AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00033
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OSKIRA-ABPM: A Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Effect of Fostamatinib 100 mg Twice Daily on 24-hour Ambulatory Blood Pressure in Patients with Rheumatoid Arthritis

Study dates: First subject enrolled: 15 May 2012
Last subject last visit: 15 January 2013

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator: [redacted]

Sponsor's Responsible Medical Officer:

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

Study centres

[redacted]

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Primary objective:	**Primary outcome variable:**
To assess the effect of fostamatinib (100 mg twice daily [*bid*] taken in combination with a disease-modifying anti-rheumatic drug [DMARD]), relative to placebo plus a DMARD, on 24-hour mean ambulatory systolic blood pressure (SBP) at Week 4, in patients with active rheumatoid arthritis (RA).	Mean change from baseline in 24-hour mean ambulatory SBP after 4 weeks of treatment with fostamatinib or placebo
Secondary objectives:	**Secondary outcome variables:**
To assess the effect of fostamatinib (100 mg *bid* taken in combination with a DMARD), relative to placebo plus a DMARD, on 24-hour mean ambulatory diastolic blood pressure (DBP) at Week 4, in patients with active RA.	Mean change from baseline in 24-hour mean ambulatory DBP after 4 weeks of treatment with fostamatinib or placebo
To describe the effect of fostamatinib on blood pressure (BP) throughout the day by comparing daytime, night-time, awake and sleeping SBP and DBP between fostamatinib and placebo groups by ambulatory BP monitoring (ABPM).	Mean change from baseline in mean daytime (6am-9.59pm) SBP and DBP, night-time (10pm-5.59am) SBP and DBP, awake and sleeping SBP and DBP after 4 weeks of treatment with fostamatinib or placebo Ratio of night-time to daytime mean SBP and DBP
To describe the effects of fostamatinib on BP as determined with clinic BP and as determined with home BP assessments.	Mean change from baseline in clinic BP Mean change from baseline in pre-dose (morning) home weekly mean SBP and DBP and post-dose (evening) home weekly mean SBP and DBP
To describe the BP effects following discontinuation of fostamatinib (persistence and/or reversibility of the effect), including subjects who stopped the treatment prematurely due to BP elevation above the predefined threshold and for other safety reasons.	Mean change from completion/discontinuation to follow-up in clinic measurement of SBP and DBP
To evaluate the efficacy of fostamatinib as measured by Disease Activity Score based on a 28 joint count (DAS28).	DAS28-C-reactive protein (CRP), DAS28-erythrocyte sedimentation rate (ESR), DAS28 European League Against Rheumatism (EULAR) response criteria, Health Assessment Questionnaire-Disability Index (HAQ-DI), individual components of DAS28, patient's global assessment of disease activity, physician's global assessment of disease activity and patient's assessment of pain, CRP, ESR

Additional safety objectives:	**Additional safety outcome variables:**
To evaluate the safety and tolerability of fostamatinib, taken in combination with a DMARD, in patients with active RA.	Adverse events (AEs), serious adverse events (SAEs), serious infective events, vital signs, laboratory safety assessments, electrocardiogram abnormalities, weight, physical examination
To investigate the relationship between variations in the gene encoding uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) and the safety and tolerability of fostamatinib in the study population.	UGT1A1 genotype
Exploratory objectives (reported separately from the CSR)**:**	**Exploratory outcome variables:**
To collect and store blood samples 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/or DMARDs; and/or susceptibility to, progression of and prognosis of RA; and/or associated biomarkers.	DNA from whole blood
To investigate the pharmacokinetics of R406 (the active moiety of fostamatinib) and to investigate the relationship between systemic exposure to R406 and AEs, safety parameters and efficacy outcomes.	Plasma R406 concentrations
To investigate systemic biomarker profiles in RA patients.	Serum and plasma biomarkers

Study design

This was a multi-centre, randomised, double-blind, placebo-controlled, parallel group study to characterise the BP effects of fostamatinib in patients with active RA. Patients received investigational product (IP) for 4 weeks, followed by a 1-week wash-out period.

Patients were randomised 1:1 to treatment with fostamatinib (100 mg *bid*) or matching placebo, both in combination with their usual DMARD (methotrexate, sulfasalazine, hydroxychloroquine or chloroquine). Randomisation was stratified according to whether patients were receiving stable anti-hypertensive medications and whether they had a prior failure to a biologic DMARD.

Blood pressure was measured by 24-hour ABPM (performed at baseline and after 4 weeks of treatment), home BP (measured over several week-long periods) and clinic BP (measured at weekly scheduled visits).

For the purposes of detecting a signal in this short-term study, both DBP and SBP were considered equally adequate measures and SBP was chosen as a well-established primary endpoint in ambulatory BP studies. During the study, safety findings were closely monitored on an ongoing basis.

A Safety Review Committee was set up to assure the safety of RA patients receiving fostamatinib and a blinded Cardiovascular Adjudication Committee reviewed pre-defined AEs of potential cardiovascular (CV) nature.

Target subject population and sample size

Male and female patients aged ≥18 years, with active RA despite current DMARD treatment. Patients with hypertension could have been included provided their BP was controlled (<140/90 mmHg) with anti-hypertensive medications being stable for at least 4 weeks prior to randomisation.

It was planned to randomise approximately 130 patients, 65 to each treatment group. Patients were to be randomised 1:1 to treatment with fostamatinib (100 mg *bid*) or placebo, both in combination with their usual DMARD.

Approximately 65 patients per randomised group were recruited in order to achieve approximately 52 evaluable patients per group. The target of 52 evaluable patients per randomised group gave 80% power to detect a treatment effect of 5 mmHg in 24-hour mean ambulatory SBP between fostamatinib and placebo at a 2-sided 5% significance level, based upon a standard deviation (SD) of 9 mmHg in the mean change in 24-hour mean ambulatory SBP. This size also gave at least 80% power to detect a treatment effect of 3.5 mmHg in 24-hour mean DBP, based on a SD of 6 mmHg.

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

Fostamatinib or matching placebo blue, film-coated, 50 mg tablets were taken orally, *bid* (once in the morning and once in the evening). Patients were to continue to take their usual prescribed DMARD (methotrexate, sulfasalazine, hydroxychloroquine or chloroquine), from their usual source. Tablets could be taken with or without food, but not with food/drink known to inhibit cytochrome P450 isoenzyme 3A4. Fostamatinib batch numbers: 11821.5/1A, 11821.3/1A. Placebo to fostamatinib batch numbers: 11821.5/1B, 11821.3/1B.

Duration of treatment

Treatment continued for 28 days unless any discontinuation criteria were met. Patients who successfully completed the scheduled treatment period, or those requiring a dose reduction, could continue to receive fostamatinib in a long-term extension study, OSKIRA-X.

Statistical methods

The full analysis set was the primary population for reporting efficacy and safety data, and comprised all randomised patients who received at least 1 dose of IP, and were analysed according to randomised treatment (intention-to-treat principle).

The primary analysis was performed by comparing change from baseline in 24-hour mean ambulatory SBP between fostamatinib and placebo using an analysis of covariance (ANCOVA) model including terms for baseline as a continuous covariate and treatment, region, prior failure to a biologic DMARD and use of anti-hypertensive medication at baseline as covariates. The change in 24-hour mean ambulatory DBP was analysed similarly. Similar ANCOVA analyses were also performed to compare the change from baseline in the other

secondary BP endpoints between fostamatinib and placebo, including those for weekly mean home BP and clinic BP.

Subgroups were defined based on baseline values for the following characteristics: gender, race, age, region and the use of medications which could have an effect on BP (anti-hypertensive medications, non-steroidal anti-inflammatory drugs [NSAIDs; including coxibs] and oral steroids).

The efficacy of fostamatinib compared to placebo was assessed by analysing the change from baseline at each clinic visit in DAS28-CRP using an ANCOVA model including terms for baseline as a continuous covariate and treatment, region, prior failure to a biologic DMARD and use of anti-hypertensive medication as factors. The change from baseline in DAS28-ESR was also analysed. The change from baseline in the individual DAS28 components and in HAQ-DI score were summarised using standard summary statistics by treatment group and timepoint.

Subject population

Overall, 135 patients were randomised, all of whom received IP (68 patients received fostamatinib and 67 patients received placebo). Sixty four (94.1%) and 65 (97.0%) patients in the fostamatinib and placebo groups, respectively, completed the study.

The mean age of the study population was 54 years (range: 25 to 83 years), 84.4% were female, and most were White (89.6%). While some imbalances in the number of patients per treatment group <50 years of age and number of Black or African American patients were observed, this was not considered to affect study interpretation. The number of Black or African American patients was small. Mean DAS28-CRP (5.43 and 5.46 in the fostamatinib and placebo groups, respectively) was well balanced between the treatment groups at baseline. The randomised treatment groups were generally well balanced with regard to demographic and baseline disease characteristics, including BP.

Medical history of current hypertension was recorded in 33 (48.5%) patients in the fostamatinib group and 31 (46.3%) patients in the placebo group and 31 (45.6%) and 32 (47.8%) patients, respectively, were receiving anti-hypertensive medication at baseline. Twenty-nine (42.6%) patients in the fostamatinib group and 32 (47.8%) patients in the placebo group were receiving oral steroids at baseline and 37 (54.4%) and 38 (56.7%) patients, respectively, were receiving NSAIDs at baseline.

Summary of safety results

Total exposure was 5.67 treatment years in the fostamatinib group and was comparable with placebo (5.59 treatment years). Most patients had no dose interruption during the study (64 [94.1%] and 66 [98.5%] patients in the fostamatinib and placebo groups, respectively).

Fostamatinib was associated with increases in BP. The primary analysis reported a treatment difference between fostamatinib and placebo in 24-hour mean ambulatory SBP of 2.93 mmHg with a 95% confidence interval (CI) of (0.40, 5.45) at Day 28 (see Table S2).

Table S2 24-hour mean ambulatory SBP (mmHg) - change from baseline, comparison between fostamatinib and placebo at Day 28

			--Comparison with Placebo--		
Treatment	**n**	**LS Mean**	**Treatment difference**	**95% CI**	**2 sided p-value**
FOSTA 100 MG BID (N=68)	65	4.68	2.93	0.40, 5.45	0.023
PLACEBO (N=67)	63	1.76			

This analysis is performed using an ANCOVA model on the change from baseline, including terms for baseline as a continuous covariate and treatment, region, prior failure to biologic DMARD and the use of anti-hypertensive medication at baseline as factors.
For patients who withdrew prematurely, ABPM was measured at the early discontinuation visit and used in place of Day 28 data.

The 24-hour mean ambulatory SBP baseline values were similar for fostamatinib and placebo (118.7 mmHg and 117.7 mmHg, respectively). After 28 days of treatment, mean changes from baseline in 24-hour mean ambulatory SBP of 4.3 mmHg and 1.3 mmHg were observed in the fostamatinib and placebo groups, respectively.

The key secondary analysis reported a treatment difference between fostamatinib and placebo in 24-hour mean ambulatory DBP of 3.53 mmHg with a 95% CI of (2.04, 5.03) at Day 28 (see Table S3).

Table S3 24-hour mean ambulatory DBP (mmHg) - change from baseline, comparison between fostamatinib and placebo at Day 28

			--Comparison with Placebo--		
Treatment	**n**	**LS Mean**	**Treatment difference**	**95% CI**	**2 sided p-value**
FOSTA 100 MG BID (N=68)	65	4.51	3.53	2.04, 5.03	<0.001
PLACEBO (N=67)	63	0.97			

This analysis is performed using an ANCOVA model on the change from baseline, including terms for baseline as a continuous covariate and treatment, region, prior failure to biologic DMARD and the use of anti-hypertensive medication at baseline as factors.
For patients who withdrew prematurely, ABPM was measured at the early discontinuation visit and used in place of Day 28 data.

The 24-hour mean ambulatory DBP baseline values were similar for fostamatinib and placebo (70.0 mmHg and 69.6 mmHg, respectively). After 28 days of treatment, mean changes from baseline in 24-hour mean ambulatory DBP of 4.4 mmHg and 0.7 mmHg were observed in the fostamatinib and placebo groups, respectively.

An increase in mean ambulatory SBP and DBP throughout the 24-hour period was seen for fostamatinib over placebo (see Figures S1[SBP] and S2 [DBP]).

Figure S1 **Ambulatory SBP (mmHg) - 24-hours profile plots of hourly group means**

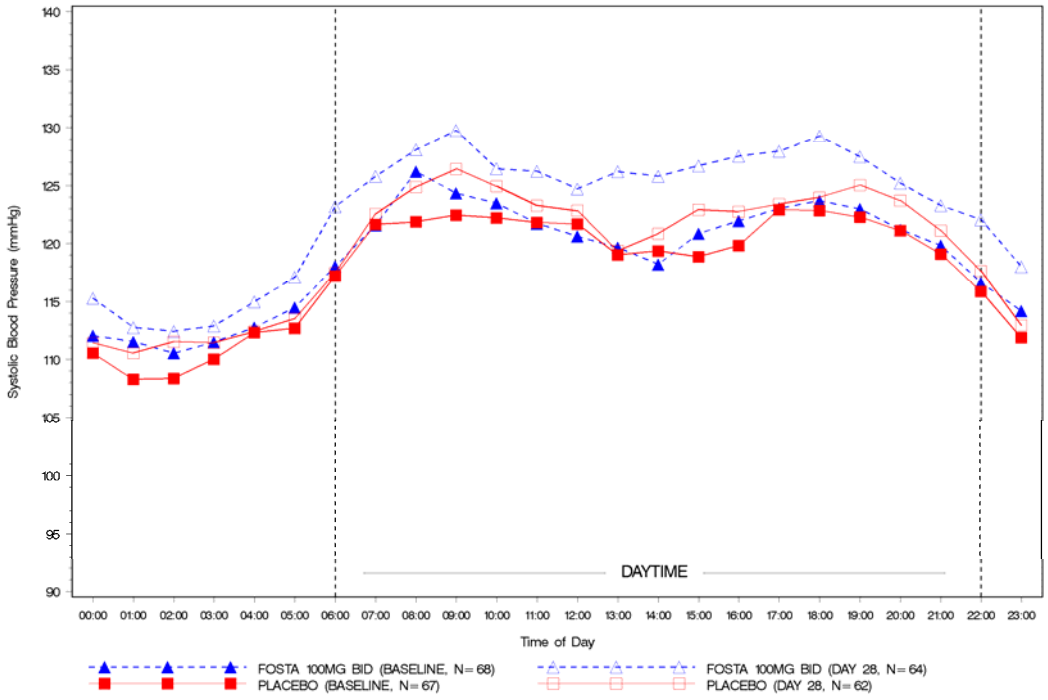
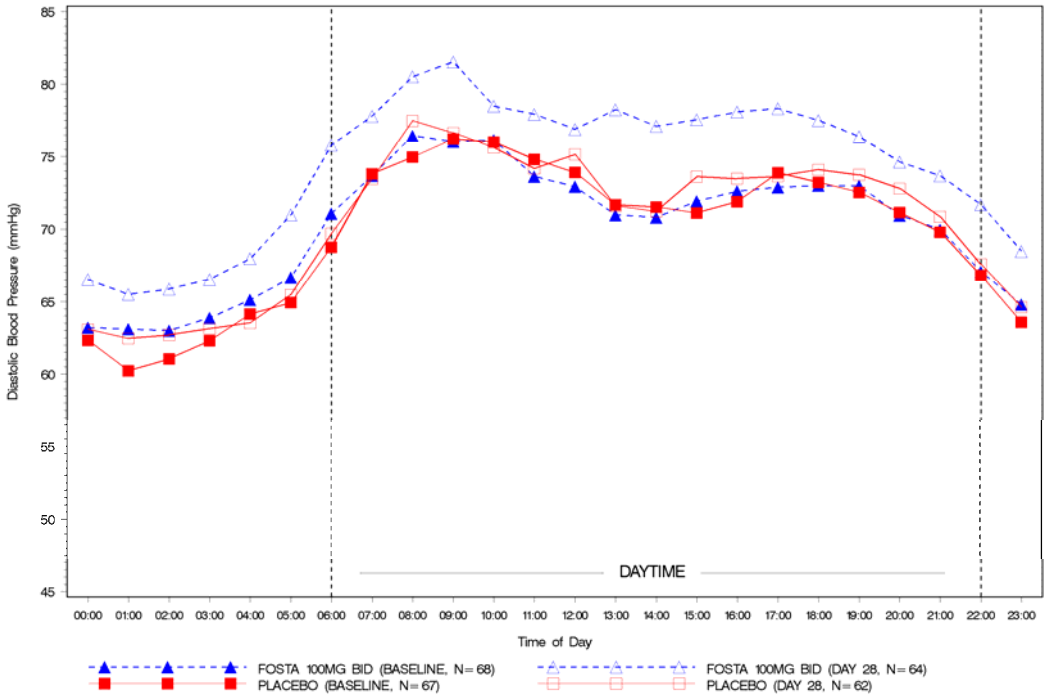


Figure S2 **Ambulatory DBP (mmHg) - 24-hours profile plots of hourly group means**



There was no indication of alteration to the circadian pattern over a 24-hour period. The extent of the BP increases were slightly larger during the daytime than the night-time, but the increases in each period of the day were of a broadly similar magnitude. After 28 days of treatment, mean changes from baseline in daytime mean ambulatory SBP of 4.9 mmHg and 1.6 mmHg were seen for the fostamatinib and placebo groups, respectively. The corresponding changes in night-time mean ambulatory SBP were 3.0 mmHg and 0.9 mmHg, respectively. After 28 days of treatment, mean changes from baseline in daytime mean ambulatory DBP of 4.7 mmHg and 0.8 mmHg were seen for the fostamatinib and placebo groups, respectively. The corresponding changes in night-time mean ambulatory DBP were 3.7 mmHg and 0.8 mmHg, respectively.

Although a small number patients in the fostamatinib group who had night-time to daytime ratios ≤0.9 at baseline were found to have ratios >0.9 at Day 28, the proportion of patients switching between these categories was less than in the placebo group. For SBP, 6 (27.3%) patients in the fostamatinib group and 11 (44.0%) patients in the placebo group had a night-time to daytime ratio ≤0.9 at baseline and >0.9 at Day 28. For DBP, 6 (18.8%) and 12 (27.3%) patients, respectively, had a night-time to daytime ratio ≤0.9 at baseline and >0.9 at Day 28.

Patients receiving anti-hypertensive medication at randomisation were noted to have numerically higher BP increases during this study compared to those not receiving such medication. Patients receiving oral steroids at baseline were also noted to have numerically higher BP increases during this study compared to those not receiving such medication. No consistent differences in BP were recorded in patients receiving NSAIDs at baseline compared to those not receiving such medication. In general, similar results were observed for each of the applicable secondary endpoints, including by clinic and home BP measurement, although with some variation in the magnitude of the changes observed. No firm conclusions could be drawn on the subgroup analysis according to age, gender and race.

Increases in BP for fostamatinib-treated patients were also observed using home BP monitoring. Pre-dose home weekly mean baseline SBP and DBP values were 119.6 and 79.3 mmHg in the fostamatinib group and 119.4 and 77.5 mmHg in the placebo group. Post-dose home weekly mean baseline SBP and DBP values were 118.4 and 78.4 mmHg in the fostamatinib group and 119.1 and 77.7 mmHg in the placebo group. At Week 4, greater increases from baseline in the morning (pre-dose) home weekly mean SBP and DBP were seen for the fostamatinib group compared to the placebo group: the mean changes from baseline in pre-dose home weekly mean SBP were 5.1 mmHg and -1.3 mmHg, respectively, and the mean changes from baseline in pre-dose home weekly mean DBP were 4.0 mmHg and -0.4 mmHg, respectively. The findings were consistent for the evening (post-dose) home weekly mean SBP and DBP: the mean changes from baseline in post-dose home weekly mean SBP were 5.3 mmHg and -1.6 mmHg for the fostamatinib and placebo groups, respectively, and the mean changes from baseline in post-dose home weekly mean DBP were 3.7 mmHg and -1.0 mmHg, respectively.

Mean baseline clinic SBP and DBP values were 121.9 and 75.6 mmHg in the fostamatinib group and 119.8 and 74.7 mmHg in the placebo group. In the fostamatinib group, mean changes from baseline were evident by Day 8, and subsequently plateaued up to Day 29. After 28 days of treatment, mean changes from baseline in clinic SBP of 3.8 mmHg and 2.9 mmHg were seen for the fostamatinib and placebo groups, respectively. After 28 days of treatment, mean changes from baseline in clinic DBP of 2.7 mmHg and 0.7 mmHg were seen, respectively.

Clinic BP ≥140/90 mmHg was experienced by 21 (30.9%) and 10 (14.9%) patients in the fostamatinib and placebo groups, respectively, during the study. No patients had clinic BP ≥180/110 mmHg. A total of 23 (35.9%) and 7 (11.3%) patients, respectively, experienced elevated 24-hour mean ambulatory BP ≥130/80 mmHg after 28 days of treatment.

Increased BP, as measured at clinic visits, appeared to be reversible after discontinuation of fostamatinib treatment. After the 1-week wash-out (Day 36), mean changes in SBP from the discontinuation visit (Day 29) of -3.3 mmHg and -0.5 mmHg were seen for the fostamatinib and placebo groups, respectively. Similarly, mean changes in clinic DBP from the discontinuation visit of -1.8 mmHg and -0.6 mmHg were seen for the fostamatinib and placebo groups, respectively. As such, mean clinic SBP and DBP returned to similar levels as baseline by Day 36.

No effect on pulse rate was observed during the study.

The number of patients that had at least 1 AE was 22 (32.4%) in the fostamatinib group and 26 (38.8%) in the placebo group. No deaths or treatment-emergent SAEs were observed during this study. The most common AEs were headache, hypertension, increased aspartate aminotransferase (AST), diarrhoea and anaemia. Overall, the incidence of AEs leading to discontinuation of IP (DAEs) was low, and a similar proportion of patients had DAEs in the fostamatinib (2 [2.9%] patients) and placebo groups (2 [3.0%] patients), of which, 1 patient in each treatment group discontinued due to hypertension or BP-related AEs. The incidence of CV AEs was low and the most commonly reported was hypertension. No patients had AEs which met the criteria for CV adjudication.

No absolute neutrophil counts <0.5 x 10^9/L were reported. Two patients experienced alanine aminotransferase (ALT) or AST values ≥3 x upper limit of normal (ULN): one patient in the fostamatinib group had ALT ≥3 to <5 x ULN and one patient in the placebo group had ALT ≥5 to <10 x ULN and AST ≥3 to <5 x ULN. No patients experienced maximum total bilirubin ≥2 x ULN and no patients met the clinical chemistry criteria for potential drug induced liver injury during the study (AST or ALT ≥3 x ULN **and** total bilirubin ≥2 x ULN).

Summary of pharmacogenetic results

While there is the potential for fostamatinib to act as a UGT1A1 inhibitor and effect certain laboratory parameters, such as bilirubin, no patients with polymorphisms in the gene encoding UGT1A1, or in this study as a whole, were reported with a potential drug induced liver injury.

No patients had a bilirubin concentration >2 x ULN. There was no evidence of clinical consequence for any genotype group in this data set.

Summary of efficacy results

A statistically significant difference in DAS28-CRP improvement was observed at Day 29 for fostamatinib compared to placebo with a treatment difference of 0.74 with 95% CI (0.4, 1.08), p<0.001. Consistent findings were observed for DAS28-ESR. Improvements from baseline were seen for fostamatinib compared to placebo in all components of DAS28 and in HAQ-DI.

Conclusions