AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00004
Edition Number	1
Date	12 July 2013
EudraCT Number	2010-023692-26

(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 Adalimumab Monotherapy in Patients with Active Rheumatoid Arthritis

Study dates: First subject enrolled: 10 February 2011
Last subject last visit: 03 October 2012

Phase of development: Therapeutic exploratory (IIB)

[redacted]

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

[redacted]

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Primary objectives:	Primary outcome variables:
Evaluate the efficacy of 3 oral dosing regimens of fostamatinib compared with placebo when used as monotherapy in patients with active rheumatoid arthritis (RA) by assessment of the signs and symptoms of RA, as measured by Disease Activity Score based on a 28 joint count (DAS28) at Week 6.	DAS28-C-reactive protein (CRP) at Week 6.
Evaluate whether the efficacy of 3 oral dosing regimens of fostamatinib are non-inferior to that of adalimumab when used as monotherapy in patients with active RA by assessment of the signs and symptoms of RA, as measured by DAS28 at Week 24.	DAS28-CRP at Week 24.
Secondary objectives:	**Secondary outcome variables:**
Further assess the efficacy of fostamatinib measured by DAS28, DAS28 response criteria, American College of Rheumatology (ACR) 20% response criteria (ACR20), ACR 50% response criteria (ACR50), ACR 70% response criteria (ACR70), ACR index of RA improvement (ACR-N) and the individual components of ACR score.	DAS28, DAS28 response criteria, DAS28 ≤3.2, DAS28 <2.6, clinically important change in DAS28 (improvement ≥1.2), ACR20, ACR50, ACR70, 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}], CRP); 'ACR/European League Against Rheumatism remission (EULAR)' based on the simplified disease activity index.
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.
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), 8 individual domain scores.
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 separately from the CSR):	
Investigate the pharmacokinetics (PK) of R406 (active metabolite of fostamatinib) and/or the PK of fostamatinib or other metabolites and to investigate the relationship between systemic exposure to these metabolites and AEs, safety parameters and efficacy outcomes.	Plasma R406 and/or fostamatinib or other metabolites concentrations, oral clearance, area under plasma concentration-time curve during dosing interval at steady state. Limited PK data due to sparse sampling.
Collect and store DNA for future exploratory research into genes/genetic variation that could influence response (ie, absorption, distribution, metabolism and excretion, safety, tolerability and efficacy) to fostamatinib and/or adalimumab; and/or susceptibility to, progression of and prognosis of RA; and/or associated biomarkers.	DNA from whole blood
To investigate systemic biomarker profiles in RA patients.	Serum and plasma biomarkers

Study design

24-week, 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. Patients were randomised to study treatment as follows:

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

Group B: Fostamatinib 100 mg *bid* for 4 weeks then 150 mg once daily (*qd*) to Week 24, plus placebo injection every 2 weeks.

Group C: Fostamatinib 100 mg *bid* for 4 weeks then 100 mg *qd* to Week 24, plus placebo injection every 2 weeks.

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

Group E: Patients were randomised to receive 1 of 2 regimens (Groups F and G, see below) plus placebo injection every 2 weeks:

- **Group F:** placebo (6 weeks), then switch to fostamatinib 100 mg *bid* to Week 24.
- **Group G:** placebo (6 weeks) then switch to fostamatinib 100 mg *bid* for 4 weeks, followed by 150 mg *qd* to Week 24.

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

In addition, up to 90 patients at selected sites were to be randomised to participate in this study, but were also to undergo magnetic resonance imaging in a sub-study (reported separately).

Target subject population and sample size

Male and female patients aged ≥18 years, with active RA and not currently receiving DMARDs (DMARD-naive, 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.

It was planned to randomise up to approximately 280 patients to ensure that approximately 250 (~50 per group) received study treatment. For comparison with placebo, 50 patients per group would provide at least 85% power to detect a difference in mean change from baseline in DAS28-CRP of 0.7 at Week 6, assuming standard deviation of 1.25. For comparison with adalimumab, a non-inferiority margin of 0.6 in mean change from baseline in DAS28-CRP was chosen, and a zero difference in mean change from baseline in DAS28-CRP between the fostamatinib dose regimens and adalimumab assumed. Fifty patients per group provided approximately 85% power to confirm non-inferiority between fostamatinib and adalimumab, with standard deviation of 1.25.

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: 9636.10/1, 9636.11/1, 9636.12/1, 9636.13/1, 9636.14/1, 9636.15/1, 9636.16/1, 9636.20/1, 9636.21/1, 9636.22/1, 9636.23/1, 9636.24/1, 9636.25/1, 9636.31/1, 9636.32/1, 9636.34/1, 9636.37/1, 9636.41/1, 9636.42/1, 9636.44/1, 9636.45/1, 9636.46/1, 9636.47/1, 9636.5/1, 9636.52/1, 9636.59/1, 9636.6/1, 9636.61/2, 9636.62/2, 9636.7/1, 9636.8/1, 9636.9/1. Placebo to fostamatinib batch numbers: 9636.14/1, 9636.8/1, 9636.10/1, 9636.16.1).

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 methyl prednisolone (or equivalent).

Duration of treatment

Treatment continued for 24 weeks unless any discontinuation criteria were met. Patients who successfully completed the scheduled treatment period could continue to receive fostamatinib in a long-term extension study, OSKIRA-X.

Statistical methods

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

Each regimen of fostamatinib (Groups A, B, C) was compared separately to placebo at all scheduled post-baseline assessments to Week 6, and to adalimumab at all scheduled post-baseline assessments to Week 24. Primary endpoints were analysed using analysis of covariance (ANCOVA) on the change from baseline, including terms for baseline as a continuous covariate and treatment, DMARD naivety and country as factors. There were no adjustments for multiplicity.

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 DMARD naïvety and by country. 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 ANCOVA on the change from baseline, including terms for baseline as a continuous covariate and treatment, DMARD naïvety and country as factors. The proportion of patients classified as having achieved DAS28 response criteria and ACR/EULAR remission at each time point was analysed using logistic regression including treatment, country and DMARD naïvety as factors. In addition to the analysis of HAQ-DI score as an individual ACR component, the proportion of patients classified as HAQ responders at each time point was analysed using logistic regression including treatment, DMARD naïvety and country as factors. The SF-36 scores were summarised as change from baseline over time. The PCS and the MCS were analysed at each time point using the ANCOVA model described for individual ACR components.

Subject population

64.3%, 71.7%, and 69.5% of patients across the fostamatinib Groups A, B, C completed the 24-week study treatment. In the adalimumab group, 84.2% of patients completed treatment.

Figure S1 Patient disposition: randomisation

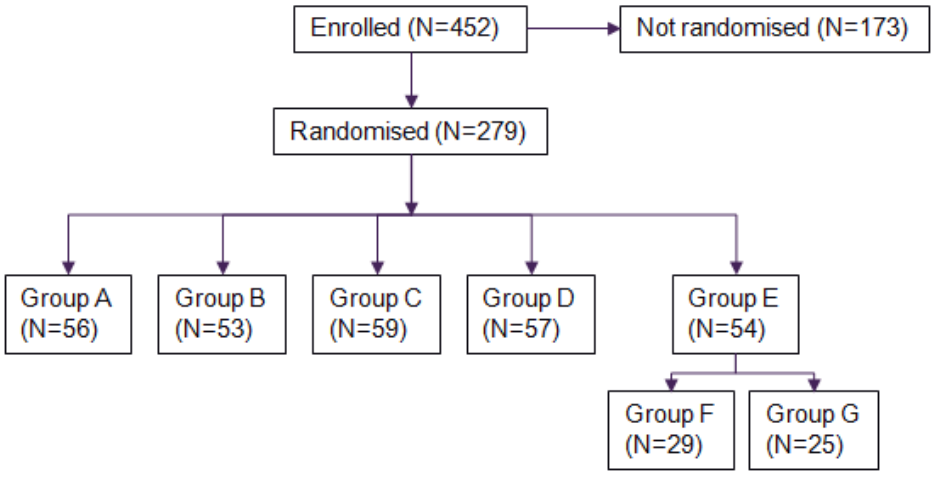
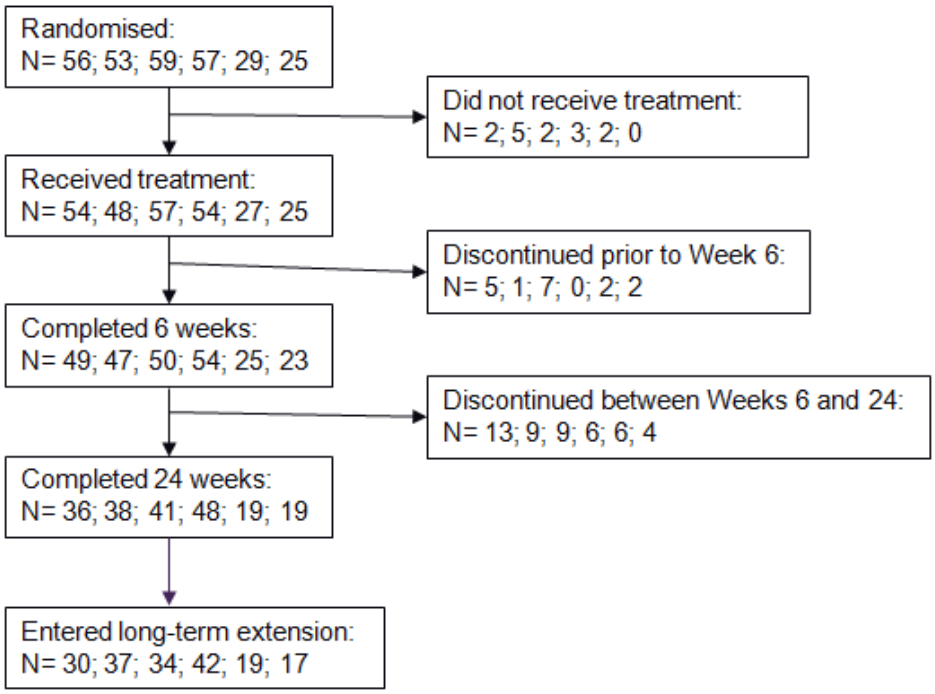


Figure S2 Patient disposition: study completion and discontinuation



N = Number of patients: Group A; Group B; Group C; Group D, Group F; Group G.

Mean age of the study population was 50 years (range: 22 to 78 years), 79.2% were female and most were White (90.6%). Mean DAS28-CRP score at baseline was 5.68. Overall, 42.6% were DMARD-naïve, and 57.4% had inadequate response/intolerance to DMARDs. The randomised treatment groups were generally well balanced with regard to demographic and baseline disease characteristics, and the stratification factor of DMARD naivety.

Summary of efficacy results

The efficacy results showed that fostamatinib monotherapy at the 2 higher dose regimens (Groups A and B) was more effective than placebo, but the lower dose (Group C) did not show consistent evidence of efficacy across the primary and secondary endpoints. Fostamatinib did not demonstrate non-inferiority versus adalimumab on the primary endpoint of DAS28 at 24 weeks, and adalimumab was statistically superior on this endpoint. Sensitivity and subgroup analyses (including whether patients were DMARD-naïve or had previously received DMARDs) also showed consistent results with the primary analyses. Although discontinuations from study treatment were more frequent on fostamatinib than adalimumab, this does not have a major influence on the efficacy conclusions.

Table S2 DAS28-CRP improvement from baseline to Week 6: comparison between fostamatinib and placebo (full analysis set)

Treatment	n	LS mean DAS28	Comparison with placebo [a]		
			Treatment difference	95% CI	2-sided p-value
Fostamatinib 100 mg *bid*	54	1.09	0.56	0.23, 0.90	0.006
Fostamatinib 100 mg *bid* (4 wks) then 150 mg *qd*	48	1.02	0.49	0.14, 0.84	0.022
Fostamatinib 100 mg *bid* (4 wks) then 100 mg *qd*	57	0.75	0.22	-0.12, 0.56	0.280
Placebo (combined placebo groups)	52	0.53			

[a] ANCOVA model on the improvement from baseline, including terms for baseline as a continuous covariate and treatment, DMARD naivety (DMARD naive vs DMARD-inadequate response/intolerant) and pooled country as factors.

Table S3 DAS28-CRP improvement from baseline to Week 24: comparison between fostamatinib and adalimumab (full analysis set)

Treatment	n	LS mean DAS28	Comparison with adalimumab [a]		
			Treatment difference	95% CI	2-sided p-value
Fostamatinib 100 mg *bid*	54	1.06	-0.72	-1.04, -0.40	0.005
Fostamatinib 100 mg *bid* (4 wks) then 150 mg *qd*	48	1.17	-0.61	-0.94, -0.27	0.020
Fostamatinib 100 mg *bid* (4 wks) then 100 mg *qd*	57	1.06	-0.72	-1.04, -0.40	0.004
Adalimumab 40 mg	54	1.78			

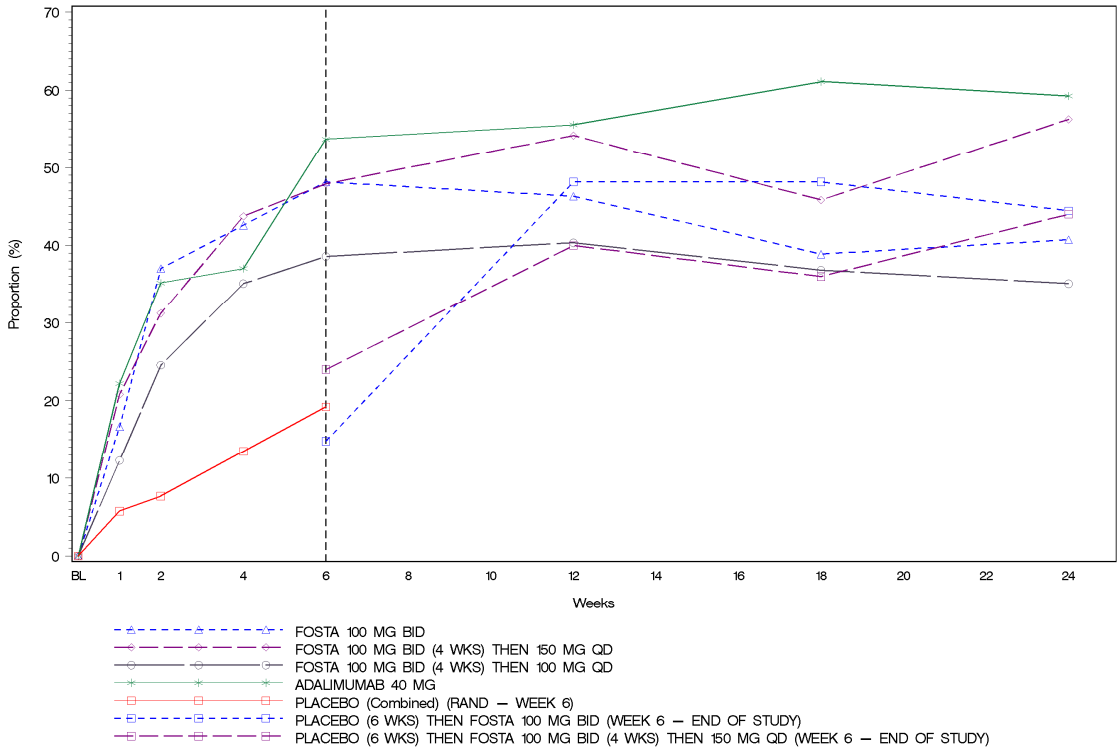
[a] ANCOVA model on the improvement from baseline, including terms for baseline as a continuous covariate and treatment, DMARD naivety (DMARD naive vs DMARD-inadequate response/intolerant) and pooled country as factors.

Broadly consistent results with the primary analyses were seen across the secondary efficacy endpoints (eg, see ACR20 response rates over time in Figure S3, with evidence of activity across the active treatment groups at Week 1, and activity maintained to Week 24). The lowest of the 3 fostamatinib doses (Group C) did not show consistent evidence of efficacy across the secondary endpoints.

ACR20, ACR50 and ACR70 response rates at Week 24:

- ACR20: 40.7%, 56.3% and 35.1% across the fostamatinib groups, and 59.3% on adalimumab.
- ACR50: 20.4%, 18.8% and 12.3% across the fostamatinib groups, and 31.5% on adalimumab.
- ACR70: 9.3%, 10.4% and 3.5% across the fostamatinib groups, and 20.4% on adalimumab.

Figure S3 Proportion of patients with ACR20 response over time



Non-responder imputation (BOCF) was applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Summary of pharmacogenetic results

While there is potential for fostamatinib to act as a UGT1A1 inhibitor and affect certain laboratory parameters, such as bilirubin, no patients with polymorphisms in the gene encoding UGT1A1 were reported with potential drug induced liver injury. One patient (a UGT1A1*28/*28 homozygote) in Group B had a total bilirubin value ≥2x ULN. For UGT1A1*1/*1 and UGT1A1*1/*28 genotypes, there was little variability in total or indirect bilirubin values and no notable differences seen over time or between treatment groups. As expected, baseline total and indirect bilirubin values were highest in UGT1A1*28/*28 homozygotes. The small group sizes (range n=1 to n=9) for the UGT1A1*28/*28 homozygotes in each treatment group limits any interpretation of variability. There is no evidence of clinical consequence for any genotype group on fostamatinib.

Summary of safety results

Total exposure was similar across fostamatinib groups (20.6, 20.8 and 21.9 treatment-years), and 24.1 treatment-years in the adalimumab group. Mean duration of exposure to Week 24 was 140, 158 and 140 days across the fostamatinib groups, and 163 days on adalimumab. Across the fostamatinib groups, 16.7%, 8.3% and 0% of patients had a dose reduction.

Table S4 Adverse events in any category, from randomisation to end of study

AE category	Number (%) of patients[a]			
	Fostamatinib 100 mg *bid* (n=54)	**Fostamatinib** 100 mg *bid* (4 wks) then 150 mg *qd* (n=48)	**Fostamatinib** 100 mg *bid* (4 wks) then 100 mg *qd* (n=57)	**Adalimumab** 40 mg (n=54)
Any AE	39 (72.2)	29 (60.4)	34 (59.6)	30 (55.6)
Any AE with outcome = death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	5 (9.3)	1 (2.1)	4 (7.0)	4 (7.4)
Any AE leading to discontinuation of IP[b]	9 (16.7)	6 (12.5)	8 (14.0)	0 (0.0)
Any AE leading to dose reduction of oral IP[c]	6 (11.1)	2 (4.2)	0 (0.0)	2 (3.7)

[a] 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.
[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.

Most common AEs on fostamatinib between randomisation and Week 24 were diarrhoea and hypertension. Incidence of diarrhoea across fostamatinib groups was 16.7%, 27.1% and 21.1%, and 1.9% on adalimumab. Incidence of hypertension was 13.0%, 6.3% and 8.8% across the fostamatinib groups, and 9.3% on adalimumab. Individual preferred terms for serious adverse events (SAEs) were generally reported at single incidences; SAEs on fostamatinib included CV and infection events. Most common AEs leading to discontinuation of IP reported on fostamatinib were diarrhoea (5.6%, 6.3% and 1.8%) and AEs related to increased liver transaminases (3.7%, 2.1% and 0%).

Gastrointestinal-related AEs reported by >1 patient in any group were diarrhoea, nausea and vomiting. For ~70% of the patients with diarrhoea, the AE was reported as resolved. Among the 14 patients with diarrhoea reported as unresolved, 10 entered OSKIRA-X and 4 had ongoing diarrhoea at time of withdrawal from study (2 of these 4 discontinued for a reason other than diarrhoea). In the overall population, there was relatively low use of anti-diarrhoeal or anti-propulsive medications (7.4%, 8.3%, 8.8% across fostamatinib groups). While this relatively small study was not designed to formally assess qualitative aspects of gastrointestinal tolerability, the data indicate that up to one-third of patients with an AE of diarrhoea may have used anti-diarrhoeal or anti-propulsive medications and suggest that for a majority of the patients who experience diarrhoea, symptoms may be manageable without adjunctive medication (ie, anti-propulsives) or discontinuation of study treatment.

No deaths or major adverse CV events were reported in any treatment group. Most common CV events were hypertension-type events. Other CV event types (arrhythmias, cardiac failure, ischaemic heart disease [angina] and thromboembolic events) were reported in small numbers of patients in Groups A and C, and in no patients on adalimumab. Nine events in 6 patients on fostamatinib were sent to the CV Adjudication Committee for adjudication, of

which 7 events in the 6 patients were adjudicated as CV. Of the 6 patients with events adjudicated as CV, 5 had multiple risk factors for CV events, including history of hypertension. No events on adalimumab or placebo met criteria for CV adjudication.

Fostamatinib is associated with elevations in blood pressure (BP). Increases in BP were evident at Week 1. The profile of elevated systolic blood pressure (SBP) from baseline over time was slightly more pronounced in Group A; 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 if they were on anti-hypertensives at baseline. Patients on anti-hypertensives at baseline showed variability in timing of their maximum SBP increase from baseline (median and means). For patients not on anti-hypertensives at baseline, maximum increases of SBP from baseline were seen by Week 10 (median and means). Across the 3 fostamatinib groups, 29.6%, 14.6% and 22.8% of patients had intervention for elevated BP. On adalimumab, 20.4% of patients had intervention for elevated BP. Initiation of new anti-hypertensive medication was the most frequent intervention. The most common anti-hypertensives starting after study entry were: ACE inhibitors, plain (9.3%, 4.2%, 7.0% of patients across fostamatinib groups), selective β-blocking agents (9.3%, 6.3%, 5.3%), and calcium channel blockers (20.4%, 6.3%, 12.3%). Two patients (both Group A) had elevated BP >160/100 mmHg that persisted beyond 2 consecutive visits. Blood pressure returned to normal on follow-up, in all patients who were discontinued from the study for elevated BP.

Incidence of serious infective events (ie, infections fulfilling criteria for SAE or requiring intravenous antimicrobials) was low (5 patients overall); none were associated with evidence of neutrophils $<1.5 \times 10^9$/L prior to the event. There was no evidence of neutropenia prior to the serious infective events and no evidence that patients were unable to mount an immune response in the face of an infection challenge. All serious infective events in fostamatinib-treated patients resolved. No absolute neutrophil counts were reported $<0.5 \times 10^9$/L.

The proportion of patients with increased ALT between 3x and 5x ULN was higher on fostamatinib (5.6%, 2.1%, 5.3% across fostamatinib groups) than on adalimumab (1.9%). Increases in ALT or AST >10x ULN were reported in Group A only (3.7% and 1.9%, respectively), and review of all individual cases showed that these resolved either on, or following, cessation of study treatment. Two of these patients had other potential explanations for their transaminase increased. No patients met the clinical chemistry criteria of ALT/AST ≥3xULN and total bilirubin ≥2xULN for potential drug induced liver injury.

[redacted]