Clinical Study Report Synopsis

Drug Substance	AZD5213
Study Code	D3030C00005
Edition Number	1
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EudraCT Number	

A Phase IIa Safety and Tolerability Study to Investigate the Effect on Sleep of 3 Doses of AZD5213 and Placebo in Patients with Mild Alzheimer's Disease and Mild Cognitive Impairment During 4 Weeks of Treatment, Designed as a Randomized, Double-Blind, Multi-Center, Parallel Group, Placebo-Controlled Study

Study dates:	First subject enrolled (informed consent signed): 24 April 2012 Last subject last visit: 14 January 2013
Phase of development:	Clinical pharmacology (I) Therapeutic exploratory (IIa)
International Co-ordinating Investigator:	Not Applicable

[redacted]

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

Study centre(s)

This study was conducted at 10 study centers in the United States (US).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To estimate the relationship of sleep duration versus dose after 4 weeks of administration of AZD5213 or placebo	Change from Baseline to 4 weeks of treatment in the total sleep time (TST), based on polysomnography (PSG) measurements
Secondary	Safety	To explore the relationship between sleep duration versus plasma exposure after 4 weeks of administration of AZD5213 or placebo	Sleep duration versus log AZD5213 concentration prior to start of PSG
Secondary	Safety	To evaluate the effect of AZD5213 on the level of insomnia compared with placebo	Change from Baseline to 4 weeks of treatment in PSG measurements
Secondary	Safety	To correlate PSG with actigraphy measurements	Correlation of nighttime actigraphy sleep parameters with PSG
Secondary	Safety	To measure the effects of AZD5213 on behavioral alertness compared with placebo	Change from Baseline in Psychomotor Vigilance Test (PVT)
Secondary	Safety	To evaluate safety and tolerability of AZD5213 compared with placebo	Frequency of adverse events (AEs) and change from Baseline and shift in category will be calculated for laboratory, electrocardiogram (ECG), and vital signs variables
Secondary	Safety	To characterize the PK of AZD5213	AZD5213 plasma concentrations
Secondary	Safety	To evaluate if treatment with AZD5213 affects the PK of donepezil	Donepezil plasma concentrations in patients receiving AZD5213 versus patients receiving placebo
Exploratory	Safety	To explore the effect of AZD5213 on subjective daytime sleepiness compared with placebo	Change from Baseline to 4 weeks of treatment in Karolinska Sleepiness Scale (KSS) and daytime actigraphy data
Exploratory	Safety	To explore the effect of AZD5213 on sleep quality during nighttime compared with placebo	Change from Baseline to 4 weeks of treatment in Time Sleep Diary (TSD)
Exploratory	Safety	To explore the effects of AZD5213 on cognition compared with placebo	Change from Baseline to 4 weeks of treatment in CogState (One Card Learning [OCL], Identification task IDN])
Exploratory	Safety	To evaluate effects of AZD5213 on sleep architecture (PSG measurement set)	Change from Baseline to 4 weeks of treatment in PSG measurements including wake time after sleep onset (total, hour 1 to 3, 4 to 6, 7 to 8), duration and %TST in sleep stages (1, 2, 3/4, rapid eye movement)

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Safety	To identify/explore genetic variations that may affect the PK and pharmacodynamics (PD), safety and/or tolerability related to AZD5213 treatment or the target (H_3 receptor) in deoxyribonucleic acid (DNA) samples taken from consenting patients. In addition, susceptibility genes and genes related to underlying disease could be explored **(data from this objective will not be included in the Clinical Study Report [CSR] and will be reported separately)**.	

Study design

This was a double-blind, multi-center, placebo-controlled, randomized, parallel group study designed to objectively assess and quantify the effects on sleep induced by AZD5213 over 4 weeks of treatment in order to facilitate dose finding in Phase IIb. In addition, the intention was to evaluate mobile sleep measurement devices (actigraphy) for future sleep measures in Alzheimer's patients.

Patients with mild Alzheimer's disease (AD) or mild cognitive impairment (MCI) who may or may not have been taking donepezil, were randomized to 1 of 3 AZD5213 dose groups (0.5 mg once daily, 2.0 mg once daily, or 6.0 mg once daily, n=18 patients each) or placebo (once daily, n=18 patients). Total sleep time in addition to other sleep parameters, as measured by PSG assessments, was determined at Baseline (Night -2 and Night -1), Week 2 (Night 13 and Night 14), and Week 4 (Night 27 and Night 28). Actigraphy, a mobile sleep measurement method, was also used to measure sleep parameters. Other measures of sleep outcome included behavioral alertness as determined by a Psychomotor Vigilance Test (PVT), subjective daytime sleepiness as assessed by the KSS, subjective self-assessed sleep quality as measured by a Time Sleep Diary (TSD), and cognition as measured by CogState tasks (One Card Learning [OCL], Identification task IDN]).

Target subject population and sample size

Male and nonfertile female patients between the ages of 50 and 85 years diagnosed with mild AD or MCI (Clinical Dementia Rating [CDR] of 0.5 to 1.0, Mini-Mental State Examination [MMSE] score of 24 to 30, Hachinski Ischemic Score ≤4).

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

AZD5213 gelatin capsules will be self-administered orally, once daily in the morning at doses of 0.5 mg, 2.0 mg, or 6.0 mg.

Duration of treatment

Study drug was self-administered orally, whole with water (not chewed or crushed), once each day, in the morning, 30 minutes prior to the first meal of the day. Study drug was to be taken at approximately the same time each morning. Study treatment lasted for 28 days.

Statistical methods

Continuous variables were summarized using descriptive statistics [number of patients (n), mean, median, standard deviation (SD), minimum, and maximum].

The primary endpoint, TST based on PSG, was analyzed with a mixed model for repeated measurements (MMRM). All pre- and post-Baseline values of sleep duration were dependent variables, while treatment group, time, treatment-by-time-interaction were fixed effects, and study center was a random effect. It was assumed that there was no treatment difference for Nights -2 and -1. Values from different patients were assumed to be independent, and missing values were assumed missing completely at random (MCAR). For the 6 values from each patient, an unstructured covariance matrix was used to model the within-subject error and the Kenward-Rogers approximation was used to estimate the degrees of freedom. From this model, the estimate of the mean of Nights 27 and 28 minus the mean of Nights -2 and -1 (Baseline) were derived as the primary endpoint.

The decision criterion of less than 30 minutes sleep reduction relative to Baseline was based on the primary analysis model. The 4 estimates of the Week 4 treatment means (ie, average of Day 27 and Day 28) from the estimates from contrast statement of the MMRM model were examined. If the results were nonmonotone, the 30 minutes criterion was applied after application of monotone regression to the least squares (LS) estimates for the treatment groups.

The statistical comparisons of each AZD5213 dose versus placebo utilized model-based point estimates, 2-sided 90% confidence intervals (CI), and p-values, with no correction for multiplicity.

The secondary endpoint of PSG variables (TST at Week 2, sleep efficiency index [SEI], number of awakenings [NAW], and latency to persistent sleep [LPS]) were analyzed using a MMRM model, where change from Baseline to each post-Baseline value at Week 2 and Week 4 were the dependent variable, while treatment group, time, treatment group -by-time-interaction were fixed effects, and study center was a random effect and corresponding baseline value as a covariate. Values from different patients were assumed to be independent, and missing values were assumed MCAR. Other continuous secondary and exploratory variables were analyzed similarly.

Subject population

A total of 164 patients were enrolled in the study and 81 patients were randomized, with 19 randomized to receive 0.5 mg AZD5213 daily (0.5 mg group), 22 randomized to receive

2.0 mg AZD5213 daily (2.0 mg group), 20 randomized to receive 6.0 mg AZD5213 daily (6.0 mg group), and 20 randomized to receive placebo daily (placebo group).

All randomized patients (100%) received treatment and 72 of 81 patients (88.9%) completed the study. The 6.0 mg group had the largest number of patients who discontinued from the study (7 patients, 35.0%), followed by the 2.0 mg group (2 patients, 9.1%). All patients from the 0.5 mg group and the placebo group completed the study.

All 81 randomized patients received at least 1 dose of study drug (either AZD5213 or placebo) and had post-Baseline data and were therefore included in the Safety analysis set.

The Primary analysis set (all randomized treated patients who provided post-Baseline PSG data classified according to the randomized treatment) included 73 patients in total. One patient in the 2.0 mg group and 6 patients in the 6.0 mg group were considered not evaluable (did not have 2 consecutive nights of valid PSG recordings at Baseline and had at least 2 TST observations based on valid post-Baseline PSG recordings) and 1 patient in the 6.0 mg group had 1 or more invalid PSG assessments, and were therefore excluded from the Primary analysis set.

In general, Baseline demographic data were similar across treatment groups and any differences were not expected to influence the data collected or interpretation of the results.

Summary of sleep and sleep-associated results

Overall, according to the primary variable, the change from Baseline to Week 4 in TST (as determined by PSG), no treatment group had a mean decrease in TST of ≥30 minutes; however, there was a relationship with dose in the change in TST from Baseline to Week 4 (LS mean), with the largest decrease seen in the 6.0 mg group (-19.41 minutes; 90% CI: -41.91, 3.08) with a statistically significant treatment difference compared with placebo (-33.89 minutes; 90% CI: -60.69, -7.09; p=0.038). Compared with placebo, there were no statistically significant differences in the TST in the 0.5 mg group (-8.04 minutes; 90% CI: -32.11, 16.03; p=0.581) or the 2.0 mg group (-27.00 minutes; 90% CI: -50.79, -3.21; p=0.062) at Week 4. Other observations included the following:

- The relationship between the plasma concentration and the PSG total sleep time had a negative slope, indicating the there was a trend for decreasing total sleep time with increasing exposure to AZD5213

- Comparing the active AZD5213 treatment groups with the placebo group, there were no statistically significant treatment differences in any of the PVT variables. The mean reaction time and the number of lapses (reaction time >500 msec) decreased at Week 4 compared with Baseline in all treatment groups

- There was little change in daytime sleepiness as determined by the KSS. There were no statistically significant treatment differences comparing the active AZD5213 treatment groups with the placebo group

- There were no clinically meaningful changes in the quality of sleep as assessed by the TSD. There were no significant treatment differences comparing the active AZD5213 treatment groups with the placebo group at Week 4

- There were only minor changes in the CogState test data from Baseline to Week 2 and Week 4 in the speed and accuracy assessments. Aside from a statistically significant treatment difference in favour of the 0.5 mg group compared with the placebo group in the speed of performance and accuracy of performance at Week 4, there were no other statistically significant treatment differences comparing the active AZD5213 treatment groups with the placebo group.

Summary of pharmacokinetic results

The exposures reported for the current study are consistent with those expected based upon the exposures seen at similar doses in other human clinical studies. There were too few patients taking donepezil with pharmacokinetic data to derive any firm conclusions regarding the effect of donepezil on AZD5213 or the effect of AZD5213 on donepezil.

Summary of safety results

Treatment with AZD5213 was safe and generally well tolerated. There were no deaths and a single SAE (moderate transient ischemic attack) that was assessed by the Investigator to be unrelated to study drug was reported. Seven patients were reported with 1 or more AE leading to discontinuation of study drug; 2 patients (9.1%) in the 2.0 mg group and 5 patients (25.0%) in the 6.0 mg group, with most of the patients discontinuing due to events associated with sleep disruption (insomnia, night sweats) and/or headache, dizziness, and nausea. Other safety findings included:

- The most frequently reported treatment-emergent AEs (TEAEs) were insomnia (19.7% of patients) and headache (16.4% of patients), both which showed an increase in the number of patients reporting with increasing AZD5213 dose. No other TEAEs were reported for more than 10% of patients

- Most TEAEs were mild or moderate. The only severe TEAEs reported were for 3 patients in the 6.0 mg group, with all 3 patients reported with severe insomnia

- No clinically meaningful differences comparing the AZD5213-treated patients with placebo-treated patients were noted for any laboratory, ECG, or vital sign parameter

- There were no Hy's Law cases (alanine aminotransferase >3 x upper limit of normal [ULN] or aspartate aminotransferase >3 x ULN and total bilirubin >2 x ULN), ie, no patient in any treatment group met the liver function test criteria indicative of drug-induced liver injury

- There were no events of suicidal ideation or behavior during the study.

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