AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00009
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An Open-label, Phase I Study to Assess the Pharmacokinetics of R406 in Subjects with Renal Impairment Compared to Healthy Subjects following Administration of a Single Dose of Fostamatinib 150 mg

Study dates: First subject enrolled: 29 November 2010
Last subject last visit: 17 June 2011

Phase of development: Clinical pharmacology (I)

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

Study centres

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 PK of R406 in subjects with renal impairment compared to healthy subjects following administration of a single dose of fostamatinib 150 mg	Primary variables: Total plasma R406 AUC and C_{max} Secondary variables: Total plasma R406 $AUC_{(0-t)}$, $AUC_{(0-48)}$, $t_{1/2\lambda z}$, t_{max}, and λ_z	Pharmacokinetic
Secondary	**Secondary**	
To examine the safety and tolerability of a single oral dose of 150 mg fostamatinib in subjects with renal impairment and in healthy subjects	Adverse events, laboratory safety variables, vital signs, 12-lead electrocardiogram, and physical examination	Safety
To assess the urinary PK of R406 and its N-glucuronide metabolite in subjects with renal impairment and in healthy subjects	Secondary variables: R406 A_e and CL_R R406 N-glucuronide A_e	Pharmacokinetic
To explore potential changes in protein binding of R406 and subsequent effects on the PK in healthy subjects with normal renal function and in subjects with varying degrees of renal impairment	Secondary variables: Unbound plasma R406 $C_{max,u}$, $AUC_{(0-t),u}$, $AUC_{(0-48),u}$, and AUC_u	Pharmacokinetic
To determine the effects of hemodialysis on the PK of R406 in patients with end stage renal disease	Secondary variables: CL_D and $A_{D(2-6)}$	Pharmacokinetic

A_e: amount of unchanged drug excreted in the urine; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-48)}$: area under the plasma concentration-time curve from zero to 48 hours post-dose; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the last quantifiable time point; CL_D: dialysis clearance; CL_R: renal clearance; C_{max}: maximum plasma concentration; A_e: amount excreted in urine; A_D: amount removed by dialysis; u: unbound; λ_z: terminal elimination rate constant; CSP: Clinical Study Protocol; NA: not applicable; PK: pharmacokinetic; $t_{1/2\lambda z}$: terminal half-life; t_{max}: time to maximum plasma concentration.

Study design

This was a single dose, open-label study designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of fostamatinib in subjects with renal impairment compared to subjects

with normal renal function using an adaptive 2-stage approach. Stage 1 investigated the PK of R406 in subjects at the extremes of renal function. In Stage 1, 8 healthy subjects with normal renal function (Group 1) and 8 subjects with end stage renal disease (ESRD) requiring dialysis were enrolled (Group 5). Stage 2 was to be conducted in up to 3 groups and could potentially include subjects with mild (Group 2), moderate (Group 3), and severe renal impairment (Group 4), with 8 subjects per group.

All available safety, tolerability, and PK data from Stage 1 were reviewed to assess the effect of renal impairment on R406 PK. While a review of the data from Stage 1 did not suggest ESRD altered R406 PK to an extent warranting dosage adjustment, given somewhat unexpectedly that lower exposure was observed for R406 in subjects with ESRD, it was decided to proceed with enrollment of a group of subjects with moderate renal impairment (Group 3) in Stage 2, in order to confirm any effect or the lack thereof of renal impairment on R406 PK and support future guidance on dosing.

Subjects in Group 5 with ESRD requiring dialysis participated in 2 treatment periods in order to study these subjects under both non-dialysis and dialysis conditions (to assess the dialysis clearance of R406). There was a wash-out period of at least 1 week between doses.

Subjects were classified at screening on the basis of renal function using the Cockroft-Gault formula to estimate creatinine clearance (CL_{CR}):

- Group 1: CL_{CR} ≥80 mL/min (control subjects with normal renal function)
- Group 3: CL_{CR} ≥30 to <50 mL/min (moderate renal impairment)
- Group 5: currently requiring dialysis

Subjects in Group 1 (single dose) and Group 5 (2 doses [non-dialysis and dialysis conditions]) received 150 mg fostamatinib in Stage 1 and subjects in Group 3 (single dose) received 150 mg fostamatinib in Stage 2.

Target subject population and sample size

Eight male or female subjects per group, with a CL_{CR} as specified for each group. Subjects in Group 1 were to be healthy and subjects in Group 5 were to have ESRD.

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

Table S2 Details of investigational product

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number
Fostamatinib	Tablet, 50 mg, oral	Patheon	C912281

Duration of treatment

A single dose for subjects in Groups 1 and 3, and 2 doses (1 dose per treatment period) for subjects in Group 5.

Each treatment period comprised 5 days (Days -1 to 4). Treatment periods in Group 5 were separated by a wash-out period of 7 days between doses.

Statistical methods

This study was not statistically powered in terms of claiming no effect of renal impairment on exposure to R406 (ie, if 90% confidence interval [CI] is within 0.8 to 1.25). Interpretation of the results is 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 subjects per group would provide at least 85% power to detect a 50% increase in area under the plasma concentration-time curve from zero to infinity (AUC) and maximum plasma concentration (C_{max}), significant at the 5% level. This was based on data from study C788-013 that suggests an inter-subject coefficient of variation (CV) of 27% for AUC and 29% for C_{max}.

Pharmacokinetic data were presented by renal function and period. The primary PK parameters (AUC and C_{max}) were compared by use of analysis of variance (ANOVA) on the log-transformed data, with renal function group as a fixed effect and body mass index (BMI) as a continuous effect. Body mass index was only included for C_{max}, as it was not significant at the 10% level for AUC. The geometric mean ratio for drug exposure (AUC and C_{max}), along with 90% CI for the ratio, were calculated between normal and ESRD off dialysis (Period 1) subjects.

To assess the potential differences between Period 1 (off dialysis) and Period 2 (on dialysis) in ESRD subjects, AUC and C_{max} were analyzed using a repeated measures ANOVA model on the log-transformed data. The model included treatment period as a repeated-fixed effect. Body mass index was removed from the model because it was not significant at the 10% significance level for both AUC and C_{max}. The results were back transformed and presented as geometric least squares means, a geometric mean ratio and its associated 90% CI.

The relationship between PK parameters (C_{max} and AUC) and CL_{CR} was also assessed using a regression model across renal function groups (with the exception of ESRD subjects for Treatment Period 2). Creatinine clearance (renal function group) was included in the model as a continuous effect. Body mass index was removed from the model because it was not significant at the 10% significance level for both AUC and C_{max}. Results were presented for the slope and the associated 90% CIs for the CL_{CR} parameter from the model. In addition, the p-value testing was presented.

Subject population

Enrolled: 24 subjects (Group 1: 8 subjects; Group 3: 8 subjects; Group 5: 8 subjects)

Completed: 24 subjects

Of the 24 subjects enrolled, 16 subjects (66.7%) were male and 8 subjects (33.3%) were female; 8 subjects (33.3%) were white, 15 subjects (62.5%) were black or African American, and 1 subject (4.2%) was native Hawaiian or other Pacific islander.

The age, gender, and BMI of subjects in Groups 1 and 5 were comparable (as required by the Clinical Study Protocol) as well as with Group 3. The CL_{CR} in Group 1 ranged from 88.5 to 192.7 mL/min, in Group 3 from 33.2 to 49.9 mL/min, and in Group 5 from 8.9 to 43.8 mL/min.

Summary of pharmacokinetic results

Table S3 Statistical comparison of R406 key pharmacokinetic parameters between renal groups in Period 1

				Comparison to normal renal function group (Group 1)	
Parameter	**Renal group[a]**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
AUC (ng*h/mL)	Group 1	8	7384		
	Group 3	6	5786	78.36	(52.40, 117.18)
	Group 5	8	5451	73.83	(50.86, 107.16)
C_{max} (ng/mL)	Group 1	8	693.9		
	Group 3	8	400.7	57.74	(35.81, 93.10)
	Group 5	8	429.8	61.94	(38.49, 99.69)

LS least-squares; CI confidence interval; RI renal impairment. Treatment Period 2 for end stage was not included in this analysis. Results based on linear mixed effect analysis of variance model with renal group as fixed effects. Body mass index was included as a continuous effect only for the C_{max} parameter.

[a]Normal: Normal renal function (Group 1). CL_{CR} >=80 mL/min; 150 mg (3 x 50 mg tablets) fostamatinib on Day 1 of single treatment period;

Moderate: Moderate RI (Group 3). CL_{CR} >=30 mL/min but < 50 mL/min; 150 mg (3 x 50 mg tablets) fostamatinib on Day 1 of a single treatment period;

End stage: (Group 5). Currently requiring dialysis.

Treatment Period 1: Group 5, 150 mg (3 x 50 mg tablets) fostamatinib on Day 1, after completion of dialysis session;

Source: Table 11.2.5.

Table S4 Statistical comparison of R406 key pharmacokinetic parameters between period for the end stage renal disease group

				Comparison Period 1 / Period 2	
Parameter	**Perioid[a]**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
AUC (ng*h/mL)	Period 1	8	5451		
	Period 2	7	6805	80.11	(52.76, 121.64)
C_{max} (ng/mL)	Period 1	8	407.4		
	Period 2	8	529.4	76.95	(48.88, 121.12)

LS least-squares; CI confidence interval. Results based on linear mixed effect analysis of variance model with renal group as fixed effects.

[a] End stage: (Group 5). Currently requiring dialysis.
Treatment Period 1: Group 5, 150 mg (3 x 50 mg tablets) fostamatinib on Day 1, after completion of dialysis session;
Treatment Period 2: Group 5, 150 mg (3 x 50 mg tablets) fostamatinib on Day 1, prior to the start of dialysis session.

Source: Table 11.2.6.

Total and unbound R406 exposure parameters were lower in the moderate renal impairment and end stage renal disease groups when compared to the normal renal function group with the exception of AUC_u being similar between groups. The $t_{1/2\lambda z}$ and t_{max} were also similar across groups.

A significant relationship between creatinine clearance and R406 exposure was not found in a regression analysis.

Renal elimination of R406 was negligible, regardless of renal function. Renal elimination of R406 N-glucuronide decreased with decreasing renal function (normal renal function group mean A_e was 1.94- and 28.4-fold higher than the moderate renal impairment and end stage renal disease groups, respectively).

When compared to Period 2 (dosed 2 hours before dialysis), R406 AUC and C_{max} were lower in the end stage renal disease group for Period 1 (dosed after dialysis) with a geometric mean least squares ratio of 80.11% and 76.95%, respectively. Additionally, CL_D was negligible (A_D less than 1% of theoretical dose).

Summary of safety results

No deaths, serious adverse events (SAEs), discontinuation due to an adverse event (DAE), or other significant adverse events (OAEs) were reported. Overall, 11 subjects (45.8%) reported at least 1 adverse event (AE). The most frequently reported AE was nausea: 1 subject (12.5%) in Group 3, 1 subject (12.5%) in Group 5 Period 1, and 1 subject (12.5%) in Group 5 Period 2.

One AE, mild in severity headache, was considered to be causally related to the investigational product by the Investigator. Four moderate in severity AEs were reported for 3 subjects: back pain and constipation (Group 3), vomiting (Group 5 Period 1), and pneumonia (Group 5 Period 2).

Based on the reported AEs, laboratory measurements, vital signs, electrocardiogram (ECG) evaluations, and physical examination findings, a single dose of fostamatinib was well tolerated in the populations studied.