AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7268
Study Code	D1151C00001
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A Phase I, Single Center, Double-blind, Randomized, Placebo-controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD7268 after Single Ascending Oral Doses in Healthy Subjects

Study dates: First healthy volunteer enrolled: 8 December 2008
Last healthy volunteer completed: 5 March 2009

Phase of development: Clinical pharmacology (1)

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

Study center

AstraZeneca Clinical Pharmacology Unit
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Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to assess the safety and tolerability of AZD7268 following administration of single ascending doses by assessment of adverse events (AEs), vital signs, physical examination, laboratory parameters, electrocardiography (ECG), and electroencephalography (EEG). The secondary objectives of this study were to evaluate and characterize pharmacokinetics of AZD7268 and its metabolites in healthy subjects following single ascending dose administration given under fasted or fed conditions and to collect blood samples for possible retrospective genotyping.

Study design

This was a Phase I randomized, double-blind, placebo-controlled single center study to assess the safety, tolerability and pharmacokinetics of AZD7268 following single ascending dose administration to healthy volunteers.

All dose cohorts received 1 oral dose of AZD7268/placebo with the exception of dose cohort 4. Cohort 4 participated in 2 periods of study. In Period 1, investigational drug was administered with the volunteers in a fasted state. After a safety review, treatment assignments were unblinded to identify who received active drug. Volunteers who received AZD7268 in Period 1 participated in Period 2 and received drug after consuming a standardized high fat meal.

Target healthy volunteer population and sample size

Healthy volunteers, either male or surgically-sterile females from 18 to 45 years old with a body mass index of 18 to 30 kg/m^2, were to be included. Major exclusion criteria limited the population to non-drug-abusers, individuals with normal ECG and EEG patterns and no family or personal history of seizure disorder, and individuals not taking prescription or over-the-counter medicines.

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

AZD7268 was supplied as powder for oral solution (Batch ST76133-001-FA01) and as capsules in 1 mg (Batch ST76129-001-FA01), 5 mg (Batch ST76131-001-FA01) and 10 mg (Batch ST76132-001-FA01) strengths. Matching placebo capsules (Batch ST76134-001-

FA01) were also supplied. Single doses were administered as a 0.2 mg oral solution or as either 1 mg, 3 mg, 10 mg (fed and fasted conditions), 15 mg, or 20 mg via oral capsules.

Duration of treatment

Cohorts 1 through 3, 5, 6 and placebo-treated volunteers in Cohort 4: Single dose.

Cohort 4 volunteers receiving AZD7268: Single dose in a fasted state with at least 7 days washout followed by second single dose in the fed state.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

The following pharmacokinetic assessments were made.

Pharmacokinetics: C_{max}, t_{max}, $t_{1/2\lambda z}$, AUC, AUC_{0-t}, CL/F, V_z/F, Ae as percent of dose, F_e, CL_R.

To assess a possible food effect on pharmacokinetics, ratios of fed to fasted C_{max}, AUC and AUC_{0-t} were evaluated by ANOVA.

Criteria for evaluation - safety (main variables)

The following safety assessments were made: adverse events, vital signs: blood pressure, pulse, body temperature, physical examinations, electrocardiography, electroencephalography, clinical chemistry, hematology, and urinalysis.

Statistical methods

All outcome variables were summarized by descriptive statistics.

Subject population

In total, 15 Caucasian, 32 African-American and 1 Asian males were randomly assigned to treatment at 1 study site. Twelve of these volunteers were randomly assigned to placebo treatment and 36, to treatment with AZD7268. Thirty of the volunteers each received 1 administration of AZD7268 during the planned treatment visit. The 6 volunteers who received AZD7268 10 mg received 2 administrations of the drug, once in the fed and again in the fasted condition. All healthy volunteers randomly assigned to treatment completed the study. The average age was 33.8 years. The cohorts were well-balanced across demographic characteristics.

Summary of pharmacokinetic results

Following a single oral administration of AZD7268 0.2 mg to 20 mg, AZD7268 was absorbed with a median t_{max} of 1.5 to 3.49 h across all dosing groups. The geometric mean of C_{max} increased from 4.29 ng/mL (3 mg dose) to 71.4 ng/mL (20 mg dose) and that of AUC, from 232 (10 mg dose) to 373 h*ng/mL (20 mg dose). The geometric means of $t_{1/2\lambda z}$ for the 10 mg, 15 mg and 20 mg dose groups were 8.21, 6.10 and 6.09 h, respectively. The geometric mean of oral clearance (CL/F) was lower in the 10 mg dose group (43000 mL/h), but consistent between the 15 and 20 mg dose groups (53600 mL/h). Due to the limited number of measurable plasma concentrations, most pharmacokinetic parameters of the parent were

estimated from data for AZD7268 doses ≥10 mg. Only T_{max} and C_{max} estimates were calculable for the 3 mg dose.

Renal excretion (A_e) of AZD7268 and its two metabolites AZ12728094 and AZ13100152 was observed across dose groups, and the amount excreted increased with the dose. Renal clearance (CLr) for AZD7268 was consistent across dose groups (10-20 mg). The geometric mean of the percentage of AZD7268 dose excreted in the urine as the parent ranged from 7.27% to 10.5% across dose groups.

Volunteers given a 10 mg dose of AZD7268 in conjunction with a high-fat breakfast exhibited a geometric mean C_{max} of 20.3 ng/mL compared to one of 29.1 ng/mL in the fasted condition. AUC was also somewhat lower in the fed condition (208 h*ng/mL) than in the fasted (232 h*ng/mL). Median T_{max} was similar in both conditions. Geometric mean oral clearance (CL/F) was lower in the fed condition than in the fasted condition and terminal half life ($t_{1/2\lambda z}$) was longer in the fed condition. The conventional 90% CI criteria for the PK ratio estimates failed to support a lack of food effect, but the small sample size precluded a rigorous evaluation of true food effect.

Summary of safety results

There were no deaths, other serious adverse events, discontinuations due to adverse events or other significant adverse events in the study. All adverse events were of mild to moderate intensity. Events including dizziness, light-headedness and syncope were noted around the time of maximal AZD7268 plasma concentrations in volunteers given the 20 mg dose, and the pre-syncopal and syncopal episodes were regarded as limiting the dosing range for this study.

Date of the report

13 July 2009

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