AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8329
Study Code	D2350C00001
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A Randomised, Single-blind, Placebo-controlled, Two-centre Phase I Study in Healthy Volunteers to Assess the Safety, Tolerability and Pharmacokinetics of AZD8329 After Single Ascending Oral Doses

Study dates: First healthy volunteer enrolled: 13 July 2009
Last healthy volunteer last visit: 19 August 2010

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)

The study was conducted at 2 centres in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of AZD8329 following administration of single ascending doses and to estimate the MTD, if within the pre-defined exposure limits	AEs, laboratory variables, vital signs (blood pressure, pulse and body temperature), physical examination, weight and ECG (resting 12-lead ECG, continuous dECG and telemetry)	Safety
Secondary	**Secondary**	
To characterise the PK of AZD8329 and provisionally assess the dose proportionality of the PK following administration of single ascending doses of AZD8329	AUC, $AUC_{(0-t)}$, CL/F, C_{max}, t_{max}, $t_{½\lambda z}$ and V_z/F. $C_{max,\ 1st\ dose}$ and $t_{max,\ 1st\ dose}$ for the fractionated doses	PK
To explore the effect of food on the PK of AZD8329	Individual ratios (fed/fasted) for AUC, $AUC_{(0-t)}$ and C_{max}	PK
Exploratory[a]		
To collect and store blood samples for potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism and metabolic diseases (not applicable for the first study cohort)	Potential biomarkers	PD

AE: Adverse events, AUC: Area under the plasma concentration-time curve from time zero to infinity, $AUC_{(0-t)}$: Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration, CL/F: Apparent oral plasma clearance, C_{max}: Maximum plasma concentration, dECG: Digital electrocardiogram, ECG: Electrocardiogram, MTD: Maximum tolerated dose, PD: Pharmacodynamic, PK: Pharmacokinetic(s), t_{max}: Time to C_{max}, $t_{½\lambda z}$: Terminal half-life, V_z/F: Apparent volume of distribution following extravascular dosing.

[a] Reported separately from the Clinical study report (CSR).

Study design

This was a randomised, single-blind, placebo-controlled, two-centre Phase I study in healthy volunteers to assess the safety, tolerability and PK of AZD8329 after single ascending oral doses. Eight cohorts (Cohort 1 to Cohort 8 [including two optional cohorts]) with a food interaction part for Cohort 3 and Cohort 4 were planned with AZD8329 or placebo in oral suspension. The study was temporarily halted after Cohort 4 (fasting treatment period) due to significantly lower plasma exposures than what was expected, and a new formulation of AZD8329 (oral solution) was developed. Five new cohorts (Cohort 9 to Cohort 13) for AZD8329 or placebo in oral solution were added to the study. After each cohort, a Safety

Review Committee (SRC) evaluated the safety, tolerability and PK of AZD8329 and decided the next dose (planned dose, increased or decreased dose, repeated dose or dose stopped).

Target subject population and sample size

The target population was healthy male volunteers aged 20 to 45 years with a body mass index (BMI) between 18 and 30 kg/m^2 (inclusive) and weight of at least 50 kg. In each cohort, 8 healthy male volunteers were planned to be randomised 6:2 to active treatment (AZD8329) or placebo. Each healthy volunteer was only allowed to participate in 1 cohort.

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

Oral suspension:
The investigational product (IP) for Cohort 1 to Cohort 4 was AZD8329 oral suspension (20 mg/mL, formulation/batch number: 09-005642AZ/p8057, manufacturer: AstraZeneca) given as single oral doses starting with a dose of 4 mg (Cohort 1) or placebo oral suspension (formulation/batch number: 09-005088AZ/p8060, manufacturer: AstraZeneca). Dose escalation continued until Cohort 4 (fasting treatment period), when the study was temporarily halted due to unexpectedly low plasma concentrations of AZD8329. The doses administered in Cohort 2 to Cohort 4 were 20 mg, 100 mg and 400 mg, respectively.

Oral solution:
The IP for Cohort 9 to Cohort 13 was AZD8329 oral solution (20 mg/mL, formulation/batch number: 10-002569AZ/p8198, manufacturer: AstraZeneca) given as single oral doses starting with a dose of 20 mg (Cohort 9) or placebo oral solution (formulation/batch numbers: 10-003159AZ/p8201 and 10-002619AZ/p8201, manufacturer: AstraZeneca). Dose escalation continued until Cohort 13 when the pre-defined maximum exposure level was reached with respect to AZD8329 AUC. The doses administered in Cohort 10 to Cohort 13 were 60 mg, 150 mg, 300 mg (fractionated into 2 doses of 150 mg given 1.5 h apart) and 500 mg (fractionated into 2 doses of 250 mg given 6 h apart), respectively.

Duration of treatment

Single dose in Cohort 1, Cohort 2, Cohort 4, Cohort 9, Cohort 10 and Cohort 13. Two single doses in Cohort 3, Cohort 11 and Cohort 12 where a food interaction treatment period was included. A washout period of 7 to 14 days separated the 2 doses.

Statistical methods

The data were summarised using descriptive statistics. Dose proportionality was analysed using an analysis of covariance (ANCOVA) model using the logarithm of AUC (and C_{max}) as the dependent variable and the logarithm of the dose as the independent variable. The relative bioavailability of AZD8329 (when administered with food compared to during fasting conditions) were presented as the geometric mean of the individual ratios (fed/fasted) for AUC, $AUC_{(0-t)}$ and C_{max} with 95% confidence interval (CI).

Subject population

In total, 139 healthy white male volunteers were screened (consented) and 72 healthy volunteers aged between 20 and 45 years were randomized to treatment in the study. Of the 72 healthy volunteers who were randomized to treatment, 32 were assigned AZD8329 or placebo oral suspension (Cohorts 1 to 4) and 40 were assigned AZD8329 or placebo oral solution (Cohorts 9 to 13). The mean weight and BMI was 78.0 kg and 24.0 kg/m^2. Overall, the dose groups were comparable with regards to demographic characteristics.

All 72 healthy volunteers who were randomized to treatment received the assigned dose(s) and completed the study. All 72 healthy volunteers were included in the safety analysis set, and 54 healthy volunteers were included in the PK analysis set (all except the healthy volunteers who received placebo). Data from 2 healthy volunteers in the 150 mg AZD8329 oral solution dose group (Cohort 11) were excluded from the descriptive statistics and statistical analyses in the fasting treatment period due to repeated vomiting shortly after dosing.

Summary of pharmacokinetic results

Administration of AZD8329 as oral suspension (dose range 4 mg to 400 mg) resulted in plasma concentrations much lower than predicted. The geometric mean plasma exposure following the highest dose was 45-fold (C_{max}) and 27-fold (AUC) lower than the respective maximum exposure limits (81.5 µmol/L for C_{max} and 927 h*µmol/L for AUC).

Administration of AZD8329 as oral solution (dose range 20 mg to 250+250 mg) resulted in plasma concentrations higher than those observed after administration as suspension. The absorption of AZD8329 was rapid and comparable between doses with a median t_{max} of 0.67 to 0.84 hours (single dose, fasting conditions) or a median $t_{max,\ 1st\ dose}$ of 0.84 h (fractionated dosing). The plasma concentration-time profiles displayed multi-phasic decline approximately in parallel between doses. Following the highest dose, the geometric mean estimates of C_{max} (71.9 µmol/L) and AUC (917 h*µmol/L) were close to, but yet below, the pre-defined maximum exposure limits. The inter-individual variability in the plasma exposure estimates was judged to be low to moderate.

Dose proportionality was evaluated using an ANCOVA model. The 95% CI for the slope parameter β included 1 both for AUC and C_{max}. A doubling of dose was predicted to result in a 2.0-fold increase in AUC and a 2.1-fold increase in C_{max}. There were no indications of any dose-dependent changes in geometric mean CL/F (1.3 to 2.1 L/h), V_z/F (24 to 54 L) or $t_{½\lambda z}$ (13 to 20 h).

The median t_{max} of AZD8329 was in approximate agreement in fed and fasting conditions. The AUC and $AUC_{(0-t)}$ were similar in the fed and fasting states following 150 mg and 150+150 mg. The C_{max} (based on first dose) was 31 to 38% lower in the fed state compared to that in the fasting state.

Summary of pharmacodynamic results

Any results from the potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism and metabolic diseases will be reported separately from the CSR.

Summary of safety results

No safety or tolerability concerns were identified in this study, and the MTD was not reached.

There were no serious adverse events, discontinuations of IP due to AEs or other significant AEs. In total, the most common PT among the healthy volunteers who received AZD8329 oral suspension was headache, and the most common PTs among the healthy volunteers who received AZD8329 oral solution were headache, fatigue and nausea. All events of fatigue occurred in the fed treatment period. The most common PT among the healthy volunteers who received placebo was headache. All AEs were of mild or moderate intensity. There was no clear trend of a higher proportion of healthy volunteers experiencing AEs, or of a higher number of AEs, after administration of increasing doses of the AZD8329 oral solution. There was a trend towards a higher number of healthy volunteers experiencing AEs after administration of the highest dose (400 mg) of the oral suspension compared to after administration of the lower doses of oral suspension. However the AZD8329 exposure was fairly low in this dose group compared to in the oral solution dose groups.

No clinically significant effects were observed based on laboratory variables, vital signs, ECG or physical examination.