AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3480
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An Open-Label Positron Emission Tomography (PET) Study Using 2-[^{18}F]-F-A85380 to Determine α4β2 Neuronal Nicotinic Receptor Occupancy of AZD3480 after Oral Administration to Healthy Male Subjects (Non-Nicotine Users)

Study dates: First healthy volunteer enrolled: 21 January 2008
Last healthy volunteer completed: 27 August 2008

Phase of development: Clinical pharmacology (I)

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

Study centre

The study was conducted at AstraZeneca Clinical Pharmacology Unit (CPU) C2-84, Karolinska University Hospital, Huddinge, SE-141 86 Stockholm, Sweden. The first healthy volunteer was enrolled on 21 January 2008, and last healthy volunteer completed on 27 August 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to determine the relation between plasma concentration of AZD3480 and the occupancy at α4β2 neuronal nicotinic receptors (NNRs) in healthy male volunteers, non-nicotine users.

The secondary objective of the study was to evaluate the safety and tolerability of AZD3480 following single doses of AZD3480 by assessment of adverse events (AEs) and vital signs.

In addition, a deoxyribonucleic acid (DNA) blood sample, that may be used for possible future exploratory genetic research aimed at identifying/exploring further genetic variations that may affect pharmacokinetics , pharmacodynamics, α4β2 NNR occupancy, safety and tolerability of AZD3480, was collected and stored. The DNA samples were obtained only from healthy volunteers who provided additional informed consent for this purpose.

Study design

This study was an open-label, non-randomised, single-centre, exploratory positron emission tomography (PET) study. The study consisted of 5 visits: enrolment, magnetic resonance imaging (MRI) scan, baseline PET scan, PET scan after treatment with AZD3480, and follow-up. The α4β2 NNR occupancy induced by AZD3480 was studied by PET examinations with the radioligand 2-[^{18}F]-F-A85380.

Target healthy volunteer population and sample size

The study recruited healthy male volunteers from the AstraZeneca Volunteer Panel at the AstraZeneca CPU, aged 20 to 80 years, non-nicotine users, who had been genotyped for cytochrome P450 (CYP) 2D6 as poor metabolisers (PMs) or extensive metabolisers (EMs) in previous clinical studies. The study was to include 9 healthy volunteers with an option of 3 additional ones.

Investigational product: dosage, mode of administration and batch numbers

The investigational product, AZD3480, was administered as a single oral dose. The dose administered to each healthy volunteer was individualised based on their CYP2D6 genotype in order to target a pre-defined plasma concentration and was in the range of 5 to150 mg in EMs and 5 to 15 mg in PMs. Seven batches of AZD3480 were used in this study (H 1895-01-

01-01, H 1828-01-01-01, H 1828-02-01-01, H 1812-01-01-01, H 1812-02-01-01, H 1813-01-01-02, and H 1813-02-01-01).

The PET radioligand 2-[^{18}F]-F-A85380 was manufactured at the PET Centre at Karolinska University Hospital Solna from the precursor, 2-Nitro-A85380, supplied by ABX advance biochemical compounds GmbH, Germany. The radioligand 2-[^{18}F]-F-A85380 was prepared just before the PET investigation and administered as an intravenous bolus injection on 2 occasions (2 PET experiments on separate days).

Duration of treatment

Single dose of AZD3480.

Criteria for evaluation – pharmacokinetics/pharmacodynamics (main variables)

- **AZD3480 pharmacokinetics**

  C_{max} and t_{max}, partial area under the curve corresponding to the duration of the PET measurement (AUC_{PET}), and the average plasma concentration of AZD3480 during PET measurement ($C_{av\ PET}$) used for occupancy determination were calculated for all healthy volunteers.

- **PET- derived pharmacokinetic/pharmacodynamic variables**

  The regional uptake and distribution of the radioligand 2-[^{18}F]-F-A85380 in regions of interest (ROIs) in the brain was assessed following a single intravenous dose of the radioligand. The ROIs were outlined based on the known distribution of α4β2 receptors in human brain and included thalamus, striatum (caudate, putamen), cerebellum, pons, cerebral cortical regions (frontal and temporal), and hippocampus. Regional radioactivity uptake, presented as time-activity curves, was used for quantification of the variable total distribution volume (V_T).

- **Relationship between AZD3480 concentration and occupancy at α4β2 NNRs**

  The individual V_T values and the AZD3480 C_{avPET} for each ROI were used for estimation of the primary study outcome variable Ki_{pl} (total plasma concentration of AZD3480 resulting in 50% receptor occupancy), using a non-linear model. The Ki_{pl} for the unbound (free) concentration of AZD3480 was calculated by multiplication of the estimated value of Ki_{pl} for total concentration by the factor of 0.3 (the unbound fraction of AZD3480 as determined *in vitro*).

Criteria for evaluation - safety (main variables)

- AEs and vital signs (blood pressure and pulse).

Statistical methods

The statistical analysis was descriptive and exploratory. Safety, tolerability and pharmacokinetic variables were analysed using listings and summary statistics.

Subject population

Twelve healthy volunteers (9 EMs and 3 PMs) were enrolled, and 9 of them completed the study. Two healthy volunteers discontinued at enrolment due to abnormal ECG and metal in the eyes, respectively. One healthy volunteer discontinued voluntarily after MRI. Nine healthy volunteers who completed the study were included in the safety and pharmacokinetics (PK) analysis sets.

Summary of pharmacokinetic results

The plasma concentrations during the PET measurements (C_{avPET}) were in the range of 2 to 377 nmol/L. The pharmacokinetic results were in line with expectations based on previous results with AZD3480.

Summary of pharmacodynamic (PET-derived) results

Brain images of regional brain uptake of radioligand 2-[^{18}F]-F-A85380 at baseline and after administration of AZD3480 were obtained. At baseline, radioligand uptake showed regional distribution corresponding to the known anatomical distribution of α4β2 NNRs, with the highest distribution volume (V_T) in the thalamus, ranging from 8.22 to 10.45, lower in pons (7.27 to 5.23), followed by dorsal striatum, hippocampus and cortical regions.

Summary of plasma concentration relationship to receptor occupancy

There was a saturable, plasma concentration-dependent reduction of the radioligand 2-[^{18}F]-F-A85380 uptake in the CNS after administration of AZD3480. The estimated Ki_{pl} for total drug concentration in plasma was 8.23 nmol/L, and the Ki_{pl} corresponding to the unbound drug in plasma was 2.46 nmol/L. The highest plasma concentrations observed in this study (approximately 400 nmol/L) is 50-fold the estimated Ki value, inducing an occupancy of 98%.

Summary of safety results

There were no serious adverse events, other significant events or discontinuations of treatment with investigational product due to AEs in this study. There were 2 AEs: orthostatic hypotension and numbness in left index finger. No clinically important changes or values were observed in any healthy volunteer in any of the laboratory variables or vital signs.