AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7268
Study Code	D1151C00003
Edition Number	1
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A Phase I, Single-center, Double-blind, Randomized, Placebo-controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of AZD7268 When Given in Multiple Ascending Oral Doses in Healthy 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 center

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and outcome variables for this study are shown in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the safety and tolerability of AZD7268 when given orally in multiple ascending doses (MAD) to healthy male subjects and healthy female subjects of non-child-bearing potential.	Assessment of adverse events, vital signs, physical examination, clinical laboratory assessments, electroencephalograms (EEGs), and electrocardiograms (ECGs), physical examinations, and Columbia Suicide Severity Rating Scale	Safety
Secondary	**Secondary**	
To characterize the pharmacokinetics (PK) of AZD7268 and its metabolites, M1 (AZ1310052) and M2 (AZ12728094), when given orally.	AZD7268 concentration in plasma and urine samples	PK
To collect blood samples for optional exploratory genetic studies focusing on the identification of genes that influence disposition, efficacy, safety, and tolerability of AZD7268.	Genetic analysis of blood sample	Exploratory
To explore the concentration of AZD7268 in cerebrospinal fluid (CSF) in healthy subjects.	AZD7268 concentration in CSF[a]	Exploratory

[a] Cohort 5 only.

Study design

In this multiple ascending dose (MAD) study, the starting dose of AZD7268 was 5 mg once daily (QD), and dose escalation continued until the Safety Review Committee (SRC) had

determined that escalation should be halted due to safety and tolerability or PK and/or the predefined maximum exposure level was reached as defined by an AZD7268 maximum plasma concentration (C_{max}) of 260 nM. In each cohort, 10 healthy volunteers were randomly assigned to active treatment or placebo in a ratio of 8:2.

Healthy volunteers were assigned to 1 of 6 ascending-dose groups beginning with Cohort 1 and continuing with Cohort 2, Cohort 3, Cohort 4, Cohort 5, and Cohort 6, in that order. Cohort 1 received a single daily dose of AZD7268 5 mg or placebo on Day 1 and Days 3 to 9. For Cohorts 2, 3, and 4, each healthy volunteer was assigned to receive AZD7268 twice daily (BID) dose of 5 mg, 10 mg, and 15 mg, respectively, or placebo. Cohorts 2 to 4 received a single dose of AZD7268 or placebo on Days 1 and 9 and received the assigned BID dose on Days 3 through 8.

For Cohort 5, AZD7268 was titrated up to a 20-mg BID oral dose. Each healthy volunteer received AZD7268 10 mg or placebo BID on Day 1; AZD7268 15 mg or placebo BID on Day 2; and AZD7268 20 mg or placebo BID on Days 3 through 8. Healthy volunteers received a single oral dose of AZD7268 20 mg or placebo on Day 9.

For Cohort 6, AZD7268 was titrated up to a 30-mg BID oral dose. Each healthy volunteer received AZD7268 10 mg or placebo BID on Day 1; AZD7268 15 mg or placebo BID on Day 2; AZD7268 20 mg or placebo BID on Day 3; and AZD7268 30 mg BID on Days 4 through 9. Healthy volunteers received a single oral dose of AZD7268 30 mg or placebo on Day 10.

Target subject population and sample size

Sixty healthy male volunteers between the ages of 18 and 45 years (inclusive) were included in this study.

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

AZD7268 was provided in capsules for oral use in doses of 5 mg and 10 mg (batch numbers ST76131-001-FA01 NB13650-14 and ST76132-001-FA01, respectively). Placebo to match the 5-mg and 10-mg capsules was provided (batch number ST76134-001-FA01).

Duration of treatment

The duration of each healthy volunteer's participation was approximately 56 days, which included a screening period of up to 30 days, an inpatient treatment period consisting of 12 days and 11 nights, and a follow-up visit 5 to 14 days after the last dose of study drug.

Statistical methods

All analyses were performed under the direction of the Biostatistics Group, AstraZeneca. All calculations were performed with the Statistical Analysis System® (SAS®) software, unless otherwise stated.

The safety analysis set included all healthy volunteers who received at least 1 dose of study medication and had data collected post-dose.

The pharmacokinetic (PK) analysis set included all healthy volunteers who received at least 1 dose of study medication and had at least 1 valid PK assessment.

The sample size was not based on formal statistical considerations, but on experience from previous similar studies to obtain initial safety, tolerability, and PK information while exposing as few healthy volunteers as possible to study medication and procedures.

The data were summarized using descriptive statistics.

Subject population

In total, 60 male healthy volunteers were randomized into the study at 1 study site; each healthy volunteer participated in 1 cohort of the study. All healthy volunteers randomized to treatment completed the study, except for 4 healthy volunteers who discontinued due to adverse events (AEs). There were no protocol deviations that led to exclusion of data from the safety analyses. Three healthy volunteers (1 healthy volunteer in the 5-mg QD group, 2 healthy volunteers in the 15-mg BID group) had data excluded from the PK analyses. The safety analysis included all randomized healthy volunteers. Overall, the treatment groups were well balanced/comparable with regard to demographic characteristics. In Cohort 5, the mean weight was approximately 8 kg higher than the other cohorts; however, the BMI was similar among groups. Although both male and female healthy volunteers could be enrolled in the study, the investigational site ultimately entered only male healthy volunteers.

Summary of pharmacokinetic results

Forty-eight healthy male volunteers completed multiple oral dose administrations with AZD7268 (6 doses in total). Eight healthy male volunteers in each cohort received QD or BID oral dose administrations. Plasma concentration of AZD7268, AZ12728094, and AZ13100152 were obtained from each healthy volunteer following oral dosing on Day 1, and Day 9 or 10; at pre-dose on Days 6, 7, and 8 for Cohort 1 to 5; and at pre-dose on Days 7, 8, and 9 for Cohort 6. Measurable plasma concentrations of AZD7268 were observed across all dose groups. However, as expected, plasma concentrations (geometric mean) of AZ12728094 and AZ13100152 were relatively low when compared to AZD7268 (on Day 10, the maximum concentration was 4.48 ng/mL for AZ12728094; 3.98 ng/mL for AZ13100152; and 154 ng/mL for AZD7268, respectively). The geometric mean pre-dose plasma concentrations of AZD7268 obtained over dosing days were between 1.30 to 1.42 ng/mL for 5 mg QD group, 3.68 to 4.42 ng/mL for 5 mg BID group, 7.87 to 9.38 ng/mL for 10 mg BID group, 14.3 to 17.1 ng/mL for 15 mg BID group, 20.0 to 22.9 ng/mL for 20 mg BID group, and 29.6 to 34.2 ng/mL for 30 mg BID group, respectively.

Following a single oral dose administration on Day 1, AZD7268 was rapidly absorbed with median time to maximum plasma concentration (t_{max}) values ranging from 2 to 3 hours for the 5 mg QD, 5 mg BID, 10 mg BID, and 15 mg BID dose groups. The geometric mean terminal half-life ($t_{1/2}$) for these dose groups was 7.74, 9.87, 9.64 and 11.6 hours, respectively. C_{max}

and area under the plasma concentration time curve (AUC) increased with dose across these dose groups. Oral clearance appeared to be comparable across dose groups 5 mg QD, 5 mg BID, 10 mg BID, and 15 mg BID. PK parameters of AZ12728094 and AZ13100152 were not estimated due to low plasma concentrations observed across dose groups. Kidney excretion of AZD7268 and its 2 metabolites in the 10-mg BID dose group was demonstrated. Based on the data from 0- to 48-hour urine collection, the geometric mean renal clearance for AZD7268 was 5460 mL/h (coefficients of variation [CV%]: 32.4), and approximately 9% of the dose was excreted in the urine as AZD7268.

Following multiple oral dose administrations, AZD7268 was rapidly absorbed after 5 mg QD, 5 mg BID, 10 mg BID, 15 mg BID, 20 mg BID, and 30 mg BID daily doses with median t_{max} values ranging from 2 to 4 hours. The Day 9 geometric mean $t_{1/2}$ values for the 5 mg QD, 5 mg BID, 10 mg BID, 15 mg BID, 20 mg BID, and 30 mg BID dose groups were 11.1, 13.9, 14.5, 16.3, 16.1 and 14.7 hours, respectively. C_{max} and AUC increased with the dose across dose groups. The geometric mean of steady state C_{max} (154 ng/mL; 307 nM) in healthy volunteers receiving AZD7268 30 mg BID surpassed the predefined exposure limit (C_{max}: 260 nM). AZD7268 accumulation in plasma, as assessed by the accumulation ratio calculated from AUC ($R_{ac(AUC)}$), was 1.30, 1.34, 1.47, and 1.77 for the 5 mg QD, 5 mg BID, 10 mg BID, and 15 mg BID dose groups. AZD7268 accumulation in plasma, as assessed by the accumulation ratio calculated from C_{max} ($R_{ac(Cmax)}$) was 1.14, 1.35, 1.36, and 1.67 for the 5 mg QD, 5 mg BID, 10 mg BID, and 15 mg BID dose groups, respectively. The ratio between peak and trough concentrations during a dosing interval on the final day of dosing was on average 10-fold for the QD dose group and 3- to 5-fold for the BID dose groups. Based on the data from 0- to 48-hour urine collection, the geometric mean renal clearance for AZD7268 on the final day of dosing was 6760 mL/h (CV%: 28.5).

Cerebrospinal fluid (CSF) and plasma samples were obtained from Cohort 5 (20 mg BID dose group; n=5) approximately 4.5 hours post-dose Day 7. The geometric mean CSF concentration of AZD7268 was approximately 0.550 ng/mL, and the geometric mean plasma concentration of AZD7268 was 69.2 ng/mL, which results in a geometric mean ratio of CSF to plasma of 0.800% (range: 0.490% to 1.02%).

Summary of pharmacogenetic results

As planned, samples were collected and results are not included in this CSR.

Summary of safety results

There were no deaths, serious adverse events (SAEs), or any other significant adverse event (OAEs) in the study. Four healthy volunteers had discontinued due to adverse events (DAEs). Most of the AEs were of mild/moderate intensity, with only 1 AE of severe intensity in the placebo group. The most common AEs reported included application site irritation, headache, back pain, and dizziness. Causally related AEs were reported more often in dose groups of 10 mg BID and above.

There were no serious clinically relevant treatment-related changes in any laboratory, vital signs, EEGs, Columbia Suicide Severity Rating Scale measurements, or dECG variables

measured in subjects exposed to AZD7268 during the study. It was noted by the investigator that a number of volunteers had elevated blood glucose (fasting values) over 110 without glycosuria. The elevation was not felt by the investigator or SRC to be of sufficient clinical concern to warrant cessation of dose escalation. Unblinded data showed instances of either single or repeated elevations of serum glucose in some subjects exposed to AZD7268. An imbalance in the number of healthy volunteers with elevated fasting serum glucose values when comparing AZD7268 with placebo was observed. None of these healthy volunteers had glycosuria. In a small number of subjects exposed to AZD7268, elevations of ALT and/or AST were observed that resolved while either still on drug or after cessation of drug administration. The elevations of ALT and AST in one volunteer resulted in discontinuation from the study. There was no clear dose-dependence for the observed changes, and the clinical significance of the observations is unclear.

There were no clinically relevant treatment related changes or trends in blood pressure or heart rate during the study in subjects exposed to AZD7268.

Date of Report

1 February 2010