AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0328
Study Code	D0190C00006
Edition Number	1
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A Phase I, Randomized, Double-blind (with-in panel), Placebo-controlled, Parallel Group Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD0328 in Healthy Elderly Volunteers After Oral Multiple Ascending Doses of AZD0328

Study dates: First healthy volunteer enrolled: 13 November 2007
Last healthy volunteer completed: 12 June 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)

Quintiles AB
Phase I Services
Strandbodgatan 1
SE-753 23 Uppsala, Sweden

Quintiles-Hermelinen AB
Varvsgatan 53
SE-972 33 Luleå, Sweden

Berzelius Clinical Research Center AB
Berzelius Science Park
SE-582 25 Linköping, Sweden

AstraZeneca Clinical Pharmacology Unit
Karolinska University Hospital Huddinge,
C2-84
SE-141 86 Stockholm, Sweden

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was

- to assess the safety and tolerability, following once-daily dosing for 13 days, of an orally administered solution of AZD0328 in healthy elderly subjects and to determine the maximum tolerated dose (MTD), if within the predefined exposure limits.

The secondary objectives of the study were:

- to determine the single and multiple dose PK of AZD0328, to assess the time required to attain steady state, to assess dose proportionality at steady state, the degree of accumulation and time dependency of the PK.

- to evaluate the cognitive dose response relationship for AZD0328 (change from baseline to 13 days).

Exploratory objectives for this study were:

- to explore blood samples for analysis of the regulation of nicotinic receptor expression after administration of AZD0328 (not reported in this Clinical Study Report).

- to collect blood and urine samples for analysis of biomarkers of cartilage, bone and synovial inflammation (not reported in this Clinical Study Report).

- to collect DNA samples that may be used for future exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK and PD (including biomarkers), safety and tolerability related to AZD0328 treatment from

subjects who have provided separate, optional written informed consent (partially reported in this Clinical Study Report).

Study design

The study consisted of 14 dose panels where each panel included 8 healthy volunteers, 6 receiving the same dose of AZD0328 and 2 healthy volunteers receiving placebo. Each dose panel was denoted either as a dose escalation panel or a dose response panel. After each dose escalation panel (0.025, 0.075, 0.23, 0.68 and 1.35 mg), a Safety Review Committee (SRC) evaluated the safety, tolerability and the pharmacokinetics of AZD0328 and decided the next dose (planned dose, increased or decreased dose, repeated dose or dose stopped). After each dose response panel, a PD Review Committee (PRC) evaluated the PD data (cognitive results) from all previous panels, and decided the dose in the next dose response panel. The doses in the dose response panels never exceeded the maximal dose administrated in a previous dose escalation panel. In order to cover a broad dose range, dose response panels included doses lower than the starting dose.

Target healthy volunteer population and sample size

The volunteers participating in the study were 112 (38 male, 46 female) Caucasian, healthy volunteers aged 60 to 78 years. The healthy volunteers were required not to use any tobacco products within 90 days of administration of investigational product.

Each dose panel consisted of 8 healthy volunteers, 6 receiving AZD0328 and 2 placebo. Some doses were repeated in two or more panels, resulting in that the number of healthy volunteers varied between different dose groups. The doses given were: 0.001 mg (n=6), 0.005 mg (n=12), 0.010 mg (n=6), 0.025 mg (n=12), 0.075 mg (n=12), 0.230 mg (n=6), 0.680 mg (n=18), 1.000 mg (n=6), 1.350 mg (n=6) and placebo (n=28).

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

The investigational product was AZD0328, powder for oral solution, manufactured by AstraZeneca (formulation number 4069-X-1, batch number 4096-3-1). The placebo used was sodium chloride solution for injection (9 mg/mL), manufactured by Fresenius Kabi or equivalent purchased locally.

Duration of treatment

AZD0328 was given as single oral doses, once-daily for 13 days, on study Day 1 and Day 3 to 14.

Criteria for evaluation - pharmacokinetics and pharmacodynamics (main variables)

Variables used for evaluation of pharmacokinetics were:

Single dose profiles AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2}$, CL/F, V_Z/F, Ae, CL_R, fe_{po}
Multiple dose profiles AUC_{τ}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, CL/F, Ae, CL_R, fe_{po}

Dose proportionality	AUC_{τ}, $C_{max,ss}$
Accumulation ratio	$AUC_{\tau}/AUC_{(0-t)}$, $C_{ss,max}/C_{max}$
Time dependency	AUC_{τ}/AUC

Secondary variable for evaluation of pharmacodynamics were standardized cognitive changes scores.

Criteria for evaluation - safety (main variables)

Variables used for the evaluation of safety and tolerability were: adverse events, laboratory variables (including clinical chemistry, haematology and urinalysis), vital signs (including blood pressure, pulse and body temperature), ECG and the Spielberger State-Trait Anxiety Inventory.

Statistical methods

The data were summarized using descriptive statistics. Dose proportionality was analysed by using the power model approach. PK parameters were analysed by a linear model (ANCOVA) in order to assess dose proportionality and dependencies on other covariates. The results of the PD assessments were analyzed using a linear model (ANCOVA) with the dose group and baseline score as covariates.

Subject population

In total, 112 Caucasian male and non-fertile female healthy volunteers were randomised into the study at 4 study sites. One healthy volunteer was discontinued from the study on Day 1 after receiving one dose of AZD0328, due to incorrect enrolment (pathological ECG findings that were already present predose on Day 1).

Of the remaining 111 healthy volunteers, 83 received study drug and 28 received placebo, in 13 administrations once daily on Day 1 and Days 3 to 14 and all completed the study. The healthy volunteers receiving AZD0328 were in total 38 men and 46 women aged from 60 to 78 years with BMI ranging from 19.2 to 30.4 kg/m^2. Overall, the dose panels were well balanced and comparable with regards to age. The frequency of women in each dose groups varied between 33% and 100%.

Summary of pharmacokinetic results

Peak plasma concentrations occurred at median times of approximately 1.5 to 2.3 h, ranging from 0.68 to 4 h (Day 1) and approximately 1 to 2.3 h, ranging from 0.5 to 6 h (Day 14). Oral plasma clearance (CL/F, Gmean) was similar between Day 1 and Day 14: 18 to 23 L/h (Day 1) and 15 to 21 L/h (Day 14). The terminal half-life ($t_{1/2}$, Gmean) of AZD0328 was 6.4 to 8.4 h with an overall mean of approximately 7 h. The oral volume of distribution during terminal phase (V_Z/F, Gmean) was 166 to 260 L. Approximately 46% of the orally administered drug (fe_{po}=0.46, overall Gmean of dose escalation panels) was excreted as unchanged AZD0328 in the urine, ranging from 38 to 53 % (Day 1 and 14). Following AZD0328 doses of 1.35 mg, the maximal AUC and C_{max} values (Day 1) or maximal AUC_{τ}

and $C_{ss,.max}$ values (Day 14) were well below the predefined exposure limits of 1500 nmol*h/L (AUC) and 600 nmol/L (C_{max}).

Following once daily administration of AZD0328, steady state was reached within three days. The mean accumulation ratio (R_{ac}, Day 14/Day 1) was 1.03 to 1.17 based on $C_{ss,.max}/C_{.max}$, and 1.11 to 1.25 based on $AUC_{\tau}/AUC_{0\text{-}t}$. The ratio AUC_{τ}/AUC was 1.01 to 1.1, indicating that the PK of AZD0328 is time-independent.

Both AUC_{τ} and $C_{ss,max}$ were considered to be approximately proportional to dose in the studied dose range (0.025 to 1.35 mg for AUC_{τ}; 0.005 to 1.35 mg for $C_{ss,max}$). Furthermore, oral clearance (CL/F) appeared to be dose independent for doses of 0.025 to 1.35 mg for Day 1 and Day 14.

Linear models were fitted by regressing log (AUC) and log (C_{max}) for Day 1 or log (AUC_{τ}) and log ($C_{ss,max}$) for Day 14 on log dose, gender, weight, age, CYP2D6 genotype and baseline creatinine clearance. For AUC and AUC_{τ}, genotype and creatinine clearance had a minor but statistically significant impact. No impact could be demonstrated for gender, age and body weight. Regarding C_{max} and $C_{ss,max}$, a minor but statistically significant impact of body weight was demonstrated. In addition, a minor impact of gender was found at Day 1 (males had 81% of the C_{max} of the females) and a minor impact of CYP2D6 genotype at Day 14.

Summary of pharmacodynamic results

No significant effects of AZD0328 on cognition were seen over time.

Summary of pharmacogenetic results

The individual level of exposure (dose normalized AUC and C_{max}) was plotted against dose for a number of drug-metabolizing enzymes. A possible tendency of increased exposure was identified for CYP2D6 poor metabolizers. The impact of CYP2D6 genotype on exposure was subsequently analysed using a statistical model, see the Summary of pharmacokinetic results. The genotype had no apparent impact on dose normalized AUC and C_{max} for the other tested genes (ABCB1, CYP2A6, CYP2B6, CYP2C9, CYP2C19, UGT1A1, UGT2B7, UGT2B15 and UGT2B17).

Summary of safety results

There were no deaths, other SAEs, DAEs, OAEs in the study. The frequency of reported AEs generally increased with dose. There was a marked increase of the average number of AEs per healthy volunteer at the highest dose level (1.35 mg). The intensity also increased at the three highest dose levels (0.68 to 1.35 mg). The most common AEs were headache, nausea, fatigue, flatulence and diarrhoea. Apart from gastrointestinal disorders and flushing, adverse events occurred with similar frequency in healthy volunteers receiving placebo and those receiving AZD0328.

In total, gastrointestinal symptoms were reported at least once by 53% of the healthy volunteers receiving AZD0328 compared to 36% of the healthy volunteers receiving placebo. Both the frequency and intensity of gastrointestinal AEs increased with the dose of AZD0328. Flushing was found only in the 2 highest dose groups (1.0 and 1.35 mg), was always observed within 2 hours after administration of AZD0328 and usually had a duration of less than 1 hour.

There were no clinically relevant treatment-related changes or trends in any vital signs, laboratory, ECG variables or Spielberger State-Trait Anxiety Inventory values, measured in healthy volunteers receiving AZD0328 during the study.