AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7325
Study Code	D1140C00002
Edition Number	1
Date	20 April 2009

A Phase I, Single-Center, Randomized, Double-Blind, Placebo-Controlled, Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD7325 When Given in Multiple Ascending Oral Doses in Healthy Male and Healthy Female Subjects of Non-child Bearing Potential

Study dates: First healthy volunteer enrolled: 11 March 2008
Last healthy volunteer completed: 7 July 2008

Phase of development: Clinical pharmacology (I)

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

Study center

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to assess the safety and tolerability of multiple ascending oral doses of AZD7325 compared to placebo by assessment of adverse events, vital signs, physical examinations, laboratory parameters, and ECGs.

The secondary objectives of the study were:

1. To evaluate and characterize the pharmacokinetics of AZD7325 when given orally in multiple ascending doses by assessment of drug concentration in plasma and urine.

2. To evaluate the pharmacodynamic effects of AZD7325 on selected psychometric (cognitive and psychomotor) assessments and subjective effect measures using VAS, Modified Wilson Sedations Scale, and CogState battery.

3. To evaluate time dependencies in the pharmacokinetics of AZD7325 after repeated dosing with regard to auto induction and indirect assessment of CYP3A4 activity.

4. To collect blood samples for optional exploratory genetic studies focusing on identification of genes that influence the disposition, efficacy, safety and tolerability of AZD7325.

Study design

This was a single-center, randomized, double-blind, placebo-controlled, multiple ascending dose study of a compound targeted for the treatment of generalized anxiety disorder.

Target healthy volunteer population and sample size

Healthy male and female volunteers of non-child bearing potential, aged 18 to 55 years (inclusive) with a body mass index ≥ 18 and ≤ 30 kg/m^2 participated in the study.

Due to the exploratory nature of the analysis, sample size calculations to a formal statistical criterion were not carried out. Dose groups of 12 subjects (to be randomized 3:1 [active: placebo] are thought to provide sufficient information to gather initial safety and PK data in humans while at the same time exposing a minimum number of subjects to AZD7325. In addition, with the stopping rule, if the true incidence of dose- limiting toxicity events is 22%, then the probability that 2 or more subjects out of a cohort of 12 will report such an event is

49%. Therefore, for each dose panel, 9 subjects received AZD7325, and 3 subjects received placebo.

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

AZD7325 was administered in doses 5, 10, 20 and 50 mg as multiples of 5 mg immediate release oral capsules or as a single 50 mg immediate release capsule. Matching placebo capsules were provided. Batch numbers for the 5 mg, 50 mg, and placebo doses were 2000115377, 2000115424 and 2000115159, respectively.

Duration of treatment

The duration of participation for each volunteer included a screening period of up to 30 days followed by residence in the testing unit for 13 days, with dosing on 8 days of residence.

Criteria for evaluation - pharmacokinetics (main variables)

Primary pharmacokinetic assessments for AZD7325 included maximum plasma concentration (C_{max}), lag time (t_{lag}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from zero to infinity(AUC), area under the total plasma concentration-time curve during 24- and 48-hour intervals (AUC_{0-24} and AUC_{0-48}), elimination half-life ($t_{1/2\lambda z}$), apparent oral clearance (CL/F), apparent fraction of dose excreted unchanged in the urine (f_e) and renal clearance (CL_R).

Assessment of the ratio of 6-beta-OH-cortisol to cortisol in urine for the exploration of the auto induction and indirect assessment of CYP3A4 activity was not carried out.

Criteria for evaluation - pharmacodynamics (main variables)

Pharmacodynamic assessments were included for exploratory purposes only. The potential effect of AZD7325 on cognition, reaction time, and attention was assessed using a computerized neurocognitive test battery (CogState). In addition, potential effects on mood, mental status, and alertness were assessed using a variation of the Bond-Lader visual analog scale. The results of the CogState assessments are not included in this report.

Criteria for evaluation – genetics

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the disposition, efficacy, safety and tolerability to AZD7325. The results of the genetic research are not included in this report.

Criteria for evaluation - safety (main variables)

Safety and tolerability, the primary objective of the study, were evaluated by the incidence and severity of adverse events and the assessment of vital signs, physical examinations, ECGs, clinical laboratory tests, and ataxia.

Statistical methods

No formal statistical hypothesis testing was performed in this study.

Data were presented by dose regimen), and volunteers receiving placebo were pooled across dose panels for the purposes of summarization of safety and PD results.

To achieve the primary objective, the safety and tolerability data were evaluated in terms of AEs, vital signs, physical examinations, ECGs, and clinical laboratory assessments. AEs were listed as well as summarized by system organ class and dose. Vital signs (including orthostatic assessments), ataxia assessment, clinical laboratory measures, and dECGs were summarized using descriptive statistics by protocol time and dose.

To achieve the secondary objectives, the pharmacokinetics of AZD7325 were evaluated by assessment of drug concentrations in plasma and urine. If possible, individual PK and PD parameters were calculated and tabulated along with descriptive statistics for each dosing group.

Descriptive summary statistics for continuous variables included N, arithmetic mean, standard deviation, median, minimum, and maximum, geometric mean, and coefficient of variation. Descriptive summary statistics for categorical data included the frequency and proportion. Graphical methods were used to explore PK and safety data (dECG and clinical laboratory results). There was no filling-in for missing data, unless otherwise specified, such as for the plasma concentration level and SAS total score.

Subject population

Forty eight male healthy volunteers were randomly assigned to study treatment, and each received study drug during the planned treatment course. Six volunteers, all in active treatment groups, discontinued the study before completion. Three of the discontinuations were associated with adverse events. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

Following multiple daily administrations of AZD7325, apparent steady state plasma levels were reached 3 to 4 days after the start of daily dosing at all doses, consistent with the drug's terminal half-life at each respective dose.

The pharmacokinetic properties of AZD7325 were time-independent, with no difference in kinetics between Day 1 and Day 9; and dose-independent, with no difference among all doses tested. These inferences were supported by the similarity in CL/F and $t_{1/2\lambda z}$ along with value of TCP.

The AUC accumulation ratios $R_{(AUC)}$ for the 5 mg QD regimen were as expected and consistent with the elimination half-life from both single-dose and multiple-dose kinetic data. Nevertheless, those for 10, 20, and 50 mg were less than the projection based upon

elimination half-life. This might be due to random variation among treatment groups or because the larger proportion of plasma AZD7325 exposure is in the distribution phase or before 12 hours, so that very little drug concentration remains at 24 hours post-dosing.

Summary of pharmacodynamic results

The Alertness and Mood subscales both showed increasing scores with increasing doses of AZD7325, with peak effect seen at the 2-hour assessment. The calmness subscale showed no clear effects at any time point. Elevations of the Alertness and Mood subscales 2 hours after AZD7325 administration persisted throughout the 9 days of dosing, but with some indication of decreasing effect. Modified Wilson Sedation Scales for all volunteers at all assessment times were scored as "oriented."

Summary of safety results

Adverse events of dizziness, euphoric mood, hypoesthesia or paresthesia, and somnolence were reported following administration of AZD7325 in a dose of 10 mg or higher. The MedDRA preferred terms "euphoric mood" and "dizziness" were both often recorded as "feels high" or a similar variant. Dizziness was also reported as "lightheaded." Two volunteers reported "feeling drunk." Vital signs data provided no indication of a loss of hemodynamic postural adjustment in volunteers with reports of "dizziness" and an ataxia rating of significant impairment was noted in only one case of dizziness. Three volunteers were discontinued from the study due to AEs of prolonged PR interval (primary AV block), elevated liver enzymes and stupor (one AE for each volunteer). There were no clinically relevant treatment-related changes or trends in any laboratory, vital signs or dECG variables measured in healthy volunteers exposed to AZD7325 during the study. There were no clinically relevant changes or trends in blood pressure or heart rate during the study.

Date of the report

20 April 2009