AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00008
Edition Number	1
Date	29 October 2013

(OSKIRA-Asia-1): A Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Dose Ranging Study in Asia Evaluating Efficacy and Safety of Fostamatinib in Patients with Active Rheumatoid Arthritis Who are Inadequate Responders to Methotrexate Therapy

Study dates: First subject enrolled: 09 April 2012
Last subject last visit: 17 July 2013

Phase of development: Therapeutic exploratory (II)

[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 has been prepared.

Study centres

[redacted]

Publications

None.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Primary objectives:	**Primary outcome variables:**
Investigate the efficacy of 4 oral dosing regimens of fostamatinib taken in combination with methotrexate, compared with placebo plus methotrexate, in patients with active RA by assessment of the signs and symptoms of RA, as measured by American College of Rheumatology 20% response criteria (ACR20) at Week 12.	ACR20 at Week 12
Secondary objectives:	**Secondary outcome variables:**
Further assess the efficacy of fostamatinib measured by ACR20, ACR 50% criteria (ACR50), ACR 70% criteria (ACR70), ACR index of RA improvement (ACRn) and the individual components of ACR score.	ACR20, ACR50, ACR70, ACRn and 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 [measured by Health Assessment Questionnaire-Disability Index; HAQ-DI], C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]).
Assess physical function status of patients after administration of fostamatinib using the HAQ-DI.	HAQ-DI score; HAQ-DI response.
To evaluate the efficacy of fostamatinib as measured by the Disease Activity Score based on a 28 joint count (DAS28) and DAS European League Against Rheumatism (EULAR) response criteria.	DAS28; DAS28≤3.2 (low disease activity); improvement in DAS28>1.2 (clinically important change); DAS EULAR response.
Investigate the effects of fostamatinib on health-related quality of life using the 36-item Short Form Health Survey (SF-36) questionnaire.	SF-36 physical and mental component scores (PCS and MCS).
Safety objectives:	**Safety outcome variables:**
Evaluate the safety and tolerability of fostamatinib.	Adverse events (AEs) (including independent adjudication of cardiovascular [CV] events), serious AEs (SAEs), serious infective events (SIEs); vital signs; electrocardiogram; clinical chemistry and urinalysis; physical examination.
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: (not reported in the CSR)	
To further assess the efficacy of fostamatinib measured by hybrid ACR response, ACR/EULAR remission (based on Simplified Disease Activity Index [SDAI]) and DAS28 remission.	Hybrid ACR response, ACR/EULAR remission based on SDAI, DAS28 remission.
To investigate the effects of fostamatinib on inflammatory biomarkers interleukin-6 (IL-6) and matrix metalloproteinase (MMP-3)	IL-6, MMP-3.
Investigate the pharmacokinetics (PK) of R406 (active metabolite of fostamatinib) and to investigate the relationship between systemic exposure to this metabolite and AEs, safety parameters and efficacy outcomes.	Plasma R406 concentrations, oral clearance, area under plasma concentration-time curve during dosing interval at steady state. Limited PK data due to sparse sampling.
Collect and store serum and plasma samples for future exploratory research the mechanism of action of fostamatinib and methotrexate and their effects upon markers of RA disease activity and its associated co-morbidities.	Serum and plasma samples.
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 methotrexate; and/or susceptibility to, progression of and prognosis of RA; and/or associated biomarkers.	DNA from whole blood

Study design

This was a 12-week, multi-centre, randomised, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of fostamatinib in patients in Asia with active RA, despite treatment with methotrexate. Patients were randomised to study treatment as follows:

Group A: Fostamatinib 100 mg twice daily (*bid*) for 12 weeks.

Group B: Fostamatinib 100 mg *bid* for 4 weeks then 150 mg once daily (*qd*) to Week 12.

Group C: Fostamatinib 75 mg *bid* for 12 weeks.

Group D: Fostamatinib 50 mg *bid* for 12 weeks.

Group E: Placebo *bid* for 12 weeks.

A reduced dosing regimen of 100 mg *qd* was available for patients in Groups A, B and C for the management of tolerability, and a reduced regimen of placebo qd was available for patients in Group E. Patients who reduced their dose were to remain on the lower dose for the remainder of the study. Patients in Group D who met the criteria for dose reduction were to be withdrawn as further dose reduction was not available. Dose re-escalation was not permitted.

All patients were to remain 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 predefined AEs of potential CV nature.

Patients who successfully completed the 12-week treatment period and whose disease was adequately controlled could, at the discretion of the investigator, be transferred to a long-term extension study (D4300C00029; OSKIRA-Asia-1X) to receive fostamatinib 100 mg *qd*.

Target subject population and sample size

Male and female patients aged ≥18 years, with active RA despite current treatment with methotrexate.

It was planned to randomise approximately 175 patients in total, 35 to each treatment group. A sample size of 35 patients per group would provide approximately 80% power to detect a 25% increase in the proportion of patients achieving an ACR20 response at Week 12 at a 2-sided significance level of 0.2, assuming a placebo response rate of 30%.

The study was terminated early due to programme closure. As of the data cut-off date (19 August 2013), 119 patients had completed the 12-week treatment period. This suggests that each treatment group would have approximately 23 patients completing the 12-week treatment period. Holding the assumptions above this should provide approximately 67% power to detect a 25% increase in the proportion of patients achieving an ACR20 response at Week 12.

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

Fostamatinib or matching placebo blue, film-coated, 50 mg or 25 mg tablets were taken orally, *bid* (once in the morning and once in the evening). Tablets could be taken with or without food, but not with food/drink known to inhibit CYP3A4. Dose reduction to fostamatinib 100 mg *qd* was available for management of tolerability. [Fostamatinib batch numbers: 11097.14/1, 11097.15/1, 11097.16/1, 11097.17/1, 11097.19/1, 11097.37/1, 11097.38/1, 11097.39/1, 11097.40/1, 11097.42/1. Placebo to fostamatinib batch numbers: 11097.13/1, 11097.18/1, 11097.36/1, 11097.41/1].

Duration of treatment

Treatment continued for 12 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 (D4300C00029).

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 investigational product; patients in the full analysis set were analysed according to randomised treatment (intention-to-treat principle).

Each regimen of fostamatinib (Groups A, B, C, D) was compared separately to placebo at all scheduled post-baseline assessments up to Week 12. The primary analysis of ACR20 at Week 12 was performed using a test of the treatment difference in the proportion of responders (patients who achieve ACR20 at Week 12) with a Mantel-Haenszel approach, stratified by country. An adjusted difference and 80% confidence interval (CI) was presented for each comparison. A 2-sided p-value of less than 0.2 was to be considered statistically significant. There were no adjustments for multiplicity.

There were 5 key secondary endpoints in this study:

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

Analysis of ACR20, ACR50, and ACR70 at each time point was performed using a test of the treatment difference in the proportion of responders with a Mantel-Haenszel approach stratified by country. ACRn scores at each timepoint were analysed using a non-parametric method (van Elteren test, stratified by country). Individual ACR components at each timepoint were analysed using an analysis of covariance (ANCOVA) on the change from baseline, including terms for baseline as a continuous covariate and treatment and country as factors. The DAS28 scores at each timepoint were analysed using the ANCOVA model described for individual ACR components. The DAS28 EULAR response (No response, Moderate response and Good response) at each time point was analysed using a proportional odds model including treatment and country as factors. The proportion of patients classified as having achieved low-disease activity (DAS28 ≤3.2) and a clinically important change in DAS28 score (improvement in DAS28 score >1.2) at each timepoint were each analysed using logistic regression 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 timepoint was analysed using logistic regression including treatment and country as factors. The SF-36 was summarised as change from baseline over time. The PCS and the MCS were analysed at each timepoint using the ANCOVA model described for individual ACR components.

During the final blinded review of the data, it was noted that Hong Kong recruitment was low (5 patients). Therefore, to ensure a more robust analysis, it was decided to pool data from Hong Kong together with data from Taiwan when applying statistical models that use country as a factor.

Given the early termination of the study, some analyses were reduced compared to those described in the protocol, with no subgroup or sensitivity analyses conducted. These changes

were specified in the Statistical Analysis Plan prior to unblinding. Individual dimensions of HAQ-DI and domain scores of SF-36 were listed only. No imputation for any scheduled visit after the discontinuation date was applied for patients who discontinued due to early study termination.

Subject population

Overall, 298 patients were enrolled into the study. Of these, 163 were randomised and received treatment: 31, 33, 33 and 33 in fostamatinib Groups A, B, C and D, respectively, and 33 in the placebo group. In total 77.4%, 72.7%, 63.6% and 75.8% of patients across the fostamatinib Groups A, B, C and D, respectively, completed the 12-week study treatment; of those patients that were randomised to placebo, 75.8% of patients completed the 12-week study treatment. The most common reason for discontinuing the study was due to project closure (34 [20.9%] patients in total; balanced across the treatment groups); 1 patient in Group B discontinued due to the study-specific discontinuation criteria of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or bilirubin rise to ≥5x upper limit of normal (ULN) at any time.

In total 66 (40.5%), 31 (19.0%), 24 (14.7%), 23 (14.1%), 14 (8.6%) and 5 (3.1%) patients were recruited in Japan, Vietnam, Thailand, Taiwan, South Korea, and Hong Kong, respectively; country representation was balanced across the groups.

Figure S1 Patient disposition: randomisation

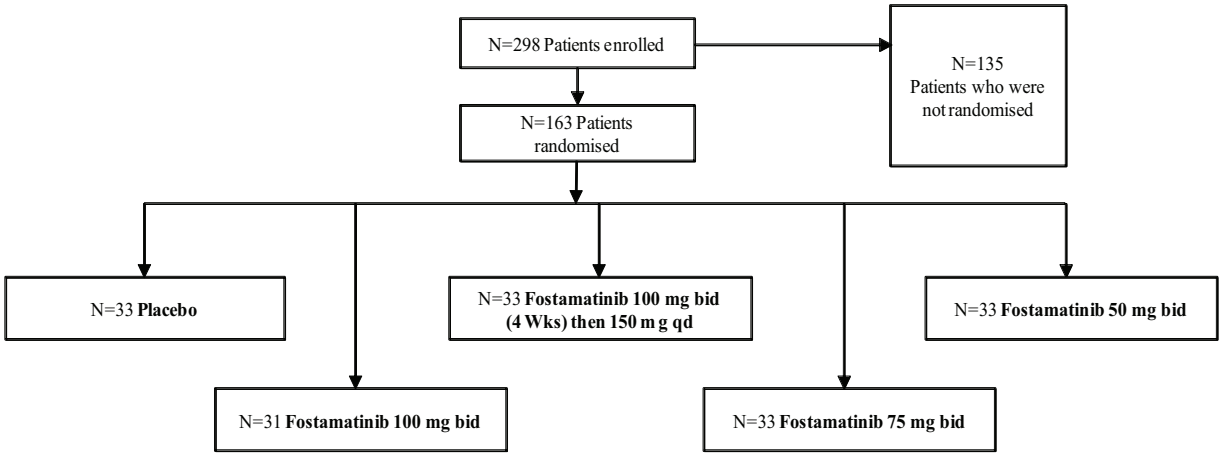
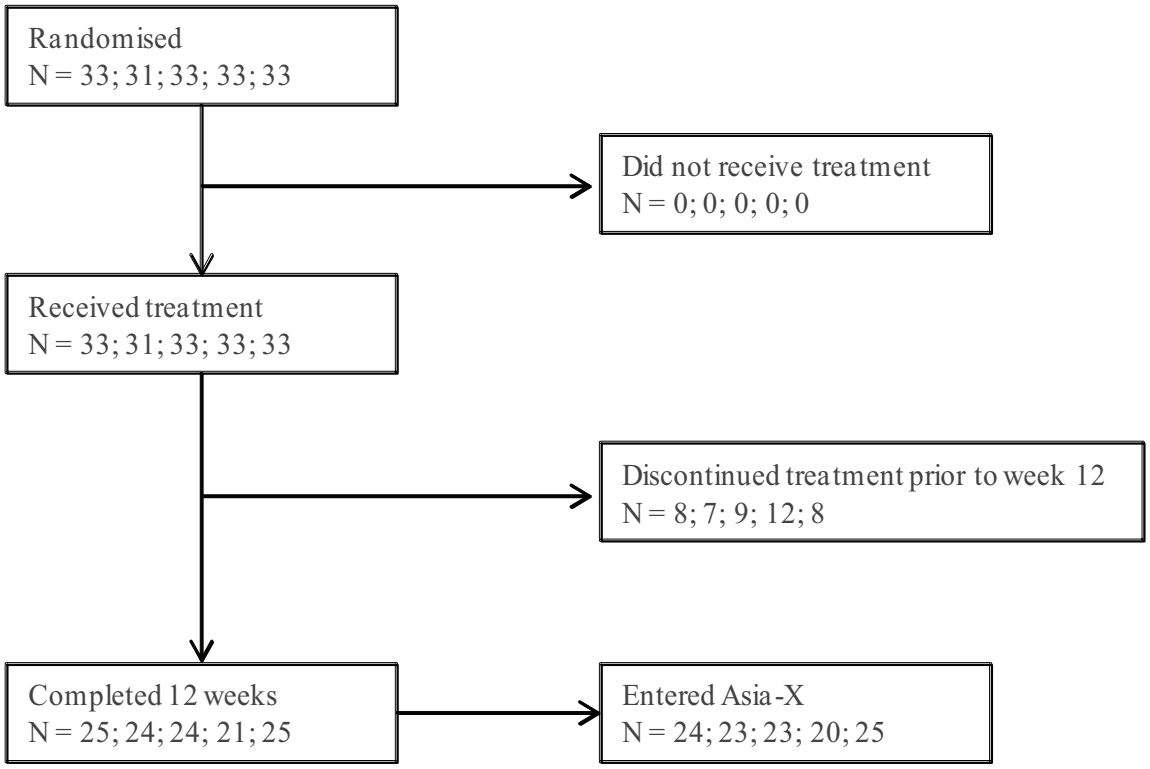


Figure S2 Patient disposition: study completion and discontinuation



N = Number of patients: placebo; Group A; Group B; Group C; Group D.

Overall, 17 patients (10.4%) had at least 1 important protocol deviation. The most common deviation (in 13 patients) was the use of oral steroids or parenteral steroids starting post-dose during the study, outside of those specified as allowed in the protocol. Of these, more were seen in Group C (5 patients) than in the other treatment groups. 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 55 years (range: 21 to 74 years), 87.1% were female, and all were Asian. The groups were generally well balanced for demographics; however due to the small size of the treatment groups some imbalances were seen in the number of male patients and those ≥65 years, although this was thought to be unlikely to have an impact on the conclusions.

In general, baseline characteristics (including CV history, RA history and previous RA treatment) were as expected in this patient population and were balanced across the groups. The mean weekly dose of methotrexate at baseline was 11.8 mg. Baseline disease activity (as illustrated by DAS28-CRP) varied between groups with higher levels of activity observed in Group B and lower levels of activity observed in Group D: mean DAS28-CRP baseline values were 5.76, 6.07, 5.59 and 5.41 in fostamatinib Groups A, B, C and D, respectively, and 5.70 in the placebo group.

Summary of efficacy results

Fostamatinib achieved statistically significant improvements in the primary variable, ACR20 response rate at Week 12, in Group A (53.8%) and Group B (55.2%), but not in Group C (25.9%) or Group D (46.4%), compared to placebo (32.1%) (Table S2).

Table S2 ACR20 – proportion of patients achieving ACR20 at Week 12, comparison between fostamatinib and placebo

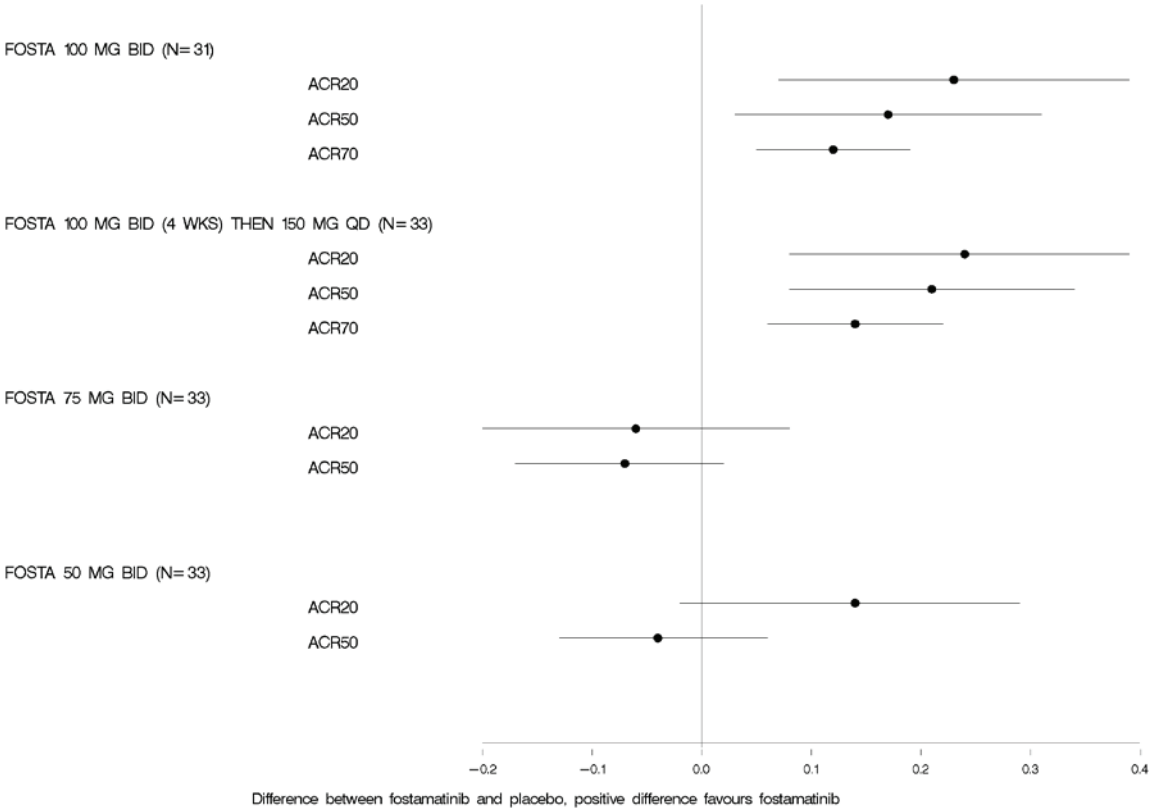
Treatment	n	Number (%) of patients	Comparison with placebo		
			Weighted difference in proportion	80% CI	2-sided p-value
Placebo (N=33)	28	9 (32.1)			
Fostamatinib 100 mg bid (N=31) - Group A	26	14 (53.8)	0.23	0.07, 0.39	0.059
Fostamatinib 100 mg bid (4 wks) then 150 mg qd (N=33) - Group B	29	16 (55.2)	0.24	0.08, 0.39	0.054
Fostamatinib 75 mg bid (N=33) - Group C	27	7 (25.9)	-0.06	-0.20, 0.08	0.570
Fostamatinib 50 mg bid (N=33) - Group D	28	13 (46.4)	0.14	-0.02, 0.29	0.262

Non-responder imputation (baseline observation carried forward) was applied following premature withdrawal, or increased dose of methotrexate or any disease-modifying anti-rheumatic drug initiation, or following receipt of any parenteral steroids, or for patients with no post baseline data. Subjects who prematurely withdrew due to project closure had no imputation applied. 80% CIs and p-values were calculated using a Mantel-Haenszel approach stratified by pooled country.

Fostamatinib achieved a statistically significant improvement over placebo for Groups A and B in the key secondary endpoints of ACR20 at Week 1 (combined Groups A and B), ACR50 at Week 12, ACR70 at Week 12, and DAS28-CRP $\leq$3.2 at Week 12. The key secondary endpoint of HAQ-DI $\geq$0.22 at Week 12 was statistically significant in Group A only.

Consistent findings to the primary endpoint were generally observed across ACR20, ACR50 and ACR70 with significant improvements seen over placebo for Groups A and B; Groups C and D generally performed similarly to placebo (Figure S3).

Figure S3 **ACR20, ACR50, ACR70 at week 12 - forest plot of the estimated difference and 80% confidence intervals comparing fostamatinib and placebo**



Non-responder imputation (BOCF) has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or following receipt of any parenteral steroids, or for patients with no post baseline data. Subjects who prematurely withdrew due to project closure have no imputation applied.
/art/prod/astrazeneca/rita/d4300/d4300c00008/prog/reports/zeff_fe4ax.sas 03Oct2013:17:55

Improvements in ACR20 response rates for Groups A and B over placebo were observed at Week 1, and were maintained up to Week 12. While Group D showed a higher proportion of patients achieving ACR20 at Week 12 than for other timepoints, Group C was similar to placebo from Week 4 onwards. The improvement over time in ACR50 and ACR70 for each dose of fostamatinib over placebo was consistent with the results observed for ACR20.

In general, improvements were seen for most other secondary variables (ACRn, ACR components, DAS28-CRP score, HAQ-DI score and SF-36 PCS and MCS) for Group A over placebo. Improvements over placebo were also seen in Group B, but were often of a smaller magnitude or were less consistent across components and timepoints. Benefits in Group B were more consistently demonstrated for ACRn and acute phase reactants (CRP and ESR) than for the remaining secondary variables.

Groups A and B generally performed better than Groups C and D. The efficacy observed in Group C was generally lower or similar to Group D and placebo (as illustrated by the ACR20

response in Figure S3), which was not as expected. Although disease activity at baseline for Group C was consistent to that seen on average in this study, more patients in Group C started oral steroids during the treatment period in comparison to the other groups and the dropout rate in Group C was slightly greater than for the other groups (implying a higher rate of non-responder imputation).

Summary of pharmacogenetic results

Out of the genotyped population (161/163 total study population), only 4 patients were found to have a functionally significant genotype (*6*6) and no individuals were found to have a *28*28 genotype. Six patients demonstrated bilirubin readings above ULN but these were all below the clinically significant level of 2xULN or above. Since only 4/161 patients had a functionally significant genotype and none of the patients in the study had a clinically significant increase in bilirubin level it is not possible to conclude any effect of UGT1A1 genotype on clinically significant bilirubin elevation from this data.

Summary of safety results

Total exposure was similar across fostamatinib groups (6.71, 6.80, 6.59 and 6.97 treatment-years), and 6.85 treatment-years in the placebo group. Mean duration of exposure to Week 12 was 79, 75, 73 and 77 days across the fostamatinib groups, and 76 days on placebo. The lower exposure in Group C was due to a greater number of discontinuations.

Across the fostamatinib groups, 5 (16.1%), 2 (6.1%), 2 (6.1%) and 0% of patients had a dose reduction, compared to 2 (6.1%) in the placebo group. Similar proportions of patients had dose reductions due to AEs and dose reductions due to protocol specified reasons. Groups A (4 [12.9%]) and D (5 [15.2%]) presented higher proportion of patients with interruption, compared to placebo (2 [6.1%]), Groups B (2 [6.1%]) and C (3 [9.1%]). The most common reason for dose interruptions was due to AEs.

Table S4 Number (%) patients who had at least 1 AE in any category

AE category	Number (%) of patients				
	Fostamatinib 100 mg bid (n=31)	**Fostamatinib** 100 mg bid (4 wks) then 150 mg qd (n=33)	**Fostamatinib** 75 mg bid (n=33)	**Fostamatinib** 50 mg bid (n=33)	**Placebo** bid (n=33)
Any AE	23 (74.2)	23 (69.7)	21 (63.6)	24 (72.7)	20 (60.6)
Any AE with outcome = death	0	0	0	0	0
Any SAE (including events with outcome = death)	1 (3.2)	1 (3.0)	0	3 (9.1)	1 (3.0)
Any AE leading to discontinuation of IP	1 (3.2)	0	3 (9.1)	0	1 (3.0)
Any AE leading to dose reduction of oral IP	5 (16.1)	0	2 (6.1)	0	2 (6.1)

Patients with multiple events in same category are counted once in that category. Patients with events in >1 category are counted once in each of those categories.
If action taken changed during the course of AE, the worst case was summarised in the order: discontinued, dose reduced, dose interrupted.

The incidence of AEs from randomisation up to Week 12 was 74.2%, 69.7%, 63.6% and 72.7% of patients in the fostamatinib groups (A, B, C and D, respectively) and 60.6% of patients in the placebo group. There were no deaths reported. The most common AEs on fostamatinib were hypertension, diarrhoea and neutropenia. The incidence of hypertension was 29.0%, 18.2%, 18.2% and 9.1% across the fostamatinib groups, and 6.1% on placebo. The incidence of diarrhoea across fostamatinib groups was 16.1%, 18.2%, 6.1% and 3.0%, and 0% on placebo. The incidence of neutropenia across fostamatinib groups was 12.9%, 6.1%, 12.1% and 15.2%, and 9.1% on placebo. The majority of AEs reported in any treatment group were mild or moderate in intensity.

The overall rate of SAEs and discontinuations due to AEs (DAEs) was low. Individual preferred terms for SAEs and DAEs were reported at single incidences per treatment group. The SAEs reported were hypertension (Group A), laryngitis viral (Group A), diarrhoea (Group B), carpal tunnel syndrome (Group D), osteoporosis (Group D) and RA (Group D and placebo). The DAEs reported were rash pustular (Group A), strongyloidiasis (Group C), neutropenia (Group C), rash macular (Group C) and vomiting (placebo).

Gastrointestinal-related AEs reported by >1 patient in any group were diarrhoea, nausea, vomiting and gastritis. For all patients with diarrhoea, the AE was reported as resolved. Only 2 patients started anti-propulsives during the study (1 each in Group A and Group B). Events of diarrhoea were observed throughout the treatment period.

No deaths or major adverse CV events were reported in any treatment group. Two SAEs in 2 patients on fostamatinib were sent to the CVAC for adjudication, neither of which were adjudicated as CV events. No events on placebo met the criteria for CV adjudication.

Fostamatinib is associated with elevations in blood pressure (BP). Increases in BP in all fostamatinib groups were evident at Week 1. The profile of elevated SBP from baseline over time was slightly more pronounced in Groups A and B. Increased BP was seen both in patients who were receiving anti-hypertensive medication at baseline, and those who were not. The proportion of patients with elevated BP ≥140/90 mmHg during the study was: 41.9%, 33.3%, 30.3%, 18.2% and 18.2% across Groups A, B, C, D and placebo, respectively. No patients had elevated BP ≥160/100 mmHg at 2 or more consecutive visits. No patients had elevated BP ≥180/110 mmHg at any visit during the study. Across the 4 fostamatinib groups, 38.7%, 36.4%, 36.4% and 18.2% of patients had intervention for elevated BP, compared to 24.2% of patients on placebo. 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) (25.8%, 18.2%, 27.3% and 12.1% in Groups A to D, respectively, and 15.2% on placebo).

No absolute neutrophil counts were reported $<0.5 \times 10^9$/L. Decreases in absolute neutrophil count below the lower limit of normal were seen in 42 patients, with a higher proportion of patients seen on fostamatinib (41.9%, 15.2%, 30.3% and 33.3% in the fostamatinib Groups A, B, C and D, respectively) compared to placebo (9.1% of patients). One patient in Group A experienced an SIE (ie, infections fulfilling criteria for SAE or requiring intravenous antimicrobials) (laryngitis viral); the patient's neutrophil count was normal throughout the study. The SIE resolved.

One patient (Group B) had an AST >10xULN and the patient was discontinued as per the study specific discontinuation criteria. This patient had accompanying ALT >3xULN and normal bilirubin at the same timepoint. No other patients had ALT or AST above 3xULN during the study. No patients met the clinical chemistry criteria of ALT/AST ≥3xULN and total bilirubin ≥2xULN for potential drug induced liver injury.

There were no reported malignancies, or tuberculosis or herpes zoster cases during the treatment period.