AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6088
Study Code	D0840C00007
Edition Number	1
Date	01 December 2009

A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Oral AZD6088 after Single Ascending Doses in Healthy Male and Non-Fertile Female Volunteers

Study dates: First healthy volunteer/patient enrolled: 08 June 2009
Last healthy volunteer/patient completed: 11 August 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 the United Kingdom at Quintiles Drug Research Unit at Guy's Hospital.

The first healthy volunteer was enrolled on 08th June 2009 and the last healthy volunteer completed the study on 11th August 2009.

Publications

None at the time of writing this report.

Primary objective

To assess the safety and tolerability of single ascending oral doses of AZD6088 and to estimate the maximum tolerated dose in healthy volunteers, if within the predefined exposure limits.

Secondary objectives

1. To characterise the pharmacokinetics (PK) of AZD6088 and assess the dose proportionality of the pharmacokinetics following administration of single ascending oral doses in healthy volunteers.

2. To assess pharmacodynamic (PD) effects of AZD6088.

Exploratory objectives

Furthermore, a blood sample for genotyping will be collected for future, possible exploratory genetic research aimed at identifying/ exploring genetic variations that may affect PK and PD, safety and tolerability related to AZD6088 (not included in the Clinical Study Report).

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to AZD6088, and response under study within the current study protocol. No other research will be performed on the samples.

Plasma and urine will be collected for determination of AZD6088, and for explorative qualitative metabolite characterisation (not included in the Clinical Study Report).

Study design

This was a Phase I, first time in human, randomised, double-blind, placebo-controlled, parallel group, single centre study to assess the safety, tolerability, pharmacokinetics and pharmacodynamic effects of AZD6088 following single ascending dose administration to healthy volunteers. The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure the safety of the healthy volunteers.

Target healthy volunteer population and sample size

Up to 64 evaluable healthy volunteers aged 18 to 55 years were to participate in the study. The study included a maximum of 8 panels (including 2 optional if needed) and aimed for 8 randomised healthy volunteers in each panel (6 AZD6088/2 placebo).

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

The investigational product for this study was AZD6088 1 mg/mL oral solution batch number 09-002214AZ and AZD6088 10 mg/mL oral solution batch number 09-002392AZ. Placebo was oral solution batch number 09-001559AZ.

Duration of treatment

Single dose.

Criteria for evaluation - pharmacokinetics (main variables)

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), lag time (t_{lag}), terminal half-life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution during terminal phase (Vz/F), amount of drug excreted unchanged (Ae; % dose), fraction of drug excreted into urine (fe) and renal clearance (CLR).

Criteria for evaluation - pharmacodynamics (main variables)

Pupil diameter, urinary frequency, S-cortisol, P-adrenaline and P-noradrenaline.

Criteria for evaluation - safety (main variables)

Adverse events, vital signs, electrocardiogram, electroencephalogram, laboratory variables and oral body temperature.

Statistical methods

Given the exploratory nature, no formal statistical hypothesis testing was performed in this study. The analysis of safety, tolerability, PK and PD were descriptively summarised, including listings, summary statistics and graphs, as appropriate.

The analysis of data was based on different subsets according to the purpose of analysis, ie, for safety, PK and PD, respectively. The decision regarding validity of data for each of the analysis sets was based on a blind review of data.

The as-treated principle was applied to all evaluations, ie subjects who received another treatment than the one assigned in the randomisation list were analysed as belonging to the actual treatment group and not that assigned by randomisation. The placebo group consisted of all subjects treated with placebo regardless of dose panel.

Any subject who withdrew prior to the last planned observation in a study period was to be included in the analyses up to the time of discontinuation

Subject population

In total, 39 healthy male subjects were randomised into the study at 1 study site, each received 1 administration of study drug during the planned treatment visit. All subjects randomised to treatment completed the study. There were no protocol deviations that led to exclusion of data from the pharmacokinetic or safety analyses. The safety analysis included all randomised subjects. Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of pharmacokinetic results

Geometric mean C_{max} and AUC following 30 mg AZD6088 given in fasting state was 81.3 nmol/L (range: 56-97 nmol/L) and 604 nmol*h/L (range: 393-771 nmol*h/L), respectively. The exposure was thus below the predefined limits for C_{max} and AUC_{0-24h}, which were 600 nmol/L and 1900 nmol*h/L, respectively. The inter individual variability (CV%) in the exposure parameters over the studied dose range 1-30 mg AZD6088 given in fasting state was low (14 and 30 mg dose group) to moderate (1 and 4 mg dose group). The % extrapolated area exceeded 20% for all subjects in the 1 mg dose group and the estimated AUC values are thus not regarded as reliable in this group. One subject in the 4 mg dose group had and extrapolated AUC area over 20% but none in the 14 or 30 mg dose group.

The absorption of AZD6088 was rapid and comparable between doses with a median t_{max} of 0.74 to 1.50 hours in fasting subjects. The geometric mean $t_{1/2\lambda z}$ was comparable between doses (3.09-4.49 hours). There were no indications of any dose-dependent changes in geometric mean CL/F (122 to 182 L/h), CL_R (5.74 to 9.54 L/h) or V_z/F (790 to 829 L).

Renal clearance constituted about 5% of oral clearance, independently of the dose. CL_R (~7.5 L/h) was approximately similar to the filtration clearance (glomerular filtration rate (GFR)*fraction unbound in plasma (ie, 7.2*0.87 = 6.3 L/h).

The PK profile following a single oral dose of 30 mg were similar in fasted compared to fed state, both regarding the absorption and elimination phase. Geometric mean C_{max} and AUC following a single oral dose of 30 mg in fed state were 15% and 18% higher, respectively, compared to in fasting state but the exposure was still below the predefined limits. Geometric mean C_{max} and AUC was 93.6 nmol/L (range: 67.0-129 nmol/L) and 714 nmol*h/L (range: 535-1095 nmol*h/L), respectively, in fed state. The inter individual variability (CV%) in the exposure parameters was 26 to 30%).

There was a 45- and 23-fold increase in the geometric mean AUC and C_{max}, respectively, with a 30-fold increase in dose during fasting conditions.

The relationships were described by a power model using analysis of covariance, in which the 90% CI of the slope for C_{max} (0.82, 1.03) and AUC (1.00, 1.21) both included 1. The plasma

exposure of AZD6088 was thus considered compatible with linear kinetics after single oral doses of 1 to 30 mg in fasting state.

Summary of pharmacodynamic results

There was no dose- or time-dependent trend in change from baseline regarding S-cortisol concentration at fixed time points or at time points related to dose. However, in the 14 mg and 30 mg fasted dose groups, there was a change in the diurnal variation in cortisol levels after dosing; the mean S-Cortisol Day 2 01:00 concentration was higher compared to the corresponding Day 1 19:00 value. There was no obvious relationship between plasma AZD6088 and S-Cortisol concentration, neither at 1, 2 or 3 hours after dose, or at fixed time points.

P-Adrenaline levels and change from baseline were low overall, and there was no dose-dependent trend in direction or magnitude of change from baseline. The highest mean change from baseline (61.5 pmol/L), was found in the 14 mg dose group. There was no obvious relationship between plasma AZD 6088 concentration and P-Adrenaline at 2 hours after dose. All subjects in the 30 mg fed and fasted dose groups exhibited non-detectable levels (<300 pmol/L) of P-Adrenaline, both at baseline and at 2 hours after dose.

An increase of mean P-Noradrenaline concentration from baseline to 2 hours after dose was noticed in the 30 mg dose groups (arithmetic mean change from baseline=733.0 pmol/L for fasted, 644.0 pmol/L for fed) compared to the other dose groups. There was a negative change from baseline of similar magnitude (arithmetic mean change from baseline=-557.5 pmol/L) in the placebo group. There was no obvious relationship between plasma AZD 6088 concentration and P-Noradrenaline at 2 hours after dose. However, P-Noradrenaline levels and variability were relatively low for the dose groups with the lowest exposure levels, i.e. the 1 mg and 4 mg dose groups.

Change from baseline in pupil diameter was relatively low overall, with a maximum increase from baseline of 2 mm in the placebo, 14 mg and 30 mg fasted dose groups and a maximum decrease from baseline of 3 mm in the placebo group. There was no obvious relationship between AZD6088 plasma concentration and pupil diameter at 1, 2, 4 or 6 hours after dose.

No dose-dependent trend in urination frequency could be detected. There was no obvious relationship between AZD6088 systemic exposure in terms of AUC and number of urinations in the 0-48h interval.

Summary of safety results

There were no deaths or other serious adverse events in the study. Most of the AEs were of mild intensity; moderate intensity AEs were reported by subjects receiving 30 mg AZD6088 and 30 mg AZD6088 under fed conditions. The most common AE reported during the study was hyperhidrosis, reported by subjects receiving 14 mg AZD6088 (4/6 subjects), 30 mg AZD6088 (6/6 subjects) and AZD6088 fed (5/6 subjects).

Dose escalation was halted after 30 mg AZD6088, as in both AZ6088 30 mg and AZ6088 30 mg fed groups, subjects experienced moderate cholinergic AEs considered by the investigator to be drug related. Although these AEs were not considered serious it was felt that they were on the edge of maximum tolerability so further dose escalation was considered inappropriate.

There were 7 subjects with AEs of moderate intensity during the study (6 subjects with single moderate AEs and 1 subject with 2 moderate AEs). The moderate AEs were hyperhidrosis (2 subjects AZD6088 30 mg and 3 subjects AZD6088 30 mg fed), nausea (1 subject AZD6088 30 mg fed), sialoadenitis (1 subject AZD6088 30 mg), and vomiting (1 subject AZD6088 30 mg). All other AEs were of mild intensity. All moderate intensity AEs were considered by the investigator to be related to treatment. Moderate intensity AEs were only reported in the highest dose groups (30 mg AZD6088 and 30 mg AZD6088 fed).

The incidence of AEs categorised as salivation, lacrimation, urination, defecation, gastrointestinal upset or emesis (SLUDGE) was relatively high; 53.3% of all subjects on active treatment reported at least one suspected SLUDGE AE. There was an increase in incidence of SLUDGE AEs with increasing dose of AZD6088. Hyperhidrosis was the most common AE within the study, reported by 66.7% of the subjects in the 14 mg dose group, by 100% in the 30 mg dose group and by 83.3% in the 30 mg fed dose group. This is consistent with the analysis of the relationship between systemic exposure and probability of hyperhidrosis, which shows a trend for increasing incidence of hyperhidrosis with increasing C_{max} and AUC, respectively.

There was a general decrease in RR and a trend towards prolonged QTcF with increasing dose. The review of the ECGs and EEGs did not show any clinically significant abnormalities and both the physical and neurological examinations were considered by the investigator to be normal.