AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00004 (sub-study)
Edition Number	1.0
Date	12 November 2013
EudraCT	2010-023692-26

(Sub-study to OSKIRA-4): A Phase IIB, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Fostamatinib Disodium Monotherapy Compared with Placebo or Adalimumab Monotherapy in Patients with Active Rheumatoid Arthritis: Magnetic Resonance Imaging Sub-Study

Study dates: First subject enrolled: 30 September 2011
Last subject last visit: 17 July 2013
Date of early study termination: 17 July 2013

Phase of development: Therapeutic exploratory (IIB)

[redacted]

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

This study was terminated early due to the closure of the fostamatinib programme in rheumatoid arthritis (RA); therefore a synoptic clinical study report (CSR) has been prepared.

[redacted]

Publications

Taylor, P et al. Ann Rheum Dis. June 2013. Vol 72 Suppl 3, OP0048, pp 65-66.
(This publication refers to the main OSKIRA-4 study. Only 2 patients were in common between the main study and the sub-study).

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Primary objective:	**Primary outcome variable:**
To assess the efficacy of fostamatinib in reducing joint synovial disease activity as measured by change from baseline to Week 6 (versus placebo) in Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Image Scoring system (RAMRIS) synovitis score.	OMERACT RAMRIS synovitis score at Week 6.
Safety objectives:	**Safety outcome variables:**
Evaluate the safety and tolerability of fostamatinib taken as monotherapy in patients with active RA.	Adverse events (AEs; including independent adjudication of cardiovascular [CV] events); clinical chemistry, haematology, urinalysis; physical examination; electrocardiogram; weight; vital signs.
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*28 genotype
Exploratory objectives (reported in this CSR):	**Exploratory outcome variables:**
To assess the efficacy of fostamatinib in reducing joint synovial disease activity measured by change from baseline to Week 24 (versus adalimumab) in OMERACT RAMRIS synovitis score.	OMERACT RAMRIS synovitis score at Week 24.
To assess the efficacy of fostamatinib in reducing osteitis as measured by change from baseline to Week 6 (versus placebo) and Week 24 (versus adalimumab) in OMERACT RAMRIS osteitis score.	OMERACT RAMRIS osteitis score at Week 6 and Week 24.
To assess the efficacy of fostamatinib in prevention of structural joint damage as measured by: - Change from baseline to Week 6 (versus placebo) and Week 24 (versus adalimumab) in OMERACT RAMRIS erosions score - Change from baseline to Week 6 (versus placebo) and Week 24 (versus adalimumab) in joint space narrowing.	OMERACT RAMRIS erosions score at Week 6 and Week 24. Joint space narrowing at Week 6 and Week 24.

Exploratory objectives (not reported in this CSR):	**Exploratory outcome variables:**
To assess the efficacy of fostamatinib in reducing joint synovial disease activity as measured by change from baseline to Week 6 (versus placebo) and Week 24 (versus adalimumab) in contrast-enhanced magnetic resonance imaging (MRI) parameters including but not limited to: - K^{trans} Volume transfer constant between blood plasma and extravascular extracellular space (also referred to as the transfer coefficient of contrast agent across the capillary membrane) (min^{-1}) - *IRE* Initial rate of enhancement (mM/sec) - $IAUC_{60}$ Initial area under the contrast agent concentration curve for the first 60 seconds post contrast agent injection (mM·sec) - $IAUC_{120}$ Initial area under the contrast agent concentration curve for the first 120 seconds post contrast agent injection (mM·sec) - *VEP* Volume of Enhancing Pannus (mL) - *ME* Maximum Enhancement of the contrast agent concentration curve during Dynamic, Contrast-enhanced Magnetic Resonance Imaging (DCE-MRI) scanning series (mM) - v_e Volume of extracellular extravascular space per unit volume of tissue accessible to contrast agent (no unit) - v_p Volume of blood plasma per unit volume of tissue (no unit)	K^{trans}, *IRE*, $IAUC_{60}$, $IAUC_{120}$, *VEP*, *ME*, v_e, and v_p at Week 6 and Week 24.
Further assessment of the MRI scan data may be made to explore any other potential effects of fostamatinib on bone and joint structure. These data may be analysed separately from the main study and described in a separate report.	Qualitative review of MRI scan data.

In addition to the pre-specified magnetic resonance imaging (MRI) treatment comparisons between fostamatinib and adalimumab at Week 24, comparisons between these 2 groups were also produced at Week 6, given the limited number of patients who completed 24 weeks of treatment. These additional comparisons were confirmed in the Statistical Analysis Plan (SAP) prior to unblinding of this sub-study.

Study design

Patients participating in the sub-study of OSKIRA-4 followed the same study schedule and study design as that of the main study, ie, a 24-week, multi-centre, randomised, double-blind (administrator unblinded), placebo-controlled (for 6 weeks), parallel-group study to investigate the efficacy and safety of fostamatinib monotherapy in patients with active RA.

In the main OSKIRA-4 study, patients were randomised to one of 5 treatment groups. In the sub-study, patients were randomised to one of only 3 of these treatment groups as follows:

Group A: Fostamatinib 100 mg twice daily (*bid*) for 24 weeks plus placebo sub-cutaneous (sc) injection every 2 weeks.

Group D: Adalimumab 40 mg (sc injection) every 2 weeks for 24 weeks, plus placebo to fostamatinib *bid*.

Group E: Placebo *bid* (6 weeks), then switch to fostamatinib 100 mg *bid* to Week 24, plus placebo sc injection every 2 weeks.

In contrast to the main study, patients participating in the sub-study assigned to Group E, only switched to 100 mg fostamatinib *bid* at Week 6. (In the main study, Group E patients were randomly assigned to switch at Week 6 to either 100 mg fostamatinib *bid* or 100 mg fostamatinib *bid* for 4 weeks followed by 150 mg fostamatinib once daily [*qd*] for the remainder of the study).

Randomisation was stratified by disease-modifying anti-rheumatic drug (DMARD) naïvety (ie, DMARD-naïve versus DMARD-inadequate response/intolerant). 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 CV Adjudication Committee (CVAC) reviewed pre-defined AEs of potential CV nature.

In addition to the main study assessments, patients in the sub-study underwent MRI assessments. All patients in the sub-study had Contrast-Enhanced MRI (CE-MRI) scans to enable RAMRIS assessments, and where participating sites had DCE-MRI capability, this more extensive scan was performed to provide both CE- and DCE-MRI parameters. The same method was used for all scans for an individual patient.

The CE-MRI or DCE-MRI measurements were made of the whole hand. The hand with most active joint disease was selected for measurement at the first scan, assessed clinically by the Investigator on the basis of swelling and tenderness. The same hand was then to be used for all measurements.

The MRI scans were performed using commercially available 1.5T/ 3T whole-body MRI scanners. Images were obtained both prior to and after intravenous injection of the contrast agent, and captured and read centrally for synovitis, osteitis, and erosions according

to OMERACT definitions by 2 experienced blinded readers. Additionally, quantitative and semi-quantitative DCE measurements were obtained for analysis.

All patients were required to undergo one baseline scan within 6 to 14 days prior to the first dose of randomised treatment to assess current disease status. In accordance with best practice guidelines, 2 baseline evaluations were recommended in order to establish intra-patient variation. Where appropriate optional patient consent was given, an additional baseline scan was to be performed at ≥2 days prior to the first dose of randomised treatment (Visit 2), with ≥3 days separating the 2 scans to ensure adequate washout of contrast medium. Patients who either did not consent to or were not able to undergo a second baseline MRI evaluation were still able to participate in the study.

Follow-up scans were performed at Week 6 (+5 days/ -2 days) and Week 24 (±5 days).

Target subject population and sample size

Male and female patients aged ≥18 years, with active RA and not currently receiving DMARDs (DMARD-naïve, intolerant to DMARDs, or had inadequate response to a maximum of 2 DMARDs). Eligibility criteria were designed to include patients with relatively early RA, within 5 years of diagnosis.

In the sub-study, patients at participating sites had to meet the main study criteria and be willing and suitable to undergo CE-MRI assessments. Patients had to have ≥1 swollen joint in the hand/wrist, and ≥1 joint with RAMRIS synovitis score of ≥+1 as determined by baseline MRI scan. If a patient's baseline scan was read (to determine patient eligibility) as synovitis score ≥+1, but when all scans were subsequently read (for final analysis) by 2 independent readers and their combined synovitis score was <1, the patient was still deemed to have met the inclusion criteria. This situation may be expected to occur in <1% of patients as a consequence of the natural variability/ assessment by different readers.

It was planned to randomise approximately 90 patients to the sub-study (approximately 30 per treatment group) to ensure that approximately 81 (~27 per group) received study treatment. With 27 patients per treatment group, the sub-study would have at least 90% power to detect a mean difference of at least 1 unit between fostamatinib compared with placebo in the change from baseline in the OMERACT RAMRIS synovitis score at Visit 6 (Week 6), using a 10% 2-sided Wilcoxon Rank Sum Test. However, the study was terminated early due to the closure of the fostamatinib programme in RA. Seventy-four patients completed Visit 6 (Week 6), of whom 67 were evaluable for the primary endpoint.

Investigational product 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) as monotherapy. Tablets could be taken with or without food, but not with food/drink known to inhibit cytochrome P450 isoenzyme 3A4. Dose reduction to fostamatinib 100 mg *qd* was available for management of tolerability. (Fostamatinib batch numbers: 9636.5/1, 9636.9/1, 9636.11/1, 9636.15/1, 9636.20/1,

9636.24/1, 9636.32/1, 9636.37/1, 9636.42/1, 9636.45/1, 9636.46/1, 9636.59/1, 9636.61/2, 9636.62/2, 9636.66/2, 9636.73/2, 9636.74/1 and 9636.76/1. Placebo to fostamatinib batch numbers: 9636.8/1, 9636.10/1, 9636.14/1, 9636.16/1, 9636.23/1, 9636.25/1, 9636.33/1, 9636.37/1, 9636.41/1, 9636.44/1, 9636.47/1, 9636.52/1, 9636.61/2, 9636.65/2, 9636.72/1, 9636.72/2 and 9636.75/1).

Adalimumab 40 mg or matching placebo injections were administered every 2 weeks.

If necessary, to control symptoms of RA, patients could have intramuscular, intravenous or intra-articular corticosteroid injections of up to 80 mg methylprednisolone (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. The sub-study was terminated early due to the closure of the fostamatinib programme in RA.

Statistical methods

An updated analysis of the main OSKIRA-4 study objectives including patients from the main study and additional patients in the sub-study was not performed as there was little overlap between the patients unblinded for the analysis of the main OSKIRA-4 CSR and those in this sub-study. Only 2 patients were in common between the main study and the sub-study analysis sets and therefore this synoptic CSR only involves sub-study patients.

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

The CE-MRI endpoints were analysed using a van Elteren test with treatment group as row variable, the change from baseline in each of the CE-MRI endpoints as column variable and DMARD naïvety (DMARD-naïve versus DMARD-inadequate response/intolerant) as a stratification variable. Country was not used as a stratification factor as insufficient numbers of patients were available.

For each of the CE-MRI endpoints, the unstratified Hodges-Lehmann non-parametric point estimate for the median difference between treatment groups of the change from baseline, together with the associated non-parametric 90% confidence interval (CI) were presented for each treatment comparison. The CE-MRI endpoints were also presented graphically using cumulative probability density plots.

Efficacy endpoints were tested at a 2-sided significance level of 10% for fostamatinib versus placebo, and for fostamatinib versus adalimumab. There were no adjustments for multiplicity. In addition to the pre-specified MRI treatment comparisons between fostamatinib and adalimumab at Week 24, comparisons between these 2 groups were also produced at Week 6,

given the limited number of patients who completed 24 weeks of treatment. These additional comparisons were confirmed in the SAP prior to unblinding of this sub-study.

The signs and symptoms outcome variables (Disease activity score based on a 28 joint count-C-reactive protein [DAS28-CRP] and components, health assessment questionnaire - disability index [HAQ-DI]) were analysed as per the main study.

Subject population

Overall, 198 patients were enrolled into the sub-study. Of these, 97 were randomised and 90 received treatment. Of the patients who were randomised, 35.3%, 42.4%, and 43.3% of patients across the 3 treatment groups (Groups A, D and E, respectively) completed the 24-week study treatment. The most common reason for discontinuing the study was due to project closure (34 [35.1%] patients; balanced across the treatment groups); 3 patients in Group A discontinued due to the study-specific discontinuation criteria of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or bilirubin rise to a value ≥5 x upper limit of normal (ULN) at any time (2 patients), or due to sustained increased systolic or diastolic blood pressure (1 patient).

The first 2 patients randomised in the sub-study were also previously reported in the main OSKIRA-4 CSR (E6906412 and E6909401).

Figure S1 Patient disposition: randomisation

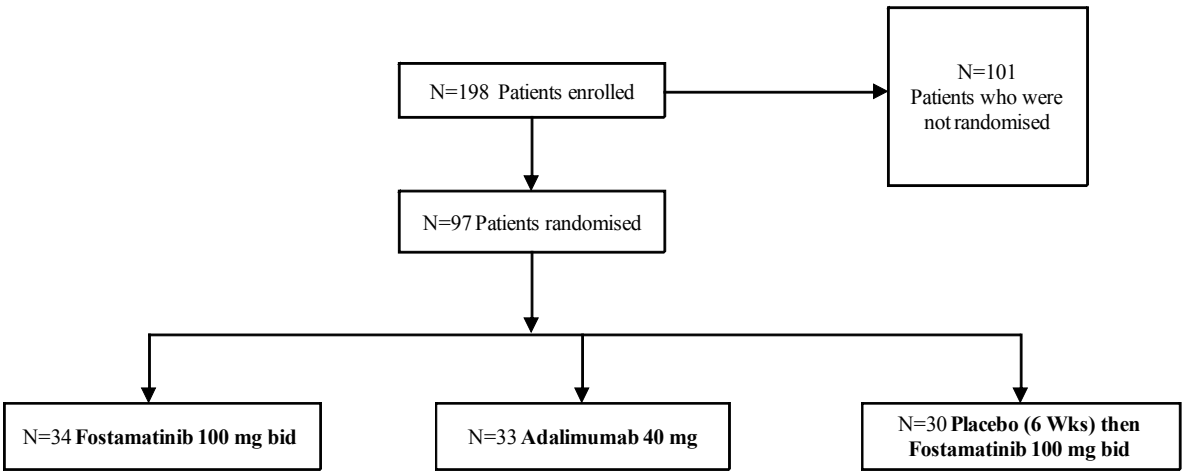
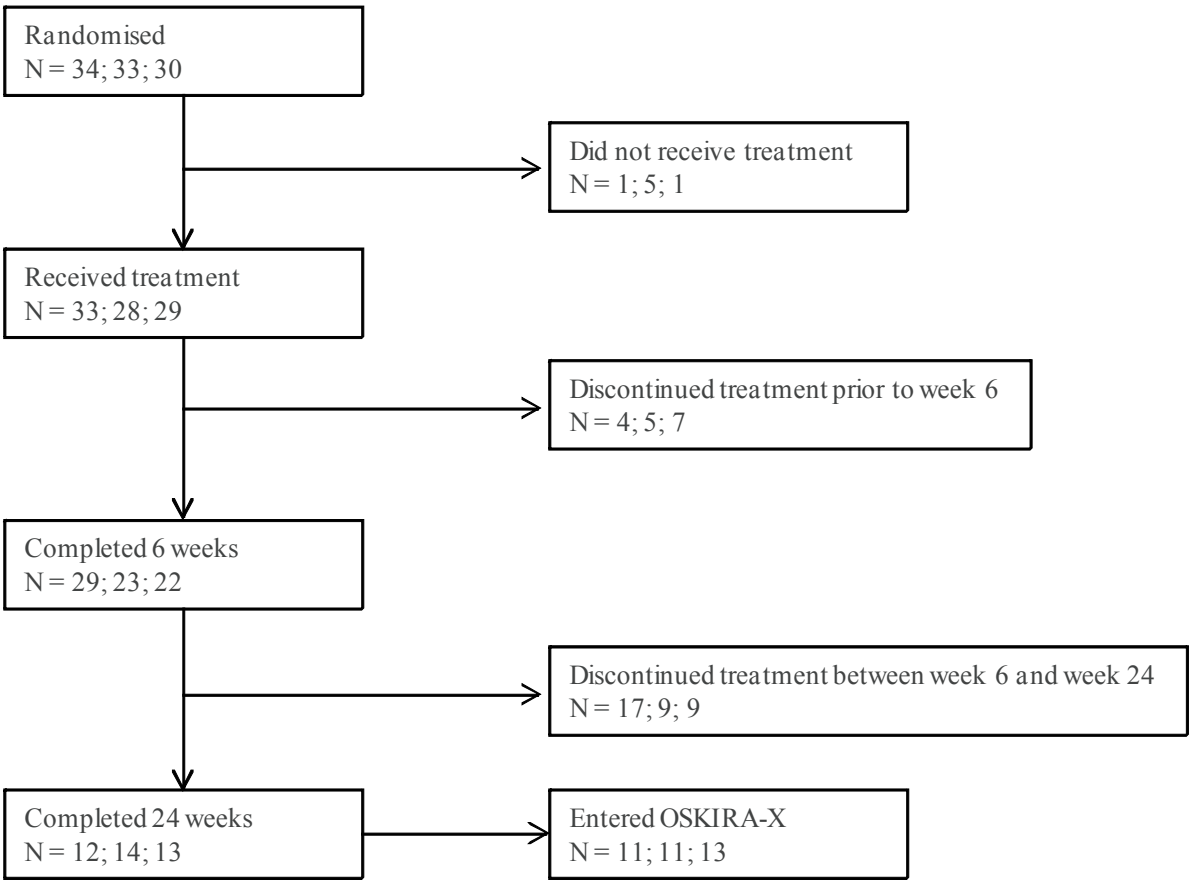


Figure S2 Patient disposition: study completion and discontinuation



N = Number of patients: Fostamatinib 100 mg *bid* (Group A); Adalimumab 40 mg (Group D); Placebo (6 weeks) then fostamatinib 100 mg *bid* (Group E).

Overall, 14 patients (15.6%) had at least one important protocol deviation. The most common protocol deviation was the use of DMARD medication at baseline or during the study (in 4 patients). Two patients used oral or parenteral steroids during the study, outside of those specified as allowed in the protocol. Patient E6909401 in Group E deviated from the protocol for use of DMARDs and disallowed steroids. There were no concerns regarding protocol deviations in terms of study conduct or the safety of patients.

In general, demographics were as expected in this patient population. The median age of the study population was 53 years (range: 23 to 75 years), 72.2% were female and 75.6% were White. The treatment groups were generally well balanced for demographics.

In general, baseline characteristics (including CV history, RA history, baseline disease activity and previous RA treatment) were as expected in this patient population and were balanced across the treatment groups. In terms of baseline disease characteristics, median tender joint count was 15, median swollen joint count was 10, median HAQ-DI score was 1.6, median CRP was 14 mg/L, median erythrocyte sedimentation rate was 42 mm/hr and median DAS28-CRP was 5.88. Median duration of RA was 0.6 years.

With regard to disease history, erosions based on previous X-radiography were present in 36.0% of patients, and 92.2% of patients had a documented positive rheumatoid factor test.

Overall, 62.2% of patients were DMARD-naïve, and 37.8% had received previous conventional DMARD therapy; the treatment groups were well balanced with regard to the stratification factor of DMARD-naïvety.

With the potential exception of dihydropyridine derivatives (anti-hypertensives) (1, 7 and 3 patients in Groups A, D and E, respectively), there was no clear imbalance in concomitant medications used between the treatment groups, given the small numbers of patients.

Small numerical differences were observed in baseline RAMRIS synovitis mean scores (7.6, 6.2 and 8.8 in Groups A, D and E, respectively), but given the small numbers of patients there was no clear imbalance between the treatment groups.

Summary of efficacy results

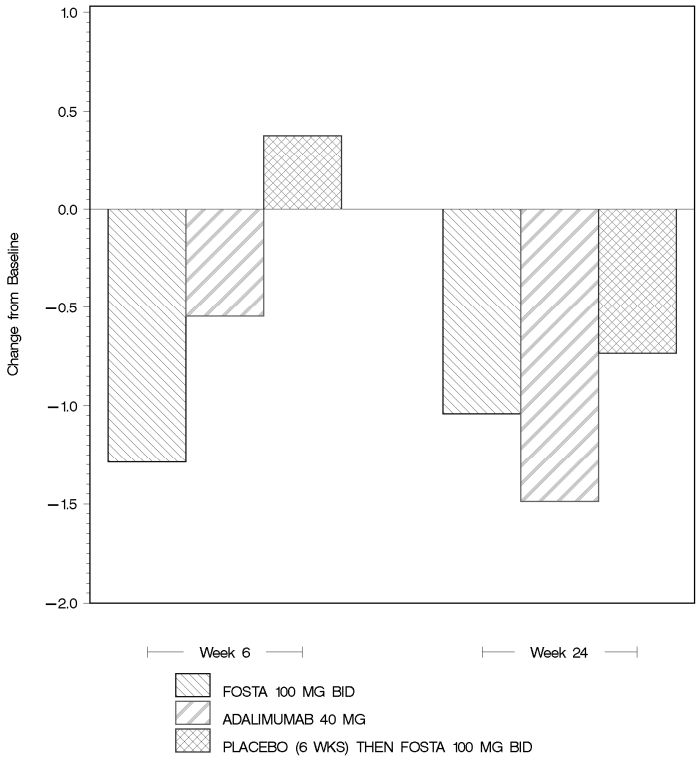
At Week 6, the primary variable RAMRIS synovitis score was reduced (median change -1.5) compared to baseline for patients treated with fostamatinib, and this treatment difference was statistically significantly better than placebo (median change 0.0) (Table S2). A negative value for the change from baseline in RAMRIS synovitis score indicates a better clinical condition. The mean changes from baseline for patients in the fostamatinib and placebo treatment groups were -1.3 and +0.4, respectively (Figure S3).

Table S2 OMERACT RAMRIS synovitis score: comparison between fostamatinib and placebo (van Elteren) (full analysis set)

						Comparison with Placebo			
Visit	**Treatment**	**n**	**Median**	**Q1**	**Q3**	**Treatment difference**	**90% CI**		**p-value**
Week 6	Fostamatinib 100 mg *bid* (N=33)	25	-1.50	-3.00	0.00	-1.75	-2.75	-0.42	0.022
	Adalimumab 40 mg (N=28)	22	-0.50	-1.00	0.00				
	Placebo (6 wks) then fostamatinib 100 mg *bid* (N=29)	20	0.00	-0.50	1.63				

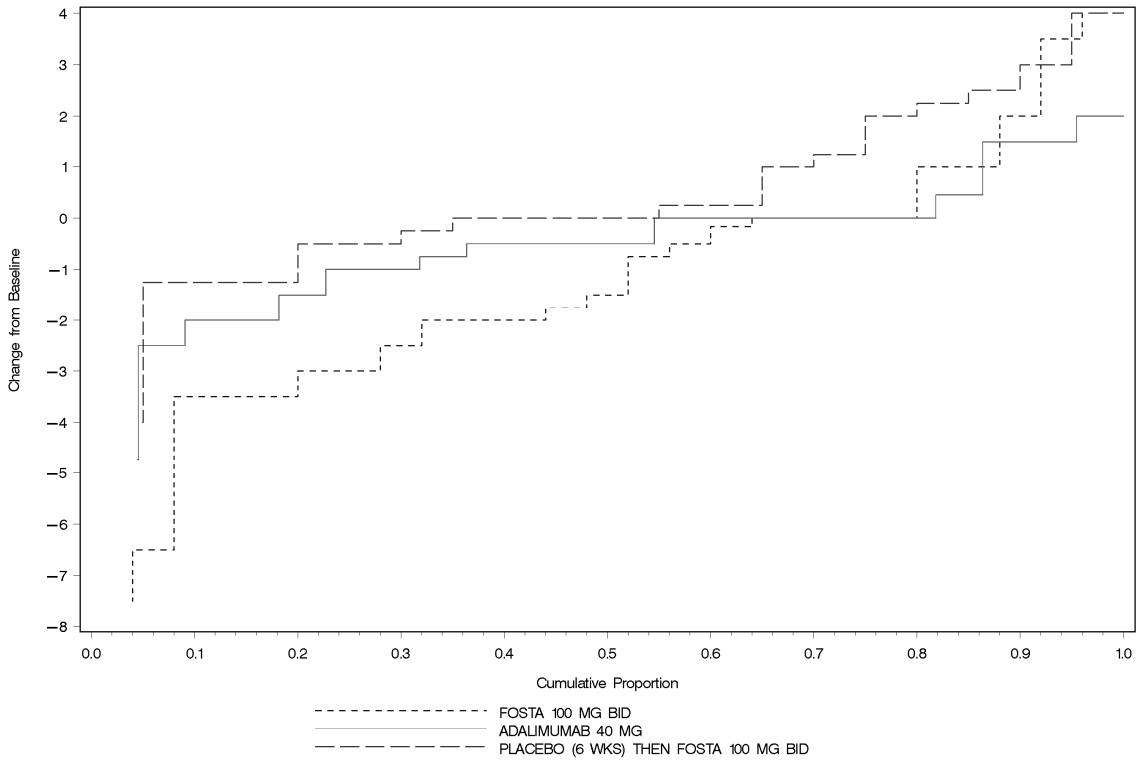
OMERACT RAMRIS synovitis score was based on 8 joints and ranged from 0 to 24 with a smaller value indicating a better clinical condition.
A negative value for change from baseline in OMERACT RAMRIS synovitis score indicates a better clinical condition.
The p-value is estimated using the van Elteren test stratified by DMARD naïvety. The point estimate for the median difference in change from baseline and associated 90% confidence interval are calculated using the method of unstratified Hodges-Lehmann.
A treatment difference <0 indicates a benefit towards fostamatinib.

Figure S3 Bar chart of mean change in synovitis (full analysis set)



OMERACT RAMRIS synovitis score was based on 8 joints and ranged from 0 to 24 with a smaller value indicating a better clinical condition.
A negative value for change from baseline in OMERACT RAMRIS synovitis score indicates a better clinical condition.

Figure S4 Synovitis score: cumulative probability plot of change from baseline at Week 6 (full analysis set)



OMERACT RAMRIS synovitis score was based on 8 joints and ranged from 0 to 24 with a smaller value indicating a better clinical condition.
A negative value for change from baseline in OMERACT RAMRIS synovitis score indicates a better clinical condition.

At Week 6, there was no significant treatment difference in RAMRIS synovitis score change from baseline between fostamatinib and adalimumab. The cumulative probability plot of change from baseline to Week 6 in RAMRIS synovitis score is shown in Figure S4.

At Week 24, RAMRIS synovitis score was reduced with both adalimumab- and fostamatinib-treated patients compared to baseline; however the treatment difference was not significant, and there were only small numbers of patients (18 and 16 patients in Group A and Group D, respectively) with assessments at this timepoint.

A bar chart of mean change from baseline in RAMRIS synovitis score at Week 6 and Week 24 is shown in Figure S3. Sensitivity analyses (including the baseline value as a covariate) confirmed the results of the primary analyses for RAMRIS synovitis score.

The RAMRIS osteitis and RAMRIS erosion results do not provide evidence that treatment with either fostamatinib or adalimumab ameliorate osteitis or erosion:

- At Week 6, RAMRIS osteitis mean score and RAMRIS erosion mean score were increased by 0.5 and 0.6, respectively, compared to baseline for patients treated with fostamatinib; there were no statistically significant differences versus placebo. Some differences in baseline observations were evident.

- Approximately 90% of patients in each treatment group had no increase in JSN score, and therefore at Week 6 and Week 24, total damage score (RAMRIS erosion score + joint space narrowing [JSN] score) results reflect the RAMRIS erosion score results.

Consistent with the reduction in RAMRIS synovitis score at Week 24, numerically, RAMRIS osteitis, RAMRIS erosion, JSN and total damage change scores with adalimumab were better (lower) than with fostamatinib; statistically significant treatment differences between fostamatinib and adalimumab were observed for RAMRIS erosion score and total damage score, although there were only small numbers of patients with assessments at this timepoint.

Results for signs and symptoms variables were consistent with findings from the main study:

- For the first 6 weeks, DAS28-CRP improvement from baseline for patients treated with fostamatinib was statistically significantly better compared to placebo (Week 6: least squares [LS] mean 1.37 with fostamatinib, LS mean 0.49 with placebo, treatment difference 0.89, 90% CI 0.36 to 1.41, p=0006); patients treated with adalimumab showed similar levels of improvement to patients treated with fostamatinib (Week 6: LS mean 1.15 with adalimumab). At Week 24, DAS28-CRP improvement from baseline LS means were 1.03, 1.37 and 1.51, for patients in Groups A, D and E, respectively.

- For American College of Rheumatology index of RA improvement (ACR) and DAS28-CRP components (including HAQ-DI), results were consistent with DAS28-CRP, showing improvements from baseline for patients treated with fostamatinib, which were numerically better than placebo at Week 6. At Week 24, patients treated with fostamatinib maintained improvement from baseline for ACR and DAS28-CRP components; however, the small numbers of patients with assessments preclude any definitive conclusions.

Summary of pharmacogenetic results

No individuals exhibited bilirubin ≥2 x ULN. Of the 10 *28/*28 individuals in the study population, 8 were treated with fostamatinib. Since no individuals exhibited bilirubin ≥2 x ULN it is not possible to determine a phenotype (bilirubin ≥2 x ULN)/genotype correlation.

Summary of safety results

Total exposure appeared consistent across the treatment groups (10.6 and 9.8 treatment-years in the fostamatinib [Group A] and adalimumab [Group D] groups, respectively, and 3.1 and 6.2 treatment-years with placebo then fostamatinib, respectively, in Group E), given the differences in numbers of patients. Mean duration of exposure to Week 24 was 117 and 128 days in Groups A and D, respectively, and 39 and 102 days with placebo then fostamatinib, respectively, in Group E.

Across the treatment groups, only 2 patients (1 [3.0%] patient in Group A and 1 [4.5%] patient in Group E) had a dose reduction, due to protocol-specified reason (Group A) and AE (Group E). In total, 5 patients (3 [9.1%] patients in Group A and 2 [7.1%] patients in Group D) had a dose interruption; 2 patients in Group A and 2 patients in Group D had a dose interruption due to AE. Across the groups, one (3.0%) patient in Group A had both a dose reduction and a dose interruption. In total, only one (3.0%) patient in Group A had a missed injection.

Table S3 Adverse events in any category

AE category	Number (%) of patients[a]			
	Randomisation to End of Study		Randomisation to Week 6	Week 6 to End of Study
	Fostamatinib 100 mg *bid* (n=33)	**Adalimumab** 40 mg (n=28)	**Placebo** (n=29)	**Placebo (6 wks) then fostamatinib** 100 mg *bid* (n=22)
Any AE	23 (69.7)	16 (57.1)	8 (27.6)	12 (54.5)
Any AE with outcome = death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	3 (9.1)	3(10.7)	1 (3.4)	0 (0.0)
Any AE leading to discontinuation of IP[b]	5 (15.2)	4 (14.3)	0 (0.0)	0 (0.0)
Any AE leading to dose reduction of oral IP[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Patients with multiple events in the same category are counted once in that category. Patients with events in >1 category are counted once in each of those categories.
[b] Patients could not discontinue oral IP and injected IP (adalimumab/adalimumab placebo) independently.
[c] If action taken changed during the course of AE, the worst case was summarised in the order: discontinued, dose reduced, dose interrupted.
IP Investigational product.

Adverse events from randomisation to end of study were reported in 23 (69.7%) patients and 16 (57.1%) patients in Group A (fostamatinib) and Group D (adalimumab), respectively. In Group E (placebo then fostamatinib), 8 (27.6%) patients and 12 (54.5%) patients had an AE from randomisation to Week 6, and from Week 6 to end of study, respectively. There were no deaths reported. The most common AE on fostamatinib was hypertension (reported in 4 [12.1%] patients on fostamatinib, 0% patients on adalimumab, 1 [3.4%] patient on placebo from randomisation to Week 6 and 1 [4.5%] patient on fostamatanib from Week 6 to end of

study). Other common AEs reported with >8% frequency in any treatment group were constipation, diarrhoea, nasopharyngitis, RA, ALT increased, and gastroenteritis.

Seven patients had serious AEs (SAEs), and 9 patients had AEs leading to discontinuation of investigational product (DAEs). Unlike the main OSKIRA-4 study, 4 patients had DAEs in the adalimumab group (0 patients in the main study).

Individual preferred terms for SAEs were reported at single incidences per group. Serious adverse events reported were gastroenteritis (Group A), post procedural haemorrhage (Group A), femoral neck fracture (Group A), musculoskeletal chest pain (Group D), orthostatic hypotension (Group D), asthma (Group D), exostosis and invertebral disc protusion (Group E; the same patient had 2 SAEs from randomisation to Week 6).

Individual preferred terms for DAEs were reported at single incidences per group, except for ALT increased and AST increased; DAEs were hypertension (Group A; patient E2821404 had a blood pressure [BP] reading of 157.5/104.5 mmHg on Day 1 and discontinued on Day 9 with a BP reading of 162.5/109.5 mmHg), colonic polyp (Group A), ALT increased (Group A; 2 patients), AST increased (Group A; in the same 2 patients with ALT increased), blood lactate dehydrogenase increased (Group A), gamma-glutamyltransferase increased (Group A), dizziness (Group D), mouth ulceration (Group D), urticaria (Group D) and musculoskeletal chest pain (Group D).

No major adverse CV events were reported in any treatment group. One SAE (orthostatic hypotension) in a patient on adalimumab was sent to the CVAC for adjudication, and was adjudicated to be a non-CV event.

Small increases in blood pressure were evident during the initial weeks in the fostamatinib treatment group (mean changes of 3.2 mmHg in systolic BP at Week 1, and 3.1 mmHg in diastolic BP at Week 2, respectively). Mean systolic BP and diastolic BP values stayed relatively constant in the fostamatinib (Group A) and adalimumab (Group D) treatment groups later in treatment. There was some variability in the placebo then fostamatinib group (Group E) with a maximum mean increase of 5.3 mmHg in systolic BP at Week 8. No patients had elevated BP >180/110 mmHg at any time during the study.

One patient in Group A experienced a serious infective event (ie, infections fulfilling criteria for SAE or requiring intravenous antimicrobials) (gastroenteritis); the patient's neutrophil count was normal throughout the study. The serious infective event resolved. No absolute neutrophil counts were $<1.0 \times 10^9$/L.

No patients met the clinical chemistry criteria of ALT/AST ≥3 x ULN and total bilirubin ≥2 x ULN for potential drug induced liver injury. A proportion of patients in the fostamatinib treatment group (Group A) had raised liver enzymes (normal baseline and high observation within randomisation to end of study period): 12 (37.5%) patients had raised ALT, 8 (25.0%) patients had raised AST, 9 (28.1%) patients had raised alkaline phosphatase, and 10 (31.3%) patients had raised creatine kinase. One patient (Group A) had ALT ≥5 and <10 x ULN, and one patient (Group A) had ALT >10 x ULN; both patients were discontinued

as per the study specific discontinuation criteria. One patient (Group E) had ALT ≥5 and <10 x ULN after switching from placebo to fostamatinib.

There were no reported malignancies, opportunisitic infections or herpes zoster reported during the treatment period.