AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7268
Study Code	D1151C00002
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A Phase I, Single Center, Randomized, Double-Blind, Placebo-Controlled Single Ascending Oral Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD7268 in Healthy Japanese Subjects

Study dates:

Phase of development:

Principal Investigator:
Sponsor's Responsible Medical Officer:

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

Study centre(s)

The study was conducted at a single-center. Forty-eight healthy Japanese male and/or female (of non-child bearing potential) volunteers 20 to 45 years of age were recruited for this study.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objective	Outcome Variables	Type
Primary		
To investigate the safety and tolerability of oral AZD7268 capsules following administration of single ascending oral doses.	Adverse events (AEs)	Safety
	Clinical chemistry, hematology and urinalysis laboratory parameters	Safety
	Vital signs: orthostatic pulse, and blood pressure, body temperature, height and weight	Safety
	Digital and paper electrocardiography (dECG/pECG): 12-lead ECG, real time telemetry	Safety
	Electroencephalography (EEG)	Safety
	Physical examination	Safety
	Neurological assessment: Columbia-Suicide Severity Rating Scale (C-SSRS)	Safety
Secondary		
To characterize the pharmacokinetics (PK) of AZD7268 and its metabolites, M1 (AZ13100152) and M2 (AZ12728094), following administration of single ascending oral doses.	Maximum plasma concentration (C_{max}), time to Cmax (t_{max}), terminal rate constant (λz); terminal half-life ($t_{½}$), area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution based on the terminal phase (Vz/F), amount of drug excreted in the urine (A_e), apparent fraction of dose excreted unchanged in urine (f_e) and renal clearance (CL_R)	PK
Exploratory		
To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes that may influence response i.e. distribution, safety, tolerability and efficacy of AZD7268 treatment	Voluntary sample donation; no results to be presented in this report.	Pharmacogenetic (PGX)

Study design

This is a Phase I, randomized, double-blind, placebo-controlled, single center study to assess the safety, tolerability and PK of AZD7268 following single ascending oral dose administration to healthy Japanese subjects. Six dose panels were run with 8 subjects allocated to each dose panel and randomized to receive AZD7268 (n=6) or placebo to match (n=2).

Target subject population and sample size

Healthy Japanese male and/or female (of non-child bearing potential) subjects 20 to 45 years of age.

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

AZD7268 was provided in immediate release 1, 5, and 10 mg capsules. Matching placebo capsules were provided for AZD7268.

Table S-2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength,	Manufacturer	Formulation number	Batch number[a]
AZD7268	1 mg opaque orange capsule	AstraZeneca	F13675	09-003020AZ
AZD7268	5 mg opaque orange capsule	AstraZeneca	F13677	09-003022AZ
AZD7268	10 mg opaque orange capsule	AstraZeneca	F13678	09-003023AZ
Placebo to match AZD7268	0 mg opaque orange capsule to match 1 mg, 5 mg and 10 mg capsules	AstraZeneca	F13680	09-003024AZ

a Batch numbers are not required for non-IP/test drug.

Duration of treatment

Each subject received a single dose of AZD7268 or placebo. The study duration for the subjects was approximately 45 days, which included up to 30 days for screening, 4 confinement days for treatment and post dose assessments, and a follow-up visit 7 to 14 days post dose.

Statistical methods

All analyses were performed under the direction of the Biostatistics Group, AstraZeneca. All calculations were performed with the SAS® (SAS Institute Inc., Cary, NC), unless otherwise stated. Given the exploratory nature, no formal statistical hypothesis testing was performed in this study.

All subjects who received at least one dose of randomized investigational product (IP), AZD7268 or placebo, and for whom any post-dose data are available, were included in the safety population.

Data for all enrolled subjects were presented in data listings. For those listings or data summaries where baseline and change from baseline measurements were presented, unless stated otherwise, the last observed measurement prior to the first dose of treatment medication was considered the baseline measurement.

To achieve the primary objective, the safety and tolerability were evaluated in terms of AEs, clinical laboratory assessments, ECG (paper and digital), EEG, vital signs, neurological assessments, and physical examinations.

To achieve the secondary objectives related to PK, drug concentrations in plasma and in urine were assessed and summarized. Individual PK parameters were summarized for each regimen. Pharmacokinetic analyses were performed using WinNonlin, Version 5.1 or later (Pharsight Corporation, Mountain View, California, USA).

All data were presented according to the dose administered (not by the cohort), and data from subjects receiving placebo were pooled across cohorts for the purposes of summarization of safety results. Pharmacokinetic data from subjects receiving placebo were not included in the summary and analysis of PK parameters.

Unless otherwise stated, descriptive summary statistics for continuous variables included N, mean (i.e., arithmetic mean), standard deviation (SD), minimum, median, and maximum, while for continuous PK variables, descriptive summary statistics included, in addition, geometric mean, arithmetic coefficient of variation (CV%), and geometric coefficient of variation (GCV%). Descriptive summary statistics for categorical data included the frequency and proportion.

There was no imputation (substitution) for missing data unless explicitly specified otherwise in this protocol, such as for missing plasma concentration. A subject who withdrew prior to the last planned observation in a study period was included in the analysis up to the time of discontinuation.

Graphical methods were used in exploring PK results.

Subject population

In total, 48 Japanese male subjects were randomized into the study at a single site; each received a single dose of IP during the planned treatment visit. Although female subjects of non-child bearing potential were allowed per protocol, no female subjects were enrolled into this study. Forty-seven subjects completed the study. Subject 304 administered AZD7268 10 mg was recorded as lost to follow-up after completing Visit 2. This subject had reportedly returned to Japan following discharge from the clinical unit. All safety assessments performed during Visit 2 were not clinically significant and the subject did not report any AEs.

Summary of pharmacokinetic results

The plasma PK profile of AZD7268 was assessed from predose to 72 hours post-dose. Following a single oral administration of 1 mg to 40 mg AZD7268, AZD7268 was absorbed with a median t_{max} of 1.25 to 4.00 hours post dose across all dose groups. The geometric mean of C_{max} increased from 1.54 ng/mL (1 mg dose) to 106 ng/mL (40 mg dose) and that of AUC increased from 19.6 ng*h/mL (1 mg dose) to 732 ng*h/mL (40 mg dose). The oral clearance varied between dose groups with CV% ≤ 44.2%. The geometric mean $t_{1/2}$ ranged from 3.75 h to 13.14 h; a longer geometric mean $t_{1/2}$ was observed in the 30 mg and 40 mg dose groups.

The exposure to either of the 2 metabolites (AZ12728094 or AZ13100152) was much lower than that to AZD7268. Due to limited measurable plasma concentrations across all dose groups, the PK parameters of the 2 metabolites analyzed (AZ12728094 and AZ13100152) were not reported.

Renal excretion (A_e) for AZD7268 and its 2 metabolites was observed across dose groups, which increased considerably as the dose increased. Renal clearance (CL_R) for AZD7268 was consistent across dose groups (1 to 40 mg). The geometric mean of the percentage of AZD7268 dose excreted in the urine as the parent ranged from 5.6 to 10.0% across dose groups.

Summary of safety results

During this study, a total of 16 AEs were reported by 9 subjects (8 [22%] subjects on active and 1 [8%] subject on placebo). There were no serious adverse events (SAEs) or AEs that led to withdrawal from the study. All AEs experienced by placebo subjects were of mild intensity; and mild (6 events) to moderate (8 events) AEs were experienced by active subjects. The 8 moderate AEs reported by active subjects (1 event at 30 mg and 7 events at 40 mg) included dizziness (3 events), orthostatic hypotension (2 events), hypotension (1 event), bradycardia (1 event), and syncope (1 event). The number and intensity of AEs in the AZD7268 40 mg group was higher as compared to the other AZD7268 dose groups.

Of the 14 AEs reported by active subjects, 86% (12 AEs) had at least a possible causality to the study treatment as judged by the Principal Investigator. Of the 2 AEs reported by the 1 placebo subject who reported an AE, neither had at least a possible causality to the study treatment as judged by the Principal Investigator.

The most frequently (≥2 subjects per dose) reported AEs at any dose level were: Cardiac Disorders (mild, related tachycardia at the 40 mg dose) and Nervous System Disorders (mild, related somnolence at the 15 mg dose and mild to moderate, related dizziness at the 40 mg dose).

AZD7268 was well tolerated when administered as single ascending oral doses up to and including 30 mg. No safety concerns were raised for the dose range of 1 mg to 30 mg. A 40 mg dose of AZD7268 was also dosed. Vital sign AEs, considered by the investigator to be related to treatment (syncope, hypotension/dizziness) observed in the AZD7268 40 mg

cohort, resulted in the cessation of dose escalation after SRC review of blinded data and the consideration of this dose as intolerable when the data were unblinded.

QT and QTcF did not exhibit any significant changes following AZD7268 administration compared to placebo. There were no clinically significant clinical laboratory parameters, ECG measurements, EEG recordings or physical examination findings following any dose of AZD7268 or placebo.

Date of Report:

26 February 2010