AstraZeneca

**STUDY REPORT SUMMARY**

**ASTRAZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:** Quetiapine XR
**ACTIVE INGREDIENT:** Risperidone

| **Study No: D1443L00039** |
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| A One-Year Randomized, Prospective, Parallel, Open Comparison of Subjective Well-being in Schizophrenic Out-patients Treated with Quetiapine XR (SEROQUEL XR™) or Oral Risperidone at Flexible Dose in a Naturalistic Setting |

**Developmental Phase:** 3b
**Study Completion Date:** 22.10.2009
**Date of Report:** 08.10.2010

**OBJECTIVES:**

**Primary objectives**

The primary objective of this study is to demonstrate the non-inferiority of quetiapine XR to risperidone assessed at month 6 in terms of responder rate using the self-report instrument SWN-K.

**Secondary objectives**

A secondary objective of particular interest is to demonstrate the non-inferiority of quetiapine XR to risperidone assessed at month 12 by evaluating the change from baseline in SWN-K mean total score.

Other secondary objectives of the study are to evaluate in both treatment groups the following outcomes throughout the study:

1. Subjective changes using the SWN-K scale.

2. Remission rate during the study using the SWN-K scale, defined as a total score of ≥80 points.

3. Severity of patient symptoms using the CGI-SCH scale.

4. Depressive symptoms changes using the CDSS.

5. Relapse rate in terms of symptoms and/or re-hospitalization.

6. Quality of life changes using the EQ-5D.

7. Resource utilization for health economics (modified vocational status index/modified location code index, loss of school/work days, total number of days of hospitalization, emergency visits and number of outpatient visits, time to re-hospitalization, need for additional treatment for schizophrenia due to symptoms of schizophrenia despite stable antipsychotic treatment for at least one month).

8. Safety and tolerability.

9. Compliance (treatment adherence).

**METHODS:**

For the primary analysis, the noninferiority of quetiapine XR versus risperidone were evaluated at Month 6 based on the difference in responder rates (quetiapine XR - risperidone) in the per protocol population at Month 6 (PP6) with an acceptance region of -9.7%. Two-sided 95% confidence intervals (CIs) for the observed responder rates of the risperidone and quetiapine XR groups were calculated.
Noninferiority of quetiapine XR compared to risperidone was to be accepted if the lower limit of the 95% CI of the adjusted difference (quetiapine XR - risperidone) was higher than the noninferiority margin set at -9.7% in the PP6 analysis set. To confirm the robustness of the result, this analysis was replicated in the intent-to-treat (ITT) population. If noninferiority was claimed for quetiapine at Month 6, superiority of quetiapine versus risperidone was tested as follows: if the observed responder rate in quetiapine was greater than the one observed in risperidone and, if the two-sided 95% CI of the adjusted difference did not contain 0 then a 2-sided test for superiority was to be conducted at a 5% significance level. The test for superiority was to be conducted on the ITT analysis set.
For the secondary analysis of particular interest, the noninferiority of quetiapine XR versus risperidone was evaluated at Month 12 (final visit) based on the difference in the mean change from baseline in Subjective Well-being under Neuroleptics scale, short version (SWN-K) total score in the per protocol population at Month 12 (PP12) with an acceptance region of -7.5 points. Change from baseline for each SWN-K subscale score and for the SWN-K total score were analyzed with repeated measurements model (visits), using treatment, visit and treatment*visit interaction as fixed effect, country as random effect, and baseline value as covariate. The 95% CI for the difference between quetiapine XR and risperidone was provided. If the lower limit of the 95% CI for the difference (quetiapine XR - risperidone) between quetiapine XR and risperidone was greater than -7.5, quetiapine XR was claimed noninferior to risperidone. If the superiority was claimed in favor of quetiapine XR in the primary analysis at Month 6, then a superiority test was

applied on the ITT analysis set. All other secondary analyses were evaluated in the ITT analysis set at Month 12.

**RESULTS:**

**Summary of efficacy results**

Primary:

A patient was considered a responder if the patient's change from baseline value in SWN-K total score was ≥ 10 or if the SWN-K total score was improved by at least 20% of the baseline value. At Month 6, 136 of 210 (64.8%) patients treated with quetiapine XR and 158 of 232 (68.1%) patients treated with risperidone were classified as responders (PP6 analysis set). The treatment difference between the groups at Month 6 was -5.7% (95% CI: -15.1; 3.7). The lower limit was less than the prespecified limit of -9.7%. The noninferiority of quetiapine XR to risperidone at Month 6 in terms of responder rate was not established. Results were similar for the ITT analysis set at Month 6 (Table S4).

**Table S4 SWN-K total score**

| | Quetiapine XR | Risperidone |
|---|---|---|
| Responders (PP6) | | |
| Least squares mean (SEM) | 136/210 (64.8%) | 158/232 (68.1%) |
| Difference (quetiapine XR - risperidone) | -5.7% (95% CI: -15.1; 3.7) | |
| Responders (PP12) | 131/173 (75.7%) | 140/191 (73.3%) |
| Least squares mean (SEM) | 23.2 (1.55) | 21.2 (1.49) |
| Difference (quetiapine XR - risperidone) | 2.1 (95% CI: -0.8; 5.0) | |
| Responders (ITT) at Month 12 | 161/210 (76.7%) | 164/227 (72.2%) |
| Least squares mean (SEM) | 22.7 (1.34) | 19.4 (1.30) |
| Difference (quetiapine XR - risperidone) | 3.3 (95% CI: 0.6; 5.9) | |

Secondary:

*SWN-K total score at Month 12*

For the PP12 analysis set, the least squares mean (SEM) of the change from baseline in SWN-K total score at Month 12 was 23.2 (1.55) for patients taking quetiapine XR and 21.1 (1.49) for patients taking risperidone. The difference (quetiapine XR - risperidone) in LS mean at Month 12 was 2.1 (95% CI: -0.8; 5.0). The lower limit for the PP12 analysis set was greater than -7.5; thus, the noninferiority of quetiapine XR to risperidone with respect to change from baseline in SWN-K total score at Month 12 was established. Results were similar for the ITT analysis set (Table S4).

*Remission and Relapse*

The SWN-K remission rate was numerically higher in the quetiapine XR group than in the risperidone group for the ITT analysis set but there was no statistically significant difference between the treatment groups (Table S5).

The ITT analysis set showed a numerically higher relapse rate in patients taking quetiapine XR than in patients taking risperidone but there was no statistically significant difference between the treatment groups. (Table S5).

*Calgary Depression Scale for Schizophrenia and Clinical Global Impression-Schizophrenia Scale – Depressive Symptoms Subscale*

The Calgary Depression Scale for Schizophrenia (CDSS) total score by visit and score group (no or mild depression, moderate depression, and moderate severe to severe depression) depicts the improvement of depressive symptoms in both treatment groups. The difference between treatment groups was statistically significant at Month 6 ($p<0.001$) and at Month 12 ($p=0.001$) in favor of quetiapine (Table S5).

The Clinical Global Impression-Schizophrenia Scale (CGI-SCH) overall severity score and change from baseline depict improvement in both treatment groups. The mean change from baseline was numerically higher for the quetiapine XR group than the risperidone group (Table S5).

**Table S5 SWN-K Remission, Relapse Rate, CDSS, and CGI-SCH Depressive Symptoms Subscale – ITT analysis set**

| | Quetiapine XR N=379 | Risperidone N=392 |
|---|---|---|
| Remission at Month 6 | 142 (54.2%) | 137 (48.1%) |
| Difference (quetiapine XR - risperidone) | 2.9% (95% CI: -5.7; 11.5) | |
| Remission at Month 12 | 139 (66.2%) | 128 (56.4%) |
| Difference (quetiapine XR - risperidone) | 6.3% (95% CI: -3.6; 16.2) | |
| Relapse at Month 6 | 35 (9.2%) | 22 (5.6%) |
| Difference (quetiapine XR - risperidone) | 1.3% (95% CI: -2.1; 4.6) | |
| Relapse at Month 12 | 43 (11.3%) | 31 (7.9%) |
| Difference (quetiapine XR - risperidone) | 0.6% (95% CI: -3.0; 4.2) | |
| CDSS mean (SD) total score at Month 6 | 2.7 (3.5) | 3.7 (4.5) |
| CDSS mean (SD) change from baseline at Month 6 | -4.3 (5.1) | -2.8 (4.8) |
| Difference (quetiapine XR - risperidone) | ($p<0.001$) | |
| CDSS mean (SD) total score at Month 12 | 1.7 (2.4) | 2.6 (3.6) |
| CDSS mean (SD) change from baseline at Month 12 | -5.3 (5.1) | -3.8 (4.6) |
| Difference (quetiapine XR - risperidone) | ($p=0.001$) | |
| CGI-SCH overall severity mean (SD) score at Month 6 | 2.6 (0.97) | 2.8 (1.14) |
| CGI-SCH overall severity mean (SD) change from baseline at Month 6 | -1.2 (1.07) | -1.0 (1.12) |
| CGI-SCH overall severity mean (SD) score at Month 12 | 2.3 (0.93) | 2.5 (1.11) |
| CGI-SCH overall severity mean (SD) change from baseline at Month 12 | -1.5 (1.07) | -1.3 (1.15) |

CDSS = Calgary Depression Scale for Schizophrenia. CGI-SCH = Clinical Global Impression-Schizophrenia Scale

No notable differences between treatment groups were observed for SWN-K subscale scores, compliance, Euro Quality of Life - 5 dimension (EQ-5D), modified vocational status index/modified location code index, resource utilization (hospitalizations, loss of work/school days, unscheduled visits), and use of psychotropic or antidepressant medications.

**Summary of safety results**

The duration of treatment was similar in both treatment groups. At Month 12, the number of patients receiving quetiapine XR at 400 mg was 154 patients, 155 patients at 600 mg, and 82 patients at 800 mg. The number of patients receiving risperidone at 2 mg was 93 patients, 216 patients at 4 mg, and 93 patients at 6 mg.

Overall Analyses of Adverse Events

The overall incidence of treatment-emergent adverse events (TEAEs) was similar in both treatment groups at Month 12 (Table S6).

**Table S6 Analysis of Treatment-emergent Adverse Events at Month 12**

| | Quetiapine XR N= 391 | | | Risperidone N= 402 | | |
|---|---|---|---|---|---|---|
| | N ( % ) | | # | N ( % ) | | # |
| Treatment-emergent adverse events (TEAE) | 238 | (60.9%) | 791 | 258 | (64.2%) | 834 |
| Drug-related TEAEs | 198 | (50.6%) | 493 | 204 | (50.7%) | 522 |
| TEAE caused patient to discontinue the study | 57 | (14.6%) | 72 | 48 | (11.9%) | 80 |
| Extra-pyramidal TEAEs | 38 | (9.7%) | 51 | 83 | (20.6%) | 112 |
| Cardiac disorder TEAEs | 22 | (5.6%) | 25 | 17 | (4.2%) | 17 |
| Serious TEAEs | 45 | (11.5%) | 49 | 26 | (6.5%) | 31 |
| - Drug-related serious TEAEs | 13 | (3.3%) | 14 | 4 | (1.0%) | 4 |
| - Serious TEAE leading to death | 0 | (0.0%) | 0 | 1 | (0.2%) | 1 |

TEAE = Treatment Emergent Adverse Event, defined as an Adverse Event occurring after the first intake of the study medication (or the same day). # = Number of events. N = number of patients with at least 1 event. % = Percentage of patients was calculated within each treatment group on the total number of patients in the treatment group.

Most Common Adverse Events:

The most common TEAEs, occurring at a rate of ≥ 5% in either or both treatment groups, were somnolence, insomnia, anxiety, constipation, headache, aptyalism, asthenia, nausea, weight increased, dizziness postural, sedation, tension, and tremor.

The most common serious TEAEs (N ≥ 3 in 1 treatment group) for quetiapine and risperidone respectively were worsening of schizophrenia (3.1% and 1.2%), worsening of psychotic disorder (2.3% and 1.2%), agitation (0.8% and 0.0%), and suicide attempt (0.8% and 0.0%).

Adverse events resulting in study withdrawal all occurred in the psychiatric disorder SOC. The most common reasons for withdrawal were the preferred terms of psychotic disorder and schizophrenia for patients taking quetiapine XR and insomnia and anxiety for patients taking risperidone.

The most common extra-pyramidal adverse events (≥ 1% in one treatment group) were tremor, hypokinesia, muscle rigidity, hyperkinesia, extra-pyramidal disorder, restlessness, akathisia, and dyskinesia. At least 1 extra-pyramidal TEAE was observed in 9.7% of patients treated with quetiapine XR and in 20.6% of patients treated with risperidone.

Clinical Laboratory Results

There was no difference in hematology and serum chemistry laboratory test results between treatment groups when comparing their respective shift tables, except for serum prolactin.

Risperidone was associated with an increase in serum prolactin levels between baseline and Month 12 (15.9 ng/mL compared with -7.7 ng/mL for quetiapine XR). Substantially more patients treated with risperidone (137 of 215 patients; 63.7%) compared to quetiapine XR (31 of 205 patients; 15.1%) shifted from a normal prolactin level at baseline to a high level at Month 12. More patients in the quetiapine XR-treated group (74 of 127 patients; 58.3%) compared to the risperidone-treated group (36 of 125 patients; 28.8%) experienced a shift in prolactin level from high at baseline to normal at Month 12.

Analysis of Individual Symptoms from the UKU

Psychic and autonomic symptomatology, as measured by a modified UKU side effect rating scale for psychotropic drugs, showed no difference between patients treated with quetiapine XR and risperidone at Month 12. Neurologic symptomatology was significantly more prevalent at Month 12 in patients treated with risperidone than in patients treated with quetiapine XR. Hyperprolactinemia was significantly more prevalent at Month 12 in female patients treated with risperidone than in patients treated with quetiapine XR. Sexual dysfunction was significantly more prevalent at Month 6 in men treated with risperidone than in men treated with quetiapine XR. There was no difference between treatment groups at Month 12 for sexual dysfunction in men.

Suicide Attempts and Suicidal Thoughts:

Suicide attempts occurred in 5 quetiapine XR-treated patients (1.3%) during the study. No patients treated with risperidone attempted suicide, and no patient in either group died as a result of a suicide attempt. The incidence of attempted suicide and suicidal thoughts was 16.1% (63 of 391 patients) for the quetiapine XR group versus 20.6% (83 of 402 patients) for the risperidone group at Month 12.