ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 06/21/2012

ClinicalTrials.gov ID: NCT01213836

Study Identification

Unique Protocol ID:	D1443L00082
Brief Title:	Compare the Effect on Cognitive Functioning of Two Formulations of Seroquel, Seroquel XR and IR in Patients With Stable Schizophrenia (eXtRa)
Official Title:	A Phase IV Prospective, Double-blind, Double-dummy, Randomised, Crossover Study to Assess the Impact on Daily Cognitive Functioning of Quetiapine Fumarate Immediate Release (Seroquel IR®) Dosed Twice Daily and Quetiapine Fumarate Extended Release (Seroquel XR®) Dosed Once Daily in the Evening in Patients With Stable Schizophrenia
Secondary IDs:	2010-020579-21 [EudraCT Number]

Study Status

Record Verification:	May 2012
Overall Status:	Completed
Study Start:	November 2010
Primary Completion:	August 2011 [Actual]
Study Completion:	August 2011 [Actual]

Sponsor/Collaborators

Sponsor:	AstraZeneca
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 18.08.2010 Board Name: Ethik-Kommission der Medizinischen Universität Wien Board Affiliation: Ethik-Kommission der Medizinischen Universität Wien Phone: 0043 1 404 00-2147 Email: Ethic-kom@meduniwien.ac.at
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Austria: Agency for Health and Food Safety Germany: Federal Institute for Drugs and Medical Devices Italy: National Monitoring Centre for Clinical Trials - Ministry of Health Spain: Spanish Agency of Medicines

Study Description

Brief Summary:	This will be a phase IV 20 –32 day prospective, double blind, double-dummy, randomised crossover study that will evaluate the effect of quetiapine XR and quetiapine IR on cognitive performance in patients with schizophrenia stabilized on a single antipsychotic medication.
Detailed Description:	

Conditions

Conditions:	Schizophrenia
Keywords:	Stable schizophrenia cognitive functioning

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase:	Phase 4
Intervention Model:	Crossover Assignment
Number of Arms:	2
Masking:	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	75 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: First Seroquel XR then Seroquel IR Patients randomised to Seroquel XR will have treatment for 10-16 days and after that cross-over to treatment with Seroquel IR for 10-16 days	Drug: Seroquel XR- quetiapine fumarate extended release Seroquel XR dose 400-700 mg (in tablet form). The investigator established the dosing schedule for each patient depending on the patient's dose when entering the study. The patients continued on the same dose during the study as they had prior to enrolment. Dose taken once a day for 10-16 days. Drug: Seroquel IR - quetiapine fumarate Seroquel IR dose 400-700 mg (in tablet form). The investigator established the dosing schedule for each patient depending on the patient's dose when entering the study. The patients continued on the same dose during the study as they had prior to enrolment. Dose taken twice a day for 10-16 days. Drug: Placebo matching Seroquel XR Placebo matching Seroquel XR dose 400-700 mg (in tablet form). Dose taken once a day for 10-16 days. Drug: Placebo matching Seroquel IR Placebo matching Seroquel IR dose 400-700 mg (in tablet form). Dose taken twice a day for 10-16 days.
Active Comparator: First Seroquel IR then Seroquel XR Patients randomised to Seroquel IR will have treatment for 10-16 days and after that cross-over to treatment with Seroquel XR for 10-16 days	Drug: Seroquel XR- quetiapine fumarate extended release Seroquel XR dose 400-700 mg (in tablet form). The investigator established the dosing schedule for each patient depending on the patient's dose when entering the study. The patients continued on the same dose during the study as they had prior to enrolment. Dose taken once a day for 10-16 days. Drug: Seroquel IR - quetiapine fumarate Seroquel IR dose 400-700 mg (in tablet form). The investigator established the dosing schedule for each patient depending on the patient's dose when entering the study. The patients continued on the same dose during the study as they had prior to enrolment. Dose taken twice a day for 10-16 days.

Arms	Assigned Interventions
	Drug: Placebo matching Seroquel XR Placebo matching Seroquel XR dose 400-700 mg (in tablet form). Dose taken once a day for 10-16 days. Drug: Placebo matching Seroquel IR Placebo matching Seroquel IR dose 400-700 mg (in tablet form). Dose taken twice a day for 10-16 days.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 50 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Provision of written informed consent prior to any study specific procedures
- Documented clinical diagnosis of schizophrenia, paranoid type, for at least 2 years before randomisation meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV, American Psychiatric Association 2000) criteria of schizophrenia (DSM-IV codes 295.3) confirmed by MINI version 5.0
- Outpatient status at enrolment
- Dose of quetiapine IR or quetiapine XR unchanged during the last 56 days before randomisation

Exclusion Criteria:

- Diagnosis of any DSM-IV Axis I disorder other than those included in inclusion criteria above within 6 months before randomisation (e.g., alcohol dependence or psychoactive substance dependence not in full remission, concurrent organic mental disorder, or mental retardation [axis II diagnosis]) of a degree that may interfere with the patient's ability to co-operate.
- Previous stable use of high dosage of benzodiazepines during one year or more
- Significant neurological medical history (complicated head trauma as judged by the investigator, epilepsy, meningo-encephalitis)
- Use of the following medication:
- other antipsychotic drug than quetiapine within 28 days prior to randomisation
- a depot antipsychotic injection within two dosing intervals (for the depot) before randomisation (Visit 2)
- other psychoactive drugs within 14 days prior to randomisation (hypnotic or anxiolytic drugs, other than those allowed)
- Use of concomitant therapy likely to affect cognition, Medication prohibited 28 days prior to randomisation: benzodiazepines, amphetamines, reboxitin, atomoxinetine, buspiron, donepezil, duloxetine, galantamine, ginko biloba, memantine, methylphenidate, modafinil, rivastigmine, tacrine, smoking cessation therapy varencicline and any dosage form

of nicotine replacement therapy. Medication prohibited 14 days prior to randomisation: irreversible monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TCA), biperiden, antoicholinergic agents (even if the indications are extra pyramidal symptoms or urinary symptoms)

Contacts/Locations

Study Officials: Eva Dencker Vansvik
Study Director
AstraZeneca

Locations: Austria
Research Site
Salzburg, Austria

Research Site
Wien, Austria

Germany
Research Site
Berlin, Germany

Research Site
Bochum, Germany

Research Site
Hamburg, Germany

Research Site
Munchen, Germany

Research Site
Rottweil, Germany

Italy
Research Site
Giarre, CT, Italy

Research Site
Genova, GE, Italy

Research Site
Lido Di Camaiore, LU, Italy

Research Site

Torre Annunziata, Italy

Research Site
Tivoli, RM, Italy

Research Site
Sant'arsenio, SA, Italy

Research Site
Sassari, SS, Italy

Research Site
Catania, Italy

Spain
Research Site
Salamanca, Castilla Leon, Spain

Research Site
Zamora, Castilla Leon, Spain

Research Site
Cuenca, Cuenca, Spain

Italy
Research Site
Barakaldo (vizcaya), Pais Vasco, Italy

Research Site
La Corredoria, Asturias, Italy

Research Site
Borgomanero, NO, Italy

Research Site
Roma, Italy

Denmark
Research Site
Middelfart, Denmark

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	Patients were recruited at 20 study centres in 5 countries: Austria (1 site), Denmark (1 site), Germany (6 sites), Italy (9 sites) and Spain (3 sites). Recruitment started 2 November 2010 and was completed 29 June 2011. The last patient completed the study on 3 August 2011.
Pre-Assignment Details	Screening (0 days to 14 days before enrolment), enrolment at Visit 1 (14 days to 3 days prior to randomisation), randomisation at Visit 2 after confirmation of eligibility. 75 patients were screened/enrolled. Of these, 9 were not randomised; 2 patients due to own decision to discontinue and 7 patients due to eligibility criteria not fulfilled.

Reporting Groups

	Description
First Seroquel XR Then Seroquel IR	Patients randomised to Seroquel XR will have treatment for 10-16 days and after that cross-over to treatment with Seroquel IR for 10-16 days
First Seroquel IR Then Seroquel XR	Patients randomised to Seroquel IR will have treatment for 10-16 days and after that cross-over to treatment with Seroquel XR for 10-16 days

Period 1, First Intervention

	First Seroquel XR Then Seroquel IR	First Seroquel IR Then Seroquel XR
Started	34	32
Completed	31	29
Not Completed	3	3
Adverse Event	2	1
Protocol Violation	0	1
Withdrawal by Subject	1	1

Period 2, Second Intervention

	First Seroquel XR Then Seroquel IR	First Seroquel IR Then Seroquel XR
Started	31	29

	First Seroquel XR Then Seroquel IR	First Seroquel IR Then Seroquel XR
Completed	31	29
Not Completed	0	0

Baseline Characteristics

Reporting Groups

	Description
First Seroquel XR Then Seroquel IR	Patients randomised to Seroquel XR will have treatment for 10-16 days and after that cross-over to treatment with Seroquel IR for 10-16 days
First Seroquel IR Then Seroquel XR	Patients randomised to Seroquel IR will have treatment for 10-16 days and after that cross-over to treatment with Seroquel XR for 10-16 days

Baseline Measures

	First Seroquel XR Then Seroquel IR	First Seroquel IR Then Seroquel XR	Total
Number of Participants	34	32	66
Age, Continuous [1] [units: participants]			
between 18 and 29 years	6	3	9
Between 30 and 50 years	26	28	54
>50 years	2	0	2
Age, Continuous [2] [units: years] Mean (Standard Deviation)	38.6 (8.2)	37.0 (5.2)	37.8 (6.9)
Gender, Male/Female [3] [units: participants]			
Female	11	9	20
Male	23	22	45
Region of Enrollment [units: participants]			
Spain	1	1	2
Denmark	1	1	2
Austria	1	2	3

	First Seroquel XR Then Seroquel IR	First Seroquel IR Then Seroquel XR	Total
Germany	18	10	28
Italy	13	18	31

[1] Of the 66 patients randomised to treatment with XR or IR only 65 patients took any study drug. One patient withdrew before taking any study drug. 65 patients were analysed for baseline age.

[2] Of the 66 patients randomised to treatment with XR or IR only 65 patients took any study drug. One patient withdrew before taking any study drug. 65 patients were analysed for baseline measure age.

[3] Of the 66 patients randomised to treatment with XR or IR only 65 patients took any study drug. One patient withdrew before taking any study drug. 65 patients were analysed for baseline measure gender.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Mean for Attentional Standardised Composite Score Based on Performance Scores From the CogState Test Battery Domains Detection (Speed of Processing)and Identification (Attention/Vigilance)
Measure Description	Attentional standardised composite score: Standardised speed of performance score. Higher Score=better performance. Score range minus infinity to plus infinity. Measured at baseline (before study drug administration) and in Period 1 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period. (Last test day not earlier than after 10 days of randomised)and in Period 2 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period. Last test day not earlier than after 10 days of crossover treatment.
Time Frame	Period 1 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period. Period 2 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period.
Safety Issue?	No

Analysis Population Description

The per protocol set (PPS) is a subset of the FAS consisting of patients who fulfilled all inclusion criteria but none of the exclusion criteria, complied with study medication dosing scheme, did not violate any of the study restrictions and completed the study without protocol violation.

Reporting Groups

	Description
Seroquel XR	Patients that took Seroquel XR in arm XR-IR and arm IR-XR.
Seroquel IR	Patients that took Seroquel XR in arm XR-IR and arm IR-XR.

Measured Values

	Seroquel XR	Seroquel IR
Number of Participants Analyzed	51	51
Mean for Attentional Standardised Composite Score Based on Performance Scores From the CogState Test Battery Domains Detection (Speed of Processing)and Identification (Attention/Vigilance) [units: standardised units] Mean (Standard Deviation)		
Post 1	0.002 (0.856)	-0.098 (0.983)
Post 2	-0.201 (1.054)	-0.131 (1.053)
Post 3	-0.194 (1.040)	-0.120 (1.100)

2. Secondary Outcome Measure:

Measure Title	Mean Treatment Satisfaction for Treatment Satisfaction Questionnaire of Medication (TSQM)
Measure Description	TSQM is a 14-item questionnaire with 4 sub-scales: effectiveness of the medication; treatment side effects; convenience of the medication; global satisfaction with the medication. Scale range 0-100 for each sub-scale, higher=greater satisfaction/milder side effects/greater convenience/greater overall satisfaction. There are 2 measurement, (after the start of taking study drug) one at end of period 1 and one at end of period 2. That is one measurement per patient per treatment. The mean of all the patients is presented, one mean value per treatment group.
Time Frame	Before taking study drug, end of Period 1 and end of Period 2
Safety Issue?	No

Analysis Population Description

Full Analysis Set (FAS)used for efficacy analysis included all patients who in both study periods, received at least 1 dose of investigational product and for whom post-dose efficacy data was available.

Reporting Groups

	Description
Seroquel XR	Patients that took Seroquel XR in arm XR-IR and arm IR-XR.
Seroquel IR	Patients that took Seroquel IR in arm XR-IR and arm IR-XR.

Measured Values

	Seroquel XR	Seroquel IR
Number of Participants Analyzed	60	59
Mean Treatment Satisfaction for Treatment Satisfaction Questionnaire of Medication (TSQM) [units: units on a scale] Mean (Standard Deviation)		
Side Effects	87.9 (20.5)	81.5 (27.5)
Effectiveness	65.4 (16.8)	62.2 (19.1)
Convenience	66.2 (19.3)	63.6 (19.7)
Overall Satisfaction	63.0 (19.7)	58.9 (21.1)

3. Secondary Outcome Measure:

Measure Title	Mean Daytime Cognitive Performance Using CogState: - Working Memory - Verbal Learning) -Reasoning and Problem Solving
Measure Description	International Shopping List Task (ISLT): measures reasoning and problem solving. Min=minus infinity, max=plus infinity, higher score=better performance. Groton Maze Learning Test (GMLT): measures reasoning and problem solving. Min=minus infinity, max=plus infinity, lower score=better performance. Lower=better performance. One Back memory task (ONB: measures working memory, min=minus infinity, max=plus infinity, lower score=better performance.
Time Frame	Period 1 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period. Period 2 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period.
Safety Issue?	No

Analysis Population Description

Per Protocol (PPS), subset of the FAS consisting of patients who fulfilled all of inclusion but none of exclusion criteria, complied with study medication dosing, did not violate any of the restrictions and completed the study without protocol violation.

Reporting Groups

	Description
Seroquel XR	Patients that took Seroquel XR in arm XR-IR and arm IR-XR.
Seroquel IR	Patients that took Seroquel IR in arm XR-IR and arm IR-XR.

Measured Values

	Seroquel XR	Seroquel IR
Number of Participants Analyzed	51	51
Mean Daytime Cognitive Performance Using CogState: - Working Memory - Verbal Learning) - Reasoning and Problem Solving [units: Units on a scale] Mean (Standard Deviation)		
ISLT post 1	24.020 (5.746)	23.588 (5.787)
ISLT post 2	23.551 (4.899)	23.152 (5.562)
ISLT post 3	23.216 (5.360)	22.920 (4.944)
GMLT post 1	64.180 (29.822)	61.040 (28.721)
GMLT post 2	59.021 (21.257)	56.956 (21.798)
GMLT post 3	57.229 (24.162)	57.300 (22.307)
ONB post 1	2.875 (0.143)	2.897 (0.134)
ONB post 2	2.896 (0.151)	2.896 (0.169)
ONB post 3	2.894 (0.161)	2.893 (0.154)

4. Secondary Outcome Measure:

Measure Title	Mean Overall Sedation as Measured by the Modified Bond-Lader Visual Analogue Scale (VAS) When Administered According to Label
Measure Description	The modified Bond-Lader VAS: The degree of sedation was marked by the patient on a 100 mm VAS ranging between Alert (=0 mm) and Drowsy (=100 mm). The marked length in millimetres. There are 3 assessments made in each period (post 1, 2 and 3 for each period). That is three measurements per patient per treatment. The mean is an overall mean of all the recordings in all patients, one mean value per treatment group.
Time Frame	Period 1 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period. Period 2 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period.
Safety Issue?	No

Analysis Population Description

The full analysis set (FAS) used for analysis of efficacy included all patients who, in both study periods, received at least one dose of investigational product and for whom post-dose efficacy data are available in both periods.

Reporting Groups

	Description
Seroquel XR	Patients that took Seroquel XR in arm XR-IR and arm IR-XR.
Seroquel IR	Patients that took Seroquel IR in arm XR-IR and arm IR-XR.

Measured Values

	Seroquel XR	Seroquel IR
Number of Participants Analyzed	60	60
Mean Overall Sedation as Measured by the Modified Bond-Lader Visual Analogue Scale (VAS) When Administered According to Label [units: units on a scale] Mean (Standard Deviation)	23.5 (19.0)	28.6 (21.4)

5. Secondary Outcome Measure:

Measure Title	Mean Overall Sedation as Measured by the Stanford Sleepiness Scale When Administered According to Label
Measure Description	Stanford Sleepiness Scale: The sleepiness was assessed by the patient on a 7 item rating scale ranging from 1 (Feeling active and vital) to 7 (Almost in reverie). There are 3 assessments made in each period (post 1, 2 and 3 for each period). That is three measurements per patient per treatment. The mean is an overall mean of all the recordings in all patients, one mean value per treatment group.
Time Frame	Period 1 at 3 visits,(post 1),(post 2),(post 3), in a 5-day (maximum 8 day) period. Period 2 at 3 visits,(post 1),(post 2), (post 3), in a 5-day (maximum 8 day) period.
Safety Issue?	No

Analysis Population Description

The full analysis set (FAS) used for analysis of efficacy included all patients who, in both study periods, received at least one dose of investigational product and for whom post-dose efficacy data are available in both periods.

Reporting Groups

	Description
Seroquel XR	Patients that took Seroquel XR in arm XR-IR and arm IR-XR.
Seroquel IR	Patients that took Seroquel IR in arm XR-IR and arm IR-XR.

Measured Values

	Seroquel XR	Seroquel IR
Number of Participants Analyzed	60	60
Mean Overall Sedation as Measured by the Stanford Sleepiness Scale When Administered According to Label [units: units on a scale] Mean (Standard Deviation)	2.4 (0.9)	2.6 (1.0)

6. Secondary Outcome Measure:

Measure Title	Number of Dropouts.
Measure Description	The number of patients who dropped out was counted.
Time Frame	Period 1 and Period 2
Safety Issue?	No

Analysis Population Description

The Safety analysis set was used, that is all patients who received at least one dose of study medication and for whom any post-dose safety data are available were included in the safety set.

Reporting Groups

	Description
Seroquel XR	Patients treated with at least one dose of Seroquel XR
Seroquel IR	Patients treated with at least one dose of Seroquel IR

Measured Values

	Seroquel XR	Seroquel IR
Number of Participants Analyzed	34	31
Number of Dropouts. [units: participants]		
Period 1	3	2
Period 2	0	0

7. Secondary Outcome Measure:

Measure Title	Mean Ratio of Morning Plasma Concentration of Quetiapine and Nor-quetiapine for Quetiapine IR and Quetiapine XR, at Steady-state Conditions in the End of Each Treatment Period 1 and 2.
Measure Description	The ratio was derived as individual plasma concentration of quetiapine divided by the plasma concentration of nor-quetiapine. The mean ratio was derived for each treatment, XR and IR, respectively.
Time Frame	End of Period 1, end of Period 2
Safety Issue?	No

Analysis Population Description

21 patients for the FAS were analysed. This outcome measure was introduced as a protocol amendment after study start and plasma concentration was not measured in all patients. FAS is all patients who, in both study periods, received at least one dose of investigational product and for whom post-dose efficacy data are available in both periods.

Reporting Groups

	Description
Seroquel XR	Patients that took Seroquel XR in arm XR-IR and arm IR-XR.
Seroquel IR	Patients that took Seroquel IR in arm XR-IR and arm IR-XR.

Measured Values

	Seroquel XR	Seroquel IR
Number of Participants Analyzed	21	21
Mean Ratio of Morning Plasma Concentration of Quetiapine and Nor-quetiapine for Quetiapine IR and Quetiapine XR, at Steady-state Conditions in the End of Each Treatment Period 1 and 2. [units: Ratio] Mean (Standard Deviation)	1.941 (1.504)	2.128 (2.369)

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	[Not specified]

Reporting Groups

	Description
Seroquel XR	Patients treated with at least one dose of Seroquel XR
Seroquel IR	Patients treated with at least one dose of Seroquel IR

Serious Adverse Events

	Seroquel XR		Seroquel IR	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	0/63 (0%)		0/62 (0%)	

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 1%

	Seroquel XR		Seroquel IR	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	4/63 (6.35%)		4/62 (6.45%)	
Blood and lymphatic system disorders				
neutropenia [A] *	0/63 (0%)	0	1/62 (1.61%)	1
Cardiac disorders				
tachycardia [A] *	0/63 (0%)	0	1/62 (1.61%)	1
Ear and labyrinth disorders				
vertigo [A] *	1/63 (1.59%)	1	0/62 (0%)	0
General disorders				
fatigue [A] *	0/63 (0%)	0	1/62 (1.61%)	1
Investigations				
heart rate increase [A] *	0/63 (0%)	0	1/62 (1.61%)	1
Nervous system disorders				
dizziness [A] *	0/63 (0%)	0	1/62 (1.61%)	1
sedation [A] *	1/63 (1.59%)	1	0/62 (0%)	0
somnolence [A] *	1/63 (1.59%)	1	2/62 (3.23%)	2

	Seroquel XR		Seroquel IR	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Psychiatric disorders				
delusion [A] *	0/63 (0%)	0	1/62 (1.61%)	1
psychotic disorder [A] *	1/63 (1.59%)	1	0/62 (0%)	0
sleep disorder [A] *	1/63 (1.59%)	1	0/62 (0%)	0

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (14.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

Results Point of Contact:

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