AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3480
Study Code	D3690C00014
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A Single-Centre, Double Blind, Randomised, Two-Way Cross-Over Study of Repeated Oral Doses of AZD3480 and Single Dose of Warfarin to Evaluate the Pharmacokinetic Interaction of AZD3480 and Warfarin and the Effect of AZD3480 on Warfarin Pharmacodynamics in Healthy Male Subjects (Phase I)

Study dates: First subject enrolled: 19 September 2007
Last subject completed: 23 February 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

The study was conducted at one study centre at ICON Development Solutions, Skelton House, Manchester Science Park, UK.

The first subject was enrolled on 19 September 2007.

The last subject completed on 23 February 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to evaluate the pharmacokinetics (PK) of warfarin during co-administration with AZD3480 by assessment of the PK variables of R- and S-warfarin.

The secondary objectives of this study were:

1. To evaluate possible changes in the anticoagulative activity of warfarin upon co-administration with AZD3480 by assessment of prothrombin time as measured by the international normalised ratio.

2. To evaluate the PK of AZD3480 during co-administration with warfarin by assessment of the PK variables of AZD3480.

3. To evaluate the safety and tolerability of AZD3480 alone and in combination with warfarin by assessment of adverse events (AEs), blood pressure, pulse, laboratory variables, and physical examination.

In addition, an optional blood sample for genotyping for possible future exploratory research aimed at identifying/exploring genetic variations that might affect PK and pharmacodynamics (PD) (including biomarkers), safety and tolerability related to AZD3480 treatment was collected and stored.

Study design

This was a double blind, randomised, 2-way cross-over, placebo-controlled (AZD3480 versus placebo, open for warfarin), single-centre study.

Target subject population and sample size

Healthy male subjects aged ≥18 to ≤45 years were recruited to ensure at least 26 evaluable subjects. Twenty-two subjects were extensive metabolisers (EMs) with 1.5 functional CYP2D6 alleles or more, and 7 subjects were poor metabolisers (PMs) with no functional allele of CYP2D6.

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

AZD3480 or placebo capsules (batch number H 1814-01-01) were administered at doses of 50 mg (1 x 50 mg capsule, batch number H 1813-01-01) to PMs and 125 mg (2 x 50 mg, batch number H 1813-01-01 and 1 x 25 mg capsule, batch number H 1812-01-01) to EMs once daily from Day 1 to Day 12. Doses were given under fasting conditions on Days 5 and 6.

Warfarin (Waran®) was administered as a 25 mg single dose (10 x 2.5 mg tablets, batch number H 0724-02-02-01) to both EMs and PMs on the morning of Day 6 in both periods of the study. Warfarin was dosed under fasting conditions.

Duration of treatment

The study consisted of an enrolment visit, within 48 days of first dosing, followed by a treatment period of 14 days (Day -1 to Day 13). A follow-up visit occurred 10 days (± 3 days) after the last PK sample in treatment Period 2.

Criteria for evaluation - pharmacokinetics (main variables)

Primary PK variables were AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, and $t_{½lambda,z}$ of R- and S warfarin.

Secondary PK variables were AUC_{τ}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, and CL_{ss}/F of AZD3480.

Criteria for evaluation - pharmacodynamics (main variables)

Primary PD variables were $AUC_{INR,\ 0-168}$ and INR_{max}.

Criteria for evaluation - safety (main variables)

The safety variables were adverse events (AEs), laboratory assessments (chemistry, haematology, urinalysis), physical examination, 12-lead electrocardiogram (ECG), vital signs (supine blood pressure and pulse).

Statistical methods

In order to show that AZD3480 did not interact with the PK of warfarin AUC, $AUC_{(0-t)}$ and C_{max} for R- and S-warfarin were analysed with mixed effects analysis of variance (ANOVA) models. PK parameters were log_e-transformed and compared between co-administration of warfarin with AZD3480 (Test) and with placebo (Reference) using ANOVA. R- and S-warfarin t_{max} was compared between treatment with AZD3480 (Test) and with placebo (Reference) using the non-parametric Wilcoxon signed rank test for matched pairs. A non-parametric 90% confidence interval (CI) was calculated for the median difference between treatments based on the Hodges-Lehmann estimator.

To show that warfarin did not interact with the steady state PK of AZD3480 AUC_{τ} and $C_{ss,max}$ for AZD3480 were analysed using an ANOVA procedure. The parameters were log_e-transformed and compared between co-administration of AZD3480 with warfarin on

Day 6 (Test) and AZD3480 alone on Day 5 (Reference) using ANOVA. AZD3480 t_{max} was compared between AZD3480/warfarin (Test) and AZD3480 alone (Reference) and using the non-parametric Wilcoxon signed rank test for matched pairs. A non-parametric 90% CI was calculated for the median difference between treatments based on the Hodges-Lehmann estimator.

In order to show that AZD3480 did not interact with the PD of warfarin $AUC_{INR, 0-168}$ and INR_{max} were analysed using ANOVA. The parameters were log_e-transformed and compared between co-administration of warfarin with AZD3480 (Test) and with placebo (Reference) using ANOVA.

Subject population

Twenty-nine subjects were randomised onto the study and received at least 1 dose of study treatment. Twenty-four subjects successfully completed the study and 5 were withdrawn.

Table S1 Summary of demographic data

Demographic and baseline characteristic		Overall (N=29)
Sex n (%)	Male	29 (100.0)
Age (years)	Mean (SD)	30.2 (8.8)
	Minimum	19
	Median	27.0
	Maximum	45
Race n (%)	Caucasian[1]	26 (89.7)
	Oriental[1]	1 (3.4)
	Other	2 (6.9)

[1] Caucasian = White, Oriental = Asian

Summary of pharmacokinetic results

For both EMs and PMs the geometric mean ratio and associated 90% CI indicated there was no effect of AZD3480 on C_{max} of R-warfarin. For AUC and $AUC_{(0-t)}$ of R-warfarin the geometric LSmean ratios and the 90% CIs indicated a possible weak inhibition of R-warfarin metabolism by AZ3480 in both EMs and PMs. However, for PMs these results must be viewed with caution due to the small number of subjects (n=4).

Table S2 PK of R-warfarin: Summary of statistical analysis (PK population)

CYP2D6 Population	Parameter	n Test	n Reference	Geometric LSmean Test	Geometric LSmean Reference	Geometric LSmean Ratio (Test/ Reference)	90% CI for Geometric LSmean Ratio [Lower - Upper]
PM	C_{max}	4	4	3784.29	3757.05	1.007	[0.874, 1.161]
	$AUC_{(0-t)}$	4	4	278681.57	216007.56	1.290	[1.180, 1.411]
	AUC	4	4	368144.86	248151.70	1.484	[1.340, 1.643]
EM	C_{max}	20	20	3669.97	3667.46	1.001	[0.940, 1.065]
	$AUC_{(0-t)}$	20	20	226765.72	192347.14	1.179	[1.134, 1.226]
	AUC	20	20	265768.89	212692.13	1.250	[1.195, 1.307]

Test = AZD3480 + warfarin
Reference = Placebo + warfarin

For both EMs and PMs the geometric mean ratios and associated 90% CIs for C_{max}, $AUC_{(0-t)}$ and AUC of S-warfarin indicated there was no effect of AZD3480 at steady state on the exposure to S-warfarin.

Table S3 PK of S-warfarin: Summary of statistical analysis (PK population)

CYP2D6 Population	Parameter	n Test	n Reference	Geometric LSmean Test	Geometric LSmean Reference	Geometric LSmean Ratio (Test/ Reference)	90% CI for Geometric LSmean Ratio [Lower - Upper]
PM	C_{max}	4	4	3737.11	3805.66	0.982	[0.836, 1.153]
	$AUC_{(0-t)}$	4	4	127120.57	120964.79	1.051	[0.969, 1.139]
	AUC	4	4	131901.64	124691.61	1.058	[0.973, 1.150]
EM	C_{max}	20	20	3587.76	3619.96	0.991	[0.924, 1.064]
	$AUC_{(0-t)}$	20	20	118400.26	114712.42	1.032	[0.996, 1.070]
	AUC	20	20	122274.43	118123.96	1.035	[0.998, 1.074]

Test = AZD3480 + warfarin
Reference = Placebo + warfarin

In EMs, the geometric mean ratios and associated 90% CIs for both $C_{ss,max}$ and AUC_{τ} indicated there was no overall effect of warfarin on the PK of AZD3480. For PMs, the geometric mean ratios were close to 1 but the 90% CIs slightly exceeded the upper limit of 1.25 for both $C_{ss,max}$ and AUC_{τ}. These results indicated a negligible inhibition of AZD3480 metabolism by warfarin in PMs. However, these results should be viewed with caution due to the small number of PM subjects (n=6).

Table S4 PK of AZD3480: Summary of statistical analysis (PK population)

CYP2D6 Population	Parameter	n Test	n Reference	Geometric LSmean Test	Geometric LSmean Reference	Geometric LSmean Ratio (Test/ Reference)	90% CI for Geometric LSmean Ratio [Lower - Upper]
PM	$C_{ss,max}$	6	6	522.77	486.59	1.074	[0.783, 1.474]
	AUC_{τ}	6	6	7350.88	6841.57	1.074	[0.900, 1.282]
EM	$C_{ss,max}$	20	20	269.19	259.98	1.035	[0.871, 1.231]
	AUC_{τ}	20	20	1004.89	1038.29	0.968	[0.878, 1.066]

Test = AZD3480 + warfarin (Day 6)
Reference = AZD3480 (Day 5)

Summary of pharmacodynamic results

For both EMs and PMs, the geometric mean ratios for $AUC_{INR,0-168}$ and INR_{max} were close to 1 and the associated 90% CIs were within 0.94 to 1.14, indicating there was no overall effect of AZD3480 on the PD of warfarin.

Table S5 Summary of statistical analysis of PD Parameters: PD population

CYP2D6 Population	Parameter	n Test	n Reference	Geometric LSmean Test	Geometric LSmean Reference	Geometric LSmean Ratio (Test/ Reference)	90% CI for Geometric LSmean Ratio [Lower - Upper]
PM	INR_{max}	4	4	2.01	1.95	1.035	[0.941,1.139]
	$AUC_{(INR, 0-168)}$	4	4	228.71	215.78	1.060	[0.992, 1.132]
EM	INR_{max}	20	20	1.70	1.66	1.023	[0.981, 1.067]
	$AUC_{(INR, 0-168)}$	20	20	202.39	197.76	1.023	[0.994, 1.054]

Test = AZD3480 + warfarin (Day 6)
Reference = AZD3480 (Day 5)

Summary of safety results

There were 6 pre-treatment AEs reported in 3 subjects (10.3%). There were no deaths during the study. There was 1 severe SAE of acute psychosis 10 days after dosing with AZD3480 and warfarin that lead to a PM subject being discontinued from the study. The final diagnosis of his condition was an acute paranoid psychotic episode (schizophreniform psychosis) which had probably pre-existed for a number of years but was subclinical in nature. The Investigator considered that there was a reasonable possibility that this SAE was caused by the study treatment. No other significant AEs were reported in this study. The majority of the AEs were mild in severity. The AEs experienced by the PMs were similar to those experienced by the EMs with nervous system disorders, general disorders and administration site conditions and gastrointestinal disorders being the most commonly reported affected system organ class in both groups. The profile of AEs was consistent with those previously recorded in the Investigator's Brochure for AZD3480.

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