AstraZeneca

**Clinical Study Report Synopsis**

| | |
|---|---|
| Drug Substance | Fostamatinib |
| Study Code | D4300C00010 |
| Edition Number | 1 |
| Date | 28 November 2011 |

# An Open-label, Single-center Study to Assess the Pharmacokinetics of R406 in Subjects with Hepatic Impairment and in Healthy Subjects Following Administration of a Single Dose of Fostamatinib 150 mg

**Study dates:** First subject enrolled: 18 October 2010
Last subject last visit: 03 June 2011

**Phase of development:** Clinical pharmacology (I)

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

## 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 plasma pharmacokinetics of R406 in subjects with varying degrees of hepatic impairment and in healthy subjects following administration of a single dose of fostamatinib 150 mg | Primary variables: R406 AUC and $C_{max}$<br>Secondary variables: R406 $t_{max}$, $\lambda_z$, $t_{1/2,\lambda z}$, $AUC_{(0-t)}$, and $AUC_{(0-48)}$ | Pharmacokinetic |
| **Secondary** | **Secondary** | |
| To examine the safety and tolerability of a single oral dose of 150 mg fostamatinib in subjects with varying degrees of hepatic impairment and in healthy subjects | Adverse events, clinical laboratory tests, physical examinations, electrocardiograms, and vital signs | Safety |
| To assess the urinary pharmacokinetics of R406 and N-glucuronide metabolite in subjects with varying degrees of hepatic impairment and in healthy subjects | $A_e$ and $CL_R$ | Pharmacokinetic |
| To explore potential changes in protein binding of R406 and subsequent effects on the pharmacokinetics in subjects with normal hepatic function and in subjects with varying degrees of hepatic impairment | $C_{max,u,}$ $AUC_{(0-t),u}$, $AUC_{(0-48),u}$, and $AUC_u$ | Pharmacokinetic |

R406 the analyte in plasma for the dephosphorylated drug.

## Study design

This was a Phase I open-label, single-center, single-dose, parallel-group study to examine the pharmacokinetics and safety and tolerability of fostamatinib in volunteers with varying degrees of hepatic impairment and in volunteers with normal hepatic function.

Following an up to 28-day screening period there was 1 admission period to the clinic from the day before dosing (Day -1) until discharge on Day 6. Volunteers received a single 150-mg dose of fostamatinib on Day 1, with blood samples collected up to 120 hours postdose for the determination of R406 plasma concentrations. The percent of R406 unbound plasma was

determined at 1, 6, and 24 hours. Urine was collected from predose to 48 hours postdose to determine R406 and N-glucuronide concentrations.

Volunteers with hepatic impairment were categorized by their medical history, physical examination, and laboratory results at screening on the basis of their Child-Pugh score. At least 4 volunteers with mild hepatic impairment (Child-Pugh Class A) were dosed prior to the recruitment of any volunteers with moderate hepatic impairment (Child-Pugh Class B), with safety and tolerability (eg, adverse events, vital signs, clinical laboratory values, and electrocardiogram data) assessed by the Safety Review Committee. After at least 4 volunteers with moderate hepatic impairment were dosed, all available safety, tolerability, and pharmacokinetic data from volunteers dosed to date were reviewed by the Safety Review Committee prior to recruiting any volunteers with severe hepatic impairment (Child-Pugh Class C). There was an option to adjust the fostamatinib dose in volunteers with severe hepatic impairment if the Safety Review Committee found a dose reduction was warranted.

Volunteers with normal hepatic function were enrolled after the majority of hepatically-impaired volunteers completed the study. Every effort was made to match healthy volunteers to the demographics of the 24 volunteers in the hepatic impairment groups based on age, gender, and body weight (ie, within the age and body weight range with approximately 50% of volunteers on each side of the median).

**Target subject population and sample size**

The target population was male volunteers and female volunteers (healthy, Child-Pugh Class A, B, and C hepatic impairment) of nonchildbearing potential greater than or equal to 18 years of age with a body weight of at least 50 kg and a body mass index between 18 and 40 $kg/m^2$. Each group under study was to contain at least 2 volunteers of each gender. Volunteers with normal hepatic function were age and body weight matched (50% of volunteers on each side of the median) to hepatically-impaired volunteers. Volunteers in the hepatically-impaired groups could not have fluctuating or rapidly deteriorating hepatic function.

This study was not statistically powered in terms of claiming no effect of hepatic impairment on exposure to R406 (ie, if 90% CI was within 0.8 to 1.25). Interpretation of the results was to be based on the size of the treatment ratio and associated 90% CI. To illustrate the size of effect that could be detected, it was estimated that 8 volunteers per group would provide at least 85% power to detect a 50% increase in AUC and Cmax, significant at the 5% level. This was based on data from study C788-013 that suggests an intersubject CV% of 27% for AUC and 29% for Cmax.

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

A single dose of fostamatinib 150 mg (three 50-mg tablets) was administered orally with 240 mL of water. Batch number: WK90520.008

**Duration of treatment**

The duration of subject participation was approximately 42 days including a screening period of up to 28 days, followed by an inpatient visit lasting 7 days, and ending with a follow-up visit up to 7 days after discharge. The duration of the study from start of screening to the last follow-up visit was approximately 7.5 months.

**Statistical methods**

To assess the potential effects of hepatic impairment on R406 pharmacokinetics, the plasma pharmacokinetic parameters of AUC and $C_{max}$ were analyzed using an analysis of variance model, with hepatic group as a fixed effect, 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.

The relationship between Child-Pugh score and AUC (and $C_{max}$) was analyzed using a regression model with the Child-Pugh score as a continuous dependent variable and the natural logarithm of AUC (or $C_{max}$) as the independent variable. The slope β together with confidence intervals (2-sided 95%) was estimated and presented.

**Subject population**

There were 32 study participants, overall and all 32 volunteers completed the study. All volunteers were included in the safety and pharmacokinetic analyses. There were 24 (75.0%) males and 8 (25.0%) females (the mild hepatic group did not enroll any females). The majority of the volunteers (28/32, 87.5%) were white; 3 (9.4%) volunteers were black; and 1 (3.1%) was American Indian or Alaska Native. The mean age was 54 years with a standard deviation of 7 years and ranged from 36 years to 66 years. Volunteers in the normal hepatic function group were considered healthy at study entry.

**Summary of pharmacokinetic results**

The results of the primary statistical comparison of R406 $C_{max}$ and AUC in hepatically-impaired volunteers versus normal hepatic function are presented in Table S2.

**Table S2 Statistical comparison of R406 primary pharmacokinetic endpoints**

| | | | | Comparison to normal subjects | |
|---|---|---|---|---|---|
| **Parameter** | **Hepatic group[a]** | **N** | **Geometric LS mean** | **Ratio (%)** | **90% CI** |
| AUC (ng*h/mL) | Normal | 8 | 8970 | | |
| | Mild | 8 | 6387 | 71.21 | (51.48, 98.49) |
| | Moderate | 8 | 6858 | 76.46 | (55.28, 105.75) |
| | Severe | 8 | 9490 | 105.80 | (74.69, 146.33) |
| $C_{max}$ (ng/mL) | Normal | 8 | 692.1 | | |
| | Mild | 8 | 614.6 | 88.81 | (60.63, 130.09) |
| | Moderate | 8 | 602.3 | 87.02 | (59.41, 127.48) |
| | Severe | 8 | 582.1 | 84.11 | (57.42, 123.20) |

CI confidence interval; LS least-squares; Results based on linear model with hepatic function group as a fixed effect. Fostamatinib 150 mg (3 x 50 mg tablets) was administered as a single oral dose with 240 mL of water.

[a] Mild: mild hepatic impairment – Child-Pugh Category A.
Moderate: moderate hepatic impairment – Child-Pugh Category B.
Severe: severe hepatic impairment – Child-Pugh Category C.
Normal: normal hepatic function.

The results showed that hepatic impairment did not have a consistent effect on R406 pharmacokinetics, with mild and moderate hepatically-impaired groups having a lower exposure (AUC and $C_{max}$) than normal hepatic function. Furthermore, although the severe hepatically-impaired group had lower $C_{max}$ than the normal hepatic function group, AUC was similar between the groups.

A significant relationship between Child-Pugh Score and R406 exposure parameters (AUC and $C_{max}$) was not found in the regression analysis.

R406 geometric mean percent unbound ranged from 0.641% to 0.969% in the mild hepatic impairment group, 0.811% to 1.30% in the moderate hepatic impairment group, 1.09% to 1.95% in the severe hepatic group, and 0.835% to 1.13% in the normal hepatic function group and did not appear to change across sampling time. However, the severe hepatically-impaired group had the highest average percent unbound, and therefore, the highest $AUC_u$ and $C_{max,u}$ (1.7- and 1.3-fold larger than the normal hepatic function group).

The mild and moderate hepatically-impaired groups had a slightly longer median $t_{max}$ (2.5 and 1.75 hours) and shorter geometric mean $t_{1/2\lambda z}$ (approximately 16 hours) than the normal hepatic function and severe hepatically-impaired groups (1.5 hours and approximately 19 hours, respectively).

Urinary excretion of R406 was minimal across groups. However, the renal clearance values in moderate and severe hepatic impairment subjects tended to be higher than the normal hepatic function and mild hepatic impairment subjects. Additionally, the amount of R406 N-glucuronide excreted into the urine was slightly increased in mild and moderate hepatic impairment groups and considerably increased in the severe hepatic impairment group.

**Summary of safety results**

All 32 volunteers enrolled in the study received a single dose of 150 mg fostamatinib on study Day 1.

There were no deaths or discontinuations due to adverse events reported during study conduct. One volunteer (E0001021, severe hepatic impairment) experienced a serious adverse event of worsening hepatic encephalopathy requiring hospitalization that began on Day 8 (2 days after discharge from clinic). The event was assessed by the Investigator as severe in intensity and not causally related to investigational product. The volunteer also experienced an adverse event of suspected gastrointestinal bleed beginning the second day of hospitalization. This event was considered by the Investigator to be moderate in intensity and not causally related to the investigational product. Both events resolved and the volunteer returned for the follow-up visit.

Following the single dose of investigational product, there were 17 adverse events reported for 10 volunteers. No trends in the frequency of AEs overall was noted with increasing hepatic dysfunction. The most frequently reported AE was sinus congestion in 2 (25.0%) volunteers in the moderate hepatically-impaired group; there were no other AEs reported by more than 1 volunteer.

Adverse events assessed by the Investigator as causally related to investigational product included: headache (1 volunteer, normal hepatic function group), dizziness (1 volunteer, moderate hepatically-impaired group), and diarrhea (1 volunteer, severe hepatically-impaired group). One volunteer (mild hepatic function group) experienced 2 adverse events that were considered moderate in intensity and not causally related to investigational product.

There were no trends or clinically meaningful changes noted in clinical laboratory, vital sign, or electrocardiogram findings throughout the study.