AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9830C00017
Edition Number	1
Date	

A Phase I, Open Label, Randomised, Parallel Group Study of Repeated Oral Doses of AZD1981 (100 mg Twice Daily and 400 mg Twice Daily) for Two Weeks and Single Doses of Warfarin (25 mg) to Evaluate the Pharmacokinetic Interaction of AZD1981 and Warfarin and the Effect of AZD1981 on Warfarin Pharmacodynamics in Healthy Male Volunteers

Study dates: First subject enrolled: 4 October 2010
Last subject last visit: 3 December 2010

Phase of development: Clinical pharmacology (I)

Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre

The study was conducted at a single centre in

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary, secondary and exploratory objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate if the exposure of warfarin is clinically significantly changed by 7 days of exposure to AZD1981	AUC and C_{max} of (R)- and (S)-warfarin.	PK
Secondary	**Secondary**	
1. To explore possible changes in the anticoagulative activity of warfarin after 7 days of exposure to AZD1981	$AUC_{INR, 0-168}$ and INR_{max}	PD
2. To estimate basic systemic steady-state PK variables of AZD1981 after a single dose of warfarin	$AUC_{(0-t)}$, t_{max}, $t_{1/2\lambda z}$, CL/F and V_z/F for (R)- and (S)-warfarin on Day 1 and Day 15	PK
3. To estimate additional basic systemic PK variables of warfarin after a single dose of warfarin with and without administration of AZD1981	AUC_{τ}, $C_{ss,max}$, t_{max} and CL_{ss}/F for AZD1981 on Day 15	PK
4. To evaluate safety and tolerability of AZD1981	AEs, blood pressure, pulse, laboratory variables, ECG and physical examination	Safety
Exploratory	**Exploratory**	
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response, ie, distribution, safety and tolerability of AZD1981 or warfarin	Not applicable	PGx

a Results not included in the Clinical Study Report.
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 of last quantifiable concentration; AUC_{τ} area under the plasma concentration-time curve during a dosing interval; $AUC_{INR, 0-168}$ area under the international normalised ratio versus time curve from time 0 to 168 h; CL/F apparent plasma clearance after a single dose; CL_{ss}/F apparent plasma clearance at steady-state; C_{max} maximum plasma concentration; $C_{ss,max}$ maximum plasma concentration during a dosing interval; ECG electrocardiogram; INR_{max} maximum INR; V_z/F apparent volume of distribution during terminal phase; PD pharmacodynamic(s); PGx pharmacogenetic(s); PK pharmacokinetic(s); t_{max} time to reach C_{max} or $C_{ss,max}$; $t_{1/2\lambda z}$ terminal half-life

Study design

This was an open label, randomised, parallel group study to assess the PK interaction between AZD1981 and warfarin.

Warfarin was administered as a single oral dose on 2 occasions, 14 days apart: on Day 1 (7 days before start of treatment with AZD1981) and on Day 15 (after 7 days of AZD1981 pre-treatment). AZD1981 100 mg or 400 mg, according to randomisation, was administered as oral tablets twice daily (bid) for 14 days from Day 8 to Day 21.

PK blood samples for warfarin assessment and PD blood samples for assessment of prothrombin complex (INR) were collected at multiple time points up to 168 h (7 days) after each warfarin single dose. PK blood samples for AZD1981 were collected at multiple time points up to 168 h (7 days) after dosing on Day 15 (at steady state).

Safety assessments were made throughout the study.

Target subject population and sample size

Healthy male volunteers, aged 18 to 55 years, with a body mass index (BMI) between 19 and 30 kg/m^2 (extremes included) and a weight of at least 65 kg and no more than 100 kg. Healthy volunteers predicted to be most sensitive to warfarin based on CYP2C9 and VKORC1 genotypes were excluded.

Twenty-eight (28) healthy volunteers were to be randomised to ensure data from 24 evaluable healthy volunteers (ie, 12 who received 100 mg AZD1981 and 12 who received 400 mg AZD1981) who completed the study.

Investigational products: dosage, mode of administration, formulation numbers and batch numbers

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD1981	Tablet 100 mg, oral, bid	AstraZeneca	D0900500	10-003598AZ
Waran® (Warfarin sodium)	Tablet 2.5 mg, oral, single dose	Nycomed	VNR 535260	10-004768AZ

Duration of treatment

Warfarin (Waran®) 25 mg was administered as 2 single doses of oral tablets (10 x 2.5 mg), given 14 days apart: pre-dose of AZD1981 (Day 1) and after 7 days of AZD1981 treatment (Day 15).

AZD1981 100 or 400 mg was administered bid (morning and evening) as oral tablets (1 x 100 mg or 4 x 100 mg) for 14 days (Days 8 to 21).

Statistical methods

AUC and C_{max} of (R)- and (S)-warfarin was analysed using a linear mixed effects model. The model included time (pre AZD1981 dose or post AZD1981 dose), group (100 or 400 mg AZD1981) and time*group as fixed factors and subject as a random factor. The analyses were based on $\log_e$-transposed variables and the results were exponentially back-transformed in order to provide estimates of the true ratios post-dose/pre-dose. Least squares means point estimates and corresponding 95% confidence intervals (CIs) were presented by dose group and time. Estimates and 90% CIs of the ratios post-dose/pre-dose were presented by dose group.

$AUC_{INR, 0\text{-}168}$ and INR_{max} were analysed using a linear mixed effects model similar to the model for AUC and C_{max} of (R)- and (S)-warfarin.

Safety was evaluated by descriptive statistics.

Subject population

A single centre was used in the study. In total, 53 healthy volunteers were screened, 29 were randomised, 28 received at least one dose of investigational product (IP) and 24 completed the study. All 28 who received at least one dose of IP were included in the safety analysis set. Twenty-four were included in the PK analysis set and 25 in the PD analysis set.

Thirteen of the volunteers who completed the study were randomised to 100 mg AZD1981 and 11 were randomised to 400 mg AZD1981. Although only 11 healthy volunteers were evaluable in one of the treatment groups, instead of the planned 12, this was judged sufficient for the purpose of the study.

There were 5 withdrawals from the study. One withdrawal was before first dose, due to near fainting during pre-dose blood sampling. This volunteer was judged not to be suitable for the study and thus not to fulfil the eligibility criteria. The volunteer was replaced. Three withdrawals were due to an INR value of 3 or above after the first dose of warfarin, which was a study specific withdrawal criterion. One withdrawal (on Day 15) was due to severe non-compliance to the protocol. The volunteer had taken 1 x 100 mg AZD1981 bid instead of 4 x 100 mg bid when dosing at home.

All healthy volunteers randomised in the study were white males, with an age range of 18 to 50 years. The two treatment groups, 100 mg and 400 mg AZD1981, were comparable with regard to demographic and baseline characteristics.

Summary of pharmacokinetic results

The statistical analysis of (R)-warfarin plasma exposure indicated that AUC and C_{max} after co-administration of AZD1981 100 mg bid, as well as AUC after co-administration of AZD1981 400 mg bid were unchanged. C_{max} increased by 12% after co-administration of AZD1981 400 mg bid. The 90% CIs for all of the comparisons were contained within 80.00 to 125.00%. The estimates of t_{max}, $t_{½\lambda z}$, CL/F and V_z/F of (R)-warfarin were similar between treatments.

The statistical analysis of (S)-warfarin plasma exposure indicated that C_{max} was unchanged, while AUC increased by 35% after coadministration of warfarin with AZD1981 100 mg bid. The AUC and C_{max} increased by 137% and 13%, respectively, after co-administration of warfarin with AZD1981 400 mg bid. The 90% CIs for C_{max} were contained within 80.00 to 125.00% while the 90% CIs for AUC (both treatment groups) were above 125.00%. The increase in AUC of (S)-warfarin was accompanied by a prolonged $t_{½\lambda z}$ and a decreased CL/F upon co-administration with AZD1981. The t_{max} of (S)-warfarin was similar and there were no relevant changes in V_z/F between treatments.

Based on a visual inspection of the pre-dose (trough) plasma concentration-time profiles, steady-state of AZD1981 was considered to have been achieved in both dose groups and also maintained during the study period, ie, up to 168 h after the warfarin dose.

Summary of pharmacodynamic results

The statistical analysis indicated that $AUC_{INR, 0-168}$ and INR_{max} after co-administration of warfarin with AZD1981 100 mg were basically unchanged. The geometric least squares means of $AUC_{INR, 0-168}$ and INR_{max} increased by 16% and 11%, respectively, after co-administration of AZD1981 400 mg. All 90% CIs for the comparisons were contained within 80.00 to 125.00%. The inter-individual variability (CV%) in $AUC_{INR, 0-168}$ and INR_{max} was <22%.

Summary of pharmacokinetic/pharmacodynamic relationships

The overall PD effect was dose-dependent with respect to AZD1981. This was in alignment with the larger increase in plasma exposure of (S)-warfarin after co-administration of AZD1981 400 mg bid as compared to AZD1981 100 mg bid.

Summary of safety results

There were no serious AEs, discontinuations due to AEs or other significant AEs in the study. The most common AEs overall were headache, pharyngitis and epistaxis. All AEs were of mild or moderate intensity. Bleeding-related AEs, ie, gingival bleeding, haematochezia, epistaxis and venipuncture site haematoma, were reported only in conjunction with the single doses of warfarin.

As expected after dosing with warfarin, mean P-activated partial thromboplastin time (P-APT) and P-prothrombin complex (INR) were increased in both treatment groups compared to baseline. The increase was higher in the 400 mg group than in the 100 mg group. There were no other trends in the clinical laboratory values in the study.

Three volunteers were withdrawn from the study after the first dose of warfarin due to INR values above the safety limit in the study (INR of 3 or above). Apart from this, there were no clinically significant findings based on vital signs, ECG, physical examinations or weight assessments during the study.