AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00013
Edition Number	1
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An Open-Label, Single Centre Study to Assess the Pharmacokinetics and Pharmacodynamics of Warfarin when Co-Administered with Fostamatinib in Healthy Subjects

Study dates: First subject enrolled: 16 March 2011
Last subject last visit: 2 June 2011

Phase of development: Clinical pharmacology (I)

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

Study centre

One study centre in the United Kingdom

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 whether R- and S-warfarin plasma concentration-time profiles and resulting PK parameters (single administration) are altered during steady-state fostamatinib administration	Primary variables: R- and S-warfarin: AUC and C_{max} (for Day 1 [warfarin alone] and Day 14 [warfarin + fostamatinib]) Secondary variables: R- and S-warfarin t_{max}, AUC_{0-t}, $t_{1/2\lambda z}$, CL/F, and V_z/F	Pharmacokinetic
Secondary	**Secondary**	
To investigate the INR after a single administration of warfarin alone and during steady-state fostamatinib administration	INR_{max} and $AUC_{INR,0-168}$ (for Day 1 [warfarin alone] and Day 14 [warfarin + fostamatinib])	Pharmacodynamic
To assess the steady-state PK of R406	R406: AUC_{ss}, $C_{max,ss}$, $t_{max,ss}$, and CL/F	Pharmacokinetic
To examine the safety and tolerability of fostamatinib in combination with warfarin	Adverse events, vital signs, electrocardiogram, laboratory safety variables, and physical examination	Safety

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 the last measurable concentration; $AUC_{INR,0-168}$: Area under the International Normalised Ratio-time curve from zero to 168 hours postdose; AUC_{ss}: Area under the plasma concentration-time curve during the dosing interval at steady-state; CL/F: Apparent clearance; C_{max}: Maximum plasma concentration; $C_{max,ss}$: Maximum plasma concentration at steady-state; CSP: Clinical Study Protocol; INR: International Normalised Ratio; INR_{max}: Maximum International Normalised Ratio; PK: Pharmacokinetic(s); R406: Analyte in plasma for the dephosphorylated drug; $t_{1/2\lambda z}$: Terminal half-life; t_{max}: Time to maximum plasma concentration; $t_{max,ss}$: Time to maximum plasma concentration at steady-state; V_z/F: Apparent volume of distribution.

Study design

This was an open-label, non-randomised, fixed sequence study conducted at a single study centre to assess the PK and PD of warfarin when co-administered with fostamatinib. The study comprised 12 visits.

All subjects were to receive 2 single 25 mg warfarin doses (separated by 14 days) on Days 1 and 14 and 100 mg fostamatinib twice daily (bid) from Days 8 to 20 (26 doses over 13 days).

Target subject population and sample size

Fifteen healthy male and female (of non-childbearing potential) subjects aged 18 to 55 years (inclusive) with a minimum weight of 50 kg and a body mass index of 18 to 35 kg/m^2 (inclusive).

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

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number
Warfarin	Tablet, 5 mg, oral	Goldshield[a]	BYD9034F
Fostamatinib	Tablet, 50 mg, oral	Patheon	10048.2/1 CK2P

[a] A generic product with an AB rating in the Food and Drug Administration Orange Book could have been used.

Duration of treatment

Single warfarin dose on Day 1; single warfarin dose on Day 14; bid fostamatinib doses from Days 8 to 20.

Statistical methods

The analyses of pharmacokinetics (PK), pharmacodynamics (PD), and safety data were summarised descriptively in tables, listings, and graphs, as appropriate. Quantitative continuous variables were summarised using descriptive statistics, including number of subjects, mean, standard deviation (SD), median, minimum, and maximum values.

Statistical analyses were performed on data from the safety analysis set, PK analysis set, and PD analysis set.

Subject population

Enrolled: 15 subjects

Completed: 14 subjects

All subjects enrolled were eligible to be included in this study.

Summary of pharmacokinetic results

This study was conducted to determine if R406 would affect the PK and PD of R- and S-warfarin.

Visual inspection of R406 trough concentrations indicated steady-state was reached 3 days prior to warfarin administration on Day 14.

The results of the primary statistical comparison of R- and S-warfarin PK parameters following administration of a single dose of warfarin 25 mg given alone and in combination with fostamatinib dosed to steady-state are presented in Table S2.

Table S2 Statistical comparison of key R- and S-warfarin pharmacokinetic parameters

					Warfarin + fostamatinib/ Warfarin alone	
Analyte	**Parameter (units)**	**Treatment**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
R-warfarin	AUC	Warfarin alone	11	65228		
	(ng·h/mL)	Warfarin + fostamatinib	11	76828	117.8	(113.0, 122.7)
	C_{max}	Warfarin alone	13	1177		
	(ng/mL)	Warfarin + fostamatinib	13	1202	102.1	(97.0, 107.5)
S-warfarin	AUC	Warfarin alone	14	43014		
	(ng·h/mL)	Warfarin + fostamatinib	14	48528	112.8	(107.4, 118.5)
	C_{max}	Warfarin alone	14	1188		
	(ng/mL)	Warfarin + fostamatinib	14	1173	98.7	(91.5, 106.4)

CI confidence interval; LS least squares. Results based on analysis of variance model on log transformed pharmacokinetic parameters with fixed effects for treatment and subject.

The results showed similar geometric mean maximum plasma concentrations for both R- and S-warfarin when warfarin administered alone and with fostamatinib.

Median t_{max} was 2 hours for each analyte and treatment, with the exception of S-warfarin median t_{max} occurring a 1 hour after the warfarin alone treatment.

Both R-and S-warfarin had a slight increase in geometric mean AUC after warfarin was coadministered with fostamatinib, however 90% confidence intervals remained within the (80, 125%) interval.

R-warfarin geometric mean $t_{1/2\lambda z}$ was 50.7 hours after warfarin was administered alone and 57.3 hours with fostamatinib coadministration. S-warfarin geometric mean $t_{1/2\lambda z}$ was 34.5 hours after warfarin was administered alone and 40.6 hours with fostamatinib coadministration.

Polymorphisms in the cytochrome P450 (CYP) 2C9 genotype did not appear to have an effect on S-warfarin exposure parameters.

Summary of pharmacodynamic results

The results of the primary statistical comparison of INR parameters following administration of a single dose of warfarin 25 mg concomitantly with multiple dose fostamatinib dosed to steady-state, compared to a single dose of warfarin 25 mg administered alone are presented in Table S3.

Table S3 Statistical comparison of key pharmacodynamic parameters

				Warfarin + fostamatinib/ Warfarin alone	
Parameter (units)	**Treatment**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
INR_{max}	Warfarin alone	14	1.65	89.7	(84.6, 95.2)
	Warfarin + fostamatinib	14	1.48		
$AUC_{INR,0-168}$ (h)	Warfarin alone	14	206.65	97.0	(95.3, 98.8)
	Warfarin + fostamatinib	14	200.44		

LS least squares; CI confidence interval

Although R-and S-warfarin exposure trended up after coadministration with fostamatinib, INR parameters trended down. However, 90% confidence intervals remained within the (80, 125%) interval.

Polymorphisms in the vitamin K epoxide reductase (VKORC1) genotype did increase INR parameters, however, trend in the population for lower INR values in the warfarin + fostamatinib treatment was also observed for these subjects.

Summary of safety results

No deaths, serious adverse events (SAEs), discontinuation due to adverse events (DAEs), or other significant adverse events (OAEs) were reported. Six adverse events (AEs) were reported for 5 subjects: pollakiuria (urinary frequency), 2 events of rash, lethargy, hypoaesthesia, and nausea.

Based on the reported AEs, laboratory measurements, vital signs, electrocardiogram (ECG) evaluations, and physical examination findings, fostamatinib can be considered well tolerated.