AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00004
Edition Number	1
Date	November 26, 2009

An Open-label Positron Emission Tomography (PET) Study using 2-[^{18}F]-F-A85380 to determine α4β2 Neuronal Nicotinic Receptor (NNR) Occupancy of AZD1446 After Oral Administration to Male and Non-fertile Female (non-nicotine users) Healthy Volunteers

Study dates: First healthy volunteer enrolled: 2009-04-08
Last healthy volunteer completed: 2009-08-25

Phase of development: Clinical pharmacology (I)

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

Study centre

AstraZeneca Clinical Pharmacology Unit (CPU)
Karolinska University Hospital Huddinge
Stockholm, Sweden

Publications

None at the time of writing this report.

Objectives

Primary objective

To determine whether and to what extent AZD1446 can displace radioligand 2 [18F] F A85380 from binding to α4β2 neuronal nicotinic receptors (NNRs) and to describe the relationship between plasma concentrations of AZD1446 and its occupancy at α4β2 NNRs.

Secondary objective

To evaluate the safety and tolerability of AZD1446.

Exploratory objective

To collect and store a blood sample for genotyping for possible future exploratory genetic research aimed at identifying/exploring genetic variations that may affect pharmacokinetic, pharmacodynamic, safety and tolerability related to AZD1446.

Study design

This was an open-label, non-randomized, single-centre, exploratory PET study, where the α4β2 nicotinic receptor occupancy induced by AZD1446 was studied by PET examinations with the radioligand 2-[^{18}F]-F-A85380.

The study comprised 3 dose panels, with 3 volunteers per panel. Each of the 9 subjects received a single dose of AZD1446 (oral solution). Using an adaptive design, doses varied to ensure that the complete plasma exposure/occupancy relationship was characterized over the course of the study.

Target healthy volunteer population and sample size

The study population was 9 healthy male and non-fertile female volunteers, aged 20 to 45 years, non-nicotine users.

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

The details of the investigational products and any study treatment are given in Table 1.

Table 1 Details of investigational product and any other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number[a]
AZD1446	Oral solution 0.5 mg/mL	AstraZeneca	D0800219	08-001659AZ
AZD1446	Oral solution 25 mg/mL	AstraZeneca	D0800218	08-001542AZ
2-[^{18}F]-F-A85380	Solution for intravenous injection	PET Centre, Karolinska University Hospital Solna		

[a] Batch numbers are not required for non-investigational product/test drug.

Duration of treatment

Single dose.

Criteria for evaluation - PK/ PD (main variables)

Table 2 Study objectives and variables

Objective	Variable
To determine whether and to what extent AZD1446 can displace radioligand 2-[18F]-F-A85380 from binding to α4β2 neuronal nicotinic receptors (NNRs).	PK: C_{max}, t_{max}, AUC_{PET}, $C_{av,PET}$; PD: total distribution volume (VT)
To describe the relationship between plasma concentrations of AZD1446 and its occupancy at α4β2 NNRs.	PK/PD Occupancy versus $C_{av,PET}$, $K_{i,plasma}$ (as plasma concentration of AZD1446 at 50% receptor occupancy)

Criteria for evaluation - safety (main variables)

Adverse Events, blood pressure, pulse rate and laboratory variables.

Statistical methods

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

The sample size was not been calculated on any statistical criteria. The data was summarized using descriptive statistics.

Subject population

A total of 11 healthy volunteers were enrolled in the study; 9 were assigned to treatment, and all 9 completed the study. The enrolled subjects were males aged between 22 and 39 years.

Summary of pharmacokinetic results

The plasma concentrations during the PET measurements (CavPET) were in the range of 99 nmol/L (10 mg AZD1446) to 2263 nmol/L (200 mg AZD1446). The pharmacokinetic results were in line with expectations based on previous results with AZD1446.

Summary of pharmacodynamic (PET-derived) results

Brain images were obtained of the regional brain uptake of radioligand 2-[^{18}F]-F-A85380 at baseline and after administration of AZD1446. At baseline, radioligand uptake showed regional distribution volumes corresponding to the anatomical distribution of α4β2 NNRs. The highest radioligand uptake (V_T) was seen in the thalamus, ranging from 4.20 to 6.98, lower in pons (2.94 to 4.77), followed by dorsal striatum (putamen, caudate nucleus), hippocampus and cortical regions. There was a plasma concentration-dependent reduction of the radioligand 2-[^{18}F]-F-A85380 uptake in the CNS after administration of AZD1446.

Summary of pharmacokinetic/pharmacodynamic relationships

Based on displacement data, receptor occupancy was predicted using the population PK/PD model, which showed that, at the doses explored, AZD1446 achieved achieved near full occupancy (>80%) of NNRs. The AZD1446 plasma concentration achieving 50% receptor occupancy, $K_{i,plasma}$ was estimated to 128 nmol/L (95% confidence interval 51.8 to 309 nmol/L). By multiplication with the unbound fraction of AZD1446 in plasma, determined in human plasma *in vitro*, the $K_{i,plasma}$ corresponding to the unbound drug in plasma was estimated to be approximately 100 nmol/L.

Summary of safety results

There were no deaths, serious adverse events, other significant events or AEs leading to discontinuation. There were 12 AEs in the study, all of mild or moderate intensity, six of which occurred prior to treatment with AZD1446. There were no clinically relevant changes or trends in any laboratory variable (haematology, clinical chemistry, urine or histamine/tryptase) or in vital signs. There were no abnormalities in ECG evaluations after treatment.