AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00015
Edition Number	1
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An Open-label, Non-randomized, 2-Period, Single-center Study to Assess the Single-dose Pharmacokinetics of R406 in Healthy Subjects when Fostamatinib 150 mg is Administered Alone and in Combination with Rifampicin

Study dates:	First subject enrolled: 26 April 2011 Last subject last visit: 1 July 2011
Phase of development:	Clinical pharmacology (I)

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

Study center(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	**Primary**	
To assess the pharmacokinetics of R406 in healthy subjects when a single dose of fostamatinib is administered alone and in combination with rifampicin	C_{max} and AUC **Secondary** t_{max}, $t_{1/2\lambda z}$, and $AUC_{(0\text{-}t)}$	Pharmacokinetic
Secondary	**Secondary**	
To examine the safety and tolerability of a single dose of fostamatinib in combination with rifampicin	Adverse events, clinical laboratory results, vital signs, electrocardiograms, and physical examinations	Safety

Two exploratory objectives were specified in the clinical study protocol, but results relating to these objectives are not included in this clinical study report.

Study design

This was an open-label, nonrandomized, 2-period study conducted at a single study center to assess the pharmacokinetics of R406 when administered alone and in combination with rifampicin in healthy subjects. In Period 1, a single 150 mg fostamatinib dose was administered on Day 1. In Period 2, a single 150 mg fostamatinib dose was administered on Day 6 and 600 mg rifampicin was administered once a day from Day 1 to Day 8.

Following an up to 28-day screening period, volunteers underwent 2 fixed-sequence treatment periods with a washout period between treatments of at least 7 days between the fostamatinib administration Period 1 and the first rifampicin dose in Period 2. In Period 1, volunteers remained in the clinic from check-in on Day -1 until Day 3, with outpatient visits on Days 4 and 5. Volunteers returned to the clinic on Day -1 of Period 2 and remained confined until Day 8; outpatient visits occurred on Days 9 and 10. A follow-up visit occurred 3 to 5 days following Period 2 discharge.

During each treatment period, serial blood samples for the determination of R406 concentrations were collected prior to and for 96 hours following fostamatinib administration (Day 1 of Period 1 and Day 6 of Period 2).

Target subject population and sample size

The target population was healthy male and female volunteers 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).

This study was not statistically powered in terms of claiming no effect of rifampicin on exposure to R406 (ie, if 90% confidence interval was within 0.80 to 1.25). Interpretation of the results was based on the size of the treatment ratio and associated 90% confidence intervals. To illustrate the size of effect that could be detected, it was estimated that 12 volunteers would provide 80% power to detect a ratio of 0.75 or less in AUC and C_{max}, significant at the 5% level. This was based on pharmacokinetic data from study C788-013 that suggests an intersubject coefficient of determination of 27% for AUC and 29% for C_{max}. Intrasubject variability could be less.

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

Each volunteer received single, oral doses of 150 mg fostamatinib (as three 50-mg tablets) on 2 separate occasions (batch number: CKZN) and 8 doses of 600 mg rifampicin administered once daily over 8 days (batch number: 68443A). Study drug was administered with 240 mL water.

Duration of treatment

This study was comprised of a screening period, 2 treatment periods (separated by a washout period), and a follow-up period. Screening took place within 28 days of the first fostamatinib administration (Period 1 Day 1), Period 1 was 6 days (including Day -1 admission and 2 outpatient visits), and Period 2 was 11 days (including Day -1 admission and 2 outpatient visits). The 2 treatment periods were separated by a washout period of at least 7 days (from Period 1 Day 1 to Period 2 Day 1). Follow-up occurred 3 to 5 days after Period 2 Day 10. The duration of the study was approximately 6 weeks from screening until the last follow-up evaluation.

Statistical methods

To assess the effect of rifampicin on R406, the primary pharmacokinetic parameters (C_{max} and AUC) of R406 were analyzed using an analysis of variance model following a natural logarithmic transformation, with fixed effects for treatment and subject. Least-squares geometric means, 2-sided 95% confidence intervals, ratios of geometric means together with 2-sided 90% confidence intervals of test treatment (fostamatinib plus rifampicin), and reference treatment (fostamatinib alone) were estimated and presented.

Subject population

There were 15 study participants overall; all 15 volunteers completed the study. All volunteers were male and 8 (53.3%) were white, 6 (40.0%) were black, and 1 (6.7%) was Asian. There were no volunteers who reported their ethnicity as Hispanic. The mean (±standard deviation) age was 33 (±10.4) years and ranged from 19 to 50 years. All volunteers were considered healthy at study entry. One volunteer received a single dose of

paracetamol for an adverse event of headache following the completion of dosing in Period 2; otherwise, there were no concomitant medications reported.

Summary of pharmacokinetic results

This study was conducted to determine the effect of rifampicin (a *CYP3A4* inducer) on the pharmacokinetics of R406 (a *CYP3A4* substrate).

The results of the primary statistical comparison of R406 primary PK endpoints following administration of a single dose of fostamatinib 150 mg given alone and in combination with rifampicin dosed to steady state are presented in Table S2.

Table S2 Statistical analysis of primary pharmacokinetic endpoints

				Fostamatinib + rifampicin/ fostamatinib alone	
Parameter (units)	**Treatment**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
AUC	Fostamatinib alone	15	6540		
(ng·h/mL)	Fostamatinib + rifampicin	15	1610	24.6	(19.1, 31.7)
C_{max}	Fostamatinib alone	15	573		
(ng/mL)	Fostamatinib + rifampicin	15	234	40.9	(29.7, 56.3)

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

The results of the statistical analysis indicate that R406 exposure (AUC and C_{max}) decreases when fostamatinib is given in combination with rifampicin. Median t_{max} decreased with the combined treatment (1 hour) when compared to fostamatinib alone (2 hours). Geometric mean $t_{1/2\lambda z}$ decreased with the combined treatment (15 hours) when compared to fostamatinib alone (10.8 hours).

Summary of safety results

All 15 volunteers received all planned doses of investigational product, including single doses of 150 mg fostamatinib administered on Day 1 of Period 1 and on Day 6 of Period 2 and once-daily doses of 600 mg rifampicin administered from Day 1 through Day 8 of Period 2.

There were no deaths, serious adverse events, withdrawals due to adverse events, or adverse events of severe intensity reported during study conduct. Overall, there were 4 adverse events in 4 (26.7%) volunteers. One adverse event of mild pollakiuria, which began during rifampicin alone treatment, was assessed by the Investigator as causally related to rifampicin administration. The remaining adverse events were assessed by the Investigator as mild in

intensity and not related to investigational product and included pain in extremity (2 volunteers) and headache (1 volunteer).

There were no trends or clinically meaningful changes noted in mean or median clinical laboratory results or vital signs throughout the study. There were no adverse events reported for abnormal laboratory, vital sign, or electrocardiogram findings. No clinically relevant changes were noted in electrocardiograms or physical examinations following dosing.