AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00003
Edition Number	1
Date	21 September 2010

A Phase I, Randomised, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1446 in Healthy Young and Elderly Japanese Volunteers after Oral Single and Multiple Ascending Doses

Study dates: First healthy volunteer enrolled: 19 December 2009
Last healthy volunteer last visit: 1 June 2010

Phase of development: Clinical pharmacology (I)

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

1 centre was planned for participation only in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of AZD1446 following single and multiple ascending oral doses of AZD1446 in healthy young and elderly Japanese subjects.	Adverse events (AE)
			Laboratory variables
			Vital signs: Blood pressure, Pulse, Body temperature
			Electrocardiogram (ECG): Paper print out, Digital ECG and telemetry
			Physical examination (including skin /mucosa inspection)
			Pulmonary function: Lung auscultation and Spirometryc
			State-Trait Anxiety Inventory (STAI) state part
Secondary	PK	To investigate pharmacokinetics (PK) of AZD1446 following single and multiple dosing of AZD1446 in healthy young and elderly Japanese subjects.	[Day 1, Day 3 and Panel 4] C_{max}, t_{max}, $t_{½λz}$, $AUC_{(0-t)}$, AUC, CL/F, V_z/F and MRT [Day 3 and Panel 4 (Day 1)] A_e, f_e and CL_R [Day 4 – Day 9] $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, $AUC_{(0-24),ss}$, CL_{ss}/F, A_e, f_e and CL_R

C_{max}: Maximum plasma concentration, t_{max}: Time to C_{max}, $t_{½λz}$: Terminal half-life, $AUC_{(0-t)}$: Area under the plasma concentration-time curve from zero to the time of the last measurable concentration, AUC: Area under the plasma concentration-time curve from zero to infinity, CL/F: Apparent oral plasma clearance, V_z/F: Apparent volume of distribution during terminal phase, MRT: Mean residence time, A_e: Cumulative amount of drug excreted unchanged in urine, f_e: Fraction of given dose excreted in urine, CL_R: Renal clearance, $C_{ss,max}$: Maximum plasma concentration at steady state, $t_{ss,max}$: Time to steady state C_{max}, $C_{ss,min}$: Minimum plasma concentration at steady state, $AUC_{(0-24),ss}$: AUC during 24 hours at steady state, CL_{ss}/F: apparent oral plasma clearance at steady state

Study design

This was a Phase I randomised double-blind placebo-controlled single centre study to assess the safety, tolerability and PK of AZD1446 following single and multiple ascending dose administration to healthy young and elderly Japanese volunteers. Three dose levels were planned for the young healthy volunteers with the possibility to add an optional fourth cohort (single dose only) and two dose levels for the elderly healthy volunteers.

Target subject population and sample size

Healthy Japanese young volunteers aged 20 to 50 years and healthy elderly male and elderly female volunteers aged 65 to 80 years.

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

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Packaged Lot ID
AZD1446	Oral solution 0.5 mg/mL	AstraZeneca	08-001659AZ	08-007789AZ
AZD1446	Oral solution 25 mg/mL	AstraZeneca	08-005519AZ	08-007790AZ
Placebo	Oral solution	AstraZeneca	08-005425AZ	08-007788AZ

Duration of treatment

Each panel except for the panel 4 consisted of a single dose period and a multiple dose period. In the single dose period, the healthy volunteers received a single dose on Day 1. In the multiple dose period, the healthy volunteers received a single dose on Day 3 and multiple doses 4-times daily from Day 4 to Day 9. Only the panel 4, the healthy young male volunteers received a single dose (300 mg) on Day 1.

Statistical methods

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

Subject population

In total 32 young (20 to 35 years) and 16 elderly healthy volunteers (66 to 76 years) were randomised to AZD1446 (n=36) or placebo (n=12) at 1 study sites. All healthy volunteers received 26 (the panels 1, 2, 3, 5 and 6) or 1 (the panel 4) administrations of study drug. All healthy volunteers completed the study.

There were no important protocol deviations that led to exclusion of data from the PK or safety analysis. The safety analysis included all randomised healthy volunteers.

Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

Following single dose administration of 10 to 300 mg AZD1446 as an oral solution to young and elderly healthy volunteers, AZD1446 was rapidly absorbed (median t_{max} around 1.0 h). The decline of AZD1446 in plasma was rapid (mean $t_{½}$ approximately 2.5 h).

Following multiple dose administration (up to 85 mg x 4 in young and 60 mg x 4 in elderly healthy volunteers), steady state was reached within a few days after start of multiple dosing. Steady state exposure to AZD1446 ($C_{ss,max}$ and $AUC_{(0-24),ss}$) increased in proportion to dose without any apparent time-dependency in AZD1446 exposure in young healthy volunteers. Steady state exposure to AZD1446 ($C_{ss,max}$ and $AUC_{(0-24),ss}$) was approximately 30% and 40% higher in elderly healthy volunteers than in young healthy volunteers. At the highest multiple dose levels (85 mg x 4 in young healthy volunteers and 60 mg x 4 in elderly healthy volunteers), geometric mean $AUC_{(0-24),ss}$ (25600 and 27400 nmol*h/L in young and elderly healthy volunteers) was slightly below the predefined maximum exposure limit (AUC 30000 nmol*h/L).

Approximately 60 to 70% of a given dose was excreted unchanged in urine (fe) in young healthy volunteers and approximately 60% of a given dose in elderly healthy volunteers, indicating that renal elimination was the major elimination pathway for both single dose and multiple doses, both in young and elderly healthy volunteers. CL_R was lower in the elderly healthy volunteers compared to young healthy volunteers.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of investigational product due to adverse events (DAEs), or any other significant adverse event (OAEs) in the study.

Overall, AEs were uncommon in each treatment group and all AEs were of mild intensity. The most common AEs during treatment with AZD1446 was nausea. AEs provoked by study specific procedure, ie, orthostatic challenge (Provoked AE) were uncommon in this study. There was no clinically significant difference in frequency of AEs between young and elderly healthy volunteers.

A few healthy volunteers had values outside the predefined project specific reference limits, but there were no clinically relevant changes or trends in any laboratory safety variables measured (haematology, clinical chemistry or histamine/tryptase) in healthy volunteers exposed to AZD1446 during the study.