Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00011
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A Phase II, Multi-center, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Pharmacodynamic Effect of Single and Multiple Oral Doses of AZD1446/ Placebo and a Single Dose of Donepezil on Quantified Electroencephalography (qEEG) and Event-Related Potentials (ERP) in Patients with Mild-to-Moderate Alzheimer's Disease

Study dates: First subject enrolled: 21 June 2010
Last subject last visit: 10 March 2011

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

A total of 10 study sites participated in the study from 2 countries: Russia (6 sites), Ukraine (4 sites).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective of this study was to evaluate the effect of single and multiple dosing of AZD1446 and a single dose of donepezil on Quantified electroencephalography (qEEG) and Event-related potentials (ERP) in patients with mild-to-moderate AD.	Quantified Electroencephalography and Event-Related Potentials measurements after single and multiple doses of AZD1446, placebo and a single dose of donepezil	Pharmaco-dynamic
Secondary	**Secondary**	
To evaluate the relationship between AZD1446/donepezil plasma concentrations and qEEG/ERP following single and multiple oral doses of AZD1446 and a single dose of donepezil, as applicable	Relationship between plasma concentrations of AZD1446/donepezil and qEEG/ERP	PK/PD
To evaluate the correlation between changes in qEEG/ERP and changes in cognition, if applicable	Correlation between changes in EEG/ERP and changes in cognition	Pharmaco-dynamic
To evaluate the time course of the effect on qEEG and ERP following different dosing regimens of AZD1446	Time course of the effect on qEEG and ERP following different dosing regimens of AZD1446	Pharmaco-dynamic
To assess the safety and tolerability of single and multiple oral doses of AZD1446 in patients with AD.	Adverse events, clinical laboratory assessments, vital signs, ECG, physical examination, Columbia suicide severity rating scale	Safety
Exploratory	**Exploratory**	
To explore cognitive effects of AZD1446 compared to placebo after both single and multiple doses using selected cognitive tests from the CogState batteries	International Shopping List (ISLT), Identification (IDN), Continuous Paired Associate Learning (CPAL), One Card Learning (OCL)	Pharmaco-dynamic
To explore effects of AZD1446 on circadian rhythm as compared to placebo after both single and multiple doses by measuring motor activity and sleep quality	Motot activity is not reported in the CSR Sleep Diary: duration of sleep during night time, quality of sleep during night time	Pharmaco-dynamic
Pharmacogenetics (optional): to collect and store deoxyribonucleic acid (DNA) samples for possible future, exploratory genetic research. This will be optional for all patients participating in the study.	Not reported in CSR.	Pharmaco-genetics

Study design

This was a double-blind, multi-national, placebo-controlled, randomized, 5-treatment, 5-period crossover study in 2 countries at 10 sites in patients with mild-to-moderate Alzheimer's Disease

Target subject population and sample size

The target population consisted of males and non-fertile females, 55 to 85 years of age (inclusive) at day of enrollment, who had: a clinical diagnosis of probable AD according to the NINCDS-ADRDA criteria, an MMSE score of 18-24 and a history of progressive worsening of memory and other cognitive functions for at least 12 months.

A total of approximately 40 male and non-fertile female patients with mild-to-moderate AD, who are aged 55 to 85 years inclusive and are non-nicotine users, planned for randomization in order to obtain approximately 30 evaluable patients.

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

AZD1446 was provided in 2.5 mg, 10 mg and 30 mg capsules. Donepezil hydrochloride was provided in 5 mg capsules. Batch numbers and further information is included in the CSR.

Duration of treatment

This was a 5-treatment, 5-period crossover study. Each period consisted of a single dose treatment on Day 1, followed by 6 days of multiple dose treatment. The 5 study periods were each followed by a 7-day washout period

Statistical methods

Statistical analysis on qEEG/ERP (using the SDT methodology) and actigraphy was performed by the biostatistics department of Forenap Pharma. Statistical analysis of CogState cognition tests was performed by CogState. Statistical analysis of sleep quality, correlation between changes in qEEG/ERP and changes in cognition, pharmacokinetics and safety was performed by AstraZeneca.

Continuous variables were summarised using descriptive statistics (n, mean, SD, min, median, max) by treatment group. Categorical variables were summarised in frequency tables (frequency and proportion) by treatment group.

The safety analysis set included all patients who received at least one dose of randomized IP, AZD1446 or donepezil and for whom any post-dose data are available. The pharmacokinetic analysis set included all patients who received IP and who have evaluable PK data appropriate for the comparison of interest (with no major protocol deviation or AE thought to significantly affect the PK of the drug). The pharmacodynamic analysis set included all patients who received IP and who have evaluable PD data appropriate for the comparison of interest (with no major protocol deviation or AE thought to significantly affect the PD variable). Whether a

given patient has data appropriate to evaluate PK or PD data or not was decided before breaking the blind.

Subject population

In total, 62 patients were enrolled in the study. 35 patients were randomized to treatment, 10 discontinued treatment and 25 completed all 5 treatment periods. 29 patients completed a follow-up visit.

A total of 35 patients were randomized to treatment and are included in the safety analysis set. The PK analysis set includes 25 patients, as 10 were excluded from the PK analysis set, due to protocol deviations. The PD analysis set includes 22 patients, as an additional 3 were excluded from this set due to study withdrawals after the first treatment period. A restricted PD analysis set has also been created, which excludes 7 additional patients with protocol deviations related to PK

The demographics and patient characteristics of the subject population were in line with the target population for the study. The number of patients excluded due to protocol deviations or not remaining on treatment over the course of the study is not considered to influence the results.

Summary of pharmacokinetic results

The concentration results show that patients in the PK analysis set received AZD1446 as intended. Overall, the PK parameters results show that AZD1446 and donepezil generally performed in-line with expectations.

Summary of pharmacodynamic results

Primary Variable

Effects of AZD1446 and donepezil on quantified electroencephalography (qEEG)

The data from Day 1 did not show any pattern of significant qEEG activity for single-dose treatment with 2.5 mg and 10 mg AZD1446, although there was a significant increase for the 10 mg dose on the alpha-2 sub-band. A single dose of 60 mg AZD1446 showed significant decreases on the delta and theta bands for both the resting and vigilance conditions after, generally, 3 hours post treatment, but no significant changes on alpha, apart from a decrease on the alpha-1 sub-band. Treatment with donepezil showed significant decreases on delta and theta, but it also showed decreases on alpha, all after 3 hours. There were significant changes on the beta band after 1 hour for all the AZD1446 doses.

A compositive analysis of the alpha band, delta and theta bands, called the Alpha Slow Wave Index (ASI), was also performed for Day 1- The analysis shows a significant increase (associated with improvement in cognitive function) for single doses of 10 mg and 60 mg AZD1446 at 3 hours (resting) and 8 hours (vigilance). Treatment with donepezil showed a significant decrease (ie worsening) after 3 hours.

After 6 days of multiple dosing (ie on Day 7), treatment with 60 mg tid AZD1446 showed indications of qEEG activity associated with improvement in cognitive function: significant increase in activity after 3 hours on the alpha-2 sub-band for both resting and vigilance conditions as well as a significant decrease on theta (resting) after 8 hours. Treatment with 60 mg od AZD1446 did not show significant changes any of the bands, and treatment with 2.5 mg AZD1446 showed significant decreases on alpha. The donepezil group, which had been treated with placebo since day 1, showed significant decreases on alpha after 3 hours and significant increases on delta There were significant changes in the beta band for the 2.5 mg and 60 mg tid AZD1446 doses.

The ASI analysis for Day 7 showed significant increases (ie improvement) after 1 hour for both the AZD1446 60 mg od (vigilance) and tid (resting and vigilance) groups. It also showed significant decreases (ie worsening) for the group treated with donepezil on Day 1.

In general, EEG effects were pronounced after multiple dosing.

Overall the relative magnitude results were in line with the absolute magnitude results across all the parameters.

Effects of AZD1446 and donepezil on event-related potentials (ERP)

For ERPs, the most salient effect is the decrease in latency by >20 milliseconds at 8 h on Day 7 for the 2.5 mg dose which was accompanied by amplitude increases on statistical maps (and P3 peak increases on Cz by +0.33 microVolt only). A similar effect on latency was observed on 60 mg od, but not on 60 mg tid.

Secondary Variables

Correlation between changes in qEEG/ERP and changes in cognition

The exploratory analysis of cogntion showed no significant effects for AZD1446 on the International Shopping List (ISLT), Identification (IDN) or Continuous Paired Associate Learning (CPAL) tasks. Significant effects were shown on the One Card Learning (OCL) task.

Consequently, an analysis was performed of the potential correlation of changes in qEEG/ERP and changes on OCL. The analysis showed no significant correlation between OCL improvements and qEEG or ERP.

On Day 7, no significant improvement compared to placebo was shown on OCL in any treatment group.

Time course of effect on qEEG/ERP and different dosing regimens of AZD1446

As noted above, occasional significant effects of AZD1446 were observed for some of the qEEG parameters, however without any obvious consistency or pattern over time on day 1 or on day 7. Consequently, it is not possible to draw any conclusion on the duration of effect or the time course of the effect of AZD1446 on any of these parameters.

As noted above in the ERP results section, the most pronounced decreases in P3 latency compared to placebo were observed for AZD1446 2.5 mg od and 60 mg od at day 7, 8 hours. The time course of these doses, with decreases on day 1 and day 7, is shown in Figure 15. There was no consistent pattern over time for these 2 dose groups from baseline to the 8-hour timepoint, although both groups exhibited significant latency increases between the 8- and 10-hour timepoints, stressing the transient nature of the effect on Day 7.

Summary of pharmacokinetic/pharmacodynamic relationships

Donepezil concentrations vs qEEG/ERP

Exploring the qEEG (resting and vigilance condition for α, β, δ waves) and ERP (P300 and LP300 effects versus donepezil plasma exposure showed statistically significance in the same direction as the dose-related effects in the primary analysis, when using a linear PK/PD model.

AZD1446 concentrations vs qEEG/ERP

Results for Day 1

When pooling concentration data from all sampling times (1, 3 and 8 hours after dose) there were no significant effects when relating qEEG (resting and vigilance condition for alpha, beta, delta waves) and ERP (P300 and LP300) effects to AZD1446 plasma exposures, when using a linear PK/PD model. When looking at each time-point separately, there were no consistent trends, even if statistical significance was observed at occasional time-points and parameters.

In additional, the findings were not consistent with the dose-related analysis of the alpha, beta and delta waves.

Results for Day 7

For alpha, there was a statistically significant increase during both resting and vigilance controlled conditions, both at one separate time-point (3h) and when pooling all time-points. This was un-consistent with the dose-related analysis, where no consistent effects were seen.

For beta, there was a statistically significant decrease during resting condition in both one separate time-point (1h) and when pooling all time-points. However, the observed effect was in opposite direction than expected.

For delta, there was a statistically significant decrease during the vigilance controlled condition only, both in one separate time-point (3h) and when pooling all time-points. This was also observed at one occasional time point (8h) for the dose-related analysis analysis.

There was no relationship between the ERP parameters P300 and LP300 and AZD1446 plasma concentrations either at any separate time-points or when pooling all time-points.

Patient reported outcomes

Duration of nightly sleep was recorded in the sleep diaries. The results showed that the mean number of hours of sleep were similar across the treatment groups. The number of patients reporting less than 5 hours or greater than 8 hours of sleep was also similar across the treatment groups.

No significant changes from baseline were shown on the sleep quality ratings in any treatment group during any period.

Summary of safety results

- The results indicated that AZD1446 single doses ranging from 2.5 mg od to 60 mg od and repeated doses ranging from 2.5 mg od to 60 mg tid during 1 week, had acceptable safety and tolerability in patients with mild or moderate Alzheimer's disease.
- There were no deaths or SAEs. There was 1 DAE.
- AEs were of mild or moderate intensity.
- There were no clinically meaningful changes in clinical laboratory measurements, vital signs, ECGs, physical findings or suicidality (C-SSRS)

Result(s)

- The EEG results showed a signal in slow wave and alpha power for 60 mg od & tid AZD1446 after both single and multiple dosing. The ERP results showed a signal for 60 mg od and 2.5 mg od AZD1446 after multiple dosing. There was no consistent pattern in the time-course of the effects after single or multiple dosing.
- There was no apparent relationship between plasma concentrations of AZD1446 and donepezil and the changes in qEEG/ERP. There was no apparent relationship between qEEG/ERP and cognition test results after a single dose of AZD1446 or donepezil or after multiple dosing with AZD1446.

- Treatment with single and multiple oral doses of AZD1446 showed acceptable safety and tolerability in patients with mild or moderate Alzheimer's disease.