AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2516
Study Code	D2080C00004
Edition Number	1
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A Phase I, Single-centre, Randomised, Double-blind, Placebo-controlled Parallel group Study to Assess the Safety, Tolerability and Pharmacokinetics after Oral Single Ascending Doses of AZD2516 in Young and Elderly Japanese Healthy Subjects

Study dates: First healthy volunteer enrolled: September 2009
Last healthy volunteer last visit: December 2009

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 assess the safety and tolerability of AZD2516 following administration of single ascending doses in Japanese healthy subjects.	Adverse events Laboratory variables Physical examinations Vital signs: Blood pressure, Pulse, Body temperature ECG, Pupil size, Ophthalmologic findings, Psychiatric interview	Safety
Secondary	**Secondary**	
To investigate the pharmacokinetic of AZD2516 and provisionally assess the dose proportionality of the pharmacokinetics following administration of single ascending doses of AZD2516 in Japanese healthy subjects.	C_{max}, t_{max}, $t_{½}\lambda z$, AUC, $AUC_{(0-t)}$, CL/F, V_Z/F, fe, CL_R	PK
Exploratory	**Exploratory**	
To identify/explore genetic variations that could affect safety, tolerability, pharmacokinetics and pharmacodynamics related to AZD2516.	Markers within genes relevant to drug response related to AZD2516	PGX*
To explore metabolites in plasma and urine if possible	Concentration of possible metabolites in plasma and urine	PK
* No genotyping results are presented in this CSR		

Study design

This was a Phase I randomised double-blind placebo-controlled single centre study to assess the safety, tolerability and pharmacokinetics of AZD2516 following single ascending dose administration to healthy Japanese volunteers.

Target subject population and sample size

Healthy Japanese young male and elderly male and female volunteers. The sample size was based on experience from previous similar Phase I studies. No formal power calculation had been performed.

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

The starting dose of AZD2516 was 2 mg and the consecutive doses were 5, 10 and 20 mg for young healthy volunteers and a single 5 mg for elderly healthy volunteers. Single oral doses of AZD2516 were dispensed as a capsule 1, 5, 10 and 20 mg (Batch numbers 08-003391AZ, 08-003387AZ, 08-003388AZ, 08-003390AZ) depending on the dose that was administered. As a comparator, placebo was administered as a capsule (Batch number 08-000861AZ).

Duration of treatment

Each healthy volunteer received a single dose of AZD2516 or placebo.

Statistical methods

The primary analysis of safety and tolerability mainly consist of descriptive statistics, including listings, summary statistics, and graphs as appropriate. The PK analysis mainly consists of descriptive statistics. The number of healthy volunteers per dose was chosen to have enough healthy volunteers to evaluate tolerability, safety and pharmacokinetics based on experience from other studies.

Subject population

In total, 117 healthy volunteers were enrolled, and of these 32 males aged between 20 and 28 years (young) and 4 males and 4 non-fertile females between 65 and 75 years (elderly), were randomized in the study in 5 panels (4 young and 1 elderly panels). Each panel consisted of 8 healthy volunteers (6 receiving AZD2516 and 2 receiving placebo). The mean age was 22.6 years in the young panel and 69.6 years in the elderly panel.

None of the healthy volunteers took any concomitant medications during the study. None of the protocol deviations was judged to have any influence on the study outcome or interpretation. There was no important protocol deviation in the study. None of the healthy volunteers was excluded from the safety or PK analysis sets.

Summary of pharmacokinetic results

Following single dose administration of 2 to 20 mg, AZD2516 was rapidly absorbed with t_{max} occurring at around 1 hour. The dose of 20 mg resulted in a mean (range) C_{max} of 878 (604-1310) nmol/L and an AUC of 2040 (1490-2630) nmol/L*h. There was a large inter-individual variability in C_{max} and AUC within each dose group, with a mean CV of 31 to 55% and 21 to 52%, respectively.

In the interval 2 to 20 mg, the plasma concentrations of AZD2516 decreased in an apparently mono-exponential manner in the majority of healthy volunteers. The terminal half-life ranged between 1.0 to 1.9 h, whilst longer half-life was observed in 3 healthy volunteers who showed β-phase.

The AUC and C_{max} of AZD2516 increased slightly more than dose-proportionally across studied dose range. Renal clearance was low. No remarkable difference was observed in pharmacokinetic parameters between young and elderly healthy volunteers.

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 the study. The 5 healthy volunteers exposed to 20 mg AZD2516 reported a total of 7 AEs (three "Dizziness" and one "Dreamy state", "Elevated mood", "Hallucination visual" and "Hypnagogic hallucination") in the study. All AEs developed within 1 hour after the administration of investigational product and resolved after 0.5-4 hours without any treatment. All AEs were mild in intensity and considered by the principal investigator as related to study treatment. There was no apparent difference in adverse events between young and elderly healthy volunteers receiving 5 mg AZD2516.

There were no clinically relevant treatment-related changes or trends in any laboratory , vital signs, ECG and pupil size during the study in healthy volunteers exposed to AZD2516.