AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00032
Edition Number	1
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A Phase I, Open-label Study to Assess the Pharmacokinetics of Oral Fostamatinib in Healthy Japanese Subjects After Single and Multiple Doses

Study dates: First subject enrolled: 11 June 2012
Last subject last visit: 06 September 2012

Phase of development: Clinical pharmacology (I)

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

Study centre

The study was conducted at a single center (Site 0001):

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	Pharmacokinetics (PK)	To determine plasma and urine PK parameters following oral administration of single and multiple doses of fostamatinib 100 mg and 200 mg twice daily in healthy Japanese subjects	The following PK parameters were determined using plasma, whole blood and dry blood spot (DBS) R406 concentration-time data from Day 1: maximum concentration (Cmax), time to Cmax (tmax), terminal rate constant (λz), terminal elimination half-life (t½), area under the plasma concentration-time curve from zero to the time of the last measurable concentration (AUC0-t), from zero to the end of the dosing interval (AUCτ, ie AUC0-12) and from zero to infinity (AUC), and percentage extrapolated AUC. In addition, the following PK parameters were determined from urine data on Day 1: renal clearance (CLR0-48) and amount of drug excreted unchanged (Ae 0-48) for R406 and Ae-0-48) for N-glucuronide of R406 The following PK parameters were determined using plasma, whole blood and DBS R406 concentration-time data from Day 4 (first day of multiple dosing): Cmax, tmax, AUC(0-t) and AUCτ (AUC(0-12)).

Table S1 Objectives and outcome variables

Objective Priority	Type	Description	Outcome Variable Description
			The following PK parameters were determined using plasma, whole blood and DBS R406 concentration-time data from Day 10: maximum plasma concentration at steady state (Css,max), time to steady state Cmax (tss,max), AUC(0-t), area under the plasma concentration-time curve from zero to the end of the dosing interval (AUCss), λz and t½,ss.
Secondary	PK	To determine whole blood and dry blood spot (DBS) concentrations and PK parameters for R406 (ie, the dephosphorylated drug) following single and multiple oral dose administration of fostamatinib 100 mg and 200 mg twice daily in healthy Japanese subjects.	See description of primary PK parameters
Secondary	Safety	To investigate the safety and tolerability of single and multiple doses of fostamatinib administered orally to healthy Japanese subjects.	Adverse events, vital sign assessments, electrocardiograms, clinical laboratory assessments, physical examinations
	Pharmacogenetics	To investigate the relationship between variations in the gene encoding uridine diphosphate (UDP) glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) and the safety and tolerability of fostamatinib in the study population.	UGT1A1 genotype for each subject

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Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Pharmacogenetics	To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, absorption, distribution, metabolism and excretion, safety, tolerability and efficacy) to fostamatinib, and associated biomarkers.	Not presented in this report
	PK	To store selected plasma and urine samples for further potential metabolism and PK investigations.	Not presented in this report

Study design

This was a Phase I, open-label, single and multiple dose study in healthy Japanese male subjects conducted at a single center.

The study was planned to consist of two groups of healthy Japanese subjects aged 20 to 45 years. Initially, a total of 12 subjects were allocated to treatment (6 subjects per group). A further 12 subjects (6 subjects per group) were allocated to treatment as planned per protocol. Therefore, a total of twelve subjects were allocated to Group A (100 mg) and twelve subjects were allocated to Group B (200 mg). All 24 subjects completed the study.

Target subject population and sample size

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

Due to the exploratory nature of the study the sample size was not based on formal statistical considerations, but on experience from previous similar Phase I studies with other compounds.

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

The investigational product fostamatinib disodium was manufactured by Patheon and supplied in a strength of 50 mg. One batch of fostamatinib was used in this study. Individual batch number and further information are included in the Clinical Study Report (CSR). Fostamatinib was administered to the subjects as oral tablets. Subjects received fostamatinib

in a fasted state on PK days. A single oral dose (100 mg in Group A and 200 mg in Group B) was administered on Day 1 followed by a 72-hour wash-out period before multiple dosing commences on Day 4. On Days 4 to 9, fostamatinib was administered as 100 mg (Group A) or as 200 mg (Group B) twice daily, with a final morning dose on Day 10.

Duration of treatment

The duration of subject participation was approximately 47 days, including a 28-day screening period, 13-day confinement period and a follow-up visit seven to nine days after the last dose.

Each subject received a single dose of fostamatinib on Day 1. Repeated dosing commenced on Day 4 with fostamatinib twice daily for six days (Day 4 to Day 9) followed by a final single dose in the morning of Day 10.

Statistical methods

No formal statistical hypothesis testing was performed. The analyses of safety, tolerability and PK data was summarized descriptively including tables, listings and graphs, as appropriate. Individual subject data were listed.

Tables and figures were produced separately for the single dose data and the multiple dose data.

The time dependency of the PK was evaluated by comparing AUC_{ss} with AUC of Day 1. The ratio between AUC_{ss} and AUC (Day 1) was calculated by back-transforming the arithmetic mean difference between the log-transformed AUCs. Using the computed estimate, 90% confidence intervals were calculated for the difference and then back-transformed.

Subject population

A total of 24 healthy Japanese male and female (of non-childbearing potential) subjects aged 20 to 45 years were randomised into this clinical study.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

- Mean AUC and C_{max} were approximately dose proportional for 100 and 200 mg following a single dose on Day 1. On Day 4 (1st day of multiple dosing) PK parameters were close to dose proportional but some variability in exposure versus Day 1.

- Steady state AUC and C_{max} were increased in a greater than dose proportional manner between 100 mg and 200 mg bid; a 2-fold increase in dose resulted in an approximate 3-fold increase in AUC.

- Steady-state appears to have been reached at 100 mg bid by 2-3 days dosing; for 200 mg group trough concentrations were rising from Days 2-5 and appear to have hit a plateau between Days 6 and 7.

- Accumulation was evident at both doses and accumulation ratio for AUC was higher at 200 mg bid than 100 mg bid (3.72 vs 2.24).

- Concentrations of R406 in blood were approximately 2.5-fold higher than plasma and the ratio of blood:plasma concentrations were consistent for the two doses and during both single dose and steady-state conditions.

- PK parameters were very consistent between whole blood, FS-DBS, and PD-DBS.

- There was very little renal excretion of R406 (<0.1% of dose) and renal clearance values were also very low for R406 at both doses (0.002 – 0.004 L/h).

- Excretion of the N-glucuronide of R406 accounted for about 9-11% of the administered dose during steady-state administration.

Summary of safety results

- A total of 9 AEs (all single occurrences) were reported by 3 subjects during the study. All AEs were observed during the multiple dose-period, none during the single-dose period.

- There were no SAEs, deaths, or AEs leading to study discontinuation.

- There were no AEs related to clinical laboratory values, vital signs or ECG measurements

- A small decrease from baseline in leukocyte and neutrophil count was observed over time with the lowest value seen at Follow-up visit. The drop was slightly larger for the higher dose.

- For several individual subjects across treatment groups liver function parameter values were noteworthy, but of no safety concern.

- For several subjects AST/ALT/bilirubin values were increased above the normal limit but to no greater than 3-fold ULN. None were considered of clinical significance.

- Vital signs did not show any changes of concern between the different assessments that might have been caused by the investigational product. There were no relevant findings for vital signs and ECG parameters.