Clinical Study Report Synopsis

Drug Substance	AZD2516
Study Code	D2080C00009
Edition Number	1
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An open label Positron Emission Tomography (PET) study with [^{11}C]AZ12713580 to determine central mGluR5 receptor occupancy of AZD2516 after oral administration to healthy subjects

Study dates: First healthy volunteer enrolled: 29 April 2009
Last healthy volunteer last visit: 8 October 2009

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 and criteria for evaluation

All objectives and outcome variables are described in Table S1.

Table S1 Objectives and outcome variables

Objectives	Outcome variables	Type
Primary		
To demonstrate that AZD2516 can displace [^{11}C]AZ12713580 in the CNS and to describe the assumed relationship between AZD2516 exposure and mGluR5 receptor occupancy in the brain	<u>PD variables/parameters</u> Radioactivity concentration in each Region of Interest (ROI) Radioactivity in blood and metabolite corrected plasma Binding potential ($BP_{ND)}$ Distribution volume (V_T) <u>PK/PD parameters</u> The relationship between plasma concentration and V_T The relationship between plasma concentration and occupancy. The plasma concentration corresponding to 50% occupancy (Ki_{pl})	PD PK/PD
Secondary		
To investigate the safety and tolerability of AZD2516	Adverse events, laboratory variables, vital signs and ECG	Safety
To investigate pharmacokinetics of AZD2516	AUC, C_{max}, t_{max}, $t_{1/2\lambda z,}$ CL/F, V_z/F and $C_{av,PET}$	PK
Exploratory	**Exploratory**	
Furthermore, a blood sample for genotyping was collected for future exploratory genetic research aimed at identifying/exploring genetic variations that affect PK and PD, safety and tolerability related to AZD2516 treatment.[a]	Gene assays	PGX

[a] Genotyping results are not presented in the CSR.

Abbreviations: mGluR Metabotropic glutamate receptor, PD Pharmacodynamics, PK Pharmacokinetics, PGX Pharmacogenetics, AUC Area under plasma concentration-time curve from zero to infinity, C_{max} Maximum plasma (peak) drug concentration, t_{max} Time to reach peak or maximum concentration, $t_{1/2\lambda z}$ Terminal half-life, CL Total body clearance of drug from plasma, F The fraction of administered dose systemically available, V_z Volume of distribution (apparent) during terminal phase, $C_{av,PET}$ Average concentration in plasma during PET measurement

Study design

This was an open-label, non-randomized, single-center PET study to determine the central mGluR5 receptor occupancy of AZD2516 after oral administration in healthy volunteers. The

study consisted of 7 visits per panel: an enrolment visit, a MRI scan visit, 4 PET visits and a follow-up visit. A total of 2 panels were planned, each containing 3 healthy volunteers

Target subject population and sample size

The study was planned to include 6 evaluable healthy male or non-fertile female volunteers, aged 20 to 45 years inclusive.

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

The details of the investigational products and study treatment are given in Table S2. The doses given are presented in Table S3.

Table S2 Details of investigational product and other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
[^{11}C]AZ12713580	Solution for iv injection, iv, 300 mBq/injection	PET center, Karolinska University Hospital, Solna	NA	9003, 9004, 9005, 9006, 9007, 9008, 9009, 9010, 9011, 9012, 9013, 9014, 9018, 9019, 9020, 9021, 9022, 9023, 9024, 9025, 9026, 9027, 9028, 9029
AZD2516	Oral capsules, 1 mg	AstraZeneca	D0800191	08-000855AZ
AZD2516	Oral capsules, 5 mg	AstraZeneca	D0800194	08-003387AZ
AZD2516	Oral capsules, 10 mg	AstraZeneca	D0800195	08-003388AZ

NA Not applicable

Table S3 Panels and doses used in this study

Panel	Fractionated Dose	Total Dose
Panel 1 – Dose A	15+5+5+5 mg	30 mg
Panel 1 – Dose B	8+3+3+3 mg	17 mg
Panel 1 – Dose C	3+1+1+1 mg	6 mg
Panel 2 – Dose D	15+5+5+5 mg	30 mg
Panel 2 – Dose E	6+2+2+2 mg	12 mg
Panel 2 – Dose F	8+3+3+3 mg	17 mg

E0001001, E0001003 and E0001004 were included in Panel 1. E0001005, E0001006 and E0001007 were included in Panel 2.

Duration of treatment

Each healthy volunteer was administered 4 single doses of [11C]AZ12713580 and 3 single fractionated doses of AZD2516. At least 7 days were planned between each dose of AZD2516.

Statistical methods

The safety analysis set included all healthy volunteers who received investigational product, and for whom at least 1 measure of safety was collected. The PK analysis set included healthy volunteers who provided sufficient PK and PD data as judged by the pharmacokineticist and PET expert.

Primary and secondary endpoints were summarized descriptively and consisted of listings, graphs and summary statistics that included geometric mean, coefficient of variation, median, min and max. High/low values and treatment emergent changes for laboratory safety variables and vital signs were defined using AstraZeneca extended/standard reference ranges.

Occupancy is defined as the relative reduction of specific binding by the radioligand. Since there is no reference region without mGluR5 receptors available representing non-specific uptake, the specific binding could not be directly assessed from each PET measurement. The analysis was therefore based on the individually estimated V_T values which represented the sum of specific (V_s) and non-displaceable (V_{ND}) uptake in the CNS (partition coefficient CNS/plasma).

The relationship between AZD2516 exposure and binding potential (BP_{ND}) was assessed assuming the following relationship.

$$BP_{ND} = BP_{BL} \cdot (1 - \frac{C_{av,PET} \cdot BP_{BL}}{C_{av,PET} + Ki_{pl}})$$

Where Ki_{pl} is the exposure corresponding to 50% occupancy, $C_{av,PET}$ is the average plasma concentration of AZD2516 during the PET-experiment and BP_{BL} is the baseline binding potential. The V_{ND} i.e. the non-specific uptake was assumed to be the same in all regions. Ki_{pl} was estimated in 2 different ways using 2 different models. In model 1, a separate BP_{BL} was estimated for each ROI. In model 2, the BP_{BL} in cerebellum was fixed to be 20% of that in caudate nucleus.

Subject population

In total, 6 healthy volunteers were administered AZD2516 at 1 study site. Each volunteer received 3 single fractionated doses of AZD2516. All healthy volunteers that were administered treatment completed the study. The safety, PK and PET analyses included all healthy volunteers. There were no protocol deviations that led to exclusion of data from the analyses. All healthy volunteers were males between the ages of 24 and 32 years. One

healthy volunteer was black (or African American) and the other healthy volunteers were white.

Summary of pharmacodynamics (PET) results

At baseline, radioligand uptake was regionally distributed corresponding to the anatomical distribution of mGluR5. After treatment with AZD2516, decreased uptake of radioligand was observed. The greatest change in radioligand uptake was seen in the regions with the highest mGluR5 density (CAU, HIP, VST). The competitive binding of AZD2516 led to the displacement of radioligand from the mGluR5 binding sites. This observation (decrease in radioligand binding, ie, occupancy) provides evidence that AZD2516 binds to mGluR5.

Summary of pharmacokinetic results

AZD2516 was rapidly absorbed. The geometric mean t_{max} occurred 1.5 to 2.0 h after administration of the first dose fraction. T_{max} was in the range of 0.72 h to 2.75 h and always occurred prior to or within 5 min of the start of the PET measurement. The PET measurement began approximately 2.5 h after administration of the first dose fraction (and 15 min after administration of the last dose fraction) and lasted for 1 h. The plasma concentration during the PET measurements was relatively stable.

The initial decline in plasma concentration was similar after all doses. In the interval 6 to 17 mg, the plasma concentrations of AZD2516 decreased in an apparently mono-exponential manner. At these doses the geometric mean terminal half-life varied from 0.92 to 1.66 h. However after 30 mg, when 4 out of 6 healthy volunteers had quantifiable concentrations at 24 h after the administration of the first dose fraction, a β-phase was found, and the geometric mean terminal half-live was longer, 2.52 h.

Summary of pharmacokinetic/pharmacodynamic (PET) relationship

There was a plasma concentration-dependent displacement of the radioligand [^{11}C]AZ12713580 in the CNS after administration of AZD2516. The total plasma concentration corresponding to a receptor occupancy of 50% (Ki_{pl}) was 510 nmol/L ($CI_{95\%}$ 391, 666). When fixing the cerebellar specific uptake to 20% of that in caudate nucleus, in accordance with literature data suggesting that mGluR5 density in the cerebellum is approximately 20% of that in caudate nucleus, the estimated Ki_{pl} was 422 nmol/L.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations due to adverse events (DAEs) or other significant adverse events (OAEs) in the study. In total, 15 mild and 4

moderate AEs were reported in the 6 healthy volunteers. The most common AE was dizziness which was reported in 4 healthy volunteers (all mild).

There were no clinically relevant treatment-related changes or trends in safety laboratory variables or vital signs during the study. There were no ECG abnormalities recorded during the study.