AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D5090C00021
Edition Number	1
Date	30 April 2010

A Single-centre, Randomised, Double-blind, Placebo-controlled, Two-part Study to Assess Safety, Tolerability, Pharmacokinetics of Orally Administered AZD1386, and the Relationship between Body Temperature and QTc in Healthy Volunteers in the Presence and Absence of Naproxen

Study dates:	First subject enrolled: 06 August 2009 Last subject last visit: 15 September 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

This was a single-centre study at the Early Phase Clinical Unit –PAREXEL International, Northwick Park Hospital, Harrow, Middlesex, United Kingdom.

Study period		Phase of development
First subject enrolled	06 August 2009	I
Last subject completed	15 September 2009	

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
To investigate safety, tolerability, pharmacokinetics and potential relationship between body temperature and QTc in healthy volunteers after oral doses of AZD1386	See details below	Safety and tolerability, pharmacokinetics, pharmacodynamics
Primary	**Primary**	
To investigate the safety and tolerability of single ascending doses of AZD1386.	Adverse events, vital signs, electrocardiograms (ECGs), telemetry, safety laboratory variables	Safety and tolerability
Secondary	**Secondary**	
To investigate the pharmacokinetic profile of AZD1386 (and if possible relevant metabolites) after single ascending doses.	Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal half-life ($t_{1/2\,\lambda z}$), area under the plasma concentration-time curve from zero to 12 hours ($AUC_{(0-12)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution during terminal phase (V_z/F), mean residence time (MRT).	Pharmacokinetics (PK)
To investigate the dose effect relationship of QTc and body temperature, respectively, after a single oral dose of AZD1386	QTc and body temperature (BT)	Safety and tolerability
To investigate the Heat Pain Threshold (HPT) and Warmth Detection Threshold (WDT) after single doses of AZD1386	HPT and WDT	Pharmacodynamics (PD)

Objectives	Outcome variables	Type
Exploratory		
A blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that could affect PK and PD, safety and tolerability related to AZD1386	Gene sequence	Pharmacogenetics
The results from this genetic research may be reported in a separate report as appropriate.		

QT - Interval from the beginning of the Q-wave (or the R-wave if Q is missing) to the end of the T-wave, in the surface ECG; QTc - QT interval corrected

Study design

This was a Phase-I clinical study divided into Part A and B, and planned to explore the safety, tolerability and PK at supra-therapeutic levels of AZD1386, and also to investigate the potential relationship between QTc and BT in 61 healthy volunteers aged 20 to 45 years, to support the design of a future clinical thorough QT (TQT) study.

Only the dose panel 1 of Part A with single dosing of 300 mg AZD1386 or placebo at a ratio of 8:3 was performed in 11 healthy volunteers aged 20 to 38 years. Single dose panels 2 and 3 of Part A, and the multiple dose regimen of Part A, as well as the entire Part B of the study were not performed due to reasons unrelated to this study.

This document further reports only on the performance and results of the part of this Phase-I clinical study that was completed, ie dose panel 1 of Part A.

Target subject population and sample size

Healthy male and female (of non-childbearing potential) volunteers aged 20 to 45 years (inclusive) with eleven volunteers included per dose panel.

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

- AZD1386, capsule, 30 mg; single oral dose administration of 300 mg (Batch number: 08-002010AZ)
- Placebo, capsule matching 30 mg AZD1386 capsule; single oral dose administration (Batch number: 09-000848AZ)

Duration of treatment

Single dose

Statistical methods

All statistical analyses were performed for descriptive purposes, since no formal hypothesis testing was conducted. The confidence intervals were calculated only for descriptive purposes. No corrections for multiplicity were done.

The statistical analyses of PK variables consist mainly of subject listings and appropriate descriptive statistics by time point and dose group, and concentration-time graphs per dose group.

An ANCOVA was performed for the variables QTcF, PR, RR and BT; with one model for each time point. Independent factors were *treatment* and the *baseline* value (as covariate) and *treatment* was a categorical factor.

Appropriate descriptive statistics were used for the presentation of the PD variables WDT and HPT variables, and these variables were analysed with a linear model to access differences between the different treatment groups (AZD1386 vs. placebo).

Categorical analysis of frequencies and certain proportions of subjects were performed by descriptive methods.

Subject population

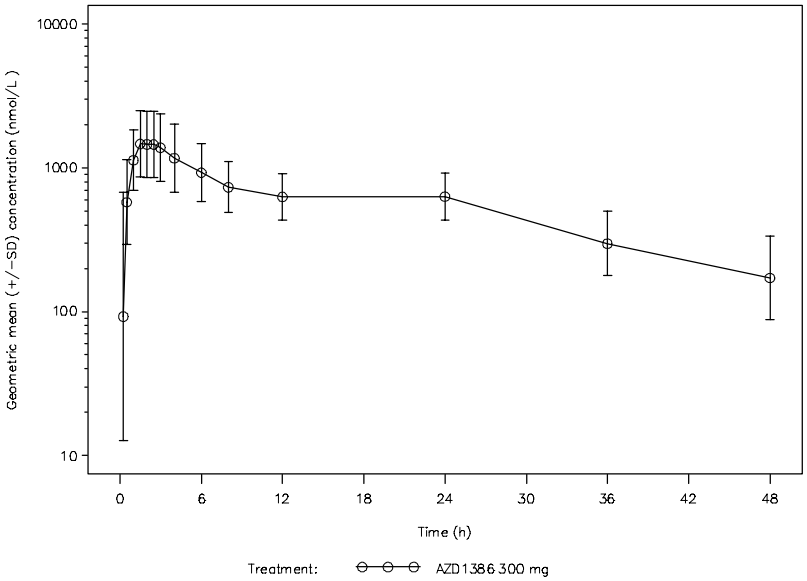
In total, 11 healthy male volunteers were randomised into 1 dose panel, each volunteer received a single administration of the investigational product (IP) (AZD1386) or placebo during the planned treatment period and all randomised subjects completed the study in accordance with the amended Clinical Study Protocol (CSP).

Overall, the treatment groups (AZD1386 and placebo) were well balanced with regards to demographic and baseline characteristics and the healthy volunteers enrolled were found eligible for this Phase I clinical pharmacology study according to all criteria defined in the CSP.

Summary of pharmacokinetic results

Following administration of 300 mg AZD1386, given as a single oral dose of 10 capsules of 30 mg each, the absorption was rapid with a median t_{max} of 2 hours. The geometric mean C_{max} and AUC was 1520 nmol/L and 31500 nmol*h/L, respectively. Post C_{max}, the plasma concentration initially declined, followed by a period when it remained rather constant. Approximately 24 hours post dose AZD1386 concentrations declined again with a geometric mean terminal $t_{1/2\lambda z}$ of 14.4 hours, see Figure S1.

Figure S1 **Geometric Mean (±SD) plasma concentrations (nmol/L) of AZD1386 on log-linear scale versus time following single dose of AZD1386 300 mg – (PK Analysis Set)**



Summary of pharmacodynamic results

Increases in mean thresholds of temperature sensations, ie of WDT and HPT, comparing active versus placebo treatments were seen from 1.0 until 24 or 48 hours post-dose. Depending on thermode size (18x18 or 25x50 mm) and site of assessment (left and right arm) maximum mean changes from baseline ranged from 2.4 to 6.7°C for WDT and from 3.6 to 5.4°C for HPT after AZD1386 treatment, while from 0.6 to 6.6°C and 0.5 to 2.0°C, respectively, after placebo treatment. A statistically significant difference of WDT between AZD1386 and placebo treatments was determined at 3.0 hours post-dose of about 3.0°C (95% CI: 0.79; 5.22).

Summary of safety results

There were 2 AEs reported, both of mild intensity; 1 AE after AZD1386 (hot flush) considered by the investigator to be related to the IP and 1 AE after placebo (nasal congestion). There were no deaths, other serious adverse events (SAEs), discontinuations of IP due to adverse events, or any other significant adverse events in the study.

Mean BT increased slightly following 300 mg AZD1386 in comparison to placebo from 1.0 hour post-dose (maximum mean change from baseline of 0.38°C after AZD1386 administration). Statistically significant differences in BT following AZD1386 versus placebo were about 0.38 to 0.49°C observed between 3.0 and 8.0 hours post-dose.

Consistent effects on QTcF, directly or in relation to BT, or any other digital ECG variable following single dose treatment with 300 mg AZD1386 did not become evident.

No clinically important changes in laboratory safety variables, 12-lead ECGs, vital signs and physical examinations were observed.