

Non-Interventional Study (NIS) Report

NIS Code	NIS-NNL-SER-2008/1
NIS Name	Xperience
Edition Number	Final
Date	05 January 2011

Xperience: A non-interventional study evaluating well-being/Quality of Life in schizophrenic patients treated with Seroquel XR® (quetiapine) and other atypical antipsychotics. A 9-month, observational, multicentric prospective study.

Study dates:

First Subject In: 18 April 2008

Last Subject Last Visit: 21 January 2010

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NON INTERVENTION STUDY REPORT SYNOPSIS

Xperience: A non-interventional study evaluating well-being/Quality of Life in schizophrenic patients treated with Seroquel XR® (quetiapine) and other atypical antipsychotics. A 9-month, observational, multicentric prospective study

National co-ordinating investigator

Not Applicable, there was no National Co-ordinating Investigator

Study centres

Practices of psychiatrists within general hospitals and within psychiatric hospitals in The Netherlands.

Publications

None to date.

Clinical Trials Registry identifier

NCT00689325

Study Dates

First Subject enrolled: 18 April 2008
Last Subject completed: 21 January 2010

Phase of Development

Phase IV

Objectives

The primary objective of this Non-Intervention Study (NIS) was:

1. to evaluate the Quality Of Life (QOL) and subjective effectiveness in patients with schizophrenia, treated with atypical antipsychotics using the Subjective Well-being under Neuroleptics Short form (SWN-K).

Secondary objectives of this study were, in these patients with schizophrenia, treated with atypical antipsychotics:

2. to evaluate symptom resolution, using the Positive and Negative Syndrome Scale-8 (PANNS-8)

3. to evaluate clinical benefit using the Global Assessment of Functioning (GAF) questionnaire
4. to evaluate disease insight as measured by the G12-item of the PANSS-8
5. to evaluate additional factors that may influence the QOL.

Study design

This was an observational, prospective, multi-centre study, defined as a Non-Intervention Study (NIS). Potential patients had been diagnosed with schizophrenia and had started treatment with one atypical antipsychotic (AAP) between 2 and 8 weeks prior to the baseline visit. This anti-psychotic treatment could be the first treatment for the schizophrenia or a changed treatment. Follow-up visits took place at approximately 3 months, 6 months and 9 months after the baseline visit while the AAP treatment was continued and a series of questionnaires were completed by the patient and the investigator. A change in AAP treatment was considered to be a protocol violation, leading to study discontinuation. The Study Protocol and the Informed Consent Form were reviewed by an Independent Ethics Committee.

Target subject population and sample size

Patients of either sex, aged between 18 and 65 years, who had been diagnosed with schizophrenia and who were being treated with one atypical antipsychotic. A total of 200 patients were aimed to be enrolled in order to have 120 fully evaluable patients, expecting a 40% drop-out rate. A difference in the Total score of the SWN-K of 8 points was regarded as clinically meaningful and with an expected Standard Deviation of maximally 20 points, a treatment difference of at least 7.2 points would be detectable with 120 evaluable patients.

Investigational product

There was not one investigational product. All AAP were prescribed through the normal routine, in whatever dosage was deemed appropriate. The AAP and all concomitant medication were recorded in the Case Report Form.

Duration of treatment

Approximately 9 months.

Criteria for evaluation (main variables)

Efficacy

Primary variable:

- Quality of Life: SWN-K (Total score) at the end of the study (9 months) as change from baseline.

Secondary variables:

- Quality of Life: SWN-K (Total score) at 3 and 6 months as change from baseline and sub-scores in SWN-K at 3, 6 and 9 months as change from baseline
- Efficacy: symptom resolution, based on the PANSS-8, defined as when all eight symptoms from PANSS-8 are scored ≤ 3
- Clinical Benefit, based on the GAF scale
- Disease insight: assessed with the G12-item of the PANSS
- Functioning: changes during the follow-up period in concomitant medication, in psychiatric hospitalisation, in substance use and substance abuse, in work or school attendance and living condition from baseline to the end of the study.

Safety

Safety was not assessed in this Non Intervention Study since normal practice was followed. Adverse effects of quetiapine could be reported spontaneously to AstraZeneca and adverse effects of other AAPs or concomitant treatments were to be reported to the manufacturer of the other medication or to the Netherlands Pharmacovigilance Centre.

Statistical methods

The calculation of the sample size was based on the width of a (two-sided) 95% confidence interval for the difference in the SWN-K-score from baseline to End of Study (visit 4 or an earlier visit in case of a missing visit 4). In the literature, mean differences between 8 and 11 points of the total score in the SWN-K scale with standard deviations (SD) between 10 and 20 points have been reported and a difference of 8 was considered clinically relevant. A sample size of 120 patients who completed the study would produce confidence intervals that were considered sufficiently small. The width of a two-sided 95% confidence interval would be 3.58 if SD=10, 5.37 if SD=15, 7.16 if SD=20. Taking into account a drop-out rate of about 40%, approximately 200 patients had to be recruited for the study.

Statistical testing (change from baseline) was performed with paired t-tests for continuous variables SWN-K, GAF, PANSS-8, and G12. Two-sided p-values below 0.05 were considered statistically significant. Mean changes were based on individual changes by patient. These changes were calculated when values were available at both the visit of interest and at baseline. Therefore, the difference between the overall means of the visits is not always equal to the mean change.

End of Study data were calculated using the Last Observation Carried Forward (LOCF) principle.

Potential differences between the different antipsychotic treatments were not analysed.

RESULTS

Subject population

After obtaining their written Informed Consent, a total of 158 patients were enrolled in the study from a total of 49 study sites. Enrolment was stopped prior to reaching the planned number of 200 patients due to a dramatic decrease in enrolment speed. All 158 patients used at least one dose of their AAP medication and thus the Safety Analysis Data Set consists of 158 patients. Of 61 patients, due to missing answers on at least one question in the SWN-K, the total score of the SWN-K was not available at baseline, leaving 97 patients for the Efficacy Analysis Data Set. Demographics are shown in Table 1. The majority of the patients was male and had the paranoid subtype of schizophrenia. One patient was enrolled erroneously, being older than 65. Of the total of 158 patients, 74 used quetiapine as antipsychotic treatment during the study, details on AAP medication are shown in Table 1. Many patients used other concomitant medication and virtually all received some sort of concomitant therapies, see Table 1. Of 69 patients the number of years since the start of antipsychotic treatment was available, the mean period was 9.6 years (SD 9.0), ranging from 0 to 32 years.

Table 1 Patient population, baseline characteristics and disposition

		Safety Analysis ^a		Efficacy Analysis ^b	
Population					
N		158		97	
Demographic characteristics					
Sex (n and % of subjects) ^d	Male	102	(65%)	67	(70%)
	Female	55	(35%)	29	(30%)
Age (years)	Mean (SD)	39.8	(11.4)	39.3	(10.7)
	Range	18 – 73		18 – 73	
Data at follow-up visits					
		Visit 1		97 (100%)	
		Visit 2		97 (100%)	
		Visit 3		72 (74.2%)	
		Visit 4		51 (52.6%)	

		Safety Analysis ^a		Efficacy Analysis ^b	
Schizophrenic subtype					
- Paranoid (P)		103 P		62 P	
- Disorganized (D)		10 D		8 D	
- Undifferentiated (U)		24 U		14 U	
- Residual (R)		21 R		13 R	
Atypic Antipsychotic used					
- Quetiapine (Q)		74 Q			
- Risperidon (R)		25 R			
- Olanzapine (O)		25 O			
- Aripiprazol (A)		21 A			
- Paliperidon (P)		14 P			
- Others (Ot)		9 Ot			
Concomitant Medication^c					
- Benzodiazepine (B)		55 B			
- Antidepressant (AD)		40 AD			
- Mood stabilizer (M)		13 M			
- Anticholinergic (AC)		11 AC			
- Other (O)		23 O			
Concomitant Therapies^e					
- Psycho-education (PE)		100 PE			
- General psychotherapy (GP)		78 GP			
- Psycho- rehabilitation (PR)		47 PR			
- Cognitive skills (CS)		23 CS			
- Cognitive therapy (CT)		18 CT			
- Family therapy (FT)		11 FT			
- Psycho-dynamic (PD)		5 PD			
Reason of discontinuation		n=82		n=51	
- Protocol deviation (PD) ^f		41 PD	(50.0%)	26 PD	(51.0%)
- Voluntary decision (VD)		24 VD	(29.3%)	12 VD	(23.5%)
- Insufficient efficacy (IE)		12 IE	(14.6%)	9 IE	(17.6%)
- Adverse effects (AE)		5 AE	(6.1%)	4 AE	(7.8%)
Disposition					
N (%) of subjects who	Completed	76	(48.1%)	46	(47.4%)
	Discontinued	82	(51.9%)	51	(52.6%)

^a Number of subjects who took at least 1 dose of study treatment

^b Number of subjects who took at least 1 dose of study treatment and had SWN-K data at baseline

^c Any change in antipsychotic treatment was considered a protocol deviation leading to withdrawal

^d One patient had missing data

^e More than one therapy was possible

Within the Efficacy analysis data set, 6 patients had a full-time job at baseline, 11 a part-time job, 11 worked in a sheltered workshop and 14 performed volunteer work, while 41 patients had no work. The living situation at enrolment was such that 47 patients lived independently, 23 patients lived with family or friends and 7 lived under supervision. Concerning substance abuse at baseline, 27 patients stated to use alcohol, 43 patients stated to use nicotine, 14 patients used soft drugs, 1 patient used hard drugs and 2 patients used other substances.

Approximately half of the patients (51.9 % of the Safety analysis data set and 52.6% of the Efficacy analysis data set) did not complete the entire study, which was more than the anticipated 40%.

Efficacy results: SWN-K

A total of 97 patients had SWN-K data at baseline, since of 61 patients at least one of the 20 questions was not answered, leading to a missing sub-score and thus to a missing Total score for SWN-K. This Efficacy Analysis data set of 97 patients is used in the presentation of all the efficacy results below. SWN-K data is shown in Table 2 below for all visits and for the End of Study (using Last Observation Carried Forward).

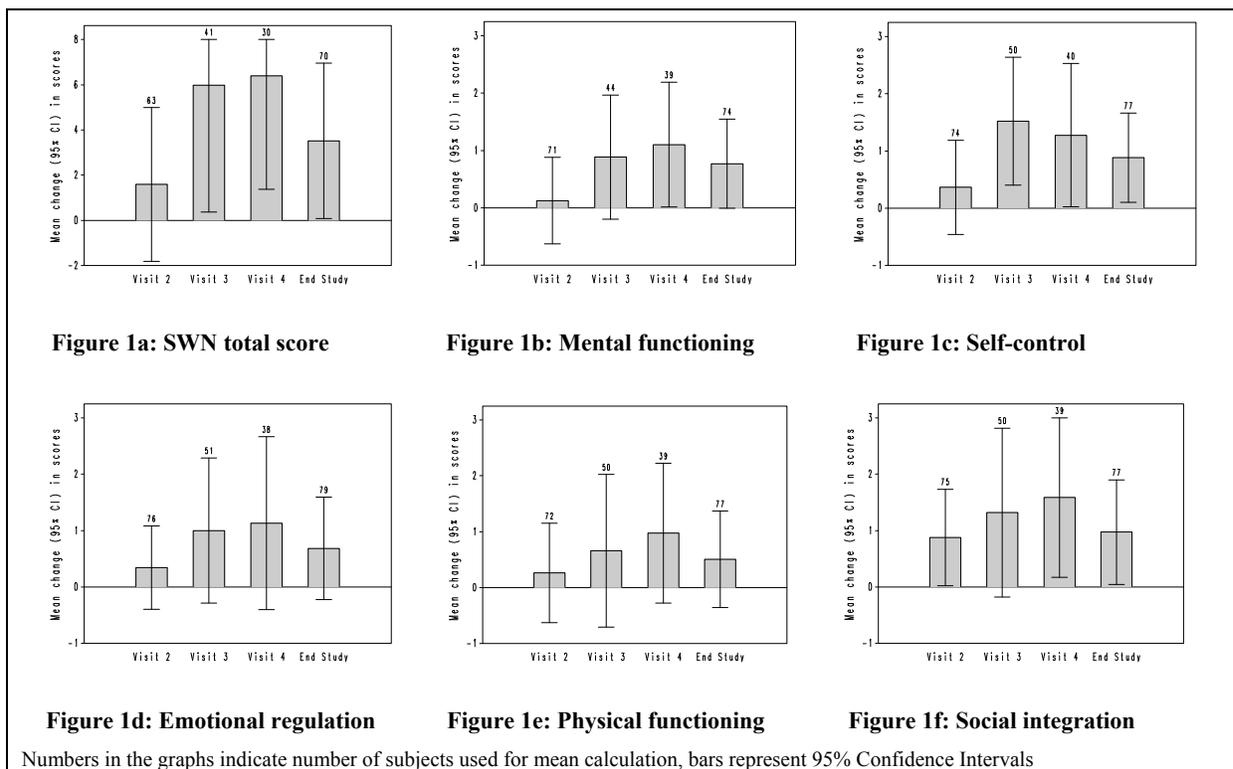
Table 2 Efficacy: SWN-K : Total score and sub-scores at all visits and at End of Study and change from baseline in Total score

	Visit 1	Visit 2	Visit 3	Visit 4	End of Study
Total Score	n = 97	n = 63	n = 41	n = 30	n = 70
Mean (SD)	74.8 (17.1)	76.7 (14.7)	78.9 (13.8)	76.1 (11.6)	77.8 (14.8)
95% CI	71.3 – 78.2	73.0 – 80.4	74.5 – 83.3	71.8 – 80.5	74.2 – 81.3
Min - max	31 – 112	49 – 110	54 – 112	45 – 104	45 – 112
Mental functioning	n = 97	n = 71	n = 44	n = 39	n = 74
Mean (SD)	14.3 (3.7)	14.3 (3.3)	15.4 (2.5)	15.2 (2.4)	14.9 (3.0)
Self Control	n = 97	n = 74	n = 50	n = 40	n = 77
Mean (SD)	15.4 (3.9)	15.7 (3.5)	16.9 (3.2)	16.1 (3.4)	16.2 (3.6)
Emotional regulation	n = 97	n = 76	n = 51	n = 38	n = 79
Mean (SD)	15.4 (4.0)	15.6 (3.9)	16.4 (4.2)	15.8 (3.7)	15.9 (4.0)
Physical functioning	n = 97	n = 72	n = 50	n = 39	n = 77
Mean (SD)	15.3 (4.5)	15.7 (3.9)	16.0 (4.2)	15.6 (4.1)	15.8 (4.4)
Social integration	n = 97	n = 75	n = 50	n = 39	n = 77
Mean (SD)	14.4 (4.4)	15.2 (3.6)	15.4 (3.9)	15.2 (3.0)	15.2 (3.6)
Change from baseline in Total score					
		n=63	n=41	n=30	n=70
Mean (SD)		1.6 (13.5)	6.0 (17.8)	6.4 (13.5)	3.5 (14.4)
95% CI:		-1.8 – 5.0	0.4 – 11.6	1.4 – 11.4	0.1 – 7.0

95% CI: 95% Confidence Interval; SD: Standard Deviation

SWN-K data (Total score and sub-scores) as change from baseline and corresponding 95% CI for visit 2, visit 3, visit 4 and End of Study is shown in the figure.

Figure 1 SWN-K as change from baseline at visit 2, 3, 4 and at End of Study



In Table 3 the change from baseline to End of Study in SWN-K (Total score and sub-scores) are also shown. All scores showed a mean improvement (increase) but the change in Total score at End of Study (a mean 3.5 points with a 95% Confidence Interval of 0.1 to 7.0) did not reach the predetermined level of clinical relevancy (the value 8), though the increase was statistically significant. Two sub-scales increased statistically significant from baseline to End of Study (Self-control and Social integration).

Table 3 Efficacy: SWN-K, Total score and sub-scores as change from Baseline to End of Study

SWN-K	N	Mean (SD)	95% CI	Min – Max
Total score	70	3.5 (14.4)	0.1 – 7.0 *	-30 – 43
Mental functioning	74	0.8 (3.3)	-0.0 – 1.5	-6 – 9
Self-control	77	0.9 (3.4)	0.1 – 1.7 *	-6 – 11
Emotional regulation	79	0.7 (4.1)	-0.2 – 1.6	-11 – 14
Physical functioning	77	0.5 (3.8)	-0.4 – 1.4	-8 – 12
Social integration	77	1.0 (4.1)	0.0 – 1.9 *	-9 – 12

*: 96% Confidence Interval (CI) entire outside zero and thus a statistically significant change from baseline

At the separate visits 2, 3 and 4 (after respectively 3, 6 and 9 months) there was a gradual increase in the change from baseline for the Total score in WSN-K: a mean increase of 1.6 after 3 months, 6.0 after 6 months and 6.4 after 9 months. The 95% confidence interval for the

change from baseline in the WSN-K Total score at 6 months and at 9 months was entirely outside zero and thus statistically significant but the difference in total WSN-K score at 6 months and at 9 months only approached the level of clinical relevance, defined as an increase of 8.

Efficacy results: PANSS-8 and symptom resolution

The Positive and Negative Symptoms Scale (PANSS-8) scores improved (decreased) during the course of the study (see Table 4), all three subscales showed a statistically significant improvement at all visits and at End of Study.

Table 4 Efficacy: PANSS-8

	Visit 1	Visit 2	Visit 3	Visit 4	End of Study	Change from baseline to End of Study
	n = 94	n = 86	n = 58	n = 46	n = 87	n = 85
Positive	8.2 (4.0)	7.1 (3.3)	6.2 (2.5)	5.6 (2.5)	6.6 (3.0)	-1.4 (3.7) [-2.2 – -0.6] *
Negative	11.0 (3.6)	9.9 (3.5)	9.4 (3.0)	9.1 (3.5)	9.4 (3.5)	-1.6 (2.7) [-2.2 – -1.0] *
General	4.8 (2.5)	4.1 (2.1)	4.0 (2.1)	3.6 (1.8)	4.0 (2.1)	-0.7 (2.0) [-1.1 – -0.2] *

Data as Mean (SD) and for the change from baseline as [95% Confidence Interval]; * statistically significant

Resolution of symptoms of schizophrenia is present when all eight questions of the PANSS (which is rated from 1 – 7) are scored ≤ 3 . The proportion of patients with symptom resolution increased from 17.2% at baseline to 43.5% of patients at visit 4. In Table 5 the number and proportion of patients in the study who fulfilled this criterion of symptom resolution is shown.

Table 5 Efficacy: Symptom resolution^a, based on PANSS-8

	Visit 1	Visit 2	Visit 3	Visit 4	End of Study
Total n	n = 93	n = 86	n = 58	n = 46	n = 87
n (%)	16 (17.2%)	27 (31.4%)	21 (36.2%)	20 (43.5%)	32 (36.8%)

^a Symptom resolution is defined as all 8 questions in PANSS-8 scored 3 or less

Efficacy results: Global Assessment of Functioning (GAF)

The Global Assessment of Functioning (GAF) is a score on functioning, ranging from 1 (persistent danger) to 100 (superior functioning). The mean GAF score improved during the course of the study (see Table 6), at all follow-up visits the change from baseline in GAF was statistically significant.

Table 6 Efficacy: GAF at study visits and as change from baseline

Visit 1	Visit 2	Visit 3	Visit 4	End of Study
n = 97	n = 88	n = 60	n = 47	n = 88
52.5 (12.6)	54.4 (11.4)	56.9 (11.6)	57.0 (10.5)	55.7 (12.2)
Change from baseline	3.1 (7.9) [1.4–4.8] *	5.1 (11.4) [2.2–8.1] *	5.8 (11.1) [2.6–9.1] *	4.4(11.5) [1.9 – 6.8] *

Data as Mean (SD) and for the change from baseline [95% Confidence Interval]; * statistically significant

Efficacy results: disease insight

Disease insight was assessed with the G12 question from the PANSS. The scores on this G12 question did not change substantially during the study. The change (a decrease, thus improvement) from baseline to Visit 4 was statistically significant, but the change to End of Study was not statistically significant.

Table 7 Efficacy: Disease insight score at study visits and as change from baseline

Visit 1	Visit 2	Visit 3	Visit 4	End of Study
n = 97	n = 88	n = 61	n = 47	n = 88
2.8 (1.4)	2.7 (1.3)	3.0 (1.3)	2.6 (1.2)	2.6 (1.2)
Change from baseline	-0.1(1.0) [-0.3 – 0.1]	-0.0 (1.3) [-0.4 – 0.3]	-0.4 (1.2) [-0.7 – -0.0] *	-0.2 (1.0) [-0.4 – 0.0]

Data as Mean (SD) and for the change from baseline [95% Confidence Interval]; * :statistically significant

Efficacy results: functioning

Most patients with data at the end of the study used the same type of concomitant medication and concomitant therapies at baseline and at the end of the study, exceptions were a net decrease of 14.4% of patients with data in the use of antidepressants, a net decrease of 16.5% in the use of benzodiazepines, a net decrease of 28.9% in the number of patients receiving general psychotherapy and a net decrease of 39.1% in the number of patients receiving psycho-education. Of patients with data at the end of the study there was a net decrease of 6.9% of patients who were substance abuser. There were limited changes in the working situation of the patients at the end of the study, compared to baseline, except for 6 patients (6.8%) having no work at baseline and working in a sheltered workshop at the end of the study. Few patients changed in their school situation, though a net increase of 2 patients following courses and 2 patients visiting a regular school at the end of the study. Similar, few patients changed in their living situation. The last year prior to the study, 24 out of the 97 patients (24.7%) had been hospitalised for some time, at visit 2, 3 and 4 respectively a decreasing number of 19 out of 89 (21.3%), 5 out of 60 (8.3%) and 1 out of 46 (2.2%) respectively of those patients available for analysis at that visit had been hospitalised since the previous visit.

Efficacy, in summary.

Of all patients enrolled, 39% had missing data at baseline for the primary efficacy analysis and of those with baseline data there was a drop-out rate of 53% during this 9-months' non-intervention study, which was larger than expected. Furthermore, enrolment into the study was ended before the anticipated number of evaluable patients was reached. These facts complicate the interpretation of the study. The analysis of the primary objective of the study (investigating the subjective well-being using the SWN-K scale) did show a statistically significant change for the Total score and for the sub-scores Self-control and Social integration. The magnitude of effect in the Total SWN-K, though gradually increasing during

continued follow-up and reaching statistical significance, was smaller than the limit of being clinically relevant. For the secondary objectives, symptoms, as assessed with the PANSS-8 showed a gradual and statistically significant decrease and there was a gradual increase in the number and proportion of patients with symptoms resolution. Clinical benefit, assessed with the GAF, gradually increased during the study and the change from baseline to End of Study in GAF was statistically significant. There was a decrease in the proportion of patients who was hospitalised. There was a modest improvement in disease insight. Functioning with respect to work, school, living situation and concomitant treatments were either unchanged or showed small improvements.

Potential differences between the different antipsychotic treatments were not analysed.

Safety results

Since this was a Non Intervention Study no safety data were actively gathered. Adverse effects noted on treatment with quetiapine could be reported to AstraZeneca. No adverse effects were reported to AstraZeneca, though 5 of the 158 enrolled patients were withdrawn from the study due to adverse effects. No information was available on the reporting of adverse effects on the other AAPs.