AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9056 hydrochloride
Study Code	D1520C00020
Edition Number	1
Date	9 December 2008

A Randomised, Double-Blind, Placebo-Controlled, 2-Period Cross-over Study in Healthy Male Volunteers, to Investigate Retinal Function Following a Single 800 mg Oral Dose of AZD9056

Study dates: First healthy volunteer enrolled: 04 June 2008
Last healthy volunteer completed: 07 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(s)

The study was conducted at a single centre in the UK: AstraZeneca Clinical Pharmacology Unit, South Block E, Queens Medical Centre, Nottingham, NG7 2UH, UK. The first healthy volunteer enrolled on 04 June 2008 and the last healthy volunteer completed on 07 August 2008.

Publications

None at the time of writing this report.

Objectives

Primary objectives

The primary objective of this study was to investigate the effects of a single oral dose of 800 mg AZD9056 on retinal function assessed by electroretinography (ERG).

Secondary objectives

The secondary objectives of the study were:

1. To investigate the effect of single oral dose of 800 mg AZD9056 on retinal function assessed by measurements of visual acuity, contrast sensitivity and colour vision.

2. To investigate the effect of single oral dose of 800 mg AZD9056 on occipital (CNS) function assessed by visual evoked potential (VEP).

3. To investigate the effect of single oral dose of 800 mg AZD9056 on cognitive function assessed by psychomotor testing.

4. To explore whether there is a relationship between any reported visual adverse events and measurements of retinal, occipital and cognitive function by assessment of ERG, visual acuity, contrast sensitivity, colour vision, VEP and psychomotor testing.

5. To measure plasma concentrations of AZD9056 to determine exposure at the time of the ERG testing and psychomotor testing.

6. To further investigate the safety and tolerability of AZD9056 by assessment of vital signs, ECG, haematology, clinical chemistry, urinalysis and adverse events.

Exploratory objectives

To provide pharmacogenetic data for the AZD9056 project that can be pooled with genetic results from other AZD9056 studies to allow the investigation of the influence of genotype on PK disposition, safety and pharmacodynamic response.

Study design

AZD9056 is being developed as a novel disease modifying anti-rheumatic drug (DMARD). This was a randomised, double-blind, placebo-controlled, 2-period cross-over study to investigate the effects of a single dose of 800 mg AZD9056 on retinal function.

Target healthy volunteer population and sample size

It was planned that up to 15 healthy males (aged 18 to 65, and with a BMI between 18 and 30 kg/m^2 inclusive) would be enrolled into the study with 12 men completing the study. All healthy volunteers were emmetropic with corrected visual acuity of 6/6 in both eyes (excluding contact lens wearers and wearers of tinted/photochromic glasses). Each had an intra-ocular pressure <25 mmHg, had not received corrective laser eye surgery and had no history or presence of neurological or ophthalmological disease. Healthy volunteers with a narrow anterior chamber of the eye were excluded as were those with colour blindness or a family history of colour blindness.

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

AZD9056 was administered orally as 200 mg uncoated tablets (formulation no. FDN272). Placebo to AZD9056 was provided as matching uncoated tablets (formulation no. FDN232).

Duration of treatment

Single dose of AZD9056, 2 period, cross-over study with 14-21 day washout period.

Criteria for evaluation - Pharmacodynamics (main variables)

Electroretinogram assessments: photopic response, oscillatory potentials, 30 Hz (flicker) response, maximal dark adapted response.

Visual assessments: Bailey-Lovie visual acuity. Colour vision. Contrast sensitivity.

Occipital (CNS) function: Visual evoked potential (VEP): onset/off-set, pattern reversal.

Cognitive (psychomotor) assessments: simple reaction time, digit vigilance, choice reaction time, Bond-Lader VAS of mood and alertness.

Visual questionnaire to identify abnormalities (reported as adverse events)

Criteria for evaluation - PK (main variables)

Determination of plasma concentrations of AZD9056. Estimation of C_4, $C_{5.5}$, $C_{8.5}$, C_{24} and C_{max}.

Criteria for evaluation - safety (main variables)

Adverse events; haematology, clinical chemistry, and urinalysis; vital signs, electrocardiograms (ECG).

Statistical methods

Continuous measurements were summarised using descriptive statistics (eg, number of observations, arithmetic or geometric mean, standard deviation or coefficient of variation, minimum, median, maximum). Categorical data were summarised using frequency tables (ie, count and percentages).

The effect of AZD9056 compared to placebo on the change from pre-dose within period for the primary and secondary outcomes (ERG, visual function, VEP and cognitive function measurements) were compared using ANOVA models. Subject, sequence and treatment were included in the ANOVA models as fixed effects. The treatment effect was tested by using the within-subject residual mean square. The least square means for each treatment (AZD9056 and placebo) and the least square mean and standard errors for treatment effect with the associated 95% confidence interval were presented.

Subject population

Twelve healthy volunteers were randomised (6 to AZD9056/placebo and 6 to placebo/AZD9056) and completed treatment. Eleven subjects completed the study, one subject was lost to follow up and completed both treatment periods but did not attend post-treatment follow up.

All 12 subjects were healthy males with age range 18 to 44 years, height range 163 to 188 cm and weight range 67 to 89 kg. Medical and surgical histories and physical examination data were as expected and the healthy volunteers recruited for this study were appropriate for this study. There were no imbalances between the treatment groups in demographics or any other baseline characteristics.

Summary of pharmacokinetic results

Analysis of post-dose plasma samples demonstrated that all subjects were exposed to AZD9056. The maximal plasma concentration (C_{max}) was determined as the highest value for each subject. C_{max} occurred at 4 h in five subjects, 5.5 h in six subjects and 8.5 h in one subject.

Summary of pharmacodynamic results

There were no clinically relevant differences in the amplitudes or latencies of electroretinographic responses between placebo or AZD9056 for the right or the left eye. Similarly, AZD9056 had no clinically relevant effect on visual acuity, colour vision and contrast sensitivity. Taken together, these data indicate that a single 800 mg oral dose of AZD9056 has no clinically relevant effect on retinal function.

Occipital (CNS) function after AZD9056 was assessed by visual evoked potentials. The amplitude and latency of onset/offset and pattern reversal responses were not significantly different for either eye after AZD9056 or placebo.

Psychomotor assessments showed that at 8.5 h and 24 h post-dosing, 800 mg AZD9056 orally had no statistically significant or clinically relevant effects on cognitive function and self-rated assessments of mood and alertness.

Summary of safety results

There were no deaths, serious adverse events (AEs), discontinuations due to AEs or other significant AEs. Eight subjects on placebo (67%) reported a total of 16 AEs; 8 subjects on AZD9056 (67%) reported a total of 20 AEs. In both treatment groups, AEs most commonly occurred in the 'gastrointestinal disorders' SOC (7 AZD9056 subjects and 3 placebo subjects). Diarrhoea was reported by 6 (50%) subjects after AZD9056 (4 with moderate and 2 with mild intensity) compared to mild diarrhoea in only one subject receiving placebo.

Headache was also commonly reported, occurring in 5 (42%) subjects receiving placebo with lower frequency in 2 (16.7%) subjects after AZD9056. Intensity of headache was mild or moderate in all cases and for both treatment sequences.

No visual adverse events were reported by any subjects during the study. The AE 'visual acuity tests abnormal' was recorded for Subject E0001999 after placebo and AZD9056. It was concluded that this was a physiological artefact arising from the test conditions.

There were no clinically important changes from baseline in the mean or individual values of any other laboratory parameter. Thus there did not appear to be any evidence of an effect of AZD9056 on haematology, clinical chemistry or urinalysis variables. Similarly, there was no evidence of any effect of AZD9056 on the vital signs or 12-lead ECG measurements.