AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00002
Edition Number	1
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A Phase I, Single-centre, Randomised, Double-blind, Parallel Group, Placebo-controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD2066 in Young and Elderly Healthy Subjects after Oral Multiple Ascending Doses

Study dates: First healthy volunteer enrolled: 09 January 2008
Last healthy volunteer completed: 19 November 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 this study was to investigate the safety and tolerability of AZD2066 in young and elderly healthy volunteers after multiple dosing by assessment of adverse events (AEs), vital signs, laboratory variables and electrocardiography (ECG).

The secondary objectives of the study were:

1. To investigate the pharmacokinetic (PK) profile (including dose proportionality, degree of accumulation and time-dependency) of AZD2066 (and possible relevant metabolites) in young and elderly healthy volunteers after multiple dosing by assessment of plasma concentrations

2. To investigate effects on CNS function of AZD2066 after multiple ascending dosing using psychometric tests

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

Furthermore, a blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK and pharmacodynamics (PD), safety and tolerability related to AZD2066 treatment.

Study design

This was a single-centre, randomised, double-blind, parallel group, placebo-controlled study to assess the safety, tolerability and PK of AZD2066 in young (8 dose panels) and elderly (3 dose panels) healthy volunteers after multiple dosing.

Target healthy volunteer population and sample size

The plan was to randomise a maximum of 110 healthy male and non-fertile female healthy volunteers: up to 80 young (aged 20 to 45 years, BMI $\geq$19 to $\leq$28 kg/m^2) and 30 elderly healthy volunteers (aged 65 to 80 years, BMI $\geq$19 to $\leq$30 kg/m^2).

In all dose panels, 10 healthy volunteers were allocated to receive either AZD2066 (n=8 in all dose panels except in the 2 first elderly dose panels where n=7) or placebo (n=2 in all dose panels except in the 2 first elderly dose panels where n=3).

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

The dose levels used in the study were 1.5 mg, 2.3 mg, 4 mg, 5.9 mg, 9 mg, 13.5 mg, 13.5+19.5 mg and 18+27 mg in young dose panels 1 to 6 and 10 to 11, and 2 mg, 7.2 mg and 10.5 mg in elderly dose panels 7 to 8 and 12.

In dose panel 10 (13.5+19.5 mg) and 11 (18+27 mg) for young healthy volunteers, the healthy volunteers received a dose level shown to be tolerated in previous dose panels on Day 1 and Day 3 to 6 before continuing with a higher dose Day 7 to 14.

Investigational product	Dosage form, strength and route of administration	Batch number
AZD2066	Oral solution, 0.1 mg/mL	4004-4-2 and 4004-5-2
AZD2066	Oral solution, 3 mg/mL	4077-3-1
Placebo	Oral solution	4073-1-1 and 4073-5-2

Duration of treatment

All healthy volunteers received an initial dose that was followed by a wash-out period of 48 hours to adequately define the single-dose PK. Thereafter the healthy volunteers were dosed once daily for another 11 doses except for healthy volunteers in dose panel 10 (13.5+19.5 mg) and dose panel 11 (18+27 mg) who received another 13 doses. In the 2 highest dose groups, 13.5+19.5 mg and 18+27 mg, the healthy volunteers received the lower dose on Day 1 and Day 3 to 6 before continuing with the higher dose on Day 7 to 14. In all other dose panels, the last dose was administered on Day 12.

Criteria for evaluation - pharmacokinetics and pharmacodynamics (main variables)

- **Pharmacokinetics**

- Single-dose: C_{max}, t_{max}, AUC_{0-24}, AUC, CL/F, V_z/F, MRT and $t_{½\lambda z}$
- Multiple dose: C_{max}, t_{max}, C_{min}, AUC_{τ}, Accumulation ratio (AUC_{τ}/AUC_{0-24} from single-dose study), time dependency of the pharmacokinetics, $t_{½\lambda z}$
- Metabolites (if applicable): C_{max}, t_{max}, AUC_{0-24}, AUC and $t_{½\lambda z}$

- **Pharmacodynamics**

Cognitive assessments (psychometric tests)

- **Pharmacogenetics (not included in the CSR)**

Any future genetic analyses will be reported separately.

Criteria for evaluation - safety (main variables)

AEs, vital signs, clinical chemistry, haematology, urinalysis, ECG, SSAI and STAI.

Statistical methods

Descriptive statistics were used to analyse safety, tolerability, PK and PD data. Dose proportionality was analysed by analysis of covariance (ANCOVA) using a power model.

Subject population

Healthy males aged between 20 and 43 years (young dose panels) and healthy male and non-fertile females aged between 65 and 79 years (elderly dose panels) were included in the study. Overall, both within the young and within the elderly dose panels, the treatment groups were comparable with regards to demographic characteristics.

Eighty (80) young and 30 elderly healthy volunteers were randomised, which was in accordance with the planned number of subjects.

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

Among the young healthy volunteers, 1 healthy volunteer in the 1.5 mg dose group discontinued the study due to AEs, and 1 healthy volunteer who received placebo voluntarily discontinued. The number of young and elderly healthy volunteers who completed the study was 78 and 30, respectively.

Summary of pharmacokinetic results

The median t_{max} ranged between 0.7 and 2.2 h. The highest t_{max}-values and a different absorption profile were observed at the highest dose. Average $t_{½\lambda z}$ following the last dose was 23 to 30 h in young and 32 to 36 h in elderly healthy volunteers. Dose-adjusted exposures were slightly higher in elderly.

The highest average C_{max} and AUC_{τ} in young healthy volunteers were 3547 nmol/L and 45828 h*nmol/L, respectively. The highest individual C_{max} and AUC_{τ} in young healthy volunteers were 4878 nmol/L and 76576 h*nmol/L, respectively. Corresponding estimates for elderly healthy volunteers were 1576 nmol/L and 21424 h*nmol/L, and 2615 nmol/L and 37269 h*nmol/L, respectively.

Fluctuations (C_{max}/C_{trough}) on Day 12/14 averaged to around 3 in young and approximately 2.5 in elderly healthy volunteers.

Steady-state was reached within approximately 3-4 days of dosing.

Steady-state exposures in young and elderly healthy volunteers were on average approximately 50 % and slightly less than 2-fold higher than single dose exposures, respectively.

Dose- and time-dependent pharmacokinetics was observed. Exposures (C_{max} and AUCs) increased slightly less than proportionally with increasing doses. The non-proportionality was significant for Days 7 and 12/14, but not on Day 1. The average AUC_{τ}(steady-state)/ AUC(Day 1) ranged between 0.8 (at higher doses) and 1.0. These dependencies were not associated with apparent decreases in $t_{½}$, indicating changes in pre-systemic processes.

Summary of pharmacodynamic results

There were no clear trends or changes in the composite scores for subjects receiving AZD2066 as compared to placebo. For the composite score Speed of Memory, a pattern of smaller improvements over time (training effect) was seen for AZD2066 as compared to the placebo group in the elderly subgroup. This effect was not seen for the young healthy volunteers.

Some changes were seen in the individual tests results. For young healthy volunteers receiving AZD2066, the Numeric Working Memory sensitivity was impaired. For elderly healthy volunteers receiving AZD2066, the Numeric Working Memory speed was impaired. Impairments were also seen in Picture Recognition Sensitivity, but not in the two highest dose groups. Detailed results from the psychometric tests are available in a separate report from Cognitive Drug Research Ltd (CDR) included in Appendix 12.1.13.

Summary of safety results

No major safety and tolerability concerns were identified in this study. There were no serious AEs and the majority of AEs were of mild to moderate intensity. One (1) young healthy volunteer in the 1.5 mg dose group discontinued due to AEs (anxiety, derealisation, restlessness and thinking abnormal).

The most common AEs in young healthy volunteers were headache, disturbance in attention, dizziness, fatigue, and AEs of psychiatric character. A similar AE profile was observed in the elderly population, where the most common AEs were headache, disturbance in attention and fatigue. However, headache, fatigue, dizziness and abnormal dreams were also reported by healthy volunteers in the placebo group, both in young and elderly panels. Nevertheless, disturbance in attention and dizziness appeared to be dose dependent. Psychiatric and nervous system AEs were increased in the 2 highest dose groups for young healthy volunteers, ie, AEs were dose dependent.

No clinically relevant changes in vital signs were observed.

In the 2.3 mg, 5.9 mg and 13.5 mg dose groups for young healthy volunteers, single healthy volunteers had alanine aminotransferase (ALAT) elevations but these were not considered clinically relevant. There were no clinically relevant changes in other laboratory safety variables.

Multiple dose administration of AZD2066 did not result in change in QTcF, and there was no evidence for QTcF prolongation.

No treatment related trends or changes in SSAI scores were identified over time.