Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00007
Edition Number	1
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A Phase I, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Tolerability and Pharmacokinetics of Oral Fostamatinib Disodium in Healthy Japanese and White Subjects After Single and Multiple Ascending Doses

Study dates: First subject enrolled: 26 July 2010
Last subject last visit: 22 May 2011

Phase of development: Clinical Pharmacology (1)

Principal Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

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

Study centre(s)

The study was conducted at a single-center (Site 100),

[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 investigate the safety and tolerability of single and multiple doses of fostamatinib administered orally to healthy Japanese subjects.	Adverse events Laboratory variables: chemistry, hematology and urinalysis Vital signs: Blood pressure, heart rate, Body temperature dECG/ECG: resting 12-lead ECG, real time telemetry Physical examinations	safety
Secondary	**Secondary**	
1. To determine plasma and urine PK parameters, including intra-subject variability, following oral administration of fostamatinib in healthy Japanese subjects compared to healthy White subjects. 2. To investigate the relationship between variations in the gene encoding UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) and the safety and tolerability of fostamatinib in the study population.	PK parameters were determined using plasma R406 concentration-time data from Day 1: C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, AUCτ (AUC from zero to the end of the dosing interval [$AUC_{(0-12)}$ for twice daily dosing; $AUC_{(0-24)}$ for once daily dosing]), $AUC_{(0-48)}$, λz, $t_{½}$, and % extrapolated AUC. PK parameters were determined from urine data: $Ae_{(0-48)}$ and $CL_{R(0-48)}$ for R406 and $Ae_{(0-48)}$ for N-glucuronide of R406. PK parameters were determined using plasma R406 concentration data from Day 8 (Day 5 of multiple dosing) (Cohorts 3, 4, 6 and 7): $C_{max,ss}$, $t_{max,ss}$, $AUC_{(0-t)}$, and AUC_{ss}. PK parameters were determined using plasma R406 concentration data from Day 10 (Day 7 of multiple dosing): $C_{max,ss}$, $t_{max,ss}$, $AUC_{(0-t)}$, AUC_{ss} (ie, 0-12 hours for twice daily dosing and 0-24 hours for once daily dosing), λz, and $t_{½}$. PK parameters were determined from urine data: for R406 $Ae_{(0-12)}$, and $CL_{R(0-12)}$), for twice daily groups and $Ae_{(0-24)}$ and $CL_{R(0-24)}$ for daily groups; Ae values were calculated for N-glucuronide of R406 Accumulation ratios (Rac) for R406 were calculated using AUC_{ss} from Day 10 and AUCτ from Day 1, as well as C_{max} from each day.	PK

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
	PK parameters were determined using plasma R788 concentration-time data on Day 1 and 10: C_{max}, t_{max}, and $AUC_{(0-t)}$ (if possible).	
Exploratory		
To determine the concentration and total amount of R406 in a single semen sample obtained during steady state for cohort 4 (White male subjects).		PK

Fostamatinib (R935788, R788), an orally bioavailable small molecule, is the pro-drug of R940406 (R406).

Study design

This was a Phase I randomized, double-blind, placebo-controlled, parallel group, single center study to assess the safety, tolerability and PK following single and multiple dose administration of fostamatinib to healthy Japanese and White subjects. The study design allowed a gradual escalation of dose in Japanese subjects with intensive safety monitoring to ensure the safety of all subjects.

Fifty-six healthy male subjects aged 20 to 45 years (inclusive) participated in 7 cohorts (8 subjects per cohort). The study consisted of 5 cohorts of Japanese together with 2 cohorts of White subjects (see Table 2 for cohort dose and regimen). Eight subjects participated in each cohort and received either fostamatinib or placebo, randomized 6:2. Each subject was dosed in one cohort. Two additional cohorts (8 subjects of each race; 6 active, 2 placebo) were included at the 150 mg dose level, in order to make a more appropriate comparison of Japanese and White subjects with respect to fostamatinib PK and increase the precision of the estimates of PK parameters.

After each Japanese cohort the Safety Review Committee (SRC) assessed available data to make a decision on the next dose level. The SRC determined the minimum number of subjects who should have completed a dose level before a higher dose was tested.

Target subject population and sample size

Healthy Japanese and White male and female (of non-childbearing potential) subjects aged 20 to 45 years.

It was planned that up to 56 healthy subjects could be enrolled. Due to the exploratory nature of the study the sample size was not based on formal statistical considerations.

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

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, , and route of administration	Manufacturer	Batch number
Fostamatinib	50 mg tablets; oral administration	Patheon	WK90520.001/C912281 WK90520.011/C912281 WK90520.012/C912281
Placebo	matching tablets; oral administration	Patheon	WK90520.002/F2WR50 GFC

Table S3 Study cohorts: ethnicity, dose level and treatment regimens

Cohort	Dose	Regimen
1 (Japanese)	50 mg or placebo	Day 1 – 50 mg or placebo (1x50 mg tablet in the morning) Days 4 to 9 – 50 mg or placebo (1x50 mg tablet twice daily) Day 10 – 50 mg or placebo (1x50 mg tablet in the morning)
2 (Japanese)	100 mg or placebo	Day 1 – 100 mg or placebo (2x50 mg tablet in the morning) Days 4 to 9 – 100 mg or placebo (2x50 mg tablet twice daily) Day 10 – 100 mg or placebo (2x50 mg tablet in the morning)
3 (Japanese)	150 mg or placebo	Day 1 - 150 mg or placebo (3x50 mg tablet in the morning) Days 4 to 10 - 150 mg or placebo (3x50 mg tablet once daily in the morning)
4 (White)	150 mg or placebo	Day 1 - 150 mg or placebo (3x50 mg tablet in the morning) Days 4 to 10 - 150 mg or placebo (3x50 mg tablet once daily in the morning)
5 (Japanese)	200 mg or placebo	Day 1 – 200 mg or placebo (4x50 mg tablet in the morning) Days 4 to 9 – 200 mg or placebo (4x50 mg tablet twice daily) Day 10 – 200 mg or placebo (4x50 mg tablet in the morning)
6 (White)	150 mg or placebo	Day 1 - 150 mg or placebo (3x50 mg tablet in the morning) Days 4 to 10 - 150 mg or placebo (3x50 mg tablet once daily in the morning)
7 (Japanese)	150 mg or placebo	Day 1 - 150 mg or placebo (3x50 mg tablet in the morning) Days 4 to 10 - 150 mg or placebo (3x50 mg tablet once daily in the morning)

Duration of treatment

The duration of subject participation was approximately 48 days, including a 28-day screening period, 13 day confinement period and a follow-up visit approximately 7 to 9 days after the last dose.

Each subject was to receive a single dose of fostamatinib or placebo on Day 1. Repeated dosing started on Day 4 with fostamatinib or placebo twice daily for 6 days (Day 4 to Day 9) for cohorts 1, 2 and 5 and once daily dosing for cohorts 3 and 4, with a final single dose on Day 10 for all cohorts. Two additional cohorts (cohort 6, 8 White subjects and cohort 7, 8 Japanese subjects) were administered 150 mg or placebo as a once daily dose on Day 1 and on Days 4 to 10.

Statistical methods

No formal statistical hypothesis testing was performed. Safety and tolerability and PK data were summarized descriptively including tables, listings and graphs, as appropriate. Where possible, individual PK parameters were calculated and summarized descriptively by dose level.

Data were presented by actual dose and by cohort. Subjects receiving placebo were pooled across dosing cohorts for the purposes of summarizing the safety results. Tables and figures were produced separately for the single and multiple dose data.

Subject population

In total, 40 Japanese male and 16 White male subjects were randomized into the study at a single study site. Female subjects were allowed per protocol, but no females were enrolled. None of the stopping criteria were met with regard to dose escalation.

Two subjects did not complete the study: Subject 1027 (Cohort 3, 150 mg Japanese) discontinued for personal reasons after dosing on Day 7, and Subject 1054 (Cohort 5, 200 mg Japanese) discontinued for personal reasons after dosing on Day 1. Discontinued subjects were not replaced.

All subjects were included in the safety analysis and all subjects up to the point of their discontinuation were included in the PK analysis. None of the subjects were excluded from safety or PK analyses due to protocol deviations.

All 40 Asian subjects enrolled were of Japanese ethnicity. All 16 White subjects were of European ethnicity (recorded as 'Other'). Demography and baseline characteristics were as expected for cohorts of Japanese and White ethnicities.

UGT1A1*6 and UGT1A1*28 genotype frequencies did not differ from expected in the ethnic groups. Thirty one of the study subjects carried more than one UGT1A1*6 and/or UGT1A1*28 alleles.

Summary of pharmacokinetic results

Single Dose

Geometric mean AUC and C_{max} increased with increase in dose for Japanese 50, 100 and 150 mg single dose cohorts.

Geometric mean AUC and C_{max} for 200 mg Japanese single dose were less than expected compared with other Japanese cohorts. The extent of exposure for the 200 mg single dose (C_{max} = 395 ng/mL and AUC = 4430 ng*hr/mL) was similar to the 100 mg single dose.

Investigations into the potential cause of this unusually low exposure with 200 mg single dose did not identify a cause (ie, dosing error, bioanalytical error, etc.).

Pharmacokinetic parameters for Japanese subjects administered a 150 mg single dose had higher values than White subjects administered a 150 mg single dose for both C_{max} (~45% higher) and AUC (~27% higher).

Half lives were similar for all cohorts and ranged from approximately 13 to 16 hours, following a single dose of fostamatinib.

Multiple Dose

Following multiple doses, steady state was achieved by Day 8 (day 5 of multiple dosing) for all dose levels. Steady state AUC and C_{max} increased with bid dosing of 50, 100 and 200 mg fostamatinib.

Higher steady state exposure was observed in Japanese subjects administered 150 mg compared with White subjects administered 150 mg on Day 10 (AUC ~18% and C_{max} ~24% higher in Japanese).

Steady state exposure for the 50 mg and 100 mg dose levels was well predicted by single dose data. For the 200 mg dose level, exposure to R406 was increased during steady state to a greater extent than predicted from single dose.

Approximately 20% higher steady state exposure (AUC and C_{max}) was observed in Japanese subjects administered 150 mg compared with White subjects administered 150 mg. The differences between Japanese and White subjects at the 150 mg dose level may be in part, be due to the difference in body weight between the White and Japanese subjects.

Half lives were similar for all cohorts and ranged from approximately 12 to 17 hours, following steady state administration.

Steady state AUC and C_{max} were approximately dose proportional across the range of bid doses studied in Japanese subjects, although the geometric mean AUC and C_{max} at 200 mg bid was greater than double that for 100 mg bid.

Plasma concentrations of R788 following single and multiple dose administration of fostamatinib were low (< 5 ng/ml) and sporadically observed over the first 2 hours post any dose. No plasma R788 was detected at 4 h after single or multiple dose administration at any dose level.

The amount of R406 excreted in urine (Ae) following single and multiple dose administration of fostamatinib was low (<0.1% of dose).

Higher amounts (Ae) of R406 N-glucuronide were excreted in urine following single and multiple dose administration, at approximately 5 to 15% of dose in molar equivalents.

Low amounts of R406 were detected in the semen samples for all White subjects administered fostamatinib in Cohort 4; these low amounts are likely to result in minimal exposure to sexual partners.

Table S4 Summary of Single Dose R406 Plasma Pharmacokinetic Parameters from Day 1 Cohorts 1 to 7 (Pharmacokinetic Population)

Treatment Group	Statistic	C_{max} (ng/mL)	t_{max}* (h)	AUC (ng.h/mL)	AUC_{0-t} (ng.h/mL)	AUC_{tau} (ng.h/mL)	$t_{1/2}$ (h)
50 mg	n	6	6	6	6	6	6
Japanese	Geo Mean	163	3	2170	2090	1080	15.2
	GCV (%)	36.5	(1-4)	14.9	15.7	29.8	22.2
100 mg	n	6	6	6	6	6	6
Japanese	Geo Mean	338	3	4150	3960	2080	15.9
	GCV (%)	39.8	(1.5-6)	33	30.4	24.9	40.3
150 mg	n	12	12	12	12	12	12
Japanese	Geo Mean	626	1.5	5870	5730	4500	12.6
	GCV (%)	39	(1-4)	27.6	27.1	31.6	34.9
150 mg	n	12	12	12	12	12	12
White	Geo Mean	431	1.5	4620	4480	3400	12.7
	GCV (%)	47.7	(0.5-4)	32.8	32.9	34.1	42.8
200 mg	n	6	6	5	5	6	5
Japanese	Geo Mean	395	1.5	4430	4300	2260	14.8
	GCV (%)	38.8	(1-4)	32.1	32.8	44.9	9.56

All dose levels were administered as a single dose on Day 1. * T_{max} presented as median, minimum and maximum only. AUC_{tau} = AUC (0-12) for twice daily dosing; AUC_{tau} = AUC (0-24) for once daily dosing. Geo Mean = geometric mean. GCV (%) = 100 x [exp (s^2)-1]^1/2, where s is the standard deviation of the data on a log scale.

Table S5 Summary of Multiple Dose R406 Plasma Pharmacokinetic Parameters from Day 10 Cohorts 1 to 7 (Pharmacokinetic Population)

Treatment Group	Statistic	$C_{max\ ss}$ Day 10 (ng/mL)	$t_{max\ ss}$* Day 10 (h)	AUC_{0-t} Day 10 (ng.h/mL)	AUC_{ss} Day 10 (ng.h/mL)	$t_{1/2}$ Day 10 (h)	$Rac_{(Cmax)}$ [1]	$Rac_{(AUC)}$ [2]
50 mg	n	6	6	6	6	6	6	6
Japanese	Geo Mean	340	2	4900	2570	16.5	2.09	2.39
	GCV (%)	16.7	(1.5-4)	16.9	12.5	19.8	38	35.4
100 mg	n	6	6	6	6	6	6	6
Japanese	Geo Mean	615	2	8930	4610	16	1.82	2.22
	GCV (%)	31.1	(1.5-4)	44.8	31	35.1	36.7	18.1
150 mg	n	11	11	11	11	11	11	11
Japanese	Geo Mean	643	4	7480	5900	14.3	1.01	1.26
	GCV (%)	37	(1-6)	34.7	33.5	30.6	38.4	25.3

Table S5 Summary of Multiple Dose R406 Plasma Pharmacokinetic Parameters from Day 10 Cohorts 1 to 7 (Pharmacokinetic Population)

Treatment Group	Statistic	$C_{max\ ss}$ Day 10 (ng/mL)	$t_{max\ ss}$* Day 10 (h)	AUC_{0-t} Day 10 (ng.h/mL)	AUC_{ss} Day 10 (ng.h/mL)	$t_{1/2}$ Day 10 (h)	$Rac_{(Cmax)}$ [1]	$Rac_{(AUC)}$ [2]
150 mg White	n	12	12	12	12	12	12	12
	Geo Mean	520	2	6670	4980	12.7	1.21	1.46
	GCV (%)	45.2	(1-4)	46.8	37.9	45.4	59.4	39.6
200 mg Japanese	n	5	5	5	5	5	5	5
	Geo Mean	1730	1.5	26500	14100	12.3	4.51	6.55
	GCV (%)	20.4	(1-4)	33.5	19.4	17.5	48.9	52.1

Dose levels 50 mg, 100 mg and 200 mg administered as single dose Day 1, bid doses Day 4 to Day 9, and single dose on Day 10. Dose level 150 mg administered as single dose Day 1 and single dose on Day 4 to Day 10.
* $T_{max\ ss}$ presented as median, minimum and maximum only. Geo Mean = geometric mean.,
GCV (%) = 100 x [exp (s^2)-1]^1/2, where s is the standard deviation of the data on a log scale.
Extent of accumulation on multiple dosing: [1] $C_{max,\ ss}$ Day 10 / C_{max}, Day 1; [2] AUC_{ss}, Day 10 / AUC_{tau}, Day 1.

Summary of safety results

There were no SAEs, deaths, or AEs leading to a change in the planned IP administration or leading to study discontinuation. A total of 17 AEs were reported by 12 subjects during the study (1 AE after single dose; 16 AEs during multiple dosing) and all were of mild intensity.

The AEs reported in this study were consistent with the nature of the study. There was no difference of note in AEs reported by Japanese or White subjects.

There were no notable differences in vital signs or clinical laboratory measurements across treatment groups vs. placebo. For several individual subjects across treatment groups, vital signs findings and liver function parameter values were noteworthy, but of no safety concern.

[redacted]