Non-Interventional Study (NIS) Report Synopsis

NIS Name/Code	CLIMAX / NIS-NKR-SER-2009-1
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A non-interventional study evaluating the CLInical Benefit and Effectiveness of Quetiapine FuMArate EXtended-Release Tablets (SEROQUEL XR®) in Subjects with Schizophrenia, an observational, multicentric prospective study

CLIMAX study

Study dates: **First Subject In: 8 Jul 2009**

Last Subject Last Visit: 10 Jan 2010

Study centre(s)

There were 1494 patients at 58 centers in Korea.

Objectives

1. Primary Endpoint

Primary Endpoint was demonstrating clinical benefits of Seroquel XR in patients treated with Seroquel XR.

- Proportion of patients with improved clinical benefit by assessment of Clinical Global Impression - Clinical Benefit Scale (CGI-CB). Improvement of Clinical benefit was defined as the decrease in CGI-CB score from baseline (visit 1) to week 8.

2. Secondary Endpoint

2-1. The efficacy of Seroquel XR improving symptoms associated with schizophrenia was assessed as follows.

- Change in Clinical Global Impression - Clinical Benefit Scale (CGI-CB) score
- Change in Clinical Global Impression - Improvement of Illness (CGI-I) score
- Change in Clinical Global Impression - Severity of illness (CGI-S) score
- Proportion of patients with Clinical Global Impression - Severity of illness(CGI-S) score less than 3

2-2. Schizophrenic Patients treated with Seroquel XR were assessed whether Seroquel XR increased well-being feature.

- Change in SWN-K(Subject Wellbeing under Neuroleptic Treatment Scale) score with antipsychotic drug treatment

Study design

This study was an 8-week, non-interventional, prospective, multi-center study

Target subject population

This study was targeted to patients who were treated with Seroquel XR for schizophrenia and who aged between 18 and 65 years. About 60 psychiatrists conducted the study. 1500 subjects were to be recruited, and 1494 Subjects were enrolled.

Statistical Analysis

Primary endpoint : CGI-CB

One sided test p-value and both sides 95 % CI were presented for the null hypothesis – the improvement ratio of CGI-CB was less than 50% and descriptive statistics of changes in CGI-CB and paired t-test were also presented.

Secondary endpoint : CGI-S

Descriptive statistics of changes of CGI-S, paired t-test, and 95% CI for changes in CGI-S were presented. Sided test p-value and 95% CI for the null hypothesis – the proportion of subjects who were lower than 3 CGI-S score lower than 50% was presented.

Secondary end point : CGI-I

Descriptive statistics of CGI-I on visit 2(week 8) was presented.

Secondary end point : SWN-K

Descriptive statistics and 95% CI for total changes in SWN-K score were presented. Paired t-test was performed. The analysis of the rest of the subsection was conducted using an identical method.

Exploratory Factor Analysis

Multiple Logistic Analysis was performed to identify the parameter involved in CGI-CB improvement.

Summary of results

CGI-CB

The proportion of subjects who showed improvement in CGI-CB score with Seroquel XR was 61.71% (743 patients), and that of subjects with no improvement in CGI-CB score with Seroquel XR was 38.29% (461 patients). More than 50% of the subjects showed improvement in CGI-CB score with Seroquel XR ($p<.0001$). In addition, the lower and upper-bound estimates of 95% CI were each 58.97% and 64.46%, and the lower-bound estimate of CI was higher than 50%. It demonstrated that the Seroquel XR treatment for schizophrenia was effective.

Table S1. Improved rate of CGI-CB between baseline and week 8

Acquire the clinical benefit	n(%)	95% CI[Low,Up]	p-value†
Yes	743(61.71)	[58.97,64.46]	<.0001

† Test of proportion

The mean and difference of CGI-CB scores of subjects at baseline(visit 1) and at week 8 (visit 2) were evaluated (table S2). As a result, the mean CGI-CB score was 6.42±2.48 at baseline (visit 1), and the mean CGI-CB score was 4.37±2.49 at week 8 (visit 2). It showed that the mean CGI-CB score decreased by 2.06±2.85 with Seroquel XR treatment for 8 weeks and it was statistically significant (p<.0001). Accordingly, it was estimated that subjects treated with Seroquel XR for 8 weeks experienced clinical benefit i.e. therapeutic efficacy.

Table S2. CGI-CB between baseline and week 8

CGI-CB	Baseline	Week 8	Difference	95% CI[Low,Up]	p-value†
Mean±SD	6.42±2.48	4.37±2.49	-2.06±2.85	[-2.22,-1.90]	<.0001

†paired t-test

CGI-S

The mean CGI-S score was 4.12±0.99 at baseline (visit 1), the mean CGI-S score was 3.03±0.88 at visit 2 (week 8). It showed that the mean CGI-S score decreased by 1.08 ±1.08 with Seroquel XR treatment for 8 weeks and it was statistically significant e(p<.0001). Accordingly, it was estimated that subjects treated with Seroquel XR for 8 weeks experienced decrease in severity of schizophrenia symptoms.

Table S3. CGI-S between baseline and week 8

CGI-S	Baseline	Week 8	Difference	95% CI[Low,Up]	p-value†
Mean±SD	4.12±0.99	3.03±0.88	-1.08±1.08	[-1.15,-1.02]	<.0001

†paired t-test

CGI-S ≤ 3

It was estimated that subjects who had 3 or lower CGI-S score were 75.66% (911 subjects), and subjects who had higher than 4 CGI-S score were 24.34%(293 subjects) (Table. S4). It was more than 50% that the proportion of subjects who had 3 or lower

CGI-S score (p<.0001). The lower and upper-bound estimates of 95% CI for subjects who were 3 or lower CGI-S score were 73.24%, 78.09%. Accordingly, the severity of schizophrenia symptoms in patients on Seroquel XR was determined not severe than 'moderately ill' which showed that Seroquel XR was effective for controlling schizophrenic symptoms.

Table S4. CGI-S ≤ 3 at week 8

CGI-S ≤ 3	n(%)	95% CI[Low,Up]	p-value†
Yes	911(75.66)	[73.24,78.09]	<.0001

† Test of proportion

CGI-I

The mean CGI-I score was 2.49±0.80 at visit 2 (week 8). It was between 2 and 3 or between "much improved" and "minimally improved". It demonstrated that the treatment response in subjects treated with Seroquel XR for 8 weeks was generally improved.

Table S5. CGI-I at week 8

CGI-I	Week 8
Mean±SD	2.49±0.80

SWN-K

The differnce of total score and mean of SWN-K between baseline and week 8 were presented in table S6. Total score of SWN-K was 65.17±14.01 at baseline (visit 1) and 78.38±13.21 was at visit 2 (week 8). The mean difference of SWN-K between baseline (visit 1) and visit 2 (week 8) was 13.21±15.04 which was statistically significant (p<.0001).

Table S6. SWN-K between baseline and week 8

SWN-K	Baseline (Mean±SD)	Week 8 (Mean±SD)	Difference (Mean±SD)	95% CI[Low,Up]	p-value†
Total	65.17±14.01	78.38±13.21	13.21±15.04	[12.36,14.06]	<.0001
Mental function	12.63±3.33	15.31±2.97	2.68±3.48	[2.48,2.88]	<.0001
Self control	13.55±3.13	15.99±2.97	2.44±3.41	[2.25,2.63]	<.0001
Emotional regulation	13.29±3.27	15.71±2.98	2.41±3.47	[2.22,2.61]	<.0001

Physical functioning	12.76±3.47	15.90±3.17	3.14±3.86	[2.92,3.36]	<.0001
Social integration	12.94±3.06	15.47±2.88	2.53±3.40	[2.34,2.73]	<.0001

†paired t-test

Specifically, 'physical function' increased from 12.76±3.47 to 15.90±3.17 with average of 3.14±3.86 where showed highest average change among SWN-K sub-domains. Besides, it was investigated that the average score increased in order of the following: 'Mental function', 'Social integration', 'Self control', 'Emotion regulation'. It was estimated that total and scores of all domains at visit 2 (week 8) significantly increased compared with those at baseline (visit 1) (p<.0001), and subjective well-being recognized by subjects increased after treatment with Seroquel XR.

Exploratory Factor Analysis

Multiple Logistic Analysis was conducted to evaluate factors affecting improvement of CGI-CB at visit 2 (week 8). As a result, it was observed that CGI-CB score, age of subjects, and types of schizophrenia of subjects at baseline (visit 1) statistically significantly influenced the improvement of CGI-CB. Specifically, the probability of improvement in CGI-CB after treatment with Seroquel XR for 8 weeks was 1.42 times higher if the CGI-CB score was high at baseline (visit 1), and 0.99 times higher if the subject was young. In addition, It was estimated the probability of improvement of CGI-CB after treatment with Seroquel XR for 8 weeks was 1.98 times higher if the type of schizophrenia was paranoid than undifferentiated, 1.26 times higher if the type of schizophrenia was catatonic than undifferentiated, and 0.46 times higher if the type of schizophrenia was residual than undifferentiated (p<.0001).

Table S7. Multiple logistic regression of CGI-B

Variable	Class	Regression coefficient estimate	SE	Odds ratio	95% CI		p-value
					Low	Up	
CGI-CB at baseline	continuous variable	0.35	0.03	1.42	1.34	1.50	<.0001
Age	continuous variable	-0.01	0.01	0.99	0.98	1.00	0.0084
Diagnosis							<.0001
	paranoid vs undifferentiated	0.65	0.16	1.98	1.46	2.67	
	catatonic vs undifferentiated	-0.82	0.41	0.46	0.15	1.35	
	residual vs undifferentiated	0.20	0.20	1.26	0.82	1.95	

The number of patients used from this analysis is 1,204.

The p-values are corresponding to the F statistics.
Multiple logistic regression model by stepwise method(Alpha:0.05)