AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00011
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An Open-label, Single-center Study to Assess the Pharmacokinetics of R406 in Healthy Volunteers when Fostamatinib Disodium 150 mg is Administered Alone and in Combination with Verapamil

Study dates: First subject enrolled: 13 September 2010
Last subject last visit: 01 November 2010

Phase of development: Clinical pharmacology (I)

Principal Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

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

Study center

[redacted]

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 assess the pharmacokinetics of R406 in healthy subjects when fostamatinib was administered alone and in combination with verapamil	Primary: R406 C_{max} and AUC Secondary: R406 $AUC_{(0-t)}$, $t_{1/2z}$, and t_{max}	Pharmacokinetic
Secondary	**Secondary**	
To examine the safety and tolerability of fostamatinib when given in combination with verapamil	Adverse events, vital signs, physical examination, clinical chemistry, hematology, urinalysis, and electrocardiograms	Safety

Two exploratory exploratory objectives were specified for this study but are not reported in the CSR

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 last quantifiable time point, C_{max}: Maximum plasma concentration, $t_{1/2z}$: Terminal half-life, t_{max}: Time to C_{max}

Study design

This was a Phase I, open-label, study to assess the PK of R406 (fostamatinib) in 15 healthy subjects. It was planned that both male and female subjects (of non-childbearing potential) aged 18 to 55 years (inclusive) were to be included in the study, however only male subjects participated. Fostamatinib was administered as a single 150 mg dose in a fixed sequence, both alone (Treatment period 1) and in combination with immediate release verapamil hydrochloride, 80 mg, administered 3 times daily (Treatment period 2).

The washout period was at least 7 days (from the single fostamatinib administration in Treatment period 1 until the first administration of verapamil in Treatment period 2).

Target subject population and sample size

The target population was healthy male and female subjects (of non-childbearing potential) between the ages of 18 and 55 years, inclusive, with a body mass index between 18 and 35 kg/m^2.

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

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Fostamatinib	Oral tablet, 50 mg, single dose, 150 mg (3 tablets)	Patheon	Not applicable	C9I2281
Verapamil hydrochloride (Immediate-release) Calan®	Oral tablet, 80 mg, 3 times daily	Pfizer	Not applicable	C090186

Duration of treatment

Subjects received a single administration of 150 mg fostamatinib on Day 1 during Treatment period 1.

During Treatment period 2, starting on Day 1 and ending on Day 4, subjects received verapamil, 80 mg, 3 times daily as well as a single dose of 150 mg fostamatinib on Day 2.

Statistical methods

Plasma concentrations of R406 and the derived pharmacokinetic parameters were summarized by Treatment period using descriptive statistics.

While this study was not statistically powered in terms of claiming no effect of verapamil on the pharmacokinetics of R406, interpretation of the results was based on the size of the treatment ratios and associated 90% confidence intervals (CIs). To assess the potential effects of verapamil on R406 pharmacokinetics, the plasma pharmacokinetic parameters of area under the plasma concentration-time curve from zero to infinity (AUC) and maximum plasma concentration (C_{max}) were analyzed using a linear-effects model with treatment and volunteer as a fixed effects, following a natural logarithmic transformation. The results were back transformed and presented as geometric least square means, the ratio of these geometric least square means and its associated 90% CI.

All continuous safety data were summarized across all treatments for the absolute value at each scheduled assessment and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each subject were presented with abnormal or out-of-range values flagged.

Subject population

All 15 enrolled male subjects were included in the safety analysis set and the pharmacokinetic analysis set. Twelve (12) of the 15 enrolled subjects completed the study and 3 subjects prematurely withdrew from the study due to non-safety reasons (subject's decision, severe non-compliance to the CSP and lost to follow-up, respectively). Although inclusion of female subjects was permitted only male subjects participated in the study.

Summary of pharmacokinetic results

The results of the stastical comparisons of the primary R406 pharmacokinetic paramaters are presented in Table S3.

Table S3 Statistical comparison of key R406 single dose pharmacokinetic parameters: Pharmacokinetic analysis set

Parameter (units)	Treatment	N	Geometric LS Mean	Ratio (%)	90% CI
AUC (ng*h/mL)	Fostamatinib Alone	13	6464		
	Fostamatinib + Verapamil	13	9007	139.33	(107.79, 180.11)
C_{max} (ng/mL)	Fostamatinib Alone	14	574.8		
	Fostamatinib + Verapamil	14	608.6	105.90	(78.12, 143.55)

Results based on linear model with fixed effects for treatment and subject
LS: Least squares, CI: Confidence interval

The results showed that the exposure of R406 (AUC) was increased by approximately 40% during verapamil co-administration. The effect of verapamil on C_{max} was marginal with an approximate 6% increase.

Higher R406 geometric mean plasma concentrations were observed after fostamatinib and verapamil co-administration compared with fostamatinib alone.

Verapamil co-administration prolonged R406's geometric mean $t_{1/2}$ by 41% (13.5 and 19.1 hours for Treatment periods 1 and 2, respectively).

While differences in individual R406 t_{max} values were observed between Treatment periods, verapamil co-administration did not show a consistent effect on t_{max}. Median (range) t_{max} values were similar across treatments with 1.48 hours (0.78, 4.03) and 1.50 hours (0.48, 4.00) in Treatment periods 1 and 2, respectively.

Summary of safety results

Based on the reported adverse events, hematology, clinical chemistry, urinalysis, vital signs, and electrocardiogram evaluations, the investigational product can be considered well tolerated. Three (3) subjects reported a single adverse event each (headache, skin bacterial infection, and superficial phlebitis), none of which were considered by the investigator to be related to the investigational product. In previous studies with fostamatinib the most commonly reported events were gastrointestinal complaints, headache, and dizziness. No serious adverse events were reported during the study and no safety concerns were raised in this study.