Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00016
Edition Number	1
Date	21 March 2011

An Open-label, Randomized, Four-way Crossover Study in Healthy Male Subjects to Assess the Relative Bioavailability of 4 Different Fostamatinib Tablets

Study dates:	First subject enrolled: 22 September 2010 Last subject last visit: 19 November 2010
Phase of development:	Clinical pharmacology (I)
International Co-ordinating Investigator:	[redacted]
Sponsor's Responsible Medical Officer:	

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

Study centre(s)

[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 relative bioavailability of R406 in healthy volunteers when fostamatinib is administered as 50-mg tablets versus 3 different 100-mg tablet batches with different dissolution profiles under low pH conditions	C_{max}, t_{max}, λ_z, $t_{1/2,\lambda z}$, AUC_{0-t}, and AUC	Pharmacokinetic
To assess the relative bioavailability of R406 in healthy volunteers when fostamatinib is administered as 3 different 100-mg tablet batches, each with a different dissolution profile under low pH conditions	C_{max}, t_{max}, λ_z, $t_{1/2,\lambda z}$, AUC_{0-t}, and AUC	Pharmacokinetic
Secondary	**Secondary**	
To examine the safety and tolerability of fostamatinib 50-mg and 100-mg tablet batches	Adverse events, clinical laboratory results, vital signs, electrocardiograms, and physical examinations	Safety
To assess the relationship between the dissolution of fostamatinib tablets and the in vivo exposure to R406	Correlation of the percent dissolved R788 after 30 min with C_{max} and AUC	Pharmacokinetic

[a] Results from exploratory objectives, including genetic and biomarker research, potential metabolism and pharmacokinetic investigations, and population pharmacokinetic modeling, will be reported separately from this clinical study report.

Study design

Fostamatinib disodium, also referred to as R788, is a prodrug that undergoes dephosphorylation in the gastrointestinal tract through the action of gut alkaline phosphatase to produce R406. This was a Phase I open-label, single-center, four-period, randomized, crossover study to assess the relative bioavailability of R406 in healthy male volunteers when fostamatinib was administered as a single dose as either two 50-mg tablets (Treatment A), or as a single 100-mg tablet from 1 of 3 different batches (Treatment B, C, or D), each with a different dissolution profile under low pH conditions.

Following an up to 28-day screening period, volunteers underwent 4 treatment periods. Volunteers were randomly assigned to 1 of 4 sequences in a crossover manner utilizing a William's design.

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 Treatment Period 4 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 35.0 kg/m^2 and a minimum body weight of 50 kg.

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

Each volunteer received single, oral doses of fostamatinib as two 50-mg tablets (Treatment A) and one 100-mg tablet from each of 3 formulation batches (Treatments B, C, and D) in 4 separate treatment periods. Study drug was administered with 240 mL water. Batch numbers: C912281, C8G0180, C9C20301, and C912283 for Treatments A through D, respectively.

Duration of treatment

The duration of volunteer participation was approximately 63 days. This included a 28-day screening period, four 5-day 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 4 visit. The duration of the study was approximately 2 months from screening until the last follow-up evaluation.

Statistical methods

Plasma concentrations of R406 and the derived pharmacokinetic parameters were summarized by treatment using descriptive statistics. This study was not formally powered. The interpretation of the results was based on the size of the treatment ratios and associated 90% confidence intervals. To assess the potential difference in bioavailability between batches, the plasma pharmacokinetic parameters were analyzed using a linear mixed-effects model, following a natural logarithmic transformation. The results were back transformed and presented as geometric least-squares means, the ratio of these geometric least-squares means, and its associated 90% confidence interval.

Sensitivity analyses of plasma pharmacokinetic parameters of AUC and C_{max} were performed using a paired t-test, following a natural logarithmic transformation. The results were back transformed and presented as geometric least-squares means, the ratio of these geometric least square means and its associated 90% confidence interval.

Adverse events were summarized by Preferred Term and System Organ Class by treatment. Tabulations and listings of data for vital signs, 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.

Subject population

There were 24 study participants overall; 22 volunteers completed all 4 treatment periods per protocol. One volunteer was withdrawn due an adverse event and 1 volunteer withdrew consent for personal reasons. All volunteers were male and the race for 17 (70.8%) volunteers was white and for 7 (29.2%) volunteers was black. The mean age was 29 ±9.3 years and ranged from 19 to 51 years. All volunteers were considered healthy and there were no ongoing concomitant medications at study entry.

Summary of pharmacokinetic results

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

Table S2 Statistical comparison of key R406 pharmacokinetic parameters

Parameter (units)	Treatment	N	Geometric Least-squares mean	Pair	Ratio (%)	90% Confidence intervals
AUC	A	24	4487	B/A	99.44	(87.68, 112.79)
(ng·h/mL)	B	24	4462	C/A	112.11	(98.67, 127.38)
	C	23	5030	D/A	100.88	(88.79, 114.63)
	D	23	4526	C/B	112.73	(99.22, 128.09)
				D/B	101.45	(89.28, 115.27)
				D/C	89.99	(79.07, 102.42)
C_{max}	A	24	345.2	B/A	100.50	(82.03, 123.11)
(ng/mL)	B	24	346.9	C/A	119.04	(96.90, 146.25)
	C	23	410.9	D/A	85.36	(69.48, 104.87)
	D	23	294.7	C/B	118.46	(96.42, 145.53)
				D/B	84.94	(69.14, 104.36)
				D/C	71.71	(58.22, 88.33)

Notes: Results based on linear mixed effect analysis of variance model with terms for sequence, period, and treatment as fixed effect, and volunteer within sequence as a random effect. Treatment A: Fostamatinib 50 mg tablet x 2; Treatment B: Fostamatinib 100 mg tablet (Batch 1); Treatment C: Fostamatinib 100 mg tablet (Batch 2); Treatment D: Fostamatinib 100 mg tablet (Batch 3).

Overall the median R406 t_{max} was 1.50, 2.00, 2.00, and 3.00 hours for Treatment A, B, C, and D, respectively, with an overlapping range of estimates across treatments (0.50, 6.00 hours). R406 geometric mean $t_{1/2\lambda z}$ estimates were similar across treatments, within a range of 13.2 to 15.3 hours.

Treatment A (two 50-mg tablets) and Treatment B (100-mg high dissolution tablet) demonstrated comparable systemic exposure for both AUC and C_{max}.

While the shape of the plasma concentration-time profile for Treatment C (medium dissolution) was similar to that for Treatments A and B, the R406 AUC and C_{max} values were approximately 12% and 19% higher, respectively. The reason for higher exposure for Treatment C is not known.

Treatment D, which had the lowest dissolution at low pH, demonstrated an altered concentration-time profile compared to the other 3 treatments with a slower absorption phase characterized by a lower C_{max} and later t_{max}. Total exposure to R406 as expressed by AUC was comparable to both Treatments A and B. This profile could be considered to be consistent with a formulation that had low dissolution at low pH (ie, conditions in the stomach).

No clear trend was noted between R406 exposure and the mean batch dissolution of fostamatinib observed at 30 minutes in vitro.

Summary of safety results

There were no deaths, serious adverse events, other significant adverse events, or adverse events of severe intensity. One volunteer was withdrawn from the study due to an adverse event of chlamydial urethritis (assessed as moderate and not related to investigational product). The number of volunteers with adverse events was higher during Treatments A (6 [25%]) and C (6 [26%]) than during Treatments B (3 [13%]) and D (2 [9%]); however, there were no treatment-related trends noted in individual preferred terms. The most frequently reported adverse events were headache and superficial thrombophlebitis occurring in 6 (25%) and 3 (13%) volunteers, respectively. There were 3 adverse events in 3 volunteers (13%) that were assessed by the Investigator as related to investigational product, including dizziness (Treatment D) and headache (1 adverse event each during Treatments B and D). The headache during Treatment D was assessed as moderate in intensity and the remaining treatment-related adverse events were of mild intensity.

There were no clinically relevant treatment-related changes or trends in any laboratory variables, vital signs, or electrocardiograms measured in volunteers exposed to fostamatinib during the study.

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