AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2516
Study Code	D2080C00001
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A Phase I, Single-centre, Randomised, Double-blind, Placebo-controlled Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD2516 in Young and Elderly Healthy Volunteers after Oral Single Ascending Doses

Study dates: First healthy volunteer enrolled: 24 September 2008
Last healthy volunteer completed: 13 December 2008

Phase of development: Clinical Pharmacology (1)

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

The primary objective of the study was to assess the safety and tolerability of AZD2516 following administration of single ascending doses and to estimate the maximum tolerated dose, if within predefined exposure and dose limits.

The secondary objective of the study was to characterise the pharmacokinetics of AZD2516 and provisionally assess the dose proportionality of the pharmacokinetics following administration of single ascending doses of AZD2516.

A blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect pharmacokinetics and pharmacodynamics, safety and tolerability related to AZD2516 treatment. No genotyping results are presented in this CSR.

In addition, there was a possibility to explore metabolism, by assessment of metabolites in urine and blood and the effect of food on the pharmacokinetics of AZD2516. However, food effect data were not collected in the study.

Study design

This study was a single centre, double-blind, randomised (within dose), parallel group, placebo controlled study. The starting dose of AZD2516 was 0.2 mg and dose escalation continued up to 40 mg, furthermore, in the last panel 41 mg was given as fractionated dosing.

Target healthy volunteer population and sample size

In total, 71 healthy volunteers participated in the study. Each panel consisted of 8 healthy volunteers (6 receiving AZD2516 and 2 receiving placebo), except for panel 3 (2 mg), where 7 healthy volunteers were included (5 receiving AZD2516 and 2 receiving placebo). There were 9 panels included in the study, 8 panels for young healthy volunteers and 1 panel for elderly healthy volunteers. Young healthy volunteers were defined by the age 20 to 45 years. Elderly healthy volunteers were defined by the age 65 to 80 years.

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

Single oral doses of AZD2516 were dispensed as a capsule 1, 1.5, 5 and 10 mg (Batch numbers 4142-1-1/08-000855AZ, 4145-1-1/08-000858AZ, 4143-1-1/08-000859AZ, 4144-1-1/08-000860AZ) depending on the dose that was administered. As a comparator, placebo was administered as a capsule (Batch number 3940-8-8/08-000861AZ). For doses lower than 1

mg, hydrochloric acid (0.01M) was used by the Pharmacy to constitute the AZD2516 capsule to an oral solution, and for the placebo oral solution. Doses administered in the study were 0.2, 0.8, 2, 5, 10, 20, 40 mg and 41 mg fractionated as 20+7+7+7 mg of AZD2516.

Duration of treatment

Each individual received a single dose of AZD2516 or placebo.

Criteria for evaluation - pharmacokinetics

Maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), time to reach C_{max} (t_{max}), terminal half-life ($t_{1/2\lambda z}$), fraction of systemically available drug excreted in urine (f_e), renal clearance (CL_R) and apparent plasma clearance (CL/F), Oral volume of distribution (apparent) during terminal (λz) phase (Vz/F), and concentration of possible metabolites in plasma and urine.

Criteria for evaluation - safety

Adverse events, laboratory variables: clinical chemistry, haematology urinalysis, supine vital signs variables: blood pressure, pulse, electrocardiogram, body temperature, pupil size.

Statistical methods

The primary analysis of safety and tolerability consisted mainly of descriptive statistics, including listings, summary statistics, and graphs as appropriate. The pharmacokinetic analysis consisted mainly of descriptive statistics, with the exception of the analysis of the dose proportionality, where a power model was used. 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

In total, 65 males and 6 non-fertile females aged between 20 to 43 years (young) and 68 to 78 years (elderly), entered the study in 9 panels (8 young and 1 elderly panels). The demographic characteristics reflect what could be expected from the study population defined by inclusion/exclusion criteria. The mean age was 26.1 years in the young, and 71.6 years in the elderly panel. The young panels did not include any female healthy volunteers, while 6 out of 8 healthy volunteers in the elderly panel were females.

Only concomitant medications allowed in the protocol were used during the study, and they did not have an impact on the interpretation of the results. There was one important protocol deviation in the study: a healthy volunteer was as included with BMI outside allowed criteria (BMI 28.7). None of the healthy volunteers were excluded from the safety or PK analysis sets.

Summary of pharmacokinetic results

AZD2516 was rapidly absorbed with t_{max} occurring at around 1 hour. An earlier t_{max} was observed for the first 2 panels (0.2 and 0.8 mg) in which AZD2516 was given as a solution as

compared to capsules in the other panels. The dose of 40 mg resulted in an average (range) C_{max} of 1320 (782-1860) nmol/L and an AUC of 3870 (2380-5530) nmol/L*h. The predefined upper exposure limit was approached at the 40 mg dose level in this study in terms of total C_{max} 1570 nmol/L, but not in terms of total AUC 20000 nmol*h/L. There was a large inter-individual variability in C_{max} and AUC within each dose group, with a mean CV of 37 to 82% and 25 to 68%, respectively. At doses 20 and 40 mg the terminal half-life ranged between 3.5 to 8.4 h, whilst the effective half-life was approximately 1 h.

The AUC and C_{max} of AZD2516 were approximately dose-proportional. Renal clearance was low. No apparent difference was observed in pharmacokinetic parameters between young and elderly subjects.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations due to AEs (DAEs) or other significant AEs (OAEs) in the study. Most AEs were reported at the doses of 20, 40 and the fractionated 41 mg. There was no apparent difference in adverse events between young and elderly healthy volunteers receiving 5 mg AZD2516.

Most AEs were mild to moderate in intensity . The AE of 'syncope vasovagal' (preferred term) of severe intensity was experienced by a healthy volunteer receiving 40 mg AZD2516 during blood sampling that lasted for 5 min, and was not considered by the investigator as related to study treatment. The proportion of adverse events assessed by the investigator as associated with study treatment was higher at higher doses.

The most common AEs observed in the study (occurring 4 or more healthy volunteers, PT) were 'Disturbance in attention', 'Dizziness', 'Headache', 'Vision blurred', 'Feeling drunk' and 'Abnormal dreams', in healthy volunteers exposed to AZD2516. All AEs resolved spontaneously and completely and the doses were tolerated.

There were no clinically relevant treatment related changes or trends in laboratory safety, vital signs, ECG and pupil size during the study in healthy volunteers exposed to AZD2516. The cardiologist did not consider it likely that the QT shortening seen 4 to 8 h after dose in the elderly group was related to study drug, as similar effects in the young treatment groups at higher doses were not observed.