Clinical Study Report Synopsis

Drug Substance	Quetiapine fumarate
Study Code	D1443C00040
Edition Number	1
Date	10 March 2010

A Phase IV, Multi-center, Double-blind, Double-dummy, Randomized, Parallel-group Study to Compare the Tolerability of Quetiapine Fumarate Immediate Release (Seroquel®) with Quetiapine Fumarate Extended Release (Seroquel XR®) During Initial Dose Escalation in Patients with Bipolar Depression

Study dates: First subject enrolled: 15 June 2009
Last subject last visit: 20 August 2009

Phase of development: Therapeutic use (IV)

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

Study centers

This study was conducted in 15 centers in the United States.

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To compare the intensity of sedation, 1 hour after the 50-mg dose administration, between quetiapine fumarate immediate release formulation (quetiapine IR, SEROQUEL®) and quetiapine fumarate extended release formulation (quetiapine XR, SEROQUEL XR®) during initial dose escalation as measured by the Modified Bond-Lader VAS	1. Modified Bond-Lader VAS score at 1 hour after 50-mg dose administration
Secondary	**Secondary**
To characterize the safety and tolerability of quetiapine XR and quetiapine IR in patients with bipolar depression during the initial titration period. This would assess AEs, including but not limited to dizziness and dry mouth, and the overall sedation profiles as measured by the Modified Bond-Lader VAS	2. Modified Bond-Lader VAS score at every time point 3. Maximum Intensity Modified Bond-Lader VAS at each day 4. Time to Maximum Intensity Modified Bond-Lader VAS at each day 5. Maximum Intensity Modified Bond-Lader VAS for overall study treatment 6. Area under the Modified Bond-Lader VAS-time curve (0 to 14 hours) at each day 7. Number of patients with AEs by Medical Dictionary for Regulatory Activities preferred term
To characterize the safety and tolerability of quetiapine XR and quetiapine IR, in patients with bipolar depression during the initial titration period by clinical assessments, including orthostatic vital signs, extrapyramidal symptoms using movement scales, and laboratory parameters	8. Vital signs; weight and body mass index; physical examination 9. Extrapyramidal symptoms (Simpson-Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale) 10. Columbia Suicidality Classification Score 11. Clinical laboratory assessments 12. Treatment Satisfaction Questionnaire of Medication

AE Adverse event; IR Immediate release; VAS Modified Bond-Lader Visual Analogue Scale; XR Extended release.

Study design

This was a 7-day, inpatient, multicenter, double-blind, double-dummy, randomized, parallel-group, Phase IV study to compare the tolerability of quetiapine immediate release (IR) with quetiapine extended release (XR) during initial dose escalation in patients with bipolar depression.

Target subject population and sample size

A total of 160 male or female patients aged 18 to 50 years inclusive with bipolar I or bipolar II disorder were planned to be enrolled to ensure 124 evaluable patients. This sample size was calculated to provide 90% power to detect a difference between the 2 formulations when using a 2-sided t-test at a significance level of 5% on the Modified Bond-Lader Visual Analogue Scale (VAS).

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

Patients were randomized to either of 2 dose regimens: quetiapine IR or quetiapine XR. Three tablets were to be taken orally each evening at approximately 7 PM. The dose schedule for both groups by study day was: Day 1, placebo; Day 2, 50 mg; Day 3, 100 mg; Day 4, 200 mg; Day 5, 300 mg; Day 6, 300 mg; Day 7 (discharged). Three batches each of quetiapine IR, quetiapine XR, quetiapine IR matching placebo, and quetiapine XR matching placebo were used in this study. Individual batch numbers and further information are included in the CSR.

Duration of treatment

There was a 7-day inpatient stay to assess tolerability during dose escalation.

Statistical methods

The primary analysis was based on the modified intention-to-treat (MITT) analysis set. The safety analysis data set included all patients who received at least 1 dose of study treatment.

The primary analysis of the Modified Bond-Lader VAS score at 1 hour after 50-mg dose administration tested the difference of the intensity of sedation between quetiapine IR and quetiapine XR using an analysis of covariance with the baseline Modified Bond-Lader VAS score as the covariate and including treatment as a fixed effect and center as a random effect in the model. The contrast of interest was the treatment difference between quetiapine IR and quetiapine XR at 1 hour after 50-mg dose administration. The experiment type I error rate was set to 0.05.

All pairwise differences between least-square means for quetiapine-treated groups were calculated and nominal 95% confidence intervals (CIs) were constructed. Point estimates of the Modified Bond-Lader VAS score for each treatment group was also presented together with corresponding 95% CIs.

Descriptive statistics were also presented for each visit for the Modified Bond-Lader VAS score. Safety assessments were reported using descriptive statistics. An additional analysis of

suicidality was undertaken in accordance with the Columbia Suicidality Classification Scale. However, the analysis of suicidality using Columbia Classification, including relative risk ratios, was to be performed on the safety data only if incidence of events did not equal 0 in any treatment arm.

Subject population

A total of 198 patients in 15 centers in the US were screened and enrolled in this study; 139 (70.2%) were randomized (70: quetiapine XR; 69: quetiapine IR) and 134 (67.7%) completed the study (67 in each treatment group). Five patients (3: quetiapine XR; 2: quetiapine IR) discontinued study treatment.

A sufficient number of patients were recruited to meet protocol requirements. There were 11 randomized patients with at least 1 important protocol deviation in this study. The safety population had 139 patients, the MITT population had 134, and the PP population had 128.

Demographic and baseline characteristics of the patients were similar between treatment groups. Patient ages ranged from 18 to 50 years with a mean age of 39 years; 73 (52.5%) were male. Approximately 60% of patients were Black.

Summary of primary outcome results

The primary outcome variable was sedation as measured by the Modified Bond-Lader VAS score at 1 hour after the 50-mg dose.

Table S2 Primary analysis of the Modified Bond-Lader VAS score at 1 hour after 50-mg dose (MITT analysis set)

Visit	Statistic	Quetiapine XR N=69	Quetiapine IR N=65
Day 2 at 1 hour post-dose	N	69	65
	LS means	32.472	45.022
	Lower CL	25.935	38.287
	Upper CL	39.009	51.758
	LS mean quetiapine IR vs quetiapine XR[a]		12.551
	Lower CL		3.147
	Upper CL		21.955
	p-value		0.009

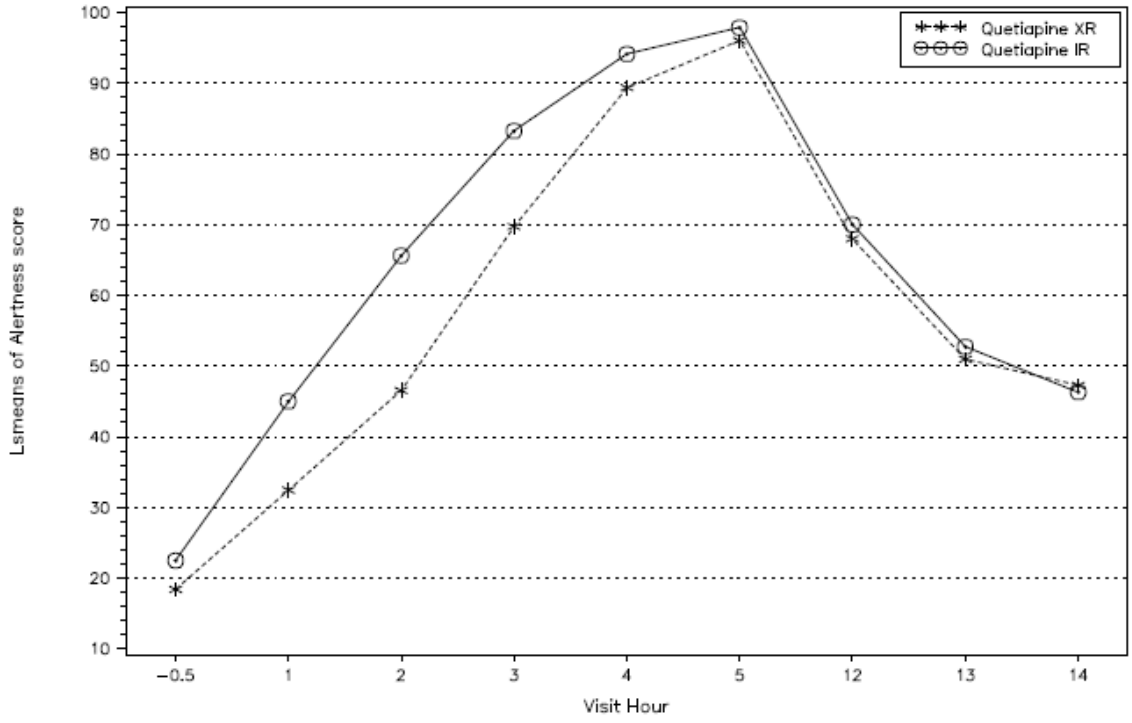
[a] A positive value means that sedation for quetiapine IR was greater than for quetiapine XR.

CL Confidence limit; IR Immediate release; LS Least squares; MITT Modified intention-to-treat; N Number of patients; SD Standard deviation; VAS Modified Bond-Lader Visual Analogue Scale; XR Extended release.

The intensity of sedation was statistically significantly lower with quetiapine XR than with quetiapine IR at 1 hour after the 50-mg dose, with a least squares (LS) mean difference between the Modified Bond-Lader VAS scores of quetiapine IR and quetiapine XR of 12.551 (p-value=0.009).

Summary of secondary outcome results

Figure S1 Modified Bond-Lader VAS score after 50-mg dose (Day 2) by visit hour (ANCOVA)



ANCOVA Analysis of covariance; LS Least squares; VAS Modified Bond-Lader Visual Analogue Scale.

The intensity of sedation was lower with quetiapine XR than with quetiapine IR, as measured by the LS mean difference between the Modified Bond-Lader VAS scores, and the results were statistically significant (p-value ≤0.050) at 1, 2, and 3 hours on each treatment day (Days 2 to 6), indicating significantly lower intensity of self-reported sedation with quetiapine XR compared with quetiapine IR in the initial dose escalation. The LS mean Modified Bond-Lader VAS scores increased from baseline to 5 hours post-dose in both treatment groups on each day. There was no statistically significant difference between treatment groups on Day 1 after receiving placebo. By post dose Hours 12 to 14, corresponding to 7 AM to 9 AM, similar levels of self-reported sedation were seen between the 2 formulations.

The overall maximum intensity of sedation was similar between the 2 treatment groups after each dose, as measured by the Modified Bond-Lader VAS score. Overall, the time to maximum intensity of sedation was longer for quetiapine XR than quetiapine IR after each

dose, but the results were not statistically significant. Quetiapine XR had a lower area under the Modified Bond-Lader VAS-time curve (0 to 14 hours) (VAS $AUC_{[0-14]}$) for each dose, but the differences were not statistically significant.

Summary of patient reported outcomes results

Patient reported outcomes results reflected safety and tolerability. The Treatment Satisfaction Questionnaire of Medication (TSQM) showed numerically fewer patients experienced side effects when taking quetiapine XR than quetiapine IR. This finding was consistent with the overall frequency of patient adverse event (AE) reporting during this study (57.1%: quetiapine XR; 71.0%: quetiapine IR). TSQM Item #5 also showed that of those patients experiencing "Any Side Effects", patients on quetiapine XR reported them to be more tolerable, reporting median score of 4.0 - "A Little Bothersome" while patients on quetiapine IR found them "Somewhat Bothersome" (median score of 3.0).

Summary of safety results

There were no patient deaths reported in this study. Three patients had serious AEs (SAEs) during this study. In addition, 1 SAE occurred before the patient was randomized to treatment. There was 1 SAE of suicide attempt; it was considered not related to investigational product. AEs leading to discontinuation were reported in 3 patients during this study (1: quetiapine XR; 2: quetiapine IR).

The incidence of patients with any AEs was lower with quetiapine XR than with quetiapine IR (57.1%: quetiapine XR; 71.0%: quetiapine IR). The most commonly (≥10%) reported AEs by preferred term for quetiapine XR were dry mouth, increased appetite, and somnolence. The most commonly (≥10%) reported AEs by preferred term for quetiapine IR were increased appetite, dizziness, dry mouth, and headache.

According to a summary table of incidence rate by classification category, there was only 1 patient with a suicidal ideation/behavior in the quetiapine XR treatment group and none in the comparison quetiapine IR treatment group. Because of this isolated event and the small number of patients exposed in this study, the analysis of suicidality using Columbia classification was unlikely to be meaningful, and thus was not performed.

Overall, it appears quetiapine XR produced fewer potentially clinically significant orthostatic changes in patients than quetiapine IR by each parameter and by the combined parameters. No other clinically meaningful findings were observed for vital signs.

AEs potentially associated with extrapyramidal symptoms (EPS) were less common with quetiapine XR (2.9%: quetiapine XR; 11.6%: quetiapine IR). The SAS total score appeared to categorically worsen in fewer patients receiving quetiapine XR than quetiapine IR.

The overall incidence of the cumulative preferred terms of lethargy, sedation, and somnolence was similar in both treatment groups.