CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022047Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	22-047
Drug:	Quetiapine fumarate sustained release tablets
Trade Name:	Seroquel SR®
Strengths:	50, 200, 300, 400 mg
Sponsor:	Astra Zeneca
Indication:	Treatment of Schizophrenia
Submission type:	Original NDA (New Formulation)
Submission dates:	7/17/06
OCP Division:	DCP 1 (HFD-860)
OND Division:	DPP (HFD-130)
PM Reviewer:	Hao Zhu, Ph.D.
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Reviewer:	Kofi A. Kumi, Ph.D.
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1. Executive Summary

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the data submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 22-047 and finds the data acceptable.

1)

- IR and SR formulations produce similar range of concentrations of the active moiety. Similar concentrations should result in similar effects, in general.
- In Study D1444C0132, a significant dose-response relationship was demonstrated (P = 0.0001) in addition to the significant effectiveness for all Seroquel SR formulation treated groups as compared to the placebo group by the end of 6th week. These results provided strong supportive evidence for the effectiveness of the Seroquel SR formulation.
- Studies D1444C0133 and 5077IL/0041 outcomes suggested that the failure to detect the difference in PANSS change between the placebo and the Seroquel SR and IR likely due to the lack of sensitivity of the trials, rather than lack of effectiveness of the Seroquel SR formulation. This is because IR, which is approved currently, failed whenever SR did.
- These two studies (5077IL/0041 and D1444C0133) which were conducted mainly in the USA failed to demonstrate significant effectiveness of Seroquel SR and IR formulations as compared to placebo. Whether this outcome reflected the differences in the expectation of US vs. non-US patient, since the primary dropout reason is lack of symptom-relief; whether it reflected the differences of clinical practice in the US vs. non-US; whether it reflected the differences of investigators/centers in the US vs. non-US is unknown. It is important to note here that since both IR and SR arms failed, the study is at best un-interpretable with respect to effectiveness conclusion. The implication of the results with respect to trial conduct and/or patient behavior differences between US and non-US sites is uncertain. Certainly this is a phenomenon to be noted in future clinical trial for this indication.

2) The proposed dissolution method and specification is acceptable

1.2. Phase IV Recommendations

The sponsor should conduct studies to investigate dose-dumping in the presence of alcohol. The sponsor should perform dissolution studies for all Seroquel XR strengths using the accepted dissolution conditions with the addition of 0%, 5%, 20% and 40% of ethanol to the dissolution media. The accepted dissolution method is:

Apparatus	USP Apparatus I (Basket)
Speed	200 RPM
Media	900 mL 0.05M Sodium Citrate and 0.09N Sodium hydroxide (pH 4.8). At 5 hours, pH adjusted to 6.6 with 100 mL medium of 0.05M Sodium Phosphate and 0.46N Sodium Hydroxide

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Regulatory Background: Seroquel (quetiapine fumarate) immediate release (IR) tablets were approved for the treatment of schizophrenia in 1997 and for acute mania associated with bipolar disorder in 2003. The sponsor is seeking approval for a quetiapine, 50 mg, 200 mg, 300 mg, 400 mg, sustained release (SR) formulation for the treatment of schizophrenia.

Therapeutic indication and Dosage Regimen: The SR tablet for the treatment of schizophrenia is intended to allow the administration of quetiapine once daily in the dose range of 400 to 800 mg/day. Therapy with quetiapine SR can be initiated at a dose of 300 mg/day, with dose increases of up to 600 mg/day on Day 2 and up to 800 mg/day on Day 3. The approved quetiapine IR tablets for the treatment of schizophrenia are administered 2 or 3 times a day in the dose range of 150 to 800 mg/day.

Exposure-Response

- IR and SR formulations produce similar range of concentrations of the active moiety. Similar concentrations should result in similar effects, in general.
- In Study D1444C0132, a significant dose-response relationship was demonstrated (P = 0.0001) in addition to the significant effectiveness for all Seroquel SR formulation treated groups as compared to the placebo group by the end of 6th week. These results provided strong supportive evidence for the effectiveness of the Seroquel SR formulation.
- Studies D1444C0133 and 5077IL/0041 outcomes suggested that the failure to detect the difference in PANSS change between the placebo and the Seroquel SR and IR likely due to the lack of sensitivity of the trials, rather than lack of effectiveness of the Seroquel SR formulation. This is because IR, which is approved currently, failed whenever SR did.
- These two studies (5077IL/0041 and D1444C0133) which were conducted mainly in the USA failed to demonstrate significant effectiveness of Seroquel SR and IR formulations as compared to placebo. Whether this outcome reflected the differences in the expectation of US vs. non-US patient, since the primary dropout reason is lack of symptom-relief; whether it reflected the differences of clinical practice in the US vs. non-US; whether it reflected the differences of investigators/centers in the US vs. non-US is unknown. It is important to note here that since both IR and SR arms failed, the study is at best un-interpretable with respect to effectiveness conclusion. The implication of the results with respect to trial conduct and/or patient behavior differences between US and non-US sites is uncertain. Certainly this is a phenomenon to be noted in future clinical trial for this indication.

Equivalence of IR and SR Formulations: Quetiapine sustained release (SR) administered as 300-mg tablets once daily and the immediate release (IR) formulation of quetiapine administered as 150-mg tablets twice daily are equivalent with respect to overall exposure (AUC) at steady state. The mean AUC was about 4% higher when the SR was compared to the IR formulation. The difference in AUC was not significant. The mean Cmax was 13% lower after administration of

quetiapine SR compared IR formulation. The difference in Cmax was significant. Switching from quetiapine IR to SR provided similar total exposures (AUC).

Dose Proportionality: The exposure to quetiapine in terms AUCss (or Cssmax) was proportional to dose after administration of quetiapine SR in doses up to 800 mg/day.

Food Effect: Administration of quetiapine SR following a standard high-fat breakfast (two eggs, 2 strips of bacon, 2 pieces of toast with approximately 5 gm of butter, 75 gm of hashed brown potatoes and 150 mL of whole milk) produced increases in Cmax (44% to 52%) and AUC (20% to 22%) relative to the fasted state. These differences were significant. In comparison, a light meal (2 slices of toast, 2 teaspoons (10g) of jelly (jam), 180 mL (6 fluids ounces) of orange juice, 1 cup (237g) of coffee, 2 tablespoons (30.6 g) of 0.1% (skim) milk and 2 teaspoons (10g) of sugar) had no significant effect on quetiapine pharmacokinetics.
It is recommended that Seroquel XR be taken without food or with a light meal.

IVIVC Development: A level A in vitro in vivo correlation (IVIVC) model which satisfies the criteria for both internal and external predictability was developed and is acceptable.

Dissolution: The following dissolution method and specification are acceptable for quetiapine SR, 50 mg, 200 mg, 300 mg, and 400 mg strengths.

Apparatus	USP Apparatus I (Basket)
Speed	200 rpm
Media	900 mL 0.05M Sodium Citrate and 0.09N Sodium hydroxide (pH 4.8). At 5 hours, pH adjusted to 6.6 with 100 mL medium of 0.05M sodium phosphate and 0.46N sodium hydroxide

Specification:

Not more than (NMT) (b) (4) at 1 hour
(b) (4) at 6 hours
(b) (4) at 12 hours
Not less than (NLT) (b) (4) at 20 hours.

The Level A IVIVC model supports these dissolution specifications.

2. Question Based Review (QBR)

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 and biopharmaceutics of this drug?

Seroquel (quetiapine fumarate immediate release) tablets were approved for the treatment of schizophrenia in 1997 (NDA 20-639). Seroquel immediate release (IR) was approved in 2003 (NDA 20-639 SE1-016/017) for acute mania associated with bipolar disorder. The sponsor is seeking approval for a quetiapine sustained release (SR) formulation for the treatment of schizophrenia. The use of quetiapine SR for the treatment of acute mania associated with bipolar disorder is not a subject of this application. The main objectives of the development plan for this application were to develop an SR formulation of quetiapine fumarate for once-daily dosing and

to establish the efficacy and safety of quetiapine SR in the treatment of schizophrenia. The clinical program comprised of clinical pharmacology, biopharmaceutics, efficacy and safety studies.

The approved quetiapine IR tablets for the treatment of schizophrenia are administered 2 or 3 times a day in the dose range of 150 to 800 mg/day. The sustained release (SR) tablets for the treatment of schizophrenia is intended to allow the administration of quetiapine once daily in the dose range of 400 to 800 mg/day.

2.1.1. What is the proposed therapeutic indication for Seroquel SR?

Seroquel SR is indicated for the treatment of schizophrenia.

2.1.2. What are the proposed dosage and route of administration?

Seroquel SR tablets are intended for oral administration. The recommended dose is 400 to 800 mg/day administered once day. Therapy with quetiapine SR can be initiated at a dose of 300 mg/day, with dose increases of up to 600 mg/day on Day 2 and up to 800 mg mg/day on Day 3. Seroquel (quetiapine) SR would be available as 50 mg, 200 mg, 300 mg and 400 mg tablets.

2.2. General clinical pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The studies used to support dosing and claims are 4 safety and tolerability studies and 3 pivotal placebo controlled safety and efficacy studies.

The safety and tolerability trials investigated 1) a starting dose of quetiapine SR considered appropriate for use in subsequent safety and efficacy studies 2) a dose escalation scheme for quetiapine SR considered appropriate for use in subsequent safety and efficacy studies. The studies were conducted in patients with schizophrenia, schizoaffective disorder, or bipolar disorder.
The studies to establish starting doses were double blind, double dummy, randomized, parallel group study with 3 or 4 treatment groups designed to establish the highest tolerable starting dose. These studies compared quetiapine SR at fixed doses with quetiapine IR doses escalated according to approved prescribing information. The doses of quetiapine SR studied were from 50 mg to 800 mg fixed starting doses.

The studies to establish the dose escalation scheme for quetiapine SR were double-blind, randomized safety and tolerability of 2 or 3 treatment groups designed to compare dose-escalation schemes for quetiapine SR with a fixed daily 300 mg dose of quetiapine SR. The sponsor reported that these studies indicated that a starting dose of 300 mg was well tolerated. The data also indicated that quetiapine SR was well tolerated when the dose was maintained at 300 mg/day, escalated to 600 mg/day or escalated to 800 mg/day. The dosing scheme adopted for the first pivotal safety and efficacy study (study 041), 600 mg/day was reached on day 5 and 800 mg/day was reached on day 8. The dosing scheme used in pivotal safety and efficacy studies 132 and 133, escalation to 800 mg/day was reached on day 3.

The first pivotal placebo controlled study in the clinical program (041) was in patients with acute exacerbation of schizophrenia conducted in US and Canada and included 6 treatment groups: quetiapine SR 300 mg/day, 600 mg/day and 800 mg/day; placebo; and quetiapine IR 300 mg/day and 600 mg/day. The primary variable was the change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at Day 42.

Two other pivotal clinical efficacy studies centered on pivotal 6-week, multicenter, double-blind, placebo- and active-controlled studies in acutely ill patients with schizophrenia (Studies 132 and 133). Each study included 3 once daily doses of quetiapine SR (400 mg, 600 mg, and 800 mg) and 1 dose of quetiapine IR given twice daily (400 mg/day in study 132, 800 mg/day in study 133). In Studies 132 and 133, the time to reach the maximum quetiapine SR dose of 800 mg/day was reduced to 3 days from 8 days in Study 041. The minimum fixed dose of quetiapine examined in 132 and 133 was 400 mg/day, compared with 300 mg/day in Study 041. Study 132 was a foreign study conducted in 7 countries (Bulgaria, Greece, India, Indonesia, the Philippines, Romania, Russia and South Africa). Study 133 was conducted in the US.

2.2.2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the active moieties in the plasma have been adequately identified and measured.

2.2.3. Exposure- Response

2.2.3.1. Are the exposures after administration of the Sustained Release formulation similar to that of the Immediate Release formulation?

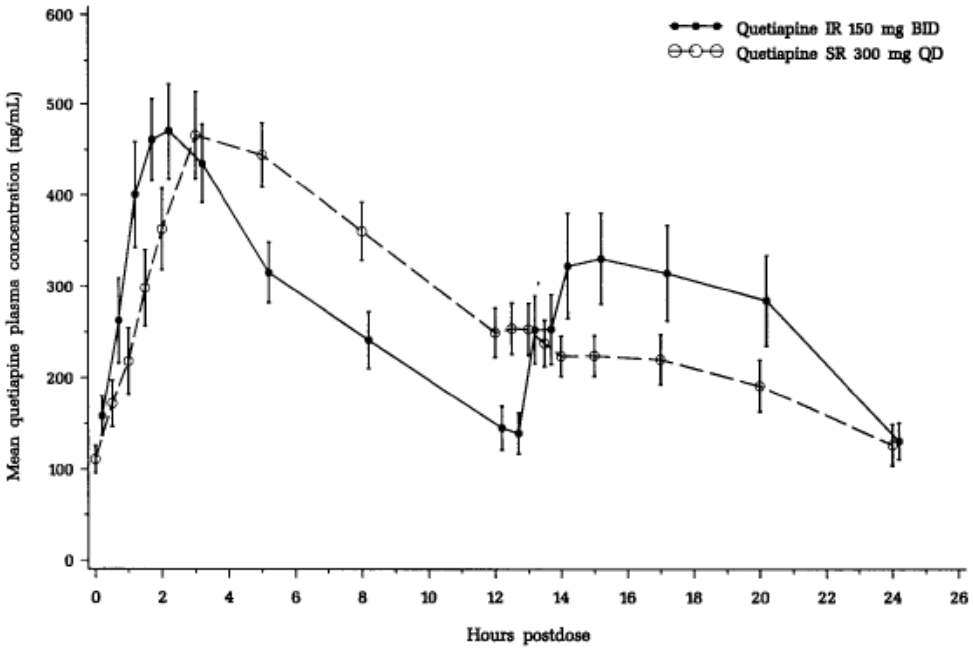
Quetiapine sustained release (SR) administered as 300-mg tablets once daily and the immediate release (IR) formulation of quetiapine administered as 150-mg tablets twice daily are equivalent with respect to overall exposure (AUC) at steady state. Switching from quetiapine IR to SR provided similar total exposures (AUC). However, Cmax was lower after administration of quetiapine SR than after IR formulation. The mean AUC was about 4% higher when the SR was compared to the IR formulation and the 90% confidence interval (CI) around the ratio of the mean was 0.92% to 1.19%, contained within the 80% – 125% regulatory limit for bioequivalence. The mean Cmax was about 13% lower after administration of the SR compared to IR formulation and the 90% CI was 0.77 to 0.99, outside the 80% to 125% limits for bioequivalence. Median DF, which is a measure of how Cmax and Cmin fluctuate around the time-averaged plasma concentration (AUC(0-24h)/24 hours), was similar for the SR and the IR formulations.

A study was conducted to compare the steady-state area under the quetiapine concentration-time curve across a 24-hour interval (AUC(0-24)) of sustained release (SR) quetiapine tablets with that of immediate release (IR) quetiapine tablets. The study was a single-center, open-label, randomized, 2-period crossover, bioavailability trial. Subjects were randomly assigned to 1 of 2 treatment-sequence groups (IR-SR or SR-IR). All subjects were given 300 mg/day of quetiapine SR on Days 1 and 2 of the Lead-in Period. Subjects assigned to the IR-SR sequence were given 150-mg doses of quetiapine IR twice daily on Days 1 through 4 of Period 1, then switched to single daily 300-mg doses of quetiapine SR on Days 1 through 4 of Period 2. Subjects assigned to the SR-IR sequence were given single daily doses 300-mg of quetiapine SR on Days 1 though 4 of Period 1, then switched to 150-mg doses of quetiapine IR twice daily on Days 1 through 4 of Period 2. Steady-state pharmacokinetic parameters of quetiapine were derived from data

collected over the 24-hour dosing interval following administration of the morning dose of quetiapine on Day 4 of Period 1 and Day 4 of Period 2.

The following figure depicts the mean plasma quetiapine concentrations over a 24-hour dosing interval for each of the two treatments.

Fig A: Mean ± SEM plasma quetiapine concentrations



IR: immediate – release quetiapine 150 mg twice daily
SR: sustained – release quetiapine 300 mg once daily

The following table summarizes the steady state pharmacokinetic parameters of quetiapine for each treatment and the results of statistical comparisons of the 2 treatments.

Table 1: Comparison of pharmacokinetic parameters for a 300-mg dose of quetiapine administered as SR tablets (300 mg once daily) or as IR tablets (150 mg twice daily)

Parameter (units)[a]	Immediate-release quetiapine (150 mg twice daily) (n=24)	Sustained-release quetiapine (300 mg once daily) (n=24)	Comparison of treatments: ratio of means[b]	
	Geometric mean (95% CI)		Ratio (SR/IR)	90% CI[c]
$AUC_{(0-24)}$ (ng·h/mL)	5882 (4729 to 7315)	6147 (5215 to 7246)	1.04	0.92 to 1.19
C_{max} (ng/mL)	568.1 (474.0 to 680.9)	495.3 (424.6 to 577.9)	0.87	0.77 to 0.99
C_{min} (ng/mL)	96.5 (66.2 to 140.4)	95.3 (69.4 to 130.8)	1.00	0.77 to 1.31
	Median (range)			
t_{max}	2.0 (0.6 to 8.0)	5.0 (0.9 to 20.0)		
Degree of fluctuation (%)	171.8 (54.9 to 430.0)	155.7 (21.0 to 566.2)		

[a] Parameters derived from data collected during the 24-hour interval following morning quetiapine administration on Day 4 of Periods 1 and 2.
[b] Based on ratio (SR/IR) of least squares means from analysis of variance.
[c] Based on log-transformed data.
CI Confidence interval.
IR Immediate release.
SR Sustained release.

2.2.3.2. What are the characteristics of the exposure-response relationships for efficacy?

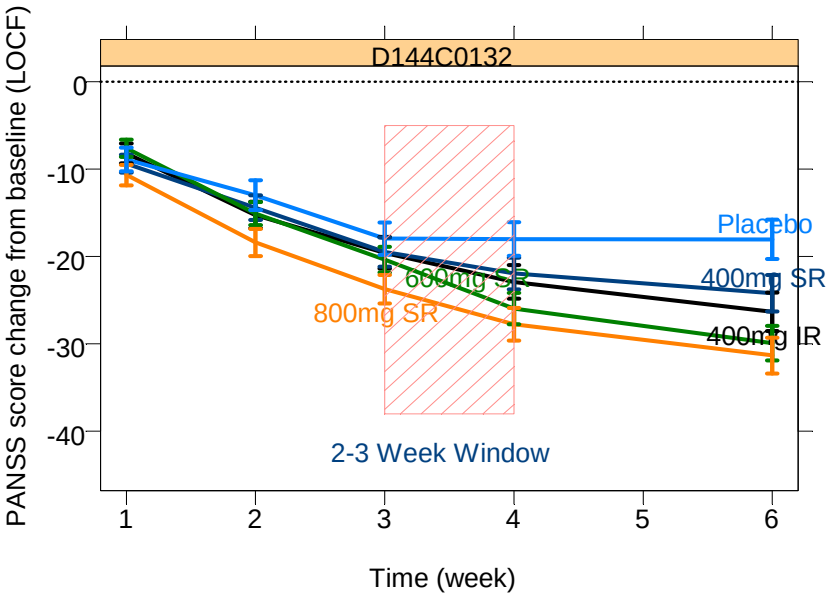
2.2.3.2.1 Overall, is there substantial evidence of effectiveness of Seroquel SR formulation?

- The sponsor demonstrated equivalence (in terms of AUC) of Seroquel SR and IR formulation, which indicates that the exposure between Seroquel IR and SR formulation is comparable (Fig A).
- Long term therapy is required to demonstrate anti-schizophrenia effect following Seroquel administration, which suggests that the cumulative overall exposure (e.g. AUC), rather than the shape of concentration time profile is more likely to be linked to

effectiveness (Fig B). Therefore, the Seroquel SR formulation is expected to produce similar effect on the symptoms as compared to IR formulation, given that the Seroquel IR formulation has been approved and the equivalence in exposure (in terms of AUC) of Seroquel SR and IR formulation was demonstrated.

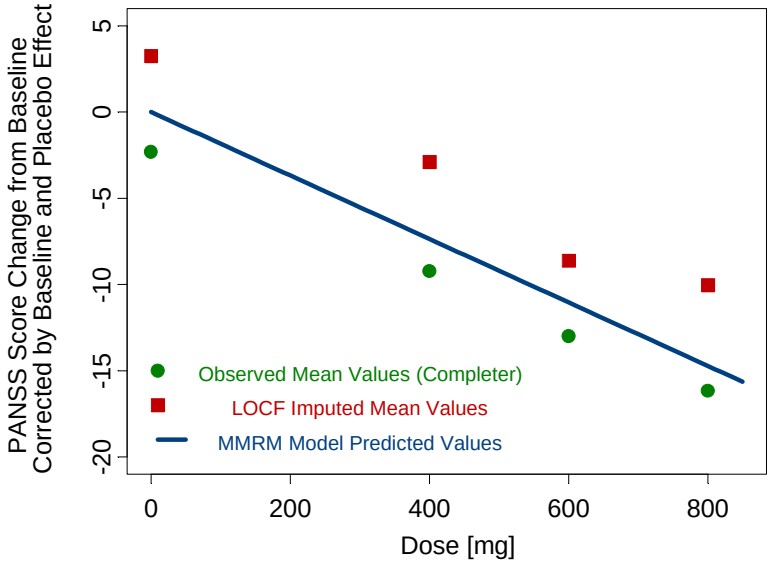
- In Study D1444C0132, a significant dose-response relationship was demonstrated (P = 0.0001) in addition to the significant effectiveness for all Seroquel SR formulation treated groups as compared to the placebo group by the end of 6^{th} week (Fig C). These results provided strong supportive evidence for the effectiveness of the Seroquel SR formulation.
- Seroquel SR and IR formulation with the same dose consistently produced similar PANSS score change from baseline values in all three pivotal trials. Additionally, in Studies D1444C0133 and 5077IL/0041, neither Serqouel SR, nor Seroquel IR demonstrated significant effectiveness compared to placebo, even though the Seroquel IR formulation has been approved for schizophrenia. The outcomes suggested that the failure to detect the difference in effectiveness between the placebo and the Seroquel SR and IR likely due to the lack of sensitivity of the trials, rather than lack of effectiveness of the Seroquel SR formulation. (Fig D)
- Two pivotal clinical studies (5077IL/0041 and D1444C0133) which were conducted mainly in the USA failed to demonstrate significant effectiveness of Seroquel SR and IR formulations as compared to placebo. Whether this outcome reflected the differences in the expectation of US vs. non-US patient, since the primary dropout reason is lack of symptom-relief; whether it reflected the differences of clinical practice in the US vs. non-US; whether it reflected the differences of investigators/centers in the US vs. non-US is unknown. It is important to note here that the since both IR and SR arms failed, the study is at best un-interpretable with respect to effectiveness conclusion. The implication of the results with respect to trial conduct and/or patient behavior differences between US and non-US sites is uncertain. Certainly a phenomenon to be noted in future clinical trial for this indication.

Fig B. PANSS Change from Baseline versus Time (LOCF)



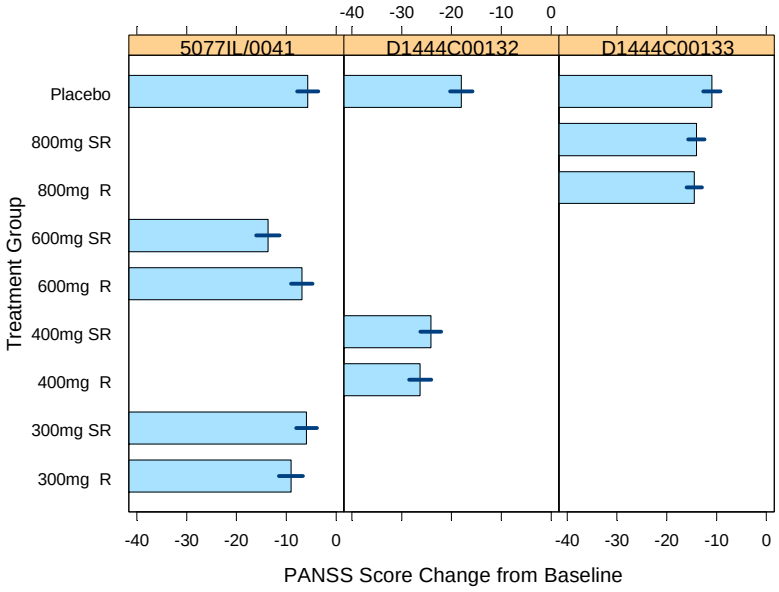
Note: At least 2-3 week treatment is needed in order to demonstrate effectiveness of Seroquel comparing to placebo**.**

Fig C. Dose-response relationship for Seroquel SR formulation



Note: Dose-response relationship has been demonstrated in Study D144C0132. (Using MMRM analysis, P = 0.0001)

Fig D. PANSS Score Change from Baseline for Seroquel IR and SR formulation with the same dose.

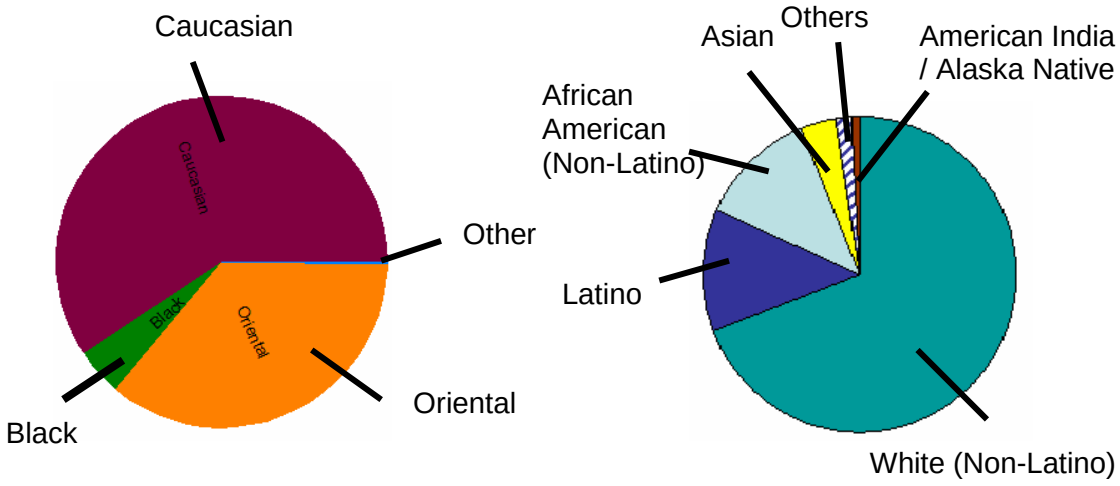


Note: Seroquel SR and IR formulation with the same dose produced similar PANSS score change from baseline. In Study 5077IL/0041 and D1444C0133, neither SR nor IR formulation demonstrated significant effectiveness as compared to placebo.

Fig E Clinical sites in the Study D144C00132

Note: Study D144C00132 mainly included clinical sites in Asia and East Europe.

Fig F Racial composition of the Study D144C0132 and American population



Note: Racial composition in Study D144C0132 is different from the American population.

2.2.3.2.2. What are the potential reasons for studies D1444C0133 and 5077IL/0041's failure?

- Most likely reason for the failure of trial D1444C0133 and 5077IL/0041 is substantial early dropout. The overall dropout rates for study 5077IL/0041 and D1444C0133 are 57% and 39% respectively (Fig G). About half of them dropped out within the 1st week of treatment (Fig H). Interpreting trials with such a high rate of drop out is extremely challenging. No one method is reliable.

Fig G. Overall Percentage of Prematurely Discontinued Subjects vs. Study

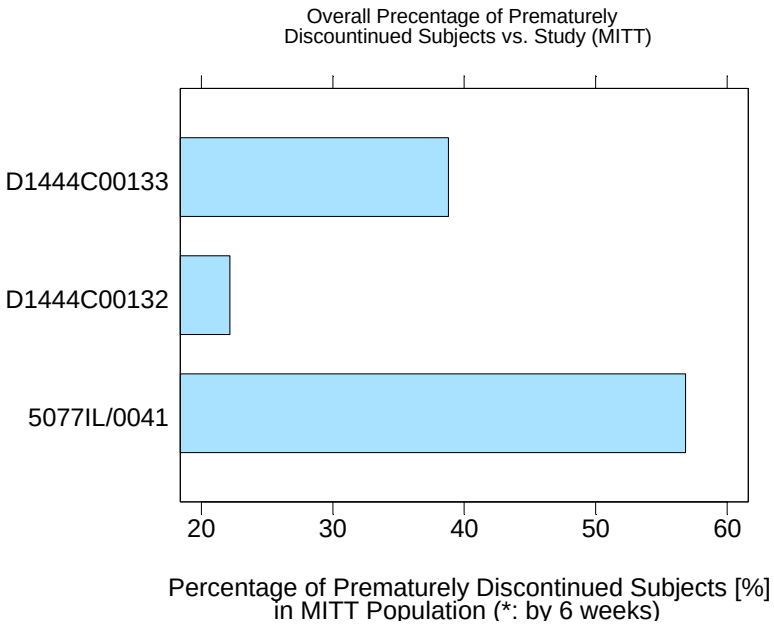


Fig H. Time Distribution of Premature Discontinuation, by Study

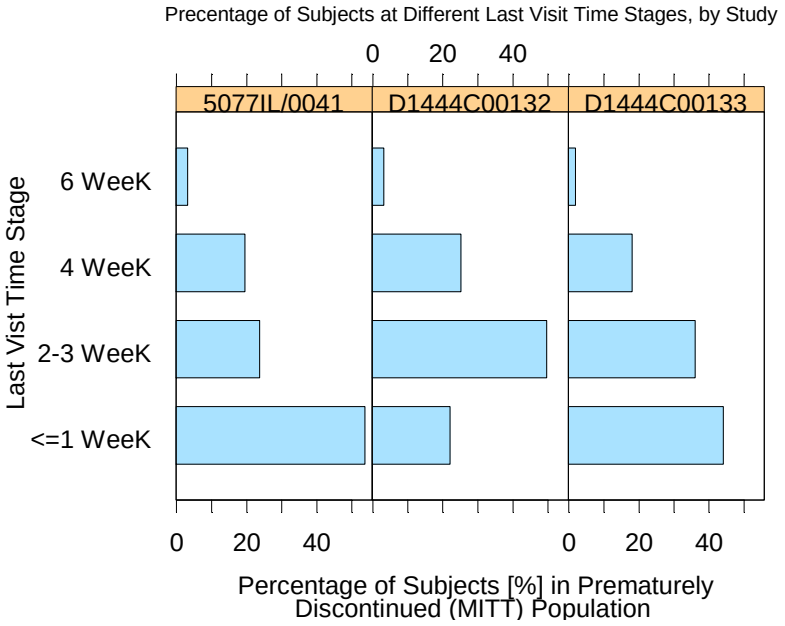

Precentage of Subjects at Different Last Visit Time Stages, by Study
0
20
40
5077IL/0041
D1444C00132
D1444C00133
Last Vist Time Stage
6 WeeK
4 WeeK
2-3 WeeK
<=1 WeeK
0
20
40
0
20
40
Percentage of Subjects [%] in Prematurely Discontinued (MITT) Population

Table 2

Summary of Clinical Trial Designs

Study	5077IL/0041	D144C0132	D144C0133
Sites	US + Canada	Non-US	US only
Teatment	Placebo 300, 600, 800mg/day SR 300, 600mg/day IR	Placebo 400, 600, 800mg/day SR 400mg/day IR	Placebo 400, 600, 800 mg/day SR 800mg/day IR
Duration	42 Day	42 Day	42 Day
Variables	PANSS Score Change from Baseline on Day 42		
Analysis	ANCOVA with LOCF		

Table 3

Summary of Clinical Outcomes

Study	5077IL/0041	D144C0132	D144C0133
Placebo	-5.19	-18.8	-12.1
300mg SR	-5.01		
400mg SR		-24.8 *	-13.8
600mg SR	-13.01*	-30.9 ***	-16.8
800mg SR	-11.17	-31.3 ***	-14.8
300mg IR	-9.42		
400mg IR		-26.6 ***	
600mg IR	-6.97		
800mg IR			-15

*: Statistical Significance

2.2.3.3. What are the characteristics of the exposure-response relationships for safety?

The sponsor reported that the type, frequency and intensity of AEs observed in the quetiapine SR and quetiapine IR groups were similar, with no apparent dose-response (safety) relationship. There were no AEs associated only with quetiapine SR treatment, and in general, there was no dose relationship with any common AE associated with drug across the dose range (300 to 800 mg/day). The sponsor reported that overall, the profile of patients treated with quetiapine SR was comparable to that of patients treated with quetiapine IR.

The sponsor reported that a total of 951 patients who were treated with quetiapine SR for up to 42 days in the 3 placebo-controlled studies provided safety data for 4 fixed doses of quetiapine SR: 300 mg/day (91 patients),400 mg/day (227 patients), 600 mg/day (310 patients), and 800 mg/day (323 patients). The sponsor reported that the most common AEs in all quetiapine dose groups were dry mouth, sedation, somnolence, and dizziness and most were rated as mild or moderate in intensity. The sponsor reported that the incidence rates across the quetiapine SR groups for all these AEs were higher than for placebo, although the rates were generally similar to those for quetiapine IR and did not appear to be related to the dose of quetiapine. The sponsor reported that sedation, somnolence, and dizziness in patients treated with quetiapine in the placebo-controlled pool occurred at rates similar to those reported for quetiapine IR in the original schizophrenia registration studies, while dry mouth was reported more frequently for both quetiapine SR and quetiapine IR in the placebo controlled pool. The sponsor reported that headache, insomnia, constipation, agitation, and dizziness postural were reported less frequently for quetiapine SR and quetiapine IR in the placebo-controlled pool than for quetiapine IR in the original schizophrenia registration studies; orthostatic hypotension was reported more frequently with quetiapine SR and quetiapine IR in the placebo-controlled pool. (Refer to the medical officer's review for the Agency's evaluation of safety)

2.2.3.4. Does this drug prolong the QT or QTc interval?

No formal QT study was conducted for this application. The sponsor reported that the data did not indicate an association between quetiapine SR and QT prolongation. The sponsor reported that there were no adverse events associated with QT prolongation.

2.2.3.5. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response?

The approved quetiapine IR tablets for the treatment of schizophrenia are administered 2 or 3 times a day in the dose range of 150 to 800 mg/day, with a recommended 4-day treatment initiation period to reach a dose of 300 to 400 mg/day. This dosing regimen was demonstrated in the original application (NDA 20-639) to be safe and effective. The sponsor has developed a sustained release (SR) tablets for the treatment of schizophrenia that will allow the administration of quetiapine once daily in the dose range of 400 to 800 mg/day. The dose selected by the sponsor is within the dose range approved for quetiapine IR. However, the dose would be administered once daily instead of 2 to 3 times a day as is the case for the IR formulation.

2.2.4. What are the Pharmacokinetic characteristics of the drug and its major metabolite?

2.2.4.1. Based on PK parameter, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The exposure to quetiapine in terms of AUCss (or Cmax) was proportional to the dose after the administration of quetiapine SR in doses from 100 to 800 mg/day.

A single-center, open-label, multiple-dose, within-subject dose escalation, comparison trial was conducted to determine the pharmacokinetics of quetiapine. Subjects were given oral doses of quetiapine fumarate once daily on Days 3 through 21. Dosages were 50 mg on Day 3, 100 mg on Days 4 to 6, 200 mg on days 7 to 10, 300 mg on Days 11 to 14, 400 mg on Day 15, 600 mg on Days 16 to 18, and 800 mg on Days 19 to 21. For analysis of dose proportionality, $AUCss_\tau$ was the primary measurement, and Cssmax was the secondary measurement. Dose proportionality was examined using linear regression of log-transformed $AUCss_\tau$ and Cssmax on log dose adjusted for subject. For the test of linearity the statistical treatment included fitting the data to a power model of the form $AUC = \alpha(DOSE)^{\beta}$, where α is the proportionality constant and β is the slope. After taking logs to linearize, dose proportionality was examined using linear regression of log-transformed $AUCss_\tau$ (and Cssmax) on log dose and testing for a null hypothesis in which the slope equaled 1.

The following table presents the values calculated for determination of dose proportionality based on the power model.

Table 4. Determination of dose proportionality for quetiapine sustained-release (SR) formulation.

Parameter (units)	Estimate of slope	SE	95% CI of estimate		p-value of H0: slope=1	Estimate of intercept α[a]
AUC^{ss}_{τ} (ng·h/ml)	0.90	0.076	0.75	1.06	0.207	13.61[a]
C^{ss}_{max} (ng/ml)	0.85	0.083	0.68	1.01	0.068	1.16[a]

[a] Based on power model AUC^{ss}_{τ} (or C^{ss}_{max})=α·(DOSE)β, where β=1 and the estimate of α (the intercept) is derived from the antilog of the average of log dose-normalized values (AUC^{ss}_{τ} and C^{ss}_{max}, doses combined).

CI Confidence interval, H0 Null hypothesis, SE Standard error, SR Sustained release formulation.

In another study using commercial scale quetiapine SR tablets, the pharmacokinetics of quetiapine SR were linear and thus proportional to dose at the dose strengths of quetiapine SR 50 to 400 mg. The results of this study are consistent to that observed when quetiapine doses of 100 mg to 800 mg were evaluated. The following table provides the regression analyses of log-transformed AUC and Cmax versus dose of quetiapine SR in this study.

Table 5. Regression analysis of quetiapine SR dose proportionality under fasting conditions.

Parameter	**n**	**Estimated slope[a]**	**95% CI**
C^{ss}_{max}, ng/mL	10	0.9247	0.7904 to 1.0591
AUC^{ss}_{τ}, ng·hr/mL	10	1.0011	0.9055 to 1.0967

[a] Based on regression analysis of log-transformed data for 4 doses of quetiapine SR: 50 mg, 200 mg, 300 mg, and 400 mg.

SR Sustained release.

The pharmacokinetic parameters after administration of quetiapine SR and IR are provided in the following table.

Table 6: Pharmacokinetic Parameters of quetiapine

		Quetiapine SR[a]						Quetiapine IR[a]
		50 mg		200 mg	300 mg		400 mg	300 mg
Parameter		Fasted	Fed	Fasted	Fasted	Fed	Fasted	Fasted
AUC^{ss}_{τ}, ng·hr/mL	GM	925.09	1112.24	3751.93	5710.83	6966.93	7287.37	4895.18
	CV (%)	47.20	35.03	34.76	37.86	32.66	34.02	34.11
	n	10	10	10	10	10	10	10
C^{ss}_{max}, ng/mL	GM	87.83	133.23	304.48	470.70	677.92	594.84	944.04
	CV (%)	75.58	23.47	41.83	33.14	28.52	38.92	28.12
	n	10	10	10	10	10	10	10
C^{ss}_{min}, ng/mL	GM	11.16	10.80	60.03	87.19	79.53	107.79	21.88
	CV (%)	80.86	60.26	63.68	71.36	59.28	59.00	78.59
	n	10	10	10	10	10	10	10
t_{max}, hr	Median	6.05	6.04	6.05	6.12	8.00	5.00	1.50
	Min	1.97	3.92	2.02	1.95	3.00	3.00	1.00
	Max	15.92	9.70	8.08	10.08	11.83	8.00	4.02
	n	10	10	10	10	10	10	10
$t_{1/2}$, hr	Mean	5.57	5.41	6.57	6.35	5.40	7.10	5.38
	SD	0.676	0.738	1.760	1.626	1.195	2.855	0.974
	n	4	7	5	7	8	5	9
CL/F, L/hr	Mean	60.15	48.02	57.56	56.79	45.29	57.97	64.68
	SD	28.937	18.937	25.784	24.210	15.083	20.330	22.266
	n	10	10	10	10	10	10	10

[a] Fasting samples for pharmacokinetic analyses of quetiapine SR 50, 200, 300, and 400 mg, and quetiapine IR 300 mg were collected on Days 3, 7, 10, 14, and 17, respectively. Samples for pharmacokinetic analyses of quetiapine SR 50 and 300 mg were taken following a high-fat meal on Days 4 and 11, respectively.

CV Coefficient of variation. GM Geometric mean. IR Immediate release. Max Maximum. Min Minimum. SD Standard deviation. SR Sustained release.

2.5. General Biopharmaceutics

2.5.1. What is the quantitative and qualitative composition of quetiapine SR formulation?

The following table provides the quantitative and qualitative composition of quetiapine sustained release formulations

Table 7: Quantitative composition of Seroquel SR tablets

Components	Amount per tablet (mg)			
	50 mg	200 mg	300 mg	400 mg
Tablet core				
Quetiapine fumarate[a]	(b) (4)			
Lactose monohydrate				
Microcrystalline cellulose				
Sodium citrate				
Hypromellose (b) (4)				
Magnesium stearate				
(b) (4)				
Core tablet weight				
Tablet coating				
Hypromellose (b) (4)	(b) (4)			
Polyethylene glycol 400[e]				
Titanium dioxide[e]				
(b) (4)				
Ferric oxide, yellow[e]				
(b) (4)				
Coated tablet weight				

[a] Quetiapine fumarate is 86.86% quetiapine free base.
[b] (b) (4)
[c]
[d]
[e]
NA Not applicable.

2.5.2. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Administration of quetiapine SR following a standard high-fat breakfast (approximately 800 to 1000 calories, with 50% derived from fat content) produced increases in Cmax (44% to 52%) and AUC (20% to 22%) relative to the fasted state. These differences were significant. In comparison, a light meal (approximately 300 calories) had no significant effect on quetiapine pharmacokinetics.

The high fat study was a multi-center, open-label, multiple-dose study. After a 2-day washout period, patients received oral doses of quetiapine SR or quetiapine immediate release (IR) orally once a day as follows: 50 mg SR on Days 1 to 4, 200 mg SR on Days 5 to 7, 300 mg SR on Days 8 to 11, 400 mg SR on Days 12 to 14, 300 mg IR on Days 15 to 17. On Days 4 (50 mg SR dose) and 11 (300 mg SR dose), patients consumed a standardized high-fat breakfast (two eggs, 2 strips bacon, 2 pieces of toast with approximately 5 g of butter, 75 g of hashed brown potatoes and 150 mL of whole milk) within 10 minutes of their scheduled quetiapine dose. The following table

summarizes the effects of a high fat meal on the pharmacokinetics of quetiapine after administration of 50-mg and 300-mg dose strengths of quetiapine SR.

Table 8: Relative bioavailability of quetiapine SR 50 mg and 300 mg in the fed and fasted states

Dose Parameter	Geometric mean (95% CI)		Mean fed/fasted ratio[a] (90% CI)
	Fasted[b]	Fed[c]	
50 mg SR (n=10)			
AUC^{ss}_{τ}, ng·hr/mL	925.09 (650.78 – 1315.02)	1112.24 (848.82 – 1457.41)	1.20 (1.01 – 1.43)
C^{ss}_{max}, ng/mL	87.83 (59.57 – 129.49)	133.22 (111.44 – 159.27)	1.52 (1.08 – 2.13)
300 mg SR (n=10)			
AUC^{ss}_{τ}, ng·hr/mL	5710.83 (4254.29 – 7666.03)	6966.93 (5479.48 – 8858.15)	1.22 (1.10 – 1.35)
C^{ss}_{max}, ng/mL	470.70 (364.88 – 607.20)	677.92 (551.36 – 833.53)	1.44 (1.24 – 1.68)

[a] Ratio (fed/fasted) based on least-squares means from analysis of variance of log-transformed parameter.
[b] Fasting samples for pharmacokinetic analysis of the 50-mg and 300-mg doses were taken on Days 3 and 10, respectively.
[c] Samples for pharmacokinetic analysis of the 50-mg and 300-mg doses were taken after a high-fat meal on Days 4 and 11, respectively.
CI Confidence interval. SR Sustained release.

The following table summarizes the effects of a low fat meal (2 slices of toast, 2 teaspoons (10g) of jelly (jam), 180 mL (6 fluids ounces) of orange juice, 1 cup (237g) of coffee, 2 tablespoons (30.6 g) of 0.1% (skim) milk and 2 teaspoons (10g) of sugar) on the pharmacokinetics of quetiapine after administration of 50-mg and 300-mg dose strengths of quetiapine SR.

Table 9: Relative bioavailability of quetiapine SR 50 mg and of quetiapine SR 300 mg in the fasted and fed states

	Healthy volunteers, Quetiapine SR 50 mg		Patients, Quetiapine SR 300 mg	
Parameter	**Fasted**	**Fed**	**Fasted**	**Fed**
AUC_{ss} , ng×hr/mL				
N	20	20	13	13
Geometric mean[a]	442.8	457.1	2906	2764
95% confidence interval	(419.7-467.1)	(433.3-482.3)	(2771-3049)	(2635-2900)
Mean fed/fasted ratio	1.03		0.95	
90% confidence interval	(0.97-1.10)		(0.90-1.01)	
$C_{ss,max}$, ng/mL				
N	20	20	13	13
Geometric mean[a]	38.1	41.4	243	235
95% confidence interval	(34.8-41.8)	(37.8-45.4)	(215-273)	(208-265)
Mean fed/fasted ratio	1.09		0.97	
90% confidence interval	(0.97-1.21)		(0.84-1.11)	

[a] Based on least square mean from analysis of variance for log-transformed parameters
SR Sustained release.

2.5.3. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

The sponsor developed an in vitro- in vivo correlation (IVIVC) model which formed the basis for dissolution specification during the product development including stability assessment.

2.5.3.1. Is the IVIVC model developed acceptable and can it be used to predict in vivo concentrations based on in vitro dissolution?

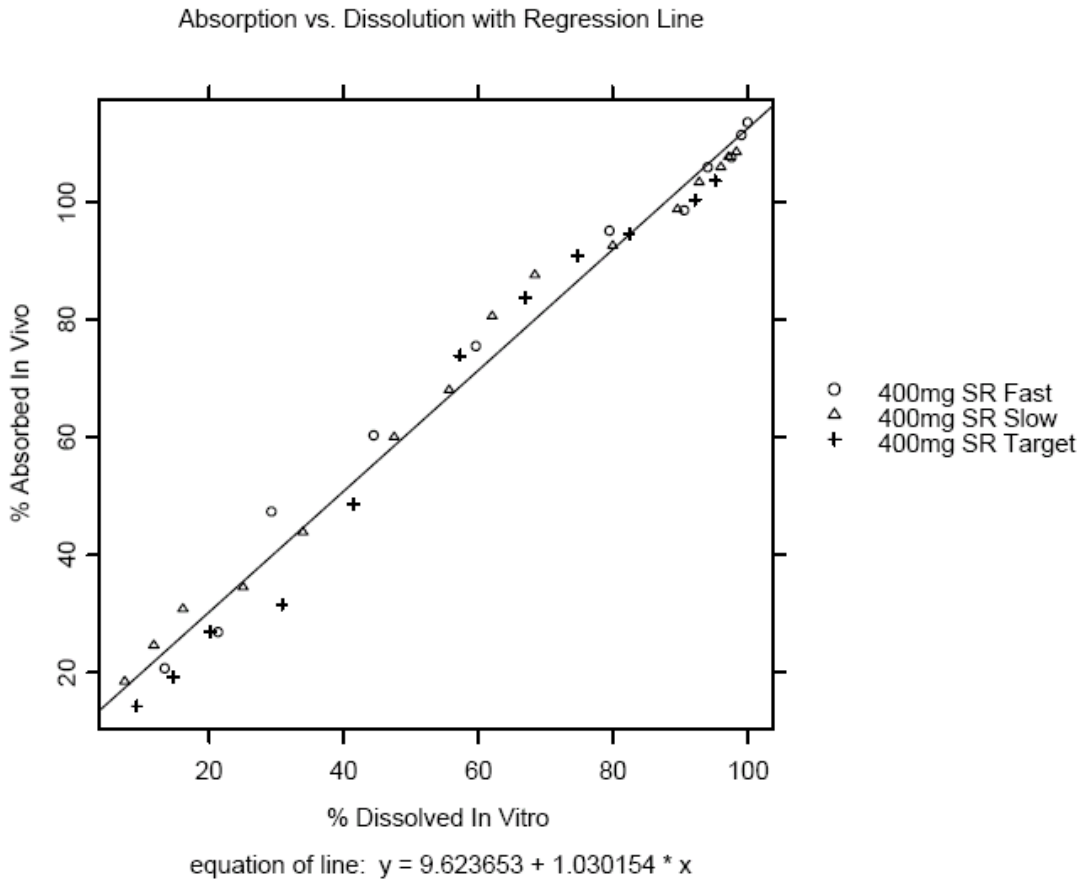
The developed IVIVC model satisfies the criteria for both internal and external predictability and is acceptable. The Level A IVIVC can be used to support the inclusion of additional manufacturing sites, as a surrogate for bioequivalence studies to support biowaiver for future relevant SUPAC/variation changes.

A simple linear model with a slope and intercept term was chosen to describe the IVIVC for Seroquel SR tablet formulations. The internal predictability of the Seroquel SR IVIVC model was assessed by predicting the average *in vivo* concentration-time profile for each of the three 400 mg SR formulations (fast, target, slow) used to develop the model. The %PE was less than 10% for each of the formulations, with the highest AUC(0-t) %PE being only 3.7% for the SR-F and the

highest Cmax %PE being only 8.7% for the SR-T. The MAPPE was 4.4% and 3.1% for Cmax and AUC(0-t), respectively. The Seroquel SR IVIVC model was also evaluated in terms of external predictability, using the average quetiapine concentration-time data for a 50 mg SR formulation. For both AUC(0-t) and Cmax, the %PE was less than 10%, satisfying the criteria for external predictability.

The following figure demonstrates absorption vs dissolution with regression line

Fig K: Average % absorbed in vivo vs. average % dissolved in vitro for 400 mg Seroquel SR tablet formulations



The following graphs show the observed and predicted concentrations for the quetiapine SR 400 and 50 mg formulations.

Fig L: IVIVC Model-predicted and average observed quetiapine concentration-time profiles for 400 mg Seroquel SR tablet formulations

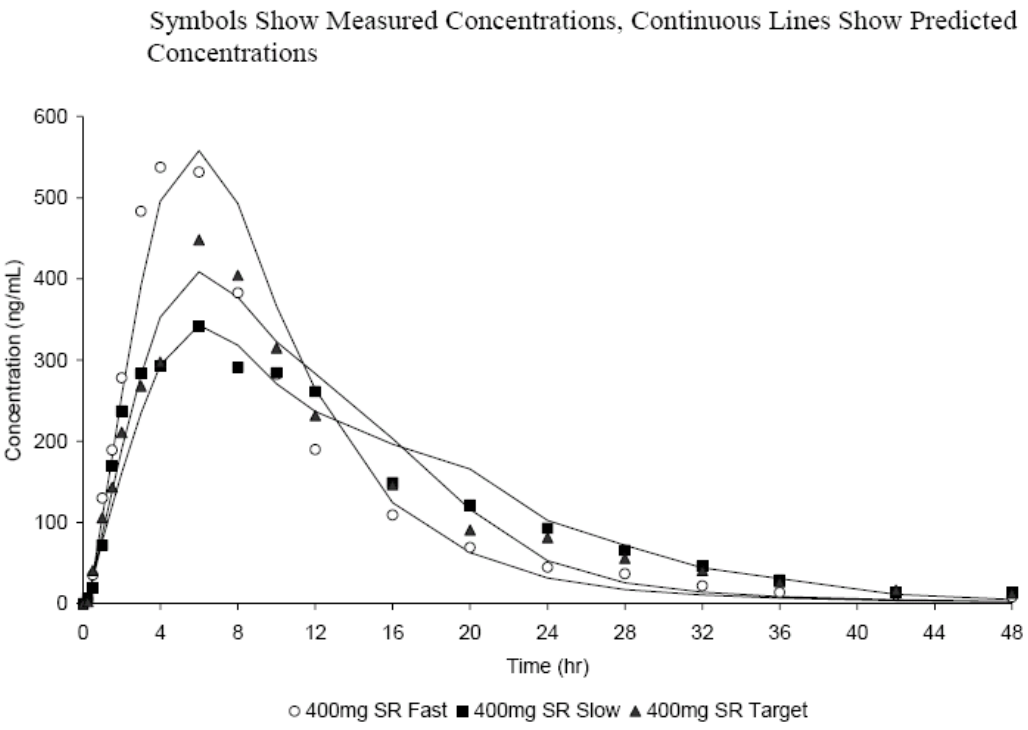
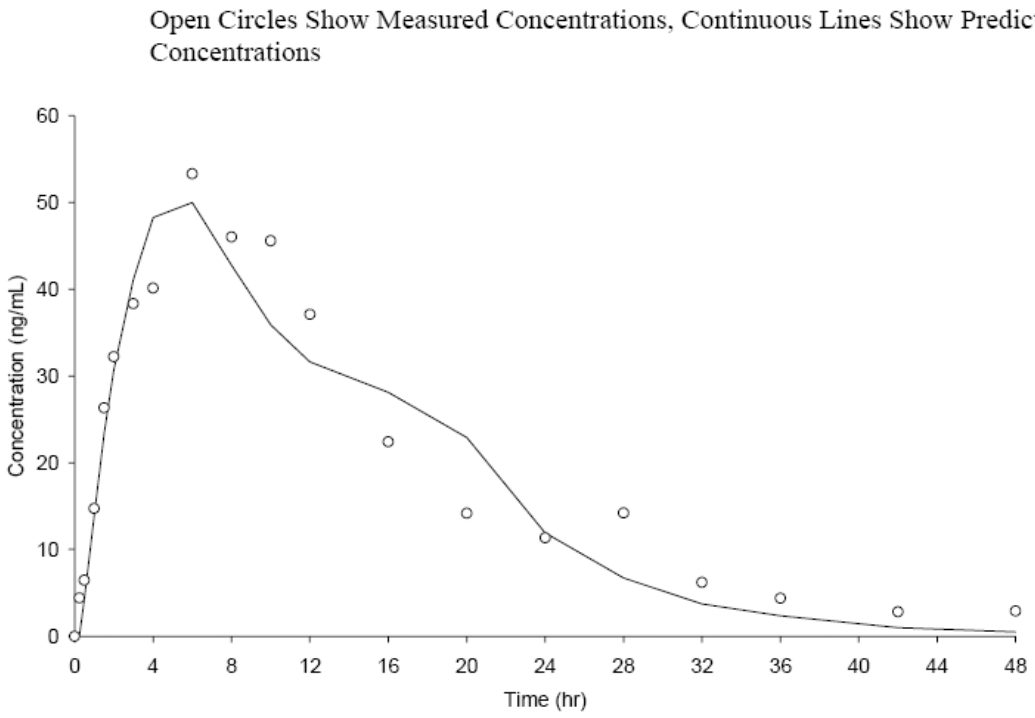


Fig M: IVIVC Model-predicted and average observed quetiapine concentration-time profiles for 50 mg Seroquel SR tablet formulation.



The following tables provide the internal and external validation for the IVIVC model.

Table 10: Internal validation statistics for Seroquel SR IVIVC model

	C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)			
Treatment	Observed	Predicted	Ratio	% PE	Observed	Predicted	Ratio	% PE
400mg SR Fast	537.39	558.16	1.04	3.86	5917.36	6135.41	1.04	3.68
400mg SR Slow	341.49	343.11	1.00	0.48	5806.90	6015.98	1.04	3.60
400mg SR Target	447.88	408.80	0.91	8.73	5971.09	5850.94	0.98	2.01
MAPPE				**4.36**				**3.10**

%PE Prediction error MAPPE Mean absolute prediction error

Table 11: External validation statistics for Seroquel SR IVIVC model

	C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)			
Treatment	Observed	Predicted	Ratio	% PE	Observed	Predicted	Ratio	% PE
50mg SR Target	53.32	51.17	0.96	4.04	869.38	819.91	0.94	5.69

2.5.3.2. Is the proposed dissolution method and specification acceptable?

The proposed dissolution method and specification are acceptable. The dissolution acceptance criteria is supported by the Level A IVIVC developed.

Using the IVIVC model, the predicted upper and lower Cmax and AUC values for the profiles defined by the SEROQUEL SR upper and lower dissolution acceptance criteria were determined. The values are provided in the following table. The predicted Cmax using the lower acceptance limits is (b) (4) different than the predicted Cmax using the upper acceptance limits. The predicted AUC using the lower acceptance limits is (b) (4) different than the predicted AUC using the upper acceptance limits. These values are within the recommended limits in the Agency's guidance on application of IVIVC in setting dissolution specifications.

Table 12: Predicted AUC and Cmax values for the proposed lower and upper Seroquel SR dissolution specifications

Specification	C_{max} (ng/mL)	C_{max} ratio	AUC (ng·h/mL)	AUC ratio
Lower				(b) (4)
Upper				

The following dissolution method and specification are acceptable for quetiapine SR, 50 mg, 200 mg, 300 mg, and 400 mg strengths. The specification is supported by the Level A IVIVC.

Apparatus	USP Apparatus I (Basket)
Speed	200 rpm
Media	900 mL 0.05M Sodium Citrate and 0.09N Sodium hydroxide (pH 4.8). At 5 hours, pH adjusted to 6.6 with 100 mL medium of 0.05M sodium phosphate and 0.46N sodium hydroxide

Specification:

Not more than (NMT) (b) (4) at 1 hour
(b) (4) at 6 hours
(b) (4) at 12 hours
Not less than (NLT) (b) (4) at 20 hours.

The dissolution method selected is performed using the basket apparatus at a rotation speed of 200 rpm. Initially, 900 mL of dissolution medium consisting of 0.05 M sodium citrate and 0.09 N sodium hydroxide are placed in each vessel. The pH of this medium is 4.8. At 5 hours, 100 mL of a medium consisting of 0.05 M sodium phosphate and 0.46 N sodium hydroxide are added to each vessel to bring the pH of the medium to 6.6 for the final duration of the dissolution analysis. Rotation speed of 200 rpm was used to provide complete release; (b) (4) rpm did not provide complete release as shown in the figure below:

The rotation speed of 200 rpm is high for USP Apparatus 1 (Basket). But, the in vitro release using this method was similar to the in vivo release of quetiapine.

2.6. Analytical Methods

2.6.1. What bioanalytical methods are used to assess concentrations?

All assay methods used to determine plasma concentrations of quetiapine and its metabolites in the studies were specific for the analytes measured. The assay employed methods that included quetiapine and metabolite extraction from alkalinized plasma by ethyl acetate, and detection by high performance liquid chromatography and tandem mass spectrometry. These assay methods provided accurate and reproducible results, with appropriate linearity and sensitivity. The within day and between day percent coefficient of variation (%CV) were less than 15%. The analytical methods are acceptable. The precision and accuracy of the assay methods are acceptable. Quality control data from each study are summarized in Analytical Methods in the Appendix.

3. Detailed Labeling Recommendations

a) The following language is recommended to be added to the Dosage and Administration section of the label.

It is recommended that Seroquel XR be taken without food or with a light meal (about 300 calories)

b) The following revision (<u>double underline</u>) of the text in the in Clinical Pharmacology Section under "Absorption" is recommended.

(b) (4)

4. Appendices

Package Insert (Proposed)
Clinical Pharmacology and Biopharmaceutics Individual Study Reviews
Consult Review (Pharmacometric Review)

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

Title (5077IL/0086): Multiple dose Pharmacokinetics and the Effect of Food and Sustained-Release (SR) Quetiapine Fumarate (Seroquel™)

Objective: To evaluate the multiple-dose pharmacokinetics of quetiapine at 5 dose levels (100 mg, 200 mg, 300 mg, 600 mg, and 800 mg) achieved by the administration of 1, 2, or 3 tablets of SR formulation (50 mg SR, 200 mg SR, or 300 mg SR); and to evaluate the effect of food on the bioavailability of SR Formulation tablets (200 mg SR and 300 mg SR). 2) To evaluate the safety and tolerability of multiple 800-mg doses of quetiapine fumarate administered as tablets of SR formulation (one 200-mg and two 300-mg tablets)

Study Design: The study was a single-center, open-label, multiple-dose, within-subject dose escalation, comparison trial to determine the pharmacokinetics with and without food; safety; and tolerability. The mean age of the 12 evaluable subjects were 40 ± 8.4 years. Most (15/16 enrolled) had a diagnosis of paranoid schizophrenia. Subjects were given oral doses of quetiapine fumarate once daily on Days 3 through 21 in the fasting state at approximately 0600, except for Days 10 and 14, when they received medication with the standardized high-fat breakfast (2 eggs, 2 strips of bacon, 2 pieces of toast with approximately 5 gm of butter, 75 gm of hashed brown potatoes and 150 mL of whole milk) at 0700. Dosages were 50 mg on Day 3, 100 mg on Days 4 to 6, 200 mg on days 7 to 10, 300 mg on Days 11 to 14, 400 mg on Day 15, 600 mg on Days 16 to 18, and 800 mg on Days 19 to 21. On Days 6, 9, 13, 18, and 21, subjects were to consume no food for 4 hours after taking their trial medication. The sponsor supplied quetiapine tablets in 3 strengths: 50 mg (formulation number F12414, lot number N83035, batch number ST72040-020-FA01), 200 mg (formulation number F12377, lot number SN83036, batch number ST72039-FA01), and 300 mg (formulation number F12359, lot number N83009, batch number ST72038-020-FA01).

It was predicted, based on previous study, that a sample size of 12 subjects was sufficient to detect a 25% difference (with a power of 80% and a significance level of 0.10) in the dose-normalized AUCssτ of quetiapine between any of the 5 dosage strengths of SR formulation.

Data Analysis: Pharmacokinetic parameters were obtained for quetiapine, ICI 213,841 (the inactive sulfoxide metabolite of quetiapine), and ICI 214,227 (the active 7-hydroxy metabolite of quetiapine) from the concentration-versus-time data obtained over the 24-hour dosing interval following the quetiapine fumarate dose administered on Days 6, 9, 10, 13, 14, 18, and 21 using noncompartmental methods

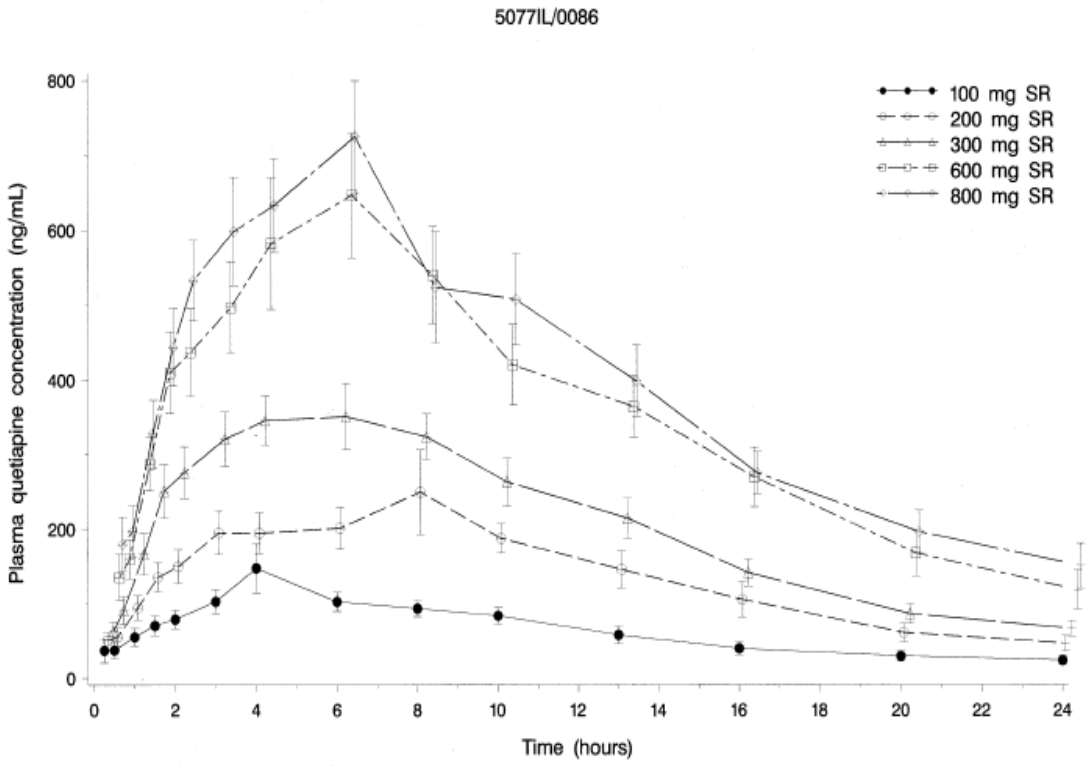
For analysis of dose proportionality, AUCss was the primary measurement, and Cmaxss was the secondary measurement; assessment of dose proportionality was based on the parameters for quetiapine only, not those for the metabolites. Dose proportionality was examined using linear regression of log-transformed AUCss and Cmaxss on log dose adjusted for subject. For the test of linearity the statistical treatment included fitting the data to a power model of the form $AUC = \alpha(DOSE)^{\beta}$, where α is the proportionality constant and β is the slope. After taking logs to linearize, dose proportionality was examined using linear regression of log-transformed AUCssτ (and Cmaxss) on log dose and testing for a null hypothesis in which the slope equaled 1. Mean Cminss values for quetiapine were analyzed by ANOVA using the effects of subject and trial day as factors to evaluate the steady-state conditions for each dose group. Steady state was examined on Days 6, 9, 13, 18, and 21. The effect of food on the bioavailability of quetiapine was assessed by constructing 90% confidence intervals (CI) for the fed/fasted ratios of AUCssτ and Cmaxss

values, based on the least-square means from the analysis of variance (ANOVA) of log-transformed AUCssτ and Cmaxss values with effects for subject and fed/fasted state. The protocol stated that if the 90% CIs for the fed: fasted ratios were within the interval 0.8 to 1.25 for AUCssτ and within the interval 0.7 to 1.43 for Cmax, then the bioavailability of quetiapine could be assumed to be similar under fed and fasted conditions; i.e., food would have had no clinically significant effect on the bioavailability of quetiapine. The analysis was performed separately for the 200-mg and 300-mg dose groups.

Analytical Method: The plasma samples were analyzed for concentrations of quetiapine, its hydroxylated metabolite, ICI214,227, and its sulfoxide metabolite, ICI213,841. The method is a validated procedure with extraction of quetiapine, ICI 214,227 and ICI 213,841 from alkalinized human plasma using ethyl acetate, and detection by HPLC with atmospheric pressure chemical ionization and tandem mass spectrometry. The method has a quantitation limit of 2.50 ng/mL with an applicable range to 5000 ng/mL by sample dilution with plasma. Recoveries of quetiapine, ICI 214,227 and ICI 213,841 from spiked plasma during method validation averaged 104%, 94.4% and 92.4%, respectively.

Results: The following figure contains the mean plasma concentration time profile for quetiapine.

Figure 1 Mean (SEM) plasma quetiapine concentrations (ng/mL) for the 100-, 200-, 300-, 600-, and 800-mg doses of the sustained-release (SR) formulation given in the fasted state



The following table contains the morning trough plasma concentrations of quetiapine.

Morning trough plasma concentrations of quetiapine from sustained-release (SR) formulation received in the fasted state on Days 5, 6, 8, 9, 12, 13, 17, 18, 20 and 21 (N=12)

Quetiapine dose (trial day)	Mean plasma concentration (ng/ml)	SEM
100 mg (Day 5)	29.31	7.21
100 mg (Day 6)	24.06	6.04
200 mg (Day 8)	48.09	8.51
200 mg (Day 9)	47.20	10.55
300 mg (Day 12)	70.99	18.81
300 mg (Day 13)	67.33	10.30
600 mg (Day 17)	124.20	26.65
600 mg (Day 18)	119.12	26.18
800 mg (Day 20)	157.12	40.92
800 mg (Day 21)	151.48	29.61

SEM Standard error of the mean.

The results showed no significant differences in pre-dose plasma concentrations of quetiapine, thus indicating that the pharmacokinetic parameters were calculated under steady-state conditions.

The following table presents pharmacokinetic parameters for quetiapine at the five dosages and two treatment conditions (fed and fasted states).

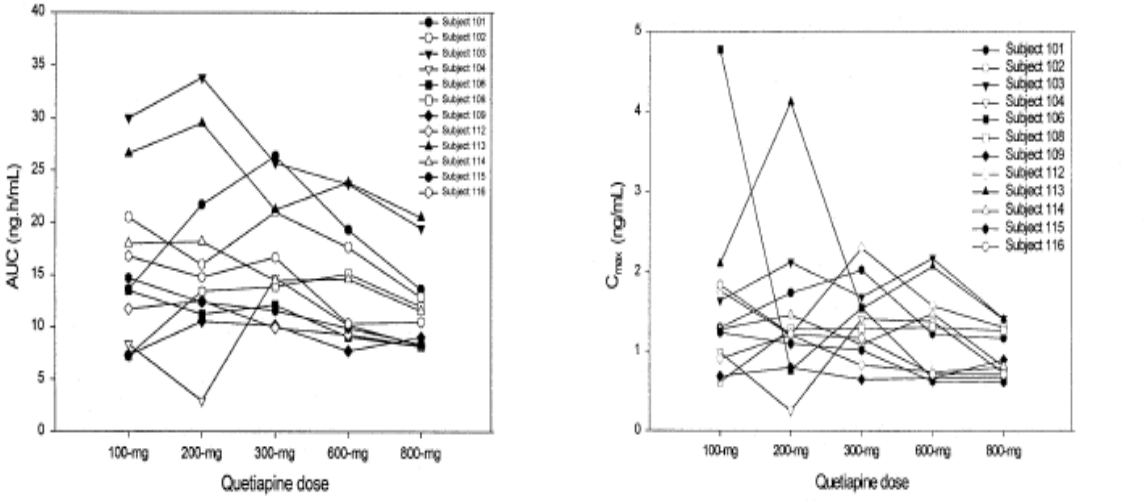
Pharmacokinetic parameters for quetiapine from sustained-release (SR) formulation at dosages of 100, 200, 300, 600 and 800 mg/day.

	Daily quetiapine dosage (treatment condition) (Trial day)						
Pharmacokinetic parameter	100 mg (fasted) (Day 6)	200 mg (fasted) (Day 9)	200 mg (fed) (Day 10)	300 mg (fasted) (Day 13)	300 mg (fed) (Day 14)	600 mg (fasted) (Day 18)	800 mg (fasted) (Day 21)
AUC_{τ}^{ss} (ng·h/ml)							
N	12	12	12	12	12	12	12
Mean	1568.58	3282.33	3279.33	4945.00	4799.17	8532.50	9492.50
SEM	208.94	489.82	469.64	499.91	568.22	997.43	985.69
C_{max}^{ss} (ng/ml)							
N	12	12	12	12	12	12	12
Mean	158.80	286.42	350.58	411.42	503.92	726.17	782.92
SEM	31.87	55.95	42.90	41.56	43.61	94.91	70.36
t_{max} (h)							
N	12	12	12	12	12	12	12
Mean	4.71	6.85	4.41	5.01	5.37	5.58	4.96
SEM	0.74	0.93	1.07	0.71	0.66	0.57	0.64
λ_Z (1/h)							
N	10	12	12	12	12	12	12
Mean	0.114	0.123	0.123	0.111	0.136	0.119	0.100
SEM	0.017	0.009	0.008	0.010	0.005	0.011	0.017
$t_{½}$ (h)							
N	10	12	12	12	12	12	12
Mean	7.41	6.05	5.91	6.84	5.16	6.46	9.87
SEM	1.09	0.54	0.36	0.60	0.19	0.65	1.95

N Number of subjects.
SEM Standard error of the mean.

The figure presents dose-normalized AUCsst and Cmaxss values for quetiapine administered in the fasted stated at each of the doses tested.

Figure 3 Individual dose-normalized AUC_{τ}^{ss} and C_{max}^{ss} values for the 100-, 200-, 300-, 600-, and 800-mg doses of the sustained-release (SR) formulation of quetiapine given in the fasted state



The following table presents the values calculated for determination of dose proportionality based on the power model.

Determination of dose proportionality for quetiapine sustained-release (SR) formulation.

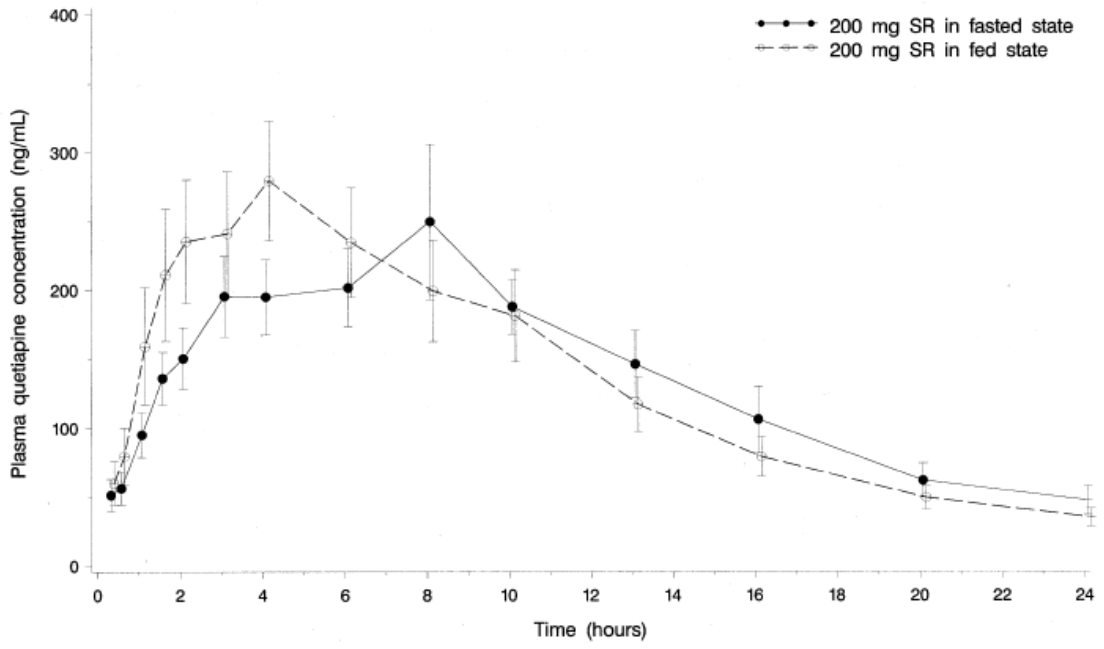
Parameter (units)	Estimate of slope	SE	95% CI of estimate		p-value of H0: slope=1	Estimate of intercept α^a
AUC^{ss}_{τ} (ng·h/ml)	0.90	0.076	0.75	1.06	0.207	13.61[a]
C^{ss}_{max} (ng/ml)	0.85	0.083	0.68	1.01	0.068	1.16[a]

[a] Based on power model AUC^{ss}_{τ} (or C^{ss}_{max})=α·(DOSE)β, where β=1 and the estimate of α (the intercept) is derived from the antilog of the average of log dose-normalized values (AUC^{ss}_{τ} and C^{ss}_{max}, doses combined).
CI Confidence interval, H0 Null hypothesis, SE Standard error, SR Sustained release formulation.

From the above table, it is observed that the estimate of the slope for $AUC_{ss\tau}$ is not significantly different from unity (slope=0.9, p-value 0.207), meaning, AUC_{τ} α DOSE or $AUC_{ss\tau}$=α.DOSE, where the estimate of the constant of proportionality α (also the intercept) is derived from the antilog of the average observed log dose-normalized AUC_{τ} values. Similarly, the slope for C_{max} is not significantly different from unity (slope=0.85, p-value 0.068). This suggests that the pharmacokinetics of quetiapine are linear in the dose range studied following administration of the sustained release tablets.

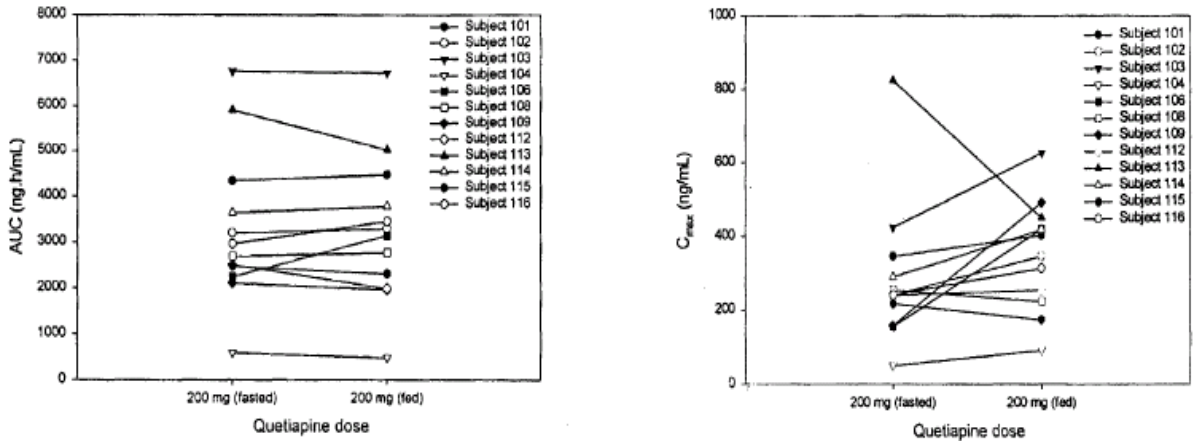
Food Effect.: The following figure shows mean plasma quetiapine concentrations during the 24-hour interval after dose administration for the 200-mg dosage in the fasted and fed states.

Mean (SEM) plasma quetiapine concentrations (ng/mL) for the 200-mg dose of the sustained release (SR) formulation given in the fasted state and in the fed state

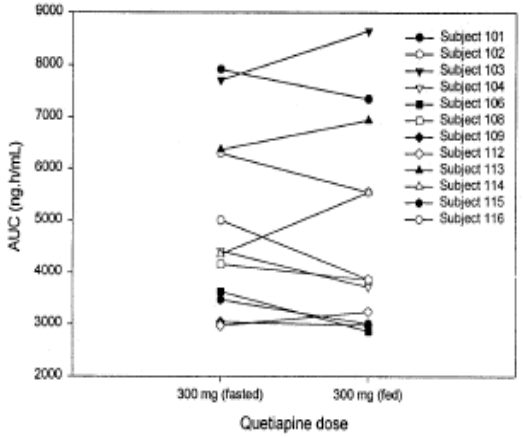


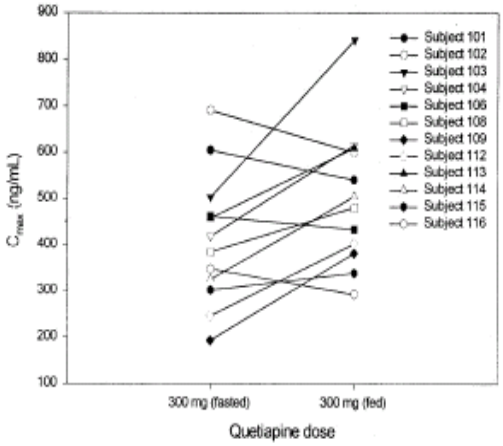
The following figure shows the individual AUC_{τ} and C_{max} values for the 200-mg dose of quetiapine given in the fed and fasted states.

Individual AUCt and Cmax values for the 200-mg dose of the sustained-release (SR) formulation of quetiapine given in the fed state (Day 10) and the fasted state (Day 9)



Individual AUC and Cmax values for the 300-mg dose of the sustained-release (SR) formulation of quetiapine given in the fed state (Day 14) and the fasted state (Day 13)





The following tables present the comparison of the pharmacokinetic parameters of quetiapine administered as the 200-mg SR formulation in the fed state or as the 200-mg SR formulation in the fasted state. And the comparison of the pharmacokinetic parameters of quetiapine administered as the 300-mg SR-C formulation under fed conditions or as the 300-mg SR-C formulation under fasted conditions.

Comparison of pharmacokinetic parameters for quetiapine administered as the 200-mg SR formulation under fed and fasted conditions

Parameter (units)	Quetiapine dose and condition (Trial day)		Ratio or difference of means[a]	90 % CI of ratio or difference
	200 mg SR (fed) (Day 10)	200 mg SR (fasted) (Day 9)		
AUC_{τ}^{ss} (ng · h/ml) geometric mean (N) (95% CI)	2804.84 (12) (1831.11 to 4296.36)	2839.04 (12) (1916.28 to 4206.16)	0.99[b]	0.80 to 1.22[c]
C_{max}^{ss} (ng/ml) geometric mean (N) (95% CI)	314.76 (12) (224.83 to 440.68)	237.76 (12) (155.92 to 362.56)	1.32[b]	1.00 to 1.74[c]
t_{max} (h) median (N) (range)	3.98 (12) (1 to 13)	6.99 (12) (3 to 13)	NA	NA
$t_{½}$ (h) arithmetic mean (N) (SEM)	5.91 (12, 0.36)	6.05 (12, 0.54)	–0.15[d]	–1.09 to 0.80

[a] Based on ratio/difference of least squares means.
[b] Ratio of quetiapine formulations SR (fed) to SR (fasted).
[c] Based on log-transformed data.
[d] Difference between formulations SR (fed) and SR (fasted).
CI Confidence interval.
NA Not applicable.
SEM Standard error of the mean.

Comparison of pharmacokinetic parameters for quetiapine administered as the 300-mg SR formulation under fed and fasted conditions

Parameter (units)	Quetiapine dose and condition (Trial day)		Ratio or difference of means[a]	90 % CI of ratio or difference
	300 mg SR-C (fed) (Day 14)	300 mg SR-C (fasted) (Day 13)		
AUC_{τ}^{ss} (ng · h/ml) geometric mean (N) (95% CI)	4466.24 (12) (3487.56 to 5719.55)	4684.02 (12) (3770.6 to 5818.7)	0.95[b]	0.77 to 1.18[c]
C_{max}^{ss} (ng/hml) geometric mean (N) (95% CI)	484.14 (12) (401.3 to 584.08)	388.0 (12) (307.75 to 489.17)	1.25[b]	0.95 to 1.64[c]
t_{max} (h) median (N) (range)	5.98 (12) (1.48 to 10)	5.00 (12) (2 to 10)		
$t_{½}$ (h) arithmetic mean (N, SEM)	5.16 (12, 0.19)	6.84 (12, 0.6)	–1.68[d]	–2.62 to –0.74

[a] Based on ratio/difference of least squares means.
[b] Ratio of quetiapine formulations SR (fed) to SR (fasted).
[c] Based on log-transformed data.
[d] Difference between formulations SR (fed) and SR (fasted).
CI Confidence interval.
NA Not applicable.
SEM Standard error of the mean.

The tables indicate that while the 90% CI for the ratio of AUC_{τ} in the fed state to AUC_{τ} in the fasted state was inside the 0.8 to 1.25 interval, for the 200-mg strength (0.80 to 1.22), it was not contained within the interval for the 300-mg dose of formulation SR-C. The 90% CI for the ratio of C_{max} in the fed state to C_{max} in the fasted state extended beyond the protocol specified limit of 0.70 to 1.43. Under fed conditions, the value for C_{max} of quetiapine increased, on average, by 32.% for the 200-mg dose and by 25% for the 300-mg dose relative to C_{max} in the fasted state. Food appeared to have no consistent effect on median t_{max}.

Pharmacokinetic Summary: The results from the analysis of the steady-state C_{max} and AUC_{τ} showed that both parameters increased in proportion to dose. This indicates that the pharmacokinetics of quetiapine were linear following the administration of quetiapine SR tablets.

The effects of food on the bioavailability of the SR tablets were examined using 200- and 300-mg tablet strengths. The results showed that food had no significant effect on quetiapine AUC_{τ} ie, the extent of absorption, with mean values being reduced by 1% and 5% in the fed state compared with the fasted state, for the 200-mg and 300-mg dose strengths, respectively. Increases in C_{max} of 32% and 25% were noted for the 200 and 300 mg tablet strengths, respectively.

Safety Summary: The following is the summary of adverse events observed in the trial as reported by the sponsor. No deaths or serious adverse events occurred during this trial. Ten subjects (63%) had 1 or more adverse events during the treatment period. The most common adverse events were headache and pain. Two subjects had dyspepsia while taking the 800-mg dosage. This adverse event is within the known profile of quetiapine. No relationship was seen between the dose of quetiapine and the occurrence of other adverse events. Two subjects had mild tachycardia attributed to treatment with quetiapine during the trial. Manually read ECGs showed that mean heart rates increased by 6 bpm between baseline and the Day 19 pre-dose assessment and by 22 bpm between the screening and post-dose assessments on Day 19. The higher heart rate at the time of peak plasma quetiapine concentrations is consistent with the known profile of quetiapine. No subjects had QT_cF values that exceeded 0.500. No clinically significant change in QT_cF occurred between baseline and either of the Day 19 ECGs. Mean QT_cF intervals before and after 800-mg doses of quetiapine, when compared with baseline, did not suggest that quetiapine had any effect of prolonging the QT interval. Changes in vital signs during the trial were generally small, except for increases in pulse rate from pre-dose to post-dose assessments, which averaged approximately 11 bpm. Post-dose assessments showed small decreases in systolic and diastolic blood pressure, as well as the increases in pulse rate, compared with pre-dose assessments. No clear effect of trial treatment on postural changes in blood pressure was seen. Overall, the safety findings in this trial showed no new safety issues related to treatment with quetiapine.

The pharmacokinetics of quetiapine were proportional to the dose after the administration of quetiapine SR in doses from 100 to 800 mg/day. Comparison of the bioavailability of 200-mg and 300-mg doses of the SR formulation of quetiapine under fed and fasted conditions showed significant effects of food on biovailability with either dosage strength. Safety and tolerability data raised no new issues related to treatment with quetiapine.

Reviewer's comments: *The pharmacokinetics of quetiapine was proportional to dose in a dose range of 100 mg to 800 mg. High fat meal (standard FDA meal) had a significant effect of the exposure of quetiapine.*

Appendix

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Table T4.1.1 Day 6 Quetiapine Pharmacokinetic Parameters
Mean and Standard Error (SEM)

Dose	Subject	Cmax (ng/ml)	Tmax (h)	AUC(0-24) (ng*h/ml)	Lambda Z (L/h/kg)	T-half (h)	DN_AUC (0-24) (ng*h/ml)	DN_Cmax (ng/ml)
100-mg fasted	101	129.000	8.000	1360.000	0.164	4.220	13.600	1.290
	102	176.000	3.970	2050.000	0.151	4.600	20.500	1.760
	103	163.000	3.000	3000.000	0.070	9.900	30.000	1.630
	104	98.100	10.000	834.000	C	C	8.340	0.981
	106	477.000	4.000	1350.000	0.200	3.460	13.500	4.770
	107	112.000	2.000	1740.000	0.131	5.290	17.400	1.120
	108	61.400	4.000	722.000	C	C	7.220	0.614
	109	67.900	8.000	727.000	0.119	5.820	7.270	0.679
	110	97.700	6.000	1110.000	0.163	4.260	11.100	0.977
	111	71.900	4.000	854.000	0.190	3.640	8.540	0.719
	112	90.200	4.000	1170.000	0.077	9.000	11.700	0.902
	113	210.000	3.000	2660.000	0.063	11.000	26.600	2.100
	114	127.000	1.500	1800.000	0.082	8.440	18.000	1.270
	115	123.000	3.000	1470.000	0.052	13.500	14.700	1.230
	116	183.000	4.000	1680.000	0.167	4.140	16.800	1.830
	N	12	12	12	10	10	12	12
	MEAN	158.800	4.706	1568.583	0.114	7.408	15.686	1.588
	SEM	31.872	0.735	208.935	0.017	1.089	2.089	0.319
	CV(%)	69.527	54.091	46.142	45.952	46.471	46.142	69.527

NOTE: DN_AUC(0-24) IS DOSE-NORMALIZED AUC
NOTE: DN_Cmax IS DOSE-NORMALIZED Cmax
NOTE: C NOT CALCULATED

NOTE: SUBJECTS 107, 110 AND 111 HAVE BEEN EXCLUDED FROM CALCULATION OF SUMMARY STATISTICS

Table T4.1.2 Day 9 Quetiapine Pharmacokinetic Parameters
Mean and Standard Error (SEM)

Dose	Subject	Cmax (ng/ml)	Tmax (h)	AUC(0-24) (ng*h/ml)	Lambda Z (L/h/kg)	T-half (h)	DN_AUC (0-24) (ng*h/ml)	DN_Cmax (ng/ml)
200-mg fasted	101	345.000	3.000	4340.000	0.083	8.310	21.700	1.725
	102	240.000	7.980	3200.000	0.122	5.680	16.000	1.200
	103	424.000	6.000	6760.000	0.140	4.940	33.800	2.120
	104	50.000	13.000	588.000	0.138	5.020	2.940	0.250
	106	155.000	10.000	2240.000	0.114	6.080	11.200	0.775
	107	275.000	6.050	2960.000	0.108	6.430	14.800	1.375
	108	254.000	8.000	2690.000	0.174	3.990	13.450	1.270
	109	158.000	10.000	2100.000	0.134	5.180	10.500	0.790
	110	C	C	C	C	C		
	111	C	C	C	C	C		
	112	240.000	6.000	2500.000	0.151	4.590	12.500	1.200
	113	824.000	8.000	5900.000	0.066	10.600	29.500	4.120
	114	289.000	3.000	3640.000	0.118	5.860	18.200	1.445
	115	217.000	4.000	2470.000	0.136	5.090	12.350	1.085
	116	241.000	3.170	2960.000	0.095	7.310	14.800	1.205
	N	12	12	12	12	12	12	12
	MEAN	286.417	6.846	3282.333	0.123	6.054	16.412	1.432
	SEM	55.953	0.931	489.822	0.009	0.536	2.449	0.280
	CV(%)	67.673	47.096	51.695	24.548	30.667	51.695	67.673

NOTE: DN_AUC(0-24) IS DOSE-NORMALIZED AUC
NOTE: DN_Cmax IS DOSE-NORMALIZED Cmax
NOTE: C NOT CALCULATED

NOTE: SUBJECTS 107, 110 AND 111 HAVE BEEN EXCLUDED FROM CALCULATION OF SUMMARY STATISTICS

Table T4.1.3 Day 10 Quetiapine Pharmacokinetic Parameters
Mean and Standard Error (SEM)

Dose	Subject	Cmax (ng/ml)	Tmax (h)	AUC(0-24) (ng*h/ml)	Lambda Z (L/h/kg)	T-half (h)	DN_AUC (0-24) (ng*h/ml)	DN_Cmax (ng/ml)
200-mg fed	101	402.000	6.000	4470.000	0.114	6.060	22.350	2.010
	102	346.000	3.980	3290.000	0.120	5.760	16.450	1.730
	103	626.000	4.000	6720.000	0.092	7.500	33.600	3.130
	104	91.000	2.980	472.000	0.107	6.500	2.360	0.455
	106	419.000	10.000	3140.000	0.108	6.430	15.700	2.095
	107	C	C	C	C	C		
	108	223.000	13.000	2770.000	0.176	3.930	13.850	1.115
	109	491.000	1.480	1960.000	0.154	4.500	9.800	2.455
	110	C	C	C	C	C		
	111	C	C	C	C	C		
	112	254.000	3.980	1980.000	0.172	4.040	9.900	1.270
	113	450.000	1.000	5020.000	0.131	5.300	25.100	2.250
	114	418.000	1.000	3780.000	0.094	7.360	18.900	2.090
	115	174.000	1.500	2300.000	0.094	7.340	11.500	0.870
	116	313.000	4.000	3450.000	0.112	6.170	17.250	1.565
	N	12	12	12	12	12	12	12
	MEAN	350.583	4.410	3279.333	0.123	5.908	16.397	1.753
	SEM	42.900	1.068	469.636	0.008	0.361	2.348	0.214
	CV(%)	42.389	83.910	49.610	23.922	21.157	49.610	42.389

NOTE: DN_AUC(0-24) IS DOSE-NORMALIZED AUC
NOTE: DN_Cmax IS DOSE-NORMALIZED Cmax
NOTE: C NOT CALCULATED

NOTE: SUBJECTS 107, 110 AND 111 HAVE BEEN EXCLUDED FROM CALCULATION OF SUMMARY STATISTICS

Table T4.1.4 Day 13 Quetiapine Pharmacokinetic Parameters
Mean and Standard Error (SEM)

Dose	Subject	Cmax (ng/ml)	Tmax (h)	AUC(0-24) (ng*h/ml)	Lambda Z (L/h/kg)	T-half (h)	DN_AUC (0-24) (ng*h/ml)	DN_Cmax (ng/ml)
300-mg fasted	101	605.000	3.000	7910.000	0.114	6.080	26.367	2.017
	102	691.000	6.000	6300.000	0.172	4.020	21.000	2.303
	103	503.000	6.000	7710.000	0.097	7.140	25.700	1.677
	104	419.000	4.000	4420.000	0.094	7.350	14.733	1.397
	106	462.000	8.000	3630.000	0.090	7.730	12.100	1.540
	107	C	C	C	C	C		
	108	385.000	6.000	4160.000	0.124	5.610	13.867	1.283
	109	193.000	10.000	3040.000	0.094	7.340	10.133	0.643
	110	C	C	C	C	C		
	111	C	C	C	C	C		
	112	246.000	4.000	2970.000	0.108	6.400	9.900	0.820
	113	458.000	3.000	6370.000	0.062	11.100	21.233	1.527
	114	325.000	2.000	4350.000	0.071	9.740	14.500	1.083
	115	302.000	6.080	3470.000	0.180	3.860	11.567	1.007
	116	348.000	2.000	5010.000	0.120	5.760	16.700	1.160
	N	12	12	12	12	12	12	12
	MEAN	411.417	5.007	4945.000	0.111	6.844	16.483	1.371
	SEM	41.564	0.708	499.907	0.010	0.604	1.666	0.139
	CV(%)	34.997	48.986	35.020	32.172	30.595	35.020	34.997

NOTE: DN_AUC(0-24) IS DOSE-NORMALIZED AUC
NOTE: DN_Cmax IS DOSE-NORMALIZED Cmax
NOTE: C NOT CALCULATED

NOTE: SUBJECTS 107, 110 AND 111 HAVE BEEN EXCLUDED FROM CALCULATION OF SUMMARY STATISTICS

Table T4.1.5 Day 14 Quetiapine Pharmacokinetic Parameters
Mean and Standard Error (SEM)

Dose	Subject	Cmax (ng/ml)	Tmax (h)	AUC(0-24) (ng*h/ml)	Lambda Z (L/h/kg)	T-half (h)	DN_AUC (0-24) (ng*h/ml)	DN_Cmax (ng/ml)
300-mg fed	101	541.000	10.000	7350.000	0.142	4.880	24.500	1.803
	102	601.000	6.000	5550.000	0.130	5.330	18.500	2.003
	103	842.000	4.000	8650.000	0.121	5.750	28.833	2.807
	104	616.000	3.000	3720.000	0.138	5.030	12.400	2.053
	106	434.000	6.000	2870.000	0.166	4.170	9.567	1.447
	107	C	C	C	C	C		
	108	481.000	6.100	3860.000	0.130	5.340	12.867	1.603
	109	382.000	4.000	2980.000	0.131	5.300	9.933	1.273
	110	C	C	C	C	C		
	111	C	C	C	C	C		
	112	403.000	3.980	3240.000	0.165	4.190	10.800	1.343
	113	610.000	5.980	6940.000	0.112	6.190	23.133	2.033
	114	505.000	5.980	5550.000	0.113	6.150	18.500	1.683
	115	339.000	7.970	3010.000	0.149	4.640	10.033	1.130
	116	293.000	1.480	3870.000	0.139	5.000	12.900	0.977
	N	12	12	12	12	12	12	12
	MEAN	503.917	5.374	4799.167	0.136	5.164	15.997	1.680
	SEM	43.612	0.655	568.221	0.005	0.190	1.894	0.145
	CV(%)	29.980	42.247	41.015	12.866	12.768	41.015	29.980

NOTE: DN_AUC(0-24) IS DOSE-NORMALIZED AUC
NOTE: DN_Cmax IS DOSE-NORMALIZED Cmax
NOTE: C NOT CALCULATED

NOTE: SUBJECTS 107, 110 AND 111 HAVE BEEN EXCLUDED FROM CALCULATION OF SUMMARY STATISTICS

Table T4.1.6 Day 18 Quetiapine Pharmacokinetic Parameters
Mean and Standard Error (SEM)

Dose	Subject	Cmax (ng/ml)	Tmax (h)	AUC(0-24) (ng*h/ml)	Lambda Z (L/h/kg)	T-half (h)	DN_AUC (0-24) (ng*h/ml)	DN_Cmax (ng/ml)
600-mg fasted	101	727.000	4.000	11600.000	0.074	9.420	19.333	1.212
	102	940.000	4.000	10600.000	0.141	4.900	17.667	1.567
	103	1300.000	6.000	14200.000	0.088	7.840	23.667	2.167
	104	819.000	6.000	6110.000	0.146	4.760	10.183	1.365
	106	395.000	6.000	5430.000	0.144	4.830	9.050	0.658
	107	C	C	C	C	C		
	108	777.000	8.000	9080.000	0.096	7.200	15.133	1.295
	109	396.000	6.000	4620.000	0.115	6.010	7.700	0.660
	110	C	C	C	C	C		
	111	C	C	C	C	C		
	112	442.000	6.000	5560.000	0.198	3.500	9.267	0.737
	113	1240.000	4.000	14300.000	0.061	11.400	23.833	2.067
	114	880.000	4.000	8770.000	0.122	5.700	14.617	1.467
	115	371.000	10.000	5930.000	0.098	7.090	9.883	0.618
	116	427.000	3.000	6190.000	0.142	4.880	10.317	0.712
	N	12	12	12	12	12	12	12
	MEAN	726.167	5.583	8532.500	0.119	6.461	14.221	1.210
	SEM	94.907	0.570	997.431	0.011	0.652	1.662	0.158
	CV(%)	45.275	35.377	40.495	32.149	34.933	40.495	45.275

NOTE: DN_AUC(0-24) IS DOSE-NORMALIZED AUC
NOTE: DN_Cmax IS DOSE-NORMALIZED Cmax
NOTE: C NOT CALCULATED

NOTE: SUBJECTS 107, 110 AND 111 HAVE BEEN EXCLUDED FROM CALCULATION OF SUMMARY STATISTICS

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Table T4.1.7 Day 21 Quetiapine Pharmacokinetic Parameters
Mean and Standard Error (SEM)

Dose	Subject	Cmax (ng/ml)	Tmax (h)	AUC(0-24) (ng*h/ml)	Lambda Z (L/h/kg)	T-half (h)	DN_AUC (0-24) (ng*h/ml)	DN_Cmax (ng/ml)
800-mg fasted	101	928.000	3.000	10900.000	0.052	13.300	13.625	1.160
	102	1040.000	3.000	10300.000	0.154	4.510	12.875	1.300
	103	1130.000	6.000	15600.000	0.025	27.600	19.500	1.413
	104	583.000	4.000	6580.000	0.093	7.480	8.225	0.729
	106	529.000	6.000	6500.000	0.070	9.840	8.125	0.661
	107	C	C	C	C	C		
	108	1010.000	6.000	9600.000	0.116	5.960	12.000	1.263
	109	710.000	6.000	7210.000	0.107	6.460	9.013	0.888
	110	C	C	C	C	C		
	111	C	C	C	C	C		
	112	635.000	8.000	6530.000	0.218	3.170	8.163	0.794
	113	1120.000	6.000	16400.000	0.045	15.400	20.500	1.400
	114	651.000	2.000	9220.000	0.061	11.400	11.525	0.814
	115	490.000	1.500	6690.000	0.073	9.500	8.363	0.613
	116	569.000	8.000	8380.000	0.181	3.840	10.475	0.711
	N	12	12	12	12	12	12	12
	MEAN	782.917	4.958	9492.500	0.100	9.872	11.866	0.979
	SEM	70.356	0.635	985.692	0.017	1.950	1.232	0.088
	CV(%)	31.130	44.365	35.971	58.861	68.418	35.971	31.130

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NOTE: DN_AUC(0-24) IS DOSE-NORMALIZED AUC
NOTE: DN_Cmax IS DOSE-NORMALIZED Cmax
NOTE: C NOT CALCULATED

NOTE: SUBJECTS 107, 110 AND 111 HAVE BEEN EXCLUDED FROM CALCULATION OF SUMMARY STATISTICS

Title (Protocol No. 5077IL/0097): A Trial to Compare the Steady State Pharmacokinetics of Quetiapine in Men and Women with Selected Psychotic Disorders Following the Administration of Sustained Release (SR) Quetiapine Fumarate (Seroquel) or Immediate Release Quetiapine Fumarate (Seroquel)

Objectives: The primary objective was to compare the steady-state area under the quetiapine concentration-time curve across a 24-hour interval (AUC(0-24)) of sustained release (SR) quetiapine tablets with that of immediate release (IR) quetiapine tablets. The secondary objectives were to compare the IR and the SR tablets with respect to steady-state maximum observed plasma quetiapine concentration (Cmax) following administration of the morning dose; plasma quetiapine concentration at the end of the 24-hour dosing interval (Cmin); time to reach Cmax (tmax); and degree of fluctuation (DF), estimated as (Cmax–Cmin)/Cav*100, with Cav=AUC(0-24h)/24. Additional objectives were to record the tolerability of switching from the IR to the SR formulation and from the SR to the IR formulation at the same daily dose and to document the safety and tolerability of both the IR and the SR formulations.

Study Design: This trial was a single-center, open-label, randomized, 2-period crossover, bioavailability trial. Twenty-four men and women with selected psychotic disorders completed all pharmacokinetic assessments (evaluable subjects). The mean age (range) and weight were 44 (18 -62) years and 87.3 (58.5 to 124.6) kg, respectively. Subjects were randomly assigned to 1 of 2 treatment-sequence groups (IR-SR or SR-IR). All subjects were given 300 mg/day of quetiapine SR on Days 1 and 2 of the Lead-in Period. Subjects assigned to the IR-SR sequence were given 150-mg doses of quetiapine IR twice daily on Days 1 through 4 of Period 1, then switched to single daily 300-mg doses of quetiapine SR on Days 1 through 4 of Period 2. Subjects assigned to the SR-IR sequence were given single daily doses 300-mg of quetiapine SR on Days 1 though 4 of Period 1, then switched to 150-mg doses of quetiapine IR twice daily on Days 1 through 4 of Period 2. All oral antipsychotic medications were discontinued at least 48 hours before Admit Day; however, lithium treatment for underlying psychiatric disorders was permitted during the trial if the lithium dose had been stable for at least 1 month before the subject entered the trial. The following trial medication were supplied by the sponsor: 25-mg tablets of quetiapine fumarate IR (Formulation number F12153,Batch number N73223), 100-mg tablets of quetiapine fumarate IR (Formulation number F12154, Batch number N83085), 300-mg tablets of quetiapine fumarate SR (Formulation number F12527, Batch number 993066)

The following table contains the administration schedule for the study.

Quetiapine administration schedule

Trial period	Day	Total daily quetiapine dose (mg)	Individual quetiapine dose (mg) and formulation[a]			
			IR-SR treatment sequence		SR-IR treatment sequence	
			at 0800	at 2000	at 0800	at 2000
Lead-in	1	300	300 SR	NA	300 SR	NA
	2	300	300 SR	NA	300 SR	NA
Period 1	1	300	150 IR	150 IR	300 SR	NA
	2[b]	300	150 IR	150 IR	300 SR	NA
	3[b]	300	150 IR	150 IR	300 SR	NA
	4[c]	300	150 IR	150 IR	300 SR	NA
Period 2	1	300	300 SR	NA	150 IR	150 IR
	2[b]	300	300 SR	NA	150 IR	150 IR
	3[b]	300	300 SR	NA	150 IR	150 IR
	4[c]	300	300 SR	NA	150 IR	150 IR
	5[d]	NA	NA	NA	NA	NA

[a] Quetiapine SR was given daily as a single 300-mg dose; quetiapine IR was given daily as two 150-mg doses.
[b] Blood samples were collected within 15 minutes before morning quetiapine administration.
[c] Blood samples were collected within 15 minutes before and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 12.5, 13, 13.5, 14, 15, 17, 20, and 24 hours after quetiapine administration. For subjects given the IR formulation, the 12-hour blood sample was collected before the evening dose was given.
[d] Day 5 of Period 2 was discharge day.
IR Immediate release.
SR Sustained release.
NA Not applicable.

On Day 4 of Periods 1 and 2, blood samples were collected before quetiapine administration (within 15 minutes before administration of the morning dose of the SR formulation); at 0.5, 1, 1.5, 2, 3, 5, 8, and 12 hours (taken before administration of the evening dose of the IR formulation); and at 12.5, 13, 13.5, 14, 15, 17, 20, and 24 hours following morning quetiapine administration. On Days 2 and 3 of Period 1 and on Days 2 and 3 of Period 2, blood samples were also obtained within 15 minutes before morning quetiapine administration. Subjects fasted overnight before predose blood samples were collected.

Analytical Method: Plasma samples were analyzed for concentrations using a validated method with extraction of quetiapine from alkalinized human plasma using ethyl acetate and detection by high-performance liquid chromatography (HPLC) with atmospheric pressure chemical ionization and tandem mass spectrometry. The method has a quantitation limit of 2.50 ng/mL with an applicable range to 5000 ng/mL by sample dilution with plasma. The method is specific against known metabolites

of quetiapine, chloral hydrate, benztropine mesylate, procyclidine, ketoconazole, diazepam, nordiazepam, carbamazepine, caffeine, aspirin, acetaminophen, nicotine, and ibuprofen. Recovery of quetiapine from spiked plasma during method validation averaged 104%. Stability of quetiapine has been established for at least 15 months in spiked samples at approximately –20°C. Quality control values for quetiapine averaged 101% of theory (7.6% between-day RSD).

Data Analysis: Predose quetiapine plasma concentrations (Cmin) obtained on Days 2, 3, and 4 of Period 1 and Days 2, 3, and 4 of Period 2 were used to determine attainment of steady-state conditions. The following steady-state pharmacokinetic parameters of quetiapine were derived from data collected over the 24-hour dosing interval following administration of the morning dose of quetiapine on Day 4 of Period 1 and Day 4 of Period 2: AUC(0-24h), Cmax, tmax, Cmin, and DF.

Noncompartmental methods were used to compute the pharmacokinetic parameters. The parameter DF was estimated as (Cmax–Cmin)/Cav x100, where Cav =AUC(0-24h)/24.
For statistical comparisons, quetiapine SR, administered as 300-mg tablets once daily, was considered the test treatment, and quetiapine IR, administered as 150-mg tablets twice daily, was considered the reference treatment.

The relative bioavailability of the SR and IR formulations at steady state was evaluated by constructing a 90% confidence interval for the SR/IR ratio for AUC(0-24h), based on the least-squares means from the ANOVA. The 2 treatments were to be considered bioequivalent if the 90% confidence interval for the ratio of geometric means (SR/IR) of AUC(0-24h) was within the range 0.80 to 1.25. The 90% confidence intervals for the ratios of geometric means (SR/IR) for Cmax and Cmin were also calculated for reference.

Pharmacokinetic Results: Statistical analyses (ANOVA) of the trough concentrations obtained on Days 2, 3, and 4 of Periods 1 and 2 showed no statistical difference in trough concentrations suggesting that quetiapine concentrations reached steady state within each treatment sequence and period. Analysis of variance did not reveal a sequence effect on any of the pharmacokinetic parameters; therefore, the data for the 2 treatment sequences were combined for comparative purposes. The following table provides the mean trough quetiapine concentrations.

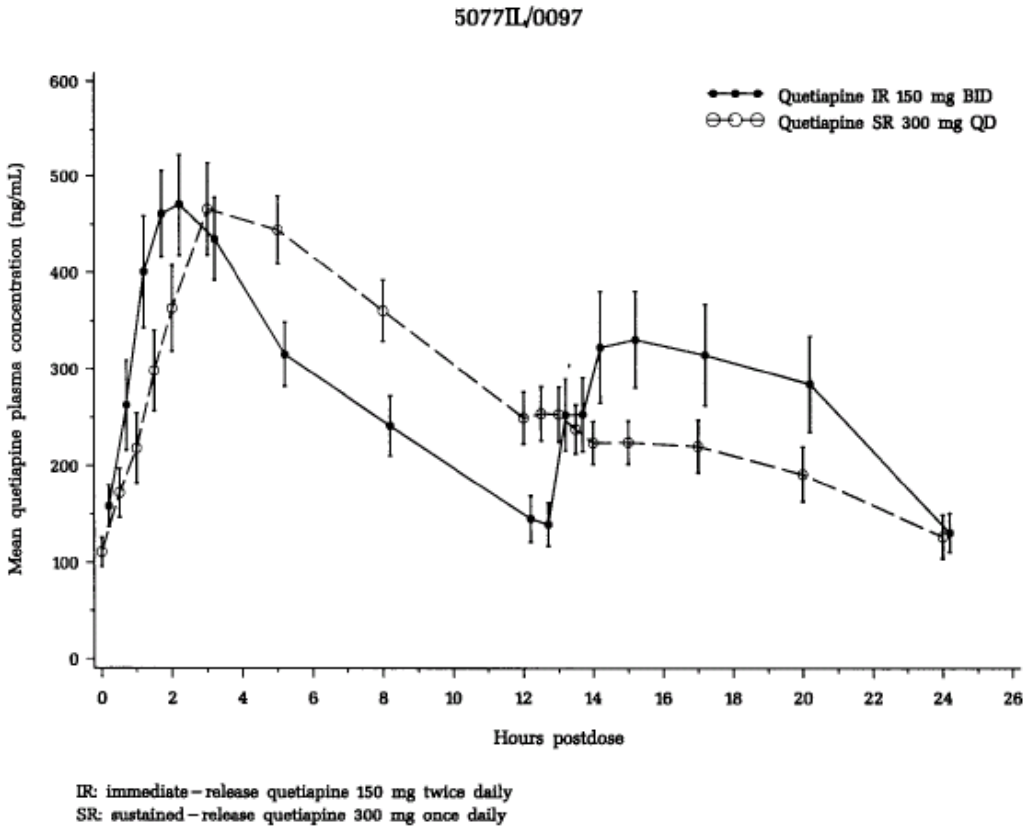
Morning trough quetiapine concentration (ng/mL) by treatment sequence, trial period, and trial day: mean (SEM)

Treatment sequence	Trial period, treatment, and day[a]					
	Period 1			Period 2		
IR-SR	IR (150 mg twice daily) (n=11)			SR (300 mg once daily) (n=11)		
	Day 2	Day 3	Day 4	Day 2	Day 3	Day 4
	85.4 (13.2)	98.5 (15.4)	113.2 (24.2)	89.5 (20.7)	77.4 (17.8)	92.5 (17.3)
SR-IR	SR (300 mg once daily) (n=13)			IR (150 mg twice daily) (n=13)		
	Day 2	Day 3[b]	Day 4	Day 2	Day 3	Day 4
	158.0 (39.6)	145.8 (23.0)	126.3 (23.3)	177.8 (27.2)	172.0 (25.3)	196.1 (31.0)

[a] Days 2, 3, and 4 of Period 1 correspond to consecutively numbered trial days 4, 5, and 6. Days 2, 3, and 4 of Period 2 correspond to consecutively numbered trial days 8, 9, and 10.
[b] n=12.
IR Immediate-release quetiapine.
SEM Standard error of the mean.
SR Sustained-release quetiapine.

The following figure depicts the mean plasma quetiapine concentrations over a 24-hour dosing interval for each of the two treatments.

Mean (± SEM) plasma quetiapine concentrations



The lower Cmax for the 2nd daily dose of the IR formulation may be the result of circadian variation in the pharmacokinetic parameters, according to the sponsor. This observation is reported by the sponsor to be consistent with other studies. The following tables summarize the steady state pharmacokinetic parameters of quetiapine for each treatment and the results of statistical comparisons of the 2 treatments.

Comparison of pharmacokinetic parameters for a 300-mg dose of quetiapine administered as SR tablets (300 mg once daily) or as IR tablets (150 mg twice daily)

Parameter (units)[a]	Immediate-release quetiapine (150 mg twice daily) (n=24)	Sustained-release quetiapine (300 mg once daily) (n=24)	Comparison of treatments: ratio of means[b]	
	Geometric mean (95% CI)		Ratio (SR/IR)	90% CI[c]
$AUC_{(0-24)}$ (ng·h/mL)	5882 (4729 to 7315)	6147 (5215 to 7246)	1.04	0.92 to 1.19
C_{max} (ng/mL)	568.1 (474.0 to 680.9)	495.3 (424.6 to 577.9)	0.87	0.77 to 0.99
C_{min} (ng/mL)	96.5 (66.2 to 140.4)	95.3 (69.4 to 130.8)	1.00	0.77 to 1.31
	Median (range)			
t_{max}	2.0 (0.6 to 8.0)	5.0 (0.9 to 20.0)		
Degree of fluctuation (%)	171.8 (54.9 to 430.0)	155.7 (21.0 to 566.2)		

[a] Parameters derived from data collected during the 24-hour interval following morning quetiapine administration on Day 4 of Periods 1 and 2.
[b] Based on ratio (SR/IR) of least squares means from analysis of variance.
[c] Based on log-transformed data.
CI Confidence interval.
IR Immediate release.
SR Sustained release.

The geometric mean SR/IR ratio for $AUC_{(0-24h)}$ was 1.04. The 90% confidence interval for the ratio was 0.92 to 1.19, which is within the 0.80 to 1.25 bioequivalence criteria. The SR and IR formulations can therefore be considered equivalent with respect to AUC. Mean C_{max} for the SR formulation was about 13% lower than mean C_{max} for the IR formulation. Median t_{max} was 5 and 2 hours for the SR and IR formulations, respectively.

The results of this trial indicate that the SR formulation administered as 300-mg tablets once daily (test treatment) and the IR formulation administered as 150-mg tablets twice daily (reference treatment) are equivalent with respect to overall exposure at steady state. The 90% confidence interval for the geometric mean SR/IR ratio for $AUC_{(0-24h)}$ was 0.92 to 1.19. Median DF, which is a measure of how C_{max} and C_{min} fluctuate around the time-averaged plasma concentration ($AUC_{(0-24h)}$/24 hours), was similar for the SR and the IR formulations; these results are consistent with the similarity of C_{max}, C_{min}, and $AUC_{(0-24h)}$ for the 2 formulations. A higher DF would normally be associated with an IR, as compared with an SR formulation.

Safety Results: In all 3 quetiapine treatment categories (lead-in treatment with SR 300 mg/day, randomized treatment with SR 300 mg/day, and randomized treatment with IR 300 mg/day), the most frequent adverse events (at least 3 subjects in each treatment category) included insomnia, tachycardia, headache, hypertension, and agitation.
The sponsor reported that no unexpected safety results were reported during this trial. Overall, the trial subjects tolerated quetiapine well, whether it was administered as an SR or an IR formulation. The trial results indicate that switching between the IR and SR

formulations of quetiapine was safe and well tolerated, as was initiation of trial treatment with quetiapine SR 300 mg/day.

Summary: The results of this 2-period crossover trial indicate that the SR formulation of quetiapine administered as 300-mg tablets once daily and the IR formulation of quetiapine administered as 150-mg tablets twice daily are equivalent with respect to overall exposure (AUC) at steady state. The sponsor reported that there was no apparent increase in the number of adverse events, cardiovascular or other, when subjects were switched from one formulation of quetiapine to the other. The study results indicate that switching between the IR and SR formulations of quetiapine was safe and well tolerated, as was initiation of trial treatment with quetiapine SR 300 mg/day during the 2-day Lead-in Period.

Reviewer Comments: *The study indicated that switching from quetiapine IR to SR provided similar total exposures (AUC). However, Cmax was lower by about 13% after quetiapine SR than after IR administration.*

TABLE T3 TROUGH PLASMA QUETIAPINE CONCENTRATIONS (NG/ML)
MEAN AND STANDARD ERROR (SEM)

SEQUENCE	CENTER/SUBJECT	PERIOD 1 DAY 4	PERIOD 1 DAY 5	PERIOD 1 DAY 6	PERIOD 2 DAY 8	PERIOD 2 DAY 9	PERIOD 2 DAY 10
IR/SR	1001/0104 1001/0108 1001/0109 1001/0112 1001/0114 1001/0115 1001/0118 1001/0120 1001/0121 1001/0124 1001/0128	(b) (4)					
	N	11	11	11	11	11	11
	MEAN	85.4	98.5	113.2	89.5	77.4	92.5
	SEM	13.2	15.4	24.2	20.7	17.8	17.3
	MIN	27.0	38.7	32.3	29.3	17.2	14.3
	MEDIAN	88.2	109.0	94.2	54.8	57.8	88.4
	MAX	163.0	200.0	299.0	252.0	201.0	205.0
SR/IR	1001/0102 1001/0103 1001/0106 1001/0107 1001/0110 1001/0111 1001/0113 1001/0116 1001/0117 1001/0119 1001/0122 1001/0125 1001/0127	(b) (4)					
	N	13	12	13	13	13	13
	MEAN	158.0	145.8	126.3	177.8	172.0	196.1
	SEM	39.6	23.0	23.3	27.2	25.3	31.0
	MIN	39.3	54.5	25.3	77.0	56.2	65.2
	MEDIAN	91.3	119.0	106.0	142.0	160.0	160.0
	MAX	497.0	311.0	321.0	418.0	375.0	395.0

TABLE T4.1 QUETIAPINE PHARMACOKINETIC PARAMETERS
MEAN AND STANDARD ERROR (SEM)

SEQUENCE	FORMULATION	CENTER/SUBJECT	AUC(0-24h) (ng*h/ml)	Cmax (ng/ml)	Tmax (h)	Cmin (ng/ml)	Degree of Fluctuation
IR/SR	IR 150 MG BID	1001/0104	2516.0	317.0	1.4	38.2	265.9
		1001/0108	5138.0	362.0	3.0	117.0	114.4
		1001/0109	6945.0	975.0	0.6	42.3	322.3
		1001/0112	3180.0	466.0	1.0	45.0	317.8
		1001/0114	5458.0	751.0	1.5	94.6	288.6
		1001/0115	6977.0	539.0	1.5	43.9	170.3
		1001/0118	13171.0	728.0	3.0	237.0	89.5
		1001/0120	11344.0	674.0	2.0	170.0	106.6
		1001/0121	5148.0	446.0	2.1	74.4	173.3
		1001/0124	6090.0	752.0	1.0	115.0	251.0
		1001/0128	2314.0	421.0	1.0	6.4	430.0
		N	11	11	11	11	11
		MEAN	6207.4	584.6	1.6	89.4	230.0
		SEM	1030.5	61.8	0.2	20.4	32.5
		MEDIAN	5458.0	539.0	1.5	74.4	251.0
		GEOMETRIC MEAN	5417.0	552.4	1.5	64.4	205.3
	SR 300 MG QD	1001/0104	5040.0	358.0	5.0	66.1	139.0
		1001/0108	6335.0	346.0	5.2	275.0	26.9
		1001/0109	3751.0	910.0	3.0	25.1	566.2
		1001/0112	4834.0	361.0	1.0	46.9	156.0
		1001/0114	6007.0	482.0	3.0	93.1	155.4
		1001/0115	5125.0	473.0	5.1	39.9	202.8
		1001/0118	8783.0	622.0	8.0	188.0	118.6
		1001/0120	10245.0	892.0	3.0	89.0	188.1
		1001/0121	3561.0	333.0	5.1	48.1	192.0
		1001/0124	6793.0	465.0	3.0	159.0	108.1
		1001/0128	3955.0	381.0	8.1	67.1	190.5
		N	11	11	11	11	11
		MEAN	5857.2	511.2	4.5	99.8	185.8
		SEM	636.2	63.4	0.7	23.2	41.0
		MEDIAN	5125.0	465.0	5.0	67.1	156.0
		GEOMETRIC MEAN	5548.5	478.9	3.9	78.3	150.8
SR/IR	SR 300 MG QD	1001/0102	2843.0	337.0	5.2	28.2	260.7
		1001/0103	5205.0	333.0	7.8	121.0	97.8
		1001/0106	4778.0	274.0	3.1	152.0	61.3
		1001/0107	8301.0	800.0	3.0	69.4	211.2
		1001/0110	11879.0	594.0	20.0	490.0	21.0
		1001/0111	7120.0	655.0	5.1	62.6	199.7
		1001/0113	4498.0	304.0	5.0	102.0	107.8

TABLE T4.1 QUETIAPINE PHARMACOKINETIC PARAMETERS
MEAN AND STANDARD ERROR (SEM)

SEQUENCE	FORMULATION	CENTER/SUBJECT	AUC(0-24h) (ng*h/ml)	Cmax (ng/ml)	Tmax (h)	Cmin (ng/ml)	Degree of Fluctuation
SR/IR	SR 300 MG QD	1001/0116	9704.0	519.0	13.0	303.0	53.4
		1001/0117	5375.0	545.0	2.1	96.3	200.3
		1001/0119	9201.0	900.0	3.0	92.6	210.6
		1001/0122	7842.0	564.0	0.9	68.9	151.5
		1001/0125	11897.0	680.0	8.1	280.0	80.7
		1001/0127	5526.0	552.0	1.6	77.9	205.9
		N	13	13	13	13	13
		MEAN	7243.8	542.8	6.0	149.5	143.2
		SEM	793.0	53.4	1.5	36.3	21.2
		MEDIAN	7120.0	552.0	5.0	96.3	151.5
		GEOMETRIC MEAN	6703.9	509.7	4.3	112.4	117.9
	IR 150 MG BID	1001/0102	2386.0	219.0	5.1	69.5	150.4
		1001/0103	5299.0	687.0	0.9	115.0	259.1
		1001/0106	3880.0	262.0	2.2	53.1	129.2
		1001/0107	5520.0	493.0	3.1	149.0	149.6
		1001/0110	9031.0	802.0	3.1	279.0	139.0
		1001/0111	6848.0	830.0	2.1	169.0	231.7
		1001/0113	5740.0	559.0	2.0	79.0	200.7
		1001/0116	7383.0	498.0	8.0	329.0	54.9
		1001/0117	4513.0	840.0	1.0	82.2	403.0
		1001/0119	12869.0	671.0	2.0	144.0	98.3
		1001/0122	4649.0	398.0	5.0	59.5	174.7
		1001/0125	14391.0	1270.0	2.0	350.0	153.4
		1001/0127	9042.0	851.0	2.0	280.0	151.6
		N	13	13	13	13	13
		MEAN	7042.4	644.6	3.0	166.0	176.6
		SEM	970.5	79.0	0.5	29.7	23.9
		MEDIAN	5740.0	671.0	2.1	144.0	151.6
		GEOMETRIC MEAN	6306.0	581.7	2.5	135.8	159.4

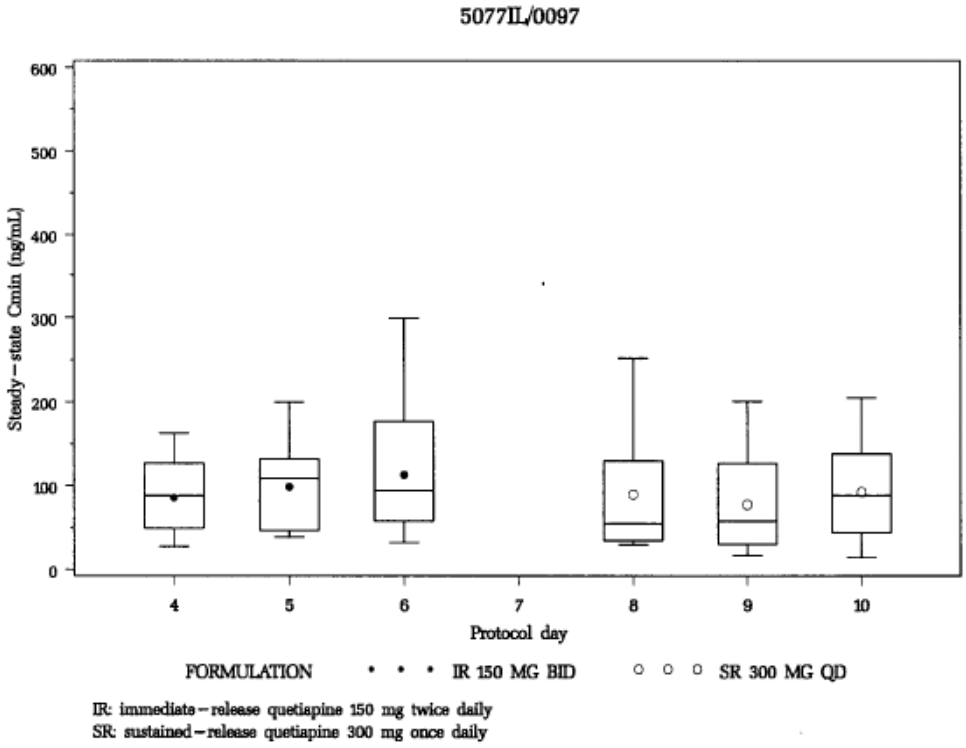
TABLE T4.2 BIOEQUIVALENCE TEST
EVALUABLE SUBJECTS

	Comparison (SR/IR)			IR 150 MG BID			SR 300 MG QD		
	Ratio (90% C.I.)			Geometric mean (95% C.I.)			Geometric mean (95% C.I.)		
Parameter	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC	1.04	0.92	1.19	5881.73	4729.17	7315.17	6147.17	5214.65	7246.46
CMAX	0.87	0.77	0.99	568.09	473.95	680.94	495.34	424.55	577.94
CMIN	1.00	0.77	1.31	96.45	66.23	140.44	95.26	69.37	130.83

TABLE T4.2 BIOEQUIVALENCE TEST
EVALUABLE SUBJECTS

	FORMULATION											
	IR 150 MG BID						SR 300 MG QD					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Tmax (HR)	24	2.4	1.7	0.6	2.0	8.0	24	5.3	4.2	0.9	5.0	20.0
DEGREE OF FLUCTUATION	24	201.1	98.3	54.9	171.8	430.0	24	162.7	107.5	21.0	155.7	566.2

Figure 1 Steady-state C_{min} (ng/mL) – treatment sequence: IR/SR



IR: immediate-release quetiapine 150 mg twice daily
SR: sustained-release quetiapine 300 mg once daily

Figure 2 Steady-state C_{min} (ng/mL) – treatment sequence: SR/IR

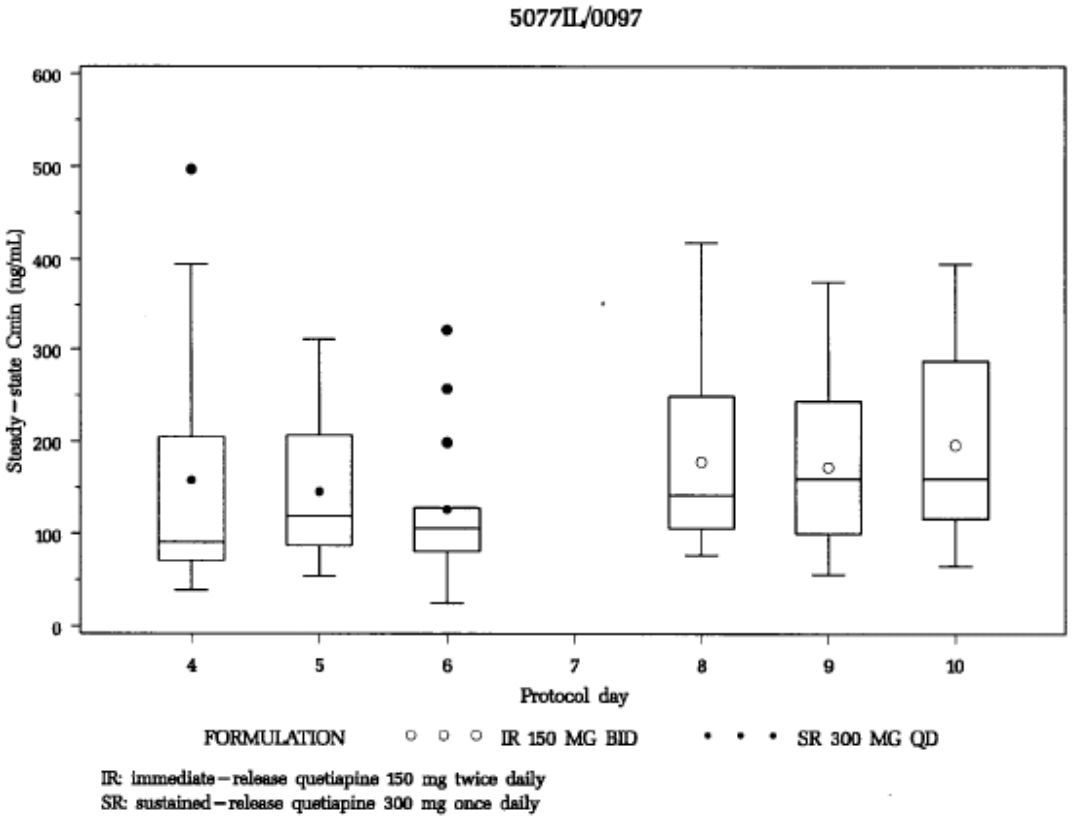
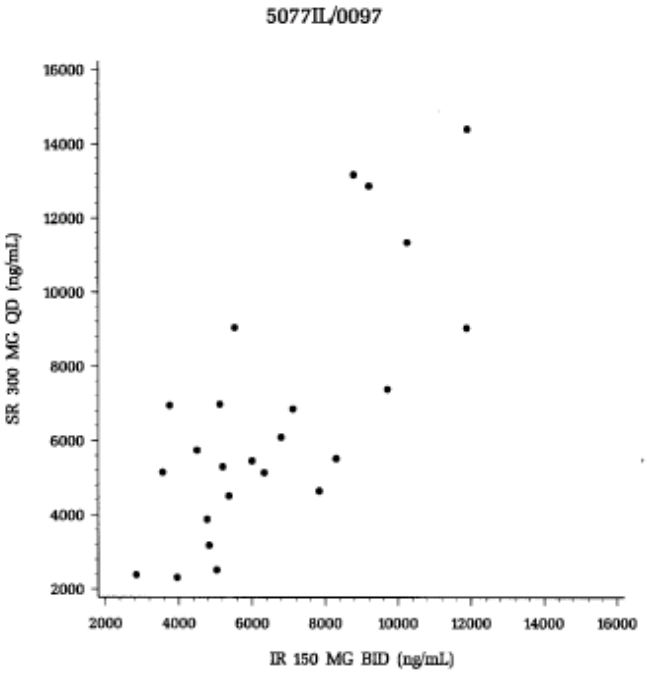


Figure 3 Scatter plot of quetiapine AUC (ng*h/mL): IR vs SR formulation



IR: immediate – release quetiapine 150 mg twice daily
SR: sustained – release quetiapine 300 mg once daily

Appendix H4 Statistical analysis of trough plasma quetiapine concentrations

Evaluable Subjects

---------- SEQUENCE=SR/IR PERIOD=1 FORMULATION=SR 300 MG QD ----------

The GLM Procedure

Dependent Variable: SSCMIN STEADY-STATE Cmin (NG/ML)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	14	319815.2732	22843.9481	6.10	<.0001
Error	23	86111.8966	3743.9955		
Corrected Total	37	405927.1697			

R-Square	Coeff Var	Root MSE	SSCMIN Mean
0.787864	42.69859	61.18820	143.3026

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SUBJECT	12	313222.4831	26101.8736	6.97	<.0001
DAY	2	6592.7901	3296.3950	0.88	0.4281

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SUBJECT	12	313197.4457	26099.7871	6.97	<.0001
DAY	2	6592.7901	3296.3950	0.88	0.4281

Parameter	Estimate	Standard Error	t Value	Pr > |t|
DAY 5 VS DAY 4	-18.9894231	24.7386189	-0.77	0.4505
DAY 6 VS DAY 4	-31.6538462	23.9999856	-1.32	0.2002
DAY 6 VS DAY 5	-12.6644231	24.7386189	-0.51	0.6136

Appendix H4 Statistical analysis of trough plasma quetiapine concentrations

Evaluable Subjects

SEQUENCE=SR/IR PERIOD=1 FORMULATION=SR 300 MG QD

The GLM Procedure
Least Squares Means

DAY	SSCMIN LSMEAN	Standard Error	Pr > |t|	LSMEAN Number
4	158.000000	16.970553	<.0001	1
5	139.010577	17.999989	<.0001	2
6	126.346154	16.970553	<.0001	3

Least Squares Means for effect DAY
Pr > |t| for H0: LSMean(i)=LSMean(j)

Dependent Variable: SSCMIN

i/j	1	2	3
1		0.4505	0.2002
2	0.4505		0.6136
3	0.2002	0.6136	

Evaluable Subjects

SEQUENCE=IR/SR PERIOD=2 FORMULATION=SR 300 MG QD

The GLM Procedure

Dependent Variable: SSCMIN STEADY-STATE Cmin (NG/ML)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	95729.2970	7977.4414	7.77	<.0001
Error	20	20542.8436	1027.1422		
Corrected Total	32	116272.1406			

R-Square	Coeff Var	Root MSE	SSCMIN Mean
0.823321	37.06912	32.04906	86.45758

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SUBJECT	10	94314.34727	9431.43473	9.18	<.0001
DAY	2	1414.94970	707.47485	0.69	0.5137

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SUBJECT	10	94314.34727	9431.43473	9.18	<.0001
DAY	2	1414.94970	707.47485	0.69	0.5137

Parameter	Estimate	Standard Error	t Value	Pr > |t|
DAY 9 VS DAY 8	-12.1272727	13.6657647	-0.89	0.3854
DAY 9 VS DAY 8	3.0272727	13.6657647	0.22	0.8269
DAY 10 VS DAY 9	15.1545455	13.6657647	1.11	0.2806

5077IL/0097
Appendix H4 Statistical analysis of trough plasma quetiapine concentrations

Evaluable Subjects

SEQUENCE=IR/SR PERIOD=2 FORMULATION=SR 300 MG QD

The GLM Procedure
Least Squares Means

DAY	SSCMIN LSMEAN	Standard Error	Pr > |t|	LSMEAN Number
8	89.4909091	9.6631549	<.0001	1
9	77.3636364	9.6631549	<.0001	2
10	92.5181818	9.6631549	<.0001	3

Least Squares Means for effect DAY
Pr > |t| for H0: LSMean(i)=LSMean(j)

Dependent Variable: SSCMIN

i/j	1	2	3
1		0.3854	0.8269
2	0.3854		0.2806
3	0.8269	0.2806	

Title (5077IL/0118): Steady State, Dose Unit Proportionality, and Food Effect Study Using Commercial Scale Sustained Release (SR) Quetiapine Fumarate (Seroquel™)

Objective: The purpose of this study was to evaluate the steady-state pharmacokinetics of 4 different commercial-scale quetiapine fumarate (SEROQUEL™, quetiapine) sustained-release (SR) tablets (50 mg, 200 mg, 300 mg, and 400 mg) and to evaluate the effect of food on the bioavailability of 50-mg and 300-mg SR tablets.

Study Design: This was a multicenter, open-label, multiple-dose study. Male or female, aged 18 to 65 years, with a diagnosis of schizophrenia or schizoaffective Disorder were eligible for enrollment. From 20 enrolled patients 13 evaluable patients (defined as those who met the patient selection criteria and who completed the study without major protocol violations or deviations) were required to provide 80% power to demonstrate dose proportionality at a 2-sided significance level of 5%.

After a 2-day washout period, patients received oral doses of quetiapine SR or quetiapine immediate release (IR) orally once a day (at approximately 0700 hours) as follows: 50 mg SR on Days 1 to 4, 200 mg SR on Days 5 to 7, 300 mg SR on Days 8 to 11, 400 mg SR on Days 12 to 14, 300 mg IR on Days 15 to 17. On Days 4 and 11, patients consumed a standardized high-fat breakfast (two eggs, 2 strips bacon, 2 pieces of toast with approximately 5 g of butter, 75 g of hashed brown potatoes and 150 mL of whole milk) within 10 minutes of their scheduled quetiapine dose. Batch numbers for quetiapine tablets were as follows: 50 mg SR, 9096F; 200 mg SR, 9077C; 300 mg SR, 9052C; 400 mg SR, 9093F; 300 mg IR, 4522C. The following table provides a summary of the daily dosage of quetiapine:

Daily Dosage of Quetiapine

Study day	Dosage and formulation [b]
1[a] through 3	1 x 50 mg sustained release
4	1 x 50 mg sustained release
5 through 7	1 x 200 mg sustained release
8 through 10	1 x 300 mg sustained release
11	1 x 300 mg sustained release
12 through 14	1 x 400 mg sustained release
15 through 17	1 x 300 mg immediate release

[a] The first administration of quetiapine was preceded by a 2-day washout.
[b] Quetiapine was administered orally once daily as a single tablet with 240 mL of water at room temperature.

The following table summarizes the pharmacokinetic variables for the study

Pharmacokinetic Variables

Objective	Summary variables for analysis (including time point and population)
To evaluate the steady-state pharmacokinetics of 4 different commercial-scale quetiapine SR tablets (50 mg, 200 mg, 300 mg, and 400 mg)	AUC^{ss}_{τ} and C^{ss}_{max} for the 24-hour dosing intervals following quetiapine administration on Days 3 (50 mg), 7 (200 mg), 10 (300 mg), and 14 (400 mg) C^{ss}_{min} measured before quetiapine administration on Days 2, 6, 9, 13, and 16
To evaluate the effect of food on the bioavailability of 50-mg and 300-mg quetiapine SR tablets	AUC^{ss}_{τ} and C^{ss}_{max} for the 24-hour dosing intervals following quetiapine administration on Days 3 and 4 (50 mg; fasted and fed, respectively) and Days 10 and 11 (300 mg; fasted and fed, respectively)

SR Sustained release.

Analytical Methods: Blood samples were collected within 15 minutes before the administration of study drug on all study days except Days 5, 8, 12, and 15. On Days 3, 4, 7, 10, 11, 14, and 17, blood samples were also collected 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after the administration of study drug. Plasma samples were analyzed for concentrations of quetiapine by using a validated procedure that employed liquid-liquid extraction of quetiapine and internal standard ($^{13}C_6$-quetiapine) from alkalinized human plasma (containing heparin anticoagulant) using ethyl acetate, followed by reverse-phase liquid chromatography and turbo ionspray ionization tandem mass spectrometry. The method has a calibration range of 0.500 ng/mL to 500 ng/mL and an applicable quantitation range to 2000 ng/mL with appropriate dilution with plasma. Accuracy and precision of quetiapine from quality control samples spiked at 0.500, 0.999, 20.0, and 400 ng/mL averaged 106% and 8.76%, respectively, across the 3 days of validation. Recovery of quetiapine from spiked plasma during method validation averaged 91.4%. Stability of quetiapine has been established previously for at least 15 months in spiked samples at approximately –20°C. The performance of the analytic method was demonstrated over the course of the analyses by monitoring the results of the spiked quality control samples assayed each day of sample analysis.

Overall precision for quality control samples, as measured by percent relative standard deviation (SD), was less than or equal to 7.97%, and the overall accuracy, as measured by percent recovery for these quality control samples ranged from 99.0% to 104%. All diluted quality control samples passed the acceptance criteria and were within 15% of theory. The precision for the dilution integrity quality control samples was δ5.07% and the overall accuracy ranged from 103% to 109%.

Data Analysis: Pharmacokinetic parameters were computed using non-compartmental methods. Dose proportionality was determined by regression analysis, using log-transformed $AUC_{ss\tau}$ and C_{ssmax} for Days 3, 7, 10, and 14. The following regression equations were used to analyze $AUC_{ss\tau}$ and C_{ssmax}, respectively: $\log (AUC_{ss\tau}) = \alpha + \beta \log (\text{dose})$; log

($C_{ssmax} = \alpha + \beta$ log (dose). The 95% confidence interval (CI) for the slope of log (dose) was constructed, and if the intervals were within the range of 0.75 to 1.25, dose proportionality was to be concluded.

The effect of food on the pharmacokinetic parameter estimates was evaluated separately for the 50-mg and 300-mg doses of quetiapine SR. The 90% CIs for the geometric mean ratios (fed/fasted) of $AUC_{ss\tau}$ and C_{ssmax} were constructed, based on the least-square means from the analysis of variance model for the log-transformed parameters. If the 90% CIs for $AUC_{ss\tau}$ and C_{ssmax} were contained within the respective predefined intervals (0.80 to 1.25 for $AUC_{ss\tau}$, 0.70 to 1.43 for C_{ssmax}), it was to be concluded that food did not have a statistically significant effect on the pharmacokinetics of quetiapine SR.

Results: Ten of the 30 enrolled patients were evaluable for pharmacokinetic analysis, ie, they met the patient selection criteria and completed the study without major protocol violations or deviations. The mean age and weight of the evaluable patients were 52.3 ± 8.63 years and 87.1 ± 13.65 kg, respectively.

Steady-state trough plasma quetiapine concentrations measured after an overnight fast on the mornings of Days 3 (50 mg SR), 7 (200 mg SR), 10 (300 mg SR), 14 (400 mg SR), and 17 (300 mg IR) are provided in the following table. The blood samples for each dose were collected after 3 days of dose administration. Plasma quetiapine trough concentrations increased as the dose of quetiapine SR was escalated.

Steady State Trough Plasma Quetiapine Concentrations

Study day	Dose and Formulation	n	Plasma quetiapine concentration (ng/mL)			
			Mean	SD	Minimum	Maximum
3	50 mg SR	10	19.61	11.050	5.30	36.40
7	200 mg SR	10	58.02	40.650	13.20	151.00
10	300 mg SR	10	116.52	91.846	30.90	311.00
14	400 mg SR	10	147.93	86.290	44.60	292.00
17	300 mg IR	10	31.95	22.062	14.70	77.90

IR Immediate release. SD Standard deviation. SR Sustained release.

Note: Patients who were evaluable for pharmacokinetic analysis were defined as those who met the patient selection criteria and who completed the study without major protocol violations or deviations, ie, they remained in the study for all blood sampling days and had sufficient data for estimation of pharmacokinetic parameters.

The estimated pharmacokinetic parameters of quetiapine are summarized in the following table.

Pharmacokinetic parameters of quetiapine

	Quetiapine SR[a]						Quetiapine IR[a]
	50 mg		200 mg	300 mg		400 mg	300 mg
Parameter	Fasted	Fed	Fasted	Fasted	Fed	Fasted	Fasted
AUC^{ss}_{τ}, ng·hr/mL							
Geometric mean	925.09	1112.24	3751.93	5710.83	6966.93	7287.37	4895.18
CV (%)	47.20	35.03	34.76	37.86	32.66	34.02	34.11
n	10	10	10	10	10	10	10
C^{ss}_{max}, ng/mL							
Geometric mean	87.83	133.23	304.48	470.70	677.92	594.84	944.04
CV (%)	75.58	23.47	41.83	33.14	28.52	38.92	28.12
n	10	10	10	10	10	10	10
C^{ss}_{min}, ng/mL							
Geometric mean	11.16	10.80	60.03	87.19	79.53	107.79	21.88
CV (%)	80.86	60.26	63.68	71.36	59.28	59.00	78.59
n	10	10	10	10	10	10	10
t_{max}, hr							
Median	6.05	6.04	6.05	6.12	8.00	5.00	1.50
Minimum	1.97	3.92	2.02	1.95	3.00	3.00	1.00
Maximum	15.92	9.70	8.08	10.08	11.83	8.00	4.02
n	10	10	10	10	10	10	10
$t_{1/2}$, hr							
Mean	5.57	5.41	6.57	6.35	5.40	7.10	5.38
SD	0.676	0.738	1.760	1.626	1.195	2.855	0.974
n	4	7	5	7	8	5	9
CL/F, L/hr							
Mean	60.15	48.02	57.56	56.79	45.29	57.97	64.68
SD	28.937	18.937	25.784	24.210	15.083	20.330	22.266
n	10	10	10	10	10	10	10

[a] Fasting samples for pharmacokinetic analyses of quetiapine SR 50, 200, 300, and 400 mg, and quetiapine IR 300 mg were collected on Days 3, 7, 10, 14, and 17, respectively. Samples for pharmacokinetic analyses of quetiapine SR 50 and 300 mg were taken following a high-fat meal on Days 4 and 11, respectively.

CV Coefficient of variation. IR Immediate release. SD Standard deviation. SR Sustained release.

The data indicated that exposure in terms of C_{ssmax}, $AUC_{ss\tau}$, and C_{ssmin} increased with dose in a dose-proportional manner for the SR dose-strengths. The quetiapine $t_{1/2}$ appeared to be similar across all dose-strengths and formulations and is consistent with

that in previous studies. The fasted median t_{max} for all SR tablet strengths ranged from 5.00 to 6.12 hours, consistently later than the median t_{max} for the 300-mg quetiapine IR tablet.

Both C_{ssmax} and $AUC_{ss\tau}$ increased following a high-fat meal when compared with the fasted state. CL/F decreased in the fed state, consistent with the observed small increases in $AUC_{ss\tau}$.

The following table provides the regression analyses of log-transformed AUC and Cmax versus dose of quetiapine SR.

Regression analysis of quetiapine SR dose proportionality under fasting conditions

Parameter	n	Estimated slope[a]	95% CI
C^{ss}_{max}, ng/mL	10	0.9247	0.7904 to 1.0591
AUC^{ss}_{τ}, ng·hr/mL	10	1.0011	0.9055 to 1.0967

[a] Based on regression analysis of log-transformed data for 4 doses of quetiapine SR: 50 mg, 200 mg, 300 mg, and 400 mg.

SR Sustained release.

The 95% CIs for the estimated regression slopes for both C_{ssmax} and $AUC_{ss\tau}$ included 1.00, and were within the pre-specified range of 0.75 to 1.25.

The following summarizes the effects of food on the pharmacokinetics of 50-mg and 300-mg dose strengths of quetiapine SR.

Relative bioavailabilityof quetiapine SR 50 mg and 300 mg in the fed and fasted states

Dose Parameter	Geometric mean (95% CI)		Mean fed/fasted ratio[a] (90% CI)
	Fasted[b]	Fed[c]	
50 mg SR (n=10)			
AUC^{ss}_{τ}, ng·hr/mL	925.09 (650.78 – 1315.02)	1112.24 (848.82 – 1457.41)	1.20 (1.01 – 1.43)
C^{ss}_{max}, ng/mL	87.83 (59.57 – 129.49)	133.22 (111.44 – 159.27)	1.52 (1.08 – 2.13)
300 mg SR (n=10)			
AUC^{ss}_{τ}, ng·hr/mL	5710.83 (4254.29 – 7666.03)	6966.93 (5479.48 – 8858.15)	1.22 (1.10 – 1.35)
C^{ss}_{max}, ng/mL	470.70 (364.88 – 607.20)	677.92 (551.36 – 833.53)	1.44 (1.24 – 1.68)

[a] Ratio (fed/fasted) based on least-squares means from analysis of variance of log-transformed parameter.

[b] Fasting samples for pharmacokinetic analysis of the 50-mg and 300-mg doses were taken on Days 3 and 10, respectively.

[c] Samples for pharmacokinetic analysis of the 50-mg and 300-mg doses were taken after a high-fat meal on Days 4 and 11, respectively.

CI Confidence interval. SR Sustained release.

Administration of quetiapine SR following a high-fat meal led to increases in $AUC_{ss\tau}$ and C_{ssmax} relative to the fasted state. For the 50-mg quetiapine SR tablet, there was a 20% increase in $AUC_{ss\tau}$ and a 52% increase in C_{ssmax} in the fed state. For the 300-mg quetiapine SR tablet, there was a 22% increase in $AUC_{ss\tau}$ and a 44% increase in C_{ssmax} in the fed state. The food effect observed in this study fell significantly outside both the equivalence intervals.

Pharmacokinetic Summary: The pharmacokinetics of quetiapine SR were linear and thus proportional to dose at the dose strengths of quetiapine SR tested (50 to 400 mg). The 95% CIs for the estimated regression slopes for both C_{ssmax} (0.7904 to 1.0591) and $AUC_{ss\tau}$ (0.9055 to 1.0967) included 1.00, and were within the protocol specified range of 0.75 to 1.25. Quetiapine $t_{1/2}$ and CL/F appeared to be independent of the dose or formulation administered.

Administration of quetiapine SR following a high-fat meal led to increases in $AUC_{ss\tau}$ and C_{ssmax} relative to the fasted state. For the 50-mg quetiapine SR tablet, there was a 20% increase in $AUC_{ss\tau}$ and a 52% increase in $C_{ss\ max}$ in the fed state. For the 300-mg quetiapine SR tablet, there was a 22% increase in $AUC_{ss\tau}$ and a 44% increase in C_{ssmax} in the fed state. The $AUC_{ss\tau}$ for the 300-mg SR tablet was approximately 17% higher than that observed for the 300-mg IR tablet.

Safety Summary: The sponsor reported that overall, the quetiapine formulations and dosages used in this study were well tolerated. The most common adverse events reported were anxiety and insomnia. The sponsor reported that no serious adverse events were reported during study treatment, and no patient discontinued treatment with the investigational product because of adverse events. Mean heart rate appeared to increase with increasing quetiapine dose. Mean pulse rate was highest 6 hours after administration of the SR formulation. Changes in hematology and clinical chemistry (hepatic function) parameters before discharge were not considered clinically important by the sponsor.

Conclusions: The different dose-strengths of quetiapine SR ranging from 50 mg to 400 mg were dose-proportional with respect to C_{ssmax} and $AUC_{ss\tau}$. Administration of quetiapine SR following a high-fat meal led to significant increases in $AUC_{ss\tau}$ and C_{ssmax} relative to the fasted state.

Reviewer comments: *Reviewer agrees with sponsor's pharmacokinetic conclusions. Refer to Medical reviewer for comments on the safety data.*

Figure 2 **Individual values of AUC^{ss}_{τ} (ng·hr/mL) of quetiapine versus quetiapine S dose under fasting conditions (evaluable patients)**

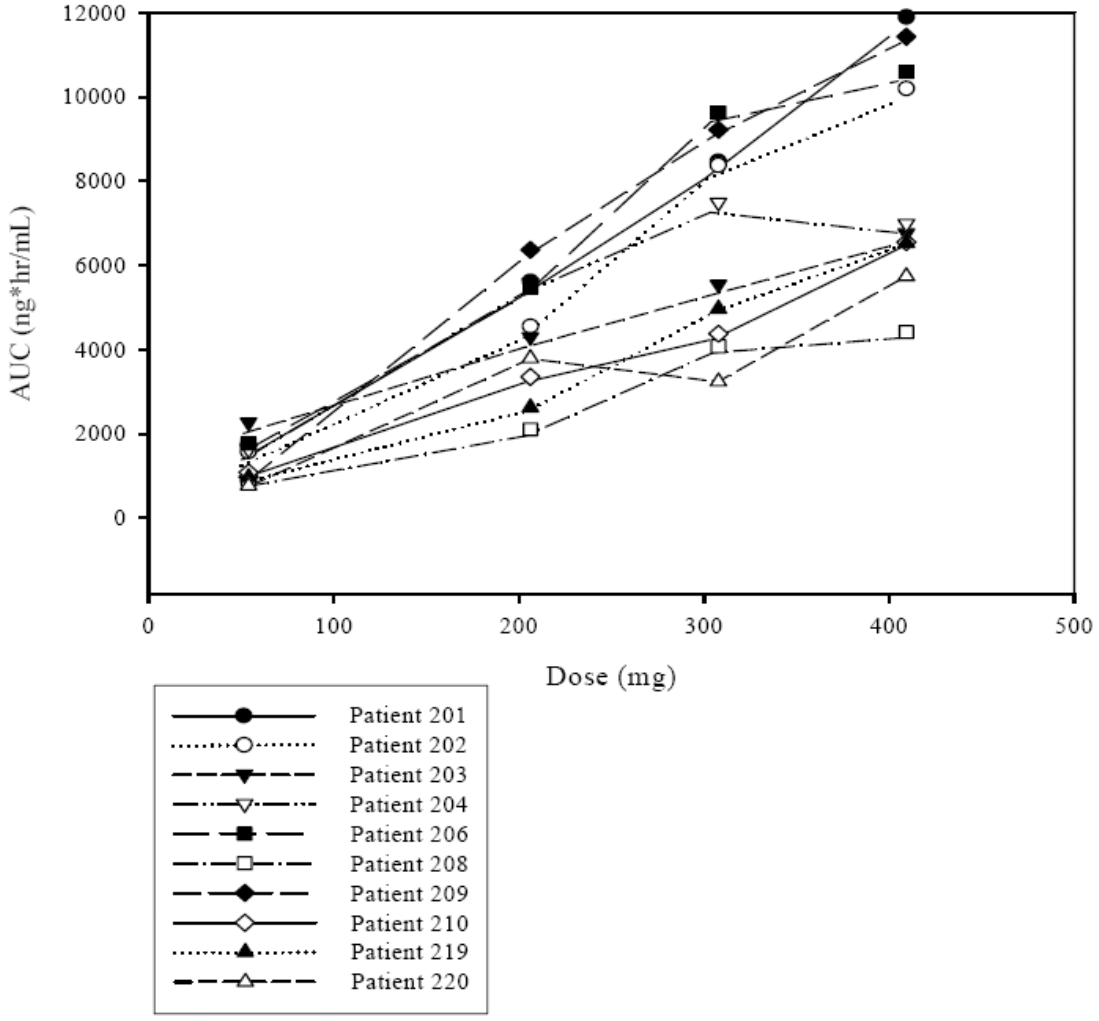


Figure 3 **Individual values of C^{ss}_{max} (ng/mL) of quetiapine versus quetiapine SR dose under fasting conditions (evaluable patients)**

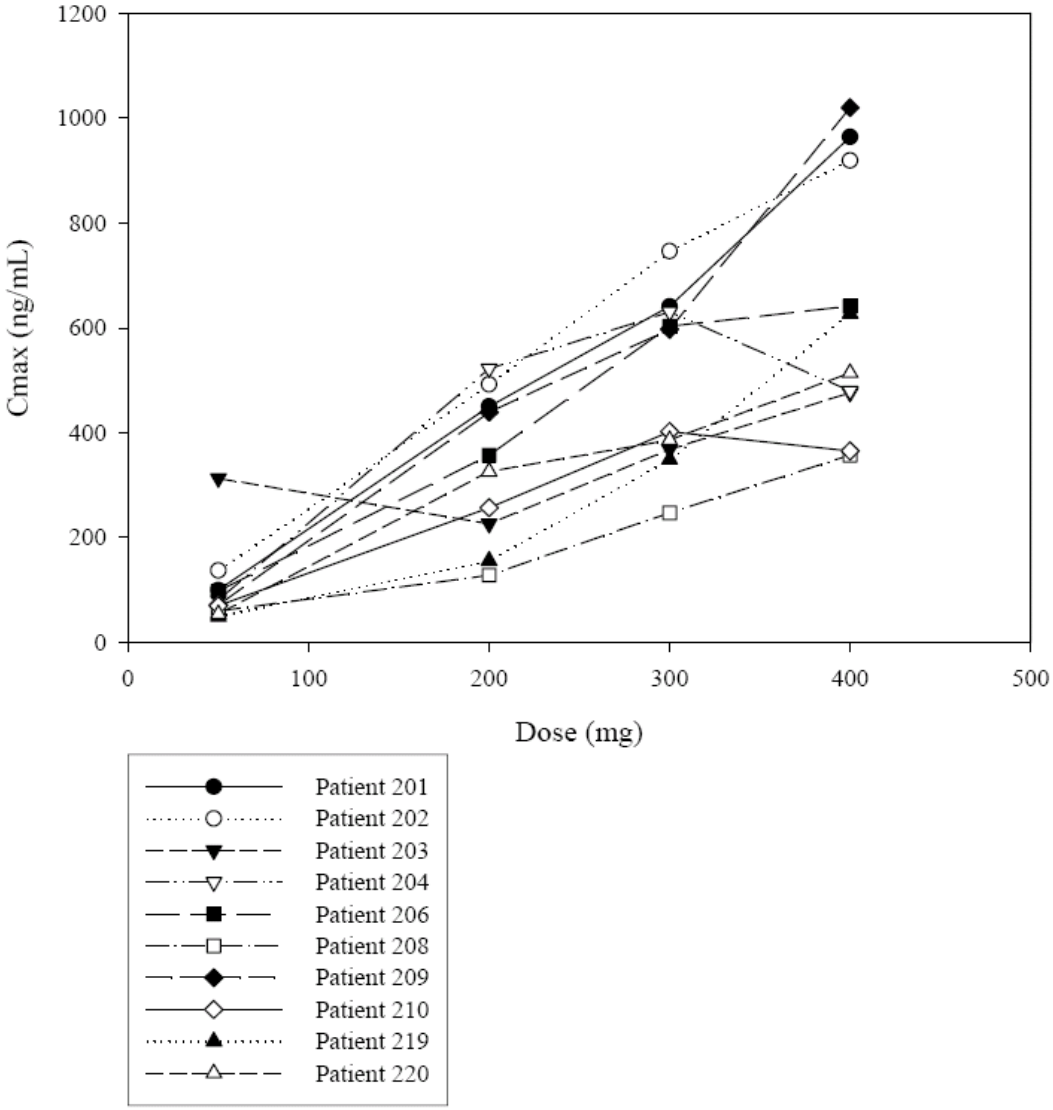


Figure 4 **Individual values of AUC^{ss}_{τ} (ng·hr/mL) of quetiapine (50 mg SR) for fasted and fed conditions (evaluable patients)**

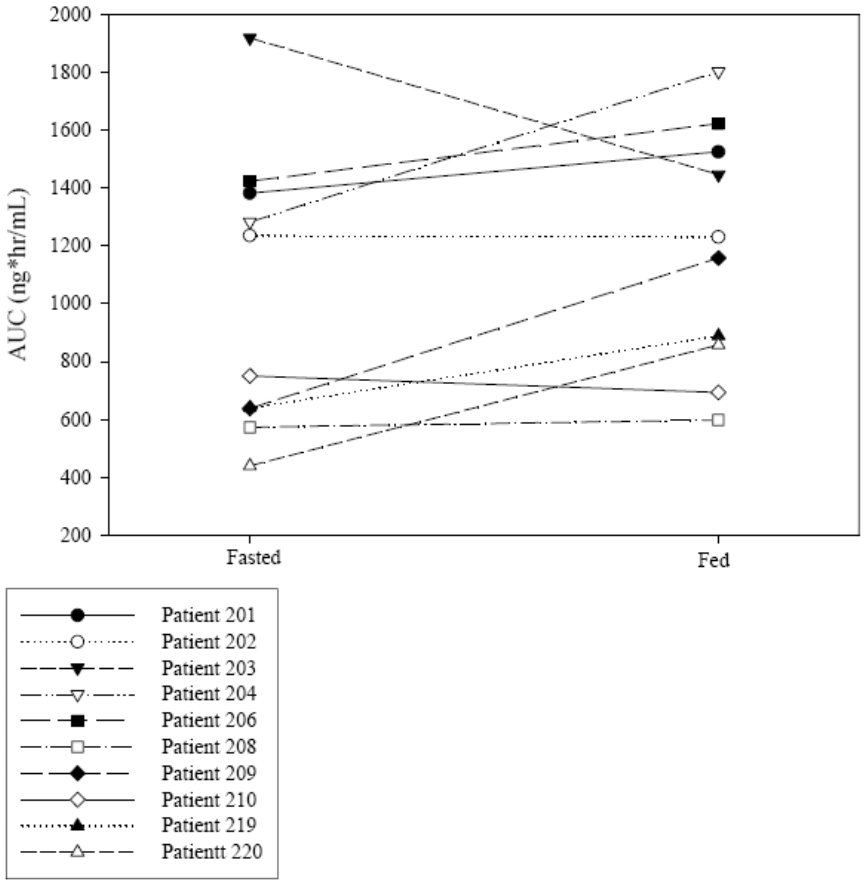
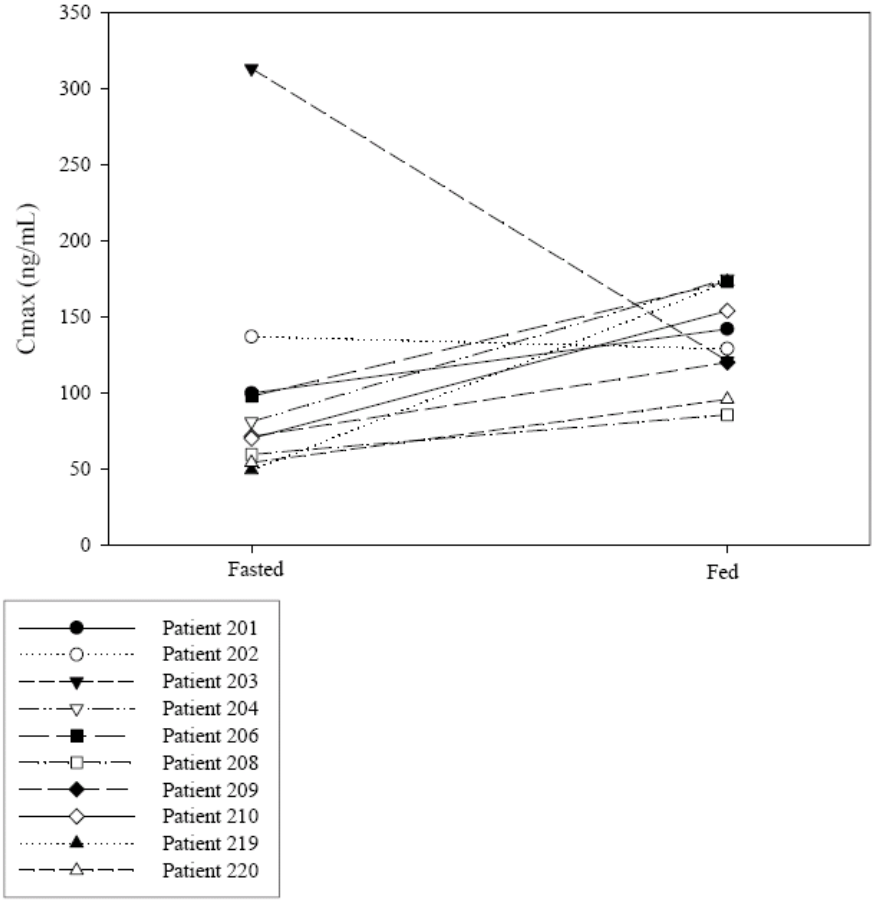
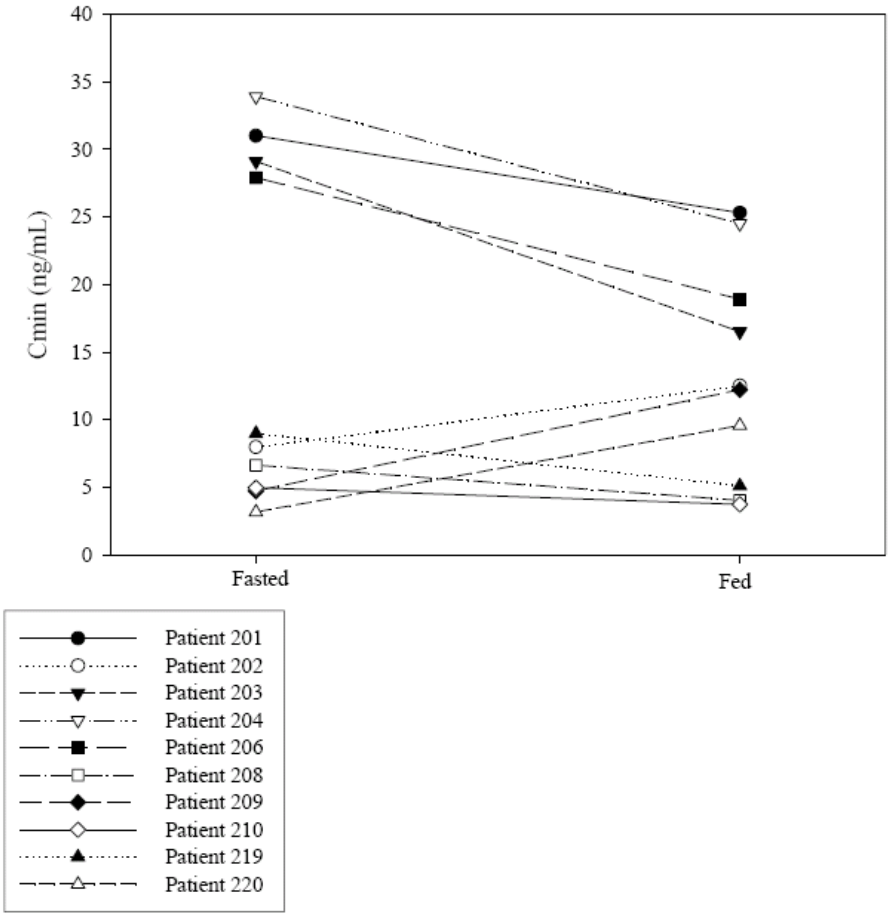


Figure 5 **Individual values of C^{ss}_{max} (ng/mL) of quetiapine (50 mg SR) for fasted and fed conditions (evaluable patients)**



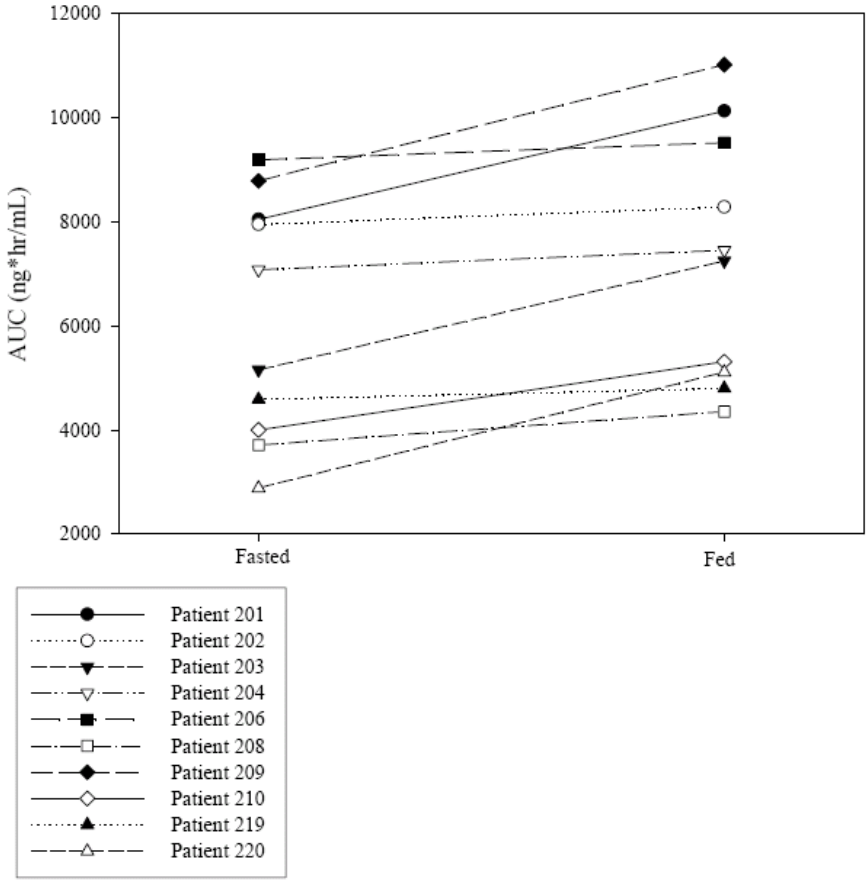
SR Sustained release.

Figure 6 **Individual values of C^{ss}_{min} (ng/mL) of quetiapine (50 mg SR) for fasted and fed conditions (evaluable patients)**



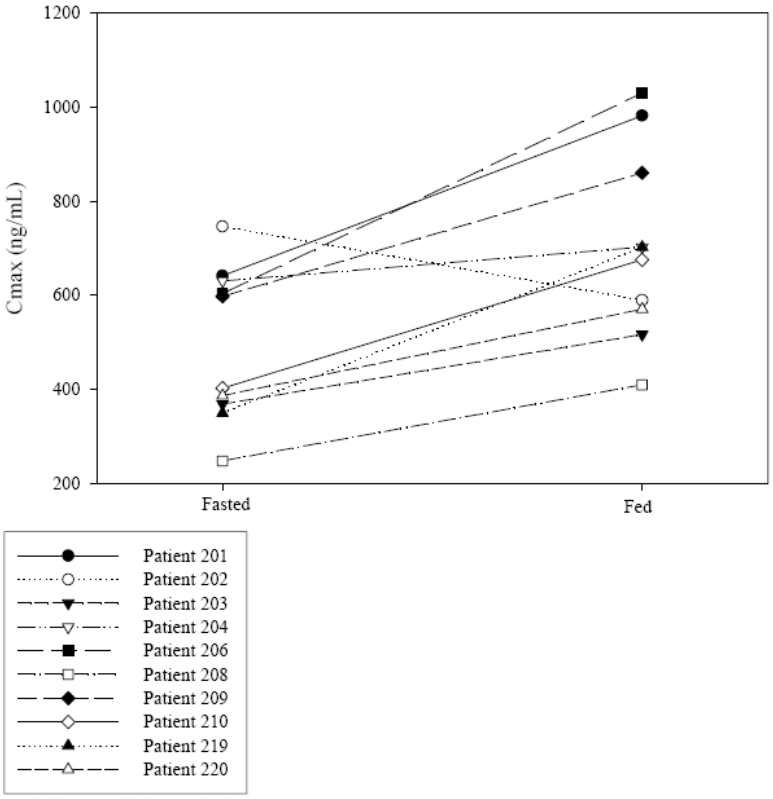
SR Sustained release.

Figure 7 **Individual values of AUC^{SS}_{τ} (ng·hr/mL) of quetiapine (300 mg SR) for fasted and fed conditions (evaluable patients)**



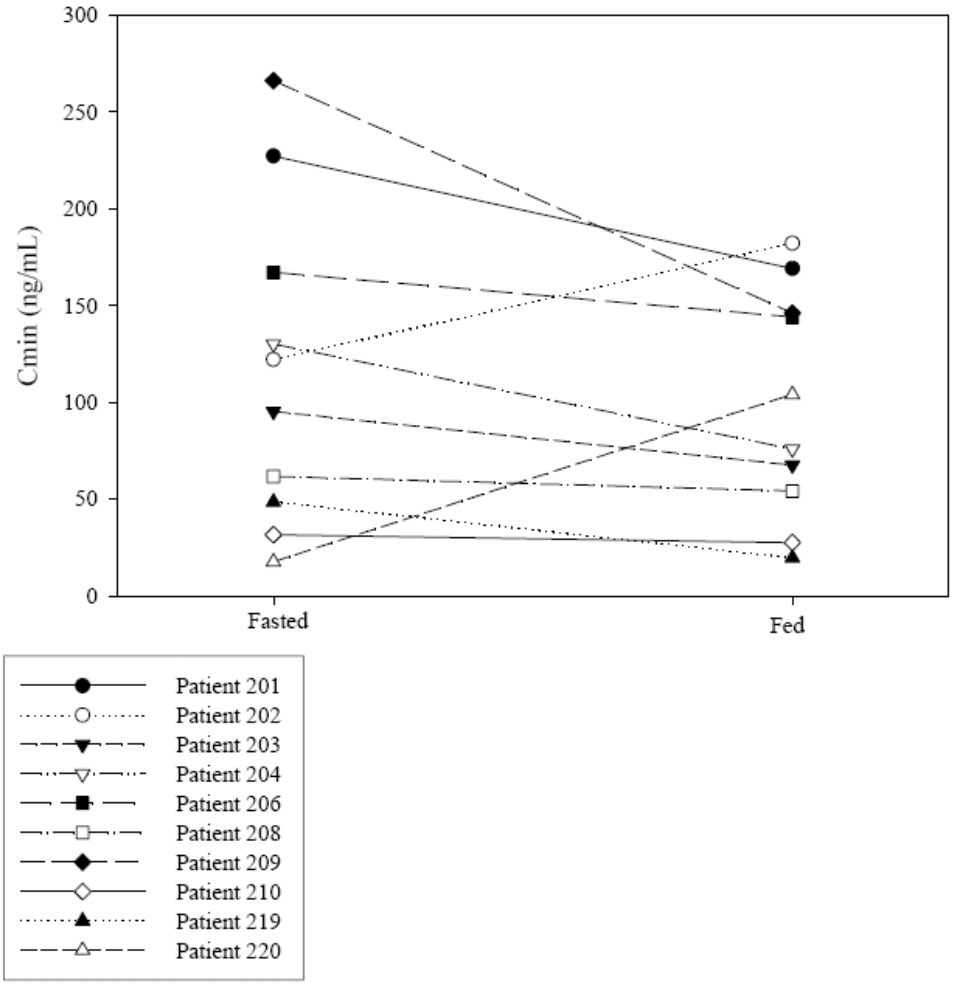
SR Sustained release.

Figure 8 **Individual values of C^{ss}_{max} (ng/mL) of quetiapine (300 mg SR) for fasted and fed conditions (evaluable patients)**



SR Sustained release.

Figure 9 **Individual values of C^{ss}_{min} (ng/mL) of quetiapine (300 mg SR) for fasted and fed conditions (evaluable patients)**



SR Sustained release.

Title (D1444C00001): A Phase I, Randomized, Open-label, 5-Treatment, 5-Period, 4-Sequence Crossover Study to Compare the Pharmacokinetics of 4 Sustained release Formulations and the Immediate release Formulation of Quetiapine Fumarate (SEROQUEL™) in Adults with Schizophrenia, Schizoaffective Disorder, or Bipolar Disorder

Objective: The primary objective of the study was to compare the single-dose pharmacokinetics of quetiapine fumarate (SEROQUEL™, quetiapine) between four sustained release (SR) tablet formulations and an immediate release (IR) tablet formulation in adults with schizophrenia, schizoaffective disorder, or bipolar disorder.

Study Design: This was an open-label, randomized, 5 treatment-period, 4-sequence crossover pharmacokinetic study conducted in the US. Approximately 20 male patients 18 to 45 years of age, inclusive, were randomized in the study in order to obtain 12 evaluable patients (3 per treatment sequence). Each patient was to be randomized to receive 1 of the following treatment sequences: ABDCE, BCADE, CDBAE, or DACBE. Each of the first 4 treatment periods was to be 4 days in duration. The fifth treatment period was to be 3 days in duration. A 2-day Washout Period was utilized for all patients who were currently taking an antipsychotic medication other than quetiapine. Following the Washout Period, patients began a 2-day Dose Titration Period. The 2-day Dose Titration Period was required to adjust the patient's dose prior to being randomized. During the Dose Titration Period, patients were given a single 100-mg dose quetiapine IR on the evening of Day –2 and quetiapine IR 100 mg twice daily on Day –1.

Treatment periods 1, 2, 3, and 4 were to begin with an initial 2-day dose of quetiapine IR 200 mg administered twice daily (Day 1 and Day 2), followed by a single oral dose of 1 of the SR 400 mg tablet formulations: SR-F (Treatment B), SR-T (Treatment C), SR-S (Treatment D) or the IR 200 mg X 2 tablet formulation (IR 400 mg-dose; Treatment A, AM only) on Day 3 according to the randomization schedule. Serial blood samples were to be obtained from each patient for 48 hours after the Day 3 study drug administration of each Treatment Period for determination of quetiapine plasma concentrations. A single oral dose of quetiapine SR 50 mg (Treatment E) was to be administered on Day 1 of Treatment Period 5. For Treatment Period 5, serial blood samples were to be obtained from each patient for 48 hours after Day 1 study drug administration for determination of quetiapine plasma concentrations. The following table provides the study medication treatments utilized.

Study Treatments

Treatment	Quetiapine formulations and dosages		
	Day 1	**Day 2**	**Day 3**
A	IR 200 mg bid	IR 200 mg bid	IR 400 mg (200 mg X 2 tablets), AM only
B	IR 200 mg bid	IR 200 mg bid	SR-F 400 mg (1 x 400 mg tablet), AM only
C	IR 200 mg bid	IR 200mg bid	SR-T 400 mg (1 x 400 mg tablet), AM only
D	IR 200 mg bid	IR 200 mg bid	SR-S 400 mg (1 x 400 mg tablet), AM only
E	SR-T 50 mg (single dose)	NA	NA

AM morning; BID twice daily; IR immediate release; NA not applicable; SR-F sustained release- fast release profile; SR-S sustained release- slow release profile; SR-T sustained release- target release profile.

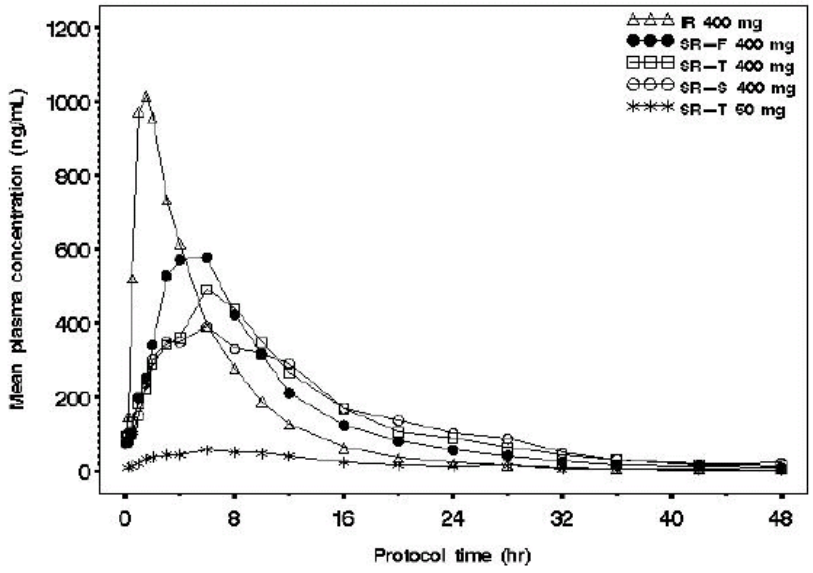
Study Patients: All of the 18 patients enrolled in this study were male, and the majority of the patients were Black (15/18). The mean age of the 18 enrolled patients was approximately 35 years (range 18 to 45 years). All but 1 of the 18 patients had a diagnosis of schizophrenia; 1 patient had a diagnosis of schizoaffective disorder. Three of the 18 patients discontinued from the study and 1 additional patient had a major protocol deviation (multiple dosing errors). As a result, 14 patients (mean weight and height = 81.14 kg and 172.5 cm) were included in the PK population. Concomitant medications used by the patients were generally as allowed by the protocol and were considered unlikely to have influenced the PK parameter estimates or safety results.

Analytical Method: A validated analytical procedure (b) (4) Report No. 160839) with liquid-liquid extraction of quetiapine, M213,841, M214,227, and M211,803 and ISTDs (^{13}C6-quetiapine, d8-M213,841, d8-M214,227, and d8-M211,803) from alkalinized human plasma (containing EDTA anticoagulant) using ethyl acetate, followed by LC/MS/MS was used. The method has a calibration range of 0.500 ng/mL to 500 ng/mL using a 100 µL aliquot, with a validated dilution of 1:20 fold with blank plasma, which extends the validated curve range to 10.0 µg/mL.

Data Analysis: Pharmacokinetic parameters were estimated by non-compartmental analysis.

Results: The mean quetiapine plasma concentrations over a 48-hour time interval for each treatment are shown in the following figure.

Figure 1 **Mean plasma concentrations of quetiapine over time (evaluable patients, N=14)**



IR 400 immediate release 200 mg X 2, AM only; SR-F sustained release-fast release profile; SR-S sustained release-slow release profile; SR-T sustained release-target release profile; .

The estimated pharmacokinetic parameters of quetiapine based on data from the 14 evaluable patients are summarized in the following table

Table 13 Pharmacokinetic parameters of quetiapine (evaluable patients; n=14)

PK parameter		Quetiapine treatment				
		IR 200 mg X 2	SR-F 400 mg	SR-T 400 mg	SR-S 400 mg	SR-T 50 mg
C_{max}, ng/ml						
Geometric	mean	1270.384	652.457	518.201	447.755	62.017
CV (%)		52.954	42.236	53.096	33.789	39.322
n		14	14	14	14	14
t_{max}, hr						
Median		1.000	4.000	6.000	6.000	6.000
Minimum		0.50	1.93	2.03	2.00	2.00
Maximum		2.00	8.00	8.00	12.02	28.00
n		14	14	14	14	14
$AUC_{(0\text{-}24hr)}$, ng.hr/mL						
Geometric	mean	5363.339	5628.922	5346.867	5172.719	691.545
CV (%)		72.258	50.192	60.391	54.302	65.286
n		14	14	14	14	14
$t_{1/2}$, hr						
Mean		6.547	6.716	7.119	7.285	7.469
SD		1.4679	2.7498	1.7037	2.0351	1.3162
n		12	12	12	12	12
CL/F, L/hr						
Mean		92.250	79.509	87.602	87.075	85.701
SD		68.5725	42.3903	57.1107	45.8388	55.0241
n		14	14	14	14	14

Note: Evaluable patients were those patients who met the patient selection criteria and who had pharmacokinetic profiles for Treatment Periods 1 to 4.
CV coefficient of variation; IR immediate release; SR-F sustained release-fast release profile; SR-S sustained release-slow release profile; SR-T sustained release-target release profile.

Equal doses of the quetiapine SR formulations produced a Cmax about 50% or more lower than the IR formulation, but the AUC(0-24hr) closely matched the IR formulation. The quetiapine half-life was approximately 7 hours, and appeared to be independent of the type of formulation administered.

Statistical analysis of Cmax and AUC(0-24hr) PK parameter estimates following quetiapine 400 mg doses for quetiapine IR and the 3 SR formulations are summarized in the following table for all evaluable patients.

Table 14 **Comparison of the estimated pharmacokinetic parameters for quetiapine SR 400 mg vs quetiapine IR 200 mg X 2, by SR formulation (evaluable patients; N=14)**

Ratio of treatments	Parameter	LS mean ratio[a]	90% CI
quetiapine SR-F/quetiapine IR	C_{max}	0.51	0.41, 0.65
quetiapine SR-F/quetiapine IR	$AUC_{(0-24)}$	1.05	0.91, 1.21
quetiapine SR-T/quetiapine IR	C_{max}	0.41	0.34, 0.49
quetiapine SR-T/quetiapine IR	$AUC_{(0-24)}$	1.00	0.87, 1.14
quetiapine SR-S/quetiapine IR	C_{max}	0.35	0.30, 0.42
quetiapine SR-S/quetiapine IR	$AUC_{(0-24)}$	0.96	0.85, 1.09

[a] Based on least-square means from ANOVA analysis of log-transformed PK parameters.
Note: Evaluable patients were those patients who met the patient selection criteria and who had pharmacokinetic profiles for Treatment Periods 1 to 4.
IR immediate release; SR-F sustained release-fast release profile; SR-S sustained release-slow release profile; SR-T sustained release-target release profile; AUC Area under the plasma concentration-time curve from zero to 24 hours; C_{max} Maximum (peak) steady state drug concentration in plasma during a dosing interval; CI Confidence interval; PK Pharmacokinetics.

The difference in the drug release rates (10% faster [SR-F] and 10% slower [SR-S]) between the different SR formulations relative to the SR-T formulation is reflected in both Cmax and AUC(0-24hr), where the LS mean ratio estimates (SR 400 mg vs IR 200 mg X 2) for the SR-T formulation fell between the SR-F and SR-S formulations. In addition, the 90% CIs for AUC from each SR 400 mg vs IR 200 mg X 2 comparison fell between 0.8 and 1.25. The SR-T formulation is designed to be dosed once daily and achieve a similar Cmax and AUC to an equivalent total daily IR dose administered twice daily.

The mean quetiapine sulfoxide, 7-hydroxy quetiapine, and N-desalkyl quetiapine plasma concentrations over a 48-hour time interval for each treatment are shown in the following figure.

Figure 3 **Mean plasma concentrations of quetiapine and 3 metabolites over time for quetiapine SR-F 400 mg (evaluable patients, N=14)**

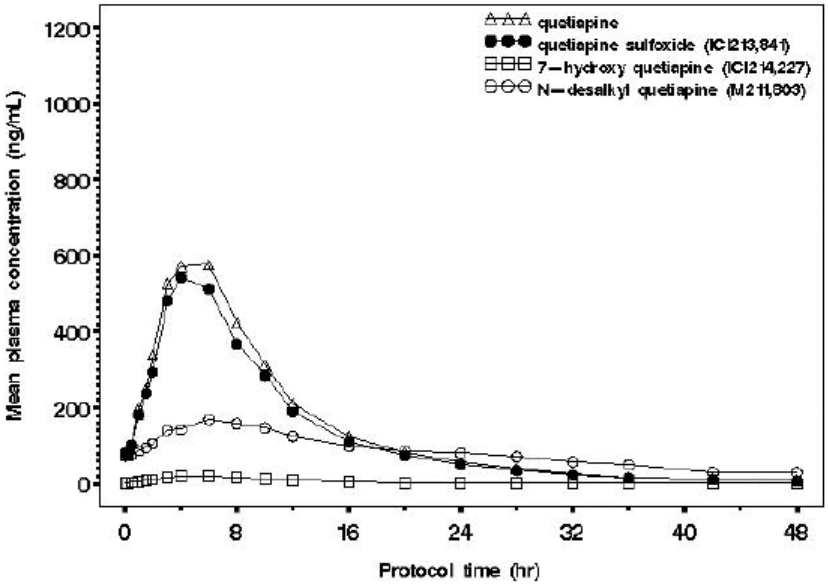


Figure 4 **Mean plasma concentrations of quetiapine and 3 metabolites over time for quetiapine SR-T 400 mg (evaluable patients, N=14)**

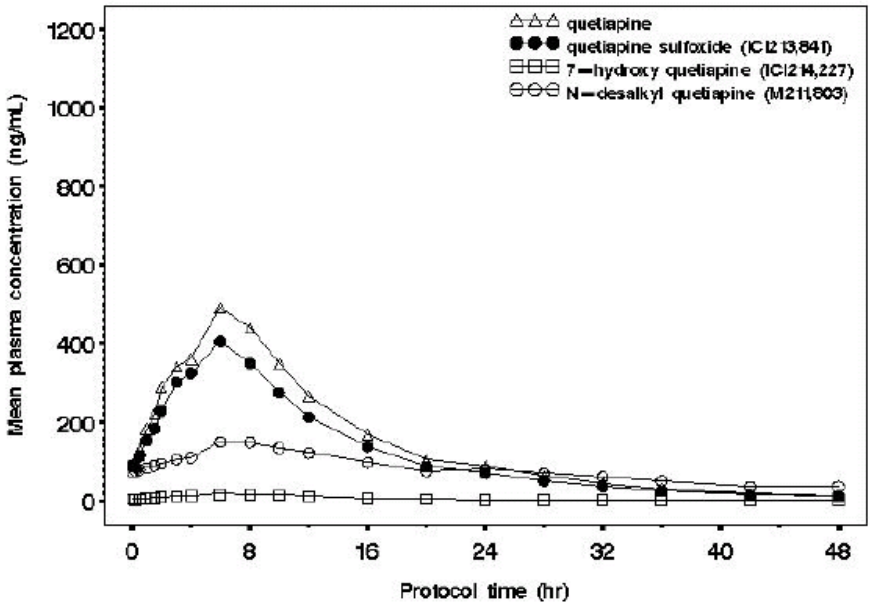


Figure 5 **Mean plasma concentrations of quetiapine and 3 metabolites over time for quetiapine SR-S 400 mg (evaluable patients, N=14)**

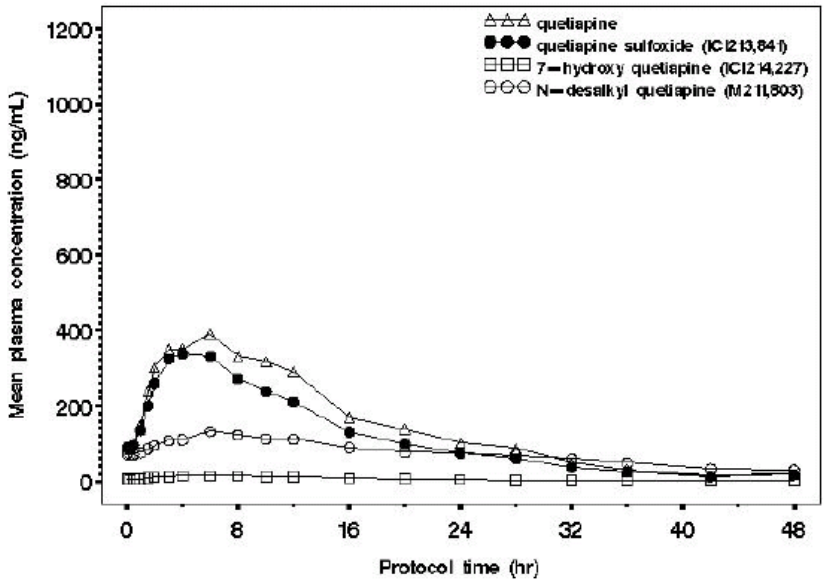
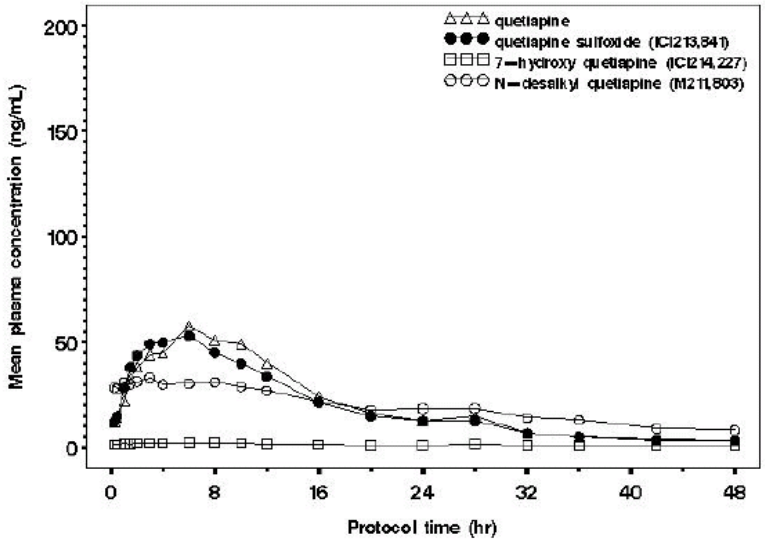


Figure 6 **Mean plasma concentrations of quetiapine and 3 metabolites over time for quetiapine SR-T 50 mg (evaluable patients, N=14)**



Quetiapine sulfoxide plasma concentrations appear to be similar for quetiapine Cmax and tmax across all the different formulations. N-desalkyl quetiapine has a half-life approximately 2-fold longer than quetiapine. The Cmax for quetiapine and all its metabolites appears to occur at approximately the same tmax for each
formulation. The plasma pharmacokinetic parameters for quetiapine sulfoxide, 7-hydroxy quetiapine and N-desalkyl quetiapine.

Pharmacokinetic parameters of quetiapine sulfoxide (N = 14)

PK Parameter	Quetiapine Treatment				
	IR 200 mg X 2	SR-F 400 mg	SR-T 400 mg	SR-S 400 mg	SR-T 50 mg
	Geometric Mean (%CV)				
Cmax (ng/mL)	1094.57 (30.26)	577.52 (37.44)	432.91 (27.42)	387.23 (27.72)	59.32 (31.43)
Tmax (hr) Median	1 (0.5 – 3.0)	4 (3.0 – 6.0)	6 (2.0 – 8)	5 (2 – 10)	4 (0- 12)
AUC (0-24hr) (ng*hr/mL)	5867.12 (36.22)	5264.48 (31.83)	4822.87 (28.46)	4551.77 (28.46)	701.22
T ½ (hr) (Mean ±SD) (N=8)	7.64 ± 2.11	6.44 ± 0.98	7.18 ± 0.90	8.29 ± 2.33	7.59 ± 1.36

CV= coefficient of variation; IR= immediate release; SR-F= sustained release- fast release profile; SR-S= sustained release- slow release profile; SR-T = sustained release target release profile.

Pharmacokinetic Parameters of 7-hydroxy quetiapine (n=14)

PK Parameter	Quetiapine Treatment				
	IR 200 mg X 2	SR-F 400 mg	SR-T 400 mg	SR-S 400 mg	SR-T 50 mg
	Geometric Mean (%CV)				
Cmax (ng/mL)	47.35 (51.82)	21.77 (59.82)	18.35 (64.86)	15.22 (68.27)	2.42 (71.69)
Tmax (hr) Median (max-min)	1 (0.5-2.0)	4 (2.9 – 8.0)	6 (3.0 – 10.0)	6 (4 – 12)	6 (0 – 28)
AUC (0-24hr) (ng*hr/mL)	342.60 (18.73)	323.69 (21.66)	309.26 (26.20)	285.68 (20.50)	49.40 (27.56)
T ½ (hr) (Mean ±SD) (N=3)	5.75 ± 1.76	5.67 ± 1.72	7.04 ± 0.62	5.72± 2.04	4.34 ± 0.69

CV= coefficient of variation; IR= immediate release; SR-F= sustained release- fast release profile; SR-S= sustained release- slow release profile; SR-T = sustained release target release profile.

Pharmacokinetic Parameters of N-desalkyl quetiapine

PK Parameter	Quetiapine Treatment				
	IR 200 mg X 2	SR-F 400 mg	SR-T 400 mg	SR-S 400 mg	SR-T 50 mg
	Geometric Mean (%CV)				
Cmax (ng/mL)	252.97 (33.15)	176.98 (23.94)	159.22 (24.85)	135.90 (29.82)	32.78 (56.88)
Tmax (hr) Median (max-min)	2 (1-10)	6 (3-10)	7 (2-8)	6 (4-10)	4.6 (0-28)
AUC (0-24hr) (ng*hr/mL)	3075.8 (24.1)	2730.6 (19.1)	2527.7 (19.75)	2293.8 (29.9)	522.92 (62.97)
T ½ (hr) (Mean ±SD) (N=5)	11.66 ± 1.53	11.15 ± 2.41	11.99 ± 2.90	12.77 ± 3.99	12.22 ± 2.12

The SR formulations achieved a lower Cmax and more sustained plasma concentrations for the metabolites as had been observed for quetiapine. The median tmax for quetiapine was similar to the tmax observed for its metabolites. Half-lives for all the metabolites appeared independent of the formulation administered. The half-life of N-desalkyl quetiapine appears to be approximately 12 hours, which is twice as long as quetiapine which led to significant carry over of residual concentrations from the 4th treatment period that confounded the PK parameters estimates for N-desalkyl quetiapine Cmax and AUC for the quetiapine SR-T 50 mg treatment.

Statistical analysis of metabolite Cmax and AUC(0-24hr) PK parameter estimates following quetiapine 400 mg doses for quetiapine IR and the 3 SR formulations are summarized in the following table.

Table 18 **Comparison of the metabolite pharmacokinetics of quetiapine SR 400 mg vs quetiapine IR 200 mg X 2, by SR formulation (evaluable patients; N=14)**

Quetiapine metabolite Ratio of treatments	Parameter	LS mean ratio[a]	90% CI
Quetiapine sulfoxide			
quetiapine SR-F/quetiapine IR	C_{max}, ng/ml	0.53	0.45, 0.61
quetiapine SR-F/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.90	0.82, 0.99
quetiapine SR-T/quetiapine IR	C_{max}, ng/ml	0.40	0.34, 0.46
quetiapine SR-T/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.82	0.74, 0.92
quetiapine SR-S/quetiapine IR	C_{max}, ng/ml	0.35	0.30, 0.42
quetiapine SR-S/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.78	0.70, 0.86
7-hydroxy quetiapine			
quetiapine SR-F/quetiapine IR	C_{max}, ng/ml	0.46	0.38, 0.55
quetiapine SR-F/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.89	0.80, 1.01
quetiapine SR-T/quetiapine IR	C_{max}, ng/ml	0.39	0.33, 0.45
quetiapine SR-T/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.86	0.76, 0.98
quetiapine SR-S/quetiapine IR	C_{max}, ng/ml	0.32	0.27, 0.39
quetiapine SR-S/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.81	0.73, 0.91
N-desalkyl quetiapine			
quetiapine SR-F/quetiapine IR	C_{max}, ng/ml	0.70	0.62, 0.79
quetiapine SR-F/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.89	0.84, 0.94
quetiapine SR-T/quetiapine IR	C_{max}, ng/ml	0.63	0.56, 0.71
quetiapine SR-T/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.82	0.77, 0.87
quetiapine SR-S/quetiapine IR	C_{max}, ng/ml	0.54	0.44, 0.65
quetiapine SR-S/quetiapine IR	$AUC_{(0-24)}$, ng.hr/mL	0.75	0.66, 0.84

Note: Evaluable patients were those patients who met the patient selection criteria and who had pharmacokinetic profiles for Treatment Periods 1 to 4.

[a] Based on least-square means from ANOVA analysis of log-transformed PK parameters.

IR immediate release; SR-F sustained release-fast release profile; SR-S sustained release-slow release profile; SR-T sustained release-target release profile.

The difference in the drug release rates (10% faster [SR-F] and 10% slower [SR-S]) between the different SR formulations is reflected in both Cmax and AUC (0-24hr), where the LS mean ratio estimates for the SR-T formulation fall between the SR-F and SR-S formulations. For all the metabolites, the Cmax for quetiapine SR-T 400 mg is approximately 37% to 61% lower than the quetiapine IR 200 mg X 2 formulation and the average AUC(0-24hr) is 14% to 18% lower than the IR formulation.

Summary of pharmacokinetic results: The quetiapine IR 200 mg X 2 formulation achieved the highest Cmax at the earliest median tmax of approximately 1 hour, followed in order by the quetiapine SR-F, SR-T, and SR-S formulations. The quetiapine SR formulations produced lower, but more sustained plasma concentrations than the quetiapine IR formulation. The quetiapine SR formulations achieved very similar overall exposure over a 24-hour time period. The half-life of quetiapine and its metabolites appear independent of the formulation administered. When the

quetiapine IR and SR-T 400 mg formulations are compared, the AUC's for all the metabolites appear lower (<20% on average) than for the IR formulation.

Safety Summary: The sponsor reported that all quetiapine IR or SR doses were generally well tolerated in this population with no unexpected AEs reported during the study. There were no deaths or discontinuations due to adverse events during the study. There was 1 SAE (worsening of schizophrenia), which occurred during the post-treatment period. The majority of AEs were rated as mild in intensity. Fourteen of the 18 patients in the safety population reported a total of 45 adverse events during study treatment. Six patients reported a total of 15 adverse events during study treatment that were considered treatment related by the investigator. Most of these treatment related events were CNS disorders and occurred similarly across the quetiapine IR or SR 400 mg formulations; no treatment-related AE was reported in the quetiapine 50 mg treatment group. Headache was the most frequently occurring AE (5 of 18 patients). Dizziness was reported in 2 patients during study treatment (IR 200 mg X 2 and SR-F 400 mg) with both cases associated with orthostatic changes in heart rates. Both events of dizziness were considered related to study treatment. The sponsor reported no clinically important changes in clinical laboratory or vital sign parameters between screening and end of treatment.

Conclusions: All 3 SR 400 mg formulations had lower maximum plasma concentrations (Cmax) and delayed times to Cmax (tmax) than obtained with quetiapine IR consistent with sustained release formulations. The rank order of the Cmax and tmax for the different SR 400 mg formulations was consistent with that expected from their in-vitro drug dissolution rates.

Reviewer's comments: *The reviewer agrees with the sponsor's conclusions.*

Appendix

Table 11.2.3.3.1 Comparison of AUC and Cmax of quetiapine and 3 metabolites for IR 400 mg and SR-S 400 mg - PK evaluable subjects

Pharmacokinetic Parameter	Comparison (SR-S 400 mg/IR 400 mg)			IR 400 mg			SR-S 400 mg		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	0.96	0.85	1.09	5363.34	3688.99	7797.64	5172.72	3857.00	6937.26
AUC (Quetiapine sulfoxide)	0.78	0.70	0.86	5867.12	4790.61	7185.53	4551.77	3874.48	5347.46
AUC (7-hydroxy quetiapine)	0.81	0.73	0.91	302.00	258.00	353.50	200.82	142.18	283.64
AUC (N-desalkyl quetiapine)	0.75	0.66	0.84	3075.79	2681.49	3528.07	2293.79	1936.20	2717.42
Cmax (Quetiapine)	0.35	0.30	0.42	1270.38	953.38	1692.79	447.76	370.33	541.36
Cmax (Quetiapine sulfoxide)	0.35	0.30	0.42	1094.57	922.62	1298.57	387.23	330.94	453.10
Cmax (7-hydroxy quetiapine)	0.32	0.27	0.39	47.35	35.73	62.75	15.22	10.65	21.75
Cmax (N-desalkyl quetiapine)	0.54	0.44	0.65	252.97	209.94	304.81	135.90	114.82	160.84

Table 11.2.3.2.1 Comparison of AUC and Cmax of quetiapine and 3 metabolites for IR 400 mg and SR-T 400 mg - PK evaluable subjects

Pharmacokinetic Parameter	Comparison (SR-T 400 mg/IR 400 mg)			IR 400 mg			SR-T 400 mg		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	1.00	0.87	1.14	5363.34	3688.99	7797.64	5346.87	3875.03	7377.75
AUC (Quetiapine sulfoxide)	0.82	0.74	0.92	5867.12	4790.61	7185.53	4822.87	4158.71	5593.10
AUC (7-hydroxy quetiapine)	0.86	0.76	0.98	302.00	258.00	353.50	213.26	149.85	303.50
AUC (N-desalkyl quetiapine)	0.82	0.77	0.87	3075.79	2681.49	3528.07	2527.70	2257.70	2829.97
Cmax (Quetiapine)	0.41	0.34	0.49	1270.38	953.38	1692.79	518.20	388.63	690.97
Cmax (Quetiapine sulfoxide)	0.40	0.34	0.46	1094.57	922.62	1298.57	432.91	370.57	505.73
Cmax (7-hydroxy quetiapine)	0.39	0.33	0.45	47.35	35.73	62.75	18.35	13.03	25.83
Cmax (N-desalkyl quetiapine)	0.63	0.56	0.71	252.97	209.94	304.81	159.22	138.24	183.40

Table 11.2.3.1.1 Comparison of AUC and Cmax of quetiapine and 3 metabolites for IR 400 mg and SR-P 400 mg - PK evaluable subjects

Pharmacokinetic Parameter	Comparison (SR-P 400 mg/IR 400 mg)			IR 400 mg			SR-P 400 mg		
	Ratio (90% C.I.)			Geometric mean (95% CI)			Geometric mean (95% CI)		
	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM	MEAN	LCLM	UCLM
AUC (Quetiapine)	1.05	0.91	1.21	5363.34	3688.99	7797.64	5628.92	4281.22	7400.88
AUC (Quetiapine sulfoxide)	0.90	0.82	0.99	5867.12	4790.61	7185.53	5264.48	4399.95	6298.87
AUC (7-hydroxy quetiapine)	0.89	0.80	1.01	302.00	258.00	353.50	224.98	163.71	309.18
AUC (N-desalkyl quetiapine)	0.89	0.84	0.94	3075.79	2681.49	3528.07	2730.55	2448.41	3045.21
Cmax (Quetiapine)	0.51	0.41	0.65	1270.38	953.38	1692.79	652.46	516.37	824.41
Cmax (Quetiapine sulfoxide)	0.53	0.45	0.61	1094.57	922.62	1298.57	577.52	468.54	711.85
Cmax (7-hydroxy quetiapine)	0.46	0.38	0.55	47.35	35.73	62.75	21.77	15.82	29.96
Cmax (N-desalkyl quetiapine)	0.70	0.62	0.79	252.97	209.94	304.81	176.98	154.43	202.83

Table 22 **Number (%) of patients in the safety population who had at least 1 adverse event on treatment, grouped by system organ class and preferred term (safety population)**

System organ class and preferred term[a]	Treatment group, n (%) of patients				
	Quetiapine IR 200 mg X 2 (N=17)	Quetiapine SR-F 400 mg (N=15)	Quetiapine SR-T 400 mg (N=15)	Quetiapine SR-S 400 mg (N=17)	Quetiapine SR-T 50 mg (N=15)
Nervous system disorders	5 (29.4)	5 (33.3)	1 (6.7)	4 (23.5)	1 (6.7)
Dizziness	1 (5.9)	1 (6.7)	0	0	0
Headache	3 (17.6)	4 (26.7)	1 (6.7)	2 (11.8)	1 (6.7)
Sedation	2 (11.8)	1 (6.7)	0	2 (11.8)	0
Psychiatric disorders	1 (5.9)	1 (6.7)	2 (13.3)	1 (5.9)	1 (6.7)
Anxiety	0	1 (6.7)	1 (6.7)	1 (5.9)	1 (6.7)
Insomnia	1 (5.9)	0	1 (6.7)	0	0
General disorders and administration site conditions	0	1 (6.7)	2 (13.3)	1 (5.9)	0
Chills	0	0	1 (6.7)	0	0
Fatigue	0	0	1 (6.7)	1 (5.9)	0
Pain	0	1 (6.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (5.9)	0	2 (13.3)	1 (5.9)	0
Nasal congestion	1 (5.9)	0	0	1 (5.9)	0
Pharyngolaryngeal pain	0	0	2 (13.3)	0	0
Gastrointestinal system disorders	0	1 (6.7)	1 (6.7)	1 (5.9)	0
Diarrhea	0	0	0	1 (5.9)	0
Dry mouth	0	0	1 (6.7)	1 (5.9)	0
Dyspepsia	0	1 (6.7)	0	0	0
Musculoskeletal and connective tissue disorders	1 (5.9)	0	0	1 (5.9)	0
Back pain	1 (5.9)	0	0	0	0
Neck pain	0	0	0	1 (5.9)	0

Title (D1444C00003): A Study to Compare the Pharmacokinetics of 50 mg and 300 mg Quetiapine Fumarate Sustained Release (SR) Tablets Administered Following a Light Meal and in the Fasted State in Adult Volunteers and Adults with Schizophrenia, Schizoaffective Disorder or Bipolar Disorder

Objective

The primary objective of the study was to estimate the effect of a light meal on the steady state pharmacokinetics of the sustained release (SR) formulation of quetiapine fumarate (SEROQUEL) (50 mg and 300 mg) using the fasting state as a comparison.

The secondary objectives of the study were:

1. To assess the safety and tolerability of quetiapine SR when administered following a light meal and in the fasted state.
2. To describe the steady-state pharmacokinetics of quetiapine metabolites: quetiapine sulfoxide, N-desalkyl quetiapine and 7-hydroxy quetiapine when administered as quetiapine SR following a light meal and in the fasted state, respectively.
3. To collect samples for pharmacogenetic analysis.

Study Design: This was a single centre, open-label, two-cohort, randomized, two-treatment, two-period crossover, steady-state pharmacokinetic study. The subject population for Cohort A was planned to be approximately 24 healthy male and female normal volunteers to ensure that 18 evaluable subjects completed the study. The patient population for Cohort B was planned to be approximately 16 adults with schizophrenia, schizoaffective disorder or bipolar disorder to ensure that 12 evaluable patients completed the study.

Each subject and patient in Cohort A and Cohort B, respectively, received two study treatments, designated Treatment L and Treatment N. Treatment L was quetiapine SR administered together with a light meal. Treatment N was quetiapine SR administered in the fasted state. Each of the two study treatments was given for 3 days in crossover fashion according to one of two randomly assigned treatment sequences: LN or NL. The total of 6 days of treatment with the study drug were divided into two periods as follows:
Administration of drug with food (L) and without food (N) was randomly allocated to study Period 1 (Days 1-3) and to study Period 2 (Days 4-6), respectively. Subjects in Cohort A were administered the 50-mg quetiapine SR tablet and patients in Cohort B received the 300-mg quetiapine SR tablet. All study drugs were administered orally, once daily in the morning. A washout study period for healthy volunteers was not required, so that they entered the study on Day –1. Patients in Cohort B entered the study on Day –2 and underwent a washout period of 2 days of their concurrent medication prior to dosing. There were 5 days between the last dose of prior anti-psychotic drug treatment and PK sampling on Day 3.

The light meal for breakfast consisted of 2 slices of toast, 2 teaspoons (10g) of jelly (jam), 180 mL (6 fluids ounces) of orange juice, 1 cup (237g) of coffee, 2 tablespoons (30.6 g) of 0.1% (skim) milk and 2 teaspoons (10g) of sugar (292 calories in total).

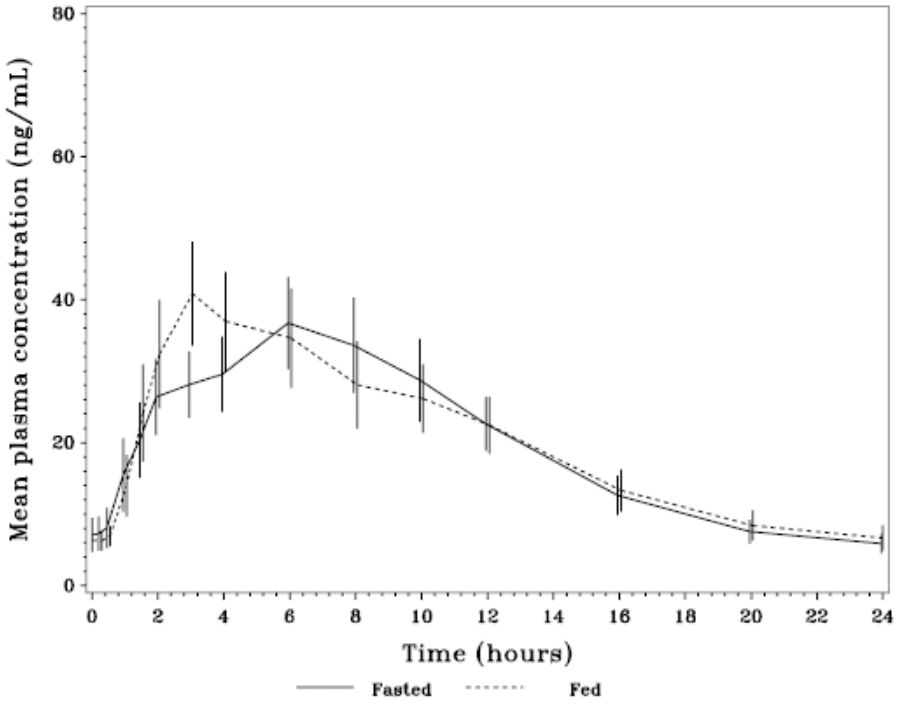
Fifteen serial blood samples were obtained from each subject between 0–24 hours at Day 3 and Day 6. The samples were analyzed for plasma concentrations of quetiapine and its metabolites.

Analytical Method: Quetiapine, M213,841 (quetiapine sulfoxide), M214,227 (7-hydroxy quetiapine), and M211,803 (N-desalkyl quetiapine) concentrations were determined in human plasma samples collected from subjects following administration of quetiapine fumarate (Seroquel™). They were analyzed using a liquid-liquid extraction of quetiapine, M213,841, M214,227, and M211,803 and internal standards (ISTDs) ($13C^6$–quetiapine, d8-M213,841, d8–M214,227, and d8-M211,803) from alkalinized human EDTA plasma using ethyl acetate, followed by reverse phase liquid chromatography and turbo ionspray ionization tandem mass spectrometry (LC/MS/MS). Analyses were performed over the range of 0.500 to 500 ng/mL in human plasma with extension of the validated curve range to 10.0 mg/mL for quetiapine, M213,841,

Data Analysis: Non-compartmental methods were used in computing the pharmacokinetic parameters.

Results: Quetiapine mean plasma concentrations following 50 mg in healthy volunteers (Cohort A) and after 300 mg quetiapine SR in patients (Cohort B) are shown in the following figures.

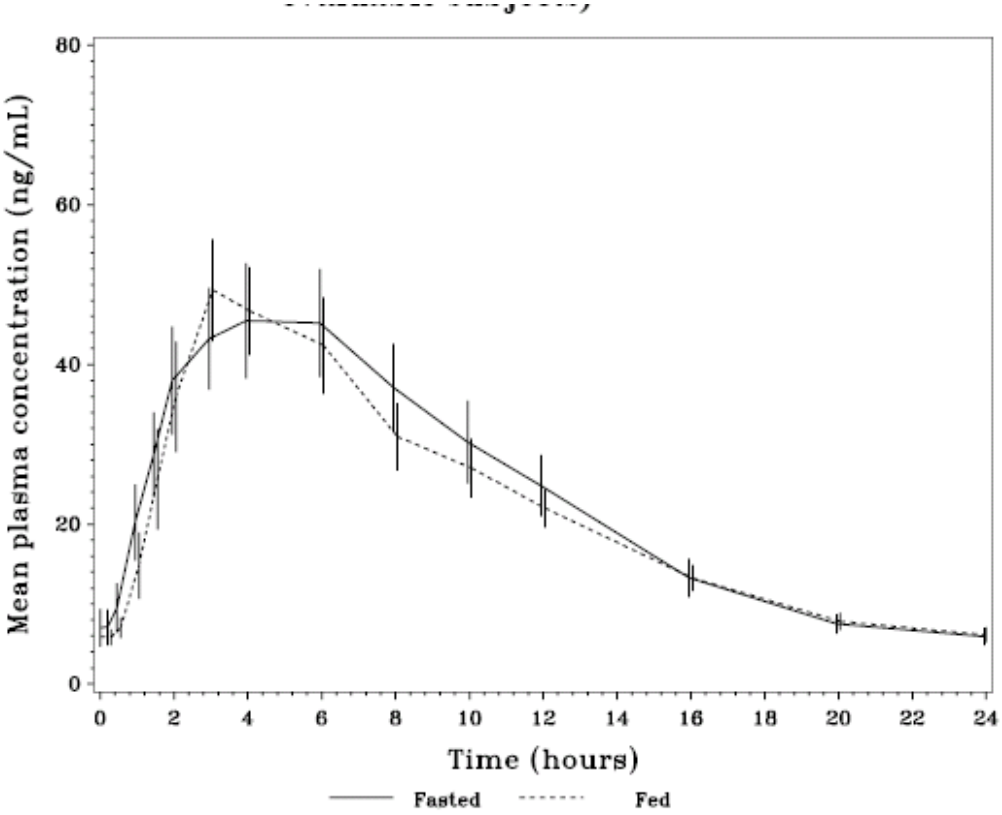
Mean plasma concentration versus time of quetiapine- Healthy volunteers, quetiapine SR 50 mg



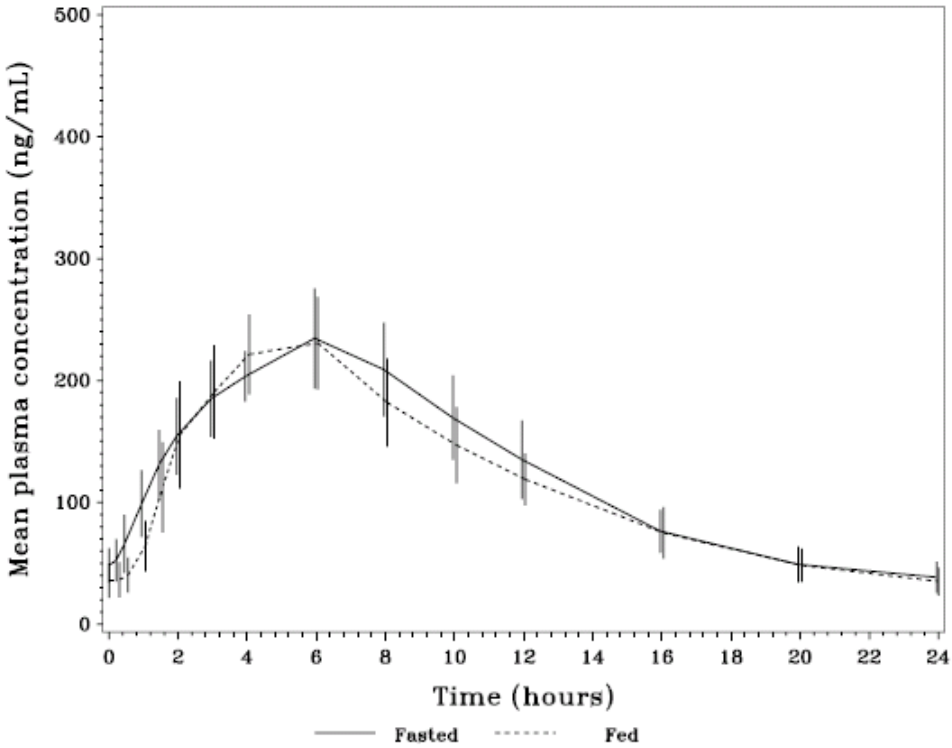
For the 50-mg tablet, the highest mean concentrations of 40.8 ±16.3 ng/mL in the fed state were achieved at 3 h post dose compared to 36.7 ±14.4 ng/mL at 6 h in the fasted state. After dosing of 300 mg quetiapine SR to the patient cohort, plasma concentrations also peaked more quickly in the fed compared to the fasted state with the highest means of 218 ±85.2 ng/mL at 6 h compared to 237 ±161 ng/mL at 8 h, respectively.

Quetiapine sulfoxide plasma concentration versus time curves for both cohorts are shown in the following figures. After 50 mg quetiapine SR, concentrations of 45.5 ±16.2 ng/mL (fasted) and 49.3 ±14.3 ng/mL (fed) were achieved at 4 h and 3 h, respectively. At the 300-mg dose level, the highest mean concentrations of 234 ±73.8 ng/mL (fasted) and 231 ±68.6 ng/mL (fed) were reached at 6 h post-dose. Quetiapine sulfoxide concentrations at 24 h post-dose were also similar (fed) or even slightly lower (fasted) than pre-dose levels, indicating that steady-state had been achieved for this metabolite.

Mean plasma concentration versus time of quetiapine sulfoxide- Healthy volunteers, quetiapine SR 50 mg

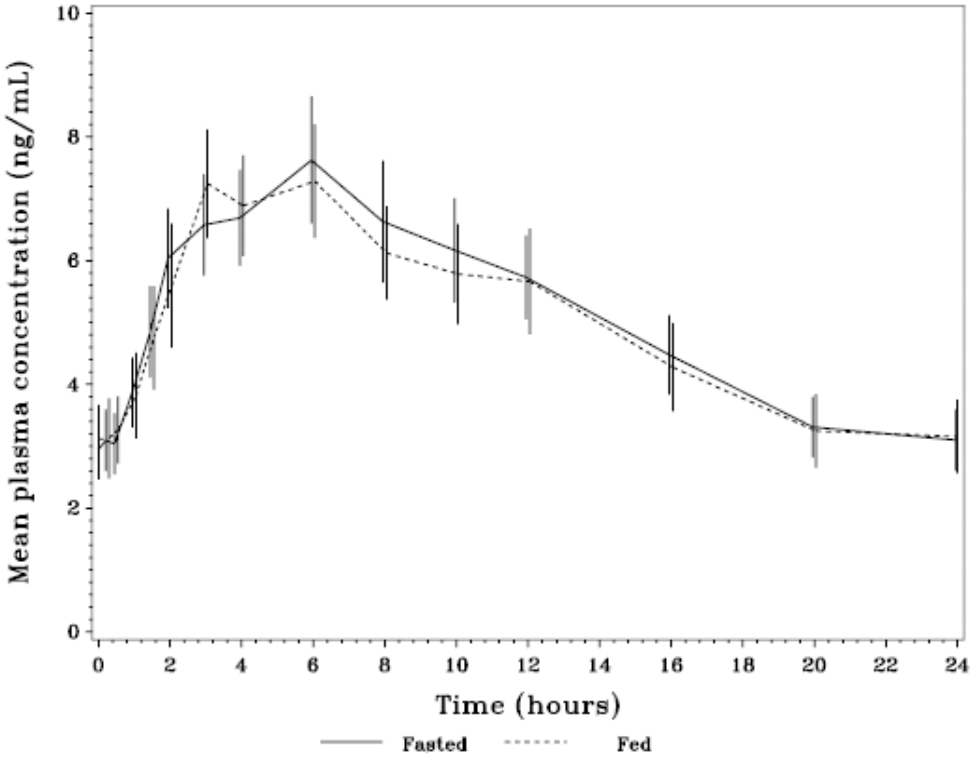


Mean plasma concentration versus time of quetiapine sulfoxide- Patients, quetiapine SR 300 mg

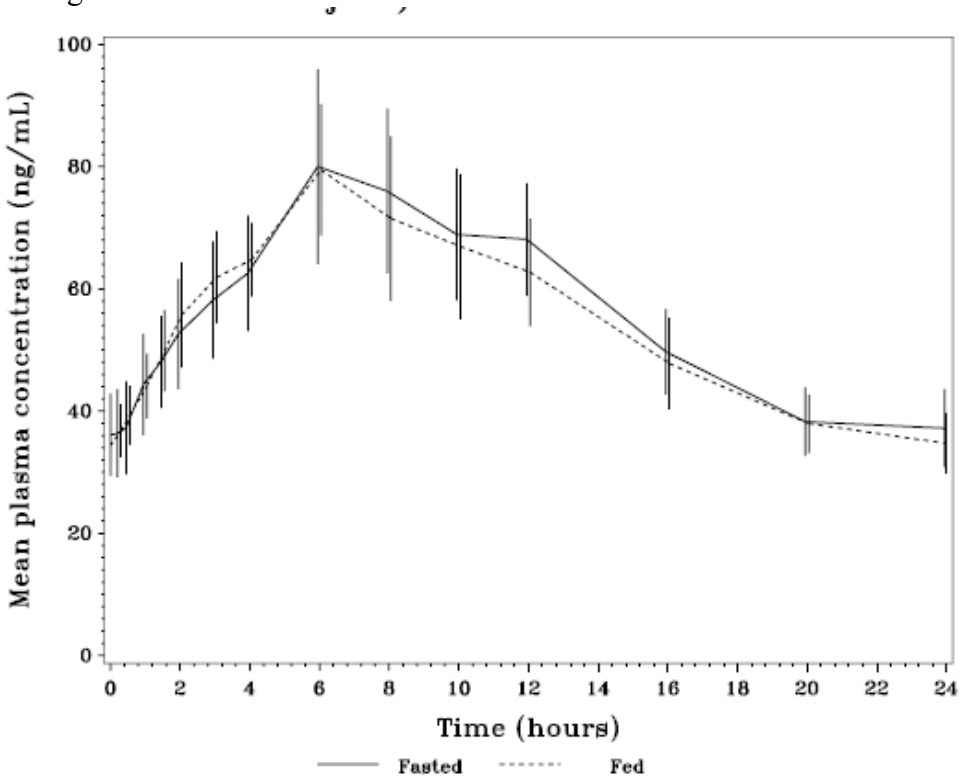


Compared to quetiapine and quetiapine sulfoxide concentrations of N-desalkyl quetiapine were lower as indicated in the following figures. The time of the highest mean concentrations of this metabolite also approximately coincided with that of the parent compound in both cohorts.

Mean plasma concentration versus time of N-desalkyl quetiapine – Healthy volunteers, quetiapine SR 50 mg

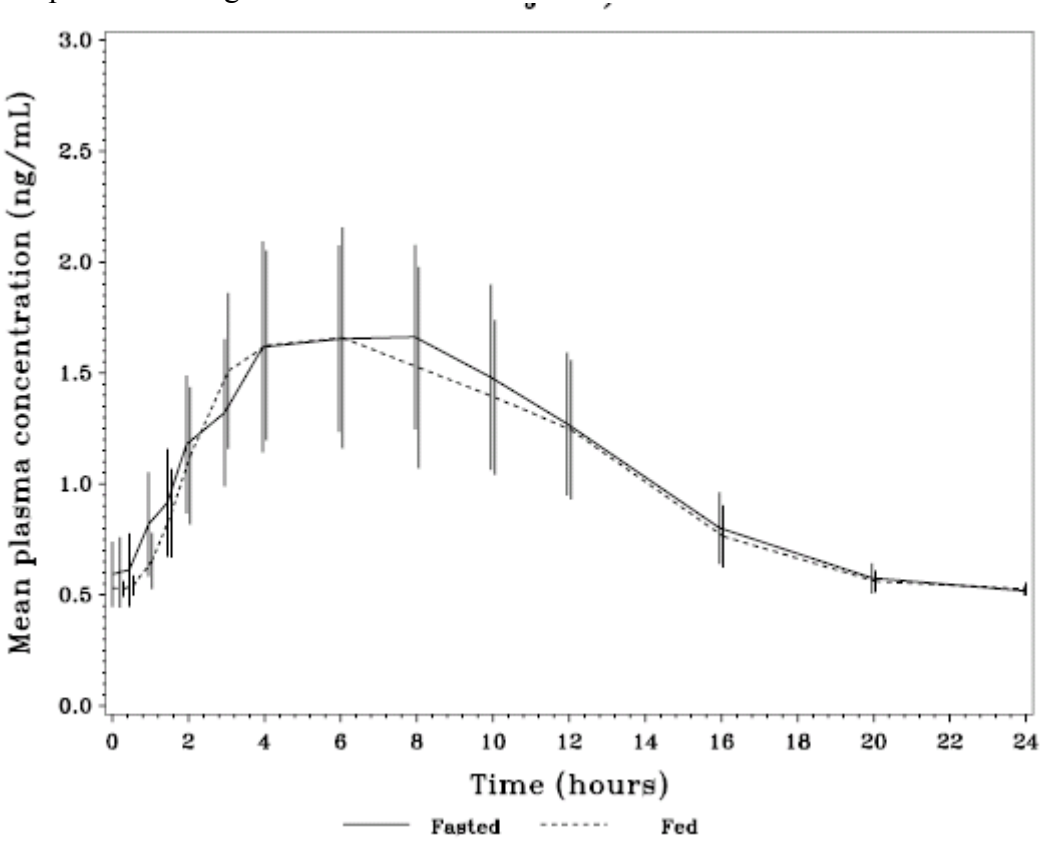


Mean plasma concentration versus time of N-desalkyl quetiapine- Patients, quetiapine SR 300 mg

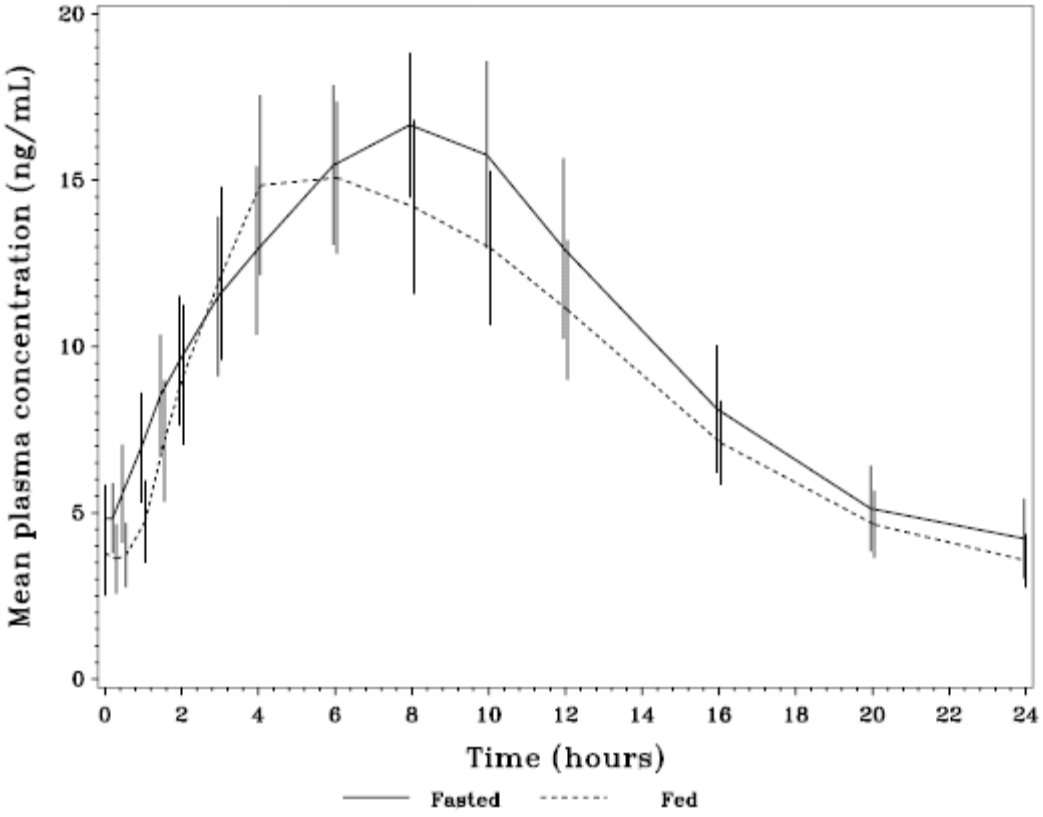


Mean plasma concentrations of 7-hydroxy quetiapine were close to the lower limit of quantification (LOQ) for 50 mg quetiapine SR following dosing and did not reach 2 ng/mL at any time. At the 300-mg dose level, all patients had quantifiable
7 hydroxy quetiapine, but the highest mean concentrations at 6 to 8 h post-dose were below 20 ng/mL.

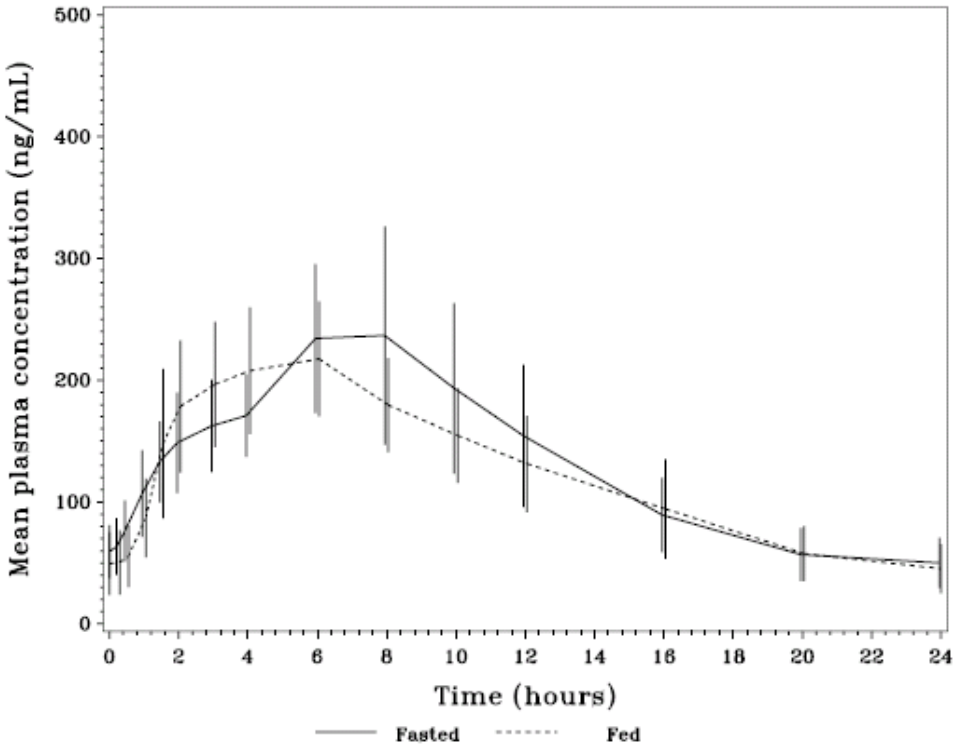
Mean plasma concentration versus time of 7-hydroxy quetiapine- Healthy volunteers, quetiapine SR 50 mg



Mean plasma concentration versus time of 7-hydroxy quetiapine- Patients, quetiapine SR 300 mg



Mean plasma concentration versus time of quetiapine- Patients, quetiapine SR 300 mg



In the fasted state in both cohorts, the median tmax was reached at approximately 6 h (range: 1.5-12 h). The tmax was reduced to 3 h (50 mg) and 4.1 h (300 mg), when quetiapine was administered in the fed state. The light meal not did produce a significant effect on Css,max nor AUCss. The apparent terminal elimination half-life, t1/2, was close to 6 h in both cohorts in the fasted state and did not change to a considerable extent, when quetiapine was given with the light meal.

Pharmacokinetic Parameters of quetiapine

	Healthy volunteers, Quetiapine SR 50 mg		Patients, Quetiapine SR 300 mg	
Parameter	**Fasted**	**Fed**	**Fasted**	**Fed**
AUC_{ss}, ng×hr/mL				
N	20	20	13	13
Geometric mean	442.8	457.1	2909	2762
CV(%)	38.6	40.9	55.2	49.7
Min to max	258.4 to 825.4	279.3 to 1072	1669 to 8681	1592 to 7366
$C_{ss,max}$, ng/mL				
N	20	20	13	13
Geometric mean	38.1	41.4	241	236
CV(%)	34.3	35.5	57.9	34.3
Min to max	18.4 to 65.9	18.6 to 76.0	163 to 749	133 to 477
$C_{ss,min}$, ng/mL				
N	20	20	13	13
Geometric mean	5.11	5.80	39.2	35.0
CV(%)	50.6	59.1	74.2	80.2
Min to max	0.94 to 13.4	2.71 to 16.8	5.73 to 154	6.83 to 138
t_{max}, hr				
N	20	20	13	13
Median	6.0	3.0	6.0	4.1
Min to max	1.5 to 12.0	1.5 to 6.1	1.5 to 12.0	1.5 to 8.0
$t_{1/2}$, hr				
N	14	14	9	9
Mean	5.9	7.2	6.1	5.8
SD	1.3	1.8	2.0	1.1
Min to max	3.5 to 8.7	4.0 to 10.0	3.3 to 10.4	3.2 to 6.9
CL/F, L/hr				
N	20	20	13	13
Mean	120.6	116.3	109.6	115.3
SD	43.60	39.70	34.87	37.38
Min to max	60.58 to 193.5	46.64 to 179.0	34.56 to 179.8	40.73 to 188.5

SR Sustained release.

The relative bioavailability of quetiapine was not significantly affected by the light meal. All 90% confidence intervals were within the equivalence limits [0.8, 1.25].

Relative bioavailability of quetiapine SR 50 mg and of quetiapine SR 300 mg in the fasted and fed states

	Healthy volunteers, Quetiapine SR 50 mg		Patients, Quetiapine SR 300 mg	
Parameter	**Fasted**	**Fed**	**Fasted**	**Fed**
AUC_{ss}, ng×hr/mL				
N	20	20	13	13
Geometric mean[a]	442.8	457.1	2906	2764
95% confidence interval	(419.7-467.1)	(433.3-482.3)	(2771-3049)	(2635-2900)
Mean fed/fasted ratio	1.03		0.95	
90% confidence interval	(0.97-1.10)		(0.90-1.01)	
$C_{ss,max}$, ng/mL				
N	20	20	13	13
Geometric mean[a]	38.1	41.4	243	235
95% confidence interval	(34.8-41.8)	(37.8-45.4)	(215-273)	(208-265)
Mean fed/fasted ratio	1.09		0.97	
90% confidence interval	(0.97-1.21)		(0.84-1.11)	

[a] Based on least square mean from analysis of variance for log-transformed parameters
SR Sustained release.

Summary of Pharmacokinetics: A total of 20 healthy volunteers who received 50-mg quetiapine SR doses with or without food in randomized order for 3 days each and 13 patients on a higher dose of 300 mg were evaluable for pharmacokinetic evaluation. Css,max and AUCss for quetiapine and its metabolites did not indicate a significant effect of a light meal. All 90% confidence intervals for the mean ratios fed versus fasted of quetiapine fell within the equivalence limits [0.8, 1.25].

All the metabolites were rapidly formed and their tmax occurred at approximately the same time as tmax of the parent drug in the fasted state or shortly later in the fed state. Half-lives for quetiapine sulfoxide and 7-hydroxy quetiapine were similar to that of the parent drug, resulting in a t1/2 of approximately 6 h. Quetiapine sulfoxide showed a similar AUCss as the parent drug after both doses, followed by N-desalkyl quetiapine. There were only low concentrations of 7-hydroxy quetiapine after both doses. The rank order of metabolite exposure in terms of Css,max and AUCss was quetiapine sulfoxide > N-desalkyl quetiapine > 7-hydroxy quetiapine.

Safety Summary: The sponsor reported that overall, no new or unexpected AEs were reported in this study. Furthermore, no SAE occurred and none of the volunteers and patients were discontinued due to an AE. Main symptoms were somnolence during the first days of treatment and tachycardia, only seen in the patients. Epistaxis was reported in healthy volunteers and was reported by the sponsor to be associated to the low relative humidity of the air in their room. Most of the AEs were judged by the investigator to be of mild intensity; however, moderate

somnolence also occurred more often. One severe AE occurred, ie, a syncope. Vital signs showed abnormal orthostatic changes in 3 healthy
volunteers on Day 1 only. The sponsor reported that results of laboratory data and ECG recordings were clinically insignificant.

Conclusions: There was no significant effect of a light meal on quetiapine SR Css,max and AUCss during treatment with 50 mg in healthy volunteers and 300 mg in patients. All 90% confidence intervals of the ratios fed/fasted for Css,max and AUCss were within the equivalence limits [0.80, 1.25].

Reviewer's comments: *The reviewer agrees with the sponsor's comment.*

Figure 11.2.3- 9 Individual AUC values of quetiapine in the fasted and fed state - Healthy volunteers, quetiapine SR 50 mg (PK evaluable subjects)

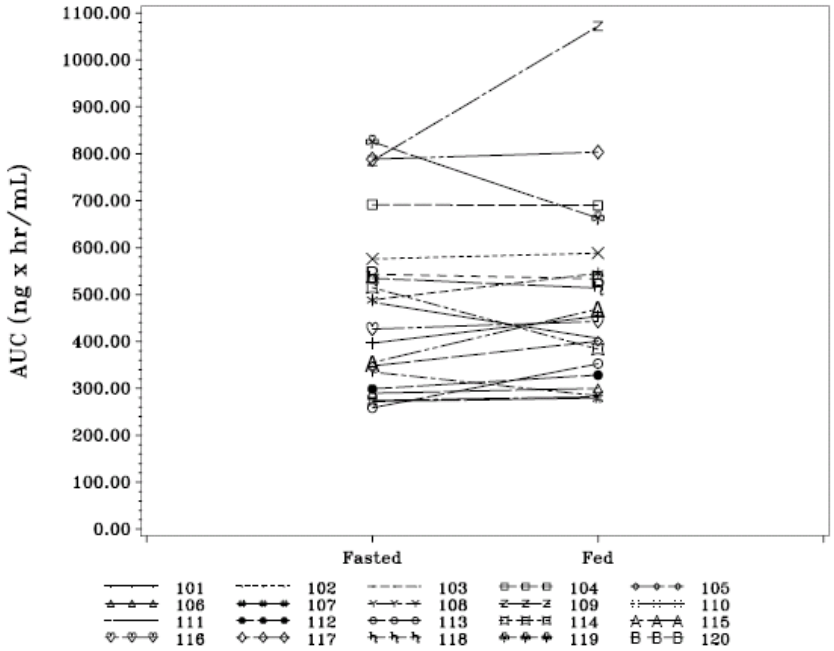


Figure 11.2.3- 10 Individual AUC values of quetiapine in the fasted and fed state - Patients, quetiapine SR 300 mg (PK evaluable subjects)

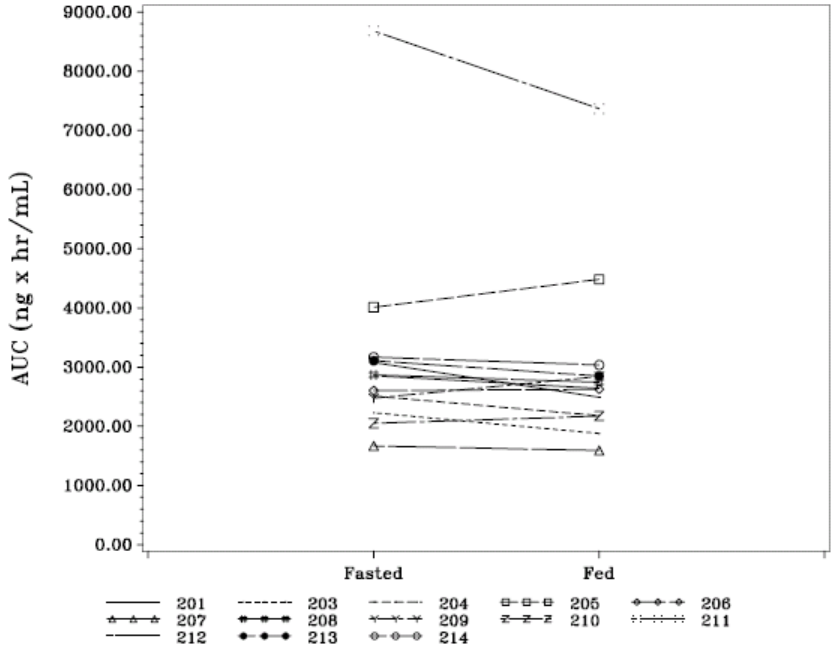


Figure 11.2.3- 11 Individual Cmax values of quetiapine in the fasted and fed state - Healthy volunteers, quetiapine SR 50 mg (PK evaluable subjects)

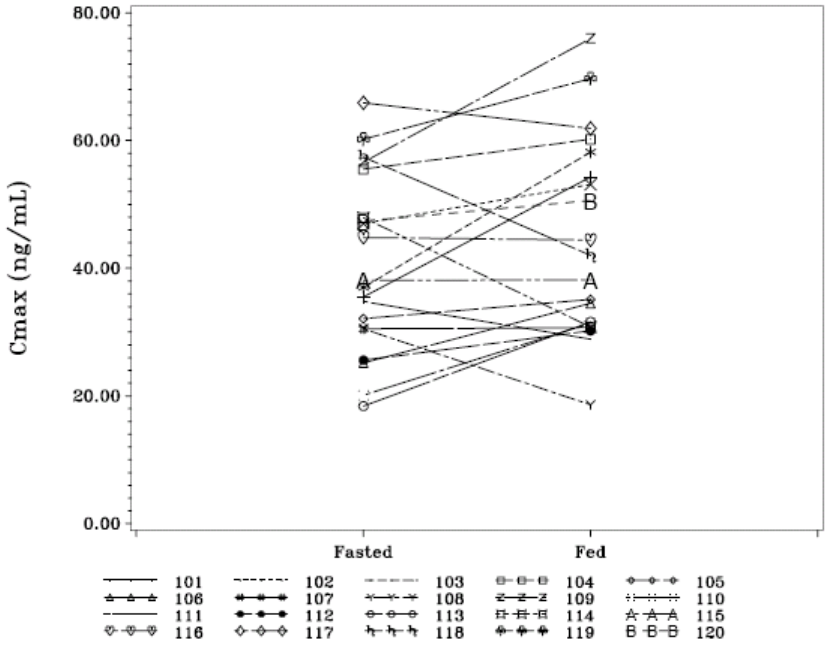


Figure 11.2.3- 12 Individual Cmax values of quetiapine in the fasted and fed state - Patients, quetiapine SR 300 mg (PK evaluable subjects)

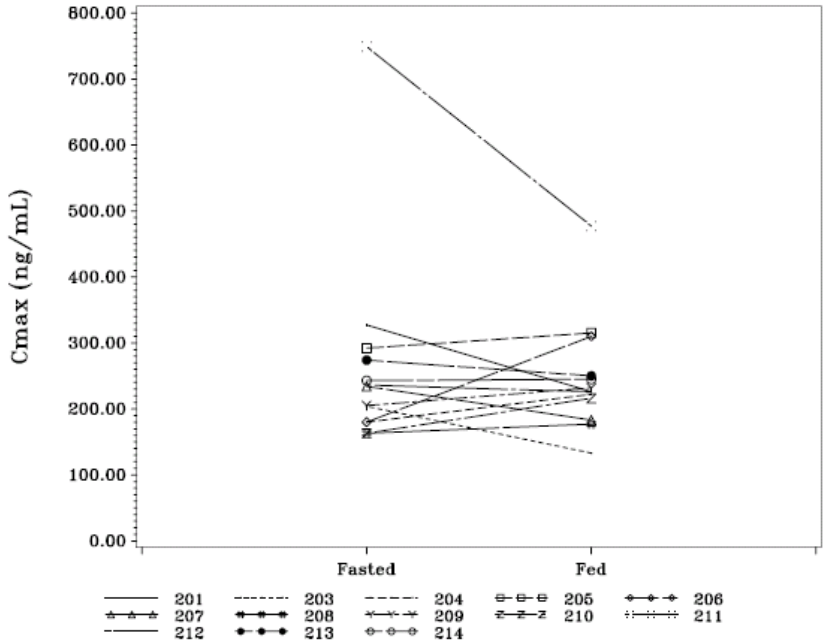


Table 11.2.1.1- 2 Pharmacokinetic parameters of quetiapine sulfoxide with extended statistics (PK evaluable subjects)

	Healthy volunteers, QTP SR 50 mg		Patients, QTP SR 300 mg	
Parameter	**Fasted**	**Fed**	**Fasted**	**Fed**
AUC_{ss}, ng×hr/mL				
N	20	20	13	13
Mean	565.1	534.6	2973	2793
SD	165.8	124.6	830.1	777.5
Geometric mean	545.2	521.8	2877	2696
CV(%)	29.4	23.3	27.9	27.8
Median	530.7	501.4	2749	2647
Min to max	370.1 to 986.9	359.4 to 789.4	2082 to 4572	1666 to 4251
$C_{ss,max}$, ng/mL				
N	20	20	13	13
Mean	50.6	52.8	249	249
SD	16.3	14.3	68.4	62.1
Geometric mean	48.2	50.9	241	241
CV(%)	32.3	27.2	27.5	25.0
Median	49.0	52.3	234	263
Min to max	27.1 to 85.0	27.0 to 85.7	168 to 386	136 to 343
$C_{ss,min}$, ng/mL				
N	20	20	13	13
Mean	5.91	6.13	38.6	35.2
SD	2.46	2.09	23.3	20.9
Geometric mean	5.42	5.79	32.2	29.9
CV(%)	41.6	34.1	60.3	59.3
Median	5.86	5.98	36.5	33.5
Min to max	1.55 to 13.5	2.25 to 11.8	7.39 to 98.9	10.3 to 78.5
t_{max}, hr				
N	20	20	13	13
Mean	4.8	3.9	5.8	5.2
SD	1.7	1.4	2.1	1.6
Median	6.0	3.5	6.0	6.0
Min to max	1.5 to 8.1	2.0 to 6.1	2.0 to 10.0	2.0 to 8.0
$t_{1/2}$, hr				
N	17	20	10	10
Mean	5.7	6.7	6.1	5.9

Table 11.2.1.1- 3 Pharmacokinetic parameters of N-desalkyl quetiapine with extended statistics (PK evaluable subjects)

	Healthy volunteers, QTP SR 50 mg		Patients, QTP SR 300 mg	
Parameter	**Fasted**	**Fed**	**Fasted**	**Fed**
AUC_{ss}, ng×hr/mL				
N	20	20	13	13
Mean	123.1	120.1	1345	1311
SD	32.92	36.75	353.6	278.2
Geometric mean	119.3	116.1	1306	1286
CV(%)	26.8	30.6	26.3	21.2
Median	117.9	108.5	1385	1219
Min to max	73.22 to 217.3	88.37 to 245.0	961.8 to 2096	971.7 to 1887
$C_{ss,max}$, ng/mL				
N	20	20	13	13
Mean	8.01	8.06	84.1	82.8
SD	2.32	1.90	26.6	22.3
Geometric mean	7.71	7.86	80.6	80.3
CV(%)	29.0	23.6	31.6	26.9
Median	7.34	7.46	78.4	77.7
Min to max	4.62 to 14.0	5.68 to 12.9	56.6 to 135	59.3 to 131
$C_{ss,min}$, ng/mL				
N	20	20	13	13
Mean	3.10	3.16	37.2	34.7
SD	1.10	1.32	11.6	8.99
Geometric mean	2.93	2.95	35.7	33.7
CV(%)	35.4	42.0	31.1	25.9
Median	2.91	2.86	32.2	33.4
Min to max	1.42 to 6.29	1.60 to 7.58	25.6 to 61.3	25.1 to 50.1
t_{max}, hr				
N	20	20	13	13
Median	6.0	4.0	6.0	6.0
Min to max	2.0 to 8.0	2.0 to 6.1	4.0 to 12.0	2.0 to 12.0

QTP Quetiapine. SR Sustained release.
Note: There was insufficient data to calculate the parameters $t_{1/2}$ and $lambda_z$ for N-desalkyl quetiapine

Table 11.2.1.1- 4 Pharmacokinetic parameters of 7-hydroxy quetiapine with extended statistics (PK evaluable subjects)

	Healthy volunteers, QTP SR 50 mg		Patients, QTP SR 300 mg	
Parameter	**Fasted**	**Fed**	**Fasted**	**Fed**
AUC_{ss} , ng×hr/mL				
N	19	19	13	13
Mean	22.35	21.47	245.7	221.8
SD	14.84	14.73	71.29	53.63
Geometric mean	17.44	16.16	235.6	215.8
CV(%)	66.4	68.6	29.0	24.2
Median	19.78	16.44	249.0	232.2
Min to max	2.090 to 61.20	2.090 to 51.50	144.6 to 354.1	156.2 to 314.1
$C_{ss,max}$, ng/mL				
N	19	19	13	13
Mean	1.99	1.91	18.2	17.0
SD	1.13	1.09	4.64	4.75
Geometric mean	1.72	1.65	17.6	16.4
CV(%)	56.8	56.9	25.5	27.9
Median	1.44	1.73	17.8	17.2
Min to max	0.70 to 4.75	0.69 to 4.90	11.7 to 24.0	10.4 to 25.8
$C_{ss,min}$, ng/mL				
N	19	19	13	13
Mean	NC	NC	4.23	3.56
SD	NC	NC	2.16	1.47
Geometric mean	NC	NC	3.68	3.22
CV(%)	NC	NC	51.0	41.3
Median	<0.5	<0.5	3.94	3.55
Min to max	<0.5 to 0.66	<0.5 to 0.71	0.74 to 9.87	0.94 to 6.58
t_{max} , hr				
N	19	19	13	13
Mean	6.7	4.7	7.8	6.2
SD	2.6	1.8	2.2	2.5
Median	6.0	4.0	8.0	6.0
Min to max	2.0 to 12.0	3.0 to 10.0	4.0 to 12.0	3.0 to 12.0
$t_{1/2}$, hr				
N	5	7	10	8
Mean	5.9	6.5	6.1	5.8

Table 11.2.1.1- 4 Pharmacokinetic parameters of 7-hydroxy quetiapine with extended statistics (PK evaluable subjects)

	Healthy volunteers, QTP SR 50 mg		Patients, QTP SR 300 mg	
Parameter	**Fasted**	**Fed**	**Fasted**	**Fed**
SD	1.5	1.6	1.2	1.0
Median	6.1	6.1	6.2	6.1
Min to max	4.3 to 8.1	4.7 to 9.1	3.7 to 7.6	3.6 to 6.7
λ_z, hr^{-1}				
N	5	7	10	8
Mean	0.12	0.11	0.12	0.12
SD	0.028	0.025	0.031	0.030
Geometric mean	0.12	0.11	0.12	0.12
CV(%)	22.7	22.8	25.5	24.2
Median	0.11	0.11	0.12	0.11
Min to max	0.090 to 0.16	0.080 to 0.15	0.090 to 0.19	0.10 to 0.19

QTP Quetiapine. SR Sustained release.
Note: NC Not calculable since more than 50% of the concentrations were non quantifiable.

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Evaluation of In Vitro In Vivo Correlation (IVIVC) for Seroquel SR Tablets

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Background: The sponsor has developed a sustained release (SR) tablet formulation of quetiapine fumarate. And has developed an in vitro in vivo correlation (IVIVC) model for the quetiapine fumarate SR tablet formulation. Validated IVIVC models may serve as surrogates for future bioequivalence studies and could enable the impact of formulation changes to be predicted from in vitro release data.

Seroquel SR strengths (50 mg, 200 mg, 300 mg and 400 mg) were being developed for the purpose of once-daily dosing. The release of the active drug is (b) (4) . For all tablet strengths, the total (b) (4) content is (b) (4). In order to achieve similar dissolution behavior for all strengths, the ratio of the (b) (4) was adjusted accordingly. Batch 400 mg 9008K exhibits typical dissolution behavior and therefore, was chosen as the target profile. In order to establish an IVIVC, "fast" and "slow" batches of 400 mg tablets were manufactured. To provide the necessary increase and decrease in dissolution, (b) (4) was adjusted to generate appropriate dissolution rates.

Objective: The primary objective was to compare the single-dose pharmacokinetics (PK) of quetiapine fumarate of four SR tablet formulations (three 400 mg SR tablets and one 50 mg SR tablet) and an IR tablet formulation in adults with selected psychotic disorders. The 400 mg SR formulations were designed to have differing drug release rates to allow

for the development of an IVIVC model and the 50 mg SR tablet was designed to match the desired target dissolution profile to provide an external validation of the IVIVC model.

Study Design: The critical elements in the design of the study use to develop the IVIVC (Study D1444C0001) was as follows:
- the study was conducted in patients.
- a single dose design PK study was considered unethical for patients so a multiple dose design was employed.
- 200 mg bid Seroquel IR was employed between the randomized treatments to help maintain patients clinically stable throughout the study. In addition, absorption of drug from the IR formulation would be completed prior to the administration of the randomized study treatments.

The study was conducted as an open-label, randomized, 5-period, 4-sequence crossover PK study. Each subject was randomized to receive one of the following treatment sequences: ABDCE, BCADE, CDBAE, or DACBE.
The first 4 treatment periods were four days in duration, while the fifth treatment period was of three days duration. The 2-day washout period was used for all subjects who were taking antipsychotic medication other than quetiapine fumarate and for those subjects who were taking quetiapine fumarate at a dose other than 200 mg twice daily. Following the washout period, subjects began the 2-day dose titration period. Subjects were given a single 100 mg dose of quetiapine fumarate on the evening of Day –2 and quetiapine fumarate 100 mg twice daily on Day –1. Treatment periods 1, 2, 3 and 4 began with an initial 2-day dose of quetiapine fumarate IR 200 mg twice daily (Day 1 and Day 2), followed by a single oral dose of one of the SR 400 mg tablet formulation (Treatment A) on Day 3 according to the randomization schedule. Serial blood samples were obtained from each subject for 48 hours after the Day 3 study drug administration of each Treatment Period for determination of quetiapine plasma concentrations. A single oral dose of quetiapine fumarate 50 mg SR (Treatment E) was administered on Day 1 of Treatment Period 5. For Treatment Period 5, serial blood samples were obtained from each subject for 48 hours after Day 1 study drug administration for determination of quetiapine plasma concentrations. Table A below summarizes the study treatments.

Table A: Study D1444C00001 Design

Treatment	Quetiapine fumarate formulations and dosages		
	Day 1	Day 2	Day 3
A	IR 200 mg bid	IR 200 mg bid	IR 400 mg (2 X 200 mg tablets), AM only
B	IR 200 mg bid	IR 200 mg bid	SR-F 400 mg tablet, AM only
C	IR 200 mg bid	IR 200 mg bid	SR-T 400 mg tablet, AM only
D	IR 200 mg bid	IR 200 mg bid	SR-S 400 mg tablet, AM only
E	SR-T 50 mg (single dose)	NA	NA

AM, morning; bid, twice daily; NA, not applicable

The possibility of developing an IVIVC for Seroquel SR tablet formulation was explored by performing deconvolution of the individual subject concentration-time data for the three 400 mg SR tablet formulations assessed in the study. The corresponding individual plasma concentration-time data following administration of the 400 mg Seroquel IR treatment were used to define the unit impulse response (UIR).

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(b) (4)

Following the Agency's guidance on IVIVC development and evaluation, the percent prediction error was estimated for each treatment according to:

$$\%PE = 100 * \left(\frac{P_{observed} - P_{predicted}}{P_{observed}} \right)$$

where $P_{observed}$ and $P_{predicted}$ were the observed and predicted C_{max} or AUC_{0-t} values. The term "mean absolute percent prediction error" (MAPPE) refers to the mean of the absolute values of the individual treatment prediction errors. The Agency criteria for internal validation of an IVIVC model state that for C_{max} and AUC_{0-t}, the absolute %PE for each formulation should not exceed 15% and MAPPE should not exceed 10% and the criteria for external validation of an IVIVC model state for C_{max} and AUC_{0-t}, the absolute %PE for each formulation should not exceed 10%.

Results:

The average *in vitro* dissolution profiles for the four Seroquel SR tablet formulations are displayed in the Appendix. The rank order in terms of release was 400 mg SR-F > 400 mg SR-T ≈ 50 mg SR-T > 400 mg SR-S. The difference between the fastest (400 mg SR-F) and the slowest (400 mg SR-S) dissolving Seroquel SR tablet formulation was 6, 13, 26, 32, 36 and 29% at 1, 2, 4, 6, 8, and 12 hours, respectively, by which time approximately 98% had been released from the 400 mg SR-F formulation.
F2 calculations clearly show that the profiles at the extremes of the dissolution range for the Seroquel SR tablet formulations (400 mg SR-F and 400 mg SR-S) were dissimilar, as indicated by an f2 value of 30 (Table 7) in Appendix. A linear IVIVC model was fit to the *in vivo* % absorbed and *in vitro* % dissolved data from the 400 mg SR formulations, by estimating the a1 (intercept) and a2 (slope) parameters of the PDx-IVIVC™ equation whilst fixing the b1 and b2 parameters to their null values of 0 and 1, respectively. The resulting model fit is presented in Figure 23 in the Appendix. The intercept and slope terms of the linear model were estimated to be 4.716% and 1.102, respectively (Table 25) in the Appendix.

The IVIVC model, developed from the 400 mg SR Seroquel formulations, was assessed in terms of internal predictability by using the model to predict the average concentration-time profiles for the 400 mg SR formulations and comparing these profiles with the corresponding average observed profiles. The validation statistics are provided in Table 28. The highest %PE for C_{max} was 8.7% for the 400 mg SR-T, with the MAPPE being 4.4%. For AUC_{0-t}, the %PE was less than 4% for all three 400 mg SR formulations, with the MAPPE of only 3.1%.

The IVIVC model was assessed in terms of external predictability by using the model to predict the average concentration-time profile for the 50 mg SR formulation and

comparing the predicted profile with the corresponding average observed profile. The validation statistics are presented in Table 30 in the Appendix. The %PE for C_{max} was 5.8% and for AUC_{0-t}, the %PE was 9.5%, satisfying the criteria for external validation of IVIVC models.

Summary: A simple linear model with a slope and intercept term was chosen to describe the IVIVC for Seroquel SR tablet formulations. The intercept (a_1 parameter) was estimated to be 4.716 % and the slope (a_2 parameter) estimated to be 1.102. The internal predictability of the Seroquel SR IVIVC model was assessed by predicting the average *in vivo* concentration-time profile for each of the three 400 mg SR formulations used to develop the model. The %PE was less than 10% for each of the formulations, with the highest AUC_{0-t} %PE being only 3.7% for the SR-F and the highest C_{max} %PE being only 8.7% for the SR-T. The MAPPE was only 4.4% and 3.1% for C_{max} and AUC_{0-t}, respectively. The Seroquel SR IVIVC model was also evaluated in terms of external predictability, using the average quetiapine concentration-time data for the 50 mg SR-T formulation. For both AUC_{0-t} and C_{max}, the %PE was less than 10%, satisfying the criteria for external predictability.

The developed IVIVC model satisfies the criteria for both internal and external predictability. The model covers potential future changes to all strengths of the SR formulation (50 – 400 mg) within the range of *in vitro* dissolution defined by the 400 mg SR-F and 400 mg SR-S.

Reviewer Comments: *The sponsor has developed an IVIVC model. The prediction error was less than 10% for both the internal and external validation of the IVIVC model. IVIVC has been demonstrated and is acceptable.*

Appendix

Figure 2. **Mean in vitro dissolution profiles for Seroquel SR tablets evaluated in Study 001.**

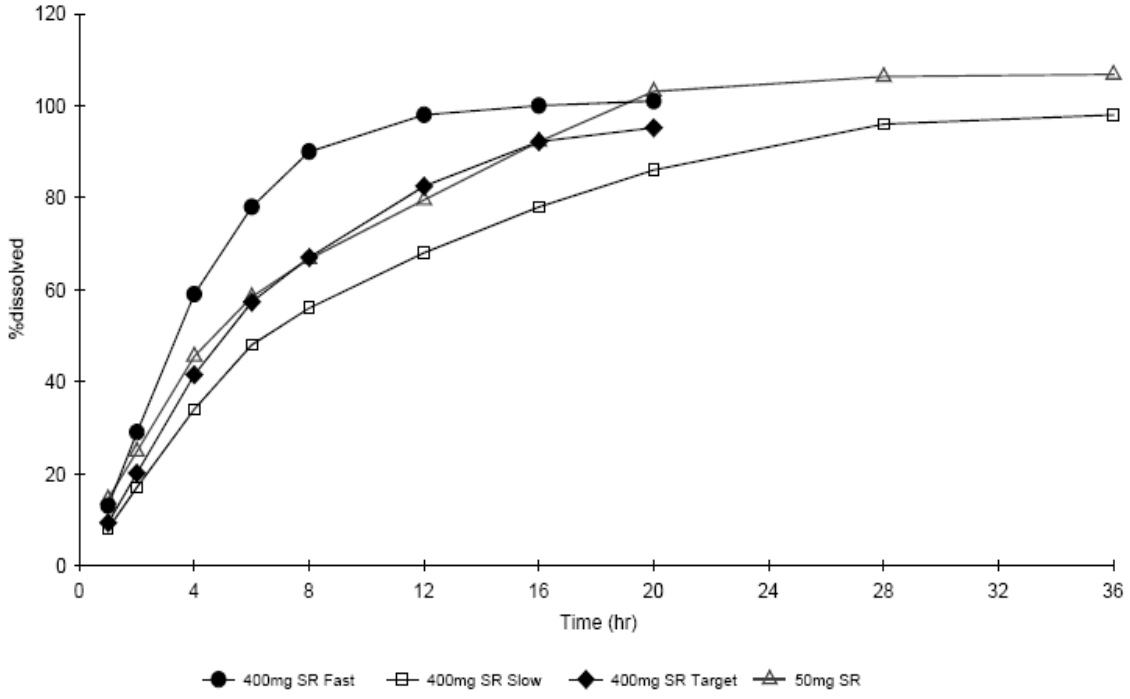


Figure 8. Average concentration-time profiles for Seroquel IR and SR treatments.

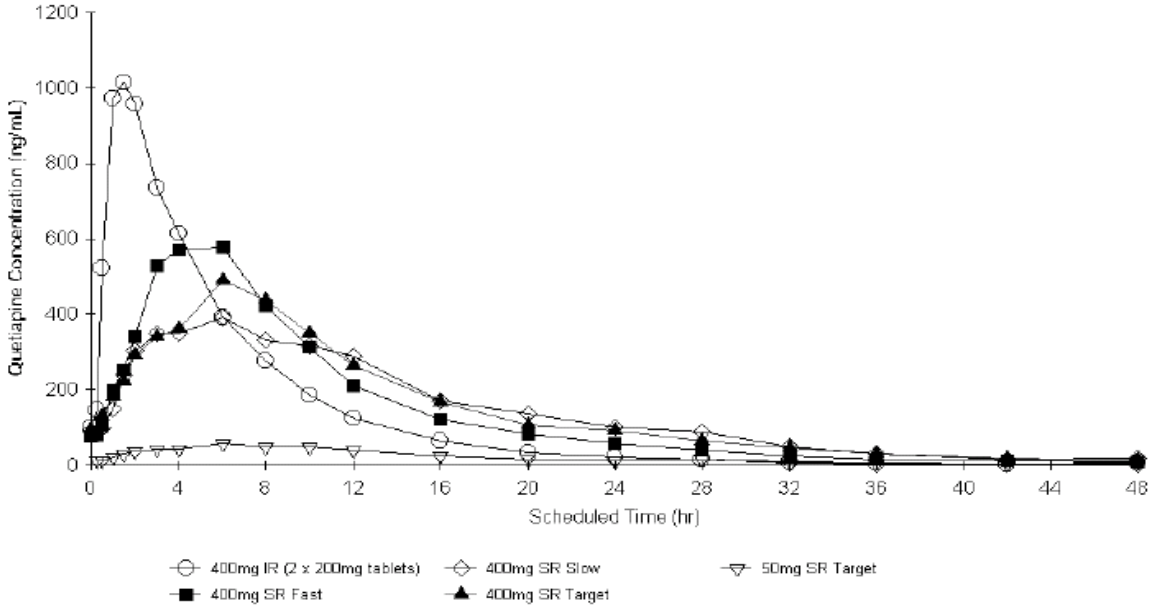


Figure 14. Average corrected quetiapine concentration-time profiles for Seroquel IR and SR treatments.

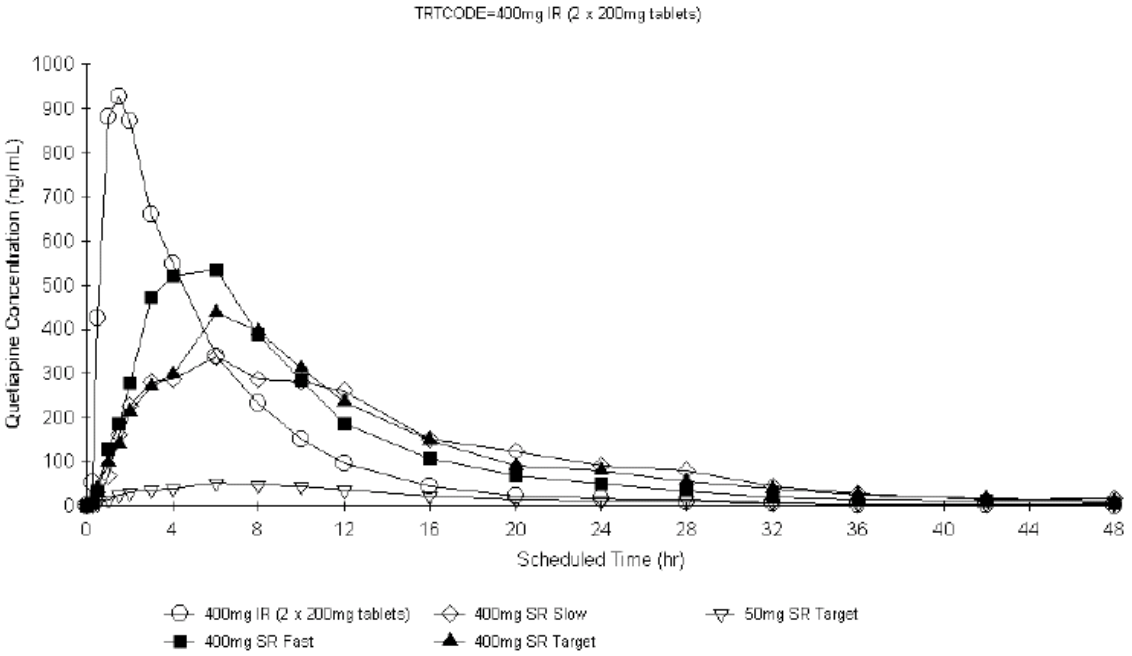


Figure 16: **Observed and predicted average quetiapine concentrations for 400 mg Seroquel IR treatment.**
Open Circles Show Mean Measured Seroquel IR Concentrations. Continuous Line Shows Predicted Concentrations.

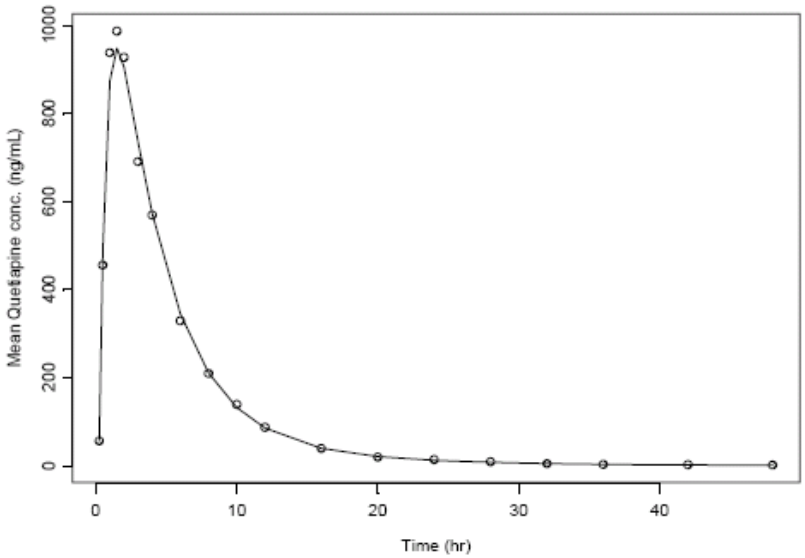


Figure 20. Average in vivo absorption profiles for 400 mg Seroquel SR tablet formulations.

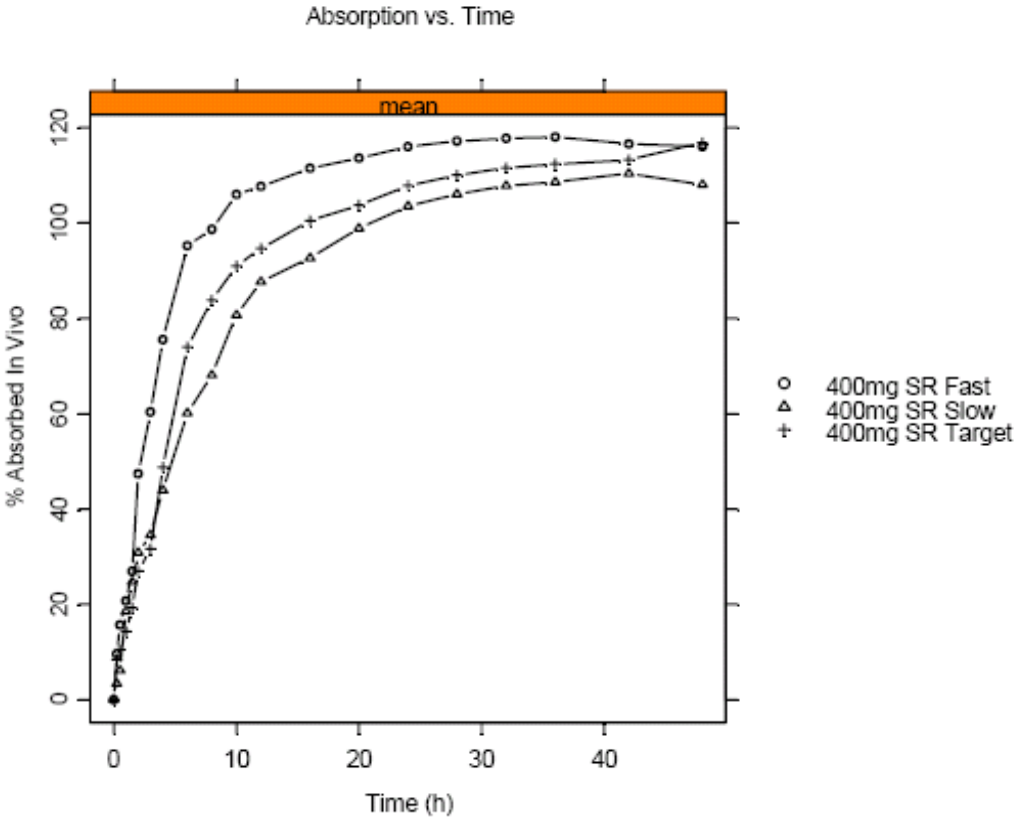


Figure 21. **Average % absorbed in vivo and average % dissolved in vitro for 400 mg plotted against time Seroquel SR tablet formulations.**

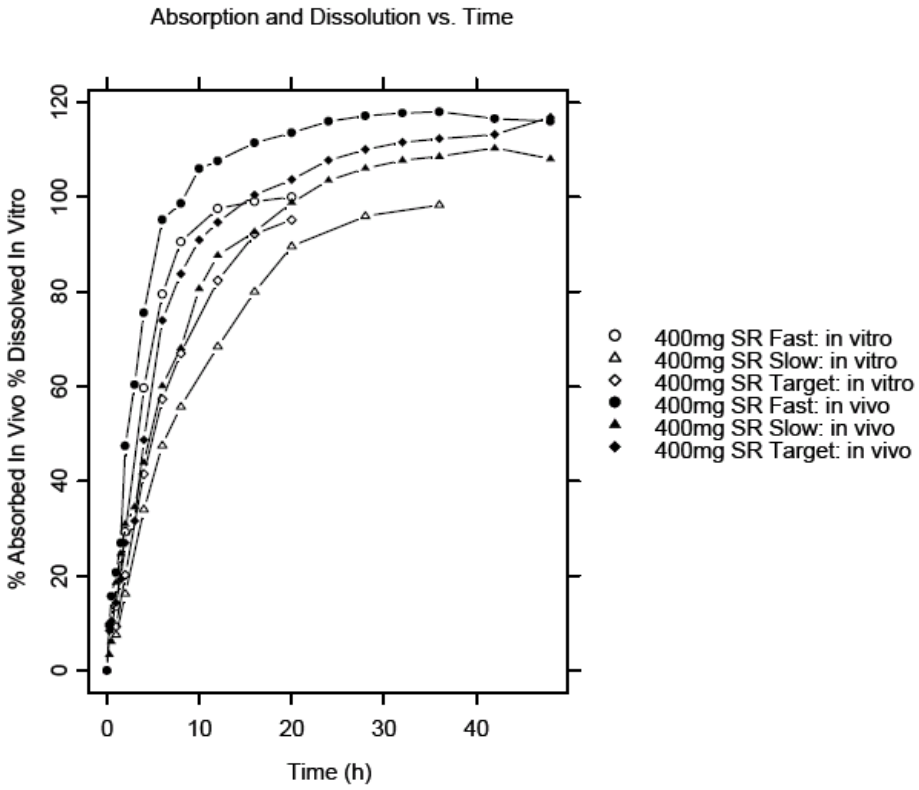


Figure 22. Average % absorbed in vivo vs. average % dissolved in vitro for 400 mg Seroquel SR tablet formulations.

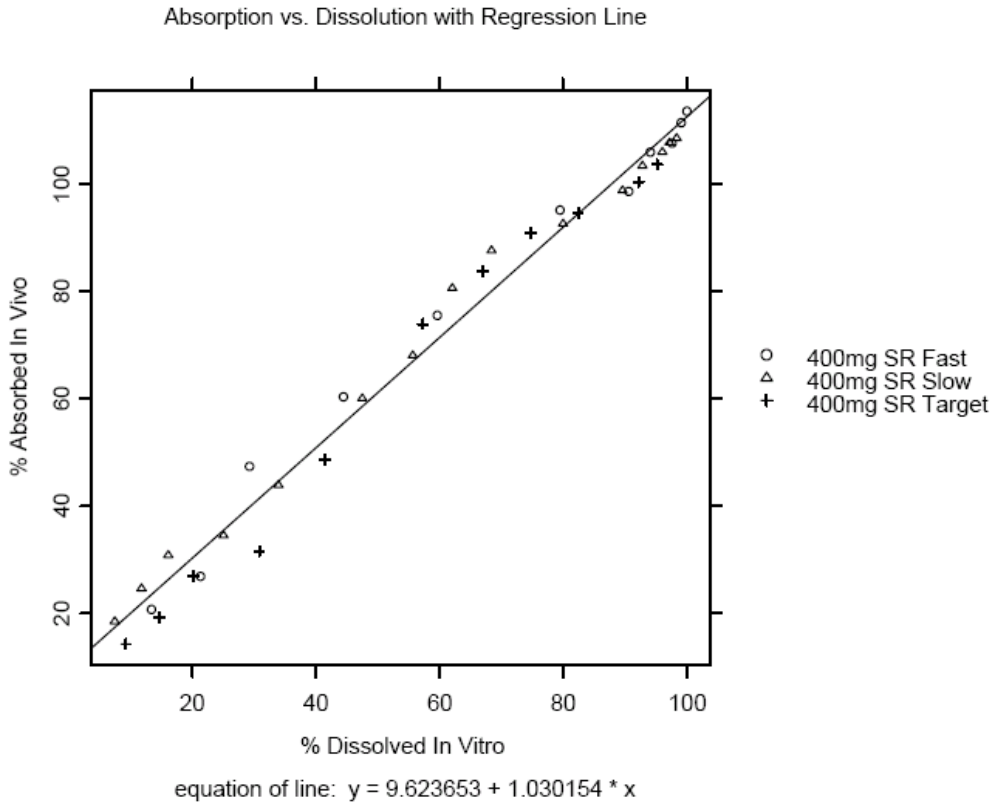


Figure 23. IVIVC Model for 400 mg Seroquel SR tablet formulations.

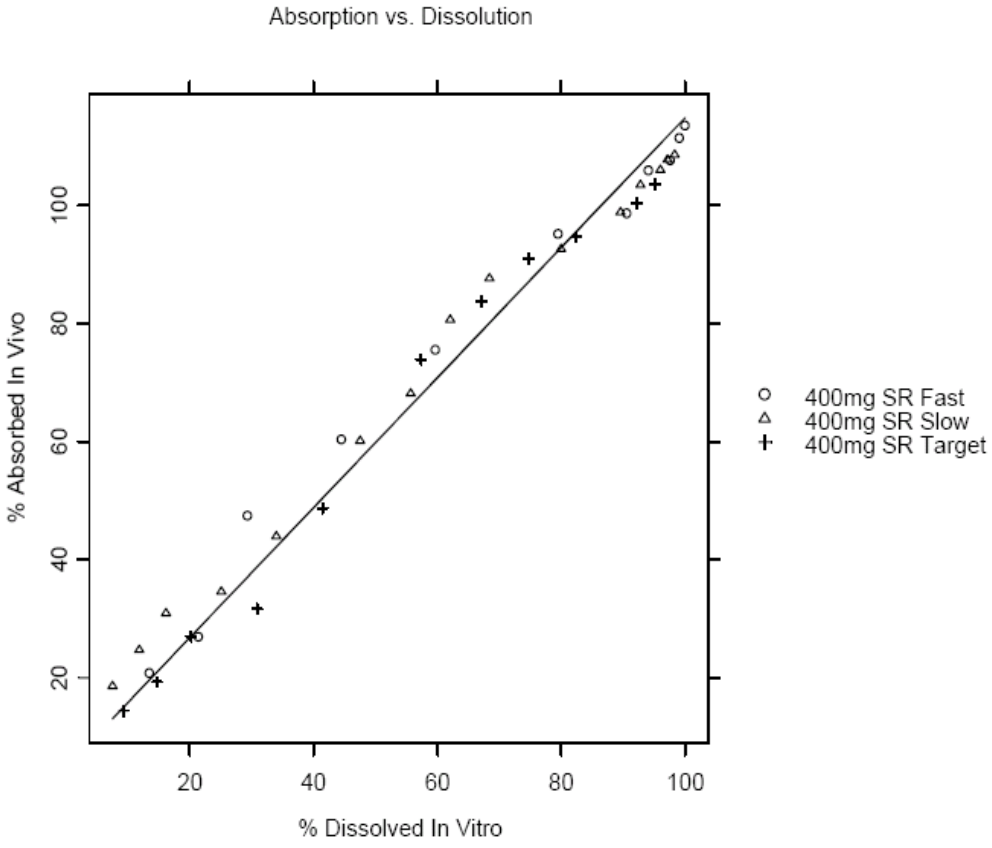


Figure 24. IVIVC Model-predicted and average observed quetiapine concentration-time profiles for 400 mg Seroquel SR tablet formulations.

Symbols Show Measured Concentrations, Continuous Lines Show Predicted Concentrations

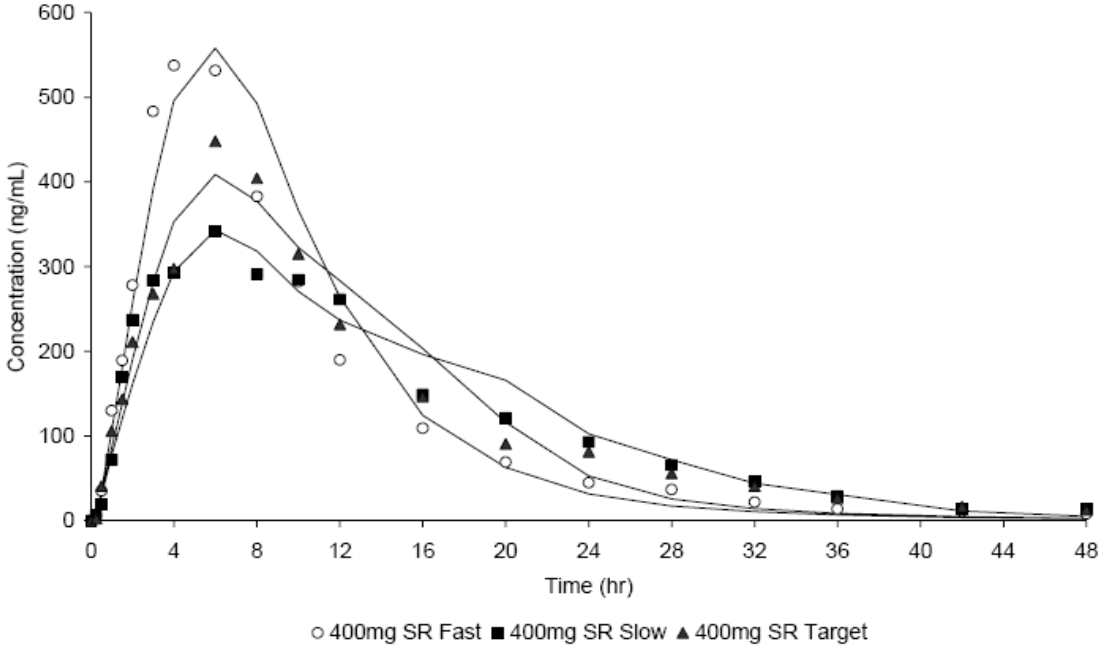
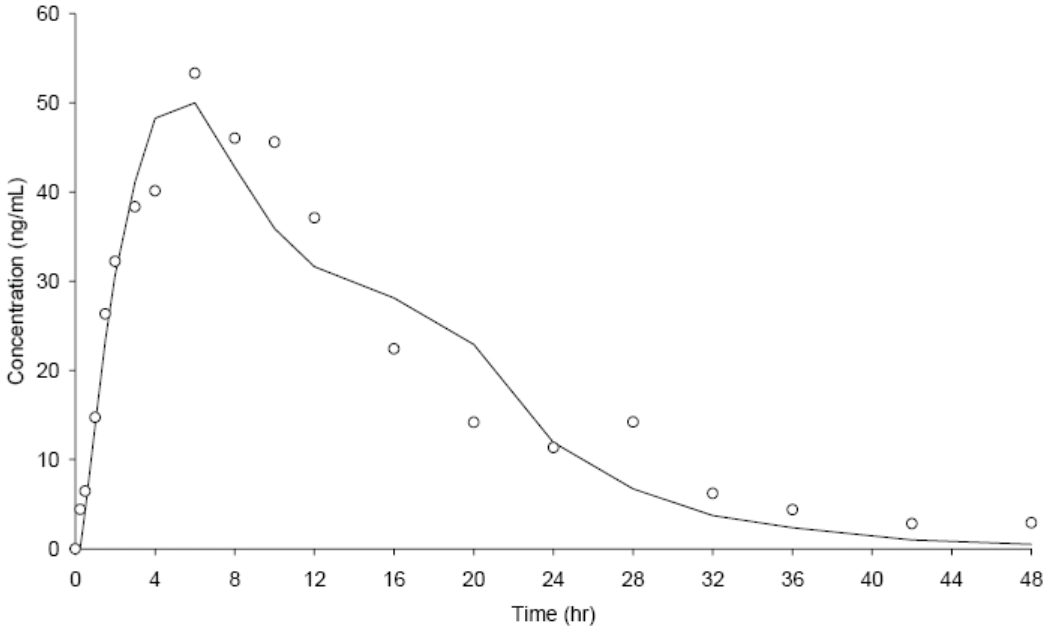


Figure 26. IVIVC Model-predicted and average observed quetiapine concentration-time profiles for 50 mg Seroquel SR tablet formulation.

Open Circles Show Measured Concentrations, Continuous Lines Show Predicted Concentrations



The following tables provide the internal and external validation for the IVIVC model.

Table 28. Internal validation statistics for Seroquel SR IVIVC model.

	C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)			
Treatment	Observed	Predicted	Ratio	% PE	Observed	Predicted	Ratio	% PE
400mg SR Fast	537.39	558.16	1.04	3.86	5917.36	6135.41	1.04	3.68
400mg SR Slow	341.49	343.11	1.00	0.48	5806.90	6015.98	1.04	3.60
400mg SR Target	447.88	408.80	0.91	8.73	5971.09	5850.94	0.98	2.01
MAPPE				**4.36**				**3.10**

Table 30. External validation statistics for Seroquel SR IVIVC model.

	C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)			
Treatment	Observed	Predicted	Ratio	% PE	Observed	Predicted	Ratio	% PE
50mg SR Target	53.32	51.17	0.96	4.04	869.38	819.91	0.94	5.69

SEROQUEL SR batches from study 5077IL/0118 were also externally predicted using the IVIVC model. Study 5077IL/0118 was an open-label, steady-state study to evaluate dose proportionality and incorporated all strengths. Each strength meets the acceptance criteria of ≤10% PE (See the following table).

Table H7 External prediction of C_{max} and AUC for SEROQUEL SR batches used in study 5077IL/0118

	C_{max} (ng/mL)				AUC_{0-t} (ng·h/mL)			
Treatment	**Observed**	**Predicted**	**Ratio**	**% PE**	**Observed**	**Predicted**	**Ratio**	**% PE**
50 mg	60.86	60.85	1.00	0.03	980.48	920.89	0.94	6.1
200 mg	257.54	238.99	0.93	7.2	3680.06	3545.66	0.96	3.7
300 mg	385.42	363.51	0.94	5.7	5784.56	5344.92	0.92	7.6
400 mg	522.67	480.77	0.92	8.0	7106.89	7048.43	0.99	0.8

Table 3. Dissolution data for 400 mg Seroquel SR Fast tablet (Batch 9006K).

Time (hours)	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Overall Mean	% RSD
1												(b) (4)	13	3.1
2													29	2.3
4													60	2.4
6													80	1.9
8													91	1.5
12													98	0.9
16													99	0.8
20													100	0.9

Table 4. Dissolution data for 400 mg Seroquel SR Target tablet (Batch 9008K).

Time (hours)	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Overall Mean	% RSD
1												(b) (4)	9.3	2.2
2													20.1	1.3
4													41.5	1.3
6													57.3	1.3
8													67.0	1.4
12													82.5	1.8
16													92.2	1.5
20													95.2	1.3

Table 5. Dissolution data for 400 mg Seroquel SR Slow tablet (Batch 9007K).

Time (hours)	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Overall Mean	% RSD
1												(b) (4)	8	3.3
2													17	3.4
4													34	2.6
6													48	2.5
8													56	2.3
12													68	2.2
16													78	2.3
20													86	1.9
28													96	1.4
36													98	1.4

Table 6. Dissolution data for 50 mg Seroquel SR Target tablet (Batch 9003K).

Time (hours)	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Tablet 11	Tablet 12	Overall Mean	% RSD
1												(b) (4)	14.7	5.5
2													25.6	5.4
4													46.2	3.1
6													58.5	2.7
8													65.9	2.5
12													79.7	3.3
16													93.9	3.5
20													103.9	1.7
28													106.6	1.6
36													107.4	1.8

Table 7. Summary of similarity factor, f2, calculations for Seroquel SR tablet formulations in vitro dissolution data.

Treatment	f2 value			
	400 mg SR-F	400 mg SR-T	400 mg SR-S	50 mg SR-T
400 mg SR-F	-	37.8	30.2	39.6
400 mg SR-T	37.8	-	50.1	70.9
400 mg SR-S	30.2	50.1	-	47.6
50 mg SR-T	39.6	70.9	47.6	-

For all comparisons involving 400 mg SR-F, the last time-point included in the calculation of the f2 statistic was 8 hours. For all other comparisons, the last time-point included was 16 hours.

Table 27. IVIVC model-predicted and average observed concentration vs. time data.

	Average observed			Model-predicted		
Time (hr)	400 mg SR-F	400 mg SR-T	400 mg SR-S	400 mg SR-F	400 mg SR-T	400 mg SR-S
0	0.00	0.00	0.00	0.00	0.00	0.00
0.25	5.67	2.44	5.99	1.70	1.67	0.98
0.5	34.84	40.56	19.23	33.57	30.15	28.16
1	129.73	105.33	71.87	105.79	85.65	76.87
1.5	189.07	143.26	169.20	180.22	138.07	119.92
2	277.92	210.90	237.09	256.74	190.24	161.31
3	483.31	267.97	283.29	391.77	281.70	234.53
4	537.39	297.50	292.44	495.65	352.69	293.58
6	531.51	447.88	341.49	558.16	408.80	343.11
8	382.72	404.25	290.80	492.90	377.44	318.10
10	282.24	315.06	284.13	366.24	322.45	270.80
12	189.75	231.60	260.97	263.96	283.09	236.45
16	109.08	146.54	148.82	124.31	203.36	196.40
20	69.05	90.43	121.30	62.93	115.93	165.82
24	44.71	81.18	92.65	31.39	52.83	102.47
28	36.50	55.55	65.46	17.13	25.44	71.94
32	21.86	40.87	45.76	10.38	14.02	43.97
36	13.70	26.79	28.64	6.72	8.56	30.54
42	11.08	16.56	13.50	3.72	4.55	11.23
48	7.87	12.62	14.00	2.12	2.56	4.89

Table 29. IVIVC model-predicted and average observed concentration vs. time data for Seroquel 50 mg SR.

Time (hr)	Average observed	Model-predicted
0	0.00	0.00
0.25	4.43	0.13
0.5	6.46	4.25
1	14.74	13.93
1.5	26.36	23.39
2	32.24	30.70
3	38.33	41.13
4	40.14	48.28
6	53.32	50.02
8	46.05	42.81
10	45.61	35.90
12	37.12	31.64
16	22.43	28.13
20	14.17	22.90
24	11.34	11.95
28	14.22	6.71
32	6.21	3.73
36	4.40	2.36
42	2.83	1.00
48	2.92	0.49

Dissolution Development

The primary objective of dissolution development was to produce a discriminatory method that serves as a control method as well as to assure in vivo performance through an in vitro in vivo correlation (IVIVC). All of the dissolution data reported in this application was generated using one of 2 methods. Method A was used during early formulation Development. Method B is the final control and bioequivalence method. The review concentrates only on Method B.

Dissolution Method B provides complete release of quetiapine and is applicable to all strengths of SEROQUEL SR tablets. The method is reported to be a sufficiently discriminating control test.

A Level A IVIVC was developed for SEROQUEL SR and which is valid for all strengths. This IVIVC has been used to justify the dissolution acceptance criteria. The Level A IVIVC will be used to support the inclusion of additional manufacturing sites, to support biowaiver for relevant SUPAC/variation changes, and as a surrogate for future bioequivalence studies.

Different dissolution systems were evaluated to better understand release dynamics of SEROQUEL SR formulations and determine if in vivo release of SEROQUEL SR could be better predicted. The media and tests evaluated consisted of single pH systems. Study designs are summarized in the following table

Table G1 Media systems used to evaluate release of SEROQUEL SR

Method	Apparatus	Composition	Rotation speed (rpm)	Detection
(b) (4)				

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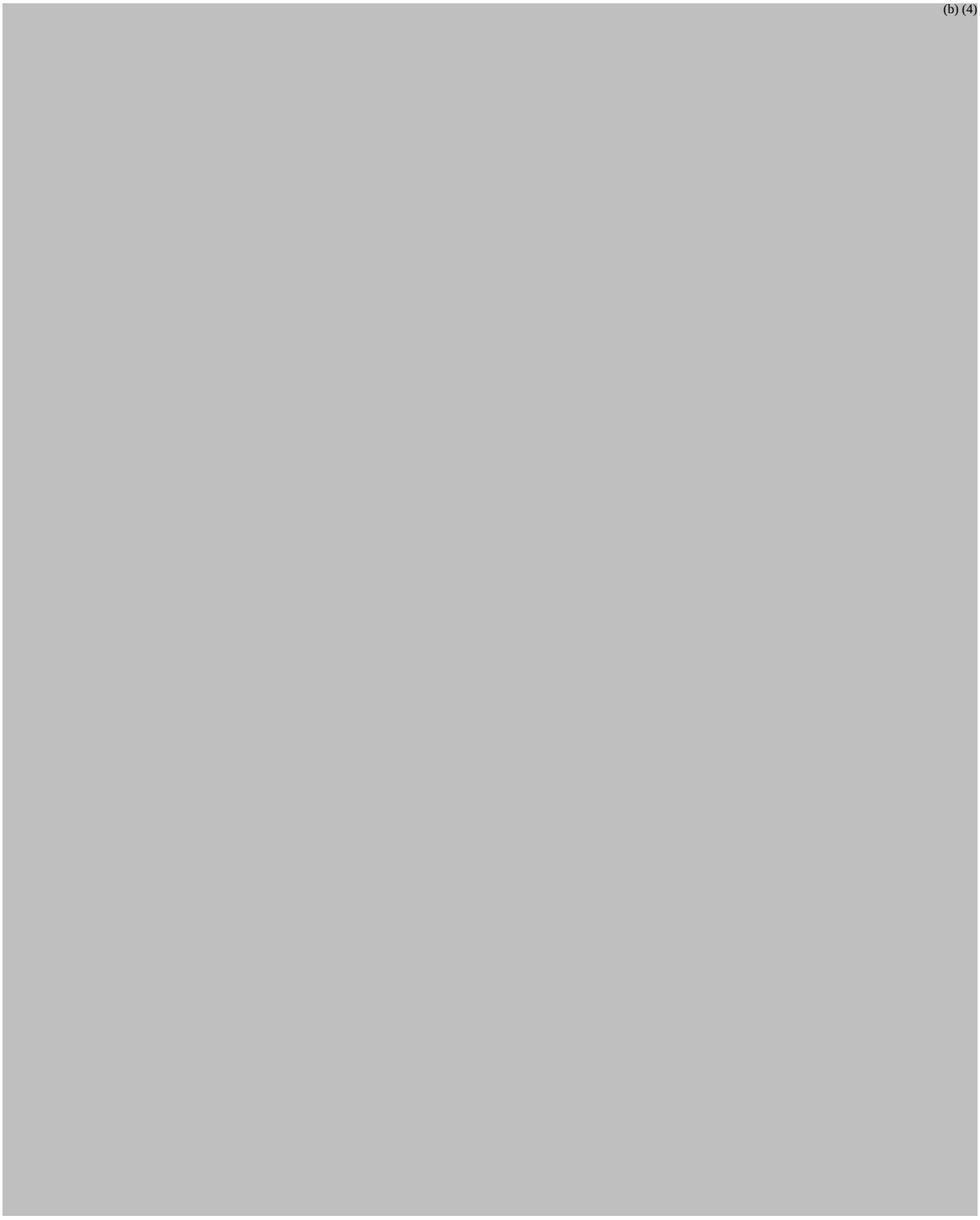
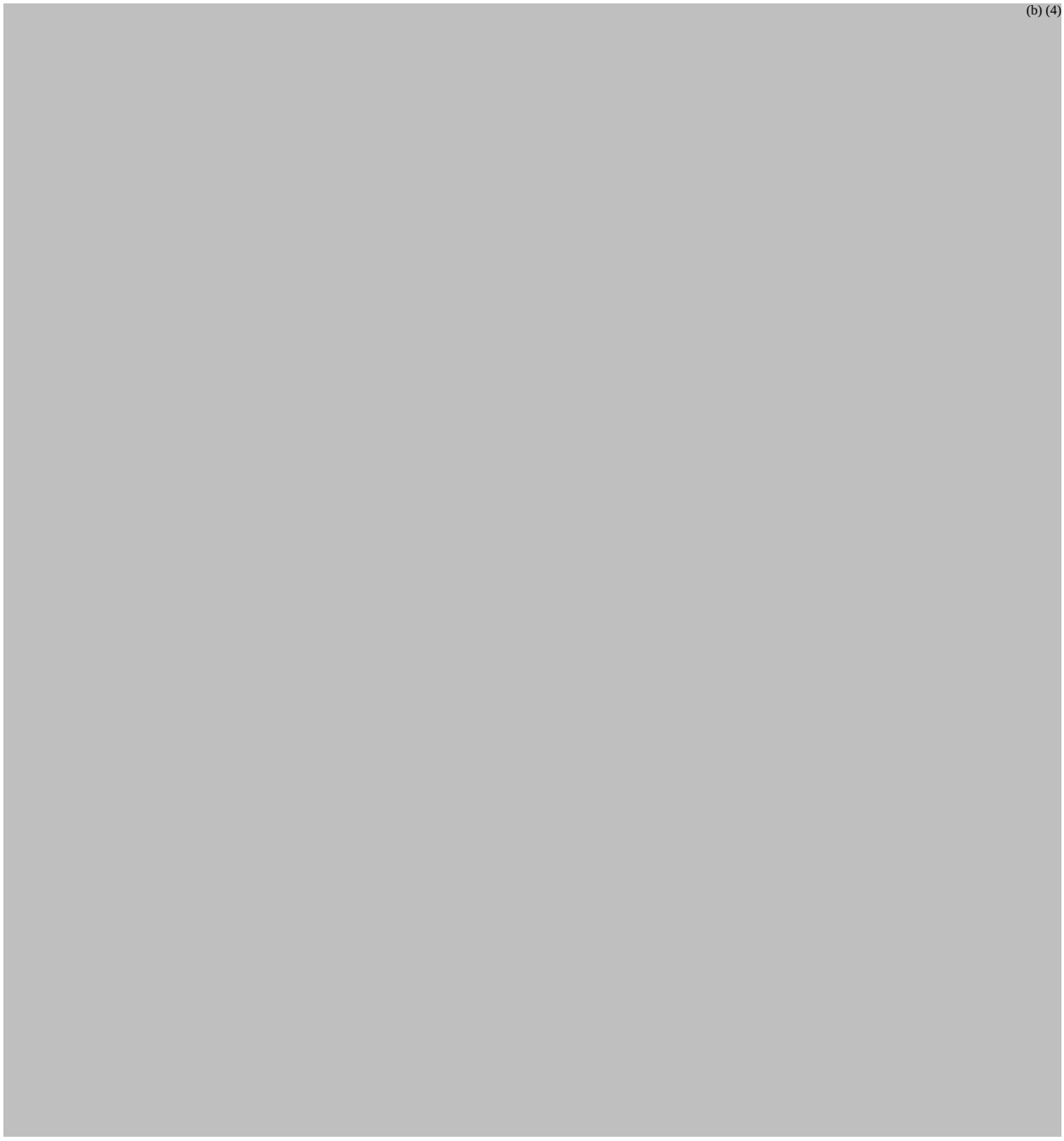


The final dissolution method selected (Method B) is performed using the basket apparatus at a rotation speed of 200 rpm. Initially, 900 mL of dissolution medium consisting of 0.05 M sodium citrate and 0.09 N sodium hydroxide are placed in each vessel. The pH of this medium is 4.8.

At 5 hours, 100 mL of a medium consisting of 0.05 M sodium phosphate and 0.46 N sodium hydroxide are added to each vessel to bring the pH of the medium to 6.6 for the final duration of the dissolution analysis. Samples are withdrawn over a 20 hour time-period and analyzed for quetiapine using ultraviolet spectrophotometric detection at 290 nm.



The dissolution method selected was used to generate the in vitro dissolution profiles, and the in vivo release profiles that are provided in the following figures. The 400 mg in vivo profile was generated during study D1444C00001 which is described in vivo in vitro correlation development. The 50, 200, and 300 mg in vivo profiles were generated from trials 5077IL/0036 and 5077IL/0037.

Figure G16 **SEROQUEL SR 400 mg tablet in vitro release compared to in vivo release, Method B**

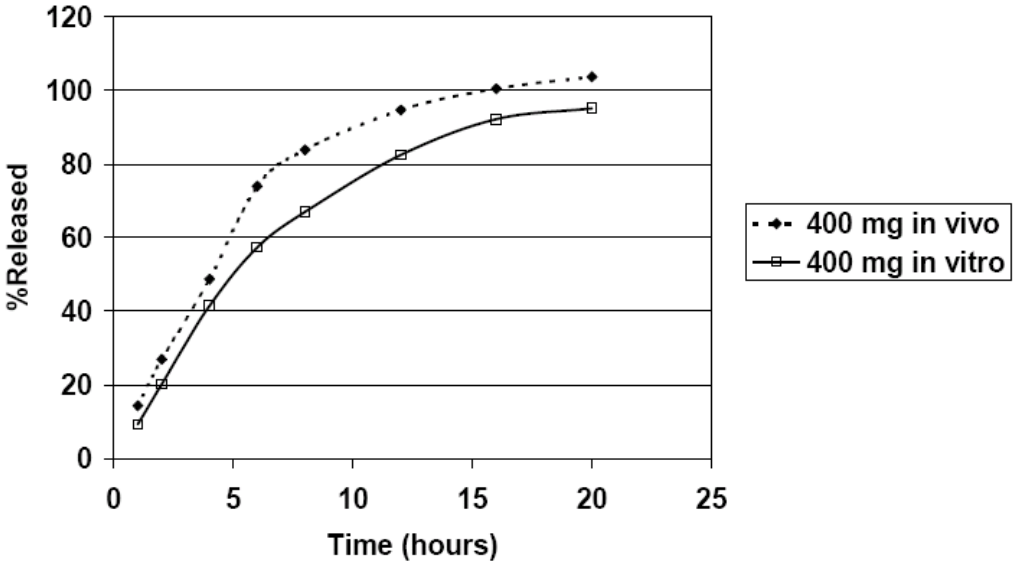


Figure G17 **SEROQUEL SR 300 mg tablet in vitro release compared to in vivo release, Method B**

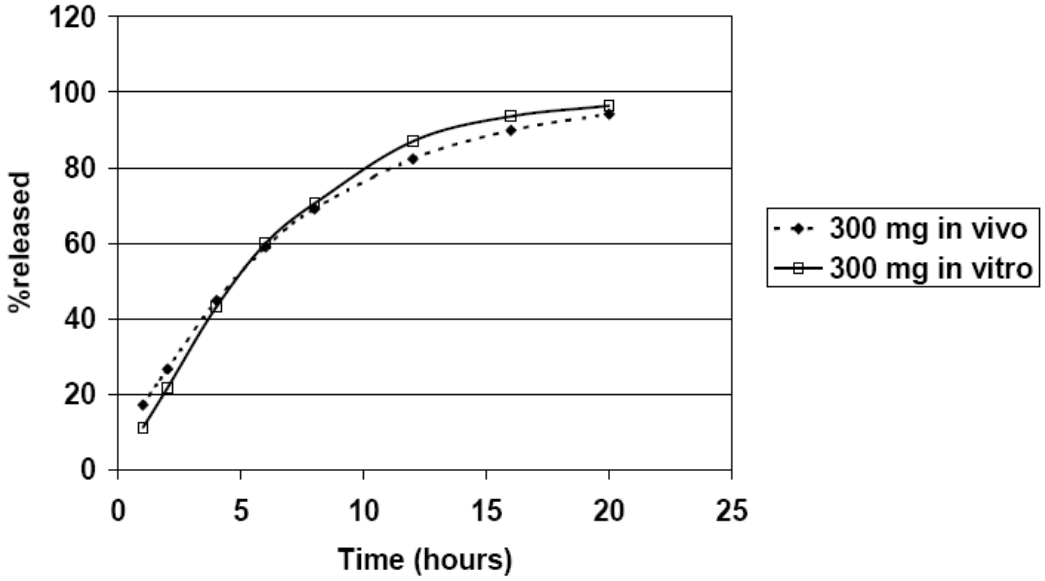


Figure G18 **SEROQUEL SR 200 mg tablet in vitro release compared to in vivo release, Method B**

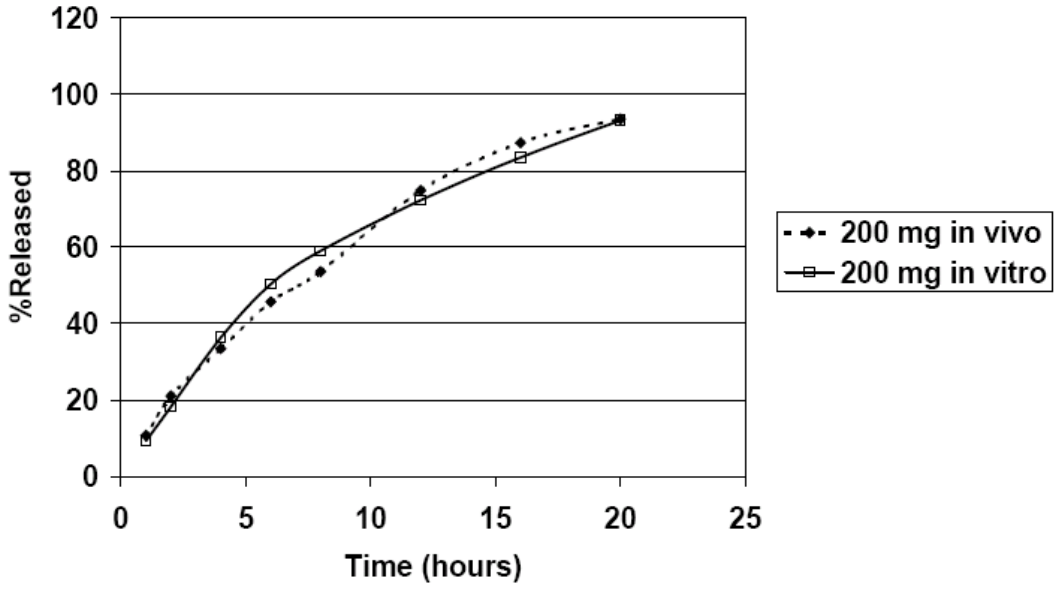
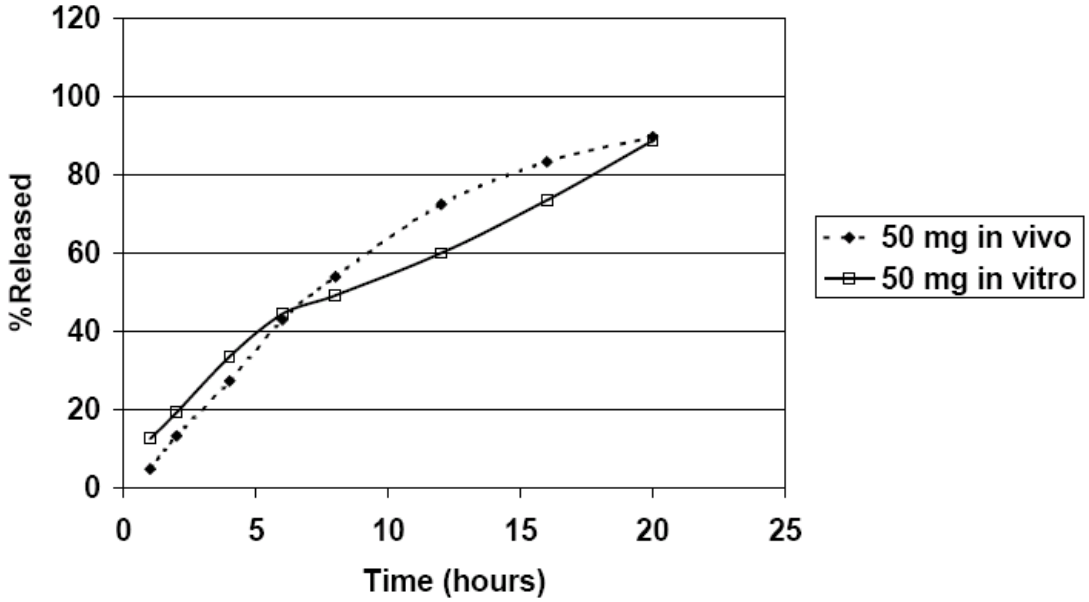


Figure G19 **SEROQUEL SR 50 mg tablet in vitro release compared to in vivo release, Method B**



The sponsor states that the method selected is discriminating and is indicative of the following parameters:

1) Formulation changes, 2) [redacted] properties and 3) Process changes. The dissolution method is reported to be a good control method. It is predictor of product performance and is discriminating against formulation and process changes for all SEROQUEL SR strengths.

Dissolution Specification: Dissolution acceptance criteria have been developed based on a Level A IVIVC. Profiles defined by the upper and lower limits of the acceptance criteria have been shown to be bioequivalent in accordance with the Agency's, 'Guidance for Industry; Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations'.

Although the IVIVC work included a batch of SEROQUEL SR 400 mg tablets (batch 9008K) with a target IVIVC dissolution profile, for the purposes of setting the dissolution acceptance criteria, all batches used in the clinical efficacy trials were examined. A batch of SEROQUEL SR 200 mg tablets (batch 9071H), was identified as having the most appropriate target dissolution profile since its profile best matched the mean profile of all batches used in the efficacy studies. While batch 9071H best matched the mean dissolution profiles for all the efficacy batches, it also is predicted bioequivalent to the

400 mg target IVIVC batch. The predicted pharmacokinetic parameters, C_{max} and AUC, for 200 mg batch (9071H) and 400 mg batch (9008K) are shown in the following table.

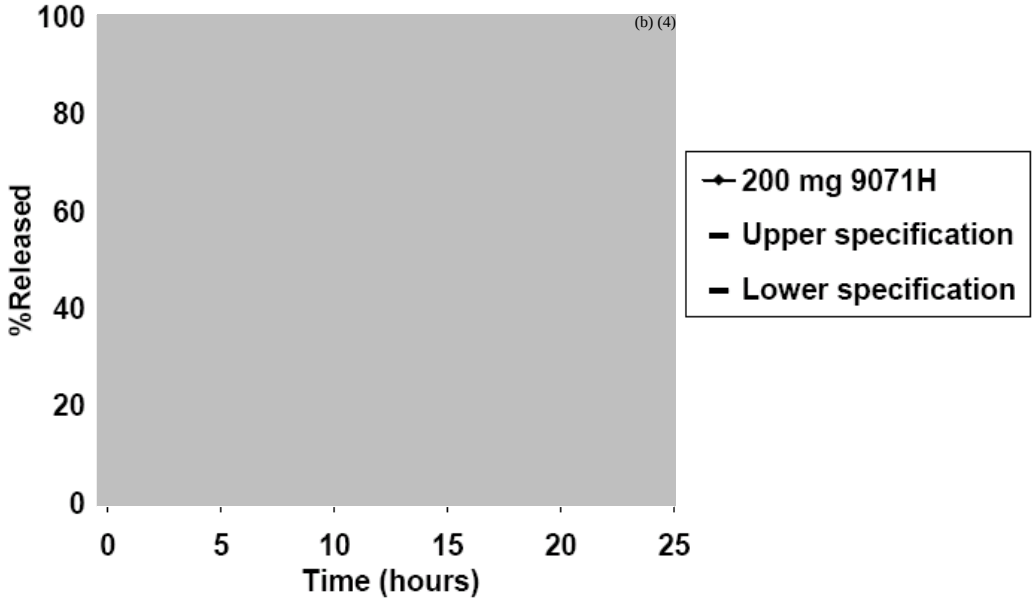
Table 3 **Comparison of C_{max} and AUC for target batch 400 mg 9008K and 200 mg target batch 9071H using the specification time-points**

Batch	C_{max} (ng/mL)	C_{max} ratio	AUC (ng'h/mL)	AUC ratio
200 mg 9071H	417.62	0.99	5941.06	1.01
400 mg 9008K	421.01	-	5859.92	-

Note The 200 mg data were treated as dosed 2 tablets to properly compare to the 400 mg strength.

The ranges for % dissolved at each sampling time point are centered about the target 200 mg batch (9071H) and was based on profile bioequivalence and dissolution results at the time of manufacture and on stability. The proposed upper and lower acceptance criteria at each of the 4 selected sampling time points along with the mean dissolution profile for the 200 mg batch (9071H) are shown the following figure,

Figure 1 **Comparison of the mean % dissolution of target batch 200 mg (9071H) to the dissolution acceptance criteria**



Using the IVIVC model, the predicted upper and lower C_{max} and AUC values for the profiles defined by the SEROQUEL SR upper and lower dissolution acceptance criteria were determined. The predicted C_{max} using the lower acceptance limits are (b) (4) different than the predicted C_{max} using the upper acceptance limits. The predicted

AUC using the lower acceptance limits are (b) (4) different than the predicted AUC using the upper acceptance limits.

Table 4 Predicted AUC and C_{max} values for the proposed lower and upper SEROQUEL SR dissolution specifications

Specification	C_{max} (ng/mL)	C_{max} ratio	AUC (ng·h/mL)	AUC ratio
Lower	(b) (4)			
Upper				

Reviewer comments: *The rotation speed of 200 rpm is high for USP Apparatus 1. However, the in vitro release using this method appears to be similar to the in vivo release of quetiapine for the 200 mg and 300 mg strength. The in vitro release using this method underestimates in vivo release for the 400 mg strength.*

The following dissolution specification is proposed by the sponsor. The specification is justified by IVIVC and is acceptable..

Not more than (b) (4) *at 1 hour*
(b) (4) *at 6 hours*
(b) (4) *at 12 hours*
Not less than (b) (4) *at 20 hours.*

The specification is acceptable.

Appendix

Table 5 **SEROQUEL SR 50 mg tablet dissolution data (% label claim) at release**

Time (hours)	**1**	**6**	**12**	**20**
Acceptance criteria	**NMT**	(b) (4)		**NLT** (b) (4)
Batch				
9002K				
Range of individuals	(b) (4)			
Mean (% RSD)	16 (5.2)	57 (1.7)	72 (2.6)	92 (3.3)
9003K				
Range of individuals	(b) (4)			
Mean (% RSD)	13 (3.2)	57 (2.0)	77 (4.4)	101 (3.2)
9038K				
Range of individuals	(b) (4)			
Mean (% RSD)	14 (10.1)	58 (2.2)	80 (2.7)	105 (1.3)
LJ4702				
Range of individuals	(b) (4)			
Mean (% RSD)	13 (4.9)	57 (4.1)	78 (5.6)	103 (1.0)
LM4622				
Range of individuals	(b) (4)			
Mean (% RSD)	14 (7.6)	55 (3.0)	71 (2.8)	94 (4.3)

NMT Not more than.
NLT Not less than.

Figure 3 **SEROQUEL SR 50 mg tablet mean dissolution**

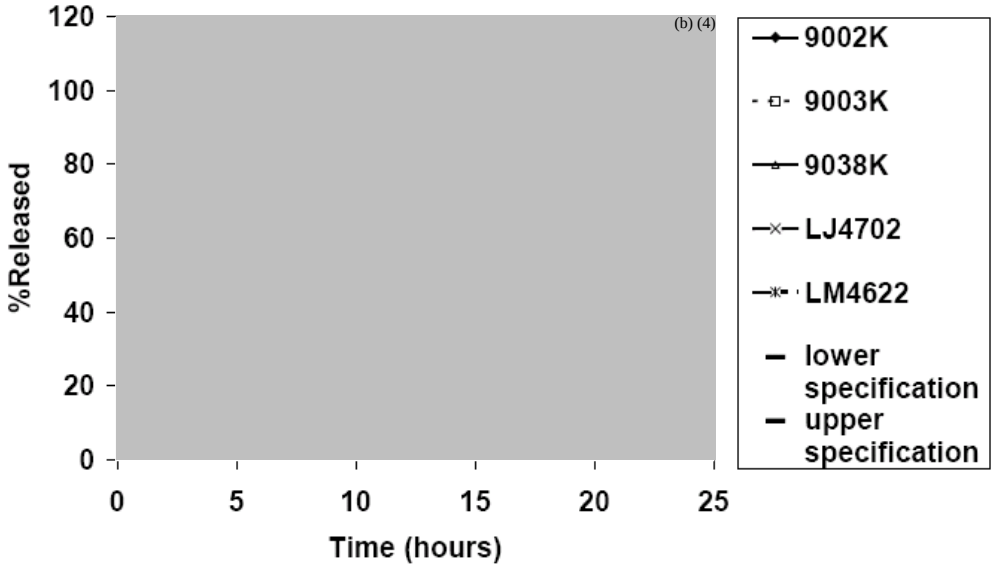


Table 6 **SEROQUEL SR 50 mg tablet (batch 9002K) summary of mean and range of individual dissolution (% label claim) stability study STB.4455**

	1	6	12	20
Acceptance criteria	**NMT** (b) (4)			**NLT** (b) (4)
Condition/time				
Initial	14 (b) (4)	58 (b) (4)	78 (b) (4)	101 (b) (4)
12 month 25°C/60% RH	15 (b) (4)	55 (b) (4)	70 (b) (4)	93 (b) (4)
12 month 30°C/65% RH	15	57	75	98

NMT Not more than.
NLT Not less than.

Table 9 **SEROQUEL SR 200 mg tablet dissolution data (% label claim) at release**

Time (hours)	**1**	**6**	**12**	**20**
Acceptance criteria	**NMT** (b) (4)			**NLT** (b) (4)
Batch				
9077C				
Range of individuals	(b) (4)			
Mean (% RSD)	11 (5.2)	56 (2.8)	79 (2.9)	95 (1.0)
9078C				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (4.0)	55 (2.2)	77 (3.4)	94 (2.8)
9099C				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (4.0)	56 (2.6)	78 (2.5)	94 (1.4)
9071H				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (6.3)	58 (3.7)	81 (3.2)	97 (1.5)
9004K				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (5.8)	54 (1.0)	73 (1.4)	93 (2.2)
9055K				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (4.2)	56 (1.9)	75 (1.6)	96 (1.3)
LK4703				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (4.2)	60 (2.9)	91 (3.4)	104 (0.7)
LK4610				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (5.3)	55 (3.4)	72 (2.9)	94 (2.2)

NMT Not more than.
NLT Not less than.

Figure 4 **SEROQUEL SR 200 mg tablet mean dissolution**

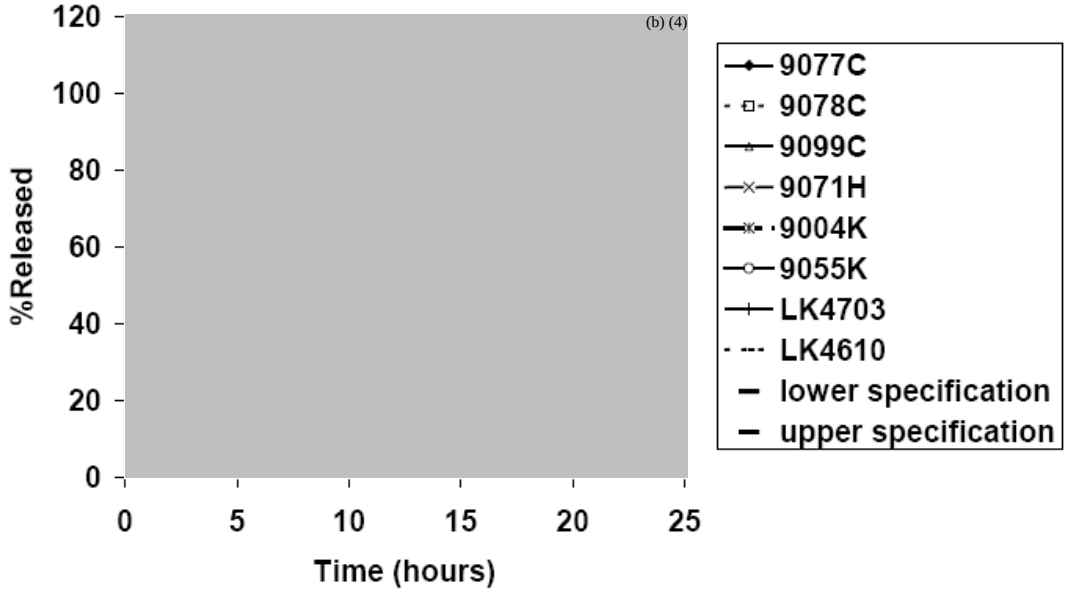


Table 10 **SEROQUEL SR 200 mg tablet (batch 9077C) summary of mean and range of individual dissolution (% label claim) stability study STB.4369**

Time (hours)	**1**	**6**	**12**	**20**
Acceptance criteria	**NMT** (b) (4)			**NLT** (b) (4)
Condition/time				
Initial	7 (6-14)	59 (52-68)	84 (77-92)	96 (90-103)
48 month 25°C/60% RH	10 (b) (4)	57 (b) (4)	82 (b) (4)	92 (b) (4)
36 month[a] 30°C/65% RH	11	59	85	95

[a] Stability testing was matrixed, 48 month data were not tested for this batch at this condition.
NMT Not more than.
NLT Not less than.

Table 13 **SEROQUEL SR 300 mg tablet dissolution data (% label claim) at release**

Time/hours	**1**	**6**	**12**	**20**
Acceptance criteria	**NMT**	(b) (4)		**NLT** (b) (4)
Batch				
9071A				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (0.0)	62 (1.2)	87 (1.6)	96 (2.0)
9072A				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (5.3)	56 (1.1)	86 (3.4)	101 (3.3)
9073A				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (5.3)	59 (1.8)	77 (2.6)	90 (3.3)
9052C				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (0.0)	58 (1.8)	83 (1.8)	96 (0.0)
9072H				
Range of individuals	(b) (4)			
Mean (% RSD)	9 (5.5)	55 (3.0)	76 (1.9)	92 (1.1)
9005K				
Range of individuals	(b) (4)			
Mean (% RSD)	9 (4.5)	57 (1.8)	77 (2.0)	92 (0.6)
LH4706				
Range of individuals	(b) (4)			
Mean (% RSD)	8 (5.0)	53 (3.0)	76 (2.7)	96 (0.6)
LH4708				
Range of individuals	(b) (4)			
Mean (% RSD)	9 (4.5)	52 (3.2)	67 (2.6)	89 (2.2)

NMT Not more than.
NLT Not less than.

Figure 5 **SEROQUEL SR 300 mg tablet mean dissolution**

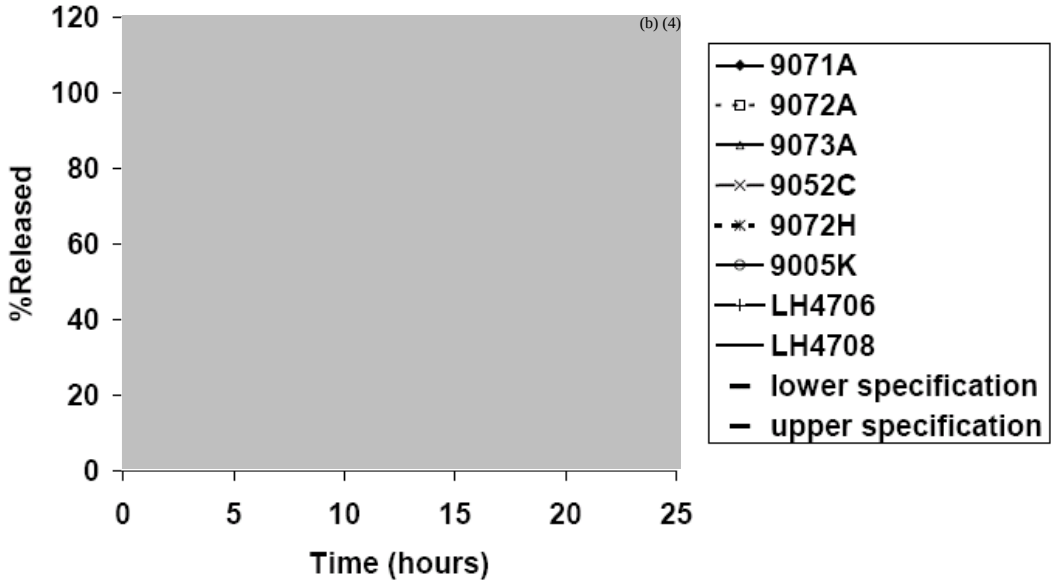


Table 14 **SEROQUEL SR 300 mg tablet (batch 9052C) summary of mean and range of individual dissolution (% label claim) stability study STB.4376**

Time (hours)	1	6	12	20
Acceptance criteria	**NMT** (b) (4)			**NLT** (b) (4)
Condition/time				
Initial	10 (b) (4)	61 (b) (4)	86 (b) (4)	93 (b) (4)
48 month 25°C/60% RH	9 (b) (4)	57 (b) (4)	83 (b) (4)	93 (b) (4)
48 month 30°C/65% RH	10 (b) (4)	59	84	93

NMT Not more than.
NLT Not less than.

Table 15 **SEROQUEL SR 400 mg tablet dissolution data (% label claim) at release**

Time (hours)	**1**	**6**	**12**	**20**
Acceptance criteria	**NMT** (b) (4)			**NLT** (b) (4)
Batch				
9104F				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (7.9)	62 (4.8)	87 (1.9)	96 (0.9)
9105F				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (5.0)	63 (3.3)	88 (2.4)	96 (1.1)
9101J				
Range of individuals	(b) (4)			
Mean (% RSD)	9 (6.4)	53 (3.2)	73 (2.3)	90 (2.2)
9008K				
Range of individuals	(b) (4)			
Mean (% RSD)	9 (4.5)	57 (1.8)	82 (1.7)	94 (0.9)
9052K				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (4.0)	61 (2.2)	87 (1.6)	96 (0.8)
9053K				
Range of individuals	(b) (4)			
Mean (% RSD)	10 (6.3)	61 (2.7)	89 (2.1)	98 (1.2)
9054K				
Range of individuals	(b) (4)			
Mean (% RSD)	9 (0.0)	56 (0.9)	78 (2.5)	96 (1.1)
LH4710				
Range of individuals	(b) (4)			
Mean (% RSD)	9 (5.5)	58 (2.0)	86 (1.6)	99 (1.3)
LL4600				
Range of individuals	(b) (4)			
Mean (% RSD)	9 (4.5)	56 (1.4)	82 (2.1)	94 (0.9)

NMT Not more than.
NLT Not less than.

Figure 6 **SEROQUEL SR 400 mg tablet mean dissolution**

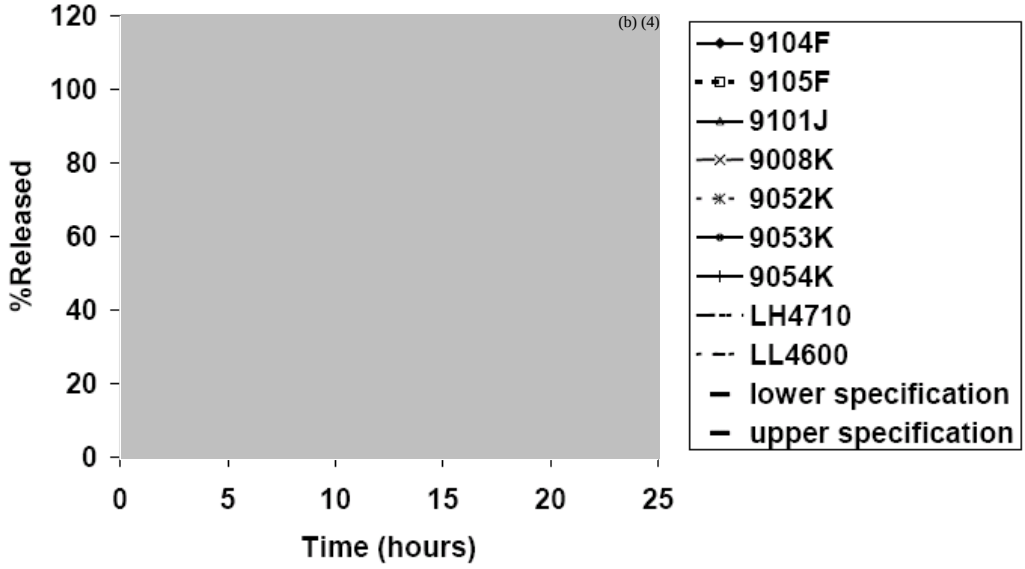


Table 16 **Summary of mean and range of individual dissolution (% label claim) of SEROQUEL SR 400 mg tablet (batch 9052K), stability study STB.4491**

Time (hours)	**1**	**6**	**12**	**20**
Acceptance criteria	**NMT** (b) (4)			**NLT** (b) (4)
Condition/time				
Initial	11 (b) (4)	65 (b) (4)	91 (b) (4)	96 (b) (4)
12 month 25°C/60% RH	10 (b) (4)	63 (b) (4)	87 (b) (4)	95 (b) (4)
12 month 30°C/65% RH	10	63	88	95

NMT Not more than.
NLT Not less than.

Analytical Methods

All assay methods used to determine plasma concentrations of quetiapine and its metabolites in the biopharmaceutics studies were for the analytes measured. The assay methods employed assay methods that included quetiapine and metabolite extraction from alkalinized plasma by ethyl acetate, and detection by high performance liquid chromatography and tandem mass spectrometry.

Assays for Studies 036, 037, 086, 097, and 109 were performed by (b) (4) For all data reported, the highest reported within-day and between-day coefficients of variation (CV%) were 7.9% and 11.9%, respectively, with an overall median CV% of 3.7% and 7.5%, respectively. With respect to the accuracy of the assay, the highest reported % deviation from quality control theoretical plasma concentrations was 14.4%, with an overall median deviation of –2.9%.

Assays for Studies 118, 001, and 003 were performed by (b) (4).
For all data reported across the 3 studies, the highest reported between-day accuracy (%RSD) and precision (%RE) results from the quality control samples were 11.5% and 8.00% (absolute), respectively.

The assay methods were accurate, reproductive results, with appropriate linearity and sensitivity. The assay methods used for the quantitation of quetiapine and related metabolites as well as the linearity and sensitivity of the assays are summarized in the following tables.

The following tables contain analytical methods used and summary quality control (accuracy and precision) data.

Analytical methods used to determine plasma concentrations of quetiapine and its metabolites (7-hydroxy quetiapine, quetiapine sulfoxide and N-desalkyl quetiapine)

Study number	Laboratory	Method	Validation study number	Method sensitivity (range, ng/mL)							
				Quetiapine		7-hydroxy quetiapine (ICI 214,227)		Quetiapine sulfoxide (ICI 213,841)		N-desalkyl quetiapine (M211,803)	
				Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower
5077IL/0036	(b) (4)	16-18	MV961002.00	5000	2.50	NM	NM	NAV	NAV	NAV	NAV
5077IL/0037		16-18	MV961002.00	5000	2.50	NM	NM	NAV	NAV	NAV	NAV
5077IL/0086		16-18(R1)	V971001	5000	2.50	5000	2.50	5000	2.50	NAV	NAV
5077IL/0097		16-18(R1)	V971001	5000	2.50	NM	NM	NM	NM	NAV	NAV
5077IL/109[b]		16-18(R1)	V971001	5000	2.50	NM	NM	NM	NM	NAV	NAV
5077IL/0118		M06.Quetiapine.hup.1, Rev. New	156492	2000	0.500	NM	NM	NM	NM	NAV	NAV
D1444C00001		M06.Quetiapine.hup.3. Rev.2 and Rev.3	160839	10000	0.500	10000	0.500	10000	0.500	10000	0.500
D1444C00003		M06.Quetiapine.hup.3. Rev.4	160839	10000	0.500	4000	0.500	10000	0.500	10000	0.500

[a] (b) (4)

[b] Plasma samples were collected in Study 109 for assay of quetiapine concentrations to support pharmacokinetic-pharmacodynamic analyses of vital signs. This study was not part of the biopharmaceutic program, and no pharmacokinetic parameter estimates were calculated. Assay information is included here for completeness.

[c] (b) (4)

NAV Not available. NM Not measured.

Assay variability for quetiapine in Study 5077IL/118

Study number	Analyte	Variability measure	QC sample concentration (ng/mL)		
			0.999	20.0	400
5077IL/0118	Quetiapine	Mean	0.989	20.5	416
		SD	0.079	0.761	15.2
		%RSD	7.97	3.71	3.65
		% recovery	99.0	103	104

QC Quality control sample. %RSD Percent coefficient of variation.

Assay variability for quetiapine and its metabolites in Studies 036, 037, 086, 097, 109

Study number / Assay method	Analyte	Variability measure	QC sample concentration (ng/mL)					
			7.50	175	350	700	1400	1750
					Dilution factor[a]			
					1X	2X	4X	5X
5077IL/0036[b]	Quetiapine	Mean	7.38	162	322	334	---	---
16-18		Within-day %RSD	3.5	2.7	3.7	2.6	---	---
		Between-day %RSD	4.8	4.4	4.0	4.0	---	---
		% theory	98.5	92.8	91.9	95.5	---	---
5077IL/0037[b]	Quetiapine	Mean	7.68	174	323	300	338	314
16-18		Within-day %RSD	4.3	5.6	3.9	1.6	2.3	3.6
		Between-day %RSD	6.8	7.0	7.5	NC	NC	NC
		% theory	102	99.2	92.3	85.6	96.6	89.8
5077IL/0086	Quetiapine	Mean	7.69	170	329	349	339	---
16-18(R1)		Within-day %RSD	4.7	4.6	2.3	1.4	1.2	---
		Between-day %RSD	3.6	5.9	7.5	NC	7.6	---
		% theory	102	97.4	94.1	99.6	96.9	---
	Quetiapine sulfoxide	Mean	7.56	170	335	351	327	---
		Within-day %RSD	5.2	4.0	2.1	2.8	1.8	---
		Between-day %RSD	9.4	6.2	7.8	NC	10.4	---
		% theory	101	97.1	95.7	100	93.5	---
	7-hydroxy quetiapine	Mean	8.07	174	340	356	NC	---
		Within-day %RSD	3.7	4.4	2.1	1.2	NC	---
		Between-day %RSD	7.7	5.7	6.7	NC	NC	---
		% theory	108	99.2	97.0	102	NC	---
5077IL/0097[b]	Quetiapine	Mean	7.53	178	337	364	358	---
16-18(R1)		Within-day %RSD	7.3	5.1	4.7	5.3	4.1	---
		Between-day %RSD	7.2	7.6	6.5	4.8	11.9	---
		% theory	100	102	96.2	104	102	---
5077IL/109[b,c]	Quetiapine	Mean	7.58	167	331	302	355	---
16-18(R1)		Within-day %RSD	7.9	4.4	7.3	0	0	---
		Between-day %RSD	8.0	9.0	8.6	8.4	6.1	---
		% theory	101	95.6	94.5	86.2	101	---

[a] Dilution factor: nX = n times dilution of original plasma sample.
[b] Metabolites were not analyzed.
NC Not calculated QC Quality control sample %RSD Percent coefficient of variation

Assay variability for quetiapine and its metabolites in Studies D14444C0001 and D1444C00003

Study number	Analyte	Variability measure	QC sample concentration (ng/mL)				Dilution factor 5x
			1.0	20.0	175	400	2000
D1444C00001	Quetiapine	Mean	0.991	20.6	173	393	2110
		SD	0.0758	0.644	6.62	15.4	97.5
		%RSD	7.65	3.13	3.83	3.92	4.62
		% RE	−0.90	3.00	−1.14	−1.75	5.50
	Quetiapine sulfoxide (M213,841)	Mean	0.986	20.5	174	390	2130
		SD	0.0760	0.549	3.99	13.1	97.4
		%RSD	7.71	2.68	2.29	3.36	4.57
		% RE	−1.40	2.50	−0.57	−2.50	6.50
	7-hydroxy quetiapine (M214,227)	Mean	1.01	21.3	171	377	2120
		SD	0.0853	1.10	10.6	20.6	133
		%RSD	8.45	5.16	6.20	5.46	6.27
		% RE	1.00	6.50	−2.29	−5.75	6.00
	N-desalkyl quetiapine (M211,803)	Mean	1.01	21.2	174	389	2110
		SD	0.0680	1.08	7.90	16.8	113
		%RSD	6.73	5.09	4.54	4.32	5.36
		% RE	1.00	6.00	−0.57	−2.75	5.50
D1444C00003	Quetiapine	Mean	0.939	20.1	167	374	2020
		SD	0.0748	0.899	6.94	15.9	70.9
		%RSD	7.97	4.47	4.16	4.25	3.51
		% RE	−6.10	0.500	−4.57	−6.50	1.00
	Quetiapine sulfoxide (M213,841)	Mean	1.01	20.3	166	378	1850
		SD	0.104	1.23	7.74	19.1	183
		%RSD	10.3	6.06	4.66	5.05	9.89
		% RE	1.00	1.50	−5.14	−5.50	−7.50
	7-hydroxy quetiapine (M214,227)	Mean	0.940	20.0	162	NAV	1840
		SD	0.0888	0.942	11.1	NAV	25.2
		%RSD	9.45	4.71	6.85	NAV	1.37
		% RE	−6.00	0.00	−7.43	NAV	−8.00
	N-desalkyl quetiapine (M211,803)	Mean	0.991	20.8	170	375	1930
		SD	0.114	0.925	9.49	31.9	131
		%RSD	11.5	4.45	5.58	8.51	6.79
		% RE	−0.900	4.00	−2.86	−6.25	−3.50

[a] Dilution factor "5x" = 5 times dilution of original plasma sample.

NAV Not available; upper limit of quantitation was 200 ng/mL for M214,227 during analysis of samples for Study D14444C00003. QC Quality control sample. R.E. Relative error. %RSD Percent coefficient of variation

4.3. Pharmacometric Review

PHARMACOMETRIC REVIEW

NDA:	22047
Drug name:	Quetiapine (Seroquel SR)
Indication:	Treatment of schizophrenia
Proposed Regimen (Sponsor):	400 to 800 mg once daily
Applicant:	AstraZeneca
OCP Reviewer	Kofi Kumi, Ph.D.
PM Reviewer:	Hao Zhu, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	NDA
Submission Date:	July 17, 2006
PDUFA Date:	May 17, 2007

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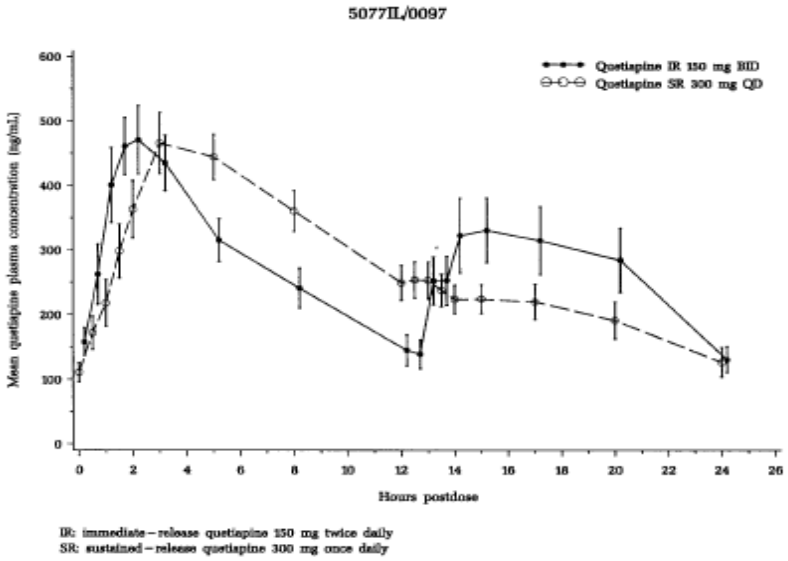
1 QUESTION BASED REVIEW

Overall, is there substantial evidence of effectiveness of Seroquel SR formulation?

- The sponsor demonstrated equivalence (in terms of AUC) of Seroquel SR and IR formulation, which indicates that the exposure between Seroquel IR and SR formulation is comparable (Fig A).
- Long term therapy is required to demonstrate anti-schizophrenia effect following Seroquel administration, which suggests that the cumulative overall exposure (eg. AUC), rather than the shape of concentration time profile is more likely to be linked to effectiveness (Fig B). Therefore, the Seroquel SR formulation is expected to produce similar effect on the symptoms as compared to IR formulation, given that the Seroquel IR formulation has been approved and the equivalence in exposure (in terms of AUC) of Seroquel SR and IR formulation was demonstrated.
- In Study D1444C0132, a significant dose-response relationship was demonstrated (P = 0.0001) in addition to the significant effectiveness for all Seroquel SR formulation treated groups as compared to the placebo group by the end of 6^{th} week (Fig C). These results provided strong supportive evidence for the effectiveness of the Seroquel SR formulation.
- Seroquel SR and IR formulation with the same dose consistently produced similar PANSS score change from baseline values in all three pivotal trials. Additionally, in Studies D1444C0133 and 5077IL/0041, neither Serqouel SR, nor Seroquel IR demonstrated significant effectiveness compared to placebo, even though the Seroquel IR formulation has been approved for schizophrenia. The outcomes suggested that the failure to detect the difference in effectiveness between the placebo and the Seroquel SR and IR likely due to the lack of sensitivity of the trials, rather than lack of effectiveness of the Seroquel SR formulation. (Fig D)
- Two pivotal clinical studies (5077IL/0041 and D1444C0133) which were conducted mainly in the USA failed to demonstrate significant effectiveness of Seroquel SR and IR formulations as compared to placebo. Whether this outcome reflected the differences in the expectation of US vs. non-US patient, since the primary dropout reason is lack of symptom-relief; whether it reflected the differences of clinical practice in the US vs. non-US; whether it reflected the differences of investigators/centers in the US vs. non-US is unknown. It is important to note here that the since both IR and SR arms failed, the study is at best un-interpretable with respect to effectiveness conclusion. The implication of the results with respect to trial conduct and/or patient behavior differences between US and non-US sites is uncertain. Certainly a phenomenon to be noted in future clinical trial for this indication.

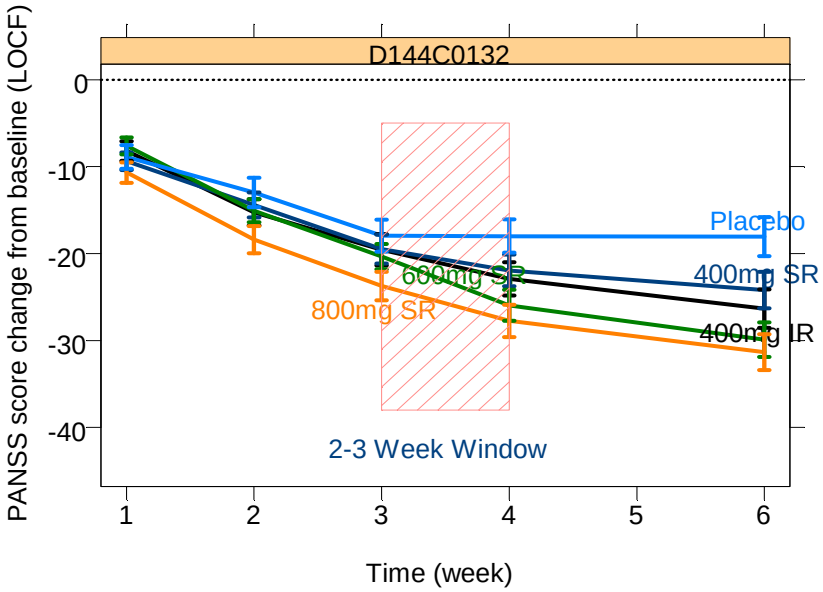
Fig A Mean Concentration time profile of Seroquel SR and IR formulation

Figure 1 Mean (±SEM) plasma quetiapine concentrations



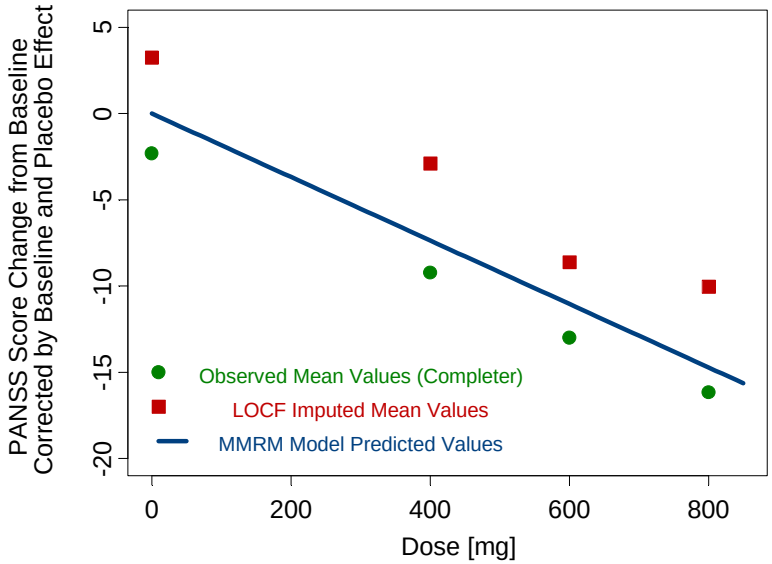
Note: Exposure between Seroquel SR and IR formulation is comparable.

Fig B. PANSS Change from Baseline versus Time (LOCF)



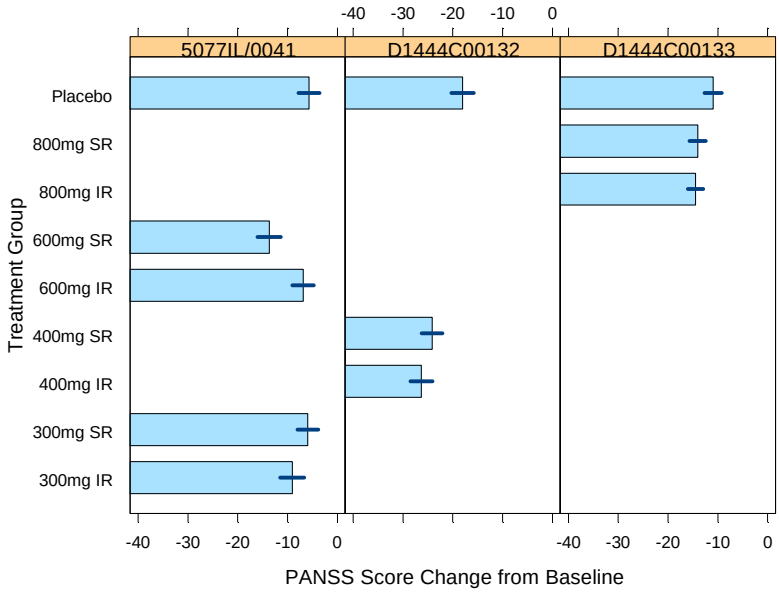
Note: At least 2-3 week treatment is needed in order to demonstrate effectiveness of Seroquel comparing to placebo**.**

Fig C. Dose-response relationship for Seroquel SR formulation



Note: Dose-response relationship has been demonstrated in Study D144C0132. (Using MMRM analysis, P = 0.0001)

Fig D. PANSS Score Change from Baseline for Seroquel IR and SR formulation with the same dose.

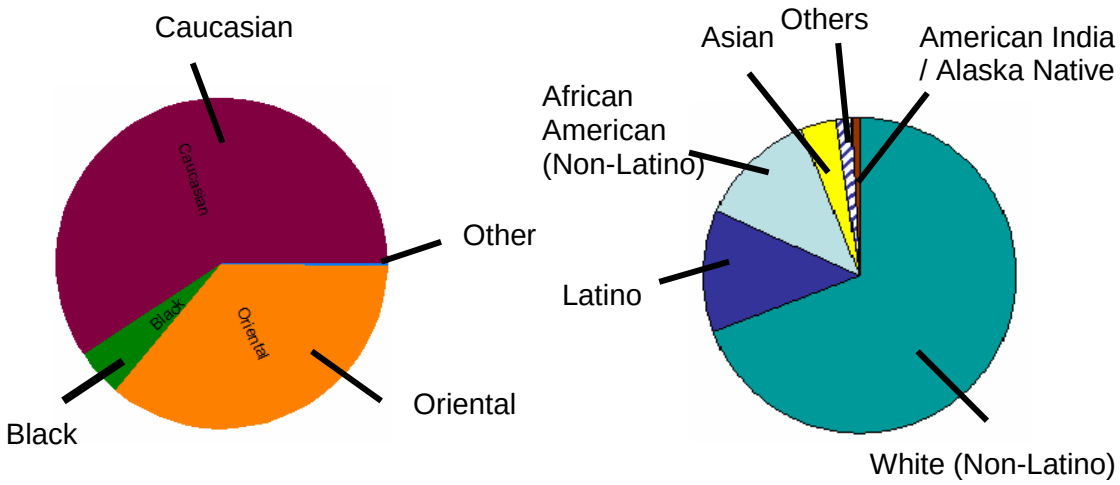


Note: Seroquel SR and IR formulation with the same dose produced similar PANSS score change from baseline. In Study 5077IL/0041 and D1444C0133, neither SR nor IR formulation demonstrated significant effectiveness as compared to placebo.

Fig E Clinical sites in the Study D144C00132

Note: Study D144C00132 mainly included clinical sites in Asian and East Europe.

Fig F Racial composition of the Study D144C0132 and American population



Note: Racial composition in Study D144C0132 is different from the American population.

What are the potential reasons for the uninterpretable studies D1444C0133 and 5077IL/0041?

- Most likely reason for the failure of trial D1444C0133 and 5077IL/0041 is substantial early dropout. The overall dropout rates for study 5077IL/0041 and D1444C0133 are 57% and 39% respectively (Fig G). About half of them dropped out within the 1st week of treatment (Fig H). Interpreting trials with such a high rate of drop out is extremely challenging. No one method is reliable.

FigG. Overall Percentage of Prematurely Discontinued Subjects vs. Study

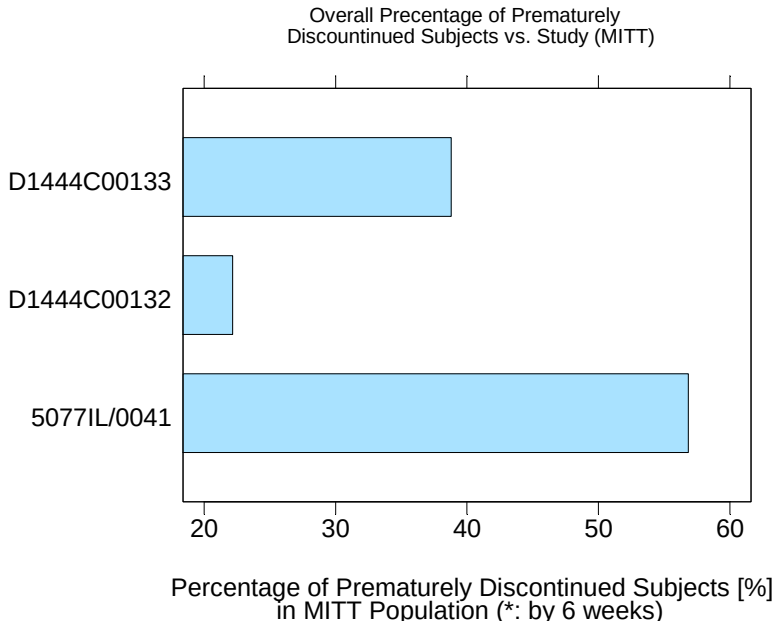
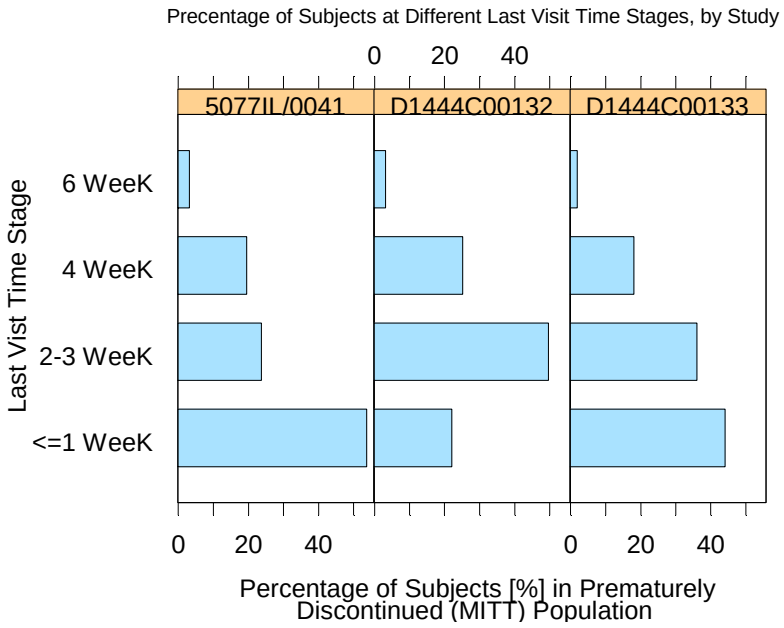


Fig H. Time Distribution of Premature Distribution, by Study



Recommendations to sponsor:

Should the sponsor conduct another effectiveness and safety trial using the same clinical end point, we recommend the following:

- In order to retain patients in the trial by educating patients, and developing a parametric model to describe the time course of PANSS score change from baseline and dropout, and then using this model to derive optimal patient retention scheme and implications on the study power, and
- In order to increase sample size to compensate the high drop out rate.

2 ANALYSIS AND RESULTS

2.1 BACKGROUND

Quetiapine fumarate (SEROQUEL™, quetiapine) is a dibenzothiazepine derivative with established effectiveness in the treatment of schizophrenia (first approved in 1997) as well as acute mania associated with bipolar disorder (first approved in 2003). Quetiapine immediate release (IR) tablets for the treatment of schizophrenia are administered 2 or 3 times a day in the dose range of 150 mg/day to 800 mg/day, with a recommended 4-day treatment-initiation period to reach a dose of 300 mg/day to 400 mg/day.

Schizophrenia is a chronic and disabling idiopathic psychotic disorder with an estimated worldwide prevalence of approximately 1%. In patients with schizophrenia, compliance with a treatment program is especially important; however, compliance is also especially problematic. While the reasons for noncompliance are varied, there is evidence that treatment complexity (eg, requirements for multiple doses per day or complex treatment initiation) is a contributing factor.

This submission is a New Drug Application (NDA) for Seroquel SR (quetiapine fumarate) sustained release tablet to obtain marketing approval so that it will allow physician to administer quetiapine once daily in a rang of 400 to 800 mg/day.

2.2 SPONSOR'S STUDIES AND ANALYSES

One of the major objectives for the sponsor's clinical development program is to establish the effectiveness and safety of quetiapine SR (sustained release) in the treatment of schizophrenia. Totally 18 clinical studies were conducted, including 7 biopharmaceutic (pharmacokinetic) studies, 5 clinical pharmacology (pharmacodynamic) studies, and 4 effectiveness and safety studies, and 2 other studies. Among them, 5077IL/0041, D1444C00132, and D1444C00133 are the key effectiveness and safety studies to demonstrate superior effectiveness of quetiapine sustained-release (SR) tablets compared with placebo in the treatment of patients with schizophrenia. Study designs and outcomes are summarized as following:

Study 5077IL/0041: This 6-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comprised a screening visit and a 42-day treatment period, which began within 7 days of screening. All patients were hospitalized for the first 10 days of treatment. After baseline assessments on Day 1, patients were assigned to 1 of 6 possible treatments: quetiapine SR at 300, 600, or 800 mg daily, quetiapine IR at 300 or 600 mg daily (in 2 divided doses), or placebo. Prohibited psychoactive medications were discontinued at least 48 hours before baseline assessments, with depot and long acting antipsychotics discontinued at least 1 dosing interval before baseline assessments. After a patient started treatment, effectiveness and safety assessments were made on Days 4, 8 (Week 1), 15 (Week 2), 28 (Week 4), and 42 (Week 6) or

last visit. Eighty evaluable patients per treatment group were sufficient for 90% power over all 3 quetiapine SR treatment groups (adjusted for multiple comparisons), assuming a mean (SD) difference of 15.5 (25.8) points between active treatment and placebo for change from baseline PANSS total score at Day 42. Therefore, 532 patients were enrolled from 49 centers both inside the US and outside US. Treatment-group sizes were as follows: placebo, n=84; quetiapine SR 300 mg, n=91; quetiapine SR 600 mg, n=92; quetiapine SR 800 mg, n=89; quetiapine IR 300 mg, n=90; and quetiapine IR 600 mg, n=86. The primary effectiveness variable is the change in PANSS total score from baseline to Day 42. The Categorical endpoints such as PANSS response or CGI Global Improvement scores were analyzed using the Cochran-Mantel-Haenszel chi-square test. During the study, at least 50% of patients in each treatment group withdrew early (placebo, 66%; quetiapine SR 300 mg, 62%; uetiapine SR 600 mg, 57%; quetiapine SR 800 mg, 51%; quetiapine IR 300 mg, 54%; and quetiapine IR 600 mg, 62%). Early withdrawal was most commonly due to lack of effectiveness or withdrawn consent and not AEs. All 532 enrolled patients were included in the safety population, and 498 were included in the primary analysis data set (modified intent to treat [MITT]). All statistical analyses used last-observation-carried-forward (LOCF) values for patients who withdrew early or had missing data. Following quetiapine SR treatment, the PANSS score change over time was demonstrated in Fig 3.2A and the statistical results were illustrated in Table 3.2A. The primary effectiveness objective was met for the quetiapine SR 600-mg dose. At the final visit, the estimated mean difference between SR 600 mg and placebo (–7.82) for change from baseline in PANSS total score (primary effectiveness variable) was significant in favor of SR 600 mg (p=0.033, ANCOVA, adjusted for multiplicity).

Study D1444C00132: This was a 6-week, multicenter, double-blind, double-dummy, randomized, placebo controlled study comparing the effectiveness and safety of quetiapine SR 400 mg/day, 600 mg/day and 800 mg/day and quetiapine IR 400 mg/day with that of placebo in the treatment of adult male and female patients with schizophrenia. This study was conducted at 39 international centers (Non-US) in South Africa, Russia, Romania, Bulgaria, Greece, India, Indonesia, and the Philippines. The primary outcome variable was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment at Day 42 (Last Observation Carried Forward [LOCF]). After a patient started treatment, effectiveness and safety assessments were made on Days 4, 8 (Week 1), 15 (Week 2), 28 (Week 4), and 42 (Week 6) or last visit. The randomized study population comprised 588 patients. A total of 446 patients completed study treatment (72% of placebo patients, 74% of quetiapine SR 400 mg/day patients, 81% of quetiapine SR 600 mg patients, 74% of quetiapine SR 800 mg/day patients and 78% of quetiapine IR patients). Of the 588 patients assigned to treatment and included in the safety analyses, 15 were excluded from the MITT population because post-baseline PANSS scores were missing. Analysis of the primary variable, the change from baseline in the PANSS total score at Day 42, showed significant improvement in all tested quetiapine SR doses (SR 400 mg/day, 600 mg/day, and 800 mg/day) compared to placebo. The magnitude of change from baseline compared to placebo was -6.1 in the quetiapine SR 400 mg/day, -12.1 in the quetiapine SR 600 mg/day group, and -12.5 in the quetiapine SR 800 mg/day group. Quetiapine IR 400 mg/day was

demonstrated to be superior to placebo (p=0.004) with a difference of -7.8. LOCF analyses based on the PP population at Day 42 as well as OC (observed cases) analyses for the MITT and PP populations supported the robustness of the primary analysis with regard to the effectiveness of the 3 quetiapine SR doses. Following quetiapine SR treatment, the PANSS score change over time was demonstrated in Fig 3.2B and the statistical results were illustrated in Table 3.2B.

Study D1444C00133: This was a 6-week, multicenter, double-blind, double-dummy, randomized, placebo controlled study comparing the effectiveness and safety of quetiapine SR 400 mg/day, 600 mg/day and 800 mg/day and quetiapine IR 800 mg/day with that of placebo in the treatment of adult male and female patients with schizophrenia. This study was conducted at 40 centers in the United States. The primary outcome variable was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment at Day 42 (Week 6) (Last Observation Carried Forward [LOCF]). After a patient started treatment, effectiveness and safety assessments were made on Days 4, 8 (Week 1), 15 (Week 2), 28 (Week 4), and 42 (Week 6) or last visit. The randomized study population comprised 565 patients, divided into 5 treatment groups of similar sizes. A total of 333 patients completed treatment. The number of patients discontinuing early ranged from 40 (35%) in the quetiapine SR 400 mg/day group through 49 (42%) in placebo to 54 (47%) in the quetiapine IR 800 mg/day group, most commonly because consent was withdrawn, AEs, or lack of effectiveness. A Cochran-Mantel-Haenszel (CMH) technique was used for the analysis of the PANSS response rate and the CGI Global
Improvement score response rate. The PANSS score change over time was demonstrated in Fig 3.2C and the statistical results were illustrated in Table 3.2C.Improvement from baseline in PANSS total score at Day 42 was seen in all groups, with greater improvement in quetiapine dose groups than in the placebo group. The change from baseline in PANSS total score in the placebo group was pronounced and continued throughout the study. However, quetiapine SR at each of the 3 doses (400 mg/day, 600 mg/day and 800mg/day) and quetiapine IR (800 mg/day) was not statistically superior to placebo at the end of treatment. Improvements were also seen at Day 42 in CGI Severity of Illness score (LOCF), PANSS response rate, CGI Global Improvement rating ≤ 3 (LOCF) and change in PANSS subscale scores (LOCF), most consistently with quetiapine SR 600 mg/day, but superiority to placebo was not demonstrated for any of the quetiapine dose groups. The quetiapine SR 600 mg/day group achieved separation from placebo in the PANSS general psychopathology, depression cluster and hostility/aggression cluster analyses, as shown by 95% CIs. At a dose of 800 mg/day, quetiapine IR, an atypical antipsychotic with proven effectiveness against the symptoms of schizophrenia, was also unable to differentiate from placebo in any of the effectiveness measurements assessed.

The time course of the mean observed, LOCF imputed, and least-square predicted PANSS score change from baseline from the same study are different because the premature discontinuations are not missing completely at random, but rather they are correlated with the disease.

The observed PANSS score change from baseline (non-dropout patient) from Seroquel SR treatment group was clearly separated from placebo group at all dose levels starting from week 4

in Study D1444C00132. Since the dropout rate in this study is very low, the time course for observed PANSS score change from baseline is similar compared with the LOCF imputed and least square predicted values. At the last visit, the apparent separation for PANSS score change from baseline in the treatment group can be demonstrated compared with placebo using either one of the plots.

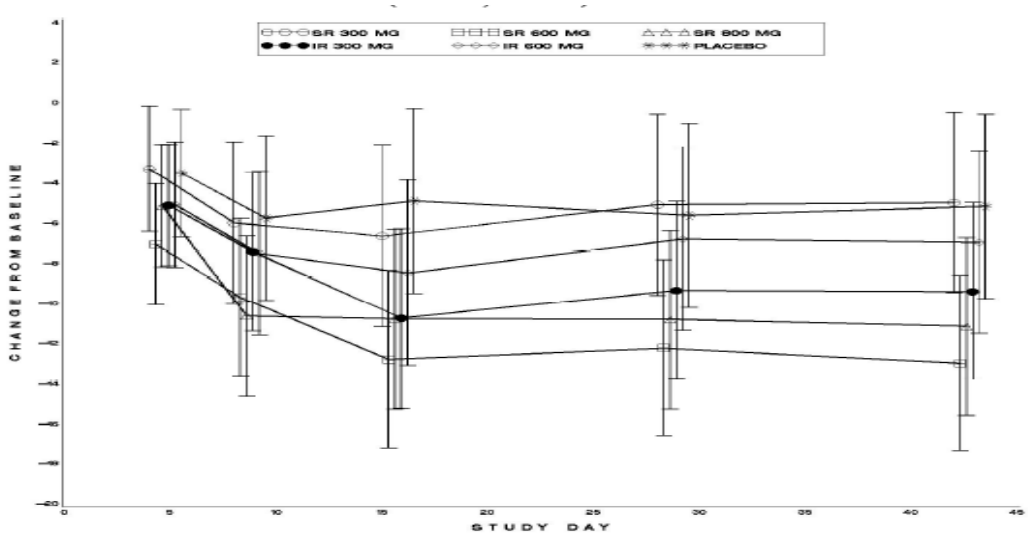
Table 3.2A Overview of effectiveness results at Day 42 (LOCF, MITT Popul ation, Study 5077IL/0041)

Summary statistic	Placebo (n=78)	QTP SR 300 mg (n=83)	QTP SR 600 mg (n=87)	QTP SR 800 mg (n=85)	QTP IR 300 mg (n=85)	QTP IR 600 mg (n=80)
PANSS total score, LSmean change from BL[a]	-5.19	-5.01	-13.01[b]	-11.17	-9.42	-6.97
PANSS response, % patients with ≥30% improvement[c]	14.1	12.0	24.1	23.5	18.8	13.8
CGI Severity of Illness score, LSmean change from BL	–0.42	–0.50	–0.66	–0.68	–0.59	–0.51
CGI Global Improvement, % patients with improvement[d]	48.7	50.6	64.4	55.3	57.6	53.8
% much/very much improved	19.2	30.1	33.3	35.3*	42.3*	26.3

[a] Mean baseline PANSS total scores across treatment groups were 91.1, 91.5, 92.4, 89.0, 89.5, and 88.6, respectively.
[b] Significantly different from placebo (analysis of covariance adjusted for multiplicity, p=0.033).
[c] In PANSS total score.
[d] Includes patients improved, much improved and minimally improved per CGI Global Improvement rating.
[e] Significantly different from placebo (Cochran-Mantel-Haenszel analysis, p=0.015 for SR 800 mg and 0.005 for IR 300 mg).

BL Baseline. CGI Clinical Global Impression. LOCF Last observation carried forward. LSmean Least-squares mean.
MITT Modified intent-to-treat. PANSS Positive and Negative Syndrome Scale.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.

Fig 3.2A PANSS score change from baseline versus time (LOCF, MITT, Study 5077IL/0041)



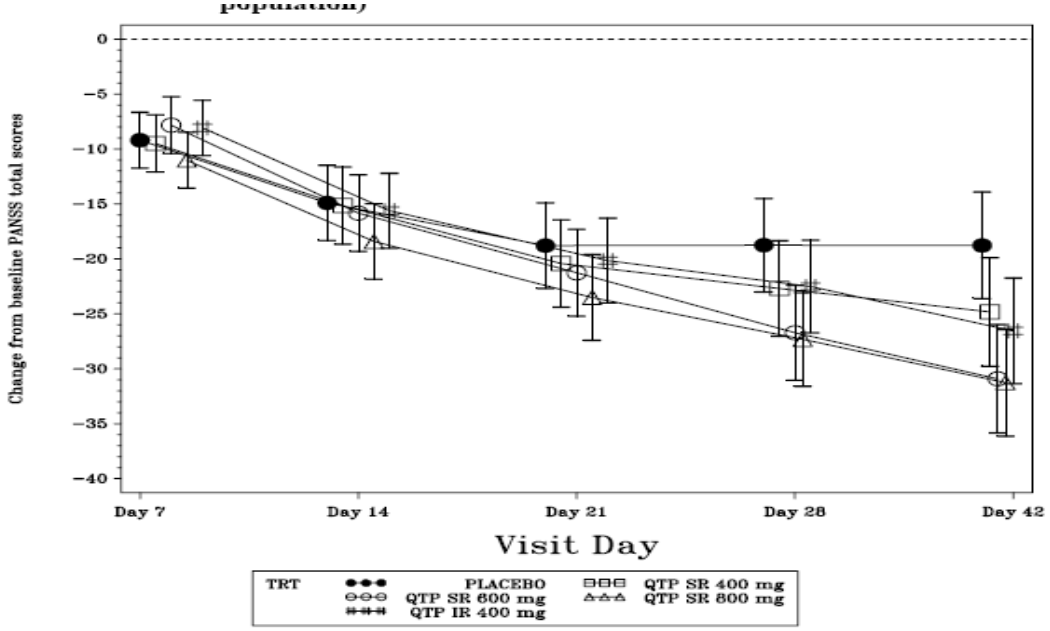
CI Confidence interval. IR Quetiapine immediate release. SR Quetiapine sustained release.
LOCF Last observation carried forward. MITT Modified intent to treat analysis population.
Data from Figure 11.2.3.1.3, Section 11.2.

Table 3.2B Overview of effectiveness results at Day 42 (LOCF, MITT Popul ation, Study D1444C00132)

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
PANSS total score, LS mean change from baseline[a]	-18.8	-24.8*	-30.9***	-31.3***	-26.6**
PANSS response, % of patients responding[b]	30.4	44.1*	60.4***	56.4***	52.9**
CGI Severity of Illness score, LS mean change from baseline	-1.0	-1.3	-1.5***	-1.6***	-1.3*
CGI Global Improvement score, % of patients showing improvement[c]	60.0	73.9*	79.3**	76.9**	75.6*

*** p<0.001 comparison with placebo
** p<0.01 comparison with placebo
* p<0.05 comparison with placebo
[a] The comparisons of QTP SR doses with placebo refer to p-values adjusted with Hommel's procedure for multiplicity.
[b] Response was defined as a ≥30% improvement in PANSS total score.
[c] Improvement was defined as a rating of 'much improved', 'improved' and 'minimally improved' on the CGI Global Improvement scale.
CGI Clinical Global Impression Improvement. LOCF Last observation carried forward. LS Least squares. MITT Modified intention-to-treat. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: The MITT population included all patients who took study medication and who had a baseline PANSS assessment and at least 1 valid post-baseline PANSS assessment.
Source document: ETC_EFF_RESULT252.SAS. Generated: 23:04:03 18May2006 DB version prod: 27.

Fig 3.2B PANSS score change from baseline versus time (LOCF, MITT, Study D1444C00132)



BL Baseline. IR Immediate-release. LOCF Last observation carried forward. MITT Modified intention to treat. QTP Quetiapine. SR Sustained-release.
Note: Data shown for each visit are least-square means and corresponding 95% confidence intervals.
Source document: S__ANCOVA_PANSS_REPPLOT.SAS. Generated: 9:18:04 22May2006 DB version prod: 27.

Table 3.2C Overview of effectiveness results at Day 42 (LOCF, MITT Popul ation, Study D1444C00133)

	PLA N=111	QTP SR 400 mg N=113	QTP SR 600 mg N=101	QTP SR 800 mg N=110	QTP IR 800 mg N=109
PANSS total score, LS mean change from baseline	-12.1	-13.8	-16.8	-14.8	-15.0
PANSS response, % of patients responding[a]	20.7	19.5	26.7	23.6	22.9
CGI Severity of Illness score, LS mean change from baseline	-0.5	-0.6	-0.6	-0.6	-0.6
CGI Global Improvement score, % of patients showing improvement[b]	56.8	65.5	67.3	62.7	61.5

Note: None of the QTP doses were statistically superior compared to placebo for any of the efficacy outcome variables at Day 42

[a] Response was defined as a ≥30% improvement in PANSS total score.

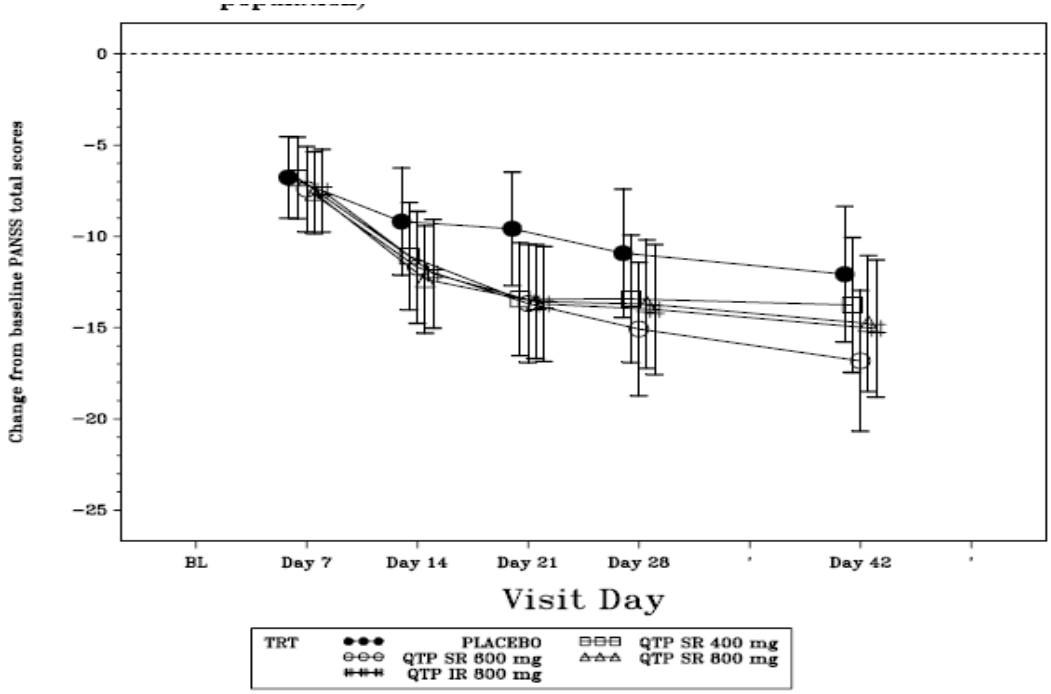
[b] Improvement was defined as a rating of 'much improved', 'improved' and 'minimally improved' on the CGI Global Improvement scale.

CGI Clinical Global Impression Improvement. LOCF Last observation carried forward. LS Least squares. MITT Modified intention-to-treat. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SR Sustained-release.

Note: The MITT population included all patients who took study medication and who had a baseline PANSS assessment and at least 1 valid post-baseline PANSS assessment.

Source document: ETC_EFF_RESULT252.SAS. Generated: 10:00:16 22May2006 DB version prod: 24.

Fig 3.2C PANSS score change from baseline versus time (LOCF, MITT, Study D1444C00133)



BL Baseline. IR Immediate-release. LOCF Last observation carried forward. MITT Modified intention to treat. QTP Quetiapine. SR Sustained-release.

Note: Data shown for each visit are least-square means and corresponding 95% confidence intervals.

Source document: S__ANCOVA_PANSS_REPPLOT.SAS. Generated: 11:41:53 22May2006 DB version prod: 24.

2.3 AIM OF THE ANALYSIS

The overall aim of this analysis is to investigate the dose-effectiveness relationship in order to:

- Explore the reason for the discrepant results that were seen among different effectiveness trials

2.4 DATA

Data used in the analysis is the effectiveness data set that comes along with the submission package. (PANSS.xpt)

2.5 METHODS AND RESULTS

2.5.1 Dose-response analysis

The developed mixed-model repeated measures (MMRM) model is described by:

Δ PANSS score = $\beta_0 + \beta_1$ Visit + β_2 Dose + β_3 BasePANSS score + β_4 Visit*Dose

Where β_0, β_1, β_2, β_3, β_4 refer to the intercept, slope in placebo group, symptomatic effect, baseline PANSS score, and the slope between the treatment and placebo groups. The time effect was treated as a categorical variable.

The time course of the mean observed, LOCF imputed, and least-square predicted PANSS score change from baseline from the same study are different because the premature discontinuations are not missing completely at random, but rather they are correlated with the disease.

Considerable data are missing in study D1444C00133 and 5077IL/0041mostly due to lack of response. Last observation carried forward (LOCF) for missing data that the sponsor used can be an inappropriate imputation technique for the data when the dropouts are related to the patient disease progression or adverse events associated with the treatment (not missing at completely at random (MCAR)). Alternative approach using mixed model repeated measures (MMRM) model was developed to evaluate the dose and time effect.

The mean observed PANSS score change from baseline, mean LOCF imputed PANSS score change from baseline, and least-square mean predicted PANSS score change from baseline for the three studies were shown in Fig 1A, Fig 1B, and Fig 1C respectively.

The observed PANSS score change from baseline (observed patient) from Seroquel SR treatment group was obviously separated from placebo group at all dose levels starting from week 4 in Study D1444C00132. Since the dropout rate in this study is low, the time course for observed

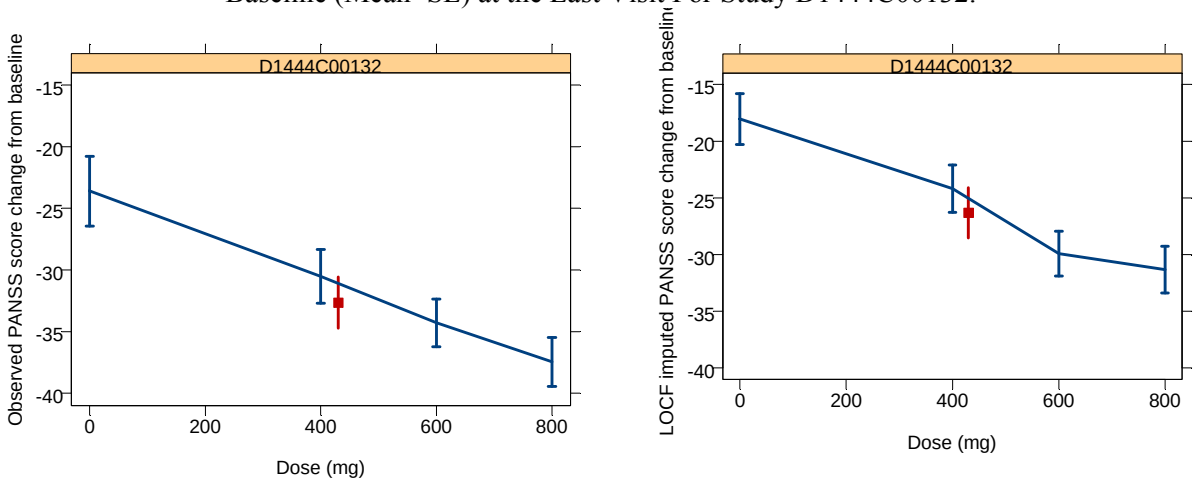
PANSS score change from baseline is similar compared with the LOCF imputed and least square predicted values. At the last visit, a clear separation for PANSS score change from baseline in the treatment group can be demonstrated compared to placebo as shown in the figures (Fig 1A to Fig 1C). Fig 1 D further illustrated the dose response for PANSS score change from baseline at the last visit by using observed data alone or using LOCF imputed data. An obvious trend with larger PANSS score change from baseline as dose increases was demonstrated. Fig 1E compared the dose response relationship from observed (for completer only), MMRM model predicted and LOCF imputed mean PANSS score change from baseline at the last visit. Since MMRM model includes the information for patients who dropped out before last visit (usually with a smaller PANSS score change from baseline), the model prediction is slightly higher than the mean observation for the completers. LOCF assumed the patients who prematurely discontinued would finish the trial under the condition that the PANSS score change from baseline would never change from the time they left trial till the end of the study. This could be a very conservative approach to evaluate the treatment effect for different dose groups, therefore LOCF imputation yielded smaller PANSS score change from baseline as compared to the observed, and MMRM predicted mean values. In summary, the dose response relationship was clearly demonstrated for study D1444C00132 at the last visit with P <0.0001 and the parameter estimates were listed in Table 2.5.1.A.

Table 2.5.1.A. Parameter estimates from MMRM analysis for Study D1444C00132.

Parameters	Estimate	Significance
Intercept	-1.609	N
Base PANSS Score	-0.2039	***
Dose of Seroquel SR Formulation	-0.0184	***
VISIT 4	12.5224	***
VISIT 5	7.7719	***
VISIT 6	2.4972	**
VISIT 7	1.4456	N
VISIT 8	0	-
DOSE*VISIT4	0.0172	***
DOSE*VISIT5	0.01274	***
DOSE*VISIT6	0.01135	***
DOSE*VISIT7	0.00531	**
DOSE*VISIT8	0	-

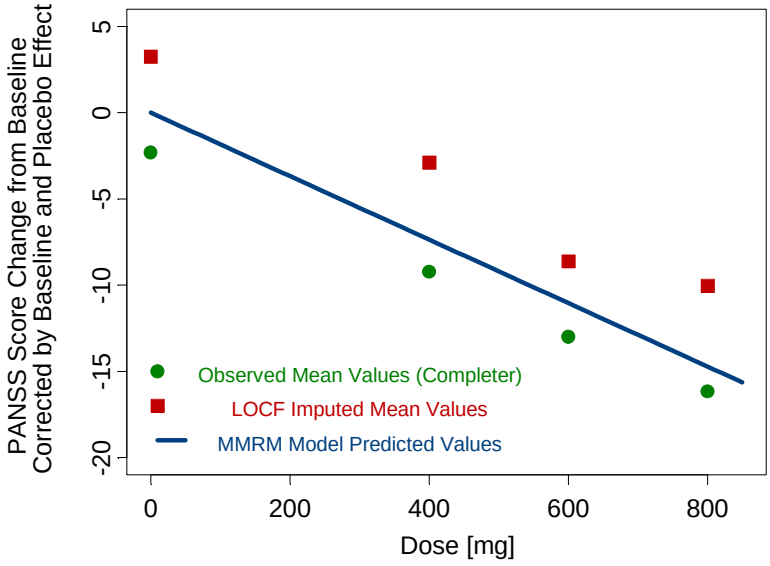
*Note: N: = not significant, ***: = P < 0.0001, **: = P < 0.05, -: Not applicable*

Fig 1A. Dose-Response Relationship for Observed and LOCF Imputed PANSS Score Change from Baseline (Mean±SE) at the Last Visit For Study D1444C00132.



Note: (Left) Observed PANSS Score Change from Baseline and (Right) LOCF Imputed PANSS Score Change from Baseline. Blue circles were dose-response relationship for Seroquel SR formulation groups, and red squares represented the Seroquel IR formulation group. Significant dose response relationship could be demonstrated for Seroquel SR formulation. (P < 0.0001)

Fig 1B. Mean PANSS Score Change from Baseline, Corrected by Baseline and Placebo Effect versus Dose of Seroquel SR Formulation at Last Visit of Study D1444C00132.



Note: Green circles represented the observed mean values for the completers. Red squares represented the LOCF imputed mean values, and the blue line was the MMRM model predicted mean values. MMRM model captured information form both completers and prematurely discontinued patients. Therefore, the model prediction was between the LOCF imputed and observed (for completer) values.

Fig 1C. Observed PANSS Score Change from Baseline (Mean ± SE) versus Time, for Study 5077IL/0041, D1444C00132 and D1444C00133

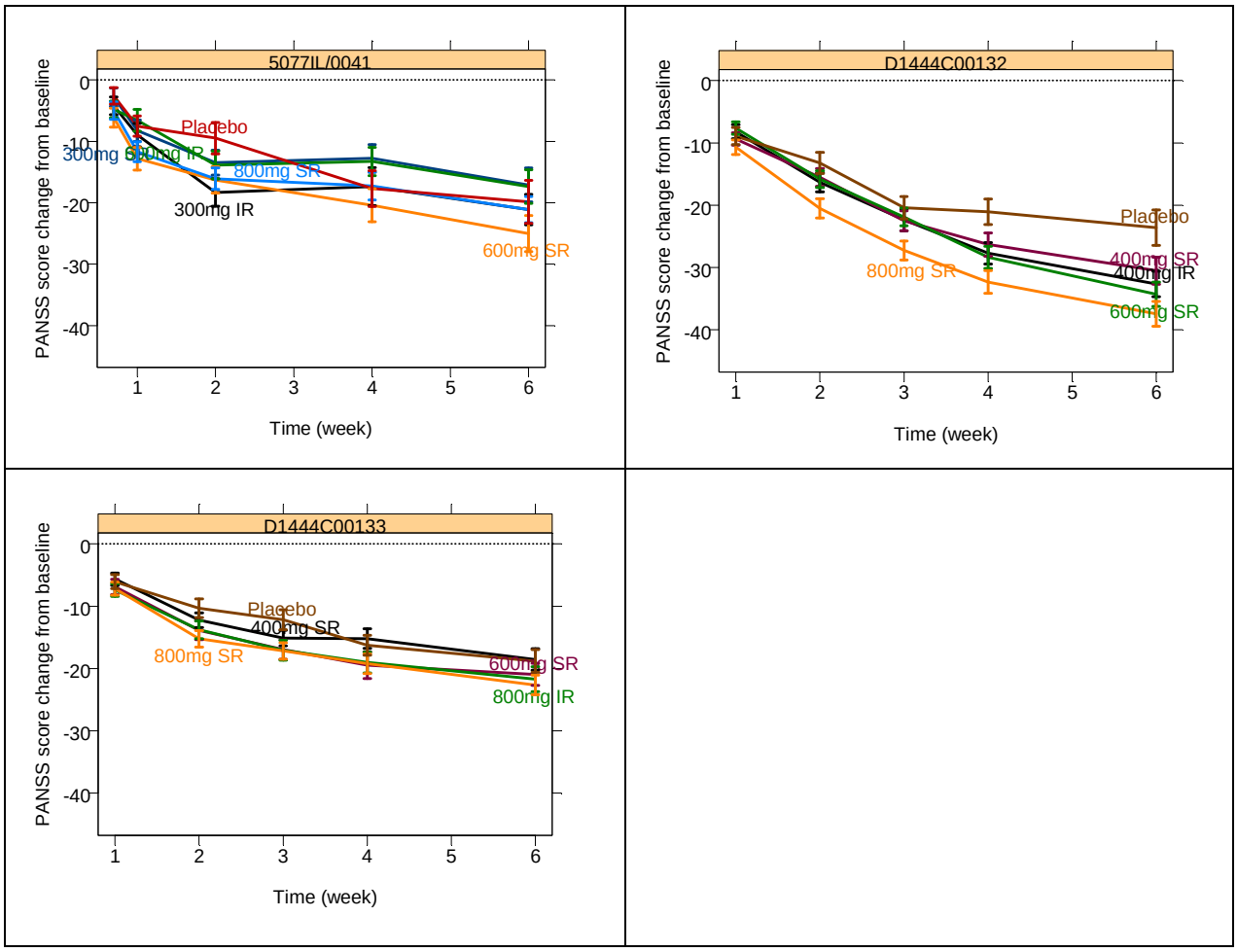

5077IL/0041
PANSS score change from baseline
0
-10
-20
-30
-40
1
2
3
4
5
6
Time (week)
Placebo
300mg IR
800mg SR
600mg SR
D1444C00132
Placebo
400mg SR
400mg IR
800mg SR
600mg SR
D1444C00133
Placebo
400mg SR
800mg SR
600mg SR
800mg IR

Fig 1D. LOCF Imputed PANSS Score Change from Baseline (Mean ± SE) versus Time, for Study 5077IL/0041, D1444C00132 and D144C00133.

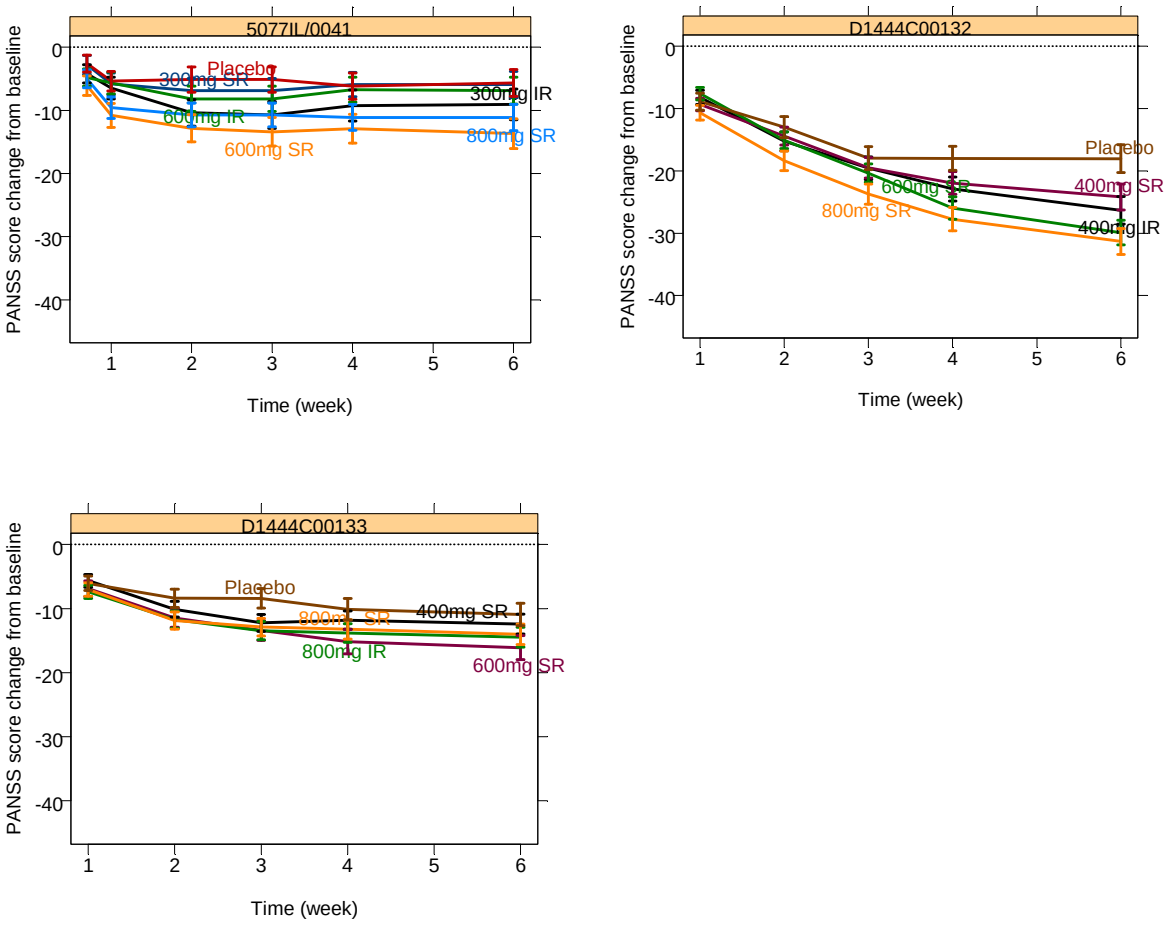
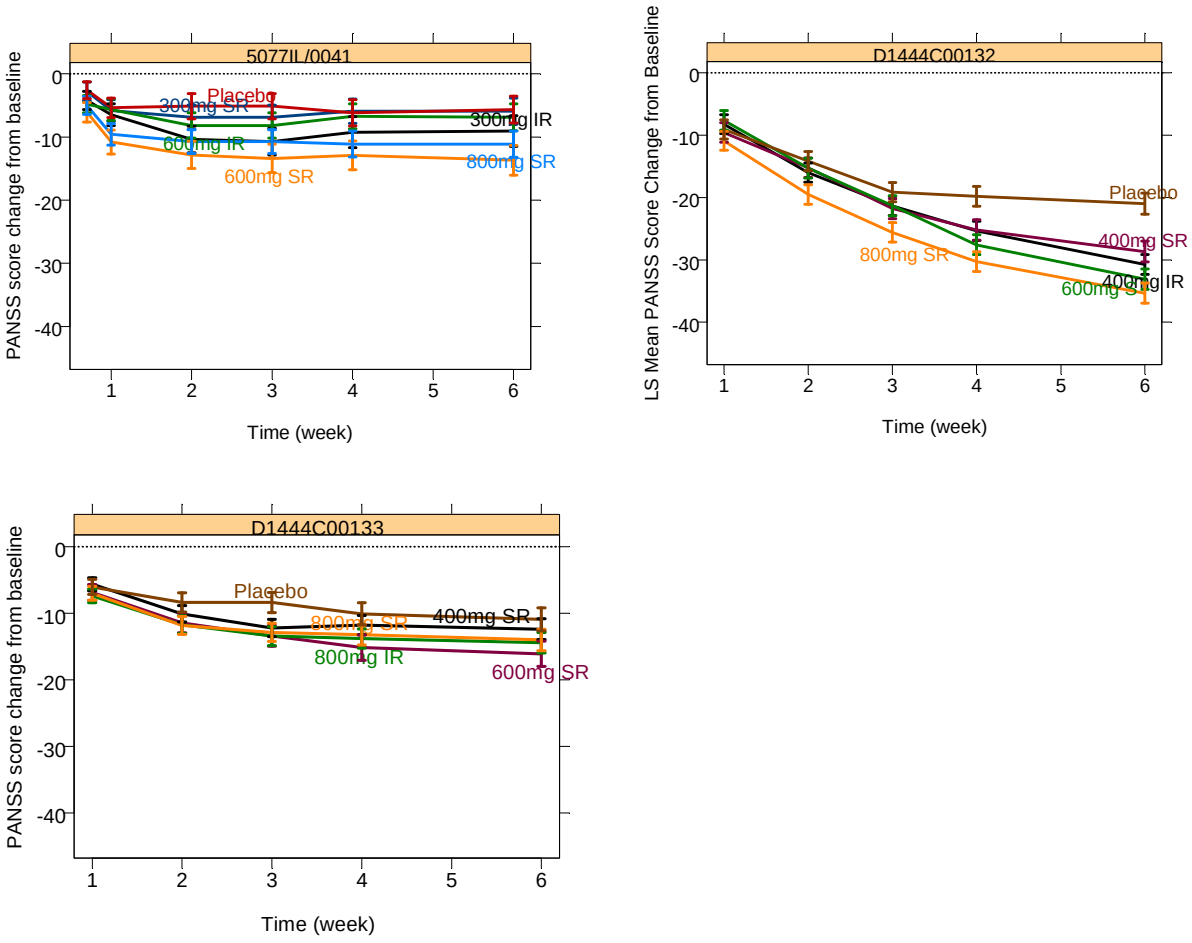


Fig 1E. Least Square Predicted PANSS Score Change from Baseline, Corrected by Placebo and Baseline Effect (Mean ± SE) versus Time,
for Study 5077IL/0041, D1444C00132, and D1444C00133.



Study 5077IL/0041 is the trial with the highest dropout rate among the three studies. No superior effectiveness of SR formulation can be demonstrated at the last visit using observed PANSS score change from baseline (non-dropout patient) and least square prediction. The only complete separation from placebo group is the 600mg SR group using LOCF imputation, which is consistent with the sponsor's primary analysis. However, LOCF imputation might not be appropriate when the dropout is not due to the worsening the symptom or drug therapy.

In study D1444C00133, no separation of the observed PANSS score change from baseline (observed patients) in the SR treatment group can be identified compared to the placebo group at the last visit. Improved separation can be found using least square prediction which accounts for the information from premature discontinuation. However, at the last visit, the difference between the treatment groups and the placebo group was still marginal.

In summary, the MMRM model clearly demonstrated significant dose response relationship for Seroquel SR treatment groups at the last visit for study D1444C00132. This provided supportive evidence for the effectiveness of Seroquel SR formulation. For study D1444C00133 and 5077IL/0041, MMRM model demonstrated improved separation of Seroquel SR treatment groups from placebo group. However, this improvement still could not be translated into significance dose response at the last visit.

2.5.2 Dropout analysis

As summarized in the section 3.2, D1444C00132 study was conducted at the centers outside US and demonstrated superior effectiveness of SR formulation at all dose levels compared with placebo in the treatment of patients with schizophrenia. D1444C00133 was conducted at 40 centers in the United States following similar design as study D1444C00132. None of the doses were superior for any of the effectiveness outcome variables compared with placebo at Day 42. 5077IL/0041 is studied at centers both inside and outside US. The primary effectiveness objective was met only for the quetiapine SR 600 mg dose. At the final visit, the estimated mean difference between SR 600 mg and placebo (–7.82) for change from baseline in PANSS total score (primary effectiveness variable) was significant in favor of SR 600 mg.

In an effort to explore the reason why the different outcomes were seen from different clinical trials, the patient premature discontinuation pattern was investigated. D1444C00132 was the only trail that demonstrated superior effectiveness for both SR and IR formulation at all dose levels compared with the placebo. As shown in Fig G, it was also the trial that had the lowest overall premature discontinuation rate (about 20%). The dropout rates for study D1444C00133 and 5077IL/0041, however, were about 40% and 60% respectively. Since the sample size of each study was determined with the assumption that 90% of all randomized patients were expected to be the evaluable patients without significant protocol violation and deviation, high premature

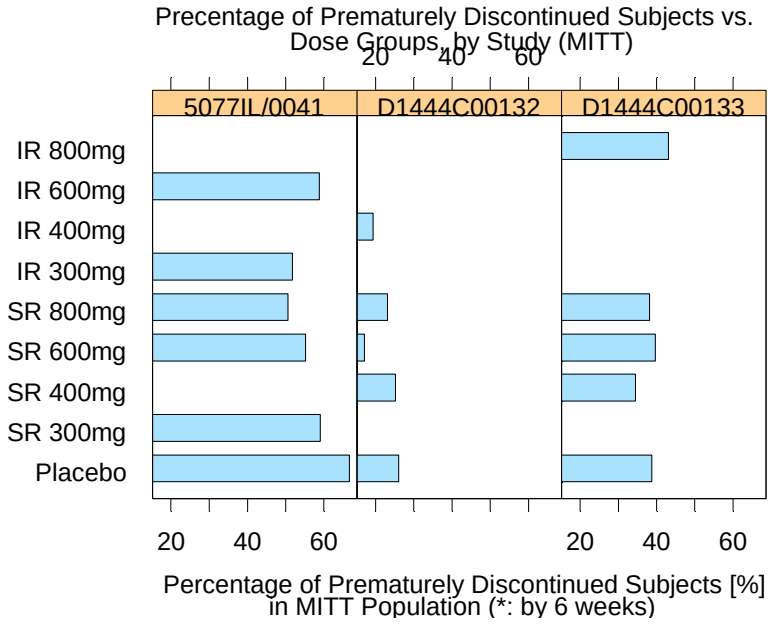
discontinuation rate can lead to insufficient power for the detection of an anticipated difference between treatment groups and placebo group at the final visit.

The distribution of premature discontinuation at various time points is different among the three pivotal trials. As illustrated in Fig H, most patients choose to withdrawal from the study after 2-3 weeks of treatment in study D1444C00132, whereas the highest premature withdrawal rate was seen during the 1st week of trail in study D1444C00133 and 5077IL/0041. Since anti-schizophrenia effect can only be seen following long-term therapy (in the time frame of weeks), patients who withdrawal from studies at early time points provided limited drug effectiveness information for data analysis.

Therefore, high dropout rate and early drop out in study D1444C00133 and 5077IL/0041 could be two potential reasons that led to the different outcomes seen from the three pivotal effectiveness studies.

Premature discontinuation was seen at all dose levels in the treatment group as well as in the placebo group. As shown in Fig 4.5.2A, no specific pattern was identified among different dose groups for a specific study.

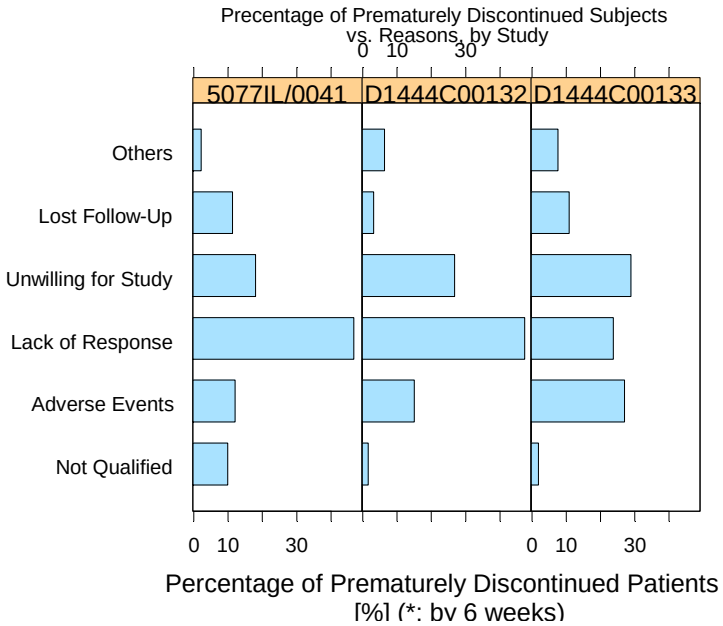
Fig 4.5.2A Premature Discontinuation versus Dose Groups, by Study



When considerable data are missing, it is important to understand the cause of the premature discontinuation. A scrutiny of premature discontinuation pattern (Fig 4.5.2B) indicated that the

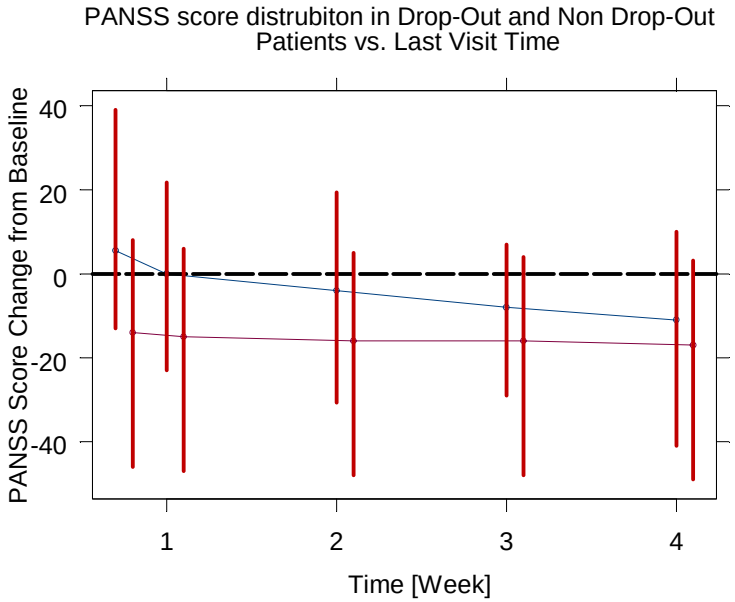
lack of symptom relief was the main reason for patients' early withdrawal from the trial for study 5077IL/0041 and study D1444C00132.

Fig 4.5.2B Reasons for Premature Discontinuation, by Study



The distribution of PANSS total score change from baseline was evaluated at each time point for patients who discontinued at the next time point versus the patients who stayed in the trial for pooled data (Fig 4.5.2.C). PANSS score change from baseline distribution for each trial was plotted in Fig 1 in Appendix. It appears that patients who dropped out from the trial had different PANSS total score change from baseline distribution as compared with those who stayed in the trials. The score distribution was especially separated at early time points.

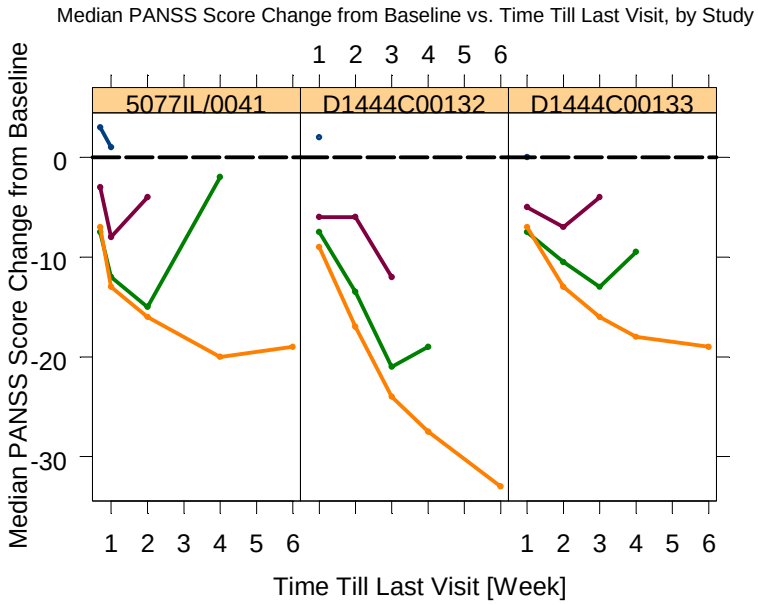
Fig 4.5.2.C PANSS Score Distribution in Premature Discontinuation and Non-Premature Discontinuation Patients versus Last Visit Time.
(Pooled Data from Study 5077IL/0041, D1444C00132, D1444C00133)



Note: At the last visit for the dropout patients, the distribution of PANSS score change from baseline was different from that from the non-dropout patients. This suggested that the patients who dropped out from study mainly due to insufficient relief from symptom.

Patients were grouped according to their last visit time; the median PANSS score change from baseline within each group was plotted at different time points during their treatment course for each study (Fig 4.5.2D). The same plot using the pooled data and for each formulation within each study were demonstrated in Fig 2 and Fig 3 in the Appendix. The results showed patients who experienced sudden worsening of their PANSS score dropped out.

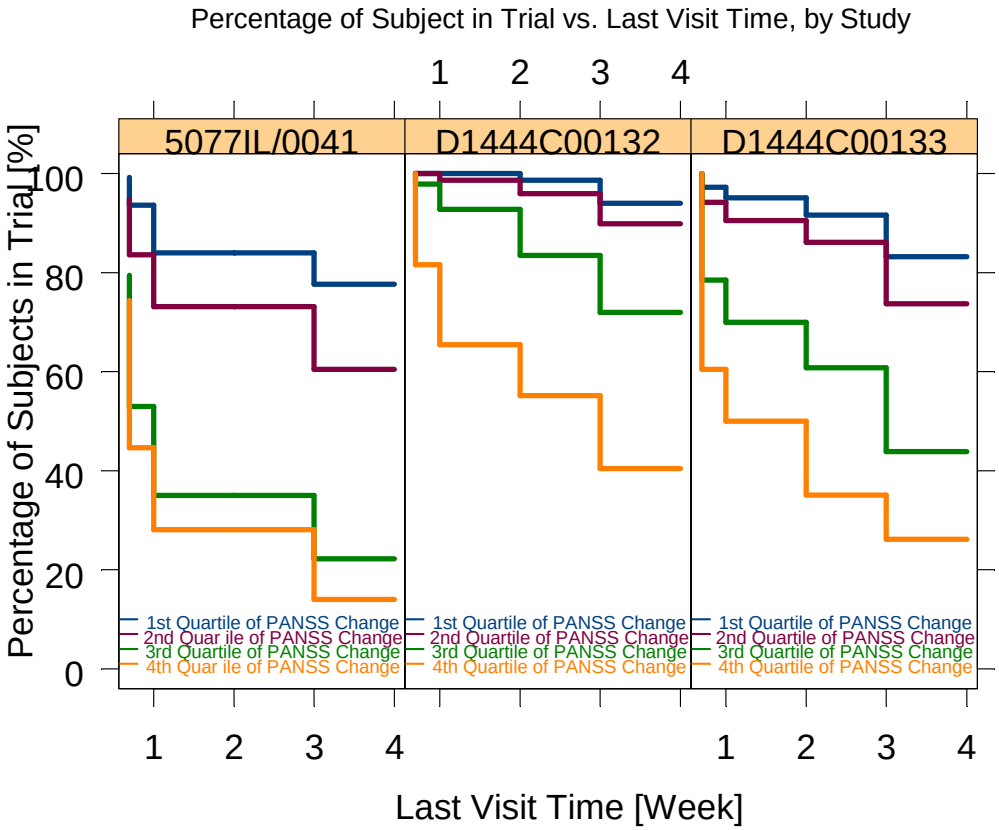
Fig 4.5.2.D Median PANSS Score Change from Baseline versus Last Visit Time
(for Study 5077IL/0041, D1444C00132, D1444C00133)



Note: Patients were grouped according to their last visit time.
Patients tended to dropout at the next visit when a rebound in their PANSS score change from the baseline was observed at the last visit.

Patients were further grouped according to their last visit PANSS score change from baseline; the percentage of subjects who stayed in the trial versus their last visit time for each study was demonstrated in Fig 4.5.2.E. The overall time trend for pooled data was shown in Fig 4 in Appendix. Patient with less relief of their syndrome following the treatment tended to discontinue the trial earlier.

Fig 4.5.2.E Percentage of Subjects Stayed in the Trial versus Last Visit Time
(for Study 5077IL/0041, D1444C00132, D1444C00133)



Note: Patients were grouped by the last visit PANSS score change from baseline Patients with less relief of symptom after starting the trial tended to drop out early.

The patterns for premature discontinuation suggested that most patients dropped out from trial due to worsening of the syndrome, the dropouts were not missing completely at random (MCAR), and rather they are correlated with the PANSS score change from baseline. The imputation based on last observation carry forward (LOCF) might be inappropriate because it can lead to biased estimator for the effectiveness at the final visit.

In summary, the premature discontinuation pattern suggested the LOCF might be an inappropriate imputation tool. Insufficient effectiveness information can be obtained from study D1444C00133 and 5077IL/0041 due to high dropout rate and early dropout.

2.6 CONCLUSION

Statistical significant dose response relationship was demonstrated for Seroquel SR formulation in study D1444C00132 at the last visit.

Most likely reason for the failure of trial D1444C0133 and 5077IL/0041 is substantial early dropout. The overall dropout rates for study 5077IL/0041 and D1444C0133 are 57% and 39% respectively. Among all premature discontinued patients, 53% and 44% of them dropped out within the 1st week of treatment for study 5077IL/0041 and D1444C0133 respectively, no imputation is reliable

In the clinical studies, the patients dropped out early mainly due to lack of relief of syndrome. The LOCF imputation, which sponsor applied in the primary analysis is not appropriate.

Should the sponsor conduct another effectiveness and safety trial, we recommend, 1.) to increase sample size to compensate the high drop out rate, and 2.) To retain patients in the trial by educating patients, and using the joint time course of PANSS score change from baseline with dropout model to derive optimal patient retention scheme and implication the power.

3 APPENDIX

Fig 1. PANSS Score Distribution in Dropout and Non Dopout Patients at the Last Visit Time for Study 5077IL/0041, D144C00132 and D144C00133.

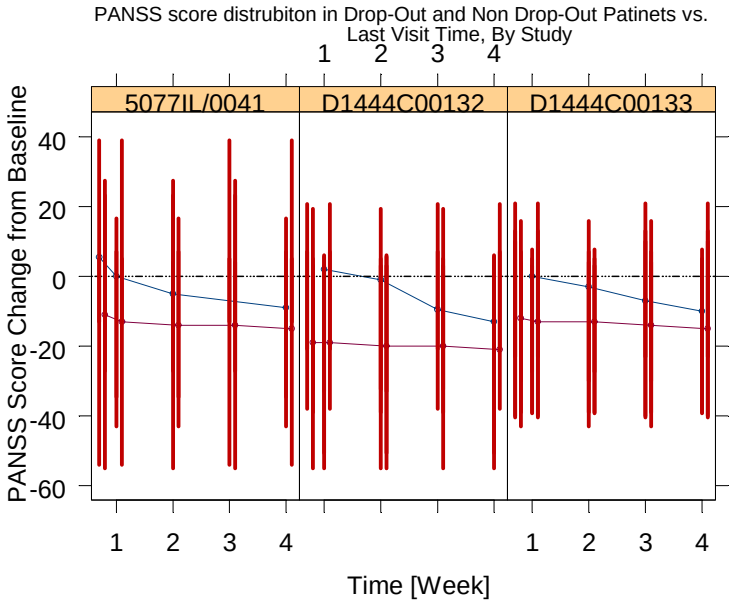
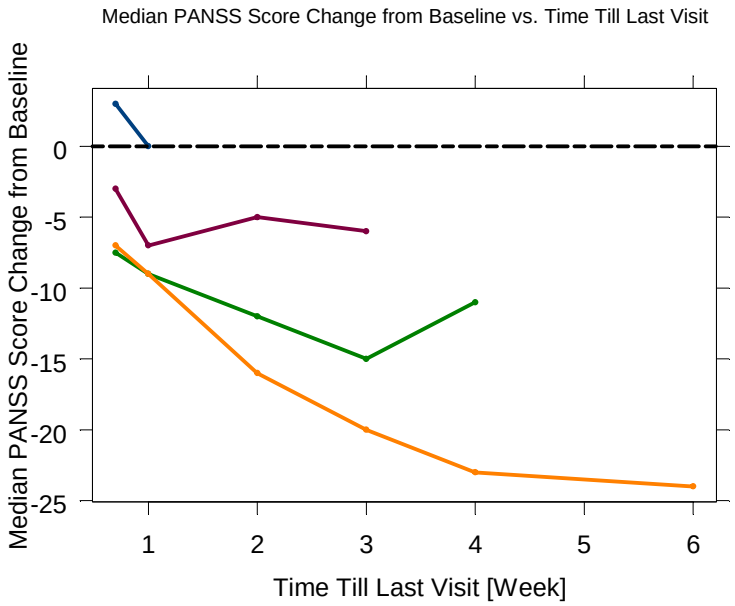
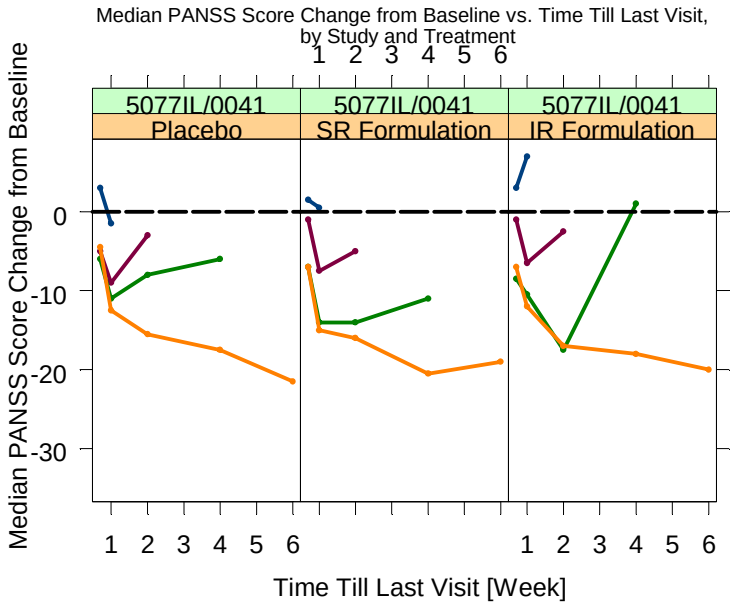


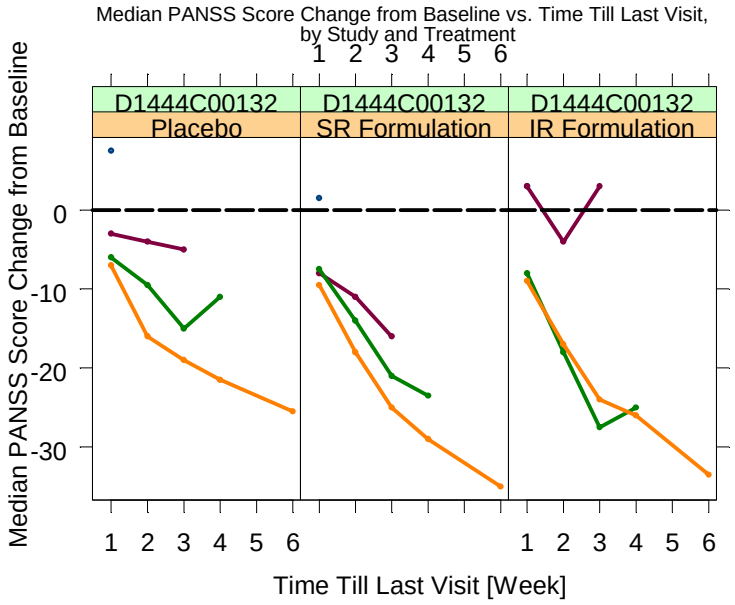
Fig 2. Median PANSS Score Change from Baseline versus Last Visit Time
(for pooled data from Study 5077IL/0041, D1444C00132, D1444C00133)

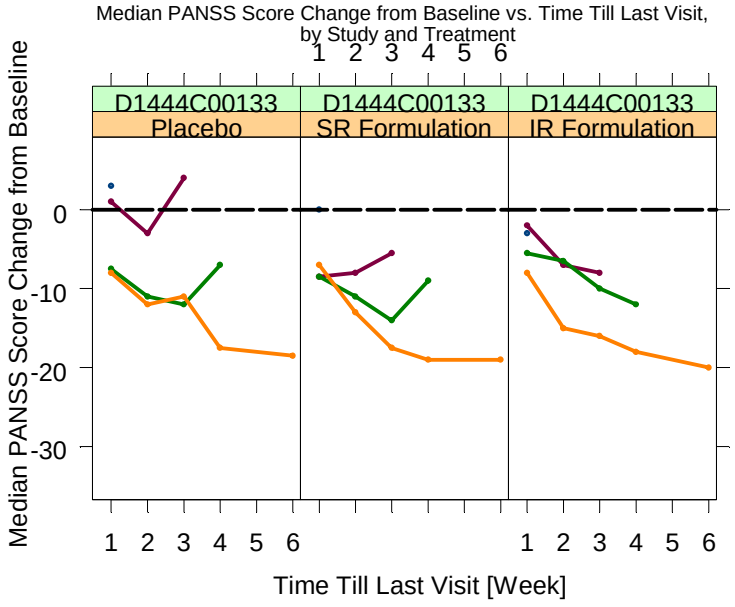


*: *Patients were grouped according to their last visit time.*

Fig 3. Median PANSS Score Change from Baseline versus Last Visit Time
(from each formulation group of Study 5077IL/0041, D1444C00132, D1444C00133)

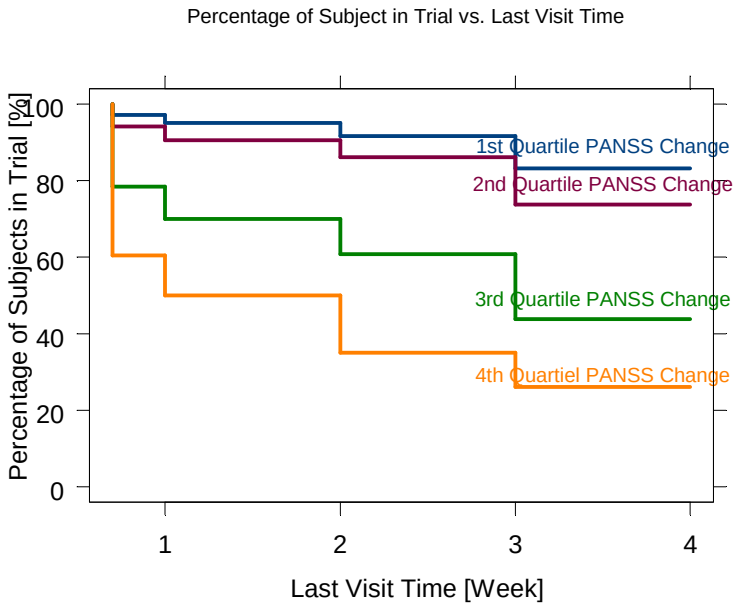






Patients were grouped by their last visit time

Fig 4. Percentage of Patients Stayed in the Trial versus Last Visit Time.
(For pooled data from Study 5077IL/0041, D1444C00132 and D1444C00133)



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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-047**	**Brand Name**	**Seroquel SR**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Quetiapine sustained release Tablets**
Medical Division	**DPP**	**Drug Class**	**Dibenzothiazepine derivative**
OCPB Reviewer	**Kofi Kumi**	**Indication(s)**	**Treatment of Schizophrenia**
OCPB Team Leader	**Raman Baweja**	**Dosage Strength and Form**	**50, 200, 300, 400 mg SR Tablet**
		Dosing Regimen	**300 to 800 mg/day**
Date of Submission	**7/17/06**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**3/17/06**	**Sponsor**	**AstraZeneca**
PDUFA Due Date	**5/17/07**	**Priority Classification**	**Standard**
Division Due Date	**3/17/07**		

Clin. Pharm. and Biopharm. Information

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

PD:				
Phase 2:	**X**	**5**		
Phase 3:	**X**	**5**		
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	**X**	**6**		
solution as reference:				
alternate formulation as reference:	**X**	**6**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**2**		
Dissolution:	**X**	**1**		
(IVIVC):	**X**	**1**		
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Effect of DVS on QTc				
Pediatric development plan				
Literature References				
Total Number of Studies		**14**		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		**1. Are the exposures (AUC, Cmin) after administration of similar total doses Seroquel SR and Seroquel IR similar?** **2. Does food have an effect on Seroquel SR** **3. Is Seroquel SR performance at steady state similar to the IR product?** **4. Is the IVIVC reported by the sponsor substantiated by the data?** **5. Is there exposure (dose, Cmax, AUC)- response (tolerability) relationship for quetiapine after administration of Seroquel SR?**
Other comments or information not included above	**This application is all electronic. Link to EDR : \\CDSESUB1\N22047\N-000\2006-07-17**	
Primary reviewer Signature and Date	**Kofi A. Kumi**	
Secondary reviewer Signature and Date		

CC: NDA 22-047, HFD-850 (Electronic Entry or Lee), HFD-130, HFD-860 (Mehta, Baweja, KumiK)), CDR (B. Murphy)

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Kofi Kumi
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Raman Baweja
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