AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Seroquel XR®
ACTIVE INGREDIENT: Quetiapine fumarate XR

Study No: D1443L00031/NCT00640562

Comparison of Quetiapine Extended-Release (Seroquel XR™) and Risperidone in the treatment of depressive symptoms, in schizophrenic or schizoaffective patients: A randomized, open label, flexible-dose, parallel group, non inferiority, 12-week study-Ex Attitude Study

Developmental Phase: Phase IIIb
Study Completion Date: February 8th 2010
Date of Report: February 3rd 2011

STUDY DESIGN

This was a randomized, open label, parallel group, flexible dose, comparative study of Seroquel XR vs. risperidone in the treatment of depressive symptoms in patients with schizophrenic or schizoaffective disorder.

OBJECTIVES AND CRITERIA FOR EVALUATION:

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the efficacy of Seroquel XR versus risperidone on depressive symptoms assessed with Calgary Depression Scale for Schizophrenia (CDSS), in schizophrenic or schizoaffective patients.	CDSS has 9 items provided is a semi-structured interview. All items are rated on a four–point scale: 0=absent; 1=mild; 2=moderate; 3=severe. Change from V2 (baseline) to V6 (week 12) in CDSS total score	Efficacy
Secondary	**Secondary**	
To evaluate negative and positive symptoms assessed by Positive and negative Syndrome Scale (PANSS)	PANSS is a 30 item scale, each item ranging 1-7. 7 items refer to positive symptoms, 7 to negative symptoms and 16 refer to general psychopathology. PANSS negative sub-scale differentiates depressive symptoms from negative symptoms of schizophrenia.	Efficacy

Objectives	Outcome variables	Type
To evaluate depressive symptoms in schizophrenic or schizoaffective patients, assessed by Hamilton Rating Scale for Depression (HAM-D)	Change from V2 to V6 in HAM-D total score, in HAM-D factors: 1 anxiety/somatisation; 2 weight; 3 cognitive disturbance; 4 diurnal variation; 5 retardation; 6 sleep disturbance, and in HAM-D domains: 1 vegetative symptoms; 2 non vegetative symptoms	Efficacy
To evaluate attitude towards treatment, assessed by Drug Attitude Inventory (DAI – 10)	DAI is a self-reported scale to measure subjective responses and attitudes of chronic schizophrenic patients towards the maintenance antipsychotic treatment. The DAI-10 is the shorter version of the original 30 items scale.	Efficacy
To evaluate the global efficacy assessed by Clinical Global Impression (CGI)	CGI a 3-part instrument. In this study only the first part Severity of Illness scale (CGI-S) is scored to rate the patient's current clinical state and the second part Global Improvement scale (CGI-I) to rate the patient's change from start of treatment.	Efficacy
Safety	**Safety**	
Neurological assessment by Simpson-Angus Scale (SAS)	SAS, containing 10 items, rated at V2 and V6 or at discontinuation on a five-point scale where 0 = normal and 4 = severe symptoms.	Safety
Prolactin Levels (PRL)	Plasma for PRL drawn prior to morning meal at V1 and at V6 or discontinuation.	Safety
AEs, SAEs, OAEs	Assessment and recording by standard method.	Safety
Laboratory, Vital signs, BMI		Safety
Anticholinergic or antidepressant medications	Measure of anticholinergic or antidepressant consumption after start of study treatment.	Efficacy

METHODS:

Inclusion criteria:

For inclusion in the study, subjects had to fulfil all of the following criteria;

1. Provision of written informed consent
2. Male or female patients aged ≥18 - ≤ 65 years.
3. Patients who satisfied the criteria for diagnosis of schizophrenia or schizoaffective disorder according to DSM-IVTR.
4. Baseline depressive symptoms, assessed by means of HAM-D (21-item) score ≥ 20, and HAM-D item 1 score ≥2.
5. Able to understand and comply with the requirements of the study.

Esclusion Criteria:

Any of the following was regarded as a criterion for exclusion from the study:

1. Any DSM-IV Axis I disorder other than schizophrenia and schizoaffective disorder.

2. Pregnancy or breast-feeding. Women of childbearing potential had to use a reliable contraceptive method.

3. Patients with previous intolerance or unresponsiveness to quetiapine or risperidone or in treatment with quetiapine or risperidone at the moment of screening visit.

4. Patients treated with depot antipsychotic medications within 1 dosing interval before day 0; patients treated with other AP oral medications during the trial except for the switch period.

5. Use of clozapine within 28 days prior to enrolment or clozapine non responders.

6. Known previous sensitivity to quetiapine IR or risperidone.

7. Any significant clinical disorder that, in the opinion of the investigator, made the subject unsuitable to be given treatment with an investigational drug.

8. Serious unstable medical conditions (patients with renal, haemopoietic, endocrinology impairments).

9. Patients with unstable or un-adequately treated medical illness, e.g. angina pectoris, hypertension, congestive heart failure, as judged by the investigators.

10. Liver function tests AST or ALT three times the upper normal limit.

11. Pre-existing organic mental disorder.

12. Involvement in the planning and conduct of the study (related to both AstraZeneca staff or staff at the study site).

13. Previous enrolment or randomisation of treatments in the present study.

14. Participation in a clinical study during the last 30 days.

15. An absolute neutrophil count (ANC) of £1.5 x 109 per liter.

16. Patients who, in the opinion of the investigator, pose an imminent risk of suicide or a danger to self or others.

17. Use of any of the following cytochrome P450 3A4 inhibitors in the 14 days preceding enrolment including but not limited to: ketoconazole, itraconazole,

fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, fluvoxamine and saquinavir.

18. Use of any of the following cytochrome P450 inducers in the 14 days preceding enrolment, including, but not limited, to: phenytoin, carbamazepine, barbiturates, rifampin, St. John's Wort, and glucocorticoids.

19. A patient with Diabetes Mellitus (DM) fulfilling one of the following criteria:

- Unstable DM defined as enrolment glycosylated hemoglobin (HbA1c) >8.5%.
- Admitted to hospital for treatment of DM or DM related illness in past 12 weeks.
- Not under physician care for DM.
- Physician responsible for patient's DM care has not indicated that patient's DM is controlled.
- Physician responsible for patient's DM care has not approved patient's participation in the study.
- Has not been on the same dose of oral hypoglycaemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones) this period had to be not lower than 8 weeks.
- Taking insulin whose daily dose on one occasion in the past 4 weeks had been more than 10% above or below their mean dose in the preceding 4 weeks.

Note: if a diabetic patient met one of these criteria, the patient had to be excluded even if the treating physician believed that the patients was stable and could participate in the study.

SUMMARY RESULTS

Population

Two-hundred and twenty eight patients were screened in 24 Italian centres and a total of 216 patients were randomized. Two centres randomized no patients; 109 patients were randomly assigned to Seroquel XR and 107 to Risperidone. Forty four patients did not complete the study: 18 in the Seroquel XR group, 26 in the Risperidone group.

Summary Efficacy

The study met its primary and secondary efficacy objective. In fact, Seroquel XR proved non inferior to standard risperidone in decreasing depressive symptoms assessed with Calgary Depression Scale for Schizophrenia (CDSS) in schizophrenic or schizoaffective patients. Not only: beyond the objectives of the study, Seroquel XR proved also statistically significant superiority over risperidone in decreasing CDSS, PANSS,HAM-D, GCI scale score.

Summary Safety.

Safety and tolerability of Seroquel XR vs. risperidone in Schizophrenic or Schizoaffective patients: during study treatment many AEs were experienced both in

Seroquel XR and in risperidone group, in particular within the SOC categories of nervous system disorders or psychiatric disorders, but no particular differences were observed between treatment groups. Nine SAEs were experienced (4 in Seroquel XR and 5 in risperidone) and two patients in Seroquel XR died for adverse events not related to study drug. Neurological side effects measured by SAS scale got better.

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