AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0328
Study Code	D0190C00009
Edition Number	1
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A Phase I, Open, Randomized, Single-Dose, Two-Treatment (Fed versus Fasting), Two-Period Cross-Over Single-Centre Study to Evaluate the Effect of Food on the Pharmacokinetics of AZD0328 Following Oral Administration (Capsule) in Healthy Male Subjects

Study dates: First healthy volunteer enrolled: 8 September 2008
Last healthy volunteer completed: 13 October 2008

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 study was conducted at AstraZeneca, Clinical Pharmacology Unit, AstraZeneca R&D Lund, SE-221 87 Lund, Sweden. The first healthy volunteer was enrolled 8 September 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was:

- To evaluate the effect of food, in comparison to fasting condition, on the extent and rate of absorption of AZD0328 following administration of a single oral dose of AZD0328 capsule in healthy male subjects.

The secondary objective of the study was:

- To evaluate the safety and tolerability of AZD0328, when given in fasting condition or in combination with food.

Exploratory objective:

- To collect and store DNA samples for possible future, exploratory genetic research. This was optional for all participants. It is not reported in the Clinical study report or in this synopsis.

Study design

This food effect study was an open, cross-over study, with single oral doses of 0.7 mg (capsule) AZD0328 during two treatment periods, one under fed (high fat meal breakfast) and one under fasting (from 10 hours before dose) condition in a randomized order. The treatment periods consisted of two days with a wash-out period of 5 to 10 days between the periods. The study consisted of 4 visits with the last visit 7 to 10 days after discharge. The intended indication for AZD0328 is symptomatic treatment of cognitive deficits, primarily in patients with Alzheimer's disease and schizophrenia.

Target healthy volunteer population and sample size

The main inclusion criteria were: healthy male Caucasian, age 20 to 45 years, a body mass index of 19 to 30 kg/m^2, clinically normal physical findings, laboratory values, vital signs, resting ECG, and age adjusted creatinine clearance. The sample size was primarily based on experience from previous similar studies with other compounds, and it was determined without formal statistical considerations or formal power calculation. This was a pilot study aiming for randomization of 14 healthy volunteers to have at least 12 evaluable healthy volunteers.

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

The investigational product was AZD0328 (capsule 0.7 mg), manufactured by AstraZeneca. One batch of AZD0328 was used in the study (formulation number 4134-X-1, batch number 4134-1-1). No placebo or other investigational products were used.

Duration of treatment

AZD0328 was given as single oral doses. The study had two treatment periods that consisted of two days with a wash-out period of 5 to 10 days between the periods.

Criteria for evaluation - pharmacokinetics (main variables)

The primary variables used for evaluation of the pharmacokinetics were: AUC, C_{max} $AUC_{fed}/AUC_{fasting}$, $C_{max\ fed}/C_{max\ fasting}$.

The other PK variables were: $AUC_{(0-t)}$, CL/F, $t_{1/2}$, t_{max}.

Criteria for evaluation - safety (main variables)

The variables used for evaluation of safety and tolerability were: adverse events (AEs), vital signs (pulse and blood pressure), laboratory variables, physical examination and Electrocardiograms (ECGs).

Statistical methods

The data were summarized using descriptive statistics. The log (C_{max}) and log (AUC) was analysed by mixed linear models, with subject, period and treatment (fed versus fasting) as factors. The inferential target was the contrast between food and fasting.

Subject population

Fourteen healthy volunteers were randomised. All healthy volunteers that were randomized, completed the study. The PK and safety analysis included all randomized healthy volunteers.

Summary of pharmacokinetic results

The mean AUC and C_{max} were approximately equal under fasting and fed conditions (geometric mean ratio fed/fasted was 0.99 and 0.93, respectively). The 95% CI for the ratio were within the equivalence limits of 0.80 to 1.25 and included 1 for both AUC and C_{max}. Thus, there was no effect of food intake on AUC and C_{max}. Following food intake, t_{max} was somewhat delayed from 2.5 to 4.0 h (median t_{max}).

Summary of safety results

There were no deaths, other SAEs, DAEs, or OAEs in the study. The vast majority of AEs were of mild intensity, few were of moderate intensity and none were of severe intensity. There was no difference in the total number of mild AEs during fasting and fed conditions. Similar numbers of healthy volunteers reported moderate AEs during fasting and fed

conditions. Most AEs were associated with gastrointestinal and nervous system disorders. There were no clinically relevant changes or trends in any laboratory, variable measured in the study. However, plasma chloride changes outside project specific laboratory reference ranges were observed more often under fed compared to fasting condition. The small changes in plasma chloride concentrations were considered not clinically relevant. There were no clinically relevant changes or trends in supine blood pressure (SBP) or pulse during the study. The observed changes of orthostatic pulse and BP were considered not clinically relevant. There were no abnormalities in the physical examinations. All ECGs were normal.