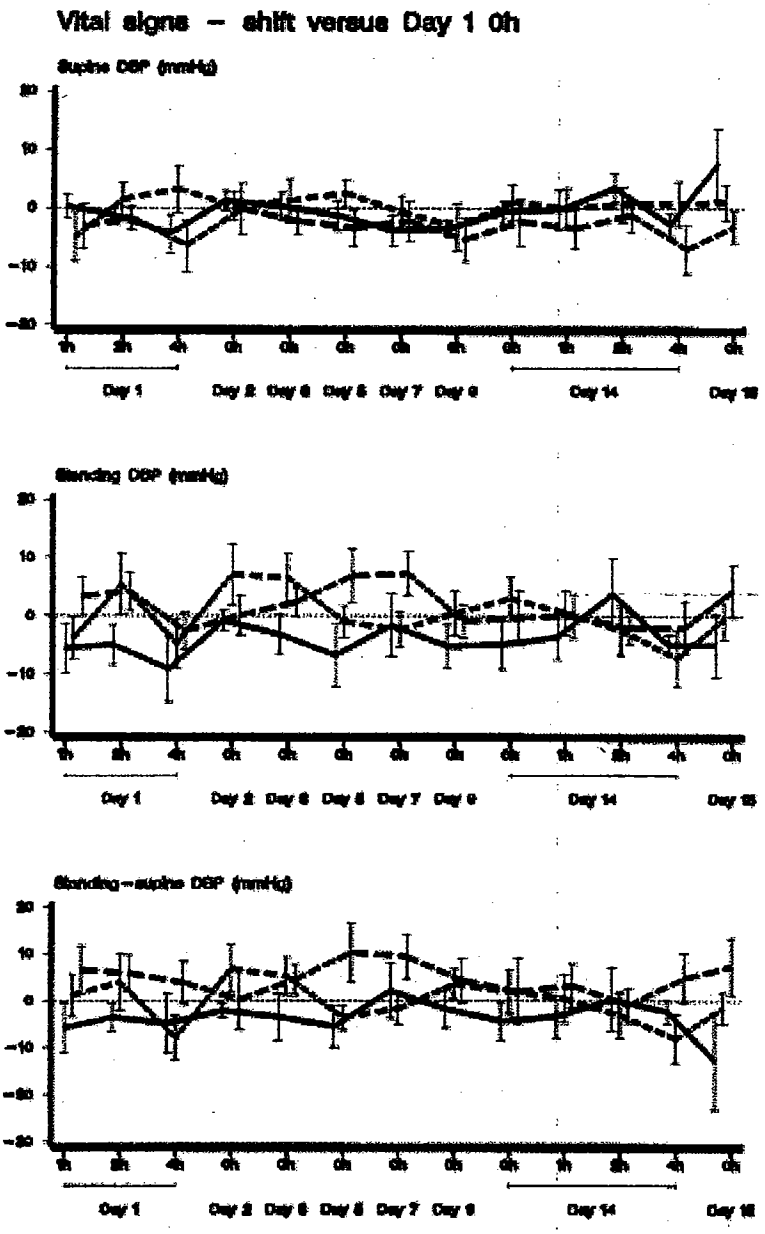
Figure 74 Change from Baseline in Diastolic Blood Pressure – Study INT-1

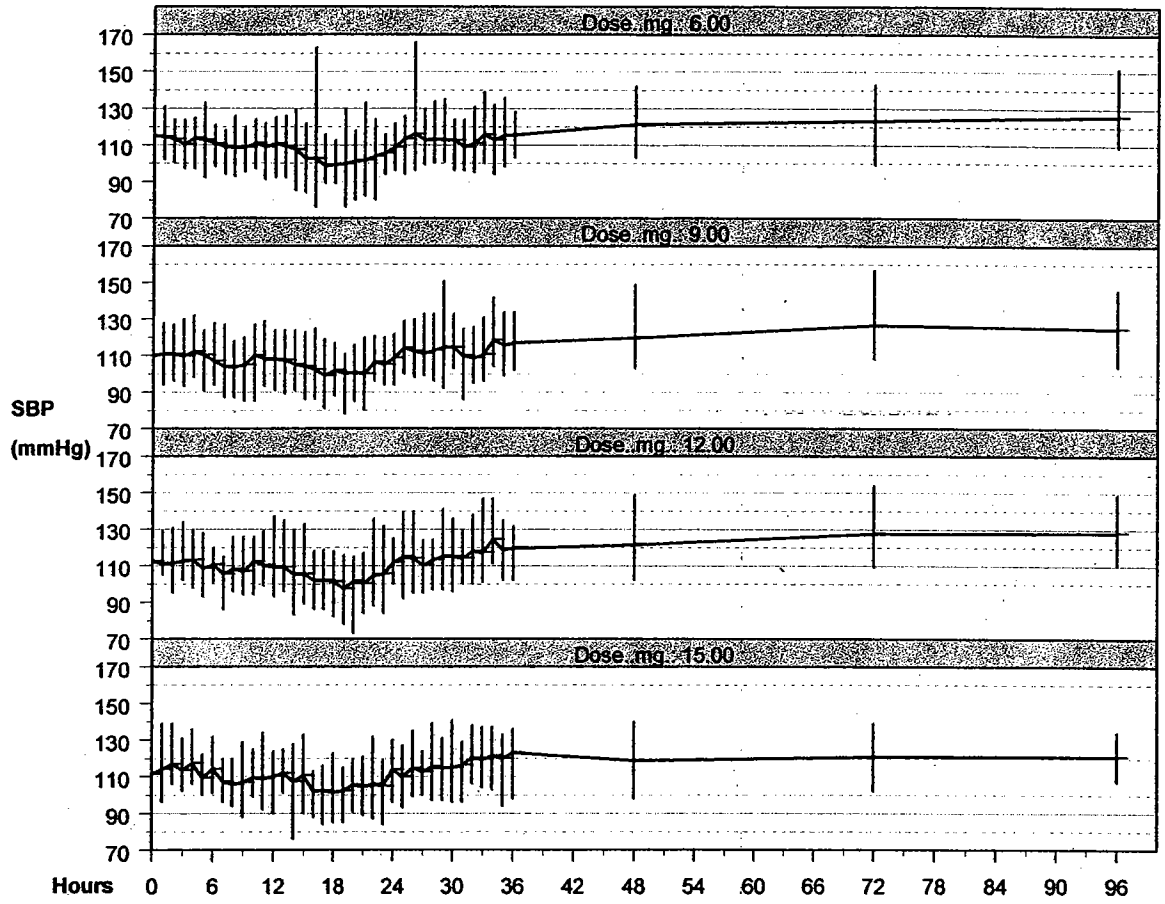
Display 24: Vital Signs - Graphical Presentation of Changes From Baseline (Day 1 Predose) (cont'd)



3.10.7.5.2.5 Systolic Blood Pressure

However when systolic blood pressure is examined after single doses of paliperidone in the same studies there appears to be a small signal for a response relationship, although this isn't apparent in the multiple dosing study, (see Figure 75 and Figure 76). However, when the incidence of potentially orthostatic changes in SBP or symptoms consistent with orthostasis from a number of studies is examined the incidence appears to track with expected changes in dose, rate, and extent of absorption, (see Figure 77, Table 85, Table 86, Table 87, and Figure 78).

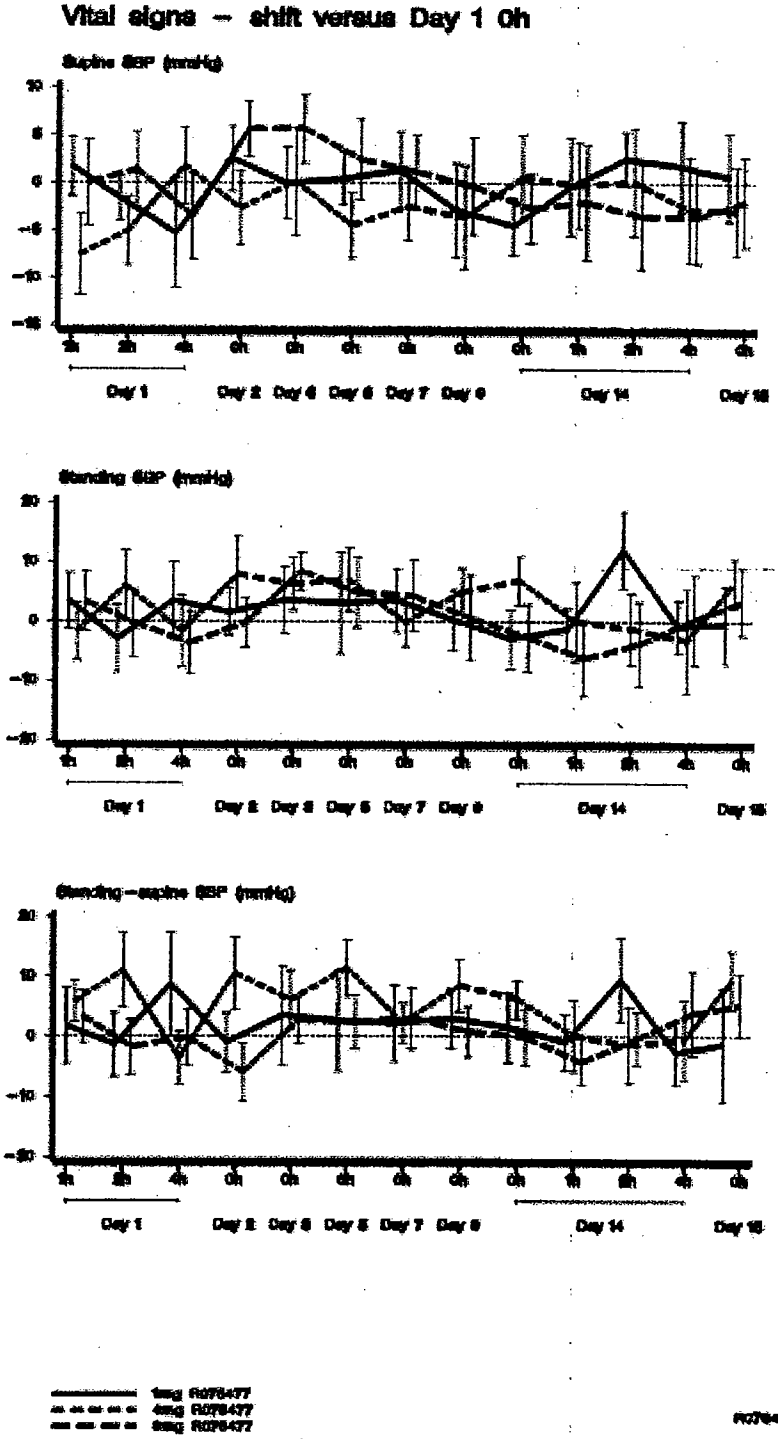
Figure 75 Effect of Single Doses of Paliperidone OROS on Systolic Blood Pressure over Time by Dosage – Study Alza-044[a]



a Values are Mean, high and low.

Figure 76 Change from Baseline in Systolic Blood Pressure – Study INT-1

Display 24: Vital Signs - Graphical Presentation of Changes From Baseline (Day 1 Predose) (cont'd)



P01-101

Figure 77 Percent of Subjects with Orthostasis by Treatment- Study P01-101

Table 7: Orthostatic Measurements - Incidence of Worst Orthostatism per Treatment (Study R076477-P01-101: All Subjects Analysis Set)

	[redacted] FASTED (N=34)	[redacted] FED (N=34)	OROS FASTED (N=35)	OROS FED (N=34)	SOLUTION FASTED (N=34)	Total (N=35)
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pulse (bpm)	18 (53)	19 (56)	17 (49)	15 (44)	18 (53)	29 (83)
SBP (mmHg)	15 (44)	15 (44)	7 (20)	8 (24)	22 (65)	29 (83)
DBP (mmHg)	17 (50)	18 (53)	9 (26)	10 (29)	20 (59)	32 (91)

Note: Percentages calculated with the no. of subjects in each group as denominator.
The incidence of worst orthostatism was calculated as the percentage of subjects for whom the maximal decrease in BP or the maximal increase in pulse was above the predefined limits, or who could not stand.
Orthostatic Hypotension criteria:
Standing-supine Pulse ≥ +50 bpm or unable to remain standing
Standing-supine SBP ≤ -20 mmHg or unable to remain standing
Standing-supine DBP ≤ -10 mmHg or unable to remain standing

Alza-039

"Pharmacodynamic Results: statistics show that the percentage of subjects with either a drop in SBP >20 mmHg at 2-minutes standing or with symptoms of orthostatic hypotension (dizziness or faintness) were similar for Ascend and IR even though the Ascend dose was greater than the IR dose (3.5 mg versus 2 mg on Day 1, respectively). A 2-mg dose was given on Day 2 in each active treatment and the incidence of >20 mm Hg drop or dizziness or faintness was lower than on Day 1."

Table 85 Drop of >20 mm Hg SBP or Symptoms of Dizziness or Faintness – Study Alza-039

	Ascend	Flat	IR	Placebo
Day 1	54%	42%	59%	23%
Day 2	50%	35%	41%	15%

Alza-019

Table 86 Percentages of subjects with either a drop in SBP >20 mmHg at 2- minutes standing or symptoms of orthostatic hypotension (dizziness or faintness)

	Ris Ascend-4 N = 22	Ris IR-2 N = 22	Pal Ascend-4 N = 21	Pal Ascend-2 N = 25	Placebo N = 27
Day 1	32%	46%	29%	32%	7%
Day 2	19%	38%	24%	36%	15%

Alza-034

"SLOW OROS (paliperidone) treatments were associated with the lowest incidence of orthostatic hypotension among the treatments in this study. [redacted] OROS (paliperidone) was associated with an incidence of orthostatic hypotension similar to that of the 2-mg dose of IR Oral Solution paliperidone. In general, the occurrence of symptoms of orthostatic hypotension (dizziness or faintness) or a drop in SBP greater than 20 mm Hg (the measurable definition of orthostatic hypotension) at any given time interval appeared to be associated with the Cmax and Tmax of the 4 treatments, although it is not possible to attribute all changes in blood pressure and heart rate to treatment because there was no placebo treatment in this study to account for diurnal changes.

The following table presents the percentage of subjects who experienced dizziness/faintness or had a drop in systolic blood pressure greater than 20 mm Hg at 2 minutes standing 0 to 24 hours after paliperidone administration. (Incidence was similar for the period 0 to 48 hours after paliperidone administration."

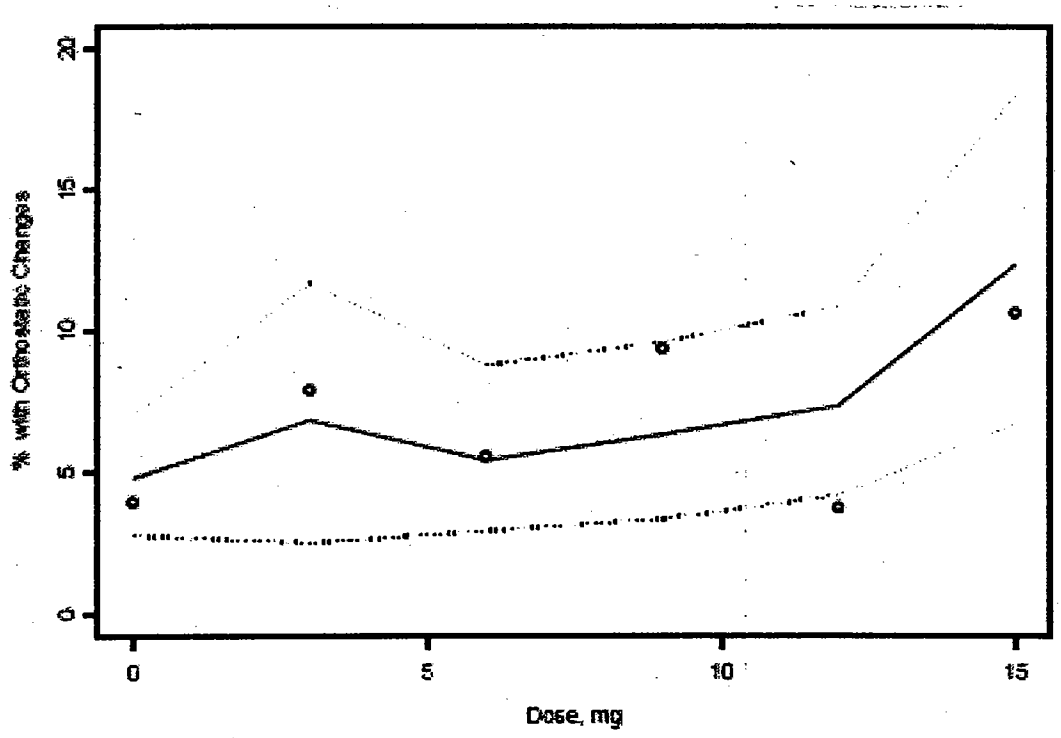
Table 87 Number (%) of Subjects Who Felt Dizzy or Faint or Had a Drop of >20 mm Hg in Systolic Blood Pressure After 2 Minutes Standing (0-24 Hours) – Study Alza-034

	OROS fasted 4 mg	SLOW OROS fasted 4 mg	SLOW OROS fed 4 mg	IR Oral Solution fasted 2 mg
N	n=28	n=30	n=31	n=29
Subjects with dizziness/faintness or >20 mm Hg drop	19 (68%)	15 (50%)	13 (42%)	21 (72%)
Subjects with >20 mm Hg drop	13 (46%)	9 (30%)	8 (26%)	11 (38%)

Population PD Analysis

Figure 78 Sponsor's Population Prediction of the Incidence of Orthostatic Changes from Phase III Study Data.

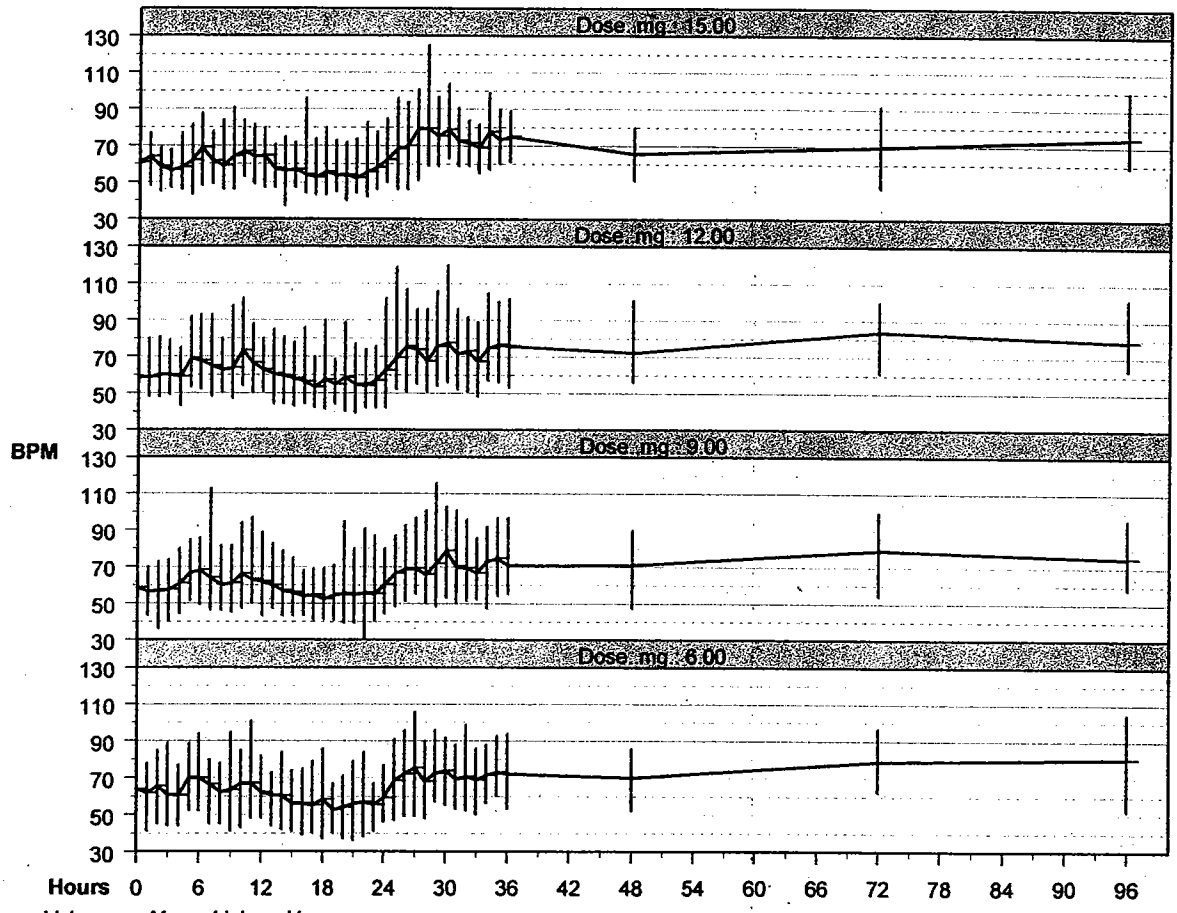
Figure 7: Predicted Incidence of Orthostatic Changes in Vital Signs With 95% Prediction Intervals in 1,000 Simulated Replicates of the Phase 3 Studies as a Function of Dose. The Circles Represent the Observed Incidences.



3.10.7.5.3 HR

As with changes in blood pressure there appears to be a diurnal pattern to changes in heart rate after single doses of paliperidone OROS. In addition, there appears to be a clear indication of a dose response relationship, (see Figure 79), and this is likely responsible for the dose response relationship seen with systolic blood pressure.

Figure 79 Effect of Single Doses of Paliperidone OROS on Heart Rate over Time by Dosage Heart Rate – Study Alza-044[a]



a Values are Mean, high and low.

3.10.8 Effects of Intrinsic Factors

3.10.8.1 Age

The effect of age was examined in study SCH-1011, an open label, parallel group study of the single and multiple dose pharmacokinetics of Paliperidone OROS 3 mg.

There is a trend for increasing exposures as age increases, such that exposures are around 1/3 higher subjects around 75 years of age compared with those around 25 years of age.

Tables on the following pages show comparative single dose and multiple dose pharmacokinetics in the young and elderly. In these tables red text highlights a progressive trend with age with differences between the elderly subjects 65 – 74 years old and the elderly 75 – 85 yo; and orange text highlights a progressive trend with age for the enantiomer ratios. Green text highlights a lack of difference by age, and a mixture of red and plum text generally indicates a difference between the young and the elderly but not between the elderly 65 – 74 yo and the elderly 75 - 85 yo, although in two cases plum text instead indicates a difference for elderly 75 - 85 yo compared to all other subjects.

After single doses, both total Cmax and total and unbound AUC for paliperidone increased progressively with age, with corresponding decreases in half-life and clearance/F, (see Table 88, Figure 80, and Figure 81).

Except for unbound Cmax and total Cmax for (+)-paliperidone similar changes were seen for both paliperidone enantiomers, (see Table 89).

On multiple dosing increases in half-life and both total and unbound Cmax and AUC with age were again seen, and there were also decreases in Cl/F and Vdss/F. In addition to the change in Cl/F probably being partially due to decreasing renal function, and possibly hepatic function with age, the decrease in Vdss/F and Cl/F might also be partially due to an increase in F due to slower GI transit in the elderly. Although differences were seen between the young and the elderly on multiple dosing there is not much difference between the elderly subjects 65 – 74 yo those 75 – 85 yo, (see Table 90 and Table 91).

No 'old' elderly, (i.e. > 85 yo), were included in this study so the pharmacokinetics in this age group are unknown, although trends suggest they may have even higher exposures.

Table 88 Single Dose Pharmacokinetic Metrics of Paliperidone OROS 3 mg by Age – Study SCH-1011

Analyte	Pop	Cmax (ng/ml)	Tmax (h)	t½ (h)	fu	AUC0-24 (ng/ml x hr^{-1})	AUClast (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	AUCinf,ex %	Enantiomer Ratio-AUCinf	CL/F (ml/min)	Vdz/F (L)	Cmax,u (ng/ml)	AUCinf,u (ng/ml x hr^{-1})	CLu/F (ml/min)
Pal	elderly subjects (75 - 85 years old)	7	7	7	7	7	7	7	7	7	7	7	7	7	7
		6.24 ± 2.27 (36.4) 2.52 - 8.68 [7.35]	22.03 ± 4.49 (20.4) 12.00 - 24.10 [24.02]	34.7 ± 8.53 (24.6) 24.3 - 45.2 [30.4]	0.236 ± 0.0370 (15.6) 0.197 - 0.302 [0.234]	74.5 ± 22.9 (30.8) 40.8 - 100 [71.5]	286 ± 98.4 (34.4) 145 - 387 [304]	325 ± 116 (35.7) 157 - 455 [359]	11.6 ± 4.41 (38.1) 5.50 - 17.2 [11.8]	1.68 ± 0.148 (8.85) 1.46 - 1.84 [1.70]	178 ± 82.5 (46.3) 110 - 318 [139]	510 ± 187 (36.5) 257 - 831 [438]	1.41 ± 0.446 (31.7) 0.660 - 2.12 [1.44]	73.8 ± 20.7 (28.1) 40.1 - 101 [76.0]	738 ± 259 (35.1) 494 - 124 [658]
	elderly subjects (≥ 65 and < 75 years)	23	23	22	20	23	21	21	21	20	21	21	23	21	21
		5.81 ± 2.55 (43.8) 2.10 - 11.7 [5.60]	23.33 ± 1.29 (5.55) 20.00 - 24.12 [24.00]	31.6 ± 6.13 (19.4) 18.7 - 43.7 [32.2]	0.238 ± 0.0363 (15.3) 0.177 - 0.307 [0.240]	68.9 ± 24.3 (35.3) 31.1 - 112 [66.5]	251 ± 101 (40.2) 85.8 - 406 [224]	275 ± 113 (41.0) 94.3 - 452 [240]	8.68 ± 3.51 (40.5) 2.84 - 16.4 [8.77]	1.64 ± 0.189 (11.5) 1.24 - 1.94 [1.61]	216 ± 99.3 (46.0) 111 - 530 [208]	577 ± 253 (43.8) 292 - 1178 [584]	1.29 ± 0.478 (37.0) 0.434 - 2.32 [1.32]	62.5 ± 20.9 (33.4) 18.9 - 97.5 [59.3]	928 ± 468 (50.4) 513 - 263 [843]
	elderly subjects (≥=65)	30	30	29	27	30	28	28	28	27	28	28	30	28	28
		5.91 ± 2.45 (41.5) 2.10 - 11.7 [5.70]	23.02 ± 2.40 (10.4) 12.00 - 24.12 [24.00]	32.4 ± 6.75 (20.8) 18.7 - 45.2 [32.1]	0.237 ± 0.0358 (15.1) 0.177 - 0.307 [0.239]	70.2 ± 23.7 (33.8) 31.1 - 112 [69.0]	260 ± 99.6 (38.4) 85.8 - 406 [254]	288 ± 114 (39.5) 94.3 - 455 [279]	9.40 ± 3.89 (41.3) 2.84 - 17.2 [8.90]	1.65 ± 0.178 (10.8) 1.24 - 1.94 [1.64]	207 ± 95.4 (46.2) 110 - 530 [179]	561 ± 237 (42.2) 257 - 1178 [491]	1.32 ± 0.466 (35.3) 0.434 - 2.32 [1.34]	65.4 ± 21.1 (32.2) 18.9 - 101 [60.9]	880 ± 429 (48.8) 494 - 263 [821]
	young subjects (18 – 45 years old)	30	30	28	28	30	29	28	28	28	28	28	30	28	28
		5.49 ± 2.24 (40.8) 0.924 - 10.1 [5.13]	21.87 ± 4.35 (19.9) 9.00 - 24.10 [24.00]	20.9 ± 6.71 (32.1) 13.4 - 42.8 [18.6]	0.258 ± 0.0473 (18.4) 0.157 - 0.350 [0.261]	67.5 ± 24.8 (36.6) 8.47 - 114 [61.9]	188 ± 79.4 (42.4) 8.25 - 363 [186]	211 ± 74.4 (35.2) 81.6 - 383 [206]	8.97 ± 3.77 (42.0) 2.13 - 19.2 [8.71]	1.42 ± 0.219 (15.4) 0.881 - 1.79 [1.40]	272 ± 115 (42.3) 130 - 613 [243]	471 ± 197 (41.9) 246 - 1059 [440]	1.37 ± 0.576 (42.0) 0.192 - 3.09 [1.34]	53.8 ± 19.5 (36.2) 16.8 - 93.7 [54.4]	1091 ± 53 (48.9) 533 - 297 [919]

Table 89 Single Dose Pharmacokinetic Metrics of Paliperidone Enantiomers after Administration of Paliperidone OROS 3 mg by Age – Study SCH-1011

Analyte	Population	Cmax (ng/ml)	Tmax (h)	t½ (h)	fu	AUC0-24 (ng/ml x hr^{-1})	AUClast (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	AUCinf,ex %	Ratio-AUCinf	CL/F (ml/min)	Vdz/F (L)	Cmax,u (ng/ml)	AUCinf,u (ng/ml x hr^{-1})	CLu/F (ml/min)
R078543 (+)-Pal	elderly subjects (75 - 86 years old)	7 4.04 ± 1.53 (38.0) 1.59 - 5.75 [4.80]	7 22.03 ± 4.49 (20.4) 12.00 - 24.10 [24.02]	7 36.4 ± 8.14 (22.3) 25.2 - 45.5 [40.2]	7 0.171 ± 0.0333 (19.4) 0.142 - 0.230 [0.154]	7 48.7 ± 16.2 (33.2) 26.4 - 67.8 [44.9]	7 180 ± 65.3 (36.4) 91.9 - 247 [191]	7 206 ± 75.0 (36.5) 108 - 295 [226]	7 12.7 ± 4.15 (32.7) 5.73 - 16.8 [14.8]	–	7 141 ± 62.6 (44.5) 84.7 - 231 [111]	7 435 ± 196 (45.1) 208 - 803 [366]	7 0.668 ± 0.240 (35.8) 0.307 - 1.09 [0.696]	7 33.7 ± 10.1 (30.0) 20.9 - 49.6 [33.2]	7 801 ± 242 (30.2) 504 - 1195 [753]
	elderly subjects (>= 65 and < 75 years)	23 3.73 ± 1.63 (43.7) 1.36 - 7.41 [3.61]	23 22.02 ± 4.40 (20.0) 6.00 - 24.12 [24.00]	22 32.1 ± 6.66 (20.8) 17.1 - 49.2 [32.7]	23 0.170 ± 0.0339 (19.9) 0.121 - 0.239 [0.164]	23 45.1 ± 16.0 (35.4) 20.8 - 75.3 [43.4]	21 156 ± 62.7 (40.3) 56.4 - 260 [142]	21 173 ± 69.0 (39.9) 64.2 - 289 [156]	21 10.0 ± 3.39 (33.8) 4.64 - 19.1 [9.59]	–	21 169 ± 71.3 (42.2) 86.4 - 390 [160]	21 457 ± 190 (41.5) 240 - 937 [489]	23 0.609 ± 0.219 (35.9) 0.204 - 1.10 [0.632]	21 28.6 ± 8.51 (29.7) 9.63 - 42.9 [27.0]	21 985 ± 444 (45.1) 582 - 2595 [926]
	elderly subjects (>= 65)	30 3.80 ± 1.59 (41.8) 1.36 - 7.41 [3.70]	30 22.02 ± 4.34 (19.7) 6.00 - 24.12 [24.00]	29 33.1 ± 7.15 (21.6) 17.1 - 49.2 [32.9]	30 0.171 ± 0.0332 (19.4) 0.121 - 0.239 [0.163]	30 46.0 ± 15.8 (34.4) 20.8 - 75.3 [44.2]	28 162 ± 63.0 (39.0) 56.4 - 260 [147]	28 181 ± 70.6 (39.0) 64.2 - 295 [162]	28 10.7 ± 3.70 (34.6) 4.64 - 19.1 [10.1]	–	28 162 ± 69.2 (42.8) 84.7 - 390 [155]	28 452 ± 188 (41.6) 208 - 937 [401]	30 0.623 ± 0.221 (35.5) 0.204 - 1.10 [0.644]	28 29.9 ± 9.03 (30.2) 9.63 - 49.6 [28.2]	28 939 ± 407 (43.3) 504 - 2595 [886]
	young subjects (18 – 45 years old)	30 3.35 ± 1.42 (42.5) 0.577 - 6.45 [2.94]	30 21.94 ± 4.36 (19.9) 9.00 - 24.10 [24.00]	28 20.9 ± 7.08 (33.9) 12.3 - 45.0 [19.6]	30 0.195 ± 0.0474 (24.3) 0.102 - 0.314 [0.196]	30 42.7 ± 16.1 (37.6) 5.78 - 74.3 [38.8]	29 111 ± 49.2 (44.3) 5.56 - 231 [109]	28 125 ± 47.4 (38.0) 50.6 - 242 [117]	28 8.64 ± 3.36 (38.9) 4.04 - 19.4 [8.14]	–	28 234 ± 101 (43.2) 103 - 494 [213]	28 400 ± 169 (42.4) 208 - 930 [344]	30 0.638 ± 0.303 (47.4) 0.0941 - 1.79 [0.558]	28 23.8 ± 9.61 (40.4) 7.79 - 54.3 [22.4]	28 1233 ± 559 (45.3) 460 - 3210 [1115]
R078544 (-)-Pal	elderly subjects (75 - 86 years old)	7 2.21 ± 0.742 (33.6) 0.939 - 2.93 [2.55]	7 22.32 ± 2.45 (11.0) 18.00 - 24.10 [24.02]	7 34.7 ± 8.92 (25.7) 23.1 - 45.9 [33.5]	7 0.344 ± 0.0407 (11.8) 0.292 - 0.408 [0.351]	7 25.7 ± 6.88 (26.8) 14.3 - 32.7 [26.5]	7 106 ± 34.4 (32.5) 50.0 - 139 [113]	7 122 ± 38.9 (32.0) 61.2 - 160 [134]	7 13.0 ± 4.94 (38.0) 5.15 - 18.3 [14.7]	–	7 232 ± 99.3 (42.7) 156 - 409 [187]	7 674 ± 263 (39.0) 340 - 1184 [619]	7 0.741 ± 0.217 (29.2) 0.355 - 1.03 [0.800]	7 40.6 ± 10.2 (25.1) 23.1 - 51.7 [42.9]	7 661 ± 216 (32.7) 484 - 1081 [582]
	elderly subjects (>= 65 and < 75 years)	23 2.10 ± 0.923 (44.0) 0.741 - 4.33 [1.98]	23 23.06 ± 1.46 (6.34) 20.00 - 24.12 [24.00]	22 31.7 ± 5.75 (18.1) 22.3 - 41.0 [32.2]	23 0.336 ± 0.0399 (11.9) 0.282 - 0.435 [0.335]	23 23.8 ± 8.57 (36.0) 10.4 - 38.4 [23.1]	21 93.8 ± 40.1 (42.7) 27.3 - 160 [79.7]	20 110 ± 39.9 (36.4) 58.5 - 172 [98.4]	20 12.4 ± 4.24 (34.1) 5.63 - 20.0 [12.0]	–	20 259 ± 92.3 (35.7) 146 - 427 [257]	20 727 ± 323 (44.4) 353 - 1392 [632]	23 0.687 ± 0.264 (38.4) 0.230 - 1.22 [0.678]	20 36.4 ± 10.8 (29.6) 20.5 - 54.5 [34.0]	20 751 ± 234 (31.1) 458 - 1217 [739]
	elderly subjects (>= 65)	30 2.12 ± 0.873 (41.1) 0.741 - 4.33 [2.14]	30 22.89 ± 1.72 (7.53) 18.00 - 24.12 [24.00]	29 32.4 ± 6.60 (20.4) 22.3 - 45.9 [32.4]	30 0.338 ± 0.0395 (11.7) 0.282 - 0.435 [0.341]	30 24.3 ± 8.13 (33.5) 10.4 - 38.4 [24.2]	28 96.8 ± 38.5 (39.7) 27.3 - 160 [105]	27 113 ± 39.3 (34.8) 58.5 - 172 [122]	27 12.6 ± 4.34 (34.5) 5.15 - 20.0 [12.0]	–	27 252 ± 93.0 (36.9) 146 - 427 [204]	27 713 ± 304 (42.7) 340 - 1392 [619]	30 0.700 ± 0.251 (35.9) 0.230 - 1.22 [0.716]	27 37.5 ± 10.6 (28.3) 20.5 - 54.5 [37.1]	27 727 ± 229 (31.4) 458 - 1217 [674]
	young subjects (18 – 45 years old)	30 2.14 ± 0.846 (39.5) 0.347 - 3.66 [2.07]	30 22.07 ± 3.90 (17.7) 9.00 - 24.10 [24.00]	28 21.1 ± 5.99 (28.3) 13.7 - 40.1 [19.1]	30 0.343 ± 0.0596 (17.4) 0.233 - 0.515 [0.346]	30 24.9 ± 9.11 (36.6) 2.69 - 40.5 [23.7]	29 76.1 ± 31.0 (40.8) 2.15 - 132 [76.2]	28 87.9 ± 29.6 (33.6) 31.0 - 141 [84.5]	28 11.2 ± 3.70 (33.0) 5.70 - 18.9 [10.3]	–	28 326 ± 144 (44.0) 177 - 806 [296]	28 580 ± 253 (43.6) 301 - 1229 [523]	30 0.735 ± 0.304 (41.3) 0.0979 - 1.30 [0.709]	28 30.5 ± 11.5 (37.8) 9.06 - 52.4 [30.0]	28 986 ± 518 (52.5) 477 - 2760 [835]

Table 90 Multiple Dose Pharmacokinetic Metrics of Paliperidone OROS 3 mg by Age – Study SCH-1011

Analyte	Pop	Cmax,ss (ng/ml)	Cmin,ss (ng/ml)	tmax,ss (h)	t½ (h)	AUCT (ng/ml x hr^{-1})	Cavg,ss (ng/ml)	AccRatio-	FI%	CLss/F (ml/min)	AUCT/ AUCinf	Vdss/F,u (L)	Cmax,ss,u (ng/ml)	AUCT,u (ng/ml x hr^{-1})	Cavg,ss,u (ng/ml)	CLss,u/F (ml/min)
Pal	elderly subjects (75 - 85 years old)	7	7	7	6	7	7	7	7	7	7	6	7	7	7	7
		12.8 ± 5.30	8.32 ± 3.65	19.30 ± 8.11	41.5 ± 9.46	251 ± 103	10.4 ± 4.30	3.40 ± 0.86	43.4 ± 10.6	224 ± 71.2	0.80 ± 0.23	800 ± 335	2.95 ± 1.00	57.6 ± 19.1	2.40 ± 0.794	938 ± 243
		(41.4)	(43.8)	(42.0)	(22.8)	(41.3)	(41.2)	(25.3)	(24.5)	(31.8)	(28.7)	(41.9)	(34.0)	(33.2)	(33.1)	(25.9)
		8.03 - 22.7	5.37 - 15.3	6.00 - 24.03	31.9 - 55.0	159 - 449	6.62 - 18.7	2.42 - 4.55	29.7 - 57.4	111 - 315	0.54 - 1.18	418 - 1283	2.24 - 4.48	43.3 - 88.5	1.80 - 3.68	565 - 1155
		[10.8]	[7.39]	[24.00]	[40.0]	[222]	[9.26]	[3.38]	[39.6]	[225]	[0.81]	[764]	[2.41]	[48.1]	[2.00]	[1039]
	elderly subjects (>= 65 & <75 years old)	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19
		12.8 ± 3.25	8.16 ± 2.32	16.53 ± 9.09	34.8 ± 6.78	248 ± 60.2	10.3 ± 2.51	3.98 ± 1.38	44.9 ± 17.2	215 ± 59.5	1.04 ± 0.45	651 ± 237	2.95 ± 0.578	57.2 ± 11.2	2.38 ± 0.466	908 ± 185
		(25.5)	(28.5)	(55.0)	(19.5)	(24.3)	(24.3)	(34.7)	(38.2)	(27.7)	(43.0)	(36.4)	(19.6)	(19.6)	(19.5)	(20.4)
		6.94 - 20.6	5.09 - 12.4	4.00 - 24.07	25.8 - 49.6	142 - 348	5.91 - 14.5	2.44 - 6.90	26.9 - 75.6	144 - 353	0.48 - 2.26	389 - 1257	1.88 - 4.16	38.6 - 80.7	1.61 - 3.36	619 - 1297
		[12.9]	[8.18]	[24.00]	[34.1]	[257]	[10.7]	[3.34]	[37.3]	[195]	[0.88]	[588]	[2.89]	[58.3]	[2.43]	[858]
	elderly subjects (>=65 years old)	26	26	26	25	26	26	26	26	26	26	25	26	26	26	26
		12.8 ± 3.79	8.20 ± 2.66	17.28 ± 8.76	36.4 ± 7.86	249 ± 72.0	10.4 ± 3.00	3.83 ± 1.27	44.5 ± 15.5	217 ± 61.5	0.98 ± 0.41	687 ± 264	2.95 ± 0.694	57.3 ± 13.3	2.39 ± 0.555	916 ± 198
		(29.6)	(32.5)	(50.7)	(21.6)	(28.9)	(28.9)	(33.3)	(34.8)	(28.3)	(42.0)	(38.4)	(23.5)	(23.3)	(23.2)	(21.6)
		6.94 - 22.7	5.09 - 15.3	4.00 - 24.07	25.8 - 55.0	142 - 449	5.91 - 18.7	2.42 - 6.90	26.9 - 75.6	111 - 353	0.48 - 2.26	389 - 1283	1.88 - 4.48	38.6 - 88.5	1.61 - 3.68	565 - 1297
		[12.5]	[8.03]	[24.00]	[34.2]	[247]	[10.3]	[3.35]	[39.3]	[202]	[0.85]	[649]	[2.82]	[56.0]	[2.33]	[894]
	young subjects (18–45 years old)	28	28	28	28	28	28	28	28	28	27	28	28	28	28	28
		10.7 ± 3.34	6.60 ± 2.03	17.04 ± 8.28	28.4 ± 5.12	199 ± 54.0	8.31 ± 2.25	3.47 ± 2.35	49.5 ± 21.8	270 ± 75.7	1.08 ± 0.53	651 ± 175	2.68 ± 0.898	50.1 ± 14.7	2.09 ± 0.613	1088 ± 337
		(31.3)	(30.7)	(48.6)	(18.0)	(27.1)	(27.1)	(67.7)	(44.0)	(28.1)	(49.0)	(27.0)	(33.5)	(29.4)	(29.4)	(31.0)
		5.42 - 21.7	2.52 - 10.6	2.00 - 24.07	19.3 - 38.8	114 - 308	4.75 - 12.8	1.46 - 13.9	19.5 - 101	162 - 439	0.53 - 3.05	370 - 1031	1.19 - 5.70	25.8 - 82.3	1.07 - 3.43	608 - 1939
		[10.6]	[6.27]	[22.00]	[28.2]	[190]	[7.93]	[3.08]	[43.6]	[263]	[0.97]	[591]	[2.64]	[49.0]	[2.04]	[1023]

Table 91 Multiple Dose Pharmacokinetic Metrics of Paliperidone Enantiomers after Administration of Paliperidone OROS 3 mg by Age – Study SCH-1011

Analyte	Pop	Cmax,ss (ng/ml)	Cmin,ss (ng/ml)	tmax,ss (h)	t½ (h)	AUCT (ng/ml x hr^{-1})	Cavg,ss (ng/ml)	AccRatio-	FI%	CLss/F (ml/min)	AUCT/ AUCInf	Vdss/F,u (L)	Cmax,ss,u (ng/ml)	AUCT,u (ng/ml x hr^{-1})	Cavg,ss,u (ng/ml)	CLss,u/F (ml/min)
R078543 (+)-Pal	elderly subjects (75 - 85 years old)	7	7	7	6	7	7	7	7	7	7	6	7	7	7	7
		8.03 ± 3.54 (44.1) 4.87 - 14.6 [6.52]	5.22 ± 2.45 (46.9) 3.28 - 9.84 [4.60]	19.30 ± 8.11 (42.0) 6.00 - 24.03 [24.00]	41.0 ± 9.13 (22.3) 31.6 - 53.2 [39.4]	157 ± 69.3 (44.1) 93.9 - 289 [138]	6.55 ± 2.88 (44.0) 3.91 - 12.0 [5.74]	3.25 ± 0.841 (25.9) 2.30 - 4.44 [3.24]	43.5 ± 10.9 (25.0) 26.3 - 59.9 [41.3]	181 ± 62.2 (34.3) 86.4 - 266 [182]	0.78 ± 0.20 (25.9) 0.54 - 1.08 [0.81]	638 ± 262 (41.1) 324 - 981 [632]	1.34 ± 0.541 (40.3) 0.879 - 2.12 [1.12]	26.2 ± 10.2 (39.1) 17.0 - 42.0 [21.6]	1.09 ± 0.426 (39.1) 0.708 - 1.75 [0.900]	1062 ± 32 (31.0) 595 - 146 [1157]
	elderly subjects (>= 65 & <75 years old)	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19
		7.87 ± 2.02 (25.7) 4.30 - 12.3 [7.61]	4.98 ± 1.44 (28.8) 3.07 - 7.89 [4.86]	16.69 ± 8.69 (52.1) 4.00 - 24.07 [24.00]	35.3 ± 7.30 (20.7) 26.5 - 52.7 [34.3]	153 ± 37.8 (24.7) 87.2 - 226 [159]	6.37 ± 1.58 (24.7) 3.63 - 9.43 [6.62]	3.79 ± 1.37 (36.0) 2.34 - 6.74 [3.26]	45.6 ± 16.8 (36.8) 25.4 - 75.5 [38.6]	174 ± 48.2 (27.7) 110 - 287 [157]	1.01 ± 0.42 (41.1) 0.48 - 2.18 [0.85]	534 ± 191 (35.8) 314 - 1014 [455]	1.32 ± 0.274 (20.7) 0.882 - 1.87 [1.24]	25.6 ± 5.30 (20.7) 17.9 - 38.0 [25.5]	1.07 ± 0.221 (20.7) 0.745 - 1.58 [1.06]	1011 ± 19 (18.8) 659 - 139 [982]
	elderly subjects (>=65 years old)	26	26	26	25	26	26	26	26	26	26	25	26	26	26	26
		7.92 ± 2.44 (30.8) 4.30 - 14.6 [7.50]	5.04 ± 1.71 (34.0) 3.07 - 9.84 [4.77]	17.39 ± 8.46 (48.6) 4.00 - 24.07 [24.00]	36.7 ± 7.97 (21.7) 26.5 - 53.2 [34.7]	154 ± 46.8 (30.3) 87.2 - 289 [150]	6.42 ± 1.95 (30.3) 3.63 - 12.0 [6.23]	3.65 ± 1.25 (34.4) 2.30 - 6.74 [3.25]	45.1 ± 15.2 (33.8) 25.4 - 75.5 [40.4]	176 ± 51.1 (29.0) 86.4 - 287 [168]	0.95 ± 0.38 (40.1) 0.48 - 2.18 [0.84]	559 ± 209 (37.4) 314 - 1014 [530]	1.33 ± 0.353 (26.6) 0.879 - 2.12 [1.24]	25.8 ± 6.75 (26.2) 17.0 - 42.0 [24.2]	1.07 ± 0.281 (26.1) 0.708 - 1.75 [1.01]	1025 ± 22 (22.4) 595 - 146 [1035]
	young subjects (18–45 years old)	28	28	28	28	28	28	28	28	28	27	28	28	28	28	28
		6.30 ± 1.97 (31.2) 2.98 - 12.5 [6.00]	3.79 ± 1.23 (32.4) 1.49 - 6.28 [3.57]	16.97 ± 8.35 (49.2) 2.00 - 24.07 [22.01]	29.3 ± 5.60 (19.1) 19.0 - 40.7 [28.7]	117 ± 33.0 (28.3) 63.2 - 178 [112]	4.86 ± 1.38 (28.3) 2.63 - 7.44 [4.66]	3.15 ± 1.85 (58.9) 1.39 - 10.9 [2.81]	52.4 ± 21.4 (40.9) 23.0 - 103 [45.2]	232 ± 68.8 (29.6) 140 - 396 [224]	1.07 ± 0.50 (46.8) 0.56 - 2.86 [0.97]	575 ± 155 (27.0) 334 - 846 [523]	1.19 ± 0.391 (32.8) 0.486 - 2.25 [1.11]	22.1 ± 6.76 (30.6) 10.3 - 36.4 [21.3]	0.92 ± 0.28 (30.6) 0.429 - 1.52 [0.886]	1248 ± 42 (33.8) 686 - 242 [1178]
R078544 (-)-Pal	elderly subjects (75 - 85 years old)	7	7	7	6	7	7	7	7	7	7	6	7	7	7	7
		4.77 ± 1.76 (37.0) 3.16 - 8.09 [4.02]	3.09 ± 1.19 (38.4) 2.09 - 5.41 [2.79]	19.30 ± 8.11 (42.0) 6.00 - 24.03 [24.00]	42.5 ± 10.4 (24.4) 31.7 - 58.7 [40.9]	93.3 ± 34.2 (36.7) 64.9 - 159 [81.8]	3.89 ± 1.42 (36.7) 2.70 - 6.63 [3.41]	3.68 ± 0.910 (24.8) 2.66 - 4.91 [3.65]	43.2 ± 11.4 (26.4) 29.2 - 60.6 [40.4]	293 ± 83.1 (28.3) 157 - 385 [306]	0.80 ± 0.21 (26.8) 0.54 - 1.11 [0.81]	1079 ± 480 (44.5) 592 - 1867 [968]	1.60 ± 0.471 (29.4) 1.24 - 2.36 [1.37]	31.3 ± 8.95 (28.6) 25.2 - 46.5 [26.5]	1.30 ± 0.372 (28.5) 1.05 - 1.94 [1.10]	845 ± 192 (22.8) 538 - 992 [944]
	elderly subjects (>= 65 & <75 years old)	19	19	19	19	19	19	19	19	19	18	19	19	19	19	19
		4.93 ± 1.32 (26.8) 2.64 - 8.26 [5.11]	3.15 ± 0.908 (28.9) 1.83 - 4.72 [3.23]	15.58 ± 9.20 (59.0) 4.00 - 24.07 [24.00]	34.1 ± 6.50 (19.0) 24.8 - 48.8 [33.3]	95.0 ± 24.0 (25.3) 54.5 - 134 [99.1]	3.96 ± 1.00 (25.3) 2.27 - 5.59 [4.13]	4.35 ± 1.45 (33.4) 2.64 - 7.47 [3.72]	45.2 ± 18.3 (40.4) 21.4 - 75.8 [45.8]	282 ± 81.8 (29.0) 186 - 459 [252]	0.95 ± 0.32 (33.7) 0.47 - 1.69 [0.85]	843 ± 324 (38.5) 511 - 1639 [772]	1.64 ± 0.352 (21.5) 1.00 - 2.33 [1.64]	31.5 ± 6.79 (21.5) 20.7 - 43.6 [34.0]	1.31 ± 0.282 (21.5) 0.861 - 1.81 [1.42]	831 ± 194 (23.4) 574 - 1210 [736]
	elderly subjects (>=65 years old)	26	26	26	25	26	26	26	26	26	25	25	26	26	26	26
		4.89 ± 1.42 (29.0) 2.64 - 8.26 [4.89]	3.13 ± 0.966 (30.8) 1.83 - 5.41 [3.12]	16.58 ± 8.92 (53.8) 4.00 - 24.07 [24.00]	36.1 ± 8.20 (22.7) 24.8 - 58.7 [33.4]	94.5 ± 26.4 (27.9) 54.5 - 159 [96.4]	3.94 ± 1.10 (27.9) 2.27 - 6.63 [4.02]	4.17 ± 1.35 (32.3) 2.64 - 7.47 [3.69]	44.6 ± 16.5 (36.9) 21.4 - 75.8 [43.1]	285 ± 80.6 (28.3) 157 - 459 [259]	0.91 ± 0.30 (32.8) 0.47 - 1.69 [0.84]	900 ± 371 (41.2) 511 - 1867 [793]	1.63 ± 0.378 (23.2) 1.00 - 2.36 [1.62]	31.5 ± 7.24 (23.0) 20.7 - 46.5 [30.9]	1.31 ± 0.301 (23.0) 0.861 - 1.94 [1.29]	835 ± 190 (22.7) 538 - 1210 [810]
	young subjects (18–45 years old)	28	28	28	28	28	28	28	28	28	27	28	28	28	28	28
		4.39 ± 1.43 (32.6) 2.50 - 9.20 [4.24]	2.79 ± 0.846 (30.3) 1.03 - 4.40 [2.73]	15.72 ± 8.50 (54.1) 4.00 - 24.07 [20.00]	27.4 ± 4.56 (16.6) 18.1 - 36.6 [27.6]	82.7 ± 22.5 (27.2) 44.0 - 132 [81.3]	3.45 ± 0.94 (27.3) 1.83 - 5.51 [3.39]	4.07 ± 3.45 (85.0) 1.61 - 20.4 [3.45]	46.5 ± 22.2 (47.8) 13.3 - 98.1 [41.4]	325 ± 93.2 (28.6) 189 - 568 [308]	1.08 ± 0.57 (53.1) 0.50 - 3.35 [0.92]	764 ± 228 (29.8) 407 - 1339 [699]	1.49 ± 0.556 (37.3) 0.692 - 3.45 [1.48]	28.0 ± 9.05 (32.3) 13.9 - 49.6 [27.4]	1.17 ± 0.377 (32.3) 0.580 - 2.07 [1.14]	991 ± 342 (34.5) 504 - 1796 [914]

Figure 80 Single Dose AUCinf vs. Age – Study SCH-1011

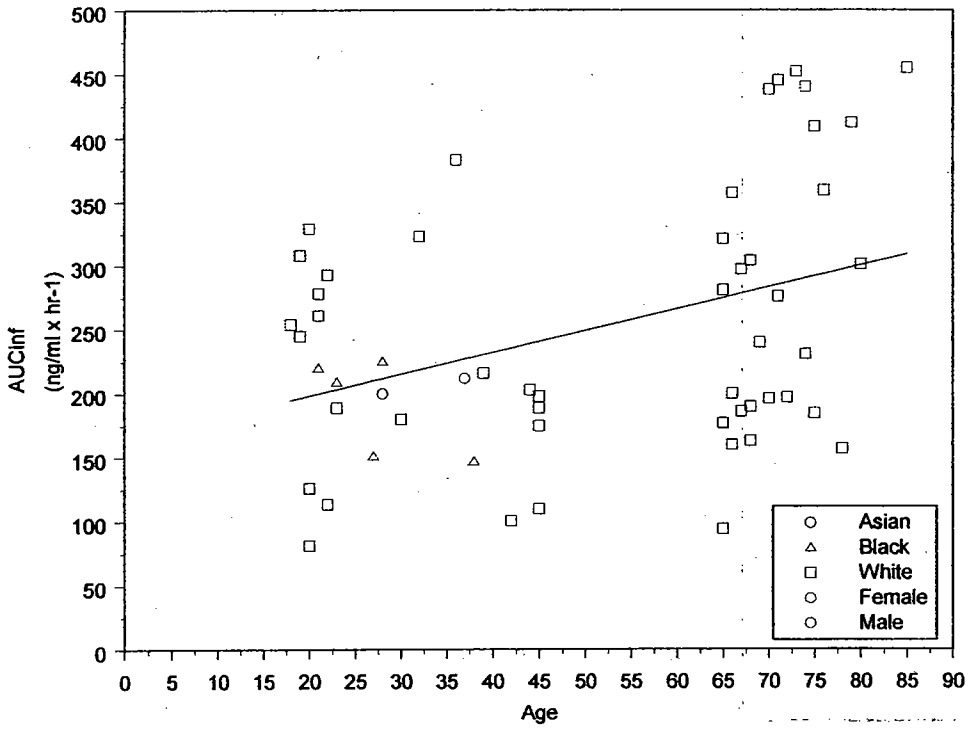


Figure 81 Single Dose Unbound AUCinf vs. Age – Study SCH-1011

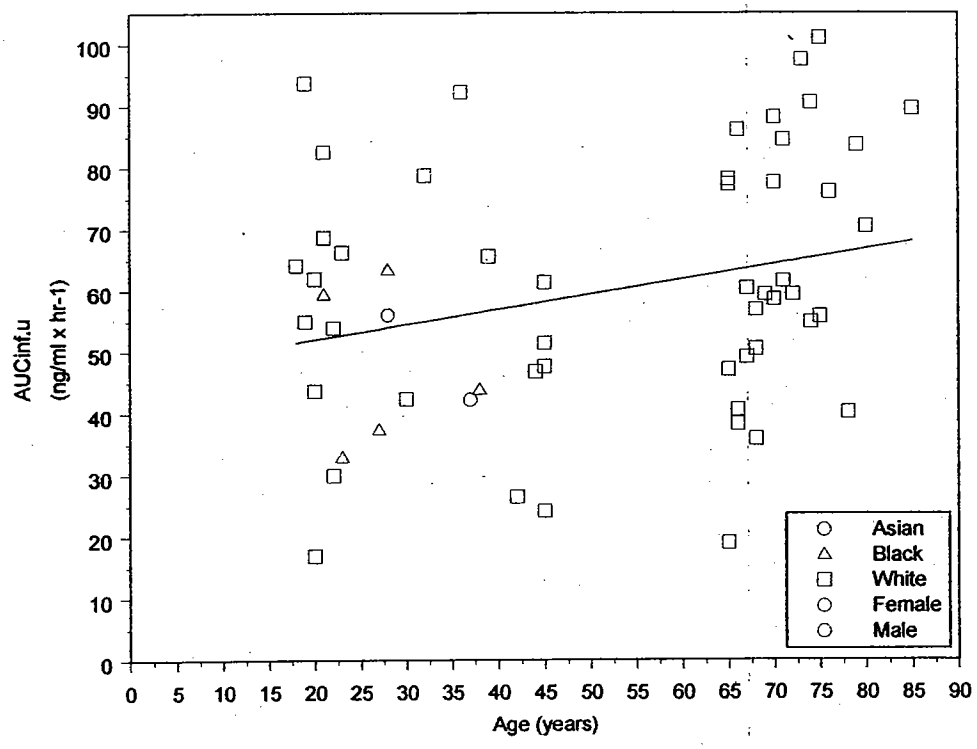


Figure 82 Steady-State AUCtau vs. Age – Study SCH-1011

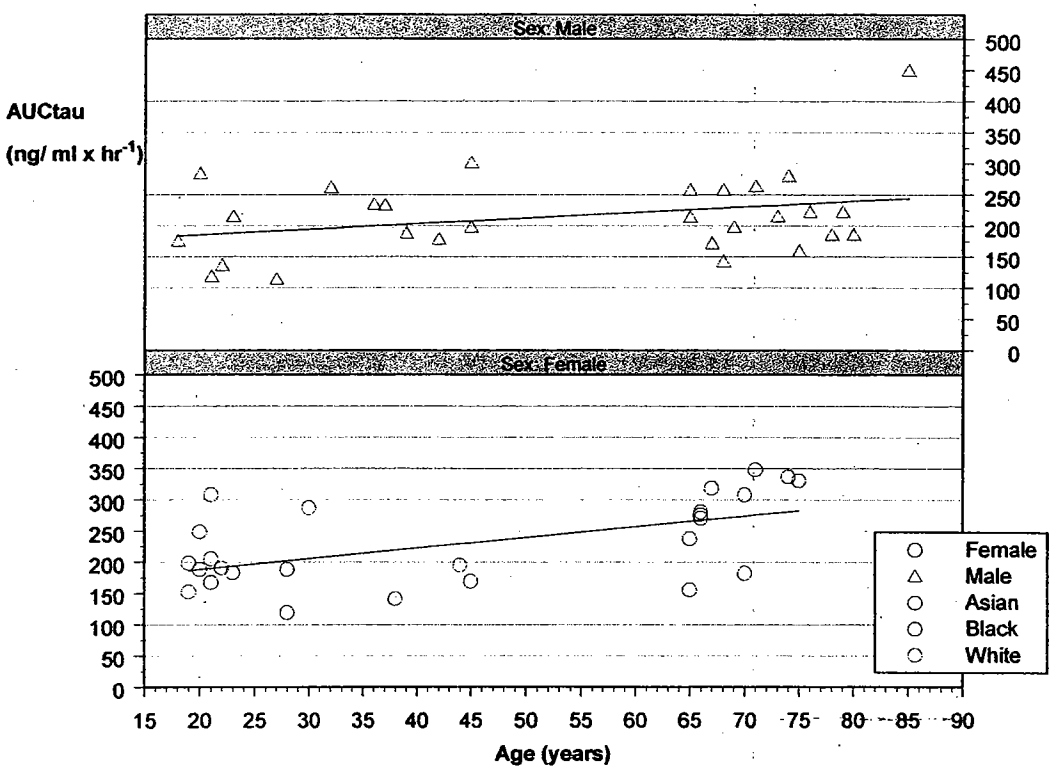
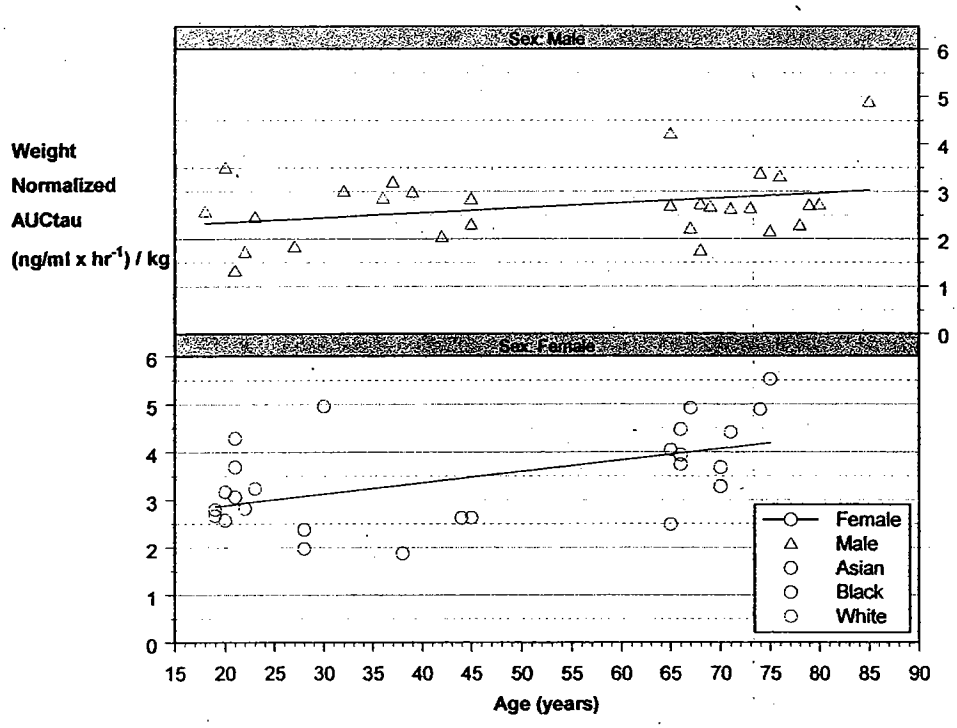


Figure 83 Weight Normalized AUCtau vs. Age by Gender – Study SCH-1011



3.10.8.2 Gender

No specific gender effect study was performed, however inspection of the data from the age effect study, (SCH-1011), indicates that there is unlikely to be a significant gender effect on pharmacokinetics, (see Figure 80 to Figure 83). There was insufficient review time to extract the data and evaluate the effect of gender from the data available in the other studies submitted.

Table 92 Comparison of Pharmacokinetic Parameter Summary Statistics for Male and Female Subjects by Age – Study SCH-1011

Sex	Age Group	Race	N	Age (yrs)	Weight (kg)	Cmax (ng/ml)	Tmax (hrs)	AUClast (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	AUCextrap (%)	AUCratio	Half-life (hrs)	Cl/F (ml/min)	Vd/F (L)	fu	Cmax,u (ng/ml)	AUCinf,u (ng/ml x hr^{-1})	Clu/F (ml/min)	AUCt (ng/ml x hr^{-1})	WtNl.AUCt (ng/ml x hr^{-1} / kg
Female	Young	Asian	1	28	80	7.1	24	186	200	7.02	1.41	13.4	250	290	0.28	1.96	56	893	189	2.4
		Black	3	29.0 ± 8.5 (29.5) 21.0 - 38.0 [28.0]	64.0 ± 10.8 (16.9) 55.0 - 76.0 [61.0]	5.6 ± 1.7 (30.5) 3.8 - 6.7 [6.5]	24.0 ± 0.0 (0.1) 24.0 - 24.0 [24.0]	181 ± 40 (22.2) 135 - 207 [202]	197 ± 44 (22.1) 147 - 225 [220]	8.1 ± 2.3 (27.8) 5.9 - 10.4 [8.1]	1.2 ± 0.1 (8.3) 1.1 - 1.3 [1.2]	16.1 ± 1.7 (10.6) 14.4 - 17.8 [16.0]	263 ± 67 (25.4) 222 - 340 [227]	366 ± 96 (26.2) 284 - 471 [342]	0.3 ± 0.0 (5.0) 0.3 - 0.3 [0.3]	1.5 ± 0.4 (26.8) 1.1 - 1.8 [1.7]	55.5 ± 10.4 (18.6) 43.8 - 63.4 [59.4]	924 ± 190 (20.6) 789 - 1142 [842]	143 ± 24 (16.8) 120 - 168 142]	2.3 ± 0.7 (28.7) 1.9 - 3.1 [2.0]
		White	11	25.8 ± 9.7 (37.7) 19.0 - 45.0 [21.0]	66.7 ± 8.9 (13.4) 55.0 - 79.0 [68.0]	5.7 ± 2.3 (40.0) 3.2 - 10.1 [5.2]	21.3 ± 4.7 (22.2) 9.0 - 24.1 [24.0]	192 ± 75 (39.1) 69 - 292 [186]	207 ± 77 (37.4) 82 - 308 [203]	8.1 ± 3.4 (42.2) 2.1 - 14.9 [8.4]	1.4 ± 0.3 (19.5) 0.9 - 1.8 [1.4]	20.3 ± 6.1 (30.0) 14.8 - 34.7 [17.4]	287.4 ± 143 (49.8) 163 - 613 [247]	475 ± 183 (38.5) 246 - 827 [489]	0.3 ± 0.1 (21.7) 0.2 - 0.4 [0.2]	1.5 ± 0.7 (46.6) 0.7 - 3.1 [1.5]	53.9 ± 23.1 (42.8) 16.8 - 93.7 [53.9]	1173 ± 727 (62.0) 533 - 2971 [928]	212 ± 49 (22.9) 153 - 308 [196]	3.2 ± 0.8 (24.5) 2.6 - 4.9 [2.8]
		All	15	26.6 ± 8.9 (33.6) 19.0 - 45.0 [22.0]	67.1 ± 9.4 (14.0) 55.0 - 80.0 [68.0]	5.8 ± 2.1 (35.8) 3.2 - 10.1 [5.9]	22.1 ± 4.2 (19.0) 9.0 - 24.1 [24.0]	189 ± 65 (34.5) 69 - 292 [186]	204 ± 68 (33) 82 - 308 [203]	8.0 ± 3.0 (37.6) 2.1 - 14.9 [8.1]	1.4 ± 0.2 (17.8) 0.9 - 1.8 [1.3]	19.0 ± 5.7 (29.9) 13.4 - 34.7 [16.9]	280 ± 124 (44.3) 163 - 613 [247]	440 ± 170 (38.6) 246 - 827 [366]	0.3 ± 0.0 (18.5) 0.2 - 0.4 [0.3]	1.5 ± 0.6 (40.4) 0.7 - 3.1 [1.6	54.4 ± 19.9 (36.6) 16.8 - 93.7 [54.9]	1105 ± 630 (5.07) 533 - 2971 [910]	197 ± 51 (25.8) 120 - 308 [189]	3.0 ± 0.8 (27.6) 1.9 - 4.9 [2.8]
	Elderly	White	13	69.1 ± 3.5 (5.0) 65.0 - 75.0 [70.0]	68.2 ± 8.2 (12.1) 56.0 - 84.0 [69.0]	6.6 ± 2.9 (43.5) 2.6 - 11.7 [6.9]	23.9 ± 0.6 (2.3) 22.0 - 24.1 [24.0]	485 ± 748 (154.3) 141 - 2841 [274]	282 ± 106 (37.4) 160 - 445 [256]	6.9 ± 2.7 (39.3) 2.8 - 12.0 [6.6]	1.6 ± 0.2 (13.1) 1.2 - 1.9 [1.6]	29.2 ± 6.1 (20.8) 23.1 - 43.7 [28.0]	200 ± 70 (35.1) 112 - 312 [197]	525 ± 279 (53.2) 257 - 1178 [396]	0.2 ± 0.0 (16.1) 0.2 - 0.3 [0.2]	1.5 ± 0.5 (35.5) 0.7 - 2.3 [1.6]	66.3 ± 20.5 (30.9) 38.2 - 101.0 [59.8]	827 ± 268 (32.4) 494 - 1310 [836]	277 ± 63 (22.6) 156 - 348 [281]	4.1 ± 0.8 (20.6) 2.5 - 5.5 [4.0]
Male	Young	Asian	1	37	73	5.64	22	193	212	9.01	1.7	17.2	235	350	0.198	1.1	42.2	1185	233	3.19
		Black	3	23.7 ± 3.1 (12.9) 21.0 - 27.0 [23.0]	79.3 ± 15.0 (19.0) 62.0 - 89.0 [87.0]	4.2 ± 3.5 (85.1) 0.9 - 7.9 [3.6]	18.4 ± 8.1 (44.3) 9.0 - 24.0 [22.0]	113 ± 96 (84.7) 8 - 196 [135]	180 ± 41 (22.8) 151 - 209 [180]	8.1 ± 2.8 (34.9) 6.1 - 10.1 [8.1]	1.5 ± 0.2 (11.9) 1.4 - 1.6 [1.5]	16.7 ± 1.5 (8.9) 15.6 - 17.7 [16.7]	286 ± 65 (22.7) 240 - 332 [286]	417 ± 131.5 (31.5) 324 - 510 [417]	0.2 ± 0.1 (31.8) 0.2 - 0.2 [0.2]	0.8 ± 0.5 (68.2) 0.2 - 1.2 [0.9]	35.2 ± 3.2 (9.1) 32.9 - 37.4 [35.2	1430 ± 129 (9.1) 1338 - 1521 [1430]	149 ± 57 (38.1) 114 - 214 [118]	1.9 ± 0.6 (30.3) 1.3 - 2.5 [1.8]
		White	11	32.9 ± 11.4 (34.6) 18.0 - 45.0 [36.0]	79.5 ± 12.5 (15.8) 63.0 - 106.0 [81.0]	5.4 ± 2.3 (42.6) 2.5 - 8.6 [4.6]	22.6 ± 3.6 (15.8) 12.1 - 24.0 [24.0]	283 ± 267 (94.3) 88 - 1041 [192]	228 ± 93 (40.9) 101 - 383 [207]	10.6 ± 4.8 (45.3) 3.1 - 19.2 [10.4]	1.5 ± 0.2 (12.0) 1.2 - 1.7 [1.5]	25.0 ± 7.4 (29.4) 13.7 - 42.8 [24.8]	260 ± 121 (46.6) 130 - 496 [242]	540 ± 247 (45.7) 287 - 1059 [510]	0.3 ± 0.0 (13.8) 0.2 - 0.3 [0.3]	1.3 ± 0.5 (34.6) 0.6 - 2.0 [1.4]	57.9 ± 20.2 (34.8) 26.4 - 92.2 [61.6]	993 ± 444 (44.7) 542 - 1894 [812]	217 ± 56 (25.6) 136 - 301 [198]	2.6 ± 0.5 (20.6) 1.7 - 3.5 [2.8]
		All	16	31.3 ± 10.5 (33.6) 18.0 - 45.0 [32.0]	79.0 ± 12.1 (15.4) 62.0 - 106.0 [81.0]	5.2 ± 2.4 (46.8) 0.9 - 8.6 [4.6]	21.7 ± 4.6 (21.4) 9.0 - 24.0 [24.0]	243 ± 239 (98.5) 8 - 1041 [192]	220 ± 84 (38.1) 101 - 383 [209]	10.1 ± 4.4 (43.1) 3.1 - 19.2 [10.1]	1.5 ± 0.2 (11.6) 1.2 - 1.7 [1.5]	23.1 ± 7.3 (31.7) 13.7 - 42.8 [23.9]	262 ± 108 (41) 130 - 496 [240]	507 ± 227 (44.8) 287 - 1059 [499]	0.2 ± 0.0 (18.2) 0.2 - 0.3 [0.3]	1.2 ± 0.5 (41.3) 0.2 - 2.0 [1.1]	53.2 ± 19.7 (37.1) 26.4 - 92.2 [51.4]	1072 ± 420 (39.1) 542 - 1894 [973]	202 ± 60 (29.4) 114 - 301 [198]	2.5 ± 0.6 (25.4) 1.3 - 3.5 [2.6]
	Elderly	White		72.4 ± 5.8 (7.9) 65.0 - 85.0 [71.0]	80.2 ± 9.9 (12.3) 61.0 - 100.0 [81.0]	5.4 ± 2.0 (37.6) 2.1 - 8.2 [5.7]	22.4 ± 3.0 (13.5) 12.0 - 24.1 [24.0]	388 ± 548.7 (141.6) 88 - 2481 [275.0]	454 ± 677 (149.3) 94 - 3041 [301]	11.7 ± 3.9 (33.0) 5.5 - 18.4 [11.8]	1.7 ± 0.1 (8.4) 1.5 - 1.9 [1.7]	34.7 ± 6.4 (18.6) 18.7 - 45.2 [35.9]	296 ± 366 (123.7) 110 - 1651 [181]	856 ± 1127 (131.6) 310 - 5161 [585]	0.2 ± 0.0 (14.5) 0.2 - 0.3 [0.2]	1.2 ± 0.4 (30.2) 0.4 - 1.8 [1.3]	64.2 ± 21.5 (33.5) 18.9 - 97.5 [61.5]	1384 ± 1978 (142.9) 513 - 8801 [813]	228 ± 73 (32.1) 142 - 449 [214]	2.9 ± 0.8 (28.1) 1.8 - 4.9 [2.7]

3.10.8.3 Race / Ethnicity

Only one study specifically addressed the effect of race /ethnicity on paliperidone pharmacokinetics study P01-1005. Study P01-1005 compared the single and multiple dose pharmacokinetics of paliperidone and its enantiomers in Caucasians and Japanese.

Single and multiple dose pharmacokinetics of 3 mg doses were examined as well as the pharmacokinetics of 6 mg single doses.

Average values for pharmacokinetic metrics were similar in Caucasians and Japanese, for the 3 mg and 6 mg single doses Japanese subjects had slightly higher mean values due to outliers, whereas for the 3 mg multiple dose Caucasians had slightly higher values due to outliers, (Table 93, Table 94, and Table 95).

Another study, P01-1006, also enrolled Japanese subjects, but was a food effect study and did not include another racial or ethnic group.

There was insufficient review time to extract data by race and ethnicity across other studies.

Table 93 Comparison of Paliperidone and Paliperidone Enantiomer Pharmacokinetics after Single Doses of Paliperidone OROS 3 mg to Caucasians and Japanese- Study P01-1005

Rx	Analyte	Subjects	Cmax (ng/mL)	DNCmax (ng/mL)	Tmax (hr)	t1/2 (hr)	CL/F (mL/min)	AUC0-24h (ng/ml x hr^{-1})	AUC0-48h (ng/ml x hr^{-1})	AUClast (ng/ml x hr^{-1})	DNAUClast (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	DNAUCinf (ng/ml x hr^{-1})	AUCinfRatio* 3mgSD/6mgSD	Cavgss (ng/ml)	Cminss (ng/ml)	AUC0-24 (ng/ml x hr^{-1})	FI (%)	AccRat
3 mg SD	Pal	Caucasian	24		23	22	24	24	24	22		22							
			5.6 ± 2.8 (50.8) 1.5 - 11.8 [5.4]		25.0 ± 2.9 (11.6) 20.0 - 36.0 [24.0]	20.8 ± 4.82 (23.2) 11.1 - 29.3 [20.7]	306 ± 194 (63.5) 97.0 - 864 [260]	59.4 ± 27.4 (46.1) 10.1 - 121 [61.5]	137 ± 71.4 (52.0) 16.6 - 287 [133]	185 ± 109 (59.1) 13.9 - 450 [171]		218 ± 114 (52.5) 57.9 - 516 [192]		0.904 ± 0.306 (33.9) 0.451 - 1.59 [0.817]					
		Japanese	**23**		**23**	**24**	**23**	**23**	**23**	**23**		**23**		**21**					
			6.6 ± 2.2 (33.1) 3.1 - 10.7 [6.2]		22.7 ± 4.3 (18.8) 9.0 - 27.2 [24.0]	19.6 ± 3.4 (17.6) 14.1 - 24.5 [21.3]	237 ± 97.2 (41.0) 121 - 490 [213]	79.9 ± 24.3 (30.5) 48.4 - 139 [75.1]	174 ± 53.8 (30.9) 86.1 - 283 [166]	223 ± 77.6 (34.8) 92.3 - 384 [217]		241 ± 84.2 (34.9) 102 - 414 [235]		0.962 ± 0.342 (35.6) 0.262 - 1.78 [0.981]					
	R078543 (+)-Pal	Caucasian	24		24	23	22	24	24	24		22		22					
			3.4 ± 1.9 (55.5) 0.8 - 7.6 [3.0]		24.7 ± 2.9 (11.7) 20.0 - 36 [24.0]	22.3 ± 4.4 (19.9) 15.7 - 33 [22.1]	263 ± 160 (61.0) 83.5 - 735 [244]	37.0 ± 18.0 (48.5) 7.83 - 81.3 [35.8]	81.4 ± 45.5 (55.8) 12.0 - 181 [74.5]	108 ± 67.4 (62.5) 10.6 - 266 [91.5]		127 ± 70.0 (55.0) 34.0 - 299 [103]		0.915 ± 0.301 (32.9) 0.470 - 1.53 [0.792]					
		Japanese	23		23	24	23	23	23	23		23		21					
			4.1 ± 1.5 (36.3) 1.9 - 7.5 [4.02		22.8 ± 4.4 (19.1) 9.0 - 27.2 [24.0]	20.0 ± 3.1 (15.6) 13.1 - 24.3 [20.9]	208 ± 98.0 (47.2) 94.1 - 488 [187]	50.3 ± 17.3 (34.4) 27.4 - 90.0 [45.6]	105 ± 37.5 (35.8) 44.3 - 184 [103]	132 ± 51.7 (39.1) 46.9 - 234 [127]		143 ± 58.4 (39.5) 51.3 - 266 [134]		0.967 ± 0.349 (36.1) 0.244 - 1.78 [0.966]					
	R078544 (-)-Pal	Caucasian	24		24	23	22	24	24	24		22		22					
			2.2 ± 1.0 (45.5) 0.62 - 4.4 [2.3]		25.1 ± 2.9 (11.6) 20.0 - 36.0 [24.0]	22.0 ± 4.7 (21.2) 12.9 - 30.6 [21.7]	344 ± 207 (60.1) 115 - 939 [271]	22.3 ± 9.72 (43.5) 2.25 - 40.0 [24.1]	55.9 ± 26.7 (47.7) 4.64 - 112 [57.7]	76.4 ± 43.0 (56.3) 3.31 - 184 [76.0]		93.1 ± 44.2 (47.5) 26.6 - 217 [92.3]		0.909 ± 0.305 (33.5) 0.499 - 1.68 [0.847]					
		Japanese	23		23	24	23	23	23	23		23		21					
			2.5 ± 0.7 (28.9) 1.25 - 3.8 [2.4]		24.2 ± 1.8 (7.3) 20.0 - 27.2 [24.0]	20.2 ± 3.5 (17.1) 14.1 - 25.2 [21.5]	278 ± 96.2 (34.6) 154 - 502 [248]	29.6 ± 7.69 (26.0) 19.1 - 49.4 [26.8]	69.2 ± 18.2 (26.3) 38.5 - 108 [66.5]	90.0 ± 28.3 (31.4) 42.2 - 150 [92.4]		99.4 ± 30.1 (30.3) 49.8 - 163 [101]		0.962 ± 0.331 (34.4) 0.289 - 1.79 [0.993]					

Table 94 Comparison of Paliperidone and Paliperidone Enantiomer Pharmacokinetics after Multiple Dosing of Paliperidone OROS 3 mg to Caucasians and Japanese- Study P01-1005

Rx	Analyte	Subjects	Cmax (ng/mL)	DNCmax (ng/mL)	Tmax (hr)	t1/2 (hr)	CL/F (mL/min)	AUC0-24h (ng/ml x hr^{-1})	AUC0-48h (ng/ml x hr^{-1})	AUClast (ng/ml x hr^{-1})	DNAUClast (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	DNAUCinf (ng/ml x hr^{-1})	AUCinfRatio* 3mgSD/6mgSD	Cavgss (ng/ml)	Cminss (ng/ml)	AUC0-24 (ng/ml x hr^{-1})	FI (%)	AccRati
3 mg MD	Pal	Caucasian	23		23	23	23	23							23	23+	23	23	21
			12.5 ± 7.0 (56.2) 4.8 - 34.0 [11.4]		13.2 ± 8.9 (67.9) 2.0 - 24.1 [9.0]	27.6 ± 4.2 (15.2) 18.0 - 35.7 [27.4]	265 ± 128 (48.5) 73.2 - 525 [244]	243 ± 140 (57.5) 95.3 - 683 [205]							10.1 ± 5.8 (57.6) 4.0 - 28.5 [8.6]	7.9 ± 4.6 (58.3) 3.2 - 22.0 [6.9]	45.8 ± 18.4 (40.1) 24.6 - 95.0 [41.2]	5.1 ± 5.0 (98.1) 1.6 - 26.6 [3.8]	1.2 ± 0.5 (39.0) 0.6 - 2.0 [1.1]
		Japanese	23		23	23	23	23							23	23	23	22	22
			11.8 ± 4.0 (33.5) 6.6 - 21.6 [11.5]		14.3 ± 9.4 (65.8) 2.0 - 24.0 [12.0]	25.4 ± 3.5 (13.8) 18.4 - 32.5 [25.5]	242 ± 80.8 (33.4) 125 - 398 [225]	230 ± 78.2 (33.9) 126 - 401 [222]							9.6 ± 3.3 (33.9) 5.23 - 16.7 [9.3]	7.9 ± 2.8 (35.3) 3.8 - 13.5 [7.6]	42.5 ± 12.6 (29.8) 20.6 - 66.1 [42.2]	3.0 ± 0.9 (29.9) 1.3 - 4.7 [2.9]	1.0 ± 0.3 (31.1) 0.5 - 1.7 [0.9]
	R078543 (+)-Pal	Caucasian	23		23	23	23	23							23	23	23	23	21
			7.5 ± 4.5 (60.8) 2.5 - 21.7 [6.9]		12.7 ± 9.2 (72.3) 2.0 - 24.1 [9.0]	28.3 ± 3.6 (12.9) 23.0 - 35.8 [27.6]	238 ± 124 (52.1) 57.8 - 501 [197]	141 ± 89.6 (63.5) 49.9 - 432 [127]							5.9 ± 3.7 (63.5) 2.1 – [5.3]	4.4 ± 3.0 (68.8) BQL – [3.9]	52.7 ± 26.0 (49.3) 30.1 – [44.7]	4.5 ± 3.9 (86.1) 1.4 – [3.4]	1.2 ± 0.4 (38.6) 0.61 – [1.1]
		Japanese	23		23	23	23	23							23	23	23	22	22
			7.1 ± 2.4 (34.2) 3.9 - 12.0 [7.3]		14.4 ± 9.3 (64.4) 2.0 - 24.0 [12.0]	26.2 ± 2.9 (11.0) 18.7 - 32.5 [26.3]	209 ± 75.2 (36.0) 116 - 365 [195]	135 ± 47.0 (34.8) 68.4 - 215 [128]							5.6 ± 2.0 (34.8) 2.8 – 9.0 [5.4]	4.5 ± 1.7 (37.2) 2.0 - 7.9 [4.4]	47.6 ± 14.6 (30.6) 21.3 - 72.7 [47.2]	2.8 ± 0.8 (30.6) 1.2 - 4.3 [2.8]	1.0 ± 0.3 (31.4) 0.5 - 1.6 [0.9]
	R078544 (-)-Pal	Caucasian	23		23	23	23	23							23	23	23	23	21
			5.1 ± 2.6 (50.3) 2.25 - 12.3 [4.3]		13.3 ± 8.9 (66.7) 2.0 - 24.1 [9.0]	27.3 ± 4.4 (16.2) 17.9 - 35.7 [26.5]	303 ± 135 (44.4) 99.7 - 551 [270]	102 ± 50.8 (50.1) 45.4 - 251 [92.8]							4.2 ± 2.1 (50.1) 1.9 - 10.4 [3.9]	3.4 ± 1.6 (47.8) 1.5 - 8.2 [3.25]	39.1 ± 12.4 (31.8) 22.0 - 77.1 [37.1]	6.4 ± 9.0 (139) 1.9 - 46.7 [4.3]	1.2 ± 0.5 (38.5) 0.6 - 1.9 [1.1]
		Japanese	23		23	23	23	23							23	23	23	22	22
			4.8 ± 1.6 (33.9) 2.8 - 9.6 [4.4]		14.2 ± 9.5 (66.8) 2.0 - 24.0 [9.0]	25.4 ± 3.5 (13.8) 18.2 - 32.7 [25.3]	292 ± 93.7 (32.1) 128 - 504 [272]	95.2 ± 33.6 (35.3) 49.6 - 195 [92.0]							4.0 ± 1.4 (35.3) 2.1 - 8.1 [3.8]	3.3 ± 1.2 (35.0) 1.6 - 6.3 [3.2]	39.1 ± 11.0 (28.0) 21.9 - 66.3 [38.2]	3.2 ± 0.9 (28.5) 1.5 - 5.2 [3.11]	1.0 ± 0.3 (30.8) 0.5 - 1.7 [0.9]

Table 95 Comparison of Paliperidone and Paliperidone Enantiomer Pharmacokinetics after Single Doses of Paliperidone OROS 6 mg to Caucasians and Japanese- Study P01-1005

Rx	Analyte	Subjects	Cmax (ng/mL)	DNCmax (ng/mL)	Tmax (hr)	t1/2 (hr)	CL/F (mL/min)	AUC0-24h (ng/ml x hr^{-1})	AUC0-48h (ng/ml x hr^{-1})	AUClast (ng/ml x hr^{-1})	DNAUClast (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	DNAUCinf (ng/ml x hr^{-1})	AUCinfRatio* 3mgSD/6mgSD	Cavgss (ng/ml)	Cminss (ng/ml)	AUC0-24 (ng/ml x hr^{-1})	FI (%)	AccRatio
6 mg SD	Pal	Caucasian	24	22	24	24	24	24	24	24		24							
			12.7 ± 6.2 (48.7) 4.2 - 31.9 [11.6]	6.4 ± 3.1 (48.7) 2.1 - 16.0 [5.8]	23.8 ± 1.9 (8.1) 16.0 - 27.1 [24.0]	23.6 ± 3.7 (15.8) 14.4 - 29.9 [23.3]	246 ± 132 (53.8) 79.8 - 862 [235]	142 ± 57.8 (40.8) 62.7 - 321 [123]	332 ± 154 (46.2) 115 - 811 [276]	465 ± 228 (49.1) 134 - 1152 [382]	232 ± 114 (49.1) 67.0 - 576 [191]	513 ± 256 (50.0) 151 - 1254 [426]	251 ± 131 (52.2) 75.6 - 627 [206]						
		Japanese	23	23	232	23	23	23	23	23		22							
			13.8 ± 8.2 (59.4) 3.1 - 44.9 [12.3]	6.9 ± 4.2 (60.4) 1.6 - 22.5 [6.2]	22.9 ± 3.8 (16.4) 6.0 - 24.1 [24.0]	22.9 ± 6.5 (28.3) 17.0 - 48.9 [21.0]	216 ± 78.6 (36.5) 48.8 - 357 [210]	173 ± 87.6 (50.7) 50.7 - 481 [150]	375 ± 215 (57.4) 84.3 - 1201 [325]	501 ± 313 (62.5) 122 - 1734 [418]	253 ± 160 (63.2) 61.2 - 867 [213]	565 ± 368 (65.0) 280 - 2049 [476]	286 ± 188 (65.8) 140 - 1025 [243]						
	R078543 (+)-Pal	Caucasian	24	22	24	24	24	24	2	24		24							
			7.8 ± 4.2 (53.8) 2.4 - 21.2 [7.0]	3.9 ± 2.1 (53.8) 1.2 - 10.6 [3.5]	23.1 ± 3.0 (13.0) 12.0 - 27.0 [24.0]	24.6 ± 3.4 (13.8) 18.8 - 33.1 [24.4]	216 ± 118 (54.7) 64.7 - 592 [199]	88.9 ± 39.5 (44.5) 38.1 - 217 [76.8]	198 ± 101 (51.1) 65.7 - 522 [162]	271 ± 146 (54.1) 75.2 - 723 [225]	135 ± 73.2 (54.1) 37.6 - 361 [112]	298 ± 161 (54.1) 84.4 - 773 [252]	145 ± 82.0 (56.5) 42.2 - 386 [117]						
		Japanese	23	23	23	23	23	23	23	23		22							
			8.4 ± 5.3 (62.8) 2.0 - 28.2 [7.6]	4.2 ± 2.7 (63.8) 1.0 - 14.1 [3.8]	21.6 ± 4.4 (20.5) 9.0 - 24.1 [24.0]	23.8 ± 6.7 (28.2) 17.7 - 50.8 [22.2]	189 ± 78.0 (41.1) 39.4 - 334 [184]	108 ± 58.7 (54.1) 32.4 - 312 [88.2]	226 ± 142 (62.6) 52.6 - 766 [199]	297 ± 202 (67.9) 76.1 - 1087 [251]	150 ± 103 (68.5) 38.1 - 544 [126]	335 ± 234 (69.9) 149 - 1268 [272]	169 ± 120 (70.6) 74.7 - 634 [138]						
	R078544 (-)-Pal	Caucasian	24	22	24	24	24	24	24	24		24							
			4.9 ± 2.0 (41.5) 1.8 - 10.7 [4.7]	2.5 ± 1.0 (41.5) 0.91-5.4 [2.4]	24.0 ± 2.2 (8.9) 16.0 - 27.1 [24.0]	24.4 ± 3.9 (16.1) 16.1 - 31.7 [24.0]	282 ± 145 (51.4) 104 - 744 [261]	52.8 ± 18.8 (35.6) 24.6 - 104 [47.5]	134 ± 53.5 (39.9) 49.7 - 288 [121]	193 ± 83.5 (43.2) 58.8 - 429 [173]	96.6 ± 41.7 (43.2) 29.4-214 [86.3]	216 ± 95.2 (44.0) 67.2 - 478 [192]	106 ± 49.0 (46.1) 33.6-239 [90.5]						
		Japanese	23	23	23	23	23	23	23	23		22							
			5.4 ± 3.0 (54.9 1.1 – 16.7 [5.1]	4.2 ± 1.5 (36.4) 1.9 – 7.5 [4.0]	23.3 ± 3.9 (16.8) 6.0 - 27.0 [24.0]	23.1 ± 6.2 (26.8) 17.2 - 46.3 [21.8]	254 ± 82.2 (32.4) 63.5 - 393 [249]	64.3 ± 29.7 (46.3) 18.3 - 169 [57.1]	149 ± 75.6 (50.7) 31.6 - 434 [133]	203 ± 113 (55.8) 46.2 - 647 [181]	103 ± 57.9 (56.5) 23.1-323 [90.6]	231 ± 137 (59.0) 127 - 787 [201]	117 ± 69.8 (59.8) 63.6-394 [105]						

3.10.8.4 Effect of CYP Genotype

Blood was collected for genotyping in a number of studies, including the phase III studies however in most cases the protocol specified that genotyping of all or most drug metabolizing genes would only be performed if there was an indication that this information would have utility, i.e. it would not be analyzed simply for exploratory purposes. However, 7 studies did examine the relationship between genotype or phenotype and these studies are listed in Table 96.

Table 96 Studies Containing Genotyping or Phenotyping Data for Drug Metabolizing Enzymes[a]

Study	How Assessed	CYP2D6	CYP3A4	CYP3A5	UTG1A1	UTG1A6
P01-1007	Phenotyped	ND	—	—	—	—
P01-101	Genotyped	ND	—	—	—	—
P01-1004	Genotyped	ND	—	—	—	—
P01-1006	Genotyped	ND	Not clear. Possibly higher AUC in *1/*1 although this could be due to larger numbers of subjects and variability	no subjects with *1/*1 *1/*3 = *3/*3	—	—
P01-1005	Genotyped	ND		poss lower *1/*1	—	—
SCH-101	Genotyped	ND		poss lower	Possibly lower AUC with *1/*1	—
SCH-102	Genotyped	ND		poss lower *1/*1		Possibly lower AUC with *1/*1

a ND – No Obvious Difference or relationship between PK and genotype
*1/*1/ higher expression

The sponsor clearly focused on the effect of CYP2D6 polymorphisms with some examination of selected CYP3A and UGT1A isozymes. These were most likely examined based on the *in vitro* and *in vivo* metabolism studies.

Figure 84 shows the relationship between CYP2D6 genotype, predicted phenotype and AUC for paliperidone and its enantiomers for study P01-1004. Examination fails to indicate any relationship between genotype and AUC. Similar results were found for CYP2D6 for the other 6 studies in Table 96.

Figure 85 and Figure 86 show the relationship between UGT1A1 genotype, the predicted level of enzyme expression and AUC for paliperidone and its enantiomers for combined data from studies SCH-101 and SCH-102. Examination of the figures indicates a possible lower AUC in some individuals who possess two wild-type alleles (*1/*1), possibly indicating a relationship between genotype and AUC.

Figure 87 and Figure 88 show the relationship between UGT1A6 genotype and AUC for paliperidone and its enantiomers for data from study SCH-102. Examination of the figures indicates a possible lower AUC in some individuals who are homozygous for *1/*1 alleles, possibly indicating a relationship between genotype and AUC.

Figure 89 show the relationship between CYP3A4 genotype and weight and dose normalized AUC for paliperidone and its enantiomers for all available data (studies P01-1005, P01-1006, SCH-101, and SCH-102). Examination of the figure indicates a possible higher AUC in some individuals who are homozygous for *1/*1 alleles, possibly indicating a relationship between genotype and AUC

Figure 90 and Figure 91 show the relationship between CYP3A5 genotype and AUC for paliperidone and its enantiomers for all available data (studies P01-1005, P01-1006, SCH-101, and SCH-102). Examination of the figures indicates trend between lower AUC and number of *1 alleles. Since there is a

known relationship between the number of *1 alleles and the degree of CYP3A5 expression, this is of potential of interest especially since the in vitro and in vivo metabolism indicates that the primary metabolic pathways are mediated by CYP2D and CYP3A. In addition, since CYP2D6 polymorphism does not correlate with AUC, this indicate that these pathways are primarily mediated by CYP3A in vivo. Consequently, it makes sense that the CYP3A5 genotype might effect paliperidone clearance and exposures to a measurable extent.

Figure 92 shows histograms of AUCs by CYP3A5 genotype. Although the numbers are small there may be higher AUCs in subjects who don't express CYP3A5. In addition, Figure 93 indicates that the presence of CYP3A5 effects both enantiomers to a similar extent.

Figure 84 Paliperidone and Enantiomer AUCs vs. CYP2D6 Genotype – Study P01-1004

Figure PK 11: Graphical Representation of the Influence of the CYP2D6 Genotype on Pharmacokinetic Parameters of Paliperidone and its Enantiomers, R078543 and R078 (Continued)

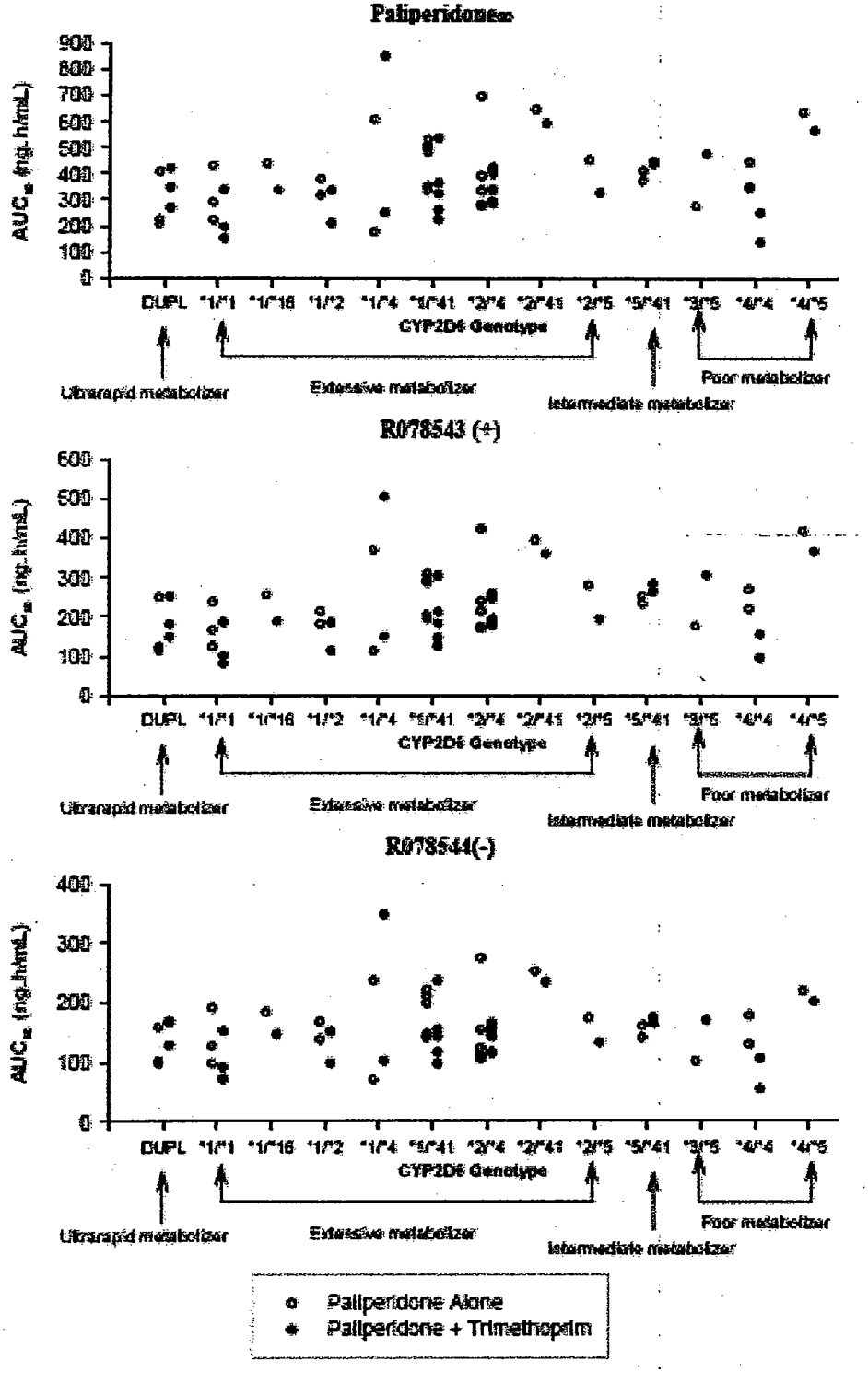


Figure 85 Scatterplot of Paliperidone and Enantiomer AUCs vs. UGT1A1 Genotype - Studies SCH-101 and SCH-102

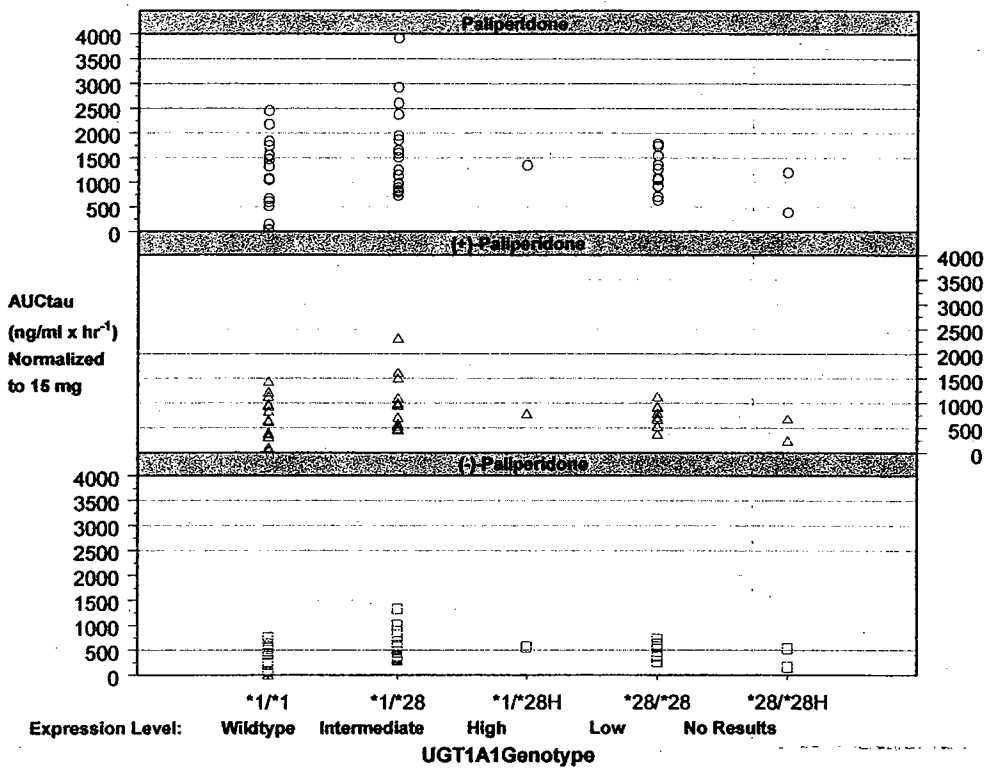


Figure 86 Boxplot of Paliperidone and Enantiomer AUCs vs. UGT1A1 Genotype- Studies SCH-101 and SCH-102

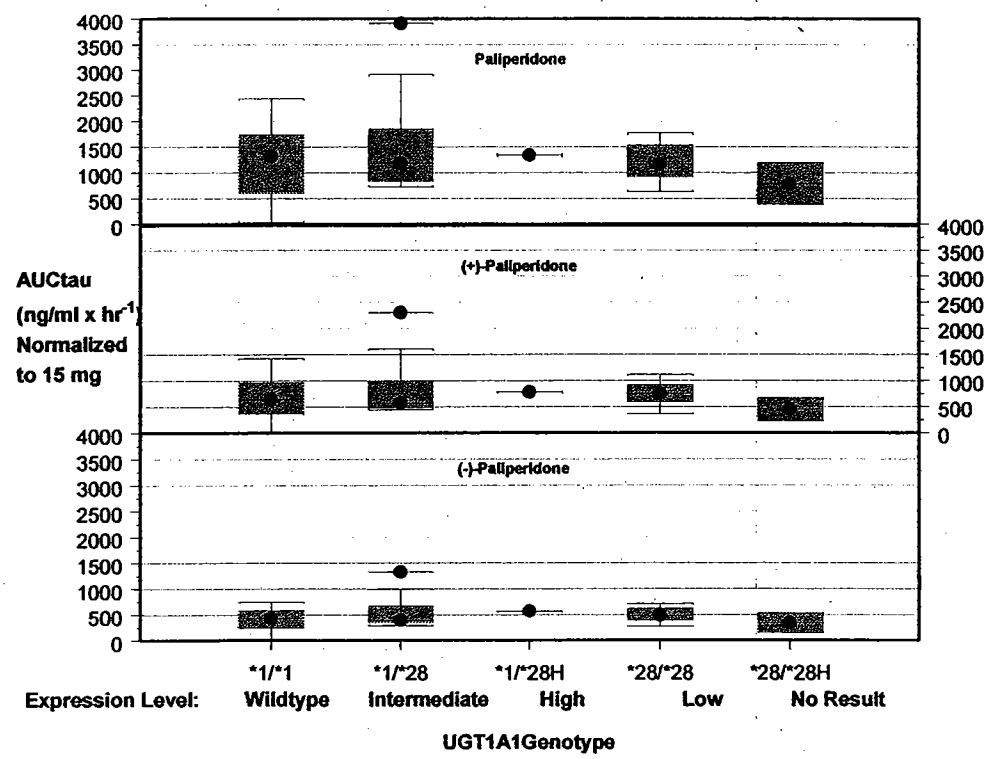


Figure 87 Scatterplot of Paliperidone and Enantiomer AUCs vs. UGT1A6 Genotype – Study SCH-102

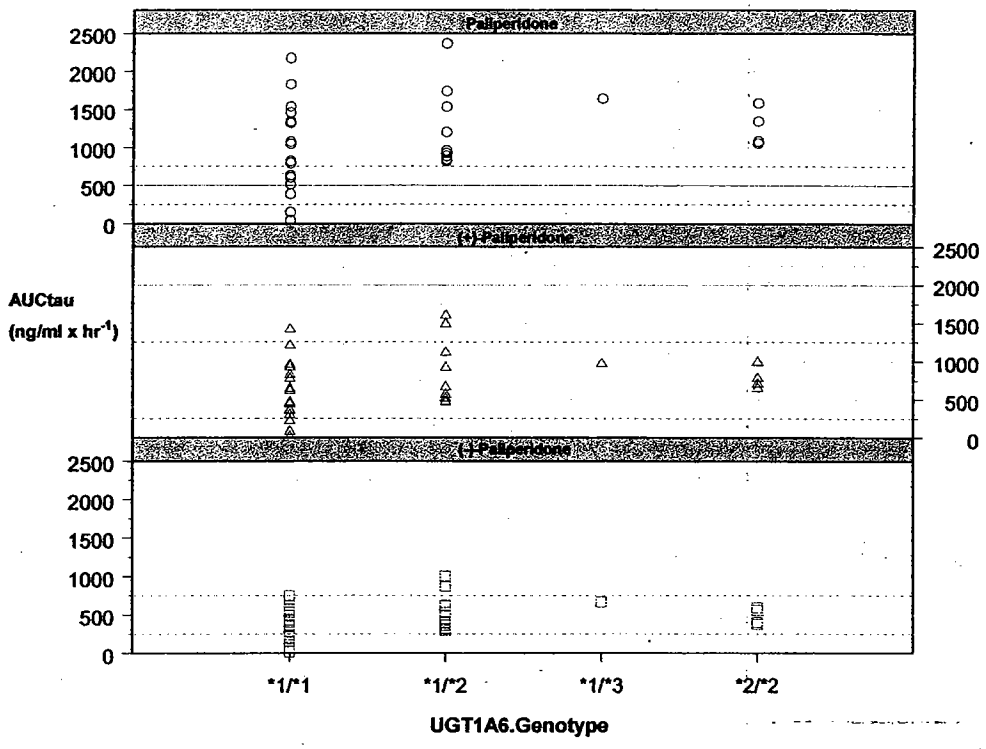


Figure 88 Boxplot of Paliperidone and Enantiomer AUCs vs. UGT1A6 Genotype - Study SCH-102

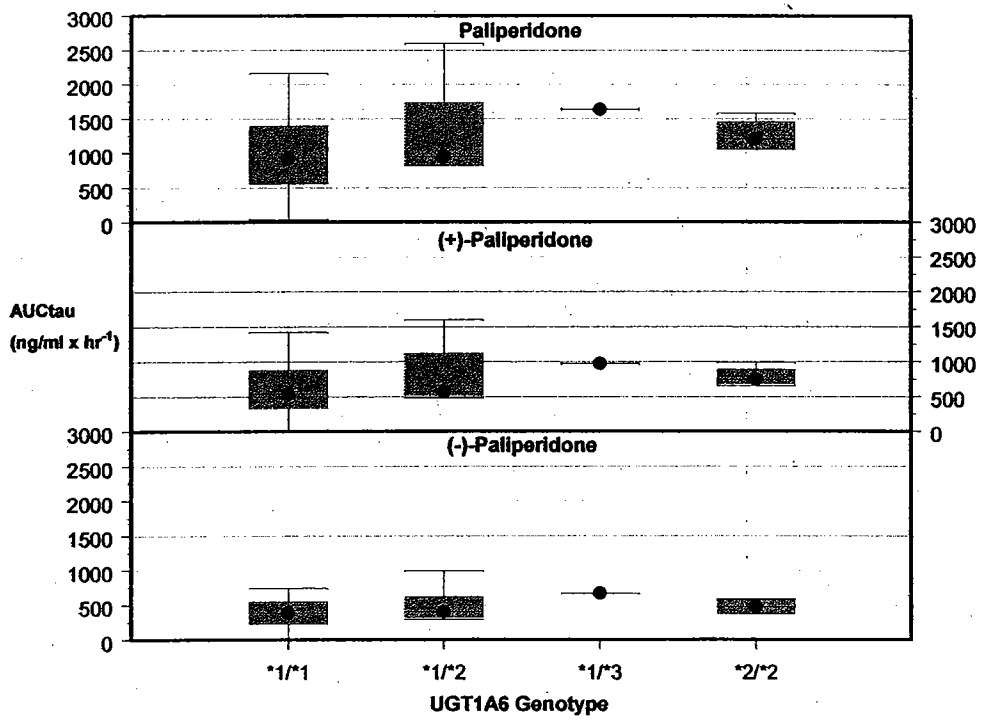


Figure 89 Scatterplot of Paliperidone and Enantiomer Dose & Weight Normalized AUCs vs. CYP3A4 Genotype – Studies P01-1005, P01-1006, SCH-101, and SCH-102

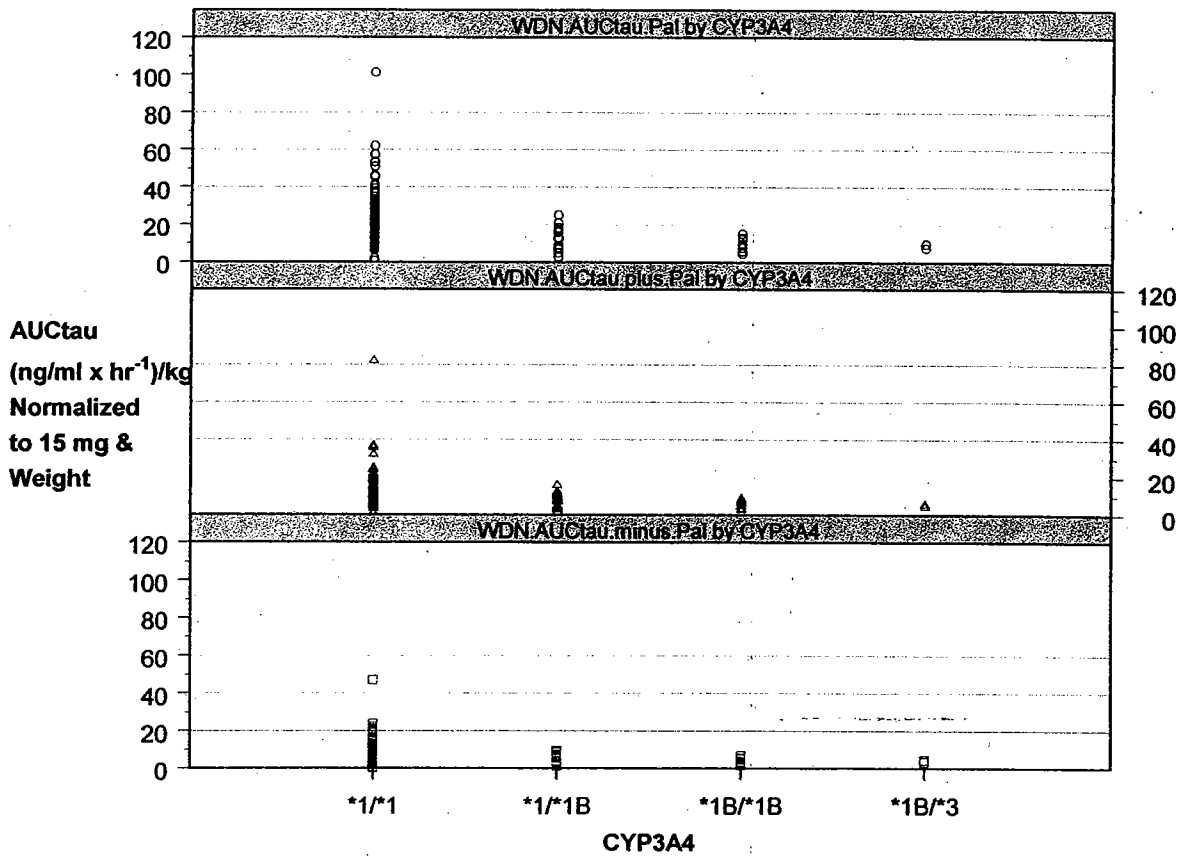


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Figure 90 Scatterplot of Paliperidone Dose & Weight Normalized AUCs vs. CYP3A5 Genotype by Gender – Studies P01-1005, P01-1006, SCH-101, and SCH-102

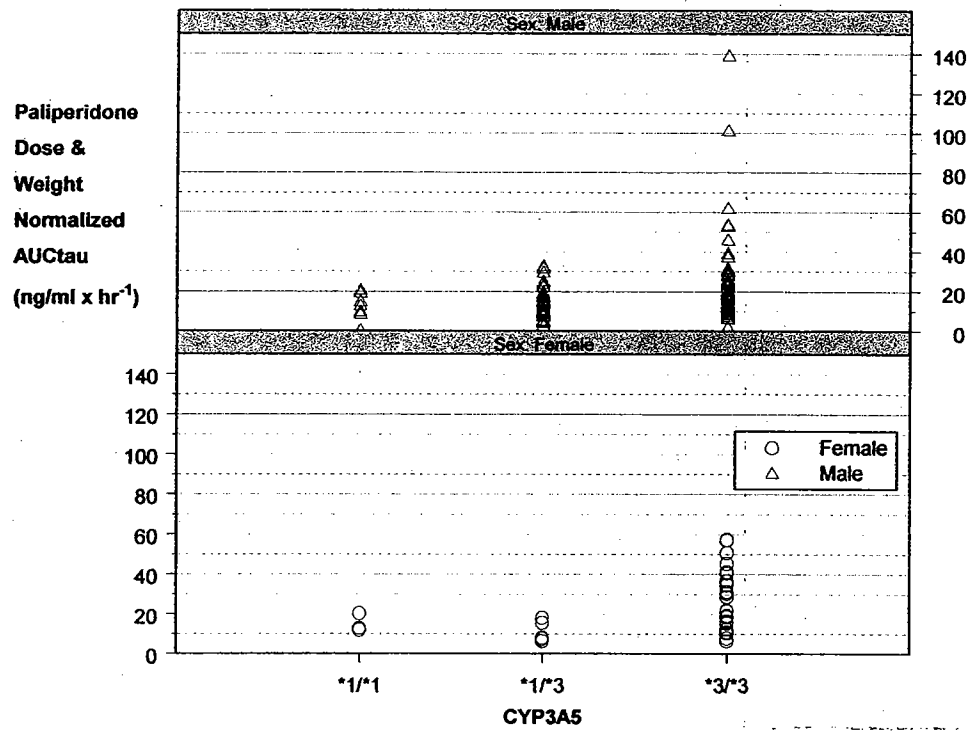


Figure 91 Boxplot of Paliperidone Dose & Weight Normalized AUCs vs. CYP3A5 Genotype – Studies P01-1005, P01-1006, SCH-101, and SCH-102

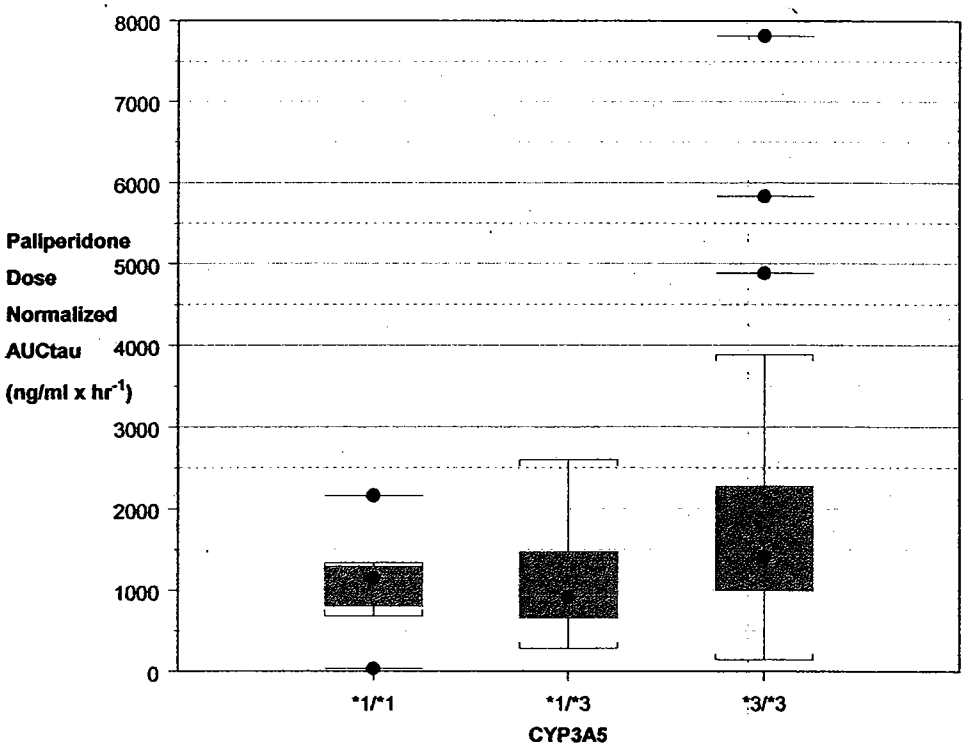


Figure 92 Distributions of Paliperidone and Enantiomer Dose and Weight Normalized AUCs by Predicted CYP3A5 Expression – Studies P01-1005, P01-1006, SCH-101, and SCH-102

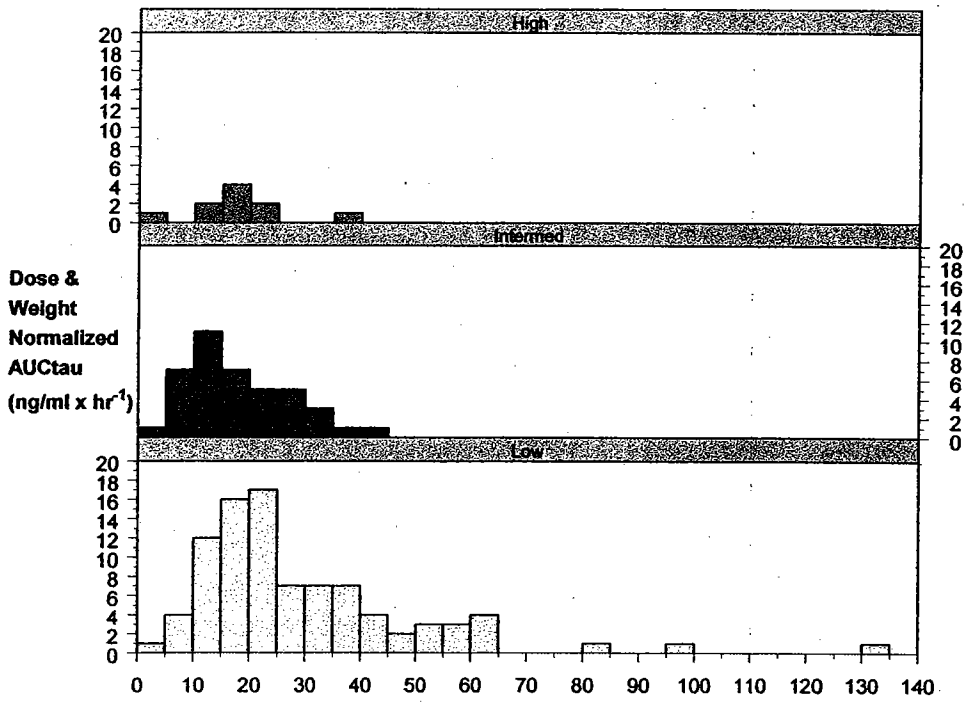
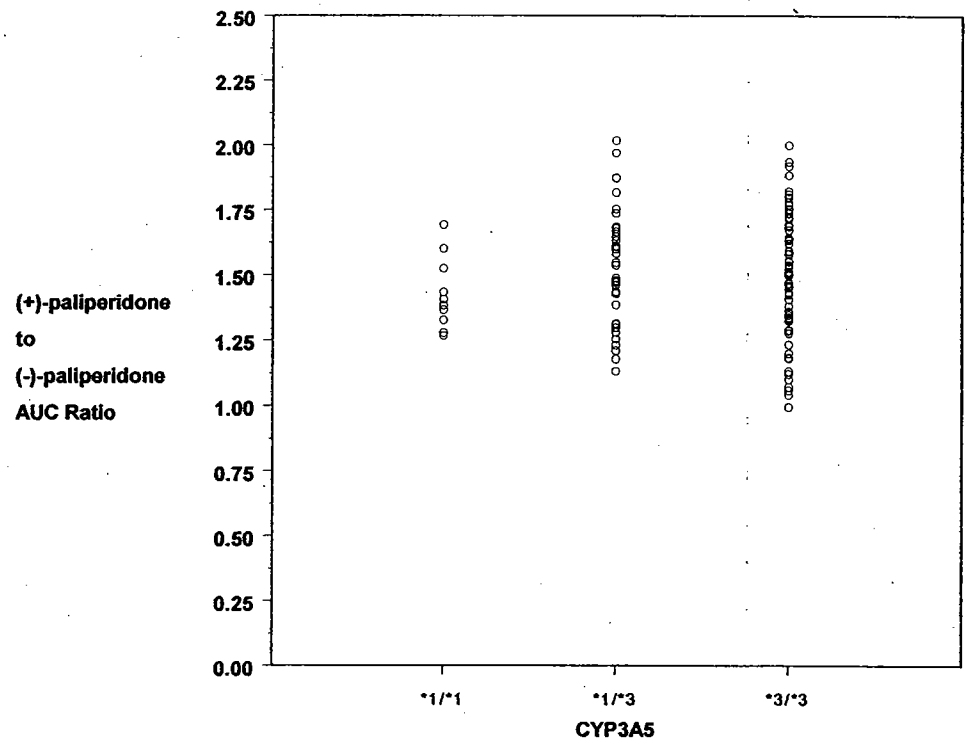


Figure 93 Scatterplot of (+)-Paliperidone : (-)-Paliperidone AUC Ratios vs. CYP3A5 Genotype – Studies P01-1005, P01-1006, SCH-101, and SCH-102



3.10.8.5 Renal Function

In both study P01-1005 and study REI-1001, renal clearance in healthy volunteers was reported as 10% - 15% of total body clearance. Thus renal insufficiency would not be expected to effect paliperidone elimination except in end state renal disease, (see Table 98 and Table 99). However, additional work with more extensive urine collection periods showed that renal clearance is approximately 60% of total body clearance.

When paliperidone elimination was examined in individuals with varying degrees of renal insufficiency there was clearly a progressive increase in exposure as renal function diminished, with an associated decrease in total body clearance, (see Table 97, Figure 94, and Figure 95).

It should be noted that the sponsor categorized subjects by estimated creatinine clearance and this did not always correspond to actual renal function, (see Figure 95).

Table 97 Change in Mean Paliperidone Clearances and Exposure with Degree of Renal Insufficiency – Study REI-1001

	Severity of Renal Insufficiency	Definition	CL_{CR} (ml/min)	AUCinf	CL/F (ml/min)	CL_{GFR}[b] (ml/min)	CL_R (ml/min)	CLpass (ml/min)	CLact (ml/min)	CL/F_{NR} (ml/min)	$CL/F_{NR,u}$ (ml/min)	$CLact/CL_R$	CLact/(CL/F)
Mean Value	Normal	Clcr ≥ 80 ml/min	107	114	561.5	32.3	70.5	32.3	38.2	491	1600	0.490	0.0659
	Mild	Clcr ≥ 50 to < 80 ml/min	79.9	169.0	433.2	21.9	49.2	21.9	27.4	384	1389	0.536	0.0790
	Mod	Clcr ≥ 30 to < 50 ml/min	40.4	301.9	289.9	10.2	21.9	10.0	11.9	268	1049	0.247	0.0403
	Severe	Clcr < 30 ml/min	20.4	541.9	216.9	5.6	12.9	5.63	7.26	204	713	0.491	0.0359
% change from Mean Value in Normals	Mild	Clcr ≥ 50 to < 80 ml/min	-25.3	1.5[a]	-22.8	-32.2	-30.2	-32.2	-28.3	-21.8	-13.2	9.4	19.9
	Mod	Clcr ≥ 30 to < 50 ml/min	-62.2	2.6[a]	-48.4	-68.4	-68.9	-69.0	-68.8	-45.4	-34.4	-49.6	-38.8
	Severe	Clcr < 30 ml/min	-80.9	4.8[a]	-61.4	-82.7	-81.7	-82.6	-81.0	-58.5	-55.4	0.2	-45.5

a Fold increase. Not % change.
b $CL_{GFR} = CL/F * fu$

Based on changes in total paliperidone clearances average dosages should probably be decreased by approximately 1/3 in mild renal insufficiency at least ½ in moderate insufficiently and by 75 – 80% in severe insufficiency.

What's interesting is that the enantiomer ratio changes as renal function decreases and is a proportionately greater change for the unbound ratio, (see Table 100). This appears to be due to differences in the elimination of the enantiomers, as evidenced by the fact that the enantiomer ratio changes to a greater extent as the time post dosing increases, (see Figure 96 and Figure 97). Thus the ultimate exposure to each enantiomer is difficult to predict. Since the enantiomer pharmacokinetic studies indicated that there may be a pharmacodynamic difference between the enantiomers in their propensity to cause toxicity even at the same exposures, we are unable to predict the risk benefit ratio with higher steady-state dosing of paliperidone in patients with renal insufficiency. Consequently, clinicians should be aware that the toxicity to efficacy profile may be different than in normals.

Hyperprolactinemia was the only clearly exposure related AE. Although as postural hypotension occurred in 1 subject with mild renal insufficiency and 2 subjects with severe renal insufficiency it might also be dose related. There were 3 cases of elevated LFTs but only in the subject with severe renal insufficiency was the increase of > 3 fold (i.e. 6 fold). Other significant laboratory changes included a 10% drop in hematocrit in the same patient who had the 6 fold increase in LFTs, and 2 other subjects had drops in RBC.

Table 98 Total and Renal Clearances for Paliperidone and its Enantiomers in Caucasian and Japanese Subjects with Normal Renal Function – Study P01-1005

	Caucasian subjects			Japanese subjects		
	Paliperidone	**R078543**	**R078544**	**Paliperidone**	**R078543**	**R078544**
	3 mg SD data (n=24 for Caucasian subjects and n=23 for Japanese subjects)					
Ae% dose (0-48 hours)	8.18 ± 4.30	3.20 ± 1.83	4.98 ± 2.50	9.43 ± 3.46[2]	3.80 ± 1.43[4]	5.63 ± 2.07[2]
CL/F (mL/min)	306 ± 194[1]	263 ± 160[1]	344 ± 207[1]	237 ± 97.2	208 ± 98.0	278 ± 96.2
CL_R (mL/min)	32.6 ± 13.9	21.6 ± 9.68	48.4 ± 19.1	29.0 ± 11.6	19.7 ± 8.15	42.5 ± 16.3
CL_{GFR} (mL/min)	26.5 ± 6.48	17.7 ± 4.32	36.3 ± 8.87	20.4 ± 3.87[2]	13.6 ± 2.58[2]	28.0 ± 5.31[2]
CL_{act} (mL/min)	6.10 ± 12.8	3.93 ± 8.92	12.1± 17.3	8.57 ± 10.8	6.14 ± 7.66	14.6 ± 14.8
	3 mg MD data (n=23 for both the Caucasian and Japanese subjects)					
Ae% dose (0-24 hours)	13.8 ± 5.09	5.24 ± 2.16	8.59 ± 2.99	12.0 ± 4.5	4.72 ± 1.94	7.30 ± 2.64
CL/F (mL/min)	265 ± 128	238 ± 124	303 ± 135	242 ± 80.8	209 ± 75.2	292 ± 93.7
CL_R (mL/min)	33.2 ± 14.1	21.8 ± 9.15	48.1 ± 20.1	27.2 ± 9.93	18.2 ± 6.76	40.1 ± 15.0
CL_{GFR} (mL/min)[1]	22.7 ± 6.80	15.1 ± 4.53	31.1 ± 9.31	16.9 ± 6.69[3]	11.3 ± 4.46[3]	23.2 ± 9.16[3]
CL_{act} (mL/min)[1]	10.5 ± 13.2	6.72 ± 8.65	17.0 ± 18.8	10.4 ± 9.74[3]	6.96 ± 6.77[3]	17.0 ± 14.1[3]
	6 mg SD data (n=24 for the Caucasian subjects and n=22 [4] for the Japanese subjects)					
Ae% dose (0-48 hours)	9.33 ± 3.72	3.68 ± 1.54	5.65 ± 2.26	9.15 ± 3.28	3.64 ± 1.41	5.51 ± 1.91
CL/F (mL/min)	246 ± 132	216 ± 118	282 ± 145	216 ± 78.6	189 ± 78.0	254 ± 82.2
CL_R (mL/min)	31.3 ± 15.0	20.8 ± 9.89	45.9 ± 21.5	27.6 ± 9.95	18.4 ± 6.88	40.9 ± 13.9
CL_{GFR} (mL/min)	23.5 ± 5.66	15.7 ± 3.77	32.2 ± 7.75	19.8 ± 4.89	13.2 ± 3.26	27.2 ± 6.70
CL_{act} (mL/min)	7.75 ± 14.2	5.16 ± 9.19	13.7 ± 20.4	7.55 ± 8.90	5.07 ± 6.16	13.4 ± 12.3

Table 99 Pharmacokinetic Metrics including Total and Renal Clearance for Paliperidone and its Enantiomers in Subjects with Varying Degrees of Renal Function – Study REI-1001

Table 5: Pharmacokinetic Parameters of Paliperidone and its Enantiomers (Study R076477-REI-1001)

	Paliperidone							
	Healthy Subjects		Mild Renal Impairment		Moderate Renal Impairment		Severe Renal Impairment	
	n	Total	n	Total	n	Total	n	Total
C_{max}, ng/mL	12	2.63 ± 1.61	11	4.29 ± 2.39	12	6.65 ± 5.46	10	5.55 ± 2.81
AUC_{∞}, ng.h/mL	12	114 ± 74.0	11	169 ± 83.1	12	416 ± 444	10	429 ± 247
t_{max}, h	12	20.5 (12.0 – 26.0)	11	24.0 (12.0 – 26.0)	12	24.0 (12.0 – 28.0)	10	24.0 (16.0 – 26.0)
$t_{1/2}$, h	12	23.2 ± 7.8	11	23.6 ± 4.9	12	40.2 ± 18.3	10	51.0 ± 15.4
CL/F, mL/min	12	561 ± 225	11	433 ± 400	12	271 ± 253	10	217 ± 261
V_{dz}, L	12	1045 ± 374	11	751 ± 349	12	770 ± 653	10	779 ± 653
CL_R, mL/min	12	70.5 ± 26.8	11	49.2 ± 16.8	11	21.9 ± 11.9	10	12.9 ± 9.64
CL_{NR}, mL/min	12	491 ± 204	11	384 ± 386	11	268 ± 250	10	204 ± 253
Ae, %dose	12	13.2 ± 3.74	11	15.2 ± 6.81	11	9.80 ± 5.40	10	7.47 ± 2.40

	(+) R078543							
	Healthy Subjects		Mild Renal Impairment		Moderate Renal Impairment		Severe Renal Impairment	
	n	Total	n	Total	n	Total	n	Total
C_{max}, ng/mL	12	1.65 ± 0.982	11	2.74 ± 1.56	12	4.30 ± 3.55	10	3.69 ± 2.03
AUC_{∞}, ng.h/mL	12	70.5 ± 44.9	11	108 ± 54.1	12	259 ± 264	10	275 ± 164
t_{max}, h	12	19.0 (12.0 – 26.0)	11	24.0 (12.0 – 24.0)	12	23.0 (12.0 – 28.0)	10	24.0 (9.0 – 26.0)
$t_{1/2}$, h	12	23.7 ± 7.8	11	24.5 ± 4.1	12	40.2 ± 16.7	10	52.6 ± 15.2
CL/F, mL/min	12	455 ± 184	11	335 ± 290	12	211 ± 203	10	161 ± 173
V_{dz}, L	12	862 ± 305	11	641 ± 389	12	593 ± 457	10	649 ± 547
CL_R, mL/min	12	45.4 ± 18.1	11	31.7 ± 9.0	11	14.3 ± 8.0	10	8.22 ± 5.41
CL_{NR}, mL/min	12	409 ± 170	11	303 ± 284	11	211 ± 201	10	152 ± 169
Ae, %dose	12	5.21 ± 1.41	11	6.40 ± 3.02	11	4.11 ± 2.27	10	3.24 ± 1.21

	(-) R078544							
	Healthy Subjects		Mild Renal Impairment		Moderate Renal Impairment		Severe Renal Impairment	
	n	Total	n	Total	n	Total	n	Total
C_{max}, ng/mL	12	1.01 ± 0.673	11	1.55 ± 0.846	12	2.40 ± 1.94	10	1.92 ± 0.844
AUC_{∞}, ng.h/mL	12	47.2 ± 29.2	11	67.3 ± 31.2	12	160 ± 179	10	157 ± 83.9
t_{max}, h	12	24.0 (12.0 – 28.0)	11	24.0 (12.0 – 28.0)	12	25.0 (16.0 – 28.0)	10	24.0 (19.0 – 30.0)
$t_{1/2}$, h	12	24.5 ± 8.0	11	24.6 ± 4.8	12	42.8 ± 21.5	10	51.0 ± 14.5
CL/F, mL/min	12	678 ± 292	11	510 ± 411	12	320 ± 263	10	273 ± 308
V_{dz}, L	12	1339 ± 493	11	971 ± 468	12	1034 ± 946	10	976 ± 709
CL_R, mL/min	12	101 ± 37.0	11	69.7 ± 20.5	11	31.3 ± 14.9	10	19.1 ± 13.4
CL_{NR}, mL/min	12	576 ± 264	11	440 ± 395	11	310 ± 257	10	254 ± 297
Ae, %dose	12	7.97 ± 2.39	11	8.75 ± 3.80	11	5.71 ± 3.17	10	4.23 ± 1.23

Mean ± SD; for t_{max}: median (range)

Table 100 Pharmacokinetic Metrics in Subjects with Varying Degrees of Renal Function as Estimated by Cockcroft and Gault Equation - Study REI-1001

	N	Total								Unbound							
		Tmax (h)	Cmax, (ng/ml(	AUClast (ng/ml x hr^{-1})	AUC∞ (ng/ml x hr^{-1})	t½ (h)	Ratio AUC∞,+/−	CL/F (ml/min)	Vdzl (L)	fu	tmax,u (h)	Cmax,u (ng/ml x hr^{-1})	AUCu,last (ng/ml x hr^{-1})	AUCu,∞ (ng/ml x hr^{-1})	Ratio AUCu,∞,+/−	CLu/F (ml/min)	Vdz,u (L)
Normal	12	19.2 ± 6.1 (31.7) 12.0 - 26.0 [20.5]	2.63 ± 1.61 (61.3) 1.36 - 7.11 [2.05]	97.5 ± 68.6 (70.3) 42.8 - 245 [68.3]	114 ± 74.0 (64.7) 56.3 - 264 [79.1]	23.2 ± 7.8 (33.8) 16.9 - 44.3 [21.2]	1.50 ± 0.177 (11.9) 1.22 - 1.72 [1.53]	561 ± 225 (40.1) 190 - 888 [632]	1045 ± 374 (35.8) 371 - 1789 [1074]	0.301 ± 0.0483 (16.1) 0.189 - 0.387 [0.302]	20.08 ± 6.24 (31.1) 12.0 - 26.0 [24.0]	0.741 ± 0.390 (52.6) 0.426 - 1.88 [0.631]	27.0 ± 15.3 (56.7) 13.4 - 65.9 [21.1]	31.7 ± 15.6 (49.1) 17.7 - 70.7 [26.3]	0.795 ± 0.131 (16.5) 0.622 - 1.0 [0.782]	1831 ± 661 (36.1) 707 - 2826 [1839]	3447 ± 978 (28.4) 1382 - 4649 [3516]
Mile	11	20.8 ± 5.2 (24.9) 12.0 - 26.0 [24.0]	4.29 ± 2.39 (55.9) 1.03 - 9.42 [4.23]	158 ± 83.7 (52.9) 28.2 - 301 [165]	169 ± 83.1 (49.3) 31.7 - 310 [174]	23.6 ± 4.9 (20.9) 11.1 - 28.0 [24.8]	1.58 ± 0.130 (8.2) 1.35 - 1.76 [1.60]	433 ± 400 (92.3) 161 - 1578 [287]	751 ± 349 (46.6) 342 - 1517 [596]	0.277 ± 0.0432 (15.6) 0.228 - 0.381 [0.271]	20.82 ± 5.19 (24.9) 12.0 - 26.0 [24.0]	1.14 ± 0.602 (52.6) 0.280 - 2.45 [1.10]	42.8 ± 21.3 (49.7) 7.91 - 73.0 [43.2]	45.2 ± 20.8 (46.2) 8.6 - 74.7 [45.1]	0.797 ± 0.0627 (7.9) 0.709 - 0.897 [0.817]	1567 ± 1430 (91.2) 661 - 5648 [1082]	2719 ± 1271 (46.7) 1401 - 5430 [2369]
Moderate	12	23.2 ± 4.1 (17.8) 12.0 - 26.0 [24.0]	6.65 ± 5.46 (82.1) 1.20 - 19.7 [5.22]	329 ± 294 (89.4) 49.7 - 1073 [281]	416 ± 444 (106.7) 64.5 - 1671 [325]	40.2 ± 18.3 (45.4) 17.3 - 92.7 [36.8]	1.63 ± 0.224 (13.7) 1.22 - 1.99 [1.63]	271 ± 253 (93.5) 29.9 - 775 [154]	770 ± 653 (84.8) 205 - 2522 [523]	0.25 ± 0.046 (18.7) 0.176 - 0.334 [0.237]	25.7 ± 7.7 (30.0) 16.0 - 48.0 [24.0]	1.52 ± 1.12 (73.3) 0.266 - 4.09 [1.26]	75.6 ± 63.0 (83.3) 11.2 - 230 [66.9]	95.5 ± 97.2 (101.8) 14.0 - 368 [76.2]	0.765 ± 0.103 (13.4) 0.571 - 0.904 [0.757]	1063 ± 963 (90.7) 136 - 3172 [658]	2086 ± 2654 (86.0) 849 - 10805 [2225]
Severe	10	22.7 ± 4.1 (18.1) 16.0 - 26.0 [24.0]	5.55 ± 2.81 (50.7) 1.05 - 9.69 [4.96]	323 ± 184 (56.9) 45.2 - 594 [277]	429 ± 247 (57.6) 54.7 - 826 [394]	51.0 ± 15.4 (30.2) 31.5 - 85.0 [48.0]	1.73 ± 0.278 (16.1) 1.38 - 2.25 [1.66]	217 ± 261 (120.3) 60.5 - 914 [128]	779 ± 653 (83.8) 269 - 2495 [672]	0.268 ± 0.0516 (19.2) 0.152 - 0.319 [0.281]	23.70 ± 3.47 (14.6) 16.0 - 26.0 [25.0]	1.38 ± 0.606 (43.9) 0.333 - 2.48 [1.34]	81.2 ± 42.1 (51.9) 14.2 - 164 [80.6]	108 ± 59.0 (54.4) 16.7 - 207 [105]	0.859 ± 0.143 (16.7) 0.650 - 1.16 [0.846]	759 ± 803 (105.7) 242 - 2896 [476]	2776 ± 1952 (70.3) 965 - 7903 [2285]

Figure 94 Mean Paliperidone Concentration vs. Time Profiles by Degree of Renal Function as Estimated by Cockcroft and Gault Equation - Study REI-1001

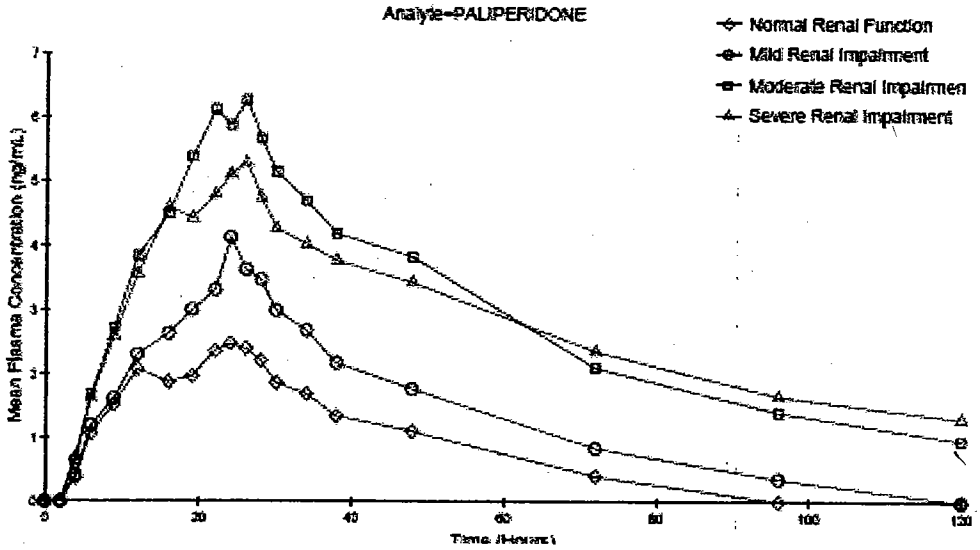


Figure 95 Paliperidone AUCinf vs. Measured Clcr and Degree of Renal Function as Estimated by Cockcroft and Gault Equation - Study REI-1001

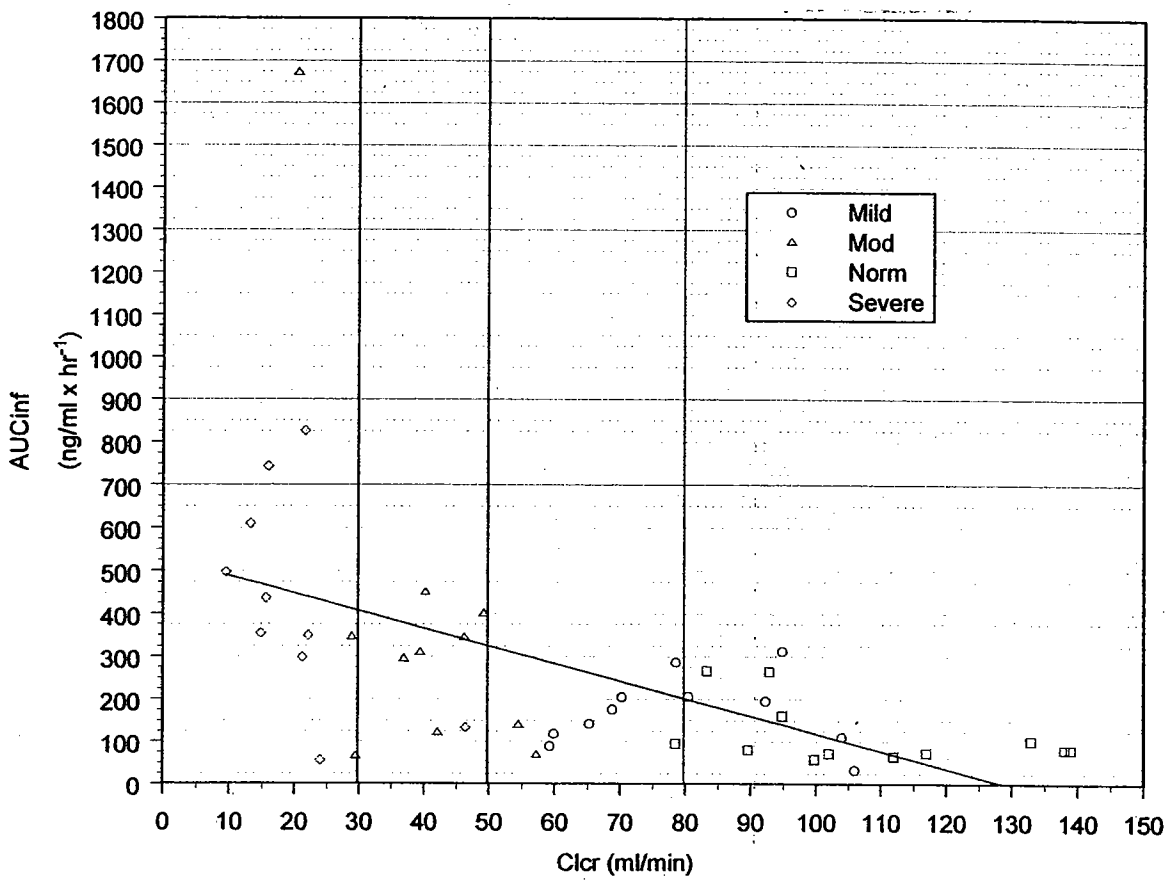
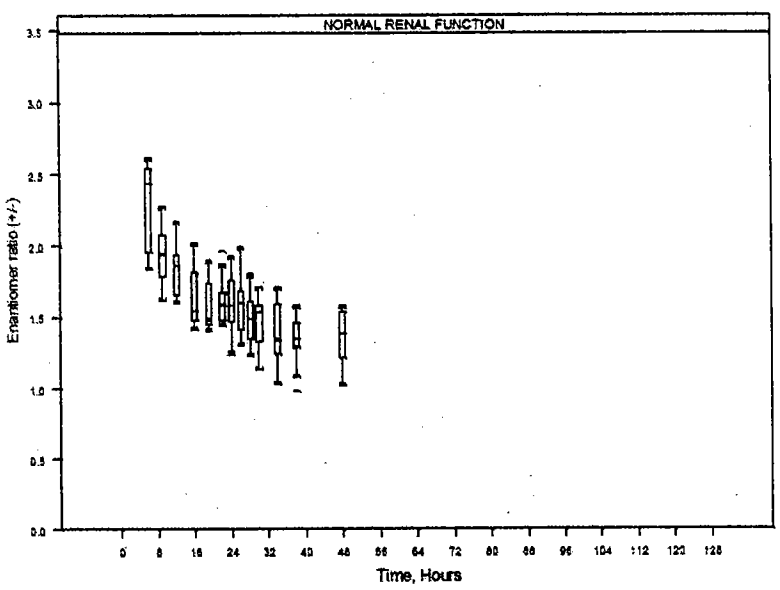
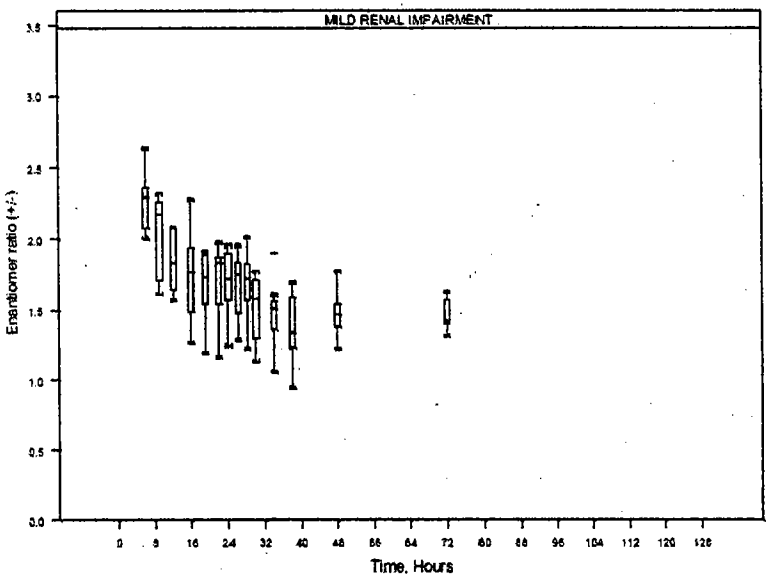
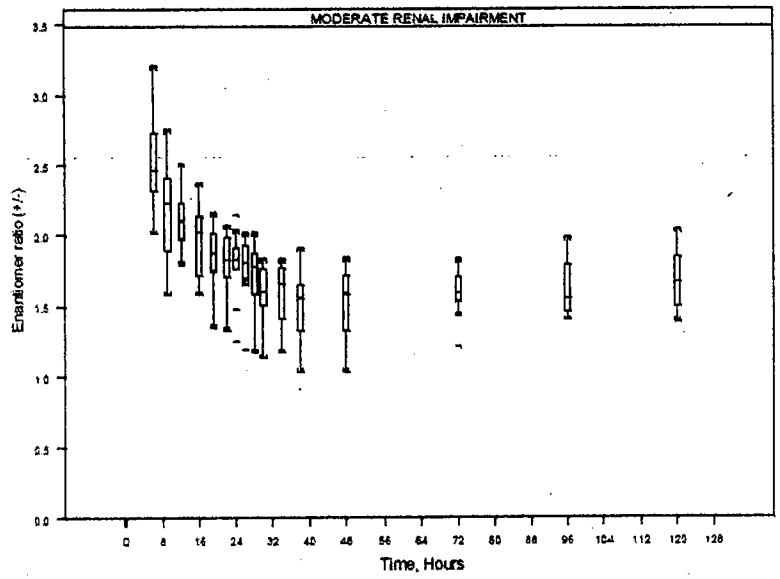


Figure 96 Distributions of Total Paliperidone Enantiomer Ratios vs. Time Post-Dose for Varying Degrees of Renal Function







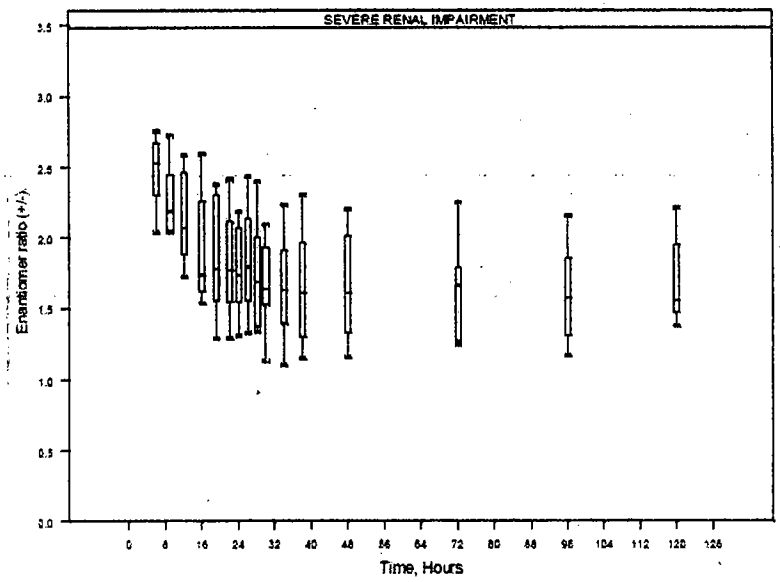


Figure 97 Distributions of Unbound Paliperidone Enantiomer Ratios vs. Time Post-Dose for Varying Degrees of Renal Function

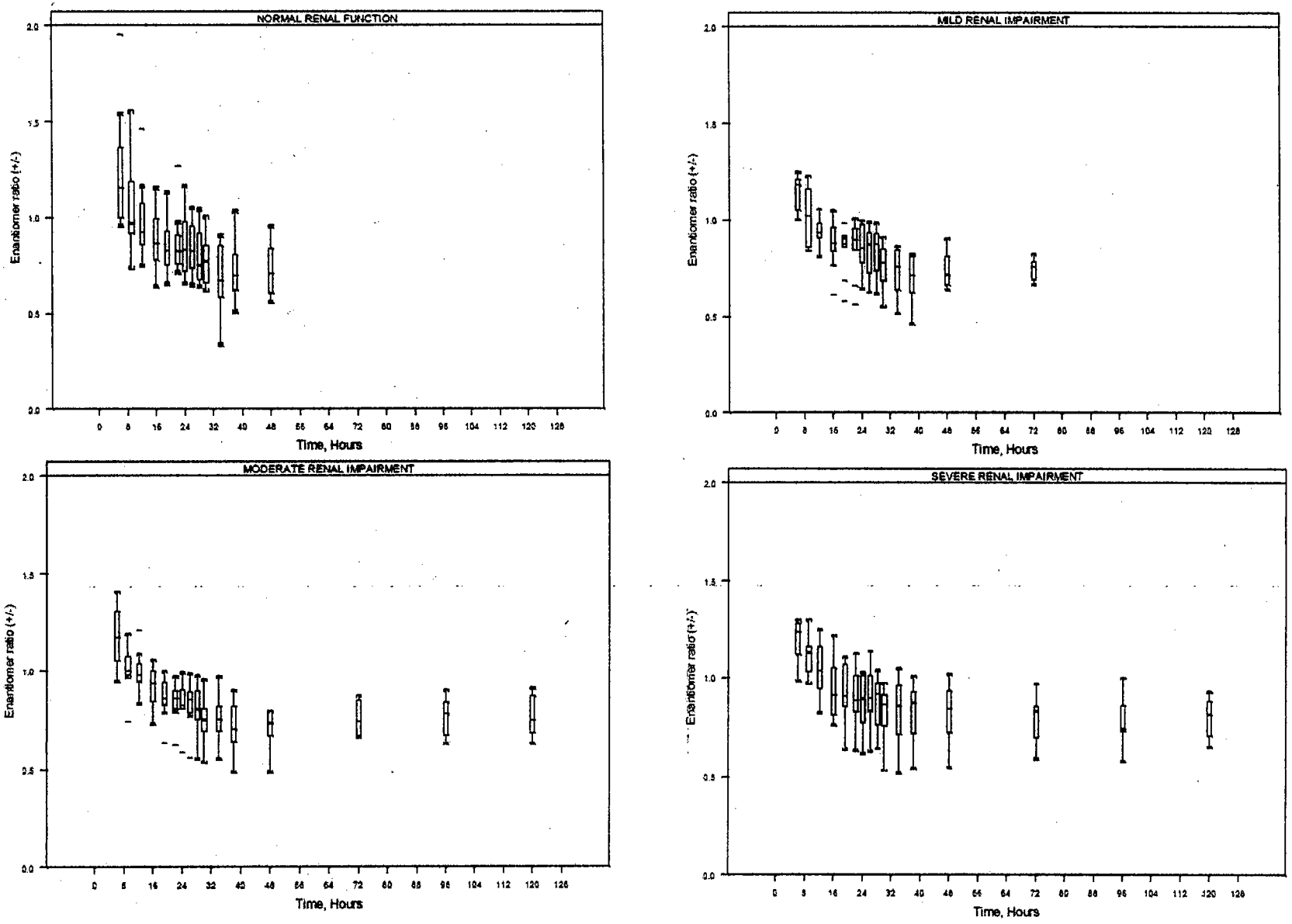


Table 101 Plasma Protein Binding of the Paliperidone Enantiomers and Predose Concentrations of Plasma Proteins, Including Descriptive Statistics- Study REI-1001

Parameter	R078543		R078544		Predose Concentrations		
	% free	% bound	% free	% bound	Albumin (g/100mL)	α1-AGP (mg/100mL)	Total Protein (g/100 mL)
Subjects with Normal Renal Function							
n	12	12	12	12	12	12	12
Mean	22.4	77.6	41.5	58.5	4.5	78.1	7.2
SD	5.25	5.25	4.51	4.51	0.2	22.2	0.5
%CV	23.5	6.8	10.9	7.7	5.4	28.4	6.6
Median	22.2	77.8	42.6	57.5	4.6	76.6	7.3
Min	12.4	65.4	30.0	53.3	4.2	55.8	6.3
Max	34.6	87.6	46.7	70.0	4.9	140.6	7.9
Subjects with Mild Renal Impairment							
n	12	12	12	12	12	12	12
Mean	20.0	80.0	39.4	60.6	4.5	78.9	7.4
SD	3.68	3.68	4.42	4.42	0.2	13.9	0.4
%CV	18.4	4.6	11.2	7.3	5.0	17.6	5.8
Median	19.3	80.8	39.7	60.3	4.5	77.3	7.5
Min	15.6	70.6	34.1	49.5	4.1	59.9	6.4
Max	29.4	84.4	50.5	65.9	5.0	98.2	7.8
Subjects with Moderate Renal Impairment							
n	12	12	12	12	12	12	12
Mean	17.3	82.8	36.3	63.7	4.4	91.8	7.1
SD	3.89	3.89	4.94	4.94	0.3	19.9	0.5
%CV	22.6	4.7	13.6	7.8	6.4	21.7	6.5
Median	16.1	83.9	36.1	63.9	4.5	89.6	7.1
Min	12.1	75.3	28.7	54.5	3.8	64.7	6.3
Max	24.7	87.9	45.5	71.3	4.7	128.1	7.9
Subjects with Severe Renal Impairment							
n	11	11	11	11	11	11	11
Mean	20.1	79.9	39.3	60.7	4.4	98.2	6.8
SD	4.57	4.57	5.03	5.03	0.2	29.70	0.4
%CV	22.7	5.7	12.8	8.3	4.9	30.2	5.4
Median	20.5	79.5	40.9	59.1	4.4	91.6	6.7
Min	10.1	73.7	26.7	55.7	4.1	60.2	6.2
Max	26.3	89.9	44.3	73.3	4.8	163.2	7.5

3.10.8.6 Hepatic Function

In subjects with moderate hepatic impairment the free fraction of (+)-paliperidone increases on average by almost 50% and of (-)-paliperidone by almost 20%, (see Table 102). Because of this the total paliperidone exposure decreases, although the exposure to unbound racemic paliperidone as well as to the unbound paliperidone enantiomers remains essentially the same, (see Table 103). Although pharmacokinetically there does not appear to be a reason to alter dosing in moderate hepatic impairment, pharmacodynamically paliperidone as a CNS active agent might induce a hepatic encephalopathy.

Table 102 Plasma Protein Binding of Paliperidone Enantiomers in Subjects with Moderate Hepatic Impairment and Controls – Study SCH-1008

n	R078543 (+)-Paliperiodone		R078544 (-)-Paliperiodone		Predose Concentrations		
	% free	% bound	% free	% bound	Albumin (g/100 ml	α1-AGP (mg/100 ml)	Total Protein (g/ 100 ml)
Subjects with Normal Hepatic Function							
10	21.5 ± 4.69 (21.8) 14.4 - 28.8 [20.5]	78.5 ± 4.69 (6.0) 71.2 - 85.6 [79.6]	38.5 ± 4.16 (10.8) 32.5 - 44.7 [37.7]	61.5 ± 4.16 (6.8) 55.3 - 67.5 [62.4]	4.3 ± 0.2 (4.6) 4.1 - 4.7 [4.3]	77.0 ± 18.8 (24.5) 55.3 - 116.8 [75.9]	7.2 ± 0.2 (3.1) 6.9 - 7.6 [7.2]
Subjects with Moderate Hepatic Impairment							
10	30.6 ± 6.87 (22.4) 20.9 - 42.5 [29.1]	69.4 ± 6.87 (9.9) 57.5 - 79.1 [71.0]	45.7 ± 5.04 (11.1) 38.6 - 54.4 [44.6]	54.4 ± 5.04 (9.3) 45.6 - 61.4 [55.5]	3.3 ± 0.6 (19.4) 2.2 - 4.3 [3.2]	46.6 ± 17.1 (36.7) 20.7 - 68.2 [51.6]	6.9 ± 0.7 (10.1) 6.1 - 8.2 [6.8]

Table 103 Pharmacokinetic parameters of Paliperidone 1 mg Oral Solution in Healthy Volunteers and Subjects with Moderate Hepatic Impairment – Study SCH-1008

Analyte		Total Paliperidone Pharmacokinetic Metrics (Bound and Unbound)								Unbound Paliperidone Pharmacokinetic Metrics							
	Sub	tmax (h)	Cmax (ng/ml)	AUClast (ng.ml x hr^{-1})	AUC∞ (ng.ml x hr^{-1})	AUC∞, +/–	t1/2 (h)	CL/F (ml/min)	Vdz (L)	fu	Tmax,u (h)	Cmax,u (ng/ml)	AUCu,last (ng.ml x hr^{-1})	AUCu,∞ (ng.ml x hr^{-1})	AUCu,∞, +/–	CLu/F (ml/min)	Vdz,u (L)
Pal	NL[a]	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
		1.35 ± 0.47 (35.1) 1.00 - 2.00 [1.00]	7.14 ± 2.28 (31.9) 4.33 - 12.1 [6.76]	165 ± 63.5 (38.6) 89.4 - 303 [158]	176 ± 64.4 (36.6) 103 - 318 [171]	1.67 ± 0.24 (14.6) 1.34 - 2.08 [1.69]	23.6 ± 3.6 (15.1) 16.5 - 27.9 [25.3]	106 ± 34.9 (33.1) 52.4 - 162 [98.6]	211 ± 59.6 (28.3) 113 - 320 [202]	0.279 ± 0.0492 (17.6) 0.203 - 0.346 [0.268]	1.4 ± 0.46 (32.8) 1.0 - 2.0 [1.25]	1.81 ± 0.292 (16.1) 1.32 - 2.33 [1.79]	43.3 ± 9.37 (21.6) 30.7 - 61.4 [42.2]	45.8 ± 8.72 (19.0) 35.4 - 63.5 [43.9]	0.914 ± 0.094 (10.3) 0.787 - 1.11 [0.923]	370 ± 67.1 (18.1) 258 - 471 [374]	748 ± 14 (19.2) 558 - 102 [716]
	Mod[b]	10	10	10	9	8	10	9	9	8	10	10	10	8	8	8	8
		1.58 ± 1.16 (73.3) 0.25 - 4.00 [1.25]	4.57 ± 1.05 (23.0) 3.19 - 6.37 [4.65]	105 ± 39.4 (37.5) 49.5 - 185 [98.8]	128 ± 42.5 (33.3) 76.9 - 213 [116]	1.38 ± 0.20 (14.8) 1.12 - 1.72 [1.39]	26.5 ± 6.4 (24.1) 17.2 - 35.3 [26.9]	143 ± 43.4 (30.5) 78.3 - 217 [144]	311 ± 65.2 (21.0) 216 - 392 [309]	0.353 ± 0.0564 (16.0) 0.285 - 0.468 [0.353]	1.58 ± 1.16 (73.3) 0.25 - 4.0 [1.25]	1.59 ± 0.318 (20.0) 1.23 - 2.23 [1.52]	37.3 ± 11.0 (29.4) 23.3 - 56.4 [32.5]	45.7 ± 12.6 (27.5) 32.6 - 65.0 [43.8]	0.886 ± 0.103 (11.6) 0.724 - 1.04 [0.907]	386 ± 99.3 (25.7) 256 - 505 [381]	857± 14 (17.0) 688 - 110 [829]
R078543 (+)	NL[a]	10	10	10	10	–	10	10	10	10	10	10	10	10	–	10	10
		1.30 ± 0.42 (32.4) 1.00 - 2.00 [1.00]	5.10 ± 1.80 (35.2) 2.98 - 9.23 [4.91]	105 ± 45.5 (43.3) 51.6 - 205 [100]	116 ± 47.7 (41.3) 58.8 - 221 [108]	–	25.0 ± 4.2 (16.6) 16.4 - 30.2 [25.6]	83.0 ± 31.7 (38.2) 37.8 - 142 [79.3]	173 ± 51.4 (29.8) 84.0 - 245 [157]	0.215 ± 0.0469 (21.8) 0.144 - 0.288 [0.205]	1.3 ± 0.42 (32.4) 1.0 - 2.0 [1.0]	1.03 ± 0.157 (15.2) 0.751 - 1.33 [1.03]	20.9 ± 4.83 (23.1) 14.0 - 29.6 [21.2]	23.1 ± 4.89 (21.2) 15.9 - 31.8 [23.6]	–	377 ± 84.2 (22.3) 262 - 523 [353]	802 ± 18 (23.4) 584 - 125 [743]
	Mod[b]	10	10	10	10	–	10	10	10	10	10	10	10	10	–	10	10
		1.48 ± 1.20 (81.7) 0.25 - 4.00 [1.00]	3.05 ± 0.781 (25.7) 1.94 - 4.46 [2.96]	61.6 ± 25.2 (40.9) 25.7 - 112 [60.6]	71.6 ± 28.2 (39.4) 32.3 - 129 [68.4]	–	26.5 ± 6.8 (25.8) 16.7 - 36.5 [26.1]	135 ± 57.9 (42.9) 64.8 - 258 [122]	290 ± 93.1 (32.1) 178 - 491 [272]	0.308 ± 0.0687 (22.4) 0.209 - 0.425 [0.291]	1.48 ± 1.2 (81.7) 0.25 - 4.0 [1.0]	0.897 ± 0.153 (17.1) 0.737 - 1.21 [0.871]	17.8 ± 5.54 (31.1) 10.4 - 26.8 [16.2]	20.8 ± 6.19 (29.8) 13.0 - 30.7 [18.6]	–	434 ± 125 (28.8) 271 - 639 [448]	943 ± 182 (19.3) 697 - 124 [920]
R078544 (-)	NL[a]	10	10	10	10	–	10	10	10	10	10	10	10	10	–	10	10
		2.25 ± 1.06 (47.1) 1.00 - 4.00 [2.00]	2.16 ± 0.564 (26.2) 1.40 - 3.26 [2.02]	56.4 ± 17.8 (31.6) 36.8 - 93.4 [58.9]	67.1 ± 18.6 (27.7) 44.0 - 106 [67.5]	–	23.8 ± 2.8 (11.7) 16.7 - 28.2 [24.2]	133 ± 35.0 (26.4) 78.5 - 189 [124]	268 ± 53.0 (19.8) 165 - 346 [263]	0.385 ± 0.0416 (10.8) 0.325 - 0.447 [0.377]	2.25 ± 1.06 (47.1) 1.0 - 4.0 [2.0]	0.812 ± 0.141 (17.4) 0.594 - 1.060 [0.800]	21.1 ± 4.62 (21.9) 16.4 - 30.4 [20.7]	25.2 ± 4.58 (18.2) 19.5 - 34.5 [24.1]	–	340 ± 57.8 (17.0) 242 - 428 [347]	692 ± 94. (13.7) 508 - 838 [674]
	Mod[b]	10	10	10	8	–	10	8	8	10	10	10	10	8	–	8	8
		2.28 ± 1.77 (77.7) 0.25 - 6.02 [1.75]	1.60 ± 0.295 (18.4) 1.25 - 1.98 [1.47]	42.5 ± 15.2 (35.8) 23.7 - 72.7 [41.9]	56.5 ± 15.8 (28.0) 36.4 - 84.3 [52.9]	–	27.5 ± 6.4 (23.2) 17.8 - 36.8 [30.1]	158 ± 43.4 (27.5) 98.9 - 229 [158]	359 ± 61.3 (17.1) 262 - 433 [366]	0.457 ± 0.0504 (11.1) 0.386 - 0.544 [0.446]	2.28 ± 1.77 (77.7) 0.25 - 6.0 [1.75]	0.727 ± 0.142 (19.5) 0.591 - 1.020 [0.676]	19.0 ± 5.81 (30.5) 12.9 - 29.6 [17.2]	24.7 ± 6.34 (25.7) 17.4 - 34.3 [24.2]	–	357 ± 89.2 (25.0) 243 - 478 [347]	814 ± 125 (15.3) 679 - 998 [827]

a NL – Normal Healthy Volunteers
b Mod - Subjects with Moderate Hepatic Impairment

3.10.9 Effects of Extrinsic Factors

3.10.9.1 Food Effect

Seven food effect studies were conducted.

Study BEL-1 conducted with an IR tablet showed that food slowed the rate, but did not affect the extent of absorption, (see section 3.10.2.2). This most likely is an effect on upper GI transit and as the OROS formulation is absorbed throughout the GI tract the effect of food on the OROS formulation would be expected to possibly be different.

Study P01-101 examined the effect of food on bioavailability from both an OROS and from an ER formulation relative to a solution under fasted conditions. Both th and the OROS formulation showed about 40 – 50% relative bioavailability under fasting conditions and a small increase in biovailability in the presence of food, (i.e. ~ 20%), (see Table 46) and a about a 2 hour delay in Tmax for the OROS formulation. However, the results from this study should be interpreted cautiously as 20% of the paliperidone OROS dose was applied as an immediate release top layer and if food has a minimal effect on the extent of absorption of the IR component,t then the net effect of the total Cmax, Tmax, and AUC will be tempered.

Study P01-102 found a delay in Tmax and decrease in Cmax but a higher AUC with 2 formulations however, the extent of applicability to the OROS formulation is unclear, (see Table 47).

Study Alza-034 showed a increase in 36% -39% increase in Cmax, and AUC with the Slow release OROS formulation, with no change in Tmax, (see Table 45).

Study Alza-034

The Slow release OROS formulation shows approximately a 33% bioavailability compared to an immediate release tablet, and also appears to show a 35% - 40% increase in Cmax and AUC under fed conditions, with no change in Tmax, (see Table 45). However, histograms of the Cmax and AUC ratios under fed and fasted conditions clearly indicate that this magnitude of increase is driven by at least partially by an outlier), (see Figure 28 and Figure 29). Indicating that a least some individuals may have large increases, (≥ 10 fold). Standard geometric mean ratios and 90% confidence intervals on log transformed data would have been a useful comparison but were not performed by the sponsor.

Study P01-1006 was a single dose food effect study of with the 3 mg OROS CTF on the effect of standard Japanese breakfast on the bioavailability of paliperidone OROS in Japanese men and women. The sponsor calculated pharmacokinetic metrics in several ways. Based on the sponsor's calculation of geometric mean ratios the extent of absorption is increased by about 35% to 40% on average but in individuals there is up to a 6.6 fold increase in bioavailability, with no change in the rate of absorption, (see Table 104 and Table 105).

Alza-C-2004-006 was a single dose food effect study at an OROS dose of 15 mg that also incorporated a pilot study of OROS 12 mg and 15 mg under fasting conditions to determine if subjects could tolerate the potential orthostatic hypotension expected with the 15 mg dose food effect study. In all treatment arms subjects were to remain sitting for 4 hours post dose then were to remain either sitting or supine for an additional 44 hours, Under these conditions bioavailability decreased when administered with a high fat meal, however it was also lower with the 15 mg dose compared to the 12 mg dose by a similar amount when both were administered under fasting conditions. Consequently, this raises the possibility that the decrease in bioavailability seen in the presence of food is not due to the food per se but rather is due to postural position, (see
Table 106 and Table 107).

To follow-up on the issue of posture, the sponsor conducted study P01-1012, a 3-way single dose cross-over study of [redacted] paliperidone OROS 12 mg in healthy young male volunteers. One treatment arm employed Paliperidone OROS 12 mg under fasted conditions while supine for 36 hours, and the other 2 arms were under fed and fasted conditions while ambulatory. Posture had no effect on bioavailability · however there was a 55% increase in the AUC with a slightly greater increase in Cmax (60%) with a slightly shorter Tmax (2 hours less), (see Table 108, Table 109, and Figure 98).

Study P01-1008 studied the bioequivalence of [redacted] formulation to the CTF, and the effect of food on the bioavailability [redacted] formulation. Taking the [redacted] formulation with a high fat meal resulted in approximately a 47% average increase in the extent of absorption without a change in the rate as indicated by similar increases in both Cmax and AUCinf without any change in the Tmax, (see Table 114)

Ta 104 Effect of a Standard Japanese Breakfast on Bioavailability paliperidone OROS 3 mg in Japanese Subjects– Study P01-1006

Summary Statistics for Treatment Groups									Summary Stats for Fed/Fasted Individual Ratios[a]		
Fed/Fasted	Subjects	N	Tlag (h)	Cmax (ng/ml)	Tmax (h)	t½ (h)	AUClast (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	N	Cmax	AUCinf
Fed	All Subjects	20	2.70 ± 0.98 (36.2) 2.0 - 4.0 [2.0]	5.49 ± 4.59 (83.6) 1.0 - 22.7 [4.79]	21.1 ± 4.1 (19.4) 9.0 - 24.2 [22.0]	19.2 ± 3.42 (17.8) 11.8 - 26.0 [19.5]	167 ± 135 (80.5) 21.3 - 673 [148]	178 ± 148 (83.1) 23.9 - 737 [153]	–	–	–
	Without Subjects 100609 and 100616[b]	18	2.78 ± 1.0 (36.1) 2.0 - 4.0 [2.0]	4.79 ± 2.11 (44.1) 1.53 - 9.06 [4.79]	21.8 ± 3.1 (14.1) 12.0 - 24.2 [22.0]	19.1 ± 3.0 (15.6) 11.8 - 23.7 [19.5]	147 ± 59.1 (40.1) 52.5 - 245 [148]	155 ± 63.3 (40.8) 58.1 - 263 [153]	–	–	–
Fasted	All Subjects[c]	18	1.8 ± 0.65 (36.4) 0.0 - 2.0 [2.0]	3.8 ± 2.2 (58.9) 1.3 - 9.3 [3.33]	22.5 ± 3.3 (14.8) 16.0 - 27.0 [24.0]	20.1 ± 4.0 (20.1) 12.6 - 26.8 [20.1]	117 ± 70.8 (60.4) 45.2 - 301 [95.2]	124 ± 74.5 (60.3) 48.2 - 324 [102]	17	1.81 ± 1.55 (85.4) 0.538 - 5.38 [1.26]	1.77 ± 1.48 (83.8) 0.547 - 6.56 [1.20]
	Without Subject 100616[d]	17	1.8 ± 0.7 (37.6) 0.0 - 2.0 [2.0]	3.8 ± 2.3 (61.0) 1.3 - 9.3 [3.0]	22.7 ± 3.2 (14.2) 16.0 - 27.0 [24.0]	20.1 ± 4.2 (20.7) 12.6 - 26.8 [20.2]	118 ± 72.9 (61.9) 45.2 - 301 [89.1]	124 ± 76.7 (61.8) 48.2 - 324 [95.2]	16	1.60 ± 1.30 (81.4) 0.538 - 4.81 [1.19]	1.49 ± 0.90 (60.7) 0.547 - 3.54 [1.18]

a These are summary statistics for individual ratios, and are not geometric mean ratios.
b Descriptive statistics were also calculated without subjects 100609 and 100616, who had unexpected low (Cmax, Tmax, and AUC) and high (Cmax, AUC) values, respectively.
c Does not include Subjects 100609 and 100636, who withdrew during or after their first treatment (=fed conditions).
d Descriptive statistics and ratios were also calculated without Subject 100616.

Table 105 Sponsor's Calculations of the Effect of a Standard Japanese Breakfast on Bioavailability of Paliperidone OROS 3 mg in Japanese Subjects– Study P01-1006

Summary of pharmacokinetic parameters for paliperidone (mean ± SD)

	FED (n=20)	FASTED (n=18)	FED/FASTED ratio (%) (n=18)	90% CI (n=18)
C_{max} (ng/mL)	5.49 ± 4.59	3.81 ± 2.24	135.58	100.06-183.70
t_{max} (h)	21.06 ± 4.08	22.46 ± 3.32	-	-
$t_{1/2}$ (h)	19.2 ± 3.42	20.1 ± 4.03	-	-
AUC_{last} (ng.h/mL)	167 ±135	117 ± 70.8	137.11	104.05-180.68
AUC_{∞} (ng.h/mL)	178 ±148	124 ± 74.5	136.52	103.50-180.08

Note: Two subjects completed only 1 of the 2 periods; these subjects were excluded from the statistical analysis.

Table 106 Paliperidone Pharmacokinetic Metrics under Fasted and Fed Conditions in Two Groups in a Sitting or Supine Position – Study Alza-C-2004-006

	Group 1 - ER OROS 12 mg Fasted (A)							Group 1 - ER OROS 15 mg (9 mg & 2 x 3 mg) Fasted (B)							
	Cmax (ng/ml)	Tmax (h)	t½ (h)	AUCt (ng/ml x hr^{-1})	AUC(0-48) (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	Cavg (ng/ml)	Cmax (ng/ml)	Tmax (h)	t½ (h)	AUCt (ng/ml x hr^{-1})	AUC(0-48) (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	Cavg (ng/ml)	F (%) AUC0-48 TrtB/TrtA
All Subjects															
n	20	20	20	20	20	20	20	16	16	16	16	16	16	16	
Mean ± SD (%CV) Min - Max [Median]	23.2 ± 7.45 (32.2) 11.9 - 37.8 [23.20]	24.8 ± 2.3 (9.20) 18.0 - 27.0 [24.0]	17.9 ± 7.15 (39.9) 8.0 - 34.1 [16.5]	580.6 ± 160.8 (27.7) 360 - 917 [567.1]	580.6 ± 160.8 (27.7) 360 - 917 [567.1]	813.4 ± 276.9 (34.0) 474 - 1424 [785.7]	33.9 ± 11.5 (34.0) 20 - 59 [32.7]	22.7 ± 6.5 (28.8) 11.3 - 33.2 [23.0]	24.9 ± 1.8 (7.3) 22.0 - 27.0 [24.0]	16.7 ± 2.75 (16.5) 12.1 - 23.6 [16.7]	626.4 ± 177.9 (28.4) 335 - 893 [604.8]	626.4 ± 177.9 (28.4) 335 - 893 [604.8]	847.7 ± 278.6 (32.9) 466 - 1494 [812.9]	35.3 ± 11.6 (32.9) 19 - 62 [33.9]	
Gmean	22.01	24.7	16.6	559.9	559.9	770.5	32.1	21.7	24.8	16.5	600.9	600.9	806.2	33.6	
Excluding Subject(s) 114 116 117 119															
n	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16
Mean ± SD (%CV) Min - Max [Median]	22.1 ± 7.2 (32.5) 11.9 - 36.4 [22.0]	25.4 ± 1.7 (6.8) 22.0 - 27.0 [25.5]	15.8 ± 6.2 (39.2) 8.0 - 34.1 [15.1]	540.3 ± 139.6 (25.8) 360 - 835 [537.6]	540.3 ± 139.6 (25.8) 360 - 835 [537.6]	720.8 ± 210.1 (29.1) 474 - 1143 [691.5]	30.0 ± 8.8 (29.1) 20 - 48 [28.8]	22.7 ± 6.5 (28.8) 11.3 - 33.2 [23.0]	24.9 ± 1.8 (7.3) 22.0 - 27.0 [24.0]	16.7 ± 2.75 (16.5) 12.1 - 23.6 [16.7]	626.4 ± 177.9 (28.4) 335 - 893 [604.8]	626.4 ± 177.9 (28.4) 335 - 893 [604.8]	847.7 ± 278.6 (32.9) 466 - 1494 [812.9]	35.3 ± 11.6 (32.9) 19 - 62 [33.9]	97.3 ± 35.4 (36.4) 37 - 198 [92.8]
Gmean	21.0	25.3	14.8	524.1	524.1	693.8	28.9	21.7	24.8	16.5	600.9	600.9	806.2	33.6	91.7
	Group 2 - ER OROS 15 mg (9 mg & 2 x 3 mg) Fasted (C)							Group 2 - ER OROS 15 mg (9 mg & 2 x 3 mg) Fed (D)							
	Cmax (ng/ml)	Tmax (h)	t½ (h)	AUCt (ng/ml x hr^{-1})	AUC(0-48) (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	Cavg (ng/ml)	Cmax (ng/ml)	Tmax (h)	t½ (h)	AUCt (ng/ml x hr^{-1})	AUC(0-48) (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	Cavg (ng/ml)	F (%) AUC0-48 TrtB/TrtA
All Subjects															
n	20	20	20	20	20	20	20	19	19	19	19	19	19	19	
Mean ± SD (%CV) Min - Max [Median]	27.5 ± 8.7 (31.6) 9.7 - 47.7 [27.3]	24.25 ± 2.22 (9.1) 22.0 - 27.0 [24.0]	16.8 ± 2.5 (14.6) 13.6 - 22.0 [16.1]	767.2 ± 244.7 (31.9) 314 - 1378 [758.0]	767.2 ± 244.7 (31.9) 314 - 1378 [758.0]	1039.0 ± 348.5 (33.5) 385 - 1681 [1008.0]	43.3 ± 14.5 (33.5) 16 - 70 [42.0]	27.4 ± 12.5 (45.8) 4.1 - 45.4 [25.8]	23.0 ± 2.1 (9.3) 18.0 - 27.0 [24.0]	16.7 ± 2.2 (13.3) 12.7 - 21.6 [16.7]	770.6 ± 333.8 (43.3) 115 - 1249 [780.3]	784.3 ± 349.5 (44.6) 115 - 1278 [780.3]	1034.3 ± 480.3 (46.4) 154 - 1755 [979.6]	43.1 ± 20.0 (46.4) 6 - 73 [40.8]	
Gmean	26.1	24.2	16.7	730.3	730.3	982.4	40.9	23.4	22.9	16.6	662.0	670.0	879.6	36.7	
Excluding Subject(s) 127															
n	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19
Mean ± SD (%CV) Min - Max [Median]	27.4 ± 8.9 (32.5) 9.7 - 47.7 [27.3]	24.1 ± 2.18 (9.1) 22.0 - 27.0 [24.0]	17.0 ± 2.5 (14.5) 13.6 - 22.0 [16.3]	763.4 ± 250.8 (32.8) 314 - 1378 [749.1]	763.4 ± 250.8 (32.8) 314 - 1378 [749.1]	1038.1 ± 358.0 (34.5) 385 - 1681 [1000.8]	43.3 ± 14.9 (34.5) 16 - 70 [41.7]	27.4 ± 12.5 (45.8) 4.1 - 45.4 [25.8]	23.0 ± 2.1 (9.3) 18.0 - 27.0 [24.0]	16.7 ± 2.2 (13.3) 12.7 - 21.6 [16.7]	770.6 ± 333.8 (43.3) 115 - 1249 [780.3]	784.3 ± 349.5 (44.6) 115 - 1278 [780.3]	1034.3 ± 480.3 (46.4) 154 - 1755 [979.6]	43.1 ± 20.0 (46.4) 6 - 73 [40.8]	103.4 ± 42.2 (40.8) 23 - 187 [110.7]
Gmean	26.0	24.0	16.8	724.9	724.9	978.6	40.8	23.4	22.9	16.6	662.0	670.0	879.6	36.7	92.4

Table 107 Statistical Analysis of Log-transformed Pharmacokinetic Parameters for Paliperidone Following Paliperidone Treatments Fasted and Fed Conditions in Two Groups in a Supine Position (Normalized to 15 mg) – Study Alza C 2004 006

Contrast	n	Parameter	B 12 mg Fed	A 12 mg Fasted	Ratio (%) 90% CI
Trt B / Trt A	16	LN(AUC0-48)	600.9	524.1	91.7 78.31 - 107.43
		LN(Cmax)	21.7	21.0	82.8 67.5 - 101.5
Contrast	**n**	**Parameter**	**D 15 mg Fed**	**C 15 mg Fasted**	**Ratio (%) 90% CI**
Trt D / Trt C	19	LN(AUC0-48)	724.9	670.0	92.4 74.5 - 114.7
		LN(Cmax)	23.4	26	90.0 73.4 - 110.2

Table 108 Single Dose Pharmacokinetic Parameters of Paliperidone OROS under Fed and Fasted Conditions while Ambulatory and under Fasted Conditions while Supine - Study P01-1012

Table 7: Mean (±SD) Pharmacokinetic Parameters of Paliperidone After Administration of ER OROS Paliperidone, 12-mg Single Dose
(Study PALIOROS-P01-1012: Pharmacokinetic Analysis Set)

Parameter	Fed Ambulant (Treatment A) (N=58)	Fasted Ambulant (Treatment B) (N=59)	Fasted Bed (Treatment C) N=62)
t_{max}, h	20.00 (9.00 - 28.00)	22.00 (6.00 - 28.00)	24.00 (6.00 - 28.00)
C_{max}, ng/mL	29.2 ± 15.9	17.4 ± 7.21	18.6 ± 7.59
AUC_{last}, ng/mL.h	1103 ± 558	685 ± 297	720 ± 303*
AUC_{∞}, ng/mL.h	1179 ± 606	741 ± 330	775 ± 331*
$t_{1/2}$, h	21.1 ± 3.1	21.9 ± 3.3	21.7 ± 3.3*

Data presented as arithmetic mean ±SD. t_{max} presented as median (range).
* N=60.

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Table 109 Geometric Mean Ratios and 90% CI for Single Dose Pharmacokinetic Parameters of Paliperidone OROS und Fed and Fasted Conditions while Ambulatory and under Fasted Conditions while Ambulatory and Supine - Study P01-1012

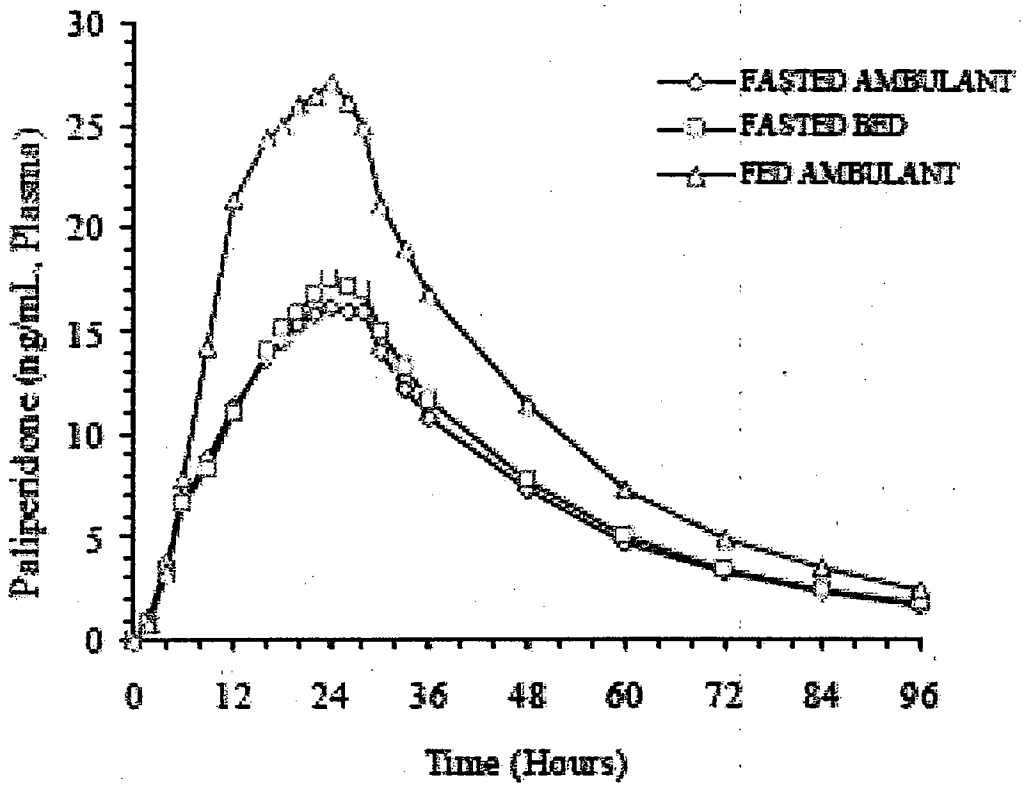
Table 8: Summary of the Statistical Analysis of the Food Effect and Posture Effect After Administration of ER OROS Paliperidone, 12-mg Single Dose (Study PALIOROS-P01-1012: Pharmacokinetic Analysis Set)

Test	Reference	Test/Reference Ratio, % (90% CI) *		
		C_{max}, ng/mL	AUC_{last}, ng h/mL	AUC_{∞}, ng h/mL
Fed Ambulant (Treatment A)	**Fasted Ambulant (Treatment B)**	159.56 (144.21 - 176.54)	155.51 (140.49 - 172.13)	153.94 (139.11 - 170.36)
Fasted **Bed** (Treatment C)	Fasted **Ambulant** (Treatment B)	106.08 (95.89 - 117.36)	103.92 (93.90 - 115.02)	103.71 (93.73 - 114.75)

* for the statistical analysis, data were analyzed on logarithmic scale, and transformed back to original scale.

Figure 98 Paliperidone OROS 12 mg Concentration vs. Time Profiles under and Fed and Fasted Conditions while Ambulatory and under Fasted Conditions while Supine - Study P01-1012

Figure 2: Mean Paliperidone Plasma Concentration-Time Profile (Study PALIOROS-P01-1012: Pharmacokinetic Analysis Set)



3.10.9.2 Drug-Drug Interactions

3.10.9.2.1 Trimethoprim

A single dose of paliperidone 6 mg was administered in combination with trimethoprim 200 mg q 12hours to determine if there is an interaction with respect to active renal secretion that might result in an increase in exposure to either paliperidone or trimethoprim. Paliperidone OROS 6 mg was administered as a single dose without trimethoprim, or on day 5 of an 8 day regimen of trimethoprim. On day 5 paliperidone and trimethoprim were administered at the same time.

When paliperidone was administered together with trimethoprim the significant changes for paliperidone included a 25% – 30% increase in the total and unbound Cmax of the paliperidone enantiomers with a decrease in total drug AUC. The average free fraction also increased by 15.5% for racemic paliperidone, 20.8% for (+)-paliperidone, and 9.4% for (-)-paliperidone. There was also a decrease in average half-life for each paliperidone species of about 5 hours. There was little change in other metrics including unbound AUC and no difference in unbound oral clearance (Clu/F), (see Table 110 to **Error! Reference source not found.**).
These observations are consistent with a protein binding displacement interaction without a change in active renal secretion. With a first dose of paliperidone or of trimethoprim or other displacers, there may be transient clinical consequences such as hypotension, somnolence ,or other cardiovascular side effects as was seen in this study, but this is likely to be less than with the food effect, (see Table 113).

The effect on trimethoprim pharmacokinetics was not fully examined. Pre-dose concentrations were obtained prior to paliperidone on all days, and 2 hour post-dose concentrations were obtained on day 6 and day 8, 26 and 74 hours after dosing with paliperidone. For each subject, 2 hour trimethoprim concentrations were lower on day 6 than on day 8. Although this possibly suggests a lack of an effect of paliperidone on trimethoprim pharmacokinetics, it is also consistent with a protein binding displacement of trimethoprim, prevention of reabsorption, some other mechanism, or assay interference.

Table 110 Paliperidone and Paliperidone Enantiomer Pharmacokinetic Metrics when Administered alone (6 mg SD) and in Combination with Trimethoprim 200 mg q12 hrs- Study P01-1004

Rx	Analyte	N	Cmax (ng/mL)	Cmax,u (ng/mL)	tmax (h)	AUClast (ng/ml x hr^{-1})	AUC∞ (ng/ml x hr^{-1})	AUC∞,u (ng/ml x hr^{-1})	t½ (h)	fu (%	CL/F (mL/min)	Clu/F (mL/min)	CL (mL/min)	Clu (mL/min)	Cmax Ratio B/A	AUClast Ratio B/A	AUC∞ Ratio B/A
Pal	Pal	30	9.78 ± 3.45 (35.3) 4.43 - 18.7 [9.53]	2.48 ± 0.840 (33.9) 1.08 - 4.28 [2.43]	23.53 ± 3.35 (14.2) 16.00 - 28.00 [24.00]	348 ± 119 (34.1) 172 - 648 [336]	391 ± 138 (35.4) 178 - 698 [376]	99.0 ± 33.2 (33.6) 43.5 - 180 [102]	26.8 ± 5.09 (19.0) 17.3 - 39.7 [25.6]	25.7 ± 3.81 (14.8) 18.8 - 32.7 [26.7]	290 ± 108 (37.2) 143 - 561 [266]	1130 ± 405 (35.8) 555 - 2300 [987]	80.3 ± 29.9 (37.2) 39.7 - 155 [73.6]	314 ± 112 (35.8) 154 - 636 [273]			
Pal + TMP		30	10.7 ± 3.67 (34.4) 3.92 - 22.6 [10.5]	3.16 ± 1.09 (34.4) 0.851 - 6.19 [3.07]	23.78 ± 2.63 (11.1) 11.42 - 28.00 [24.00]	330 ± 130 (39.3) 133 - 754 [317]	356 ± 148 (41.7) 141 - 854 [336]	106 ± 44.0 (41.7) 30.7 - 234 [97.2]	21.8 ± 3.57 (16.4) 13.3 - 29.9 [21.4]	29.7 ± 3.77 (12.7) 21.7 - 36.2 [30.0]	327 ± 135 (41.2) 117 - 707 [298]	1130 ± 567 (50.0) 427 - 3260 [1030]	90.7 ± 37.3 (41.2) 32.4 - 196 [82.5]	314 ± 157 (50.0) 118 - 903 [285]	1.18 ± 0.448 (37.8) 0.356 - 1.99 [1.12]	1.01 ± 0.376 (37.2) 0.343 - 1.80 [1.03]	0.966 ± 0.350 (36.3) 0.352 - 1.71 [0.968]
Pal	R078543 (+)-Pal	30	6.11 ± 2.23 (36.6) 2.88 - 11.7 [6.10]	1.13 ± 0.423 (37.5) 0.452 - 1.96 [1.10]	23.20 ± 3.13 (13.5) 16.00 - 28.00 [24.00]	209 ± 75.7 (36.2) 104 - 396 [209]	235 ± 87.2 (37.2) 113 - 424 [227]	43.3 ± 15.9 (36.7) 17.8 - 76.8 [41.8]	27.2 ± 5.18 (19.0) 17.7 - 39.5 [26.4]	18.7 ± 3.55 (18.9) 12.4 - 24.8 [18.3]	244 ± 95.0 (38.9) 118 - 442 [221]	1330 ± 540 (40.5) 651 - 2820 [1200]					
Pal + TMP		30	6.51 ± 2.38 (36.6) 2.63 - 14.2 [6.44]	1.47 ± 0.562 (38.1) 0.410 - 2.98 [1.47]	23.50 ± 3.12 (13.3) 9.00 - 28.00 [24.00]	195 ± 81.3 (41.7) 75.9 - 448 [176]	210 ± 92.8 (44.2) 80.1 - 506 [185]	47.8 ± 22.1 (46.2) 14.8 - 106 [43.3]	22.0 ± 3.71 (16.9) 12.9 - 30.2 [21.7]	22.6 ± 3.67 (16.2) 15.6 - 28.9 [23.1]	282 ± 121 (42.8) 98.8 - 624 [270]	1300 ± 677 (52.1) 471 - 3390 [1160]			1.16 ± 0.457 (39.4) 0.320 - 2.00 1.08	0.990 ± 0.375 (37.9) 0.331 - 1.84 1.01	0.946 ± 0.346 (36.6) 0.336 - 1.73 0.946
Pal	R078544 (-)-Pal	30	3.71 ± 1.25 (33.8) 1.61 - 7.04 [3.67]	1.32 ± 0.414 (31.3) 0.620 - 2.20 [1.34]	24.00 ± 2.63 (10.9) 18.00 - 28.00 [24.00]	138 ± 44.5 (32.2) 64.4 - 252 [134]	156 ± 51.9 (33.2) 70.1 - 274 [150]	55.8 ± 17.9 (32.1) 27.0 - 103 [57.8]	26.5 ± 5.15 (19.5) 16.9 - 39.4 [25.8]	36.1 ± 4.43 (12.3) 28.2 - 43.6 [36.7]	357 ± 125 (35.1) 183 - 713 [332]	990 ± 321 (32.4) 485 - 1850 [866]					
Pal + TMP		30	4.17 ± 1.33 (31.9) 1.31 - 8.38 [4.14]	1.65 ± 0.525 (31.9) 0.423 - 3.08 [1.64]	24.11 ± 2.66 (11.1) 11.42 - 28.00 [24.00]	135 ± 50.4 (37.4) 45.1 - 306 [137]	147 ± 56.5 (38.4) 55.0 - 348 [145]	58.2 ± 22.3 (38.3) 17.8 - 128 [55.8]	21.7 ± 3.58 (16.5) 13.8 - 29.4 [21.4]	39.5 ± 3.84 (9.7) 31.6 - 46.3 [39.0]	387 ± 151 (39.1) 144 - 909 [345]	999 ± 462 (46.2) 391 - 2810 [897]			1.22 ± 0.444 (36.6) 0.409 - 2.02 [1.19]	1.04 ± 0.382 (36.8) 0.358 - 1.78 [1.03]	0.997 ± 0.349 (35.0) 0.372 - 1.88 [0.999]

Table 111 Fraction Unbound in Plasma (fu %) for Paliperidone, its' Enantiomers, and Trimethoprim – Study P01-1004

N	Paliperidone		R078543 (+)		R078544 (-)		Trimethoprim
	Without Trimethoprim	With Trimethoprim	Without Trimethoprim	With Trimethoprim	Without Trimethoprim	With Trimethoprim	
30	25.7 ± 3.81 (14.8%) 18.8 - 32.7 [26.7]	29.7 ± 3.77 (12.7%) 21.7 - 36.2 [30.0]	18.7 ± 3.55 (18.9%) 12.4 - 24.8 [18.3]	22.6 ± 3.67 (16.2%) 15.6 - 28.9 [23.1]	36.1 ± 4.43 (12.3%) 28.2 - 43.6 [36.7]	39.5 ± 3.84 (9.7%) 31.6 - 46.3 [39.0]	57.7 ± 1.93 (3.4%) 52.7 - 61.2 [58.0]
Approximate Average Increase	1.09x		1.21x		1.16x		–

Table 112 Geometric Means and Geometric Mean Ratio for Paliperidone and Paliperidone Enantiomer Pharmacokinetic Metrics when Administered Alone (6 mg SD) and in Combination with Trimethoprim 200 mg q12 hours- Study P01-1004

Analyte	Parameter	Treatment A Paliperidone Alone	Treatment B Paliperidone + Trimethoprim	Geometric Mean Ratio (90% CI)	p - value
Paliperidone	Cmax (ng/ml)	9.19 (8.21 - 10.28)	10.06 (8.99 - 11.26)	109.53 (96.20 - 124.71)	0.24
	Cmax,u (ng/ml)	2.34 (2.08 - 2.63)	2.96 (2.64 - 3.33)	126.63 (111.36 - 144.01)	0.0041
	AUClast (ng/ml x hr^{-1})	328.4 (292.8 - 368.3)	307.4 (274.0 - 344.7)	93.59 (82.39 - 106.32)	0.38
	AUC∞ (ng/ml x hr^{-1})	367.4 (326.4 - 413.6)	329.8 (292.9 - 371.2)	89.75 (79.37 - 101.51)	0.15
	AUC∞,u (ng/ml x hr^{-1})	93.56 (82.86 - 105.6)	97.09 (85.98 - 109.6)	103.78 (91.96 - 117.12)	0.61
	CLR (mL/min)	49.99 (45.34 - 55.13)	56.61 (51.34 - 62.43)	113.24 (108.23 - 118.47)	<0.001
R078543 (+) Paliperidone	Cmax (ng/ml)	5.71 (5.08 - 6.43)	6.10 (5.42 - 6.87)	106.86 (93.37 - 122.31)	0.41
	Cmax,u (ng/ml)	1.05 (0.93 - 1.19)	1.36 (1.20 - 1.55)	129.64 (112.58 - 149.27)	0.0041
	AUClast (ng/ml x hr^{-1})	196.4 (173.8 - 221.8)	179.8 (159.1 - 203.1)	91.55 (80.47 - 104.15)	0.25
	AUC∞ (ng/ml x hr^{-1})	219.4 (193.6 - 248.5)	192.7 (170.1 - 218.3)	87.86 (77.63 - 99.43)	0.086
	AUC∞,u (ng/ml x hr^{-1})	40.39 (35.30 - 46.22)	43.05 (37.63 - 49.26)	106.58 (93.68 - 121.26)	0.41
	CLR (mL/min)	33.24 (30.05 - 36.76)	37.32 (33.74 - 41.27)	112.28 (107.04 - 117.79)	<0.001
R078544 (-) Paliperidone	Cmax (ng/ml)	3.50 (3.14 - 3.90)	3.96 (3.55 - 4.41)	112.95 (99.65 - 128.03)	0.11
	Cmax,u (ng/ml)	1.26 (1.13 - 1.40)	1.56 (1.40 - 1.73)	123.91 (109.80 - 139.85)	0.0054
	AUClast (ng/ml x hr^{-1})	131.2 (117.6 - 146.5)	126.2 (113.1 - 140.9)	96.19 (84.67 - 109.28)	0.61
	AUC∞ (ng/ml x hr^{-1})	148.1 (132.7 - 165.3)	138.0 (123.6 - 154.0)	93.17 (82.75 - 104.91)	0.32
	AUC∞,u (ng/ml x hr^{-1})	53.07 (47.47 - 59.34)	54.25 (48.52 - 60.65)	102.21 (91.20 - 114.55)	0.75
	CLR (mL/min)	74.59 67.97 - 81.85)	82.86 (75.51 - 90.92)	111.08 (106.51 - 115.86)	<0.001

Figure 99 Paliperidone and Enatiomer Naïve Pooled Concentration vs. Time Profiles in the Presence and Absence of Trimethoprim – Study P01-1004

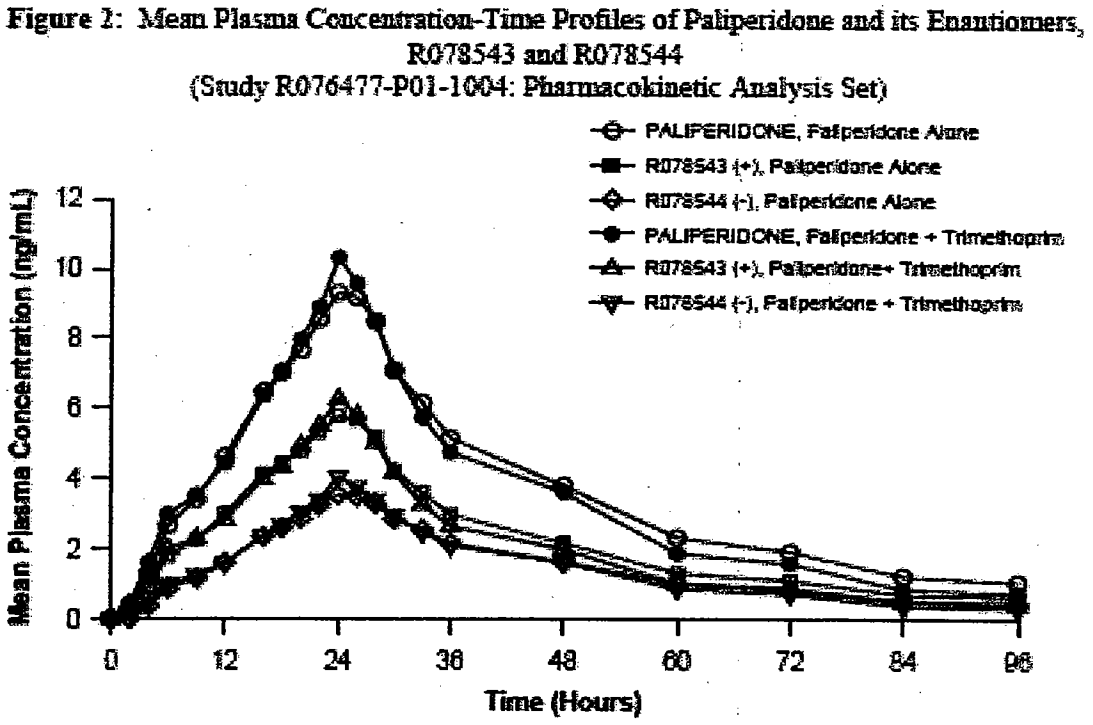
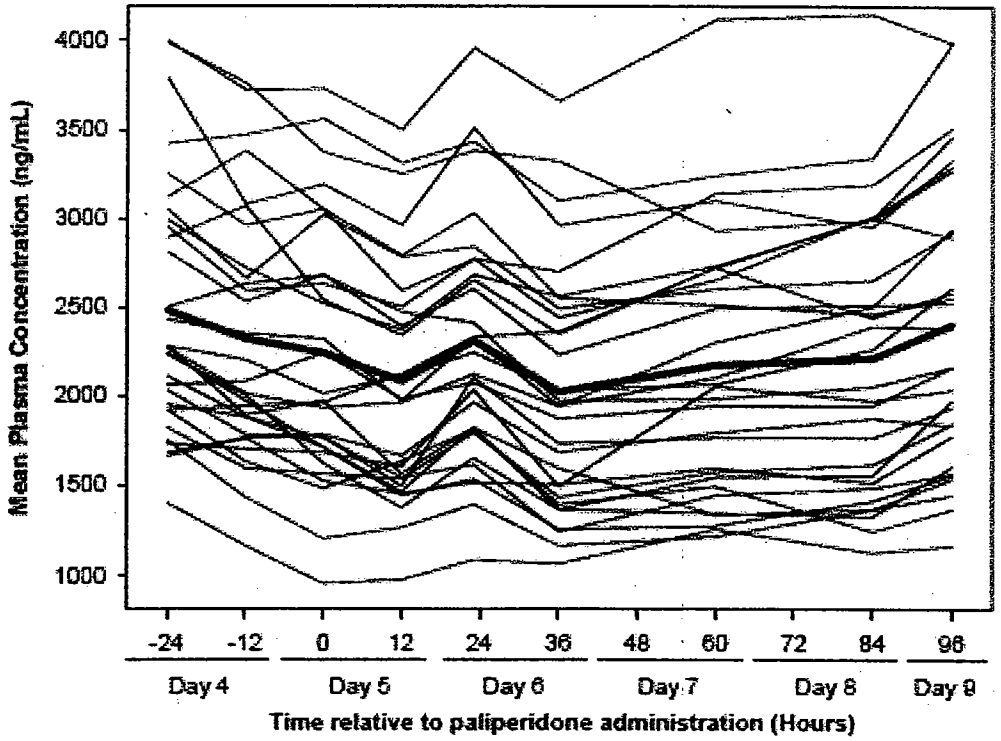


Figure 100 Trimethoprim Concentrations Morning and Evening – Study P01-1004



Bold line is arithmetic mean

Table 113 Incidence of Treatment-Emergent Adverse Events by Body System and Preferred Term by Treatment – Study P01-1004

Body System Preferred Term	TRIM ONLY (N=30) n (%)	TRIM+PAL (N=30) n (%)	PAL ONLY (N=30) n (%)	Total (N=30) n (%)
Total no. subjects with adverse events	**5 (16.7)**	**22 (73.3)**	**18 (60.0)**	**25 (83.3)**
Gastro-intestinal system disorders	**2 (6.7)**	**11 (36.7)**	**6 (20.0)**	**14 (46.7)**
Flatulence	1 (3.3)	10 (33.3)	4 (13.3)	11 (36.7)
Diarrhoea	1 (3.3)	1 (3.3)	1 (3.3)	3 (10.0)
Mouth dry	0	3 (10.0)	0	3 (10.0)
Nausea	0	1 (3.3)	0	1 (3.3)
Tooth ache	0	0	1 (3.3)	1 (3.3)
Cardiovascular disorders, general	**0**	**8 (26.7)**	**3 (10.0)**	**9 (30.0)**
Hypotension postural	0	8 (26.7)	3 (10.0)	9 (30.0)
Centr & periph nervous system disorders	**1 (3.3)**	**5 (16.7)**	**3 (10.0)**	**7 (23.3)**
Headache	1 (3.3)	4 (13.3)	3 (10.0)	6 (20.0)
Dizziness	0	2 (6.7)	1 (3.3)	3 (10.0)
Psychiatric disorders	1 (3.3)	5 (16.7)	3 (10.0)	7 (23.3)
Somnolence	1 (3.3)	5 (16.7)	3 (10.0)	7 (23.3)
Concentration impaired	0	1 (3.3)	0	1 (3.3)
Body as a whole - general disorders	**0**	**3 (10.0)**	**5 (16.7)**	**6 (20.0)**
Fatigue	0	2 (6.7)	5 (16.7)	5 (16.7)
Back pain	0	0	1 (3.3)	1 (3.3)
Injury	0	1 (3.3)	0	1 (3.3)
Skin and appendages disorders	**1 (3.3)**	**2 (6.7)**	**0**	**3 (10.0)**
Acne	0	1 (3.3)	0	1 (3.3)
Dermatitis	1 (3.3)	0	0	1 (3.3)
Rash	0	1 (3.3)	0	1 (3.3)
Urinary system disorders	**1 (3.3)**	**1 (3.3)**	**0**	**2 (6.7)**
Micturition disorder	0	1 (3.3)	0	1 (3.3)
Polyuria	1 (3.3)	0	0	1 (3.3)
Vision disorders	**0**	**2 (6.7)**	**0**	**2 (6.7)**
Conjunctivitis	0	1 (3.3)	0	1 (3.3)
Vision abnormal	0	1 (3.3)	0	1 (3.3)
Hearing and vestibular disorders	**0**	**1 (3.3)**	**0**	**1 (3.3)**
Ear ache	0	1 (3.3)	0	1 (3.3)
Resistance mechanism disorders	**0**	**1 (3.3)**	**0**	**1 (3.3)**
Infection viral	0	1 (3.3)	0	1 (3.3)

Note: Incidence is based on the number of subjects, not the number of events

3.10.10 Pivotal Bioequivalence Study

Study P01-1008 was a single dose, randomized, 3 treatment, 3 period, 3-way crossover study of the bioequivalence of the 15 mg [redacted] to the phase III clinical trial formulation (CTF), and of the effect of a high fat breakfast on the [redacted] formulation in healthy males.

Treatments were as follows:

Treatment A	Paliperidone ER OROS 15 mg Phase 3 CTF formulation administered as 3 mg and 9 mg tablets in the fasted state	
Treatment B	Paliperidone ER OROS 15 mg [redacted]	in the fasted state
Treatment C	Paliperidone ER OROS 15 mg [redacted]	in the fed state

Results are shown in Table 114. The CTF and [redacted] formulations were bioequivalent, however administration with a high fat meal resulted in approximately a 45% increase in bioavailability as indicated by similar increases in both Cmax and AUCinf without any change in the Tmax.

Table 114 Bioequivalence of Paliperidone OROS [redacted] and CTF and the Effect of a High Fat Meal [redacted] · Study P01-1008

	All Subjects			Subjects Used in Inferential Analyses				
Treatment Code	A	B	C	A	B	C	Geometric Mean Ratio (90% CI)	
Formulation	CTF	[redacted]	[redacted]	CTF	[redacted]	[redacted]	[redacted] CTF Fasted	[redacted] Fed / Fasted
Strengths	3 mg & 9 mg	15 mg	15 mg	3 mg & 9 mg	15 mg	15 mg		
Food	Fasted	Fasted	Fed	Fasted	Fasted	Fed		
N	66	63	71	58	58	58		
Tmax (h)	22.67 ± 2.59 (11.4) 16.00 - 28.05 [22.07]	22.70 ± 3.09 (13.6) 12.00 - 28.00 [24.00]	21.30 ± 4.58 (21.5) 12.00 - 33.52 [22.00]	22.56 ± 2.67 (11.8) 16.00 - 28.05 [22.03]	22.52 ± 3.12 (13.9) 12.00 - 28.00 [23.99]	21.01 ± 4.27 (20.3) 12.00 - 28.00 [22.00]		
Cmax (ng/ml)	22.1 ± 8.16 (36.9) 9.10 - 50.1 [21.5]	22.8 ± 9.84 (43.1) 5.12 - 52.0 [22.1]	32.1 ± 15.6 (48.4) 11.6 - 95.5 [27.9]	21.5 ± 7.35 (34.2) 9.10 - 37.8 [21.5]	22.1 ± 9.25 (41.8) 5.12 - 51.8 [22.1]	32.3 ± 16.8 (51.9) 11.6 - 95.5 [27.5]	100.7 (91.6 - 110.6)	142.3 (129.4 - 156.4)
AUClast ($ng/ml \times hr^{-1}$)	815 ± 294 (36.0) 361 - 1493 [784]	799 ± 320 (40.0) 178 - 1783 [753]	1162 ± 533 (45.9) 410 - 2907 [1016]	796 ± 281 (35.3) 361 - 1385 [784]	774 ± 302 (39.1) 178 - 1783 [737]	1161 ± 572 (49.3) 410 - 2907 [1006]	96.1 (88.4 - 104.5)	145.6 (133.9 - 158.3)
AUCinf ($ng/ml \times hr^{-1}$)	886 ± 329 (37.2) 389 - 1608 [869]	867 ± 349 (40.2) 185 - 1957 [797]	1262 ± 598 (47.4) 439 - 3269 [1091]	862 ± 320 (37.1) 389 - 1608 [867]	838 ± 336 (40.2) 185 - 1957 [784]	1263 ± 644 (51.0) 439 - 3269 [1076]	96.00 (88.21-104.48)	145.78 (133.91-158.68)
AUC_{extrap} (%)	7.53 ± 2.97 (39.4) 3.59 - 16.2 [7.17]	7.54 ± 2.98 (39.6) 3.35 - 17.6 [7.08]	7.39 ± 2.80 (37.9) 2.45 - 16.5 [6.86]	7.59 ± 3.06 (40.3) 3.59 - 16.2 [7.17]	7.49 ± 3.02 (40.3) 3.35 - 17.6 [7.01]	7.43 ± 2.96 (39.8) 2.45 - 16.5 [6.88]		
$t_{1/2}$ (h)	22.9 ± 3.55 (15.5) 16.9 - 33.0 [22.6]	22.7 ± 3.82 (16.8) 17.2 - 35.2 [22.1	23.0 ± 3.40 (14.8) 16.8 - 33.5 [22.6]	23.0 ± 3.64 (15.8) 16.9 - 33.0 [22.6]	22.9 ± 3.88 (16.9) 17.2 - 35.2 [22.0]	23.0 ± 3.58 (15.6) 16.8 - 33.5 [22.6]		

10 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 13

32 Page(s) Withheld

_____ Trade Secret / Confidential

V Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 14

4.4 Appendix 4: Consults

4.4.1 Pharmacometric QT Consult

4.5 Appendix 5: Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-999	**Brand Name**	[redacted]
OCPB Division (I, II, III)	I	**Generic Name**	Paliperidone Extended Release Tablets
Medical Division	Psychiatry	**Drug Class**	Antipsychotic
OCPB Reviewer	Ron Kavanagh	**Indication(s)**	Schizophrenia
OCPB Team Leader	Ray Baweja	**Dosage Form**	MR Tablet
INDs	65,850 [redacted]	**Dosing Regimen**	QD
Date of Submission	November 30, 2005	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	July 30, 2005	**Sponsor**	Jannsen, L.P
PDUFA Due Date	September 30, 2005	**Sponsor's Agent**	J&JPRD Titusville, NJ
Division Due Date	August 30, 2005	**Priority Classification**	S

Clin. Pharm. and Biopharm. Information	**"X" if included at filing**	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments if any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	5		
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	2		
Blood/plasma ratio:		0		
Plasma protein binding:	X	2		
Cell Transport:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	11		
multiple dose:	X	2		
Patients-				
single dose:		0		
multiple dose:	X	3		
Dose proportionality -				
fasting / non-fasting single dose:	X	4		
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:		0		
In-vitro:	X	2		
Subpopulation studies -				
ethnicity:	X	1		
gender:	X	6		
pediatrics:		0		
geriatrics:	X	1		
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	8		

Phase 3 clinical trial:	X	5		
Population Analyses -				
Data rich:				
Data sparse:	X	5		
II. Biopharmaceutics				
Absolute bioavailability:	X	1		
Relative bioavailability -	X	4		
solution as reference:	X	5		
alternate formulation as reference:	X	3		
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:		0		
Food-drug interaction studies:	X	5		
Dissolution:	X	2		
(IVIVC):	X	3		
Bio-wavier request based on BCS		0		
BCS class		0		
III. Other CPB Studies				
Genotype/phenotype studies:	X	8		
Chronopharmacokinetics		0		
Pediatric development plan	X			
Literature References	X			
Total Number of Studies		**95/44**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	Are exposure similar to exposures obtained with risperidone? [redacted]	
Other comments or information not included above	Many studies with multiple objectives.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-999, HFD-850 (P. Lee, GobburuJ), HFD-860 (KavanaghR, JacksonA, BawejaR, M. Mehta), Psychiatry (KeidrowK), CDR

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/s/

Ron Kavanagh
9/12/2006 06:30:06 PM
BIOPHARMACEUTICS

Raman Baweja
9/12/2006 07:03:08 PM
BIOPHARMACEUTICS