AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00019
Edition Number	1
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An Open-label, Single-center, 2-Part, Randomized Study to Assess the Pharmacokinetics of R406 in Healthy Subjects when Fostamatinib 150 mg is Administered Alone in Fed and Fasted State and in Combination with Ranitidine in Fasted State, and to Assess the Relative Bioavailability of Process Variants of Tablets

Study dates: First subject enrolled: 11 September 2012
Last subject last visit: 21 December 2012

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)

This study was conducted at 1 study center in the United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	To assess the pharmacokinetics of R406 in healthy subjects when fostamatinib (one 150-mg mannitol-based 38% drug-loaded tablet [orange]) was administered alone and in combination with ranitidine in the fasted state	AUC, $C_{max,}$ $AUC_{(0-t),}$ $t_{1/2\lambda z}$, and t_{max}
	Pharmacokinetic	To assess the pharmacokinetics of R406 in healthy subjects when fostamatinib (one 150-mg mannitol-based 38% drug-loaded tablet [orange]) was administered with food and in the fasted state	AUC, $C_{max,}$ $AUC_{(0-t),}$ $t_{1/2\lambda z}$, and t_{max}
	Pharmacokinetic	To assess the pharmacokinetics of R406 in healthy subjects when fostamatinib (three 50-mg microcrystalline cellulose-based 13% drug-loaded tablets [blue]) was administered with food and in the fasted state	AUC, $C_{max,}$ $AUC_{(0-t),}$ $t_{1/2\lambda z}$, and t_{max}
	Pharmacokinetic	To assess the relative bioavailability of R406 in healthy subjects between 2 process variants and a reference batch of fostamatinib tablets (one 150-mg mannitol-based 38% drug-loaded tablet [orange]) in the fasted state	AUC and C_{max}
Secondary	Safety	To examine the safety and tolerability of fostamatinib	Adverse events, laboratory safety assessments, physical examinations, electrocardiograms, and vital signs
Exploratory		To store selected plasma and urine samples for further potential metabolism and pharmacokinetic investigations	If performed, will be reported separately from this clinical study report.
		To collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to fostamatinib and/or associated biomarkers	If performed, will be reported separately from this clinical study report.

AUC area under the plasma concentration-time curve; $AUC_{(0-t)}$ area under the plasma concentration-time curve from zero extrapolated to the time of the last measurable concentration; C_{max} maximum plasma concentration; $t_{1/2\lambda z}$ terminal half-life; t_{max} time to C_{max}.

Study design

The study was conducted as a 2-part, 5-period, 7-treatment, open-label, randomized study.

The 7 treatments administered were as follows:

- Treatment A: one 150-mg mannitol-based 38% drug-loaded tablet (orange, batch variant A), fasted
- Treatment B: one 150-mg mannitol-based 38% drug-loaded tablet (orange, batch variant B), fasted
- Treatment C: one 150-mg mannitol-based 38% drug-loaded tablet (orange, reference), fasted
- Treatment D: one 150-mg mannitol-based 38% drug-loaded tablet (orange, reference), fed
- Treatment E: three 50-mg microcrystalline cellulose-based 13% drug-loaded tablets (blue), fed
- Treatment F: one 150-mg mannitol-based 38% drug-loaded tablet (orange, reference) + antacid (ranitidine), fasted
- Treatment G: three 50-mg microcrystalline cellulose-based 13% drug-loaded tablets (blue), fasted

All 28 volunteers participated in Parts A and B.

Part A included 2 periods (Periods 1 and 2) during which blue tablets were administered either fed or fasted and orange tablets were administered either fed or fasted with ranitidine. Volunteers were enrolled into 1 of 2 treatment pools (Pool I and Pool II) in a 1:1 ratio, and received 2 treatments in a fixed order: volunteers in Pool I received Treatments D and F during Periods 1 and 2, respectively, and volunteers in Pool II received Treatments E and G during Periods 1 and 2, respectively. For Treatments D and E (Period 1, fed), volunteers received a high-fat/high-calorie breakfast 30 minutes prior to investigational product administration. For Treatments F and G (Period 2, fasted), volunteers were fasted from 10 hours prior until 4 hours following investigational product administration.

Part B included 3 periods (Periods 3, 4, and 5) and immediately followed Part A. Part B included the randomized administration of orange tablets, batch variant A tablets, and batch variant B tablets all in the fasted state. This part allowed comparison of the in vitro and in vivo performance of a reference batch versus batch variants and also provided orange tablet fasted data as a reference for comparison to Treatments D and F. All 28 volunteers received Treatments A, B, and C during Periods 3, 4, and 5 in a randomized order. Volunteers were fasted from 10 hours prior until 4 hours following investigational product administration for all treatments.

Screening took place within 28 days of the first investigational product administration in Period 1 (Part A). In both Parts A and B, volunteers were admitted to the clinical pharmacology unit on Day -1 of each period and were resident until discharge on Day 3 of each period (3 days and 3 nights). Volunteers received investigational product on Day 1 of each period, followed by safety and serial pharmacokinetic assessments. Volunteers returned for 2 outpatient visits on Days 4 and 5 of each period for pharmacokinetic sample collection and safety assessments. All periods were separated by a washout period of at least 7 days (from investigational product administration on Day 1 of the previous period until investigational product administration on Day 1 of the next period). There was a follow-up visit 3 to 5 days after discharge from Period 5, which included routine safety assessments.

Target subject population and sample size

Healthy male and female (nonchildbearing potential) volunteers aged between 18 and 55 years (inclusive), with body mass index of between 18 and 30 kg/m^2, and minimum weight of 50 kg were eligible for study participation.

This study was not statistically powered in terms of claiming no effect of ranitidine or food on the 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 interval. To illustrate the size of effect that could be detected, 12 volunteers would provide 80% power to detect a ratio of 0.75 or less in AUC and C_{max}, using a 2-sided 5% significance test. This is based on pharmacokinetic data from a bioequivalence study (D4300C00018) that suggests an intrasubject coefficient of variation of 33.4% for C_{max}.

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

The following 4 fostamatinib formulations were administered as single oral doses during this study:

- one 150-mg mannitol-based 38% drug-loaded tablet (orange, batch variant A, Lot Number 12-002953AZ [P/5289/40], primary 12-002959AZ)
- one 150-mg mannitol-based 38% drug-loaded tablet (orange, batch variant B, Lot Number 12-002472AZ/10751I12, blister strips)
- one 150-mg mannitol-based 38% drug-loaded tablet (orange, reference, Lot Number 3201, 10219D12)
- three 50-mg microcrystalline cellulose-based 13% drug-loaded tablets (blue, Lot Number GPKZ)

Additionally, a single 150-mg ranitidine tablet (Lot Number 2ZP2286) was administered concomitantly with 1 of the fostamatinib formulations (one 150-mg mannitol-based 38% drug-loaded tablet, orange, reference) during 1 treatment (Treatment F).

There was no active comparator.

Duration of treatment

The study consisted of a screening period of up to 28 days before the first administration of fostamatinib in Treatment Period 1. Volunteers received a single dose of fostamatinib in each of the 5 periods, with at least a 7-day washout between doses. The follow-up visit occurred 3 to 5 days after discharge from Period 5 and included routine safety assessments.

Duration of participation was approximately 10 weeks for each volunteer.

Statistical methods

Plasma concentrations of all analytes and their derived pharmacokinetic parameters were summarized by treatment using descriptive statistics and presented in listings, tables, and figures as appropriate. For the primary objectives to assess food effect and drug-interaction with antacid, plasma pharmacokinetic parameters of AUC and C_{max} were analyzed for each treatment comparison of interest using a paired t-test, following a natural logarithmic transformation. To assess the relative bioavailability, plasma pharmacokinetic parameters of AUC and C_{max} were analyzed using a linear fixed-effects analysis of variance model with treatment, period, volunteer nested within sequence, and sequence included as the fixed effect in the model. The results were back transformed and presented as geometric least-squares means, the ratio of these geometric least-squares means, and the associated 90% confidence intervals.

Tabulations and listings of data for vital signs, electrocardiograms, physical examinations, and clinical laboratory tests were presented. For clinical laboratory tests, listings of values for each volunteer were presented with abnormal or out-of-range values flagged. Adverse events were summarized by Preferred Term and System Organ Class for each treatment.

Subject population

Twenty-eight (28) healthy male and female (nonchildbearing potential) volunteers (mean age of 31 years) were randomly assigned to receive treatment. Of the 28 randomized volunteers, 26 (92.9%) completed all planned study treatments. One (3.6%) volunteer who experienced a nonserious adverse event of hematochezia (blood in stool) was withdrawn from the study. One (3.6%) volunteer discontinued due to subject decision. All 28 volunteers were included in both the pharmacokinetic and safety analysis sets.

Summary of pharmacokinetic results

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

Table S2 Statistical comparison of key R406 pharmacokinetic parameters for all treatment groups

					Pairwise Comparisons		
Parameter (unit)	**Treatment**	**N**	**Geometric LS Mean**	**95% CI**	**Pair**	**Ratio%**	**90% CI**
Treatment A, B, and C (bioavailability)							
AUC (ng·h/ml)[a]	A	28	7263	(6652,7931)	A/C	103.71	(93.35, 115.22)
	B	28	7107	(6509, 7761)	B/C	101.48	(91.33, 112.76)
	C	27	7003	(6397,7667)			
C_{max} (ng/ml)[a]	A	28	620.1	(531.3, 723.8)	A/C	102.07	(84.83, 122.80)
	B	28	593.5	(508.6, 692.7)	B/C	97.69	(81.18, 117.56)
	C	27	607.6	(518.2,712.4)			
Treatment C versus D (fasted versus fed)							
AUC (ng·h/ml)[b]	C	13	6561	(5483,7850)	D/C	123.26	(102.13, 148.77)
	D	13	8087	(6749,9690)			
C_{max} (ng/ml)[b]	C	13	594.3	(450.3,784.3)	D/C	114.53	(88.68, 147.91)
	D	13	680.6	(546.0,848.5)			
Treatment E versus G (fed versus fasted)							
AUC (ng·h/ml)[b]	E	14	9575	(7869,11650)	E/G	113.96	(98.88,131.33)
	G	14	8403	(6715,10510)			
C_{max} (ng/ml)[b]	E	14	754.5	(668.9,851.1)	E/G	93.41	(77.30, 112.88)
	G	14	807.8	(621.5,1050)			
Treatment C versus F (fostamatinib plus ranitidine versus fostamatinib alone)							
AUC (ng·h/ml)[b]	C	13	6561	(5483,7850)	F/C	97.22	(79.84, 118.39)
	F	13	6378	(4876,8344)			
C_{max} (ng/ml)[b]	C	13	594.3	(450.3,784.3)	F/C	97.59	(70.85, 134.40)
	F	13	579.9	(427.3,787.1)			

CI confidence interval; LS least-squares.
Treatment A: one 150-mg mannitol-based 38% drug-loaded tablet (orange, batch variant A), fasted
Treatment B: one 150-mg mannitol-based 38% drug-loaded tablet (orange, batch variant B), fasted
Treatment C: one 150-mg mannitol-based 38% drug-loaded tablet (orange, reference), fasted
Treatment D: one 150-mg mannitol-based 38% drug-loaded tablet (orange, reference), fed
Treatment E: three 50-mg microcrystalline cellulose-based 13% drug-loaded tablets (blue), fed
Treatment F: one 150-mg mannitol-based 38% drug-loaded tablet (orange, reference) + antacid, fasted
Treatment G: three 50-mg microcrystalline cellulose-based 13% drug-loaded tablets (blue), fasted

[a] Results based on linear fixed-effect model with treatment, period, sequence, and subject nested within sequence included as fixed effects for log transformed pharmacokinetic parameters.

[b] Results based on paired t-test. Subjects who completed both treatment periods were included in the paired treatment comparison.

When Treatment A was compared to the reference formulation Treatment C, the AUC and C_{max} geometric least-square mean ratios were approximately 104% and 102%, respectively.

When Treatment B was compared to Treatment C, the AUC and C_{max} geometric least-squares mean ratios were approximately 101% and 98%, respectively.

When Treatment D (one 150-mg reference tablet, fed) was compared to Treatment C (one 150-mg reference tablet, fasted) to assess the effect of food, the AUC and C_{max} geometric least-squares mean ratios showed a slight increase of approximately 23% and 15%, respectively.

When Treatment E (three 50-mg tablet formulation, fed) was compared to Treatment G (three 50-mg tablet formulation, fasted) to assess the effect of food, the geometric least-squares mean ratio for AUC showed a slight increase of approximately 14% and for C_{max} showed a slight decrease of approximately 7%.

When Treatment F (one fostamatinib 150-mg reference tablet, with 150 mg ranitidine, fasted) was compared to Treatment C (one 150-mg reference tablet, fasted) to assess a drug-drug interaction, the geometric least-squares mean ratio for AUC and C_{max} showed a slight decrease of approximately 3% for both.

The observed data for the reference formulation (Treatment C) is similar to what has been previously observed with fostamatinib clinical pharmacokinetic studies.

Summary of safety results

There were no deaths or serious adverse events reported. One (3.6%) volunteer was withdrawn from the study due to a nonserious adverse event of hematochezia (blood in stool, thought on examination to be due to internal hemorrhoids) that occurred on Day 1 of Period 4. The adverse event of hematochezia was assessed by the Investigator as mild in severity and not related to investigational product.

In Part A, adverse events were reported for 9 (32.1%) volunteers during the study. Adverse events were reported for 5 (35.7%) volunteers during Treatment D, 3 (21.4%) volunteers during Treatment E, and 2 (14.3%) volunteers during Treatment F. No volunteers experienced adverse events during Treatment G. In Part A, all AEs were reported for only 1 volunteer each. The most frequently reported adverse events were skin and subcutaneous tissue disorders (contact dermatitis, ecchymosis, and erythema) which were reported for 3 (10.7%) volunteers overall. In Part A, adverse events assessed by the Investigator as causally related to investigational product were reported for 2 (7.1%) volunteers overall. Causally related adverse events included dizziness in 1 volunteer who received Treatment F and nausea in 1 volunteer who received Treatment D. All adverse events in Part A were mild in severity.

In Part B, adverse events were reported for 13 (46.4%) volunteers during the study. Adverse events were reported for 6 (21.4%) volunteers during Treatment A, 3 (10.7%) volunteers during Treatment B, and 4 (14.8%) volunteers during Treatment C. In Part B, the most frequently reported adverse events overall were excoriation, nasal congestion, and ecchymosis, each of which was reported for 2 (7.1%) volunteers overall. In Part B, adverse

events assessed by the Investigator as causally related to investigational product were reported for 2 (7.1%) volunteers overall. Causally related adverse events included abdominal pain and diarrhea in 1 volunteer who received Treatment A, and nausea in 1 volunteer who received Treatment B. All adverse events in Part B were mild in severity with the exception of a moderate AE of abdominal pain in 1 subject which was moderate in severity.

Overall, there were no trends or clinically relevant changes noted in clinical laboratory, vital sign, electrocardiogram, or physical examination findings.