AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9831C00003
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An Open, Single-dose, Phase I, 4-period partly Crossover Study in Healthy Men or Women to Assess Relative Bioavailability of Oral Administration of AZD1981 via Tablets Compared with Suspension and Basic Systemic Pharmacokinetic Parameters after Intravenous Administration

Study dates: First subject enrolled: 1 June 2009
Last subject last visit: 13 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)

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: To estimate relative bioavailability (F_{rel}) of AZD1981 after oral administration via 2 tablet formulations compared with suspension by assessment of area under the plasma concentration-time curve from zero to infinity (AUC) for the tablet and the suspension.	**Primary:** F_{rel} based on AUC for the tablet and suspension formulations.	Pharmacokinetic
To evaluate basic systemic pharmacokinetic (PK) parameters of orally and intravenously administered AZD1981.	Oral administrations: C_{max}, t_{max}, $t_{1/2\lambda z}$, $AUC_{(0-t)}$, AUC, MRT, MAT Intravenous (iv) infusion: C_{max}, t_{max}, $t_{1/2\lambda z}$, $AUC_{(0-t)}$, AUC, MRT, CL, V_z, V_{ss} Oral and iv outcomes were cross-correlated to assess MAT and F (based on AUC).	Pharmacokinetic
Safety: To evaluate the safety and tolerability of AZD1981 in healthy volunteers.	**Safety:** Adverse events (AEs), clinical laboratory tests, vital signs, ECG.	Safety
Exploratory: To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie distribution, safety, tolerability and efficacy) to AZD1981. The results are not part of the main report for this study.	**Exploratory:** Genotype	Pharmacogenetic

Study design

This was an open, randomised, 4-period partly crossover, single dose, phase I study comprising 6 visits. Four (4) different AZD1981 formulations were administered at

4 occasions: iv infusion (100 mg at Visit 2), oral suspension (514 mg at Visit 3) and two tablet formulations (500 mg each at Visit 4 and 5 or vice versa) of which one, Tablet A, had optimal dissolution properties and the other, Tablet B, had slower dissolution properties. There was a washout period of at least 1 week between the doses. Screening was performed at Visit 1 and follow-up examinations were done at Visit 6.

Target subject population and sample size

The target population was to consist of healthy male and female volunteers, aged 18 to 55 years with a body mass index between 19 and 30 kg/m^2 and a weight of 50 to 100 kg. The subjects were to be non-smokers or should have stopped smoking more than 6 months prior to Visit 1 (pre-entry). Female volunteers had to be post-menopausal or surgically sterile.

A total of 14 subjects were planned to be randomised in order to have at least 12 evaluable subjects.

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

Four single doses of each AZD1981 formulation listed in Table S2 were administered at 4 occasions. Subjects fasted for at least 10 h before administration until 4 h post dose.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
AZD1981 (Tablet A)	Film-coated tablet 250 mg (optimal dissolution)	AstraZeneca	D0900142	09-003203AZ/ DKM 461
AZD1981 (Tablet B)	Film-coated tablet 250 mg, Variant 1 (slower dissolution)	AstraZeneca	D0900163	09-003202AZ/ DLC 486
AZD1981	Suspension 50 mg/g	AstraZeneca	D0800359	09-000872AZ/ DKE 431
AZD1981	Solution for infusion, 2.6 mg/mL	AstraZeneca	D0900178	09-002437AZ

Duration of treatment

Four single doses of AZD1981 were administered at 4 occasions with a washout period of at least 1 week in between. The total duration of participation (from pre-entry to follow up) was in general around 6 weeks.

Statistical methods

Relative bioavailability (F_{rel}) of AZD1981 for each of the tablet formulations was computed by the geometric mean ratio of dose corrected tablet vs suspension AUC, including 95% confidence interval (CI), calculated from the student's t distribution.

Relative bioavailability (F_{rel}) between oral tablet formulations of AZD1981 was computed by the geometric mean ratio of Tablet A vs Tablet B AUC, including 95% CI. The model for estimation of F_{rel} and corresponding 95% CI was a mixed ANOVA model with subject, treatment and period as fixed factors. The analyses were based on log_e-transposed response variables and the results were exponentially back-transformed in order to provide estimates of the true ratios.

Absolute bioavailability (F) of AZD1981 for each of the oral formulations was computed by geometric mean ratio of dose corrected oral vs iv AUC, including 95% CIs, calculated from the student's t-distribution.

Mean absorption time (MAT) of AZD1981 for each of the oral formulations was computed as the arithmetic mean difference between mean residence time (MRT) after oral and iv administration, including 95% CI, calculated from the student's t distribution.

Basic systemic PK parameters after iv administration of AZD1981 were described with mean and 95% confidence limits for the mean, calculated from the student's t distribution. Geometric mean was used for all parameters except for MRT where arithmetic mean was presented.

Subject population

In total, 23 subjects were enrolled (consented) at a single centre, 14 were randomised and 14 completed the study. All 14 subjects were included in the safety analysis set and plasma PK analysis set.

The number of subjects and their demography and baseline characteristics were in line with the population that was intended to be included in the study. The dose groups were comparable in terms of demographics.

Summary of pharmacokinetic results

Relative oral bioavailability (F_{rel}) of AZD1981 via tablet formulations A and B (95% CI) was estimated to 147% (125% to 174%) and 117% (99% to140%), respectively, of that via oral suspension.

Mean absolute bioavailability of AZD1981 after administration of the oral suspension (95% CI) was estimated to 36% (29% to 44%). Mean absolute bioavailability of AZD1981 after administration of Tablet A and Tablet B (95% CI) was estimated to 53% (46% to 61%) and 42% (37% to 49%), respectively.

Geometric means for plasma clearance (CL) and volume of distribution (V_{ss}), at steady state were estimated to 16 L/h and 24 L, respectively, following iv administration of AZD1981.

Mean terminal half life ($t_{½λz}$) and MRT after iv administration (2.8 and 1.5 h, respectively) were shorter than the mean $t_{½λz}$ and MAT after oral administration (overall means 15 h and 8.6 h, respectively).

Due to problems with the urinalysis method, urine PK data are not reported in this report.

Summary of pharmacogenetic results

Any future genetic analyses will be reported separately.

Summary of safety results

No safety or tolerability concerns were identified in this study. The number of reported AEs was low. The most common AE was headache and 4 incidences of headache were judged to be causally related to treatment. All AEs were of mild to moderate intensity and were not associated with a certain formulation. There was no clear relation between the exposure levels of the active drug and the AEs judged to be potentially related to the treatment. There were no clinically relevant effects on clinical laboratory values, ECG or vital signs.