AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7268
Study Code	D1151C00004
Edition Number	1
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A Phase I, Single-Centre, Randomised, Double-Blind, Placebo-controlled, Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD7268 When Given in Multiple Ascending Oral Doses in Japanese Healthy Male Subjects

Study dates: First healthy volunteer enrolled: 19 April 2010
Last healthy volunteer last visit: 29 July 2010

Phase of development: Clinical pharmacology (I)

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 and criteria for evaluation

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 to Japanese healthy male subjects by assessment of adverse events (AEs), vital signs, physical examination, clinical laboratory assessments, electroencephalogram (EEG), Columbia Suicide Severity Rating Scale (C-SSRS) and electrocardiogram (ECG).	Assessment of AEs, vital signs, EEGs, ECGs, clinical laboratory assessments, C-SSRS, and physical examinations	Safety
Secondary	**Secondary**	
To characterize the pharmacokinetics (PK) of AZD7268 and its metabolites (AZ13100152 and AZ12728094) in Japanese healthy male subjects when given orally.	AZD7268, AZ13100152 and AZ12728094 concentrations and PK parameters in plasma and urine samples	PK
Exploratory	**Exploratory**	
To collect blood samples for possible retrospective genotyping focusing of the identification of genes that influenced disposition, efficacy, safety, and tolerability of AZD7268.	Pharmacogenetic analysis of blood sample	Pharmacogenetic

Study design

This was a single center, double-blind, placebo-controlled, randomized within each dose group, multiple ascending dose (MAD) study. Healthy volunteers were assigned to 1 of 3 ascending dose groups beginning with Cohort 1 and continuing with Cohort 2 and Cohort 3 in that order. Each dose group were comprised of 10 healthy volunteers with treatment assignment randomized in such a way that 8 healthy volunteers received AZD7268 and 2 healthy volunteers received placebo to match AZD7268.

Cohort 1- Healthy volunteers received a single oral dose of AZD7268 5 mg or placebo on Day 1 and Day 9. Healthy volunteers received an oral dose of AZD7268 5 mg or placebo, twice

daily (BID), on Day 3 through 8. Cohort 2- Healthy volunteers received a single oral dose of AZD7268 15 mg or placebo on Day 1 and Day 9. Healthy volunteers received an oral dose of AZD7268 15 mg or placebo BID on Day 3 through 8. Cohort 3- Healthy volunteers received an oral dose of 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 or placebo BID on Day 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

Japanese healthy male volunteers 20 to 45 years of age were enrolled.

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

AZD7268 was provided in capsules for oral use in dose of 5 mg (batch number 10-000397AZ). Placebo to match the 5 mg capsules was provided (batch number 09-006431AZ).

Duration of treatment

The duration of each healthy volunteer's participation was up to 54 or 55 days which included a screening period of up to 30 days prior to Day -1, n subject treatment period consisting of 12 days and 11 nights (cohort 1-2) or 13 days and 12 nights (cohort 3), and a follow-up visit 5 to 14 days after the last dose of study drug.

Statistical methods

Statistical and statistical programming activities required for this trial were performed by Statistics & Programming Department, AstraZeneca KK using statistical analysis system® (SAS®) (version 8 or higher). Given the exploratory nature, no formal statistical hypothesis testing was performed in this study.
The safety analysis set included all randomized healthy volunteers who took at least one dose of study medication. Healthy volunteers were classified according to treatment regimen (placebo, AZD7268 5 mg BID, etc.) actually received.

The PK analysis set included all randomized healthy volunteers who took at least one dose of study medication and had at least one valid PK assessment (ie, sufficient dose and concentration data to derive PK parameters).

The primary objective of this study was to investigate the safety and tolerability of AZD7268. No hypotheses were posited for testing a priori. Therefore, due to the exploratory nature of the study, the sample size was not based on formal statistical considerations, however 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.

Subject population

In total, 30 male healthy volunteers were randomised into the study at 1 study site, each 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 AEs. There were no protocol deviations that led to exclusion of data from the PK or safety analyses. The safety analysis included all randomised healthy volunteers. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

Twenty four healthy male volunteers (n=8 for each cohort) were treated with AZD7268 at 3 dose levels (5mg BID, 15 mg BID and 30 mg BID). Seven and eight healthy volunteers completed single and multiple oral dose administrations of AZD7268 in 5 mg BID group and 15 mg BID group, respectively. Six healthy volunteers completed multiple oral dose administrations of AZD7268 in 30 mg BID group. Plasma concentrations of AZD7268, its 2 metabolites AZ12728094 and AZ13100152 were obtained from each healthy volunteer following oral dosing from pre-dose to 48 hr post-dose on Day 1 and Day 9 or 10. Trough plasma concentrations were obtained at pre-dose of both AM and PM doses from Days 6 to Day 8 in the 5 mg BID group and 15 mg BID group and at pre-dose of both AM and PM doses from Days 7 to Day 9 in the 30 mg BID group. Conclusively, plasma concentrations following single dose were available from seven healthy volunteers in 5 mg BID group and eight healthy volunteers in 15 mg BID group and plasma concentrations following multiple dose were available from seven healthy volunteers in 5 mg BID group and eight healthy volunteers in 15 mg BID group and six healthy volunteers in 30 mg BID group.

Following a single oral dose administration of 5 mg and 15 mg AZD7268 on Day 1, AZD7268 was rapidly absorbed for both dose groups. The geometric means of terminal half-life ($t_{½λz}$) ranged from 7.4 to 10.6 hrs for these two dose groups.

Following multiple oral dose administrations, AZD7268 was rapidly absorbed across the dose groups (5 mg BID, 15 mg BID and 30mg BID groups). The geometric mean of $t_{ss\ ½λz}$ ranged from 11.5 to 13.4 hrs across the dose groups. Steady state appeared to be achieved in 5 to 6 days after the first dose across dose groups. Exposure of AZ13100152 and AZ12728094 was minimal when compared to the exposure of AZD7268. By BID doses of AZD7268, $AUC_{(0-12)}$ and C_{max} of AZD7268 increased 2.0 folds and 1.9 folds for 5 mg BID group, respectively, and increased 1.7 folds and 1.4 folds for 15 mg BID group, respectively. However temporal change parameter (TCP) values suggested no marked time-dependency. The geometric mean of steady state C_{max} (120.7 ng/mL) in healthy volunteers receiving AZD7268 30 mg BID didn't surpass the predefined exposure limit (C_{max}: 130 ng/mL=260 nM).

Urine excretion of AZD7268 and its 2 metabolites in the 15 mg BID group was demonstrated.

Exposure ($C_{ss\ max}$, $AUC_{ss\ (0-t)}$ and AUC_{ss}) of AZD7268 following BID doses increased with the dose of AZD7268. However, it was difficult to assess the dose proportionality due to the nature of the study design.

Summary of pharmacogenetic results

As planned, samples were collected and results are not included in this clinical study report (CSR).

Summary of safety results

Overall, 2(33.3%), 6 (75.0%), 6 (75.0%), 5 (62.5%) healthy volunteers in placebo, 5 mg BID, 15 mg BID, and 30 mg BID groups, respectively reported a total of 39 AEs (in all healthy volunteers on active drug) during the study. Total number of AEs in the 15 mg BID group was greater than other groups. There were no deaths, other serious adverse events (SAEs), or any other significant adverse events (OAEs) in the study. Four healthy volunteers discontinued due to adverse events (DAEs) (1 healthy volunteer in placebo and 1 healthy volunteer in the 5 mg BID group and 2 healthy volunteers in the 30 mg BID group). Most of the AEs were of mild intensity, with 3 AEs of moderate intensity. The most common AEs (≥2 healthy volunteers on active drug) reported included dermatitis contact, dizziness postural, headache, constipation, malaise, dizziness, syncope, atrioventricular block second degree, and orthostatic hypotension. Causally related AEs were reported more often in the 15 mg BID group.

There were no clinically relevant treatment-related changes in any laboratory, EEGs, or C-SSRS measurements or ECG variables measured in healthy volunteers exposed to AZD7268 during the study.

The mean change from baseline in standing and orthostatic blood pressure tended to decrease more in the 15 mg BID and 30 mg BID groups compared to the placebo and 5 mg BID groups. However, there were no clear trends in supine blood pressure and pulse rate. Overall, the changes in blood pressure and pulse rate seen during the study were not considered to be clinically important.