AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4017
Study Code	D2060C00001
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A Randomized, Single-blind, Placebo-controlled, Single-centre, Phase 1 Study in Healthy Volunteers to Assess the Safety, Tolerability and Pharmacokinetics of AZD4017 after Single Ascending Oral Doses

Study dates: First healthy volunteer enrolled: 17 November 2008
Last healthy volunteer completed: 16 March 2009

Phase of development: Clinical Pharmacology (1)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

This study was performed at one study centre in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table 1 presents the primary and secondary objectives in this study and the related outcome variables. The study had also an exploratory objective to collect blood samples for genotyping for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect pharmacokinetics, pharmacodynamics, safety and tolerability related to AZD4017 treatment. Blood samples for future, possible exploratory research aimed at exploring biomarkers involved in nutrient metabolism and metabolic disease (such as cortisone, POMC and DHEA) were also collected. This exploratory objective is not reported in the CSR.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To assess the safety and tolerability of AZD4017 following administration of single ascending doses.	Adverse events, laboratory variables, vital signs, ECG, physical examination
Secondary	**Secondary**
To evaluate the pharmacokinetics of AZD4017 and assess the dose proportionality of the pharmacokinetics following administration of single ascending doses of AZD4017.	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2\lambda z}$, CL/F
To explore the effect of food on the pharmacokinetics of AZD4017.	

Study design

This is a Phase I, first time in human, randomized, single-blind, placebo-controlled, single ascending dose study in healthy male subjects conducted at a single centre.

Target subject population and sample size

It was planned to include a total of 40 evaluable healthy male subjects in the study. Eight different dose escalation panels were planned, (with the option of adding up to two extra panels if needed). Two of the doses were to be repeated together with food. At each dose level, 6 subjects were to be randomized to receive AZD4017 and 2 to placebo.

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

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

Table 1 Details of investigational product and other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD4017	20 mg/mL oral suspension	AstraZeneca	F13666	62314J08
Placebo	0 mg/mL oral suspension	AstraZeneca	F13639	62313B08

In each dose panel 8 healthy volunteers were randomised to active treatment (6 healthy volunteers) or placebo (2 healthy volunteers). The dose panels received: A: 2 mg; B: 10 mg; C: 40 mg; D: 160 mg; E: 500 mg; F: 1000 mg; G: 1000 mg fractionated into 2 doses separated by 3 h; and H: 1500 mg fractionated into 2 doses separated by 3 h. The effect of food on the pharmacokinetics of AZD4017 was also studied (160 mg and 500 mg).

Duration of treatment

Each healthy volunteer received no more than 2 single doses of IP.

Statistical methods

The data were summarized using descriptive statistics. Dose proportionality was analyzed using an ANCOVA model using the logarithm of AUC (and C_{max}) as the dependent variable and the logarithm of the dose as the independent variable.

Subject population

In total, 42 Caucasian healthy male volunteers were randomised into the study at 1 study site. Each healthy volunteer received a maximum of two single doses of AZD4017 or placebo, separated by a wash-out period of at least 12 days. Two healthy volunteers discontinued the study prematurely: 1 healthy volunteer due to an adverse event (AE; vasovagal reaction) and the other healthy volunteer due to none-compliance of the restrictions in the wash-out period. All other healthy volunteers randomised to treatment completed the study.

Summary of pharmacokinetic results

The plasma concentration versus time profile for AZD4017 seems to be bi-phasic with a similar profile over the dose range studied. The predefined maximum exposure limit for AUC (189 µmol*h/L) was reached in one healthy volunteer at the 1500 mg dose level. There was considerable variability in the exposure data at individual dose levels, but based on the fit of the power model to the data from the whole dose range AUC and C_{max} seemed to increase approximately proportionally with dose.

There was a large variability in the effect of food on AUC and C_{max} of AZD4017 at both dose levels at which the effect of food was investigated. For the 160 mg dose group food did not have any clear effect on either AUC or C_{max}, whereas for the 500 mg dose group there was a tendency towards an increase in AUC and C_{max} when AZD4017 was administered together with food. The estimated ratio (fed/fasting) at this dose level was 1.43 (95% CI 1.0-2.06) for AUC and 1.37 (95% CI 0.85-2.21) for C_{max}.

Summary of safety results

There was 1 serious adverse event in the study: 1 healthy volunteer in the lowest dose group (2 mg AZD4017) experienced a vasovagal reaction with sinus arrests. The event occurred in conjunction with pain during manipulation of the venous cannula and was assessed as related to study procedures, but there was no suspicion of a relationship to treatment with study drug, as judged by the investigator.

There were no deaths, discontinuation of study treatment due to AEs, or any other significant AEs in the study. The majority of AEs were of mild or moderate intensity. The most commonly reported AEs in both the placebo and the AZD4017 treatment groups were gastrointestinal disorders and headache.

There were no clinically relevant treatment–related changes or trends in any laboratory variables measured, in blood pressure, heart rate or temperature nor in any dECG variables in the healthy volunteers exposed to AZD4017 during the study.