AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7325
Study Code	D1140C00007
Date	05 August 2009

An open-label positron emission tomography (PET) study with [^{11}C]flumazenil to determine central $GABA_A$ receptor occupancy of AZD7325 after oral administration to healthy volunteers

Study dates: First healthy volunteer/patient enrolled: 25 February 2008
Last healthy volunteer/patient completed: 14 July 2008

Phase of development: Clinical pharmacology (I)

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

Study centers

The study was conducted as a research collaboration between the AstraZeneca Clinical Pharmacology Unit, Karolinska University Hospital Huddinge and the Karolinska Institutet, Department of Clinical Neuroscience, Karolinska University Hospital Solna in Stockholm, Sweden.

The first healthy volunteer was enrolled on 25 February 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to determine the relationship between the dose and the plasma concentration of AZD7325 and gamma-aminobutyric acid type A ($GABA_A$) receptor occupancy in the brain by using positron emission tomography (PET) and the radioligand [^{11}C]flumazenil, by assessment of the time course of radioactivity in brain and AZD7325 plasma concentrations.

The secondary objectives of the study were to assess safety and tolerability of AZD7325 following single doses of AZD7325 by assessment of adverse events (AEs), vital signs, electrocardiogram (ECGs) measurements, physical examination, psychometric tests, and laboratory variables and to investigate the pharmacokinetics (PK) of AZD7325 following single doses of AZD7325 by assessment of drug concentration in plasma.

Study design

The study comprised 2 sequential panels, Panel 1 and Panel 2, with 2 healthy volunteers in each. In Panel 1, 2 healthy volunteers received 3 different doses of AZD7325 (A, B, and C). In Panel 2, each healthy volunteer received 3 dose levels (D, E, and F) selected to complement the information obtained from Panel 1.

Target healthy volunteer population and sample size

The target population for this study was 4 healthy male volunteers between the ages of ≥20 to ≤45 years with a Body Mass Index (BMI) of ≥18 to ≤30 kg/m^2 and weight of ≥60 to ≤100 kg. Volunteers were required to have

- Clinically normal physical findings, medical history, and laboratory values as judged by the investigator.
- Negative results to the urine drug screen and normal resting ECG.
- Normal magnetic resonance imaging (MRI) scan at Visit 2.

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

Four batches of AZD7325 and 1 batch of [^{11}C] flumazenil were used in this study. Individual batch numbers forAZD7325 were 2000114911, 2000114004, 2000114002, and 2000114000. The batch number for [^{11}C]flumazenil was 221201.

Duration of treatment

Two healthy volunteers were to be dosed with single doses of 0.2, 5, and 20 mg of AZD7325 and 2 were to be dosed with 1, 2, and 30 mg of AZD7325. Each volunteer was to receive a microdose of the radioligand [^{11}C]flumazenil with each dose of AZD7325.

The duration for participation in the study was planned for up to 75 days.

Criteria for evaluation - pharmacokinetics and PET (main variables)

Pharmacokinetic variables included average plasma concentration during the PET assessment ($C_{av,PET}$), area under the plasma concentration versus time curve from zero to infinity (AUC), partial area under the curve corresponding to the duration of the PET assessment, apparent oral clearance of the drug, maximum plasma concentration (C_{max}), and time to reach the maximum plasma concentration. PET variables included distribution volume (VT), and binding potential (BP). PK/PET variables included occupancy and plasma concentration resulting in 50% receptor occupancy (Ki_{pl}).

Criteria for evaluation - safety (main variables)

Safety variables included AEs, vital signs, ECGs, and clinical laboratory parameters.

Statistical methods

The study was exploratory and the statistical analysis was descriptive. The pharmacokinetic, PET, safety, and tolerability variables were analyzed using subject listings and summary tables. An exploratory analysis was made of the relationship between concentration of AZD7325 in plasma and occupancy through a nonlinear mixed-effects model.

Subject population

Four nonsmoking, healthy, white, male volunteers were randomly assigned treatment sequences in the study at 1 study site. Their ages ranged from 23 to 34 years, weights ranged from 71 to 98 kg, and BMI ranged from 23.0 to 28.6.

The safety analysis included all the randomly assigned healthy volunteers. One volunteer was not dosed during a planned second treatment visit because of an AE that occurred during the preceding dosing. He received the third dose at the next visit.

The PK analysis set included all volunteers.

Summary of positron emission tomography imaging-derived results

Dose dependent decrease in binding of the radioligand [^{11}C]flumazenil to the $GABA_A$ receptors in human brain was found after treatment with single oral doses of AZD7325.

Summary of pharmacokinetic results

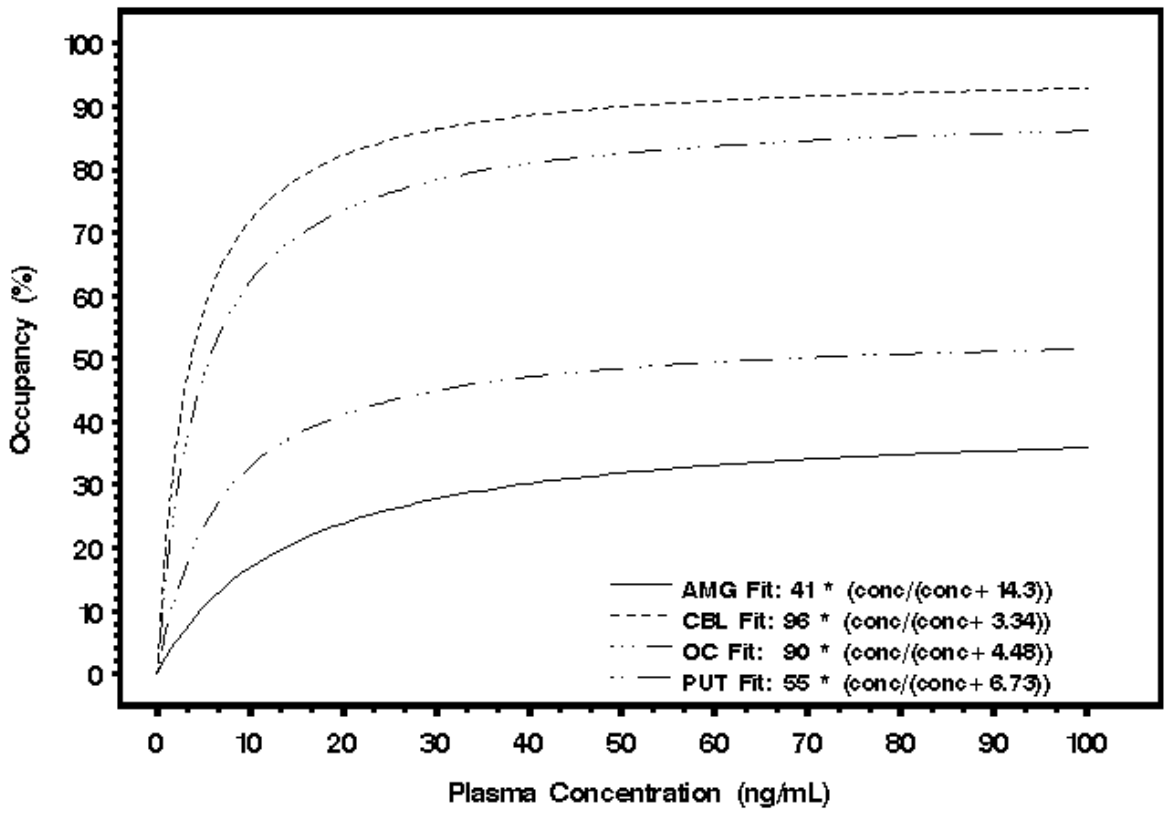
Following administration of AZD7325, the plasma concentrations reached a maximum within 5 hours and were characterized by a rapid decline.

The range for cumulative and peak exposures for the AUC and C_{max} were 2.69 to 847 h ng/mL and 0.81 to 109 ng/mL, respectively. Peak plasma concentrations occurred at 0.47 to 3 hours, and the mean apparent elimination half-life ranged from 2.25 to 25.8 hours.

Summary of pharmacokinetic/PET relationship

There was a plasma concentration-dependent reduction in the uptake in the central nervous system of the radioligand [^{11}C]flumazenil after administration of AZD7325. The maximum apparent occupancy of AZD7325 was reached at doses of 20 mg and above (see Figure 1).

Figure 1 **Estimated percent $GABA_A$ receptor occupancy of different brain regions versus the AZD7325 plasma concentration (estimated by BP method)**



AMG Amygdala; Conc Concentration; CBL Cerebellum; OC Occipital cortex; PUT Putamen.

The maximum displacement of radioligand varied between the brain regions, giving highest apparent receptor occupancy in the cerebellum and cortical regions (with a gradient of high to low from the occipital cortex to the frontal cortex), lower in striatal regions, and very low in the amygdala and hippocampus.

Summary of safety results

Fourteen AEs (5 mild, 8 moderate, and 1 severe) were observed among the 4 volunteers. All but 3 of these AEs were considered possibly related to study drug. There were no deaths, other serious AEs, discontinuations due to AEs, nor other significant AEs reported. There were also no clinically relevant treatment-related changes or trends in any laboratory evaluations, vital signs, ECGs, or physical examinations.