AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00013
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An open label, non-randomized Positron Emission Tomography (PET) study with [^{11}C]AZ12713580 to determine central mGluR5 receptor occupancy of AZD2066 after oral administration to healthy subjects

Study dates: First healthy volunteer enrolled: 1 April 2008
Last healthy volunteer completed: 25 June 2008

Phase of development: Clinical pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives

Primary objectives

The primary objectives were to demonstrate that AZD2066 can displace [^{11}C]AZ12713580 from mGluR5 binding-sites in the CNS and to describe the relationship between AZD2066 exposure and mGluR5 receptor occupancy in the brain.

Secondary objectives

Secondary objectives were:

- To investigate the safety and tolerability of AZD2066 by assessment of Adverse Events (AEs), vital signs measurements (blood pressure and pulse), electrocardiogram (ECG), physical examination, clinical chemistry, haematology, urinalysis and Spielberger State Anxiety Inventory (SSAI).

- To investigate pharmacokinetics of AZD2066.

Furthermore, a blood sample for genotyping will be collected for future exploratory genetic research aimed at identifying/exploring genetic variations that affect PK and pharmacodynamics (PD), safety and tolerability related to AZD2066 treatment. No genotyping results are presented in this Clinical Study Report (CSR).

Study design

This was an open-label, non-randomised, single centre, exploratory positron emission tomography (PET) study, comprising 2 panels with an interim analysis in between for dose selection for panel 2. Each subject went through 4 PET measurements.

Target subject population and sample size

The target population was 6 subjects, 3 in each panel, males or non-fertile females aged 20 to 45 years, with an body weight of at least 50 kg and a maximum of 100 kg.

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

In Panel 1, each 3 subjects received 3 oral doses of AZD2066 (3.5mg, 6.9mg, and 13.5mg). In Panel 2, each 3 subjects received 2 oral doses of AZD2066 (13.5mg, and 6.9 mg). The radioligand, [^{11}C]AZ12713580, was administered iv at each PET measurement (300 MBq per injection).

Duration of treatment

The subjects received 2 or 3 single oral doses of AZD2066 with at least 7 days in between the dosing.

Criteria for evaluation - PET imaging and pharmacokinetics (main variables)

PET measurement variables

Regional uptake and distribution of [^{11}C]AZ12713580 in regions of interest (ROI) in CNS was assessed following single intravenous doses of the radioligand. Regional radioactivity uptake, presented as time-activity curves (TAC) was used to derive the variable, total distribution volume (DV_{tot}), for calculation of the occupancy.

Pharmacokinetics of AZD2066

Maximum plasma (peak) drug concentration (C_{max}), time to reach C_{max} following administration (t_{max}), average drug concentration in plasma during PET measurement ($C_{av,PET}$), total clearance of drug from plasma/fraction of administered dose systemically (CL/F) and terminal half-life ($t_{1/2\lambda z}$).

Criteria for evaluation - safety (main variables)

AEs, vital signs, clinical chemistry, haematology, urinalysis and SSAI.

Statistical methods

The statistical analysis was descriptive and exploratory. The pharmacokinetic, PET, safety and tolerability variables were analysed using subject listings, summary tables and presented graphically, as appropriate.

Subject population

Altogether 7 subjects were enrolled in this single centre study. One subject was screened but was excluded according to inclusion criterion no 4. In total, 6 subjects completed the study, 3 in each of the 2 panels and all 6 were analysed for PK, PET and safety.

Summary of pharmacokinetic results

The pharmacokinetic results were in line with expectations. The $t_{1/2\lambda z}$ was approximately 20 hours and CL/F was around 1.3 L/h. T_{max} was in the range 20 minutes to 2 hours and always occurred prior to the PET measurement, which was performed at 3 to 4 hours post

dose. The plasma concentration during the PET measurement was relatively stable and proportional to the dose of AZD2066.

Summary of PET results

It was shown that AZD2066 is able to diminish the total uptake of the radioligand in a dose-dependently gradual manner, suggesting that AZD2066 can displace [^{11}C]AZ12713580 from mGluR5 binding sites in the CNS.

Summary of pharmacokinetic/PET relationships

The regional DV_{tot} values confirm the effect of AZD2066 pre-treatment on the total binding of [^{11}C]AZ12713580. The dose dependent decrease in specific binding is evident from the decrease of the difference in total uptake between the highest and lowest density regions. The Ki_{pl} was estimated to 936 nmol/L with a 90% CI of 572-1800 nmol/L. The estimated binding potential (BP) in caudate nucleus was estimated to 3.23. The estimated BP in cerebellum corresponded to 45% of that in cortex and 35% of that in caudate nucleus.

Summary of safety results

There were no deaths, other SAEs, discontinuations due to AEs, or OAEs reported in the study. The non-procedure related AEs were similar to those reported in previous SAD study up to 13.5 mg of AZD2066. AEs were in general of mild to moderate intensity.

There were no clinically relevant treatment related changes in vital signs (blood pressure and pulse), ECG or physical examination.

There were no clinically important changes in individual values over time in any laboratory variables.

There were no changes from baseline in SSAI scores judged to be clinically relevant in any of the doses of AZD2066.