Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00009
Edition Number	1
Date	09 March 2010

A Phase I, Randomised, Double-blind, Placebo-controlled, Parallel Group, Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1446 in Healthy Elderly Male and Female Volunteers During 4 Weeks of Treatment

Study dates: First subject enrolled: 06 October 2009
Last subject last visit: 18 December 2009

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This study was conducted at AstraZeneca R&D, Clinical Pharmacology Unit CPU, Tunavägen 22a, S-221 87 Lund.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of AZD1446 dosed for 4 weeks as compared to placebo in healthy elderly male and female volunteers, aged 65 to 85 years.	Adverse events (AE), vital signs [pulse, blood pressure (BP) and body temperature], clinical chemistry, haematology and urinalysis, electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS), Spielberger, State trait anxiety scale, state part.	Safety
Secondary	**Secondary**	
To determine the pharmacokinetics (PK) of AZD1446 dosed for 4 weeks in healthy elderly male and female volunteers, using population analysis.	Population PK (PoP PK) analysis using a Non-linear Mixed Effects Model (NONMEM). The effect of covariates on the PK of AZD1446. Area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0\text{-}24h),ss}$, predicted maximum plasma concentration at steady state ($C_{ss,max,pred}$), effective half-life ($t_{½,eff}$), apparent total plasma clearance (CL/F), apparent volume of distribution (V/F) and renal clearance (CL_R). Other parameters may be calculated as appropriate.	PK

Study design

This study was a randomised, double-blind, placebo-controlled, parallel group, single centre study to evaluate the safety, tolerability, and PK of AZD1446 when given 3-times daily for 4 weeks. Healthy elderly volunteers, aged 65 to 85 inclusive, nicotine and non-nicotine users, were randomised, 1:1:1, to AZD1446 40 mg x 3, AZD1446 75 mg x 3, or to placebo.

AZD1446 is intended for treatment of Alzheimer's disease and Attention deficit and hyperactivity disorder.

Target subject population and sample size

The main inclusion criteria were healthy male and/or female healthy volunteer aged ≥65 to ≤85 years, a body mass index (BMI) between 18 and 30 kg/m^2, clinically normal findings on physical examination in relation to age and a normal ECG.

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

The investigational product was AZD1446 (oral solution), manufactured by AstraZeneca. One (1) batch of AZD1446 was used [oral solution, 25 mg/ml (formulation number: D0800218, batch number: 08-001542AZ)] and 1 batch of placebo [oral solution (formulation number: D0800011, batch number: 09-005981AZ)].

Duration of treatment

The investigational product (IP) was administered 3-times daily during 4 weeks.

Statistical methods

The safety, tolerability and data for concentrations of AZD1446 in plasma and urine were summarized using descriptive statistics. Population PK (PoP PK) data was analysed with a NONMEM.

Subject population

The planned number of randomised healthy volunteers was 51 to ensure 45 evaluable healthy volunteers. Due to operational reasons (research unit being closed down) the actual number of randomised as well as evaluable healthy volunteers was 34. Sixteen (16) and 18 female white healthy volunteers, were randomised at 1 study site. Of the 34 randomised healthy volunteers 33 completed the study. One (1) healthy volunteer randomised to AZD1446 40 mg x 3 entered the study even though entry criteria was not satisfied and was therefore withdrawn on study day 3. Overall, the treatment groups were well balanced/comparable with regards to demographic and baseline characteristics. The safety and PK analysis included all randomised healthy volunteers. The final number of healthy volunteers being lower than planned is not considered to have any impact on the conclusions drawn in this study.

Summary of pharmacokinetic results

A PoP PK model, based on data from the AZD1446 multiple ascending dose (MAD) study (D1950C00002) could describe the PK results from the present study well. Therefore no further PoP PK model development was performed and an effect of covariates was not explored. Individual estimates of PK parameters were derived using the POSTHOC step in NONMEM. The geometric mean of $AUC_{(0\text{-}24),ss,pred}$ was 23100 h*nmol/L for the dose AZD1446 75 mg x 3, and 12200 h*nmol/L for the dose AZD1446 40 mg x 3 (AUC exposure limit for AZD1446 (30000 h*nmol/L). AZD1446 was rapidly absorbed with a $t_{max,pred}$ less than 1 h after dose. Effective half-life ($t_{½,eff}$), was in the range of 1.7 to 2.7 h. Steady state was reached within 1 day of repeated dosing. The geometric mean of fraction of given drug excreted in urine (f_e) was 48% and 51% on day 28 for the 40 mg x 3 and 75 mg x 3 dose groups respectively.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of investigational product (IP) due to adverse events (DAEs), or any other significant adverse event (OAEs) in

the study. All adverse events (AEs) were mild to moderate in intensity. Most of the AEs of moderate intensity, were reported at the highest dose of AZD1446, 75 mg x 3. The most common AEs during treatment with AZD1446 as compared to placebo were nausea and dizziness. Headache was as common in healthy volunteers receiving AZD1446 as in those receiving placebo. There were few values outside predefined project specific reference limits with regards to laboratory variables, vital signs and the Spielberger State trait anxiety scale, state part, with no apparent differences between placebo and AZD1446. All ECGs were normal. No healthy volunteer had any suicidal behaviour or any indication of suicidal ideation (as measured with C-SSRS).