AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00002
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A Phase I, Randomised, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD1446 in Male and Non-fertile Female, Young and Elderly Healthy Volunteers, After Oral Multiple Ascending Doses

Study dates: First healthy volunteer enrolled: 27 April 2009
Last healthy volunteer completed: 11 September 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 in Sweden at AstraZeneca Clinical Pharmacology Unit C2-84 Karolinska University Hospital, Huddinge, SE-141 86 Stockholm and AstraZeneca Clinical Pharmacology Unit, Avd. 102, Gröna Stråket 12 Sahlgrenska Sjukhuset SE-413 45 Göteborg. The first healthy volunteer was enrolled 27 April 2009. The last healthy volunteer completed the study 11 September 2009.

Publications

None at the time of writing this report.

Objectives

Primary objective: To assess the safety and tolerability of AZD1446 following multiple ascending doses of an orally administered solution of AZD1446 in male and non-fertile female, young and elderly healthy volunteers.

Secondary objective: To determine the single and multiple dose PK of AZD1446 in male and non-fertile female healthy volunteers.

Study design

This was a randomised, double-blind, placebo-controlled, parallel-group, multiple ascending dose study. Young (aged ≥18 to ≤50 years) and elderly (aged 65 to ≤80 years) healthy volunteers were randomised to AZD1446 or placebo with a ratio of 6:2, to 8 dose panels in total.

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, young or elderly, a body mass index of 19 to 30 kg/m^2, clinically normal findings on physical examination in relation to age, normal ECG, and normal forced expiratory volume during 1 second (FEV_1) as measured by spirometry. Up to 10 dose panels with 8 subjects (AZD1446 n=6, placebo n=2) in each were planned. 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.

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

The investigational product was AZD1446 (oral solution), manufactured by AstraZeneca. Dosage in young healthy volunteers: 10 mg x 4, 30 mg x4, 100 mg x 4, and 300 mg x 1. Dosage in elderly healthy volunteers: 10 mg x 4, 30 mg x 4, 75 mg x 4, and 200 mg x 1.

Two batches of AZD1446 were used [0.5 mg/ml oral solution (formulation number: D0800219, batch number: 08-001659AZ) 25 mg/ml oral solution (formulation number: D0800218, batch number: 08-001542AZ)] and 1 of placebo [oral solution (formulation number: D0800011, batch number: 08-000018AZ).

Duration of treatment

AZD1446 was given for 7 days. In dose panels 1 to 6, single oral doses were administered on day 1 and multiple doses 4-times daily for the 6 following days. In dose panels 7 to 8, the investigational product was given once daily for 7 days.

Criteria for evaluation - pharmacokinetics (main variables)

AUC_{pred}, $AUC(0\text{-}24)_{pred,ss}$, $C_{max,pred}$, $C_{ss,max,pred}$, $t_{max,pred}$, $t_{max,ss,pred}$, $t_{1/2,eff,pred}$, CL, F, V/F, CL_R, f_e

Criteria for evaluation - safety (main variables)

Adverse events (AEs), laboratory variables, vital signs, electrocardiogram (ECG), physical examination, FEV_1, and State-Trait Anxiety Inventory (STAI), state part.

Statistical methods

The safety, tolerability and data for concentrations of AZD1446 in plasma and urine were summarized using descriptive statistics. PK data was analysed with a Non-linear Mixed Effects Model including dose and time-dependency as well as covariates e.g, age and creatinine clearance.

Subject population

In total, 32 young and 33 elderly healthy volunteers were randomised to AZD1446 (n=48) or placebo (n=17) to 8 dose panels. Two elderly healthy volunteers were discontinued after administration of study drug on study day 1 because of difficulties blood sampling. One of the healthy volunteers was replaced. Consequently, 9 healthy volunteers were randomised into 1 of the dose panels. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics. The PK and safety analysis included all randomised healthy volunteers.

Summary of pharmacokinetic results

The geometric mean $AUC_{(0\text{-}24),ss,pred}$ following the highest dose for young (100 mg x 4) and elderly (75 mg x 4) healthy volunteers approached the AUC exposure limit for AZD1446 (30000 h*nmol/L), whereas the highest $C_{ss,max,\ pred}$ was below the C_{max} exposure limit (8000 nmol/L) with once daily dosing. With the dose-regimen in this study, 4 doses equally distributed within 12 h, steady state was reached within the first day of dosing, which is consistent with the estimate of $t_{1/2eff}$ of approximately 2 h. $AUC_{(0\text{-}24),ss,pred}$ increased in proportion to dose according to the model, whereas $t_{ss,max,pred}$ increased from 20 min to approximately 1 h and $C_{ss,max,pred}$ increased from 2700 to 4600 nmol/L when doubling the dose from 80 mg to 160 mg. The model predicted a 10% higher exposure in terms of AUC after repeated dosing as compared to a single dose. Exposure was 25 to 30% higher in elderly

healthy volunteers than in young healthy volunteers. The fraction of given drug excreted in urine (f_e) of AZD1446 was lower in elderly healthy volunteers (45%) compared to young healthy volunteers (55%). The between-subject variability was generally low, in the range 4% to 18% for AUC_{pred} and 6% to 35% for $C_{max,pred}$.

Summary of safety results

There were no deaths, other serious AEs, discontinuations due to AEs or other AEs in the study. The majority of AEs were of mild or moderate intensity while 1 AE was of severe intensity. The most common AEs were associated with gastrointestinal disorders (nausea) and nervous system disorders (headache). AEs in healthy volunteers receiving AZD1446 were mainly associated with nausea, diarrhoea, and dizziness. 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, (state part)], variables measured in the study.