

CHAPTER 4

RESULTS

Subjects

The demographic characteristics of the 24 subjects were illustrated in Table 4. The mean \pm SD of age, weight, height, and BMI of the subjects were 21.08 ± 5.06 y, 64.02 ± 6.09 kg, 172.50 ± 5.28 m, and 21.41 ± 2.24 kg/m², respectively. All subjects were healthy on the basis of medical history, physical, hematological and biochemical investigations (Table 5). None was withdrawn from this study.

Method Validation

1. Specificity

Quetiapine and IS were clearly separated from the plasma with the retention times of 6.091 and 8.612 min, respectively. The chromatograms of blank plasma and quetiapine and IS were shown in Figure 7 and 8, respectively. Both peaks were clearly separated and no interference from endogenous substances was observed.

2. LLOQ

LLOQ with acceptable accuracy of 109.68% and precision of 2.45%, was 9 ng/ml (Table 6).

3. Calibration curve and linearity

The calibration curve of standard quetiapine was linear over the range of 9-1,737 ng/ml (Table 7 and Figure 9). The regression equation for the calibration curve of peak area ratio of quetiapine and IS (y) versus plasma quetiapine concentration (x) was $y = 0.0118x - 0.0338$. The correlation coefficient (r^2) of calibration curve was 0.9997 (Figure 9).

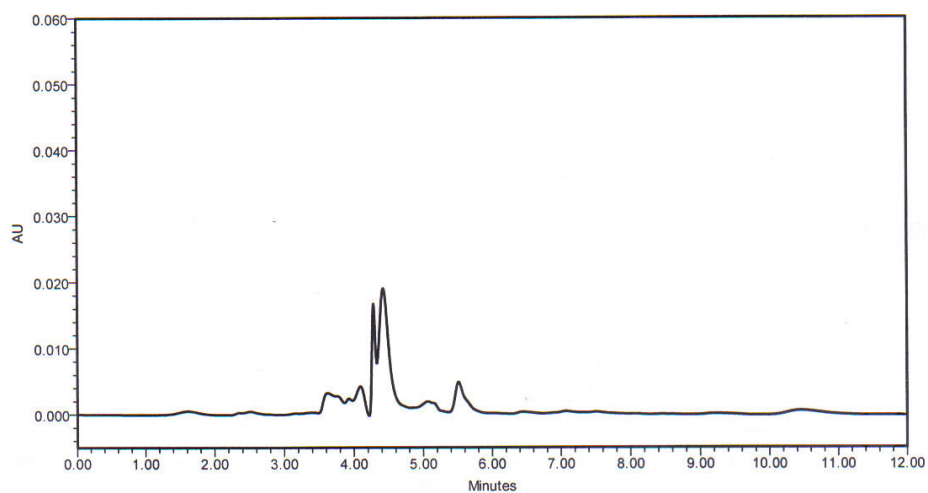


Figure 7. Chromatogram of blank plasma.

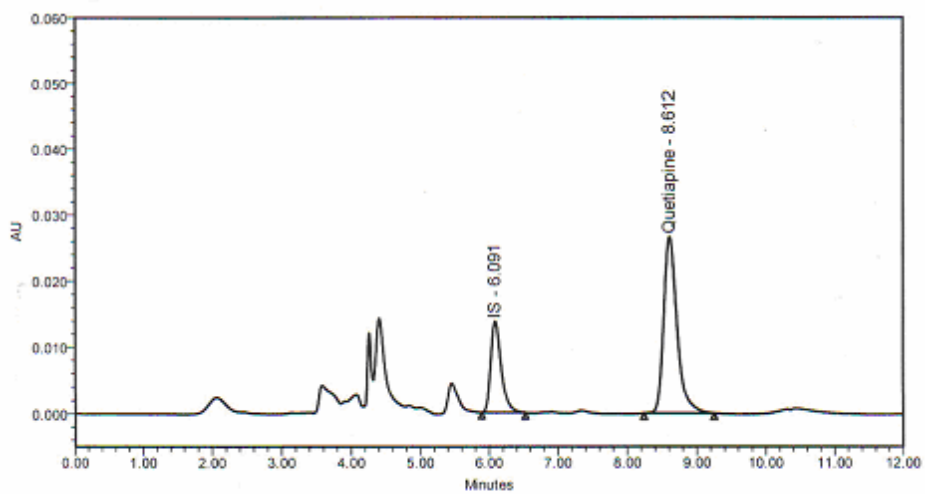


Figure 8. Chromatogram and retention time of IS and quetiapine 217 ng/ml in plasma sample

Table 4. Demographic data of 24 healthy male volunteers enrolled in the study.

Subject No.	Age (y)	Weight (kg)	Height (cm)	BMI (kg/m²)
1	20	60	169	21.01
2	24	64	165	23.50
3	20	65	168	20.51
4	19	53	171	18.12
5	19	59	176	19.04
6	20	61	176	19.69
7	20	59	175	19.27
8	23	70.5	168	24.98
9	19	66.5	168	23.56
10	21	60	174	19.82
11	21	64	170	22.15
12	20	70	178	22.09
13	20	63.5	173	21.21
14	20	54	167	19.36
15	21	69	170	23.86
16	21	72	170	24.91
17	20	57	174	18.82
18	18	77	181	23.50
19	44	64	160	25.00
20	19	60	181	18.31
21	19	67	175	21.00
22	20	63	180	19.44
23	19	63	173	21.05
24	19	75	178	23.67
Mean	21.08	64.02	172.50	21.41
SD	5.06	6.09	5.28	2.24

Table 5. Laboratory data of 24 healthy volunteers enrolled in the study.

Subject No.	FBS	BUN	Cr	DBI	TBL	SGPT	SGOT	ALP	TP	ALB	WBC	Hct	Hb	PMN	E	Lymp
1	78	14.85	1.09	0.20	0.96	20	27	82	8.20	5.29	8,150	48	16.0	41	2	54
2	70	11.00	1.00	0.20	1.00	23	23	108	7.60	4.90	5,000	46	15.3	45	2	46
3	78	8.00	0.90	0.20	0.82	25	21	104	7.00	5.20	6,200	44	14.6	58	6	33
4	75	10.00	0.80	0.19	0.89	12	17	96	7.50	4.90	6,250	48	16.0	40	4	51
5	75	13.00	0.90	0.20	0.94	13	22	102	7.20	5.10	6,750	45	15.0	63	6	24
6	77	18.00	1.00	0.35	0.60	10	20	118	8.10	5.70	6,150	44	14.6	52	4	40
7	76	11.00	1.00	0.18	0.90	14	17	77	7.50	5.20	7,700	45	15.0	49	1	45
8	84	10.00	1.20	0.30	1.13	18	29	120	7.90	5.20	9,650	47	15.6	56	2	39
9	82	12.00	1.00	0.25	1.00	13	18	67	7.10	5.00	7,300	45	15.0	52	3	37
10	75	8.38	1.07	0.20	0.94	11	20	106	7.55	5.04	7,600	45	15.0	46	2	44
11	80	8.20	1.00	0.21	1.10	28	23	76	7.27	5.21	4,500	46	15.3	37	3	55
12	80	11.48	0.84	0.20	1.00	14	21	83	7.53	4.90	5,000	40	13.3	53	5	39
13	83	10.45	0.92	0.20	0.77	11	20	65	6.81	4.61	7,050	44	14.6	47	4	43
14	77	10.97	0.80	0.19	1.00	23	24	86	6.90	4.85	5,150	48	16.0	53	3	39
15	81	12.35	0.96	0.17	1.00	40	30	79	7.64	5.08	6,000	47	15.6	50	2	43
16	85	10.53	1.02	0.19	0.72	23	24	70	7.50	4.67	6,950	43	14.3	50	5	43
17	79	7.00	0.90	0.18	0.97	14	17	70	6.80	4.50	5,050	42	14.0	53	2	40
18	77	9.00	0.90	0.20	1.00	28	21	90	7.10	5.00	7,350	43	14.3	43	3	52
19	84	12.10	1.01	0.20	0.89	31	27	88	7.10	4.60	5,950	42	14.0	43	2	51
20	85	11.00	1.03	0.31	1.18	10	22	77	7.90	5.00	5,500	45	15.0	66	2	29
21	81	9.80	0.89	0.20	0.84	15	17	102	7.50	4.70	7,400	45	15.0	46	6	44
22	78	10.40	1.01	0.20	0.90	13	18	67	7.10	4.70	5,550	41	13.6	62	2	33
23	79	7.00	0.83	0.20	1.00	23	23	85	7.10	4.80	7,500	48	16.0	43	1	54
24	86	9.50	0.95	0.20	1.00	36	26	91	7.00	4.80	5,000	42	14.0	62	3	34
Mean	79.38	10.67	0.96	0.21	0.94	19.50	21.96	87.88	7.37	4.96	6445.83	44.71	14.88	50.42	3.13	42.17
S.D.	3.93	2.43	0.10	0.04	0.13	8.52	3.83	16.11	0.39	0.27	1257.49	2.31	0.78	7.82	1.54	8.16

Table 6. LLOQ of quetiapine in plasma.

No	Peak area		Peak area ratio	Concentration (ng/ml)
	Quetiapine	IS		
1	7,203	99,652	0.072	9.41
2	8,646	118,477	0.073	9.49
3	7,197	102,991	0.070	9.23
4	7,452	97,076	0.077	9.84
5	7,140	95,203	0.075	9.66
			Mean	9.53
			SD	0.23

% CV = 2.45
% Accuracy = 109.68

Table 7. Calibration curve data of quetiapine in plasma.

No.	Conc. (ng/ml)	Peak area of quetiapine	Peak area of IS	Peak area ratio
1	9	10,893	104,449	0.10
2	35	46,878	114,205	0.41
3	109	121,171	109,338	1.11
4	217	285,179	117,498	2.43
5	434	522,382	105,198	4.97
6	869	1,112,395	106,333	10.46
7	1,737	2,070,574	101,463	20.41

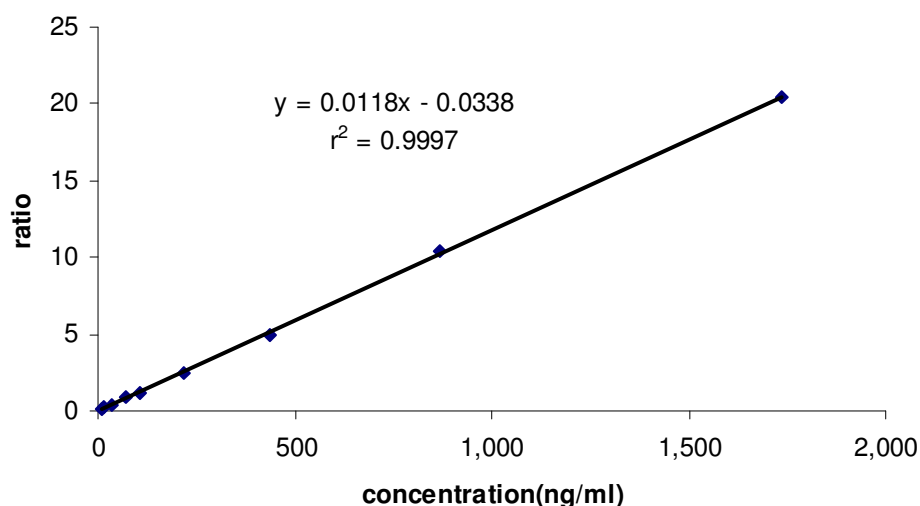


Figure 9. The calibration curve of standard quetiapine.

4. Precision and accuracy

Precision and accuracy for this method were controlled by calculating the intra-day and inter-day at three concentrations (13, 347 and 1,042 ng/ml) in five replicates. As shown in Table 8, the intra-day accuracy ranged between 87.48 - 100.77% with a precision (%CV) of 1.71- 5.79%. The inter-day accuracy ranged between 99.61- 102.40% with a precision (%CV) of 2.92 - 8.31% (Table 9).

5. Recovery

Mean extraction recoveries of quetiapine at concentrations of 13, 347 and 1,042 ng/ml were 99.17, 90.38 and 94.09%, respectively, and the extraction recovery of the IS was 101.55% (Table 10).

Table 8. The intra-day variance of three different quetiapine concentrations in plasma

Theoretical conc. (ng/ml)	Calculated conc. (ng/ml)								
	1	2	3	4	5	Mean	SD	% CV	% Accuracy
13	11.52	11.13	12.07	10.59	11.68	11.40	0.56	4.96	87.48
347	332.46	382.15	334.26	345.66	355.98	350.10	20.27	5.79	100.77
1,042	984.73	957.92	939.94	953.72	965.23	960.31	16.47	1.71	92.14

Table 9. The inter-day variance of three different quetiapine concentrations in plasma

Theoretical conc. (ng/ml)	Calculated conc. (ng/ml)								
	Day 1	Day 2	Day 3	Day 4	Day 5	Mean	SD	% CV	% Accuracy
13	14.49	11.44	13.09	12.91	12.96	12.98	1.08	8.31	99.61
347	371.56	332.46	385.41	353.61	327.48	354.10	24.81	7.01	101.92
1,042	1,070.36	1,046.43	1,106.95	1,027.92	1,085	1,067.33	31.15	2.92	102.40

Table 10. Recovery of quetiapine and IS in plasma

Theoretical conc.(ng/ml)	Sample	Calculated conc. (ng/ml)					Mean	SD	% CV	% Accuracy
		1	2	3	4	5				
Low (13)	in plasma	8.92	12.43	10.99	11.08	11.89	11.06	1.34	12.1	84.90
	in mobile phase	11.47	11.73	10.23	12.00	10.58	11.20	0.76	6.79	85.98
	% recovery	77.76	105.95	107.44	92.34	112.36	99.17	14.08	14.19	
Medium (347)	in plasma	358.83	360.81	368.2	372.70	377.48	367.60	7.86	2.14	105.81
	in mobile phase	419.52	424.57	376.42	375.54	447.57	408.73	31.71	7.76	117.65
	% recovery	85.53	84.98	97.81	99.24	84.34	90.38	7.47	8.26	
High (1,042)	in plasma	984.73	957.92	939.94	953.72	965.24	960.31	16.47	1.71	92.14
	in mobile phase	992.38	1,024.98	1,030.19	1,041.03	1,017.25	1,021.17	18.27	1.79	97.98
	% recovery	99.23	93.46	91.24	91.61	94.89	94.09	3.23	3.43	
IS (150)	in plasma	157.06	174.28	145.39	166.50	155.39	159.72	11.06	6.92	106.48
	in mobile phase	139.83	162.61	145.39	184.28	155.94	157.61	17.35	11.01	105.07
	% recovery	112.32	107.17	100.00	90.35	99.64	101.90	8.34	8.19	

6. Stability

6.1 Freeze-thaw stability

Stability of quetiapine at the concentrations of 13, 347, and 1,042 ng/ml kept frozen at -70 °C before and after freeze and thaw was presented in Table 11. After 3 cycles of freezing and thawing, the percentages of quetiapine change at the concentrations of 13, 347, and 1,042 ng/ml were 1.38, 7.42 and 4.10%, respectively

6.2 Short-term stability

Short-term stability was investigated to ensure that quetiapine was not degraded in plasma samples at room temperature for the time period covering the sample preparation. QC samples at concentrations of 13, 347, and 1,042 ng/ml were left at room temperature for 2 and 6 h. The samples were then processed and analyzed. The results showed in Table 12, indicated that quetiapine was stable during the exposure period. The percentages of quetiapine change at the concentrations of 13, 347, and 1,042 ng/ml after standing at room temperature were 7.57, 6.94 and 3.32%, respectively.

6.3 Long-term stability

The stability of quetiapine was evaluated by analyzing QC samples kept at -70 °C for 15 days and 1 month. Quetiapine was stable for 1 month with 4.11, 8.68 and 10.91% change at the concentrations of 13, 347, and 1,042 ng/ml, respectively (Table 13).

6.4 Post-preparative stability

As delayed injection may occasionally occur, therefore stability of quetiapine was evaluated by leaving the samples in the autosampler for 6 h before injection into the HPLC system. The quantitative results indicated that quetiapine was stable in the autosampler up to at least 6 h with 0, 2.74 and 1.58% change at the concentrations of 13, 347, and 1,042ng/ml, respectively (Table 14).

7. Stock solution stability

Stock solutions of quetiapine (43 µg/ml) and IS (10 µg/ml) in methanol were stable, when kept for at least 14 days at -70 °C. The stability test of sample solutions showed that quetiapine and IS were stable in the mobile phase for at least 6 h

at room temperature. There was no evidence of degradation of quetiapine and IS under these conditions (Table 15).

Pharmacokinetics and bioequivalence assessment

The plasma concentration-time profiles of the two quetiapine products of each subject were shown in Figures 10-33. The mean plasma concentration-time curves of the two quetiapine formulations in 24 healthy male volunteers with a single 200-mg oral dose were shown in Figure 34. The individual and mean values with SD of plasma quetiapine concentrations at various sampling times from 24 subjects after a single oral dose of 200 mg of Seroquel[®] and Quantia 200[®] were presented in Tables 16 and 17, respectively. Quetiapine pharmacokinetic parameters of individual subjects following after single oral dose of 200-mg of Seroquel[®] and Quantia 200[®] were presented in Tables 18 and 19, respectively.

Comparison of quetiapine pharmacokinetic parameters of individual subjects following a single oral dose of 200 mg of Quantia 200[®] and Seroquel[®] was shown in Table 20. The means \pm SD of C_{max} for the test and reference formulations were 886.60 ± 356.50 and 811.34 ± 323.37 ng/ml, respectively. The extent of absorption, as determined from AUC_{0-48} and $AUC_{0-\infty}$ values, were $3,754.41\pm 1,453.00$ and $3,520\pm 1,229.61$ ng.h/ml, respectively after the administration of the test formulation, and $4,015.35\pm 1,528.25$ and $3,769.45\pm 1,296.69$ ng.h/ml, respectively, after the administration of the reference formulation. $T_{1/2}$ for the test and reference formulations were 5.26 ± 2.63 and 5.53 ± 2.83 , respectively.

Mean \pm SD of T_{max} of the test and reference formulations were 1.08 ± 0.78 and 1.10 ± 0.79 , respectively. The difference of T_{max} of the test and reference formulations was 1.82% which was less than 20%.

The mean extrapolate portion of the plasma concentration-time curves of Quantia 200[®] and Seroquel[®] were 6.55 and 6.58%, respectively, which were less than the acceptable value of 20%.

Statistical analysis of BE

The results of two-way ANOVA test of the ln-transform data of C_{max} , AUC_{0-48} , and $AUC_{0-\infty}$ of quetiapine were shown in Table 21. C_{max} , AUC_{0-48} , and

AUC_{0-∞} of Quantia 200[®] were not significantly different from the reference drug (Seroquel[®]).

BE analysis showed that the 90% CI of C_{max}, AUC₀₋₄₈ and AUC_{0-∞} for ratios of Quantia 200[®] and Seroquel[®] were 98.21-124.37, 94.43-117.03 and 94.77-116.61%, respectively (Table 22) which fell within the acceptable range for BE of the Thai FDA criteria, i.e. 80-125%.

Table 11. Freeze-thaw stability of quetiapine in plasma.

Sample	Theoretical conc. (ng/ml)	Calculated conc.* (ng/ml)			N
		t = 0	t = 72 h (3 cycle)	% change	
Quetiapine	13	13.06 ± 0.13	12.88 ± 0.42	1.38	3
	347	379.99 ± 22.84	351.78 ± 8.19	7.42	3
	1,042	1,072.82 ± 12.42	1,028.83 ± 18.47	4.10	3

* mean conc. ± SD

Table 12. Short-term stability of quetiapine in plasma.

Sample	Theoretical conc. (ng/ml)	Calculated conc. * (ng/ml)					N
		t = 0	t = 2 h	% change	t = 6 h	% change	
Quetiapine	13	12.94 ± 0.95	12.82 ± 0.92	0.93	11.96 ± 0.18	7.57	3
	347	396.98 ± 14.65	393.67 ± 7.81	0.83	369.43 ± 3.78	6.94	3
	1,042	1,028.83 ± 18.47	1,022.05 ± 24.63	0.66	994.71 ± 28.57	3.32	3

* mean conc. ± SD

Table 13. Long-term stability of quetiapine in plasma.

Sample	Theoretical conc. (ng/ml)	Calculated conc. * (ng/ml)					N
		t = 0	t =15 days	% change	t = 1 month	% change	
Quetiapine	13	13.15±1.18	12.71±0.99	3.35	12.61±1.93	4.11	3
	347	384.93±4.45	356.84±19.30	7.29	351.52±17.98	8.68	3
	1,042	1,085.80±13.99	1,048.96±20.78	3.39	967.39±50.73	10.91	3

* mean conc. ± SD

Table 14. Post-preparative stability of quetiapine in plasma.

Sample	Theoretical conc.(ng/ml)	Calculated conc. * (ng/ml)			N
		t = 0	t = 6 h	% change	
Quetiapine	13	13.06±0.13	13.06±0.77	0	3
	347	379.98±22.84	369.58±30.51	2.74	3
	1,042	1,115.72±8.75	1,098.10±32.82	1.58	3

* mean conc. ± SD

Table 15. Stock solution stability of quetiapine and IS

Sample	Theoretical conc.($\mu\text{g/ml}$)	Calculated conc. * ($\mu\text{g/ml}$)							N
		At room temperature					At -70°C for 14 days	% change	
		0 h	2 h	% change	6 h	% change			
Quetiapine	43	43.99 \pm 0.54	43.89 \pm 0.18	0.23	43.88 \pm 0.05	0.25	43.64 \pm 0.11	0.79	3
IS	10	9.93 \pm 0.01	9.92 \pm 0.01	0.10	9.89 \pm 0.04	0.40	9.91 \pm 0.07	0.20	3

* mean conc. \pm SD

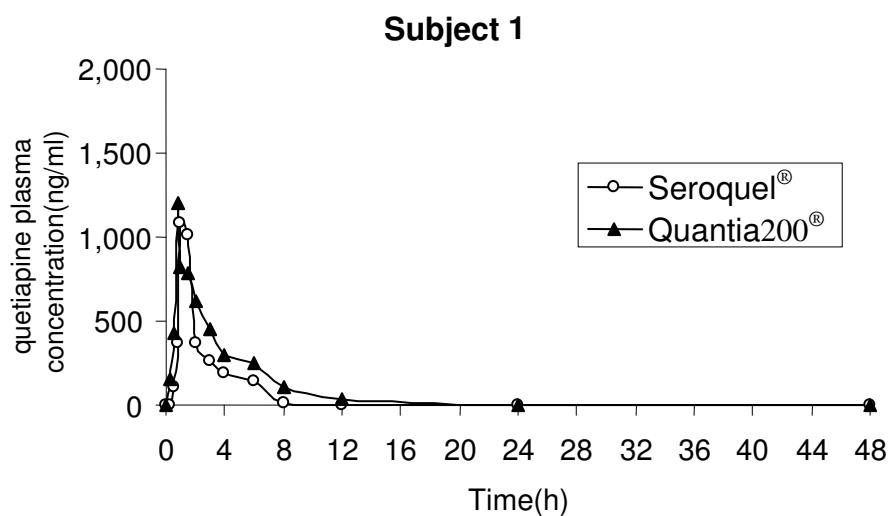


Figure 10. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 1.

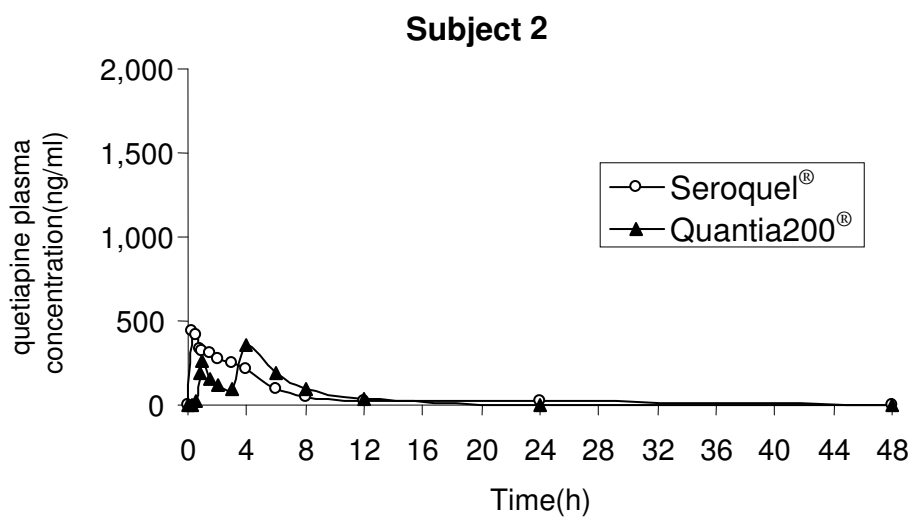


Figure 11. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 2.

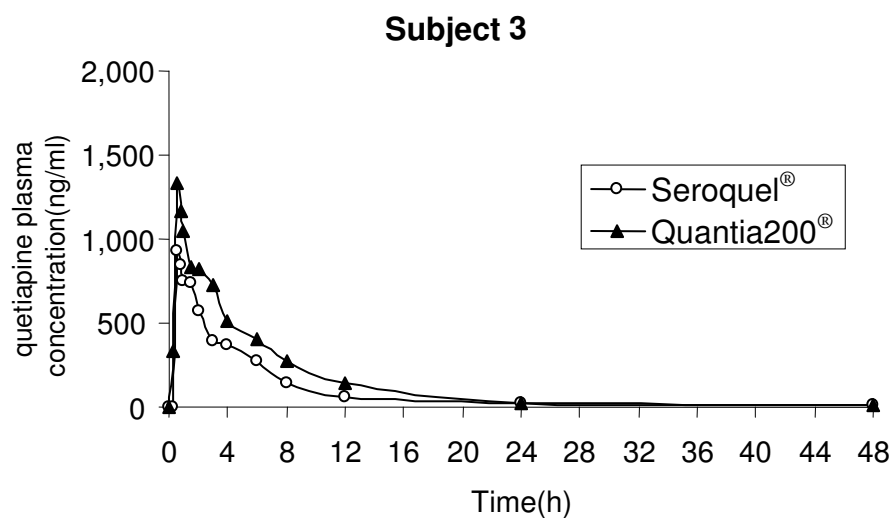


Figure 12. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 3.

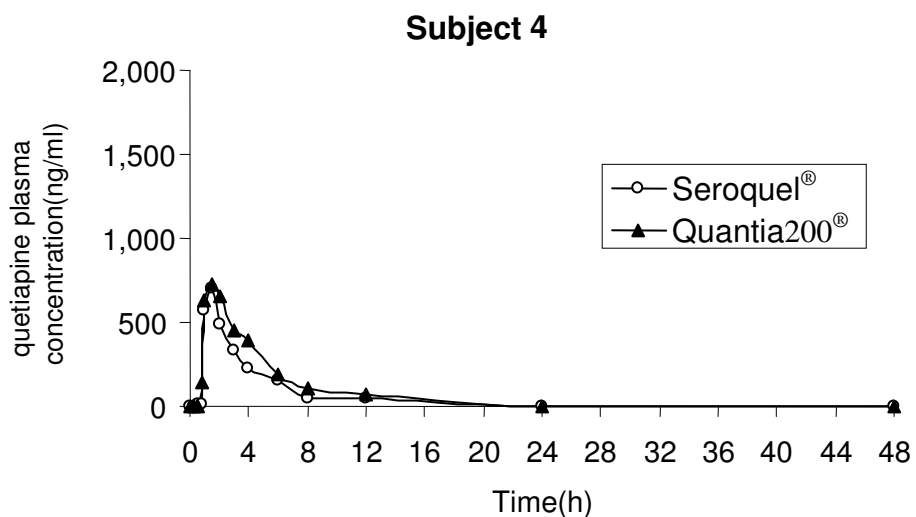


Figure 13. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 4.

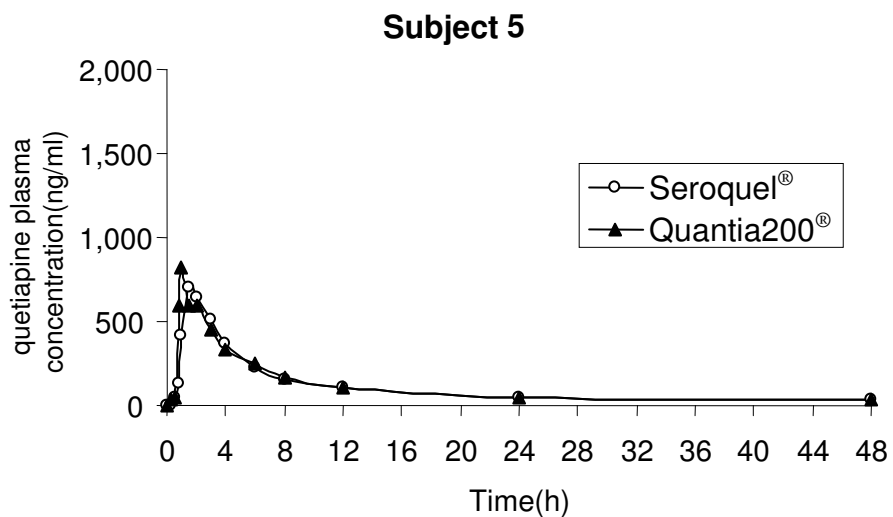


Figure 14. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 5.

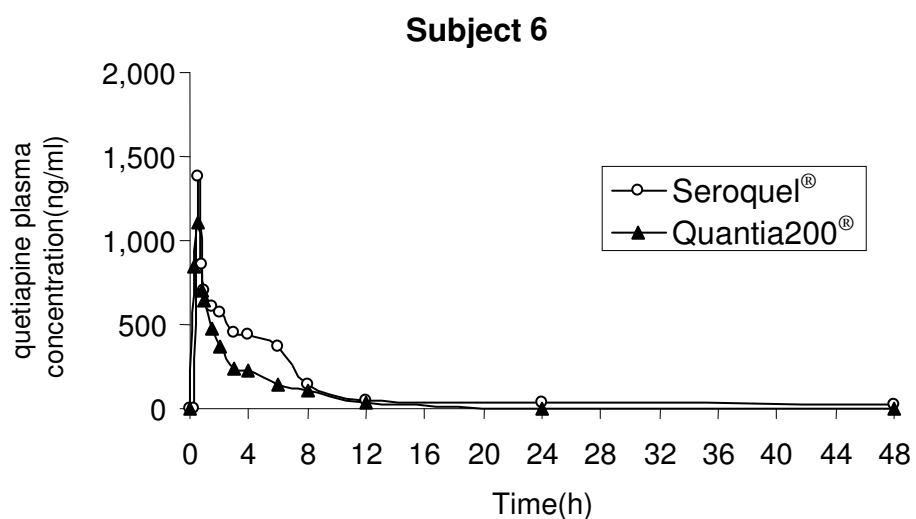


Figure 15. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 6.

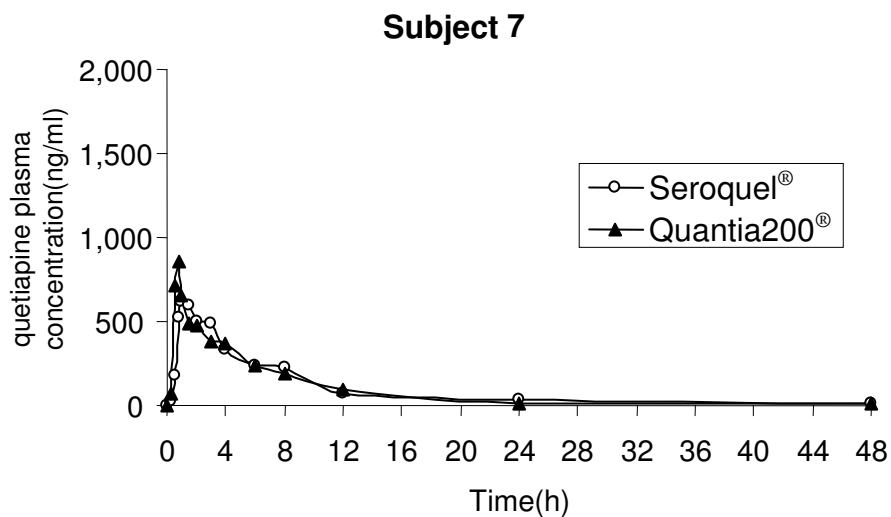


Figure 16. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 7.

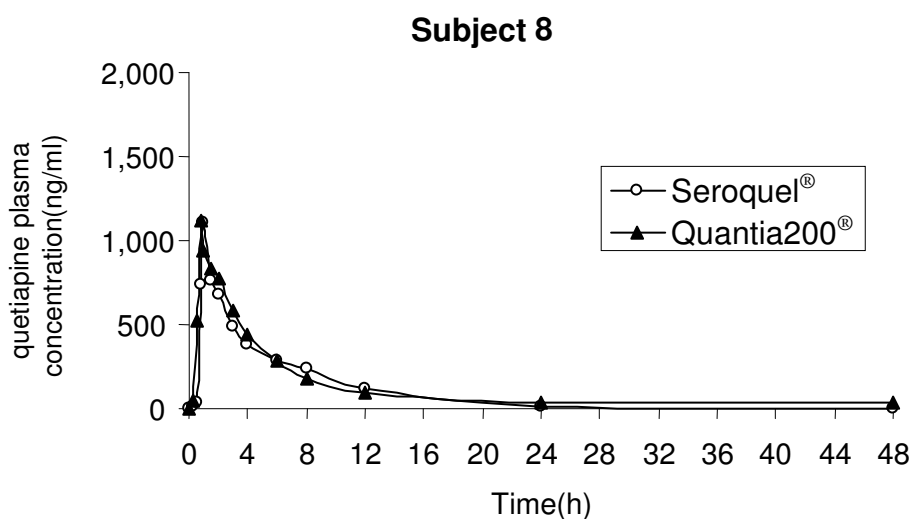


Figure 17. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 8.

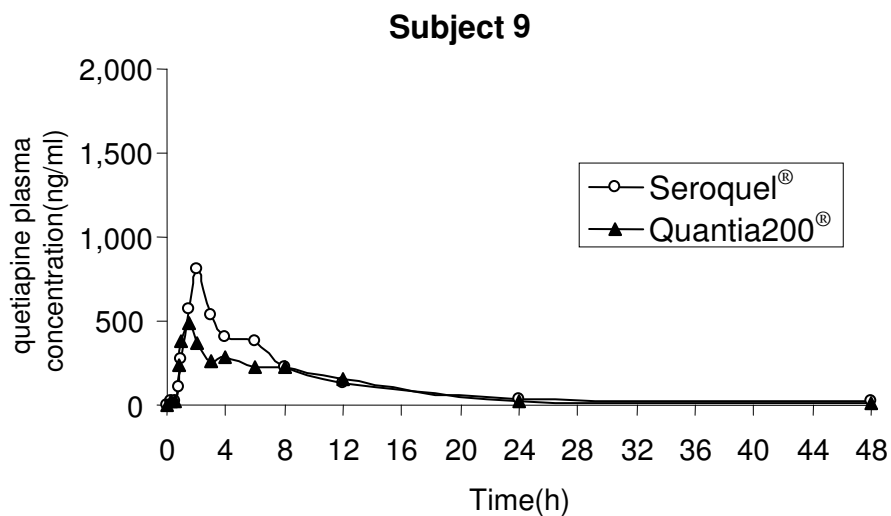


Figure 18. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 9.

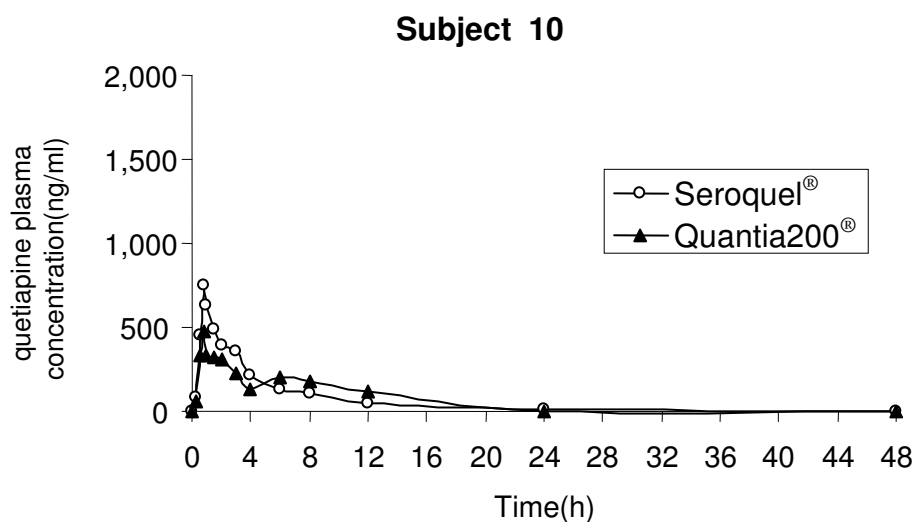


Figure 19. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 10.

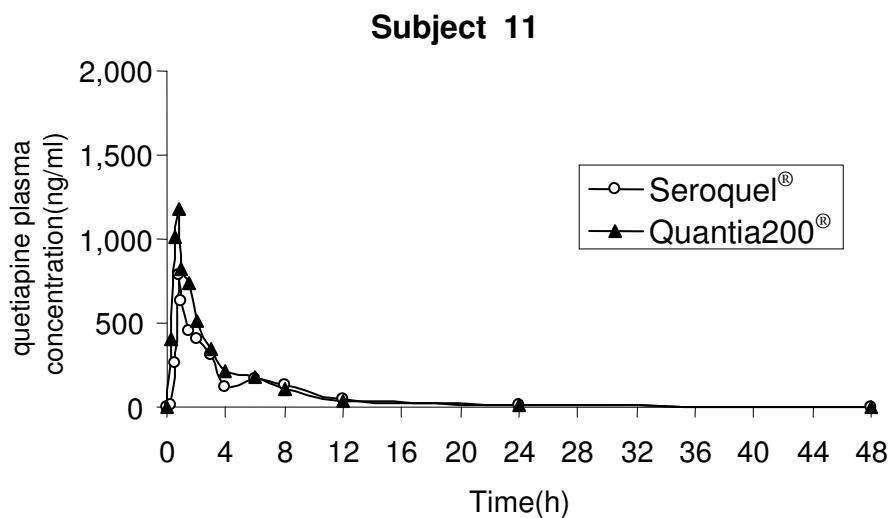


Figure 20. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 11.

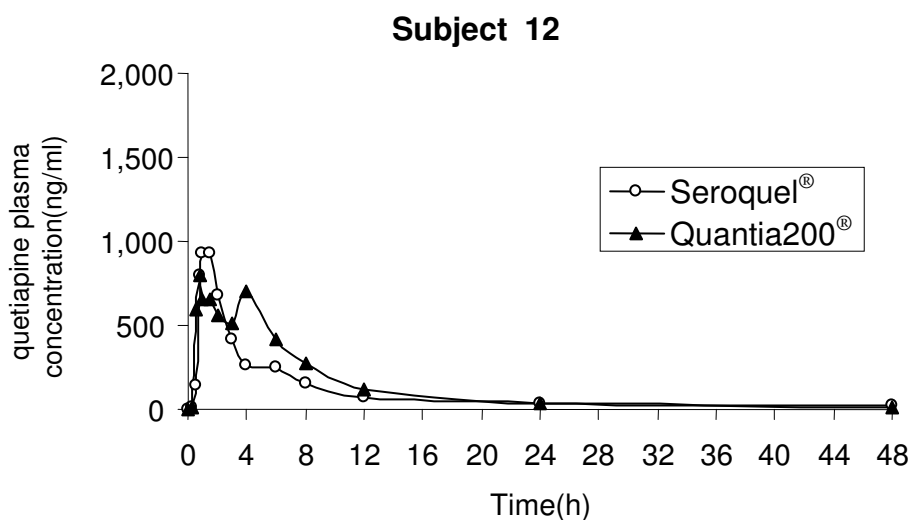


Figure 21. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 12.

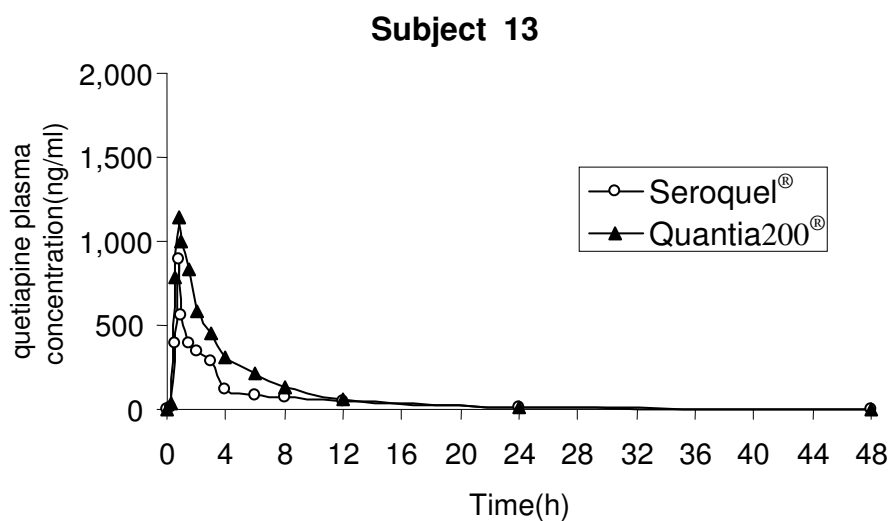


Figure 22. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 13.

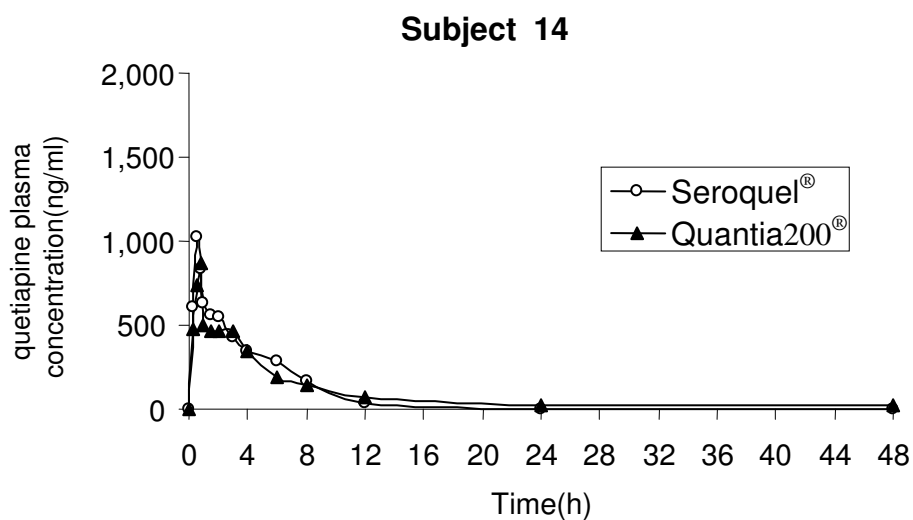


Figure 23. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 14.

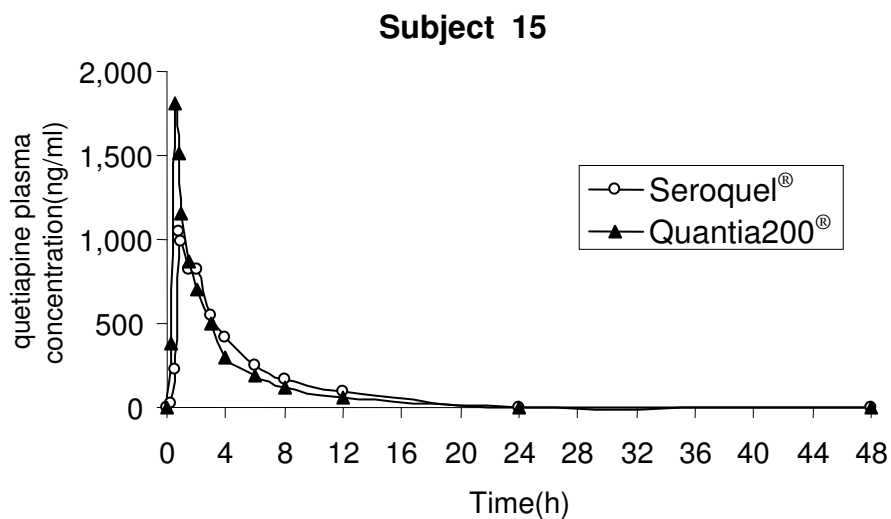


Figure 24. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 15.

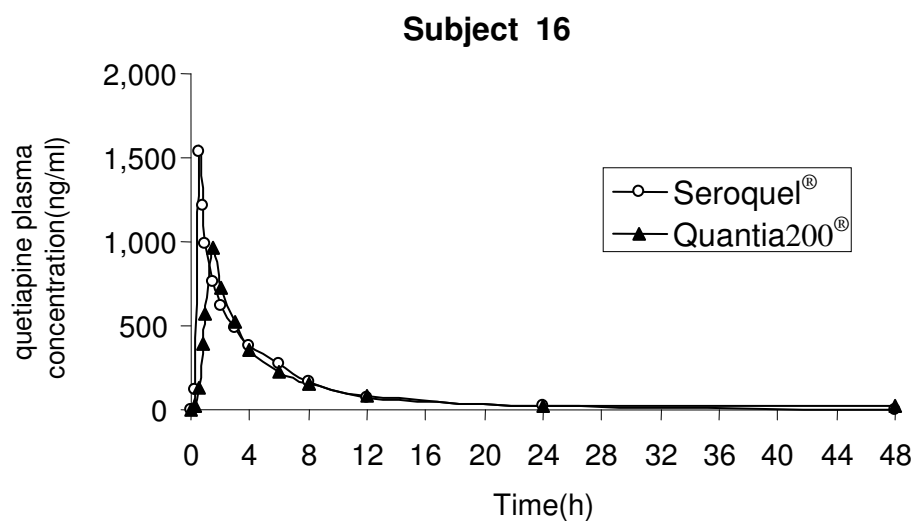


Figure 25. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 16.

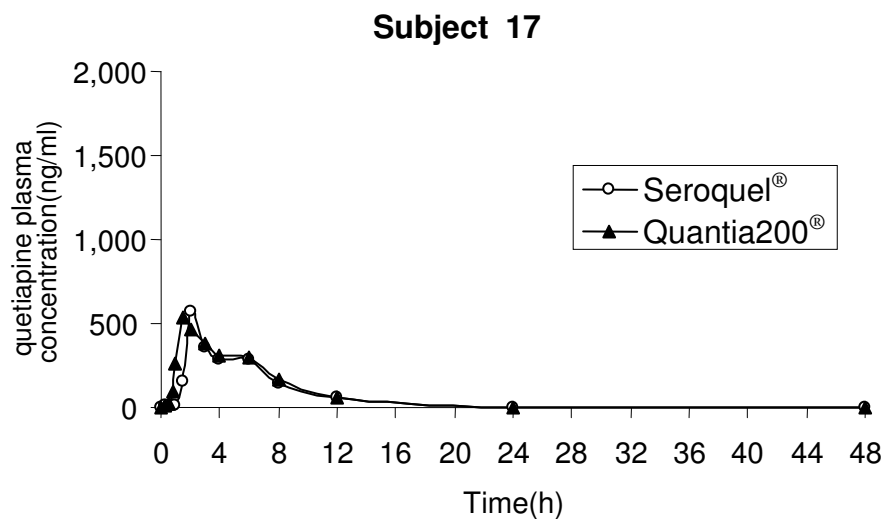


Figure 26. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 17.

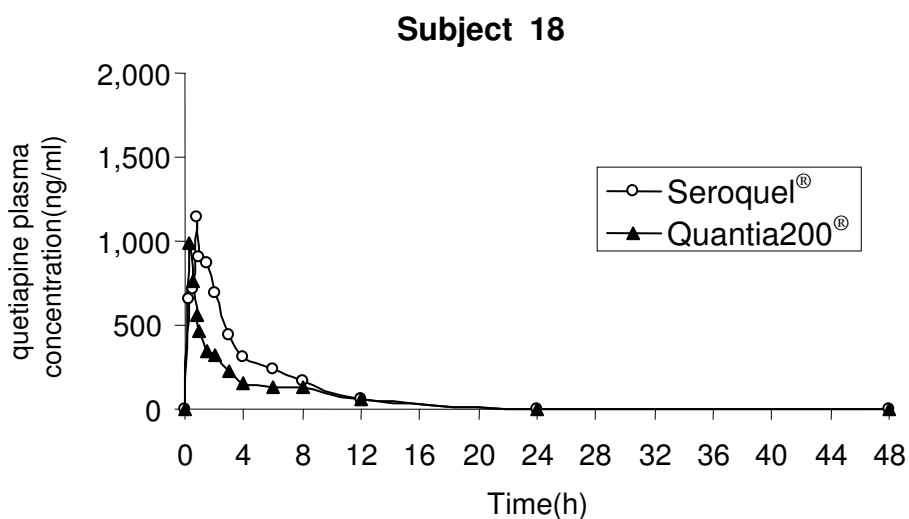


Figure 27. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 18.

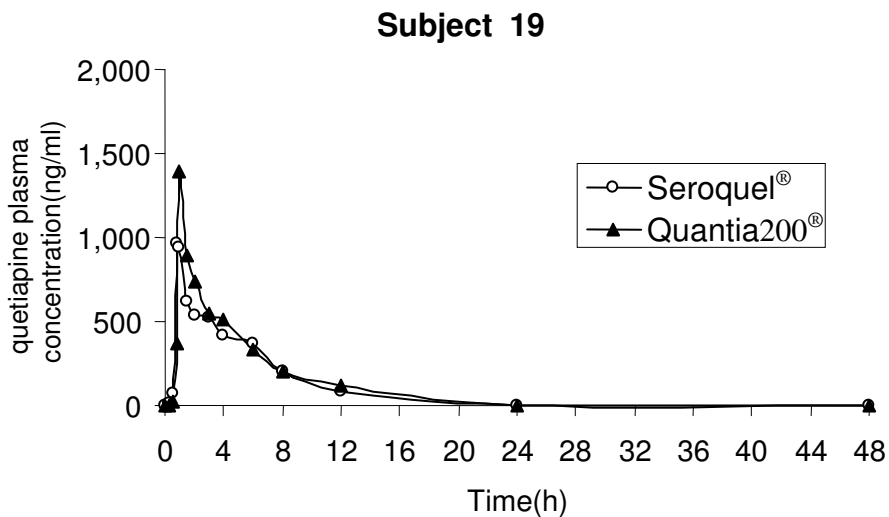


Figure 28. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 19.

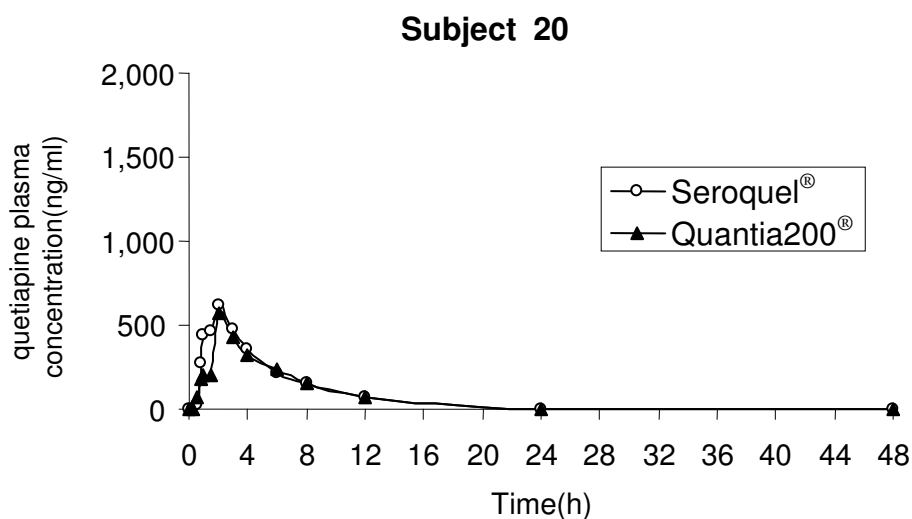


Figure 29. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 20.

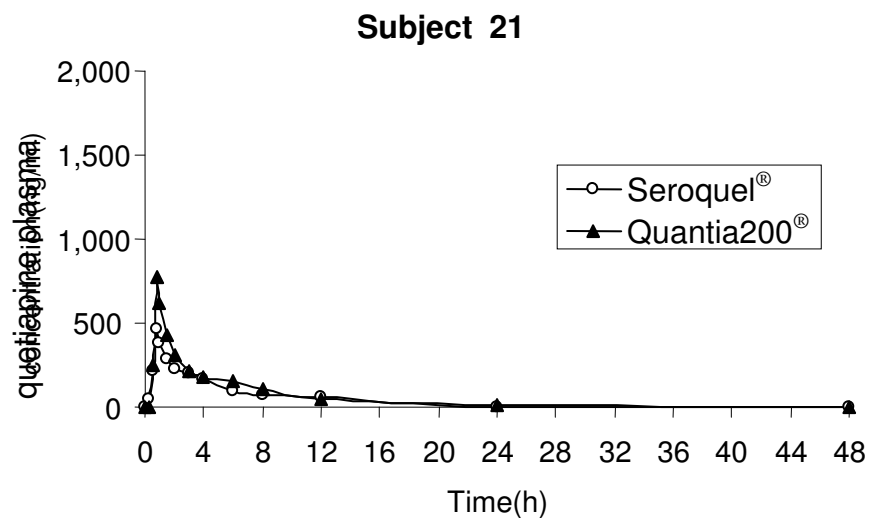


Figure 30. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 21.

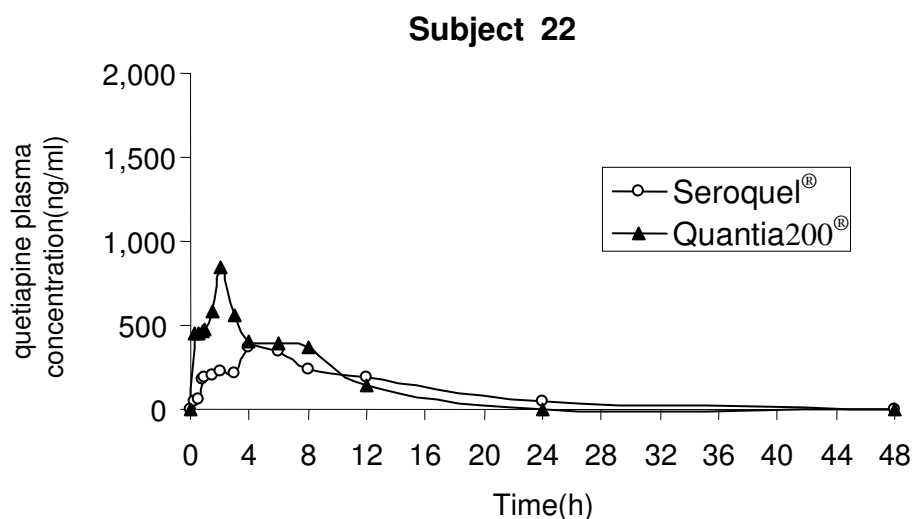


Figure 31. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 22.

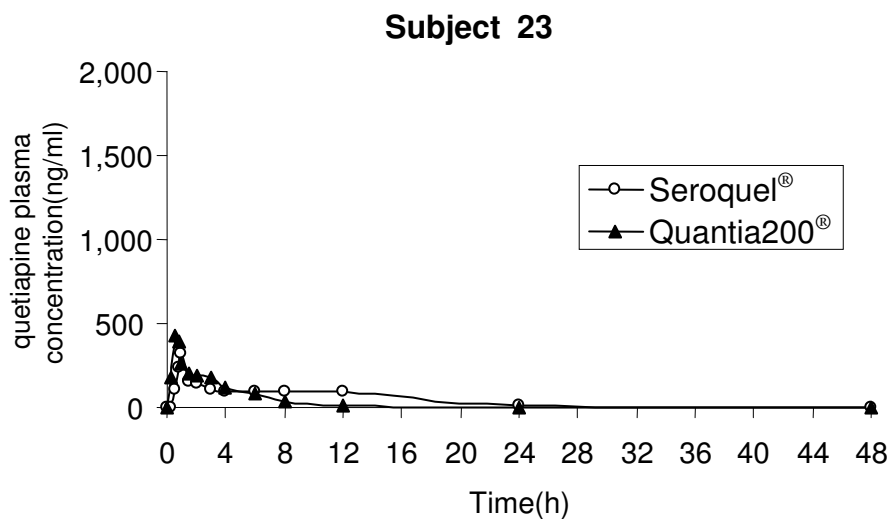


Figure 32. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 23.

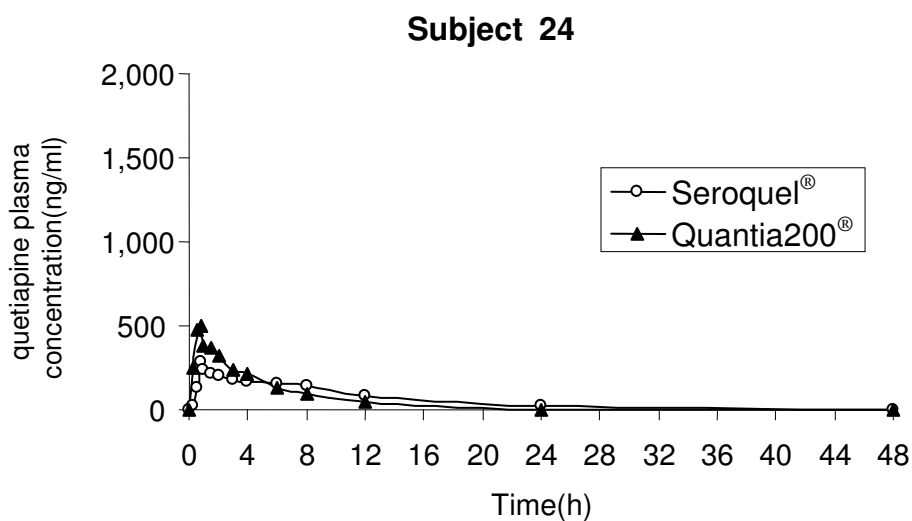


Figure 33. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel[®] and Quantia 200[®] in subject No. 24.

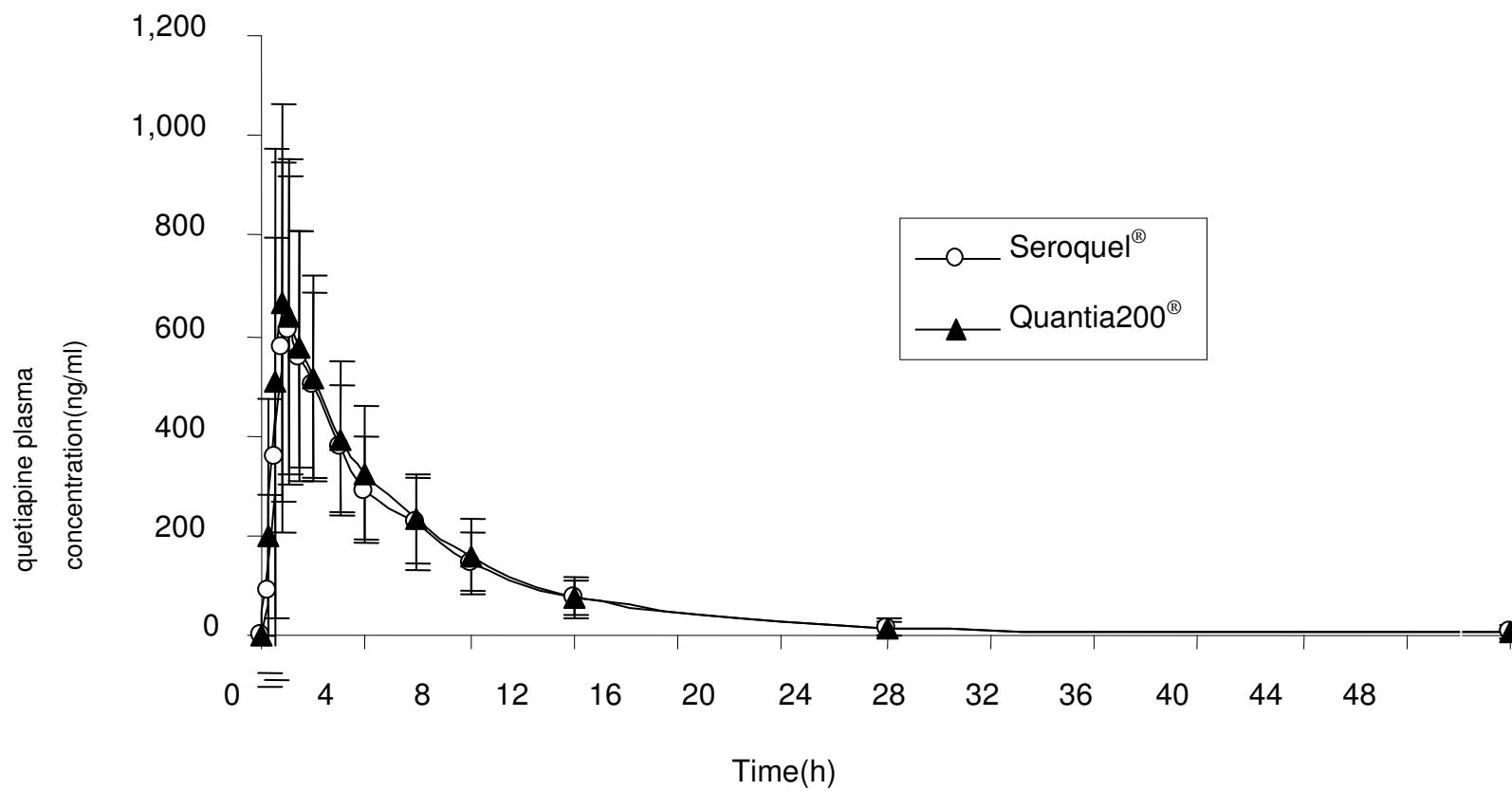


Figure 34. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Quantia 200® in the 24 subjects.

Table 16. The plasma concentrations of quetiapine at various sampling times after the administration of Seroquel[®], 200-mg single dose in 24 subjects.

Subject No.	P1	P2	Plasma concentration of quetiapine (ng/ml)													
			0	0.33 h	0.5 h	0.75 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	12 h	24 h	48 h
1	/		0	<LLOQ	104.16	365.47	1,083.72	1,011.46	366.20	262.55	196.13	138.47	13.65	<LLOQ	<LLOQ	<LLOQ
2		/	0	438.18	417.87	329.59	321.77	310.84	278.02	248.34	212.40	94.43	50.68	28.02	27.16	<LLOQ
3	/		0	<LLOQ	924.99	845.46	745.46	741.53	572.24	393.50	368.30	279.32	148.61	62.79	17.91	15.07
4		/	0	<LLOQ	<LLOQ	11.20	576.74	707.40	485.50	330.76	228.57	151.93	51.93	47.55	<LLOQ	<LLOQ
5	/		0	<LLOQ	41.76	132.27	411.10	704.53	646.87	508.91	366.58	227.16	159.28	101.61	45.41	38.84
6		/	0	<LLOQ	1,378.51	862.27	701.59	610.14	565.69	451.16	446.03	374.24	145.18	52.02	31.50	28.09
7	/		0	21.08	178.10	518.45	617.57	589.50	503.54	489.50	334.24	236.87	226.34	76.34	35.11	<LLOQ
8		/	0	9.38	35.81	741.06	1,108.39	758.88	672.74	489.57	384.62	286.60	243.04	124.13	10.96	<LLOQ
9	/		0	19.33	23.64	112.91	271.44	566.85	814.38	539.33	400.16	385.02	229.24	133.83	30.16	19.61
10		/	0	82.99	450.84	745.33	628.13	483.46	392.99	358.32	211.12	134.49	102.43	43.46	9.06	<LLOQ
11	/		0	13.93	264.99	788.62	627.73	456.05	403.13	312.83	116.73	166.32	133.23	43.13	14.55	<LLOQ
12		/	0	<LLOQ	147.68	796.37	934.00	927.33	672.77	417.25	263.91	253.30	152.68	70.67	31.81	20.84
13	/		0	12.67	392.84	888.28	556.34	392.54	346.81	283.79	115.67	86.81	75.86	45.69	13.53	<LLOQ
14		/	0	609.23	1,022.93	837.31	636.23	553.92	546.98	422.84	340.61	280.14	165.07	35.98	<LLOQ	<LLOQ
15	/		0	23.46	222.73	1,043.14	990.37	822.81	817.12	543.46	411.02	246.15	169.89	100.46	<LLOQ	<LLOQ
16		/	0	117.14	1,533.00	1,220.03	988.39	766.67	624.09	482.69	380.34	276.75	170.03	72.45	24.02	<LLOQ
17	/		0	9.65	10.52	11.57	12.78	149.83	569.22	352.26	291.39	284.61	143.04	59.48	<LLOQ	<LLOQ
18		/	0	651.78	713.29	1141.24	907.13	870.17	693.74	440.44	314.54	236.51	169.10	54.46	<LLOQ	<LLOQ
19	/		0	<LLOQ	77.29	969.52	942.82	619.52	537.46	526.13	413.89	370.68	204.52	86.84	<LLOQ	<LLOQ
20		/	0	<LLOQ	24.39	273.54	441.86	461.38	624.08	473.62	359.31	212.78	159.14	72.78	<LLOQ	<LLOQ
21	/		0	52.82	208.90	461.46	379.38	290.34	230.90	198.74	161.06	100.82	72.10	57.86	<LLOQ	<LLOQ
22		/	0	44.87	64.97	176.52	194.79	197.31	226.54	219.57	366.41	350.75	235.67	191.20	49.70	<LLOQ
23	/		0	<LLOQ	105.48	242.15	320.00	156.67	139.03	105.91	100.86	97.53	96.67	89.46	<LLOQ	<LLOQ
24		/	0	19.15	131.91	287.31	236.28	209.84	205.47	176.39	165.93	158.23	148.80	85.24	28.23	<LLOQ
Mean			0	89.16	353.56	575.04	609.75	556.62	497.31	376.16	289.58	226.25	144.42	72.31	15.71	5.40
S.D.			0	189.39	440.56	372.63	307.04	250.47	191.41	126.64	107.35	93.09	61.50	39.37	15.94	10.82

P1: Phase1; P2: phase 2; LLOQ = 9 ng/ml

Table 17. The plasma concentrations of quetiapine at various sampling times after the administration of Quantia200[®], 200-mg single dose in 24 subjects.

Subject No.	P1	P2	Plasma concentration of quetiapine (ng/ml)													
			0	0.33 h	0.5 h	0.75 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	12 h	24 h	48 h
1		/	0	152.34	429.71	1,203.4	816.57	790.29	622.41	450.15	299.78	248.69	111.46	34.82	<LLOQ	<LLOQ
2	/		0	<LLOQ	23.34	195.21	258.49	158.49	117.09	98.34	356.93	192.09	89.74	33.49	<LLOQ	<LLOQ
3		/	0	337.59	1,329.7	1,169.0	1,045.15	829.72	821.06	731.29	510.82	402.16	277.75	140.74	25.78	11.76
4	/		0	<LLOQ	<LLOQ	142.44	627.84	721.25	654.12	446.82	392.80	189.15	110.32	67.99	<LLOQ	<LLOQ
5		/	0	30.08	43.95	595.04	819.13	597.23	593.58	451.98	335.92	246.14	164.39	106.72	46.87	41.03
6	/		0	841.76	1,108.4	696.46	646.03	473.38	363.13	232.36	220.39	148.60	106.72	38.34	<LLOQ	<LLOQ
7		/	0	76.34	717.57	852.66	656.17	491.25	481.61	385.11	363.18	240.38	193.89	96.52	11.87	<LLOQ
8	/		0	45.02	529.18	1,113.3	938.09	830.17	768.78	581.65	435.91	291.55	173.73	89.57	31.55	29.97
9		/	0	22.82	28.32	241.72	386.39	486.39	366.54	259.51	283.83	228.32	225.57	151.07	20.43	<LLOQ
10	/		0	59.91	330.75	477.38	334.11	325.70	306.54	230.47	136.45	203.93	177.85	117.57	<LLOQ	<LLOQ
11		/	0	399.50	1,007.7	1,180.0	825.96	735.69	511.45	349.02	219.59	183.75	108.83	40.12	9.77	<LLOQ
12	/		0	<LLOQ	589.79	795.93	653.30	651.46	556.11	507.33	707.25	415.05	269.35	121.98	40.75	10.67
13		/	0	36.64	788.19	1,146.1	1002.67	833.71	587.76	452.93	311.64	211.03	126.64	54.22	<LLOQ	<LLOQ
14	/		0	473.67	741.36	872.48	500.36	470.12	465.49	459.54	344.46	194.08	147.39	69.62	23.59	21.02
15		/	0	384.93	1,806.5	1,510.7	1,151.92	870.21	701.11	498.42	300.29	191.76	118.34	64.85	<LLOQ	<LLOQ
16	/		0	25.97	129.64	397.45	571.13	961.13	721.44	522.57	359.80	224.41	152.84	88.24	27.06	22.69
17		/	0	10.17	23.57	93.65	262.52	533.39	468.87	384.00	310.26	292.17	160.96	57.22	<LLOQ	<LLOQ
18	/		0	991.06	763.47	555.88	460.08	343.56	319.90	229.46	157.76	134.37	129.19	62.40	<LLOQ	<LLOQ
19		/	0	<LLOQ	21.39	367.91	1,398.36	898.18	740.14	544.96	513.54	335.32	207.11	116.48	<LLOQ	<LLOQ
20	/		0	<LLOQ	71.51	179.14	205.92	207.02	568.90	428.80	324.22	236.08	158.88	67.36	<LLOQ	<LLOQ
21		/	0	<LLOQ	251.14	777.38	613.94	424.58	308.82	216.02	178.50	153.46	112.74	51.22	16.90	<LLOQ
22	/		0	454.62	456.54	462.80	478.60	579.39	849.88	555.04	402.73	394.90	372.36	146.35	<LLOQ	<LLOQ
23		/	0	173.67	430.89	388.00	261.33	202.11	196.00	175.56	118.33	80.11	39.78	14.22	<LLOQ	<LLOQ
24	/		0	252.25	477.20	497.54	382.71	372.94	319.03	232.94	217.20	133.29	93.98	47.20	<LLOQ	<LLOQ
Mean			0	198.96	504.16	662.99	637.37	574.47	517.07	392.68	325.07	232.12	159.57	78.26	11.11	6.39
S.D.			0	273.90	469.84	398.85	312.58	237.98	199.82	154.53	133.19	86.73	72.05	38.80	14.53	11.31

P1: Phase1; P2: phase 2; LLOQ = 9 ng/ml

Table 18. Quetiapine pharmacokinetic parameters of individual subject following a single oral dose of 200-mg of Seroquel[®].

Subject No.	C _{max} (ng/ml)	AUC ₀₋₄₈ (ng/ml)	AUC _{0-∞} (ng/ml)	AUC extrapolate (%)	T _{max} (h)	T _{1/2} (h)	Vd (L)	Cl (L/h)
1	1,083.72	2,147.36	2,172.14	1.14	1	1.26	167.20	92.10
2	438.18	2,059.30	2,261.89	8.96	0.33	5.17	659.50	88.40
3	924.99	4,440.99	4,600.77	3.47	0.5	7.35	460.90	43.50
4	707.41	2,167.11	2,346.77	7.66	1.5	2.62	322.00	85.20
5	704.53	5,120.68	5,744.04	10.85	1.5	11.12	558.80	34.80
6	1,378.51	5,121.96	5,486.25	6.64	0.5	8.99	472.90	36.50
7	617.57	4,547.21	4,653.45	2.28	1	10.45	648.20	43.00
8	1,108.39	4,922.40	4,978.42	1.12	1	3.54	205.30	40.20
9	814.38	5,480.02	5,721.04	0.21	2	8.52	429.80	35.00
10	745.33	2,727.09	2,785.47	2.09	0.75	4.46	462.30	71.80
11	788.62	2,674.66	2,782.35	3.87	0.75	5.13	532.00	71.90
12	934.00	4,716.01	5,043.53	6.49	1	10.89	623.20	39.70
13	888.27	2,277.92	2,405.14	5.28	0.75	6.52	782.00	83.2
14	1,022.93	3,563.45	3,666.98	2.82	0.5	1.99	156.90	54.5
15	1,043.14	4,071.92	4,756.25	14.39	0.75	4.72	286.50	42
16	1,533.00	4,718.79	4,880.31	3.30	0.5	4.66	275.60	41
17	569.22	2,420.79	2,704.13	10.48	2	3.30	352.30	74
18	1,141.24	3,895.09	4,113.08	5.30	0.75	2.77	194.70	48.6
19	969.52	4,002.42	4,367.42	8.36	0.75	2.91	192.50	45.8
20	624.08	2,999.05	3,400.71	11.81	2	3.83	324.60	58.8
21	461.46	1,607.09	1,974.77	18.62	0.75	4.40	643.60	101.3
22	366.41	4,416.08	4,904.84	9.96	4	6.82	401.00	40.8
23	320.00	1,891.25	1,939.37	2.48	1	4.17	620.40	103.1
24	287.31	2,491.41	2,777.58	10.30	0.75	7.02	729.90	72
Mean	811.34	3,520.00	3,769.45	6.58	1.10	5.53	437.59	60.30
S.D.	323.37	1,229.61	1,296.69	4.68	0.79	2.83	191.42	22.64

Table 19. Quetiapine pharmacokinetic parameters of individual subject following a single oral dose of 200-mg of Quantia200®.

Subject No.	C _{max} (ng/ml)	AUC ₀₋₄₈ (ng/ml)	AUC _{0-∞} (ng/ml)	AUC extrapolate (%)	T _{max} (h)	T _{1/2} (h)	Vd (L)	Cl (L/h)
1	1,203.43	3,398.55	3,520.43	3.46	0.75	2.43	198.90	56.80
2	356.93	1,671.81	1,784.43	6.31	4	2.33	376.90	112.10
3	1,329.72	6,944.69	7,059.68	1.63	0.5	6.77	276.90	28.30
4	721.25	3,003.52	3,297.35	8.91	1.5	2.99	262.10	60.70
5	819.13	5,347.55	5,986.03	10.66	1	10.79	519.90	33.40
6	1,108.43	2,625.61	2,801.23	6.27	0.5	3.17	327.00	71.40
7	852.66	4,301.59	4,370.52	1.58	0.75	6.54	431.70	45.80
8	1,113.34	5,728.22	6,101.59	6.12	0.75	8.64	408.40	32.80
9	486.39	4,237.60	4,340.19	2.36	1.5	7.93	527.40	46.10
10	477.38	3,068.03	3,090.49	0.73	0.75	3.21	299.70	64.70
11	1,180.03	3,419.68	3,480.97	1.76	0.75	4.35	360.40	57.50
12	795.93	6,356.11	6,517.73	2.48	0.75	10.50	465.00	30.70
13	1,146.12	3,894.49	3,935.57	1.04	0.75	3.93	288.30	50.80
14	872.48	4,304.41	4,562.35	5.65	0.75	8.50	537.80	43.80
15	1,806.53	4,063.27	4,402.52	7.71	0.5	3.63	237.70	45.40
16	961.13	4,803.80	5,091.25	5.65	1.5	8.78	497.70	39.30
17	533.39	2,778.74	3,059.18	9.17	1.5	3.40	320.40	65.40
18	991.06	2,378.49	2,787.14	14.66	0.33	4.54	469.90	71.80
19	1,398.36	4,465.25	5,093.76	12.34	1	3.74	211.90	39.30
20	568.90	2,665.86	2,986.87	10.75	2	3.30	319.10	67.00
21	777.38	2,561.38	2,698.85	5.09	0.75	5.64	602.70	74.10
22	849.88	4,790.52	5,779.39	17.11	2	4.68	233.80	34.60
23	430.89	1,238.01	1,289.46	3.99	0.5	2.51	561.10	155.10
24	497.54	2,058.56	2,331.50	11.71	0.75	4.01	496.1	85.80
Mean	886.60	3,754.41	4,015.35	6.55	1.08	5.26	384.62	58.86
S.D.	356.50	1,453.00	1,528.25	4.55	0.778	2.63	122.78	28.55

Table 20. Comparison of quetiapine pharmacokinetic parameters of individual subject following a single oral dose of 200 mg of Quantia200[®] and Seroquel[®]

Sub ject No.	C _{max}		F _{rel} (T/R)	AUC ₀₋₄₈		F _{rel} (T/R)	AUC _{0-∞}		F _{rel} (T/R)
	T	R		T	R		T	R	
1	1,203.43	1,083.72	1.11	3,398.55	2,147.36	1.58	3,520.43	2,172.14	1.62
2	356.93	438.18	0.81	1,671.81	2,059.30	0.81	1,784.43	2,261.89	0.79
3	1,329.72	924.99	1.44	6,944.69	4,440.99	1.56	7,059.68	4,600.77	1.53
4	721.25	707.41	1.02	3,003.52	2,167.11	1.39	3,297.35	2,346.77	1.41
5	819.13	704.53	1.16	5,347.55	5,120.68	1.04	5,986.03	5,744.04	1.04
6	1,108.43	1,378.51	0.80	2,625.61	5,121.96	0.51	2,801.23	5,486.25	0.51
7	852.66	617.57	1.38	4,301.59	4,547.21	0.95	4,370.52	4,653.45	0.94
8	1,113.34	1,108.39	1.00	5,728.22	4,922.40	1.16	6,101.59	4,978.42	1.23
9	486.39	814.38	0.60	4,237.60	5,480.02	0.77	4,340.19	5,721.04	0.76
10	477.38	745.33	0.64	3,068.03	2,727.09	1.13	3,090.49	2,785.47	1.11
11	1,180.03	788.62	1.50	3,419.68	2,674.66	1.28	3,480.97	2,782.35	1.25
12	795.93	934.00	0.85	6,356.11	4,716.01	1.35	6,517.73	5,043.53	1.29
13	1,146.12	888.27	1.29	3,894.49	2,277.92	1.71	3,935.57	2,405.14	1.64
14	872.48	1,022.93	0.85	4,304.41	3,563.45	1.21	4,562.35	3,666.98	1.24
15	1,806.53	1,043.14	1.73	4,063.27	4,071.92	1.00	4,402.52	4,756.25	0.93
16	961.13	1,533.00	0.63	4,803.80	4,718.79	1.02	5,091.25	4,880.31	1.04
17	533.39	569.22	0.94	2,778.74	2,420.79	1.15	3,059.18	2,704.13	1.13
18	991.06	1,141.24	0.87	2,378.49	3,895.09	0.61	2,787.14	4,113.08	0.68
19	1,398.36	969.52	1.44	4,465.25	4,002.42	1.12	5,093.76	4,367.42	1.17
20	568.90	624.08	0.91	2,665.86	2,999.05	0.89	2,986.87	3,400.71	0.88
21	777.38	461.46	1.68	2,561.38	1,607.09	1.59	2,698.85	1,974.77	1.37
22	849.88	366.41	2.32	4,790.52	4,416.08	1.08	5,779.39	4,904.84	1.18
23	430.89	320.00	1.35	1,238.01	1,891.25	0.65	1,289.46	1,939.37	0.66
24	497.54	287.31	1.73	2,058.56	2,491.41	0.83	2,331.50	2,777.58	0.84
Mean	886.60	811.34	1.17	3,754.41	3,520.00	1.10	4,015.35	3,769.45	1.09
S.D.	356.50	323.37	0.43	1,453.00	1,229.61	0.32	1,528.25	1,296.69	0.30

T (Test product): Quantia 200[®]; R (Reference product): Seroquel[®]

Table 21. Two-way ANOVA test for ln-transformed data of C_{\max} , AUC_{0-48} and $AUC_{0-\infty}$ of Quantia 200[®] and Seroquel[®].

Dependent variable	Source	df	SS	MS	F	p values
C_{\max}	Subject*Sequence	22	7.075	0.322	5.642	0
	Sequence	1	0.085	0.085	1.484	0.236
	Period	1	0.217	0.217	3.806	0.064
	Drug	1	0.108	0.108	1.898	0.182
	Error	22	1.254	0.057		
	Total	48	2,137.26			
AUC_{0-48}	Subject*Sequence	22	6.200	0.282	6.040	0
	Sequence	1	0.002	0.002	0.044	0.836
	Period	1	0.101	0.101	2.166	0.155
	Drug	1	0.031	0.031	0.654	0.427
	Error	22	1.027	0.047		
	Total	48	3,177.57			
$AUC_{0-\infty}$	Subject*Sequence	22	6.078	0.276	6.267	0
	Sequence	1	0.007	0.007	0.165	0.689
	Period	1	0.061	0.061	1.380	0.253
	Drug	1	0.028	0.028	0.635	0.434
	Error	22	0.970	0.044		
	Total	48	3,232.15			

Table 22. Pharmacokinetic parameters (mean \pm SD) and 90% CI for quetiapine, after the administration of single oral dose of 200-mg of Quantia 200[®] and Seroquel[®] to 24 healthy volunteers.

Pharmacokinetic parameters	Quantia 200[®]	Seroquel[®]	90% CI
AUC ₀₋₄₈ (ng h/ml)	3,754.41 \pm 1,453.00	3,520.00 \pm 1,229.61	94.43-117.03
AUC _{0-∞} (ng h/ml)	4,015.35 \pm 1,528.25	3,769.45 \pm 1,296.69	94.77-116.61
C _{max} (ng/ml)	886.60 \pm 356.50	811.34 \pm 323.37	98.21-124.37
T _{max} (h)	1.08 \pm 0.78	1.10 \pm 0.79	-
T _{1/2} (h)	5.26 \pm 2.63	5.53 \pm 2.83	-
CL (L/h)	58.86 \pm 28.55	60.30 \pm 22.64	-
V _{z/f} (L)	384.62 \pm 122.78	437.59 \pm 191.42	-
AUC extrapolated (%)	6.55 \pm 4.55	6.58 \pm 4.68	-

Adverse events

Somnolence was observed in all subjects within 1 h after taking 200 mg of Seroquel[®] and Quantia 200[®]. Three subjects developed orthostatic hypotension after taking Seroquel[®] and four subjects in Quantia 200[®] group. Two subjects experienced agitation in Seroquel[®] and one in Quantia 200[®] group (Table 23). These adverse events were mild in intensity and subsided within 1 day. Moreover, all subjects tolerated both drugs well throughout the study. No marked laboratory abnormality was observed in all subjects and physical examinations revealed no abnormal finding at the end of the study. No subjects withdrew from the study because of adverse events.

Table 23. Adverse events of 200-mg of Seroquel[®] and Quantia 200[®] in the 24 subjects.

Side effect	Seroquel [®]		Quantia 200 [®]	
	Number	%	Number	%
Sedation	24	100	24	100
Orthostatic hypotension	3	12.5	4	16.67
Agitation	2	8.34	1	4.17