AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Seroquel XR
Study Code	D1443L00025
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A Multicentre, Open-label, Prospective Long-term Study Evaluating the Clinical Benefit and Effectiveness of Quetiapine Fumarate Extended-Release Tablets (SEROQUEL XR®) in Subjects with Schizophrenia

Study dates: First subject enrolled: 14 March 2008
Last subject last visit: 8 July 2010

Phase of development: IIIb

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

Study centre(s)

This study was performed at thirty sites across Canada, two sites across Australia, three sites in Hong Kong and five sites across Korea.

Publications

None.

Objectives and criteria for evaluation

The study objectives and outcome variables are summarized in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective was to document the clinical benefit of seroquel XR after switching from another ongoing antipsychotic treatment.	Proportion of subjects who, at Visit 8 (Week 24), have an improvement in clinical benefit defined as a decrease from baseline in CGI-CB score.	Efficacy
Secondary	**Secondary**	
The secondary objective assessed the effectiveness, safety and tolerability of seroquel XR tablets administered once daily in the treatment of schizophrenic patients	Proportion of subjects who, at Visit 8 (Week 24), have a numerical improvement on CGI-CB, PANSS total, positive, negative and general score, CGI-I, GAS, SOFAS, and SSTICS.	Efficacy
	Proportion of subjects who, at Visit 8 (Week 24) and in-remission subjects have an improvement on CGI-S≤3.	
	Proportion of subjects using anticholinergic medication.	
	Proportion of subjects who, at Visit 8 (Week 24) have an improvement on SAS, BARS, PSS, BMI, Waist-Circumference and Waist-to-Hip ratio.	Safety
	Proportion of subjects who at Visit 8 (Week 24) have no clinical changes to their ECG or lab assessments.	
Exploratory	**Exploratory**	PRO
	Proportion of subjects who, at Visit 8 (Week 24), have an improvement on PSQ, DAI, PETiT, VAS, SSTICS, PSS.	

Study design

This was a 24-week multi-centre, open-label, effectiveness and clinical benefit study of seroquel XR in the treatment of schizophrenia. The trial consisted of a cross-titration period of 2-3 days, followed by a 24 week flexibly dosed period.

Seroquel XR tablets (200 or 300 mg) were administered orally, once a day, preferably in the evening. Subjects started on 300 mg/day, and titrated up to 600 mg/day by Day 2, and 600 - 800 mg/day by Day 3. During Days 1-4, subjects were down-titrated from their other antipsychotic treatment, reaching a target dose of 0 mg by Day 4. Subjects on seroquel IR were allowed to be switched directly to their equivalent dose of seroquel XR. Study drug was open-label.

Target subject population and sample size

Female and male subjects between the ages of 18 and 65 years, inclusive, who fulfilled criteria for schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) were eligible for enrolment. Subjects were outpatients and recruited from specialist care. First episode and drug naive subjects were excluded. Subjects who in their own and/or in the Principal Investigator's opinion considered their ongoing antipsychotic treatment inadequate because of insufficient efficacy, poor tolerance, and/or non acceptability of their actual dosage regimen. In addition, subjects were required to be receiving monotherapy with their current antipsychotic for at least 7 days prior to initiating treatment (i.e., could not be on more than one antipsychotic during the 7 day period prior to initiating study medication). If subjects were on combination therapy, they could taper down to one antipsychotic over a 14-day period prior to enrolment. Subjects on a b.i.d. regimen of seroquel IR at least 7 days prior to enrolment were eligible to participate in the study.

The sample size calculation was based on the primary outcome variable namely, CGI-CB. It was considered important to have power enough to detect a difference from 50% in the primary outcome variable for the analysis of completers. Therefore, the sample size was based on the population of completers. The null hypothesis was that the proportion of subjects with an improved clinical benefit is 50% or less. Given a true proportion of at least 58%, a sample size of 295 treated subjects was thought to have 85% power to detect that the proportion were greater than 50% with a one-sided significance level of 0.025. To account for withdrawals, a total of 331 subjects were recruited.

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

The details of the investigational products and any study treatment are given in Table S2. All investigational products had to be kept in a secure place under appropriate storage conditions. No comparator was used.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Description	Batch number
Seroquel XR	200 mg	AstraZeneca	Yellow, film-coated, biconvex tablets, plain-faced	12840

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Description	Batch number
Seroquel XR	300 mg	AstraZeneca	Pale yellow, film-coated, biconvex tablets, plain-faced	12527

Duration of treatment

The total duration of treatment with seroquel XR was 24 weeks (168 days). Treatment with the seroquel XR started on Treatment Day 1 (baseline), with a 3-day cross-titration phase where ongoing antipsychotic medication was phased out and seroquel XR was phased in. Seroquel XR 300 mg/day was given on Treatment Day 1; 600 mg/day was given on Day 2. On Day 3, the dose could be increased to 800 mg/day or maintained at 600 mg/day according to clinical judgment. Note that dose changes were fixed at 200 mg doses, and changes were able to be made via telephone or in person at unscheduled visits.

On Day 4 the 800 mg dose could be maintained or if not tolerated, the dose could be decreased to a target dose of 600 mg, or if medically necessary further decreased to 400 mg/day. For the remaining 24-week treatment period, a flexible dosing between 400 mg and 800 mg/day was permitted with minimum dose adjustments of 200 mg/day.

Statistical methods

Primary analysis

The statistical method for the primary analysis tested that the primary variable, CGI-CB, to be greater than 50% of clinical improvement, against the null hypothesis that the primary variable was less than or equal to this response percentage.

The primary variable was the proportion of subjects who achieved an improvement in CGI-CB from baseline. A two-sided 95% confidence interval was calculated for the response percentage. If the lower limit of this confidence interval was greater than 50% and equivalently the corresponding one-sided p-value was less than or equal to 0.025, then the null hypothesis was rejected and the treatment considered successful.

The confidence interval for the proportion of subjects achieving an improvement in CGI-CB was computed using the asymptotic normal approximation to the binomial distribution. The corresponding one-sided p-value resulting from a test of the null hypothesis was also presented.

The intention to treat population was the population for the primary analysis. Missing values for the primary analysis were handled using the last observation carried forward (LOCF) approach.

For a consistency check, the primary analysis was repeated using the per-protocol population (with LOCF) and the completers' population.

Factors associated with the probability of achieving improvement were also explored using a logistic regression model with success in achieving improvement as response and center, baseline value of CGI-CB and other background data as explanatory variables. The results of the model were not used inferentially.

Secondary analysis

For the analysis of numerical CGI-CB, PANSS total, positive, negative and general score, CGI-I, GAS, SOFAS, and SSTICS an analysis of covariance (ANCOVA) model with mixed effects was used to observe the change from baseline to the end of treatment. Fixed effects included baseline value.

Two-sided 95% confidence intervals for the change from baseline were presented. One-sided p-values with significance level of 2.5%, for the one-sided test of the null hypothesis that the change from baseline was less than or equal to 0, were calculated. The ITT population with a LOCF approach were used for the analyses.

The development over time (change from baseline to Day 7, 14, 28, 56, 84 and 168) of these variables, are presented descriptively in tables and graphs. CGI-CB, PANSS, CGI-S, CGI-I and SSTICS were analyzed also using descriptive statistics. The development over time, changes from baseline to Day 7, 14, 42, 84, 126 and 168, are shown descriptively in tables. The ITT population was used and missing values handled by using the LOCF approach.

The analysis of the additional outcome, proportion of subjects CGI-S≤3 at Week 24 and in-remission subjects, was performed as for the primary outcome. The ITT population was used and missing values handled by using the LOCF approach. Two-sided 95% confidence intervals for the % response of CGI-S≤3 and in-remission subjects have been calculated.

The analysis of proportion of subjects using anticholinergic medication, was performed as for the primary outcome. The ITT population was used and missing values handled using the LOCF approach. Hence, for anticholinergic medication, the proportion was calculated as the number of subjects who took some anticholinergic medication after administration of the first dose of the investigational product.

PROs and Safety scales analyses

For the analysis of PROs, PSQ, DAI, PETiT, VAS, SSTICS, BMI, SAS, BARS, PSS, Waist-Circumference and Waist-to-Hip ratio, an ANCOVA model with mixed effects was used for the analysis of the change from baseline to the end of treatment. Fixed effects included baseline value and centre as covariates.

The development over time (changes from baseline to Day 7, 14, 42, 84, 126 and 168) is shown descriptively in tables. The ITT population was used and missing values handled using the LOCF approach.

Analyses of adverse events and vital signs were performed by means of descriptive statistics as appropriate. Adverse events were coded using the MedDRA dictionary.

Subject population

Subject disposition is summarized in Table S3. A total of N=300 subjects were enrolled into this trial. Of those, 140 subjects were eligible due to insufficient efficacy, 115 due to insufficient tolerability and an additional 44 due to non-acceptability, while one additional subject did not report any reason. Of the 300 subjects, 5 were discontinued before the administration of seroquel XR: 3 due to voluntary discontinuations by the subject, one due to an adverse event and one additional subject due to loss of follow-up. Of those, n=183 subjects were able to complete the study.

The 300 subjects enrolled were split depending on what medication they had received before entering the study: 91 subjects had been on olanzapine, followed by 86 subjects on seroquel IR, 64 subjects on risperidone, 28 subjects on other atypicals, 24 subjects on typicals and 7 additional subjects on other medications (subjects were on combination therapy or discontinued before obtaining monotherapy data).

The majority of subjects were located in Canada (n=227), followed by South Korea (n=35), Hong Kong (n=27) and Australia (n=6).

Table S3 Subject Disposition (Completion or Discontinuation) by Reason for Switching to Seroquel XR

	Insufficient efficacy	Insufficient tolerability	Non acceptability	Not Reported	Overall
Eligible for enrolment (Visit 1)	140	115	44	1	300
Discontinued before administration of seroquel XR (Visit 2)	2	3	0	0	5
Incorrect enrolment	0	0	0	0	0
Severe non-compliance to protocol	0	0	0	0	0
Safety reasons	0	0	0	0	0
Adverse event	1	0	0	0	1
Lack of therapeutic response	0	0	0	0	0
Voluntary discontinuation by Subject	1	2	0	0	3
Subject lost to follow-up	0	1	0	0	1
Other	0	0	0	0	0
Switched to seroquel XR (Visit 2)	138	112	44	1	295

	Insufficient efficacy	Insufficient tolerability	Non acceptability	Not Reported	Overall
Discontinued after switch of seroquel XR	53	43	15	1	112
Incorrect enrolment	4	1	0	1	6
Severe non-compliance to protocol	2	4	2	0	8
Safety reasons	0	0	0	0	0
Adverse event	21	16	6	0	43
Lack of therapeutic response	10	5	1	0	16
Voluntary discontinuation by Subject	10	8	2	0	20
Subject lost to follow-up	3	5	1	0	9
Other	3	4	3	0	10
Completed study	85	69	29	0	183

A total of n=295 subjects were included into the Safety / ITT Population. Of those, a total of n=195 subjects were able to be included into the Per Protocol Population, and n=183 were able to complete the study. The subject population recruited was adequate for this study and representative of the target population. The two subgroups, subjects switching due to insufficient efficacy and subjects switching due to insufficient tolerability, were well balanced with respect to demographic and baseline disease characteristics. The Safety / ITT population was similar to the PP population in the distribution of demographic and baseline disease characteristics.

With regards to key demographic characteristics, n=182 subjects (61.7%) of the Safety / ITT Population were male and the remaining 113 subjects (38.3%) were female. Subjects had an average age of 37.8 ± 12.12 years. Most subjects were of white ethnic background (62.7%) followed by Asian ethnic background (29.2%). A large majority of subjects were single (76.2%), while 10.2% were married and 9.2% were divorced. Only 9.5% of subjects were full-time employed and 14.6% part-time employed, while a majority (54.9%) were reported to be unemployed. The distribution of demographics between sub-groups were balanced whether subjects were divided by reasons to switch to seroquel XR or whether they were divided by their previous antipsychotic treatment.

Key baseline characteristics showed a mean disease duration of 10.95 ± 10.351 years with an average of 4.48 ± 6.431 schizophrenic episodes over the subject's lifetime. A total of 83 subjects (28.5%) had direct family members (i.e. parent, sibling, child) who also suffered from schizophrenia. According to the DSM-IV codes, 84.1% of subjects were classified as paranoid, 13.6% as undifferentiated, 2.4% as disorganized and none as catatonic. A total of 15 subjects (5.1%) had a known history of diabetes. The distribution of key baseline

characteristics between subjects was balanced between sub-groups whether they were divided by their reasons to switch to seroquel XR or by their previous antipsychotic treatments.

Amongst the 138 subjects who had switched to seroquel XR due to insufficient efficacy, a large number had experienced positive symptoms (72.5%), followed by negative symptoms (59.4%) and general psychopathology (50.0%). Amongst the 112 subjects who had switched to seroquel XR due to insufficient tolerability, 41.1% had experienced weight gain, followed by other reasons (31.3%), sexual dysfunction (8.0%) and anti-cholinergic side effects (4.5%).

Summary of efficacy results

Primary variable

Of the 295 subjects in the Safety / ITT population, 157 (56.88%) demonstrated an improvement in their CGI-CB score (Table S4), with a 95% confidence interval of [0.508, 0.628] indicating a significant improvement in the CGI-CB score over what might be expected due to chance (p=0.0222). With regards to subjects' reasons for switching to seroquel XR, only those switching for insufficient efficacy were able to show a statistically significant improvement (60%, [0.510, 0.685], p=0.0226), while those who switched due to insufficient tolerability and non-acceptability did not manage to gain a statistically significant improvement in their CGI-CB (54.4%, [0.443, 0.642], p=0.3752; and, 52.4% [0.364, 0.680]; p = 0.7576, respectively).

Table S4 Proportion of Subjects with Improvement on CGI-CB at Day 168 (LOCF) by Reason for Switching to Seroquel XR (Safety/ITT Population)

	Insufficient efficacy (n=138)	Insufficient tolerability (n=112)	Non acceptability (n=44)	Overall (n=295)
N[1]	130	103	42	276
Proportion (%)	78 (60.00)	56 (54.37)	22 (52.38)	157 (56.88)
95% CI	[0.510, 0.685]	[0.443, 0.642]	[0.364, 0.680]	[0.508, 0.628]
P-value	0.0226	0.3752	0.7576	0.0222

[1]Number of subjects with non-missing CGI-CB at Day 168.
Note: One subject with no reported reason for switching to seroquel XR is included in the Overall column.

When subjects in the Safety / ITT population were divided based on their previous antipsychotic medications before switching to seroquel XR, only those subjects previously on olanzapine showed an improvement with 62.65% (p=0.0212) as well as those previously treated with seroquel IR with 61.25% (p=0.0442).

Secondary variables

With regards to secondary variables, subjects showed continuous improvements in their CGI-CB scores. At week one, 27.5% of subjects showed an improvement in their CGI-CB score, that increased to 45.8% at week 2, 48.8% at week 6, then stayed in that range during weeks 12 and 18, and finally reached 53.2% at week 24. Percentages are based on the total Safety / ITT population (n=295), while percentages reported as part of the primary analysis are based on subjects with non-missing CGI-CB scores at week 24. When subjects were divided based on their reasons for switching to seroquel XR, similar increases were noted. The same was true when subjects were categorized by their previous antipsychotic treatment regimen.

At baseline, subjects had an average CGI-CB score of 6.33 ± 2.568 (mean ± standard deviation) that decreased by an average of 1.41 ± 3.843 points at week 24. This improvement in mean CGI-CB scores was statistically significant (p<0.0001). Similar reductions were observed when subjects were divided by reasons for switching to seroquel XR (all statistically significant). When subjects were divided by previous antipsychotic treatment, all subgroups showed improvement ranging from a decrease in CGI-CB of 0.68 to 2.52. These improvements were statistically significant for the olanzapine (p<0.0001), the seroquel IR (p=0.0002), and other atypicals subgroups (p=0.0066), but not for the risperidone (p=0.2351) and the typicals subgroups (p=0.3299).

For all subjects, CGI-S scores decreased by an average of 0.13 ± 0.574 between baseline and day 7 and by an average of 0.51 ± 1.174 between baseline and week 24 / early withdrawal. Reductions were also observed when subjects were divided by reasons for switching to seroquel XR: Between baseline and week 24, subjects who switched due to insufficient efficacy had the highest reduction in CGI-S scores by an average of 0.81 ± 1.149, followed by subjects switched due to insufficient tolerability (0.27 ± 1.122) and those switched due to non acceptability (0.21 ± 1.200). When subjects were divided by previous antipsychotic treatment, all subgroups showed a reduction in CGI-S scores between baseline and week 24 ranging from a reduction of 0.30 to 0.71.

All subjects in the Safety / ITT population had an average PANSS total score of 74.45 ± 22.523 points at baseline. At week 24, this score had decreased by 10.95 ± 20.899 points. This improvement was statistically significant (p<0.0001). When subjects were divided based on their reason for switching to seroquel XR, those subjects who had switched due to a lack of efficacy (p<0.0001) and those who had switched due to a lack of tolerability (p=0.0007) were able to show statistically significant improvements, but not those who had switched due to non-acceptability (p=0.1573). When subjects were sub-grouped based on their previous antipsychotic treatment, all subgroups were able to show statistically significant improvements ranging from an average of 7.92 to 12.64 points (p values ranging from p<0.0001 to p=0.0058).

Statistically significant improvements were also observed for all subjects with regards to the PANSS positive scale scores. Subjects improved by an average of 2.36 ± 6.061 points which

was statistically significant (p<0.0001). However, when subjects were divided by the reason to switch to seroquel XR, only those who switched due to a lack of efficacy showed a statistically significant improvement (p<0.0001), while both other subgroups did not (p=0.2124 and p=0.0948, respectively). When subjects were divided by their previous antipsychotic treatment, only those who were previously on olanzapine (p=0.0006), risperidone (p=0.0016) and seroquel IR (0.0008) showed a statistically significant improvement.

PANSS negative scale scores were an average of 20.71 ± 7.314 points at baseline and improved by an average of 3.67 ± 6.135 points at week 24 which was statistically significant (p<0.0001). For subjects divided by their reason for switching to seroquel XR, those who had switched due to a lack of efficacy (P<0.0001) and those who had switched due to a lack of tolerability (P<0.0001) showed statistically significant improvements, but not those who had switched due to non-acceptability (p=0.1665). When subjects were divided based on their previous antipsychotic treatment, all sub-groups displayed statistically significant improvements ranging from an average of 2.3 to 4.59 points (p-values ranging from p<0.0001 to p=0.0034).

The average PANSS general scale score was 36.89 ± 11.718 points at baseline for all subjects. This score improved by an average of 4.92 ± 10.721 points by week 24. When subjects were divided by their reason to switch to seroquel XR, all sub-groups showed improvements ranging from an average of 1.98 to 7.19 points. However, these improvements were only statistically significant for those subjects who had switched due to a lack of efficacy (p<0.0001) and due to a lack of tolerability (p=0.0005), but not for those who had switched due to non-acceptability (p=0.2842). If the subject population was sub-divided by previous anti-psychotic treatments, all sub-groups showed improvements that were statistically significant.(p-values ranging from p<0.0001 to p=0.008).

The average GAS score was 53.81 ± 14.847 points for all subjects at baseline. By week 24, that score increased by an average of 5.54 ± 14.866 points which was a statistically significant improvement (p<0.0001). When subjects were divided by their reason for switching to seroquel XR, all sub-groups showed an improvement ranging from an average of 1.67 to 8.55 points. However, this improvement was only statistically significant for those subjects who had switched due to lack of efficacy (p<0.0001) and due to lack of tolerability (p=0.0107), but not for those who had switched due to non-acceptability (p=0.4342). When subjects were divided based on their previous antipsychotic treatment, all sub-groups showed a statistically significant improvement (p-values ranging from p=0.0001 to p=0.0236) with the exception of those subjects who had been treated with typicals (p=0.2555).

The average SOFAS score was 54.09 ± 14.788 points for all subjects at baseline. By week 24, that score increased by an average of 6.45 ± 13.820 points which was a statistically significant improvement (p<0.0001). When subjects were divided by their reason for switching to seroquel XR, all sub-groups showed an improvement ranging from 1.98 to 9.36 points. However, this improvement was statistically significant only for those subjects who had switched to seroquel XR due to a lack of efficacy (p<0.0001) and due to a lack of tolerability (p<0.0001), but not for those who had switched due to non- acceptability (p=0.3483). When subjects were divided based on their previous usage of antipsychotic medications, all sub-

groups showed a statistically significant improvement (p-values ranging from p=0.0001 to p=0.0361).

Of the n=183 subjects who had a CGI-S score ≥ 4 at baseline, 124 subjects (67.76%) experienced an improvement by week 24. An improvement had been defined as the CGI-S score being ≤ 3 for that particular subject. This improvement was statistically significant (p<0.0001). When these 183 subjects were divided by their reason for switching to seroquel XR, the proportions of subjects were similar in the sub-groups as they were in the overall population, ranging from 66.0% to 68.18% improvement. These improvements were statistically significant for those subjects who had switched due to a lack of efficacy (p=0.0001) and for those who had switched due to a lack of tolerability (p=0.0237), but not for those who had switched for non-acceptability (p=0.0881). When these 183 subjects were divided based on their previous antipsychotic treatment, only those who had been treated with olanzapine (p=0.0086), risperidone (p=0.0080) and seroquel IR (p=0.0113) showed a statistically significant improvement, but not those who had been treated with other atypicals (p=0.2253) and typicals (p=0.4386). Of all n=275 subjects who provided non-missing CGI-S scores at week 24, n=103 (37.45%) had a CGI-S score ≤ 3 and were in remission at week 24. That change was statistically significant (p<0.0001).

For CGI-I scores, the average score was 3.54 ± 0.783 points at baseline (Day 7) and decreased by an average of 0.55 ± 1.556 points at week 24. This improvement was statistically significant (p=0.0001). When subjects were divided by their reasons to switch to seroquel XR, all subgroups also experienced an improvement in mean scores ranging from 0.25 to 0.66 points. However, this was only statistically significant for the insufficient efficacy and the insufficient tolerability subgroups (p<0.0001 and p=0.0032, respectively), but not for the non-acceptability subgroup (p=0.2434). When subjects were divided by their previous antipsychotic treatments, all subgroups experienced improvements in their average CGI-I scores ranging from 0.20 to 0.74. These improvements were statistically significant for subjects treated with olanzapine (p<0.0001), risperidone (p=0.0017), seroquel IR (p=0.0132), but not for subjects treated with other atypicals (p=0.0764) and typicals (p=0.6058).

Patient Reported Outcomes

- Mean SSTICS scores were 32.58 ± 16.339 points at baseline for all subjects in the Safety / ITT population. At the week 24 / early withdrawal visit, there was a reduction by an average of 3.10 ± 13.751 points.
- At baseline, 8.6% of all subjects were extremely satisfied with their medication and 21.4% were very satisfied, as assessed by the PSQ. At week 24 / early withdrawal, these percentages had increased to 15.8% being extremely satisfied and 32.3% being very satisfied with their medication. Similarly, 10.4% of all subjects had described their medication as extremely helpful and an additional 30.1% as very helpful at baseline, while at the end of study that had increased to 17.0% of subjects describing their medication as extremely helpful and 35.9% as very helpful. Finally, 47.1% of subjects would like to continue with their current medication at baseline, while even 78.0% would like to do the same at the end of study.
- All subjects had an average DAI score of 4.33 ± 4.142 points at baseline. By week 24 early withdrawal visit, the average DAI score had increased by 0.64 ± 4.462 points.

- For all subjects, the average PETiT score was 32.81 ± 5.628 points at baseline. By week 24 / early withdrawal visit, the PETiT score had decreased by an average of 1.04 ± 6.089 points.

- For all subjects, the average VAS score was 48.20 ± 27.705 points at baseline. By week 24 / early withdrawal visit, the VAS score had decreased by an average of 5.03 ± 31.173 points, meaning a substantial improvement in dealing with work or relationship with others.

- For all subjects, the average PSS score was 7.16 ± 3.1 points at baseline. By week 24 / early withdrawal visit, the PSS score had decreased by an average of 0.62 ± 3.762 points, indicating little changes from baseline.

Safety Rating Scales

- For all subjects, the average SAS score was 3.09 ± 4.537 points at baseline. By week 24 / early withdrawal visit, the SAS score was unchanged in 43.5% of subjects, had worsened in 10.4% of subjects, but had improved in 46.1% of subjects.

- For all subjects, the average BARS score was 1.58 ± 2.652 points at baseline, indicating the presence of restlessness in our study population as assessed by investigators. By week 24 / early withdrawal visit, the BARS score was unchanged in 63.7% of subjects, had worsened in 8.2% of subjects, but had improved in 28.1% of subjects.

Summary of safety results

Adverse events

A total of 224 subjects (75.9%) of the Safety / ITT population experienced at least one adverse event during the course of the study. The most frequent system organ classes reported are nervous system disorders (51.2%), followed by gastrointestinal disorders (31.9%) and psychiatric disorders (30.2%).

The preferred terms most frequently reported were somnolence (18.0%), followed by dizziness (14.6%) and sedation (14.2%). There were no clinically marked differences between the sub-groups with regards to adverse events, whether subjects were categorized by their reason for switching to seroquel XR or by their previous antipsychotic treatment.

No adverse events leading to death were reported. A total of 33 subjects (11.2%) of the Safety / ITT population experienced at least one serious adverse event during the course of the study. The most frequent system organ classes reported were psychiatric disorders (10.5%). Within that system organ class, the most frequent preferred terms reported were psychotic disorders (2.7%) and schizophrenia (2.7%). There were no clinically marked differences between the sub-groups with regards to serious adverse events, whether subjects were categorized by their reason for switching to seroquel XR or by their previous antipsychotic treatment.

A total of 53 subjects (18.0%) of the Safety / ITT population experienced at least one adverse event during the course of the study that resulted in discontinuation from the study. The most frequent system organ classes reported were psychiatric disorders (11.2%) followed by nervous system disorders (6.1%). Within the system organ class of psychiatric disorders, the most frequent preferred term reported was anxiety (1.0%), while for nervous system disorders, it was somnolence (2.4%) and sedation (1.7%). There were no clinically marked differences between the sub-groups with regards to adverse events leading to study discontinuation, whether subjects were categorized by their reason for switching to seroquel XR or by their previous antipsychotic treatment.

Clinical laboratory evaluation

No clinically marked differences between baseline and Week 24 hematology assessments were observed with regards to hematocrit, erythrocytes, haemoglobin, leukocytes, platelets, neutrophils, eosinophils, basophils, lymphocytes and monocytes for any study subjects. In addition, no individual clinically important abnormalities in haematology were observed.

No clinically marked differences between baseline and Week 24 clinical chemistry assessments were observed with regards to glucose, ALT, AST, alkaline phosphatase, creatinine, bilirubin, sodium, potassium, calcium, chloride, albumin, TSH, urea, total cholesterol, triglycerides, free T4, free T3, HDL, LDL, insulin, HBA1C, prolactin and bicarbonates. In addition, no individual clinically important abnormalities in clinical chemistry were observed.

Vital signs, ECGs, and physical findings

With regards to weight parameters, there were no clinically marked differences between the sub-groups with regards to change in weight, waist and hip circumference, waist to hip ratio, BMI or BMI category.

For pulse and blood pressure parameters, there were also no clinically marked abnormalities observed

Similarly, no medically important changes were observed for the QTc intervals within the ECG.