AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00027
Edition Number	1
Date	27 March 2013
EudraCT Number	2012-001214-42

A Study to Assess the Absolute Bioavailability of a Single Oral Dose of Fostamatinib with Respect to an Intravenous Micro Tracer Dose of [^{14}C] R406 in Healthy Male Volunteers

Study dates: First subject enrolled: 13 July 2012
Last subject last visit: 10 August 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

One study centre in the United Kingdom

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 absolute bioavailability and to evaluate the pharmacokinetic parameters of a single oral dose of fostamatinib and a radiolabelled intravenous micro tracer dose of [^{14}C] R406 in healthy male volunteers	R406: AUC, $AUC_{(0-t)}$, C_{max}, $t_{1/2\lambda z}$, t_{max}, MRT, MAT, F [^{14}C] R406: AUC, $AUC_{(0-t)}$, C_{max}, $t_{1/2\lambda z}$, t_{max}, MRT, CL, V_z, V_{ss}
Secondary	Safety	To assess the safety and tolerability of healthy volunteers exposed to the investigational product	Adverse events, laboratory assessments, vital signs, physical examination, 12-lead electrocardiogram
Exploratory[a]	Pharmacogenetic	To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to fostamatinib and/or associated biomarkers	-

[a] These results, if performed, are not reported in this Clinical Study Report.

AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the last quantifiable concentration; CL: total body clearance; C_{max}: maximum plasma concentration; F: oral percent bioavailability; MAT: mean absorption time; MRT: mean residence time; R406: the active metabolite of fostamatinib; $t_{1/2\lambda z}$: terminal half-life; t_{max}: time of maximum plasma concentration; V_{ss}: volume of distribution at steady state; V_z: volume of distribution during the terminal phase.

Study design

This was a Phase I, open-label study performed at a single study centre in 10 healthy male volunteers aged 18 to 55 years (inclusive). This study was performed to assess the absolute bioavailability and evaluate the pharmacokinetic (PK) parameters of a single oral dose of fostamatinib and a radiolabelled intravenous micro tracer dose of [^{14}C] R406 in healthy volunteers. The study comprised 3 visits: Visit 1 (screening, Day -21 to Day -2); Visit 2 (the healthy volunteers were admitted to the study centre on Day -1, received the investigational

product on Day 1, were discharged from the study centre after the 30 hours postdose PK sample collection on Day 2, and returned to the study for PK sample collections); and Visit 3 (follow-up 5 to 7 days after the last PK sample collection on Day 5 [96 hours postdose]).

On Day 1, the healthy volunteers received a single oral dose of 3 x 50 mg fostamatinib tablets with 240 mL of water under fasting conditions. At 1.75 hours after the oral dose, healthy volunteers received a 100 μg [^{14}C] R406 intravenous micro tracer dose, infused over 15 minutes. The intravenous micro tracer dose was infused such that the end of the infusion was coincidental with the expected median oral time of maximum plasma concentration (t_{max}) (the estimated t_{max} was 2 hours).

Target subject population and sample size

Healthy male volunteers aged 18 to 55 years (inclusive) with a body mass index (BMI) of 18 to 30 kg/m^2.

Planned: 10 healthy volunteers

Screened: 37 healthy volunteers

Completed: 10 healthy volunteers

Analysed: 10 healthy volunteers

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

The details of the investigational product are presented in Table S2.

Table S2 Details of the investigational product

Investigational product	Dosage form and strength	Manufacturer	Batch number
Fostamatinib	50 mg oral tablets	Patheon	12114.2/1
[^{14}C] radiolabelled R406 containing no more than 270 nCi (10 kBq) ^{14}C	100 μg solution for infusion	Quotient Clinical	112696/C/01

Duration of treatment

Single dose

Statistical methods

All oral and intravenous PK data were listed and summarised using standard summary statistics. The geometric mean 90% confidence interval (CI) for oral percent absolute bioavailability was calculated.

Demography and baseline data were summarised and listed using appropriate summary statistics.

All safety data, including adverse events (AEs), were summarised by descriptive statistics. The safety data addressed the secondary objective to assure the safety of all healthy volunteers by assessment of pulse rate and blood pressure, electrocardiogram (ECG), clinical chemistry, haematology, urinalysis, and AEs.

No formal statistical hypothesis testing was performed in this study.

Subject population

The age of the healthy volunteers ranged from 21 to 53 years (mean 34 years and median 33 years) and the BMI from 19 to 30 kg/m^2 (mean 25 kg/m^2 and median 26 kg/m^2). All healthy volunteers were white and male with a minimum weight of 61 kg.

Summary of pharmacokinetic results

The study was conducted to assess the absolute bioavailability of the oral formulation of fostamatinib 150 mg (administered as 3x50 mg tablets). The mean absolute bioavailability of R406 following oral dosing of fostamatinib was approximately 55% (90% CI: 42.48, 70.29). A summary of key R406 and [^{14}C] R406 pharmacokinetic parameters are presented below in Table S3.

Table S3 Summary of key R406 and [^{14}C] R406 pharmacokinetic parameters

Parameter (unit)	Statistic	R406 (N = 10)	[^{14}C] R406 (N = 9)
AUC (ng·h/mL)	Geo. mean (CV%)	4430 (64.5%)	6.35 (25.1%)
C_{max} (ng/ml)	Geo. mean (CV%)	313 (81.0%)	1.35 (24.8%)
T_{max} (h)	Median (min,max)	1.95 (0.5,3.5)	-
$t_{1/2}$ (h)	Geo. mean (CV%)	15.5 (36.0%)	15.3 (30.2%)
MRT (h)	Geo. mean (CV%)	22.2 (43.4%)	16.3 (33.5%)
MAT (h)	Geo. mean (CV%)	2.8 (186.7%)	-
F (%)	Geo. mean (CV%)	54.6 (42.4%)	
	(90% CI)	(42.48, 70.29)	-
CL (L/h)	Geo. mean (CV%)	-	15.7 (25.3%)
V_z (L)	Geo. mean (CV%)	-	345 (39.2%)
V_{ss} (L)	Geo. mean (CV%)	-	256 (37.4%)

Summary of safety results

No deaths, serious adverse events (SAEs), or discontinuations due to an AE were reported in this study. At least 1 AE was reported for 6 healthy volunteers.

At least 1 event of headache was reported for 3 healthy volunteers. Application site pain was reported for 2 healthy volunteers: a mild burning sensation during the infusion, considered related to the investigational product, and mild stinging around the cannula, considered related to the investigational product at approximately 1 minute after the infusion. No other AEs were considered to be related to the investigational product by the Investigator. All AEs were mild in severity.

No laboratory changes outside the predefined criteria were reported. Variation in mean and median vital signs measurements were reported over time. None of the changes were considered to be clinically relevant by the Investigator. No abnormal ECG readings were considered to be clinically significant by the Investigator. No normal physical examination findings at screening were reported as abnormal at follow-up.