AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00004
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A Phase I, Single-centre, Randomised, Double-blind, Parallel Group, Placebo-controlled Study to Assess the Safety, Tolerability and Pharmacokinetics after Multiple Oral Doses of AZD2066 in Japanese Healthy Male Subjects

Study dates: First healthy volunteer enrolled: 20 September 2008
Last healthy volunteer last visit: 21 July 2009

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.	– Adverse event (AE)s – Laboratory variables: Clinical chemistry, Haematology and Urinalysis – Vital signs: Blood pressure (BP), Pulse, Body temperature (BT) – Electrocardiogram (ECG)	Safety
Secondary	**Secondary**	
To investigate the pharmacokinetic profile of AZD2066 after multiple oral doses of AZD2066 solution in Japanese healthy male volunteers, by assessment of drug concentrations in plasma.	Single-dose profile: Typically non-compartmental analysis (NCA)–derived C_{max}, t_{max}, AUC_{0-24}, AUC, CL/F, Vz/F, MRT and $t_{½λz}$. Multiple-dose phase: Inspect trough concentrations to assess if steady state has been achieved. NCA-derived steady-state C_{max}, t_{max}, C_{min}, AUC_t. Assess accumulation ratio (AUC_t /AUC_{0-24} from single-dose study) and time dependency of the pharmacokinetics (ie, Is AUC_t equivalent to AUC after a single dose) Determine the $t_{½λz}$ from the washout phase.	Pharmaco kinetic (PK)
To investigate effects on Central nervous system (CNS) function of AZD2066 after multiple oral dosing in Japanese healthy male volunteers, using psychometric tests.	Cognitive assessments including simple reaction time, digit vigilance, choice reaction time, numeric working memory, immediate word recall, delayed word recall, word recognition, picture recognition and Bond-Lader VAS of mood and alertness.	Pharmaco dynamic (PD)

C_{max}, t_{max}, AUC_{0-24}, AUC, CL/F, Vz/F, MRT, $t_{½λz}$, C_{min}, AUC_t: see List of Abbreviations and definition of terms in CSR.

Study design

This was a randomised (within dose-group), double-blind, parallel group, placebo-controlled study to assess the safety, tolerability and pharmacokinetics of AZD2066 when given as multiple doses to Japanese healthy male volunteers. Six (6) consecutive multiple-ascending groups were planned. The enrolment was performed within 30 days before the residential stay, which lasted up to 16 days (18 days for the third and fourth dose groups and 20 days for the fifth and sixth dose group) including the admission day and the healthy volunteers came back for a follow-up visit 8-15 days after the last dose of the investigational product.

Target subject population and sample size

In total 60 healthy, as judged by the investigator(s), Japanese males aged ≥ 20 to ≤ 45 years.

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

The intended multiple doses of AZD2066 and placebo were given as an oral solution, the healthy volunteers were dosed once daily. The ascending doses were 2.3 mg (dose level 1), 6 mg (dose level 2), 9 mg (dose level 3) and 12 mg (dose level 4). For the fifth group, 10.2 mg was administered once daily for 5 days (including the first single dose followed by a wash-out period of 96 hours) followed by 15 mg once daily for 8 days. For the sixth dose group, 12 mg was administered once daily for 5 days (including the first single dose followed by a wash-out period of 96 hours) followed by 18 mg once daily for 8 days. Dose escalation was determined by a safety review committee (SRC) that evaluated safety, tolerability and pharmacokinetics of AZD2066 between each dose level. For the fifth and sixth groups, the SRC also decided if the higher dose level in the second half of or the overall dose level of each group had to be reduced, in consideration of the results in the previous dose group. For the third, fourth and sixth dose levels, the SRC reviewed the safety results after the single dose prior to the multiple dosing to decide if the healthy volunteers could receive the multiple doses.

The following investigational products were supplied:

- AZD2066 oral solution 0.1 mg/mL
- AZD2066 oral solution 3 mg/mL
- Placebo oral solution

Duration of treatment

Healthy volunteers started with an initial single dose that was followed by a wash-out period of 48 hours to adequately define the single-dose pharmacokinetics. For the third, fourth, fifth and sixth dose groups, the wash-out period was extended to be 96 hours and, for the third, fourth and sixth dose groups, the safety of healthy volunteers were evaluated during this washout period. Thereafter the healthy volunteers were dosed once daily for 10 days for the first, second, third and fourth dose groups and 12 days for the fifth and sixth dose groups (11 days of dosing for the first, second, third and fourth dose groups and 13 days of dosing for the fifth and sixth dose groups, including first single dose given).

Statistical methods

Safety, tolerability, pharmacokinetic and pharmacodynamic data were listed and summarised for each dose using descriptive statistics. Graphical representations of data were presented as was deemed appropriate.

Subject population

A total of 60 Japanese healthy volunteers with mean age of 24.9 were randomised to each treatment group (48 and 12 in AZD2066 and placebo group, respectively) and treated with investigational product. Of these, 59 healthy volunteers completed the study, and one healthy volunteer in the AZD2066 12+18 mg dose group was withdrawn prematurely due to Serious AE (SAE) 2 days after the last administration of investigational product.

Data from all randomised healthy volunteers who received treatment was included in the safety and pharmacodynamic analyses. Data from all randomised healthy volunteers receiving active drug was included in the pharmacokinetic analyses.

Overall, the demographic and baseline characteristics were well balanced with regards to the treatment groups.

Summary of pharmacokinetic results

The median t_{max} ranged between 0.33 and 1.00 h after once-daily dosing (od). The median t_{max} was dose-independent. The highest average $C_{ss,max}$ and AUC_{τ} in young healthy volunteers were 3889 nmol/L (CV 16%) and 51195 h*nmol/L (CV 19%) following administration of 12+18 mg od, respectively. Average (range) $t_{½\lambda z}$ after single and once daily dosing were 17 to 28 (11 to 37) h and 32 to 45 (19 to 89) h, respectively. The average $t_{½\lambda z}$ after once daily dosing was dose-independent.

Based upon the pre-dose level data collected, steady state was achieved within approximately 6 days after the start of once daily dosing at the dose levels of 2.3 to 12 mg od. The systemic exposure at steady state ($C_{ss,max}$ and AUC_{τ}) increased approximately dose proportionally. At 2.3 to 12 mg od, the mean accumulation ratio (R_{ac}) (last dosing day/single dosing day) was 1.4 to 1.8 based on $C_{ss,max}/C_{max}$ and 1.9 to 2.1 based on AUC_{τ}/AUC_{0-24}. There was no indication of time-dependent pharmacokinetics after once daily dosing.

Summary of pharmacodynamic results

In the psychometric tests, the effects seen with AZD2066 were impairments to measures of attention which were seen in Groups 1 to 4, primarily with the 9 and 12 mg doses, and were most evident on the measure of focused attention (Power of Attention), though impairments were also seen to sustained attention (Continuity of Attention). For Groups 5 and 6, there were some overall declines to both the attention composite scores for the 12+18 mg group, and for the 10.2+15 mg group for Continuity of Attention, but there were also drops in the placebo group which resulted in there being no overall differences between the placebo and active conditions.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable

Summary of safety results

There was no death, other significant AE (OAE) or AE leading to discontinuation of study treatment in this study. An SAE (diverticulitis) were reported in one healthy volunteer, which was considered severe and not related to the study treatment by the investigator.

The overall incidence of AEs was 64.6% in all AZD2066 groups and 25.0% in placebo group. AZD2066 showed a dose dependent increase of the incidence of AEs in nervous system disorders and psychiatric disorders.

The most common AEs (observed in 5 or more healthy volunteers) were somnolence (54.2%), dizziness (16.7%), head discomfort (14.6%), disturbance in attention (10.4%) and abnormal dreams (10.4%) in all AZD2066 groups. Each incidence of these AEs in AZD2066 12+18 mg dose group was higher than that of other AZD2066 treatment groups.

The majority of AEs were mild intensity and all of AEs except for an SAE were transient and resolved during the study without any treatment. Regarding laboratory variables, vital signs and physical examination, there were no clinically relevant trends. Multiple dose administration of AZD2066 did not result in change in QT interval corrected for heart rate using Fridericia's fomula (QTcF) and there was no evidence for QTcF prolongation.

In this study, no major safety or tolerability concerns were identified. However, due to high frequency of mild AEs, further dose escalation was stopped after AZD2066 12+18 mg multiple administration. The maximum tolerated dose (MTD) was not determined.