AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D2600C00004
Edition Number	1
Date	28 June 2011

A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Oral AZD2423 Solution after Administration of Multiple Ascending Doses for 12 days in Young and Elderly Healthy Japanese Volunteers

Study dates: First volunteer enrolled: 24 November 2010
Last volunteer last visit: 23 March 2011

Phase of development: Clinical pharmacology (I)

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

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
Primary	**Primary**	
To investigate the safety and tolerability of AZD2423 in healthy Japanese volunteers following administration of multiple ascending doses at steady state.	Adverse events (AEs), vital signs (pulse, blood pressure and body temperature), ophthalmological findings (fundoscopy and near/distant visual acuity), electrocardiograms (ECGs, including digital ECGs), laboratory variables	Safety
Secondary	**Secondary**	
To characterise the single and multiple dose pharmacokinetics (PK) of AZD2423 in healthy Japanese volunteers.	**Single dose part:** Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal half-life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution during terminal phase (V_z/F) **Multiple dose part:** Maximum plasma concentration at steady state ($C_{ss,max}$); time to steady state C_{max} ($t_{ss,max}$); minimum plasma concentration at steady state ($C_{ss,min}$); average plasma concentration at steady state ($C_{ss,avg}$); terminal half-life at steady state ($t_{½\lambda z,ss}$); area under the plasma concentration-time curve from zero to the end of the dosing interval ($AUC_{\tau,ss}$); apparent plasma clearance at steady state (CL_{ss}/F); extent of accumulation on multiple dosing (R_{ac}); fluctuation ratio (%) and time dependency of the pharmacokinetics.	PK

Objectives	Outcome variables	Type
Exploratory	**Exploratory**	
1. To collect blood samples to allow for possible post hoc analysis of additional potential effect markers, such as cytokines, chemokines, other inflammatory mediators or patterns of inflammatory mediators. The results only were to be reported in the clinical study report (CSR) in case of unexpected findings.*	Plasma samples were collected and stored appropriately to allow for possible post hoc analysis of potential effect markers: Pro-inflammatory and anti-inflammatory cytokines (such as tumor necrosis factor [TNF] α and interleukin [IL] 6) and chemokines (such as interleukin 8) and other inflammatory mediators and patterns of inflammatory mediators	PD
2. To obtain blood samples for possible AZD2423 metabolite identification. The results of any metabolite analysis will be reported separately from the CSR for the study.	Plasma samples were collected and stored for possible future assessments of possible metabolites of AZD2423.	PK
3. To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD2423. The results of any genetic analyses will be reported separately from the CSR for the study.	Optional blood samples were collected for future exploratory genetic research.	Pharmacogenetics

* As no unexpected findings were observed in the study, the samples were not analyzed.

Study design

This was a Phase I, randomised, double-blind, placebo-controlled, multiple ascending dose study in young and elderly healthy Japanese volunteers conducted at a single centre to investigate the safety, tolerability and pharmacokinetics (PK) of AZD2423.

Target subject population and sample size

In total, 32 healthy Japanese male volunteers aged ≥20 to ≤45 years and male and female volunteers aged ≥65 to ≤80 years.

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

The following investigational products were supplied:

- AZD2423 10 mg/mL oral solution (batch number: 10-005502AZ, 10-005505AZ and 10-005514AZ)
- Placebo oral solution (batch number: 10-005726AZ and 10-005728AZ)

AZD2423 or placebo were administered as single and multiple oral doses of an oral solution. The ascending doses were 72 and 150 mg for both young and elderly volunteers.

Duration of treatment

Each volunteer received a single dose of AZD2423 or placebo on Day 1. Repeated dosing commenced on Day 4 with AZD2423 or placebo once daily for 11 days.

Statistical methods

No formal statistical hypothesis testing were performed. The analyses of safety, tolerability and pharmacokinetic data were summarised descriptively including tables, listings and graphs, as appropriate.

Subject population

In total, 90 (37 young and 53 elderly) healthy Japanese volunteers were enrolled and 32 (16 young and 16 elderly) volunteers were randomized into 4 (2 young and 2 elderly) cohorts. During the course of the study 8 volunteers (each) who were eligible to participate were included in each cohort and received either AZD2423 or placebo, randomised 6:2. All randomised healthy volunteers received a single dose on Day 1 and repeated dosing from Day 4 to Day 14. No volunteers discontinued this study. There were no protocol deviations that led to exclusion of data from the safety or PK analyses. All ranodomised healthy volunteers were included in the safety and PK analysis sets.

The young healthy male volunteers were aged between 20 and 41 (mean: 26.3) years for AZD2423 group and between 20 and 32 (mean: 25.0) years for placebo group. Body Mass Index (BMI) values ranged from 19.7 to 27.0 kg/m^2 (mean: 23.27 kg/m^2) for AZD2423 group and from 19.6 to 26.0 kg/m^2 (mean: 22.35 kg/m^2) for placebo group. All 16 young healthy volunteers were men.

The elderly healthy male and female volunteers were aged between 65 and 75 (mean: 68.3) years for AZD2423 group and between 67 and 71 (mean: 68.3) years for placebo group. BMI values ranged from 19.75 to 25.8 kg/m^2 (mean: 22.85 kg/m^2) for AZD2423 group and from 22.1 to 26.5 (mean: 24.68 kg/m^2) for placebo group. Ten of the 16 elderly healthy volunteers were men and 6 were women.

Overall, the treatment groups were well balanced within age category in terms of age, sex, height, weight and BMI.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations due to adverse events (DAEs) or other significant adverse events (OAEs) in neither young nor elderly volunteers. In total, 6 adverse events were reported in 5 of 24 healthy volunteers who were received 72 mg or 150 mg AZD2423, while no adverse events were reported in 8 healthy volunteers who received placebo.

Six adverse events included diarrhoea (72 mg) and upper respiratory tract infection (150 mg) in the young group, and oedema peripheral (72 mg), nausea, vomiting and otitis externa (150 mg) in the elderly group. All adverse events were mild in intensity.

There were no clinically relevant treatment-related changes or trends in laboratory safety variables, vital signs and ECG during the study in young and elderly healthy Japanese volunteers exposed to AZD2423. Reversible elevations of liver enzymes were observed in 1 volunteer receiving AZD2423.

There were no clinically significant abnormal findings in ophthalmological examination during the study in healthy young and elderly Japanese volunteers exposed to AZD2423.

Summary of pharmacokinetic results

- Single-dose pharmacokinetics

Following single dose administration of 72 and 150 mg AZD2423, the median t_{max} was between 0.67 and 0.83 hours in young healthy volunteers and between 0.33 and 0.50 hours in elderly healthy volunteers. Moderate-to-large inter-subject variability was seen in the C_{max}. Young healthy volunteers showed geometric mean values of 1040 and 2760 h·nmol/L for AUC and 156 and 473 nmol/L for C_{max}, respectively. Elderly healthy volunteers showed geometric mean values of 1510 and 2900 h·nmol/L for AUC and 244 and 797 nmol/L for C_{max}, respectively.

The geometric mean apparent terminals half-lives ($t_{½\lambda z}$) after 72 and 150 mg AZD2423 were 23.7 and 23.4 hours in young healthy volunteers, and were 36.7 and 30.5 hours in elderly healthy volunteers, respectively. The corresponding geometric mean CL/F values were 162 and 127 L/h in young healthy volunteers, and were 112 and 122 L/h in elderly healthy volunteers, respectively.

- Multiple-dose pharmacokinetics

Following once daily administration of AZD2423 starting on Day 4, steady state was reached within 8 to 9 days (Day 12 or Day 13) at the latest, as supported by AZD2423 pre-dose plasma concentration values. The maximum exposure levels achieved by individual healthy volunteers following multiple dosing of 150 mg AZD2423 were below the predefined exposure limits of 2200 nmol/L (C_{max}) and 13000 h·nmol/L (AUC).

Following multiple dosing, the geometric means of $AUC_{\tau,ss}$ and $C_{ss,max}$ at Day 14 increased with ascending dose of 72 and 150 mg AZD2423 in young healthy volunteers with $AUC_{\tau,ss}$ of 1130 and 3300 h·nmol/L and $C_{ss,max}$ of 192 and 569 nmol/L, and in elderly healthy volunteers with $AUC_{\tau,ss}$ of 1550 and 3640 h·nmol/L and $C_{ss,max}$ of 291 and 1200 nmol/L, respectively. The $C_{ss,max}$ values in elderly healthy volunteers were approximately 1.5 to 2.1-fold greater than those obtained in young healthy volunteers at the same dose levels. The geometric mean $AUC_{\tau,ss}$ after 72 mg AZD2423 in elderly healthy volunteers was approximately 1.4-fold greater compared to young healthy volunteers, whereas the geometric mean $AUC_{\tau,ss}$ after 150 mg AZD2423 was similar between young and elderly healthy volunteers.

The geometric mean $t_{½\lambda z,ss}$ values after 72 and 150 mg AZD2423 were 30.6 and 51.5 hours in young healthy volunteers, and were 47.5 and 49.0 hours in elderly healthy volunteers, respectively. The corresponding geometric mean CL_{ss}/F values were 150 and 106 L/h in young healthy volunteers, and were 109 and 96.7 L/h in elderly healthy volunteers, respectively.

The steady state exposure to AZD2423 on Day 14 was slightly higher than predicted from single-dose data on Day 1. However, the systemic exposure to AZD2423 appeared to be time-independent and accumulation was minimal for C_{max}, whereas the accumulation ratio was approximately 1.6 for AUC_{τ}.