AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00001
Date	07 May 2008

A Phase I, Single-centre, Randomised, Double-blind, Placebo-controlled Parallel group Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD2066 in Young and Elderly Healthy Volunteers after Oral Single Ascending Doses

Study dates: First subject enrolled: 24 September 2007
Last subject completed: 17 January 2008

Phase of development: Clinical Pharmacology (I)

This study was performed in compliance with Good Clinical Practice

Drug Substance	AZD2066	**SYNOPSIS**	(For national authority use only)
Study Code	D0475C00001		
Date	20080508		

A Phase I, Single-centre, Randomised, Double-blind, Placebo-controlled Parallel group Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD2066 in Young and Elderly Healthy Volunteers after Oral Single Ascending Doses

Objectives

The primary objective of this study was to investigate the safety and tolerability of single ascending oral doses of AZD2066, by assessment of adverse events, blood pressure, pulse, body temperature, laboratory variables and electrocardiography (ECG).

The secondary objectives of the study were:

1. To investigate the pharmacokinetic profile of AZD2066 in young and elderly subjects after single ascending oral doses by assessment of drug concentrations in plasma and urine.

2. To investigate effects on central nervous system (CNS) function of AZD2066 after single ascending dosing using psychometric tests.

In addition, there was a possibility to analyze metabolites and potential food interaction, however these were not explored and is therefore not reported in this Clinical Study Report (CSR).

Also, the usefulness of Spielberger State Anxiety Inventory (SSAI) for measuring anxiety symptoms and Spielberger Trait Anxiety Inventory (STAI) for measuring trait, were explored.

Furthermore, a blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect pharmacokinetics and pharmacodynamics, safety and tolerability related to AZD2066 treatment. No genotyping results are presented in this CSR.

Study design

This was a first time in man (FTIM) study to assess the safety, tolerability and pharmacokinetics of AZD2066 when given as single doses to healthy young and healthy elderly subjects. The study was a randomised (within dose-group), double-blind, placebo-controlled parallel group study. In each panel 6 subjects received AZD2066 and 2 subjects received placebo.

Target subject population and sample size

In total 48 healthy volunteers participated in this study, 42 males and 6 females. The age of the young subjects ranged between 20 to 42 years and the elderly subjects between 65 to 80 years.

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

Single oral doses of AZD2066 were dispensed from either a solution of 0.1 mg/mL (Batch number 3973-2-1) or 3 mg/mL (Batch number 3957-3-2) depending on the dose that was administered. As a comparator, placebo was administered as an oral solution (Batch number 4073-1-1). Doses administered in the study were 1.3, 3.25, 6.9, 13.5 and 27 mg of AZD2066.

Variables

Safety

Adverse events (AEs, including a psychiatric interview), SSAI, 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 ($t_{1/2\lambda z}$),

free (unbound) fraction of drug in plasma (f_u), fraction of systemically available drug excreted in urine (f_e), 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 primary analysis of safety and tolerability consisted mainly of descriptive statistics, including listings, summary statistics, and graphs as appropriate. The pharmacokinetic analysis consisted mainly of descriptive statistics, with the exception of the analysis of the dose proportionality, where a power model was used. The number of subjects per dose was chosen to have enough subjects to evaluate tolerability and safety based on experience from other studies. Cognitive assessments were analyzed as stated in the Statistical Analysis Plan from Cognitive Drug Research Appendix 12.1.9.

Subject population

Healthy male and non-fertile female volunteers.

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

Panel [a]	Dose (mg)	n [b]	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	13.5	6	0	NA
5	27	6	2	Two stopping criteria were met: (1) If 2 or more of the 8 subjects show significant intolerance considered likely to be drug related the code will be broken. If the cases are within the actively treated group, the dose escalation will be stopped. (2) If 2 or more subjects in a dose group, on active compound, have an increase in SSAI exceeding 13 points, judged to be drug-related, the dose escalation should be stopped.
6	3.25	6		NA

[a] Panel 1 to 5 consisted of young subjects between the ages of 20-42. Panel 6 consisted of elderly subjects between the ages of 65-80.

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

Summary of pharmacokinetic results

AZD2066 was rapidly absorbed with t_{max} occurring at around 1 hour. The AUC and C_{max} were approximately dose-proportional. The terminal half-life was approximately 24 hours. Renal clearance was very low. No apparent difference in pharmacokinetic parameters was observed between young and elderly subjects.

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 decrements for the highest dose level (27 mg) versus placebo across most of the composite scores and subtask measures, although the decrements were primarily statistically supported on the attention tasks. The next highest dose level (13.5 mg) showed no consistent decrements across the CDR composite scores in both the primary (young subjects only) and secondary (young and elderly subjects) analyses.

Summary of pharmacokinetic/pharmacodynamic correlations

An exploratory logistic regression analysis of AEs causally related to treatment as a function of plasma concentration indicated that a C_{max} concentration of approximately 1250 nmol/L was associated with 50% probability (with a 95 % confidence interval between 25 to 75%) of developing an AE classified as psychiatric or nervous system disorder. The mean C_{max} in this study was 1095 nmol/L at the maximum tolerated dose (MTD) (13.5 mg).

Summary of safety results

No major safety and tolerability concerns were identified in this study. The MTD for single dose administration of AZD2066 to healthy subjects was determined to 13.5 mg as defined by the frequency and intensity of AEs.

There were no deaths, Serious Adverse Events (SAEs) or Other Significant Adverse Events (OAEs) in the study. AEs were of mild or moderate intensity. The 48 subjects that participated in the study reported 70 AEs in all. Of these, 55 AEs (79%) were reported in 15 out of 36 subjects in total receiving AZD2066 and 40 of these AEs were reported at the highest dose, 27 mg.

The most common AEs (AEs that occurred in more than 2 subjects, described by preferred term) observed were somnolence, mydriasis, abnormal dreams and derealisation. Headache was also common but was not dose related and was also observed among placebo treated subjects. AEs that were seen only in 1 or 2 subjects, but which were important for the estimation of maximum tolerated dose were fear, anxiety, bradyphrenia, disturbance in attention, delusion, tension and euphoric mood.

There were no clinically important or systematic changes in laboratory variables, vital signs or ECG with the exception of an increased pulse rate in the highest dose group.

Two subjects in the highest dose group (27 mg) had changes in the SSAI. One subject (Subject 504) had an increase in the score by 25 units from baseline. In another subject (Subject 505) the increase from baseline was by 8 units and the increase from the 2 hour assessment was 14 units. Dosing was stopped as the stopping criterion preventing further dose escalation was an increase in SSAI exceeding 13 units from baseline observed in 2 subjects and judged to be drug-related. No relevant effect on the SSAI variables was observed at the other dose levels. In the placebo group one subject (Subject 702) had an increase in score of 17 units from baseline.