AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00039
Edition Number	1
Date	11 June 2013

An Open-label, Nonrandomized, 2-Period Fixed Sequence, Single-center Study to Assess the Pharmacokinetics of Rosuvastatin and Simvastatin in Healthy Subjects when Administered Alone and in Combination with Fostamatinib 100 mg Twice Daily

Study dates: First subject enrolled: 12 November 2012
Last subject last visit: 18 January 2013

Phase of development: Clinical pharmacology (I)

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

Study center(s)

This was a single-center study in the United States.

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 pharmacokinetics of rosuvastatin in healthy subjects when administered alone and in combination with fostamatinib	Primary: AUC, C_{max} Secondary: AUC ratio, C_{max} ratio, $AUC_{(0-t)}$, $AUC_{(0-t)}$ ratio, $t_{1/2,\lambda z}$, λz, t_{max}, CL/F, V_z/F
	Pharmacokinetic	To assess the pharmacokinetics of simvastatin acid in healthy subjects when administered alone and in combination with fostamatinib	Primary: $AUC_{(0-t)}$, C_{max}, Secondary: AUC ratio, AUC, C_{max} ratio, $AUC_{(0-t)}$ ratio, $t_{1/2,\lambda z}$, λ_z, t_{max},
Secondary	Pharmacokinetic	To assess the pharmacokinetics of simvastatin in healthy subjects when administered alone and in combination with fostamatinib	Primary: AUC, C_{max}, Secondary: AUC ratio, C_{max} ratio, $AUC_{(0-t)}$, $AUC_{(0-t)}$ ratio, $t_{1/2,\lambda z}$, λ_z, t_{max}, CL/F, V_z/F
	Pharmacokinetic	To assess the steady-state pharmacokinetics of R406 in healthy subjects following administration of fostamatinib alone or in combination with rosuvastatin or simvastatin	AUCτ, C_{max}, t_{max}
	Safety	To examine the safety and tolerability of fostamatinib in combination with rosuvastatin or simvastatin	Adverse events, vital sign measurements, electrocardiograms, physical examination results, laboratory assessments (chemistry, hematology, and urinalysis)
Exploratory	Pharmacogenetic	To collect deoxyribonucleic acid samples to investigate variations in the genes encoding breast cancer resistance protein and organic anion-transporting polypeptide 1B1 transporters, which are involved in rosuvastatin disposition	*ABCG2(421C>A), SLCO1B1(521T>C)* and *SLCO1B1(388A>G)* gene variants

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Pharmacogenetic	If optional genetic consent was given, the deoxyribonucleic samples may also be stored and used for future exploratory research into other genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to fostamatinib and/or rosuvastatin and/or simvastatin	Not applicable. Results of this analysis, if performed, will be reported separately from this clinical study report.

Study design

The study was an open-label, 2-group, fixed-sequence, 2-period study in 42 healthy male and female volunteers. Volunteers were screened for eligibility up to 28 days prior to the first dose of investigational product in Period 1. Eligible volunteers were assigned to either Group A (N = 21) or Group B (N = 21) to receive rosuvastatin or simvastatin, respectively, alone (Period 1) and in combination with fostamatinib (Period 2). For both groups, routine safety assessments were performed at screening, clinic check-in, periodically throughout the study, and at the follow-up visit 3 to 5 days after discharge from Period 2.

Group A (rosuvastatin)

The 4 treatments administered to volunteers in Group A included:

- Treatment A (Group A, Period 1, Day -1 to Day 5):
  - Day 1: single, oral dose of rosuvastatin 20 mg
- Treatment B (Group A, Period 2, Day -1 to Day 10):
  - Day 1 to Day 5: oral dosing of fostamatinib 100 mg twice daily
  - Day 6: single, oral dose of rosuvastatin 20 mg plus continued oral dosing of fostamatinib 100 mg twice daily
  - Day 7 to Day 9: continue fostamatinib dosing 100 mg twice daily

Group B (simvastatin)

The 4 treatments administered to volunteers in Group B included:

- Treatment C (Group B, Period 1, Day -1 to Day 3):

  - Day 1: single, oral dose of simvastatin 40 mg

- Treatment D (Group B, Period 2, Day -1 to Day 8):
  - Day 1 to Day 5: oral dosing of fostamatinib 100 mg twice daily
  - Day 6: single, oral dose of simvastatin 40 mg plus continued oral dosing fostamatinib 100 mg twice daily
  - Day 7: continue fostamatinib dosing 100 mg twice daily

Blood samples were collected prior to dosing and serially postdose for up to 96 hours (Group A) and up to 48 hours (Group B) on Day 1 of Period 1 and Day 6 of Period 2 for the determination of rosuvastatin and simvastatin/simvastatin acid concentrations, respectively. Trough samples for R406 concentrations were collected prior to the morning dose on Days 1 through 4 of Period 2. On Days 5 and 6 of Period 2, samples for R406 concentrations were collected prior to the morning dose and serially postdose for 12 hours.

There was a nonresident washout period of between 5 (Group A) or 3 (Group B) and 30 days from the dose of rosuvastatin or simvastatin, respectively, in Period 1 before starting Period 2.

Target subject population and sample size

Healthy male and female volunteers between 18 and 55 years of age (inclusive) with a body mass index between 18 and 30 kg/m^2 and a minimum weight of 50 kg were eligible for study participation. Forty-two volunteers were enrolled in the study with 21 volunteers in each group.

This study was not statistically powered in terms of claiming no effect of fostamatinib on exposure to rosuvastatin or simvastatin (ie, if 90% confidence interval was within 0.8 to 1.25). Interpretation of the results was based on the size of the treatment ratio and associated 90% confidence interval. To illustrate the size of effect that could be detected, it was estimated that 18 completed volunteers would provide approximately 80% power to detect a ratio of 1.27 or more in AUC and C_{max}, using a 2-sided 5% significance test. This is based on data from various studies that suggest an approximate intrasubject coefficient of variation of 21% and 27% for AUC and 34% and 38% for C_{max} for rosuvastatin and simvastatin, respectively.

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

Fostamatinib (100 mg as two 50-mg tablets; batch no. DNNK), rosuvastatin (one 20-mg tablet; lot no. AM0055), and simvastatin (one 40-mg tablet; lot no. H005468) were administered orally with 240 mL water.

The time for dosing in relation to food intake followed the same schedule on Day 5 and Day 6 of Treatment B and Treatment D. Volunteers were fasted 10 hours before and 4 hours after the coadministration of the rosuvastatin or simvastatin and fostamatinib morning dose on

Day 6 of Treatment A or Treatment C. Volunteers were fasted 10 hours before and 4 hours after the administration of the morning fostamatinib dose on Day 5 of Treatment B and Treatment D.

Duration of treatment

The duration of the study for each volunteer in Group A and Group B was up to 80 days, and 76 days, respectively, including a screening period of up to 28 days, 2 residential treatment periods, a nonresident washout period, and a follow-up visit 3 to 5 days from clinic discharge after the last treatment period. For Group A (rosuvastatin), the residential treatment periods were 6 and 11 days in duration with a washout of between 5 and 30 days. For Group B (simvastatin), the residential treatment periods were 4 and 9 days with a washout of between 3 and 30 days.

Statistical methods

The rosuvastatin, simvastatin acid, and simvastatin pharmacokinetic parameters of AUC, $AUC_{(0-t)}$, and C_{max} were formally analyzed using an analysis of variance model. 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. Additionally, AUC_T and C_{max} for R406 were analyzed for both groups separately using the same statistical approach as above.

Subject population

Overall, 42 study volunteers met the study entry criteria and were enrolled in the study. Forty volunteers completed the study and 2 volunteers were withdrawn due to adverse events. There were no important protocol deviations and all 42 volunteers were included in the safety and pharmacokinetic analysis sets.

Summary of pharmacokinetic results

The results for primary statistical comparison for rosuvastatin AUC, $AUC_{(0-t)}$, and C_{max} and R406 AUC_T and C_{max} are presented in Table S2.

Table S2 Statistical comparison of key pharmacokinetic parameters for Group A

						Pairwise Comparisons		
Analyte	**Parameter (unit)**	**Trt[a]**	**n**	**Geo LS mean**	**Geo LS mean 95% CI**	**Pair**	**Ratio (%)**	**90% CI**
Rosuva-statin	AUC (ng·h/mL)	A	21	46.90	(43.19, 50.92)			
		B	21	91.70	(84.46, 99.57)	B/A	195.55	(177.62, 215.29)
	$AUC_{(0-t)}$ (ng·h/mL)	A	21	46.06	(42.37, 50.06)			

Table S2 Statistical comparison of key pharmacokinetic parameters for Group A

						Pairwise Comparisons		
Analyte	**Parameter (unit)**	**Trt[a]**	**n**	**Geo LS mean**	**Geo LS mean 95% CI**	**Pair**	**Ratio (%)**	**90% CI**
		B	21	90.80	(83.53, 98.69)	B/A	197.14	(178.84, 217.33)
	C_{max} (ng/mL)	A	21	5.284	(4.824, 5.789)			
		B	21	9.958	(9.090, 10.91)	B/A	188.43	(169.39, 209.62)
R406	AUC_{τ}	Day 5	21	5667	(5422, 5293)	Day		
	(ng·h/mL)	Day 6	21	6228	(5959, 6509)	6/5	109.90	(104.37, 115.72)
	C_{max}	Day 5	21	790.0	(725.6, 860.3)	Day		
	(ng/mL)	Day 6	21	892.3	(819.4, 971.6)	6/5	112.94	(102.24, 124.76)

CI confidence intervals; Geo geometric; LS least-squares; n number of observations included in the analysis; Trt treatment. Results based on fixed effects model with fixed-effects for treatment and subject.

[a] Treatment A: Rosuvastatin 20 mg single oral dose on Day 1 only; Treatment B: Fostamatinib 100 mg twice daily on Days 1 to 9; Day 6: single oral dose of rosuvastatin 20 mg plus continued oral dosing of fostamatinib 100 mg twice daily; Day 5: Treatment B, Day 5, fostamatinib 100 mg twice daily; Day 6: Treatment B, Day 6, fostamatinib 100 mg twice daily plus single oral dose of rosuvastatin 20 mg.

When a single dose of rosuvastatin administered alone on Day 1 (Treatment A) was compared to a single dose of rosuvastatin administered with fostamatinib at steady state on Day 6 (Treatment B), the geometric least-squares mean ratio for rosuvastatin AUC and $AUC_{(0-t)}$ increased by 96% and 97%, respectively. The geometric least-squares mean ratio for C_{max} increased by 88%.

When fostamatinib administered alone through Day 5 was compared to fostamatinib administered with a single dose of rosuvastatin on Day 6, the geometric least-squares mean ratio for R406 AUC_{τ} and C_{max} increased by 10% and 13%, respectively.

The results for primary statistical comparison for simvastatin acid and simvastatin AUC, $AUC_{(0-t),}$ and C_{max} and R406 AUC_{τ} and C_{max} are presented in Table S3.

Table S3 Statistical comparison of key pharmacokinetic parameters for Group B

						Pairwise Comparisons		
Analyte	**Parameter (Unit)**	**Trt[a]**	**n**	**Geometric LS Mean**	**Geometric LS Mean 95% CI**	**Pair**	**Ratio (%)**	**90% CI**
Simvasta-tin acid	AUC (ng·h/mL)	C	13	16.80	(14.96, 18.88)			
		D	15	27.98	(25.25, 31.00)	D/C	166.49	(146.21, 189.58)

Table S3 Statistical comparison of key pharmacokinetic parameters for Group B

						Pairwise Comparisons		
Analyte	**Parameter (Unit)**	**Trt[a]**	**n**	**Geometric LS Mean**	**Geometric LS Mean 95% CI**	**Pair**	**Ratio (%)**	**90% CI**
	$AUC_{(0-t)}$ (ng·h/mL)	C	21	12.64	(11.19, 14.27)			
		D	19	22.01	(19.25, 25.15)	D/C	174.16	(150.04, 202.16)
	C_{max} (ng/mL)	C	21	1.435	(1.266, 1.627)			
		D	19	2.624	(2.285, 3.013)	D/C	182.83	(156.68, 213.34)
Simvastatin	AUC (ng·h/mL)	C	21	27.50	(23.18, 32.62)			
		D	19	45.12	(37.39, 54.46)	D/C	164.11	(133.06, 202.40)
	$AUC_{(0-t)}$ (ng·h/mL)	C	21	26.11	(21.91, 31.12)			
		D	19	44.41	(36.61, 53.87)	D/C	170.07	(137.11, 210.95)
	C_{max} (ng/mL)	C	21	6.545	(5.317, 8.056)			
		D	19	13.91	(11.07, 17.48)	D/C	212.54	(164.71, 274.26)
R406	AUC_T (ng·h/mL)	Day 5	19	6056	(5589, 6562)	Day		
		Day 6	19	6701	(6185, 7261)	6/5	110.66	(100.77, 121.52)
	C_{max} (ng/mL)	Day 5	19	876.1	(784.0, 978.9)	Day		
		Day 6	19	977.7	(875.0, 1093)	6/5	111.60	(98.04, 127.04)

CI confidence intervals; LS least-squares; n number of observations included in the analysis. Results based on fixed effects model with fixed-effects for treatment and subject.

[a] Treatment C: Simvastatin 40 mg single oral dose on Day 1 only; Treatment D: Fostamatinib 100 mg twice daily on Days 1 to 7; Day 6: single oral dose of simvastatin 40 mg plus continued oral dosing of fostamatinib 100 mg twice daily. Day 5: Treatment D, Day 5, fostamatinib 100 mg twice daily; Day 6: Treatment D, Day 6, fostamatinib 100 mg twice daily plus single oral dose of simvastatin 40 mg..

When a single dose of simvastatin administered alone on Day 1 (Treatment C) was compared to a single dose of simvastatin administered with fostamatinib at steady state on Day 6 (Treatment D), the geometric least-squares mean ratio for simvastatin acid AUC and $AUC_{(0-t)}$ increased by approximately 66% and 74%, respectively. The geometric least-squares mean ratio for C_{max} increased by 83%.

When a single dose of simvastatin administered alone on Day 1 (Treatment C) was compared to a single dose of simvastatin administered with fostamatinib on Day 6 (Treatment D), the geometric least-squares mean ratio for simvastatin AUC and $AUC_{(0-t)}$ increased by approximately 64% and 70%, respectively. The geometric least-squares mean ratio for C_{max} increased by more than 2-fold.

When multiple doses of fostamatinib administered alone through Day 5 were compared to fostamatinib coadministration with a single dose of simvastatin with fostamatinib at steady state on Day 6, the geometric least-squares mean ratio for AUC_{τ} and C_{max} increased by 11% and 12%, respectively.

Summary of pharmacogenetic results

Due to the small number of study samples and distribution of the respective genotype groups, definitive conclusions regarding PK and safety could not be drawn based on the available genetic data.

Summary of safety results

Of the 42 volunteers enrolled in the study, 21 volunteers participated in Group A and received all planned doses of investigational product. In Group B, 19 volunteers received all planned doses of investigational product; 1 volunteer was withdrawn after receiving only a single dose of simvastatin in Period 1 and 1 volunteer was withdrawn after receiving simvastatin in Period 1 and 1 day of twice-daily dosing with fostamatinib in Period 2.

There were no deaths, serious adverse events, or adverse events of severe intensity reported during study conduct. Two volunteers were withdrawn for adverse events; 1 volunteer for an adverse event of influenza (moderate intensity) and 1 volunteer for an adverse event of increased alanine aminotransferase (mild intensity). Both of these adverse events were assessed by the Investigator as not related to investigational product.

There were no clinically-relevant trends observed in the frequency of individual adverse events for any treatment. There was 1 adverse event of moderate intensity (influenza); otherwise, all adverse events were assessed by the Investigator as mild in intensity. The most commonly reported adverse events overall were constipation, diarrhea, vessel puncture site reaction, upper respiratory infection, cough, and nasal congestion, occurring in 2 volunteers each. There were 2 adverse events of contact dermatitis that occurred in a single volunteer in Group B. A summary of the most frequently reported adverse events is presented in Table S4.

Table S4 Number (%) of subjects with most frequently reported adverse events (safety analysis set)

	Group A			Group B		
Preferred term[a]	**Rosuvastatin N = 21**	**Fostamatinib alone N = 21**	**Rosuvastatin + Fostamatinib N = 21**	**Simvastatin N = 21**	**Fostamatinib alone N = 20**	**Simvastatin + Fostamatinib N = 19**
Any AE	3 (14.3)	2 (9.5)	3 (14.3)	3 (14.3)	6 (30.0)	2 (10.5)
Constipation	1 (4.8%)	0	0	0	1 (4.8%)	0
Diarrhea	0	0	1 (4.8%)	0	1 (4.8%)	0
Vessel puncture site reaction	0	0	2 (9.5%)	0	0	0
Upper respiratory tract infection	0	0	1 (4.8%)	0	1 (4.8%)	0
Cough	0	0	0	1 (4.8%)	1 (4.8%)	0
Nasal congestion	0	0	0	1 (4.8%)	0	1 (5.3%)
Contact dermatitis	0	0	0	0	1 (4.8%)	1 (5.3%)

[a] Includes preferred terms occurring in at least 2 subjects overall, except contact dermatitis, where both events occurred in the same subject.

There were no trends or clinically meaningful changes in mean or median clinical laboratory and vital sign findings throughout the study or between the treatments. Adverse events for abnormal laboratory findings included a decreased platelet count of 121 $\times 10^9$/L (normal range: 150 to 400 $\times 10^9$/L), which began 2 days following the concurrent administration of fostamatinib and rosuvastatin and resolved approximately 1 week later. The Investigator assessed this event as mild and at least possibly related to investigational product. In addition, 1 volunteer was withdrawn from the study for an adverse event of increased alanine aminotransferase (105 U/L; normal range: 0 to 50 U/L) that began at admission to Period 2 (19 days following simvastatin administration in Period 1 and prior to administration of fostamatinib in Period 2) and was improved 3 days later. This event was assessed by the Investigator as mild in intensity and not causally related to investigational product. Otherwise, individual clinical laboratory values and vital signs remained generally stable during the study. There were no clinically relevant changes in electrocardiograms from screening to follow-up.