AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8931
Study Code	D0102C00011
Edition Number	1
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A Randomised, Open-label, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Oral AZD8931 Tablets in Healthy Volunteers

Study dates: First healthy volunteer enrolled: 30 March 2009
Last healthy volunteer last visit: 10 July 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)

AstraZeneca Clinical Pharmacology Unit, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK.

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 investigate the effect of food on the pharmacokinetics of AZD8931	AZD8931 concentrations in plasma Derived PK parameters for AZD8931: C_{max}, t_{max}, $t_{½}$, $AUC_{(0-t)}$, AUC, CL/F and V/F	PK
Secondary	**Secondary**	
To further investigate the safety and tolerability of AZD8931.	AEs, clinical chemistry, haematology, urinalysis, physical examination, 12-lead ECG, vital signs, and ophthalmic assessments	Safety

AE: adverse event; AUC: area under the plasma-concentration time curve from zero to infinity; $AUC_{(0-t)}$: area under the plasma-concentration time curve from zero to time t; CL/F: oral clearance; C_{max}: maximum plasma concentration; ECG: electrocardiogram; PK: pharmacokinetics; $t_{½}$: terminal half-life; t_{max}: time to maximum plasma concentration; V/F: apparent volume of distribution at steady state after an oral dose.

Study design

This was a Phase I, randomised, open-label, 3-period crossover study in healthy male volunteers in order to investigate the effect of food on the pharmacokinetics of AZD8931. Healthy volunteers received a single oral dose of AZD8931 160 mg in each of 3 periods (once in the fasted state, once immediately following a high fat breakfast and once immediately following a standard breakfast).

Target subject population and sample size

It was planned that 24 healthy male volunteers aged between 18 and 55 years with a body mass index of 19 to 30 kg/m^2 would be enrolled. In order to provide adequate information for the primary objective, the study was sized based on the estimate of the coefficient of variation (CV) of 0.425 on a log-scale for plasma AUC from the single ascending dose study of AZD8931. Twenty evaluable healthy volunteers would give 80% power of observing the 80% confidence interval (CI) for the ratio of the food effect entirely within the range 0.67 to 1.5.

Investigational product: dosage, mode of administration and batch numbers

Oral AZD8931 160 mg (comprised of 4 x 40 mg tablets). Formulation number: F013394 (D0800061). Batch number: 51733J07.

Duration of treatment

Three single doses with a minimum of 7 days washout between doses.

Statistical methods

Following log-transformation, C_{max} and AUC of AZD8931 were separately analyzed by analysis of variance (ANOVA) fitting terms for treatment group (fasted, high fat breakfast and standard breakfast), sequence and period. Healthy volunteer within sequence was treated as a random effect in the model. Point estimates and adjusted 80% and 90% confidence intervals for the difference in treatment (fasted or high fat breakfast or standard breakfast) were constructed. The point estimate and adjusted 80% and 90% confidence intervals were then exponentially back transformed to provide point and confidence interval estimates for the ratios of interest appropriately (eg, C_{max} and AUC of AZD8931 following the high fat breakfast to C_{max} and AUC of AZD8931 in the fasted state, or C_{max} and AUC of AZD8931 following the standard breakfast to C_{max} and AUC of AZD8931 in the fasted state). If the 80% confidence intervals for the ratios of AUC were contained within the pre-specified equivalence range of 0.67 to 1.5 then no effect of food on the PK of the AZD8931 would be concluded.

Subject population

A total of 24 healthy male volunteers, from a single centre in the United Kingdom, were enrolled and randomised to receive a single oral dose of AZD8931 160 mg in each of 3 periods. All 24 volunteers received at least one dose of AZD8931 and 22 volunteers completed the study. All 24 healthy volunteers were included in the full analysis set and the safety analysis set. Two healthy volunteers were excluded from the PK analysis set as they did not complete at least two periods with evaluable and calculated PK data. Both of these healthy volunteers were withdrawn due to an AE after the first dose of AZD8931. Demographic and baseline characteristics were similar across each of the treatment sequences.

Summary of pharmacokinetic results

Geometric mean AUC was found to be similar under fasted conditions (2877 ng.h/mL), after a standard breakfast (2882 ng.h/mL) and after a high fat breakfast (2880 ng.h/mL). The variability in AUC was between 37 and 44 CV%.

Geometric mean C_{max} was decreased approximately 23% under fed (344 ng/mL after a standard breakfast and 338 ng/mL after a high fat breakfast), compared with fasted conditions (443 ng/mL). The variability in C_{max} was between 33 and 56 CV%.

Median t_{max} was prolonged under fed (3 hours after a standard breakfast and 2 hours after a high fat breakfast), compared with fasted conditions (1 hour).

Arithmetic mean $t_{½}$ was found to be similar under fasted conditions (14.3 hours), following a standard breakfast (13.7 hours) or following a high fat breakfast (13.7 hours).

Arithmetic mean CL/F and V/F, respectively, were found to be similar under fasted conditions, following a standard breakfast or following a high fat breakfast.

The 80% confidence intervals for the ratios of plasma AZD8931 AUC were contained within the pre-defined equivalence range of 0.67 to 1.5 for the comparison of fed high fat versus fasted (point estimate: 1.005; 80% CI: 0.962, 1.049), fed standard versus fasted (point estimate: 1.003; 80% CI: 0.954, 1.053) and fed high fat versus fed standard (point estimate: 0.999; 80% CI: 0.947, 1.054), indicating that the AUC of AZD8931 was not affected by food.

C_{max} was 23% lower when AZD8931 160 mg was administered after a high fat breakfast than under fasted conditions (point estimate: 0.770; 80% CI: 0.670, 0.885). C_{max} was also 23% lower when AZD8931 160 mg was administered after a standard breakfast than under fasted conditions (point estimate: 0.774; 80% CI: 0.680, 0.881).

Summary of safety results

AEs were reported for 21 of 24 (88%) healthy volunteers participating in this study. The number of healthy volunteers reporting AEs was similar across the three regimens. In total, 110 AEs were reported, of which 41 were considered to be causally related to AZD8931 by the investigator.

No deaths or serious adverse events were reported. Two healthy volunteers discontinued due to an AE: candida balantitis (considered by the investigator to be unrelated to AZD8931) and macular rash (considered by the investigator to be related to AZD8931).

The most commonly reported AEs by MedDRA preferred term (>10% of healthy volunteers) with onset after any AZD8931 treatment period were application site rash (42%), headache (33%), macular rash (25%), dermatitis acneiform (21%), abdominal pain (21%), dry skin (17%), vessel puncture site haematoma (17%), diarrhoea (17%), catheter site haematoma (13%), nausea (13%) and epistaxis (13%). All AEs were of CTCAE grade 1 or 2.

Sixty-five AEs of special interest (skin-type AEs, eye-type AEs and diarrhoea) were reported for 20 healthy volunteers. Skin-type AEs were reported in 18 (75%) volunteers and skin-type AEs, excluding application site reactions were reported in 16 (67%) volunteers; all of the skin-type AEs were of CTCAE grade 1, except for macular rash for 1 volunteer who was discontinued from the study. Eye-type AEs were reported in 5 (21%) volunteers; all were of CTCAE grade 1 and none was of clinical concern. Diarrhoea was reported in 4 (17%) volunteers; all episodes were of CTCAE grade 1 and none was of clinical concern.

There were no clinically relevant changes in safety laboratory variables, vital signs, ECG and physical examination.