AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00020
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An Open-label, Single-center, Randomized, 4-way Crossover Study to Assess the Bioequivalence of R406 in Healthy Volunteers When 100 and 150 mg of Fostamatinib are Administered as the 13% Drug-loaded Tablet Versus the 38% Drug-loaded Tablet in the Fasted State (Part A)

An Open-label, Single-center, Randomized, 2-way Crossover Study to Assess the Bioequivalence of R406 in Healthy Volunteers When 150 mg of Fostamatinib is Administered as the 13% Drug-loaded Tablet Versus the 38% Drug-loaded Tablet in the Fed State (Part B)

Study dates: First subject enrolled: 19 July 2012
Last subject last visit: 05 March 2013

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 center in the United States.

Publications

None at the time of this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables for Part A

Objective		Outcome Variable
Priority	**Description**	**Description**
Primary	To assess the bioequivalence of R406 in healthy subjects when fostamatinib is administered as two 50-mg microcrystalline cellulose (MCC)-based 13% drug-loaded tablets versus one 100-mg mannitol-based 38% drug-loaded tablet and three 50-mg MCC-based 13% drug-loaded tablets versus one 150-mg mannitol-based 38% drug-loaded tablet	R406 area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC) and observed maximum plasma concentration (C_{max}) were the primary parameters
Secondary	To assess the exposure (AUC and C_{max}) proportionality for mannitol-based 38% drug-loaded tablets and MCC-based 13% drug-loaded tablets	R406 area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{0-t}), terminal half-life ($t_{1/2,\lambda z}$), lambda z, and time to C_{max} (t_{max}) were the secondary parameters. Additionally, dose normalized AUC, AUC_{0-t}, and C_{max} were reported for Part A.
	To examine the safety and tolerability of fostamatinib 50-, 100-, and 150-mg tablets	Adverse events, blood pressure, pulse rate, physical examinations, electrocardiograms, and laboratory assessments (chemistry, hematology, and urinalysis)
Exploratory	To store selected plasma samples for further potential metabolism and pharmacokinetic investigations	Exploratory pharmacokinetic research
	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	Genetic and biomarker exploratory research

Table S2 Objectives and outcome variables for Part B

Objective		Outcome Variable
Priority	**Description**	**Description**
Primary	To assess the bioequivalence of R406 in healthy subjects when fostamatinib is administered orally under fed conditions as three 50-mg MCC-based 13% drug-loaded tablets versus one 150-mg mannitol-based 38% drug-loaded tablet	R406 area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC) and observed maximum plasma concentration (C_{max}) were the primary parameters
		R406 area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{0-t}), terminal half-life ($t_{1/2,\lambda z}$), and time to C_{max} (t_{max}) were the secondary parameters
Secondary	To examine the safety and tolerability of fostamatinib 50- and 150-mg tablets when administered orally under fed conditions	Adverse events, blood pressure, pulse rate, physical examinations, electrocardiograms, and laboratory assessments (chemistry, hematology, and urinalysis)
Exploratory	To store selected plasma samples for further potential metabolism and pharmacokinetic investigations	Exploratory pharmacokinetic research
	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	Genetic and biomarker exploratory research

Study design

Part A (fasted)

This was a Phase I, open-label, single-center, 4-treatment, 4-period, randomized, crossover study to assess the bioequivalence of R406 in healthy volunteers when 100 and 150 mg of fostamatinib were administered as an MCC-based 13% drug-loaded tablet versus the mannitol-based 38% drug-loaded tablet.

The 4 treatments in this part of the study were administered orally under fasted conditions and included:

- Treatment A: two 50-mg MCC-based 13% drug-loaded tablets
- Treatment B: one 100-mg mannitol-based 38% drug-loaded tablet
- Treatment C: three 50-mg MCC-based 13% drug-loaded tablets
- Treatment D: one 150-mg mannitol-based 38% drug-loaded tablet

Up to 44 male and female volunteers were enrolled in the study and randomly assigned to 1 of 8 treatment sequences. Treatment sequences were determined using two 2x2 crossover designs in sequence, one for Treatments A and B, and one for Treatments C and D.

Following a screening period of up to 28 days, volunteers were admitted to the study center on Day -1 of each treatment period and remained resident until completion of Day 3 procedures. Volunteers returned to the study center on Days 4 and 5 of each treatment period on an outpatient basis. There was at least a 7-day washout period between doses. A follow-up visit was conducted 3 to 5 days after the study center discharge in Treatment Period 4.

Serial blood samples for the determination of R406 concentrations were collected up to 96 hours following fostamatinib dosing in each treatment period. Safety and tolerability assessments included adverse events, blood pressure, pulse rate, physical examinations, electrocardiograms, and laboratory assessments (chemistry, hematology, and urinalysis).

Part B (fed)

This was a Phase I, open-label, single-center, 2-treatment, 2-period, randomized, crossover study to assess the bioequivalence of R406 in healthy volunteers when 150 mg of fostamatinib was administered orally under fed conditions as three 50-mg MCC-based 13% drug-loaded tablets versus one 150-mg mannitol-based 38% drug-loaded tablet. This was the second portion (Part B) of a 2-part study.

The 2 treatments in this part of the study were administered orally under fed conditions and included:

- Treatment E: three 50-mg MCC-based 13% drug-loaded tablets
- Treatment F: one 150-mg mannitol-based 38% drug-loaded tablet

Up to 44 male and female volunteers were enrolled in Part B of the study (38 to complete) and randomly assigned to 1 of 2 treatment sequences (EF or FE). Following a screening period of up to 28 days, volunteers were admitted to the study center on Day -1 of each treatment period and remained resident until completion of Day 3 procedures. Volunteers returned to the study center on Days 4 and 5 of each treatment period on an outpatient basis. There was at least a 7-day washout period between doses. A follow-up visit was conducted 3 to 5 days after the study center discharge in Treatment Period 2.

Serial blood samples for the determination of R406 concentrations were collected up to 96 hours following fostamatinib dosing in each treatment period. Safety and tolerability assessments included adverse events, blood pressure, pulse rate, physical examinations, electrocardiograms, and laboratory assessments (chemistry, hematology, and urinalysis).

Target subject population and sample size

The target population for both parts was healthy male and female volunteers; females were not lactating and were not of childbearing potential. Volunteers were from 18 to 55 years of age,

inclusive, with a body mass index from 18 to 30 kg/m^2, inclusive, and a minimum body weight of 50 kg.

Based on the estimate of within-subject coefficient of variation (%) from Study D4300C00018 (33.4%), to achieve 80% power to show bioequivalence required 38 volunteers. Up to 44 healthy volunteers were to be recruited to ensure 38 completed.

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

Batch numbers: Fostamatinib 50 mg blue tablet: GPKZ; fostamatinib 100 mg orange tablet: 2201, 10216B12; fostamatinib 150 mg orange tablet: 3201, 10219D12

Part A: Fostamatinib as 50-, 100-, and 150-mg tablet(s) was administered orally under fasted conditions as a single dose on Day 1 during each treatment period. Each volunteer received Treatments A, B, C, and D according to a randomized sequence.

Part B: Fostamatinib as 50- and 150-mg tablet(s) was administered orally under fed conditions as single doses on Day 1 during each treatment period. Each volunteer receive Treatments E and F according to a randomized sequence.

Duration of treatment

Part A: The duration of the study for each volunteer was up to 59 days, including a screening period (Visit 1) of up to 28 days, 4 treatment periods consisting of 4 residential days and 2 nonresidential days (Visits 2, 3, 4, and 5), washout periods of at least 7 days between each dose, and a follow-up visit (Visit 5) 3 to 5 days from clinic discharge after the last treatment period.

Part B: The duration of the study for each volunteer was up to 50 days, including a screening period (Visit 1) of up to 28 days, 2 treatment periods consisting of 4 residential days and 2 nonresidential days (Visits 2 and 3), washout periods of at least 7 days between each dose, and a follow-up visit (Visit 4) 3 to 5 days from clinic discharge after the last treatment period.

Statistical methods

Part A: Bioequivalence was assessed between Treatments A (reference) and B (test) and between Treatments C (reference) and D (test). Analyses were performed using a linear fixed-effects analysis of variance model using the natural logarithm of AUC and C_{max} as the response variables. Geometric means together with confidence intervals (2-sided 95%) for AUC and C_{max} were estimated and presented. Also, ratios of geometric means together with confidence intervals (2-sided 90%) were estimated and presented. For each comparison separately, if the 90% confidence intervals for both AUC and C_{max} were entirely contained within 80.00% and 125.00%, it was concluded that the 2 formulations were bioequivalent. However, if the 90% confidence intervals for both AUC and C_{max} were not entirely contained within 80.00% and 125.00%, it was concluded that the 2 formulations were not bioequivalent.

The analysis described above for AUC and C_{max} were repeated for AUC_{0-t}. Ratios of geometric means together with confidence intervals (2-sided 90%) were estimated and presented; however, no conclusions were drawn with regard to bioequivalence.

Exposure proportionality was explored by graphical assessment of dose-normalized exposure parameters (AUC and C_{max}).

Part B: Bioequivalence was assessed between Treatments E (reference) and F (test). Analyses were performed using a linear fixed-effects analysis of variance model using the natural logarithm of AUC and C_{max} as the response variables. Geometric means together with confidence intervals (2-sided 95%) for AUC and C_{max} were estimated and presented. Also, ratios of geometric means together with confidence intervals (2-sided 90%) were estimated and presented. For each comparison separately, if the 90% confidence intervals for both AUC and C_{max} were entirely contained within 80.00% and 125.00%, it was concluded that the 2 formulations were bioequivalent. However, if the 90% confidence intervals for both AUC and C_{max} were not entirely contained within 80.00% and 125.00%, it was concluded that the 2 formulations were not bioequivalent.

The analysis described above for AUC and C_{max} were repeated for AUC_{0-t}. Ratios of geometric means together with confidence intervals (2-sided 90%) were estimated and presented; however, no conclusions were drawn with regard to bioequivalence.

Subject population

All 88 study volunteers met the study entry criteria and were enrolled in the study (44 volunteers each in Part A and Part B). Overall, there were 84 (95.5%) male and 4 (4.5%) female volunteers; 44 (50.0%) volunteers were white, 40 (45.5%) volunteers were black, 3 (3.4%) volunteers were American Indian/Alaskan, and 1 (1.1%) volunteer was Asian.

In Part A, 42 volunteers completed the study per protocol: 1 volunteer was discontinued due to an adverse event, and 1 volunteer was considered lost to follow-up. In Part B, 43 volunteers completed the study per protocol and 1 volunteer was withdrawn due to severe noncompliance with the protocol (positive test for amphetamines). All 88 volunteers were included in the safety and pharmacokinetic analysis sets.

Summary of pharmacokinetic results

Table S3 Statistical comparison of key R406 pharmacokinetic parameters

Parameter	Treatment	N	Geometric LS Mean	Pair	Ratio	90% CI
AUC (ng·h/mL)	A	44	4966			
	B	44	5468	B/A	110.10	(103.30, 117.36)
	C	43	7710			
	D	42	7669	D/C	99.47	(93.21, 106.15)
	E	44	9372			
	F	43	8597	F/E	91.73	(84.85, 99.17)
$AUC_{(0-t)}$ (ng·h/mL)	A	44	4820			
	B	44	5320	B/A	110.38	(103.24, 118.02)
	C	43	7549			
	D	42	7460	D/C	98.82	(92.31, 105.78)
	E	44	9125			
	F	43	8361	F/E	91.62	(84.48, 99.36)
C_{max} (ng/mL)	A	44	454.0			
	B	44	497.1	B/A	109.49	(97.35, 123.15)
	C	43	656.2			
	D	42	625.4	D/C	95.31	(84.55, 107.43)
	E	44	621.1			
	F	43	538.2	F/E	86.66	(75.48, 99.50)

CI confidence intervals; n as number of observations; LS least-squares. Results based on linear fixed-effects analysis of variance model using the natural logarithm of AUC and Cmax as the response variables, sequence, Period, Treatment, and volunteer nested within sequence as fixed effects.
Treatment A: two 50-mg MCC-based 13% drug-loaded tablets (fasted conditions);
Treatment B: one 100-mg mannitol-based 38% drug-loaded tablet (fasted conditions);
Treatment C: three 50-mg MCC-based 13% drug-loaded tablets (fasted conditions);
Treatment D: one 150-mg mannitol-based 38% drug-loaded tablet (fasted conditions);
Treatment E: three 50-mg MCC-based 13% drug-loaded tablets (fed conditions);
Treatment F: one 150-mg mannitol-based 38% drug-loaded tablet (fed conditions).
Source: Table 11.2.4 and Table 11.2.8

Under fasted conditions, both the 100 -and 150-mg mannitol-based 38% drug-loaded fostamatinib tablets (Treatments B and D) are bioequivalent to respective doses of MCC-based 13% drug-loaded tablets (Treatments A and C) with the 90% confidence intervals for AUC and C_{max} completely within the 80.00% to 125.00% bioequivalence window. Additionally, R406 appears to display dose proportionality regardless of formulation, at the 100 mg and 150 mg fostamatinib dose level.

Under fed conditions, the R406 geometric least squares mean ratio (90% confidence interval) was 91.73 (84.85, 99.17) and within the bioequivalence window for AUC but 86.66 (75.48, 99.50) and outside the bioequivalence window for C_{max} when comparing the 150-mg mannitol-based 38% tablet (Treatment F) to three 50-mg MCC-based 13% drug-loaded tablets (Treatment E).

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 for an adverse event of increased alanine aminotransferase after participating in 3 study periods. There were no trends observed in the frequency of adverse events between treatments or in individual preferred terms during either study part. There were 3 adverse events of moderate intensity (increased alanine aminotransferase and increased creatine kinase in a single volunteer and infectious mononucleosis in 1 volunteer); otherwise, all adverse events were assessed by the Investigator as mild in intensity. There were 6 volunteers overall who experienced adverse event related to infections (upper respiratory tract infection, oral herpes, infectious mononucleosis, and folliculitis); the duration and intensity of the infections for these subjects was not unusual.

There were no trends or clinically relevant changes following dosing in mean or median clinical laboratory, vital sign, or electrocardiogram values.

One volunteer was withdrawn from the study for increased alanine aminotransferase values beginning at the admission visit for Period 2 (approximately 20 days after the dose given in Period 3). This volunteer had a concurrent increase in creatine kinase; the increase in creatine kinase resolved 12 days later and the increased alanine aminotransferase was ongoing, but improving, at study conclusion. The volunteer admitted to recent strenuous work activity as well as recent alcohol intake prior to returning for Treatment Period 4.

Otherwise, there were no clinically relevant changes in individual clinical laboratory, vital sign, or electrocardiogram findings following dosing.