AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00018
Edition Number	1
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An Open-label, Partially Randomized, Five-way Crossover Study in Healthy Male Subjects to Assess the Relative Bioavailability of 100 and 150 mg Fostamatinib Tablets Compared with 50 mg Fostamatinib Tablets

Study dates: First subject enrolled: 4 August 2011
Last subject last visit: 13 October 2011

Phase of development: Clinical pharmacology (I)

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

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 relative bioavailability of R406 in healthy volunteers when fostamatinib is administered as a reformulated 100-mg tablet versus 2 of the Phase III 50-mg tablets	Primary endpoints: R406 plasma AUC and C_{max} Secondary endpoints: R406 $AUC_{(0-t)}$, $t_{1/2,\lambda z}$, and t_{max}	Pharmacokinetic
To assess the relative bioavailability of R406 in healthy volunteers when fostamatinib is administered as a reformulated 150-mg tablet versus 3 of the Phase III 50-mg tablets	Primary endpoints: R406 plasma AUC and C_{max} Secondary endpoints: R406 $AUC_{(0-t)}$, $t_{1/2,\lambda z}$, and t_{max}	Pharmacokinetic
Secondary	**Secondary**	
To estimate the within-subject variability in R406 exposure when fostamatinib 50-mg tablets are administered on 2 separate occasions	Primary endpoints: R406 plasma AUC and C_{max}	Pharmacokinetic
To examine the safety and tolerability of fostamatinib 50-, 100-, and 150-mg tablets	Adverse events, clinical laboratory variables, vital signs, electrocardiograms, and physical examinations,	Safety

R406 is the analyte in plasma for the dephosphorylated drug.
[a] Exploratory objectives, if performed, will be reported outside of this clinical study report.

Study design

This was a Phase I open-label, single-center, 5-period, partially-randomized, crossover study to assess the relative bioavailability of R406 in up to 24 healthy male volunteers when fostamatinib was administered as a single dose as two 50-mg tablets (Treatment A), three 50-mg tablets (Treatment B), one 100-mg tablet (Treatment C), or one 150-mg tablet (Treatment D). Each volunteer was to receive Treatment A on 2 separate occasions.

Following an up to 28-day screening period, volunteers underwent 5 treatment periods. Using a William's design, volunteers were randomly assigned to 1 of 4 sequences for the first 4 periods. Treatment A was given to all volunteers during Period 5.

There was at least a 7-day washout period between doses. For each treatment period, blood samples were collected from predose to 96 hours postdose for the determination of R406 plasma concentrations. Volunteers were admitted to the clinic from the day before dosing (Day -1) to 48 hours postdose (Day 3). Volunteers returned to the clinic on Days 4 and 5 for the 72- and 96-hour blood sample collections. Volunteers participated in a poststudy follow-up visit 3 to 7 days after discharge from the Period 5 visit.

Target subject population and sample size

The target population was healthy male volunteers between the ages of 18 and 55 years, inclusive, with a body mass index between 18.0 and 30.0 kg/m^2 and a minimum body weight of 50 kg. The sample size of 24 healthy volunteers was based on previous experience with fostamatinib and not based on statistical consideration.

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

Fostamatinib was administered orally, as tablets, and as a single dose with 240 mL of water during each treatment period. Each volunteer received the following treatments:

- Treatment A – fostamatinib, two 50-mg tablets (Phase III tablets; batch number C9I2281); once during Periods 1 through 4 (Treatment A1) and again during Period 5 (Treatment A2)
- Treatment B – fostamatinib, three 50-mg tablets (Phase III tablets; batch number: C9I2281)
- Treatment C – fostamatinib, one 100-mg tablet (new formulation with 25% drug loading; batch number: P/5406/04)
- Treatment D – fostamatinib, one 150-mg tablet (new formulation with 38% drug loading; batch number: P/5406/05)

Volunteers were required to fast from 10 hours prior until 4 hours after the fostamatinib dose. Volunteers were restricted from drinking any water from 1 hour predose to 2 hours postdose (excluding the water required for IP administration).

Duration of treatment

The duration of volunteer participation was approximately 90 days. This included a 28-day screening period, five 6-day (including Day -1) treatment periods with at least 7 days of washout between doses, and a follow-up visit 3 to 7 days after discharge from their Period 5 visit. The duration of the study was approximately 2 months from screening until the last follow-up evaluation.

Statistical methods

The relative bioavailability between treatments was assessed between test (Treatments C or D) and reference (Treatments A or B) treatments. Analyses were performed using a linear mixed-effect analysis of variance model using the logarithm of AUC and C_{max} as the response variables.

Using Treatment A data only, estimates of between- and within-subject variability were obtained by employing a linear mixed-effect analysis of variance model. Estimates for the between- and within-subject variability were presented together with the associated 90% confidence intervals for each estimate.

Additional analyses comparing A2 to A1were performed using a linear fixed-effect analysis of variance model using the logarithm of AUC and C_{max} as the response variables.

Subject population

There were 24 study participants overall, 22 volunteers completed the study and 2 volunteers were withdrawn; 1 volunteer due to urticaria and 1 volunteer at the Investigator's discretion. All volunteers were male and 15 (62.5%) were white, 8 (33.3%) were black, and 1 (4.2%) was Asian. One (4.2%) volunteer reported his ethnicity as Hispanic. The mean (±standard deviation) age was 28 (±7) years and ranged from 18 to 51 years. All volunteers were considered healthy at study entry.

There were no important protocol deviations and no cause for concern with respect to concomitant medications received.

Summary of pharmacokinetic results

The results of the primary statistical comparison of R406 AUC and C_{max} are presented in Table S2.

Table S2 Statistical comparison of key R406 pharmacokinetic parameters

Parameter (units)	Treatment	N	Geometric least-squares mean	Pair	Ratio (%)	90% confidence interval
AUC	A1	23	4188	C/A1[a]	111.87	(100.88, 124.06)
(ng·h/mL)	B	24	6135	D/B[a]	107.63	(97.19, 119.18)
	C	23	4685			
	D	23	6603			
	A2	22	4071	A2/A1[b]	97.56	(87.86, 108.33)
C_{max}	A1	23	394.5	C/A1[a]	111.45	(95.00, 130.74)
(ng/mL)	B	24	587.1	D/B[a]	97.04	(82.90, 113.59)
	C	23	439.6			
	D	23	569.7			
	A2	22	380.8	A2/A1[b]	96.62	(81.61, 114.40)

Treatment A1: fostamatinib, two 50-mg tablets (Phase III batch); Treatment B: fostamatinib, three 50-mg tablets (Phase III batch); Treatment C: fostamatinib 100-mg tablet (new formulation); Treatment D: fostamatinib 150-mg tablet (new formulation); Treatment A2: fostamatinib, two 50-mg tablets (Phase III batch) during Period 5.

[a] Results are based on a linear fixed effects model with sequence, period, treatment and subject nested within sequence as fixed effects.

[b] Results are based on a linear fixed effects model with treatment and subject as fixed effects.

Overall, the median R406 t_{max} was 2.00 hours for Treatment A1, and 1.50 hours for Treatments B, C, D, and A2, with an overlapping range of estimates across treatments (0.50, 6.00). R406 geometric mean $t_{1/2,\lambda z}$ estimates were similar across all treatments, within a range of 13.3 hours to 14.8 hours.

At a dose level of 100 mg, based on geometric least-squares mean ratios, the new fostamatinib 100-mg tablet 25% drug-loading formulation R406 AUC was 12% higher (C/A1 ratio of 111.87%) and C_{max} was 11% higher (C/A1 ratio of 111.45%) than the reference (two 50-mg tablets from the Phase III tablet batch).

For the newly formulated 150-mg fostamatinib (Treatment D, 38% drug loading) tablet compared to three 50-mg Phase III tablets (Treatment B) the geometric least-squares mean ratio was 107.63% for R406 AUC, and 97.04% for R406 C_{max}.

Exposure was similar between the 2 occasions when the two 50-mg Phase III batch tablets were administered, with geometric least-squares mean ratios of 97.56% for R406 AUC and 96.62% for R406 C_{max}.

For both AUC and C_{max}, the intersubject and intrasubject variability was estimated from the comparison of Treatment A1 versus Treatment A2 only. The intersubject and intrasubject coefficients of variation for R406 AUC were 23.1% and 20.7%, respectively. The intersubject and intrasubject coefficients of variation for R406 C_{max} were 28.0% and 33.4%, respectively.

Summary of safety results

There were no deaths, serious adverse events, or adverse events of severe intensity reported during study conduct. One volunteer was withdrawn from the study due to an adverse event.

Volunteer E0001002, a 21-year-old, black male, experienced an adverse event of mild urticaria beginning on Study Day 16 (Day 2 of Period 3), which led to study discontinuation. This volunteer had a concurrent adverse event of moderate generalized pruritus and adverse events of mild peripheral edema and mild pyrexia that began on Day 18. Treatment for these adverse events included diphenhydramine and paracetamol and all adverse events were resolved by Day 22. The Investigator assessed these events as at least possibly related to investigational product.

Overall, there were 24 adverse events in 16 (66.7%) volunteers. No clinically meaningful trends were noted in the number of subjects with adverse events overall or for any preferred term. The most frequently reported (2 volunteers or more) adverse events overall were headache in 4 (16.7%) volunteers; nasal congestion in 3 (12.5%) volunteers; and upper respiratory tract infection, laceration, and ecchymosis in 2 (8.3%) volunteers each. Apart from the moderate pruritus, all adverse events were of mild intensity.

There were no trends or clinically meaningful changes noted in mean or median clinical laboratory parameters, vital signs, or electrocardiograms throughout the study. There were no adverse events reported for abnormal clinical laboratory, vital sign, or electrocardiogram findings.