AstraZeneca

Clinical Study Report Synopsis

Drug substance:	Quetiapine fumarate
Study code:	D1443C00033
Edition number:	1
Date:	15 January 2009

A Double-blind, Double-dummy, Randomized, Crossover Study to Compare the Tolerability of Quetiapine Fumarate Immediate Release (SEROQUEL®) with Quetiapine Fumarate Extended Release (SEROQUEL XR®) During Initial Dose Escalation in Healthy Volunteers

Study dates: First healthy volunteer enrolled: 26 June 2008
Last healthy volunteer completed: 5 August 2008

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

An abbreviated (synopsis-only) clinical study report was considered to be appropriate for this Phase I study, which is not intended to support a marketing application.

Study center(s)

This study was conducted at a single center in the United States.

Publications

None at the time of writing this report.

Objectives

- *Primary:* To compare the intensity of sedation, 1 hour after the first dose in each period, between quetiapine fumarate immediate release (IR) formulation and quetiapine fumarate extended release (XR) formulation during initial dose escalation as measured by the Modified Bond-Lader Visual Analog Scale (VAS).

- *Secondary:* To characterize the difference in sedation profile for quetiapine IR and quetiapine XR over the period of initial dose escalation as measured by the Bond-Lader VAS. The sedation profile includes measures such as maximum intensity of somnolence, time to maximum intensity to somnolence, and area under the curve (AUC) over the following time periods after dose: 0 to 4 hours, 8 to 14 hours, 0 to 24 hours.

- *Secondary:* To characterize the pharmacokinetics of quetiapine and its metabolite (norquetiapine) on Day 5 over an 11 hour interval by measuring maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), and AUC_{0-t}, for each treatment.

- *Secondary:* To explore the relationship between systemic exposure to quetiapine and its metabolites (norquetiapine) and measures of sedation.

Study design

This was a double blind, randomized, double-dummy, 2-period crossover study.

Target subject population and sample size

A total of 60 healthy volunteers, aged 18 to 50 years inclusive, were to be enrolled to ensure that at least 52 healthy volunteers completed the study. This sample size was calculated to provide 90% power to detect a difference between the 2 formulations of 10 mm on the Bond-Lader VAS.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

During each treatment period, subjects received either quetiapine IR or quetiapine XR according to the randomization schedule. The dosing was as follows: Day 1, 50 mg; Day 2, 100 mg; Day 3, 200 mg; Days 4 and 5, 300 mg. Study drug was administered orally at

approximately the same time each morning. The batch numbers for quetiapine IR were MC4601 for the 25 mg tablet (LC4618 for matching placebo), LK4600 for the 100 mg tablet (ST70142-015-FA06 for matching placebo), and LK4608 for the 200 mg tablet (ST70142-016-FA09 for matching placebo). The batch numbers for quetiapine XR were MH4600 for the 50 mg tablet (CE888X for matching placebo), LK4613 for the 200 mg tablet (CE889X for matching placebo), and LH4708 for the 300 mg tablet (CE891X for matching placebo).

Duration of treatment

Two 7-day treatment periods (5 days of active drug dosing in each), separated by a washout period of ≥6 days.

Criteria for evaluation - pharmacodynamic (PD) and pharmacokinetic (PK) variables

Modified Bond-Lader VAS and standard PK parameters (C_{max}, T_{max}, AUC).

Criteria for evaluation - safety variables

Standard safety assessments: adverse events (AEs), vital signs, physical examinations, and laboratory parameters

Statistical methods

The per protocol (PP) analysis set, which comprised those healthy volunteers who completed both treatment periods, was used for all PD and PK analyses. The safety analysis set comprised all patients who received ≥1 dose of the study medication.

For each patient, the difference between VAS_{XR} and VAS_{IR} was calculated as follows: VAS_{XR}-VAS_{IR} = VAS_{DIFF}, where VAS_{IR} = the VAS value on IR and VAS_{XR} = the corresponding value for XR. The hypothesis that $VAS_{DIFF} = 0$ was tested by means of the Student's paired t-test. There was no significant period effect, treatment-by-period interaction, or carryover effect. As a robustness analysis, the hypothesis was tested by means of the Wilcoxon signed rank test as well, for the primary analysis only.

The significance level was set to 5% for all hypotheses tested. No adjustment for multiplicity was made. Safety assessments were reported using descriptive statistics.

Standard PK analysis methodology was used to calculate geometric mean parameters and confidence intervals, in addition to the protocol-specified comparison of arithmetic means. The results of the standard analysis are presented in this Synopsis.

Subject population

As shown in Table S1, of the 63 randomized subjects, 58 completed the study and were included in the PP population. These healthy volunteers were predominantly Black males with a mean age of 31.8 years.

Table S1 Subject disposition and demographics

Disposition			
N (%) randomized		63	(100.0%)
N (%) of subjects who:	Completed	58	(92.1%)
	Discontinued:	5	(7.9%)
	Voluntary discontinuation	4	(6.3%)
	Other reason[a]	1	(1.6%)
N (%) included in the safety analysis[b]		63	(100.0%)
N (%) included in the pharmacodynamic analysis (PP)[c]		58	(92.1%)
Demographic characteristics (PP population)			
Gender, n (%):	Male	46	(79.3%)
	Female	12	(20.7%)
Age (years):	Mean (SD)	31.8	(7.5)
	Range	18	to 50
Race, n (%):	Black/African American	39	(67.2%)
	Caucasian	14	(24.1%)
	Asian	2	(3.4%)
	American Indian/Alaska native	2	(3.4%)
	Other	1	(1.7%)
BMI (kg/m^2)	Mean (SD)	26.5	(3.6)
	Range	18	to 38

[a] Subject was caught stealing from another subject and was discontinued.
[b] Number of subjects who took ≥1 dose of study treatment.
[c] Number of subjects who completed both treatment periods.
N Number; PP Per-protocol; SD standard deviation.

Summary of pharmacodynamic results

As shown in Table S2, quetiapine XR was less sedating than quetiapine IR at 1 hour post-dose, based on the VAS scores.

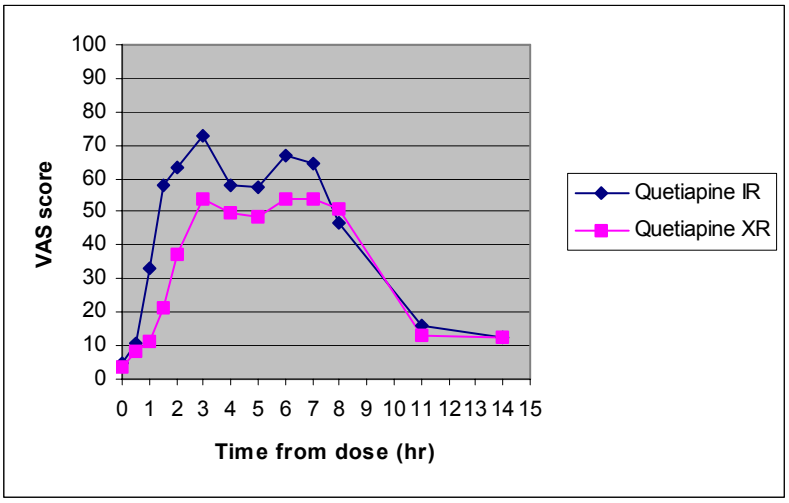
Table S2 Mean sedation score (VAS) 1 hour post-dose on Day 1 (PP analysis set, N=58)

	Quetiapine IR	Quetiapine XR	Quetiapine XR-Quetiapine IR[a]
Mean (SD)	33.2 (41.3)	11.3 (26.2)	-21.9 (44.9)
Median	8.5	1.0	0.0
Range	0.0 – 100.0	0.0 – 100.0	-100.0 – 95.0
p-value[b]			<0.001

[a] The mean, SD, and median for the change were calculated on the within-patient difference.
[b] The p-value is based on Student's paired t-test. No correction for period effect, treatment-period interaction, or multiplicity was done.
IR Immediate-release; PP Per protocol; SD Standard deviation; VAS Visual analog scale; XR Extended-release.
Note: The VAS scale ranged from 0 ('alert') to 100 ('drowsy').

The mean VAS score for each treatment over time is illustrated in Figure S1.

Figure S1 Sedation profiles (mean VAS scores over time) on Day 1 (PP analysis set)



hr Hours; IR Immediate-release; PP Per protocol; VAS Visual analog scale; XR Extended-release.

Statistical analysis indicated that the XR formulation had a longer time to maximum VAS score and a lower VAS AUC_{0-14} than the IR formulation. The maximum scores for the 2 formulations were similar.

Summary of pharmacokinetic results

As shown in Table S3, on Day 5, the 2 formulations had a similar $AUC_{(0-11)}$ for quetiapine, while the XR formulation had a somewhat lower $AUC_{(0-11)}$ for norquetiapine than the IR formulation. As expected, quetiapine XR had a lower C_{max} and longer T_{max} than quetiapine IR for both quetiapine and norquetiapine. Note that due to the dose escalation schedule, Day 5 should not be considered steady-state.

Table S3 Plasma concentrations on Day 5 (PP analysis set, N=58)

Pharmacokinetic parameter	Quetiapine XR/ Quetiapine IR Ratio (90% CI)	Quetiapine IR Geometric mean (95% CI)	Quetiapine XR Geometric mean (95% CI)
Quetiapine concentrations			
$AUC_{(0-11)}$ (ng*hr/mL)	0.89 (0.82, 0.96)	2835.89 (2517.92, 3194.02)	2515.21 (2281.76, 2772.55)
C_{max} (ng/mL)	0.55 (0.49, 0.62)	689.19 (605.83, 784.02)	381.70 (341.40, 426.76)
T_{max} (hours)	2.69 (2.35, 3.08)	1.81 (1.58, 2.06)	4.85 (4.41, 5.34)
Norquetiapine concentrations			
$AUC_{(0-11)}$ (ng*hr/mL)	0.82 (0.78, 0.86)	1074.42 (985.29, 1171.62)	880.22 (820.27, 944.55)
C_{max} (ng/mL)	0.70 (0.66, 0.75)	153.47 (137.94, 170.74)	107.69 (99.65, 116.38)
T_{max} (hours)	2.26 (2.03, 2.53)	2.73 (2.39, 3.12)	6.18 (5.70, 6.69)

$AUC_{(0-11)}$ Area under the plasma concentration-time curve from 0 to 11 hours post-dose; C_{max} Maximum plasma concentration; CI Confidence interval; IR Immediate-release; norQTP norquetiapine; PP Per protocol; QTP quetaipine; T_{max} Time to maximum plasma concentration; XR Extended-release.
Note: Due to the dose-escalation schedule, Day 5 should not be considered steady-state.

Similar results were obtained in the comparisons of arithmetic means, except that the AUCs for both quetiapine and norquetiapine were lower for quetiapine XR than for quetiapine IR.

Summary of pharmacokinetic/pharmacodynamic relationships

The secondary objective of exploring the relationship between plasma concentration and sedation was not addressed in a formal analysis. However, the sedation profiles of the 2 formulations appeared to be consistent and correlated with the plasma concentration-time profiles.

Summary of safety results

As shown in Table S4 and Table S5, while both treatments were well tolerated, there was a lower incidence of AEs with the XR formulation than with the IR formulation.

Table S4 Number (%) of subjects who had an adverse event in each category on treatment (safety analysis set)

Category	Quetiapine IR only (N=60)	Quetiapine XR only (N=61)	On both treatments[a] (N=58)[b]
Any AE	25 (41.7%)	15 (24.6%)	14 (24.1%)
Serious AE	0	0	0
AEs leading to discontinuation	0	0	0
Treatment-related AE	22 (36.7%)	12 (19.7%)	13 (22.4%)

[a] Subjects with at ≥1 event on each treatment or 1event that began during Period 1 and continued into Period 2.
[b] Includes subjects who received ≥1 dose of study drug during each period (ie, ≥1 dose of each formulation).
AE Adverse event; IR Immediate-release; XR Extended-release.
Note: This table excludes events occurring before Period 1, during the washout period, or after Period 2. Subjects with multiple events in the same category are counted only once in that category. Subjects with events in >1 category are counted once in each of those categories.

Table S5 Number (%) of subjects with the most commonly reported adverse events on treatment (safety analysis set)

AE (preferred term)	Quetiapine IR only (N=60)	Quetiapine XR only (N=61)	On both treatments[a] (N=58)[b]
Dry mouth	7 (11.7%)	4 (6.6%)	6 (10.3%)
Dizziness	7 (11.7%)	1 (1.6%)	3 (5.2%)
Constipation	0	1 (1.6%)	2 (3.4%)
Headache	5 (8.3%)	2 (3.3%)	2 (3.4%)
Nausea	5 (8.3%)	4 (6.6%)	0
Vomiting	2 (3.3%)	0	0
Coordination abnormal	2 (3.3%)	0	0
Dysarthria	3 (5.0%)	0	0
Hypoaesthesia	2 (3.3%)	0	0
Abnormal dreams	3 (5.0%)	1 (1.6%)	0
Anxiety	2 (3.3%)	0	0
Nightmare	2 (3.3%)	0	0
Nasal congestion	3 (5.0%)	1 (1.6%)	1 (1.7%)
Pharyngolaryngeal pain	2 (3.3%)	0	0

[a] Subjects with ≥1 event on each treatment or 1event that began during Period 1 and continued into Period 2.
[b] Includes subjects who received ≥1 dose of study drug during each period (ie, ≥1 dose of each formulation).
AE Adverse event; IR Immediate-release; XR Extended-release.
Note: This table excludes events occurring before Period 1, during the washout period, or after Period 2. Subjects with multiple episodes of an AE are counted only once for that AE. Events are ordered by decreasing frequency in the last column. Events that occurred in at least 2 subjects on a given treatment are included in this table.

Isolated changes were observed in (nonfasting) clinical laboratory test values, physical examinations, and vital signs, none associated with clinically important trends within or between treatments. There was a mean decrease in Free T4, but there were no clinically important changes for any patient.. The findings did not raise any new safety concerns.