AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3480
Study Code	D3690C00010
Edition Number	1
Date	11 March 2009

A Multi-centre, Double-blind, Double-Dummy, Placebo-controlled, Parallel Group, Randomised, Phase IIb Proof of Concept Study with 3 oral dose groups of AZD3480 or donepezil during 12 weeks treatment in patients with Alzheimer's Disease

Study dates: First patient enrolled: 18 July 2007
Last patient completed: 08 August 2008

Phase of development: IIb

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

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Study centre(s)

84 sites participated in the study from 10 countries: Austria, Belgium, Bulgaria, Canada, Czech Republic, Germany; Romania, Russia, Spain and United Kingdom.

Publications

No publications of the study results have appeared at the time of writing this report.

Objectives

The primary objective of this study was to prove the concept that AZD3480 improves cognition in Alzheimer's disease (AD) patients in relation to placebo and donepezil, assessed as change from baseline on Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS Cog).

The secondary objectives were:

1. to compare donepezil to placebo, as assessed by change from baseline on ADAS Cog, to provide assay sensitivity in the event that AZD3480 is not able to ensure this

2. to assess dose response relationship in cognitive effects of 3 dose groups of AZD3480 compared to placebo in changes from baseline on ADAS-Cog and Alzheimer's disease Cooperative Study- Clinical Global Impression of Change (ADCS-CGIC)

3. to assess effects on cognition of 3 dose groups of AZD3480 compared to placebo in changes from baseline by use of computerised cognitive test battery (CDR) and Mini Mental State Examination (MMSE)

4. to assess effects on cognition of 3 dose groups of AZD3480 compared to placebo in changes from baseline evaluated by the following Patient/ Proxy Reported Outcomes (PROs):

    - Disability Assessment for Dementia (DAD) for evaluation of activities of daily living
    - Cohen-Mansfield Agitation Inventory (CMAI)
    - Activity and Affect Indicators of Quality of Life (AAIQOL)
    - Zarit Burden Interview (ZBI) for evaluation of burden for caregivers
    - Overall Treatment Evaluation (OTE)

5. to assess the population pharmacokinetics and exposure response relationship of AZD3480

6. to evaluate safety and tolerability of AZD3480 by assessment of adverse events, laboratory variables, vital signs and physical examinations

Study design

This was a Multi-centre, Double-blind, Double-Dummy, Placebo-controlled, Parallel Group, Randomised, Phase IIb study, with 3 oral dose groups of AZD3480 or donepezil during 12 weeks treatment in patients with Alzheimer's Disease.

Target population and sample size

The main criteria for inclusion in the study were:

Female and male, aged 60 to 85 years, at day of enrolment with a clinical diagnosis of probable AD according to the NINCDS-ADRDA criteria and an MMSE score of 12-26

The planned sample size for evaluable patients is shown in Table S 1:

Table S 1 Sample size for evaluable patients

	AZD3480 5 mg	AZD3480 20 mg	AZD3480 35/100 mg[b]	Donepezil 10 mg	Placebo	Total
Evaluable[a]	67	67	67	134	134	469
Mild	43	43	43	86	86	301
Moderate	24	24	24	48	48	168

[a] Evaluable: assumption of 10% drop-out rate from randomisation to end of treatment
[b] High exposure group: 35 mg for slow metabolizers and 100 mg for rapid metabolizers

With these sample sizes, the probabilities of making erroneous conclusions were: probability to declare PoC for a placebo like drug (10%), probability not to declare PoC for an efficacious drug (6%), probability that donepezil will not be statistically significant better than placebo (10%)

The following assumptions were made in order to derive these error probabilities: AZD3480 was judged to be an efficacious drug if it was superior as compared to placebo (3 points on ADAS-Cog in mild patients and 4 points in moderate patients), donepezil was superior to placebo (2 points on ADAS-Cog in mild patients and 3 points in moderate patients). The standard deviation was assumed to be 6 points.

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

In this study, AZD3480 was administered as opaque, white, hard gelatine capsules of the 4-hydroxybensoate salt (TC 1734-226), for which 1 mg corresponds to 0.629 mg free base.

The capsule strengths were 5 mg, 10 mg, 25 mg and 50 mg of the salt, containing 3.1 mg, 6.3 mg, 15.7 mg, and 31.5 mg of free base, respectively.

Donepezil was administered as opaque, grey, hard gelatine capsules and the capsule strengths were 5 mg and 10 mg. The number and size of capsules were identical for the five treatment arms. The details of the investigational products (eg batch numbers) are given in the CSR.

Duration of treatment

Patients treated with AZD3480 were randomized into 3 dose groups: low, medium and high. In the low and medium dose groups, all patients received 5 and 20 mg AZD3480 over the 12 weeks, respectively, irrespective of being rapid or slow metabolizers. In the high dose group, all patients received 35 mg AZD3480 for the first 4 weeks; after 4 weeks the dose was increased to 100 mg for rapid metabolizers, while it remained at 35 mg for slow metabolizers throughout the 12-week treatment period.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Table S 2 summarizes the main efficacy and pharmacokinetics variables of this study, and shows how they relate to the study objectives.

Table S 2 Efficacy and Pharmacokinetics objectives and main variables

Objective	Main Variables
Primary objective	Mean change from baseline to EOT (Week 12) on ADAS-Cog (11-item) Total Score
Secondary Objective 1 (assess assay sensitivity)	Mean change from baseline to EOT (Week 12) on ADAS-Cog (11-item) Total Score
Secondary Objective 2 (assess dose response relationship in cognitive effects on ADAS-Cog and ADCS-CGIC)	Mean change from baseline to EOT (Week 12) on ADAS-Cog (11-item) Total Score and ADCS-CGIC
Secondary Objective 3 (assess effects on cognition in CDR and MMSE)	Mean change from baseline to EOT (Week 12) on CDR (Power of Attention, Continuity of Attention, Quality of Working Memory, Quality of Episodic Secondary Memory) and MMSE Total Score
Secondary Objective 4 (assess effects on cognition by PROs)	Mean change from baseline to EOT (Week 12) on DAD Total Score, CMAI (Aggressive Behaviour, Physically Non-Aggressive Behaviour, CMAI Verbal Inappropriate Behaviour), AAIQOL (Activity, Positive Affect, Negative Affect), ZBI Score and OTE
Secondary Objective 5 (assess PK and PK/PD)	The results are reported separately. Only descriptive statistics of plasma concentration are reported in the CSR.

EOT End of treatment; PRO Patient/ proxy reported outcomes

Criteria for evaluation - safety (main variables)

The safety objective was to evaluate safety and tolerability of AZD3480 by assessment of adverse events, laboratory variables, vital signs and physical examinations. The main variables were AEs, laboratory variables, vital signs and physical examinations from baseline to end of treatment (EOT)/ end of study (EOS) and from EOT to EOS. For safety parameters, EOT was defined as the last post-randomization visit prior to follow-up assessment.

Statistical methods

The concept was proven if in any of the two sub-populations (mild and moderate AD patients) there is at least one dose, which is both statistically significant better than placebo (one-sided $p<0.1$) and numerically better than Donepezil as assessed by mean change from baseline in ADAS-Cog (LS mean change AZD3480 > LS mean change donepezil).

The change from baseline to the end of the randomised treatment period was analysed with a linear model using analysis of variance (ANOVA) or covariance (ANCOVA). The results were reported as p-values, estimates and confidence intervals.

For the combined efficacy analyses (ie by group of all patients), the model included treatment, baseline ADAS-Cog total score, country, severity group, as explanatory variables. Country was treated as a random effect while severity group was treated as a fixed effect. Interaction effects could be added to model if deemed appropriate.

For the efficacy analyses by AD severity, the model included treatment, country and baseline ADAS-Cog total score as explanatory variables. Country was treated as a random effect.

The PRO analyses followed the same methods as the analyses of the other efficacy variables, except for the analysis of OTE. Used in Germany only, OTE for patient and caregiver at Week 12 was analyzed with a linear model ANOVA with severity as explanatory variables. Severity was treated as a fixed effect. If assumptions for parametric analysis were clearly violated, a non-parametric approach was to be applied.

Subject population

In general, the study population was similar to the targeted patient population and was well-balanced across the treatment groups.

The 569 patents randomized to treatment, and the 545 patients evaluable for the primary analysis, provided an adequate number to meet the design requirements for statistical power.

There were few important protocol deviations, and there were no apparent findings in the use of concomitant medication that could have influenced the evaluation of safety or efficacy.

Summary of efficacy results

<u>Primary efficacy variables</u>

The analysis of the primary endpoint, change from baseline in ADAS-Cog total score at week 12 (LOCF), is shown for all patients (FAS) in Table S 3.

Table S 3 ADAS-Cog Total Score Change from Baseline vs Placebo at Week 12 (LOCF) - ANCOVA (FAS)

		Baseline	Change from baseline		Difference versus Placebo		
Treatment	**N**	**Mean (SE)**	**LS Mean(SE)**	**95% CI**	**LS Mean(SE)**	**95% CI**	**One-Sided P-Value**
AZD3480 5 mg	77	22.4 (1.02)	0.1 (0.60)	-1.1, 1.23	0.4 (0.73)	-1.0, 1.81	0.701
AZD3480 20 mg	77	22.5 (1.08)	-1.0 (0.60)	-2.2, 0.13	-0.7 (0.73)	-2.1, 0.73	0.166
AZD3480 35/100 mg	81	22.7 (1.12)	0.8 (0.58)	-0.4, 1.90	1.1 (0.72)	-0.3, 2.49	0.936
Placebo	157	24.0 (0.92)	-0.3 (0.42)	-1.2, 0.50	na	na	na
Donepezil 5/10 mg	153	23.8 (0.83)	-1.1 (0.43)	-1.9, -0.21	-0.7 (0.59)	-1.9, 0.44	0.111

ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale; FAS: Full Analysis Set
Note: ADAS-Cog Total Score is calculated using the 11- item ADAS-Cog measure.
Source: Table 11.2.1.1.1.2.1
//csre/dev/azd3480/d3690c00010/sp/output/tlf/csr07.rtf adcs400.sas 28NOV2008:09:00 russoja

At Week 12 (LOCF), treatment with AZD3480 was not statistically superior to placebo for any dose group, in respect to LS mean (ie. adjusted for baseline covariates) changes from baseline on ADAS-Cog total score. However, treatment with AZD3480 20mg was numerically better than placebo, with an LS mean difference to placebo of -0,7 (SE 0.73; 95% CI -2.1, 0.73). Results for the AZD3480 5mg and 35/100mg groups were numerically worse than placebo: 0.4 (SE 0.73) and 1.1 (SE 0.72) respectively. The results were supported by the PP Analysis.

When analyzed by AD severity, at Week 12 (LOCF), treatment with AZD3480 was not statistically superior to placebo for any dose group in either mild or moderate AD subgroups, in respect to LS mean changes from baseline in ADAS-Cog total score. The results were supported by the PP Analysis.

AZD3480 was not numerically better than donepezil, assessed as change from baseline on ADAS-Cog, in the group of all patients or when the mild and moderate AD subgroups were analyzed separately, except for AZD3480 20 mg in the mild AD subgroup, which showed a numerical but minimal advantage (-0.1 points).

Secondary efficacy variables

- Treatment with donepezil did not show a statistically significant difference to placebo, assessed by change from baseline on ADAS-Cog, in the group of all patients. Therefore donepezil did not provide assay sensitivity for this study.

- No consistent dose response relationship could be established. AZD3480 showed trends to improvement vs. placebo for some doses on the secondary outcome scales MMSE, ADCS-CGIC and DAD.

  - No dose-response could be established among patients treated with AZD3480 on ADAS-Cog and ADCS-CGIC. The greatest numerical effect was shown by the 20mg group in the group of all patients on both ADAS-Cog and ADCS-CGIC: -0.7 (SE 0.73; 95% CI -2.1, 0.73) and -0.5 (SE 0.14; 95% CI -0.8, -0.21) respectively.

  - Treatment with AZD3480 did not show improvement in the CDR composite scores in the group of all patients. The variability in the composite scores was very high.

  - Treatment with AZD3480 showed improvement (unadjusted p-value < 0.1) in MMSE by the 5mg and 20mg dose groups, in the group of all patients: 0.5 (SE 0.38; 95% CI -0.2, 1.27) and 0.9 (SE 0.38; 95% CI 0.2, 1.67) respectively.

  - Treatment with AZD3480 did not show consistent improvement compared to placebo on any of the PROs (DAD, CMAI, AAIQOL, ZBI, OTE) in the group of all patients. Improvement (unadjusted p-values < 0.1) was shown in the 35/100 mg dose group on DAD 2.9 (SE 2.15; 95% CI -1.3, 7.11) and the 20 mg dose group on CMAI aggressive behaviour (0.5; SE 0.34; 95% CI -1.1, 0.18).

Summary of pharmacokinetic results

Overall, treatment with AZD3480 achieved individual exposures that were within the predicted range and, as expected, higher in SMs than in RMs within the same dose group. Similar individual exposures were achieved when SMs were treated with 35mg and RMs were treated with 100mg, as expected.

Summary of safety results

- The overall frequency of AEs among patients treated with AZD3480 was similar to placebo.

- There was an indication that patients treated with the highest dose of AZD3480 (35/100mg) had a higher frequency of AEs than those treated with a lower dose (5mg or 20mg).

- Among patients treated with AZD3480, AEs of dizziness and fatigue were slightly more common in the 35/100mg dose group than in the other treatment groups (5mg or 20mg).

- There were few SAEs and few DAEs within the AZD3480 groups, and the overall frequencies among patients treated with AZD3480 were similar to placebo.
- There were no clinically significant changes in laboratory values, vital signs or physical examinations.
- There were no signs of withdrawal symptoms.
- The pattern of AEs for donepezil was as expected, while the incidence was relatively low.
- All doses of AZD3480 given in the study were well tolerated and showed a good safety profile.