AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Seroquel XR
ACTIVE INGREDIENT: Quetiapine extended release

Study No: D1443L00058
EFFECTIVENESS OF QUETIAPINE XR VS. SERTRALINE IN ACUTE BIPOLAR DEPRESSION AS ADD-ON THERAPY TO PREVIOUS MOOD STABILIZER TREATMENT: A PILOT STUDY

Developmental Phase: IIIb
Study Completion Date: 08/FEB/2011
Date of Report: 17/JAN/2012

OBJECTIVES:

Primary

- To assess the early effectiveness of quetiapine extended release (quetiapine XR) vs. sertraline in the treatment of bipolar depression, as measured by the change from baseline to week 2 in the Montgomery Asberg Depression Rating Scale (MADRS) total score.

Secondary

- To evaluate the effectiveness of quetiapine XR vs. sertraline in the treatment of bipolar depression, measured by the change from baseline to weeks 1, 4, and 8 in the MADRS total score.

- To evaluate the effectiveness of quetiapine XR vs. sertraline in the treatment of bipolar depression, measured by the change from baseline to weeks 1, 2, 4, and 8 in the Clinical Global Impression Scale - Bipolar (CGI-BP-M).

- To evaluate the effectiveness of quetiapine XR vs. sertraline in the control of anxiety symptoms associated with bipolar depression, measured by the change in the Hamilton Anxiety Rating Scale (HARS) score from baseline to weeks 4 and 8.

- To evaluate the response ($\geq$ 50% reduction in MADRS total score) and remission (MADRS total score $\leq$ 10) rates of quetiapine XR vs. sertraline at weeks 1, 2, 4, and 8.

METHODS:

Prospective, open-label, controlled (active comparator), randomized, 8-week study to assess the efectiveness of quetiapine XR vs. sertraline in addition to previous mood stabilizer treatment (lithium or valproate at stable and clinically therapeutic blood levels) in bipolar depression.

Target subject population

Male and female outpatients, between the ages of 18 and 65 years, with a documented clinical diagnosis of bipolar I or II disorder, under treatment with a mood stabilizer (lithium or valproate at stable and clinically therapeutic blood levels), and a current acute depressive episode according to DSM-IV criteria. To qualify for enrollment, patients were required to have a total score on the 17-item Hamilton Rating Scale for Depression (HAM-D17) of ≥20.

The investigational drug was quetiapine extended release (quetiapine XR). Titration was as follows: 50 mg on day 1; 100 mg on day 2; 200 mg on day 3; 300 mg on day 4; and flexible doses between 300-600 mg/day from day 5 to the end of the study according to investigator judgment. Active comparator was sertraline. Titration was as follows: 50 mg on day 1, 2 and 3; 100 mg on day 4; and flexible doses between 50-200 mg/day from day 5 to the end of the study according to investigator judgment. Complete doses were administered once a day in the morning.

RESULTS:

Subject population

A total of 27 patients were randomized from five centres: 13 patients to sertraline and 14 to quetiapine XR. A total of 18 patients completed the study.

Variable		Sertraline (N=13)	Quetiapine XR (N=14)	Total (N=27)
Randomized patients				
Yes	N(%)	13(100.00%)	14(100.00%)	27(100.00%)
Withdrawal				
Yes	N(%)	5(38.46%)	4(28.57%)	9(33.33%)
Reason of withdrawal				
Lack of efficacy of medication	N(%)	2(40.00%)	1(25.00%)	3(33.33%)
Tolerability problems	N(%)	1(20.00%)	2(50.00%)	3(33.33%)
Safety problems	N(%)	1(20.00%)	0(0.00%)	1(11.11%)
Other	N(%)	1(20.00%)	1(25.00%)	2(22.22%)

Mean age was 46 years (SD), 63% were male. Baseline socio-demographic and clinical characteristics of the sample are shown in the following table:

Variable		Sertraline (N=13)	Quetiapine XR (N=14)	Total (N=27)	p-valor
Age					0.2534
	Mean	43.38	48.57	46.07	
	SD	12.64	12.54	12.62	
	95%CI	(35.75,51.02)	(41.33,55.81)	(41.08,51.07)	
Gender					0.6946
Male	N(%)	9(69.23%)	8(57.14%)	17(62.96%)	
Educational level					0.3367
No school	N(%)	0(0.00%)	2(14.29%)	2(7.41%)	
Primary School	N(%)	6(46.15%)	8(57.14%)	14(51.85%)	
Secondary School	N(%)	5(38.46%)	2(14.29%)	7(25.93%)	
Universitary	N(%)	2(15.38%)	2(14.29%)	4(14.81%)	
Working status					0.2365
Yes	N(%)	10(76.92%)	7(50.00%)	17(62.96%)	
MADRS total score					0.5926
	Mean	28.2	29.5		
	95%CI	(26.7, 31.7)	(26.6, 32.4)		
CGI-BP-M total score					0.6964
	Mean	5.3	5.1		
	95%CI	(4.8, 5.9)	(4.7, 5.6)		
HARS total score					0.1777
	Mean	17.6	22.4		
	95%CI	(13.02, 22.2)	(18.5, 26.4)		

Primary efficacy variable

A greater but not significant reduction in MADRS total score was observed among patients treated with quetiapine XR compared with sertraline after 2 weeks of treatment. The mean changes in MADRS total score from baseline to week 2 were -13.1 (95%CI -18.6, -7.6) and -6.6 (95%CI -12.6, -0.6) in the quetiapine XR and sertraline groups, respectively (p=0.0878).

Secondary efficacy variables

The mean changes in MADRS total score from baseline to week 1 were -9.5 (95%CI -13.8, -5.1) and -8.6 (95%CI -14.5, -2.6) in the quetiapine XR and sertraline groups, respectively (p=0.5926). At week 4, mean changes in MADRS total score were -16.1 (95%CI -21.4, -10.9) and -17.7 (95%CI -25.8, -9.7), respectively (p=0.9344). At week 8, mean changes in MADRS total score were -19.4 (95%CI -24.2, -14.5) and -18.2 (95%CI -24.8, -11.6), respectively (p=0.5248).

The mean changes in CGI-BP-M total score from baseline to week 1 were -0.79 (95%CI -1.47, -0.10) and -1.08 (95%CI -2.14, -0.02) in the quetiapine XR and sertraline groups, respectively (p=0.8646). At week 2, mean changes in CGI-BP-M total score were -1.36 (95%CI -2.19, -0.52) and -1.00 (95%CI -2.20, -0.20), respectively (p=0.0979). At week 4, mean changes in CGI-BP-M total score were -2.09 (95%CI -3.19, -0.99) and -2.56 (95%CI -4.15, -0.97), respectively (p=0.8194). At week 8, mean changes in CGI-BP-M total score were -2.9 (95%CI -4.14, -1.66) and -2.88 (95%CI -4.25, -1.5), respectively (p=0.4594).

The mean changes in HARS total score from baseline to week 4 were -13.4 (95%CI -17.6, -9.1) and -8.9 (95%CI -14.3, -3.4) in the quetiapine XR and sertraline groups, respectively (p=0.6141). At week 8, mean changes in HARS total score were -13.1 (95%CI -18.01, -8.2) and -10.6 (95%CI -15.5, -5.7), respectively (p=0.8011).

At weeks 1, 2, 4, and 8, 28.5, 57.1, 72.7, and 80% of patients in the quetiapine XR group had responded to treatment respectively compared with 30.7, 18.8, 66.6, and 62.5% of the sertraline group. At week 8, the proportion of patients achieving remission was 37.5% (n=3) in the quetiapine XR group versus 57.1% (n=4) in the sertraline group (p=0.6193).

Summary of safety results

In total 21 patients (77.8%) presented adverse events (AEs), 9 (69.2%) in sertraline group and 12 (85.7%) in quetiapine XR group. No patients experienced serious adverse events (SAEs).

Adverse Events. Summary

Variable		Sertraline (N=13)	Quetiapine XR (N=14)	Total (N=27)	p-valor
Number of AEs					0.9380
	N	17	20	37	
	Mean	0.94	0.95	0.95	
	SD	0.24	0.22	0.23	
	CI95%	(0.82,1.07)	(0.85,1.05)	(0.87,1.02)	
	Median(IQR)	1(0)	1(0)	1(0)	
	[Min, Max]	[0,1]	[0,1]	[0,1]	
Number of patients with at least one AE					0.3033
Yes	N(%)	9(69.23%)	12(85.71%)	21(77.78%)	
No	N(%)	4(30.77%)	2(14.29%)	6(22.22%)	
Number of patients with at least one AE related to treatment					0.1733
Yes	N(%)	7(53.85%)	11(78.57%)	18(66.67%)	
No	N(%)	6(46.15%)	3(21.43%)	9(33.33%)	
Number of patients with at least one serious AE					N/A
No	N(%)	13(100.00%)	14(100.00%)	27(100.00%)	
Number of patients with at least one AE leading to study withdrawal					0.6862
Yes	N(%)	2(15.38%)	3(21.43%)	5(18.52%)	
No	N(%)	11(84.62%)	11(78.57%)	22(81.48%)	

Adverse Events. Summary

Variable		Sertraline (N=13)	Quetiapine XR (N=14)	Total (N=27)	p-valor
Number of patients with at least one severe AE					0.4959
Yes	N(%)	2(15.38%)	1(7.14%)	3(11.11%)	
No	N(%)	11(84.62%)	13(92.86%)	24(88.89%)	

Details of Adverse Events related to treatment

System Organ Class (SOC) and Preferred Term (PT)		Sertraline (N=13)	Quetiapine XR (N=14)	Total (N=27)
Gastrointestinal disorders	N(%)	3 (23.1%)	3 (23.1%)	6 (22.2%)
Dry mouth	N(%)	0 (0.0%)	3 (21.4%)	3 (11.1%)
Diarrhoea	N(%)	2 (14.3%)	0 (0.0%)	2 (7.4%)
Dyspepsia	N(%)	2 (14.3%)	0 (0.0%)	2 (7.4%)
General disorders and administration site conditions	N(%)	0 (0.0%)	1 (7.7%)	1 (3.7%)
Chest discomfort	N(%)	0 (0.0%)	1 (7.1%)	1 (3.7%)
Metabolism and nutrition disorders	N(%)	0 (0.0%)	1 (7.7%)	1 (3.7%)
Hyperphagia	N(%)	0 (0.0%)	1 (7.1%)	1 (3.7%)
Nervous system disorders	N(%)	2 (15.4%)	8 (61.5%)	10 (37.0%)
Somnolence	N(%)	1 (7.1%)	5 (35.7%)	6 (22.2%)
Tremor	N(%)	1 (7.1%)	2 (14.3%)	3 (11.1%)
Dysarthria	N(%)	0 (0.0%)	1 (7.1%)	1 (3.7%)
Psychiatric disorders	N(%)	3 (23.1%)	1 (7.7%)	4 (14.8%)
Insomnia	N(%)	2 (14.3%)	0 (0.0%)	2 (7.4%)
Anxiety	N(%)	1 (7.1%)	0 (0.0%)	1 (3.7%)
Disorientation	N(%)	0 (0.0%)	1 (7.1%)	1 (3.7%)
Libido decreased	N(%)	1 (7.1%)	0 (0.0%)	1 (3.7%)