AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6765
Study Code	D2285C00001
Edition Number	1
Date	09 November 2011

A phase I, multi-centre, double-blind, placebo-controlled parallel group study to assess the pharmacoMRI effects of AZD6765 in male and female subjects fulfilling the criteria for Major Depressive Disorder

Study dates: First subject enrolled: 30th November 2009
Last subject last visit: 17th March 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)

The study was conducted at two centres in the United Kingdom.

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 for this study is to assess the effect of a single dose iv infusion of ketamine (Part 1) and AZD6765 (Part 2) compared to placebo on the Blood Oxygen Level Dependent (BOLD) signal in brain area BA25 using functional Magnetic Resonance Imaging (fMRI) in subjects meeting the criteria for Major Depressive Disorder (MDD).	BOLD signal in the BA25 area.	PD
Secondary	**Secondary**	
To assess whether a single dose iv infusion of ketamine (Part 1) and AZD6765 (Part 2) alter the effects of emotional processing on the BOLD signal in various brain areas such as BA25, amygdala and other areas of interest.	BOLD signal in the BA25 area and other areas associated with mood in response to an emotional test battery.	PD
Safety	**Safety**	
To evaluate the safety and tolerability of 100 mg AZD6765 given as a single dose iv infusion.	Adverse events (AEs), vital signs, physical examinations, ECGs, C-SSRS and clinical laboratory assessments.	Safety

Exploratory	**Exploratory**	
To assess whether a single dose iv infusion of ketamine (Part 1) and AZD6765 (Part 2) improves symptoms of depression in subjects meeting the criteria for MDD as assessed by a change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) total score.	MADRS and BDI	PD
To assess whether a single dose iv infusion of ketamine (Part 1) and AZD6765 (Part 2) alter the responses on the emotional test battery, a computer-based battery of behavioural tasks.	Facial expression recognition task, Dot Probe and Emotional Memory	PD
To evaluate the pharmacokinetics of 100 mg AZD6765 given as a single dose iv infusion.	Cmax, Tmax, AUC(0-24), AUC(0-tlast) of AZD 6765	PK
To assess whether a single dose iv infusion of ketamine (Part 1) and AZD6765 (Part 2) alter the cerebral blood flow responses as measured by arterial spin labelling (ASL).	ASL flow	PD
An optional blood sample for genotyping will be collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK and pharmacodynamic (PD), safety and tolerability related to AZD6765.	DNA Exploratory Research	PG

Study design

This was a multi-centre, double-blind, placebo-controlled, parallel group study in males and females with Major Depressive Disorder (MDD). The maximum study period is approximately 42 days (6 weeks) for individual subjects.

The study was divided into two parts. Subjects in Part 1 were randomised 1:1 to ketamine or placebo. Subjects in Part 2 were randomised 2:2:5 to ketamine, placebo or AZD6765. Study procedures were the same in both Part 1 and Part 2.

Target subject population and sample size

Sixty-four male and female subjects between the ages of 18 and 45 years old with MDD were to be randomized to obtain 60 evaluable subjects. Twenty-four evaluable subjects in Part 1 (12 per arm; ketamine and placebo) and 36 evaluable subjects in Part 2 (20 AZD6765, 8 ketamine and 8 placebo).

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

AZD6765: Subjects received a single infusion of AZD6765 100 mg (15 mg/mL, IV infusion) intravenously. The infusion was of a final maximum volume of 40 mL given over 60 minutes. Batch number(s): 10-003824AZ and 10-005001AZ.

Ketamine: Subjects received a single infusion of ketamine 0.5 mg/kg (10 mg/mL Injection) intravenously. The infusion was of a final maximum volume of 40 mL given over 60 minutes. Batch number(s): 42800A and 09-008003AZ.

Duration of treatment

Single dose.

Statistical methods

Pharmacodynamic: In general, all variables were presented using descriptive statistics and graphs as appropriate.

For BOLD fMRI images, linear regression was used to estimate experimentally induced signal changes. Regression analysis modelled mutually orthogonal aspects of brain activation at each voxel with contrasts suitable for the particular paradigms.

Significant activations in different brain regions involved during processing of each variable were determined using whole brain analysis and analysis of variance (ANOVA) or group t-tests.

Between-group analyses were conducted at two levels of anatomical resolution - regional (or region of interest) and whole brain levels. At both levels potential differences between the groups were investigated where significant or trend-significant effects of group were identified. Effects of treatment on mood-related indices were evaluated by conducting planned t-tests (ketamine versus placebo; AZD6765 versus placebo), for each variable, at each time point. Region of interest analysis were performed either using cluster level or small volume corrections.

For PhMRI data, a time series analysis using a pseudo block design was used. For Facial expression processing and Emotional counting stroop data, a block design analysis random effects analysis was used.

For all measured variables, where appropriate, potential differences between the treatment groups were investigated using one-way analysis of variance (ANOVA) with follow-up t-tests where significant or trend-significant effects of group were identified.

Safety data was generally summarized using descriptive statistics.

Pharmacokinetic: For AZD6765 maximum plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve from zero to 24 hour (AUC(0-24)),

area under the plasma concentration-time curve from zero to last quantifiable plasma concentration (AUC(0-tlast)). At least 3 data points were required for AUC determination.

Subject population

Sixty-six subjects were randomized. Twenty-one subjects were randomized to AZD6765, 23 were randomized to ketamine and 22 were randomized to placebo. Part 1 had 11 evaluable subjects per arm (ketamine and placebo). Part 2 had 34 evaluable subjects (19 AZD6765, 8 ketamine and 7 placebo).

There were 61 subjects in the Safety Analysis Set (20 AZD6765, 21 ketamine and 20 placebo). The PK Analysis set was 41 (20 AZD6765 and 21 ketamine).

The mean age for the randomized subjects in each group were: AZD6765: 27 years (range 18-44), ketamine: 28 years (range 18-44) and Placebo: 26 years (range 18-45).

The mean baseline Body Mass Index for the randomized subjects in each group were: AZD6765: 23 kg/m^2 (range 18-29), ketamine: 23 kg/m^2 (range 17-33) and Placebo: 23 kg/m^2 (range 18-30).

Summary of pharmacokinetic results

AZD6765 and ketamine were detected in plasma of all patients receiving the corresponding dose with Cmax theoretically observed at the end of infusion. Except for 2 patients which exhibited very high AZD6765 Cmax levels, most patients had AZD6765 Cmax levels in the expected range. Plasma levels for AZD6765 at other time points as well as ketamine at all time points were consistent with the PK properties of these compounds.

Table S2 Plasma concentrations (ng/mL) of AZD6765 and ketamine at various sample time post infusion. Safety analysis set.

Protocol schedule	Statistic	AZD6765 100 mg (N=20)	Ketamine 0.5 mg/kg (N=21)
End of infusion	n	19	21
	Mean	1229	168
	SD	1089	101
	Min	616	48
	Median	746	134
	Max	4630	519
4 hrs after infusion	n	19	21
	Mean	623	27.9
	SD	94.3	12.2
	Min	429	12.8

Protocol schedule	Statistic	AZD6765 100 mg (N=20)	Ketamine 0.5 mg/kg (N=21)
	Median	626	25.3
	Max	779	55.1
24hr end of infusion	n	19	7
	Mean	206	2.96
	SD	81.5	1.4
	Min	69	0.6
	Median	200	2.54
	Max	416	4.82

The pharmacokinetic 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 fMRI.

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 and be subjected to a "population PK analysis approach" to estimate individual PK parameters.

Summary of pharmacodynamic results

The open-channel N-metyl-D-aspartate antagonist (NMDA) ketamine and AZD6765 produced significant changes in the BOLD functional magnetic resonance imaging (fMRI) signal in the sub-genual cingulate cortex (SCG or BA25) in un-medicated mildly depressed subjects at plasma concentrations similar to those observed in previous antidepressant studies. Contrary to the original hypothesis however, ketamine and AZD6765 increased, rather than decreased, the SCG BOLD signal.

In the covert emotional faces task, 100 mg AZD6765 significantly attenuated the activation of the right amygdala in response to fearful or sad faces. Ketamine showed trends in the same direction. Effects in the amygdala were similar to those seen with reference antidepressants in other studies.

The average Montgomery-Asberg Depression Rating Scale (MADRS) scores improved in all 3 groups. AZD6765 improved the most on Day 1 after treatment, but the baseline depression ratings were higher in the AZD6765 group.

There was a correlation between the increase in the BOLD fMRI signal in the SCG and the decrease in Beck Depression Inventory scores for AZD6765 and ketamine.

Summary of pharmacogenetic results

None at the time of writing this report.

Summary of safety results

Eleven adverse events were reported in the Safety Set. The majority of adverse events occurred early in treatment and were transient. The only adverse event to persist was tension headache associated with AZD6765 100 mg treatment in one subject.

Adverse events by preferred term were: throat tightness (n=1 subject, placebo group, mild), hypoaesthesia (n=1, ketamine 0.5mg/kg group, mild), somnolence (n=1, ketamine 0.5mg/kg group, severe; n=1, placebo group, mild; n=1, AZD6765 100mg group, moderate), feeling drunk (n=1, ketamine 0.5mg/kg group, moderate), influenza (n=1, 0.5 mg/kg ketamine group, mild), headache (n=1, AZD6765 100mg group, mild), tension headache (n=1, AZD6765 100 mg group, mild), nausea (n=1, AZD6765 group, moderate), and dizziness (n=1, AZD6765 group, mild).

There were no overall clinically significant changes within each treatment arm for haematological and chemical parameters; nor were any individually clinically significant changes identified across the subjects viewed individually.

There were no notable individual clinically important abnormalities in any vital sign parameter after any treatment.

No clinically relevant changes in physical examination were noted after any treatment.

No clinically relevant changes in the C-SSRS were noted after any treatment, either for individuals or treatment arms collectively.

Administration of ketamine was associated with a greater mean increase in Clinician Administered Dissociative States Scale (CADSS) scores than that produced by AZD6765 in comparison to placebo.