AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00001
Edition Number	1
Date	02 Aug 2013
EudraCT Number	2010-020743-12

(OSKIRA-1): 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 Methotrexate

Study dates: First subject enrolled: 21 September 2010
Last subject last visit: 26 November 2012

Phase of development: Therapeutic confirmatory (III)

[redacted]

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

Study centres

Patients were recruited at 141 study centres: 11 in Argentina, 3 in Australia, 2 in Belgium, 5 in Brazil, 7 in Bulgaria, 2 in Chile, 4 in Estonia, 1 in France, 11 in Hungary, 11 in India, 9 in Mexico, 10 in Peru, 9 in Poland, 4 in Slovakia, 14 in Ukraine, 5 in the United Kingdom and 33 in the United States.

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) and the prevention of structural joint damage, when taken in combination with methotrexate, compared with methotrexate alone in patients with active RA.	American College of Rheumatology (ACR) 20% response criteria (ACR20) at Week 24 and change from baseline in Modified Total Sharp Score (mTSS) at Week 24.
Secondary objectives:	**Secondary outcome variables:**
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 score of ≤3.2, DAS28 score of less than 2.6, clinically important change in DAS28 score (improvement of at least 1.2).
To further assess the efficacy of fostamatinib in the prevention of structural joint damage, as measured by change in the components of mTSS.	mTSS, joint space narrowing (JSN) and erosion score (ES).
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; Work Limitations Questionnaire (WLQ) – WLQ index and WLQ productivity loss; Medical Outcomes Study -Sleep – 2 sleep problem indices and the Sleep Disturbance Scale; 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 methotrexate in patients with active RA.	Adverse events (AEs, including independent adjudication of cardiovascular [CV] events); clinical chemistry, haematology and urinalysis; physical examination; electrocardiogram; 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 (reported separately from 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. Only limited PK data will be available due to sparse sampling (Weeks 4 and 24).
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 blood pressure (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 methotrexate; 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 methotrexate. 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 who had been receiving treatment with oral, subcutaneous or intramuscular methotrexate for at least 6 months prior to randomisation.

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%, and approximately 80% power to detect a difference in the mean change from baseline in mTSS of 1 at Week 24, assuming a standard deviation of 4.

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 methotrexate therapy.

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 methotrexate, were to be compared separately to placebo, in combination with methotrexate, 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.

There were 2 primary efficacy endpoints in this study: the proportion of patients achieving ACR20 at Week 24 and the change in mTSS at Week 24. A hierarchical (fixed sequence) approach was used within each dosing regimen, and the Hochberg procedure was used across the 2 dose groups. The order of the statistical testing for the primary endpoints was:

1) Proportion of patients achieving ACR20 at Week 24.

2) Change in mTSS at Week 24.

Adjusted p-values were calculated using the hierarchical approach within each of the 2 dose groups. If the adjusted 2-sided p-value for mTSS was ≤ 0.05 in favour of fostamatinib for both dose groups, then both primary endpoints were to be considered statistically significant for both dose groups. If the adjusted 2-sided p-value for mTSS for either dose group was >0.05, then for the other dose group, an adjusted 2-sided p-value ≤ 0.025 in favour of fostamatinib was to be considered statistically significant.

There were 6 key secondary endpoints in this study; however, statistical significance was not achieved on the mTSS primary endpoint at either dose of fostamatinib, therefore, formal statistical interpretation of the key secondary endpoints could not be done.

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. The primary analysis of change in mTSS at Week 24 was performed using an analysis of covariance (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.

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

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 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 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 and country 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 and country as factors.

Changes in JSN and ES at Week 24, and changes in mTSS, JSN and ES at Week 12 and Week 52 were summarised and analysed as described for the primary analysis of change in mTSS at Week 24. 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

67.2%, 62.7%, and 52.9% of patients across Groups A, B and C, respectively, completed the study.

Figure S1 Patient disposition: randomisation

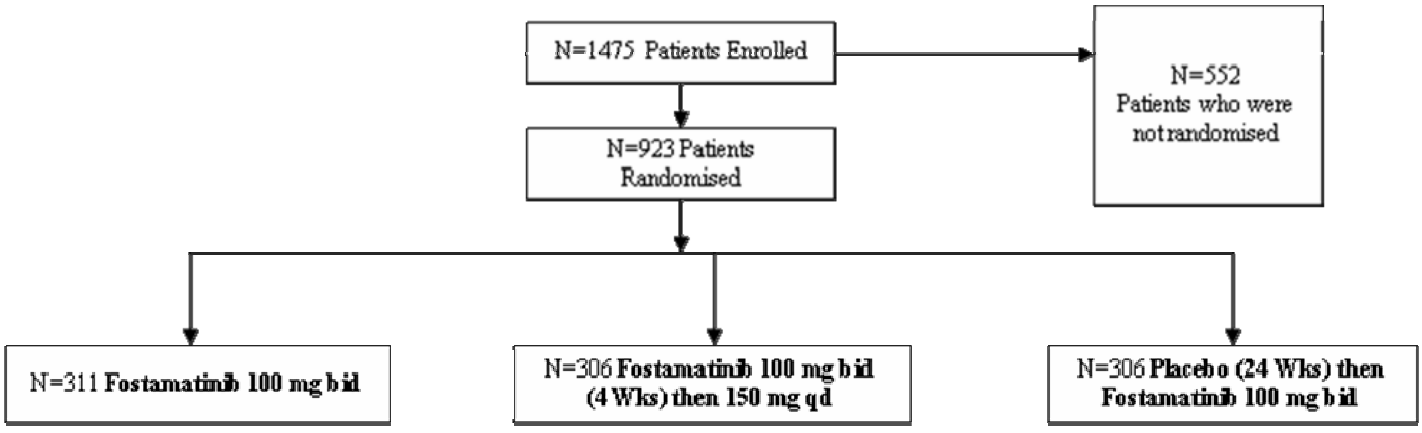
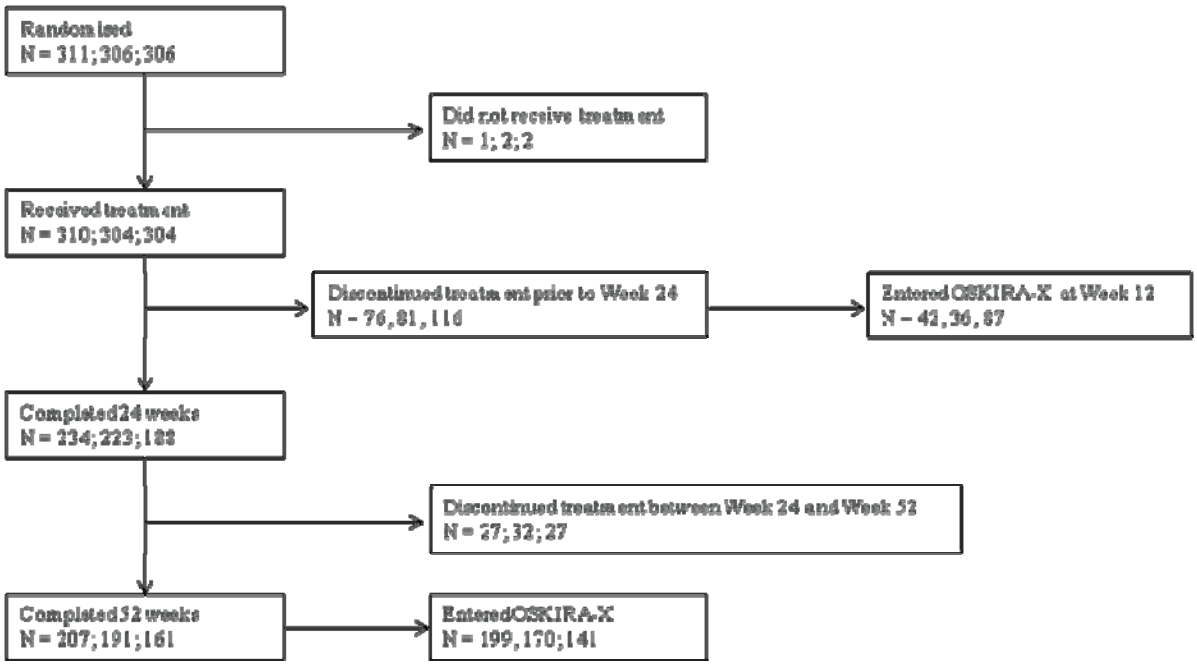


Figure S2 Patient disposition: study completion and discontinuation



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 52 years (range: 18 to 86 years), 83.9% were female, and most were White (69.7%). Mean DAS28-CRP score at baseline was 5.81. Demographic and baseline disease characteristics were generally well balanced across the randomised 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 (49.0% and 44.4% of patients, respectively) compared to placebo (34.2% of patients). The onset of effect was seen as early as Week 1 and was generally more evident in Group A compared to Group B. The improvement in ACR50 and ACR70 for each dose of fostamatinib over placebo was consistent with the results observed for ACR20 and the effects observed at Week 24 were maintained up to Week 52.

Fostamatinib did not achieve a statistically significant difference in on the primary endpoint of mTSS at Week 24 compared to placebo, at either dose. As statistical significance was not achieved on the mTSS endpoint at either dose of fostamatinib, formal statistical interpretation of the key secondary endpoints could not be done.

In reviewing the secondary signs and symptoms and patient reported outcome (PRO) endpoints, they generally suggested benefit on fostamatinib treatment compared to placebo.

The secondary structural progression endpoints were consistent with the primary endpoint (change in mTSS at Week 24) and showed no difference between the treatment groups.

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, only 2 patients (1 in Group B and 1 in Group C, post-switch), both with polymorphisms in the gene encoding UGT1A1 (*28/*28), had alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and bilirubin levels that met the clinical chemistry criteria for potential drug induced liver injury. For both patients there was an alternative explanation for the elevations in total bilirubin other than drug induced liver injury: both patients were homozygous for UGT1A1*28.

For UGT1A1*1/*1 and UGT1A1*1/*28 genotypes, there was little variability in total or indirect bilirubin values and no notable changes differences were observed over time or between treatment groups. Five patients had bilirubin concentration >2 upper limit of normal (ULN): all were *28/*28 and, with the exception of 1 patient (Group B), 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 (123.74 and 119.56 treatment years) and was 111.23 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 (146 and 144 days in Groups A and B, respectively), and was lower in the placebo group (134 days).

In the fostamatinib groups, from randomisation up to Week 24, the proportions of patients who had dose interruptions were 15.2% and 18.8%, and the proportions with dose reductions were 9.4% and 10.5%. In the placebo group, the proportion of patients who had at least 1 dose interruption was 9.5% and the proportion with dose reductions was 5.6%.

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

AE Category	--Number (%) of patients[a]--		
	Fostamatinib 100 mg bid (n=310)	Fostamatinib 100 mg bid (4 Wks) then 150 mg qd (n=304)	Placebo (24 Wks) then Fostamatinib 100 mg bid (n=304)
Any AE	207 (66.8)	216 (71.1)	165 (54.3)
Any AE with outcome = death	0 (0.0)	0 (0.0)	1 (0.3)
Any SAE (including events with outcome = death)	9 (2.9)	15 (4.9)	5 (1.6)
Any AE leading to discontinuation of IP	16 (5.2)	28 (9.2)	8 (2.6)
Any AE leading to dose reduction of IP[b]	28 (9.0)	30 (9.9)	14 (4.6)

[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 (15.8% and 15.1% of patients in the fostamatinib groups and 3.9% of patients in the placebo group), diarrhoea (13.9%, 15.1% and 3.9% of patients, respectively), nausea (4.2%, 6.9% and 3.6% of patients, respectively), headache (3.2%, 6.3% and 3.9% of patients, respectively) and nasopharyngitis (3.5%, 5.3% and 3.6% of patients, respectively). With the exception of gastroenteritis (reported in 2 patients in Group B), all individual preferred terms for serious AEs (SAEs) from randomisation up to Week 24 were reported at single incidences. Most common discontinuation of IP due to an AE reported on fostamatinib from randomisation up to Week 24 were diarrhoea (1.0% and 2.6% of patients) and AEs related to transaminase/hepatic enzyme increases (1.3% and 2.3% of patients).

Most common gastrointestinal (GI)-related AEs from randomisation up to Week 24 were diarrhoea, nausea, abdominal pain upper, dyspepsia, and vomiting. Most events of diarrhoea were mild or moderate in intensity and resolved on treatment with minimal intervention. There were no SAEs of diarrhoea reported. Among the 6 patients with diarrhoea reported in the period from randomisation up to Week 24 that was unresolved/ongoing at end of study, 3 continued into OSKIRA-X and all 6 received treatment for the diarrhoea. In the overall population, there was relatively low use of anti-diarrhoeal or anti-propulsive medications: 3 (1.0%), 3 (1.0%) and 1 (0.3%) patients in Groups A, B and C, respectively, started anti-diarrhoeal treatment, and 7 (2.3%), 13 (4.3%) and 2 (0.7%) patients, respectively, started anti-propulsive treatment in the period from randomisation up to Week 24. While this study was not designed to formally assess qualitative aspects of GI 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.

There were 6 deaths during the study reporting period. Most common CV events were hypertension-type events. Other CV event types (arrhythmias, cardiac failure, myocardial infarction and thromboembolic events) were reported in very small numbers of patients across all 3 treatment groups. Overall, the incidence of adjudicated CV events, including major adverse CV events, was low and generally similar between the fostamatinib and placebo treatment groups. No events were adjudicated as CV events in Group A.

Fostamatinib is associated with elevations in BP. Increases in BP were evident at Week 1. The profile of elevated systolic BP (SBP) from baseline over time was slightly more pronounced in Group A than Group B and this treatment difference was observed from Week 6; changes in diastolic BP from baseline were generally smaller than changes in SBP. 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, 24.8%, 22.7% and 7.9% 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) (14.2%, 16.4% and 6.9% of patients in Groups A, B and C, respectively), acetylcholinesterase inhibitors, plain (11.0%, 10.2% and 1.6% of patients, respectively) and selective β-blocking agents (4.2%, 3.6% and 3.7% of patients, respectively). Between randomisation and Week 24, 7 patients (3 and 4 patients in the fostamatinib groups) had elevated BP ≥160/100 mmHg that persisted beyond 2 consecutive visits. These visits generally occurred within the first 6 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 (6 patients overall in the period from randomisation up to Week 24); none were associated with evidence of neutrophils $<1.5 \times 10^9$/L prior to the event. No patients in any group experienced a neutrophil count $<0.5 \times 10^9$/L, and no patients randomised to fostamatinib experienced an SAE due to or associated with neutropenia/decreased absolute neutrophil count.

Increases in ALT or AST >10x ULN were reported for 4 patients: 3 in Group B and 1 in Group C (pre-switch); review of individual cases showed that these occurred in the period from randomisation up to Week 24 and resolved either on or following cessation of study treatment. The proportion of patients with increased ALT or AST between 3x and 5x ULN was similar across the 3 treatment groups in the period from randomisation up to Week 24: 3.5%, 3.6% and 3.0% of patients in Groups A, B and C, respectively, had increased ALT ≥3x and <5x ULN, and 1.6%, 1.6% and 2.0% of patients, respectively, had increased AST ≥3x and <5x ULN. Two patients (1 in Group B and 1 in Group C, post-switch) met the clinical chemistry criteria for potential drug induced liver injury during the study. For both patients

there was an alternative explanation for the elevations in total bilirubin other than drug induced liver injury: both patients were UGT1A1*28 homozygotes (UGT1A1*28*28).