AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00006
Edition Number	1
Date	7 December 2010

Safety, Tolerability and Pharmacokinetics of 3 Dose regimens of AZD1446 vs. Placebo as an Add-on Treatment to Donepezil:

A Multi-centre, Double-blind, Randomised, Placebo controlled, Parallel group Phase IIa Study in Patients with Mild to Moderate Alzheimer's Disease during 4 weeks of Treatment

Study dates: First patient enrolled: 21 December 2009
Last patient last visit: 29 July 2010

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was conducted in 3 European countries at 13 recruiting centres.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives[a]	Outcome variables
Primary	Primary
To evaluate the safety and tolerability of 3 dose regimens of AZD1446 compared to placebo as an add-on treatment to donepezil for 4 weeks in patients with mild to moderate Alzheimer's disease (AD).	Adverse events (AEs), laboratory variables, vital signs, physical examination, electrocardiogram, Columbia Suicide Rating Scale (C-SSRS)
Secondary	Secondary
To evaluate any effect of AZD1446 as an add-on treatment to donepezil on the pharmacokinetics (PK) of donepezil.	Donepezil plasma concentrations.
To characterize the PK of AZD1446 as an add-on treatment to donepezil in AD patients	AZD1446 population PK parameters.
To analyse Apolipoprotein E genotype in relation to drug response and other clinical endpoints	D-KEFS Verbal Fluency Condition 1, Letter Fluency, D-KEFS Verbal Fluency Condition 2, Category Fluency, Trail making test A and B
To explore the effects of 3 dose regimens of AZD1446 compared to placebo as an add-on treatment to donepezil on changes from baseline in cognitive functioning using selected tests from the Neuropsychological Test Battery (NTB)(Delis-Kaplan Executive Function Systems (D-KEFS), Verbal Fluency Condition 1, Letter fluency and D-KEFS Verbal Fluency Condition 2, Category Fluency) and Trail making tests A and B.	D-KEFS Verbal Fluency Condition 1, Letter Fluency, D-KEFS Verbal Fluency Condition 2, Category Fluency, Trail making test A and B
To explore the effects of 3 dose regimens of AZD1446 compared to placebo as an add-on treatment to donepezil on changes from baseline in global functioning using Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC).	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC).

a Exploratory objectives are not listed in the table and are reported separately outside the Clinical study report (CSR).

Study design

This was a double-blind, randomised, placebo controlled, parallel group multi-centre, multi-national study including patients with mild or moderate AD.

Target subject population and sample size

Patients with a clinical diagnosis of probable AD with a MMSE score of 12-24, males and females aged 60 to 85 years were included in the study. The planned sample size of 12 patients per group (48 in total) was based on experience from previous similar studies with other compounds. No formal statistical sample size calculation was done.

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

The investigational products were: AZD1446 capsules 30 mg (batch number 09-005444AZ manufacturer AstraZeneca), and placebo capsules (batch number 09-005693AZ manufacturer AstraZeneca).

Duration of treatment

The treatment duration of the study was 4 weeks.

Statistical methods

Continuous variables were summarised using descriptive statistics by treatment group and categorical variables were summarised in frequency tables by treatment group. PK data were analysed with a Non-linear Mixed Effects Model. Analysis of donepezil PK data were based on a comparison of observed plasma concentrations at baseline and at last day of treatment. A population PK model was used for the AZD1446 PK analysis. Efficacy data were analysed with Fisher's exact test and ANCOVA as appropriate.

Subject population

Overall, 99 patients with mild or moderate AD were enrolled, whereof 56 were randomised into the study. The treatment groups were generally well balanced with regards to demographic (mean age was for; placebo 78 years and AZD1446 70.3 years) and patient characteristics (mean MMSE was for; placebo 17.85 and AZD1446 20.00). All patients assigned to treatment received study drug, and all patients received the study drug to which they were assigned.

The safety and PK analysis included all randomised patients. One (1) patient (within the AZD1446 30 mg x 3 treatment group) that withdrew consent at day 21 was excluded from the efficacy analysis since there was no post-baseline efficacy data. One (1) patient (within the AZD1446 60 mg x 3 treatment group) discontinued the study at day 23 due to AEs.

Summary of efficacy results

The analyses of the efficacy variables were performed for exploratory purposes, as the sample size of the study was insufficient for statistical evaluation of the effects.

No statistically significant differences could be seen in global functioning [ADCS-CGIC] or cognition [Verbal fluency, and Trail making test] between AZD1446 treatment groups or placebo irrespective of APOE ε4 genotype.

Summary of pharmacokinetic results

Donepezil: The mean ratio between day 28 and baseline for the placebo treatment group was 0.98 indicating that exposure to donepezil in the absence of AZD1446 was similar at baseline and at day 28. The confidence intervals for all AZD1446 treatment groups versus placebo comparisons included 1, indicating that AZD1446 did not influence the exposure to donepezil.

AZD1446: The predicted time to maximum concentration, $t_{max,pred}$, ranged from 0.7 to 1 hour and the half-life ranged from 2.5 to 3.2 hours. The geometric mean of predicted $C_{ss,max,pred}$ and $AUC_{(0-24),ss,pre}$ ranged between 1550 and 1950 nmol/L and 7790 to 23800 nmol*h/L, respectively.

Summary of safety results

There were no deaths, other serious adverse events or any other significant AEs in the study. One (1) patient in the AZD1446 60 mg x 3 treatment group, discontinued treatment of investigational product (IP) due to AEs. AEs were more common in the AZD1446 60 mg x 1 and AZD1446 60 mg x 3 treatment groups than in the AZD1446 30 mg x 3 treatment group. All AEs were mild to moderate in intensity. There were no AEs in the placebo group. Few values were outside predefined project specific reference limits with regards to laboratory variables, vital signs, and ECGs. There was no pattern of changes in mean values in any of these variables in any of the treatment groups. No patient had any suicidal behaviour, as measured by Columbia-suicidal severity rating scale (C-SSRS), or any indication of suicidal ideation during the treatment period.