Clinical Pharmacology and Biopharmaceutics Review

NDA:	20639 SE5-045/046
Drug:	Quetiapine fumarate
Trade Name:	Seroquel®
Indication:	Treatment of schizophrenia and bipolar mania in pediatric patients
Sponsor:	Astra-Zeneca
Submission Type:	Pediatric Efficacy Supplement
Submission Date:	10/28/08, 10/30/08,10/31/08, 2/27/09
PM Reviewer:	Hao Zhu, Ph.D.
PM Secondary Reviewer:	Christine Garnett, Ph.D.
PM Team Leader:	Yaning Wang, Ph.D.
Reviewer:	Kofi A. Kumi, Ph.D,
Team Leader:	Raman Baweja, Ph.D.

Tale of Contents

1. Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the data submitted to the Clinical Pharmacology section of this supplemental NDA and finds it acceptable. The following are the general conclusions from the data OCP reviewed:

1. There was a tendency for children aged 10 -12 years old to have higher exposures of quetiapine (AUC was 36% – 55% and Cmax was 54% - 71% higher) than adolescents aged 13 to 17 years old.
2. Dose normalized exposures were generally lower (AUC = 12% lower and Cmax = 8% lower) in pediatric/adolescent patients than adult. These differences are not expected to be clinically relevant.
3. Dose normalized, weight-normalized AUC and Cmax decreased by about 40% when pediatric children ages 10 to 17 were compared to adults. The decrease in exposure are not expected to be clinically relevant.
4. Quetiapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses.

1.2 Phase IV Commitments recommended

There are no phase IV recommendations from OCP

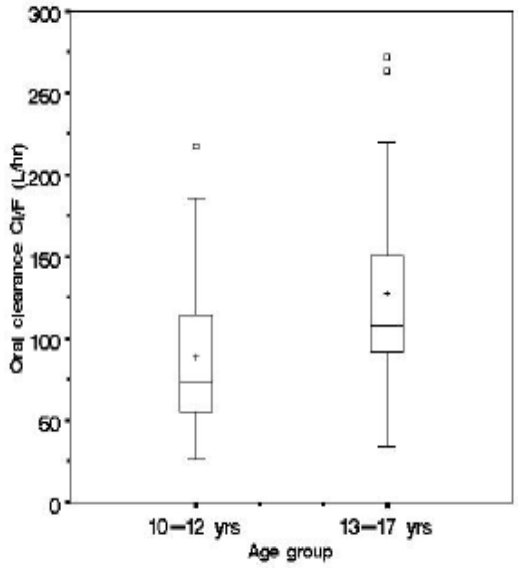
1.3 Summary of Clinical Pharmacology Findings

Background: In response to a Written Request issued by the Agency, the sponsor submitted a supplemental New Drug Administration containing, pharmacokinetic, efficacy and safety data for the use of Seroquel in the treatment of schizophrenia and bipolar mania in pediatric patients.

Comparison of exposures between pediatric patients aged 10 -17 years old.

In a pharmacokinetic study in which pharmacokinetic data was obtained on days 7 and 13 of dosing, exposure to quetiapine in terms of AUCss and Css,max appeared to be higher in 10- to 12-year-old subjects than in the 13- to 17-year-old subjects. The geometric means for AUCss on Days 7 and 13 were 55% and 36% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 – 17 year old. The geometric means for Css,max on Days 7 and 13 were 71% and 54% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 -17 year olds. The apparent oral clearance (CL/F) was 38% and 30% lower for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to 13 to 17 year olds.

Figure 1: Box plots of oral clearance of quetiapine on Day 7 and Day 13 by age group



Note: The horizontal lines in the graph indicate the 10th,25th,50th,75th,and 90th percentiles

Comparison of exposures between pediatric patients aged 10 -17 years and Adults.

Comparison of dose normalized exposures (AUCss and Cmax) to quetiapine showed a 12% decrease in exposure (AUC) in pediatric children ages 10 to 17 years old compared to adults. Approximately a 40% decrease in AUC was also observed when exposures were adjusted for dose and weight of patients. The decrease in exposure may not be clinically relevant.

Table 1: Comparison of dose-normalized exposure (AUCss and Cmax) to quetiapine and 3 metabolites in children/adolescents with exposure in adults

	Dose-normalized AUC_{ss}		Dose-normalized $C_{ss,max}$	
Analyte	Mean ratio[a]	90% CI	Mean ratio[a]	90% CI
Quetiapine	0.88	0.76, 1.03	0.92	0.79, 1.06
Quetiapine sulfoxide	1.27	1.15, 1.39	1.30	1.16, 1.44
7-hydroxy quetiapine	1.08	0.92, 1.26	1.11	0.94, 1.31
N-desalkyl quetiapine	1.45	1.30, 1.61	1.31	1.15, 1.49

[a] Ratio (10- to 17-year-olds:adults) of least squares means from ANOVA model.
ANOVA analysis of variance. AUC_{ss} area under the curve at steady-state. CI confidence interval. $C_{ss,max}$ maximum plasma concentration at steady-state.

Table 2: Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites in children/adolescents with exposure in adults

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.59	0.50 – 0.70	0.61	0.53 – 0.72
Quetiapine sulfoxide	0.85	0.77 – 0.93	0.86	0.79 – 0.95
7-hydroxy quetiapine	0.72	0.61 – 0.84	0.74	0.63 – 0.87
N-desalkyl quetiapine	0.96	0.86 – 1.07	0.87	0.76 – 1.00

Figure 2: Box plot of Dose-normalized, weight-normalized AUC of quetiapine versus age on combined data from children and adults

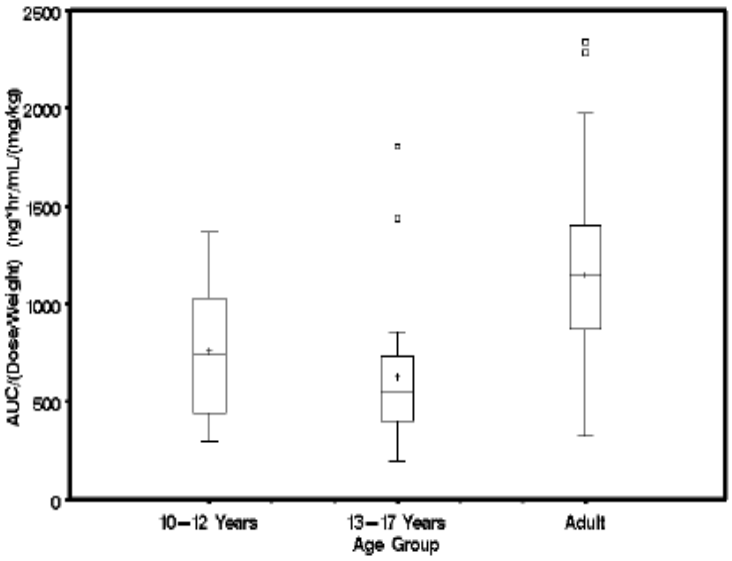
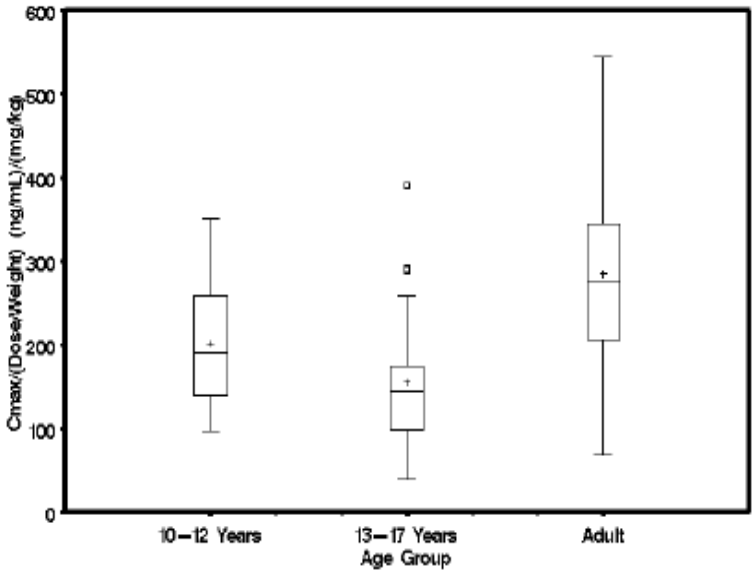


Figure 3: Box plot of Dose-normalized, weight-normalized Cmax of quetiapine versus age on combined data from children and adults



Does quetiapine prolong QTc interval in children and adolescents at the proposed clinical doses?

Quietapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses. The potential for QTc prolongation at the proposed doses was evaluated by using the quetiapine concentration-QTcF relationship derived from a thorough QT study in healthy adults. Assuming the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-corrected, baseline-adjusted QTc (ΔΔQTc) intervals are less than 10 ms following the highest dose (i.e. 400 mg BID) tested in the two pivotal pediatric studies (Study D1441C00112 and Study D1441C00149). In addition, the largest observed mean QTc interval change from baseline (ΔQTcF) observed in the clinical trials was around 2 ms. No patients had QTcF values larger than 500 ms or ΔQTcF greater than 60 ms.

Table 3: Model Predicted ΔΔQTcF Values

Daily Dose (mg/day)	Dose (mg)	Dosing	C_{max} (ng/mL)	Predicted QTcF (90% CI) (ms)
400	200	BID	520.9	5.4 (3.6 - 7.1)
600	300	BID	1023.6	6.8 (4.9 - 8.7)
800	400	BID	1113.4	6.9 (5.0 - 8.9)

2. Question Based Review

The QBR section of the review has used a deductive approach (i.e. starts with conclusions followed with supportive details) as instructed by CDER Review template MaPP 4000.4

2.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology?

The sponsor submitted this supplemental New Drug Application (sNDA) for Seroquel® (quetiapine fumarate) Tablets for Pediatric Exclusivity determination in response to a Pediatric Written Request issued by the Agency. The supplement contains, pharmacokinetic, efficacy and safety data for the use of Seroquel in the treatment of schizophrenia and bipolar mania in pediatric patients. No new information was included in the CMC (chemistry, manufacturing, and control), biopharmaceutics or preclinical, sections of this sNDA. These sections are cross-referenced to NDA 20-639 and associated supplements. The purpose of the clinical pharmacology evaluation was to characterize the steady-state pharmacokinetics (PK) of Seroquel™ , administered twice daily as quetiapine immediate-release tablets (up to total daily doses of 800 mg) in children and adolescents 10 to 17 years of age with diagnoses of bipolar I or schizoaffective disorder.

Quetiapine is a dibenzothiazepine derivative marketed in the US and a number of other countries for the treatment of adult patients with schizophrenia and bipolar disorder, including bipolar depression, bipolar mania and bipolar maintenance. The recommended dose range of quetiapine in adults is between 150 mg and 750 mg; safety data are available for doses up to 800 mg per day.

The sponsor conducted a study to characterize the steady-state pharmacokinetics (PK) of quetiapine administered as quetiapine tablets in children and adolescents 10 to 17 years of age with schizoaffective or bipolar 1 disorder. This study was conducted in response to a Pediatric Written Request issued by the Agency for information on quetiapine in subjects aged 10 to 17 years. The PK results in this pediatric study was compared to a study (Study D1441C00130) in adults (18 to 45 years) to determine if there are differences in the exposure between the pediatric and adult patients. The overall objective and design of the two studies (Studies D1441C00028 and D1441C00130) were similar.

2.2 General Clinical Pharmacology

2.2.1 What is the proposed therapeutic indication for quetiapine IR in this submission?

This sNDA seeks approval of the use of Seroquel® (quetapine fumarate) in treatment of schizophrenia and bipolar mania in pediatric patients

2.2.2 What are the proposed dosing recommendations for Seroquel in pediatric patients?

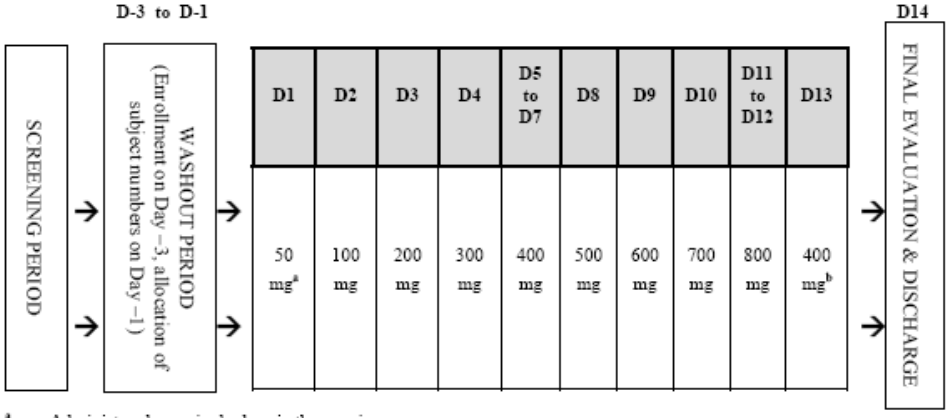
The total daily dose for the initial five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After Day 5, the dose should be adjusted within the recommended dose range of 400 to 600 mg for mania and 400 to 800 mg/day for schizophrenia based on response and tolerability. Dose adjustments should be in increments of no greater than 100 mg/day.

2.2.3 What is the Pharmacokinetics of Quetiapine and its Metabolites in Pediatric patients aged 10 – 17 years?

Exposure to quetiapine in terms of AUCss and Css,max appeared to be higher in the 10- to 12-year-old subjects than in the 13- to 17-year-old subjects on Days 7 and 13. The geometric means for AUCss on Days 7 and 13 were 55% and 36% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 – 17 year old. The geometric means for Css,max on Days 7 and 13 were 71% and 54% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 -17 year olds.

The study in pediatric patients was a multicenter, open-label, inpatient, steady-state, PK, safety and tolerability study in children and adolescents (10 to 17 years) with confirmed clinical diagnoses of schizophrenia, schizoaffective disorder or bipolar disease. Subjects received ascending total daily doses of quetiapine, administered in equally divided doses twice daily unless noted otherwise. Plasma and urine concentrations of quetiapine and its metabolites were measured after the morning doses were administered on Day 7 (200-mg dose) and Day 13 (400-mg dose). Safety was assessed by recording adverse events (AEs) and collecting vital signs measurements, electrocardiographic (ECG) data and clinical laboratory tests. The following figure depicts the design of the study.

Figure 4: Flow chart depicting the design of study in pediatric patients



[a] Administered as a single dose in the evening.
[b] Administered as a single dose in the morning.
D Day.
Note: Doses shown are total daily doses administered in equally divided doses twice daily unless noted otherwise.

Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 7 and Day 13 for subjects who received the 200 and 400 mg morning dose are provided in the following figures

Figure 5: Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 7 for subjects who received the 200 mg morning dose

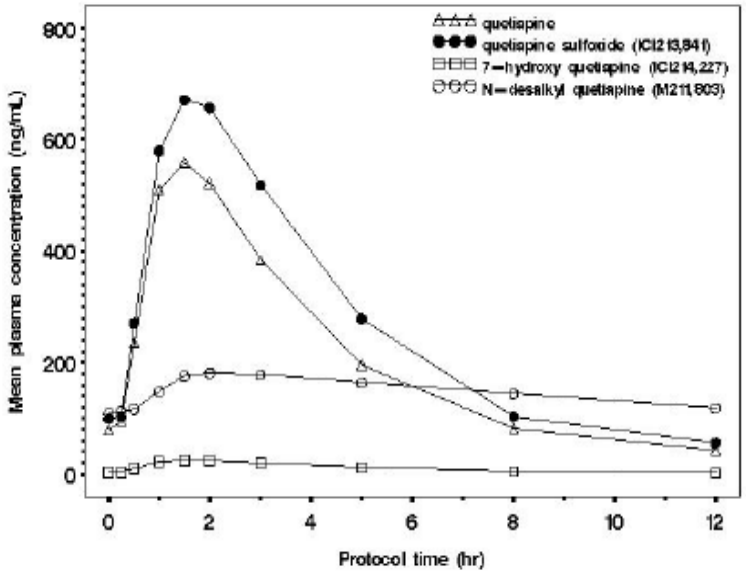


Figure 6: Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 13 for subjects who received the 400 mg morning dose

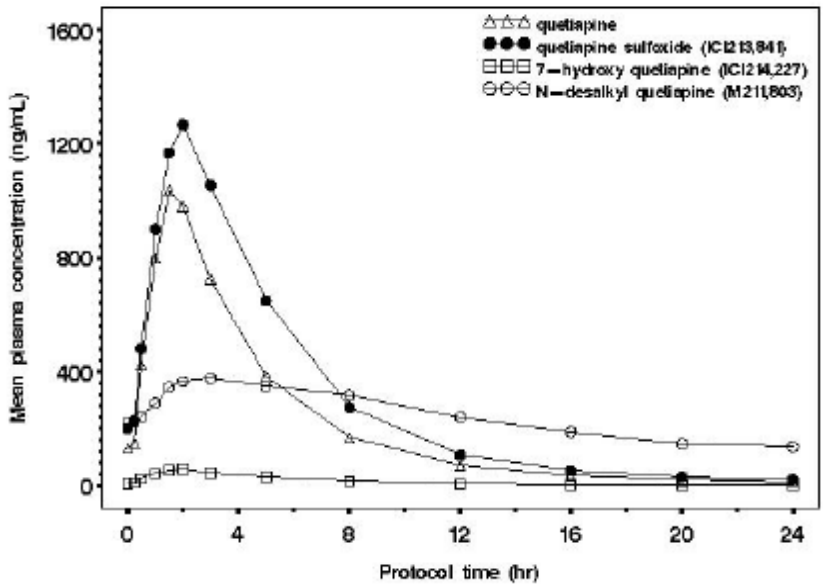
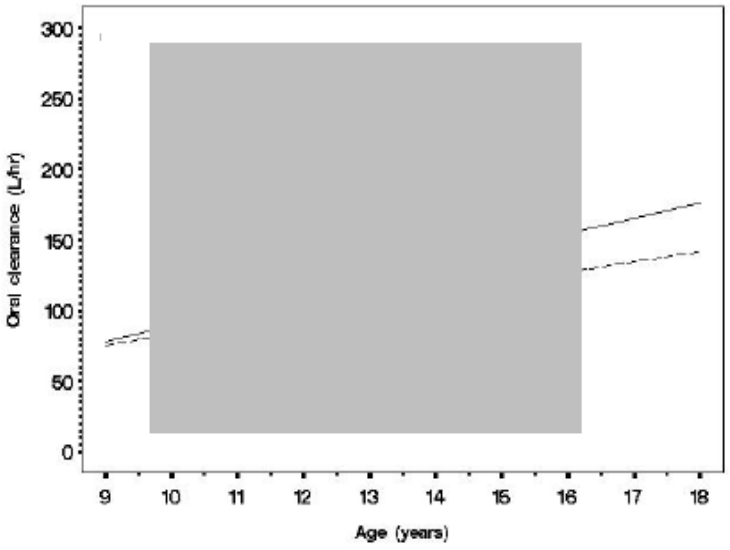
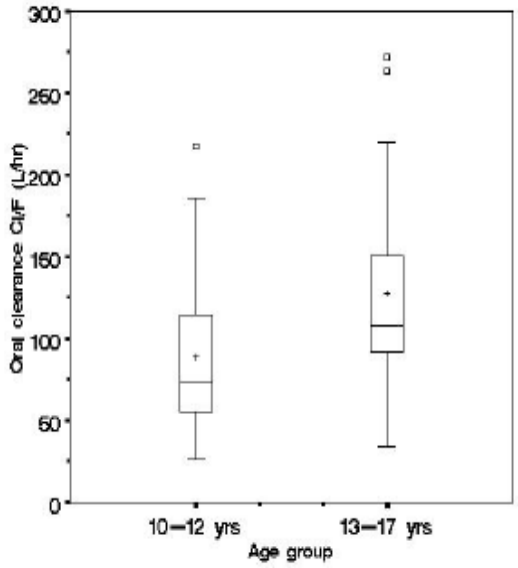


Figure 7: Scatter plot of oral clearance of quetiapine by age for Day 7 and Day 13



Triangle: Observed values for Day 7
Dot: Observed values for Day 13
Solid line: Linear regression for Day 7
Dash line: Linear regression for Day 13

Figure 8: Box plots of oral clearance of quetiapine on Day 7 and Day 13 by age group



Note: The horizontal lines in the graph indicate the 10th,25th,50th,75th,and 90th percentiles

Pharmacokinetic parameters for quetiapine are presented in the following table.
Exposure to quetiapine in terms of AUCss and Css,max appeared to be higher in the 10- to 12-year-old subjects than in the 13- to 17-year-old subjects on Days 7 and 13. The geometric means for AUCss on Days 7 and 13 were 55% and 36% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 – 17 year old. The geometric means for Css,max on Days 7 and 13 were 71% and 54% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 -17 year olds. The quetiapine Css,min was 22% and 21% higher for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to the 13 to 17 year olds. The apparent oral clearance (CL/F) was 38% and 30% lower for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to 13 to 17 year olds.

Table 4: Mean Pharmacokinetic parameters for quetiapine by age group

PK parameter	Statistic	Age group					
		10-12 yrs (n=9)[a]		13-17 yrs (n=12)		Total (n=21)[a]	
		Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC_{ss} (ng*hr/mL)	Geometric mean	2560.0	5145.0	1651.4	3784.8	1992.8	4317.1
	CV (%)	56.8	29.1	64.5	46.6	65.0	42.4
$C_{ss,max}$ (ng/mL)	Geometric mean	707.0	1426.3	414.3	924.7	520.9	1113.4
	CV (%)	37.5	33.9	69.4	51.6	63.9	49.8
t_{max} (hr)	Median	1.08	1.50	1.57	1.50	1.50	1.50
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Maximum	2.00	2.00	3.00	2.00	3.00	2.00
$C_{ss,min}$ (ng/mL)	Geometric mean	33.1	66.7	27.2	54.9	29.6	59.7
	CV (%)	113.5	74.4	99.9	66.9	102.9	69.0
CL/F (L/hr)	Mean	87.1	80.7	140.1	115.8	117.4	100.8
	SD	39.0	24.8	75.6	55.4	66.9	47.4
$t_{1/2}$ (hr)	Mean	3.17	5.52	2.77[b]	5.52[b]	2.96[c]	5.52[c]
	SD	0.99	1.38	0.56	0.77	0.80	1.07
$Ael_{(ss)}$ (µg)	Mean	143.7	281.9	101.8	253.0	119.8	265.4
	SD	145.3	217.2	50.5	99.4	101.5	156.6
Fu (%)	Mean	0.072	0.070	0.051	0.063	0.060	0.066
	SD	0.073	0.054	0.025	0.025	0.051	0.039
CL_R (L/hr)	Mean	0.063	0.053	0.070	0.077	0.067	0.067
	SD	0.083	0.036	0.052	0.058	0.065	0.050

[a] Number of subjects who received 400-mg morning dose on Day 13.
[b] Excludes 2 of 12 subjects for whom $t_{1/2}$ could not be calculated.
[c] Excludes 2 of 21 subjects for whom $t_{1/2}$ could not be calculated.

$Ael_{(ss)}$ amount of metabolite eliminated. AUC_{ss} area under the curve at steady-state. CL/F apparent oral clearance. CV coefficient of variation. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

The pharmacokinetic parameters of the active metabolite, N-desalkyl quetiapine is provided in the following table.

Table 5: Pharmacokinetic parameters for N-desalkyl quetiapine for subjects who received the 200 mg and 400 mg morning dose

		Age group					
		10-12 yrs (n=9)[a]		13-17 yrs (n=12)		Total (n=21)[a]	
PK parameter[b]	Statistic	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC_{ss} (ng*hr/mL)	Geometric mean	1977.4	4074.0	1497.1	3380.7	1686.7	3662.1
	CV (%)	13.7	20.6	34.1	33.3	30.3	29.5
$C_{ss,max}$ (ng/mL)	Geometric mean	214.9	460.3	164.7	347.7	184.6	392.1
	CV (%)	18.8	23.4	33.8	36.5	31.0	34.2
t_{max} (hr)	Median	2.00	2.00	3.00	3.00	3.00	3.00
	Minimum	1.00	1.50	1.00	1.50	1.00	1.50
	Maximum	12.00	8.00	8.00	8.00	12.00	8.00
$C_{ss,min}$ (ng/mL)	Geometric mean	126.9	250.4	100.2	223.5	110.8	234.7
	CV (%)	20.0	22.1	34.3	25.3	30.9	24.1
$Ael_{(ss)}$ (µg)	Mean	2231.1	5069.6	2328.3	5806.0	2286.7	5490.4
	SD	1813.9	3131.1	1776.0	4021.5	1747.4	3599.4
Fu (%)	Mean	1.448	1.645	1.511	1.884	1.484	1.782
	SD	1.178	1.016	1.153	1.305	1.134	1.168
CL_R (L/hr)	Mean	1.052	1.210	1.610	1.755	1.371	1.521
	SD	0.776	0.704	1.514	1.466	1.258	1.207

[a] Number of subjects who received 400-mg morning dose on Day 13.
[b] $t_{1/2}$ results are omitted from this table as there were only 5 subjects who provided data on both Days 7 and 13.
$Ael_{(ss)}$ amount of metabolite eliminated. AUC_{ss} area under the curve at steady-state. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. NA not applicable. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

The means for AUCss for N-desalkyl quetiapine on Days 7 and 13 were 32% and 21% higher, respectively, for the 10- to 12-year-old subjects compared to 13 to 17 year olds. The means for Css,max on Days 7 and 13 were 30% and 32% higher, respectively, for 10- to 12-year-old subjects compared to the 13 to 17 year old.

In terms of in vivo exposure, the rank order of exposure with respect to both AUCss and Css,max was: quetiapine sulfoxide>quetiapine> N-desalkyl quetiapine>7-hydroxy quetiapine. Quetiapine sulfoxide and 7-hydroxy quetiapine are inactive metabolites.

2.2.4 How does the exposure to quetiapine in pediatric patients compare to adults?

The comparison of pharmacokinetics between pediatric patients and adults was done across two studies. The study designs for the two studies were similar.

2.2.4.1 Dose normalized exposure comparison
Comparison of dose normalized exposures (AUCss and Cmax) to quetiapine showed a 12% decrease in AUC and 8% decrease in Cmax in pediatric children ages 10 to 17 years old compared to adults (ages 18 to 45 years).

Dose normalized AUC increased by about 6% and Cmax increased by 16% when children 10 – 12 years are compared to adults. But when children 13 – 17 years are compared to adults, dose normalized AUC and Cmax decreased by about 27% and 28% respectively.

Table 6: Comparison of dose-normalized exposure (AUCss and Cmax) to quetiapine and 3 metabolites in children/adolescents with exposure in adults

	Dose-normalized AUC_{ss}		Dose-normalized $C_{ss,max}$	
Analyte	Mean ratio[a]	90% CI	Mean ratio[a]	90% CI
Quetiapine	0.88	0.76, 1.03	0.92	0.79, 1.06
Quetiapine sulfoxide	1.27	1.15, 1.39	1.30	1.16, 1.44
7-hydroxy quetiapine	1.08	0.92, 1.26	1.11	0.94, 1.31
N-desalkyl quetiapine	1.45	1.30, 1.61	1.31	1.15, 1.49

[a] Ratio (10- to 17-year-olds:adults) of least squares means from ANOVA model.
ANOVA analysis of variance. AUC_{ss} area under the curve at steady-state. CI confidence interval. $C_{ss,max}$ maximum plasma concentration at steady-state.

Table 7: Comparison of dose-normalized AUC and Cmax of quetiapine and 3 metabolites in children (10 -12 years) with exposure in adults (18 – 45 years)

Analyte	Dose- Normalized AUC		Dose –Normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	1.06	0.88 – 1.26	1.16	0.99 – 1.35
Quetiapine sulfoxide	1.43	1.29 – 1.58	1.53	1.37 – 1.72
7-hydroxy quetiapine	1.16	0.97 – 1.40	1.23	1.00– 1.51
N-desalkyl quetiapine	1.63	1.44 – 1.84	1.49	1.26 – 1.75

Post hoc analyses with no control for multiplicity.

Table 8: Comparison of dose-normalized AUC and Cmax of quetiapine and N-desalkyl quetiapine in adolescents (13 - 17 years) with exposures in adults (18 – 45 years)

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.73	0.61 – 0.88	0.72	0.60 – 0.86
Quetiapine sulfoxide	1.11	0.99 – 1.25	1.06	0.94 – 1.21
7-hydroxy quetiapine	1.00	0.81 – 1.22	0.98	0.78 – 1.22
N-desalkyl quetiapine	1.28	1.12 – 1.47	1.14	0.96 – 1.35

Post hoc analyses with no control for multiplicity.

The following figures provide a comparison of the pediatric populations to adults in an across studies comparison.

Figure 9: Box plot of Dose-normalized AUC of quetiapine versus age on combined data from children and adults

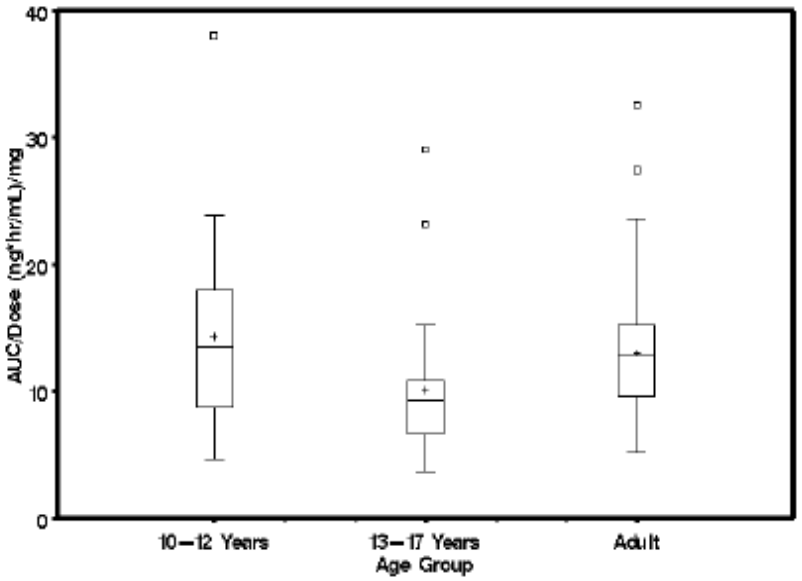
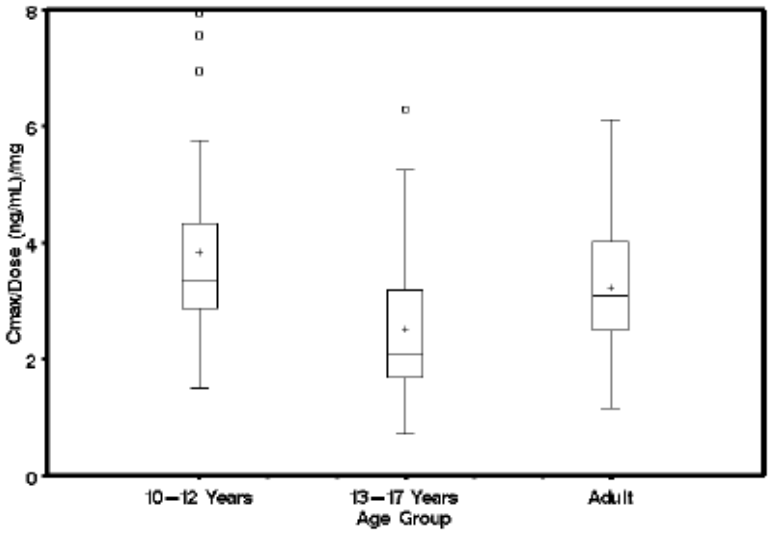


Figure 10: Box plot of Dose-normalized Cmax of quetiapine versus age on combined data from children and adults



2.2.4.2 Dose normalized, weight normalized exposure comparison
Dose normalized, weight-normalized AUC decreased by 41% and Cmax decreased by 39% when pediatric children ages 10 to 17 were compared to adults. The decrease in exposure may not be clinically relevant.

Dose normalized, weight normalized AUC decreased by about 35% and Cmax decreased by 28% when children 10 – 12 years are compared to adults. When children 13 – 17 years are compared to adults, dose normalized, weight-normalized AUC and Cmax decreased by about 47% and 48% respectively. These decreases in exposure are not expected to be clinically relevant.

The following tables provide a comparison of the pediatric populations to adults in an across studies comparison.

Table 9: Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites in children/adolescents with exposures in adults

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.59	0.50 – 0.70	0.61	0.53 – 0.72
Quetiapine sulfoxide	0.85	0.77 – 0.93	0.86	0.79 – 0.95
7-hydroxy quetiapine	0.72	0.61 – 0.84	0.74	0.63 – 0.87
N-desalkyl quetiapine	0.96	0.86 – 1.07	0.87	0.76 – 1.00

Post hoc analyses with no control for multiplicity.

Table 10: Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites in children, 10 – 12 years with exposures in adults

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.65	0.53 – 0.80	0.72	0.60 – 0.85
Quetiapine sulfoxide	0.89	0.79 – 1.00	0.95	0.85 – 1.06
7-hydroxy quetiapine	0.72	0.59 – 0.88	0.76	0.62 – 0.94
N-desalkyl quetiapine	1.00	0.87 – 1.16	0.92	0.78 – 1.10

Post hoc analyses with no control for multiplicity.

Table 11: Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites in adolescents, 13 - 17 years with exposures in adults

Analyte	Dose- Weight Normalized AUC		Dose –Weight normalized Cmax	
	Mean Ratio	90% CI	Mean Ratio	90% CI
Quetiapine	0.53	0.43 – 0.65	0.52	0.43 – 0.63
Quetiapine sulfoxide	0.81	0.71 – 0.91	0.77	0.68 – 0.87
7-hydroxy quetiapine	0.72	0.59 – 0.89	0.71	0.57 – 0.88
N-desalkyl quetiapine	0.92	0.80 – 1.07	0.82	0.69 – 0.98

Post hoc analyses with no control for multiplicity.

Figure 13: Box plot of Dose-normalized, weight normalized AUC of quetiapine versus age on data from children versus adults

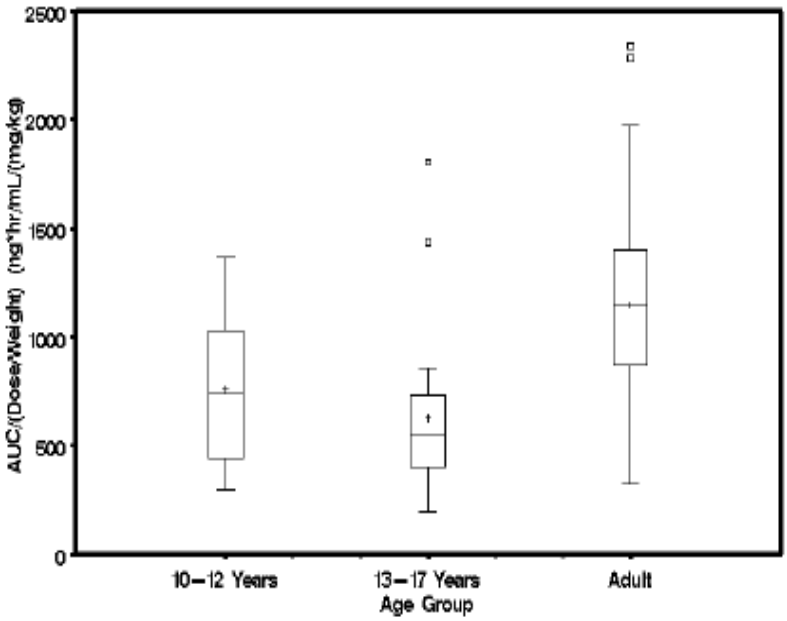


Figure 14: Box plot of Dose-normalized, weight-normalized Cmax of quetiapine versus age on children and adults

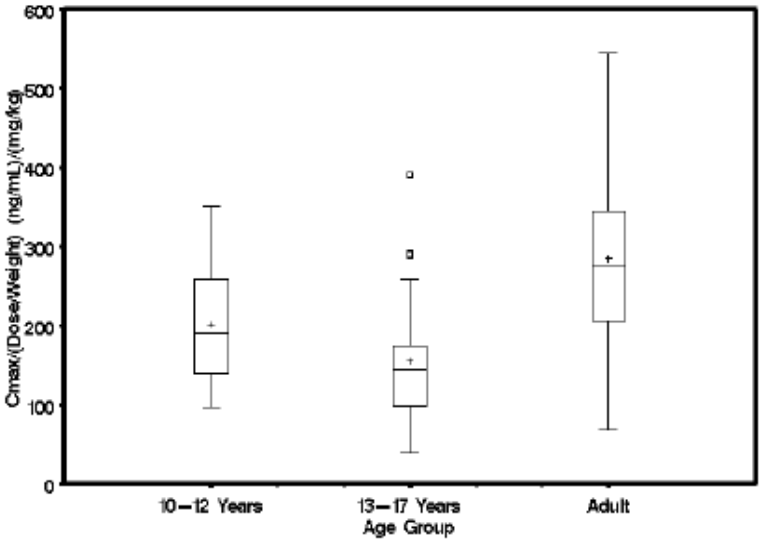


Figure 15: Box plot of Dose-normalized, weight-normalized Cmin of quetiapine versus age of data from children and adults

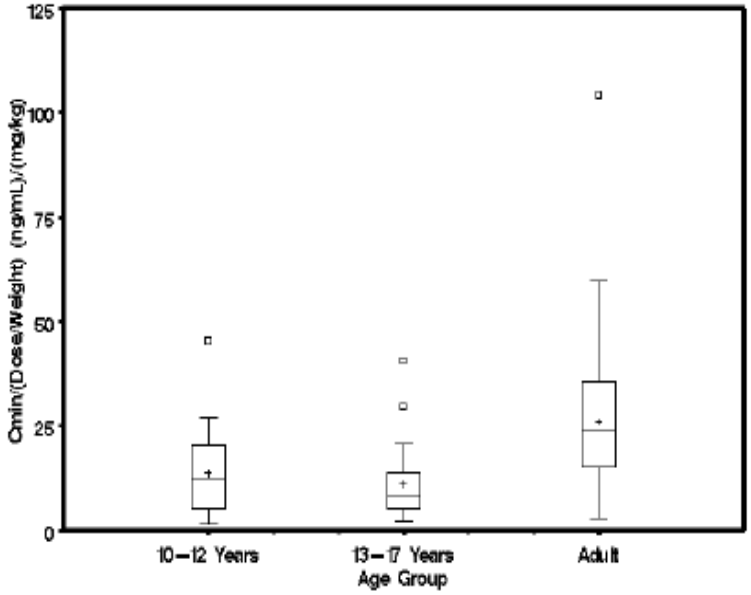
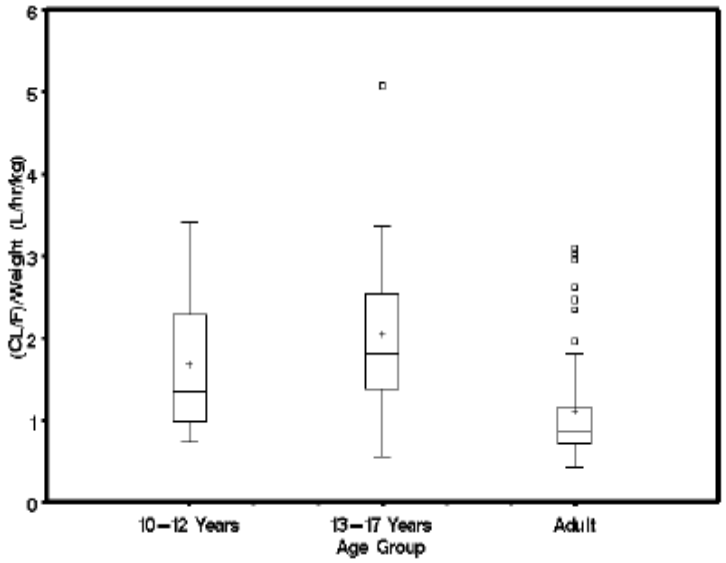


Fig 16: Box plot of Weight-normalized Oral Clearance (Cl/F) of quetiapine versus age on combined data from children and adults



Comparisons of weight-adjusted, dose normalized exposure showed evidence of significant age-related differences in exposure to quetiapine, with about 41% lower exposures seen in children/adolescents. These comparisons of weight-adjusted, dose-normalized exposure showed no evidence for age-related differences in exposure to N-desalkyl quetiapine metabolites. The differences in exposures between the pediatric patients and adults may not be clinically relevant.

2.2.5. Does quetiapine prolong QTc interval in children and adolescents at the proposed clinical doses?

Quetiapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses. The potential for QTc prolongation at the proposed doses was evaluated by using the quetiapine concentration-QTcF relationship derived from a thorough QT study in healthy adults. Assuming the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-corrected, baseline-adjusted QTc (ΔΔQTc) intervals are less than 10 ms (Table 12) following the highest dose (i.e. 400 mg BID) tested in the two pivotal pediatric studies (Study D1441C00112 and Study D1441C00149). In addition, the largest observed mean QTc interval change from baseline (ΔQTcF) observed in the clinical trials was around 2 ms (Table 13). No patients had QTcF values larger than 500 ms or ΔQTcF greater than 60 ms.

Table 12: Model Predicted ΔΔQTcF Values

Daily Dose (mg/day)	Dose (mg)	Dosing	C_{max} (ng/mL)	Predicted QTcF (90% CI) (ms)
400	200	BID	520.9	5.4 (3.6 - 7.1)
600	300	BID	1023.6	6.8 (4.9 - 8.7)
800	400	BID	1113.4	6.9 (5.0 - 8.9)

Table 13: Summary of the QTcF change from Baseline Values

Study		D1441C00112	D1441C00149
Patients		schizophrenia	Bipolar I mania
Treatment	Age	13 ~ 17	10 ~ 17
Placebo	Mean (SD)	-2.1 (18.1)	-1.2 (17.6)
	N	71	81
400 mg/day	Mean (SD)	1.96 (16.2)	-0.11 (16.1)
	N	72	94
600 mg/ day	Mean (SD)	-	-1.1 (16.8)
	N	-	98
800 mg/day	Mean (SD)	1.96 (18.1)	-
	N	73	-

2.2.6. What were overall adverse events profile in Study 28 reported by the sponsor?

In this pharmacokinetic study, the sponsor reported that quetiapine was well tolerated in this subject population and no new safety concerns were identified. There were no deaths or serious AEs during or after treatment. There were no apparent differences between younger and older subjects' safety profiles. Somnolence was the most frequently occurring adverse event during treatment. The majority of cases were considered treatment related, were rated as mild in intensity by the investigator, and were transient. A comparison of the occurrence of AEs in children and adolescents in the present study with AE occurrence in adults in Study D1441C00130 showed adult subjects reported 1 or more AEs more frequently than children. Dizziness was reported more frequently in adults than in children and adolescents. The sponsor stated that there were no other obvious differences between children and adults in the types or severity of AEs reported; however, the small sample sizes in both studies limit the comparisons that can be made between the safety profiles. The sponsor reported that increases in mean ALT and mean heart rates were seen in children and adolescents in the present study; however these changes were not unexpected and were not clinically meaningful. No other trends were seen in other clinical laboratory tests, vital signs measurements or ECG parameters.

3. Detailed Labeling Recommendations

Detailed OCP Labeling recommendations are incorporated in the proposed label attached under Appendices. The following recommended revisions is to the paragraph under "Children and Adolescents" under section 12.3. The proposed label is provided in the Appendix.

(b) (4)

4. Appendix

Proposed Label with OCP recommendations. OCP edits are noted as “Track Changes: in the proposed label

Clinical Pharmacology Individual Reports

Pharmacometric Review

FOLLOWING THIS PAGE, 55 PAGES WITHHELD IN FULL - DRAFT LABELING - B4

4.2 Individual Reports

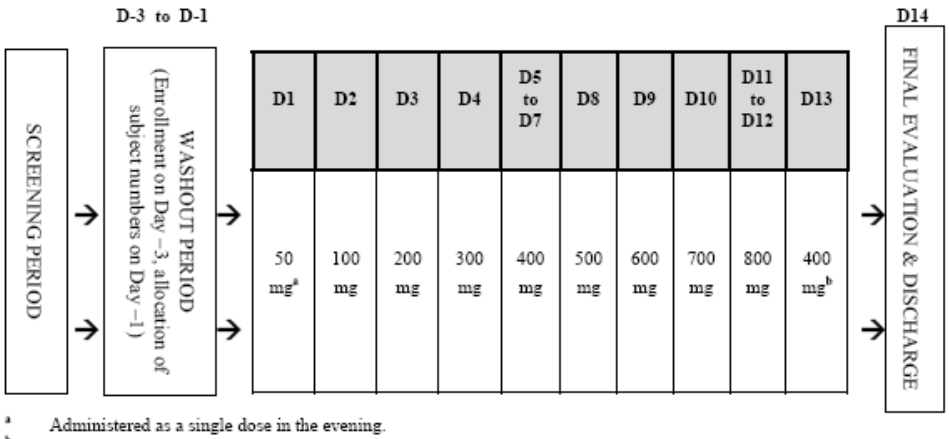
Title (Protocol D1441C00028): A Study to Characterize the Steady-State Pharmacokinetics, Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) in Children and Adolescents with Selected Psychotic Disorders

Objectives: To characterize the steady-state pharmacokinetics (PK) of quetiapine fumarate (SEROQUEL™, quetiapine) administered as quetiapine tablets in children and adolescents 10 to 17 years of age. The secondary objectives were:

1. To monitor the tolerability and safety of titrating doses of quetiapine
2. To determine the dose-proportionality for quetiapine
3. Compare the AUC and Cmax between the subjects in this trial and D1441C00130
4. To characterize the PK of 3 metabolites: quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine

Study Design: This was a multicenter, open-label, inpatient, steady-state, PK, safety and tolerability study in children and adolescents (10 to 17 years) with confirmed clinical diagnoses of schizophrenia, schizoaffective disorder or bipolar disease. Subjects received ascending total daily doses of quetiapine, administered in equally divided doses twice daily unless noted otherwise, as follows: Day 1 (a single 50-mg dose in the evening), Day 2 (100 mg), Day 3 (200 mg), Day 4 (300 mg), Days 5 to 7 (400 mg), Day 8 (500 mg), Day 9 (600 mg), Day 10 (700 mg), Days 11 and 12 (800 mg), and Day 13 (a single 400-mg dose in the morning). Plasma and urine concentrations of quetiapine and its metabolites were measured after the morning doses were administered on Day 7 (200-mg dose) and Day 13 (400-mg dose). The study used intact quetiapine 25-mg tablets (formulation number F12804; batch number 2000058452; lot number 7527F) and 100-mg tablets (formulation number F12689; batch number 2000058452; lot number 7511H) that were administered orally, every 12 hours. Safety was assessed by recording adverse events (AEs) and collecting vital signs measurements, electrocardiographic (ECG) data and clinical laboratory tests.

The following figure is a flow chart depicting the design of the study.



[a] Administered as a single dose in the evening.
[b] Administered as a single dose in the morning.
D Day.
Note: Doses shown are total daily doses administered in equally divided doses twice daily unless noted otherwise.

Multiple blood samples for determining plasma concentrations were drawn as follows:
• On Day 7 immediately prior to the 200-mg morning dose (time 0) and 0.25, 0.5, 1, 1.5, 2, 3, 5, 8 and 12 hours after this dose
• On Day 13 immediately prior to the 400-mg morning dose (time 0) and at 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 20, and 24 hours after this dose

To verify that steady-state was achieved, pre-dose blood samples were obtained as follows:
• On Days 6 and 7 prior to the 200-mg morning dose
• On Day 7 12 hours after dosing
• On Days 12 and 13 prior to the 400-mg morning dose
• On Day 13 12 hours after the 400-mg morning dose

Subjects were not permitted to take any concurrent antipsychotic or psychotropic medications, with the exception of valproic acid and lithium. Subjects who were stabilized on either of these medications for at least 1 month prior to the first administration of study treatment were permitted to continue these treatments at their current dose. All other antipsychotic and psychotropic medications were to be discontinued for at least 3 days before beginning study treatment. Acetaminophen was the only medication allowed for analgesia without prior consultation with the sponsor. Oral lorazepam was permitted for acute agitation or severe insomnia, with the dosage determined at the discretion of the principal investigator.

Analytical Methods: The concentrations of quetiapine, quetiapine sulfoxide (M213,841), 7-hydroxy quetiapine (M214,227), and N-desalkyl quetiapine (M211,803) in plasma and urine were determined using a validated reverse-phase liquid chromatography and turbo ionspray ionization tandem mass spectrometry (LC/MS/MS). The method has a validated assay range of 0.500 to 500 ng/mL for all analytes, utilizing a 100 µL sample aliquot with extension of the validated curve range to 10.0 µg/mL (50 µg/mL for urine) with appropriate dilution.

Data Analysis: The following pharmacokinetic parameters were computerized by non-compartmental methods: Blood samples: AUCss, Css,max, Css,min, T1/2, Tmax, CL/F, Fu, Ael(m), CLR, and λz for quetiapine and AUCss, Css,max, Css,min, t1/2, tmax, Fu, Ael(m), CLR, and λz for 3 metabolites (quetiapine sulfoxide, 7-hydroxy quetiapine, and N-desalkyl quetiapine). AUCss and Css,max following the 200-mg and 400-mg morning doses on Days 7 and 13 were the primary variables. Urine samples: Fu and Ael(m) for quetiapine 4 metabolites (quetiapine sulfoxide, 7-hydroxy quetiapine, N-desalkyl quetiapine and 7-hydroxy N-desalkyl quetiapine).

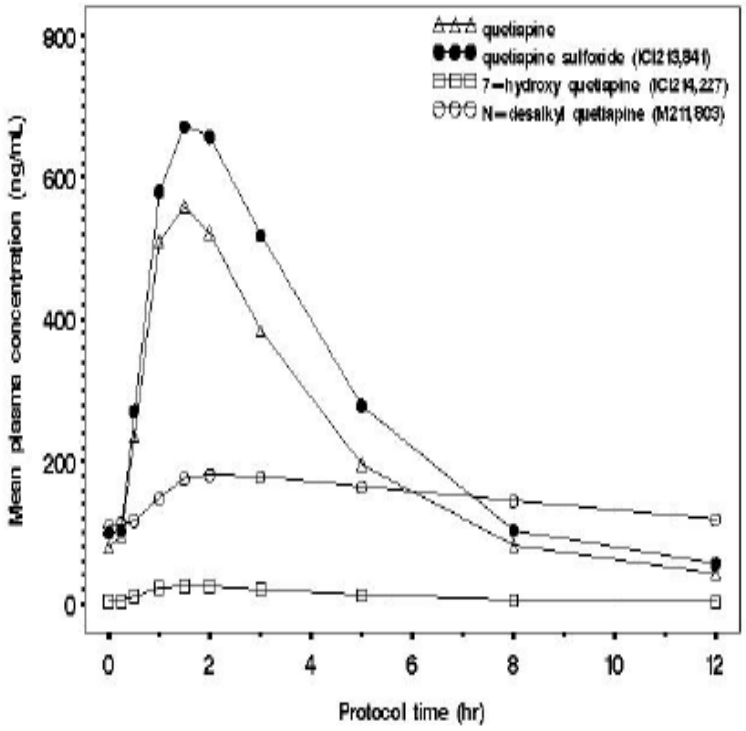
Plasma concentrations and PK parameters for quetiapine and its metabolites were summarized descriptively for each dose for all subjects and by age group (10-12 years and 13-17 years). To assess the dose-proportionality of quetiapine, log-transformed AUCss and Css,max for the 400-mg morning dose were compared to the log-transformed AUCss and Css,max for the 200-mg morning dose, respectively, using analysis of variance (ANOVA) methods. Comparisons of exposure in children/adolescents with that in adults (from Study D1441C00130) used the following models: log-transformed, dose-normalized AUCss and Css,max were analyzed separately using ANOVA with a term for age group (ie, 10- to 17-year-old subjects or adult subjects). Least squares means and 90% confidence intervals for the ratios of interest (ie, AUCss for 10- to 17-year-olds: AUCss for adults and Css,max for 10- to 17-year-olds:Css,max for adults) were calculated. If the 90% confidence intervals for both AUCss and Css,max were completely contained within the interval 0.71 to 1.41, it was concluded that there was no difference in exposure between adults and 10- to 17-year-old subjects.

Results: Twenty-eight subjects were enrolled in this study. Twenty-seven of the 28 subjects received the study medication; 1 subject was withdrawn from the study after enrollment but prior to receiving study medication. As a result, 27 subjects were included in the safety population. Three additional subjects withdrew from the study prior to completion; therefore, 24 subjects were evaluable for PK analyses. Three subjects in the 10- to 12-year age group were unable to tolerate daily doses above 600 mg and remained on 600 mg per day from Day 11 onward, as allowed by the protocol. Of the 27 subjects in the safety population, 13 were in the 10- to 12-year age range, and 14 were in the 13- to 17-year age range. The median age of subjects in the safety population was 13 years. In the 13- to 17-year-old age group, 10 of the 14 subjects were 13 or 14 years old. Approximately one-half of the subjects in each age group were male. Approximately one-half of all subjects were black; the proportion of blacks was slightly higher in the 13- to 17-year-old age group. All but 1 of the subjects had a diagnosis of bipolar I disorder; 1 subject in the 10- to 12-year-old age group had a diagnosis of schizoaffective disorder.

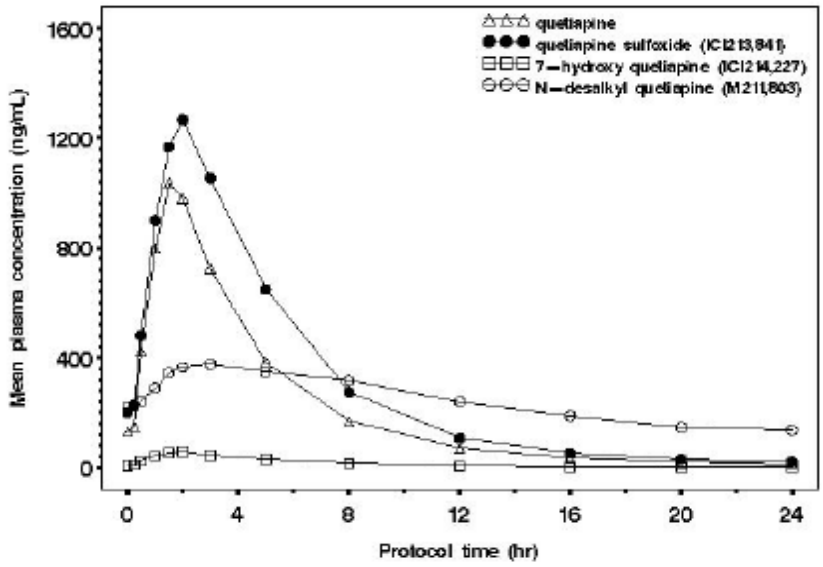
Pharmacokinetic Results

Mean plasma concentrations over time for quetiapine and 3 metabolites on Days 7 and 13.

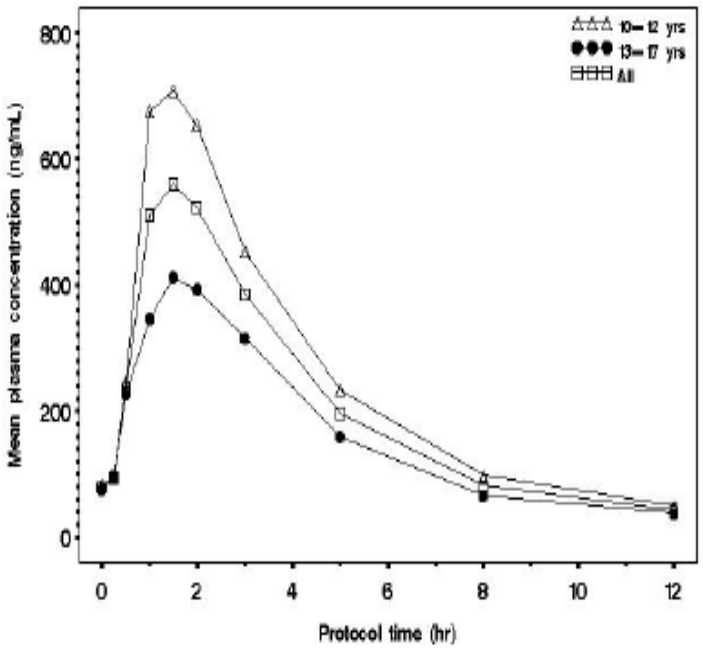
Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 7 for subjects who received the 200 mg morning dose



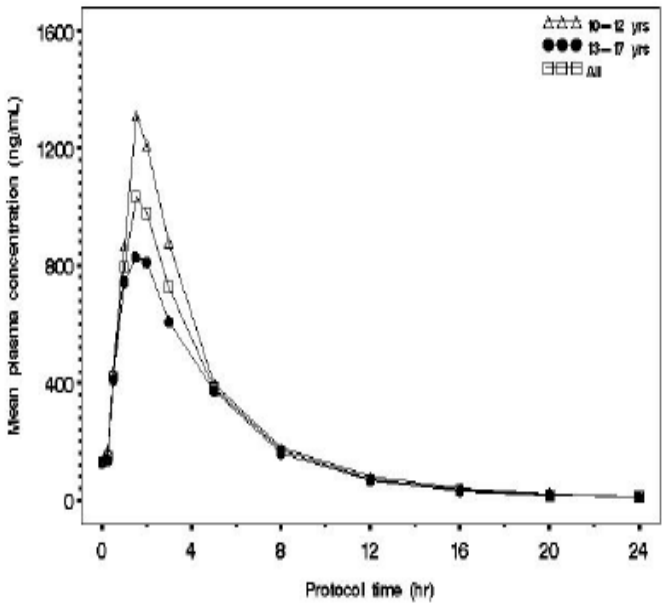
Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 13 for subjects who received the 400 mg morning dose



Mean plasma concentrations of quetiapine over time in Day 7 for PK population subjects who received the 200 mg morning dose



Mean plasma concentrations of quetiapine over time on Day 13 for PK population subjects who received the 400 mg morning dose



Descriptive statistics of the pharmacokinetic parameters for quetiapine are presented in the following table.

Pharmacokinetic parameters for quetiapine for subjects who received the 200 and 400-mg morning dose

		Age group					
		10-12 yrs (n=9)[a]		13-17 yrs (n=12)		Total (n=21)[a]	
PK parameter	Statistic	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC_{ss} (ng*hr/mL)	Geometric mean	2560.0	5145.0	1651.4	3784.8	1992.8	4317.1
	CV (%)	56.8	29.1	64.5	46.6	65.0	42.4
$C_{ss,max}$ (ng/mL)	Geometric mean	707.0	1426.3	414.3	924.7	520.9	1113.4
	CV (%)	37.5	33.9	69.4	51.6	63.9	49.8
t_{max} (hr)	Median	1.08	1.50	1.57	1.50	1.50	1.50
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Maximum	2.00	2.00	3.00	2.00	3.00	2.00
$C_{ss,min}$ (ng/mL)	Geometric mean	33.1	66.7	27.2	54.9	29.6	59.7
	CV (%)	113.5	74.4	99.9	66.9	102.9	69.0
CL/F (L/hr)	Mean	87.1	80.7	140.1	115.8	117.4	100.8
	SD	39.0	24.8	75.6	55.4	66.9	47.4
$t_{1/2}$ (hr)	Mean	3.17	5.52	2.77[b]	5.52[b]	2.96[c]	5.52[c]
	SD	0.99	1.38	0.56	0.77	0.80	1.07
$Ael_{(ss)}$ (µg)	Mean	143.7	281.9	101.8	253.0	119.8	265.4
	SD	145.3	217.2	50.5	99.4	101.5	156.6
Fu (%)	Mean	0.072	0.070	0.051	0.063	0.060	0.066
	SD	0.073	0.054	0.025	0.025	0.051	0.039
CL_R (L/hr)	Mean	0.063	0.053	0.070	0.077	0.067	0.067
	SD	0.083	0.036	0.052	0.058	0.065	0.050

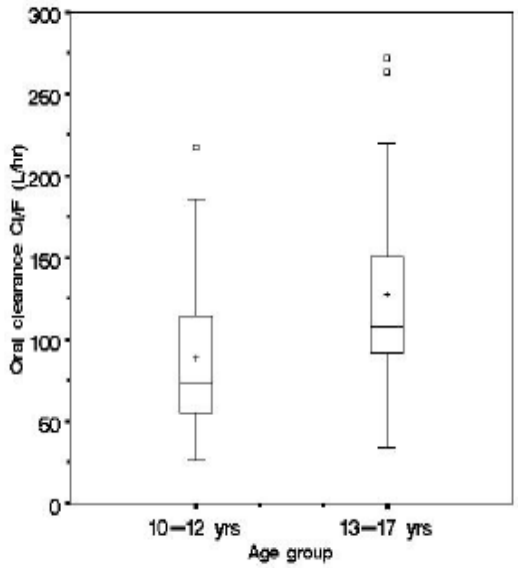
[a] Number of subjects who received 400-mg morning dose on Day 13.
[b] Excludes 2 of 12 subjects for whom $t_{1/2}$ could not be calculated.
[c] Excludes 2 of 21 subjects for whom $t_{1/2}$ could not be calculated.
$Ael_{(ss)}$ amount of metabolite eliminated. AUC_{ss} area under the curve at steady-state. CL/F apparent oral clearance. CV coefficient of variation. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

Exposure to quetiapine in terms of AUCss and Css,max appeared to be higher in the 10- to 12-year-old subjects than in the 13- to 17-year-old subjects on Days 7 and 13. The geometric means for AUCss on Days 7 and 13 were 55% and 36% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 – 17 year old. The geometric means for Css,max on Days 7 and 13 were 71% and 54% higher, respectively, for the 10- to 12-year-old subjects as compared to the 13 -17 year olds. The quetiapine Css,min was 22% and 21% higher for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to the 13 to 17 year olds. The apparent oral clearance (CL/F) was 38% and 30% lower for the 10- to 12-year-old subjects on Days 7 and 13, respectively as compared to 13 to 17 year olds.

Box plots of CL/F for all PK population subjects in each age group on Days 7 and 13 are presented in the following figure. A scatter plot of CL/F by age for Days 7 and 13 for all PK population subjects is presented in the following figure. The median CL/F was lower among 10- to 12-year-old subjects relative to the 13 to 17 year olds. Regression lines showed CL/F tended to

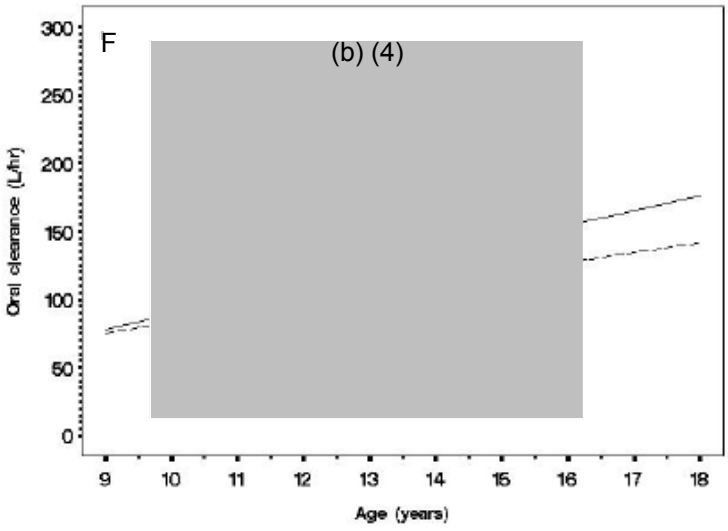
increase with age. However, there was large amount of overlap in the distributions of CL/F at all ages. Dose normalized AUC or Cmax does not appear to indicate a change in exposure when compared to the weight of the patient.

Box plots of oral clearance of quetiapine on Day 7 and Day 13 by age group



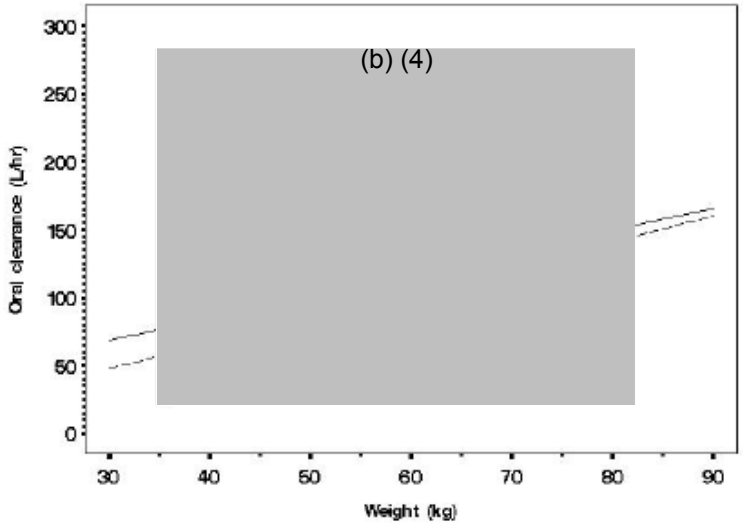
Note: The horizontal lines in the graph indicate the 10th,25th,50th,75th,and 90th percentiles

Scatter plot of oral clearance of quetiapine by age for Day 7 and Day 13



Triangle: Observed values for Day 7
Dot: Observed values for Day 13
Solid line: Linear regression for Day 7
Dash line: Linear regression for Day 13

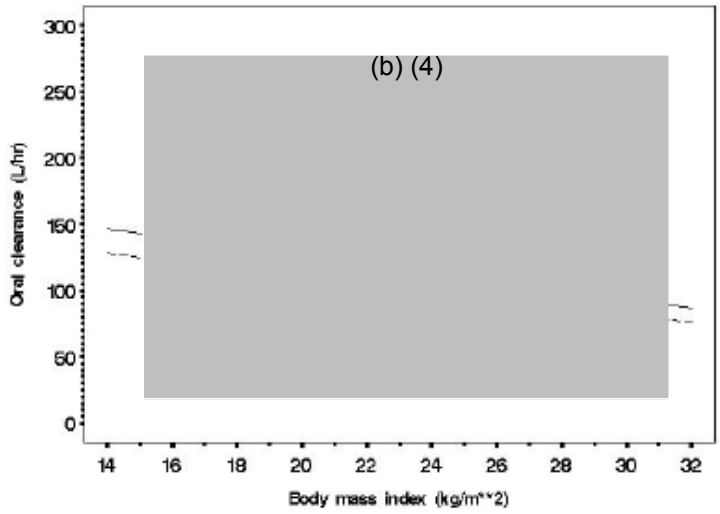
Scatter plot of oral clearance of quetiapine by weight for Day 7 and Day 13



Triangle: Observed values for Day 7
Dot: Observed values for Day 13
Solid line: Linear regression for Day 7
Dash line: Linear regression for Day 13

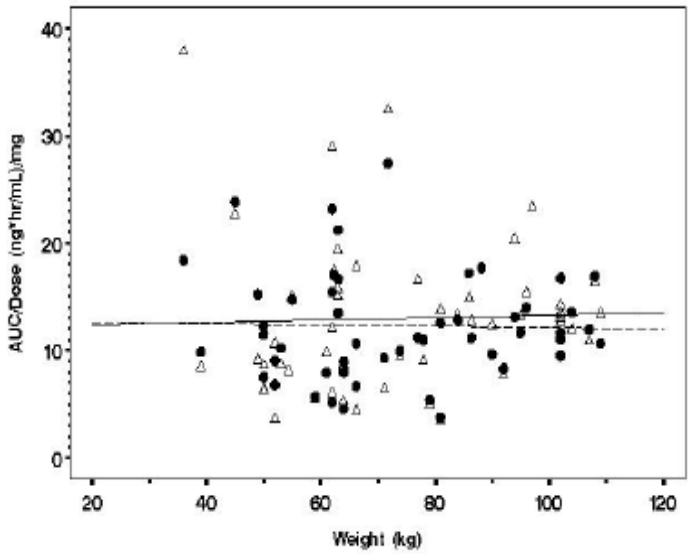
The clearance of quetiapine increase with age and weight of the patients. There was large inter-patient variability in the data.

Oral Clearance (CL/F) of quetiapine versus body mass index



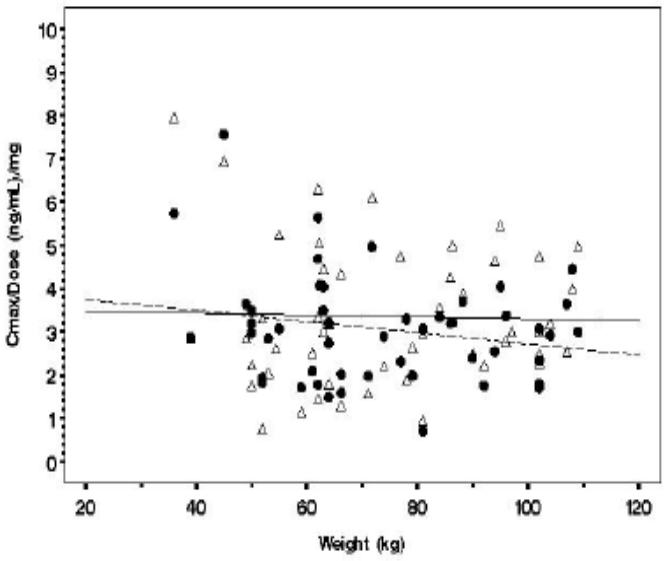
Triangle: Observed values for Day 7
Dot: Observed values for Day 13
Solid line: Linear regression for Day 7
Dash line: Linear regression for Day 13

Dose-normalized AUC of quetiapine versus weight on combined data from children/adolescents and adults (data from study 41441C00130)



Triangle: Observed values on combined data from Day 7 (Children/Adolescents) and Day 6 (Adults)
Dot: Observed values on combined data from Day 13 (Children/Adolescents) and Day 12 (Adults)
Solid line: Linear regression on combined data from Day 7 (Children/Adolescents) and Day 6 (Adults)
Dash line: Linear regression on combined data from Day 13 (Children/Adolescents) and Day 12 (Adults)

Dose-normalized Cmax of quetiapine versus weight on combined data from children/adolescents and adults

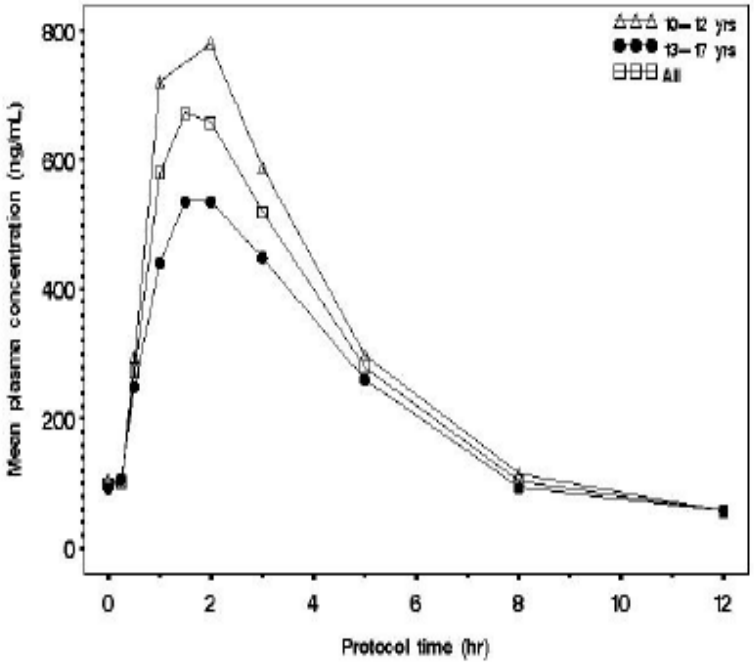


Triangle: Observed values on combined data from Day 7 (Children/Adolescents) and Day 6 (Adults)
Dot: Observed values on combined data from Day 13 (Children/Adolescents) and Day 12 (Adults)
Solid line: Linear regression on combined data from Day 7 (Children/Adolescents) and Day 6 (Adults)
Dash line: Linear regression on combined data from Day 13 (Children/Adolescents) and Day 12 (Adults)

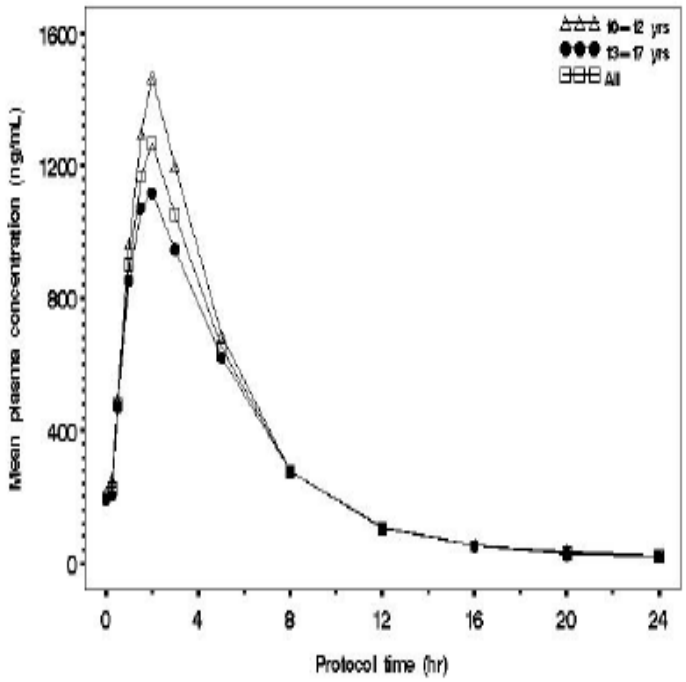
Metabolite pharmacokinetics

The following figures contain the plasma concentration time profile for the metabolites.

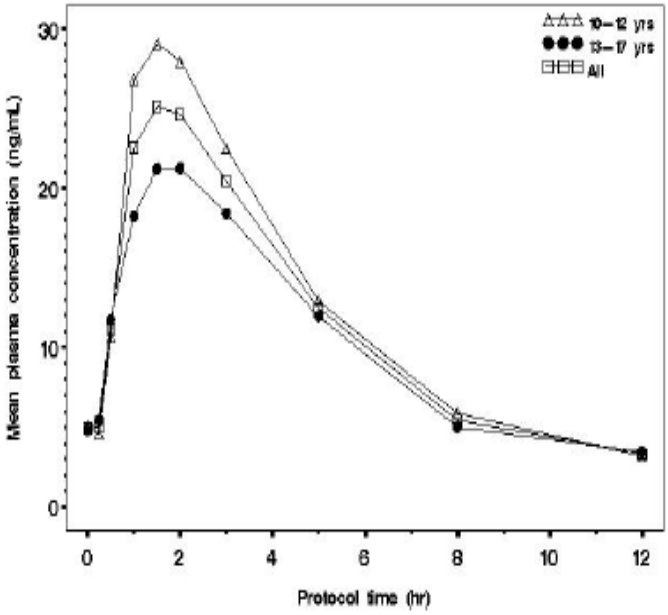
Mean plasma concentrations of quetiapine sulfoxide (IC1213841) over time on Day 7 for PK population subjects who received the 200 mg morning dose



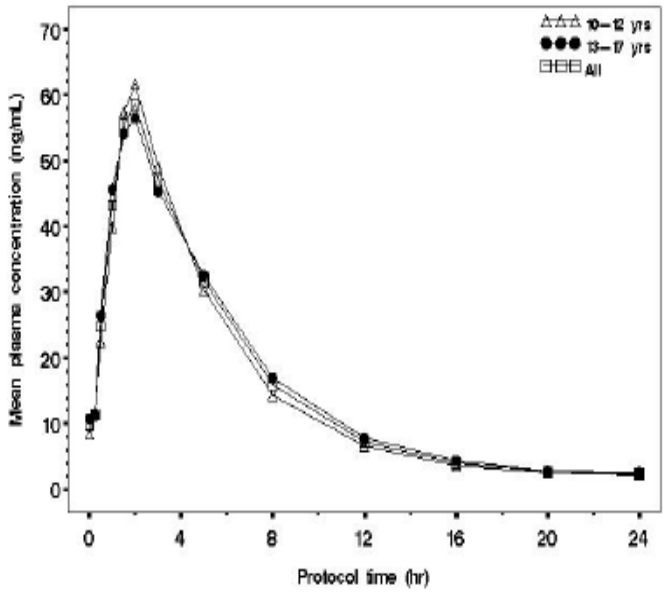
Mean plasma concentrations of quetiapine sulfoxide (ICI213,841) over time on Day 13 for PK population subjects who received the 400 mg morning dose



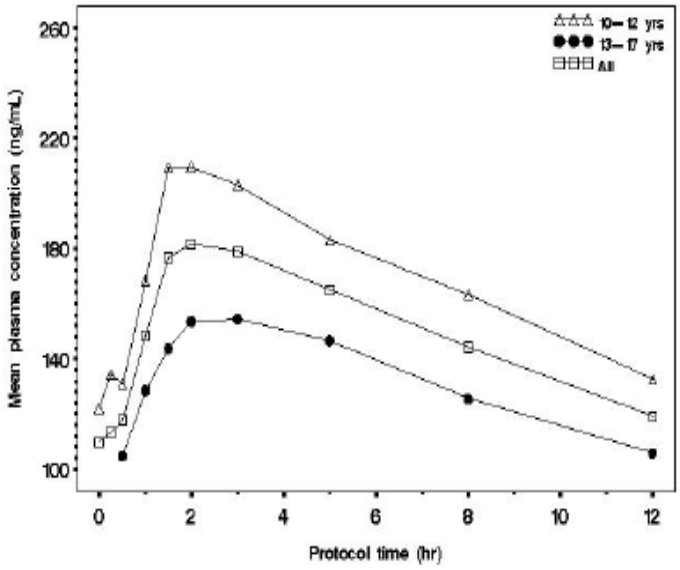
Mean plasma concentrations of 7-hydroxy quetiapine (ICI214,227) over time on Day 7 for PK population subjects who received the 200 mg morning dose



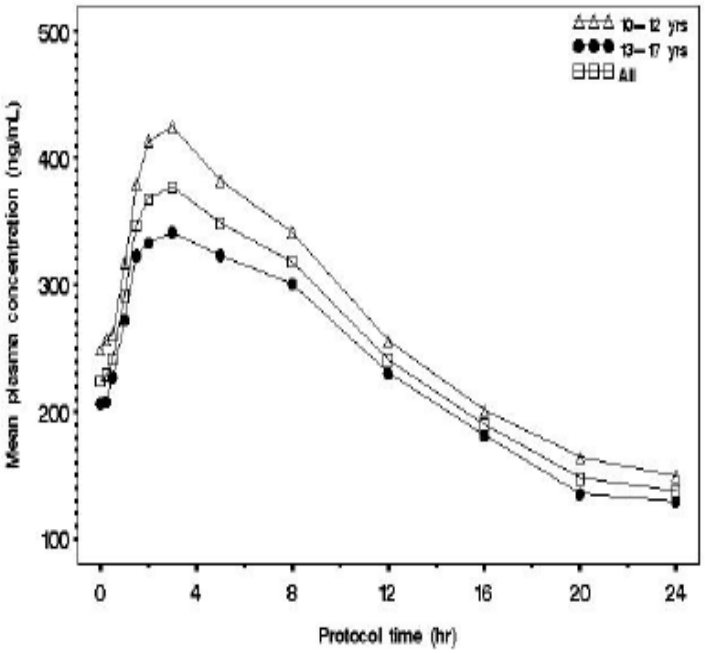
Mean plasma concentrations of 7-hydroxy quetiapine (ICI214,227) over time on Day 13 for PK population subjects who received the 400 mg morning dose



Mean plasma concentrations of N-desalkyl quetiapine (M211,803) over time on Day 7 for PK population subjects who received the 200 mg morning dose



Mean plasma concentrations of N-desalkyl quetiapine (M211,803) over time on Day 13 for PK population subjects who received the 400 mg morning dose



Pharmacokinetic parameters at steady-state are summarized for the 3 metabolites, quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine in the following tables.

Pharmacokinetic parameters for quetiapine sulfoxide for subjects who received 200 and 400-mg morning dose on Day 13

		Age group					
		10-12 yrs (n=9)[a]		13-17 yrs (n=12)		Total (n=21)[a]	
PK parameter	Statistic	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC_{ss} (ng*hr/mL)	Geometric mean	3374.8	6967.0	2585.8	5946.9	2898.4	6364.4
	CV (%)	21.5	26.5	40.3	33.0	35.5	30.8
$C_{ss,max}$ (ng/mL)	Geometric mean	795.9	1560.7	560.9	1170.5	651.7	1324.1
	CV (%)	25.5	24.1	34.4	37.6	35.4	35.2
t_{max} (hr)	Median	1.67	1.50	1.57	1.75	1.63	1.50
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Maximum	2.02	3.00	3.00	5.00	3.00	5.00
$C_{ss,min}$ (ng/mL)	Geometric mean	45.2	92.3	44.5	96.4	44.8	94.7
	CV (%)	45.8	71.0	79.2	48.9	64.1	57.1
$t_{1/2}$ (hr)	Mean	2.79[b]	5.64[b]	2.53[c]	4.98[c]	2.64[d]	5.27[d]
	SD	0.45	0.98	0.50	1.17	0.49	1.11
$Ael_{(ss)}$ (µg)	Mean	1073.5	3253.8	1168.9	3910.2	1128.0	3628.9
	SD	806.4	2801.4	523.0	2193.9	642.6	2428.4
Fu (%)	Mean	0.515	0.781	0.561	0.938	0.541	0.871
	SD	0.387	0.672	0.251	0.527	0.308	0.583
CL_R (L/hr)	Mean	0.301	0.409	0.467	0.649	0.395	0.546
	SD	0.219	0.193	0.246	0.307	0.244	0.285

[a] Number of subjects who received 400-mg morning dose on Day 13.
[b] Excludes 1 of 9 subjects for whom $t_{1/2}$ could not be calculated.
[c] Excludes 2 of 12 subjects for whom $t_{1/2}$ could not be calculated.
[d] Excludes 3 of 21 subjects for whom $t_{1/2}$ could not be calculated.
$Ael_{(ss)}$ amount of metabolite eliminated. AUC_{ss} area under the curve at steady-state. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

Exposure to quetiapine sulfoxide in terms of AUCss and Css,max were 30% and 40%, respectively higher on day 7 and 17% and 33% , respectively higher on day 13 in 10- to 12-year-old subjects than in 13- to 17-year-old subjects.

Pharmacokinetic parameters for 7-hydroxy quetiapine for subjects who received the 200 mg and 400 mg dose on day 13.

		Age group					
		10-12 yrs (n=9)[a]		13-17 yrs (n=12)		Total (n=21)[a]	
PK parameter	Statistic	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC_{ss} (ng*hr/mL)	Geometric mean	128.7	298.0	109.6	290.8	117.4	293.8
	CV (%)	31.3	40.8	50.3	54.8	42.8	47.9
$C_{ss,max}$ (ng/mL)	Geometric mean	28.2	62.6	21.3	57.7	24.0	59.7
	CV (%)	39.2	37.4	46.5	57.5	45.1	48.5
t_{max} (hr)	Median	2.00	2.00	1.57	1.50	1.82	1.50
	Minimum	1.00	1.00	0.52	0.50	0.52	0.50
	Maximum	3.00	3.00	3.00	2.00	3.00	3.00
$C_{ss,min}$ (ng/mL)	Geometric mean	2.32	5.75	2.62	6.41	2.49	6.12
	CV (%)	53.2	58.0	87.7	71.9	72.0	64.5
$t_{1/2}$ (hr)	Mean	2.92[b]	5.87[b]	3.43[c]	5.89[c]	3.19[d]	5.88[d]
	SD	0.44	1.33	0.61	1.36	0.58	1.29
$Ael_{(0)}$ (µg)	Mean	111.5	348.0	138.5	526.6	126.9	450.1
	SD	62.7	282.3	73.6	405.7	68.9	361.4
Fu (%)	Mean	0.054	0.084	0.066	0.126	0.061	0.108
	SD	0.030	0.068	0.035	0.097	0.033	0.087
CL_R (L/hr)	Mean	0.853	1.049	1.204	1.531	1.053	1.324
	SD	0.500	0.426	0.620	0.738	0.586	0.658

[a] Number of subjects who received 400-mg morning dose on Day 13.
[b] Excludes 3 of 9 subjects for whom $t_{1/2}$ could not be calculated.
[c] Excludes 5 of 12 subjects for whom $t_{1/2}$ could not be calculated.
[d] Excludes 8 of 21 subjects for whom $t_{1/2}$ could not be calculated.
$Ael_{(0)}$ amount of metabolite eliminated. AUC_{ss} aren under the curve at steady-state. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

There was about 17% and 3% higher AUCss for 7-hydroxy quetiapine in 10- to 12-year-old compared to 13 to 17 year old subjects on day 7 and 13, respectively. The Css,max was 32% higher in 10- to 12-year-old compared to 13 to 17 year olds on Day 7 and about 9% on Day 13.

Pharmacokinetic parameters for N-desalkyl quetiapine for subjects who received the 200 mg and 400 mg morning dose

		Age group					
		10-12 yrs (n=9)[a]		13-17 yrs (n=12)		Total (n=21)[a]	
PK parameter[b]	Statistic	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC_{ss} (ng*hr/mL)	Geometric mean	1977.4	4074.0	1497.1	3380.7	1686.7	3662.1
	CV (%)	13.7	20.6	34.1	33.3	30.3	29.5
$C_{ss,max}$ (ng/mL)	Geometric mean	214.9	460.3	164.7	347.7	184.6	392.1
	CV (%)	18.8	23.4	33.8	36.5	31.0	34.2
t_{max} (hr)	Median	2.00	2.00	3.00	3.00	3.00	3.00
	Minimum	1.00	1.50	1.00	1.50	1.00	1.50
	Maximum	12.00	8.00	8.00	8.00	12.00	8.00
$C_{ss,min}$ (ng/mL)	Geometric mean	126.9	250.4	100.2	223.5	110.8	234.7
	CV (%)	20.0	22.1	34.3	25.3	30.9	24.1
$Ael_{(ss)}$ (µg)	Mean	2231.1	5069.6	2328.3	5806.0	2286.7	5490.4
	SD	1813.9	3131.1	1776.0	4021.5	1747.4	3599.4
Fu (%)	Mean	1.448	1.645	1.511	1.884	1.484	1.782
	SD	1.178	1.016	1.153	1.305	1.134	1.168
CL_R (L/hr)	Mean	1.052	1.210	1.610	1.755	1.371	1.521
	SD	0.776	0.704	1.514	1.466	1.258	1.207

[a] Number of subjects who received 400-mg morning dose on Day 13.
[b] $t_{1/2}$ results are omitted from this table as there were only 5 subjects who provided data on both Days 7 and 13.
$Ael_{(ss)}$ amount of metabolite eliminated. AUC_{ss} area under the curve at steady-state. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. NA not applicable. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

The means for AUCss for N-desalkyl quetiapine on Days 7 and 13 were 32% and 21% higher, respectively, for the 10- to 12-year-old subjects compared to 13 to 17 year olds. The means for Css,max on Days 7 and 13 were 30% and 32% higher, respectively, for 10- to 12-year-old subjects compared to the 13 to 17 year old.

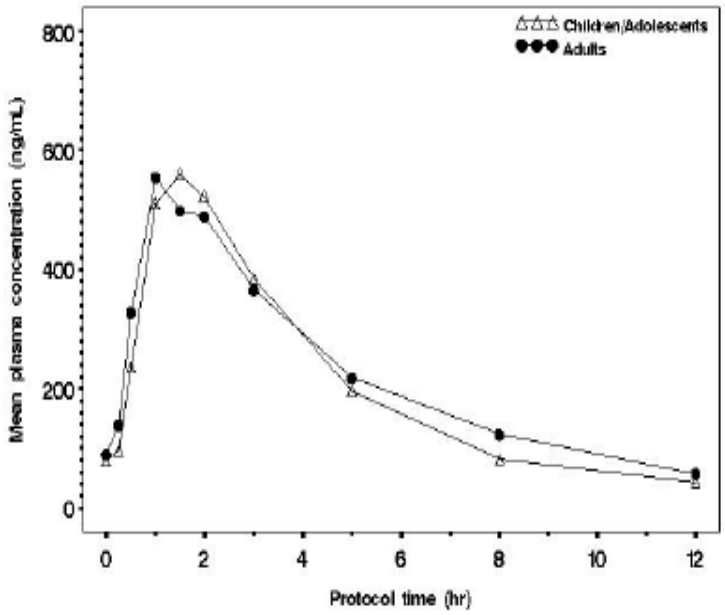
Summary of Pharmacokinetics

Two of the metabolites, quetiapine sulfoxide (t ½ = 5.27 hrs) and 7-hydroxy quetiapine (t ½ = 5.88 hrs), had estimates of t1/2 similar to quetiapine (5.52 hrs). The N-desalkyl quetiapine metabolite (t ½ = 11. 32 hrs) had a longer t ½ than quetiapine (t ½ = 5.52).
In terms of in vivo exposure, the rank order of exposure with respect to both AUCss and Css,max was: quetiapine sulfoxide>quetiapine> N-desalkyl quetiapine>7-hydroxy quetiapine.
Quetiapine AUCss and Css,max appeared to be higher in 10- to 12-year-old subjects than in 13- to 17-year-old subjects. Similar trends were observed for the quetiapine sulfoxide and N-desalkyl quetiapine metabolites. There was high degree of inter-subject variability in exposure to quetiapine and its metabolites in both subject populations. There was no apparent association between AUC and Cmax with weight for quetiapine.

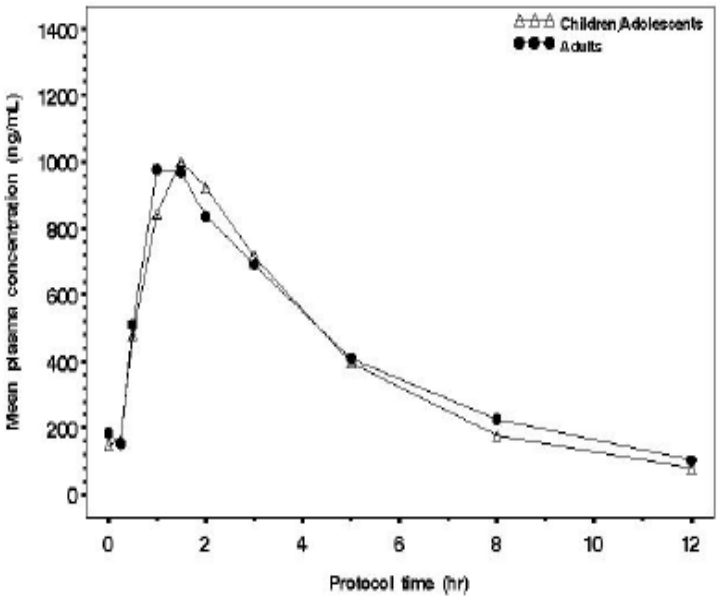
Comparison of pharmacokinetic results with those from Study D144C100130

The following figures contain the mean plasma concentrations over time for quetiapine in subjects who received 200 mg morning dose on combined data from children/adolescents and adults from study D1441C00130

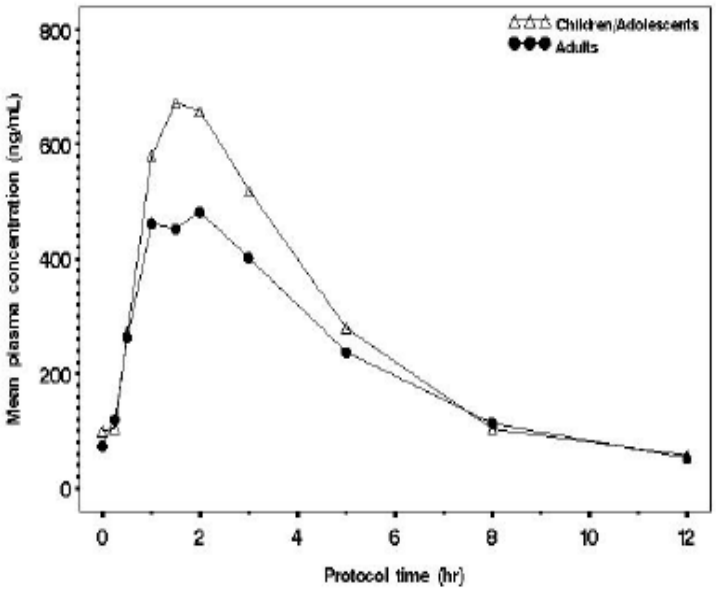
Mean plasma concentrations for quetiapine over time for PK population subjects who received the 200 mg morning dose on combined data from children/adolescents and adults



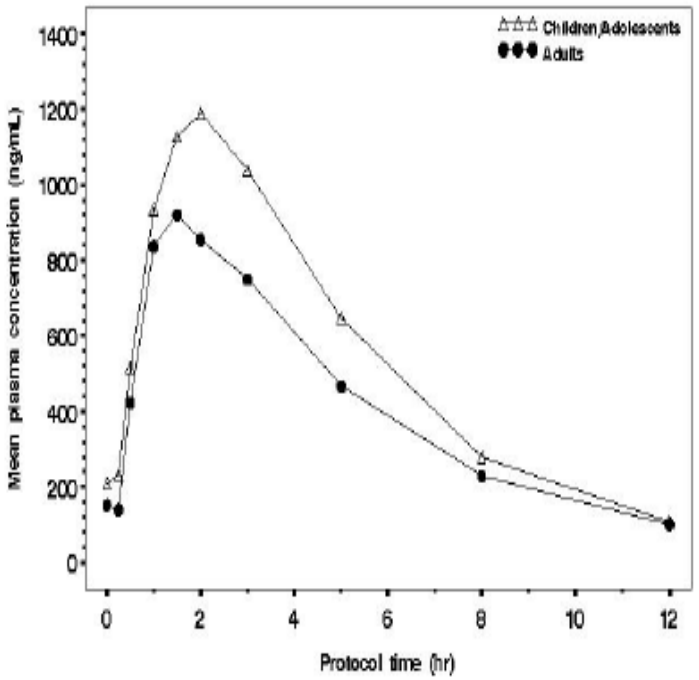
Mean plasma concentrations of quetiapine over time for PK population subjects who received the 400 mg morning dose on combined data from children/adolescents and adults



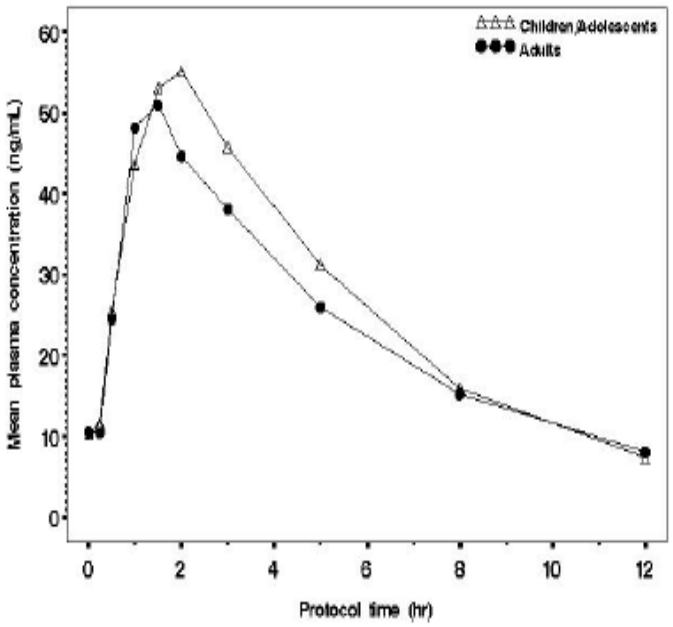
Mean plasma concentrations of quetiapine sulfoxide over time for subjects who received 200 mg morning dose on combined data from children/adolescents and adults



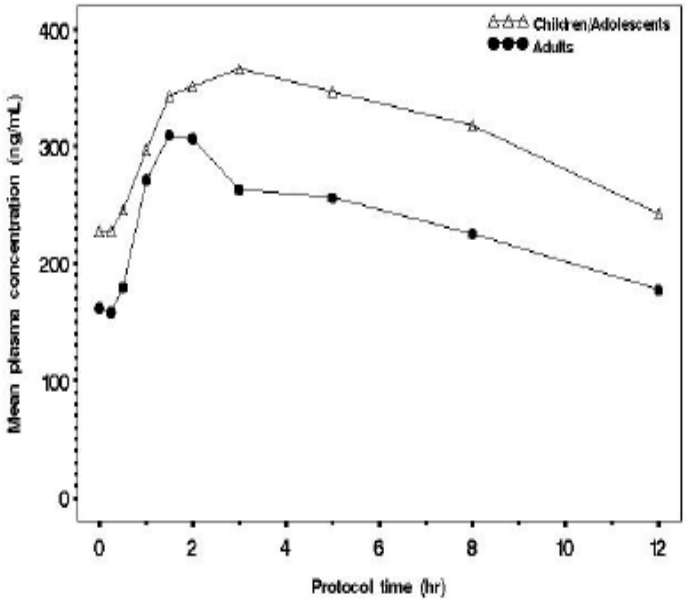
Mean plasma concentrations of quetiapine sulfoxide over time for subjects who received 400 mg morning dose on combined data from children/adolescents and adults



Mean plasma concentrations of 7-hydroxy quetiapine (ICI214,227) over time for PK population subjects who received the 400 mg morning dose on combined data from children/adolescents and adults (data from study D1441C00130)



Mean plasma concentrations of N-desalkyl quetiapine (M211,803) over time for PK population subjects who received the 400 mg morning dose on combined data from children/adolescents and adults (data from study D1441C00130)



The results of the comparisons of dose-normalized AUCss and Css,max for quetiapine and the 3 metabolites between children/adolescents and adults are presented in the following table.

Comparison of dose-normalized exposure (AUCss and Cmax) to quetiapine and 3 metabolites in children/adolescents with exposure in adults in Study D1441C00130

	Dose-normalized AUC_{ss}		Dose-normalized $C_{ss,max}$	
Analyte	Mean ratio[a]	90% CI	Mean ratio[a]	90% CI
Quetiapine	0.88	0.76, 1.03	0.92	0.79, 1.06
Quetiapine sulfoxide	1.27	1.15, 1.39	1.30	1.16, 1.44
7-hydroxy quetiapine	1.08	0.92, 1.26	1.11	0.94, 1.31
N-desalkyl quetiapine	1.45	1.30, 1.61	1.31	1.15, 1.49

[a] Ratio (10- to 17-year-olds:adults) of least squares means from ANOVA model.
ANOVA analysis of variance. AUC_{ss} area under the curve at steady-state. CI confidence interval. $C_{ss,max}$ maximum plasma concentration at steady-state.

The comparisons of dose-normalized exposure in children/adolescents with that in adults showed no evidence for age-related differences in exposure to quetiapine or its CYP2D6 metabolite, 7-hydroxy quetiapine. The effect of age on exposure to quetiapine sulfoxide, as measured by AUCss, showed statistical significance, with about 27% higher exposure seen in younger subjects. The effect of age on exposure to quetiapine sulfoxide, as measured by Css,max, was statistically significant, with about 30% higher peak exposure seen in younger subjects.

When AUCss and Css,max were normalized by the weight-adjusted dose (i.e, were divided by [dose/weight]), no differences in exposure with age were apparent for quetiapine sulfoxide or N-desalkyl quetiapine. For quetiapine and 7-hydroxy significant differences were observed.

Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites on combined data from children/adolescents and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children and Adolescents/Adults)			Children/Adolescents			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.59	0.50	0.70	610.69	527.56	706.92	1035.06	900.34	1189.93
AUC (Quetiapine sulfoxide)	0.85	0.77	0.93	905.16	832.58	984.08	1070.64	989.32	1158.65
AUC (7-hydroxy quetiapine)	0.72	0.61	0.84	39.19	34.34	44.73	54.50	47.40	62.66
AUC (N-desalkyl quetiapine)	0.96	0.86	1.07	515.11	472.96	561.01	537.17	483.67	596.59
Cmax (Quetiapine)	0.61	0.53	0.71	160.07	139.17	184.10	261.76	232.12	295.19
Cmax (Quetiapine sulfoxide)	0.86	0.79	0.95	198.50	183.40	214.85	229.59	211.40	249.34
Cmax (7-hydroxy quetiapine)	0.74	0.63	0.87	7.99	7.04	9.07	10.83	9.31	12.59
Cmax (N-desalkyl quetiapine)	0.87	0.76	1.00	55.64	50.60	61.19	63.79	56.24	72.36

Comparisons of weight-adjusted, dose normalized exposure showed evidence for statistically significant age-related differences in exposure to quetiapine and 7-hydroxy quetiapine, with (41% lower AUC, 39 % lower Cmax for quetiapine; 28% lower AUC, 26% lower Cmax for 7-hydroxyquetiapine) lower exposures seen in younger children/adolescents. These comparisons of weight-adjusted, dose-normalized exposure showed no evidence for age-related differences in exposure to the quetiapine sulfoxide or N-desalkyl quetiapine metabolites.

Conclusions:

The sponsor concluded that comparisons of dose-normalized exposure in children/adolescents with that in adults showed no evidence for age-related differences in exposure to quetiapine or its CYP2D6 metabolite, 7-hydroxy quetiapine. However, these analyses showed statistically significant differences in the quetiapine sulfoxide and N-desalkyl quetiapine metabolites, with higher exposures seen in children/adolescents.

Comparisons of weight-adjusted, dose normalized exposure showed evidence for statistically significant age-related differences in exposure to quetiapine and 7-hydroxy quetiapine, with lower exposures seen in younger children/adolescents ((41% lower AUC, 39 % lower Cmax for quetiapine; 28% lower AUC, 26% lower Cmax for 7-hydroxyquetiapine). The comparisons of weight-adjusted, dose-normalized exposure showed no evidence for age-related differences in exposure to the quetiapine sulfoxide (27% increase in AUC) or N-desalkyl quetiapine (45% increase in AUC) metabolites. There was large variability in the data.

Safety summary: The sponsor reported that quetiapine was well tolerated in this population of children and adolescents ages 10 to 17 years with diagnoses of bipolar I disorder or schizoaffective disorder. There were no deaths or other serious AEs during study treatment. There were no unexpected AEs reported during the study. The sponsor reported that there were no obvious differences between the age groups in the types of adverse events that occurred, or in their intensity. Three subjects in the 10- to 12-year-old age group had their study medication doses restricted to 600 mg/day from Day 11 onward. Somnolence was the most frequently occurring AE during study treatment. Most of the cases of somnolence occurred shortly after initiation of study treatment (ie, Day 1 or 2) and resolved prior to study completion; all cases were rated by the investigators as mild in intensity and were considered treatment related.

Reviewer comments: There was a trend towards higher exposures (36% to 55% higher AUC) in the younger children (10- 12 years old) when compared to adolescents (13 -17 year olds). There was large inter patient variability in the data.

Comparisons across studies indicated that dose normalized exposures in children/adolesecents (10-17 years) were 12% lower AUC than adults. When adjusted for weight and dose, there appears to be significant differences in exposure to quetiapine and its 7-hydroxy metabolite with children/adolescents having lower (about 30-40% lower) than adults.

Appendix

Figure 11.2.1.1.2 Individual values of Cmax of quetiapine versus quetiapine dose

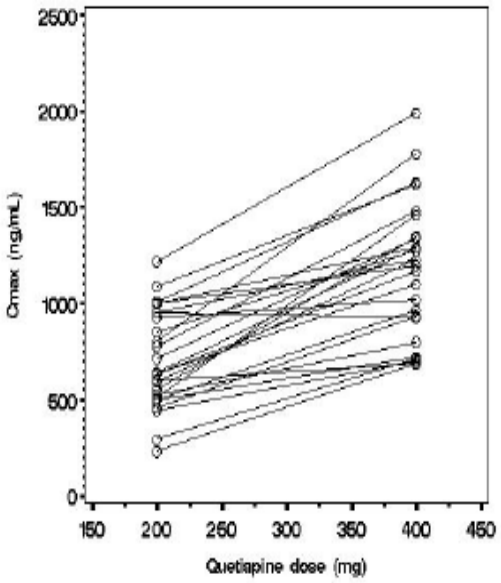


Figure 11.2.1.1.1.1 Individual values of AUC of quetiapine versus quetiapine dose

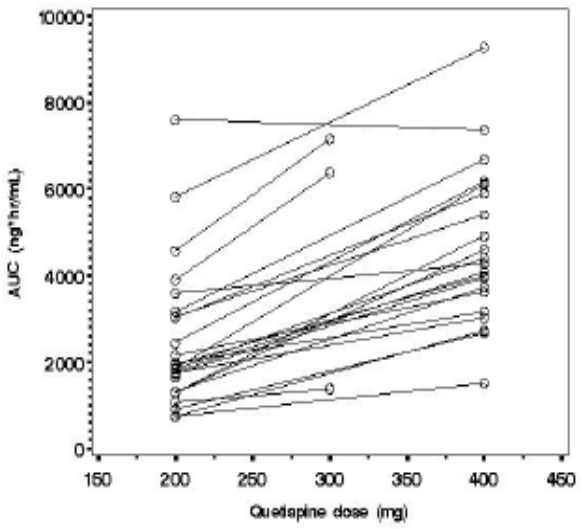


Figure 11.2.1.3.1.3 Box-plot of oral clearance (CL/F) of quetiapine on Day 7 and Day 13 by age group

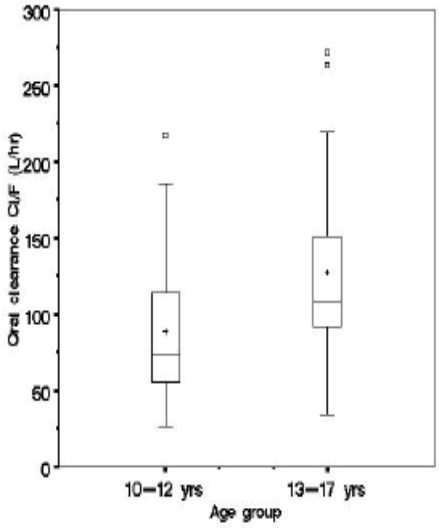


Table 11.2.1.1.1 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	2944.446	5324.121	1962.911	4143.432	2383.569	4649.442
	SD	1911.482	1406.690	1383.731	1956.123	1662.026	1804.024
	Minimum	1302.25	3024.48	735.90	1517.21	735.90	1517.21
	Median	2443.15	5404.50	1806.18	3860.78	1860.32	4267.48
	Maximum	7603.48	7371.14	5821.13	9273.16	7603.48	9273.16
	Geometric Mean	2560.018	5144.961	1651.433	3784.823	1992.752	4317.077
	CV(%)	56.825	29.120	64.538	46.617	65.048	42.348
Cmax (ng/mL)	N	9	9	12	12	21	21
	Mean	755.667	1496.667	498.583	1016.083	608.762	1222.048
	SD	338.116	498.322	338.859	422.324	354.793	506.771
	Minimum	449.00	810.00	150.00	288.00	150.00	288.00
	Median	658.00	1400.00	396.00	989.00	570.00	1190.00
	Maximum	1590.00	2300.00	1260.00	1880.00	1590.00	2300.00
	Geometric Mean	707.001	1426.254	414.267	924.704	520.917	1113.416
	CV(%)	37.455	33.860	69.351	51.606	63.852	49.802
tmax (hr)	N	9	9	12	12	21	21
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Median	1.08	1.50	1.57	1.50	1.50	1.50

Table 11.2.1.1.1 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group 10-12 (N=9) Day 7	10-12 (N=9) Day 13	13-17 (N=12) Day 7	13-17 (N=12) Day 13	All (N=21) Day 7	All (N=21) Day 13
tmax (hr)	Maximum	2.00	2.00	3.00	2.00	3.00	2.00
Cmin (ng/mL)	N	9	9	12	12	21	21
	Mean	44.998	79.922	37.618	66.167	40.781	72.062
	SD	31.026	48.526	35.297	48.250	32.928	47.655
	Minimum	8.68	21.40	7.07	21.30	7.07	21.30
	Median	51.90	57.50	28.10	48.55	29.60	53.70
	Maximum	86.20	168.00	131.00	192.00	131.00	192.00
	Geometric Mean	33.141	66.680	27.186	54.911	29.595	59.677
	CV(%)	113.547	74.366	99.946	66.851	102.917	68.953
CL/F (L/hr)	N	9	9	12	12	21	21
	Mean	87.088	80.743	140.070	115.785	117.363	100.767
	SD	38.995	24.764	75.579	55.366	66.872	47.403
	Minimum	26.30	54.27	34.36	43.14	26.30	43.14
	Median	81.86	74.01	110.78	103.73	107.51	93.73
	Maximum	153.58	132.25	271.78	263.64	271.78	263.64
	Geometric Mean	78.124	77.746	121.107	105.685	100.364	92.655
	CV(%)	56.825	29.120	64.538	46.617	65.048	42.348
t1/2 (hr)	N	9	9	10	10	19	19
	Mean	3.173	5.519	2.770	5.520	2.961	5.519

Table 11.2.1.2.1 Summary statistics for quetiapine sulfoxide (ICI213,841) pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group 10-12 (N=9) Day 7	10-12 (N=9) Day 13	13-17 (N=12) Day 7	13-17 (N=12) Day 13	All (N=21) Day 7	All (N=21) Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	3447.097	7214.171	2774.863	6204.493	3062.963	6637.212
	SD	797.009	2339.193	1134.961	1725.542	1038.637	2022.003
	Minimum	2610.65	5614.28	1302.39	2669.27	1302.39	2669.27
	Median	3292.88	6383.88	2425.70	5919.73	2847.62	6120.56
	Maximum	5170.39	13188.45	5175.32	8972.51	5175.32	13188.45
	Geometric Mean	3374.796	6966.982	2585.777	5946.904	2898.398	6364.391
	CV(%)	21.511	26.514	40.262	33.025	35.542	30.787
Cmax (ng/mL)	N	9	9	12	12	21	21
	Mean	818.556	1600.000	591.667	1232.917	688.905	1390.238
	SD	206.484	374.066	212.464	375.599	234.775	410.136
	Minimum	543.00	1090.00	316.00	435.00	316.00	435.00
	Median	738.00	1650.00	549.50	1205.00	640.00	1300.00
	Maximum	1130.00	2170.00	1020.00	2070.00	1130.00	2170.00
	Geometric Mean	795.937	1560.748	560.943	1170.454	651.695	1324.087
	CV(%)	25.482	24.129	34.432	37.634	35.432	35.196
tmax (hr)	N	9	9	12	12	21	21
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Median	1.67	1.50	1.57	1.75	1.63	1.50

Table 11.2.1.2.1 Summary statistics for quetiapine sulfoxide (ICI213,841) pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
Pharmacokinetic Parameter		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
tmax (hr)	Maximum	2.02	3.00	3.00	5.00	3.00	5.00
Cmin (ng/mL)	N	9	9	12	12	21	21
	Mean	48.622	108.356	56.900	106.767	53.352	107.448
	SD	17.103	62.397	47.903	52.488	37.373	55.437
	Minimum	19.30	26.80	17.70	45.80	17.70	26.80
	Median	55.50	105.00	34.50	88.00	51.20	102.00
	Maximum	69.30	249.00	185.00	204.00	185.00	249.00
	Geometric Mean	45.195	92.339	44.452	96.441	44.769	94.661
	CV(%)	45.801	71.011	79.188	48.917	64.074	57.054
t1/2 (hr)	N	8	8	10	10	18	18
	Mean	2.791	5.636	2.526	4.980	2.644	5.272
	SD	0.453	0.979	0.504	1.170	0.487	1.110
	Minimum	2.28	4.48	1.83	3.77	1.83	3.77
	Median	2.72	5.77	2.53	4.60	2.54	4.99
	Maximum	3.45	7.13	3.54	7.32	3.54	7.32
Lambda_z (hr-1)	N	8	8	10	10	18	18
	Mean	0.254	0.126	0.284	0.145	0.271	0.137
	SD	0.039	0.021	0.055	0.030	0.050	0.027
	Minimum	0.20	0.10	0.20	0.09	0.20	0.09

Table 11.2.1.3.1 Summary statistics for 7-hydroxy quetiapine (ICI214,227) pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group 10-12 (N=9) Day 7	10-12 (N=9) Day 13	13-17 (N=12) Day 7	13-17 (N=12) Day 13	All (N=21) Day 7	All (N=21) Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	134.394	320.233	123.825	331.137	128.338	326.464
	SD	43.633	138.037	76.473	192.565	63.297	167.472
	Minimum	87.56	170.42	72.63	145.44	72.63	145.44
	Median	120.46	283.60	90.05	263.14	109.61	263.99
	Maximum	225.30	628.31	333.59	762.56	333.59	762.56
	Geometric Mean	128.691	297.995	109.590	290.751	117.402	293.834
	CV(%)	31.321	40.804	50.299	54.806	42.787	47.856
Cmax (ng/mL)	N	9	9	12	12	21	21
	Mean	29.933	66.233	23.625	66.092	26.329	66.152
	SD	10.380	23.400	13.557	37.923	12.427	31.781
	Minimum	15.70	34.90	13.50	28.90	13.50	28.90
	Median	29.90	61.50	18.60	54.70	22.70	61.50
	Maximum	43.80	99.20	61.30	139.00	61.30	139.00
	Geometric Mean	28.199	62.563	21.260	57.694	23.996	59.732
	CV(%)	39.178	37.404	46.464	57.452	45.099	48.461
tmax (hr)	N	9	9	12	12	21	21
	Minimum	1.00	1.00	0.52	0.50	0.52	0.50
	Median	2.00	2.00	1.57	1.50	1.82	1.50

Table 11.2.1.4.1 Summary statistics for N-desalkyl quetiapine (M211,803) pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	1994.622	4151.463	1573.816	3543.345	1754.161	3803.967
	SD	290.800	874.543	519.091	1115.114	477.033	1041.603
	Minimum	1703.13	3027.50	850.90	2048.61	850.90	2048.61
	Median	1874.17	4020.25	1399.49	3272.07	1840.85	3716.88
	Maximum	2631.19	5845.24	2431.36	5638.58	2631.19	5845.24
	Geometric Mean	1977.446	4073.993	1497.113	3380.731	1686.737	3662.090
	CV(%)	13.718	20.605	34.072	33.284	30.289	29.485
Cmax (ng/mL)	N	9	9	12	12	21	21
	Mean	218.222	470.778	173.333	368.667	192.571	412.429
	SD	40.567	101.335	60.527	136.030	56.492	130.253
	Minimum	155.00	287.00	108.00	209.00	108.00	209.00
	Median	212.00	474.00	152.50	336.00	201.00	430.00
	Maximum	281.00	613.00	308.00	649.00	308.00	649.00
	Geometric Mean	214.891	460.291	164.651	347.667	184.557	392.097
	CV(%)	18.818	23.440	33.812	36.533	30.988	34.189
tmax (hr)	N	9	9	12	12	21	21
	Minimum	1.00	1.50	1.00	1.50	1.00	1.50
	Median	2.00	2.00	3.00	3.00	3.00	3.00

Table 11.2.1.4.1 Summary statistics for N-desalkyl quetiapine (M211,803) pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group: 10-12 (N=9) Day 7	10-12 (N=9) Day 13	13-17 (N=12) Day 7	13-17 (N=12) Day 13	All (N=21) Day 7	All (N=21) Day 13
tmax (hr)	Maximum	12.00	8.00	8.00	8.00	12.00	8.00
Cmin (ng/mL)	N	9	9	12	12	21	21
	Mean	129.222	255.667	105.825	230.000	115.852	241.000
	SD	27.317	54.884	40.048	58.429	36.351	57.026
	Minimum	101.00	170.00	68.40	148.00	68.40	148.00
	Median	120.00	248.00	97.80	221.00	104.00	225.00
	Maximum	186.00	351.00	204.00	356.00	204.00	356.00
	Geometric Mean	126.895	250.400	100.150	223.523	110.842	234.669
	CV(%)	20.000	22.060	34.285	25.262	30.905	24.076
t1/2 (hr)	N	2	2	3	3	5	5
	Mean	9.260	14.695	8.153	8.750	8.596	11.128
	SD	1.131	6.682	0.815	1.217	1.010	4.744
	Minimum	8.46	9.97	7.61	7.35	7.61	7.35
	Median	9.26	14.70	7.76	9.34	8.46	9.56
	Maximum	10.06	19.42	9.09	9.56	10.06	19.42
Lambda_z (hr-1)	N	2	2	3	3	5	5
	Mean	0.075	0.055	0.087	0.077	0.082	0.068
	SD	0.007	0.021	0.006	0.012	0.008	0.018
	Minimum	0.07	0.04	0.08	0.07	0.07	0.04

Table 11.2.1.1.2 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects who received 300 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group 10-12 (N=3) Day 7	10-12 (N=3) Day 13	All (N=3) Day 7	All (N=3) Day 13
AUC (ng*hr/mL)	N	3	3	3	3
	Mean	3181.950	4971.420	3181.950	4971.420
	SD	1851.644	3136.711	1851.644	3136.711
	Minimum	1078.96	1377.86	1078.96	1377.86
	Median	3899.20	6376.15	3899.20	6376.15
	Maximum	4567.60	7160.25	4567.60	7160.25
	Geometric Mean	2678.508	3977.076	2678.508	3977.076
	CV(%)	93.313	115.348	93.313	115.348
Cmax (ng/mL)	N	3	3	3	3
	Mean	880.667	1256.667	880.667	1256.667
	SD	514.578	927.434	514.578	927.434
	Minimum	361.00	450.00	361.00	450.00
	Median	891.00	1050.00	891.00	1050.00
	Maximum	1390.00	2270.00	1390.00	2270.00
	Geometric Mean	764.657	1023.629	764.657	1023.629
	CV(%)	77.659	96.204	77.659	96.204
tmax (hr)	N	3	3	3	3
	Minimum	1.00	1.00	1.00	1.00
	Median	1.00	1.00	1.00	1.00

Table 11.2.1.1.2 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects who received 300 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group 10-12 (N=3) Day 7	10-12 (N=3) Day 13	All (N=3) Day 7	All (N=3) Day 13
tmax (hr)	Maximum	1.33	3.00	1.33	3.00
Cmin (ng/mL)	N	3	3	3	3
	Mean	61.833	126.067	61.833	126.067
	SD	28.899	94.716	28.899	94.716
	Minimum	31.00	27.20	31.00	27.20
	Median	66.20	135.00	66.20	135.00
	Maximum	88.30	216.00	88.30	216.00
	Geometric Mean	56.588	92.566	56.588	92.566
	CV(%)	58.276	150.163	58.276	150.163
CL/F (L/hr)	N	3	3	3	3
	Mean	93.481	102.226	93.481	102.226
	SD	79.662	100.062	79.662	100.062
	Minimum	43.79	41.90	43.79	41.90
	Median	51.20	47.05	51.20	47.05
	Maximum	185.36	217.73	185.36	217.73
	Geometric Mean	74.668	75.432	74.668	75.432
	CV(%)	93.313	115.348	93.313	115.348
t1/2 (hr)	N	2	2	2	2
	Mean	3.360	4.185	3.360	4.185

Table 11.2.1.1.2 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects who received 300 mg morning dose on Day 13

Pharmacokinetic Parameter		Age Group 10-12 (N=3) Day 7	Age Group 10-12 (N=3) Day 13	All (N=3) Day 7	All (N=3) Day 13
Fu (%)	Mean	0.038	0.050	0.038	0.050
	SD	0.046	0.061	0.046	0.061
	Minimum	0.01	0.01	0.01	0.01
	Median	0.04	0.05	0.04	0.05
	Maximum	0.07	0.09	0.07	0.09
CLr(L/hr)	N	2	2	2	2
	Mean	0.023	0.029	0.023	0.029
	SD	0.018	0.021	0.018	0.021
	Minimum	0.01	0.01	0.01	0.01
	Median	0.02	0.03	0.02	0.03
	Maximum	0.04	0.04	0.04	0.04

Table 11.2.5.1 Comparison of dose-normalized AUC and Cmax of quetiapine and 3 metabolites on combined data from children/adolescents and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children and Adolescents/Adults)			Children/Adolescents			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.88	0.76	1.03	10.64	9.13	12.41	12.05	10.77	13.48
AUC (Quetiapine sulfoxide)	1.27	1.15	1.39	15.78	14.37	17.32	12.46	11.62	13.38
AUC (7-hydroxy quetiapine)	1.08	0.92	1.26	0.68	0.60	0.78	0.63	0.55	0.73
AUC (N-desalkyl quetiapine)	1.45	1.30	1.61	8.98	8.23	9.79	6.21	5.65	6.82
Cmax (Quetiapine)	0.92	0.79	1.06	2.79	2.39	3.26	3.05	2.76	3.37
Cmax (Quetiapine sulfoxide)	1.30	1.16	1.44	3.46	3.14	3.82	2.67	2.45	2.91
Cmax (7-hydroxy quetiapine)	1.11	0.94	1.31	0.14	0.12	0.16	0.13	0.11	0.15
Cmax (N-desalkyl quetiapine)	1.31	1.15	1.49	0.97	0.88	1.07	0.74	0.66	0.84

Table 11.2.5.2 Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites on combined data from children/adolescents and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children and Adolescents/Adults)			Children/Adolescents			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.59	0.50	0.70	610.69	527.56	706.92	1035.06	900.34	1189.93
AUC (Quetiapine sulfoxide)	0.85	0.77	0.93	905.16	832.58	984.08	1070.64	989.32	1158.65
AUC (7-hydroxy quetiapine)	0.72	0.61	0.84	39.19	34.34	44.73	54.50	47.40	62.66
AUC (N-desalkyl quetiapine)	0.96	0.86	1.07	515.11	472.96	561.01	537.17	483.67	596.59
Cmax (Quetiapine)	0.61	0.53	0.71	160.07	139.17	184.10	261.76	232.12	295.19
Cmax (Quetiapine sulfoxide)	0.86	0.79	0.95	198.50	183.40	214.85	229.59	211.40	249.34
Cmax (7-hydroxy quetiapine)	0.74	0.63	0.87	7.99	7.04	9.07	10.83	9.31	12.59
Cmax (N-desalkyl quetiapine)	0.87	0.76	1.00	55.64	50.60	61.19	63.79	56.24	72.36

Table 4.1 Comparison of dose-normalized AUC, Cmax and Cmin of quetiapine and 3 metabolites on combined data from children (10-12 years old) and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children (10-12 years old)/Adults)			Children (10-12 years old)			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	1.06	0.88	1.26	12.72	10.34	15.65	12.05	10.77	13.48
AUC (Quetiapine sulfoxide)	1.43	1.29	1.58	17.86	16.19	19.70	12.48	11.61	13.41
AUC (7-hydroxy quetiapine)	1.16	0.97	1.40	0.74	0.63	0.86	0.63	0.55	0.73
AUC (N-desalkyl quetiapine)	1.63	1.44	1.84	10.08	9.17	11.08	6.20	5.63	6.82
Cmax (Quetiapine)	1.16	0.99	1.35	3.52	2.96	4.19	3.05	2.76	3.37
Cmax (Quetiapine sulfoxide)	1.53	1.37	1.72	4.15	3.78	4.55	2.70	2.48	2.94
Cmax (7-hydroxy quetiapine)	1.23	1.00	1.51	0.16	0.13	0.18	0.13	0.11	0.15
Cmax (N-desalkyl quetiapine)	1.49	1.26	1.75	1.11	0.98	1.25	0.74	0.66	0.84
Cmin (Quetiapine)	0.79	0.59	1.04	0.19	0.13	0.26	0.24	0.20	0.28
Cmin (Quetiapine sulfoxide)	1.12	0.91	1.37	0.26	0.20	0.32	0.23	0.20	0.26
Cmin (7-hydroxy quetiapine)	0.86	0.69	1.08	0.01	0.01	0.02	0.02	0.01	0.02
Cmin (N-desalkyl quetiapine)	1.59	1.41	1.78	0.65	0.59	0.72	0.41	0.38	0.45

Table 4.2 Comparison of dose-normalized AUC, Cmax and Cmin of quetiapine and 3 metabolites on combined data from adolescents (13-17 years old) and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Adolescents (13-17 years old)/Adults)			Adolescents (13-17 years old)			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.73	0.61	0.88	8.84	7.11	10.99	12.05	10.77	13.48
AUC (Quetiapine sulfoxide)	1.11	0.99	1.25	13.86	11.93	16.11	12.48	11.61	13.41
AUC (7-hydroxy quetiapine)	1.00	0.81	1.22	0.63	0.51	0.78	0.63	0.55	0.73
AUC (N-desalkyl quetiapine)	1.28	1.12	1.47	7.95	6.93	9.13	6.20	5.63	6.82
Cmax (Quetiapine)	0.72	0.60	0.86	2.19	1.73	2.76	3.05	2.76	3.37
Cmax (Quetiapine sulfoxide)	1.06	0.93	1.21	2.86	2.48	3.31	2.70	2.48	2.94
Cmax (7-hydroxy quetiapine)	0.98	0.78	1.22	0.12	0.10	0.15	0.13	0.11	0.15
Cmax (N-desalkyl quetiapine)	1.14	0.96	1.35	0.85	0.73	0.97	0.74	0.66	0.84
Cmin (Quetiapine)	0.58	0.44	0.76	0.14	0.10	0.18	0.24	0.20	0.28
Cmin (Quetiapine sulfoxide)	1.01	0.82	1.25	0.23	0.18	0.30	0.23	0.20	0.26
Cmin (7-hydroxy quetiapine)	0.84	0.66	1.08	0.01	0.01	0.02	0.02	0.01	0.02
Cmin (N-desalkyl quetiapine)	1.29	1.14	1.46	0.53	0.47	0.60	0.41	0.38	0.45

Table 4.3 Comparison of dose-normalized AUC, Cmax, and Cmin of quetiapine and 3 metabolites on combined data from children (10-12 years old) and adolescents (13-17 years old)

Pharmacokinetic Parameter	Comparison (Children/Adolescents)			Children (10-12 years old)			Adolescents (13-17 years old)		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	1.44	1.13	1.84	12.72	10.34	15.65	8.84	7.11	10.99
AUC (Quetiapine sulfoxide)	1.29	1.11	1.49	17.86	16.19	19.70	13.86	11.93	16.11
AUC (7-hydroxy quetiapine)	1.17	0.94	1.44	0.74	0.63	0.86	0.63	0.51	0.78
AUC (N-desalkyl quetiapine)	1.27	1.11	1.45	10.08	9.17	11.08	7.95	6.93	9.13
Cmax (Quetiapine)	1.61	1.27	2.04	3.52	2.96	4.19	2.19	1.73	2.76
Cmax (Quetiapine sulfoxide)	1.45	1.26	1.66	4.15	3.78	4.55	2.86	2.48	3.31
Cmax (7-hydroxy quetiapine)	1.26	1.02	1.55	0.16	0.13	0.18	0.12	0.10	0.15
Cmax (N-desalkyl quetiapine)	1.31	1.12	1.52	1.11	0.98	1.25	0.85	0.73	0.97
Cmin (Quetiapine)	1.37	0.95	1.96	0.19	0.13	0.26	0.14	0.10	0.18
Cmin (Quetiapine sulfoxide)	1.10	0.84	1.45	0.26	0.20	0.32	0.23	0.18	0.30
Cmin (7-hydroxy quetiapine)	1.02	0.76	1.38	0.01	0.01	0.02	0.01	0.01	0.02
Cmin (N-desalkyl quetiapine)	1.23	1.08	1.39	0.65	0.59	0.72	0.53	0.47	0.60

Table 5.1 Comparison of dose-normalized, weight-normalized AUC, Cmax and Cmin of quetiapine and 3 metabolites on combined data from children (10-12 years old) and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Children (10-12 years old)/Adults)			Children (10-12 years old)			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.65	0.53	0.80	676.76	550.13	832.53	1035.06	900.34	1189.93
AUC (Quetiapine sulfoxide)	0.89	0.79	1.00	950.04	851.17	1060.39	1069.14	986.39	1158.82
AUC (7-hydroxy quetiapine)	0.72	0.59	0.88	39.21	32.50	47.29	54.23	47.05	62.50
AUC (N-desalkyl quetiapine)	1.00	0.87	1.16	536.46	477.46	602.74	535.20	480.97	595.53
Cmax (Quetiapine)	0.72	0.60	0.85	187.38	159.52	220.11	261.76	232.12	295.19
Cmax (Quetiapine sulfoxide)	0.95	0.85	1.06	220.59	201.42	241.59	231.69	213.43	251.51
Cmax (7-hydroxy quetiapine)	0.76	0.62	0.94	8.29	7.01	9.82	10.88	9.34	12.69
Cmax (N-desalkyl quetiapine)	0.92	0.78	1.10	58.82	51.54	67.13	63.67	56.00	72.40
Cmin (Quetiapine)	0.49	0.35	0.67	9.93	6.92	14.26	20.37	16.49	25.16
Cmin (Quetiapine sulfoxide)	0.69	0.55	0.88	13.57	10.40	17.71	19.59	16.77	22.89
Cmin (7-hydroxy quetiapine)	0.54	0.42	0.69	0.79	0.60	1.04	1.47	1.25	1.74
Cmin (N-desalkyl quetiapine)	0.98	0.85	1.12	34.57	30.33	39.40	35.39	32.06	39.08

Table 5.2 Comparison of dose-normalized, weight-normalized AUC and Cmax of quetiapine and 3 metabolites on combined data from adolescents (13-17 years old) and adults (data from study D1441C00130)

Pharmacokinetic Parameter	Comparison (Adolescents (13-17 years old)/Adults)			Adolescents (13-17 years old)			Adults		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.53	0.43	0.65	548.72	443.28	679.24	1035.06	900.34	1189.93
AUC (Quetiapine sulfoxide)	0.81	0.71	0.91	860.67	754.30	982.04	1069.14	986.39	1158.82
AUC (7-hydroxy quetiapine)	0.72	0.59	0.89	39.18	32.05	47.89	54.23	47.05	62.50
AUC (N-desalkyl quetiapine)	0.92	0.80	1.07	493.77	432.76	563.40	535.20	480.97	595.53
Cmax (Quetiapine)	0.52	0.43	0.63	135.84	108.59	169.93	261.76	232.12	295.19
Cmax (Quetiapine sulfoxide)	0.77	0.68	0.87	177.84	157.47	200.84	231.69	213.43	251.51
Cmax (7-hydroxy quetiapine)	0.71	0.57	0.88	7.69	6.29	9.40	10.88	9.34	12.69
Cmax (N-desalkyl quetiapine)	0.82	0.69	0.98	52.51	45.52	60.58	63.67	56.00	72.40
Cmin (Quetiapine)	0.42	0.31	0.57	8.48	6.20	11.60	20.37	16.49	25.16
Cmin (Quetiapine sulfoxide)	0.73	0.58	0.93	14.37	11.22	18.40	19.59	16.77	22.89
Cmin (7-hydroxy quetiapine)	0.61	0.47	0.79	0.90	0.67	1.20	1.47	1.25	1.74
Cmin (N-desalkyl quetiapine)	0.93	0.81	1.06	32.84	29.08	37.08	35.39	32.06	39.08

Table 5.3 Comparison of dose-normalized, weight-normalized AUC, Cmax, and Cmin of quetiapine and 3 metabolites on combined data from children (10-12 years old) and adolescents (13-17 years old)

Pharmacokinetic Parameter	Comparison (Children/Adolescents)			Children (10-12 years old)			Adolescents (13-17 years old)		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	1.23	0.97	1.57	676.76	550.13	832.53	548.72	443.28	679.24
AUC (Quetiapine sulfoxide)	1.10	0.96	1.27	950.04	851.17	1060.39	860.67	754.30	982.04
AUC (7-hydroxy quetiapine)	1.00	0.80	1.25	39.21	32.50	47.29	39.18	32.05	47.89
AUC (N-desalkyl quetiapine)	1.09	0.94	1.25	536.46	477.46	602.74	493.77	432.76	563.40
Cmax (Quetiapine)	1.38	1.10	1.72	187.38	159.52	220.11	135.84	108.59	169.93
Cmax (Quetiapine sulfoxide)	1.24	1.10	1.40	220.59	201.42	241.59	177.84	157.47	200.84
Cmax (7-hydroxy quetiapine)	1.08	0.87	1.33	8.29	7.01	9.82	7.69	6.29	9.40
Cmax (N-desalkyl quetiapine)	1.12	0.96	1.31	58.82	51.54	67.13	52.51	45.52	60.58
Cmin (Quetiapine)	1.17	0.79	1.73	9.93	6.92	14.26	8.48	6.20	11.60
Cmin (Quetiapine sulfoxide)	0.94	0.70	1.27	13.57	10.40	17.71	14.37	11.22	18.40
Cmin (7-hydroxy quetiapine)	0.88	0.64	1.21	0.79	0.60	1.04	0.90	0.67	1.20
Cmin (N-desalkyl quetiapine)	1.05	0.91	1.22	34.57	30.33	39.40	32.84	29.08	37.08

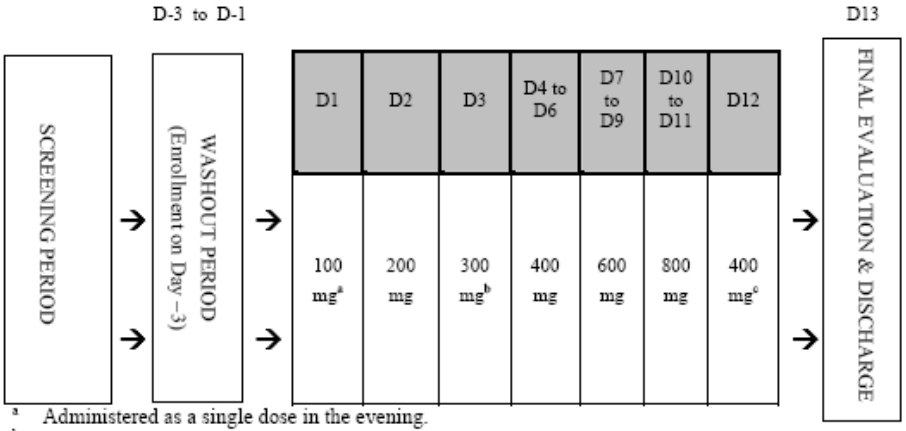
Title (D1441C00130): A Study to Characterize the Steady-State Pharmacokinetics and Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) in Adults with Selected Psychotic Disorders

Background: In response to a pediatric written request from the Agency, the sponsor originally designed a study to be conducted in subjects ages 10 to 17 years and in adults (ages 18 to 45). Adult subjects were included in order to provide concurrent PK data for quetiapine and its metabolites that could be compared with the PK data obtained in the pediatric and adolescent subjects .All subjects were to be titrated to steady-state doses using the same 10-day titration schedule, the safety and tolerability of which had not been previously studied. After a review of the original study protocol, the FDA requested that the titration schedule for 10- to 17-year-old subjects be extended to 11 days. As a result of this recommendation, the original study protocol was amended to include only pediatric and adolescent subjects (Study D1441C00028) using the 11-day titration schedule, and a separate study protocol (the present study) was developed for the adult subjects, retaining the 10-day titration schedule. The comparison of exposure to quetiapine and its metabolites in children 10 to 17 years of age to that seen in adults was conducted.

Objectives: The primary objective of this study was to characterize the steady-state PK of quetiapine administered as quetiapine tablets. The secondary objectives were: 1. Monitor the tolerability and safety of titrating doses of quetiapine, 2. Determine the dose-proportionality for quetiapine 3. Characterize the pharmacokinetics of 3 metabolites: quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine

Study Design: This was an open-label, multicenter, inpatient, steady-state, safety and tolerability study that characterized the pharmacokinetics of quetiapine in adults between 18 and 45 years of age. Steady-state PK design was chosen for the study because quetiapine is titrated based on tolerability until an adequate response is obtained. The study consisted of a 16-day/15-night inpatient stay at the clinical research center (CRC), including a 3-day pre-treatment washout period, a 12-day quetiapine treatment period, and 1 additional day for final evaluation. The following figure illustrates the design of the study. The 3-day washout period was included in order to wash subjects out from their current antipsychotic medications before beginning study drug administration on Day 1.

Study Flow Chart



[a] Administered as a single dose in the evening.
[b] Administered as 100 mg in the morning and 200 mg in the evening.
[c] Administered as a single dose in the morning.
D Day.
Note: Doses shown are total daily doses administered in equally divided doses twice daily unless noted otherwise.

Subjects were dosed according to the following titration schedule:

Study medication titration schedule

Study day	Quetiapine dose and time of administration[a]
Day 1	100 mg at 2100 hr
Day 2	100 mg at 0900 hr and 100 mg at 2100 hr
Day 3	100 mg at 0900 hr and 200 mg at 2100 hr
Day 4	200 mg at 0900 hr and 200 mg at 2100 hr
Day 5	200 mg at 0900 hr and 200 mg at 2100 hr
Day 6	200 mg at 0900 hr and 200 mg at 2100 hr
Day 7	300 mg at 0900 hr and 300 mg at 2100 hr
Day 8	300 mg at 0900 hr and 300 mg at 2100 hr
Day 9	300 mg at 0900 hr and 300 mg at 2100 hr
Day 10	400 mg at 0900 hr and 400 mg at 2100 hr
Day 11	400 mg at 0900 hr and 400 mg at 2100 hr
Day 12	400 mg at 0900 hr

[a] Dose times are approximate.

Subjects were instructed not to chew or crush the tablets. On Days 6 and 12, subjects were administered their morning doses of quetiapine with 240 mL of water following an overnight fast of at least 8 hours. Subjects were provided standard meals no less than 4 hours after drug administration. Subjects were allowed water as required except for 1 hour before and after drug administration. Subjects were to remain in an upright or sitting position for at least 1 hour following dosing.

To verify that steady-state was achieved, plasma concentrations for the 200-mg morning dose were obtained before dosing on Days 5 and 6 and 12 hours after dosing on Day 6. Plasma concentrations for the 400-mg morning dose were obtained before dosing on Days 11 and 12 and 12 hours after dosing on Day 12. In order to characterize the PK profile of quetiapine and its metabolites, 2 mL serial blood sampling was done on Days 6 and 12 at 0, 0.25,1,1.5,2,3,5,8 and 12 hours post dose. In addition, 2 mL blood samples were taken at 16, 20 and 24 hours on Day 12 in order to calculate terminal half-life. A total urine collection was taken over the morning 12-hour, steady-state dosing interval on Days 6 and 12. Total urine PK samples were collected on Days 6 and 12, which included all urine collected following the morning dose and throughout the 12-hour dosing interval.

The details of the investigational product and any study treatment are given in the following table.

Details of investigational product

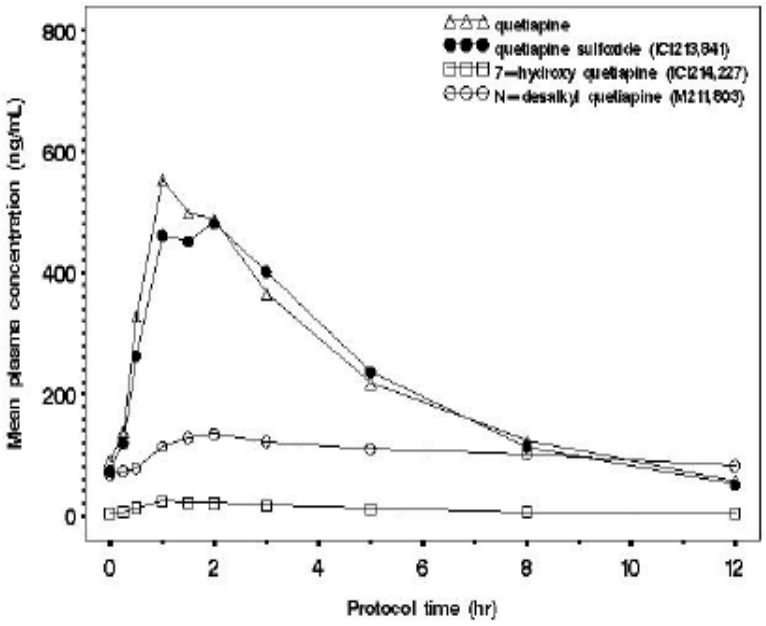
Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch and lot number
Quetiapine	100-mg tablets	AstraZeneca	F12689	Batch No. 2000048407 Lot No. 6084C; Batch No. 2000053517 Lot No. 7511H

Analytical Method: The concentrations of quetiapine, quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine in plasma were determined by a validated method utilizing a liquid-liquid extraction from alkalinized human EDTA plasma using ethyl acetate, followed by reverse-phase liquid chromatography and turbo ionspray ionization tandem mass spectrometry (LC/MS/MS). The method has a validated assay range of 0.500 to 500 ng/mL for all analytes, utilizing a 100 µL or 500 µL sample aliquot.

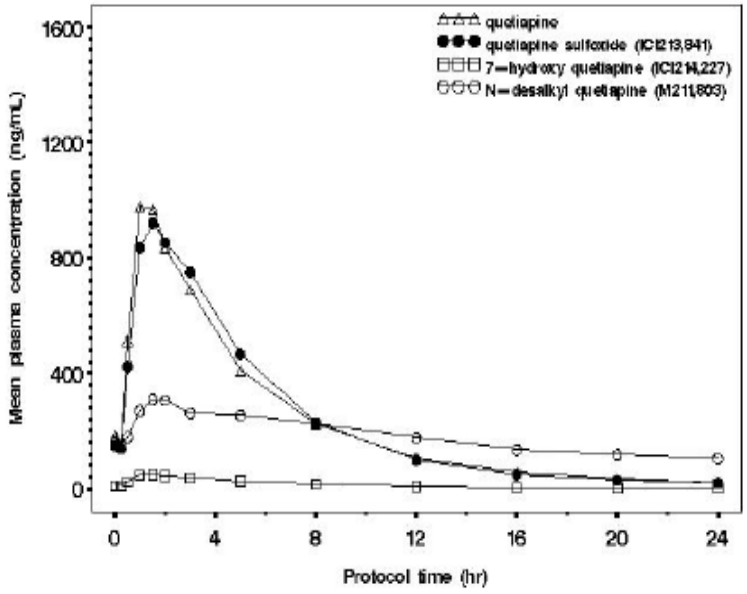
Data Analysis: Pharmacokinetic parameters for quetiapine and its metabolites were derived using non-compartmental methods from the plasma concentration versus time data. Quetiapine plasma concentration-time profiles were obtained on Day 6 (200-mg morning dose) and Day 12 (400-mg morning dose). The area under the plasma concentration versus time curve during the dosing interval at steady-state (AUCss) and the maximum observed steady-state plasma concentration during a dosing interval (Css,max) following the 200-mg and 400-mg morning doses on Days 6 and 12 were the primary variables.

Results: Mean plasma concentrations of quetiapine and 3 quetiapine metabolites are plotted over time in the following figures.

Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 6 (200-mg morning dose)



Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 12 (400-mg morning dose)



Descriptive statistics for quetiapine PK parameters are presented in the following table.

Pharmacokinetic parameters on Day 6 (200 mg) and Day 12 (400 mg) for quetiapine

PK parameter	Statistic	Day 6 (200-mg am dose) n=26	Day 12 (400-mg am dose) n=26
AUC_{ss} (ng*hr/mL)	n[a]	25	25
	Geometric mean	2469.7	4508.9
	CV (%)	42.5	39.8
$C_{ss,max}$ (ng/mL)	n	26	26
	Geometric mean	660.3	1124.6
	CV (%)	41.9	31.9
t_{max} (hr)	n	26	26
	Median	1.00	1.23
	Minimum	0.32	0.50
	Maximum	3.00	3.00
$C_{ss,min}$ (ng/mL)	n[a]	25	25
	Geometric mean	47.8	86.8
	CV (%)	72.1	65.9
CL/F (L/hr)	n[a]	25	25
	Mean	88.0	95.4
	SD	39.7	39.2
$t_{1/2}$ (hr)	n[b]	22	22
	Mean	3.34	5.10
	SD	0.62	0.91
$Ael_{(ss)}$ (µg)	n[c]	19	19
	Mean	318.0	629.6
	SD	529.5	634.2
Fu (%)	n[c]	19	19
	Mean	0.159	0.157
	SD	0.265	0.159
CL_R (L/hr)	n[d]	18	18
	Mean	0.126	0.134
	SD	0.180	0.099

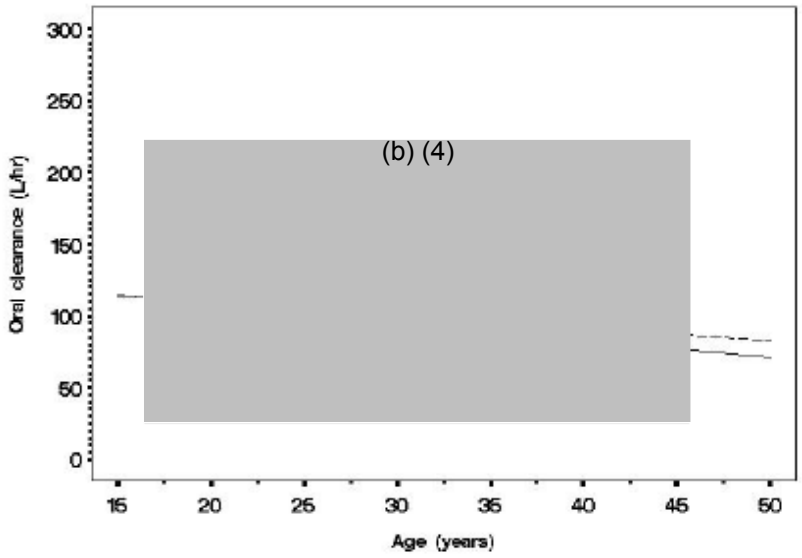
[a] Excludes 1 subject for whom no 12-hr sample on Day 6 was obtained.
[b] Excludes 4 subjects for whom the parameter could not be calculated.
[c] Excludes 7 subjects for whom the parameter could not be calculated.
[d] Excludes 8 subjects for whom the parameter could not be calculated.

$Ael_{(ss)}$ amount of metabolite eliminated. am morning. AUC_{ss} area under the curve at steady-state. CL/F apparent oral clearance. CV coefficient of variation. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

7

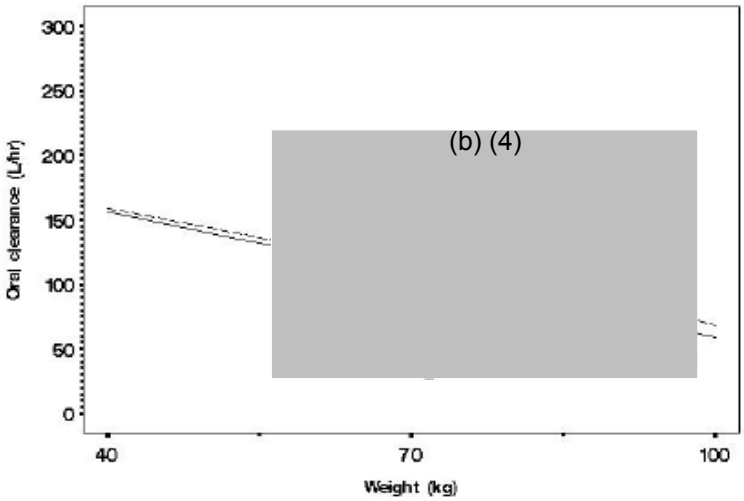
A scatter plot of Cl/F by age, weight and body mass index are provided in the following figures.

Scatter plot of oral clearance (CL/F) of quetiapine by age for Day 6 (200-mg morning dose) and Day 12 (400-morning dose)

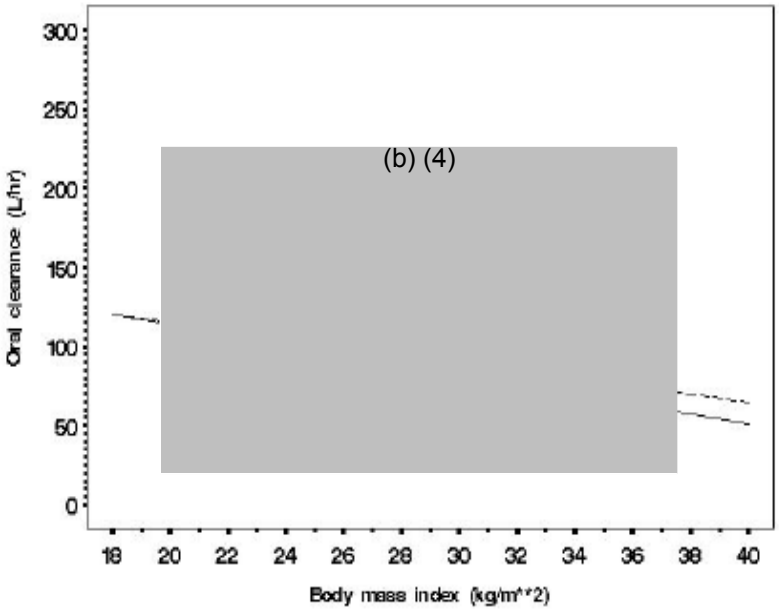


Triangle: Observed values for Day 6
Dot: Observed values for Day 12
Solid line: Linear regression for Day 6
Dash line: Linear regression for Day 12

Scatter plot of oral clearance (CL/F) of quetiapine by weight for Day 6 (200-mg) and Day 12 (400-mg morning dose)



Scatter plot of oral clearance (CL/F) of quetiapine by body mass index for Day 6 (200-mg) and Day 12 (400-mg morning dose)



The regression lines showed that CL/F tended to decrease with age, weight and body mass index (BMI). There was great variability in the data.

Pharmacokinetic parameters at steady-state are summarized for the 3 metabolites, quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine, are provided in the following tables.

Pharmacokinetic parameters for quetiapine sulfoxide on day 6 (200 mg) and day 12 (400 mg)

PK parameter	Statistic	Day 6 (200-mg am dose) n=26	Day 12 (400-mg am dose) n=26
AUC_{ss} (ng*hr/mL)	n[a]	25	25
	Geometric mean	2547.3	4889.5
	CV (%)	28.1	24.8
$C_{ss,max}$ (ng/mL)	n	26	26
	Geometric mean	580.5	1006.2
	CV (%)	33.8	26.4
t_{max} (hr)	n	26	26
	Median	1.26	1.50
	Minimum	0.32	0.50
	Maximum	3.00	5.00
$C_{ss,min}$ (ng/mL)	n[a]	25	25
	Geometric mean	46.1	90.4
	CV (%)	52.4	51.9
$t_{1/2}$ (hr)	n[b]	21	21
	Mean	3.05	4.84
	SD	0.48	0.83
$Ael_{(u)}$ (µg)	n[c]	19	19
	Mean	1748.2	3754.2
	SD	1349.2	1495.3
Fu (%)	n[c]	19	19
	Mean	0.839	0.901
	SD	0.648	0.359
CL_R (L/hr)	n[d]	18	18
	Mean	0.706	0.809
	SD	0.473	0.324

[a] Excludes 1 subject for whom no 12-hr sample on Day 6 was obtained.
[b] Excludes 5 subjects for whom the parameter could not be calculated.
[c] Excludes 7 subjects for whom the parameter could not be calculated.
[d] Excludes 8 subjects for whom the parameter could not be calculated.

$Ael_{(u)}$ amount of metabolite eliminated. am morning. AUC_{ss} area under the curve at steady-state. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

Pharmacokinetic parameters for 7-hydroxy quetiapine on Day6 (200 mg) and Day 12 (400 mg)

PK parameter	Statistic	Day 6 (200-mg am dose) n=26	Day 12 (400-mg am dose) n=26
AUC_{ss} (ng*hr/mL)	n[a]	25	25
	Geometric mean	123.3	272.7
	CV (%)	51.7	45.7
$C_{ss,max}$ (ng/mL)	n	26	26
	Geometric mean	24.5	52.7
	CV (%)	64.1	57.0
t_{max} (hr)	n	26	26
	Median	1.01	1.23
	Minimum	0.32	0.50
	Maximum	3.0	3.0
$C_{ss,min}$ (ng/mL)	n[a]	25	25
	Geometric mean	3.41	7.30
	CV (%)	56.2	59.2
$t_{1/2}$ (hr)	n[b]	15	15
	Mean	3.95	5.58
	SD	0.65	0.94
$Ael_{(0)}$ (µg)	n[c]	19	19
	Mean	169.0	392.1
	SD	129.4	209.9
Fu (%)	n[c]	19	19
	Mean	0.081	0.094
	SD	0.062	0.050
CL_R (L/hr)	n[d]	18	18
	Mean	1.313	1.386
	SD	0.560	0.432

[a] Excludes 1 subject for whom no 12-hr sample on Day 6 was obtained.
[b] Excludes 11 subjects for whom the parameter could not be calculated.
[c] Excludes 7 subjects for whom the parameter could not be calculated.
[d] Excludes 8 subjects for whom the parameter could not be calculated.

$Ael_{(0)}$ amount of metabolite eliminated. am morning. AUC_{ss} area under the curve at steady-state. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

Pharmacokinetic parameters for N-desalkyl quetiapine on Day 6 (200 mg) and Day 12 (400 mg)

PK parameter[a]	Statistic	Day 6 (200-mg am dose) n=26	Day 12 (400-mg am dose) n=26
AUC_{ss} (ng*hr/mL)	n[b]	24	24
	Geometric mean	1154.7	2585.4
	CV (%)	33.9	35.1
$C_{ss,max}$ (ng/mL)	n	26	26
	Geometric mean	144.1	306.2
	CV (%)	44.9	49.6
t_{max} (hr)	n	26	26
	Median	2.00	2.00
	Minimum	0.25	1.00
	Maximum	8.00	8.00
$C_{ss,min}$ (ng/mL)	n[b]	24	24
	Geometric mean	77.9	169.0
	CV (%)	32.2	30.3
$Ael_{(ss)}$ (µg)	n[c]	19	19
	Mean	3555.4	7930.5
	SD	2532.8	4933.5
Fu (%)	n[c]	19	19
	Mean	2.308	2.574
	SD	1.644	1.601
CL_R (L/hr)	n[d]	17	17
	Mean	2.511	2.473
	SD	1.686	1.328

[a] $t_{1/2}$ results are omitted from this table as there were only 3 subjects who provided data on both Days 6 and 12.
[b] Excludes 1 subject for whom no 12-hr sample on Day 6 was obtained and 1 subject for whom the parameter could not be calculated.
[c] Excludes 7 subjects for whom the parameter could not be calculated.
[d] Excludes 9 subjects for whom the parameter could not be calculated.

$Ael_{(ss)}$ amount of metabolite eliminated. am morning. AUC_{ss} area under the curve at steady-state. CL_R renal clearance from plasma. $C_{ss,max}$ maximum plasma concentration at steady-state. $C_{ss,min}$ minimum plasma concentration at steady-state. Fu mole fraction (percent) of dose excreted in the urine. NA not applicable. SD standard deviation. t_{max} time of maximum plasma concentration. $t_{1/2}$ terminal elimination half-life.

Pharmacokinetic summary

Quetiapine was rapidly absorbed with a Tmax between 1 and 1.2 hours after dosing, and had a t1/2 of approximately 5 hours. Two of the metabolites, quetiapine sulfoxide and 7-hydroxy quetiapine, had estimates of t1/2 similar to quetiapine. The N-desalkyl quetiapine metabolite had a longer t1/2 than quetiapine. Estimates of the t1/2 for N-desalkyl quetiapine ranged from 7.6 to 20.8 hours. In terms of in vivo exposure, the rank order of exposure with respect to AUCss was: quetiapine sulfoxide≈quetiapine>N-desalkyl quetiapine>7-hydroxy quetiapine. The rank order of in vivo exposure with respect to Css,max was: quetiapine≈quetiapine sulfoxide>N-desalkyl quetiapine>7-hydroxy quetiapine. Urinary excretion of quetiapine and its metabolites appeared to be minor.

Summary of Safety

The sponsor reported that quetiapine was well tolerated in this study population. The sponsor reported that one subject was withdrawn from the study on Day 3 as a result of severe agitation that was considered unrelated to the study treatment. Dizziness was the most frequently occurring AE during study treatment (13 of 29 subjects). The majority of occurrences of dizziness were considered treatment related. Dizziness tended to occur shortly after study treatment began, was typically rated by the investigators as mild in intensity, and was transient. Slightly over one-half of the subjects reporting dizziness had accompanying vital signs changes consistent with orthostatic hypotension. Other frequently occurring AEs included anxiety, lethargy, dry mouth, and insomnia. The majority of these events were rated by the investigators as mild in intensity. The majority of occurrences of lethargy and dry mouth were considered treatment related.

Reviewer Summary: *The steady-state pharmacokinetics of quetiapine and 3 metabolites were characterized in adults from 18 to 45 years of age with primary diagnoses of schizophrenia, schizoaffective disorder, or bipolar I disorder. The rank order of exposure with respect to AUCss was: quetiapine sulfoxide≈quetiapine>N-desalkyl quetiapine>7-hydroxy quetiapine. The rank order of in vivo exposure with respect to Css,max was: quetiapine≈quetiapine sulfoxide>N-desalkyl quetiapine>7-hydroxy quetiapine. Exposure (AUCss, Cmax) to quetiapine tended to increase with an increase in age and weight. Urinary excretion of quetiapine and its metabolites appeared to be minor.*

Table 11.2.1.1 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter		Study Day: Day 6 (N=26)	Study Day: Day 12 (N=26)
AUC (ng*hr/mL)	N	25	25
	Mean	2667.551	4831.602
	SD	1101.697	1881.882
	Minimum	1025.28	2083.33
	Median	2666.94	4661.12
	Maximum	6516.77	10986.38
	Geometric Mean	2469.650	4508.947
	CV(%)	42.470	39.768
Cmax (ng/mL)	N	26	26
	Mean	708.808	1176.808
	SD	254.859	355.749
	Minimum	231.00	686.00
	Median	639.00	1215.00
	Maximum	1220.00	1990.00
	Geometric Mean	660.266	1124.564
	CV(%)	41.942	31.909
tmax (hr)	N	26	26
	Minimum	0.32	0.50
	Median	1.00	1.23
	Maximum	3.00	3.00

Table 11.2.1.1 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter		Study Day: Day 6 (N=26)	Study Day: Day 12 (N=26)
Cmin (ng/mL)	N	25	25
	Mean	57.604	101.664
	SD	34.866	58.360
	Minimum	13.70	19.30
	Median	52.20	89.60
	Maximum	155.00	298.00
	Geometric Mean	47.849	86.834
	CV(%)	72.146	65.875
CL/F (L/hr)	N	25	25
	Mean	88.012	95.362
	SD	39.747	39.205
	Minimum	30.69	36.41
	Median	74.99	85.82
	Maximum	195.07	192.00
	Geometric Mean	80.983	88.713
	CV(%)	42.470	39.768
t1/2 (hr)	N	22	22
	Mean	3.341	5.097
	SD	0.617	0.910
	Minimum	2.53	3.77

Table 11.2.1.2 Summary statistics for quetiapine sulfoxide (ICI213,841) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter		Study Day: Day 6 (N=26)	Study Day: Day 12 (N=26)
AUC (ng*hr/mL)	N	25	25
	Mean	2642.927	5031.802
	SD	755.389	1264.530
	Minimum	1418.05	2471.85
	Median	2523.88	4730.36
	Maximum	4577.72	8675.72
	Geometric Mean	2547.334	4889.533
	CV(%)	28.076	24.781
Cmax (ng/mL)	N	26	26
	Mean	610.000	1037.077
	SD	189.920	248.792
	Minimum	272.00	438.00
	Median	572.50	997.50
	Maximum	1080.00	1580.00
	Geometric Mean	580.529	1006.217
	CV(%)	33.847	26.426
tmax (hr)	N	26	26
	Minimum	0.32	0.50
	Median	1.26	1.50
	Maximum	3.00	5.00

Table 11.2.1.2 Summary statistics for quetiapine sulfoxide (ICI213,841) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter		Study Day: Day 6 (N=26)	Study Day: Day 12 (N=26)
Cmin (ng/mL)	N	25	25
	Mean	51.652	101.216
	SD	26.251	50.143
	Minimum	16.70	37.70
	Median	47.10	96.00
	Maximum	137.00	234.00
	Geometric Mean	46.077	90.448
	CV(%)	52.374	51.859
t1/2 (hr)	N	21	21
	Mean	3.054	4.836
	SD	0.478	0.832
	Minimum	2.16	3.22
	Median	3.07	4.95
	Maximum	3.96	6.51
Lambda_z (hr-1)	N	21	21
	Mean	0.233	0.148
	SD	0.037	0.027
	Minimum	0.18	0.11
	Median	0.23	0.14
	Maximum	0.32	0.22

Table 11.2.1.3 Summary statistics for 7-hydroxy quetiapine (ICI214,227) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter		Study Day: Day 6 (N=26)	Study Day: Day 12 (N=26)
AUC (ng*hr/mL)	N	25	25
	Mean	136.688	295.886
	SD	59.378	112.367
	Minimum	35.82	90.74
	Median	135.41	303.74
	Maximum	239.59	519.35
	Geometric Mean	123.273	272.714
	CV(%)	51.707	45.698
Cmax (ng/mL)	N	26	26
	Mean	28.422	59.119
	SD	14.712	25.646
	Minimum	7.55	15.90
	Median	25.10	56.35
	Maximum	60.00	101.00
	Geometric Mean	24.479	52.661
	CV(%)	64.058	57.028
tmax (hr)	N	26	26
	Minimum	0.32	0.50
	Median	1.01	1.23
	Maximum	3.00	3.00

Table 11.2.1.3 Summary statistics for 7-hydroxy quetiapine (ICI214,227) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter		Study Day: Day 6 (N=26)	Study Day: Day 12 (N=26)
Cmin (ng/mL)	N	25	25
	Mean	3.859	8.305
	SD	1.924	3.979
	Minimum	1.12	2.28
	Median	3.79	7.71
	Maximum	8.77	15.30
	Geometric Mean	3.411	7.295
	CV(%)	56.158	59.234
Lambda_z (hr-1)	N	15	15
	Mean	0.181	0.127
	SD	0.030	0.023
	Minimum	0.13	0.09
	Median	0.18	0.13
	Maximum	0.24	0.18
	Geometric Mean	0.178	0.126
	CV(%)	16.837	17.671
t1/2 (hr-1)	N	15	15
	Mean	3.949	5.581
	SD	0.645	0.943
	Minimum	2.87	3.75

Table 11.2.1.4 Summary statistics for N-desalkyl quetiapine (M211,803) pharmacokinetic parameter estimates - PK evaluable subjects

Pharmacokinetic Parameter		Study Day	
		Day 6 (N=26)	Day 12 (N=26)
AUC (ng*hr/mL)	N	24	24
	Mean	1214.005	2723.560
	SD	379.854	848.683
	Minimum	602.61	1263.54
	Median	1151.78	2665.03
	Maximum	1986.37	4057.61
	Geometric Mean	1154.690	2585.400
	CV(%)	33.933	35.075
Cmax (ng/mL)	N	26	26
	Mean	156.350	338.731
	SD	60.395	151.242
	Minimum	62.70	126.00
	Median	150.50	306.50
	Maximum	287.00	710.00
	Geometric Mean	144.107	306.160
	CV(%)	44.877	49.604
tmax (hr)	N	26	26
	Minimum	0.25	1.00
	Median	2.00	2.00
	Maximum	8.00	8.00

Figure 11.2.1.1.1 Individual values of AUC of quetiapine versus quetiapine dose

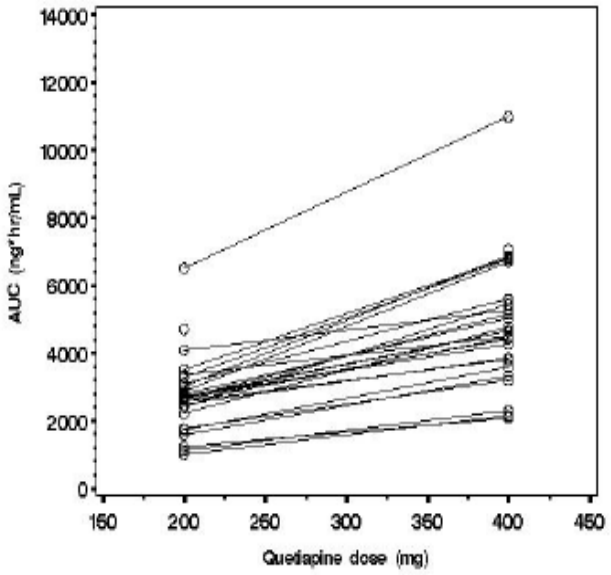
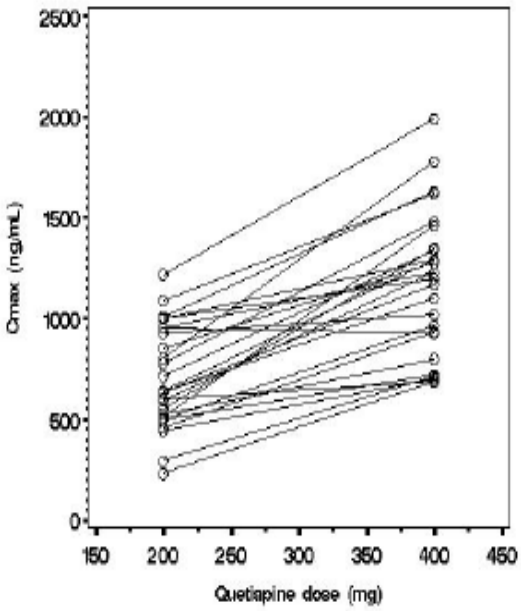


Figure 11.2.1.1.2 Individual values of Cmax of quetiapine versus quetiapine dose



4.3.

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

8 SUMMARY OF FINDINGS

8.1 Key Review Questions

The purpose of this review is to address the following key questions.

8.1.1 Does quietapine prolong QTc interval in children and adolescents at the proposed clinical doses?

Quietapine does not appear to prolong QTc interval in children and adolescents at the proposed clinical doses. The potential for QTc prolongation at the proposed doses was evaluated by using the quietiapine concentration-QTcF relationship derived from a thorough QT study in healthy adults. Assuming the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-corrected, baseline-adjusted QTc (ΔΔQTc) intervals are less than 10 ms (**Table 2Error! Reference source not found.**) following the highest dose (i.e. 400 mg BID) tested in the two pivotal pediatric studies (Study D1441C00112 and Study D1441C00149). In addition, the largest mean QTc interval change from baseline (ΔQTcF) observed in the clinical trials was around 2 ms (Table 3). No patients had QTcF values larger than 500 ms or ΔQTcF greater than 60 ms.

Table 2: Model Predicted ΔΔQTcF Values

Daily Dose (mg/day)	Dose (mg)	Dosing	C_{max} (ng/mL)	Predicted QTcF (90% CI) (ms)
400	200	BID	520.9	5.4 (3.6 - 7.1)
600	300	BID	1023.6	6.8 (4.9 - 8.7)
800	400	BID	1113.4	6.9 (5.0 - 8.9)

The two pivotal pediatric studies (Study D1441C00112 and Study D1441C00149) had slightly different results for ΔQTc following quietapine treatment. As shown in Table 3, a larger (i.e., approximately 2 ms) ΔQTcF was seen in quietapine treated groups as compared to the placebo group in Study D1441C00112. However, ΔQTcF for quietapine treated groups (e.g. -1.1 ms in 600 mg/day dose group) was similar to the placebo group (i.e. -1.2 ms in placebo group) in Study D1441C00149.

Suboptimal ECG sampling may lead to the difference in QTc results. Firstly, it has been found that the change in QTc interval is driven by drug concentration. If the ECGs were not taken at the same time post-dose between the two trials, the results may be different. Secondly, diurnal effect has been shown to affect QTc intervals. If the ECGs were not collected in time-matched fashion between the placebo group and treatment group or between the final visit and baseline visit, the results can be variable. Thirdly, QTc intervals may change over weeks. In the two studies, the baseline values were collected either 3 weeks or 6 weeks prior to the final visit. Different lag time between the ECGs observed at baseline and at the final visit may lead to different results. Furthermore, the QTc itself is highly variable, especially when ECGs were not taken in triplicates.

Table 3 Summary of the QTcF change from Baseline Values

Study		D1441C00112	D1441C00149
Patients		schizophrenia	Bipolar I mania
Treatment	Age	13 ~ 17	10 ~ 17
Placebo	Mean (SD) N	-2.1 (18.1) 71	-1.2 (17.6) 81
400 mg/day	Mean (SD) N	1.96 (16.2) 72	-0.11 (16.1) 94
600 mg/ day	Mean (SD) N	- -	-1.1 (16.8) 98
800 mg/day	Mean (SD) N	1.96 (18.1) 73	- -

9 PERTINENT REGULATORY BACKGROUND

Quetiapine (Seroquel®) has been approved as monotherapy for the treatment of depressive episodes associated with bipolar disorder in adults. It has also been approved as either monotherapy or adjunctive therapy for the treatment of the acute episodes of bipolar I disorder in adults. Additionally, it is used for the maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex in adults.

The sponsor provided the pediatric study reports in the current submission to fulfill the pediatric Written Request originated on 11 February 2003, and subsequently amended on 7 May 2004 and 3 February 2005. The sponsor is seeking an additional six-month marketing exclusivity and the indication for the treatment of acute maniac episodes associated with bipolar I disorder in children and adolescents (10 – 17 years) and schizophrenia in adolescent (13 – 17 years).

10 RESULTS OF SPONSOR’S ANALYSIS

Study D1441C00112 was a 6-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in patients aged 13 to 17 years with schizophrenia. The double-blind study was preceded by a medication washout period of 1 to 28 days based on the current medications at screening. Of the 268 patients enrolled in this study, 222 were randomly assigned to study treatment. With 73 patients in the 400 mg/day quetiapine group, 74 patients in the 800 mg/day quetiapine group, and 75 patients in the placebo group, the randomization goals were considered to be adequately satisfied. Treatment began with a 50-mg

dose on the evening of Day 1. The dose was escalated daily in increments of 100 mg thereafter, to reach a target fixed dose of 400 mg/day by Day 5 or 800 mg/day by Day 9, according to randomized treatment assignment. The overall treatment duration was 6 weeks. Twelve-lead ECGs were preformed at screening and on Day 42 (or withdrawal). QTc intervals were calculated using the Fridericia formula. Based on the clinical observation, the QT results were shown in Table 4.

Study D1441C00149 was a 3-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 600 mg/day) and placebo, given in divided doses (either twice daily [bid] or three times daily [tid], per the judgment of the investigator), in patients aged 10 to 17 years with Bipolar I mania. Of the 393 patients screened for this study, 284 were randomly assigned to study treatment. With 95 patients in the 400 mg quetiapine group, 98 patients in the 600 mg quetiapine group, and 91 patients in the placebo group, the randomization goals were considered to be adequately satisfied.
Treatment began with a 50 mg dose on the evening of Day 1. On Day 2, the dose was increased to 50 mg twice daily (i.e., 100 mg/day). Thereafter, the dose was escalated in 100 mg increments daily to reach a target of 400 mg/day by Day 5 or 600 mg/day by Day 7, according to randomized treatment assignment. Placebo to match 25 mg and 100 mg quetiapine tablets was administered orally in blinded fashion, according to randomized treatment assignment. The overall treatment duration was 21 days (3 weeks). QTc intervals were calculated using the Fridericia formula. ECGs were administered at screening period and by the end of the treatment. Based on the clinical observation, the QT results were demonstrated in Table 6.
Reviewer's Comments: The reviewer preformed additional analysis to further evaluate the quetiapine's QTc effect. There are several factors which may contribute to the inconsistent results. Firstly, the mean QTcF interval change from baseline following various doses of quietapine is not expected to be large. Assuming the concentration-QT relationships are similar between the pediatric patients and healthy adults, the model predicted mean placebo-corrected, baseline-adjusted QTc (ΔΔQTc) intervals were less than 7 ms. Secondly, it has been found that the change in QTc interval is driven by drug concentration. If the ECGs were not taken at the same time post-dose between the two trials, the results may be different. Thirdly, diurnal effect has been shown to affect QTc intervals. If the ECGs were not collected in time-matched fashion between the placebo group and treatment group or between the final visit and baseline visit, the results can be variable. Fourthly, QTc intervals may change over weeks. In the two studies, the baseline values were collected either 3 weeks or 6 weeks prior to the final visit. Different lag time between the ECGs observed at baseline and at the final visit may lead to inconsistent results. Furthermore, the QTc itself is highly variable, especially when it is measured in triplicates .

Table 4 Vital Signs and Change from Baseline to the Final Visit

(Study D1441C00112)

	Quetiapine 400 mg/day (N=73)			Quetiapine 800 mg/day (N=74)			Placebo (N=75)		
	n	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Vital signs									
Supine pulse (bpm)	73	6.0	12.32	74	3.9	12.16	73	-1.4	11.31
Supine systolic BP (mmHg)	73	2.0	10.30	74	1.0	9.72	73	-1.6	7.41
Supine diastolic BP (mmHg)	73	1.3	8.37	74	0.2	12.37	73	0.1	8.48
Standing pulse (bpm)	73	6.3	13.12	74	2.2	17.08	73	-2.5	13.14
Standing systolic BP (mmHg)	73	2.3	10.78	74	-0.4	10.26	73	-1.7	9.10
Standing diastolic BP (mmHg)	73	2.1	8.65	74	1.1	10.24	73	-1.2	7.68
Temperature (°C)	73	0.01	0.562	73	0.05	0.773	73	-0.03	0.563
Weight (kg)	73	1.9	2.47	73	1.5	2.63	73	-0.1	2.84
Height (cm)	73	0.3	0.81	73	0.3	0.88	73	0.2	0.69
ECG									
Heart rate (bpm)	64	3.78	16.52	64	11.16	14.88	65	-3.32	12.04
RR interval (msec)	64	-42.06	148.30	64	-101.09	127.59	65	33.23	128.34
PR interval (msec)	64	-1.97	32.10	64	2.77	12.97	65	1.12	12.51
QRS interval (msec)	64	0.30	8.54	64	-0.09	6.11	65	-0.25	6.38
QT interval (msec)	64	-4.88	26.39	64	-12.97	28.46	65	2.63	26.46
Fridericia's corrected QTc interval (msec)	64	1.41	16.47	64	3.13	17.48	65	-2.55	18.41
Bazett's corrected QTc interval (msec)	64	5.08	22.45	64	12.22	18.86	65	-5.57	20.93

Table 5 Vital Signs and Change from Baseline to the Final Visit

(Study D1441C00112)

	Quetiapine 400 mg (N=95)			Quetiapine 600 mg (N=98)			Placebo (N=90)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
ECG									
Heart rate (bpm)	90	12.76	12.37	87	13.36	15.52	79	-1.73	11.64
RR interval (msec)	90	-121.24	123.38	87	-136.11	165.14	79	18.20	138.03
PR interval (msec)	90	0.62	14.12	88	-0.76	13.72	81	-0.23	13.88
QRS interval (msec)	90	-0.98	6.31	87	-0.32	5.99	79	1.33	6.33
QT interval (msec)	90	-19.84	23.61	87	-22.84	24.70	79	1.39	27.65
Fridericia's corrected QTc interval (msec)	90	-0.80	15.90	87	-2.41	16.42	79	-1.68	17.57
Bazett's corrected QTc interval (msec)	90	10.22	19.89	87	9.16	24.29	79	-3.43	19.72

11 REVIEWER'S ANALYSIS

11.1 Introduction

The reviewer preformed additional analysis to evaluate the QT interval change following quetiapine treatment.

11.2 Objective

Analysis objective was to evaluate quietapine's QTc effect in pediatrics.

11.3 Methods

We compared the QTc interval change from the baseline in the quetiapine treatment group with the placebo group by the final day of the treatment.

11.3.1 Data Sets

Data sets used are summarized in Table 6.

Table 6. Analysis Data Sets

Study Number	Name	Link to EDR
Study 112	Ecg_e xpt	**\\cdsnas\pharmacometrics**
Study 149	Ecg_e xpt	**\\cdsnas\pharmacometrics**

11.3.2 Software

The analysis was conducted by using S_Plus (Version 7.0, Insightful, Inc.).

11.4 Results

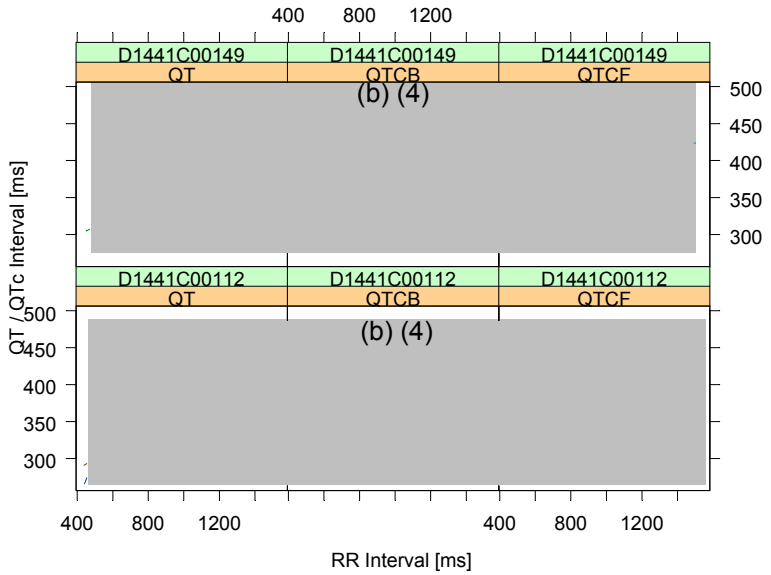
A scrutiny of the data indicated minimal QTcF change from baseline from the two pivotal trials (

Table 7).

The observed QT-RR interval relationship was presented in

Figure 1 together with the Bazett's (QTcB) and Fridericia (QTcF) stratified by different study (patient population). It appeared that QTcF was the best correction method to remove the heart rate effect. Therefore it was chosen for further analyses.

Figure 1 QT, QTcB, QTcF, and QTcS vs. RR, by Study (or Patient Population)
(Each Subject's Data Points are Connected with a Line)



Note:
Study D1441C00112 is conducted in patients aged 13 to aged 13 to 17 years with schizophrenia
Study D1441C00149 is conducted in patients aged 10 to 17 years with Bipolar I mania

Table 7 Summary of the Number of Patients with different QTcF change from Baseline

Study	Dose Group	Dosing	Total Number of patients	Number of patients		
				dQTcF > 30 ms	dQTcF > 60 ms	QTcF > 500 ms
D1441C00112	Placebo	0	68	2	0	0
D1441C00112	400 mg / day	200 mg BID	70	2	0	0

D1441C00112	800 mg / day	300 mg BID	72	2	0	0
D1441C00149	Placebo	0	80	1	0	0
D1441C00149	400 mg / day	200 mg BID	92	1	0	0
D1441C00149	600 mg / day	400 mg BID	87	5	0	0

We compared the QTc change from the baseline in different dose groups and the results were shown in Table 8. It appears that QTc values are inconsistent between the two pivotal trials (Study D1441C00112 and Study D1441C00149). As shown in Table 8, a larger (i.e., approximately 4 ms) ΔQTcF was seen in quietapine treated groups as compared to the placebo group in Study D1441C00112. However, ΔQTcF for quietapine treated groups was similar to the placebo group in Study D1441C00149.

Table 8: Summary of the QTcF change from Baseline Values

Study		D1441C00112	D1441C00149
Patients		schizophrenia	Bipolar I mania
Treatment	Age	13 ~ 17	10 ~ 17
Placebo	Mean (SD)	-2.1 (18.1)	-1.2 (17.6)
	N	71	81
400 mg/ day	Mean (SD)	1.96 (16.2)	-0.11 (16.1)
	N	72	94
600 mg/ day	Mean (SD)	-	-1.1 (16.8)
	N	-	98
800 mg/ day	Mean (SD)	1.96 (18.1)	-
	N	73	-

In an effort to understand the different QTc results between the two pivotal studies. We applied the concentration-QTc model derived from the thorough QT study in healthy adults. (Please refer to QT-IRT report for NDA 21999: paliperidone). Briefly, this thorough QTc study was a placebo- and active-controlled, 3-arm parallel study. All subjects underwent a 6-day placebo washout phase, and then received 1-day of open-label moxifloxacin treatment. They were then randomized 2:2:1 to 10 days of double-blind treatment of INVEGA™, SEROQUEL®, or placebo ( ). The 4 treatment arms were listed as the following:

- Moxifloxacin: 400 mg (Day 1)
- Placebo: Day 2-11
- Quetiapine IR : 100 mg bid (Day 2), 200 mg bid (Day 3), 300 mg bid (Day 4),and 400 mg bid (Day 5-11)
- Paliperidone ER: 12 mg qd (Day 2-5) and 18 mg qd (Day 8-11)

Blood samples and ECGs were collected at various time points (Table 9).

Table 9 Highlights of Schedule of Intervention

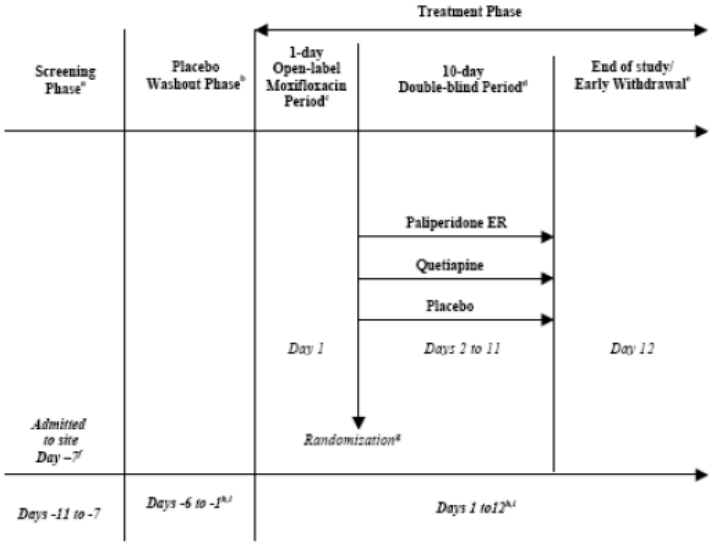
Study Day	-11 to -7	-2 to -1	1	2 to 11	12
Intervention	Screening	Baseline	Moxifloxacin	Multiple dosing	No treatment (Washout)
12-Lead ECGs	None recorded	Record ECGs[###]	Record ECGs[***]	Record ECGs[###]	None recorded
PK Samples for drug	None collected	None collected	None collected	Collected[###]	None collected

[###]0, 1, 2, 3, 4, 4.5, 5, 6, 8, 9, 12, 24 hours postdose

[***]0, 1, 1.5, 2.5, and 3.5 hours postdose for moxifloxacin

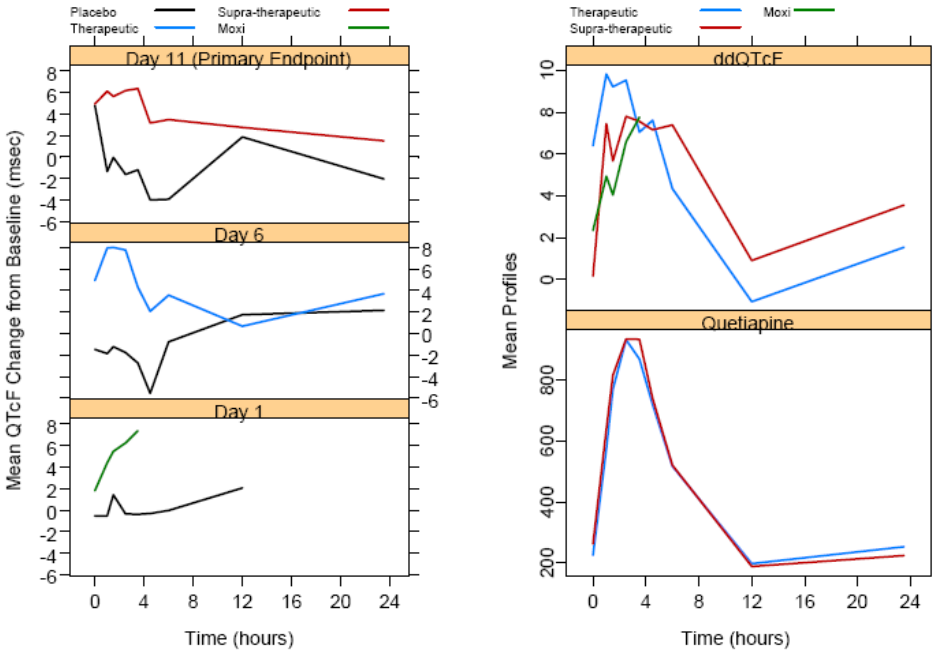
The quietapine concentration-time profile and placebo-adjusted, baseline-corrected QTcF profile were shown in Figure 3. The relationship between quetiapine concentrations and QT interval was investigated by using log-linear mixed-effects models. Data collected from the 400 mg bid Quetiapine dose group at day 6 and 11 was used for the Quetiapine concentration-QTcF analysis.

Figure 2 Schematic Illustration of the Study Design



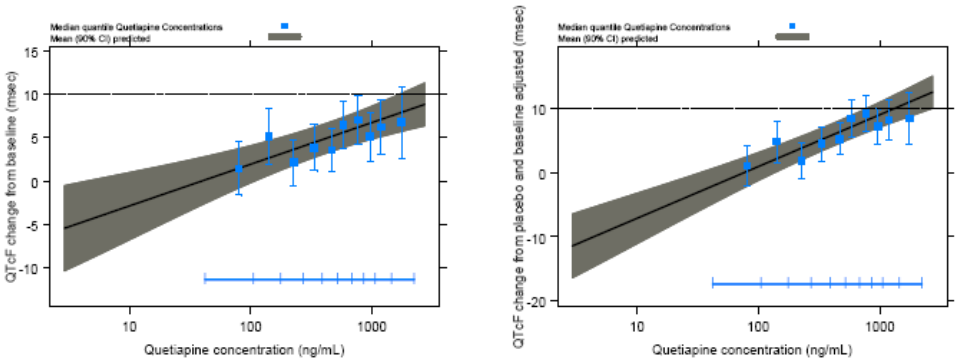
[a] Screening lasts up to 5 days.
[b] Subjects will receive placebo for 6 days.
[c] Subjects will receive a single dose of open-label 400-mg moxifloxacin in the morning for 1 day.
[d] Subjects will receive paliperidone ER, quetiapine, or placebo for 10 days. Paliperidone ER was administered beginning with a 12 mg dose on Days 2 to 6, 15 mg dose on Day 7, and an 18 mg dose on Days 8 to 11. Quetiapine was administered beginning with 100 mg twice daily (bid) on Day 2, 200 mg bid on Day 3, 300 mg bid on Day 4, and 400 mg bid on Days 5 to 11, as described in Section 3.6.
[e] End of study evaluations will be performed on subjects at the final visit on Day 12 and on those subjects who withdraw early from the study.
[f] Subjects will be admitted to the site on Day –7 and will remain until study completion on Day 12, or until early withdrawal from the study. Subjects can remain hospitalized longer based on the judgment of the investigator. If more than 3 additional days of hospitalization is required, the additional days must be discussed with the Medical Monitor.
[g] Randomization will occur after study drug administration on Day 1.
[h] Pharmacokinetic blood samples (4 mL each) will be collected on Days –2, –1, 1, 6, 7, 11, and 12 for the determination of plasma concentrations of paliperidone ER and quetiapine. Blood samples will be collected within 5 min after each triplicate ECG recording, where applicable. Refer to the table in Section 9.1, Study Procedures-Overview, for the specific time points of pharmacokinetic blood samples.
[i] Triplicate 12-lead ECG recordings will be obtained on Days –2, –1, 1, 6, 7, 11 and 12. Refer to the table in Section 9.1, Study Procedures-Overview, for the specific time points of ECG recordings.

Figure 3 Mean ΔQTcF (Change from Baseline) from day 1 to 11 (left), ΔΔQTcF (top right), and Quetiapine concentration (bottom right) profiles for placebo (black line), 400 mg bid at day 6 (blue line) and day 11 (red line), and moxifloxacin (green line)



(Source: QT-IRT Review for NDA 21999)

Figure 4 ΔQTcF (left) and ΔΔQTcF (right) vs. quetiapine concentration with observed median-quantile concentrations and associated mean QT (90% CI) prolongation overlaid (blue dots).



(Source: QT-IRT Review for NDA 21999)

Table 10 Exposure-Response Analysis of Quietapine associated ΔQTcF and ΔΔQTcF

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ΔQTcF = Intercept + slope*log(Quetiapine Concentration)		
Intercept, ms	-7.64 (-13.5, -1.80) 0.034	16.3
Slope, ms per log ng/mL	2.08 (1.15, 3.01) 0.0006	2.56
Residual Variability, ms	7.68	--
Model 2: ΔΔQTcF = Intercept + slope*log(Quetiapine Concentration)		
Intercept, ms	-15.2 (-21.2,-9.29) 0.0001	16.7
Slope, ms per log ng/mL	3.52 (2.57, 4.46) <0.0001	2.62
Residual Variability, ms	7.72	--

(Source: QT-IRT Review for NDA 21999)

Based on the concentration-QT relationship, the predicted ΔΔQTcF values when children and adolscents are administered queitiapine 200 mg, 300 mg, and 400 mg BID are shown in Table 11. Under 200 mg, 300mg, and 400 mg BID dosing, the mean baseline-corrected, placebo-adjusted QTcF values are 5.4, 6.8, and 6.9 ms respectively. The maximal upper bound of 90% confidence interval is less than 9 ms under 400 mg BID dosing.

Table 11 Model Predicted ΔΔQTcF Values

Daily Dose (mg/day)	Dose (mg)	Dosing	C_{max}* (ng/mL)	Predicted QTcF (90% CI) (ms)
400	200	BID	520.9	5.4 (3.6 - 7.1)
600	300	BID	1023.6	6.8 (4.9 - 8.7)
800	400	BID	1113.4	6.9 (5.0 - 8.9)

(Note: * please refer to Dr. Kofi Kumi's review on NDA 20639 for the C_{max} values)

12 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
QTanalysis.ssc	Analysis Script File	\\cdsnas\PHARMACOMETRICS\Seroquel\Analysis\SPlus

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