AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00001
Edition Number	1
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A Phase I, Randomised, Double-blind, Placebo-controlled, Parallel-group Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics of AZD1446 including an Open Food Effect Panel in Healthy Male and Non-fertile Female Volunteers

Study dates: First healthy volunteer enrolled: 04 December, 2008
Last healthy volunteer completed: 24 April, 2009

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 Clinical Pharmacology Unit C2-84 Karolinska University Hospital, Huddinge, SE-141 86 Stockholm. The first healthy volunteer was enrolled 4 December 2008.

Publications

None at the time of writing this report.

Objectives

Primary objective

1. To determine the safety and tolerability of single ascending doses of AZD1446 administered as an oral solution, and to estimate the maximum tolerated dose (MTD), if within predefined exposure and dose limits, in male and non-fertile female subjects (Dose escalation part).

Secondary Objectives

1. To determine the single dose pharmacokinetic (PK) of orally administered solution of AZD1446 in healthy male and non-fertile female volunteers (Dose escalation part).

2. To evaluate the safety and tolerability of AZD1446 if within predefined exposure and dose limits, by assessment of adverse event (AE) and vital signs in subjects administered AZD1446 with or without food (Food interaction part).

3. To perform an initial assessment of the effect of food on the PK of AZD1446 after administration of AZD1446 as an oral solution, (Food interaction part).

Study design

This study consisted of two parts, one dose escalation part and one food interaction part.

Dose escalation part: randomised, parallel-group, sequential (ascending dose panels), placebo-controlled, double-blind.

Food interaction part: randomised, open-label food interaction study with cross-over design conducted after completion of the dose escalation part. AZD1446, 125 mg was administered during two treatment periods, one under fed (high fat meal breakfast) and one under fasting (from at least 10 h before dose and 4 h after dose) condition.

AZD1446 is intended for treatment of Alzheimer's disease and Attention deficit and hyperactivity disorder.

Target healthy volunteer population and sample size

The main inclusion criteria were: healthy male and non-fertile female Caucasian, age 18 to 50 years, a body mass index of 19 to 30 kg/m^2, clinically normal findings on physical examination in relation to age, normal ECG, and a normal FEV_1 as measured by spirometry.

Dose escalation part; Six dose panels with 8 subjects (AZD1446 n=6, placebo n=2) in each was planned with an option for additional 3 dose panels ie, leading to a maximum of 72 randomised subjects. The sample size was primarily based on experience from previous similar studies with other compounds, and was determined without formal statistical considerations or formal power calculation.

Food interaction part; One dose panel with 8 subjects was planned. The dose was based on the results in the dose escalation part. This part of the study was a pilot food effect study to help design a definitive study if needed and to provide dosing information for future studies.

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

The investigational product was AZD1446 (oral solution), manufactured by AstraZeneca. Two batches of AZD1446 were used [0.5 mg/ml oral solution (formulation number: D0800219, batch number 08-0011659AZ) 25 mg/ml oral solution (formulation number: D0800218, batch number 08-001542AZ)] and one of placebo [oral solution (formulation number: D0800011, batch number 08-000018AZ)].

Duration of treatment

Dose escalation part: AZD1446 was given as single doses.

Food interaction part: AZD1446, 125 mg, was given as single doses during two treatment periods that consisted of two days each with a wash-out period of 4 days.

Criteria for evaluation - pharmacokinetics (main variables)

Dose escalation part: AUC, AUC_{0-t}, C_{max}, t_{max}, $t1/2\lambda z_{\lambda z}$, CL/F, Ae; f_e, CL_R.

Food interaction part: AUC, AUC_{0-t}, C_{max}, t_{max}, $t1/2\lambda z_{\lambda z}$, CL/F, point estimate and 95% CI of ratios (fed/fasting) of AUC and C_{max}.

Criteria for evaluation - safety (main variables)

Dose escalation and food interaction parts: Adverse events (AEs), laboratory variables (clinical chemistry, haematology and urinalysis), vital signs (blood pressure, body temperature, pulmonary function), Electrocardiogram (ECG), physical examination, Forced expiratory volume during one second (FEV_1) and State-Trait Anxiety Inventory (STAI).

Statistical methods

Dose escalation and food interaction parts: The safety, tolerability and PK data were summarized using descriptive statistics.

Dose escalation part: Dose proportionality was analysed by using the power model approach.

Food interaction part: The log (C_{max}) and log (AUC) were analysed by mixed linear models, with healthy volunteer, period, and treatment (fed versus fasting) as factors. The inferential target was the contrast between fed and fasting.

Subject population

Dose escalation part: In total 72 male [AZD1446 (n=54) or placebo (n=18)] Caucasian healthy volunteers aged 21 to 50 years were randomised to 9 dose panels. The starting dose 0.5 mg of AZD1446 was escalated to 350 mg.

Food interaction part: In total 8 male Caucasian healthy volunteers aged 21 to 41 were randomised. A dose of 125 mg of AZD1446 was administered.

In both the dose escalation and food interaction parts all randomised healthy volunteers completed the study. The PK and safety analysis included all randomised healthy volunteers.

Summary of pharmacokinetic results

Dose escalation part: The maximum plasma concentration generally occurred between 0.5 and up to 3 h after dose. At the highest dose level, AZD1446 350 mg, the average AUC was approximately 28300 h*nmol/L, just below the predefined maximum exposure limit (AUC 30000 h*nmol/L). The exposure limit for C_{max} (8000 nmol/L) was not reached.

The geometric mean terminal elimination half-life ($t1/2\lambda z_{\lambda z}$) was 2 to 3 h and the geometric mean total oral clearance was 46 to 63 L/h across the total dose range studied. The geometric mean fraction of the dose excreted unchanged in urine was 51 to 64 % across doses. The variability for the PK parameters was relatively low with a coefficient of variation (CV) of about 15% for AUC and about 29% for C_{max}. The systemic exposure in terms of AUC, increased proportionally to the dose, and C_{max} increased approximately dose proportionally. The relationships were well described by a power model, predicting a 2-fold increase in exposure in AUC with a 2-fold increase in dose, and a 1.92-fold increase in C_{max} with a 2-fold increase in dose.

Food interaction part: In general, the AUC was unaffected when AZD1446 was given with food, while C_{max} decreased somewhat (geometric mean ratio fed/fasting was 1.01 and 0.73 for AUC and $C_{max,}$ respectively). The 95% CI for the ratio were within the equivalence limits of 0.80 to 1.25 and included 1 for AUC. Following food intake, the median t_{max} was slightly delayed from 1.0 to 1.5 h.

Summary of safety results

Dose escalation part: There were no deaths, other serious adverse events (SAEs), or any other significant events. All AEs were mild (n=39) to moderate in intensity (n=11). No AEs were severe. Most of the mild AEs (n= 26) and all AEs of moderate intensity were reported at the three highest doses of AZD1446 (187.5 mg, 250 mg, and 350 mg). Most AEs were associated with gastrointestinal (n=12) and nervous system disorders (n=12). There were no clinically relevant changes or trends in any laboratory variables, vital signs, ECG, physical findings or other safety variables (including physical examination, FEV_1, and STAI), variables measured in the study.

Food interaction part: There were no deaths, other SAEs, or any other significant events. All observed AEs were of mild (n=9 fasting, n=5 fed) or moderate intensity (n=1 fasting). Fasting healthy volunteers experienced a greater number of AEs [including causually related AEs (as judged by the investigator), n=4 and n=8, respectively] than fed healthy volunteers. Most AEs were associated with gastrointestinal disorders (n=5 fasting, n=2 fed). There were no clinically relevant changes or trends in any laboratory variables, vital signs, ECG, physical findings or other safety variables (including physical examination, FEV_1, and STAI), variables measured in the study.