AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00003
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A Phase I, Single-centre, Randomised, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Tolerability and Pharmacokinetics after Single Ascending Oral Doses of AZD2066 in Japanese Healthy Male Subjects

Study dates: First healthy volunteer enrolled: 19 January 2008
Last healthy volunteer completed: 24 Apr 2008

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

The primary objective of the study was to investigate the safety and tolerability after single ascending oral doses of AZD2066 in Japanese healthy male subjects, by assessment of adverse events (AEs), blood pressure (BP), pulse, body temperature, laboratory variables and electrocardiography (ECG).

The secondary objectives of the study were:

1. To investigate the pharmacokinetic (PK) profile of AZD2066 following single ascending oral doses of AZD2066 solution in Japanese healthy male subjects, by assessment of drug concentration in plasma and urine.

2. To investigate effects on CNS function of AZD2066 following single ascending dosing in Japanese healthy male subjects, using psychometric tests

The usefulness of Spielberger State Anxiety Inventory (SSAI), for measuring anxiety symptoms and Spielberger Trait Anxiety Inventory (STAI) for measuring trait, were explored (Spielberger 1970, See Section 4.4.4 in the CSP, CSR Appendix 12.1.1).

In addition, a blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that might affected PK and pharmacodynamics (PD), safety and tolerability related to AZD2066 treatment. Data from this exploratory research will not be presented in this CSR.

Study design

This was a randomised (within dose-group), double-blind, placebo-controlled parallel group study to assess the safety, tolerability and pharmacokinetics of AZD2066 when given as single doses to Japanese healthy male subjects. Four consecutive ascending dose panels were planned. In each panel 6 subjects received AZD2066 and 2 subjects received placebo.

Target healthy volunteer population and sample size

In total 32 Japanese healthy male subjects participated in this study. The age of the subjects ranged between 20 to 29 years.

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

Single oral doses of AZD2066 were dispensed from either a solution of 0.1 mg/mL or 3 mg/mL depending on the dose that was administered. As a comparator, placebo was administered as an oral solution. Doses administered in the study were 1.3, 3.25, 6.9 and 7.8 mg of AZD2066.

Duration of treatment

Each subject received a single dose of AZD2066 or placebo.

Variables

Safety

Adverse events, psychiatric interview, Spielberger State and Trait Anxiety Inventory (SSAI and STAI), vital signs, ECG parameters, body temperature, clinical chemistry, haematology and urinalysis.

Pharmacokinetic

Maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from zero to infinity (AUC), time to reach C_{max} (t_{max}), terminal half-life ($t_{1/2\lambda z}$), fraction of systemically available drug excreted in urine (f_e*F), renal clearance (CL_R) and apparent plasma clearance (CL/F)

Pharmacodynamic

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 Visual Analogue Scale (VAS) of mood and alertness.

Statistical methods

The analysis of safety, tolerability, pharmacokinetic and pharmacodynamic data consisted mainly of descriptive with listings, summary statistics and graphs as appropriate.

Dose proportionality was analysed using the power model approach. Cognitive assessments were analyzed as stated in the Statistical Analysis Plan (SAP) from Cognitive Drug Research (CDR).

Subject population

Japanese healthy male subject.

Table S 1 Summary of cohorts and dose escalation, based on stopping criteria

Panel	Dose (mg)	n [a]	Number of stopping criteria	Stopping criteria information
1	1.3	6	0	NA
2	3.25	6	0	NA
3	6.9	6	0	NA
4	7.8 [b]	6	0	NA

[a] Each panel consisted of 6 subjects on study drug and 2 subjects on placebo.

[b] Originally, 13.5 mg was planned for Panel 4. However, 7.8 mg was substituted for 13.5 mg since stopping criteria No.7 was met after completion of Panel 3 (Estimated C_{max} for 7.8 mg in Japanese subjects was considered to be identical with C_{max} for 13.5 mg in Caucasian subjects calculated in study D0475C00001).

Summary of pharmacokinetic results

Following single doses of 1.3 to 7.8 mg AZD2066 as an oral solution without food, AZD2066 was rapidly absorbed with t_{max} occurring at 40 minutes post-dose, except for only 2 subjects with t_{max} of 20 minutes (7.8 mg dose panel) and 1 hour (6.9 mg dose panel). At 3.25 mg or higher, plasma AZD2066 concentrations at the follow-up visit were quantifiable in all subjects. In these subjects, the terminal phase was reached at 36 hours and the geometric mean terminal half-life was approximately 30 hours. The power model analysis showed that the AUC and C_{max} increased in a dose proportional manner for doses between 1.3 and 7.8 mg. At 3.25 mg or higher, the variability for the PK parameters was relatively low. The geometric mean CL/F was around 1.0 L/h, and was similar across doses.

Only very small amounts of unchanged AZD2066 were recovered in the urine, and the renal clearance of AZD2066 was very low suggesting that the drug is not eliminated unchanged to any significant degree.

Summary of pharmacodynamic results

A Cognitive Drug Research (CDR) computerised assessment system was used to evaluate the effects of AZD2066 on the quality of cognitive functioning in the subjects. The data revealed numerical decrements for the highest dose level (7.8 mg) versus placebo across the composite scores. However, the decrements were not statistically supported. The next highest dose level (6.9 mg) only showed a numerical decrement in one of the composite scores (Quality of Episodic Secondary Memory). The 3.25 mg dose showed a numerical benefit in most the composite scores and contributing subtasks.

Summary of safety results

No major safety and tolerability concerns were identified in this study. There were no deaths, serious adverse events (SAEs), or other significant adverse events (OAEs) in the study. There were no subjects who discontinued the study due to an adverse event in the study.

A total of three subjects reported 3 AEs (one each in 6.9 mg [headache], 7.8 mg [somnolence] and placebo [palpitation]) in total, all of them were transient and of mild in intensity. The principal investigator considered that the 3 AEs were related to treatment.

The results of clinical laboratory variables, vital signs, ECG and physical examinations have not given rise to any safety concerns in the study.

One subject (Subject 405) in the highest dose group (7.8 mg) had an increase in the score by 14 units from baseline in SSAI. The amount of increase was met definition of one of stopping criteria for dose escalation (an increase in SSAI exceeding 13 units). No relevant effects on the SSAI variables were observed at the other dose levels or placebo during the study.