AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D2285M00021
Edition Number	1
Date	25 March 2011

A single-centre, randomised, double-blind, placebo-controlled, four-period cross-over study to evaluate the scopolamine cognition model in healthy male subjects using AZD1446 and donepezil versus placebo

Study dates: First subject enrolled: 22 December 2009
Last subject last visit: 29 April 2010

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This was a single-centre study.

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**	
Evaluate the scopolamine cognition model with single oral administration of AZD1446 and donepezil, respectively, versus placebo in healthy male subjects as assessed through the absolute alpha-power of the two occipital leads of the quantified electroencephalography (qEEG)	Absolute alpha-power (average over time)	PD
Secondary	**Secondary**	
To evaluate the scopolamine cognition model with single oral administration of AZD1446 and donepezil versus placebo in healthy male subjects as assessed through the relative alpha-power of the two occipital leads of the quantified electroencephalography (qEEG)[a]	Relative alpha-power (average over time)	PD
To evaluate the scopolamine cognition model with single oral administration of AZD1446 and donepezil versus placebo in healthy male subjects as assessed through the absolute and relative AUC $_{0\text{-}6}$ h alpha-power of the two occipital leads of the quantified electroencephalography (qEEG). Post-hoc analysis	Absolute and relative AUC $_{(0\text{-}6h)}$ alpha-power (extraction of the surface estimation AUC from 0 to 6 hours, (AUC $_{(0\text{-}6h)}$)	PD
Evaluate the ability of single oral administration of AZD1446 and donepezil, compared to placebo in reversing scopolamine-induced changes in brain electrical activity in healthy male subjects through event-related potentials (ERPs) by means of mismatch negativity (MMN) and P300[b].	MMN parameters: -mean latency of N100 and N2 peak on the vertex lead -integrated amplitude of negative deflection with the latency range 76 – 112 ms for N100 and 180 – 240 ms for MMN ERP parameters : -mean latency of P3 peak (maximum between 260 and 420 ms), on the vertex lead (Cz) -mean amplitude of P3 peak (maximum between 260 and 420 ms), on the vertex lead (Cz) -mean amplitude (surface or S300) comprised in the latency ranges: 232-352 ms.	PD
To evaluate the scopolamine cognition model with single oral administration of AZD1446 and donepezil versus placebo in healthy male subjects as assessed through absolute and relative magnitude of qEEG frequency bands	Effects on absolute and relative magnitude of qEEG frequency bands and on additional spectral characteristics of qEEG	PD

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Investigate the ability of single oral administration of AZD1446 and donepezil compared to placebo in reversing scopolamine-induced cognitive impairment in healthy male subjects as assessed through Cogstate computerized cognitive tests.	Visual learning and memory measured by Continuous Paired Associate Learning task (CPAL Executive function & spatial problem solving assessed by Groton Maze Learning Task (GMLT) Visual attention/vigilance assessed by Identification task (IDN).	PD
Evaluate the subjective effects of single oral administration of AZD1446 and donepezil respectively, compared to placebo by means of ARCI-49 and Bond/Lader (B&L VAS) scales	ARCI-49: 49-items "true-false" questionnaire divided in five empirically-derived scales: MBG scale (Morphine Benzedrine Group scale) measures drug-induced euphoria -LSD scale (Lysergic Acid Diethylamine group scale) estimates dysphoria -PCAG scale (Pentobarbital Chlorpromazine Alcohol Group scale) measures sedation -BG scale (Benzedrine Group scale) is a stimulant-sensitive scale -A scale (Amphetamine scale) B&L VAS is analysed using three factor subscores: alertness, contentedness (well-being) and calmness.	PD
Explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship between qEEG alpha frequency band and AZD1446 plasma concentrations compared to donepezil	No variables were pre-specified due to the exploratory nature of the objectives. The following variables were analysed: $C_{max,}$ $t_{max,}$, AUC_{0-t} and AUC were calculated for AZD1446 and donepezil	PK/PD
Evaluate the safety and tolerability of single oral administration of AZD1446 and donepezil respectively, in combination with scopolamine administered to healthy male subjects	Adverse events, laboratory variables, vital signs, 12-lead ECG, and physical examination	Safety

a The variables relating to this objective were included in the CSP and the SAP (CSR Appendix 12.1.9a) but by mistake no objective was listed in the CSP. The objective has been added in this table and the results relating to this objective are reported in the results section.

b To evaluate the effect of AZD1446 has been added to the objective as stated in the CSP since by mistake only donepezil was included.

Study design

This was a single-centre, randomised, double blind, placebo-controlled, four-period crossover study. AZD1446 is being developed for symptomatic treatment of Alzheimer's disease.

Target subject population and sample size

Male healthy volunteers aged 18 to 45 years. A total of 21 subjects were planned to be included.

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

Investigational product	Route of administration	Manufacturer	Batch number
Placebo	Oral	AstraZeneca	09-000848AZ
Placebo	Oral	Fisher	09-005354AZ

Investigational product	Route of administration	Manufacturer	Batch number
AZD1446 80 mg	Oral	AstraZeneca	09-005446AZ
AZD1446 10 mg	Oral	AstraZeneca	09-005442AZ
Donepezil 5 mg	Oral	Fischer	09-005442AZ

Duration of treatment

Single doses of investigational product were administered during each of the four treatment periods. Scopolamine 0.5 mg s.c. was administered 2 h after donepezil or in parallel with AZD1446. There was a wash-out period of at least 21 days between the treatment periods. Each treatment period lasted for three days.

Statistical methods

Primary analysis (PD): The effect on the alpha power of the two occipital leads O1 and O2 were analysed by an average, over time, of the mean of O1 and O2 alpha power, expressed in changes from baseline. Differences between treatment groups were analysed on the average effect by an analysis of variance. Secondary analysis (PD): In general a mixed model analysis of variance was used. Analyses of brain maps (EEG/ ERPs mapping) were done using the methodology standard decision tree. PK/PD relationship: Explored graphically by plotting the individual maximum decrease from baseline. Safety was generally summarized using descriptive statistics.

Subject population

24 males aged 18 to 45 years were randomised into the study at 1 study site. All subjects 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 while 5/24 subjects were excluded from the PD analysis set. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacodynamic results

Absolute alpha power (average over time) of occipital leads, during vigilance controlled condition, was reversed by 1.4 μV with AZD1446 10 mg, by 0.9 μV with AZD1446 80 mg, and by 1.4 μV with donepezil 5 mg. During resting condition the corresponding values were 1.3μV, 1.2μV, and 1.3μV. The effects were not statistically significant.
In a post-hoc analysis of effects on relative $AUC_{(0\text{-}6h)}$, (extraction of the surface estimation (AUC) from 0 to 6 hours) during vigilance controlled condition, donepezil 5 mg significantly ($p<0.05$) reversed alpha power by 20.1 μV*h. No statistically significant effects were seen with either dose of AZD1446. Latency of N2 (LN2) was statistically significantly reversed with AZD1446 80 mg on F4 at 3h by -20 milliseconds (ms) and on F3 at 3h by -17 ms compared to placebo. Also, there was a statistically significant effect of donepezil 5 mg across assessment time on LN2 with trends of statistically significant effects on F4 at 3 h by 11.4 ms and on F4 at 24 h by –12.7 ms. Latency of P300 (LP300) was statistically significantly reversed with AZD1446 80 mg at 6h by 24.4 ms compared to placebo. For peak amplitude of P300 (P300) there was a trend for a reversal with AZD1446 80 mg by -1.7 μV ($0.05<p<0.10$) and with donepezil by 1.8 μV ($0.05<p<0.1$).

qEEG mapping analysis showed that both doses of AZD1446 significantly reversed the scopolamine induced delta increase and alpha suppression during vigilance controlled condition. ERP mapping analysis of S300 supported the mixed model analysis by showing significant increases with a centro-parietal topography at 6h for AZD1446 80 mg.

Treatment with scopolamine 0.5mg was associated with a large decline in performance as assessed with CogState. For the measure of executive function (GMLT) AZD1446, 10 mg and 80 mg, was associated with a statistically significant improvement of performance at the 2 and 3 h post-dose assessments and there was a close to statistically significant effect of donepezil 5 mg at 1 h. For the measure of visual attention/vigilance (IDN), AZD1446 80 mg was associated with a statistically significant improvement of performance at 1, 2, 3 and 6 h. No statistically significant effects were observed on the measure of visual learning and memory (CPAL) for any of the treatment groups.

There were no statistically significant differences in subjective mood, between treatments at any time points as assessed with ARCI-49. For the Bond-Lader scale, there was a significant decrease as compared to placebo in the contentedness score for AZD1446 10 mg at 1 h ($p<0.05$) and 2 h ($p<0.05$) after dosing and for donepezil at 2 h ($p<0.05$) after dosing as compared to placebo. For the calmness score there was a significant decrease ($p<0.05$) for both AZD1446 80 mg and donepezil at 3 h after dosing.

Summary of pharmacokinetic/pharmacodynamic relationships

There was no apparent relationship between individual maximum decrease from baseline of the relative alpha power and C_{max} neither for AZD1446 nor for donepezil.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), or any other significant AEs in the study. Two subjects discontinued the study due to adverse events (DAEs). The majority of the AEs were of moderate intensity and were most common in the AZD1446 80 mg group. There were no obvious differences in number or intensity of AEs between the other treatment groups. The most common AEs were associated with somnolence, dry mouth, and blurred vision. Few values were outside reference limits with regards to laboratory variables, vital signs, and ECG. There was no pattern of changes in mean values in any of the treatment groups.