AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Quetiapine Fumarate
Study Code	D1443C00038
Edition Number	1
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An open label, 1-sequence cross-over, Positron Emission Tomography (PET) study with [^{11}C]raclopride to determine central D_2 dopamine receptor occupancy of Quetiapine Fumarate Immediate Release (SEROQUEL®) with Quetiapine Fumarate Extended Release (SEROQUEL XR®) in healthy male volunteers

Study dates: First healthy volunteer enrolled: 19 January 2009
Last healthy volunteer completed: 2 September 2009

Phase of development: Clinical pharmacology Phase 1

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

Study centre

AstraZeneca Clinical Pharmacology Unit (CPU), C2 84, Karolinska University Hospital, Huddinge, SE-141 86 Huddinge, Sweden.

The PET measurements were performed at the Department of Clinical Neuroscience, Karolinska University Hospital, Solna, SE-171 76 Stockholm, Sweden.

Publications

None at the time of writing this report.

Objectives

Primary objectives

- To determine occupancy of striatal D_2 receptors by the same dose of SEROQUEL XR™ and SEROQUEL IR™ following repeated once daily administration.

- To determine the relationships between plasma concentrations of quetiapine (QTP), its main active metabolite norquetiapine (N-QTP) and D_2 receptor occupancy.

Secondary objectives

- To characterize the pharmacokinetics (PK) of QTP and its metabolite N-QTP in the subjects undergoing PET analysis.

- To assess Adverse Events (AEs), vital signs and changes in laboratory parameters, physical examinations and Modified Bond-Lader Visual Analogue Scale (VAS).

Study design

This was an open labeled, 1-sequence cross-over, exploratory PET study with the radioligand [^{11}C]raclopride to determine central dopamine D_2 receptor occupancy of quetiapine XR and quetiapine IR in healthy male volunteers.

Target healthy volunteer population and sample size

The study was to include up to 14 healthy male volunteers, age 20 to 45 years, in order to obtain evaluable data of at least 10 subjects.

Investigational product: mode of administration

Quetiapine XR and IR tablets were commercially obtained and were given orally once daily.

Duration of treatment

Quetiapine XR was titrated once daily from 50 mg up to 300 mg over a period of 5 days. 300 mg was maintained during day 5 to 8. After the PET measurements at the supposed C_{max} and trough the first dose of quetiapine IR was administrated. Quetiapine IR 300 mg was given once daily on day 9 to 12.

Criteria for evaluation - PET and pharmacokinetics (main variables)

CL_{ss}/F, t_{max}, C_{max}, $AUC_{(0-24)}$, $t_{½}$, $C_{av,PET,peak}$, $C_{av,PET,trough}$. K_i for the PK-PD evaluation

Criteria for evaluation - safety (main variables)

Standard safety assessments included adverse events, vital signs and changes in laboratory parameters and Modified Bond-Lader Visual Analogue Scale (Alertness - Drowsiness).

Statistical methods

The PK-PET data were analyzed using non-linear mixed effects modeling. Safety and tolerability variables were analyzed using listings.

Subject population

Altogether 12 male healthy volunteers were enrolled in the study. One was kept as reserve and never entered the study. Ten subjects completed the study while one discontinued prematurely due to an AE and the PET measurements in connection to the administration of quetiapine IR were not performed.

Summary of pharmacokinetic results

The table below shows the main pharmacokinetic parameters. The estimated parameters were in accordance with what has been reported previously for quetiapine XR and IR.

Summary statistics of pharmacokinetic parameters of quetiapine and norquetiapine (PK analysis set)

			Geometric mean (CV%)		Median (Range)
Analyte	**Treatment**	**n**	**AUC_{0-24} (h*ng/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Quetiapine	XR	11	3045.65 (51.42)	297.27 (51.94)	4.0 (3.0-12.0)
	IR	10[a]	2743.43 (39.53)	619.55 (41.33)	1.6 (1.0-3.1)
Norquetiapine	XR	11	1525.93 (49.70)	92.98 (40.93)	5.4 (3.0-12.0)
	IR	10[a]	1679.94 (26.68)	177.52 (17.17)	2.0 (1.0-3.1)

[a] Subject 105 discontinued study.
DATA DERIVED FROM: T_PK4.SAS GENERATED: 13:39:38 11NOV2009 DB version prod: 2

Summary of PET results

Higher displacement of radioligand was observed at C_{max} of quetiapine IR as compared to C_{max} for quetiapine XR. For both quetiapine formulations, higher decrease in [^{11}C]raclopride binding was observed at C_{max} as compared to the trough concentrations of quetiapine.

Summary of pharmacokinetic/PET relationships

The observed BP values were reduced with increasing exposure of quetiapine. The quetiapine plasma concentration achieving 50% D_2 receptor occupancy was estimated to 582 ng/mL (95% confidence interval 516 to 656 ng/mL). A reliable measure of maximal occupancy parameter, Max, was not possible to estimate from the data since the highest observed occupancy was 59%. This parameter was therefore fixed to 1 since, when estimated, Max was considered not to be different from 1.

Summary of safety results

There were no SAEs or AEs leading to death reported in the study. One subject discontinued from the study (DAE) due to a severe panic attack. There were no clinically relevant changes in vital signs or laboratory parameters.