AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D5090C00012
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A Phase I, Randomised, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1386 in Healthy Japanese young and elderly subjects after oral multiple doses.

Study dates: First healthy volunteer/patient enrolled: 21 June 2008
Last healthy volunteer/patient completed: 20 September 2008

Phase of development: Clinical Pharmacology (1)

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 study centre, Kyushu Clinical Pharmacology Research Clinic, Medical Co. LTA, Japan. The first subject was enrolled on 21 June 2008 and the last subject completed on 20 September 2008.

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 Japanese subjects by assessment of adverse events, vital signs, ECG parameters, body temperature, clinical chemistry, haematology and urinalysis.

The secondary objective of the study was to determine the PK profile of AZD1386 after multiple dosing by assessment of plasma concentrations.

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

Furthermore, a blood sample for genotyping was collected (if consent given) for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that were able to affect PK and pharmacodynamic (PD), safety and tolerability related to AZD1386.

Study design

This was a single centre, double-blind, randomised, parallel group, placebo controlled study to assess the safety, tolerability and pharmacokinetics of AZD1386 when given as multiple doses to 32 (24 healthy young and 8 healthy elderly) Japanese subjects. For young healthy subjects (aged 20 to 45) 3 consecutive multiple ascending dose panels were planned. For elderly healthy subjects (aged 65 to 80) 1 multiple dose panel was planned. Each panel consisted of 8 subjects receiving either AZD1386 (n=6) or placebo (n=2). The enrolment was performed within 30 days before the administration of investigational product. The residential period was last up to 15 days including the admission day and the subjects came back for a follow-up visit 7-10 days after discharged from the study site.

Target healthy volunteer population and sample size

A total of 32 (24 young and 8 elderly) healthy Japanese subjects, aged 20 and 45 years for young or 65 to 80 for elderly, were to be randomised in the study. The number of subjects per dose was chosen to have enough subjects to evaluate tolerability and safety based on experience from other similar Phase I studies.

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

Single and multiple doses of AZD1386 (batch no. 4059-5-2 and 4059-6-2) and placebo (batch no. 4073-2-2) were given as an oral solution without food. During the multiple dose period, the subjects were dosed twice daily. The starting dose was 20 mg. Doses were escalated from 20 mg to 50 mg and 100 mg in young panels 1 to 3. The dose in elderly panel 4 was 50 mg.

Duration of treatment

Each subject received 1 single dose (Day 1) that was followed by a wash-out period of 48 hours to adequately define the individual single-dose pharmacokinetics. The dosing continued twice daily for 9 days (Day 3 to Day 11) and ended with a single dose in the morning Day 12.

Criteria for evaluation - pharmacokinetics (main variables)

- Single-dose profile: C_{max}, t_{max}, AUC_{0-12}, AUC, CL/F, V_z/F, MRT and $t_{½\lambda z}$.
- Multiple-dose phase: $C_{max,ss}$, $t_{max,\ ss}$, $C_{min,ss}$, AUC_{τ}, $t_{½\lambda z}$, and accumulation ratio (calculated as AUC_{τ} /AUC_{0-12} (Day 1)).

Criteria for evaluation - parmacodynamics (main variables)

Subjective perception of body temperature by VAS.

Criteria for evaluation - safety (main variables)

Adverse events, vital signs, ECG parameters, body temperature, clinical chemistry, haematology and urinalysis.

Statistical methods

The primary analysis of safety and tolerability mainly consisted of descriptive statistics, including listings, summary statistics, and graphs as appropriate. The PK analysis mainly consisted of descriptive statistics.

The number of subjects per dose was chosen to have enough subjects to evaluate tolerability and safety based on experience from other studies.

Subject population

The first subject was enrolled in the study on 21 June 2008 and the last subject completed the study on 20 September 2008. In total, 60 Japanese subjects were enrolled and 32 of them were randomised and received AZD1386/placebo according to protocol. All randomised subjects completed the study.

All randomised subjects were included in the analysis of PK, PD and safety. Overall, the dose panels were well balanced with regard to demography and subject characteristics with the exception of sex. All subjects in the young panels were male, whereas 5 of 8 subjects in the elderly panel were female. The treatment code was not prematurely broken for any subjects.

Summary of pharmacokinetic results

AZD1386 was rapidly absorbed following single- and multiple-dose administration at each dose level. Peak plasma concentrations occurred at median times of approximately 0.67 to 1.00 h. Median t_{max} was similar on Days 1, 5 and 12 in all dose panels. The geometric mean C_{max} and AUC_{τ} on Day 12 were higher than the values in corresponding dose groups on Day 1. Following AZD1386 doses of 100 mg, the maximal AUC_{τ} and $C_{max,ss}$ values (Day 12) were well below the predefined exposure limits of 98000 nmol*h/L (AUC_{0-24}) and 16000 nmol/L (C_{max}).

In young subjects, apparent plasma clearance (CL/F, Gmean) was slightly higher on Day 1 than on Day 12: 23 to 26 L/h (Day 1) and 20 to 22 L/h (Day 12). Overall terminal half-life ($t_{½\lambda z}$, Gmean) of AZD1386 was approximately 6 h on Day 1 and Day 12. The $t_{½\lambda z}$ and CL/F were independent of dose. The oral volume of distribution during terminal phase (V_z/F, Gmean) on Day 1 ranged from 194 to 240 L. On Day 12, AUC_{τ} and $C_{max,ss}$ increased in a dose-proportional manner for doses from 20 mg to 100 mg.

In elderly subjects who received 50 mg AZD1386, the geometric mean CL/F (Day1) and CL_{ss}/F (Day 12) were 13.3 and 12.6 L/h respectively, and the geometric mean $t_{½\lambda z}$ was 10.0 h (Day 1) and 10.8 h (Day 12). The steady-state systemic exposure (AUC_{τ} and C_{max}) was higher and $t_{½\lambda z}$ was longer in elderly subjects compared to young subjects at the same dose (50 mg).

Following twice daily administration of AZD1386, steady state was generally achieved within five days of multiple dose administration, based upon the trough level data collected. The mean R_{acc} (Day 12/Day 1) was approximately 1.25 based on $C_{max,ss}/C_{max}$, and 1.40 to 1.50 based on AUC_{τ}/AUC_{0-12} in young subjects. In elderly subjects, the mean R_{acc} (Day 12/Day 1) was 1.44 based on C_{max} and 1.66 based on AUC_{τ}. The ratio AUC_{τ}/AUC on Day 12 was 1.13 to 1.21 in young subjects, and 1.06 in elderly subjects. The mean R_{acc} and the ratio AUC_{τ}/AUC were generally similar between Day 5 and Day 12 for all dose panels. Since the exposure increase was proportional to dose over the studied dose range on Days 1 and 12 and elimination of AZD1386 appeared to be time independent in young subjects, there was no indication of time-dependent nonlinearity in PK after multiple oral dose administration in this study.

Summary of pharmacodynamic results

There was a decrease in VAS-temp score in subjects receiving AZD1386 between time points 0.33 and 2 h post dose on Day 1. The lowest means between these time points were 49.8 mm (placebo total, at 0.67 and 1 h), 34.3 mm (20 mg young, at 0.67 h), 28.5 mm (50 mg young, at 0.67 h), 21.5 mm (100 mg young, at 0.33 h), and 34.3 mm (50 mg elderly, at 0.67 h) (Table 11.2.3.1). In each active group, the lowest mean was observed just before or at the time point of the median t_{max}. Unlike Day 1, a large decrease in mean VAS-temp was not observed on Days 5 and 12.

Summary of pharmacokinetic/pharmacodynamic relationships

There was no apparent relationship between change in VAS-temp and plasma concentration of AZD1386 on Days 1, 5 and 12.

Summary of pharmacogenetic results

Blood samples for genotyping were collected for future, possible exploratory genetic research which will be described in supplementary reports when available.

Summary of safety results

There were no SAEs or discontinuations due to AEs. All AEs were mild in intensity. No AEs were reported in young subject with 20 mg, 50 mg and placebo. AEs were reported only in young subjects with 100 mg (6 of 6 subjects) and in elderly subjects with 50 mg (5 of 6 subjects) and placebo (1 of 2 subjects). Feeling cold and peripheral coldness were the most common AEs in both young and elderly subjects.

There were no clinically important changes in mean or individual values over time in any haematology, clinical chemistry or urinalysis variable.

There were no clinically important changes in mean or individual blood pressure and pulse values in any of the treatment groups.

Body temperature increased in subjects receiving AZD1386 with a maximum mean temperature of 37.5°C in the young group with 100 mg at 6 h after first dosing. The highest temperature observed in a single subject was 37.9°C, which occurred in a young subject at 3.5 and 6 h after dosing with 100 mg AZD1386 on Day 1. The peak in body temperature appeared later than the peak in plasma concentration, the lowest VAS-temp score and the experience of feeling cold/peripheral coldness.

A statistically significant decrease of QTcF compared to combined placebo group was present at 2 h post dose on Day 1 in all active groups except for 20 mg young group. No statistically significant decrease was present on Day 12 in any group. The maximum mean effect was a shortening by approximately 20 ms compared to placebo in the highest dose group (100 mg young) and in no individual did the shortening exceed 30 ms.