0.234 [0.185]	360 ± 111 (30.8) 234 - 560 [336]	
	R078544 (-)	All Subjs	20	2.38 ± 1.59 (66.9) 1.00 - 8.00 [2.00]	3.07 ± 0.705 (23.0) 1.26 - 4.07 [3.17]	80.3 ± 22.3 (27.8) 41.9 - 113 [80.7]	91.3 ± 23.3 (25.5) 50.0 - 128 [89.9]	25.9 ± 4.2 (16.1) 19.4 - 33.1 [24.9]		97.7 ± 27.6 (28.3) 65.1 - 167 [92.8]			31.4 ± 6.77 (21.6) 20.6 - 49.4 [31.5]	0.350 ± 0.0362 (10.3) 0.292 - 0.411 [0.349]	277 ± 60.3 (21.8) 169 - 406 [265]	
		PM	10	2.15 ± 1.03 (47.8) 1.00 - 4.00 [2.00]	2.99 ± 0.617 (20.6) 2.36 - 4.07 [2.89]	81.9 ± 22.1 (27.0) 50.1 - 113 [79.3]	92.5 ± 21.8 (23.6) 63.8 - 124 [90.0]	25.8 ± 3.8 (14.9) 19.4 - 31.8 [25.9]		94.7 ± 22.1 (23.3) 67.2 - 131 [93.1]			31.0 ± 5.30 (17.1) 23.8 - 37.1 [31.6]	0.341 ± 0.0376 (11.0) 0.292 - 0.404 [0.341]	276 ± 50.1 (18.1) 225 - 350 [265]	
		EM	10	2.60 ± 2.04 (78.4) 1.50 - 8.00 [2.00]	3.15 ± 0.809 (25.7) 1.26 - 4.00 [3.34]	78.7 ± 23.6 (30.0) 41.9 - 112 [80.7]	90.0 ± 25.8 (28.7) 50.0 - 128 [89.9]	26.1 ± 4.7 (17.9) 20.4 - 33.1 [24.2]		101 ± 33.2 (33.0) 65.1 - 167 [92.8]			31.8 ± 8.27 (26.0) 20.6 - 49.4 [31.5]	0.359 ± 0.0341 (9.5) 0.301 - 0.411 [0.361]	278 ± 71.9 (25.9) 169 - 406 [265]	

Treatment	Analyte	Subj	N	Tmax, h	Cmax, ng/ml	AUClast, ng/ml x hr^{-1}	AUC∞, ng/ml x hr^{-1}	t1/2, h	AUC∞, Ratio+/-	CL/F, ml/min	Fabs	CL, ml/min	AUCu,∞, ng/ml x hr^{-1}	fu	CLu/F, ml/min	CLu, ml/min
Treatment B: Paliperidone ER OROS 3 mg	Pali	All Subjs	20	23.46 ± 4.89 (20.9) 6.00 - 28.00 [24.00]	4.90 ± 2.14 (43.7) 1.22 - 9.04 [4.88]	187 ± 88.7 (47.4) 27.0 - 325 [184]	210 ± 100 (47.7) 31.7 - 357 [194]	25.2 ± 4.2 (16.7) 14.8 - 30.5 [26.5]	1.67 ± 0.201 (12.0) 1.27 - 2.00 [1.68]	356 ± 340 (95.4) 140 - 1577 [258]	31.0 ± 12.3 (39.5) 5.15 - 47.6 [31.3]	83.2 ± 34.7 (41.7) 40.6 - 159 [77.9]	53.8 ± 16.3 (30.3) 16.5 - 84.0 [51.5]	0.240 ± 0.0285 (11.9) 0.188 - 0.285 [0.242]	1060 ± 538 (50.7) 595 - 3025 [971]	319 ± 97.2 (30.5) 152 - 522 [307]
		PM	10	24.30 ± 3.65 (15.0) 15.00 - 28.00 [24.01]	5.75 ± 2.01 (35.0) 2.45 - 9.04 [5.68]	215 ± 80.2 (37.2) 61.0 - 325 [207]	240 ± 91.6 (38.2) 73.4 - 357 [232]	25.1 ± 4.1 (16.3) 14.8 - 29.3 [26.0]	1.81 ± 0.125 (6.9) 1.68 - 2.00 [1.81]	257 ± 162 (62.9) 140 - 681 [216]	31.0 ± 11.0 (35.5) 10.2 - 45.8 [32.5]	68.8 ± 25.1 (36.5) 40.6 - 104 [62.9]	55.0 ± 16.5 (30.1) 16.5 - 75.0 [56.7]	0.233 ± 0.0317 (13.6) 0.188 - 0.285 [0.234]	1082 ± 697 (64.4) 666 - 3025 [883]	288 ± 85.0 (29.5) 152 - 455 [288]
		EM	10	22.61 ± 5.97 (26.4) 6.00 - 26.00 [24.00]	4.05 ± 2.01 (49.6) 1.22 - 7.61 [3.55]	159 ± 91.9 (57.7) 27.0 - 303 [137]	179 ± 103 (57.6) 31.7 - 356 [158]	25.3 ± 4.6 (18.0) 14.8 - 30.5 [26.5]	1.51 ± 0.146 (9.7) 1.27 - 1.68 [1.49]	456 ± 443 (97.1) 140 - 1577 [318]	31.1 ± 14.0 (45.1) 5.15 - 47.6 [29.1]	97.6 ± 38.0 (39.0) 52.7 - 159 [82.5]	52.3 ± 17.0 (32.5) 36.5 - 84.0 [47.3]	0.249 ± 0.0230 (9.2) 0.217 - 0.283 [0.246]	1033 ± 277 (26.8) 595 - 1371 [1059]	357 ± 103 (28.9) 244 - 522 [327]
		All Subjs Except #5	19	24.37 ± 2.73 (11.2) 15.00 - 28.00 [24.00]	5.05 ± 2.08 (41.1) 1.22 - 9.04 [5.12]	196 ± 82.5 (42.2) 49.7 - 325 [188]	219 ± 93.3 (42.6) 58.3 - 357 [197]	25.7 ± 3.53 (13.7) 14.8 - 30.5 [26.6]	1.67 ± 0.201 (12.0) 1.27 - 2.00 [1.68]	292 ± 187 (63.9) 140 - 858 [254]	32.4 ± 10.9 (33.8) 10.2 - 47.6 [31.5]	83.3 ± 35.6 (42.8) 40.6 - 159 [74.4]	53.8 ± 16.3 (30.3) 16.5 - 84.0 [51.5]	0.240 ± 0.0285 (11.9) 0.188 - 0.285 [0.242]	1060 ± 538 (50.7) 595 - 3025 [971]	319 ± 97.2 (30.5) 152 - 522 [307]
	R078543 (+)	All Subjs	20	23.56 ± 4.88 (20.7) 6.00 - 28.00 [24.00]	3.16 ± 1.45 (45.7) 0.733 - 6.06 [3.15]	119 ± 58.4 (49.3) 16.7 - 218 [119]	133 ± 64.7 (48.5) 21.2 - 237 [128]	25.3 ± 5.0 (19.7) 14.4 - 33.2 [26.6]	277 ± 252 (91.1) 105 - 1179 [195]				23.0 ± 9.46 (41.1) 3.84 - 37.7 [23.7]	0.180 ± 0.0241 (13.4) 0.136 - 0.234 [0.181]	1502 ± 1347 (89.7) 664 - 6515 [1054]	
		PM	10	24.30 ± 3.65 (15.0) 15.00 - 28.00 24.01	3.79 ± 1.37 (36.2) 1.61 - 6.06 3.68	140 ± 54.4 (38.8) 38.9 - 218 132	157 ± 61.0 (38.9) 46.1 - 237 147	24.9 ± 4.5 (18.2) 14.4 - 30.3 26.6	199 ± 130 (65.2) 105 - 542 171				26.4 ± 8.31 (31.5) 7.65 - 37.1 27.2	0.174 ± 0.0260 (15.0) 0.136 - 0.215 0.174	1143 ± 763 (66.8) 673 - 3267 921	
		EM	10	22.81 ± 5.98 (26.2) 6.00 - 26.00 [24.00]	2.53 ± 1.28 (50.7) 0.733 - 4.81 [2.19]	97.0 ± 56.7 (58.5) 16.7 - 188 [82.8]	110 ± 62.4 (56.8) 21.2 - 219 [95.4]	25.8 ± 5.6 (21.7) 14.6 - 33.2 [26.6]	354 ± 322 (90.9) 114 - 1179 [262]				19.7 ± 9.74 (49.5) 3.84 - 37.7 [18.4]	0.187 ± 0.0213 (11.4) 0.158 - 0.234 [0.185]	1862 ± 1721 (92.4) 664 - 6515 [1359]	
		All Subjs Except #5	19	24.48 ± 2.67 (10.9) 15.00 - 28.00 [24.00]	3.26 ± 1.41 (43.3) 0.73 - 6.06 [3.34]	124 ± 54.7 (44.2) 30.7 - 218 [120]	139 ± 60.7 (43.6) 40.7 - 237 [128]	25.9 ± 4.41 (17.0) 14.4 - 33.2 [26.7]	229 ± 139 (60.8) 105 - 614 [195]				24.0 ± 8.54 (35.5) 7.65 - 37.7 [24.4]	0.180 ± 0.0247 (13.7) 0.136 - 0.234 [0.181]	1239 ± 669 (54.0) 664 - 3267 [1023]	
	R078544 (-)	All Subjs	18-20	23.56 ± 4.97 (21.1) 6.00 - 28.00 [24.00]	1.74 ± 0.712 (41.0) 0.485 - 2.98 [1.77]	67.4 ± 31.5 (46.7) 9.84 - 117 [64.7]	85.3 ± 29.0 (33.9) 27.4 - 136 [81.3]	25.5 ± 3.8 (15.0) 15.3 - 30.9 [26.6]							981 ± 498 (50.7) 539 - 2816 [909]	
		PM	10	24.30 ± 3.65 (15.0) 15.00 - 28.00 [24.01]	1.95 ± 0.648 (33.2) 0.842 - 2.98 [1.99]	73.9 ± 26.9 (36.4) 22.1 - 108 [74.6]	85.5 ± 29.1 (34.1) 27.4 - 119 [83.9]	25.2 ± 3.9 (15.7) 15.3 - 29.4 [27.0]							1027 ± 640 (62.3) 659 - 2816 [848]	
		EM	8-10	22.81 ± 6.13 (26.9) 6.00 - 28.00 [24.00]	1.52 ± 0.739 (48.6) 0.485 - 2.83 [1.41]	60.9 ± 35.7 (58.7) 9.84 - 117 [56.3]	85.2 ± 30.8 (36.1) 55.2 - 136 [75.8]	25.7 ± 3.9 (15.1) 17.2 - 30.9 [25.8]							923 ± 261 (28.2) 539 - 1348 [933]	
		All Subjs Except #5	18-19	24.48 ± 2.83 (11.6) 15.00 - 28.00 [24.00]	1.80 ± 0.68 (37.8) 0.49 - 2.98 [1.83]	70.4 ± 29.2 (41.5) 15.9 - 117 [65.4]	85.3 ± 29.0 (33.9) 27.4 - 136 [81.3]	25.9 ± 3.4 (13.0) 15.3 - 30.9 [26.9]							981 ± 498 (50.7) 539 - 2816 [909]	

Treatment	Analyte	Subj	N	Tmax, h	Cmax, ng/ml	AUClast, ng/ml x hr^{-1}	AUC∞, ng/ml x hr^{-1}	t1/2, h	AUC∞, Ratio+/-	CL/F, ml/min	Fabs	CL, ml/min	AUCu,∞, ng/ml x hr^{-1}	fu	CLu/F, ml/min	CLu, ml/min
Treatment C: Paliperidone 30-min. I.v. infusion 1 mg	Pal	All Subjs	20	0.50 ± 0.00 (0.00) 0.50 - 0.50 [0.50]	17.8 ± 4.46 (25.0) 9.45 - 25.7 [19.0]	213 ± 82.1 (38.6) 86.0 - 374 [206]	233 ± 89.0 (38.3) 105 - 411 [215]	24.6 ± 4.8 (19.5) 17.0 - 34.4 [24.4]	1.66 ± 0.222 (13.4) 1.24 - 2.00 [1.66]	–	–	83.2 ± 34.7 (41.7) 40.6 - 159 [77.9]	56.7 ± 16.9 (29.9) 29.9 - 104 [55.8]	0.242 ± 0.0285 (11.8) 0.189 - 0.287 [0.243]		319 ± 97.7 (30.6) 161 - 558 [299]
		PM	10	0.50 ± 0.00 (0.0) 0.50 - 0.50 [0.50]	18.8 ± 3.99 (21.2) 11.3 - 24.9 [19.5]	248 ± 85.4 (34.5) 142 - 374 [241]	272 ± 93.1 (34.3) 161 - 411 [265]	26.1 ± 5.3 (20.2) 17.0 - 34.4 [27.3]	1.82 ± 0.117 (6.4) 1.63 - 2.00 [1.81]	–	–	68.8 ± 25.1 (36.5) 40.6 - 104 [62.9]	62.0 ± 19.1 (30.8) 36.8 - 104 [62.5]	0.233 ± 0.0314 (13.5) 0.189 - 0.287 [0.235]		291 ± 84.9 (29.2) 161 - 453 [267]
		EM	10	0.50 ± 0.00 (0.0) 0.50 - 0.50 [0.50]	16.9 ± 4.90 (29.1) 9.45 - 25.7 [16.1]	178 ± 65.0 (36.5) 86.0 - 291 [188]	194 ± 68.2 (35.2) 105 - 316 [202]	23.1 ± 4.0 (17.2) 17.6 - 32.3 [23.1]	1.47 ± 0.152 (10.3) 1.24 - 1.66 [1.47]	–	–	97.6 ± 38.0 (39.0) 52.7 - 159 [82.5]	50.8 ± 12.7 (24.9) 29.9 - 69.0 [52.4]	0.251 ± 0.0226 (9.0) 0.218 - 0.284 [0.248]		351 ± 106 (30.3) 242 - 558 [318]
	R078543 (+)	All Subjs	20	0.50 ± 0.00 (0.0) 0.50 - 0.50 [0.50]	11.5 ± 2.94 (25.6) 6.02 - 16.3 [12.2]	135 ± 56.4 (41.9) 48.8 - 251 [124]	148 ± 60.5 (41.0) 58.4 - 274 [133]	25.0 ± 4.7 (18.8) 17.6 - 34.1 [25.8]		–	–	67.2 ± 30.8 (45.8) 30.4 - 143 [62.8]	25.7 ± 9.16 (35.7) 11.8 - 52.3 [23.3]	0.180 ± 0.0241 (13.4) 0.136 - 0.234 [0.181]		365 ± 134 (36.8) 159 - 706 [357]
		PM	10	0.50 ± 0.00 (0.0) 0.50 - 0.50 [0.50]	12.3 ± 2.70 (22.1) 7.14 - 16.1 [12.6]	161 ± 58.2 (36.1) 88.7 - 251 [156]	177 ± 62.8 (35.5) 102 - 274 [171]	26.1 ± 5.0 (19.1) 17.6 - 34.1 [27.3]		–	–	53.4 ± 20.2 (37.8) 30.4 - 81.7 [48.9]	29.9 ± 9.86 (33.0) 17.0 - 52.3 [29.8]	0.174 ± 0.0260 (15.0) 0.136 - 0.215 [0.174]		305 ± 93.7 (30.7) 159 - 489 [280]
		EM	10	0.50+ 0.00 (0.0) 0.50- 0.50 [0.50]	10.7 ± 3.09 (28.9) 6.02 - 16.3 [10.5]	108 ± 41.6 (38.6) 48.8 - 180 [115]	119 ± 43.7 (36.8) 58.4 - 195 [122]	24.0 ± 4.4 (18.5) 17.9 - 32.0 [24.1]		–	–	81.0 ± 34.2 (42.2) 42.7 - 143 [68.3]	21.5 ± 6.42 (29.9) 11.8 - 32.6 [22.4]	0.187 ± 0.0213 (11.4) 0.158 - 0.234 [0.185]		425 ± 146 (34.4) 256 - 706 [373]
	R078544 (-)	All Subjs	1920	0.50 ± 0.00 (0.0) 0.50 - 0.50 [0.50]	6.34 ± 1.57 (24.7) 3.43 - 9.36 [6.54]	77.0 ± 26.9 (35.0) 35.7 - 131 [77.8]	89.4 ± 26.7 (29.8) 47.0 - 141 [87.6]	25.4 ± 4.7 (18.5) 18.0 - 34.7 [25.5]		–	–	102 ± 32.5 (31.9) 59.1 - 177 [95.1]	30.5 ± 8.06 (26.4) 18.1 - 51.4 [32.4]	0.350 ± 0.0362 (10.3) 0.292 - 0.411 [0.349]		291 ± 78.2 (26.8) 162 - 461 [257]
		PM	10	0.50 ± 0.00 (0.0) 0.50 - 0.50 [0.50]	6.54 ± 1.31 (20.1) 4.17 - 8.79 [6.74]	86.0 ± 28.1 (32.7) 51.7 - 131 [85.0]	95.6 ± 29.7 (31.1) 59.7 - 141 [94.5]	26.5 ± 5.3 (19.9) 18.0 - 34.7 [27.5]		–	–	95.6 ± 30.9 (32.4) 59.1 - 140 [88.3]	32.1 ± 9.33 (29.0) 19.8 - 51.4 [32.7]	0.341 ± 0.0376 (11.0) 0.292 - 0.404 [0.341]		279 ± 77.8 (27.9) 162 - 422 [255]
		EM	9-10	0.50 ± 0.00 (0.0) 0.50 - 0.50 [0.50]	6.15 ± 1.84 (29.9) 3.43 - 9.36 [5.69]	68.0 ± 23.7 (34.8) 35.7 - 111 [73.0]	82.6 ± 22.5 (27.3) 47.0 - 121 [85.9]	24.3 ± 4.0 (16.6) 19.0 - 32.7 [23.8]		–	–	109 ± 34.6 (31.8) 68.9 - 177 [97.0]	28.8 ± 6.44 (22.4) 18.1 - 36.4 [30.3]	0.359 ± 0.0341 (9.5) 0.301 - 0.411 [0.361]		306 ± 80.7 (26.4) 229 - 461 [275]

Treatment	Analyte	Subj	N	Tmax, h	Cmax, ng/ml	AUClast, ng/ml x hr^{-1}	AUC∞, ng/ml x hr^{-1}	t1/2, h	AUC∞, Ratio+/-	CL/F, ml/min	Fabs	CL, ml/min	AUCu,∞, ng/ml x hr^{-1}	fu	CLu/F, ml/min	CLu, ml/min
Treatment D: R078543 (+) paliperidone (+) oral solution 1 mg	Pal	All Subjs	20	1.80 ± 1.53 (85.2) 1.00 - 8.00 [1.50]	13.1 ± 5.34 (40.6) 5.42 - 25.2 [12.7]	256 ± 102 (39.8) 93.7 - 508 [250]	275 ± 109 (39.6) 112 - 554 [259]	24.0 ± 4.2 (17.6) 18.3 - 32.6 [24.1]	2.81 ± 0.397 (14.1) 2.23 - 3.72 [2.69]	71.1 ± 31.3 (44.1) 30.1 - 149 [64.5]			63.8 ± 16.6 (26.1) 41.9 - 105 [62.3]	0.223 ± 0.0270 (12.1) 0.174 - 0.267 [0.225]	276 ± 63.9 23.1 158 - 398 [268]	
		PM	10	2.15 ± 2.14 (99.3) 1.00 - 8.00 [1.50]	14.1 ± 5.30 (37.7) 8.84 - 25.2 [13.5]	279 ± 106 (38.0) 159 - 508 [262]	298 ± 115 (38.6) 173 - 554 [281]	24.6 ± 4.1 (16.8) 18.3 - 32.6 [25.0]	3.02 ± 0.357 (11.8) 2.61 - 3.72 [3.06]	62.8 ± 21.3 (33.9) 30.1 - 96.3 [59.6]			62.8 ± 15.4 (24.6) 45.8 - 97.1 [62.3]	0.216 ± 0.0310 (14.4) 0.174 - 0.267 [0.217]	279 ± 61.4 22.0 172 - 364 [268]	
		EM	10	1.45 ± 0.37 (25.4) 1.00 - 2.00 [1.50]	12.2 ± 5.48 (45.0) 5.42 - 24.5 [11.9]	233 ± 97.2 (41.8) 93.7 - 419 [240]	251 ± 102 (40.8) 112 - 442 [252]	23.4 ± 4.4 (19.0) 18.8 - 31.4 [22.3]	2.58 ± 0.313 (12.1) 2.23 - 3.23 [2.50]	79.3 ± 38.3 (48.2) 37.7 - 149 [66.3]			65.1 ± 19.1 (29.3) 41.9 - 105 [62.5]	0.231 ± 0.02043 (8.8) 0.205 - 0.267 [0.227]	273 ± 70.9 (26.0) 158 - 398 [269]	
	R078543 (+)	All Subjs	20	1.55 ± 0.58 (37.6) 1.00 - 3.00 [1.50]	12.2 ± 4.98 (40.7) 4.88 - 23.6 [11.9]	192 ± 79.8 (41.5) 64.8 - 392 [182]	205 ± 84.0 (40.9) 73.6 - 420 [193]	24.4 ± 4.9 (20.1) 16.1 - 33.0 [25.2]		96.9 ± 46.6 (48.1) 39.7 - 226 [86.4]			35.4 ± 11.2 (31.6) 14.9 - 60.1 [36.3]	0.180 ± 0.0241 (13.4) 0.136 - 0.234 [0.181]	523 ± 196 (37.4) 277 - 1121 [459]	
		PM	10	1.65 ± 0.75 (45.3) 1.00 - 3.00 [1.50]	13.2 ± 5.00 (37.9) 8.11 - 23.6 [12.8]	214 ± 83.4 (38.9) 118 - 392 [198]	228 ± 87.9 (38.6) 131 - 420 [212]	24.3 ± 4.6 (18.9) 16.2 - 33.0 [25.2]		82.5 ± 28.7 (34.8) 39.7 - 127 [79.0]			37.8 ± 9.39 (24.9) 27.4 - 57.1 [36.9]	0.174 ± 0.0260 (15.0) 0.136 - 0.215 [0.174]	465 ± 109 (23.4) 292 - 609 [452]	
		EM	10	1.45 ± 0.37 (25.4) 1.00 - 2.00 [1.50]	11.3 ± 5.04 (44.6) 4.88 - 22.5 [11.1]	170 ± 73.4 (43.2) 64.8 - 313 [181]	182 ± 77.6 (42.5) 73.6 - 332 [190]	24.4 ± 5.4 (22.3) 16.1 - 31.3 [24.0]		111 ± 57.4 (51.6) 50.2 - 226 [88.0]			33.1 ± 12.8 (38.7) 14.9 - 60.1 [33.5]	0.187 ± 0.0213 (11.4) 0.158 - 0.234 [0.185]	581 ± 248 (42.7) 277 - 1121 [501]	
	R078544 (-)	All Subjs	17-20	9.40 ± 5.28 (56.2) 6.00 - 24.03 [8.00]	1.49 ± 0.500 (33.5) 0.759 - 2.86 [1.40]	62.2 ± 23.8 (38.2) 27.3 - 115 [62.4]	79.2 ± 23.3 (29.4) 49.8 - 137 [73.7]	27.6 ± 3.6 (13.1) 22.7 - 34.4 [27.1]					26.4 ± 7.28 (27.6) 18.3 - 45.2 [23.8]	0.350 ± 0.0362 (10.3) 0.292 - 0.411 [0.349]		
		PM	9-10	11.21 ± 6.95 (62.0) 6.00 - 24.03 [8.00]	1.54 ± 0.577 (37.4) 0.969 - 2.86 [1.38]	63.1 ± 24.1 (38.2) 33.3 - 115 [62.4]	78.2 ± 25.8 (33.1) 49.8 - 137 [72.6]	27.9 ± 3.5 (12.6) 22.9 - 34.4 [27.7]					25.0 ± 6.39 (25.5) 18.3 - 40.0 [23.0]	0.341 ± 0.0376 (11.0) 0.292 - 0.404 [0.341]		
		EM	8-10	7.60 ± 1.84 (24.2) 6.00 - 12.00 [8.00]	1.45 ± 0.435 (30.1) 0.759 - 2.22 [1.44]	61.3 ± 24.7 (40.3) 27.3 - 105 [60.7]	80.4 ± 21.7 (27.0) 52.0 - 117 [78.0]	27.3 ± 3.9 (14.4) 22.7 - 33.7 [26.1]					28.1 ± 8.37 (29.8) 19.5 - 45.2 [27.1]	0.359 ± 0.0341 (9.5) 0.301 - 0.411 [0.361]		

Treatment	Analyte	Subj	N	Tmax, h	Cmax, ng/ml	AUClast, ng/ml x hr^{-1}	AUC∞, ng/ml x hr^{-1}	t1/2, h	AUC∞, Ratio+/-	CL/F, ml/min	Fabs	CL, ml/min	AUCu,∞, ng/ml x hr^{-1}	fu	CLu/F, ml/min	CLu, ml/min
Treatment E: R078544 (-) paliperidone (-) oral solution 1 mg	Pal	All Subjs	20	3.30 ± 1.91 (57.8) 1.50 - 8.00 [2.50]	6.14 ± 1.88 (30.7) 2.84 - 9.87 [6.01]	198 ± 68.9 (34.7) 69.8 - 366 [198]	219 ± 77.9 (35.6) 87.0 - 418 [206]	26.3 ± 5.0 (19.0) 19.5 - 40.5 [26.3]	1.01 ± 0.143 (14.3) 0.719 - 1.26 [1.01]	86.9 ± 36.2 (41.6) 39.9 - 192 [81.1]			59.2 ± 13.0 (21.9) 35.3 - 86.1 [56.9]	0.263 ± 0.0330 (12.6) 0.205 - 0.324 [0.264]	296 ± 71.2 24.1 193 - 472 [293]	
		PM	10	2.80 ± 1.46 (52.0) 1.50 - 6.00 [2.00]	6.40 ± 1.70 (26.5) 4.43 - 9.84 [5.93]	216 ± 71.8 (33.3) 150 - 366 [182]	239 ± 85.1 (35.6) 168 - 418 [197]	27.6 ± 5.7 (20.5) 20.1 - 40.5 [27.2]	1.08 ± 0.142 (13.2) 0.808 - 1.26 [1.12]	76.3 ± 21.4 (28.0) 39.9 - 99.2 [84.6]			60.9 ± 13.1 (21.6) 45.5 - 86.1 [55.1]	0.251 ± 0.0336 (13.4) 0.205 - 0.309 [0.253]	284 ± 56.2 (19.8) 193 - 366 [303]	
		EM	10	3.80 ± 2.24 (58.9) 1.50 - 8.00 [3.50]	5.89 ± 2.11 (35.9) 2.84 - 9.87 [6.10]	181 ± 64.9 (35.8) 69.8 - 245 [201]	199 ± 68.2 (34.3) 87.0 - 277 [216]	25.0 ± 4.1 (16.3) 19.5 - 30.1 [24.6]	0.935 ± 0.109 (11.7) 0.719 - 1.06 [0.962]	97.5 ± 45.3 (46.5) 60.2 - 192 [77.3]			57.6 ± 13.4 (23.2) 35.3 - 77.3 [57.0]	0.274 ± 0.0298 (10.9) 0.234 - 0.324 [0.266]	307 ± 85.6 (27.9) 216 - 472 [292]	
	R078543 (+)	All Subjs	18-20	10.00 ± 5.19 (51.9) 6.00 - 24.00 [8.00]	2.35 ± 1.64 (70.0) 0.807 - 8.27 [1.98]	96.7 ± 39.7 (41.0) 27.4 - 200 [94.0]	118 ± 43.5 (37.0) 49.4 - 234 [107]	29.5 ± 5.0 (17.0) 20.8 - 42.7 [29.8]					20.1 ± 5.20 (25.8) 9.53 - 31.8 [19.5]	0.180 ± 0.0241 (13.4) 0.136 - 0.234 [0.181]		
		PM	9-10	10.00 ± 5.33 (53.3) 6.00 - 24.00 [8.00]	2.32 ± 1.03 (44.4) 1.51 - 4.55 [1.85]	108 ± 43.2 (39.8) 69.2 - 200 [88.6]	131 ± 51.1 (38.9) 86.5 - 234 [111]	31.1 ± 5.8 (18.5) 20.8 - 42.7 [30.8]					21.5 ± 5.65 (26.3) 14.4 - 31.8 [20.2]	0.174 ± 0.0260 (15.0) 0.136 - 0.215 [0.174]		
		EM	9-10	10.00 ± 5.33 (53.3) 6.00 - 24.00 [8.00]	2.37 ± 2.15 (90.7) 0.807 - 8.27 [2.04]	85.0 ± 33.9 (39.9) 27.4 - 117 [94.2]	104 ± 31.4 (30.2) 49.4 - 140 [103]	28.1 ± 4.0 (14.3) 23.7 - 34.3 [26.8]					18.8 ± 4.62 (24.6) 9.53 - 23.5 [19.3]	0.187 ± 0.0213 (11.4) 0.158 - 0.234 [0.185]		
	R078544 (-)	All Subjs	20	1.88 ± 0.48 (25.8) 1.00 - 3.00 [2.00]	4.88 ± 1.32 (27.1) 2.33 - 7.37 [4.80]	100 ± 30.8 (30.7) 42.3 - 167 [101]	110 ± 32.8 (29.8) 48.9 - 186 [110]	24.1 ± 5.58 (23.1) 16.9 - 37.5 [23.6]		167 ± 59.8 (35.9) 89.6 - 341 [152]			37.8 ± 9.13 (24.2) 18.8 - 54.3 [36.7]	0.350 ± 0.0362 (10.3) 0.292 - 0.411 [0.349]	471 ± 137 (29.0) 307 - 885 [454]	
		PM	10	1.80 ± 0.54 (29.9) 1.00 - 3.00 [1.75]	5.16 ± 1.23 (23.9) 3.56 - 7.37 [4.84]	106 ± 30.4 (28.7) 79.3 - 167 [96.9]	116 ± 33.4 (28.7) 87.0 - 186 [104]	25.2 ± 6.30 (25.0) 17.3 - 37.5 [23.6]		153 ± 35.8 (23.5) 89.6 - 192 [160]			38.7 ± 7.57 (19.6) 29.4 - 54.3 [35.7]	0.341 ± 0.0376 (11.0) 0.292 - 0.404 [0.341]	444 ± 77.7 (17.5) 307 - 566 [467]	
		EM	10	1.95 ± 0.44 (22.5) 1.50 - 3.00 [2.00]	4.59 ± 1.41 (30.7) 2.33 - 6.17 [4.80]	94.8 ± 31.7 (33.4) 42.3 - 130 [105]	104 ± 32.7 (31.5) 48.9 - 140 [114]	23.1 ± 4.86 (21.0) 16.9 - 31.2 [22.9]		181 ± 76.3 (42.1) 119 - 341 [147]			36.8 ± 10.8 (29.3) 18.8 - 53.8 [38.1]	0.359 ± 0.0341 (9.5) 0.301 - 0.411 [0.361]	498 ± 178 (35.8) 310 - 885 [437]	

Figure 34 Exposures to both (+)- and (-)-Paliperidone after Solutions of each Single Enantiomer

A

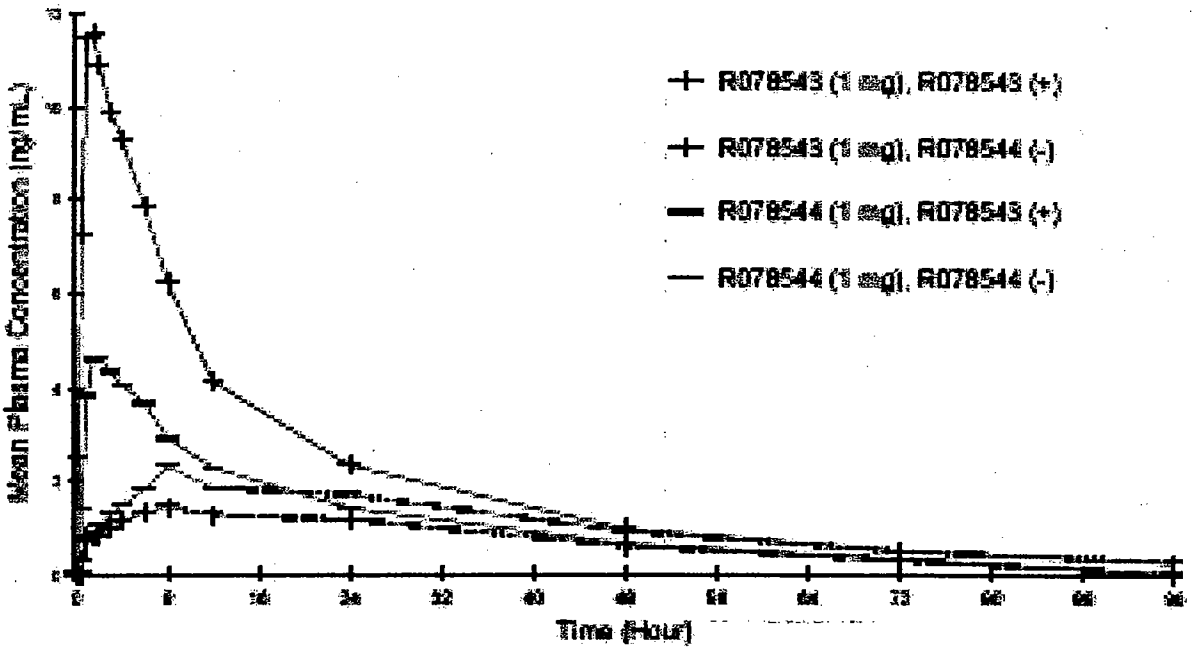


Figure 35 Exposures to Unbound Moieties of both (+)- and (-)-Paliperidone after Solutions of each Single Enantiomer

B

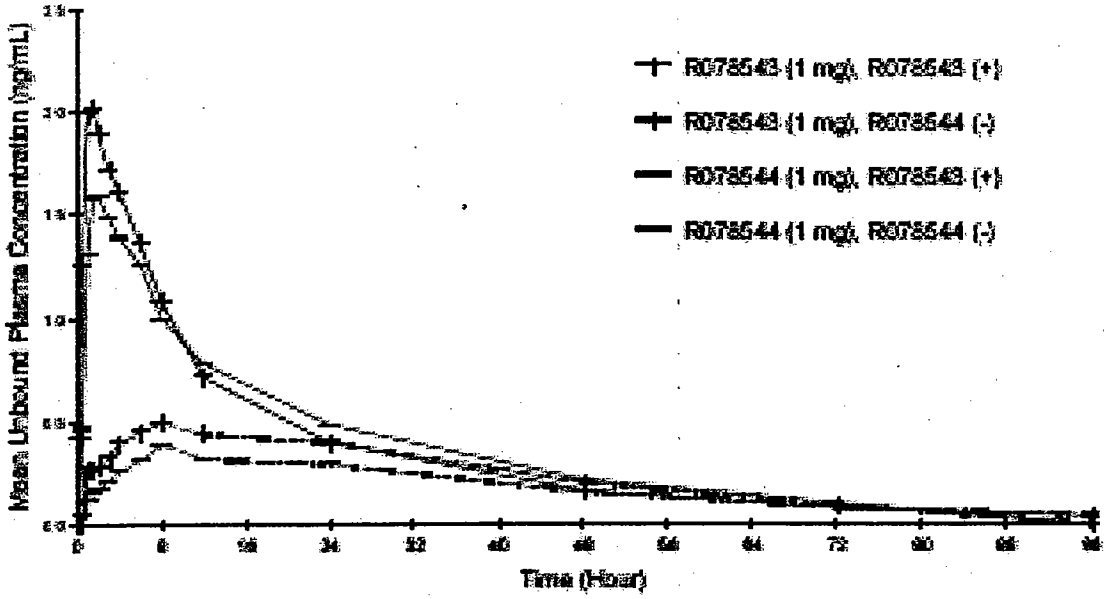
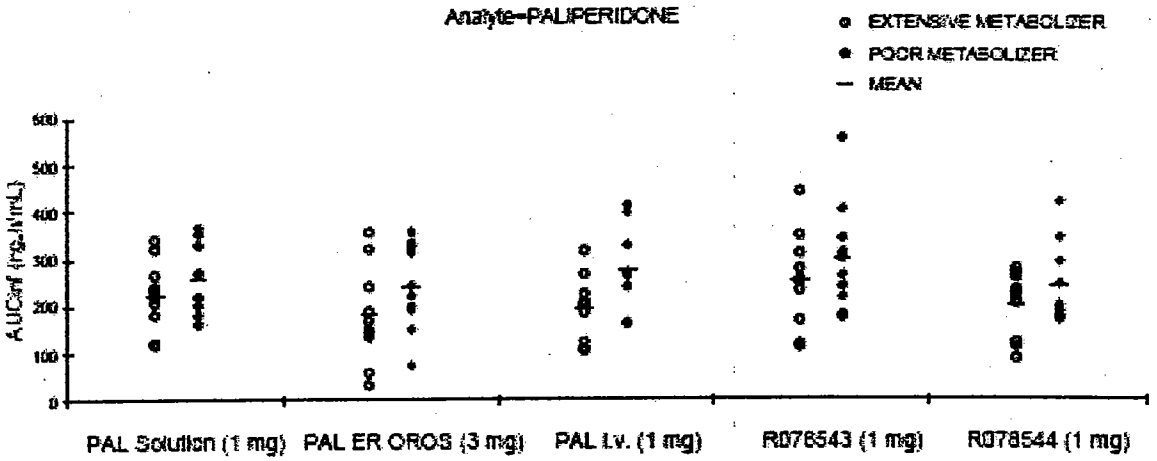
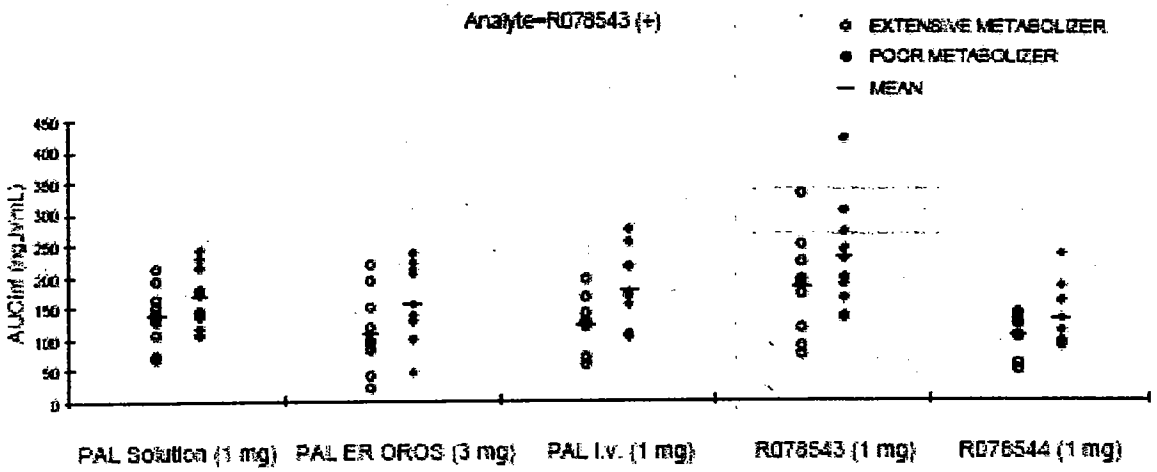
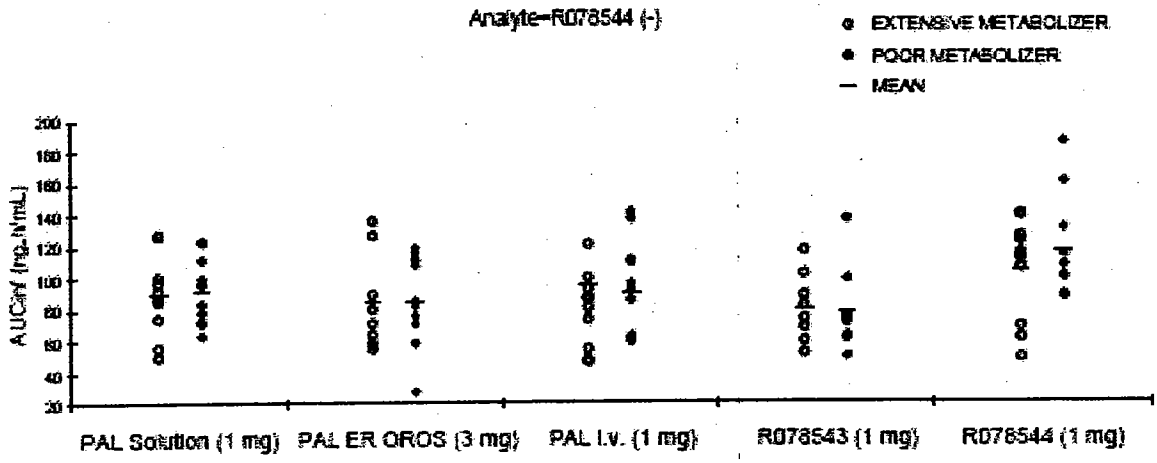


Figure 36 Graphical Representation of the Pharmacokinetic Parameters C_{max} and AUC_{inf} of Paliperidone and its Enantiomers, R078543 and R078544 by CYD2D6 Phenotype







Adverse Effects

Adverse events by treatment for study P01-1007 are shown in Table 51.

Table 51 Incidence of Common Treatment-Emergent Adverse Events (Study R076477-P01-1007: Safety Analysis Set

Body System Preferred Term	+PAL 1 MG ORAL SOL	-PAL 1MG ORAL SOL	PAL 1 MG ORAL SOL	PAL 1 MG IV	PAL 3 MG OROS	Total
	(N=20)	(N=20)	(N=20)	(N=20)	(N=20)	(N=20)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects with adverse events	13 (65)	14 (70)	15 (75)	18 (90)	14 (70)	20 (100)
Psychiatric disorders	6 (30)	11 (55)	12 (60)	12 (60)	7 (35)	18 (90)
Somnolence	6 (30)	11 (55)	11 (55)	12 (60)	6 (30)	18 (90)
Cardiovascular disorders, general	5 (25)	2 (10)	4 (20)	9 (45)	3 (15)	12 (60)
Hypotension postural	5 (25)	2 (10)	4 (20)	9 (45)	3 (15)	12 (60)
Body as a whole - general disorders	3 (15)	2 (10)	3 (15)	2 (10)	4 (20)	9 (45)
Fatigue	3 (15)	2 (10)	2 (10)	1 (5)	3 (15)	6 (30)
Back pain	0	0	0	1 (5)	1 (5)	2 (10)
Centr & periph nervous system disorders	5 (25)	2 (10)	3 (15)	5 (25)	2 (10)	9 (45)
Headache	4 (20)	1 (5)	2 (10)	3 (15)	2 (10)	7 (35)
Dizziness	0	0	1 (5)	1 (5)	0	2 (10)
Migraine	1 (5)	0	0	1 (5)	0	2 (10)
Platelet, bleeding & clotting disorders	1 (5)	1 (5)	0	0	0	2 (10)
Haematoma	1 (5)	1 (5)	0	0	0	2 (10)

For racemic paliperidone the incidence of somnolence and orthostatic hypotension was related to the rate of absorption and the Cmax, with the incidence by formulation in the following order: IV > IR > OROS, (see Table 51).

In contrast the incidence for somnolence is lower after administration of (+)-paliperidone compared with after administration of (-)-paliperidone or the racemate. The incidence of hypotension, fatigue, and headache is slightly higher after administration of (+)-paliperidone compared to with the racemic solution, the (-)-enantiomer and the OROS formulation. Although the Cmax for each individual enantiomer is higher when the enantiomer is given by itself, for the (+) enantiomer the Cmax is much higher than after administration of the racemate, (see Table 50). Looking at the incidence of AEs and the exposures by treatment in Table 51 and Table 49, there may be some advantage in terms of side effects for the (+) enantiomer compared to the racemate when both are administered as OROS formulations, whether there is similar or differential efficacy would need to be determined.

3.10.5 MR OROS Formulation - Single Dose Pharmacokinetics (Dose Linearity)

Two single dose, dose linearity studies were conducted. Study Alza-044 studied a range of 6 mg to 15 mg by using combinations of 3 and 9 mg phase III clinical trial formulations and study P01-1010 studied a 3 mg to 15 mg range using the phase III clinical trial formulation for the 3 mg dose and the [redacted] formulations for the other 4 strengths. Study Alza-044 was a sequential and study P01-1010 employed a crossover design. Both studies were conducted in healthy adult males.

Study Alza-044 was initially designed only to examine the two lowest doses and the tow higher doses were added to the design later. Consequently, not all subjects were available to participate in all four treatment arms. Thirty subjects were enrolled in the study Alza-044 and received the first two treatments (6 and 9 mg ER OROS® paliperidone, respectively). Of these subjects, 23 continued in the study and received Treatment C (12 mg ER OROS® paliperidone), and fifteen subjects continued on to complete all treatments, including Treatment D (15 mg ER OROS® paliperidone). Since Periods 3 and 4 were initially

unplanned, none of the subjects was considered to have withdrawn from the study due to an AE, withdrawn consent, or lost to follow-up.

Examination of the pharmacokinetic data from study Alza-044 and study P01-1010 reveal dose linearity for single doses over the range of 3 mg to 15 mg, (see Table 52, Figure 37, Figure 38, Figure 39, Table 53, Table 54, and Figure 40).

Table 52 Paliperidone Pharmacokinetic Metrics Following Single Doses of Paliperidone OROS – Study Alza-044

Rx	Regimen	Population (i.e. Excluding)	N	Tmax (h)	Cmax (ng/mL)	AUCt (ng/ml x hr^{-1})	AUC_∞ (ng/ml x hr^{-1})	$t_{1/2}$ (hr)
6 mg		None	30	24.3 ± 1.78 (7.3) 20.0 - 27.0 [24.0]	11.85 ± 3.68 (31.08) 6.7 - 23.4 [11.30]	444.9 ± 145.0 (32.6) 223 - 872 [407.9]	484.9 ± 159.4 (32.9) 238 - 937 [439.1]	23.44 ± 2.75 (11.73) 19.1 - 29.0 [23.53]
				24.241	11.36	424.6	462.0	23.29
		108 110 111 112 119 120 121	23	23.9 ± 1.6 (6.8) 20.0 - 27.0 [24.0]	12.44 ± 3.71 (29.83) 8.5 - 23.4 [11.80]	465.8 ± 144.1 (30.9) 314 - 872 [421.6]	507.1 ± 155.9 (30.7) 327 - 937 [444.1]	23.54 ± 2.64 (11.23) 19.1 - 29.0 [23.88]
				23.823	11.99	447.9	487.5	23.40
		102 104 108 110 111 112 116 117 119 120 121 123 127 128 130	15	23.7 ± 1.3 (5.5) 22.0 - 27.0 [24.0]	11.93 ± 4.16 (34.88) 8.5 - 23.4 [9.64]	436.8 ± 119.4 (27.3) 314 - 736 [386.2]	479.5 ± 133.4 (27.8) 327 - 806 [434.1]	24.18 ± 2.85 (11.80) 19.1 - 29.0 [24.15]
				23.643	11.39	423.5	464.1	24.02
9 mg		None	30	24.9 ± 3.1 (12.4) 16.0 - 30.0 [27.0]	16.77 ± 5.55 (33.09) 8.7 - 31.0 [15.85]	647.0 ± 219.9 (34.0) 364 - 1170 [597.1]	711.0 ± 246.3 (34.6) 398 - 1297 [659.8]	24.53 ± 3.01 (12.25) 18.2 - 29.8 [24.33]
				24.721	15.96	615.0	674.4	24.35
		108 110 111 112 119 120 121	23	25.3 ± 3.0 (11.8) 16.0 - 30.0 [27.0]	16.84 ± 5.71 (33.88) 8.7 - 31.0 [16.50]	647.7 ± 225.8 (34.9) 364 - 1170 [617.9]	710.5 ± 251.5 (35.4) 398 - 1297 [688.3]	24.47 ± 2.46 (10.03) 20.5 - 29.8 [23.93
				25.146	16.01	614.7	673.2	24.36]
		102 104 108 110 111 112 116 117 119 120 121 123 127 128 130	15	25.4 ± 2.3 (9.0) 20.0 - 27.0 [27.0]	15.12 ± 4.34 (28.73) 8.7 - 25.8 [14.30]	592.3 ± 188.8 (31.9) 364 - 1130 [550.8]	652.7 ± 211.2 (32.4) 398 - 1247 [631.4]	24.63 ± 2.23 (9.07) 21.6 - 29.5 [23.93
				25.297	14.57	568.6	625.3	24.54
12 mg		110 111 112 116 117 119 120 121 123 127 128 130	15	25.2 ± 2.1 (8.4) 22.0 - 27.0 [27.0]	20.61 ± 6.47 (31.39) 8.5 - 30.6 [21.40]	824.2 ± 233.8 (28.4) 355 - 1195 [873.3]	908.8 ± 268.5 (29.5) 395 - 1369 [940.6]	24.92 ± 3.09 (12.39) 20.1 - 30.5 [24.48]
				25.1	19.53	787.8	865.9	24.74
15 mg		102 104 108 110 111 112 116 117 119 120 121 123 127 128 130	15	24.9 ± 2.4 (9.5) 22.0 - 27.0 [27.0]	31.04 ± 5.62 (18.11) 21.9 - 41.2 [31.90]	1358.6 ± 281.5 (20.7) 831 - 1766 [1430.3]	1478.3 ± 309.2 (20.9) 910 - 1934 [1531.5]	24.65 ± 2.86 (11.61) 20.5 - 29.0 [24.28]
				24.8	30.55	1328.9	1445.7	24.50

Figure 37 Mean Paliperidone Single Dose Concentration vs. Time Profiles by Paliperidone OROS Dose – Study Alza 044

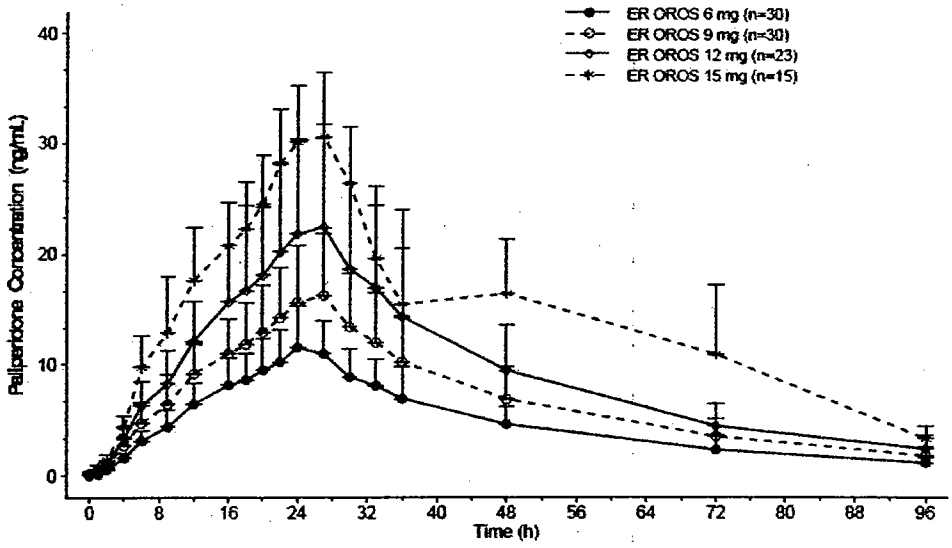


Figure 38 Dose Normalized Paliperidone Single Dose Concentration vs. Time Profiles – Study Alza 044

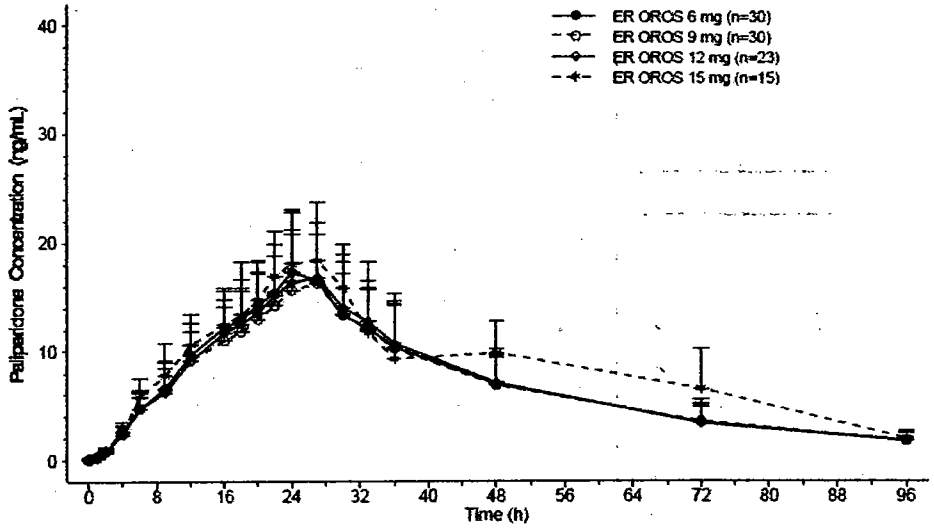


Figure 39 Paliperidone Single Dose AUCs by Paliperidone OROS Dose – Study Alza 044

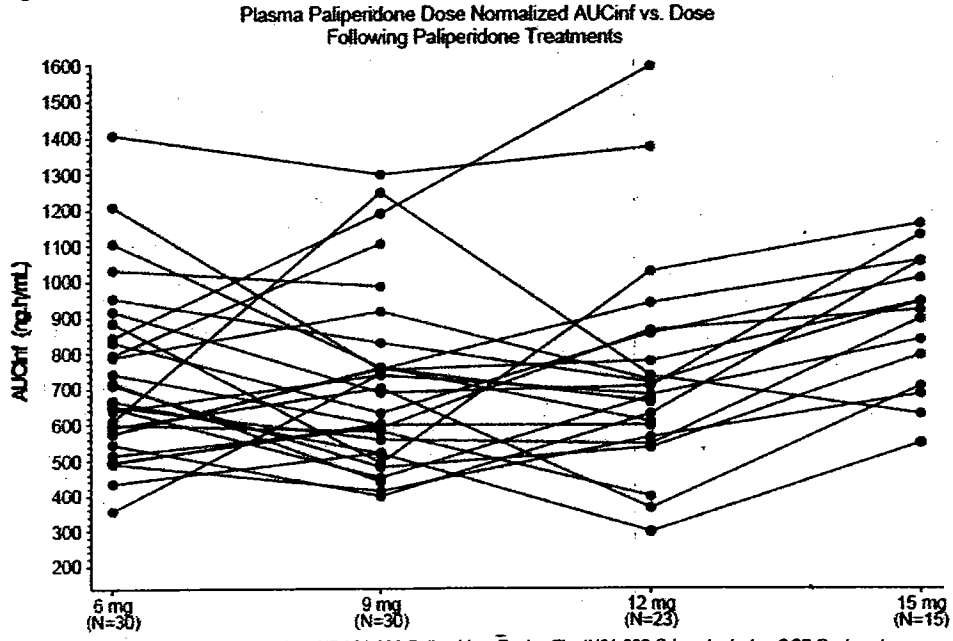


Table 53 Comparative Pharmacokinetic Metrics for Single Dose Paliperidone OROS Dose Proportionality - Study P01-1010

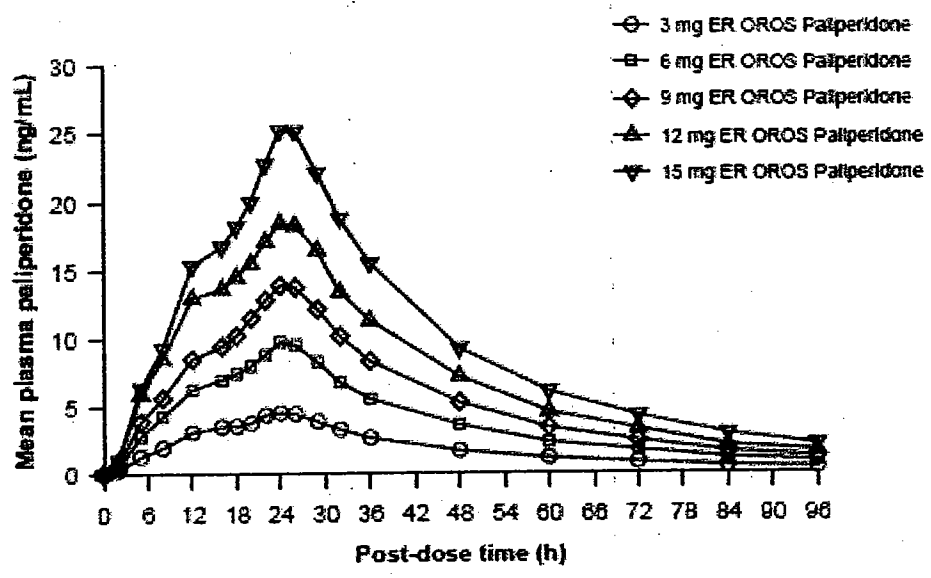
Treatment	N	Cmax (ng/ml)	Tmax (h)	AUClast (ng/ml x hr^{-1})	AUC∞ (ng/ml x hr^{-1})	t½ (h)	Dose-normalized to15-mg		
							Cmax (ng/mL)	AUClast (ng/ml x hr^{-1})	AUC∞ (ng/ml x hr^{-1})
Treatment A: 3 mg ER OROS	46	4.85 ± 2.16 (44.5) 2.23 - 11.7 [4.43]	22.50 ± 3.88 (17.2) 12.00 - 29.00 [24.00]	176 ± 76.2 (43.2) 73.1 - 365 [163]	192 ± 85.0 (44.2) 76.6 - 389 [177]	23.5 ± 5.2 (22.2) 15.6 - 38.1 [22.2]	24.3 ± 10.8 (44.5) 11.2 - 58.5 [22.2]	882 ± 381 (43.2) 366 - 1824 [815]	962 ± 425 (44.2) 383 - 1947 [884]
Treatment B: 6 ER OROS	46	10.2 ± 3.90 (38.3) 3.66 - 21.3 [9.72]	22.70 ± 4.48 (19.7) 12.00 - 29.00 [24.00]	368 ± 146 (39.8) 134 - 773 [329]	401 ± 167 (41.7) 145 - 829 [346]	23.4 ± 4.5 (19.4) 15.5 - 37.8 [23.6]	25.4 ± 9.74 (38.3) 9.15 - 53.3 [24.3]	919 ± 366 (39.8) 335 - 1933 823]	1003 ± 418 (41.7) 363 - 2074 865]
Treatment C: 9 ER OROS	46	14.8 ± 6.90 (46.7) 3.88 - 34.2 [13.1]	23.08 ± 4.86 (21.0) 8.00 - 32.02 [24.00]	525 ± 243 (46.2) 146 - 1114 [465]	567 ± 269 (47.4) 156 - 1184 [505]	22.0 ± 3.4 (15.5) 16.4 - 31.4 [21.5]	24.6 ± 11.5 (46.7) 6.47 - 57.0 [21.8]	875 ± 404 (46.2) 243 - 1857 775]	945 ± 448 (47.4) 259 - 1973 841]
Treatment D: 12 ER OROS	47	19.6 ± 8.01 (40.9) 6.18 - 38.6 [18.1]	23.45 ± 3.92 (16.7) 12.00 - 29.00 [24.00]	720 ± 327 (45.4) 252 - 1727 [648]	778 ± 370 (47.6) 274 - 1921 [685]	22.1 ± 4.5 (20.2) 15.3 - 33.0 [21.2]	24.5 ± 10.0 (40.9) 7.73 - 48.3 [22.6]	901 ± 409 (45.4) 315 - 2159 [810]	973 ± 463 (47.6) 342 - 2402 [856]
Treatment E: 15 ER OROS	48	26.6 ± 11.8 (44.5) 11.5 - 70.6 [24.5]	24.71 ± 2.82 (11.4) 12.00 - 29.05 [24.00]	938 ± 410 (43.7) 424 - 2172 [849]	1014 ± 454 (44.8) 443 - 2223 [887]	22.3 ± 4.4 (19.7) 15.8 - 33.1 [21.3]	26.6 ± 11.8 (44.5) 11.5 - 70.6 [24.5]	938 ± 410 (43.7) 424 - 2172 [849]	1014 ± 454 (44.8) 443 - 2223 [887]

Table 54 Dose Proportionality Geometric Mean Ratios for Single Dose Paliperidone OROS Pharmacokinetic Metrics - Study P01-1010

Comparison	Paliperidone Metric	ANOVA p-value	Ratio (%)	
			Estimate	90% CI
12 mg : 15 mg	Cmax, ng/ml	0.19	91.83	(82.41 - 102.32)
	AUClast, ng/ml x hr^{-1}	0.36	94.76	(86.10 - 104.30)
	AUC∞, ng/ml x hr^{-1}	0.33	94.49	(85.80 - 104.05)
9 mg : 15 mg	Cmax, ng/ml	0.090	89.44	(80.27 - 99.67)
	AUClast, ng/ml x hr^{-1}	0.080	90.30	(82.05 - 99.39)
	AUC∞, ng/ml x hr^{-1}	0.074	90.06	(81.78 - 99.17)
6 mg : 15 mg	Cmax, ng/ml	0.66	97.16	(87.19 - 108.27)
	AUClast, ng/ml x hr^{-1}	0.91	99.34	(90.25 - 109.34)
	AUC∞, ng/ml x hr^{-1}	0.99	100.09	(90.89 - 110.21)
3 mg : 15 mg	Cmax, ng/ml	0.18	91.64	(82.24 - 102.12)
	AUClast, ng/ml x hr^{-1}	0.30	94.09	(85.49 - 103.56)
	AUC∞, ng/ml x hr^{-1}	0.37	94.85	(86.14 - 104.45)
3 mg : 6 mg	Cmax, ng/ml	0.37	94.32	(84.64 - 105.10)
	AUClast, ng/ml x hr^{-1}	0.35	94.72	(86.05 - 104.25)
	AUC∞, ng/ml x hr^{-1}	0.36	94.77	(86.06 - 104.36)
6 mg : 9 mg	Cmax, ng/ml	0.21	108.63	(97.48 - 121.04)
	AUClast, ng/ml x hr^{-1}	0.10	110.01	(99.95 - 121.08)
	AUC∞, ng/ml x hr^{-1}	0.072	111.13	(100.92 - 122.38)
9 mg : 12 mg	Cmax, ng/ml	0.69	97.41	(87.41 - 108.54)
	AUClast, ng/ml x hr^{-1}	0.41	95.29	(86.58 - 104.88)
	AUC∞, ng/ml x hr^{-1}	0.41	95.31	(86.55 - 104.96)

Log-transformed parameters dose-normalized to 15-mg

Figure 40 Mean Single Dose Plasma Concentration-vs Time Profiles of Paliperidone OROS by Dose – Study P01-1010



Adverse events for studies Alza-044 and P01-1010 are shown in Table 55 and Table 56. Adverse events that were observed in both studies and/or that either clearly have or appear to have, a dose response are shown in red text and include: somnolence, rhinitis, dyspneas, and agititation. AEs shown in green text occurred in both studies but cannot be said to be dose related. These include dizziness, insomnia, and possible bleeding disorders. In study P01-1010 text in blue appears to be dose related but were not observed in study Alza-044, and **text in plum and orange are potentially worrisome**. The myalgia and and increase in CPK are signs consistent with neuroleptic malignant syndrome and rhabdomyolysis, **This needs to be evaluated by the safety reviewer to see if they occurred in the same individual.**

Plots of changes in pulse and systolic blood pressure for study Alza-044 are shown in Figure 41 and Figure 42 and overlaid on a probable circadian rhythm are decreases in both pulse and SBP.

Table 55 Adverse Events by Body System and Preferred Term Reported in 2 or More Subjects by Treatment – Study Alza-044

Body System COSTART Term	ER OROS 6 mg (n=30)	ER OROS 9 mg (n=30)	ER OROS 12 mg (n=23)	ER OROS 15 mg (n=15)
Subjects reporting at least one AE	**12 (40.0)**	**20 (66.7)**	**18 (78.3)**	**15 (100)**
Somnolence	2 (6.7)	4 (13.3)	8 (34.8)	12 (80.0)
Rhinitis	4 (13.3)	7 (23.3)	4 (17.4)	8 (53.3)
Dyspnea	3 (10.0)	3 (10.0)	4 (17.4)	6 (40.0)
Agitation	0	0	4 (17.4)	8 (53.3)
Dizziness	1 (3.3)	4 (13.3)	3 (13.0)	1 (6.7)
Headache	0	3 (10.0)	4 (17.4)	0
Asthenia	2 (6.7)	3 (10.0)	0	0
Thinking abnormal	1 (3.3)	2 (6.7)	1 (4.3)	0
Insomnia	1 (3.3)	2 (6.7)	1 (4.3)	1 (6.7)
Nausea	0	2 (6.7)	1 (4.3)	0
Epistaxis	2 (6.7)	1 (3.3)	0	0

Table 56 Incidence of Treatment-Emergent Adverse Events by Body System and Preferred Term Categorized by Dose – Study P01-1010

Body System Preferred Term	3 mg	6 mg	9 mg	12 mg	15 mg	Total
	(N=47)	(N=46)	(N=46)	(N=48)	(N=49)	(N=50)
	n (%)	n (%)	n (%)	n (%)	n (%)	n(%)
Total no. subjects with adverse events	12 (25.5)	19 (41.3)	14 (30.4)	19 (39.6)	28 (57.1)	45 (90.0)
Centr & periph nervous system disorders	4 (8.5)	9 (19.6)	5 (10.9)	14 (29.2)	10 (20.4)	27 (54.0)
Headache	2 (4.3)	7 (15.2)	4 (8.7)	6 (12.5)	5 (10.2)	19 (38.0)
Dizziness	0	2 (4.3)	1 (2.2)	5 (10.4)	4 (8.2)	10 (20.0)
Hyperkinesia	0	0	0	3 (6.3)	1 (2.0)	4 (8.0)
Dyskinesia	0	0	0	0	1 (2.0)	1 (2.0)
Dystonia	0	0	0	0	1 (2.0)	1 (2.0)
Hypertonia	1 (2.1)	0	0	0	0	1 (2.0)
Speech disorder	0	0	0	1 (2.1)	0	1 (2.0)
Tremor	1 (2.1)	0	0	0	0	1 (2.0)
Body as a whole - general disorders	2 (4.3)	6 (13.0)	6 (13.0)	2 (4.2)	9 (18.4)	20 (40.0)
Fatigue	0	5 (10.9)	4 (8.7)	2 (4.2)	7 (14.3)	15 (30.0)
Chest pain	1 (2.1)	1 (2.2)	0	1 (2.1)	1 (2.0)	4 (8.0)
Back pain	0	0	2 (4.3)	0	1 (2.0)	3 (6.0)
Hot flushes	0	0	0	0	1 (2.0)	1 (2.0)
Injury	1 (2.1)	0	0	0	0	1 (2.0)
Syncope	0	0	0	0	1 (2.0)	1 (2.0)
Psychiatric disorders	3 (6.4)	4 (8.7)	4 (8.7)	5 (10.4)	8 (16.3)	19 (38.0)
Somnolence	2 (4.3)	3 (6.5)	2 (4.3)	1 (2.1)	4 (8.2)	10 (20.0)
Anxiety	0	0	0	3 (6.3)	0	3 (6.0)
Depression	0	2 (4.3)	0	0	1 (2.0)	3 (6.0)
Dreaming abnormal	1 (2.1)	0	0	1 (2.1)	1 (2.0)	3 (6.0)
Agitation	0	0	0	1 (2.1)	1 (2.0)	2 (4.0)
Concentration impaired	0	0	0	1 (2.1)	1 (2.0)	2 (4.0)
Amnesia	0	0	1 (2.2)	0	0	1 (2.0)
Euphoria	0	0	0	1 (2.1)	0	1 (2.0)
Insomnia	0	0	0	0	1 (2.0)	1 (2.0)
Thinking abnormal	0	0	1 (2.2)	0	0	1 (2.0)
Respiratory system disorders	2 (4.3)	3 (6.5)	2 (4.3)	4 (8.3)	3 (6.1)	13 (26.0)
Rhinitis	0	1 (2.2)	2 (4.3)	4 (8.3)	3 (6.1)	9 (18.0)
Pharyngitis	2 (4.3)	2 (4.3)	0	0	0	4 (8.0)
Coughing	0	0	1 (2.2)	0	0	1 (2.0)
Gastro-intestinal system disorders	2 (4.3)	2 (4.3)	3 (6.5)	4 (8.3)	4 (8.2)	10 (20.0)
Constipation	1 (2.1)	1 (2.2)	1 (2.2)	0	1 (2.0)	4 (8.0)
Mouth dry	0	0	1 (2.2)	2 (4.2)	1 (2.0)	4 (8.0)
Nausea	0	1 (2.2)	0	0	2 (4.1)	3 (6.0)
Melaena	0	0	0	2 (4.2)	1 (2.0)	2 (4.0)
Abdominal pain	0	0	0	1 (2.1)	0	1 (2.0)
Diarrhoea	1 (2.1)	0	0	0	0	1 (2.0)
Increased stool frequency	0	0	1 (2.2)	0	0	1 (2.0)
Vomiting	0	0	0	1 (2.1)	0	1 (2.0)
Heart rate and rhythm disorders	1 (2.1)	0	0	0	3 (6.1)	4 (8.0)
Palpitation	1 (2.1)	0	0	0	1 (2.0)	2 (4.0)
Tachycardia	0	0	0	0	2 (4.1)	2 (4.0)
Cardiovascular disorders, general	1 (2.1)	0	1 (2.2)	0	1 (2.0)	3 (6.0)
Hypotension postural	1 (2.1)	0	1 (2.2)	0	0	2 (4.0)
Hypotension	0	0	0	0	1 (2.0)	1 (2.0)
Platelet,bleeding & clotting disorders	0	0	1 (2.2)	0	2 (4.1)	3 (6.0)
Bleeding time increased	0	0	1 (2.2)	0	1 (2.0)	2 (4.0)
Haematoma	0	0	0	0	1 (2.0)	1 (2.0)
Metabolic and nutritional disorders	0	1 (2.2)	1 (2.2)	0	1 (2.0)	2 (4.0)
Creatine phosphokinase increased	0	1 (2.2)	1 (2.2)	0	1 (2.0)	2 (4.0)
LDH increased	0	0	0	0	1 (2.0)	1 (2.0)
Skin and appendages disorders	0	0	0	1 (2.1)	1 (2.0)	2 (4.0)
Dermatitis fungal	0	0	0	0	1 (2.0)	1 (2.0)
Eczema	0	0	0	1 (2.1)	0	1 (2.0)
Liver and biliary system disorders	0	0	0	0	1 (2.0)	1 (2.0)
SGOT increased	0	0	0	0	1 (2.0)	1 (2.0)
Musculo-skeletal system disorders	0	0	1 (2.2)	0	0	1 (2.0)
Myalgia	0	0	1 (2.2)	0	0	1 (2.0)
Resistance mechanism disorders	0	1 (2.2)	0	0	0	1 (2.0)
Infection	0	1 (2.2)	0	0	0	1 (2.0)
Urinary system disorders	0	0	0	1 (2.1)	0	1 (2.0)
Micturition frequency	0	0	0	1 (2.1)	0	1 (2.0)
Vision disorders	0	0	0	1 (2.1)	0	1 (2.0)
Vision abnormal	0	0	0	1 (2.1)	0	1 (2.0)

Figure 41 Mean Pulse Profile by Dose - Study Alza-044

Figure 7
Mean (SD) Pulse Profile Following Paliperidone Treatments

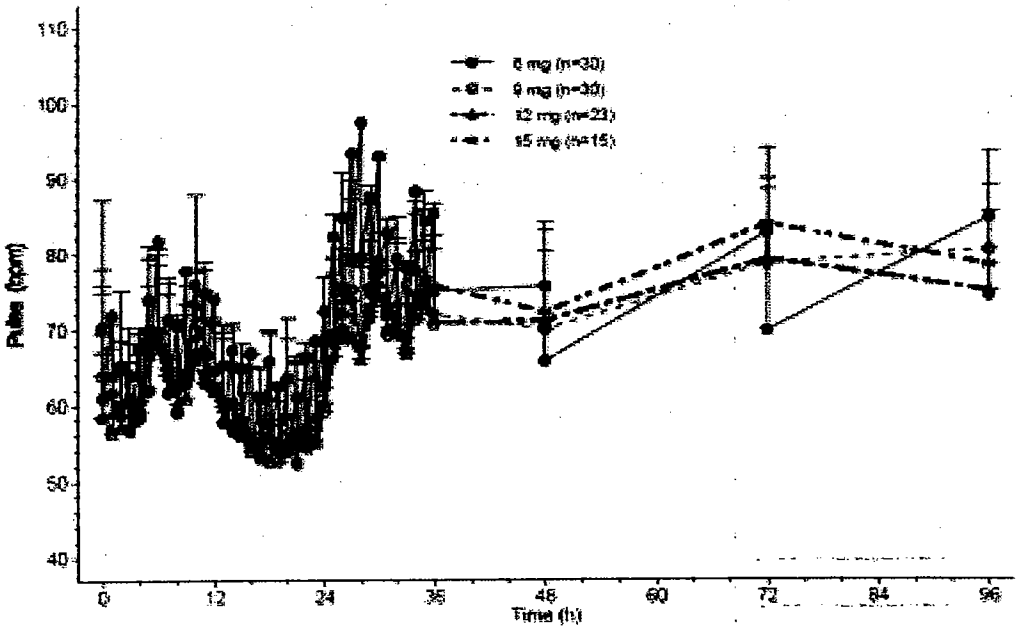
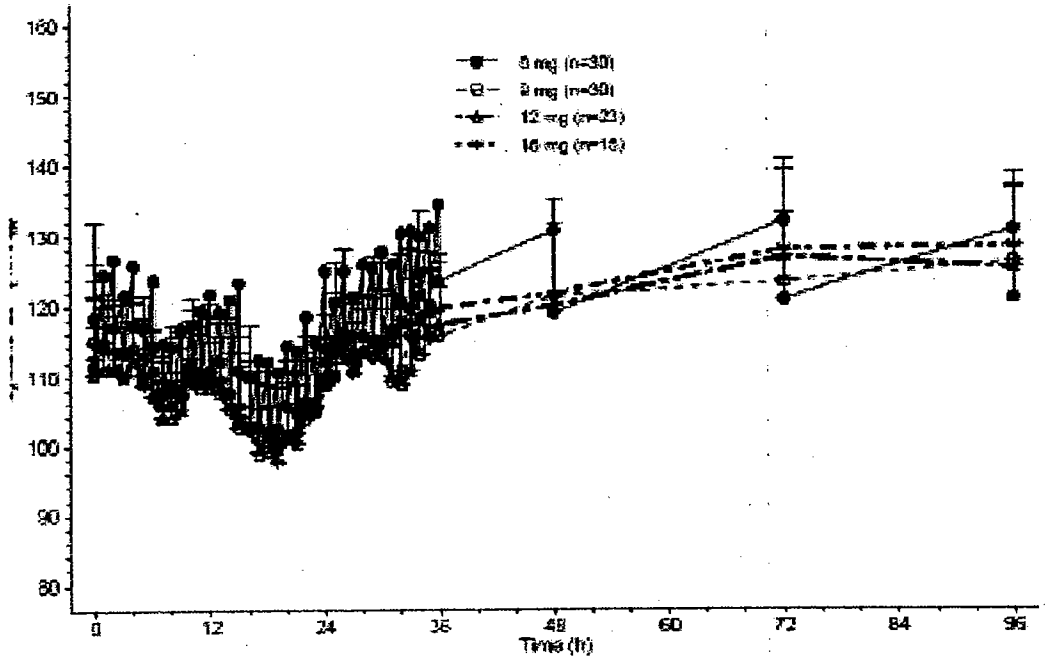


Figure 42 Mean Systolic Blood Pressure Profile by Dose - Study Alza-044

Figure 5
Mean (SD) Systolic Profile Following Paliperidone Treatments



3.10.6 Multiple Dose Pharmacokinetics

Six multiple dose studies were conducted and are outlined in Table 57. Studies INT-1 and SCH-1009 were conducted with the IR formulation were an early exploratory study and the QT study respectively. They are reviewed in detail in §3.10.2.3 and §3.10.7.5.1. The remainder of the studies used the OROS formulation. Studies SCH-102 and SCH-101 are reviewed in detail in this section and the remaining studies are either PD or special population studies and are reviewed in detail in their respective sections, i.e. §3.10.7.3 for study SCH-1010, §3.10.8.1 for study SCH-1011, and §3.10.8.3 for study P01-1005.

Table 57 Overview of Multiple Dose Paliperidone Studies

Study	Design	Formulation	"SS" Dosages	Duration	Population	Comparator	Comment
INT-1	Parallel	IR	1 mg 4 mg 8 mg	7 – 14 days	Pxts		
SCH-1009		IR	8 mg	4			QTc study
SCH-102	Parallel	OROS CTF	9 mg 15 mg	7 days "		Ris 8 mg IR q12h x 7 days	Dosages administered sequentially
SCH-101		OROS 'Slow'	12 mg	5 or 6 days	Pxts	Ris IR 4 mg	
SCH-1010		over-encapsulated OROS CTF	9 mg			PBO	Sleep study
SCH-1011		OROS CTF	3 mg				elderly
P01-1005		over-encapsulated OROS CTF	3 mg				Japanese fed

A summary of the Paliperidone OROS pharmacokinetics from studies SCH-102 and SCH-101 are shown in Table 59 to Table 62.

3.10.6.1 Time Invariance

The following is a summary of the conclusions obtained from these studies:

- First dose pharmacokinetics metrics were not provided for study SCH-102. For study SCH-101 only AUCτ were reported so AUC accumulation cannot be determined, however mean first dose Cmax is approximately half of the steady-state Cmax, which is consistent with what was reported for the IR formulation. (Data not shown).
- Cmax and AUC are roughly dose proportional, (see Figure 43 and Figure 44)
- First dose pharmacokinetics are not provided
- There does not appear to be any differences by CYP2D6 genotype.
- The exposure to the (+) enantiomer is approximately 50% higher than to the (-) enantiomer.
- Mean half-life is 34 hours which is consistent with the accumulation ratios.
- Mean paliperidone Cmax and AUCτ with the maximum proposed dose of paliperidone OROS 15 mg are approximately half of the values for paliperidone observed with the maximum approved dose of risperidone IR (8 mg bid), and approximately 1/3 of the values observed for the total active moieties.
- Mean paliperidone Cmax and AUCτ with the maximum proposed dose of paliperidone OROS 15 mg are less than or similar to values for total active moieties seen with typically maximally efficatious doses of risperidone, (i.e. risperidone IR 6 mg po qd).
- First dose pharmacokinetics are not provided
- so for time in Enantiomer study p01-1007 in §3.10.4 Table 50

SCH-101 HR BP changes relative to Risperidone 4 mg IR qd

Doesn't look like any consistent differences except in 1st dose higher HR with pal oros.

Also more QTc prolongation with Pal than with moxifloxacin

See also SCH-101 in PK/PD

However, simply examining the summary metrics fails to tell the entire story. In addition, concentration vs. time profiles must also be examined. After single dosing peak concentrations are achieved after an average of around 24 hours with a range of 9 to 36 hours, (see Table 58).

Table 58 Comparison of Paliperidone OROS Single Dose and Steady-State Tmaxs

Study	Formulation	Dose	Analyte	Tmax		Comments
				Median	Range	
Single Dose Values						
Alza-044	OROS CTF	6 mg	Pal	24	16 - 30	
		9 mg		27		
		12 mg				
P01-1010	OROS [redacted]	3 mg – 15 mg		24	8 - 32	3 mg arm used OROS CTF
SCH-1011	OROS CTF	3 mg		24	9 - 24	
P01-1005	over-encapsulated OROS CTF	3 mg		24	9 - 36	
Steady-State Values						
SCH-102	OROS CTF	9 mg	Pal	9	2 - 24	Dosages administered sequentially
		15 mg		22	2 - 24	
SCH-101	OROS 'Slow'	12 mg	Pal	4	1 - 24	
			(+)-Pal	22		
			(-)-Pal	15		
SCH-1010	over-encapsulated OROS CTF	9 mg	Pal	12	2 - 24	Sleep study
SCH-1011	OROS CTF	3 mg		24	2 - 24	Elderly
P01-1005	over-encapsulated OROS CTF	3 mg		9 12	2 - 24	Japanese & Caucasians

Table 59 Multiple Dose Paliperidone OROS Paliperidone and Enantiomer Pharmacokinetic Metric Summary Statistics -- Study SCH-101

Arm	Rx	Day	Analyte	N	Cpredose, (ng/ml)	Cmin, (ng/ml)	Cmax, (ng/ml)	Tmax, (h)	AUCτ (ng.ml x hr^{-1})	MRT (h)	Vd,ss (L)	Cavg,ss (ng/ml)	FI (%)	Acc. Ratio	CL/F (ml/min)
A	Paliperidone OROS 12 mg qd post bkfst	5	Paliperidone	34	42.7 ± 20.8 (48.7) 17.1 - 98.0 [36.9]	31.3 ± 16.6 (53.0) 9.17 - 81.9 [28.2]	44.1 ± 23.7 (53.7) 19.4 - 127 [36.5]	10.4 ± 10.4 (100.0) 1.0 - 24.3 [4.3]	877 ± 454 (51.8) 371 - 2332 [777]	11.8 ± 0.6 (5.1) 10.9 - 13.0 [11.9]	198 ± 82 (41.4) 66.9 - 353 [186]	36.6 ± 18.9 (51.6) 15.5 - 97.2 [32.4]	36.1 ± 13.4 (37.1) 18.3 - 71.8 [33.9]		279 ± 118 (42.3) 85.8 - 539 [257]
			R078543 (+)-paliperidone	16	30.7 ± 17.6 (57.3) 14.7 - 86.7 [25.1]	22.2 ± 11.8 (53.2) 9.11 - 56.6 [20.6]	34.7 ± 20.3 (58.5) 16.6 - 95.9 [28.6]	14.5 ± 10.3 (71.0) 1.0 - 24.0 [22.2]	665 ± 381 (57.3) 309 - 1839 [568]	12.0 ± 0.7 (5.8) 10.8 - 13.6 [12.1]	267 ± 109 (40.8) 84.2 - 419 [253]	27.7 ± 15.8 (57.0) 12.9 - 76.6 [23.7]	43.6 ± 17.3 (39.7) 25.6 - 90.4 [40.4]	4.18 ± 1.80 (43.1) 1.91 - 7.96 [4.01]	188 ± 82 (43.6) 54.4 - 324 [177]
			R078544 (-)-paliperidone	16	19.5 ± 9.5 (48.7) 10.7 - 46.0 [16.0]	14.5 ± 6.7 (46.2) 6.96 - 31.8 [12.9]	21.5 ± 10.8 (50.2) 10.2 - 51.2 [16.9]	12.8 ± 10.5 (82.0) 1.0 - 24.0 [15.1]	423 ± 216 (51.1) 217 - 1058 [353]	12.0 ± 0.7 (5.8) 10.9 - 13.5 [12.1]	406 ± 155 (38.2) 145 - 657 [408]	17.6 ± 9.0 (51.1) 9.04 - 44.1 [14.7]	38.7 ± 17.3 (44.7) 15.3 - 85.5 [32.8]	4.90 ± 1.94 (39.6) 2.31 - 9.03 [4.59]	285 ± 113 (39.6) 94.5 - 461 [284]
			R078543 / R078544 (+ / -)				1.59 ± 0.24 (15.1) 1.20 - 2.07 [1.59]		1.55 ± 0.20 (12.9) 1.23 - 1.94 [1.52]						
B	Paliperidone OROS 12 mg qd post bkfst	6	Paliperidone	34	41.5 ± 22.4 (54.0) 15.9 - 135 [36.0]	31.4 ± 15.9 (50.6) 13.2 - 92.4 [28.6]	45.6 ± 27.1 (59.4) 16.6 - 166 [38.4]	14.7 ± 10.1 (68.7) 0.9 - 24.0 [22.2]	896 ± 507 (56.6) 359 - 3126 [769]	12.1 ± 0.5 (4.1) 10.9 - 13.3 [12.1]	197 ± 81 (41.1) 49.5 - 394 [186]	37.3 ± 21.1 (56.6) 15.0 - 130 [32.1]	36.4 ± 12.2 (33.5) 18.8 - 72.7 [34.7]	3.83 ± 2.04 (53.3) 1.73 - 12.4 [3.12]	273 ± 113 (41.4) 64.0 - 557 [260]
C	Risperdione 4 mg IR x 5 days	6	Active	34	20.1 ± 7.8 (38.8) 7.19 - 36.6 [20.2]	18.9 ± 7.7 (40.7) 7.00 - 36.6 [18.9]	56.8 ± 18.0 (31.7) 26.2 - 95.3 [55.4]	2.8 ± 0.6 (21.4) 2.0 - 4.1 [3.0]	760 ± 276 (36.3) 321 - 1433 [748]	10.1 ± 0.5 (5.0) 9.3 - 11.0 [10.1]	59.8 ± 22.0 (36.8) 29.9 - 127 [52.3]	31.7 ± 11.5 (36.3) 13.4 - 59.7 [31.2]	125 ± 29 (23.2) 81.5 - 189 [122]	3.36 ± 0.69 (20.5) 1.35 - 5.10 [3.26]	100 ± 38 (38.0) 46.5 - 208 [89.2]
			Paliperidone	34	17.1 ± 6.9 (40.4) 7.19 - 33.7 [16.3]	15.9 ± 6.7 (42.1) 6.94 - 33.3 [15.7]	31.2 ± 10.8 (34.6) 8.60 - 53.0 [31.4]	5.2 ± 4.7 (90.4) 2.0 - 22.3 [4.0]	539 ± 196 (36.4) 179 - 975 [519]	11.0 ± 0.7 (6.4) 10.0 - 12.5 [11.0]	95.1 ± 46.1 (48.5) 48.2 - 273 [85.0]	22.5 ± 8.1 (36.0) 7.46 - 40.6 [21.6]	69.1 ± 29.5 (42.7) 22.3 - 142 [68.9]	4.11 ± 1.26 (30.7) 1.61 - 7.96 [3.97]	143 ± 63 (44.1) 68.4 - 372 [129]
			Risperidone	34	3.0 ± 5.55 (185.0) NQ - 24.6 [0.66]	2.67 ± 5.37 (201.1) NQ - 24.6 [0.46]	28.0 ± 15.2 (54.3) 6.15 - 75.8 [26.6]	2.5 ± 0.5 (20.0) 1.1 - 4.0 [2.3]	221 ± 227 (102.7) 24.1 - 1122 [124]	6.4 ± 2.0 (31.3) 3.1 - 10.7 [6.2]	212 ± 164 (77.4) 37.8 - 863 [161]	9.23 ± 9.48 (102.7) 1.00 - 46.8 [5.17]	419 ± 198 (47.3) 102 - 814 [413]	2.24 ± 0.69 (30.8) 1.00 - 4.68 [2.08]	673 ± 623 (92.6) 59.4 - [539]

Table 60 Risperidone and Metabolite Multiple Dose After Risperidone 8 mg BID – Study SCH-102

Rx	Regimen	Day	Analyte	POP	N	Cmin,ss ng/mL	tmin,ss h	Cmax,ss ng/mL	Tmax,ss h	AUCτ,ss, ng.h/mL	Cavg,ss, ng/mL	Cmax,ss: Cmin,ss Ratio	FI %	CL/F mL/min	t1/2 h	Cmax (R078543/ R078544)	AUC (R078543/ R078544)
RIS	Dose-escalation up to 7 mg IR b.i.d. Days 8-14, followed by 8 mg IR b.i.d. Days 15-21.	21	Paliperidone	All	14	78.8 ± 35.7 (46.6) 33.8 - 137 [71.5]		122 ± 41.4 (33.9) 73.2 - 195 [113]	5.28 ± 4.48 (85.0) 2.00 - 15.00 [3.50]	2392 ± 896 (37.5) 1414 - 4046 [2260]	100 ± 37.3 (37.5) 58.9 - 169 [94.2]	1.73 ± 0.49 (28.5) 1.21 - 3.1 [1.56]	49.9 ± 23.2 (46.5) 18.8 - 107 [44.7]	126 ± 43.6 (34.6) 65.9 - 189 [118]	29.7 ± 3.0 (9.9) 23.9 - 35.3 [29.9]	2.85 ± 0.453 (15.9) 2.33 - 3.78 [2.74]	2.53 ± 0.501 (19.8) 1.77 - 3.19 [2.48]
				except #027 & #053d	12	83.6 ± 34.0 (40.6) 38.9 - 137 [79.2		127 ± 42.8 (33.7) 73.2 - 195 [118	4.57 ± 3.81 (83.3) 2.00 - 14.83 [3.00	2539 ± 884 (34.8) 1414 - 4046 [2343	106 ± 36.8 (34.8) 58.9 - 169 [97.6		43.2 ± 15.3 (35.5) 18.8 - 72.1 [39.5	117 ± 40.8 (34.7) 65.9 - 189 [113.9	29.4 ± 3.1 (10.7) 23.9 - 35.3 [29.5]	2.78 ± 0.400 (14.3) 2.33 - 3.45 [2.70]	2.57 ± 0.481 (18.7) 1.89 - 3.19 [2.48]
			R078543 (+)	All	14	51.0 ± 26.7 (52.3) 16.5 - 95.1 [46.7]		92.5 ± 32.9 (35.6) 52.0 - 153 [83.2]	5.35 ± 4.44 (82.9) 2.00 - 15.00 [3.50]	1716 ± 686 (40.0) 962 - 2889 [1588]	71.5 ± 28.6 (40.0) 40.1 - 120 [66.1]		64.9 ± 33.4 (51.4) 24.5 - 151 [56.7]	179 ± 67.3 (37.5) 92.3 - 277 [169]	29.6 ± 2.3 (7.9) 26.2 - 32.2 [30.9]		
				except #027 & #053d	12	56.2 ± 25.2 44.9 21.5 - 95.1 [52.7]		95.7 ± 34.6 36.2 52.0 - 153 [88.4]	4.65 ± 3.76 80.8 2.00 - 14.83 [3.00]	1829 ± 677 37.0 962 - 2889 [1757]	76.2 ± 28.2 37.0 40.1 - 120 [73.2]		54.9 ± 20.8 37.8 24.5 - 92.6 [50.3]	166 ± 63.6 38.3 92.3 - 277 [152]	29.3 ± 2.4 8.2 26.2 - 32.2 [29.2]		
			R078544 (-)	All	14	24.3 ± 9.10 (37.4) 12.8 - 46.3 [22.6]		32.6 ± 10.5 (32.2) 17.8 - 56.7 [29.6]	10.48 ± 8.85 (84.5) 1.00 - 24.00 [8.04]	676 ± 235 (34.8) 365 - 1263 [614]	28.1 ± 9.81 (34.8) 15.2 - 52.6 [25.6]		30.2 ± 7.7 (25.6) 19.8 - 48.6 [29.2]	436 ± 137 (31.4) 211 - 730 [435]	30.7 ± 2.6 (8.5) 26.5 - 35.5 [30.9]		
				except #027 & #053d	12	25.9 ± 8.87 (34.3) 16.2 - 46.3 [23.1]		34.0 ± 10.3 (30.3) 21.2 - 56.7 [30.4]	9.55 ± 8.63 (90.4) 1.00 - 23.92 [6.00]	710 ± 233 (32.9) 452 - 1263 [643]	29.6 ± 9.72 (32.9) 18.8 - 52.6 [26.8]		28.4 ± 5.97 (21.0) 19.8 - 38.1 [27.0]	409 ± 116 (28.3) 211 - 591 [415]	30.7 ± 2.8 (9.2) 26.5 - 35.5 [31.0]		
			Risperidone	All	14	12.0 ± 21.5 (179.4) 0.281 - 75.1 [2.51]		59.7 ± 35.8 (60.0) 17.6 - 125 [50]	4.21 ± 5.05 (120.0) 0.98 - 14.00 [1.50]	668 ± 704 (105.3) 143 - 2492 [329]	27.9 ± 29.3 (105.3) 5.95 - 104 [13.7]		281 ± 164 (58.6) 48.1 - 567 [252]	813 ± 551 (67.8) 107 - 1869 [811]	15.8 ± 12.7 (81.1) 2.1 - 40.6 [14.8]		
				except #027 & #053d	12	13.9 ± 22.7 (163.4) 0.296 - 75.1 [4.59]		62.1 ± 38.0 (61.2) 17.6 - 125 [50.1]	3.66 ± 4.72 (129.2) 0.98 - 14.00 [1.00]	748 ± 732 (97.8) 168 - 2492 [447]	31.2 ± 30.5 (97.8) 7.00 - 104 [18.6]		233 ± 121 (52.1) 48.1 - 526 [235]	699 ± 484 (69.3) 107 - 1587 [631]	15.9 ± 12.8 (80.4) 2.1 - 40.6 [14.8]		
			Active Moiety	All	14	89.9 ± 47.2 (52.4) 34.1 - 161 [74.9]		176 ± 66.3 (37.9) 92.7 - 290 [161]	2.99 ± 3.62 (120.8) 1.00 - 15.00 [2.00]	3060 ± 1326 (43.3) 1621 - 4789 [2710]	127 ± 55.3 (43.3) 67.5 - 200 [113]		73.7 ± 28.2 (38.3) 33.1 - 138 [70.7]	104 ± 44.0 (42.2) 55.7 - 165 [99.2]	29.3 ± 3.1 (10.5) 24.3 - 35.1 [29.8]		
				except #027 & #053d	12	98.9 ± 44.9 45.4 39.4 - 161 [86.7]		183 ± 68.8 37.7 92.7 - 290 [167]	2.08 ± 1.16 55.9 1.00 - 4.00 [1.98]	3288 ± 1297 39.5 1621 - 4789 [2980]	137 ± 54.1 39.5 67.5 - 200 [124]		64.2 ± 15.4 24.0 33.1 - 88.2 [64.3]	95.4 ± 41.1 43.1 55.7 - 165 [89.5]	29.1 ± 3.3 11.2 24.3 - 35.1 [29.3]		

Table 61 Paliperidone and Enantiomer Multiple Dose Pharmacokinetics after Paliperidone OROS 9 mg qd – Study SCH-102

Rx	Regimen	Day	Analyte	POP	N	Cmin,ss ng/mL	tmin,ss h	Cmax,ss ng/mL	tmax,ss h	AUCτ,ss, ng.h/mL	Cavg,ss, ng/mL	Cmax,ss: Cmin,ss Ratio	FI %	CL/F mL/min	t1/2 h	Cmax (R078543/ R078544)	AUC (R078543/ R078544)	DN Cmax,ss, ng/mL	DN AUCτ,ss, ng.h/mL
Pal	9 mg ER OROS paliperidone q.d. from Day 8-14 Following a 7 days washout period.	14	Paliperidone	All	32	25.3 ± 16.2 (63.8) 3.86 - 76.9 [21.7]		40.2 ± 24.1 (59.9) 8.79 - 130 [35.0]	10.90 ± 8.88 (81.4) 1.87 - 24.00 [8.99]	762 ± 464 (60.9) 173 - 2331 [638]	31.7 ± 19.3 (60.9) 7.19 - 97.1 [26.6]	1.69 ± 0.49 (28.8) 1.15 – 3.07 [1.6]	51.9 ± 31.3 (60.4) 14.0 - 166 [48.3]	274 ± 169 (61.6) 64.4 - 869 [235]		1.59 ± 0.218 (13.7) 1.23 - 2.18 [1.55]	1.56 ± 0.204 (13.1) 1.21 - 2.02 [1.51	67.1 ± 40.1 (59.9) 14.7 - 217 [58.3]	1270 ± 773 (60.9) 288 - 3885 [1083]
				EM	25	24.5 ± 17.2 (70.4) 3.86 - 76.9 [21.1]		40.0 ± 25.9 (64.8) 8.79 - 130 [32.0]	10.39 ± 8.81 (84.8) 1.87 - 24.00 [5.95]	746 ± 499 (66.9) 173 - 2331 [598]	31.1 ± 20.8 (66.9) 7.19 - 97.1 [24.9]		55.8 ± 34.1 (61.0) 14.0 - 166 [52.1]	289 ± 180 (62.4) 64.4 - 869 [251]		1.58 ± 0.198 (12.6) 1.23 - 1.95 [1.54]	1.53 ± 0.177 (11.5) 1.21 - 1.87 [1.50	66.7 ± 43.2 (64.8) 14.7 - 217 [53.3]	1244 ± 832 (66.9) 288 - 3885 [997]
				IM & PM	6	27.4 ± 13.0 (47.6) 10.7 - 47.7 [28.0]		38.8 ± 18.0 (46.3) 18.4 - 67.3 [39.2]	11.66 ± 10.04 (86.1) 2.00 - 23.98 [9.00]	780 ± 350 (44.8) 349 - 1339 [820]	32.5 ± 14.6 (44.8) 14.5 - 55.8 [34.2]		35.9 ± 11.5 (32.0) 19.9 - 53.0 [37.2]	233 ± 118 (50.8) 112 - 430 [183]		1.68 ± 0.293 (17.4) 1.39 - 2.18 [1.68]	1.69 ± 0.278 (16.5) 1.30 - 2.02 [1.76]	64.7 ± 30.0 (46.3) 30.7 - 112 [65.3]	1301 ± 583 (44.8) 581 - 2232 [1367]
			R078543 (+)	All	32	15.2 ± 9.99 (65.7) 2.14 - 48.4 [13.3]		25.0 ± 15.7 (63.0) 5.39 - 86.2 [21.7]	11.60 ± 8.58 (73.9) 1.87 - 24.00 [9.00]	467 ± 295 (63.2) 103 - 1499 [390]	19.4 ± 12.3 (63.2) 4.29 - 62.5 [16.2]		55.1 ± 31.3 (56.8) 18.3 - 168 [53.9]	229 ± 145 (63.5) 50.0 - 728 [192]				41.6 ± 26.2 (63.0) 8.98 - 144 [36.1]	778 ± 492 (63.2) 172 - 2498 [650]
				EM	25	14.6 ± 10.5 (72.1) 2.14 - 48.4 [12.0]		24.8 ± 17.0 (68.6) 5.39 - 86.2 [19.8]	10.69 ± 8.72 (81.6) 1.87 - 24.00 [8.97]	455 ± 316 (69.4) 103 - 1499 [367]	18.9 ± 13.1 (69.4) 4.29 - 62.5 [15.3]		59.3 ± 33.7 (56.8) 18.4 - 168 [56.0]	242 ± 154 (63.8) 50.0 - 728 [205]				41.3 ± 28.3 (68.6) 8.98 - 144 [33.0]	758 ± 526 (69.4) 172 - 2498 [611]
				IM & PM	6	17.2 ± 8.80 (51.2) 6.03 - 30.9 [16.7]		24.6 ± 11.7 (47.7) 10.7 - 41.9 [24.6]	14.18 ± 8.25 (58.2) 2.00 - 23.97 [14.04]	494 ± 238 (48.2) 197 - 873 [502]	20.6 ± 9.93 (48.2) 8.20 - 36.4 [20.9]		37.8 ± 13.9 (36.8) 18.3 - 57.0 [38.0]	191 ± 108 (56.6) 85.9 - 381 [151]				41.1 ± 19.6 (47.7) 17.8 - 69.8 [40.9]	824 ± 397 (48.2) 328 - 1456 [837]
			R078544 (-)	All subjects	32	10.1 ± 6.31 (62.7) 1.72 - 28.5 [8.72]		15.5 ± 8.61 (55.7) 3.40 - 44.1 [13.9]	11.37 ± 8.89 (78.2) 1.87 - 24.00 [9.00]	295 ± 172 (58.2) 69.7 - 834 [247]	12.3 ± 7.16 (58.2) 2.90 - 34.7 [10.3]		49.0 ± 31.2 (63.7) 9.22 - 164 [43.9]	345 ± 205 (59.3) 90.0 - 1076 [304]				25.8 ± 14.4 (55.7) 5.67 - 73.5 [23.2]	492 ± 286 (58.2) 116 - 1389 [412]
				EM	25	9.86 ± 6.82 (69.1) 1.72 - 28.5 [8.00]		15.4 ± 9.19 (59.7) 3.40 - 44.1 [12.2]	10.47 ± 8.57 (81.8) 1.87 - 24.00 [8.97]	292 ± 186 (63.7) 69.7 - 834 [238]	12.1 ± 7.74 (63.7) 2.90 - 34.7 [9.90]		52.3 ± 34.5 (65.9) 9.22 - 164 [45.6]	362 ± 220 (60.8) 90.0 - 1076 [316]				25.7 ± 15.3 (59.7) 5.67 - 73.5 [20.3]	486 ± 310 (63.7) 116 - 1389 [396]
				IM & PM	6	10.0 ± 4.27 (42.5) 4.71 - 16.8 [10.7]		14.5 ± 6.53 (45.0) 7.68 - 25.5 [15.1]	13.83 ± 10.73 (77.6) 2.00 - 23.98 [15.50]	286 ± 115 (40.2) 152 - 466 [303]	11.9 ± 4.79 (40.2) 6.32 - 19.4 [12.6]		36.6 ± 8.93 (24.4) 24.5 - 47.0 [36.4]	304 ± 132 (43.4) 161 - 494 [248]				24.2 ± 10.9 (45.0) 12.8 - 42.5 [25.1]	477 ± 191 (40.2) 253 - 776 [505]

Table 62 Paliperidone and Enantiomer Multiple Dose Pharmacokinetics after Paliperidone OROS 15 mg qd – Study SCH-102

Rx	Regimen	Day	Analyte	POP	N	Cmin,ss ng/mL	tmin,ss h	Cmax,ss ng/mL	tmax,ss h	AUCτ,ss, ng.h/mL	Cavg,ss, ng/mL	Cmax,ss: Cmin,ss Ratio	FI %	CL/F mL/min	t1/2 h	Cmax (R078643/ R078644)	AUC (R078643/ R078644)	DN Cmax,ss, ng/mL	DN AUCτ,ss, ng.h/mL
Pal	9 mg ER OROS paliperidone q.d. from Day 8-14, followed by 15 mg ER OROS paliperidone q.d. from Day 15-21.	21	Paliperidone	All	31	37.0 ± 19.0 (51.3) 1.27 - 76.1 [35.4]	8.52+8.56 100.5 0-24 5	57.4 ± 30.1 (52.4) 1.82 - 146 [54.0]	17.53 ± 7.97 (45.5) 2.00 - 24.03 [21.87]	1111 ± 539 (48.5) 35.0 - 2363 [1053]	46.3 ± 22.5 (48.5) 1.46 - 98.5 [43.9]	1.61 ± 0.43 (26.8) 1.17 - 2.68 [1.47]	44.2 ± 22.3 (50.4) 15.4 - 91.9 [40.7]	522 ± 1262 (242.0) 106 - 7147 [237]	34.0 ± 10.5 (30.9) 22.1 - 70.0 [31.4]	1.61 ± 0.225 (14.0) 1.22 - 1.97 [1.59]	1.57 ± 0.203 (12.9) 1.26 - 1.97 [1.53]		
				except #106	30	38.2 ± 18.1 (47.4) 5.06 - 76.1 [37.0]		59.2 ± 28.7 (48.5) 9.30 - 146 [58.0]	18.05 ± 7.56 (41.9) 2.00 - 24.03 [21.93]	1147 ± 510 (44.4) 146 - 2363 [1063]	47.8 ± 21.2 (44.4) 6.09 - 98.5 [44.3]		44.4 ± 22.6 (50.9) 15.4 - 91.9 [41.1]	301 ± 291 (96.7) 106 - 1710 [235]	34.0 ± 10.5 (30.9) 22.1 - 70.0 [31.4]	1.60 ± 0.221 (13.8) 1.22 - 1.97 [1.59]	1.56 ± 0.205 (13.1) 1.26 - 1.97 [1.52]		
				EM	24	33.9 ± 17.8 (52.6) 1.27 - 65.8 [34.1]		52.8 ± 30.4 (57.6) 1.82 - 146 [48.0]	16.40 ± 8.60 (52.4) 2.00 - 24.00 [21.86]	1015 ± 531 (52.3) 35.0 - 2363 [938]	42.3 ± 22.1 (52.3) 1.46 - 98.5 [39.1]		44.1 ± 23.5 (53.3) 16.7 - 91.9 [39.2]	618 ± 1426 (230.7) 106 - 7147 [267]	34.8 ± 11.1 (31.8) 22.4 - 70.0 [31.4]	1.57 ± 0.208 (13.2) 1.22 - 1.92 [1.55]	1.54 ± 0.166 (10.8) 1.29 - 1.82 [1.50]		
				IM & PM	6	48.4 ± 22.1 (45.7) 16.9 - 76.1 [47.8]		71.0 ± 26.4 (37.2) 40.7 - 117 [66.7]	21.84 ± 3.50 (16.0) 15.97 - 24.03 [24.00]	1425 ± 500 (35.1) 822 - 2168 [1327]	59.4 ± 20.8 (35.1) 34.3 - 90.4 [55.3]		41.0 ± 18.0 (43.9) 15.4 - 69.5 [41.2]	195 ± 68.9 (35.4) 115 - 304 [190]	30.3 ± 8.9 (29.5) 22.1 - 41.7 [26.5]	1.75 ± 0.271 (15.5) 1.34 - 1.97 [1.88]	1.68 ± 0.315 (18.7) 1.26 - 1.97 [1.82]		
			R078543 (+)	All	31	22.4 ± 12.3 (54.8) 0.808 - 49.2 [21.4]		35.8 ± 19.8 (55.3) 1.20 - 95.6 [34.1]	17.41 ± 7.98 (45.8) 2.00 - 24.03 [21.85]	682 ± 351 (51.4) 22.0 - 1493 [648]	28.4 ± 14.6 (51.4) 0.916 - 62.2 [27.0]		47.5 ± 24.0 (50.6) 15.2 - 98.0 [44.2]	427 ± 1006 (236.0) 83.7 - 5688 [193]	34.3 ± 10.3 (29.9) 22.0 - 67.3 [31.6]				
				except #106	30	23.2 ± 11.8 (51.0) 2.95 - 49.2 [22.4]		36.9 ± 19.0 (51.6) 5.71 - 95.6 [34.8]	17.92 ± 7.58 (42.3) 2.00 - 24.03 [21.86]	704 ± 335 (47.5) 86.1 - 1493 [652]	29.4 ± 13.9 (47.5) 3.59 - 62.2 [27.2]		47.7 ± 24.4 (51.2) 15.2 - 98.0 [45.4]	251 ± 248 (98.9) 83.7 - 1452 [192]	34.3 ± 10.3 (29.9) 22.0 - 67.3 [31.6]				
				EM	24	20.3 ± 11.1 (54.8) 0.808 - 42.5 [20.3]		32.6 ± 19.6 (60.2) 1.20 - 95.6 [29.4]	16.32 ± 8.65 (53.0) 2.00 - 24.02 [20.43]	618 ± 336 (54.4) 22.0 - 1493 [569]	25.7 ± 14.0 (54.4) 0.916 - 62.2 [23.7]		47.2 ± 25.5 (54.0) 15.2 - 98.0 [42.3]	505 ± 1137 (224.9) 83.7 - 5688 [220]	34.9 ± 10.6 (30.3) 22.1 - 67.3 [31.6]				
				IM & PM	6	30.5 ± 15.4 (50.4) 9.26 - 49.2 [28.6]		45.8 ± 18.9 (41.2) 23.6 - 77.9 [41.7]	21.50 ± 3.35 (15.6) 15.97 - 24.03 [22.99]	901 ± 362 (40.1) 466 - 1426 [817]	37.5 ± 15.1 (40.1) 19.4 - 59.4 [34.1]		44.8 ± 18.9 (42.1) 16.8 - 73.8 [47.9]	160 ± 66.1 (41.4) 87.7 - 268 [156]	31.0 ± 10.2 (33.0) 22.0 - 44.1 [26.4]				
			R078544 (-)	All	31	14.4 ± 6.79 (47.2) 0.459 - 26.3 [14.6]		22.1 ± 10.7 (48.6) 0.624 - 51.3 [20.8]	17.62 ± 8.11 (46.0) 2.00 - 24.02 [21.97]	429 ± 193 (45.0) 13.0 - 870 [401]	17.9 ± 8.05 (45.0) 0.542 - 36.2 [16.7]		42.5 ± 21.0 (49.4) 18.2 - 92.3 [34.7]	676 ± 1693 (250.6) 144 - 9607 [312]	33.3 ± 10.8 (32.4) 22.2 - 75.0 [30.8]				
				Except #106	30	14.8 ± 6.39 (43.0) 1.97 - 26.3 [14.8]		22.8 ± 10.1 (44.5) 3.59 - 51.3 [22.4]	18.14 ± 7.71 (42.5) 2.00 - 24.02 [21.97]	443 ± 180 (40.7) 60.1 - 870 [413]	18.4 ± 7.50 (40.7) 2.50 - 36.2 [17.2]		42.9 ± 21.2 (49.4) 18.2 - 92.3 [36.1]	378 ± 351 (92.9) 144 - 2080 [303]	33.3 ± 10.8 (32.4) 22.2 - 75.0 [30.8]				
				EM	24	13.4 ± 6.70 (50.1) 0.459 - 25.1 [13.4]		20.7 ± 11.2 (54.2) 0.624 - 51.3 [19.8]	16.81 ± 8.64 (51.4) 2.00 - 24.00 [21.92]	397 ± 198 (49.8) 13.0 - 870 [393]	16.6 ± 8.25 (49.8) 0.542 - 36.2 [16.4]		43.0 ± 22.1 (51.4) 18.2 - 92.3 [34.2]	800 ± 1915 (239.2) 144 - 9607 [318]	34.3 ± 11.6 (33.9) 22.6 - 75.0 [30.8]				
				IM&P M	6	17.8 ± 6.98 (39.1) 7.61 - 26.3 [19.2]		25.6 ± 7.95 (31.0) 17.6 - 39.6 [25.0]	20.65 ± 6.06 (29.3) 8.97 - 24.02 [23.96]	524 ± 146 (27.8) 356 - 743 [529]	21.9 ± 6.08 (27.8) 14.8 - 31.0 [22.0]		37.7 ± 17.5 (46.3) 19.9 - 67.4 [35.8]	255 ± 72.5 (28.4) 168 - 351 [236]	29.4 ± 7.3 (24.9) 22.2 - 38.8 [26.5]				

Figure 43 Steady-State Paliperidone OROS Cmax vs. Dose – Studies P01-1005, SCH-1011, SCH-101, and SCH-102

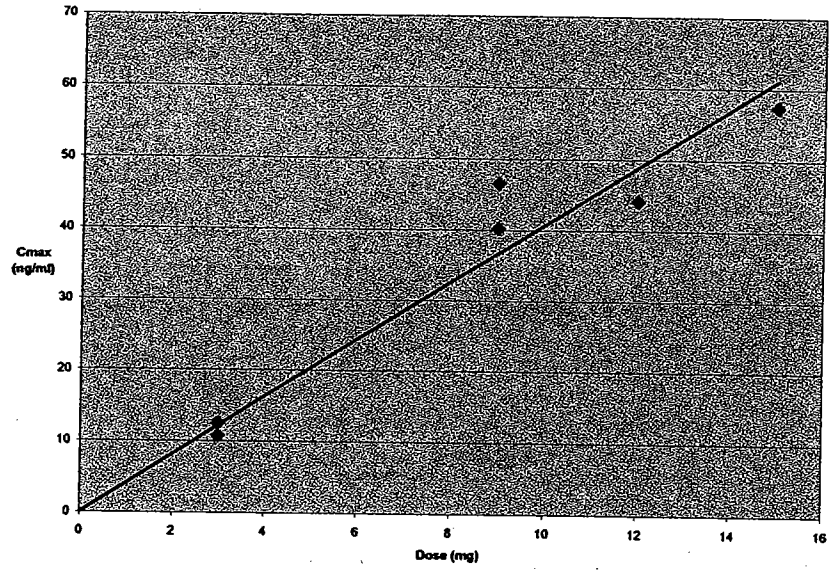


Figure 44 Steady-State Paliperidone OROS AUCtau vs. Dose – Studies P01-1005, SCH-1011, SCH-101, and SCH-102

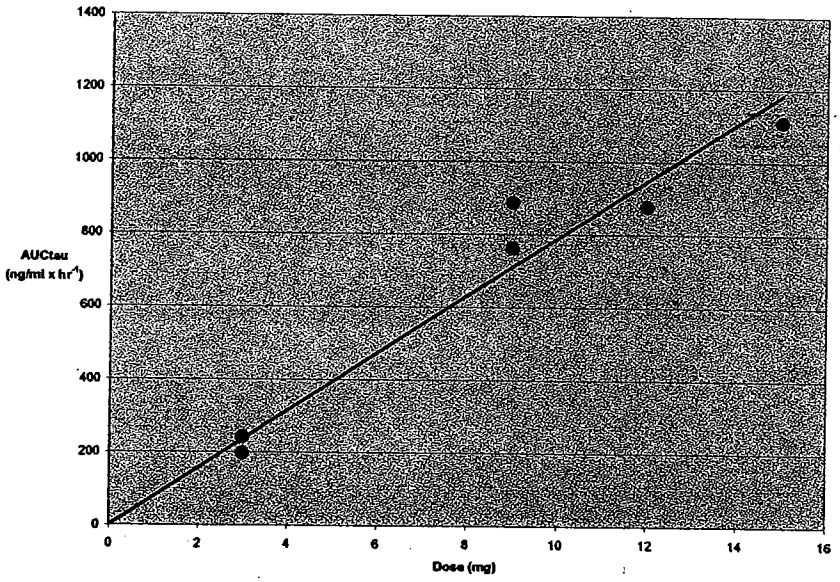


Figure 45 Mean Single Dose and Day 12 Multiple Dose Paliperidone OROS 3 mg Concentration vs. Time Profiles in Elderly and Young Subjects - Study SCH-1011

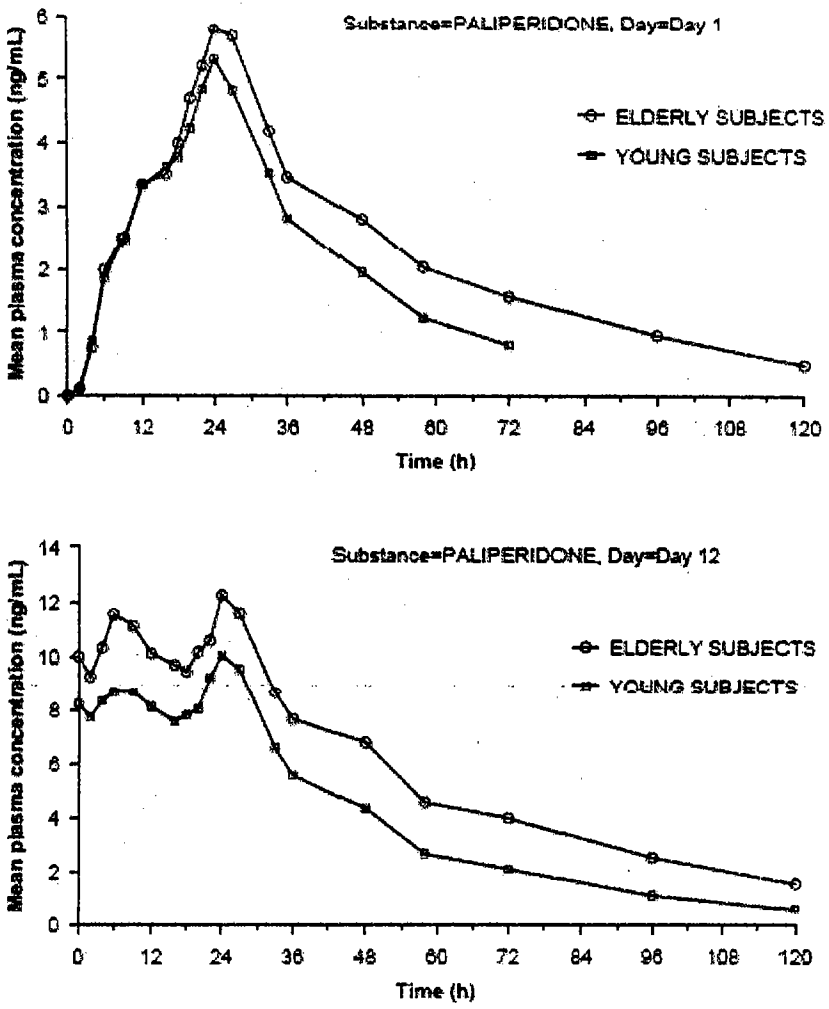


Figure 46 Individual Single Dose and Day 12 Multiple Dose Paliperidone OROS 3 mg Concentration vs. Time Profiles in Elderly and Young Subjects - Study SCH-1011

Figure PK 3: Linear and Semi-Logarithmic Overlay of Individual Plasma Concentration-Time Profiles of Paliperidone and its Enantiometers
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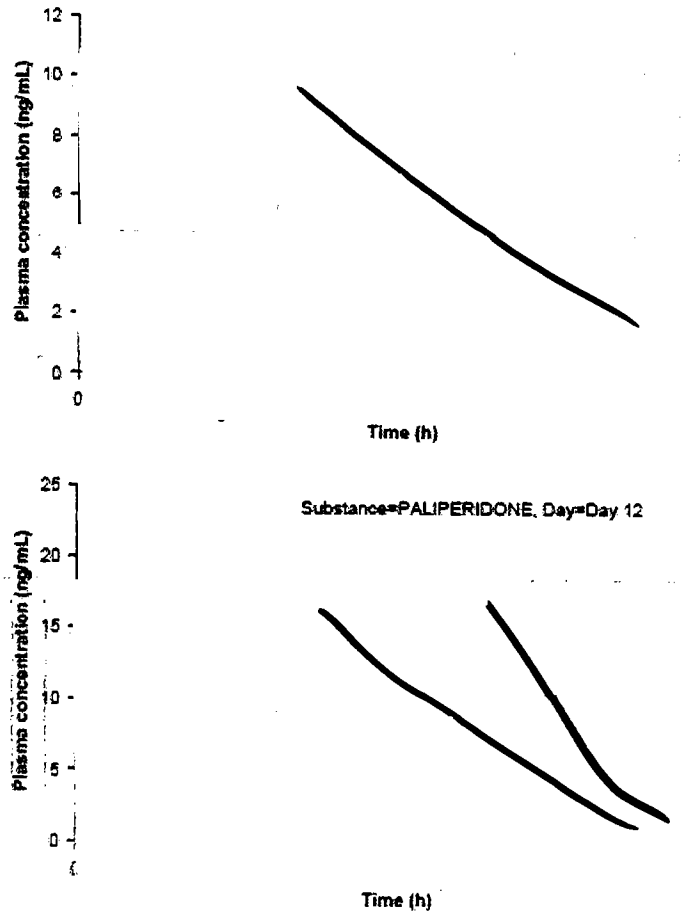


Dotted line: Elderly subjects, Unbroken line: Young subjects

Figure 47 Individual Single Dose and Day 11 Multiple Dose Paliperidone OROS 3 mg Concentration vs. Time Profiles in Caucasian Subjects -P01-1005

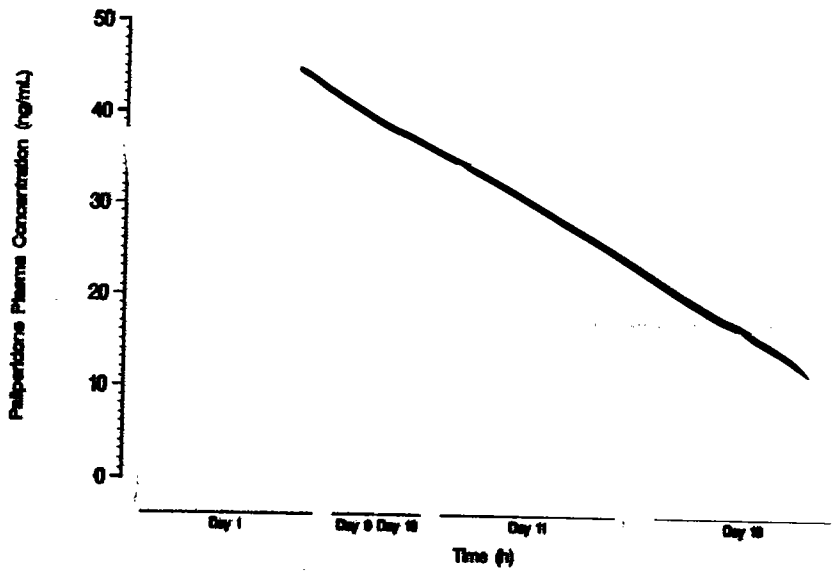


Figure 48 Individual Single Dose and Day 11 Multiple Dose Paliperidone OROS 3 mg Concentration vs. Time Profiles in Japanese Subjects -P01-1005

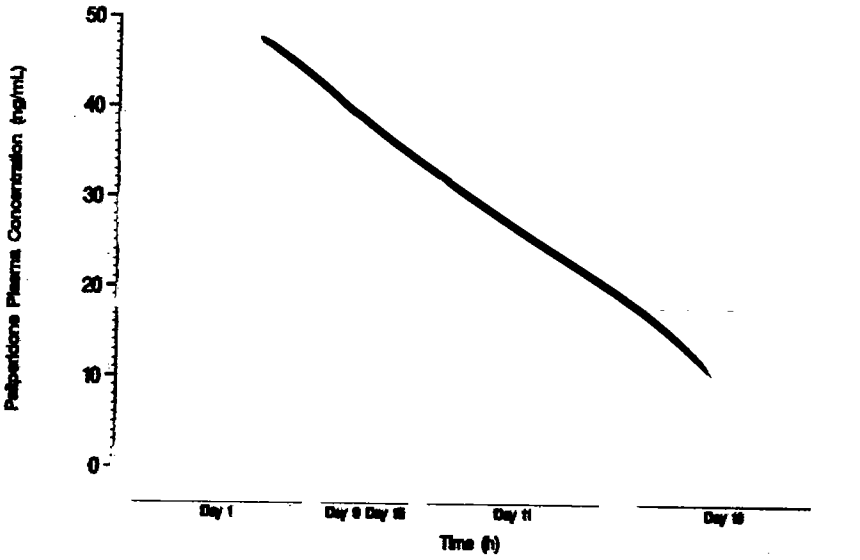
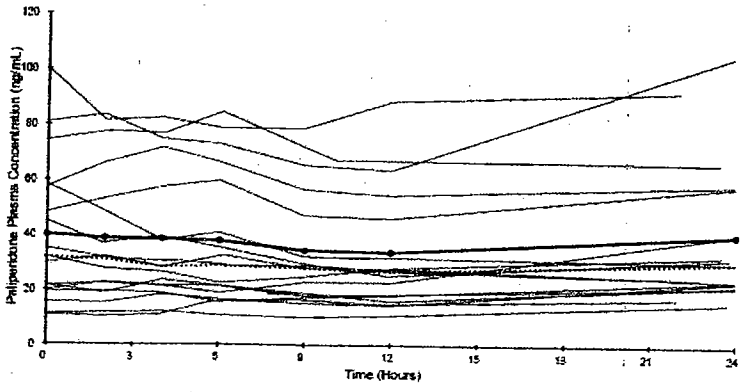


Figure 49 Multiple Dose Paliperidone OROS 9 mg Day 10 Concentration vs. Time Profiles – Study SCH-1010 Sleep study



3.10.6.2 *Paliperidone Exposure with Paliperidone OROS Compared to Exposures of Paliperidone and Active Moeity with Risperidone Tablets*

When steady-state exposures of paliperidone OROS at a dose of 15 mg daily, which is 25% higher than the proposed maximum daily dose of 12 mg, is compared to steady-state exposures of the approved maximum daily dose of risperidone IR tablets 8 mg BID, (i.e. 16 mg daily). The exposures to total 'active' moieties after risperidone, (i.e. risperidone and paliperidone), is approximately triple the exposure to paliperidone after administration of paliperidone OROS 15 mg daily. Of the total active moieties, 2/3's are due to paliperidone, so even if paliperidone alone is compared, the exposure after dosing of risperidone is still twice as high as after dosing with paliperidone OROS. After dosing with both risperidone and paliperidone OROS 2/3 of the paliperidone in plasma is composed of the (+) enantiomer and 1/3 of the exposure is due to the (-) enantiomer, (see Table 60 and Table 62). Consequently, even accounting for increases in bioavailability due to food, etc.. Exposures to paliperidone with paliperidone OROS are still probably less than after maximal exposures with risperidone. If we consider more typical clinical dosages of 6 mg daily of paliperidone OROS and 6 mg daily of risperidone the exposure ratios are only about 10% less, consequently there is still an adequate margin.

3.10.7 Pharmacokinetic / Pharmacodynamic Relationships

3.10.7.1 Positive and Negative Symptom Score (PANSS) Modeling

According to the sponsor:

> *"The effect of the drug on the endpoint PANSS and responder rates was best described by an Emax model. For PANSS, the placebo effect was estimated to be an 8% drop in PANSS, with an additional maximal drug effect of 26.6% on top of the placebo response. Both effects are proportional to the baseline PANSS score. The ED50 was estimated at 2.42 mg, although with high uncertainty (relative standard error, RSE 74%). For the responder analysis, the placebo response was different between studies: 19.3% for R076477-SCH-305 and 31.3% for R076477-SCH-303 and R076477-SCH-304.*

3.10.7.1.1 Dose and Concentration Response Modeling

The three Phase 3 studies (Studies R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305) in subjects with schizophrenia or schizoaffective disorder were included in the sponsor's PD analysis of PANSS and responder rates. Both dose and model-predicted average steady-state concentrations at endpoint were tested as drivers of the response.

According to the sponsor:

"The endpoint PANSS data of all subjects in the three studies were included in the current analysis. For subjects who dropped out of the study before the 6-week period, the LOCF methodology was applied to impute the endpoint PANSS. The percent change in PANSS at endpoint from baseline was calculated by subtracting the baseline PANSS from the endpoint PANSS, and dividing the difference by baseline-30. Responders were defined as those subjects who had an improvement (=drop) in PANSS of at least 30%.

In order to perform the concentration-response analysis, average steady-state exposure (Css) was calculated. This calculation used the individual clearance values obtained through the POSTHOC step (Bayesian estimation) from the final population PK analysis run. The following formula: dose(ng)/CL(L/h)/24,000(h.mL/L) provides the Css in ng/mL.

Several structural models were tested, starting with a linear model, followed by a log-linear, and finally an Emax and sigmoid Emax model. The effect was modeled as the sum of a placebo contribution and on top of that a drug effect. It was tested in two different ways: as an additive effect, and as a proportional effect to the baseline. In total, data from 1304 subjects from 3 Phase 3 studies were included in the analysis, including 500, 326 and 478 subjects from Studies R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305, respectively."

However, these reported results in the summary section don't match the reported values in the results section where an additive model was selected as the best model, (see Table 65). The sponsor's results for the dose response model, including placebo response is shown in Table 63, and the lack of improvement in the model estimates using concentration is shown in Table 64.

Table 63 PANSS Modeling -Dose-Response: Central Tendency and Interindividual Variability

Parameter	Central tendency (RSE, %)	Interindividual variability (SD) (RSE, %)
Baseline PANSS	93.5 (0.35)	11.0 (7.0)
Placebo effect (%)	5.07* (23.1)	19.3* (4.8)
Emax (%)	16.9* (17.0)	
ED_{50}, mg	2.42 (74.0)	
Residual error (SD)	4.17 (41.5)	

* recalculated to the baseline PANSS value of 93.5 points

Table 64 PANSS Modeling -Concentration-Response: Central Tendency and Interindividual Variability

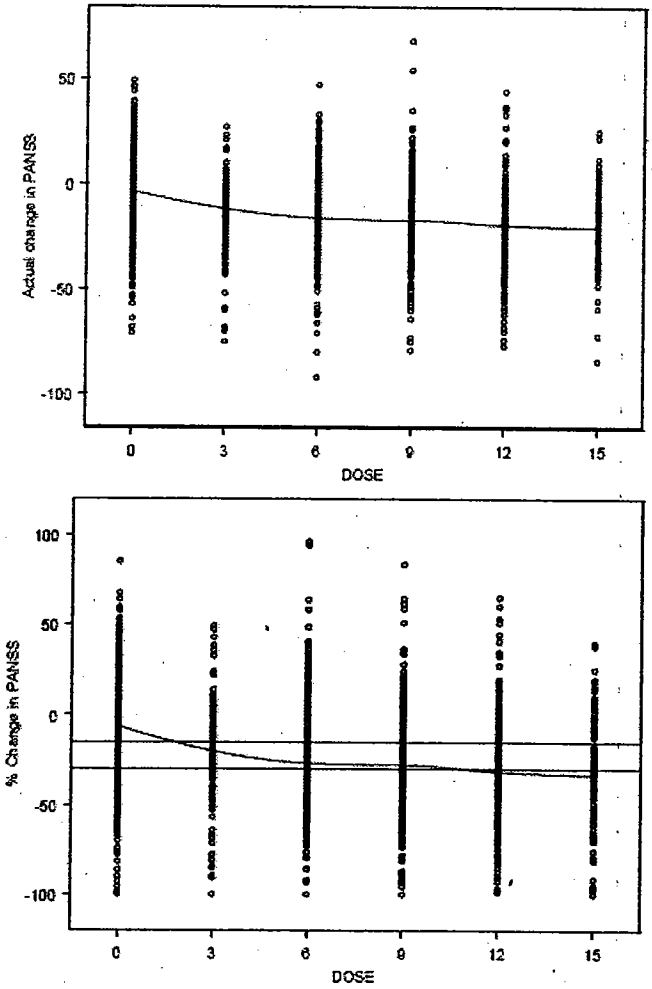
Parameter	Central tendency (RSE, %)	Interindividual variability (SD) (RSE, %)
Baseline PANSS	93.5 (0.36)	10.9 (7.46)
Placebo effect	5.16* (22.8)	19.1* (5.06)
Emax	16.7* (13.4)	
ED_{50}, mg	4.24 (83.5)	
Residual error (SD)	4.25 (41.9)	

* recalculated to the BSL PANSS value of 93.5 points

Plots of PANSS Scores and Change from Baseline vs. Dose are shown in Figure 50

Figure 50 Plots of PANSS Scores and Change from Baseline vs. Dose

Figure 1: Plots of Actual PANSS (Upper Panel) and Change from Baseline PANSS (Lower Panel) at Endpoint *vs.* Dose.



The red line represents a local smoother. The thin and the thick blue horizontal lines indicate a 15% and 30% drop in PANSS, respectively.

3.10.7.1.2 Responder Modeling

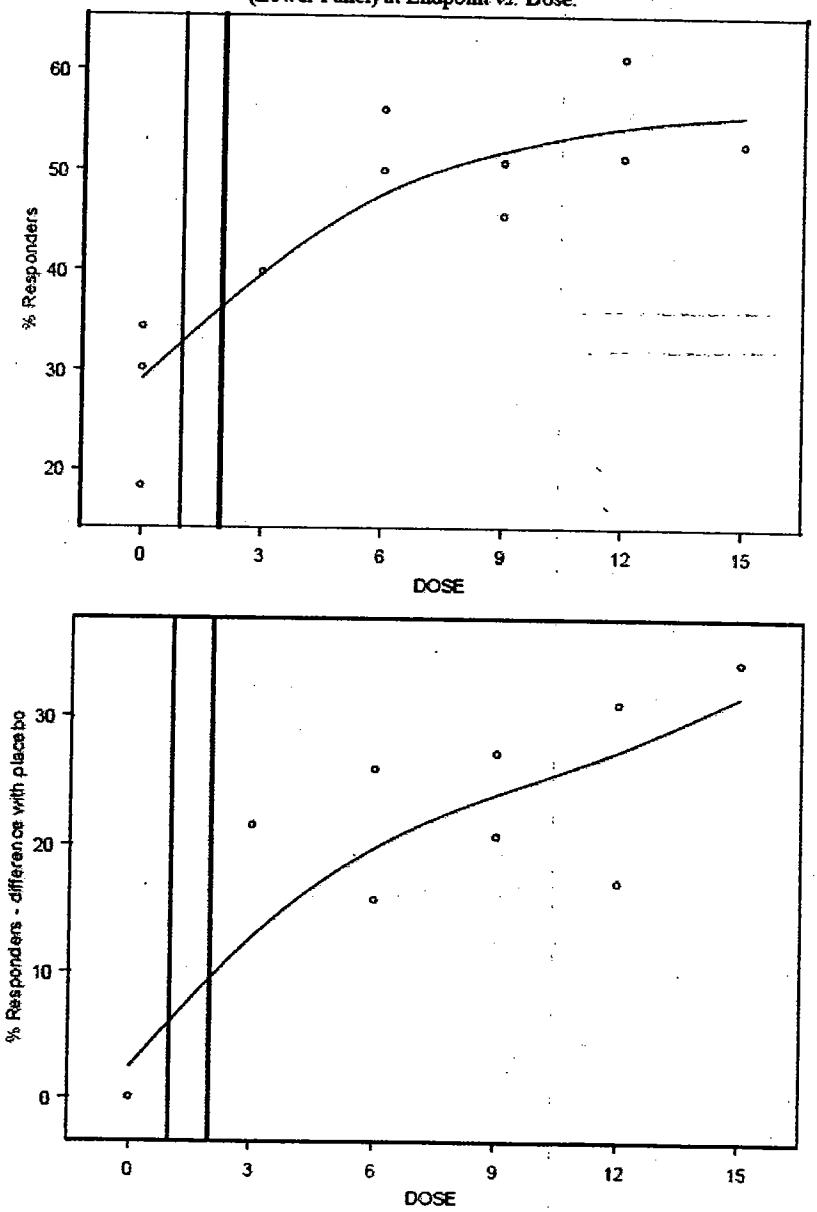
According to the sponsor:

"The best model to describe the responder data turned out to be a logistic regression model, with the probability to be a responder expressed as an Emax function of drug dose. Treatment with placebo also results in a probability of response. As such, the drug effect is generated on top of the placebo response.

When looking at the placebo response from the different Phase 3 studies, it is clear that Study R076477-SCH-305 has a much lower placebo response (Figure 51), which is accounted for in the model and found to be statistically significant. Essentially, it also means that if one corrects for the placebo response in a given study, the drug effect is the same (Figure 52)."

Figure 51 Plots of Actual % Responders and % Change from Placebo Responders at Endpoint vs. Dose

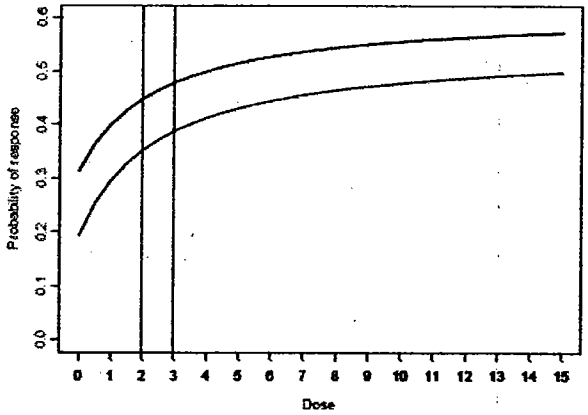
Figure 5: Plots of Actual % Responders (Upper Panel) and % Change from Placebo Responders (Lower Panel) at Endpoint *vs.* Dose.



The red line represents a local smoother. The thin and the thick blue vertical lines indicate the 1 and the 2 mg dose, respectively.

Figure 52 Percent Responders vs. Dose as Predicted by Final Dose Response Model

Figure 6: Percent Responders vs. Dose, as Predicted by the Final Dose-Response Model.



The blue line shows the prediction for Studies R076477-SCH-303 and R076477-SCH-304, the red line shows the prediction for Study R076477-SCH-305.

According to the sponsor:

"The probability to show response after placebo is estimated to be 31.3% for Studies R076477-SCH-303 and R076477-SCH-304, and 19.3% for Study R076477-SCH-305. The maximum probability of response upon drug treatment is 43.9, while the ED50 is estimated at 2.45 mg. All parameters are estimated with good precision, except for the ED50." (See Table 65)

Table 65 Sponsor's Claimed PANSS Dose and Concentration Response Modeling Parameter Estimates

Parameter	*Dose* Response Rate Model		*Concentration* Response Rate Model		Claimed Mean Maximal Response Corrected for Placebo
	Mean Placebo Response Rate% (%CV)	Mean *Dose* Response Rate Parameters Estimates (%CV)	% Placebo Response (%CV)	Mean *Concentration* Response Rate Parameters Estimates (%CV)	
Study R076477-SCH-303 and R076477-SCH-304 (% Responders)	31.3 (8.47%)	—	32.8 (8.4%)	—	—
Study R076477-SCH-305 (% Responders)	19.3 (16.7%)	—	17.9 (17.4%)	—	—
Emax (% Responders)	—	43.9 (20.8)	—	39.8 (18.5)	26.6
ED50 (mg; or ng/ml as appropriate)	—	2.45 (89.4)	—	1.82 (235%)	—

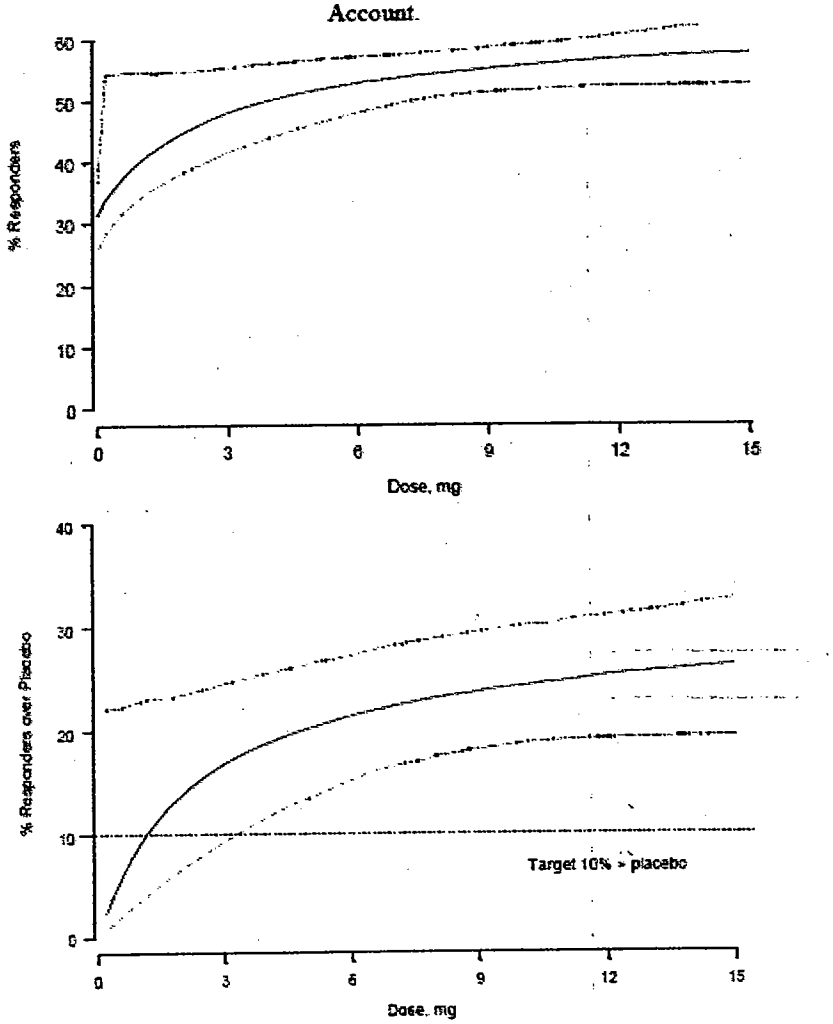
"Using the model with its associated uncertainties to simulate the dose response, the lowest dose for which the lower bound of the 95% prediction limits exceeds the target response of 10% above the placebo response is 3.2 mg. For the 3 mg-dose itself, the probability that the true drug effect exceeds 10% is 0.96. For a dose of 2 mg, this is 0.80 and for 1 mg it is 0.39. Summarizing, the dose-response modeling suggests that 3 mg is close to the minimal effective dose, whereas it is uncertain whether 2 mg would yield a relevant response rate. A dose of 1 mg is likely to be an ineffective dose."

"

Figure 53 *(upper panel) shows the predicted dose-response for percent responders in the case of a high placebo-response (31.3%) with 95%-prediction limits. These limits take into account the uncertainty of all model parameters jointly. They indicate the range of possible Emax dose-response relationships that are consistent with the data. The figure in the lower panel shows the dose-response of the drug-effect, i.e. the additional percent of responders on top of the placebo effect. The horizontal dashed line indicates the target response level for a minimal effective dose (10%)."*

Figure 53 Final Dose Response Model Percent Responders vs. Dose with 95% CI

Figure 7: Percent Responders vs. Dose, as Predicted by the Final Dose-Response Model With 95% Prediction Limits Around it. The Uncertainty in All the Model Parameters Jointly is Taken into Account.



The upper panel shows the predicted percent responders, while the lower panel shows predicted percent responders on top of the placebo response.

"The lowest dose for which the lower bound of the prediction limit exceeds the target response of 10% above the placebo response is 3.2 mg. For the 3 mg-dose itself, the probability that the true drug effect exceeds 10% is 0.96. For a dose of 2 mg, this is 0.80 and for 1 mg it is 0.39. It is therefore very likely that 3 mg reaches the target level of 10% whereas for 2 mg this is less certain. For 1 mg it is unlikely to be the case.

For doses above 6 mg, there is no major increase in response rate, and at 9 mg there is no significant increase in the precision of the prediction.

"A similar model was used to analyze the concentration-response curve. The ED50 parameter is replaced by an EC50, but for the rest, the model is similar to the model developed based on dose." (see Table 65)

"The probability to show response after placebo is estimated to be 32.8% for Studies R076477-SCH-303 and R076477-SCH-304, and 17.9% for Study R076477-SCH-305. The maximum probability of response upon drug treatment is 39.8, while the EC50 is estimated at 1.82 ng/mL. All parameters are estimated with good precision, except for the EC50, where the RSE was 235%."

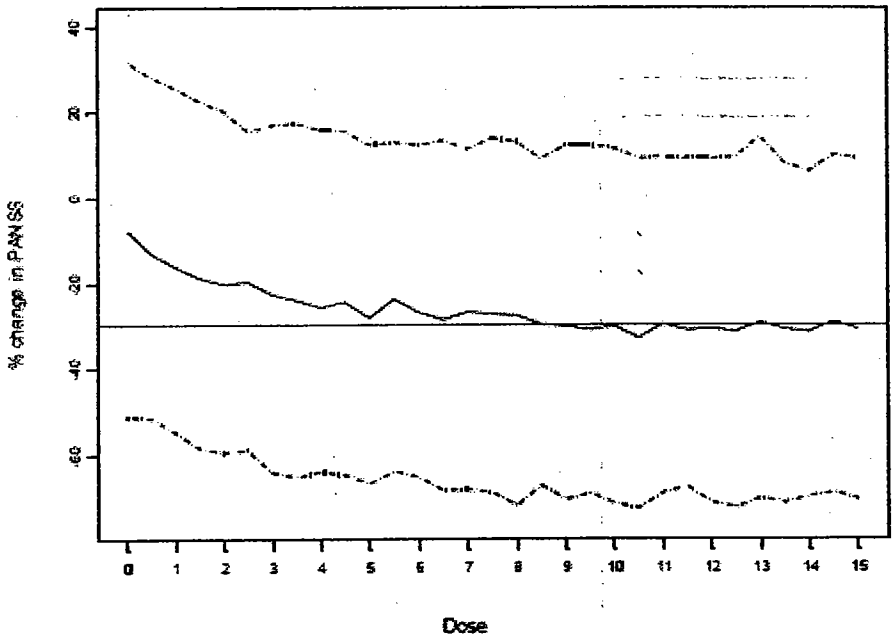
Sponsor's Conclusions

"The focus of the current analysis was on endpoint data, either PANSS or responder status, and as such, has limitations associated with it, one of it being the way drop-outs are handled. As the intent of the current analysis was to be complementary to the standard statistical analysis as defined per the statistical analysis plan, and to provide alternative viewpoints to the MED question, it was decided not to analyze longitudinal PANSS profiles, but rather to use endpoint data only. Nevertheless, baseline PANSS data were also included in the model, so that raw data could be analyzed, rather than changes from baseline. This allowed to test two versions of the model, one where the drug effect was added to the baseline, and another one where the drug effect was proportional to the baseline. The latter model described the PANSS data best, and was retained as the final model.

For PANSS, the drug effect was of the Emax type, and was added to the placebo effect. All parameters were estimated with good precision, except the ED50. This could be expected based upon the shape of the dose-response (Figure 51): all doses equal to or higher than 6 mg either approach or are close to Emax. This implies that there is essentially only one dose that determines the slope of the dose-response curve, i.e. the 3 mg dose. When the current model is used to predict the dose response curve by simulating n=1000 subjects for each dose level, taking into account the interindividual and residual variability, a wide prediction interval can be observed (Figure 54)."

Figure 54 Median Predicted Drop in PANSS vs Dose with 80% CI per Final Dose-Response Model

Figure 8: Median Predicted Drop in PANSS for Each Dose as Predicted by the Final Dose-Response Model, and 80% Prediction Interval Around the Median.



"Similar to what was observed for the dose-response analysis, the uncertainty in the EC50 for the concentration-response analysis was fairly high, precluding firm conclusions to be drawn from that value. All other parameters obtained from both the dose- and concentration-response analysis of the PANSS are in very good agreement.

With respect to the responder analysis, a clear difference in placebo response was observed between the different studies. Studies R076477-SCH-303 and R076477-SCH-304 had essentially a similar placebo response, and Study R076477-SCH-305 had a much lower placebo response. This was implemented in the model and found to be statistically significant. The drug effect, which is added to the placebo effect, was found to be best described by an Emax type model, and was constant over the different studies. Again, the uncertainty in ED50 was high, in line with what was found using the PANSS scores, and which can be explained in a similar way. Note that although the uncertainty in ED50 is very high, the two analyses (PANSS and responder analysis) yield a very consistent ED50

value. Due to the high uncertainty (>200%) in determination of the EC50-value, the concentration-responder analysis is of limited value.

The dose-response model of the responder rate shows that it is highly likely that the 3-mg dose reaches the target of a minimal effective dose, whereas for a 2-mg dose this is less certain. For the 1-mg dose it is unlikely that the response would reach the minimal target.

In conclusion, the dose-response modeling suggests that 3 mg is close to the minimal effective dose, whereas it is uncertain whether 2 mg would yield a relevant response rate. A dose of 1 mg is likely to be an ineffective dose."

3.10.7.2 Extrapyramidal Symptoms (EPS)

3.10.7.2.1 Model Development

A PK/PD model was developed relating the log of the risk of having any type of extrapyramidal symptom at time t after beginning paliperidone.

The data contributing to this model come from 3 placebo-controlled, double-blind Phase 3 clinical studies (R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305) in subjects with schizophrenia who were randomized to either fixed doses of oral ER OROS Paliperidone, placebo or olanzapine for 6 weeks. The first objective was to establish a model-based characterization of the relationship between paliperidone exposure and the risk to develop an EPS-related adverse event. The second objective was to use the PK/PD-model to investigate the impact of the food effect on the dose response of the EPS incidence.

The hazard (λ), the risk of having the event of interest at time *t*, given that it had not occurred before, is modeled as a function of the change in the underlying risk over time, the paliperidone concentration, and the dropout rate.

The time to onset of the first EPS-related adverse event was modeled as the outcome of interest, through hazard modeling, as follows:

$$log\ \lambda(t, c_i) = f(t) + g(c_i)$$

where:

c_i: individual measure of exposure
t: time since trial start
λ: hazard

f(t) describes how the hazard changes over time in a population of patients treated with placebo.

g(ci) quantifies the drug effect and is a function of an individual measure of drug exposure.

It is assumed that the time effect and the drug effect on the log hazard are additive.

The form of *f(t)* was first explored graphically using Kaplan-Meier plots of the time to EPS for the placebo patients only. The derived plots of the cumulative hazard over time give an indication of the appropriate baseline hazard model.

Two common cases, i.e. that log λ decreases linearly with *t* or with log (*t*), were fit to the data and the better model per Akaike's Information Criteria (AIC) was selected, see examples.

EX 1 $f(t) = \beta_0 + \beta_1 t$
EX 2 $f(t) = \beta_0 + \beta_1 \log(t)$

$g(c_i)$ was fit to a Hill equation,

where:

$$g(c_i) = Emax / (1 + (EC_{50}/C_i)^{\wedge}\theta_3)$$

and where c_i is the individual estimated steady state concentration.

A dropout model was also incorporated, otherwise there would be an over-prediction of EPS based on the number of subjects randomized, or an under-prediction of EPS based on the number of subjects still in the study, (see Figure 55 and Figure 56).

Figure 55 Sponsor's Dropout Model

$$\log \lambda = \beta_0 + \beta_1 R + D21.\beta_2 + (\beta_3 + \beta_4 R) \cdot dose$$

λ : hazard

β_0 : intercept for North - America

β_1 : effect of region on intercept

β_2 : effect of Day 21

β_3 : slope for North America

β_4 : effect of region on slope

R = indicator for region (0 = North - America, 1 = Other)

D21 = indicator for Day 21

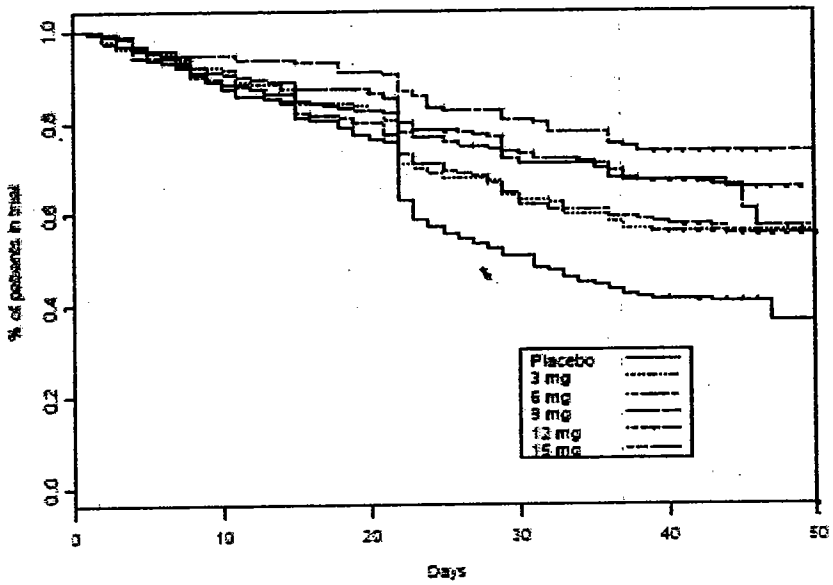
The parameter estimates of this model are given below.

Table 14: Parameters of the Dropout Model

Parameter	Estimate	Stand. Error
β_0	-4.01	0.09
β_1	-0.14	0.12
β_2	2.05	0.10
β_3	-0.026	0.012
β_4	-0.067	0.017

Figure 56 Kaplan-Meier Curves for Dropouts by Dose Group

Figure 13: Kaplan-Meier Curve of the Time to Dropout by Dose Group.



The dropout model assumes there is no difference in dropouts between subjects with EPS and subjects without EPS. Although the sponsor claims this is a reasonable assumption based on data presented in Table 66, this reviewer is not convinced as this is only a breakdown of the reasons given for dropouts, also as there is no correction for dropout rate with dose.

Table 66 Reasons for Discontinuation in Subjects With and Without Treatment Emergent EPS-Like Adverse Events

Reason for Discontinuation	EPS	No EPS
Adverse Event	18%	11%
Lack of efficacy	46%	54%
Subject withdrew consent	22%	26%
Other	1%	4%
Lost to follow-up	8%	5%
Non-compliance	5%	1%
Total Dropout Rate	100%	101%
Potential Difference in Dropouts due to EPS	7%	

Preferred Terms for various are EPS are shown in Table 67.

Table 67 EPS-Related Adverse Events – Preferred Terms

WHO-ART Preferred Term	Corresponding MEDRA 8.1 Dictionary-derived term
Bradykinesia	Bradykinesia
Dyskinesia	Dyskinesia
Dyskinesia tardive	Tardive dyskinesia
Dystonia	Dystonia/hypertonia
Extrapyramidal disorder	Extrapyramidal disorder parkinsonism cogwheel rigidity
Hyperkinesia	Akathisia dyskinesia hyperkinesia restless legs syndrome
Hypertonia	Hypertonia muscle rigidity muscle spams musculoskeletal stiffness
Hypokinesia	Hypokinesia
Muscle contractions involuntary	Extrapyramidal disorder muscle twitching
Oculogyric crisis	Oculogyration
Tetany	Hypertonia
Tongue paralysis	Tongue disorder
Tremor	Tremor

3.10.7.2.2 Concentration Response

The average paliperidone steady-state concentration was estimated at the end of the study by nonlinear mixed effects modeling, however due to a number of factors this is not expected to be a very reliable estimate. When this estimated value is compared to the number and percent of subjects with at least one EPS-related adverse event, there appears to be a rough concentration response relationship, (see Table 68, Figure 57, and Figure 58).

Table 68 Estimated Average Steady-State Concentration Grouping vs. Treatment Emergent EPS Rate (%)

Css (ng/ml)	Median Css (ng/ml)	N	#EPS	EPS-rate (%)
0	0	355	38	10.7
[0-10]	7.3	84	11	13.1
[10-15]	12.5	94	11	11.7
[15-20]	17.7	121	15	12.4
[20-25]	22.1	98	18	18.3
[25-30]	27.3	101	18	17.8
[30-35]	32.0	99	27	27.3
[35-40]	37.5	68	18	26.5
[40-50]	44.3	99	29	29.3
[50-60]	54.5	57	18	31.6
>60	69.4	51	14	27.4

Figure 57 Plot of Treatment Emergent EPS Rate (%) by Estimated Steady-State Concentration Grouping

Figure 3: Observed Incidence of EPS by Exposure Group.

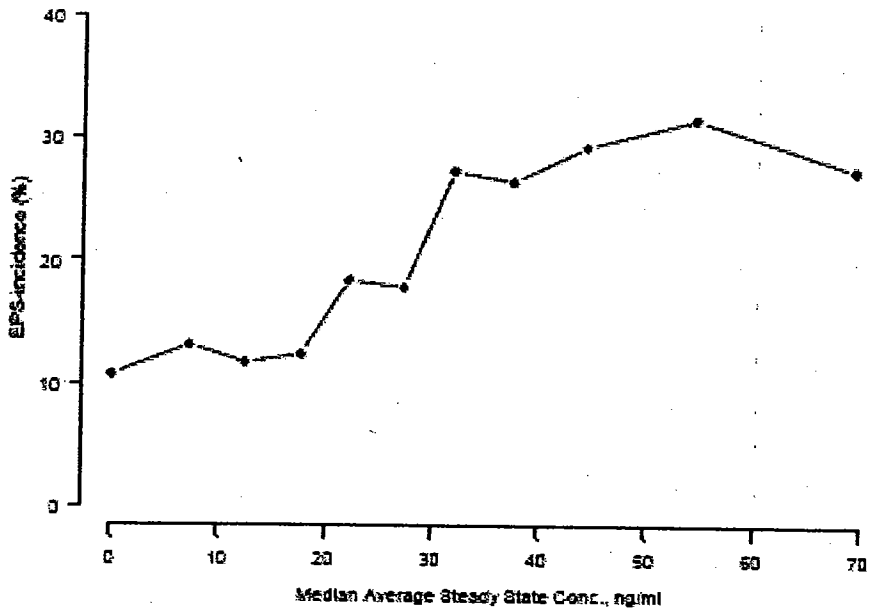


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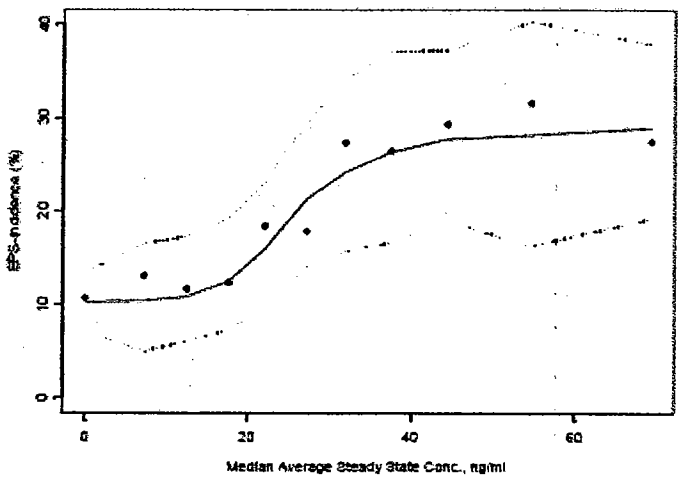
Figure 58 Plot of Treatment Emergent EPS Rate (%) by Estimated Steady-State Concentration Grouping with Mean Model Predicted Concentration Response and 95% Confidence Interval

Figure 6: Predicted EPS Incidence in 1,000 Simulated Replicates of the Phase 3 Studies as a Function of Exposure.

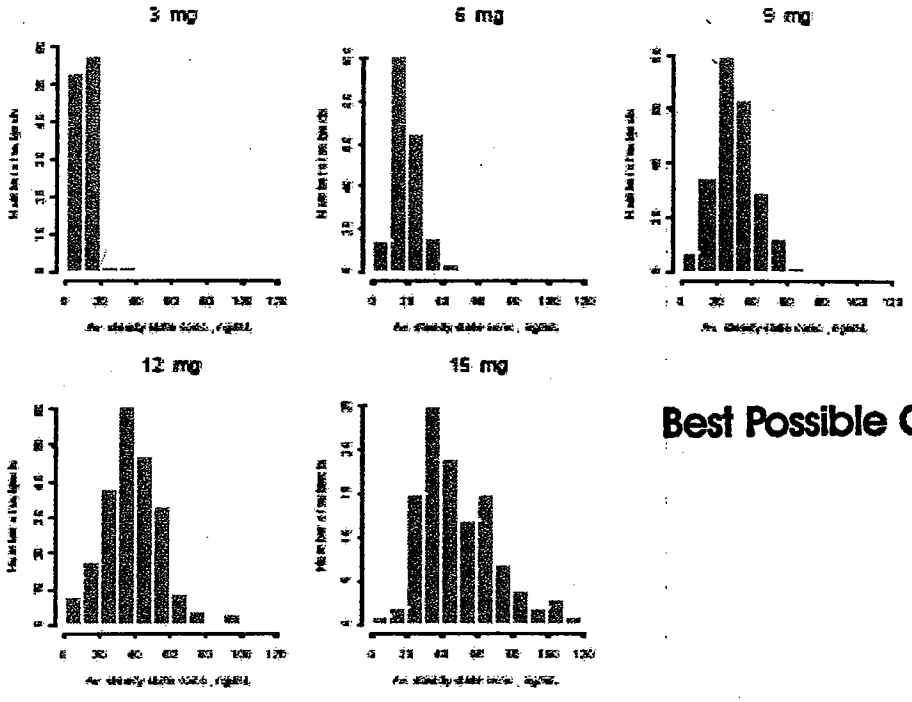


The dotted lines indicate the 95% prediction interval. The dots are the observed values.

However, histograms of estimated average steady-state concentrations suggest that a dose of 6 mg or 9 mg may be a good dividing line in order to avoid EPS, (see Figure 59):

Figure 59 Plot of Treatment Emergent EPS Rate (%) by Estimated Steady-State Concentration Grouping

Figure 2: Distribution of the Average Steady State Concentration per Dose Group.



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3.10.7.2.3 Dose Response

When dose is used as the predictor variable instead of the estimated steady-state concentration the dose response is close to what is expected based on the concentration response based on the estimated steady-state concentrations, however it does provide additional informative and clinically significant information.

Table 69 shows the total incidence of EPS by dose in all 3 phase III studies and for the pooled data, and Table 70 shows the incidence of each sub-type of EPS by dose for the pooled data.

What's noteworthy is that the incidence of EPS in both tables is no different placebo at doses up to 6 mg and increases significantly at doses of 9 mg and above. This is shown graphically in Figure 60 - Figure 62.

Table 69 Incidence of EPS by Dose in the Paliperidone ER OROS Phase 3 Studies

Study	Dose (mg)	N[a]	N-EPS[b]	%[c]
SCH-303	0	126	8	6.3
	6	123	13	10.6
	9	122	24	19.7
	12	130	36	27.7
SCH-304	0	106	16	15.0
	6	112	10	8.9
	12	112	28	25.0
SCH-305	0	123	14	11.4
	3	127	16	12.6
	9	124	39	31.5
	15	113	26	23.0
Pooled	0	355	38	10.7
	3	127	16	12.6
	6	235	23	9.8
	9	246	63	25.6
	12	242	64	26.5
	15	113	26	23.0

a N: number of patients randomized;
b N-EPS: number of patients with at least 1 treatment-emergent EPS-related adverse event.
c Number of subjects with treatment-emergent EPS-related AEs / number of subjects randomized

Table 70 Pooled EPS Incidence by Subtype vs Dose from the Paliperidone ER OROS Phase 3 Studies

EPS Group	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg
Dyskinesia[a]	3 (0.85%)	0	0	2 (0.81%)	4 (1.65%)	1 (0.88%)
Dystonia[b]	11 (3.1%)	4 (3.1%)	5 (2.1%)	27 (11.0%)	22 (9.0%)	5 (4.4%)
Hyperkinesia[c]	14 (3.9%)	5 (3.9%)	8 (3.4%)	20 (8.1%)	24 (9.9%)	11 (9.7%)
Parkinsonism[d]	8 (2.3%)	6 (4.7%)	6 (2.6%)	23 (9.4%)	21 (8.8%)	11 (9.7%)
Tremor[e]	12 (3.4%)	4 (3.1%)	6 (2.6%)	11 (4.5%)	8 (3.3%)	3 (2.6%)

a Includes: dyskinesia, dyskinesia tardive
b Includes: dystonia, hypertonia, oculogyric crisis, involuntary muscle contractions, tetany, tongue paralysis
c Includes: akathisia, hyperkinesia
d Includes: parkinsonism, parkinsonism aggravated, bradykinesia, hypokinesia, extrapyramidal disorder
e Includes: tremor

Figure 60 Rate of EPS by Dose in the Paliperidone ER OROS Phase 3 Studies

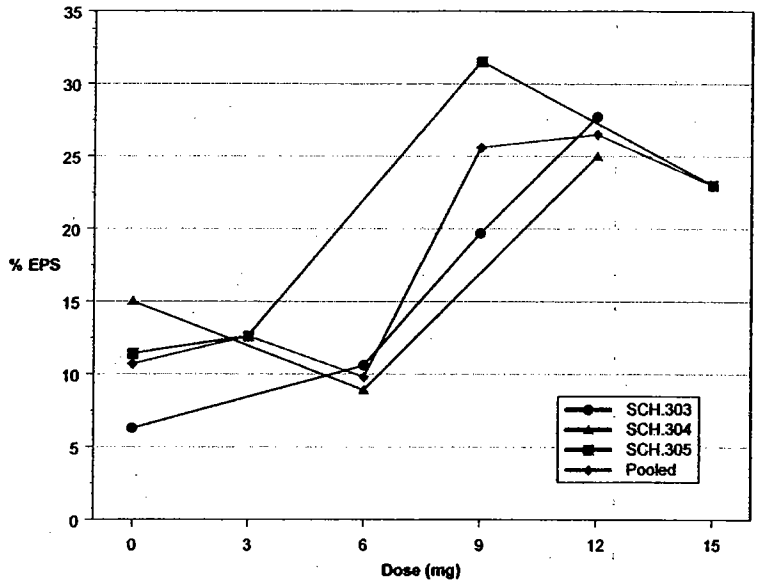


Figure 61 Rate of EPS in the Paliperidone ER OROS Phase 3 Studies vs Dose by Type of EPS

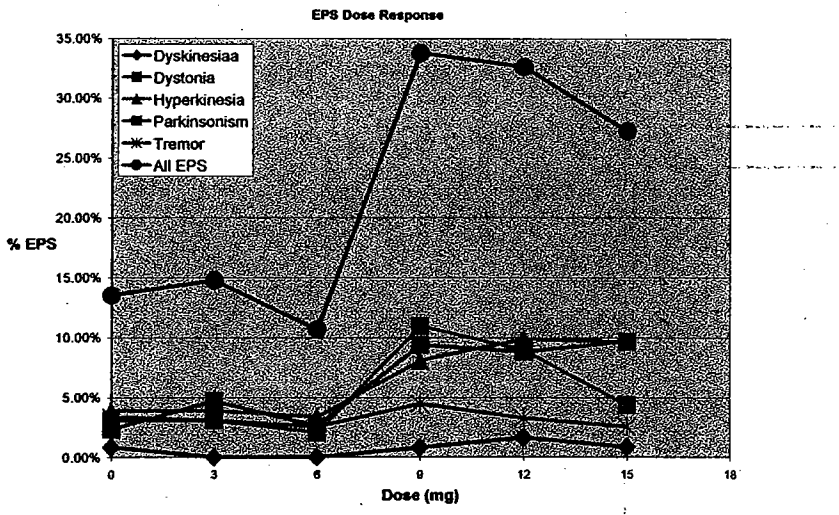
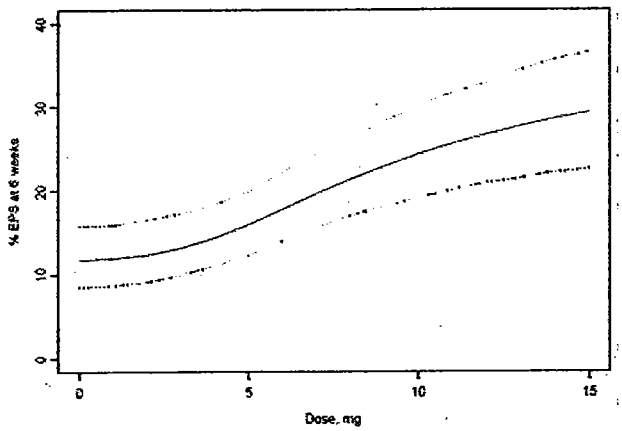


Figure 62 Predicted Population Average Rate of EPS (with 95% CI) vs. Paliperidone OROS Dose after 6 weeks of Treatment

Figure 6: Predicted Population Averaged Dose-Response Relationship of EPS Incidence in a 6-Week Clinical Study With Baseline Incidence and Dropout Patterns Representative for North America.



The dotted lines indicate the 95% confidence interval due to uncertainty of the model parameter estimates.

3.10.7.2.4 Effect of Food on EPS

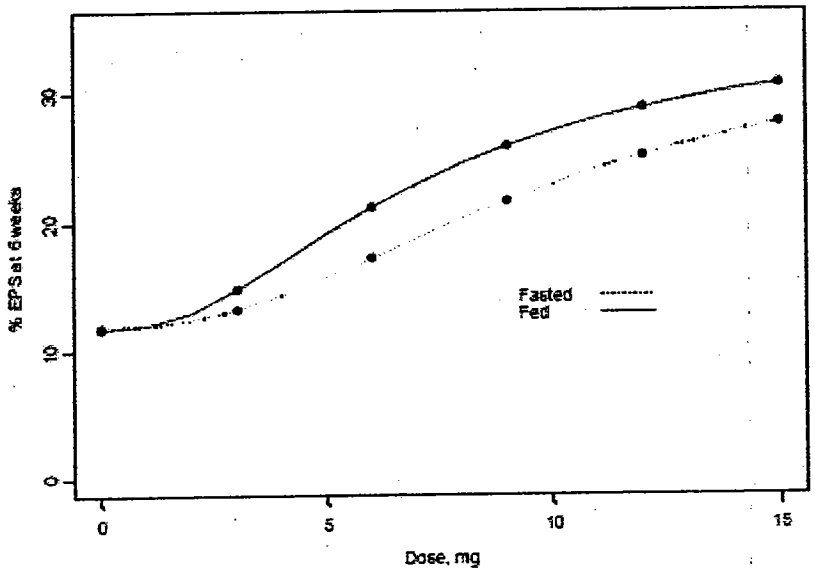
Table 71, Table 72, and Figure 63 show the sponsor's predicted change in the incidence of EPS due to a 50% increase in exposure when paliperidone OROS is taken with a high fat meal. Although the absolute difference is small, at 6 mg there is a 74% increase in the incidence of EPS due to the steepness of the dose response curve around this dose, Since, the efficacy response curve is not as steep around 6 mg the risk to benefit ratio likely decreases when paliperidone OROS is taken with food. In addition, even though the absolute rate of EPS is relatively low, i.e. an additional 4% of patients at 6 weeks, we don't know about the long term effects and a 4% greater incidence of tardive dyskinesia in a large population taking paliperidone would result in a significant increase in the total number of cases of a major debilitating side effect.

Table 71 Comparison of the Predicted Incidence of EPS (%) in a 6-Week Clinical Study in Between Fasted and Fed Conditions

Dose	% of Subjects with EPS			% of Subjects with EPS in Excess of Placebo Rate		
	Fasted	Fed	Difference	Fasted	Fed	Odds Ratio
0 mg	11.8	11.7	—	—	—	—
3 mg	13.2	14.8	1.6	1.4	3.1	2.21
6 mg	17.2	21.1	3.9	5.4	9.4	1.74
9 mg	21.6	25.8	4.3	9.8	14.1	1.44
12 mg	25.0	28.8	3.8	13.2	17.1	1.30
15 mg	27.6	30.7	3.0	15.8	19	1.20

Figure 63 Predicted Effect of Food on Phase III Study EPS Rate

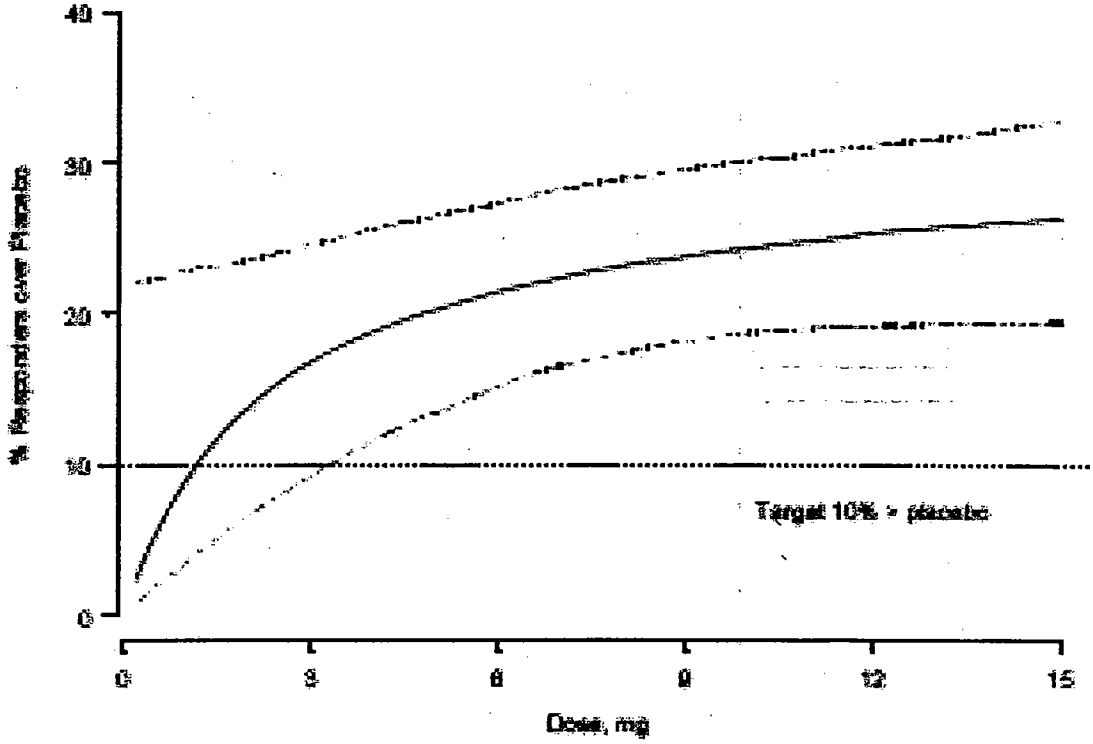
Figure 10: Predicted Dose-Response of the Incidence of EPS in a 6-Week Clinical Study Under Fed and Fasted Conditions.



3.10.7.2.5 Therapeutic Index

Comparing the sponsor's plots of overall response rate over placebo vs. dose and EPS rate vs. dose and side by side seems to indicate that a dose of 6 mg provides the best ratio of efficacy to risk of EPS with little additional benefit to higher doses, (see Figure 64). However, when this reviewer attempted to use the parameter estimate values provided by the sponsor to replicate the response and EPS rates, this reviewer was unable to do so.

Figure 64 Comparison of Sponsor's Plots of Overall Response Rate over Placebo vs. Dose and EPS Rate vs. Dose



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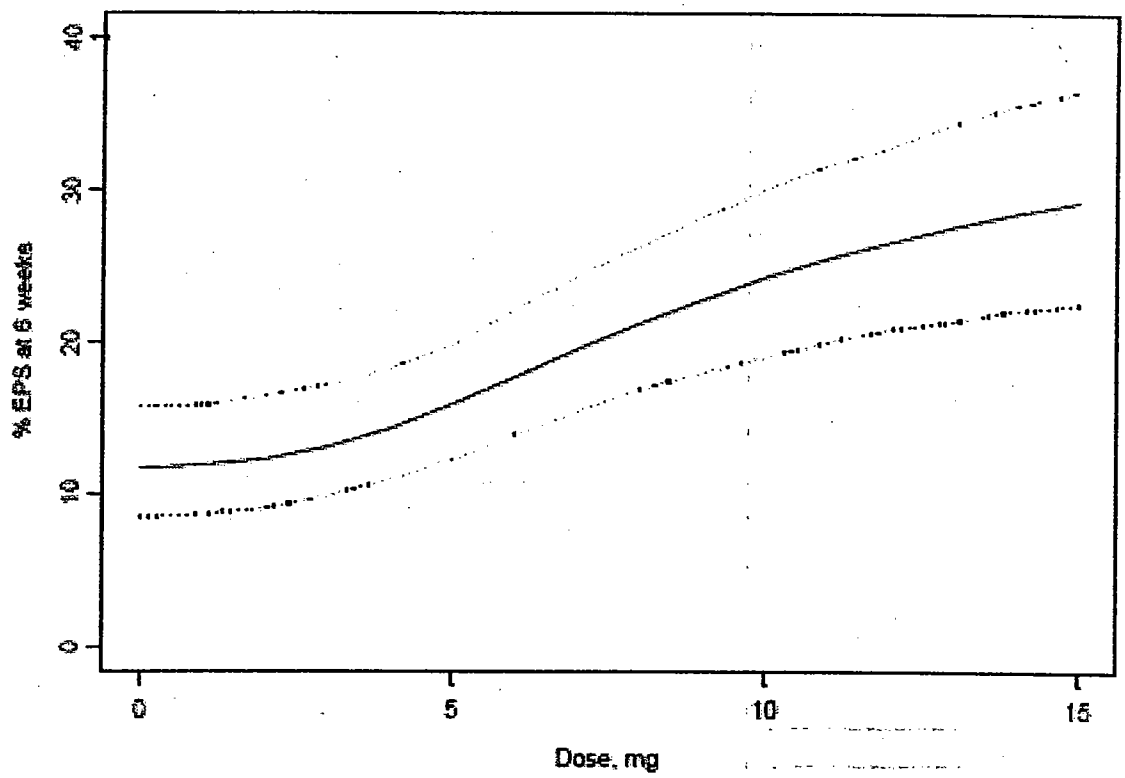

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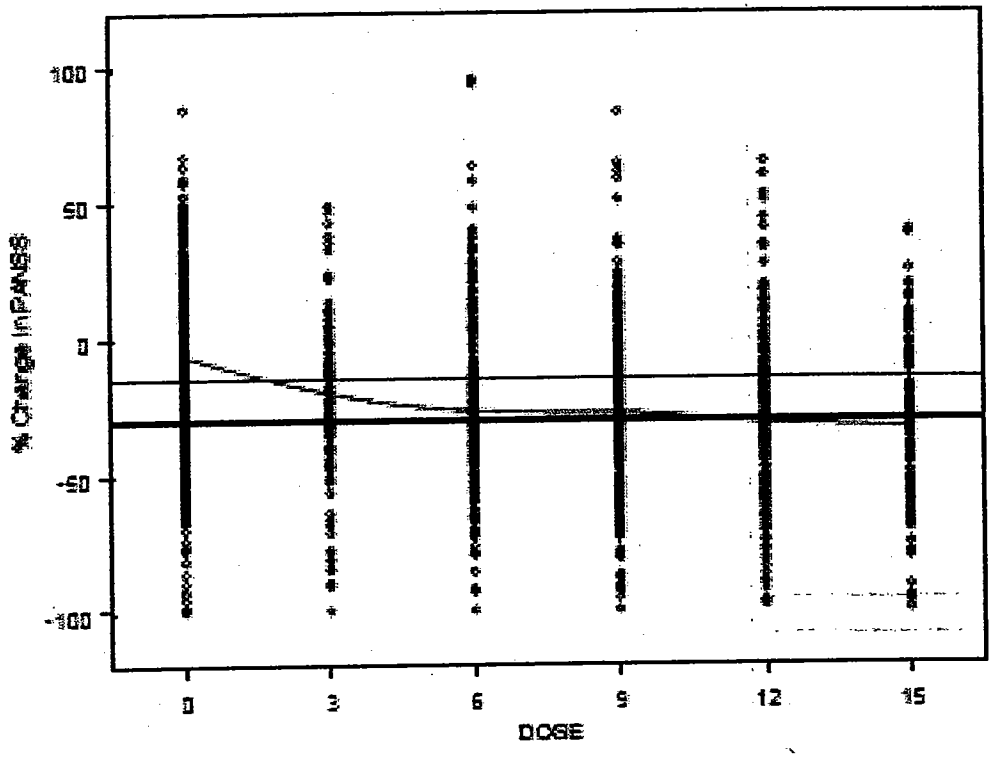
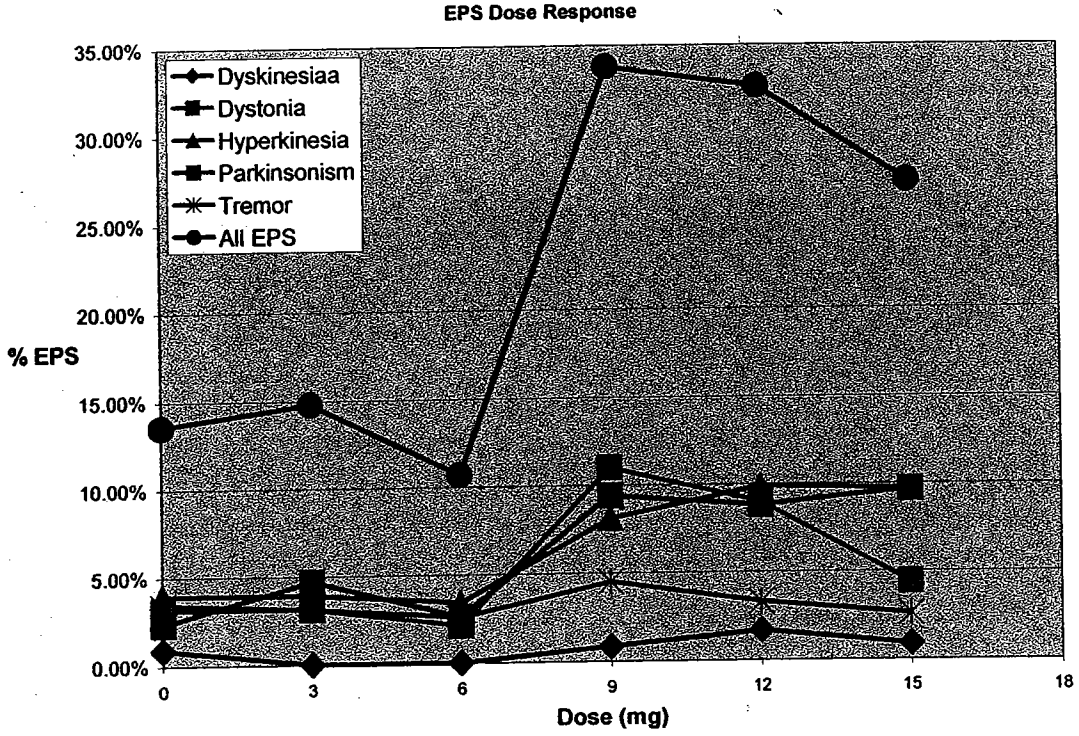
Although when plots of the actual data are compared it's clear that a dose of 6 mg does provide the best ratio of efficacy to risk of EPS with little additional benefit to higher doses, (see Figure 65).

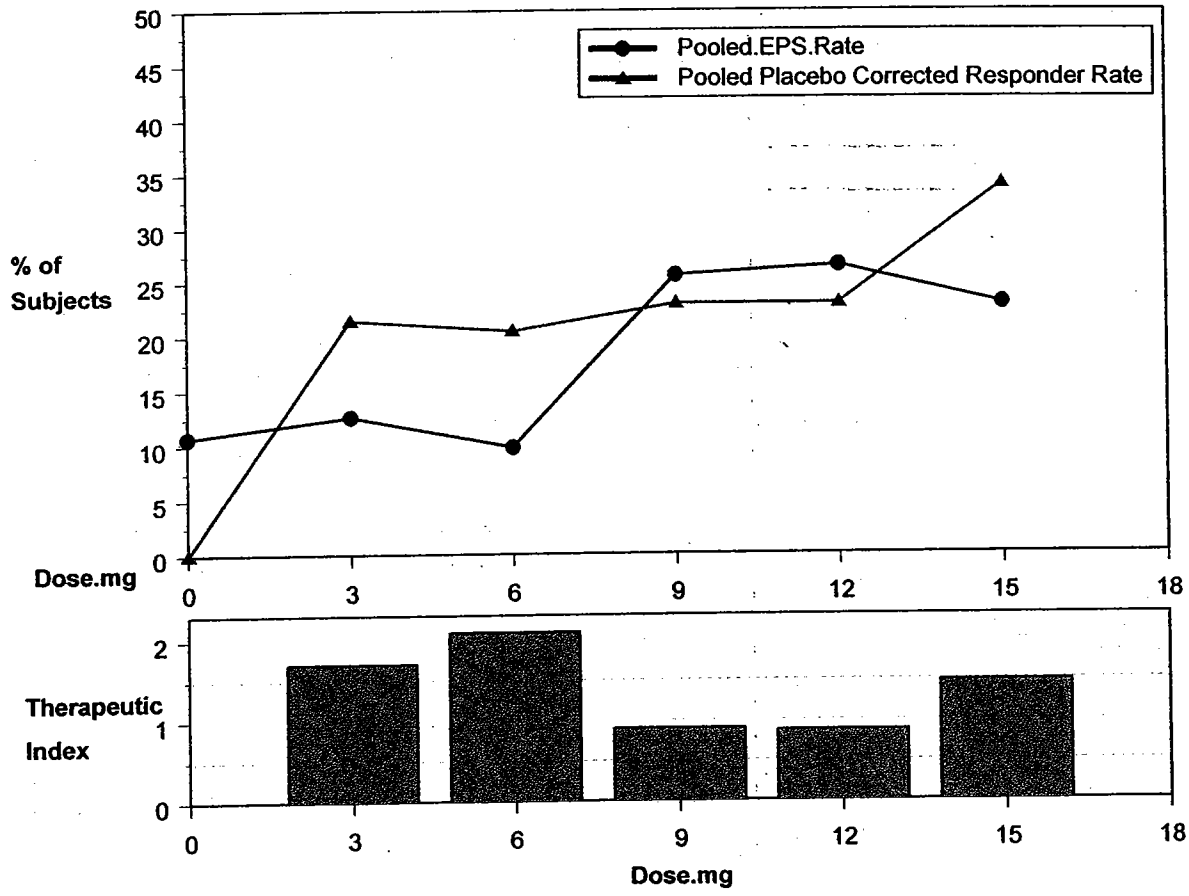
Figure 65 Comparison of % Change in PANSS and EPS Rate vs Dose in Phase 3 Studies





The therapeutic index is shown more clearly in Figure 66. It's clearly apparent that the therapeutic index of the pooled average responder rate over the pooled EPS rate drops from approximately 2 to 1 when going from a dose of 6 mg to 9 mg. Although this superficially suggests a maximum dose of 6 mg, when we consider the risk benefit ratio most of the EPS rate is due to EPS other than dyskinesia's which may be manageable or where if intolerable back titration would be a reasonable option. The higher EPS rate is more worrisome for what it may portend in terms of the risk for tardive dyskinesia with long term treatment. In addition, comparison of AUCs in subjects with varying degrees of normal renal function and other variables suggest that estimated creatinine clearance along with other variables such as drug metabolizing genotype may allow prediction of who is not likely to respond due to high clearances and thus more likely to respond with higher doses without an increased risk of side effects. In addition, these therapeutic indexes are naïve pooled values and additional evaluation of individuals and whether they have a response and or EPS and the severity of each needs to be done. Finally clinicians need to make assessment of the risk benefit in each individual patient. Consequently, additional analysis needed to be performed before we can make appropriate recommendations as to the maximum recommended dose. However, based on the side effect profile it seems that there is not an undue risk of a maximum dose of 12 mg at present when compared to currently marketed products.

Figure 66 Comparison of Pooled Placebo Corrected PANSS Responsder Rate and Pooled EPS Rates by Dose from Phase III Studies and Naïve Pooled Unweighted Therapeutic Indices



3.10.7.3 Sleep Architecture

Study SCH-1010 was a randomized, double-blind, placebo-controlled parallel group study in pharmacodynamic study that examined the effect of paliperidone OROS 9 mg on sleep after 2 weeks in schizophrenic subjects as measured by polysomnogaphy.

Table 72 shows a comparison of the duration and proportion of sleep stages as measured by polysomnography. The time to onset of sleep is decreased by 10 minutes and stage 2 sleep is increased by 30 minutes, however the sponsor indicates that these differences are not clinically relevant as the differences could be due to differences between the two groups at baseline with random changes after 2 weeks.

Table 73 shows a comparison of measure of sleep continuity. Sleep continuity relates to the duration of uninterrupted sleep and evaluations in this study included sleep duration, latency to sleep onset or persistent sleep, sleep efficiency index, awakenings, and microarousals, as well as time awake. There were no clinically significant differences between groups.

Table 74 shows a comparison of sleep onset and arousal between groups. There were no clinically significant differences between groups.

Figure 67 shows the lack of any association between paliperidone exposure as measured by AUCt and various sleep measurements and Figure 68 shows individual paliperidone concentration vs. time plots on day 10.

Table 72 Comparison of Duration and Proportion of Sleep Stages by Polysomnography in Patients Receiving Paliperidone OROS 9 mg and Placebo – Study SCH-1010

Sleep Stage	Description	N	Rx	Minutes				Proportion of Sleep %				Reviewers Description of Results	Sponsor's Assessment
				Baseline	Endpoint	Change from Baseline	Difference in LS Means ± SE (90% CI)	Baseline	Endpoint	Change from Baseline	Difference in LS Means ± SE (90% CI)		
Stage 1	Transition between wakefulness and sleep	19	Placebo	22.6 ± 12.64 [20.5] (4 - 55)	24.0 ± 12.02 [22.0] (6 – 57)	1.4 ± 9.44 [-1.0] (-20 - 15)	-	5.2 ± 2.75 [4.7] (1 - 12)	5.8 ± 2.90 [5.0] (2 - 12)	0.6 ± 2.09 [0.9] (-4 – 4)		Decrease by 10 minutes or approximately 1/3.	Sponsor claims not clinically relevant
		17	PAL OROS 9 mg	29.3 ± 27.76 [16.0] (6 - 119)	18.8 ± 17.13 [13.5] (6 – 72)	-10.5 ± 16.59 [-4.5] (-48 - 12)	11.9 ± 4.44 (-19.37 - -4.37)	7.1 ± 6.46 [3.8] (2 – 28)	4.4 ± 4.28 [3.0] (1 - 19	-2.7 ± 3.65 [-1.3] (-10 - 2)	-3.3 ± 0.98 (-4.99 - -1.69)		
Stage 2	Light Sleep.	19	Placebo	228.4 ± 42.12 [237.3] (156 - 330)	213.1 ± 58.24 [222.3] (38 - 289)	-15.3 ± 48.26 [-1.0] (-139 - 54)		53.2 ± 10.35 [51.9] (34 - 79)	51.2 ± 12.58 [50.5] (17 - 76	-2.1 ± 9.69 [-0.1] (-31 - 9)		Increased by 30 minutes or approximately 1/6	Sponsor claims not clinically relevant
		17	PAL OROS 9 mg	183.9 ± 60.17 [203.3] (56 - 248	219.3 ± 52.52 [219.5] (130 - 308	35.4 ± 57.73 [28.3] (-68 - 155	50.7 ± 17.67 (20.86 – 80.62)	45.8 ± 14.14 [45.5] (19 - 70)	50.7 ± 9.89 [50.0] (30 - 67)	4.9 ± 11.54 [3.8] (-10 - 30)	7.0 ± 3.54 (0.98 - 12.95)		
Stage 3	Part of Delta (short wave sleep)	19	Placebo	10.9 ± 7.19 [11.5] (0 – 27)	9.0 ± 7.20 [8.3] (0 - 27)	-1.9 ± 10.04 [-2.8] (-27 - 16)		2.6 ± 1.73 [2.8] (0 – 7)	2.2 ± 1.56 [2.2] (0 – 6)	-0.4 ± 2.37 [-0.1] (-7 – 3)		–	No Statistically significant Change.
		17	PAL OROS 9 mg	10.8 ± 7.52 [10.3] (0 – 34)	13.1 ± 11.17 [13.0] (0 – 50)	2.4 ± 11.75 [-1.5] (-13 - 38)	4.2 ± 3.63 (-1.91 - 10.38)	2.7 ± 1.74 [2.3] (0 – 7)	3.0 ± 2.49 [3.1] (0 - 11)	0.3 ± 2.56 [-0.2] (-3 – 8)	0.7 ± 0.82 (-0.71 - 2.07)		
Stage 4	Deep Non-Rem Sleept	19	Placebo	31.9 ± 22.84 [31.0] (0 – 73)	34.3 ± 31.62 [27.5] (0 – 94)	2.4 ± 21.82 [0.0] (-44 - 49		7.4 ± 5.19 [7.3] (0 - 16)	8.0 ± 7.13 [8.1] (0 - 20)	0.7 ± 4.84 [0.0] (-10 - 11)		–	No statistically significant differences at endpoint.
		17	PAL OROS 9 mg	45.3 ± 37.57 [45.0] (0 - 115)	39.0 ± 28.24 [43.3] (0 - 103)	-6.2 ± 27.02 [0.5] (-63 - 34)	-8.6 ± 8.15 (-22.39 - 5.16)	11.7 ± 11.24 [10.7] (0 – 40)	9.2 ± 6.68 [9.3] (0 - 24)	-2.6 ± 9.57 [0.1] (-28 - 9)	-3.2 ± 2.49 (-7.45 - 0.96)		
Total Non-REM Sleep	Stages 1 – 4 combined.	19	Placebo	293.9 ± 37.01 [304.5] (225 - 352	280.4 ± 63.06 [295.3] (78 - 354)	-13.5 ± 58.31 [-8.0] (-147 - 85)		68.4 ± 8.19 [68.0] (54 - 81)	67.2 ± 10.89 [68.9] (30 - 78)	-1.2 ± 10.02 [-1.4] (-30 - 15)		Total NonRem sleep similar at endpoint. NonRem sleep increased. due to increase in stage 2 sleep, but proportion unchanged.	Difference not clinically significant.
		17	PAL OROS 9 mg	269.2 ± 59.93 [292.0] (104 - 342)	290.2 ± 60.30 [306.0] (137 - 365)	21.0 ± 55.54 [15.0] (-85 - 115)	34.5 ± 19.04 (2.30 - 66.68	67.4 ± 12.98 [68.8] (35 - 90)	67.2 ± 11.60 [69.9] (32 - 82)	-0.1 ± 11.17 [-0.6] (-32 - 22)	1.1 ± 3.53 (-4.91 - 7.03)		
REM Sleep	Rapid eye movements and intense dreaming.	19	Placebo	87.0 ± 24.64 [81.5] (52 - 135)	76.1 ± 31.52 [78.0] (15 - 128)	-10.9 ± 27.92 [-7.5] (-67 - 36)		20.1 ± 4.87 [20.2] (12 - 30)	17.8 ± 6.02 [18.2] (7 – 28)	-2.3 ± 5.99 [-2.1] (-15 - 8)		Increased in Treatment group.	Difference at endpoint not clinically significant.
		17	PAL OROS 9 mg	72.7 ± 31.09 [74.8] (7 - 127)	80.1 ± 24.63 [84.8] (20 - 130)	7.4 ± 27.84 [10.0] (-40 - 58)	18.3 ± 9.31 (2.58 - 34.06)	17.6 ± 6.83 [18.9] (2 – 27)	18.6 ± 5.68 [18.7] (5 – 31)	1.0 ± 6.55 [-0.2] (-9 - 14)	3.3 ± 2.09 (-0.19 - 6.88)		
Slow Wave Sleep	Stages 3 and 4 combined. Deepest and most restorative sleep.	19	Placebo	42.8 ± 24.95 [47.3] (0 – 87)	43.3 ± 36.77 [38.3] (0 - 116)	0.5 ± 26.20 [-3.8] (-42 - 65)		10.0 ± 5.71 [10.7] (0 – 19)	10.2 ± 8.14 [10.9] (0 – 25)	0.3 ± 5.78 [-0.1] (-10 - 14)		–	No statistically or clinically significant changes.
		17	PAL OROS 9 mg	56.0 ± 41.69 [55.5] (0 - 128)	52.2 ± 29.54 [50.5] (0 - 123)	-3.9 ± 30.78 [0.0] (-65 - 40)	-4.4 ± 9.50 (-20.44 - 11.68)	14.5 ± 12.06 [13.4] (0 – 42)	12.1 ± 6.97 [11.3] (0 – 28)	-2.3 ± 10.29 [0.0] (-26 - 11)	-2.6 ± 2.74 (-7.21 - 2.07)		

Table 73 Comparison of Sleep Continuity Measures in Patients Receiving Paliperidone OROS 9 mg and Placebo – Study SCH-1010

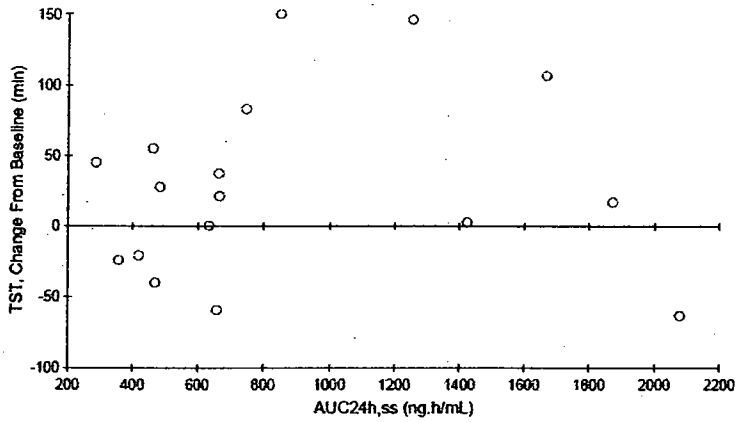
Sleep Parameter	N	Rx	Baseline	Endpoint	Change from Baseline	Difference in LS Means ± SE (90% CI)	Reviewer's Assessment
Latency to REM Sleep (Minutes)	19	Placebo	74.0 ± 29.06 [67.8] (7 - 121)	104.1 ± 48.58 [80.8] (31 - 190)	30.1 ± 46.87 [15.0] (-32 - 116)		Not statistically different.
	17	PAL OROS 9 mg	88.2 ± 53.01 [81.5] (14 - 246)	101.8 ± 70.15 [73.5] (30 – 322)	13.6 ± 61.16 [6.3] (-120 - 181)	-16.5 ± 18.05 (-47.07 - 13.98)	
REM Activity (number)	19	Placebo	369.0 ± 455.77 [261.0] (7 – 1856	230.0 ± 185.74 [192.0] (5 - 531)	-139.0 ± 358.02 [-1.5] (-1325 – 60)		Statistically different but not clinically different.
	17	PAL OROS 9 mg	181.2 ± 131.77 [168.5] (6 - 461)	211.9 ± 167.33 [155.0] (45 - 617)	30.8 ± 127.38 [14.0] (-145 - 312)	169.7 ± 91.73 (14.63;324.85)	
REM Density (# of REM /hr)	19	Placebo	239.2 ± 232.05 [210.6] (5 - 824)	177.2 ± 125.85 [183.1] (10 - 414)	-62.0 ± 157.94 [-29.3] (-580 – 119)		No statistical or clinical differences.
	17	PAL OROS 9 mg	144.0 ± 102.36 [154.2] (13 - 334)	148.1 ± 99.71 [118.6] (35 - 356)	4.1 ± 81.86 [21.8] (-187 – 110)	66.1 ± 42.70 (-6.12 - 138.29	
Total Sleep Time (Minutes)	19	Placebo	380.9 ± 45.30 [390.3] (288 - 449)	356.6 ± 87.70 [393.8] (93 – 452)	-24.4 ± 77.97 [-6.8] (-196 – 105)		Increased in Paliperidone Group.
	17	PAL OROS 9 mg	341.9 ± 77.50 [355.0] (136 – 424	370.4 ± 74.30 [400.0] (157 – 460)	28.5 ± 64.41 [21.3] (-63 - 150)	52.8 ± 24.01 (12.22 - 93.40)	
Sleep Period Time (Minutes) (Stage 2 to last sleep epoch prior to final awakening)	19	Placebo	431.9 ± 37.15 [437.3] (317 - 473)	414.8 ± 53.66 [436.3] (274 - 476)	-17.0 ± 48.77 [-5.8] (-115 - 63)		Increased in Paliperidone Group.
	17	PAL OROS 9 mg	404.0 ± 58.52 [417.5] (282 - 464)	428.8 ± 30.77 [437.3] (358 - 469)	24.7 ± 63.48 [10.3] (-59 - 142)	41.7 ± 18.75 (10.03 -73.46)	
Latency to Sleep Onset (Minutes) (lights out until sleep onset)	19	Placebo	42.3 ± 33.64 [40.0] (5 - 147)	55.1 ± 45.39 [41.3] (3 - 152)	12.8 ± 37.20 [10.8] (-57 - 95)		Shorter in Paliperidone group.
	17	PAL OROS 9 mg	58.3 ± 47.83 [46.3] (17 - 194)	35.9 ± 20.61 [34.3] (3 - 69)	-22.5 ± 52.22 [-8.3] (-149 - 47)	-35.2 ± 14.99 (-60.58 - -9.89)	
Latency to Persistent Sleep (Minutes) (10 consecutive minutes in stage 2-4 or REM without microarousals).	19	Placebo	50.3 ± 34.04 [48.5] (11 - 155)	65.2 ± 55.23 [46.0] (3 - 194)	14.9 ± 47.27 [5.0] (-58 - 116)		Shorter in Paliperidone group.
	17	PAL OROS 9 mg	68.0 ± 55.82 [49.0] (17 - 223)	41.9 ± 23.74 [43.0] (6 - 102)	-26.1 ± 64.43 [-10.5] (-178 - 79)	-41.0 ± 18.70 (-72.62 - -9.40)	
Efficiency Index (%) (Fraction of time in bed asleep)	19	Placebo	79.3 ± 9.37 [81.3] (61 - 94)	74.3 ± 18.13 [81.9] (20 - 94)	-5.0 ± 16.18 [-0.4] (-41 - 21)		Increased in Paliperidone group.
	17	PAL OROS 9 mg	71.5 ± 16.18 [73.9] (28 - 88)	77.5 ± 15.55 [83.4] (33 - 96)	6.0 ± 13.51 [4.4] (-13 - 31)	11.0 ± 5.00 (2.57 - 19.48)	
Number of Awakenings After Sleep Onset	19	Placebo	24.2 ± 16.75 [20.0] (5 - 83)	24.5 ± 11.17 [27.5] (8 – 48)	0.3 ± 11.60 [2.5] (-35 - 18)		Decreased in paliperidone group.
	17	PAL OROS 9 mg	24.9 ± 14.85 [20.0] (8 - 54)	18.1 ± 9.37 [14.5] (7 – 41)	-6.7 ± 11.66 [-7.5]] (-27 - 21)	-7.0 ± 3.88 (-13.59 - -0.46)	

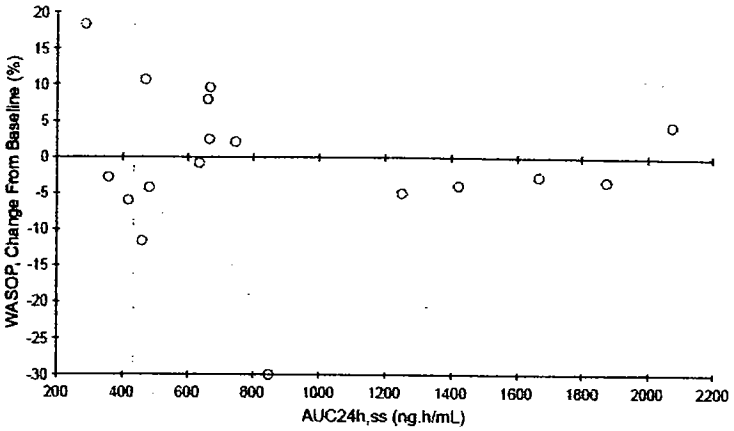
Table 74 Comparison Sleep Onset and Arousal in Patients Receiving Paliperidone OROS 9 mg and Placebo – Study SCH-1010[a]

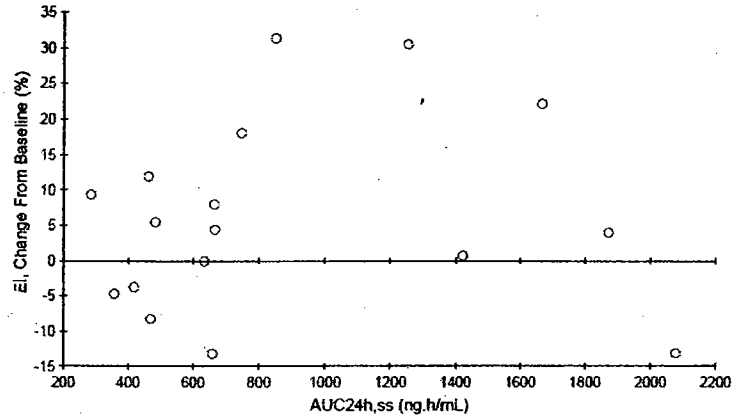
Sleep Parameter	Rx	N	Duration (minutes)				PROPORTION OF TIME				Reviewer's Assessment
			Baseline	Endpoint	Change from Baseline	Difference in LS Means ± SE (90% CI)	Baseline	Endpoint	Change from Baseline	Difference in LS Means ± SE (90% CI)	
TIME AWAKE AFTER SLEEP ONSET	PBO	19	50.93 ± 37.4 [38.25] (4.5 - 140.0)	58.25 ± 3.3 [38.75] (20.8 - 181.3)	7.32 ± 43.9 [1.00] (104.3 to 87.0)		11.49 ± 8.1 [8.35] (1.2 - 30.3)	15.02 ± 14.2 [9.41] (4.4 - 62.9)	3.5 ± 13.4 [0.20] (-22.5 to 40.3)		No statistical or clinical differences.
	Pal	17	62.13 ± 57.2 [42.25] (14.0 - 211.3)	58.38 ± 60.2 [39.50] (9.0 - 260.3)	-3.75 ± 45.5 [-4.50] (-120.3 to 84.3)	-11.1 ± 14.92 (-36.29 to 14.16)	15.05 ± 13.9 [11.33] (3.3 - 53.5)	14.18 ± 14.8 [10.01] (1.9 - 63.2)	-0.87 ± 10.6 [-2.73] (-30.0 to 18.4)	-4.4 ± 4.05 (-11.26 to 2.44)	
TIME AWAKE DURING TIME IN BED	PBO	19	96.93 ± 44.7 [84.75] (29.8 - 185.5)	119.93 ± 85.0 [84.50] (28.0 - 371.3)	23.00 ± 76.0 [0.25] (-97.5 to 185.8)		131.88 ± 78.2 [118.00] (41.5 - 339.3)	105.12 ± 74.8 [78.50] (16.3 - 321.3)	-26.8 ± 64.0 [-19.75] (-147.8 to 65.5)		**Not clinically significant.**
	Pal	17	23.41 ± 13.4 [19.86] (6.3 - 61.4)	35.74 ± 41.5 [19.50] (5.9 -188.3)	12.33 ± 37.2 [0.21] (-25.7 to 140.4)	-49.8 ± 23.58 (-89.64 to -9.89)	36.48 ± 26.7 [25.79] (9.2 - 93.9)	26.0 ± 19.8 [19.12] (3.5 - 77.9)	-10.5 ± 23.6 [-6.54] (-60.9 to26.0)	-22.8 ± 10.53 (-40.62 to-5.0)	
NUMBER OF MICROAROUSALS DURING TOTAL SLEEP TIME	PBO	19	79.71 ± 31.6 [75.00] (30.5 - 142.5)	82.11 ± 48.5 [74.50] (9.5 - 180.0)	2.39 ± 35.5 [8.50] (-63.5 to 77.0)						No statistical or clinical differences.
	Pal	17	51.29 ± 26.0 [41.50] (19.0 - 115.5)	49.68 ± 14.8 [48.50] (28.0 - 91.0)	-1.62 ± 33.0 [-0.50] (-78.5 to 72.0)	-4.0 ± 11.46 (-23.38 to 15.36)					
MICROAROUSAL INDEX DURING TOTAL SLEEP TIME (number/hour)	PBO	19	12.82 ± 5.6 [11.66] (4.2 - 23.9)	13.53 ± 7.8 [11.86] (5.6 - 35.8)	0.71 ± 7.0 [1.81] (-12.6 to 17.1)						No statistical or clinical differences.
	Pal	17	9.7 ± 5.1 [8.77] (3.4 - 21.8)	8.18 ± 3.1 [7.67] (4.2 - 17.5)	-1.48 ± 5.3 [-0.37] (-14.0 to 5.8)	-2.2 ± 2.10 -5.74 to 1.36					
NUMBER OF MICROAROUSAL DURING SLEEP PERIOD TIME	PBO	19	80.4 ± 32.7 [75.00] 30.5 – 143.0	82.11 ± 48.5 [74.50] 9.5 - 180.0	1.68 ± 36.4 [8.50] (-63.5 to 77.0)						No statistical or clinical differences.
	Pal	17	51.6 ± 26.0 [43.00] 19.5 - 116.0	49.79 ± 14.7 [48.50] 28.0 - 91.0	-1.82 ± 32.9 [-0.50] (-78.0 to 71.5)	-3.5 ± 11.60 (-23.12 to 16.11)					

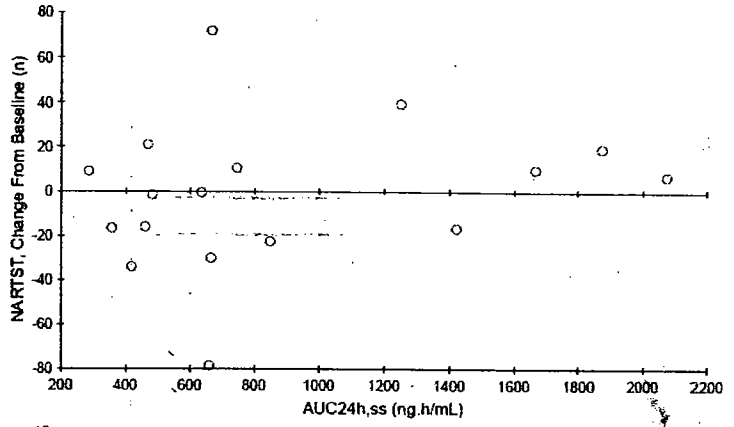
a Not shown microarousals during SWS and REM sleep.

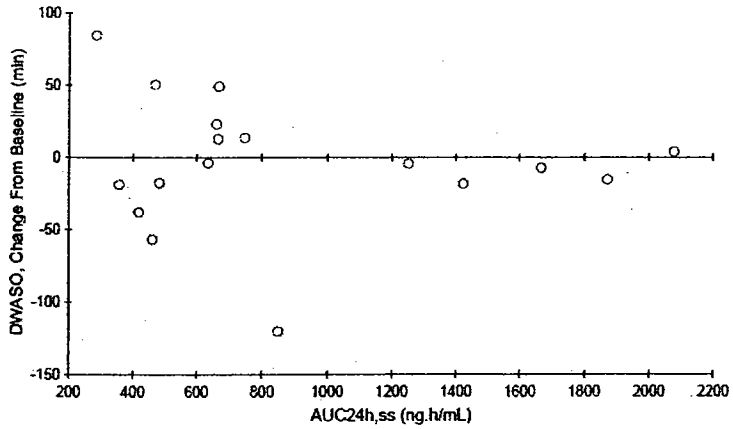
ure 67 Distribution of Sleep Measurements vs. Exposure to Paliperidone (AUCtau) – Study SCH-1010

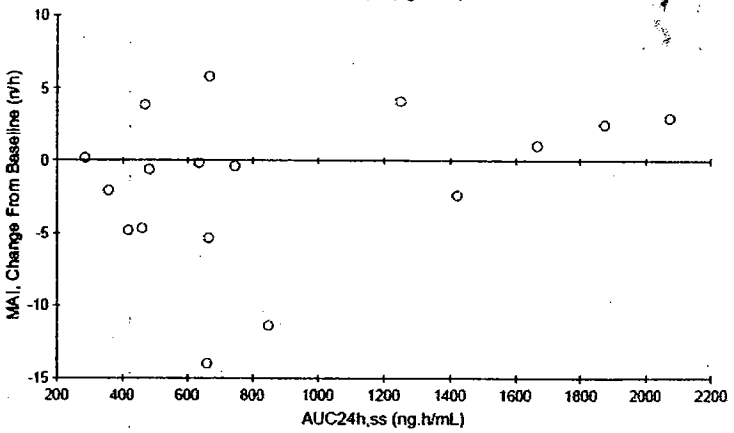


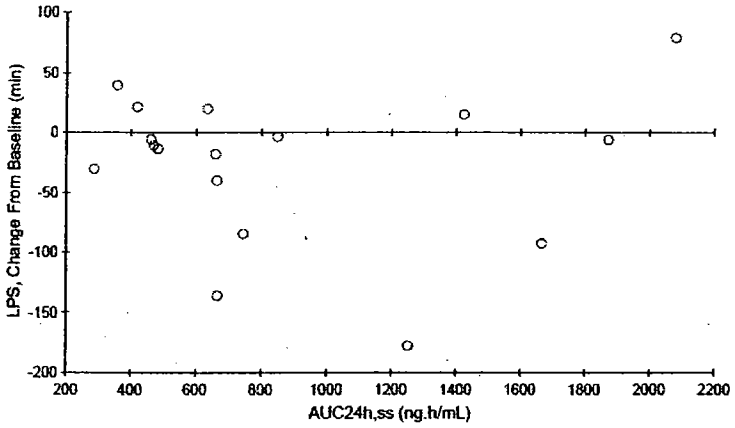


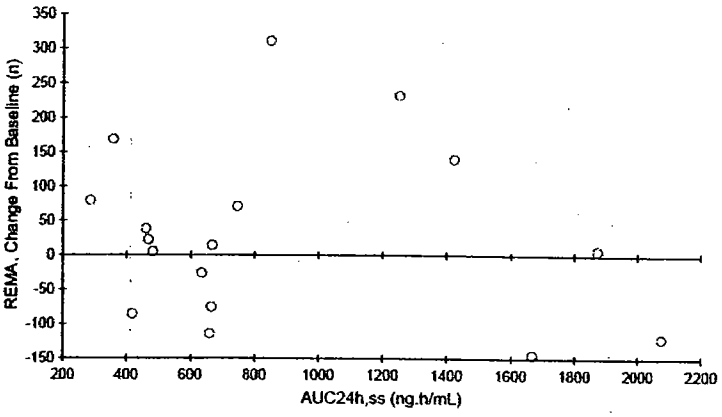


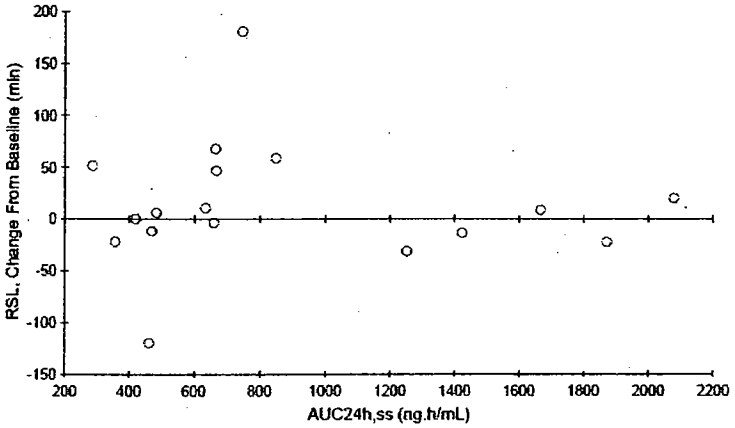


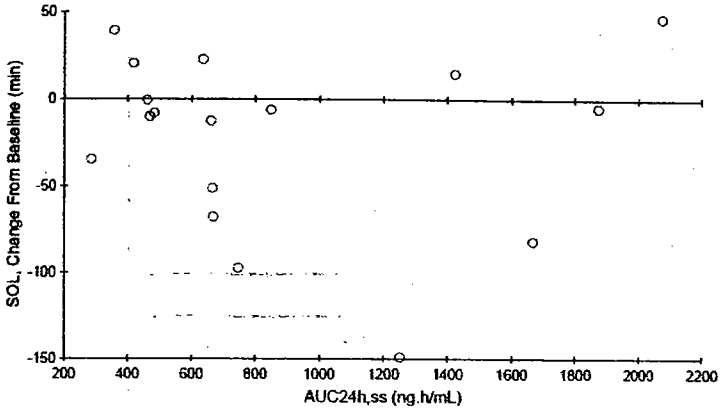


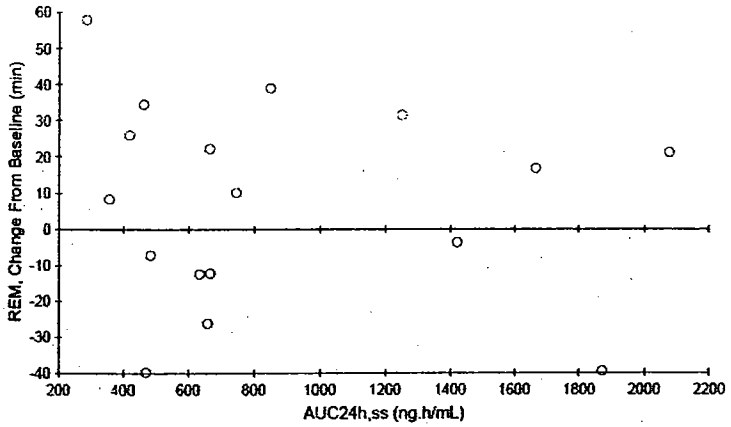



LPS, Change From Baseline (min)
AUC24h,ss (ng.h/mL)


REMA, Change From Baseline (n)
AUC24h,ss (ng.h/mL)


RSL, Change From Baseline (min)
AUC24h,ss (ng.h/mL)


SOL, Change From Baseline (min)
AUC24h,ss (ng.h/mL)


REM, Change From Baseline (min)
AUC24h,ss (ng.h/mL)

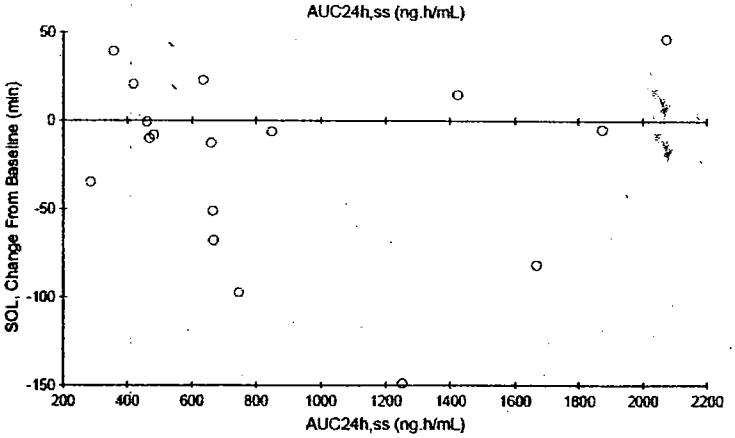
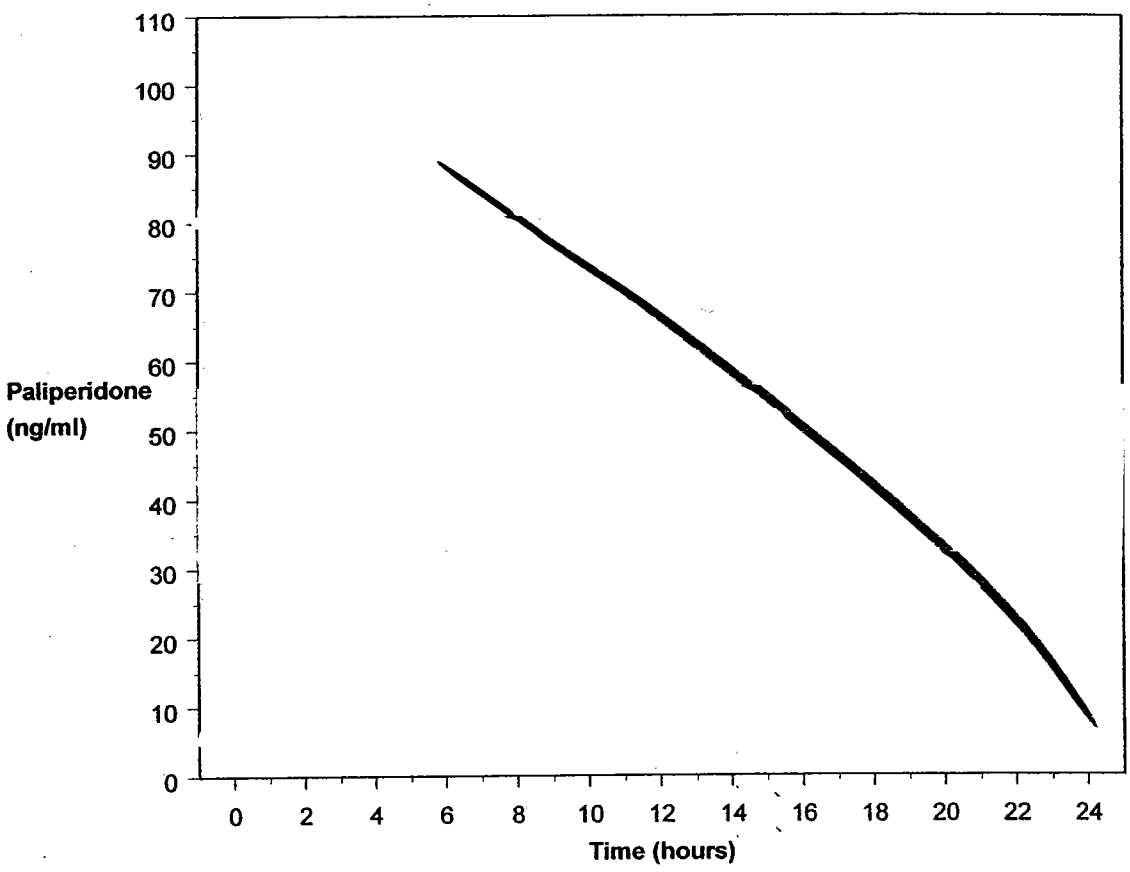

SOL, Change From Baseline (min)
AUC24h,ss (ng.h/mL)

Figure 68 Individual Subject Day 10 Paliperidone Concentration vs. Time Profile Following Paliperidone OROS 9 mg QD - Study SCH-1010



3.10.7.4 Prolactin

The effect of paliperidone on prolactin levels was examined in 5 studies, Alza-039, Alza-019,INT-1, SCH-101, and SCH-1008.

Studies Alzo-039 and Alza-019 were exploratory studies comparing the adverse event profile with several administration regimens of paliperidone to various administration regiments of risperidone.

Prolactin in both studies prolactin exposures after both risperidone and paliperidone were greater than with placebo, but were not significantly different between treatments, i.e. by drug or dosage regimen, suggesting that Emax may be close to being achieved, although this would mean Emax occurs at around the 15 mg OROS dose or less. In addition, although the plasma drug concentrations for active moiety peaked at 22 to 23 h on Day 1 following the Ascend treatments, the prolactin peak occurred much earlier (from 2.5 to 5.5 h), (see Table 75 and Table 76).

Also of note, is that in study Alza-039 the two subjects (126 and 127) reporting early menses had the highest peak prolactin levels.

Table 75 Serum Prolactin Metrics by Treatment - Study Alza-039 (n = 24)

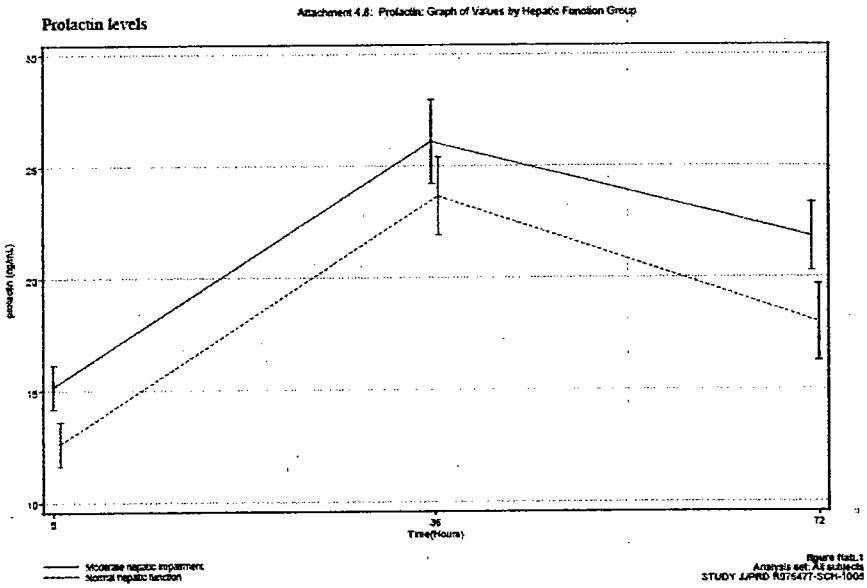
Parameters	Ascend	Flat	IR	Placebo
	Pal 5.5 mg	Pal 4.5 mg	Pal 4 mg	—
	Day 1: 3.5 mg solution in divided doses over 20.25 hrs Day 2: Pal 2 mg Soln	Day 1: 2.5 mg solution in divided doses over 20.25 hrs Day 2: Pal 2 mg Soln	Day 1: Ris 2 mg Soln Day 2: Ris 2 mg Soln	—
Cmax Day 1 (mIU/L)	1594 (1194)	2614 (2525)	2956 (2857)	449 (195)
Cmax Day 2 (mIU/L)	877 (443)	982 (632)	1059 (867)	332 (117)
Tmax Day 1 (h)	3.6 (1.7)	1.2 (0.4)	1.0 (0.2)	16.7 (5.2)
Tmax Day 2 (h)	15.6 (8.4)	9.7 (9.0)	8.3 (9.5)	10.9 (5.5)
AUC0-48 (mIU.h/L)	41,012 (22,998)	46,077 (33,105)	45,370 (33,083)	12,258 (4,379)

Table 76 Serum Prolactin Metrics by Treatment - Study Alza-019

Treatment	Ris Ascend-4	Ris IR-2	Pal Ascend-4	Pal Ascend-2	Placebo
Total Dose	Ris 6 mg	Ris 4 mg	Pal 6 mg	Pal 4 mg	—
Regiment	Day 1: Ris 4 mg solution in divided doses over 21 hrs Day 2: Ris 2 mg Soln	Day 1: Ris 2 mg Soln Day 2: Ris 2 mg Soln	Day 1: Pal 4 mg solution in divided doses over 21 hrs Day 2: Pal 2 mg Soln	Day 1: Pal 2 mg solution in divided doses over 21 hrs Day 2: Pal 2 mg Soln	—
N	N = 19	N = 20	N = 20	N = 23	N = 25
Cmax Day 1 (mIU/L)	1543 (765)	2848 (1710)	1271 (422)	1203 (513)	455 (167)
Cmax Day 2 (mIU/L)	850 (538)	1208 (864)	780 (250)	873 (506)	348 (185)
Tmax Day 1 (h)	2.5 (3.6)	1.0 (0.2)	2.5 (1.7)	5.5 (6.8)	16.3 (3.5)
Tmax Day 2 (h)	10.6 (6.3)	2.5 (3.3)	12.3 (6.2)	6.9 (8.0)	7.4 (5.4)
AUC0-48 (mIU.h/L)	39,520 (25,778)	47,965 (30,007)	35,637 (11,538)	37,685 (19,448)	12,488 (5,190)

Although the effect on prolactin concentration is not likely to be maximal at the 3 mg paliperidone OROS dose as subjects with hepatic impairment have higher prolactin exposures with 1 mg oral soln indicating that prolactin production is increased with increasing concentrations at the lower end of the dose range, (see Figure 69).

Figure 69 Mean Prolactin Concentrations after Paliperidone 1 mg Oral Solution in Normals and Subjects with Hepatic Impairment - Study SCH-1008



Prolactin exposures after multiple dosing with paliperidone IR 1 mg qd for 14 days, 4 mg for 10 days, and 8 mg for 7 days in study INT-1, and with paliperidone OROS 12 mg qd on Days 2 – 6, paliperidone OROS 12 mg qd on Days 1 – 6, and risperidone 2 mg on day 1 and 4 mg qd on days 2-6 in study SCH-101, indicate that the effect on prolactin is likely maximal with paliperidone OROS 12 mg and steady-state is reached in approximately 7 – 10 days, (see Table 77 and Figure 70).

Table 77 Prolactin Concentrations and AUCs after Single and Multiple Dosing of Paliperidone IR - Study INT-1

Table 4-5: Prolactin Levels (ng/mL) – Summary Table for Mean Raw Data and Changes From Baseline (Day 1 Predose)

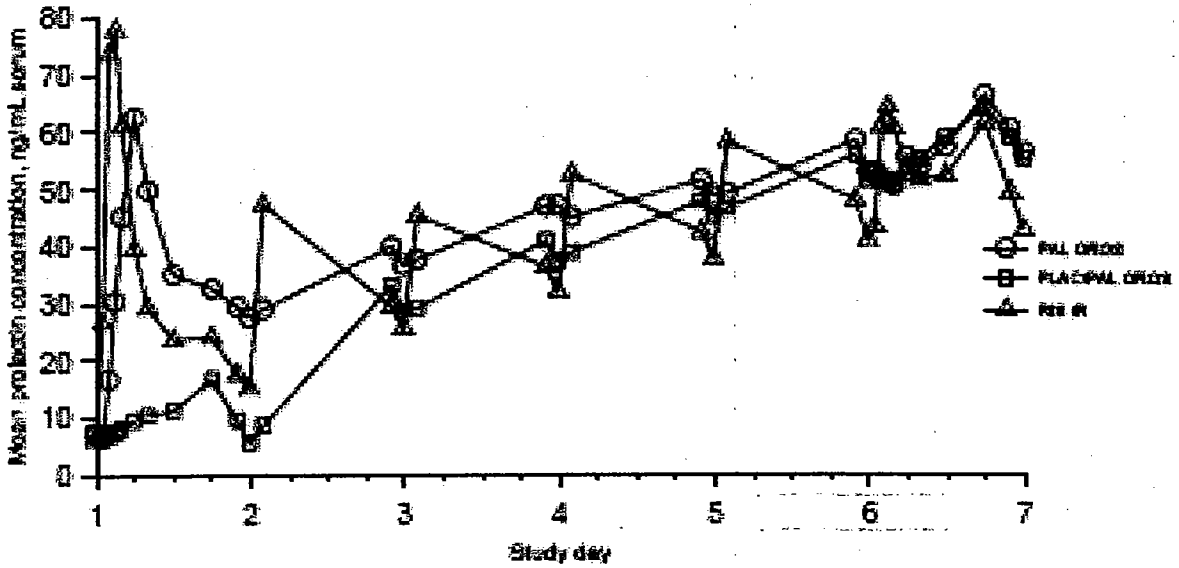
		R076477					
		1 mg (N=11)		4 mg (N=11)		8 mg (N=12)[a]	
Timepoint		mean	change	mean	change	mean	change
Day 1	0h	27.7		20.0		24.4	
	1h	52.1	24.3*	60.7	40.7*	71.9	47.6*
	2h	49.6	21.9*	64.5	44.4*	67.9	43.5*
	4h	45.3	17.5*	48.5	28.4*	55.7	31.3*
	8h	32.8	5.1*	34.9	14.9*	36.4	12.0*
	12h	33.8	6.1*	28.4	8.3*	33.7	9.3*
AUC_{0-24h}		854.1		835.2		941.2	
Day 14	0h	31.6	3.9	35.6	15.5*	61.8	37.0*
	1h	42.5	14.7*	47.9	27.9*	81.9	57.1*
	2h	42.6	14.9*	52.0	32.0*	81.8	57.0*
	4h	42.1	14.3*	48.0	27.9*	71.7	46.3*
	8h	32.4	4.6	39.2	19.1*	56.7	31.9*
	12h	38.1	10.3*	39.0	18.9*	60.4	35.6*
AUC_{0-24h}		866.9		970.6		1517.0	
Day 15	0h	30.7	3.0	35.7	15.7*	59.7	34.9*

[a] N=10 on Day 14.

* denote that the 95% confidence interval for the mean change from baseline does not contain zero.

Figure 70 Mean Prolactin vs. Time Profiles after Multiple Dosing of Risperidone and Paliperidone OROS – Study SCH-101

Figure 7: Mean Serum Concentration-Time Profiles of Prolactin
(Study PAL-SCH-101: Pharmacokinetic Analysis Set)



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3.10.7.5 Cardiovascular Effects

3.10.7.5.1 QT Effect

Overall it appears that there is an effect on QTc but it may not be large enough to be of concern in the vast majority of patients. This is supported by the limited number reports of Torsades with risperidone, which produces even higher concentrations of paliperidone, in patients with other risk factors.

3.10.7.5.1.1 Thorough QT Study

The sponsor conducted a multiple dose QT study using immediate release paliperidone and moxifloxacin as the active control. Dosing, PK, and ECG sampling are shown in Table 78 below.

Table 78 Dosing, PK, and ECG Sampling in Thorough QT Study – SCH-1009

Day	Paliperidone Treatment Group	Control Group	PK & ECG Samples[a,b] (Hours post-dose)
1	PBO	PBO	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12
2	Pal 4 mg IR	PBO	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12
3	Pal 6 mg IR	PBO	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12
4	Pal 8 mg IR	PBO	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12
5	Pal 8 mg IR	PBO	Predose
6	Pal 8 mg IR	PBO	Predose
7	Pal 8 mg IR	PBO	Predose
8	Pal 8 mg IR	Moxifloxacin 400 mg	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12
9	–	–	24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 30, 36
10	–	–	48, 48.5, 49, 49.5, 50, 50.5, 51, 51.5, 52, 54, 60

a ECGs obtained in triplicate in 10 second recordings collected at 60 second intervals
b PK samples obtained within 5 minutes after ECG are shown in red

3.10.7.5.1.2 QT Correction Methods

Several QT correction methods were used and are indicated in Table 79. However a linearly corrected QT based on QT vs. RR for the study populations examined was the primary comparison. The linearly corrected QTc is indicated by QTcLC where $QT = \alpha + \beta * RR$ for the study population.

Table 79 QT Correction Methods Employed by Sponsor in Thorough QT Study – SCH-1009

QT Correction Method	Abbreviation	Correction	References
Linearly Corrected	QTcLC	QT + b[1 - RR]	Hodges M, Salerno D, Erlien D. Bazett's QT correction reviewed: evidence that a linear QT correction for heart rate is better. J Am Coll Cardiol 1983;1:694. 34. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation. Drug Safety 2001;24(5):323-351. 35.
Bazett	QTcB	$QT/RR^{0.5}$	Bazett HC. An analysis of the time-relationship of electrocardiograms. Heart 1920;7:353-370. 36.
Fridericia	QTcF	$QT/RR^{1/3}$	Fridericia LS. Die Systolendauer im Electrokardiogramm bei normalen Menchen und bei Herzkranken. Acta Med Scand 1920;53:469-486.
QTlc	Sagie		

To detect effects on QT by paliperidone the sponsor constructed 2-sided 90% confidence intervals around the mean difference in day-averaged QTcLD on day 8 of paliperidone treatment (8 mg IR at steady-state) compared with day-averaged QTcLD during placebo treatment (Day 1). The confidence interval itself was constructed using the estimated least-squares means and variances from the models of QT vs. RR determined from the day 1 placebo treatment. Thus there is some question if this is the most appropriate way to construct the confidence interval during the drug treatment phase. Insufficient data was provided to determine if this would produce an over- or under-estimate.

The measure used the mean change in QTcLC when receiving of 8 mg IR paliperidone at steady-state (Day 8) compared to baseline.

The sponsor's assessment criteria for a 'negative' effect on QTc were if the upper limit of the 2-sided 90% confidence interval excluded 10 milliseconds. However, the criteria used for the positive control, (moxifloxacin 400 mg), were if the lower limit of the 2-sided 90% confidence interval was greater than 0 milliseconds. Thus the assessment criteria for determining if there were QT effects were inconsistent between the test and control groups.

Table 80 shows the results of the sponsor's primary QTc analysis with the QTcLD values for paliperidone in red and for the control in blue, along with the relevant pharmacokinetic metrics including Cmax in orange. What's most interesting is that although the upper limit of the 90% CI for QTcLD at steady-state dosing of the paliperdone 8 mg IR is less than 10 mSec, the change in QTcLD is still greater for paliperidone than for the active control moxifloxacin.

Other factors that should be kept in mind are that these are averaged values across the entire dosage interval, thus these QTcLD values are lower than the actual changes in QTcLD observed around the concentration peak, and that QTc by other methods may be larger.

When change from baseline in QTcLD is examined by time post dose it clearly occurs around the peak concentration, there appears to be a dose response with a prolongation in QTcLD even with the lowest dose of 4 mg IR, and that even with the lowest dose studied the effect on QTcLD is greater than for the active control, (see Table 81). However, it appears that the changes in the moxifloxacin group is driven by QTc effects in fewer individuals and that the relative degree of effect varies by the correction method used.

Hysteresis plots of mean QTcLD Versus mean paliperidone plasma concentrations also show a clear concentration response relationship without any appreciable hysteresis. This is what is expected for a direct effect of paliperidone on cardiac tissue, (see Figure 71).

Figure 72 shows the dose, concentration, and time course of effect much more clearly. Plus the effect is seen not only with the QTcLD correction, but also with Fridericia's and Bazett's method.

According to the sponsor none of the subjects in either the IR paliperidone or moxifloxacin treatment group had a QTcLD increase >60 mSec. Nineteen (26%) of 72 subjects in the IR paliperidone group and 12 (17%) of 69 subjects in the moxifloxacin group had a 30-60 ms increase in QTcLD. No subject in either treatment group had a QTcLD, QTcF, or QTlc interval ≥450 ms at any time during the study. This information was not verified nor was any independent PK/PD performed by the reviewer as the raw data was provided as 945 pages in pdf format without any associated electronic data files, although electronic data files were provided for most other studies.

The greatest mean change in QTcLD occurred on Day 8 at 1.5 hours after an 8 mg IR dose when paliperidone plasma concentrations at that time averaged 98 ng/ml. In addition significant QTcLD changes were also seen with IR doses of 4 mg and 6 mg which are associated with mean peak concentrations around 35 – 60 ng/ml respectively, (see Table 80 and Table 82).

The present study was conducted with an IR formulation however the proposed ER OROS formulation has lower bioavailability and a lower Cmax. In spite of this, there does to be overlap of the concentrations

associated with a QT effect in the controlled QT study and the peak concentrations likely to be seen with clinical dosing of the Paliperidone OROS formulation, even without accounting for the elderly who have slightly higher peak concentrations and patients with organ dysfunction that might result in higher exposures than is typical.
In normal adults when we examine the highest observed exposures (i.e. 166 ng/ml) and the other available data we can be comfortable that this concentration would also be near maximal in cases of increased bioavailability due to food at a dose of 12 mg. Extrapolating along the hysteresis curve, (see Figure 71), we can predict an average maximal QTc of around 425 mSec at this concentration, although QTc in individual subjects will be higher.

In addition, other risk factors such as the added effect on QT due to quinidine which is also expected to increase paliperidone bioavailability also need to be taken into account.

The sponsor claims that the increase in QTcLD interval exceeds the 5 mSec threshold for regulatory concern but is considerably less than the >20 mSec increase associated with a substantially increased risk for arrhythmia. There is no support for this statement. There were also a number of changes in ECG morphology that are not addressed in this review. It's recommended that the cardio-renal division be consulted to aid in assessing the clinical implications of the QTc and other changes.

Table 80 Least Square Mean Differences and 90% Confidence Intervals from Day 1 for Day-Averaged QTcLD by Treatment with Associated Pharmacokinetic Metrics – Study SCH-1009

Day	Rx	Metrics	Cpre (ng/ml)	Cmax (ng/ml)	Tmax (hr)	C 1.5 hr (ng/ml)	Cmin (ng/ml)	AUCT (ng/ml x hr^{-1})	Cavg,ss (ng/ml)	FI	t½ (hrs)	Day Averaged QTcLD				
												Paliperidone		Control		
												LSMean (SE)	LSMeanDiff (SE) 90% CI	Rx	LSMean (SE)	LSMeanDiff (SE) 90% CI
1	Placebo	n										44				
			–	–	–		–	–	–	–	–	387.6 (2.22)	–	PBO	391.8 (1.87)	–
2	4 mg IR q.d.	n	63	63	63			58								
		mean ± SD (CV%) Range [median]	BQL (?) BQL - 26.2 [BQL]	35.2 ± 14.9 (42.3) 16.0 - 89.3 [32.7]	2.07 ± 0.90 (43.4) 0.65 - 4.08 [2.05]			437 ± 198 (45.4) 109 - 1398 [420]				390.6 (2.23)	3.0 (1.10) (1.18; 4.79)	PBO	391.8 (1.87)	-0.0 (0.84) (- 1.40; 1.36)
3	6 mg IR q.d.	n	58	59	59		59	58								
		mean ± SD (CV%) Range [median]	10.4 ± 4.77 (45.9) BQL - 26.9 [9.86]	60.7 ± 24.3 (40.1) 29.4 - 147.0 [56.5]	2.25 ± 1.11 49.2 1 - 4 [2]		11.1 ± 5.7 (51.1) 0 – 26.9 [10.1]	535.5 ± 218.2 (40.7) 248.9 - 1396.5 [508.8]				388.1 (2.22)	0.6 (1.09) (-1.23; 2.36)	PBO	390.6 (1.87)	-1.2 (0.84) (- 2.59; 0.17)
4	8 mg IR q.d.	mean ± SD (CV%) Range [median]	58	58	58		58	49								
			20.7 ± 10.1 (48.7) 8.82 - 61.8 [18.7]	86.4 ± 39.2 (45.3) 0 - 226 [84.4]	2.12 ± 1.23 (60.0) 0 - 4 [2]		21.2 ± 12.2 (57.3) 0 - 63.2 [18.5]	811.2 ± 358.2 (44.2) 280.2 - 2267.9 [721.5]				390.5 (2.23)	2.9 (1.10) (1.13; 4.75)	PBO	391.1 (1.87)	-0.7 (0.84) (- 2.09; 0.67)
5			30.2 ± 14.1 (46.8) 9.90 - 78.7 [27.1]													
6			35.0 ± 18.2 (52.1) BQL - 82.3 [29.9]													
7			36.9 ± 18.3 (49.6) 8.55 - 88.6 [33.1]													
8		n	46	42	42	45	43	42	42	42	40					58
		mean ± SD (CV%) Range [median]	37.1 ± 18.7 (50.4) 6.95 - 92.0 [33.4]	113 ± 43.3 (38.4) 59.8 - 218 [102]	2.15 ± 1.12 (52.1) 0.52 - 6.08 [2.08]	98.0 ± 41.6 (42.4) 41.7 – 218 [85.6]	34.6 ± 18.4 (53.3) 6.95 - 90.9 [30.7]	1531 ± 647 (42.2) 649 - 3454 [1353]	63.8 ± 26.9 (42.2) 27.1 - 144 [56.4]	128 ± 30.9 (24.3) 84.2 - 209 [124]	23.2 ± 6.6 (28.4) 10.6 - 51.1 [23.2]	393.0 (2.22)	5.5 (1.09) (3.66; 7.25)	Moxi 400 mg qd	396.1 (1.87)	4.3 (0.84) (2.88; 5.64)

Table 81 Least Squates Mean Change from Baseline ± SE and (90% CI) in QTcLD by Time Post-Dose – Study SCH-1009

Time Postdose	Day 2	Day 3	Day 4	Day 8	
	PAL 4 mg	PAL 6 mg	PAL 8 mg	PAL 8 mg	Moxi 400 mg
n	44	44	44	44	58
Predose	0.70 ± 1.66 (-2.00 - 3.45)	0.40 ± 1.66 (-2.36 - 3.11)	1.00 ± 1.66 (-1.77 - 3.68)	2.50 ± 1.66 (-0.27 - 5.18)	-1.1 ± 1.5 (-3.55 – 1.39)
0.5 h	4.70 ± 1.66 (2.02 - 7.46)	2.80 ± 1.65 (0.07 - 5.49)	5.50 ± 1.65 (2.75 - 8.17)	6.90 ± 1.65 (4.21 - 9.62)	3.3 ± 1.49 (0.83 – 5.72)
1.0 h	4.90 ± 1.64 (2.22 - 7.60)	4.30 ± 1.64 (1.58 - 6.96)	5.60 ± 1.64 (2.90 - 8.28)	8.10 ± 1.64 (5.40 - 10.78)	1.8 ± 1.49 (-0.69 - 4.21)
1.5 h	9.30 ± 1.65 (6.56 - 11.98)	6.70 ± 1.64 (4.04 - 9.42)	9.60 ± 1.64 (6.92 - 12.31)	10.90 ± 1.64 (8.24 - 13.62)	3.7 ± 1.49 (1.24 -6.16)
2.0 h	5.50 ± 1.65 (2.76 - 8.18)	4.60 ± 1.64 (1.94 - 7.33)	7.30 ± 1.64 (4.56 - 9.94)	8.90 ± 1.64 (6.22 - 11.60)	3.5 ± 1.49 (1.05 - 5.95)
2.5 h	3.40 ± 1.64 (0.67 - 6.06)	4.00 ± 1.64 (1.35 - 6.74)	4.70 ± 1.65 (1.98 - 7.40)	7.50 ± 1.65 (4.83 - 10.24)	5.5 ± 1.49 (3.05 – 7.97)
3.0 h	4.00 ± 1.64 (1.33 - 6.71)	2.80 ± 1.64 (0.10 - 5.49)	7.20 ± 1.66 (4.52 - 9.97)	7.70 ± 1.64 (4.99 - 10.37)	6.1 ± 1.49 (3.64 – 8.53)
3.5 h	3.40 ± 1.64 (0.74 - 6.12)	-0.10 ± 1.64 (-2.83 - 2.56)	3.70 ± 1.65 (0.95 - 6.37)	5.00 ± 1.64 (2.29 - 7.67)	4.7 ± 1.49 (2.26 -7.18)
4.0 h	2.90 ± 1.64 (0.22 - 5.60)	2.00 ± 1.64 (-0.65 - 4.74)	3.20 ± 1.65 (0.52 - 5.93)	5.80 ± 1.64 (3.06 - 8.44)	5.7 ± 1.5 (3.25 – 8.19)
6.0 h	2.00 ± 1.64 (-0.74 - 4.65)	-1.30 ± 1.64 (-3.94 - 1.44)	1.30 ± 1.64 (-1.37 - 4.01)	4.80 ± 1.64 (2.08 - 7.46)	5.0 ± 1.49 (2.57 – 7.47)
12.0 h	1.80 ± 1.65 (-0.86 - 4.55)	-1.10 ± 1.66 (-3.82 - 1.63)	1.30 ± 1.65 (-1.45 - 3.96)	3.60 ± 1.65 (0.93 - 6.35)	3.5 ± 1.5 (1.07 – 6.01)

Figure 71 Hysteresis Plots of Mean QTcLD versus Mean Paliperidone Plasma Concentration – Study SCH-1009

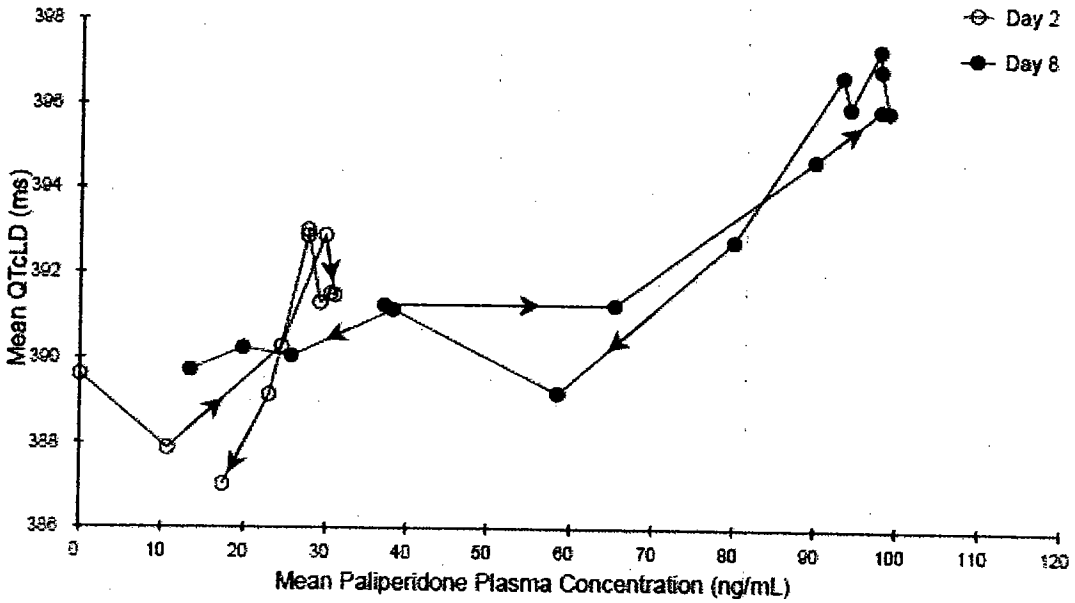


Figure 72 Electrocardiogram - Model-Adjusted Mean Differences From Day 1 with 90% Confidence Intervals By Treatment Arm, Parameter and Visit Treatment Arm: IR Paliperidone (N=44), Parameter: QTcF (ms), Visit: Day 8 – Study SCH-1009

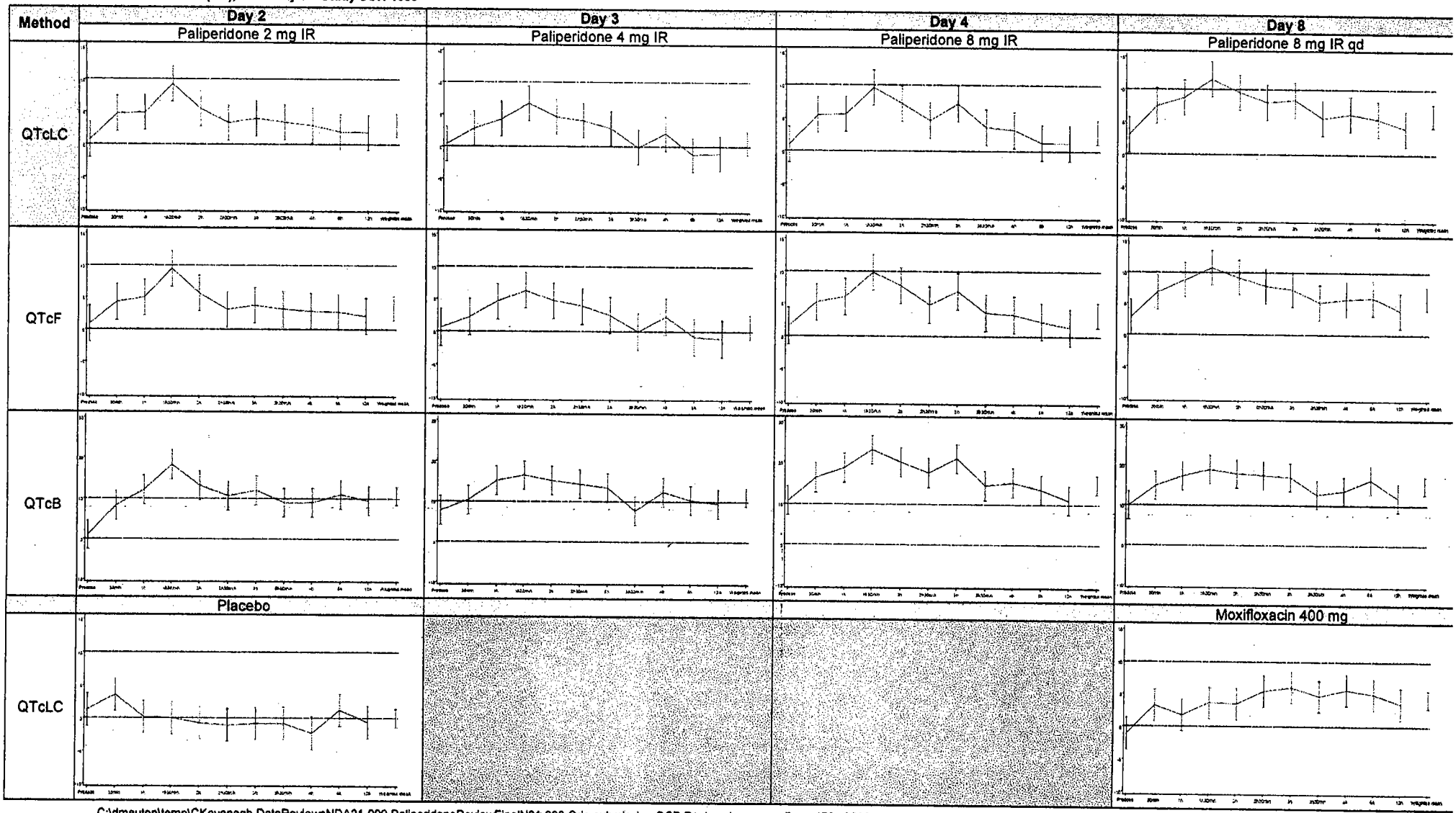


Table 82 Summary Statistics for Paliperidone OROS Peak Concentrations seen in Pharmacokinetic Studies[a]

SD / MD	Dose (mg)	Study							
		Alza-044	P01-1010	P01-1008			ALZA-006		
				–	–	Fed			Fed
SD	6 mg	11.8 ± 3.7 (31.1) 6.7 - 23.4 [11.3]	10.2 ± 3.9 (38.3) 3.66 - 21.3 [9.72]	–	–	–	–	–	–
	9 mg	16.8 ± 5.6 (33.1) 8.7 - 31.0 [15.8]	14.8 ± 6.9 (46.7) 3.88 - 34.2 [13.1]	–	–	–	–	–	–
	12 mg	20.6 ± 6.5 (31.4) 8.5 - 30.6 [21.40]	19.6 ± 8.0 (40.9) 6.18 - 38.6 [18.1]	–	–	–	23.2 ± 7.45 (32.2) 11.9 - 37.8 [23.20]	–	–
	15 mg	31.0 ± 5.6 (18.1) 21.9 - 41.2 [31.90]	26.6 ± 11.8 (44.5) 11.5 - 70.6 [24.5]	22.1+8.2 (36.9) 9.1 - 50.1 [21.5]	22.8+9.8 (43.1) 5.1 - 52 [22.1]	32.1+15.6 (48.4) 11.6 - 95.5 [27.9]	22.7 ± 6.5 (28.8) 11.3 - 33.2 [23.0]	27.5 ± 8.7 (31.6) 9.7 - 47.7 [27.3]	27.4 ± 12.5 (45.8) 4.1 - 45.4 [25.8]
		SCH-101		SCH-102	SCH-1010				
MD	9 mg	–	–	40.2 ± 24.1 (59.9) 8.79 - 130 [35.0]	46.5 + 28.7 (61.8) 15.5 - 105 [35.0]	–	–	–	–
	12 mg	44.1 + 23.7 (53.7) 19.4 - 127 [36.5]	45.6 + 27.1 (59.4) 16.6 - 166 [38.4]	–	–	–	–	–	–
	15 mg	–	–	57.4 ± 30.1 (52.4) 1.82 - 146 [54.0]	–	–	–	–	–

a Values for Cmax are in ng/ml and summary statistics include mean ± SD, (%CV), range, and [median].

3.10.7.5.1.3 Other Studies

ECGs were obtained in a number of other studies however they were usually obtained pre- and post-study. The following four studies mentioned potential cardiac findings.

Study Alza-039

Cardiovascular system events were more common with the Ascend treatment (5 subjects) compared with the Flat (3 subjects) and IR or placebo treatments (1 subject each). No subject reported an AE of hypotension. There was one AE report of syncope (Subject 121, during Ascend treatment). One subject each experienced tachycardia (Subject 122 after Ascend and after Flat treatments), bradycardia (Subject 102 after IR treatment), and arrhythmia that was described as an irregular pulse lasting eight minutes, (Subject 120 after Ascend treatment and with normal ECG at baseline, during each treatment, and per AE CRF). Subject 123, a 55 year-old male, had ectopic beats on his ECG first during IR treatment and again during both Ascend and placebo treatments.

Alza-034

A higher incidence of palpitations was noted in study Alza-034 with a more rapidly absorbed paliperidone OROS development formulation, (see Table 83).

Table 83 Adverse Events Reported in >10% of Subjects During Any Treatment – Study Alza 034

Adverse Event	[redacted] OROS fasted n=28 No. (%)	SLOW OROS fasted n=30 No. (%)	SLOW OROS fed n=31 No. (%)	IR Oral Solution fasted n=29 No. (%)
Headache	6 (21.4)	3 (10.0)	3 (9.7)	7 (24.1)
Insomnia	2 (7.1)	3 (10.0)	3 (9.7)	4 (13.8)
Nausea	8 (28.6)	3 (10.0)	3 (9.7)	2 (6.9)
Palpitation	*5 (17.9)*	*1 (3.3)*	*1 (3.2)*	*3 (10.3)*

Trimethoprim Interaction Study

Twelve-lead ECGs were performed at screening, at baseline (predose in period 1), at predose in period 2, and at the end of the study.

None of the subjects had a QTc interval increase >60 ms from baseline, and none of the subjects had a QTc interval >500 ms. One subject (100401) with normal QTcF, QTlc and QTcB at baseline had increases of 47, 45 and 96 ms, respectively at the end of the study. The end-of-study QTcB (466 ms) was prolonged according to the criteria used in the study (>450 ms). The end-of-study QTcF and QTlc were 425 ms and 419 ms, respectively. This subject also had an above-normal heart rate (HR) at the end of the study (HR=104 bpm).

One subject (100418) with normal QTcF, QTlc and QTcB at baseline had increases of 32, 39 and 41 ms respectively, at the end of the study. However, none of these end-of-study QTc values was borderline or prolonged, according to the criteria used in the study (430-450 ms and >450 ms, respectively). One subject (100422) with a normal QTcB at baseline had an increase of 3 ms at the end of the study. The end-of-study QTcB (431 ms) was borderline according to the criteria used in the study (430-450 ms). One subject (100429) had borderline QTcF, QTlc and QTcB

STUDY SCH-1011 Young vs. Elderly Study

Also in study SCH-1011 there were a number subjects who had prolongations of of QTcF between 30 – 60 milliseconds while receiving paliperidone OROS 3 mg qd. With more instances in elderly subjects than in young subjects,

Table 84 ECG Descriptive Statistics on Raw Data and Changes from Baseline – Study SCH-1011

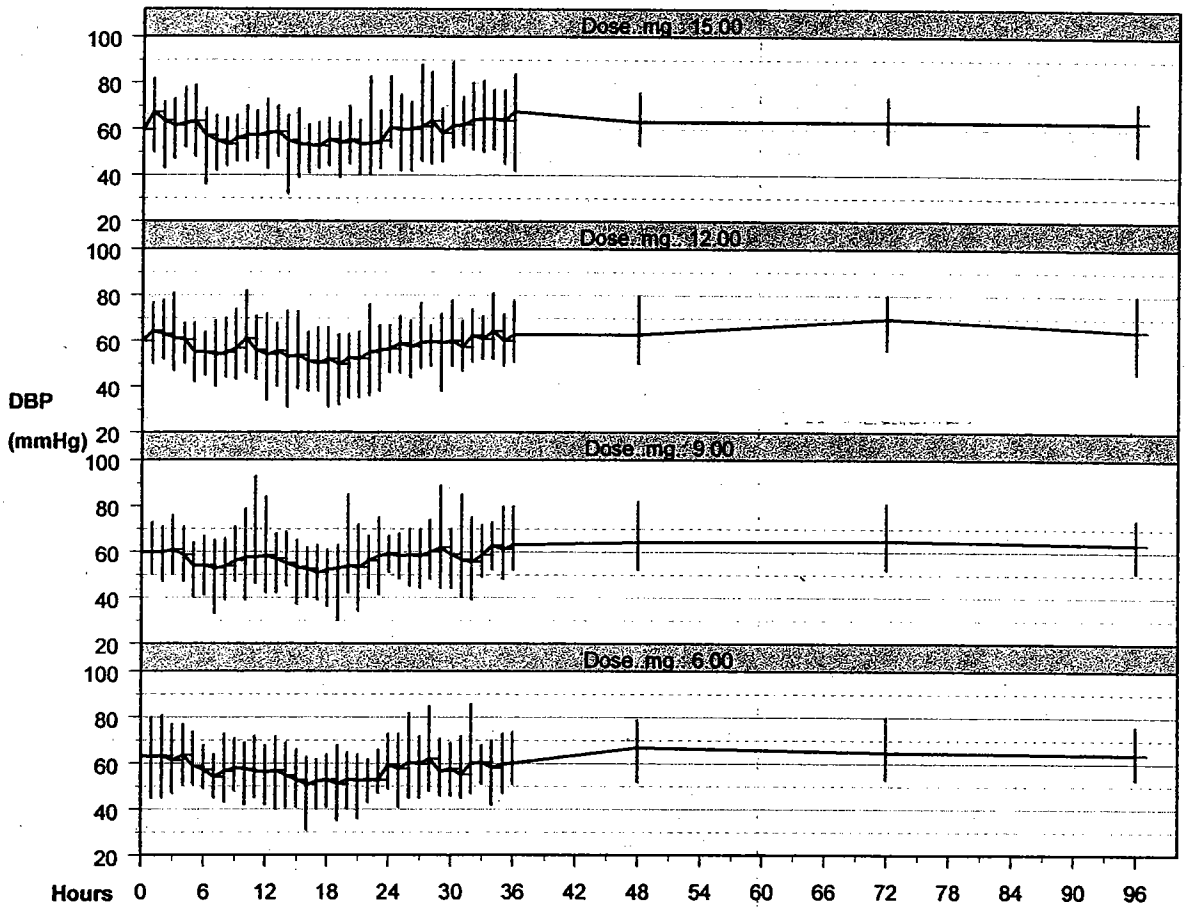
	QTcF (msec)							Change in QTcF (msec)						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
ELDERLY SUBJECTS														
Screening	30	418.93	16.700	419.00	380.0	455.0								
Single dose														
Day 1	30	418.73	15.109	420.00	390.0	445.0	418.73							
Day 2	30	421.13	12.982	420.00	391.0	**454.0**	418.73	30	2.40	2.246	12.300	0.50	-23.0	**38.0**
Day 3	30	413.73	14.818	413.00	384.0	445.0	418.73	30	- 5.00	2.364	12.948	-7.50	-27.0	21.0
Repeated dosing														
Day 12	26	419.12	15.387	422.50	386.0	447.0	418.96	26	0.15	2.711	13.824	0.50	-29.0	**32.0**
Day 13	26	421.35	11.761	424.00	397.0	**458.0**	418.96	26	2.38	2.787	14.213	5.00	-27.0	**31.0**
Day 14	26	424.12	17.284	423.00	396.0	**468.0**	418.96	26	5.15	3.311	16.885	5.50	-26.0	**40.0**
End of study	30	418.83	17.798	418.50	372.0	459.0	418.73	30	0.10	2.534	13.877	-0.50	-27.0	30.0
YOUNG SUBJECTS														
Screening	30	411.93	17.106	413.50	382.0	447.0								
Single dose														
Day 1	30	411.87	20.199	411.00	385.0	**472.0**	411.87							
Day 2	30	414.03	17.435	415.50	381.0	**451.0**	411.87	30	2.17	2.489	13.633	2.00	-25.0	**33.0**
Day 3	30	410.53	20.920	414.50	370.0	445.0	411.87	30	-1.33	2.568	14.067	0.00	-28.0	23.0
Repeated dosing														
Day 12	28	411.50	21.118	410.50	364.0	**455.0**	413.04	28	-1.54	2.720	14.393	-2.50	-34.0	**39.0**
Day 13	28	413.39	17.877	414.50	365.0	**450.0**	413.04	28	-0.36	2.440	12.911	0.50	-33.0	22.0
Day 14	28	409.96	17.244	411.00	376.0	448.0	413.04	28	3.07	2.383	12.611	-4.00	- 35.0	16.0
End of study	30	411.73	20.296	413.50	363.0	441.0	411.87	30	-0.13	3.320	18.186	-1.00	-38.0	43.0

3.10.7.5.2 BP

3.10.7.5.2.4 Diastolic Blood Pressure

When diastolic blood pressure is examined after single or multiple dosing of paliperidone there does not appear to be any obvious dose response relationship, (see Figure 73 and Figure 74).

Figure 73 Effect of Single Doses of Paliperidone OROS on Diastolic Blood Pressure over Time by Dosage – Study Alza-044 [a]



a Values are Mean, high and low.