AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00003
Edition Number	1
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(OSKIRA-3): A Phase III, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study of Two Dosing Regimens of Fostamatinib Disodium in Rheumatoid Arthritis Patients with Inadequate Response to a TNF-alpha antagonist

Study dates: First subject enrolled: 12 October 2010
Last subject last visit: 11 February 2013

Phase of development: Therapeutic confirmatory (III)

[redacted]

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

[redacted]

Publications

None.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Primary objective:	**Primary outcome variables:**
To evaluate the efficacy of 2 oral dosing regimens of fostamatinib taken in combination with methotrexate, compared with placebo plus methotrexate in patients with active rheumatoid arthritis (RA) who have had inadequate response to a single tumour necrosis factor- alpha (TNF-α) antagonist.	Proportion of patients who achieve American College of Rheumatology 20% response criteria (ACR20) at Week 24 (primary outcome variable).
Secondary objectives:	**Secondary outcome variables:**
To compare the efficacy of fostamatinib versus placebo measured by ACR20, ACR50, ACR70, ACR-N and the individual components of the ACR score.	ACR20, ACR50, ACR70, ACR-N, individual components of ACR (swollen joint count, tender joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function [as measured by the Health Assessment Questionnaire – Disability Index; HAQ-DI] and C-reactive protein [CRP]), ACR/ European League Against Rheumatism (EULAR) remission based on Simplified Disease Activity Index.
To compare physical function status of patients after administration of fostamatinib using the HAQ-DI.	HAQ-DI score; HAQ-DI response, individual dimensions of HAQ-DI.
To compare the efficacy of fostamatinib versus placebo as measured by Disease Activity Score based on a 28 joint count (DAS28) and DAS28 EULAR response criteria.	DAS28 response, DAS28 EULAR response criteria, DAS28 <3.2, DAS28 <2.6, clinically important change in DAS28 (improvement of at least 1.2).
To compare the efficacy of fostamatinib versus placebo in the prevention of structural joint damage, as measured by change in radiographic modified total sharp score (mTSS) at Week 24.	Change from baseline in mTSS, joint space narrowing (JSN) and erosion score (ES) at Week 24.
To compare the effects of fostamatinib on patient reported health outcomes measures.	Short form-36 (SF-36) – physical component score (PCS), mental component score (MCS), 8 individual domain scores. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score. Medical Outcomes Study (MOS)-Sleep – 2 sleep problem indices (SPI, SPII) and the Sleep disturbance scale (SDS). EuroQoL-5 Dimension health status questionnaire (EQ-5D).

Safety objectives:	**Safety outcome variables:**
To evaluate the safety and tolerability of fostamatinib taken in combination with methotrexate in patients with active RA.	Adverse events (AEs) (including independent adjudication of cardiovascular events); clinical chemistry, haematology, urinalysis; physical examination; electrocardiogram (ECG); weight; vital signs.
Investigate the relationship between variations in the gene encoding UGT1A1 and the safety and tolerability of fostamatinib in the study population.	UGT1A1*28 genotype
Exploratory objectives (not reported in the CSR):	
Investigate the pharmacokinetics (PK) of R406 (active metabolite of fostamatinib) and/or the PK of fostamatinib or other metabolites and to investigate the relationship between systemic exposure to these metabolites and AEs, safety parameters and efficacy outcomes.	Plasma R406 and/or fostamatinib or other metabolites concentrations, oral clearance, area under plasma concentration-time curve during dosing interval at steady state. Limited PK data due to sparse sampling.
To assess overall cardiovascular risk according to risk models such as the Framingham model and/or SCORE model.	Demographics, medical history, lipids and blood pressure (BP).
Collect and store DNA for future exploratory research into genes/genetic variation that could influence response (ie, absorption, distribution, metabolism and excretion, safety, tolerability and efficacy) to fostamatinib and/or adalimumab; and/or susceptibility to, progression of and prognosis of RA; and/or associated biomarkers.	DNA from whole blood
To investigate systemic biomarker profiles in RA patients.	Serum and plasma biomarkers

Study design

This was a 24-week, multi-centre, randomised, double-blind, placebo-controlled, parallel group study to investigate the efficacy and safety of fostamatinib in patients with active RA who have had an inadequate response or intolerance to a single TNF-α antagonist.

Patients were randomised to study treatment as follows:

Group A: Fostamatinib 100 mg twice daily (*bid*).

Group B: Fostamatinib 100 mg bid for 4 weeks then 150 mg once daily (*qd*) thereafter.

Group C: Placebo.

In addition, all patients were on stable background methotrexate (7.5 to 25 mg per week) during the study. Randomisation was stratified by country. An experienced independent joint assessor, blinded to other study assessments and to dosing regimen, was used at each site to perform the swollen and tender joint counts. A Safety Review Committee reviewed the accumulating safety data, and a blinded Cardiovascular Adjudication Committee (CVAC) reviewed pre-defined AEs of potential cardiovascular nature.

Patients who successfully completed the scheduled treatment period and patients who did not show adequate response by Week 12 (defined as not achieving at least a 20% reduction from

baseline in either swollen or tender joint count) could, at the discretion of the investigator, be transferred to a long-term extension study to receive fostamatinib 100 mg *bid*.

Target subject population and sample size

Male and female patients aged ≥18 years, with active RA and who had shown inadequate response or intolerance to a single TNF-α antagonist. Eligibility criteria were designed to allow demonstration of a clinically meaningful treatment effect.

Assuming an ACR20 response rate in the placebo group of 15% (as typically observed in previous studies of patients with prior biologic use), a sample size of 450 patients (150 in each arm) was planned. Clinical study protocol amendment 4 revised the planned total number of randomised patients to approximately 300 (100 in each arm). This would provide approximately 85% power to detect a difference of 20% or more between a dose regimen and placebo in the proportion of patients achieving ACR20 at Week 24 using a 2-sided test at the 2.5% level of significance.

Investigational product (IP) and comparator: dosage, mode of administration, 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) on a background of methotrexate. Tablets could be taken with or without food, but not with food/drink known to inhibit cytochrome P450 3A4. Dose reduction to fostamatinib 100 mg *qd* was available for management of tolerability.

Individual batch numbers and further information are included in the CSR.

If necessary, to control symptoms of RA, patients could have intramuscular, intravenous, or intra-articular corticosteroid injections of up to 80 mg methyl prednisolone (or equivalent).

Duration of treatment

Treatment continued for 24 weeks unless any discontinuation criteria were met. Patients who successfully completed the scheduled treatment period 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).

Each regimen of fostamatinib (Groups A and B) in combination with methotrexate was compared separately to placebo in combination with methotrexate at all scheduled post-baseline assessments to Week 24.

The primary analysis of ACR20 at Week 24 was to be performed using a test of treatment difference in proportion of responders (patients who achieved ACR20 at Week 24) with a

Mantel-Haenszel approach stratified by country. If the 2-sided p-value for ACR20 was ≤0.05 in favour of fostamatinib for both dose regimens, then the primary endpoint was to be considered statistically significant for both dose regimens. If the p-value for either dose regimen was >0.05, then for the other dose regimen, a 2-sided p-value ≤0.0262 in favour of fostamatinib was considered statistically significant.

There were 6 key secondary endpoints in this study:

- Proportion of patients achieving ACR20 at Week 1.
- Proportion of patients achieving ACR50 at Week 24.
- Proportion of patients achieving ACR70 at Week 24.
- Proportion of patients achieving DAS28<2.6 at Week 24.
- Proportion of patients achieving DAS28≤3.2 at Week 12.
- Proportion of patients achieving reduction in HAQ-DI≥0.22 at Week 24.

If the primary endpoint was statistically significant for both dose regimens using the above procedure, the Hommel procedure was to be applied across the key secondary endpoints for both dose regimens at the overall 2-sided 5% level. Otherwise, if the primary endpoint was statistically significant for 1 dose regimen only, the Hommel procedure was to be applied across the key secondary endpoints for that dose regimen only at the overall 2.5% level.

Further secondary endpoints were to be tested at a 2-sided significance level of 5% for each dose regimen versus placebo, and interpreted in the context of the significance level of the primary and key secondary endpoints for each dose regimen.

Analysis of ACR20, ACR50, and ACR70 at each timepoint was performed using a test of the treatment difference in the proportion of responders as described for ACR20. ACR-N scores at each timepoint were analysed using a non-parametric method. Individual ACR components at each timepoint were analysed using analysis of covariance (ANCOVA) on the change from baseline, including terms for baseline as a continuous covariate and treatment and country as factors. The proportion of patients classified as having achieved DAS28 response criteria at each timepoint was analysed using logistic regression including treatment and country as factors. The DAS28 EULAR response at each timepoint was to be analysed using a proportional odds model including treatment and country as factors. In addition to the analysis of HAQ-DI score as an individual ACR component, the proportion of patients classified as HAQ responders at each time point was analysed using logistic regression including treatment and country as factors. Changes in mTSS and its components, JSN and ES, at Week 24 were to be summarised and analysed using an ANCOVA model on the ranks of the change from baseline, including terms for the rank of the baseline score as a covariate and treatment and country as factors. SF-36 was summarised as change from baseline over

time. The PCS and the MCS were analysed at each time point using the ANCOVA model described for individual ACR components.

Subject population

In total, 63.8% and 60.2% of patients in the fostamatinib Groups A and B completed treatment; of those patients who were randomised to placebo (Group C), 50.0% completed the 24-week study treatment.

Figure S1 Patient disposition: randomisation

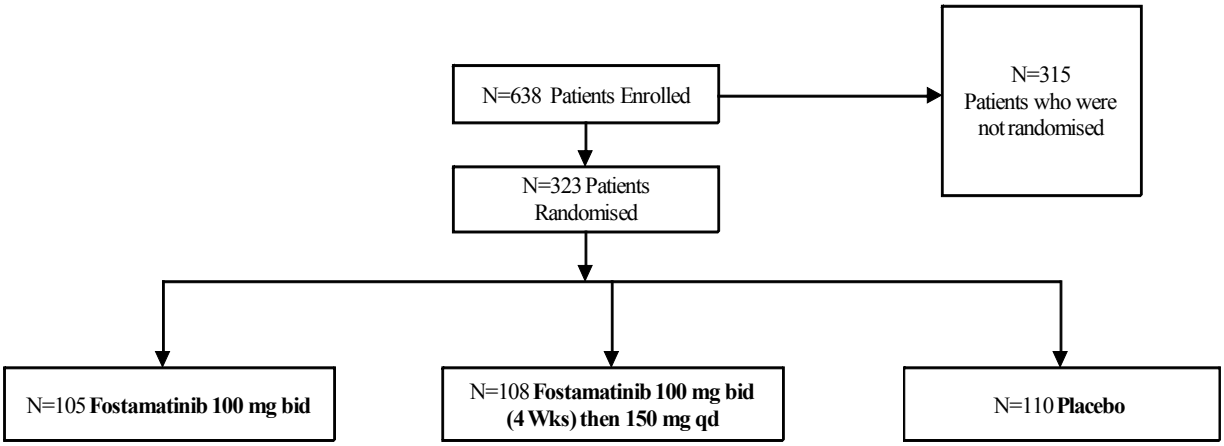
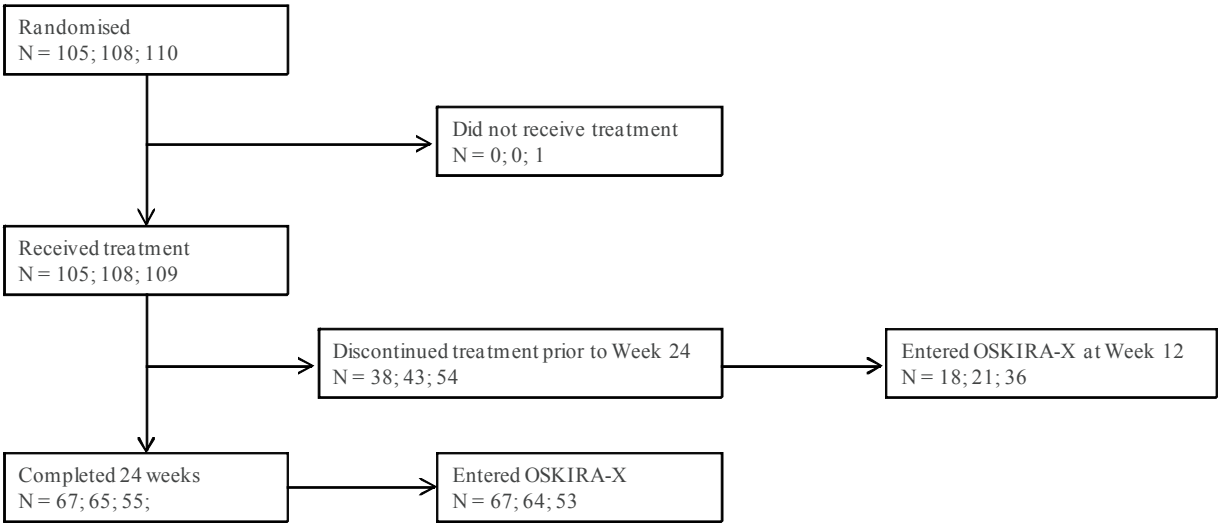


Figure S2 Patient disposition: study completion and discontinuation



N = Number of patients: Group A; Group B; Group C

"Completed" includes those patients who had a dose reduction in their study treatment.

The mean age of the study population was 53 years (range: 19 to 79 years), 81.1% were female, and most were White (83.5%). Mean DAS28-CRP score at baseline was 5.86. All

patients had prior use of a TNF-α antagonist. The randomised treatment groups were generally well balanced with regard to demographic and baseline disease characteristics.

Summary of efficacy results

Fostamatinib achieved statistically significant improvements in the primary variable, ACR20 response rate at 24 weeks, in Group A (36.2%; p=0.004) but not in Group B (27.8%; p=0.168) compared to Group C (21.1%). Subgroup results were consistent with the overall population.

Fostamatinib achieved a statistically significant improvement over placebo for all of the signs and symptoms key secondary endpoints for Group A (ACR20 at Week 1, ACR50 at Week 24, ACR70 at Week 24, DAS28-CRP<2.6 at Week 24, DAS28-CRP≤3.2 at Week 12 and reduction in HAQ-DI ≥0.22 at Week 24). Formal statistical interpretation could not be performed for the key secondary endpoints of the study for Group B, as the comparison for the primary variable was not significant at that dose.

For a further secondary endpoint (not part of the multiple testing procedure), fostamatinib did not show a difference in mTSS at 24 weeks for Group A (nominal p=0.729) compared to placebo. Although there is a suggestion of a difference versus placebo for Group B (nominal p=0.019), this is not consistent with the signs and symptoms results.

Results for further secondary signs and symptoms endpoints not included within the multiple testing procedure were consistent with findings for the primary and key secondary endpoints, including patient reported outcomes.

Summary of pharmacogenetic results

While there is potential for fostamatinib to act as a UGT1A1 inhibitor and affect 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 potential drug induced liver injury. One patient (a UGT1A1*28/*28 homozygote) had a total bilirubin concentration >2x the upper limit of normal (ULN). Variability in total or indirect bilirubin values was similar across the groups, regardless of genotype, and no notable changes in variability were observed over time or between treatment groups. There was a slight increase in bilirubin (total and indirect) concentration observed following fostamatinib dosing, regardless of genotype, however, this was more marked in the *28*28 group; the observed increases were sustained throughout the study. There was no evidence of further increases in bilirubin (total and indirect) during the study. There was no evidence of clinical consequence for any genotype group on fostamatinib treatment.

Summary of safety results

Total exposure was similar in the fostamatinib groups (39.58 and 39.78 treatment years) and was 35.60 treatment years in the placebo group. Mean duration of exposure was similar in the fostamatinib groups (138 and 135 days in Groups A and B, respectively), and was lower in the placebo group (119 days). The proportions of patients with dose reductions were 9.5%, 6.5% and 1.8%, in Groups A, B and C, respectively.

Table S2 Number (%) patients who had at least 1 AE in any category

AE Category	--Number (%) of patients[a], Event rate (per 100 pt years)[b]-- --Rand - End of Study-- Fostamatinib 100 mg bid (N=105) (tot. dur=40.9)	Fostamatinib 100 mg bid (4 Wks) then 150 mg qd (N=108) (tot. dur=41.3)	Placebo (N=109) (tot. dur=36.9)
Any AE	87 (82.9) 212.6	81 (75.0) 196.3	78 (71.6) 211.2
Any AE with outcome = death	0 (0.0) 0.0	1 (0.9) 2.4	1 (0.9) 2.7
Any SAE (including events with outcome = death)	7 (6.7) 17.1	7 (6.5) 17.0	6 (5.5) 16.2
Any AE leading to discontinuation of IP	10 (9.5) 24.4	11 (10.2) 26.7	9 (8.3) 24.4
Any AE leading to dose reduction of IP	8 (7.6) 19.6	6 (5.6) 14.5	2 (1.8) 5.4

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] Number of patients with AEs divided by the tot.dur (total duration of exposure in years) across all patients in the full analysis set within each treatment group and period, multiplied by 100.

If action taken changed during the course of the AE then the worst case is summarised in the order: discontinued, dose reduced, dose interrupted. Percentages are based on the number of patients in the full analysis set within each treatment group and period.
MedDRA version 15.1.
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The most common AEs on fostamatinib and greater than placebo were diarrhoea, hypertension, dizziness, flatulence, gastritis, nasopharyngitis, arthralgia, vomiting and upper respiratory tract infection. Incidence of diarrhoea in the fostamatinib groups was 20.0% and 26.9%, compared to 6.4% on placebo. The incidence of hypertension was 13.3% and 13.9% in the fostamatinib groups, and 8.3% on placebo. Individual preferred terms for serious AEs (SAEs) were generally reported in single patients; the only event reported in more than 1 patient was gastroenteritis/gastroenteritis bacterial which was reported in 4 patients. Serious adverse events on fostamatinib included CV and infection events. The most common discontinuation due to AE (DAE) reported on fostamatinib was diarrhoea (1.0% and 3.7%, compared to 0% on placebo).

Gastrointestinal-related AEs reported by >1 patient in any group included diarrhoea, nausea, and vomiting. For approximately 80% of the fostamatinib patients with diarrhoea, the AE was reported as resolved. Among the 9 fostamatinib patients with diarrhoea reported as unresolved at the final visit, 8 entered the long term extension study. Relatively few patients started anti-propulsive medications (8.6% and 11.1% in fostamatinib groups) during the study. While this study was not designed to formally assess qualitative aspects of gastrointestinal tolerability, this finding suggests that, for a majority of the patients who experience diarrhoea, symptoms may be manageable without adjunctive medication (ie, anti-propulsive agents) or discontinuation of study treatment.

Two deaths were reported in the study; 1 was a major adverse cardiovascular event (MACE) (cardiorespiratory arrest) in Group B, and the other was due to diabetes mellitus (CV adjudication undetermined) in Group C. Most common CV events were hypertension-type events. Other CV event types (cardiac failure, myocardial infarction and other ischaemic heart disease) were reported in small numbers of patients across the 3 treatment groups. Ten SAEs in 8 patients were sent to the CVAC for adjudication, of which 3 events in 3 patients in Group B were adjudicated as CV.

Fostamatinib is associated with elevations in blood pressure (BP). Increases in BP were evident at Week 1. Increased BP was seen both in patients who were receiving anti-hypertensive medication at baseline, and those who were not, though patients were more likely to develop elevated BP≥140/90 mmHg if they were on anti-hypertensives at baseline. In the 2 fostamatinib groups, 25.7% and 29.6% of patients had intervention for elevated BP. In placebo, 12.8% of patients had intervention for elevated BP. Initiation of new anti-hypertensive medication was the most frequent intervention. The most common anti-hypertensives starting after study entry were: calcium channel blockers (dihydropyridine derivatives) (15.2%, 14.8% and 4.6%), ACE inhibitors, plain (7.6%, 12.0% and 1.8% of patients in Groups A, B and C, respectively) and selective β-blocking agents (3.8%, 4.6% and 4.6% of patients, respectively). Three patients (2 in Group A and 1 in Group B) had elevated BP >160/100 mmHg that persisted for at least 2 consecutive visits, 1 for whom it persisted for 3 consecutive visits. BP returned to normal on follow-up, in all patients who were discontinued from the study for elevated BP. Two patients in Group A had elevated BP≥180/110 mmHg.

Incidence of serious infective events (SIEs) (ie, infections fulfilling criteria for SAE or requiring intravenous antimicrobials) was low (7 patients overall); none were associated with evidence of neutrophils $<1.0 \times 10^9$/L. There was no evidence of neutropenia prior to the SIEs and no evidence that patients were unable to mount an immune response in the face of an infection challenge. No absolute neutrophil counts were reported $<0.5 \times 10^9$/L.

The proportion of patients with increased alanine aminotransferase (ALT) between 3xULN and 5xULN was higher on fostamatinib (3.8% and 1.9% in Groups A and B, respectively) than on placebo (0.9%). One patient in the placebo group had an increase in ALT or aspartate aminotransferase (AST) >5-≤10xULN reported; there were no increases in ALT or AST>10xULN. No patients met the clinical chemistry criteria of ALT/AST ≥3xULN and total bilirubin ≥2xULN for potential drug induced liver injury.