AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D5090C00008
Edition Number	1
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A Phase I, Randomised, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1386 in Healthy Caucasian Young and Elderly Subjects after Oral Multiple Doses

Study dates: First healthy volunteer enrolled: 25 February 2008
Last healthy volunteer completed: 29 October 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

This study was conducted at a single centre in the United Kingdom: AstraZeneca Clinical Pharmacology Unit Alderley Park, Macclesfield, Cheshire SK10 4TG, England. The first healthy volunteer was enrolled on 25 February 2008. Healthy volunteers are hereafter referred to as subjects.

Publications

None at the time of writing this report

Objectives

The primary objective of the study was to investigate the safety and tolerability of AZD1386 after multiple dosing in young and elderly healthy subjects by assessment of adverse events (AEs), vital signs, electrocardiogram (ECG) variables, body temperature, clinical chemistry, haematology and urinalysis.

The secondary objectives were:

1. To determine the pharmacokinetic (PK) profile of AZD1386 after multiple dosing by assessment of plasma concentrations

2. To explore the potential of AZD1386 to affect the CYP3A activity by assessment of urine 6β-OH-cortisol/cortisol ratio at baseline and last day of treatment and by assessment of plasma 4β-OH-cholesterol at baseline, Day 6 and last day of treatment Day 12

The exploratory objectives were:

- The effect of AZD1386 on skin heat perception using warm detection threshold (WDT) was explored.

- The effect of AZD1386 on skin heat perception using heat pain threshold (HPT) was explored.

- The effect of AZD1386 on subjective perception of body temperature by visual analogue scale (temp-VAS) was explored.

- To investigate relevant metabolites from AZD1386 in subjects after multiple dosing by assessment of PK plasma samples (objective added in Amendment 5 of the Clinical Study Protocol, the results are not reported in this CSR)

Furthermore, a blood sample for genotyping was collected (if consent given) for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK and PD, safety and tolerability related to AZD1386. (Any results will be reported separately.)

Study design

This was a single centre, double-blind, randomised, parallel group, placebo controlled study to assess the safety, tolerability and PK of AZD1386 when given as multiple doses to healthy young and elderly subjects. For young subjects, 4 to 5 consecutive multiple ascending dose panels were planned. However, due to a temporary halt in the study, dosing was stopped in the first young panel before multiple dosing had begun. Therefore, this dose panel only received a single dose of 20 mg. The second panel of young subjects received multiple doses as planned but at the same dose level (20 mg) as the first young panel. The following 3 panels of young subjects were used for dose escalation. For elderly subjects 1 single dose panel followed by 2 multiple dose panels were planned and performed.

Target subject population and sample size

The plan was to randomise a total of 64 to 69 subjects: 40 to 45 young subjects (aged ≥20 to ≤45 years) and 24 elderly subjects (aged >65 to <80 years).

Each panel consisted of 8 subjects receiving either AZD1386 (n=6) or placebo (n=2).

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

The dose levels in the study were 20 mg single dose (SD), 20 mg multiple dose (MD), 50 mg MD, 90 mg MD, 150 mg MD for the young panels and 48 mg SD, 40 mg MD and 80 mg MD for the elderly panels.

Investigational product	Dosage form, strength and route of administration	Batch numbers
AZD1386	Oral solution 2.5 mg/mL (as AZD1386 hydrogen sulphate 3.16 mg/ml), vials of 100 ml containing 100 ml	4059-3-2 4059-4-2 4059-6-2
Placebo	Oral solution (Bitrex), vials of 100 ml containing 100 ml	4073-1-1 4073-5-2

Duration of treatment

All subjects in the multiple dose panels received 1 initial dose of investigational product (IP), which was followed by a wash-out period of 48 h to adequately define the individual single-dose PK. Thereafter the subjects were dosed twice daily for 9 days and ended with a single dose the next day. In total the subjects were dosed for 11 days.

All subjects participating in the elderly single dose panel and all subjects who received dose in the first young panel (originally planned as a multiple dose panel) received 1 single dose of IP. Thereafter the subjects stayed for 48 h before they were discharged from the clinic.

Criteria for evaluation - pharmacokinetics and pharmacodynamics (main variables)

- **Pharmacokinetics**

- Single-dose profile: C_{max}, t_{max}, AUC_{0-12}, AUC, CL/F, V_z/F, MRT and $t_{½\lambda z}$ of AZD1386

- Multiple-dose phase: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, AUC_{τ}, $t_{½\lambda z}$, CL/F and accumulation ratio (calculated as AUC_{0-12} [Day 5 and Day 12]/AUC_{0-12} [Day 1] and similarly for C_{max}) of AZD1386

- Plasma concentrations and if applicable C_{max}, t_{max}, AUC_{0-12}, AUC and $t_{½\lambda z}$ of metabolites of AZD1386

- Urine 6β-OH-cortisol/cortisol ratio at baseline and on the last day of treatment

- Plasma 4β-OH-cholesterol at baseline, Day 6 and on the last day of treatment

- **Pharmacodynamics**

  WDT, HPT and subjective perception of body temperature (temp-VAS)

- **Genetics (not included in the CSR)**

  Any future genetic analyses will be reported separately.

Criteria for evaluation - safety (main variables)

- **Safety**

  AEs, vital signs, ECG variables, body temperature, clinical chemistry, haematology and urinalysis

Statistical methods

Descriptive statistics, as well as formal statistical inferential analyses, were used to analyse safety, tolerability, PK and PD data.

Subject population

Healthy males aged between 21 and 45 years (young panels) and healthy male and non-fertile females aged between 65 and 76 years (elderly panels) were included in accordance with the CSP. There were no apparent differences in composition between the different dose groups within the young/elderly panels. However, females were only included in the elderly panels.

One (1) subject in the first young panel (20 mg SD) was discontinued due to AEs (see Summary of safety results). This led to a temporary halt in the study and to the discontinuation of the other 7 subjects in the first young panel. One (1) subject discontinued voluntarily in the 90 mg MD young panel and 1 subject discontinued due to an AE in the 40 mg MD elderly panel. Thus, 10 subjects discontinued the study in total.

All subjects except 1 in the first young panel received a single dose of AZD1386/placebo before the study was temporarily halted (see study design). The subject who did not receive investigational product (IP) was excluded from all analysis sets. The analysis sets are summarised in Table S 1 and Table S 2.

Table S 1 Analysis sets, single dose

	Number of subjects (%)				
Analysis set	**Placebo SD young N=2**	**AZD1386 20 mg SD N=6**	**Placebo SD elderly N=2**	**AZD1386 48 mg SD elderly N=6**	**Total**
Subjects randomised	2 (100%)	6 (100%)	2 (100%)	6 (100%)	16
Subjects included in safety analysis set	2 (100%)	5 (83.3%)	2 (100%)	6 (100%)	15
Subjects excluded from the safety analysis set	0	1 (16.7%)	0	0	1
- Never received study drug due to temporary halt	0	1 (16.7%)	0	0	1
Subjects included in PK analysis set	2 (100%)	5 (83.3%)	2 (100%)	6 (100%)	15
Subjects excluded from the PK analysis set	0	1 (16.7%)	0	0	1
- Never received study drug due to temporary halt	0	1 (16.7%)	0	0	1
Subjects included in PD analysis set	2 (100%)	5 (83.3%)	2 (100%)	6 (100%)	15
Subjects excluded from the PD analysis set	0	1 (16.7%)	0	0	1
- Never received study drug due to temporary halt	0	1 (16.7%)	0	0	1

SD Single Dose

Table S 2 Analysis sets Multiple Dose

	Number of subjects (%)								
		AZD1386					AZD1386		
Analysis set	**Placebo MD young N=8**	**20 mg MD N=6**	**50 mg MD N=6**	**90 mg MD N=6**	**150 mg MD N=6**	**Placebo MD elderly N=4**	**40 mg MD elderly N=6**	**80 mg MD elderly N=6**	**Total**
Subjects randomised	8 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	6 (100%)	6 (100%)	48
Subjects included in safety analysis set	8 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	6 (100%)	6 (100%)	48
Subjects excluded from the safety analysis set	0	0	0	0	0	0	0	0	0
Subjects included in PK analysis set	8 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	6 (100%)	6 (100%)	48
Subjects excluded from the PK analysis set	0	0	0	0	0	0	0	0	0
Subjects included in PD analysis set	8 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	6 (100%)	6 (100%)	48
Subjects excluded from the PD analysis set	0	0	0	0	0	0	0	0	0

MD Multiple Dose

Summary of pharmacokinetic results

The median time for peak plasma concentration, t_{max}, was 1.0 to 1.5 h on Day 1 and 0.7 to 1.0 h on Day 12. The geometric mean apparent elimination half-life, $t_{½\lambda z}$, was 6.9 to 7.7 h on Day 1 and 7.5 to 8.7 h on Day 12 in young subjects and 8.0 to 10.7 h on Day 1 and 8.4 to 11.7 h on Day 12 in elderly subjects. The t_{max} and $t_{½\lambda z}$ were independent of dose. The mean exposure, AUC and C_{max} was slightly higher in elderly than in young subjects.

Following twice daily administration of AZD1386, steady state was reached after 3 to 4 days, based on trough concentrations, at all doses. The accumulation was higher than expected from single-dose data. The ratio AUC_{0-12} Day 12/AUC Day 1 was 1.57 after the lowest multiple dose in young subjects. This accumulation decreased with increasing dose to 1.04 after the highest multiple dose in young subjects. The corresponding ratios for elderly subjects were 1.53 and 1.37. This indicates that the PK properties of AZD1386 may be time-dependent, at least after lower doses. The systemic exposure (AUC and C_{max}) on Day 12 increased slightly less than proportionally to the dose. The relationships were well described by a power model, with an estimated β of 0.77 with 95% CI (0.55, 0.98) for AUC_{0-12} and an estimated β of 0.78 with 95% CI (0.62, 0.95) for $C_{max,ss}$. There was no effect on the 6β-OH-cortisol/cortisol ratio in urine or on 4β-OH-cholesterol in plasma.

Summary of pharmacodynamic results

Mean WDT tended to increase on all days and was higher than placebo in dose groups given 50 mg or higher. The maximum mean WDT was around 44°C, which was observed at different time points in the 80 mg, 90 mg and 150 mg dose groups.

Mean HPT increased in all dose groups with a maximum usually at 20 min to 2 h after dose on all days. The HPT around the time for maximum was generally significantly higher than placebo in all dose groups except the 20 mg SD group. In the 90 mg and 150 mg dose groups a majority of subjects reported an HPT of 50 degrees or higher at 20 min to 2 h after dose.

Mean temp-VAS values decreased after dosing and were significantly lower than placebo during the first hours after dose on Day 1 in young subjects receiving 150 mg and in elderly subjects given 40 or 80 mg. The maximum decreases in temp-VAS were observed at around the same time points as the maximum increases in body temperature, ie, within the first few hours after dose on Day 1. This also corresponded to when most AEs in the preferred term 'feeling cold' were reported.

The effect on WDT and HPT remained after multiple doses of AZD1386, while effects on temp-VAS decreased during multiple dosing.

Summary of safety results

No major safety and tolerability concerns were identified in this study. There were no SAEs and most AEs were of mild to moderate intensity. Two (2) subjects discontinued due to AEs, 1 in the 20 mg SD young dose group due to chills, hypoventilation, nausea, palpitations, paraesthesia and tremor and 1 in the 40 mg MD elderly dose group due to hyperglycaemia.

The most common AEs in subjects exposed to multiple doses of AZD1386 and observed in 7 or more subjects were feeling cold, headache, iv catheter site reaction, feeling hot and oral hypoaesthesia. Feeling cold/peripheral coldness were of a higher intensity in the elderly than in the young subjects.

A few mild elevations of liver markers were observed but not considered to be clinically significant. Otherwise there were no major changes in laboratory variables.

Body temperature increased slightly after each dose administration compared to placebo. The amplitude diminished over time. No other clinically relevant findings were observed for vital signs (pulse and BP).

The QTcF was shortened by up to 16 ms (150 mg group) after the first dose of AZD1386 but this effect was not sustained on Day 12.