AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Quetiapine fumarate
Study Code	D1443L00082
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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

Study dates: First patient enrolled: 2 November 2010
Last patient last visit: 3 August 2011

Phase of development: Therapeutic use (IV)

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

Study centre(s)

In total, 20 study centres recruited patients in this study. The following 5 countries participated: Austria (1 site), Denmark (1 site), Germany (6 sites), Italy (9 sites) and Spain (3 sites).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives and criteria for evaluation are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To demonstrate that patients with stable schizophrenia show superior daytime cognitive performance when taking quetiapine XR once daily in the evening compared to taking quetiapine IR twice daily by using the CogState Test Battery domains Detection (speed of processing) and Identification (attention/vigilance) administered according to existing label.	Attentional standardised composite score based on performance scores from the CogState Test Battery domains Detection (speed of processing) and Identification (attention/vigilance)	Efficacy
Secondary	**Secondary**	
To assess treatment satisfaction for patients with stable schizophrenia on quetiapine XR and quetiapine IR by using the Treatment Satisfaction Questionnaire of Medication (TSQM)	Treatment Satisfaction Questionnaire of Medication (TSQM)	PRO
To assess differences in daytime cognitive performance with quetiapine IR and XR administered according to label using CogState: One back memory task (working memory) International shopping list task (verbal learning) Groton Maze learning test (reasoning and problem solving)	One back memory task (working memory) International shopping list task (verbal learning) Groton Maze learning test (reasoning and problem solving) Detection (speed of processing) and Identification (attention/vigilance),	Efficacy
To assess differences with quetiapine IR and XR (when administered according to label) in overall sedation as measured by the modified Bond-Lader visual analogue scale (VAS)	The modified Bond-Lader VAS	PRO

Objectives	Outcome variables	Type
To assess differences with quetiapine IR and XR (when administered according to label) in overall sedation as measured by the Stanford Sleepiness Scale (SSS)	Stanford Sleepiness Scale (SSS)	PRO
To evaluate the difference in dropout rate between treatment with quetiapine IR or quetiapine XR when administered according to label overall and taking into consideration treatment (quetiapine IR or quetiapine XR) prior to enrolment in the study	Difference in dropout rate	Efficacy
To determine 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	The ratio of plasma concentration of quetiapine/nor-quetiapine in steady state conditions will be estimated for each treatment regimen (IR and XR) within each patient)	Pharmaco kinetic
Safety	**Safety**	
To assess the safety and tolerability during treatment with quetiapine XR and treatment with quetiapine IR administered according to label in patients with stable schizophrenia by incidence of Adverse Events (AE) and changes in laboratory values, vital signs and weight from enrolment to end of study.	Incidence of AEs (including SAEs and AEs of special interest[a]) Changes in laboratory values, vital signs and weight	Safety

[a] AEs of special interest included suicidality, including events of suicide attempts, suicidal ideation, completed suicides and suicidal behaviour.

AE Adverse event; IR Instant release; PRO Patient reported outcomes; SAE Serious adverse event; XR Extended release

Study design

This was a phase IV, 20 –32 day prospective, double-blind, double-dummy, randomised crossover study evaluating the effect of quetiapine XR and quetiapine IR on cognitive performance in patients with schizophrenia stabilized on a single antipsychotic medication.

Target subject population and sample size

The target patient population was males and females, ≥18 and ≤50 years old, with documented diagnosis of schizophrenia and currently treated with quetiapine IR twice daily or quetiapine XR once daily in the evening (i.e. treated with quetiapine IR or XR according to label in a dose range between 400-750 mg).

The total number of patients n* required for a two-period crossover study with a specified power was defined by formula $n^*=n(1-R)/2$, where $R=\sigma_s^2 / \sigma_s^2 + \sigma_e^2$ and σ_s - patient-to-patient variability and σ_e - intrasubject variability, and n number of patients per group required for a parallel groups study with the same power according to Fleiss (Source: The design and analysis of clinical experiments, Joseph L. Fleiss, p.369 Sample Size Determination).

Assuming medium effect on primary response variable in patients with stable schizophrenia, estimated as a change of 0.6 to 1.0 on Cohen's d, and R-intraclass correlation coefficient=0.1, 29 patients per group were needed to reject the statistical null hypothesis of no difference at a power of 80% when using a 2-sided t-test at a significance level of 5%. Thus, a total of 58 evaluable patients were needed. In order to ensure 29 evaluable patients in each treatment arm, enrolment continued until 90 patients (corresponding to a drop-out rate of 35%) had been randomised or 60 patients had completed the study, which ever came first.

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

Details of investigational product are shown in Table S2.

Table S2 Details of investigational product

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Formulation number	Batch number	Formulation number	Batch number
			Labelled Lot: E07790-01		Labelled Lot: E07790-02	
Quetiapine IR	Quetiapine IR 25 mg tablets	AstraZeneca	F012804	PJ4600	F012804	PJ4600
	Quetiapine IR 25 mg placebo tablets		F012636	NH4604	F012636	NN4604
	Quetiapine IR 100 mg tablets		F012689	NN4601	F012689	NN4600
	Quetiapine IR 100 mg placebo tablets		F012637	NH4605	F012637	TM4601
	Quetiapine IR 200 mg tablets		F012690	NN4601	F012690	NN4601
	Quetiapine IR 200 mg placebo tablets Administered orally		F012638	NH4607	F012638	TM4602
Quetiapine XR	Quetiapine XR 50 mg tablets	AstraZeneca	F013219	FY301X	F013219	FY301X
	Quetiapine XR 50 mg placebo tablets		F012903	DT835X	F012903	FY897X
	Quetiapine XR 200 mg tablets		F012840	NL4621	F012840	NL4621
	Quetiapine XR 200 mg placebo tablets		F012422	DT841X	F012422	DT841X
	Quetiapine XR 300 mg tablets		F012527	NL4603	F012527	NL4603
	Quetiapine XR 300 mg placebo tablets Administered orally		F012416	DT843X	F012416	FY900X

The tablets contained lactose monohydrate, which may have caused discomfort in lactose-intolerant patients.
Labelled Lot: the batch number printed on the wallets
IR Immediate release; XR Extended release

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. The site personnel filled in the number of tablets the patient were to take each day on the wallet inside label. The IR/placebo tablets were to be taken twice daily (in the morning between 8.00 and 10.00 and in the evening between 20.00 and 22.00) and the XR tablets were to be taken once daily in the evening (between 20.00 and 22.00). It was recommended that the morning dose were taken in the clinic the days of CogState testing. The dosing schedule is described in detail in Table S3.

Table S3 Dosing schedule

Daily dose (mg)	Quetiapine IR/placebo		Quetiapine XR/placebo
	Morning	Evening	Evening
400	1×200 mg	1×200 mg	2×200 mg
450	1×25 mg 1×200	1×25 mg 1×200	1×50 mg 2×200 mg
500	2×25 mg 1×200 mg	2×25 mg 1×200 mg	1×200 mg 1×300 mg
550	3×25 mg 1×200 mg	3×25 mg 1×200 mg	1×50 mg 1×200 mg 1×300 mg
600	1×100 mg 1×200 mg	1×100 mg 1×200 mg	2×300 mg
650	1×25 mg 1×100 mg 1×200 mg	1×25 mg 1×100 mg 1×200 mg	1×50 mg 2×300 mg
700	2×25 mg 1×100 mg 1×200 mg	2×25 mg 1×100 mg 1×200 mg	2×200 mg 1×300 mg
750	3×25 mg 1×100 mg 1×200 mg	3×25 mg 1×100 mg 1×200 mg	1×50 mg 2×200 mg 1×300 mg

IR Immediate release; XR Extended release

Duration of treatment

This was a phase IV, 20 –32 day prospective, double-blind, double-dummy, randomised crossover study evaluating the effect of quetiapine XR and quetiapine IR on cognitive performance in patients with schizophrenia stabilized on a single antipsychotic medication.

The patients remained on the dose (400-750 mg) of quetiapine they were taking prior to enrolment, and they were randomised to quetiapine XR or quetiapine IR (Period 1). The patients were treated for five to eight days (5-8 days) and then underwent CogState Cognition testing three times during the next 5-8 days. At the conclusion of the testing, the patients were crossed over to 5-8 days of the alternate quetiapine treatment arm (Period 2) and underwent CogState Cognition testing three times over the next 5-8 days, and continued taking their dose of quetiapine XR or IR.

Statistical methods

The primary efficacy data was analysed using a linear mixed model, where the Period 1 baseline score was modelled as a covariate, with treatment, period, sequence, assessment and the stratification factor (i.e. treatment prior to study start) as fixed factors in the model. Patient within period and centre were modelled as random effects. The Per Protocol Set (PPS) was the primary analysis set used for the primary variable, whereas the Full Analysis Set (FAS) was used for a secondary analysis.

Secondary variables were analysed using the same linear mixed model as the primary variable, but was based on the FAS. This analysis was to be regarded as an exploratory analysis. The significance level was not adjusted for secondary endpoints.

Summary statistics and graphic methods were used to display the data.

Subject population

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.

In total, 75 patients were enrolled in this crossover study and 66 patients (88%) were randomised. Nine patients discontinued during the enrolment period. The reasons for discontinuing were voluntary discontinuation (2 patients) and eligibility criteria not fulfilled (7 patients). The disposition of the randomised patients starting on either quetiapine XR in Period 1 and then crossed over to quetiapine IR in Period 2 (hereafter referred to as treatment sequence quetiapine XR-IR), or starting on quetiapine IR in Period 1 and then crossed over to quetiapine XR in Period 2 (hereafter referred to as treatment sequence quetiapine IR-XR) is shown in Table S4:

Table S4 Disposition of randomised patients and reasons for not completing the treatment period

	Quetiapine XR in Period 1 – Quetiapine IR in Period 2	Quetiapine IR in Period 1 – Quetiapine XR in Period 2	Total
Number of patients entering the treatment sequences	34 (51.5%)	32 (48.5%)	66
Number of patients completing the study	31 (91.2%)	29 (90.6%)	60 (90.9%)
Number of patients discontinuing the study	3 (8.8%)	3 (9.4%)	6 (9.1%)
Main reason for discontinuation			
Patient decision	1	1	2
Adverse event	2	1	3
Severe non-compliance to CSP		1	1

[a] One randomised patient never started study treatment.
CSP Clinical study protocol; IR Immediate release; XR Extended release

Of the 66 randomised patients, one patient never took any dose of study medication after randomisation, i.e. the safety analysis set comprised 65 patients (98.5%) with 34 patients (100%) in the treatment sequence quetiapine XR-IR and 31 patients (96.9%) in the treatment sequence quetiapine IR-XR. The FAS comprised 60 patients (90.9%) excluding three patients from each treatment sequence, all due to not being treated with at least one dose of study drug in both periods, and not having CogState data in both periods and at baseline. The PPS comprised 51 patients (77.3%) with 26 patients (76.5%) in the treatment sequence quetiapine XR-IR and 25 patients (78.1%) in the treatment sequence quetiapine IR-XR.

In general, the treatment sequences were balanced with respect to demographics and baseline characteristics. Of the 65 randomised patients who took at least one dose of study medication, 69.2% (n=45) were male and 30.8% (n=20) were female. The mean (sd) age was 37.8 (6.9) years. Overall, 83.1% (n=54) of the patients were in the age category between 30 and 50 years. The majority of patients were white (95.4%, n=62).

Summary of efficacy results

Primary variable

There were no differences between treatment with quetiapine XR and quetiapine IR for the primary objective of cognitive function in CogState attentional composite score (domains Detection - speed of processing and Identification -attention/vigilance). The data indicated that quetiapine XR was not significantly superior to quetiapine IR in daytime cognitive

performance, measured by CogState Test domains Detection (speed of processing) and Identification (attention/vigilance) as a combined standardised attentional composite score.

The adjusted mean difference for the comparison between quetiapine XR versus quetiapine IR on the CogState standardised attentional composite score was 0.005 with 95% Confidence Intervals (CI) ranging from -0.087 to 0.098 (p- value 0.907) and Cohen's effect size 0.008 for the PPS.

The adjusted mean difference for the comparison between quetiapine XR versus quetiapine IR on the CogState standardised attentional composite score was 0.024 with 95% CI ranging from -0.056 to 0.104 (p- value 0.553) and Cohen's effect size 0.034 for the FAS.

Secondary variables

It should be noted that p-values for these parameters should be regarded as descriptive since tests are not adjusted for multiplicity.

There were no differences between quetiapine IR and quetiapine XR in the secondary objectives verbal memory, executive function or working memory as measured by the CogState end points; ISLT (95% CI [-0.220, 1.055], p- value 0.199 and Cohen's effect size 0.094 for the PPS), GMLT (95% CI [-2.714, 3.791], p- value 0.745 and Cohen's effect size 0.024 for the PPS) and ONB (95% CI [-0.026, 0.009], p- value 0.341 and Cohen's effect size 0.096 for the PPS).

Quetiapine XR was associated with improvement in the TSQM side effects and TSMQ overall satisfaction sub-scale scores compared to quetiapine IR. No or smaller differences were observed in the TSQM effectiveness and TSQM convenience sub-scale scores between quetiapine XR and quetiapine IR. TSQM side effect (95% CI [-12.0, -2.5], p=0.0035) and TSQM overall satisfaction (95% CI [-8.0, -0.2], p=0.042) all in favour of quetiapine XR. The treatment effect of the observed size is judged to be of clinical relevance. No or smaller differences were observed in TSQM effectiveness (95% CI [-8.3, 1.7], p=0.190) or TSQM convenience (95% CI [-5.3, 0.13], p=0.062)

Quetiapine XR was associated with a lower degree of sedation than quetiapine IR, as measured by the Bond-Lader VAS Sedation and SSS, when dosed according to label. Numerical differences were observed in the Bond Lader VAS Sedation scale (95% CI [2.3, 8.2], p<0.001 [p=0.0009]) and SSS (95% CI [0.12, 0.43], p<0.001 [p=0.0008].

The drop-out rates were similar with 3 drop-outs on quetiapine XR and 2 drop-outs on quetiapine IR.

Summary of pharmacokinetic results

The small sample size and the differences in sampling time relative to last dose do not permit conclusions regarding the concentrations obtained with the two formulations.

Summary of safety results

There were a similar number of AEs in the patients receiving with quetiapine XR (4 [6.3%]) compared to the patients treated with quetiapine IR (4 [6.5%]). The number of AEs judged to be related to the investigational product were similar in patients receiving quetiapine XR (2 [3.2%]) and quetiapine IR (4 [6.5%]). At System Organ Class level, the greatest proportions of patients reported events categorised in the category for nervous system disorders and were similar for patients receiving quetiapine XR (2 patients [3.2%]) and quetiapine IR (3 patients [4.8%]).

There were 3 AEs leading to discontinuation, 2 (3.2%) in patients receiving quetiapine XR and 1 (1.6%) in a patient receiving quetiapine IR.

There were no SAEs, deaths, AEs of special interest (classified as suicide attempts or suicide) or other significant AEs reported in this study.

There were no clinically important changes over time and no individual clinically important abnormalities for clinical laboratory evaluations (haematology, clinical chemistry and urinalysis), vital signs, physical findings or other observations related to safety in this study.