AstraZeneca

Exploratory Study Report Synopsis

Drug Substance	AZD6765
Study Code	D2285M00008
Edition Number	1
Date	26 July 2011

A Phase I Randomized, Double-Blind, Four-way Cross-over Study in Healthy Subjects to Assess Quantitative Electroencephalography (qEEG) Parameters after the Administration of Ketamine, two Doses of AZD6765 and Placebo

Study dates: First subject enrolled: 25 May 2010
Last subject last visit: 26 January 2011

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 center study conducted at FORENAP Pharma, Rouffach France.

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**	
To assess the effect of a single iv dose of ketamine (0.5 mg/kg), and 2 doses of AZD6765; 150 mg and 75 mg compared to placebo on the change in magnitude of gamma-band qEEG in healthy young male subjects	Change in magnitude of the gamma-band qEEG	PD
Secondary	**Secondary**	
To assess the safety and tolerability of AZD6765 in healthy male subjects through adverse event (AE) monitoring, physical examinations, vital signs, electrocardiograms (ECGs) and Columbia-Suicide Severity Rating Scale (C- SSRS)	Adverse events, physical examination, vital signs, 12-lead ECG, and C-SSRS- prospective rating of suicidal idealization	Safety
To evaluate the subjective effects of single iv dose of ketamine 0.5 mg/kg, and 2 doses of AZD6765; 150 mg, and 75 mg compared to placebo by means of Clinician Administered Dissociative States Scale (CADSS), Bond/Lader Visual Analogue Scale (VAS) scales and eVAS	-CADSS measures perceptual, behavioural, and attentional alterations occurring during dissociative experiences -VAS is analysed using three factors; alertness, contentedness and calmness -eVAS-assesses emotional stability	PD
To assess the effect of a single iv dose of ketamine 0.5 mg/kg, and 2 doses of AZD6765; 150 mg, and 75 mg compared to placebo on the change in pupil size and electronystagmus	Change in pupil size and electronystagmus	PD
Exploratory	**Exploratory**	
To explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship between qEEG bands power and ketamine and its metabolite, and AZD6765 plasma concentrations	Reported in a separate report outside the Exploratory Study Report	PK/PD

Study design

This was a single-centre, randomised, double blind, placebo controlled, four-period crossover study in young male subjects, 30 to 45 years of age.

Target subject population and sample size

Approximately 19 healthy subjects were to be enrolled at a single centre to obtain 16 completed subjects.

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

Subjects received a single 60 minute iv infusion of ketamine (0.5 mg/kg), AZD6765 75 mg, AZD6765 150 mg and placebo. Subjects were randomized to receive all of the treatment sequences, active and placebo, during the 4 treatment periods.

Concentrated AZD6765 was manufactured by AstraZeneca in bulk supply (15 mg/mL, 10.7 mL in each 10 mL vial) and the concentrate was diluted at the investigational site to obtain the protocol doses of 75 and 150 mg for intravenous infusion. The ketamine and isotonic sterile saline (used as placebo and as diluents for AZD6765/ketamine) were supplied by the investigational site. The batch number for AZD6765 was 10 002708AZ and for ketamine J90417.

Duration of treatment

The healthy subjects were randomly assigned to receive a sequence of four treatments as determined by a randomisation schedule. Each treatment administration was a 60 minute iv infusion. For each treatment period, the subjects spent 1 night and 2 days in the Clinical Research Unit with a washout period of at least 7 days between treatment periods.

Statistical methods

Primary Analysis (PD): The analysis of brain maps (EEG) was performed using a methodology called Standard Decision Tree (SDT) and presented as SDT maps. SDT maps were created for eyes closed and eyes open conditions. Secondary Analysis (PD): Pupil size and Electronystagmography were analysed by mixed model on absolute values. For all other endpoints a mixed model was used to analyse change from baseline values. Safety was generally summarized using descriptive statistics. Exploratory PK/PD: Concentration-effect between plasma concentration and qEEG bands relationship were explored through scatter plots by regimen and protocol times.

Subject population

A total of 36 healthy subjects were enrolled (informed consent received) of which 23 were randomised. Twenty-two subjects were dosed in treatment period 1, 16 of these subjects were dosed also in period 2, 15 subjects were dosed in treatment period 3 and 12 subjects completed all 4 treatment periods and the study.

Fourteen subjects received treatment with AD6765 at 75 mg, 19 subjects were treated with AZD6765 at 150 mg, 17 subjects were treated with ketamine and 15 subjects received placebo treatment.

There were 22 subjects in the Safety Analysis set and PK Analysis set and 15 subjects in the PD Analysis set.

The mean age for the 22 subjects in the Safety Analysis set was 37.0 years (range 32-45 years). The mean baseline Body Mass Index was 24.3 kg/m^2 (range 20-29 kg/m^2).

Summary of pharmacodynamic results

The study met primary objective of demonstrating statistically significant elevations in spontaneous gamma following administration of NMDAR antagonists. Overall, all three active drug arms exhibited the largest change in gamma at the stop of infusion (C_{max}) and typically produced a change in gamma of ~1 uV. This magnitude of change corresponds to an effect size (at 1–hour) of 1.6, 1.58, and 1.22 for ketamine, AZD6765 (150 mg), and AZD6765 (75 mg) respectively.

For AZD6765, fluctuations in gamma were not correlated with electronystagmography (ENG) variables; a result consistent with a neuronal origin for AZD6765 associated gamma.

Analysis of key secondary and exploratory variables including broad spectrum changes in spontaneous EEG and visual analogue scale (VAS) measurements provide quantitative differentiation between 75 mg and 150 mg doses of AZD6765.

Despite producing similar levels of gamma-EEG, ketamine but not AZD6765 was associated with a significant elevation in disassociative effects as measured by the Clinician Administered Dissociative States Scale (CADSS) score.

Summary of pharmacokinetic results

Plasma concentration for AZD6765 (75 mg and 150 mg) and ketamine (0.5 mg) were analysed at 1, 3 and 8 hours post dose. Arithmetic mean results (ng/mL) are as follows: AZD6765 (75 mg) 509.29 at 1h, 369.29 at 3h and 289.57 at 8h; AZD6765 (150 mg) 970.47 at 1h, 732.42 at 3h, and 566.26 at 8h; and ketamine (0.5) 164.66 at 1h, 49.94 at 3h and 14.42 at 8h.

The PK profile for AZD6765 is well established from previous Phase I studies so the PK measurements primarily aim to describe the relationship between AZD6765 plasma concentration and ketamine concentration and effect on qEEG.

Because of the limited PK sample collections in this study, individual PK parameters could not be estimated. However, PK data obtained in this study will be combined with other Phase I study PK data.

Summary of pharmacokinetic/pharmacodynamic relationships

Concentration-effect between plasma concentration and qEEG bands relationships were explored. Scatter plots were produced by regimen (dose of ketamine (0.5 mg/kg), 2 doses of AZD6765: 150 mg, and 75 mg) and protocol time (1h, 3h and 8h) to look at correlations between plasma concentration at protocol time (1h, 3h and 8h) on x-axis versus placebo-adjusted qEEG bands parameters on y-axis.

Correlation coefficients and associated p-values also were calculated by visit (protocol time) and tabulated. These analyses were carried out for each treatment group separately (dose of ketamine (0.5 mg/kg), 2 doses of AZD6765: 150 mg, and 75 mg). Linear regression analysis was also performed on placebo corrected EEG gamma band responses and plasma AZD6765 concentrations combined across protocol time (1h, 3h and 8h).

Summary of safety results

There were in total 11 subjects (11/23, 47.8%) that withdrew from the study. Three (3/23, 13.0%) of them due to serious AE after ketamine treatment, 2 subjects (2/23, 8.7%) due to AE after treatment with AZD6765 at 150 mg, 4 subjects (4/23, 17.4%) since the study was terminated prematurely, one subject (1/23, 4.3%) withdrew consent after treatment with AZD6765 at 150 mg and one subject (1/23, 4.3%) withdrew before the start of treatment since an eligibility criteria was not fulfilled.

In this double blind, four way crossover qEEG study in healthy volunteers, AZD6765 (at doses of 75 mg and 150 mg) and ketamine (0.5 mg) were generally well-tolerated by the majority of subjects. The AZD6765 75 mg dose in particular was associated with fewer and less severe AEs and other clinically important findings than the other dose groups. There were 3 SAEs reported in ketamine subjects and 2 DAEs reported in AZD6765 150 mg subjects. There were no deaths in the study.

Subjects receiving ketamine were more likely to report at least one AE (15/17, 88.2%) than those on AZD6765 at 150 mg (11/19, 57.9%) or 75 mg (6/14, 42.9%) or placebo (3/15, 20.0%), with central nervous system (CNS) type events being in general the most commonly reported. Events such as dizziness, somnolence and asthenia were generally more frequently reported with AZD6765 whereas events potentially closely related to abuse potential were generally more frequently reported with ketamine.

While the majority of all AEs were mild-to-moderate in intensity, it was noted that total AEs reported with ketamine were more often severe in intensity (13/35, 37.1%) than with AZD6765 at 150 mg (7/31, 22.6%) or 75 mg (0/11) or placebo (1/3, 33.3%).

Clinically relevant hypotension, typically in the context of upright or semi-upright body position adopted for study procedures, emerged as a safety topic of interest during this study. Two SAE reports of vascular collapse with documented low blood pressures shortly after receiving ketamine were observed. In addition, two other subjects were also reported to have non-serious AEs of vascular collapse with documented low blood pressures shortly after

receiving AZD6765 150 mg and were withdrawn from the study. All of these subjects recovered.

In addition to the documented cases of hypotension noted above, additional analyses of vital signs demonstrated a trend towards transient increases in mean supine semi-sitting SBP for ketamine subjects compared to AZD6765 and placebo subjects. For mean diastolic blood pressure, increases were noted for both ketamine and to a lesser extent AZD6765 150 mg compared to AZD6765 mg and placebo. EGG analysis was unremarkable. Analyses of clinical laboratory values, while limited in utility due to trial design, were unremarkable.

The study was subject to a health authority suspension, which was primarily based on 2 SAEs of “cardiovascular collapse” with the comparator arm of the study (ketamine). AstraZeneca responded in full to the health authority, including proposals to amend the protocol to include additional safeguards to ensure continued patient safety. However, to avoid delays in the developmental program, AstraZeneca elected to terminate the study early when analysis indicated that sufficient data were available to meet the study objective.