AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00002
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(OSKIRA-2): 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 an Inadequate Response to DMARDs

Study dates: First subject enrolled: 13 October 2010
Last subject last visit: 19 March 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 at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Primary objective:	**Primary outcome variables:**
To evaluate the efficacy of 2 different dose regimens of fostamatinib on the signs and symptoms of rheumatoid arthritis (RA), when taken in combination with a disease-modifying anti-rheumatic drug (DMARD), compared with a DMARD alone in patients with active RA.	American College of Rheumatology (ACR) 20% response criteria (ACR20) at Week 24.
Secondary objectives:	**Secondary outcome variables:**
To assess the efficacy of fostamatinib in the prevention of structural joint damage, as measured by change in radiographic modified Total Sharp Score (mTSS) and the components of mTSS at Week 24 and Week 52	Change from baseline in mTSS, erosion score (ES) and joint space narrowing (JSN) at Week 24 and Week 52.
To further assess the efficacy of fostamatinib measured by ACR20, ACR 50% response criteria (ACR50), ACR 70% response criteria (ACR70), major clinical response, ACR index of RA improvement (ACR-N), the individual components of the ACR score and ACR/European League Against Rheumatism (EULAR) remission.	ACR20, ACR50, ACR70, major clinical response, ACR-N 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] or erythrocyte sedimentation rate); 'ACR/EULAR remission' based on Simplified Disease Activity Index.
To assess 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 evaluate the efficacy of fostamatinib 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 $\leq$3.2, DAS28 <2.6, clinically important change in DAS28 (improvement of at least 1.2).
To investigate the effects of fostamatinib on patient reported health outcomes measures.	36-item Short Form Health Survey (SF-36) –Physical component score (PCS), Mental component score (MCS), 8 individual domain scores; Functional Assessment of Chronic Illness Therapy-Fatigue score; EuroQoL-5 Dimension health status questionnaire (reported separately from the Clinical Study Report [CSR]).

Safety objectives:	**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, including independent adjudication of cardiovascular [CV] events); clinical chemistry, haematology and urinalysis; physical examination; electrocardiogram (ECG); weight; vital signs.
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*28 genotype
Exploratory objectives (not reported in the CSR):	
To investigate the pharmacokinetics (PK) of R406 (the active metabolite of fostamatinib) and/or the PK of R788 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 R788 or other metabolites concentrations, oral clearance and area under plasma concentration-time curve during the dosing interval at steady-state. Since only sparse sampling for PK was scheduled for most patients participating in the study (Weeks 4 and 24), additional PK samples were also taken at Weeks 0, 4 and 8 in a subset of patients (blood pressure [BP]/PK/ECG subset) in order to provide more extensive data for exploratory analysis of any potential association between R406 plasma concentration and BP.
To assess overall CV risk according to risk models such as the Framingham model and/or Systematic Coronary Risk Evaluation model.	Demographics, medical history, lipids and BP.
To 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 DMARD; 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

A 52-week, multi-centre, randomised, double-blind, placebo-controlled (for 24 weeks), parallel group study to investigate the efficacy and safety of fostamatinib in RA patients with active disease despite current treatment with a DMARD (methotrexate, sulfasalazine, hydroxychloroquine or chloroquine). Patients were randomised to study treatment as follows:

Group A: Fostamatinib 100 mg twice daily (*bid*) for 52 weeks.

Group B: Fostamatinib 100 mg *bid* for 4 weeks, followed by once a day (*qd*) dosing with 150 mg up to Week 52.

Group C: Placebo *bid* for 24 weeks followed by fostamatinib 100 mg *bid* up to Week 52.

An experienced, independent joint assessor, blinded to other study assessments as well as the dosing regimen, was to be identified at each site to perform the swollen and tender joint counts. X-rays were to be centrally read in a blinded manner by independent assessors. A Safety Review Committee reviewed the accumulating safety data, and a blinded Cardiovascular Adjudication Committee reviewed pre-defined AEs of potential CV 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 despite current treatment with a DMARD.

In total it was planned to randomise approximately 900 patients, 300 patients to each treatment group. A sample size of 900 patients (300 per treatment group) provides greater than 90% power to detect a 20% increase in the proportion of patients achieving an ACR20 response at Week 24, assuming a placebo response rate of 30%.

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

Fostamatinib or matching placebo blue, film-coated, 50 mg tablets were taken orally 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. Individual batch numbers and further information are included in the CSR.

Although the study was placebo-controlled for the initial 24-week period, all patients were to continue to receive an appropriate standard of care by continuing to take their regular DMARD therapy (methotrexate, sulfasalazine, hydroxychloroquine or chloroquine).

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 52 weeks unless any of the criteria for discontinuation 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 investigational product (IP) and were analysed according to randomised treatment (intention-to-treat principle).

Both dose groups of fostamatinib (Groups A and B), in combination with a DMARD, were to be compared separately to placebo, in combination with a DMARD, at all scheduled post-baseline assessments up to Week 24. Since the 2 fostamatinib dose groups were identical for the first 4 weeks of dosing, all analyses comparing the efficacy of fostamatinib versus

placebo up to and including Week 4 were to be performed using pooled data from the 2 dose groups.

Following the Week 24 assessment, all patients were to be on active treatment. The efficacy data for the Week 24 to Week 52 assessments were to be summarised by randomised treatment group at all scheduled assessments, but no hypothesis testing was to be carried out, except for radiographic endpoints.

The primary endpoint in this study was the proportion of patients achieving ACR20 at Week 24. The overall type I error rate was controlled at 5% using the Hochberg procedure across the 2 dose groups, allowing for the correlation due to the shared placebo data.

If the 2-sided p-value for ACR20 was ≤0.05 in favour of fostamatinib for both dose groups, then the primary endpoint was to be considered statistically significant for both dose groups. If the p-value for either dose group was >0.05, then for the other dose group, a 2-sided p-value ≤0.0262 in favour of fostamatinib was to be considered statistically significant.

There were 7 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 <2.6 at Week 12, proportion of patients achieving reduction in HAQ-DI ≥0.22 at Week 24 and change in mTSS at Week 24.

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

The primary analysis of ACR20 at Week 24 was performed using a test of treatment difference in the proportion of responders (patients who achieved ACR20 at Week 24) with a Mantel-Haenszel approach stratified by country and use of background DMARD treatment (methotrexate or other DMARD).

Logistic regression modelling of ACR20 response at Week 24 was performed including terms for baseline characteristics (gender, race, age, region, weight, DAS28, HAQ-DI, duration of disease and rheumatoid factor), in addition to treatment, country and use of background DMARD treatment (methotrexate or other DMARD).

Analysis of ACR20, ACR50 and ACR70 at all scheduled assessments up to Week 24 was performed using a test of the treatment difference in the proportion of responders, as described for ACR20 at Week 24. The ACR-N scores at each time point were analysed using a non-parametric method. Individual ACR components at each time point were analysed using an analysis of covariance (ANCOVA) on the change from baseline, including terms for baseline as a continuous covariate and treatment, country and use of background DMARD treatment (methotrexate or other DMARD) as factors. The proportion of patients classified as

having achieved ACR/EULAR remission at each time point was summarised. The DAS28 scores at each timepoint were analysed using the ANCOVA model described for the individual ACR components and the DAS28 EULAR response at each timepoint was analysed using a proportional odds model including treatment, country and use of background DMARD treatment (methotrexate or other DMARD) as factors. The primary interpretation of DAS28 was based on DAS28-CRP. In addition to the analysis of HAQ-DI scores, the proportion of patients classified as HAQ responders at each time point was analysed using logistic regression including treatment, country and use of background DMARD treatment (methotrexate or other DMARD) as factors.

Changes in mTSS and its components (JSN and ES) at Weeks 24 and 52 were 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, country and use of background DMARD treatment (methotrexate or other DMARD) as factors. For the analyses at Week 52, patients who were randomised to placebo were to have their data up to Week 24 linearly extrapolated to Week 52 to allow active versus placebo comparisons.

The SF-36 was summarised in terms of 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

57.1%, 56.3%, and 42.3% of patients across Groups A, B and C, respectively, completed the study.

Figure S1 Patient disposition: randomisation

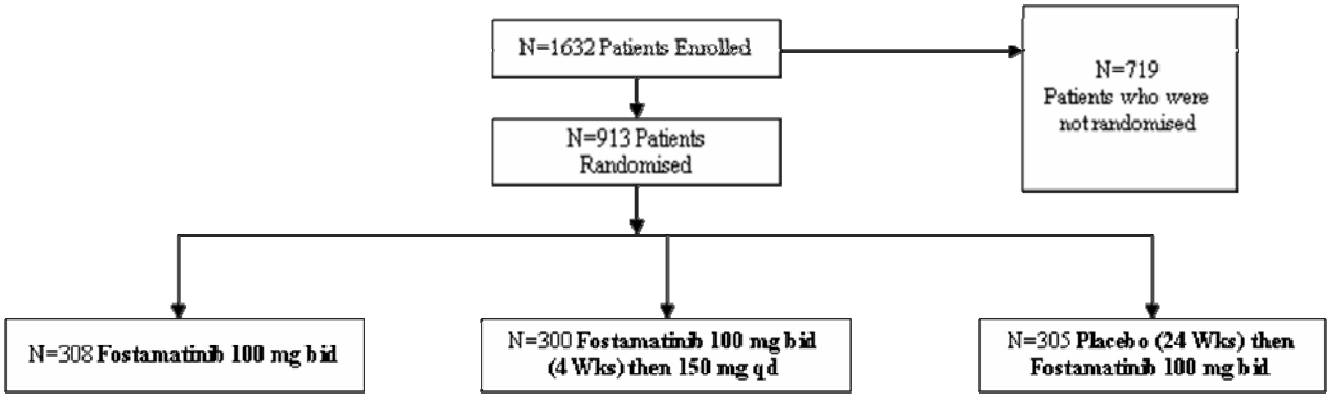
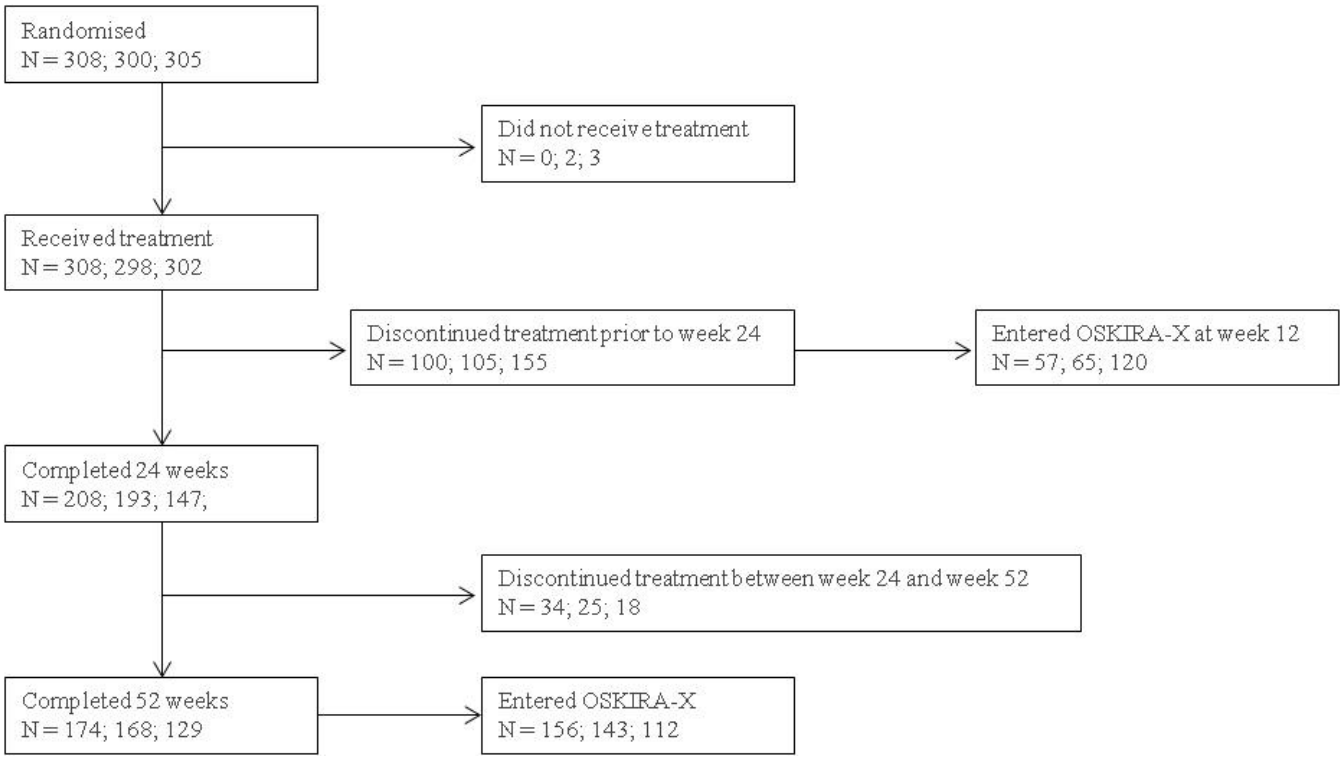


Figure S2 Patient disposition: study completion and discontinuation



N = Number of patients: Group A; Group B; Group C.
"Completed" includes those patients who had a dose reduction in their study treatment.

Mean age of the study population was 53 years (range: 18 to 84 years), 81.7% were female, and most were White (80.4%). Mean DAS28-CRP at baseline was 5.57. Demographic and baseline disease characteristics were generally well balanced across the randomised treatment groups.

At baseline, the majority of patients (82.8%) were on background methotrexate, with the remaining 17.2% of patients on other DMARDs (sulfasalazine, hydroxychloroquine or chloroquine). The proportions of patients on different background DMARD therapy was balanced between the treatment groups.

Summary of efficacy results

For the primary endpoint of ACR20 response rates at Week 24, fostamatinib achieved statistically significant improvements in both fostamatinib groups (39.6% of patients in both groups) compared to placebo (24.5% of patients). The onset of effect was seen as early as Week 1 and the effect seen at Week 24 was maintained up to Week 52.

Fostamatinib did not achieve a statistically significant difference in the key secondary endpoint of mTSS at Week 24 compared to placebo, at either dose.

Fostamatinib achieved statistical significance for all of the signs and symptoms key secondary endpoints for Group A, and for Group B all were significant except for ACR70. A dose response was generally observed across the signs and symptoms endpoints.

Findings for the secondary signs and symptoms and patient reported outcome endpoints were consistent with the primary endpoint, suggesting benefit on fostamatinib treatment compared to placebo.

Summary of pharmacogenetic results

While there is the potential for fostamatinib to act as a UGT1A1 inhibitor and thus have an effect on certain laboratory parameters, such as bilirubin, no patients in this study had alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and bilirubin levels that met the clinical chemistry criteria for potential drug induced liver injury.

For UGT1A1*1/*1 and UGT1A1*1/*28 genotypes, there was little variability in total or indirect bilirubin values and no notable changes were observed over time or between treatment groups. Four patients had bilirubin concentration >2 upper limit of normal (ULN): 2 were *28/*28, 1 was *1/*28 and 1 was not genotyped due to withdrawal of consent; all were in Group A and had baseline values in the upper half of the reference range. There was no evidence of clinical consequence for any genotype group on fostamatinib treatment.

Summary of safety results

Total exposure from randomisation up to Week 24 was similar in the fostamatinib groups (118.16 and 111.00 treatment years) and was 102.66 treatment years in the placebo group. The lower total patient years exposure observed in the placebo group was mainly due to the higher rate of discontinuation from IP up to Week 24 in this group compared to the fostamatinib groups, which included patients who were transferred to the long-term extension study at Week 12.

Mean duration of exposure at Week 24 was similar in the fostamatinib groups (140 and 136 days in Groups A and B, respectively), and was lower in the placebo group (124 days).

In the fostamatinib groups, from randomisation up to Week 24, the proportions of patients who had at least 1 dose interruption were 10.4% and 11.1%, and the proportions with dose reductions were 14.6% and 13.4%. In the placebo group, the proportion of patients who had at least 1 dose interruption was 7.9% and the proportion with dose reductions was 3.3%.

Table S2 Adverse events in any category, from randomisation to Week 24

AE Category	--Number (%) of patients[a]--		
	Fostamatinib 100 mg bid (n=308)	**Fostamatinib 100 mg bid (4 Wks) then 150 mg qd (n=298)**	**Placebo (24 Wks) then Fostamatinib 100 mg bid (n=302)**
Any AE	214 (69.5)	212 (71.1)	166 (55.0)
Any AE with outcome = death	2 (0.6)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	21 (6.8)	14 (4.7)	10 (3.3)
Any AE leading to discontinuation of IP	33 (10.7)	29 (9.7)	13 (4.3)
Any AE leading to dose reduction of IP[b]	36 (11.7)	37 (12.4)	7 (2.3)

[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] If action taken changed during the course of the AE then the worst case is summarised in the order: discontinued, dose reduced, dose interrupted.

Most common AEs (reported in >5% of patients in at least 1 of the fostamatinib groups) from randomisation up to Week 24 were hypertension (19.2% and 15.8% of patients in the fostamatinib groups and 5.3% of patients in the placebo group), diarrhoea (9.7%, 12.4% and 4.3% of patients, respectively), nasopharyngitis (11.0%, 7.4% and 5.3% of patients, respectively), nausea (6.2%, 4.4% and 2.3% of patients, respectively) and ALT increased (5.2%, 3.4% and 1.3% of patients, respectively). With the exception of atrial fibrillation, gastritis, RA, gastroenteritis bacterial, renal failure acute, respiratory failure, cholelithiasis, pulmonary embolism and syncope, all individual preferred terms for serious AEs (SAEs) from randomisation up to Week 24 were reported at single incidences. Most common discontinuations of IP due to an AE reported on fostamatinib from randomisation up to Week 24 were due to diarrhoea (2.6% and 3.0% of patients), AEs related to transaminase/hepatic enzyme increases (3.6% and 1.3% of patients) and hypertension/BP increased (1.3% and 1.0% of patients).

Most common gastrointestinal (GI)-related AEs from randomisation up to Week 24 were diarrhoea, nausea, abdominal pain, abdominal pain upper, dyspepsia, vomiting and constipation. Most events of diarrhoea were mild or moderate in intensity and resolved on treatment with minimal intervention. There was 1 patient (in Group A) with an SAE of diarrhoea reported during the period from randomisation up to Week 24. Among the 9 fostamatinib treated patients with diarrhoea reported in the period from randomisation up to Week 24 that was unresolved/ongoing at end of study, 7 continued into OSKIRA-X and 6 received treatment for the diarrhoea. In the overall population, there was relatively low use of anti-propulsive medications: 9 (2.9%), 10 (3.4%) and 4 (1.3%) patients in Groups A, B and C, respectively, started anti-propulsive treatment in the period from randomisation up to Week 24.

The most common CV events were hypertension-type events. Other CV event types (arrhythmias, cardiac failure, cerebrovascular events, myocardial infarction, other ischaemic

heart disease and thromboembolic events) were reported in small numbers of patients across the 3 treatment groups. Overall, the incidence of adjudicated CV events was low. There were no major adverse CV events (MACE) reported during the period from randomisation up to Week 24 and there were 2 MACE during the Week 24 to end of study period: 1 patient in Group A was adjudicated to have died due to cardiac arrhythmia and 1 other patient in Group C died due to sudden cardiac death. Overall, there were 4 deaths reported during the study.

Fostamatinib is associated with elevations in BP. Increases in BP were evident at Week 1. By Week 6, a smaller change from baseline in systolic BP and diastolic BP was seen in Group B compared to Group A. 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 general, patients were responsive to commonly used anti-hypertensive treatment, with few patients requiring dose reduction or discontinuation of IP. Where discontinuation of IP was necessary, BP elevations were generally reversible. Across Groups A, B and C, 31.8%, 27.5% and 12.9% of patients, respectively, had intervention for elevated BP during the period from randomisation up to Week 24. 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) (19.8%, 15.8% and 8.2% of patients in Groups A, B and C, respectively), acetylcholinesterase inhibitors, plain (12.0%, 8.4% and 8.2% of patients, respectively) and selective β-blocking agents (6.8%, 5.4% and 3.4% of patients, respectively). Between randomisation and Week 24, 8 patients (4 [1.3%], 3 [1.0%] and 1 [0.3%] in Groups A, B and C, respectively) had 2 consecutive visits with BP ≥160/100 mmHg. These visits generally occurred within the first 12 weeks of the study. In general, BP elevations were manageable or returned to baseline upon discontinuation of fostamatinib.

Incidence of serious infective events (SIEs, ie, infections fulfilling criteria for SAE or requiring intravenous antimicrobials) was low: 8 (2.6%), 6 (2.0%) and 2 (0.7%) patients in Groups A, B and C, respectively, in the period from randomisation up to Week 24. There was evidence of neutropenia prior to the event in 2 of the patients with SIEs during the study: 1 patient in Group A from randomisation up to Week 24 and 1 patient in Group C following switch to fostamatinib at Week 24 had an absolute neutrophil count (ANC) of between 1.0 and $1.5x10^9$/L around the time of the event. No patients had an SIE associated with an ANC $<1.0x10^9$/L during the study. Two patients (Group A) experienced a neutrophil count $<0.5 \times 10^9$/L during the period from randomisation up to Week 24. Most SIEs in fostamatinib treated patients resolved. In the period from randomisation up to end of study, there was 1 death attributed to an SIE (reported in the period from randomisation up to Week 24 for a patient in Group A). There were no reports of active TB or *pneumocystis carinii* pneumonia during the study.

Increases in ALT or AST >10xULN were reported for 4 patients: 3 in Group A and 1 in Group B during the period from randomisation up to Week 24. Up to end of study, 1 additional patient in Group B had ALT and/or AST >10xULN and no patients in Group C

had ALT and/or AST >10xULN during the entire study period. Review of the individual cases showed that all incidences resolved either on or following cessation of study treatment (resolved with sequelae for 1 patient in Group A). From randomisation up to Week 24, 8, 5 and 1 patients in Groups A, B and C, respectively, had either ALT and/or AST ≥5 to <10xULN.

No patients met the clinical chemistry criteria for potential drug induced liver injury during the study.