Clinical Study Report Synopsis

Drug Substance	Quetiapine XR
Study Code	D1443L00017
Edition Number	1.0
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A Phase IV Study of the Effectiveness of Quetiapine Extended Release 600 mg Once A Day to Control the Symptoms of Manic Phase of Bipolar Disorder

Study dates: First subject enrolled: 20 May 2008
Last subject last visit: 12 Aug 2009

Phase of development: Therapeutic use (IV)

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

Study centre(s)

8 centres participated in this trial all of them in Mexico.

Publications

Poster was presented at the 2010 Western Pharmacology Society Meeting.

Objectives and criteria for evaluation

The objectives are indicated in the following table.

Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
The primary objective of this study is to assess the efficacy of Quetiapine Extended release 600 mg per day either as monotherapy or combined therapy in the treatment of patients with Mania associated to Bipolar Disorder.	The efficacy of Quetiapine Extended Release 600 mg per day either as monotherapy or combined therapy in the treatment of patients with Mania associated to Bipolar Disorder; will be assessed by changes in the Young Mania Rating Scale Score (YMRS) total score and in the Clinical Global Impression (CGI) score, from inclusion to Day 21.
Secondary	**Secondary**
To evaluate if quetiapine improves health related quality of life of patients with Bipolar Mania	Change in the Quality of Life Questionnaire EQ5D total score from inclusion to Day 21
To evaluate the safety and tolerability of quetiapine in the treatment of patients with Bipolar Mania assessed by:	Change from baseline in physical examinations, laboratory values (if any), vital signs and electrocardiograms (if any) Change from baseline in physical examinations, laboratory values (if any), vital signs and electrocardiograms (if any) • Adverse events (AEs) • AEs leading to withdrawal from the study • AEs related to somnolence, i.e., incidence, severity, time, and withdrawals due to AE of somnolence • Change in weight from inclusion to Day 21 • Change in waist circumference from inclusion to Day 21 • Proportion of patients with >7% increase in weight from inclusion to Day 21 • AEs of special interest [sexual dysfunction, nausea, vomiting, Extra Pyramidal Symptoms (EPS) including akathisia, diabetes mellitus, QT prolongation, neutropenia/agranulocytosis, suicidal and syncope] • Change from inclusion to Day 21 in Simpson-Angus Scale (SAS) and in Barnes Akathisia Rating Scale (BARS)

Study design

This was a multi-centre, national, prospective, longitudinal, non-randomized, non-comparative study, to evaluate de efficacy of a 600 mg/day dose of Quetiapine Extended Release administrated once a day at evening as monotherapy or in combination with lithium or valproate, for 21 days

Target subject population and sample size

The study was conducted in 98 patients and obtained 88 evaluable patients (mITT) nationwide, from 8 participating investigational sites (12 patients per site in average) in Mexico City, Guadalajara, Monterrey, San Luis Potosí, and Mérida.

Patients must have Type I Bipolar Disorder in manic phase with a YMRS score ≥12 at study entry. Patients of both genders, 18 - 65 years old, with bipolar disorder I according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, whether first episode or chronic that based on the investigating physician are in a manic episode, confirmed by a YMRS score of ≥12 at study entry.

Patients that do not have relevant medical or psychiatric co-morbidities that require other medications to treat different disorders from the proposal of this study.

Evaluable patient is defined as that who has received at least a dose of the investigational product and has had at least one valid YMRS assessment after Visit 1 (mITT population).

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

Quetiapine fumarate, bottle with 48 extended release tablets of 300 mg and an extra bottle containing 48 tablets of 300 mg quetiapine fumarate extended release tablets.

Duration of treatment

The treatment was Quetiapine Extended Release administrated once a day at evening as monotherapy or in combination with lithium or valproate, for 21 days

Once the patient was enrolled, he/she was provided with a bottle that contains enough tablets to complete up-titration regime and whole treatment as follows:

- Day 1: One 300 mg tablet in the evening
- Day 2: Two 300 mg tablet in the evening
- Day 3 and onwards: Two 300 mg tablets in the evening, efforts must be done to maintain a daily dose of 600 mg/day.

Statistical methods

All data analysis, both primary and secondary was performed using at least one of the following analysis sets.

The safety analysis based on the safety population. This population includes all patients who took study medication at least once.

The efficacy analyses based on the modified intention-to-treat (mITT) population (Full Analysis Set). This population include all patients who received study medication and who have an YMRS assessment at inclusion, and at least one YMRS valid assessment after inclusion.

The per-protocol (PP) population, a subset of the mITT population, will include patients who completed the study treatment with no major protocol violations or deviations affecting efficacy. Data from this population will be used as a consistency check only for analysis of the primary objective.

Descriptive statistics including frequency tables (n, mean, median, standard deviation, minimum and maximum for continuous variables and n, frequency and percentage for categorical values) and graphs will be provided for all variables, as well as for the changes from baseline within each treatment and the differences between the treatment groups at each visit, for both OC and LOCF, as appropriate.

Primary analysis

- Change in total YMRS scale from inclusion to day 21 will be analyzed with the Wilcoxon signed-rank test

Secondary analyses supporting the primary objective are listed below.

- Change in total YMRS scale from inclusion to each visit will be analyzed with the Wilcoxon signed-rank test
- Change in total Clinical Global Impression-Severity (CGI-S) scale from inclusion to day 21 will be analyzed with the Wilcoxon signed-rank test
- Total Clinical Global Impression-Improvement (CGI-I) score at day 21 will be analyzed with descriptive statistics
- Number of patients with YMRS response at Day 21
- Number of patients with YMRS remission at Day 21

Subject population

Subject population are showed in the following tables:

Study analysis sets

	Number (%) of patients
Enrolled	98

	Number (%) of patients
Received study treatment	89
Safety set	89(100%)
Modified intent to treat population (mITT)	88(98.88%)
Per protocol (PP)	77(86.51%)
Number (%) of patients who discontinued after randomization	11(12.36%)
Number (%) of patients who completed the study	78(87.64%)

*Percentages calculated for each reason for discontinuation are based on the number of patients that received study treatment.

Demographic characteristics of the full data set

Demographic characteristic	Safety analysis set (N=89)
Sex (n and % of patients)	
Male	35(39.33%)
Female	54(60.67%)
Age (years)	
Mean (SD)	36.51(12.75)
Median	35
Range	18 , 65

Summary of efficacy results

The following table shows the efficacy results:

Statistical analysis of changes from baseline to final visit, modified intention to treat (mITT) population

	Baseline		Change from baseline to last visit		95% CI of change	P value
	Mean	(SD)	Mean	(SD)		
YMRS	32.05	(9.15)	-20.55	(10.75)	(-22.82 , -18.27)	<0.0001

	Baseline		Change from baseline to last visit		95% CI of change	P value
	Mean	(SD)	Mean	(SD)		
Quality of Life Questionnaire (EQ5D) Index	0.66	(0.24)	0.21	(0.24)	(0.16 , 0.27)	<0.0001
EQ5D Vas	0.55	(0.28)	0.23	(0.32)	(0.16 , 0.31)	<0.0001
CGI-S	4.98	(0.86)	-2.41	(1.33)	(-2.69 , -2.13)	<0.0001
SAS	1.16	(2.16)	-0.67	(1.91)	(-1.08 , -0.27)	=0.004
BARS	1.76	(2.44)	-0.82	(2.82)	(-1.42 , -0.22)	=0.0037

Summary of safety results

Only patients who took at least one dose of the investigational product and for whom data were collected were included in the analysis. Patients who never took the investigational product were not included in the analysis.

Of the 98 patients enrolled in the study, 9 did not take the treatment; wherefore 89 patients remained and were evaluable for safety:

The mean exposure time and the overall pattern of patients reporting AEs was similar across the treatment. On a preferred term level, somnolence was the most frequently reported AEs, followed by cephalea, dizziness and gastritis, as summarized over all treatment. The majority of AEs were of mild or moderate intensity. The incidence of AEs of severe intensity was overall low across the treatment.

No deaths were reported in this study.

In total, one non-fatal SAE was reported. The event reported by preferred term was acute mania increased, which was reported as per protocol indication (numeral 4.6.1.2 “events of worsening of mania may not be reported unless they reach one of the serious criteria); and it was considered by the investigator to be not causally related to the investigational product.

The number of discontinuations of treatment with investigational drug due to an AE was of 1. No OAEs were identified in the study.