Clinical Study Report Synopsis	
Drug Substance	Fostamatinib
Study Code	D4300C00005
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(OSKIRA-X): A Long-term Extension Study to Assess the Safety and Efficacy of Fostamatinib Disodium in the Treatment of Rheumatoid Arthritis

Study dates:	First subject enrolled: 10 January 2011
	Last subject last visit: Trial ongoing (data cut-off: 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.

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.

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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 long-term safety and tolerability of fostamatinib in patients with active rheumatoid arthritis (RA).	Adverse events (AEs; including independent adjudication of cardiovascular [CV] events); laboratory safety assessments (clinical chemistry, haematology and urinalysis); physical examination; electrocardiogram; weight abnormalities; and vital signs.
Secondary objectives:	**Secondary outcome variables:**
To assess the long-term efficacy of fostamatinib on the signs and symptoms of RA as measured by components of American College of Rheumatology (ACR) response criteria and Disease Activity Score based on a 28 joint count (DAS28).	Individual components of ACR response criteria (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, as measured by the Health Assessment Questionnaire – Disability Index [HAQ-DI], C-reactive protein and erythrocyte sedimentation rate) and DAS28.
To assess the long-term efficacy of fostamatinib on structural joint damage as measured by radiographic Modified Total Sharp Score (mTSS) and components of mTSS.	mTSS, joint space narrowing (JSN) and erosion score (ES).[a]
To assess physical function status of patients after administration of fostamatinib using the HAQ-DI.	HAQ-DI score; individual dimensions of HAQ-DI.
To investigate the effects of fostamatinib on patient reported health outcome measures.	36-item Short Form Health Survey (SF-36) –Physical component score, Mental component score, 8 individual domain scores.[b]
Exploratory objectives (not reported in this Clinical Study Report [CSR]):	**Exploratory outcome variables:**
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).[c]
To describe effects of fostamatinib on BP as determined by clinic and home BP measurements.[d]	BP (clinic and home).

[a] X-rays were not required for patients who participated in studies D4300C00004 or D4300C00033 prior to entering this extension study.

[b] SF-36 was not performed for patients who participated in study D4300C00033 prior to entering this extension study.

[c] Demographic and medical status data could be collected at Visit 1 of this extension study as a follow-up to the data collected at baseline of the qualifying study, if required.

[d] Applicable only for patients who participated in study D4300C00033 prior to entering this extension study.

Study design

A multi-centre, parallel group extension study to assess the long-term safety and efficacy of fostamatinib in patients with active RA who had participated in a qualifying study.

The qualifying studies were D4300C00001, D4300C00002, D4300C00003, D4300C00004 and D4300C00033 (also known as OSKIRA-1, -2, -3, -4 and –ABPM, respectively).

The intent was for eligible patients to enter this study directly from their qualifying study, without dose interruption. Matched placebo tablets were provided to maintain the blinding of treatment allocation.

In this extension study, patients received 1 of 3 oral dosing regimens of fostamatinib: 100 mg twice daily (*bid*), 150 mg once daily (*qd*) or 100 mg *qd*. Treatment allocation depended upon the treatment that the patient was receiving in the qualifying study.

- Patients receiving 100 mg *bid*, 150 mg *qd* or 100 mg *qd* in their qualifying study were to continue on that dose in the extension study.

- Patients who had a dose reduction to 100 mg *qd* in their qualifying study were to continue on this reduced dose in the extension study. Patients from study D4300C00033 who required a dose reduction were to be allocated to 100 mg *qd* in the extension study.

- Patients who were receiving either placebo or adalimumab in their qualifying study were to be allocated to 100 mg *bid* in the extension study. The exception to this was patients who had a "dose reduction" whilst receiving either placebo or adalimumab. In order to maintain the treatment blind, these patients were to receive the reduced active dose of 100 mg *qd*.

- Patients who entered the long-term extension study as non-responders at Week 12 from studies D4300C00001, D4300C00002 or D4300C00003 were to be allocated to fostamatinib 100 mg *bid* regardless of their original randomised dosing regimen, unless they had previously had a dose reduction. Patients who entered the study as non-responders who had a dose reduction to 100 mg *qd* were to continue at this reduced dose in the extension study.

The visit schedule and study procedures for each patient varied depending on the reason they were entering this extension study from their qualifying study. It was recognised that some patients could be switching from placebo to active treatment on entry to this study, so they were initially to have a more frequent visit schedule (Schedule I) than those patients who were already receiving active treatment (Schedule II).

Schedule I applied to patients who could have been receiving placebo on entry to the extension study, ie:

- Patients designated as non-responders at Week 12 in studies D4300C00001, D4300C00002 or D4300C00003.
- Patients who had successfully completed studies D4300C00003, D4300C00004 or D4300C00033.
- Patients who had required a dose reduction in study D4300C00033.

Schedule II applied to patients who had been receiving active treatment with fostamatinib for at least 24 weeks on entry to the extension study, ie:

- Patients who had successfully completed studies D4300C00001 or D4300C00002.

Patients entering from qualifying studies D4300C00001, D4300C00002, D4300C00003 and D4300C00033 were to continue to take their study treatment in combination with their regular disease-modifying anti-rheumatic drug (DMARD) therapy, at the discretion of the investigator.

Target subject population and sample size

Patients who had successfully completed a qualifying study (ie, studies D4300C00001, D4300C00002, D4300C00003, D4300C00004 or D4300C00033) with fostamatinib; or patients who had participated in a qualifying study and who had been classified as non-responders due to pre-defined lack of efficacy at Week 12 (D4300C00001, D4300C00002, D4300C00003); or patients who had participated in D4300C00033 and who required a dose reduction.

Since the objective of this study was to assess the long-term safety of fostamatinib, all eligible patients from the qualifying studies could be recruited. In particular, there was neither a minimum nor a maximum number of patients required.

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.

All patients were to continue to receive an appropriate standard of care by continuing to take their usual prescribed concomitant medications as allowed by the CSP, including any DMARD.

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

This extension study (also known as OSKIRA-X) was intended to continue until fostamatinib was commercially licensed in the relevant country for the indication under investigation. This report includes data up to the cut-off date of 19 March 2013, at which point the study was ongoing. However, further development of fostamatinib has since been discontinued.

Statistical methods

The full analysis set was used as the primary population for reporting safety and efficacy data. This comprised all patients who received at least 1 dose of investigational product (IP), and were summarised according to treatment first received in this study (intention-to-treat principle).

The data collected in this study, along with the data from the qualifying studies, were intended to allow assessments of safety and efficacy of fostamatinib over time. Data were summarised by visit and treatment. An additional CSR addendum will be generated after closure of this study summarising all of the data collected during the study.

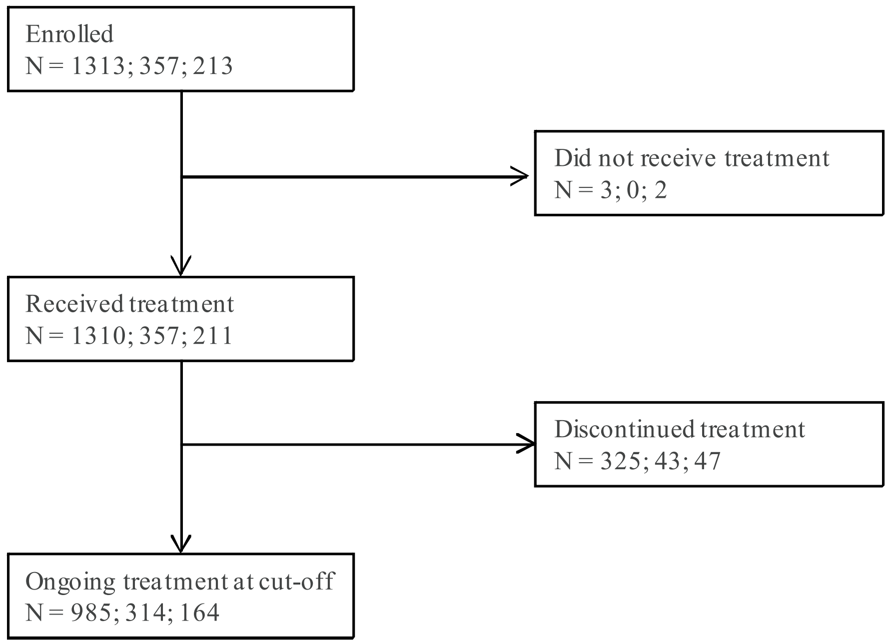
No formal statistical analysis was to be conducted in this extension study.

Subject population

Overall, 35.8% of patients were enrolled from study D4300C00001, 34.7% were enrolled from study D4300C00002, 13.8% were enrolled from study D4300C00003, 9.5% were enrolled from study D4300C00004 and 6.2% were enrolled from study D4300C00033.

75.0%, 88.0% and 77.0% of patients in the 100 mg *bid*, 150 mg *qd* and 100 mg *qd* groups, respectively, were ongoing treatment at data cut-off.

Figure S1 Patient disposition



N = Number of patients: Fostamatinib 100 mg *bid*; Fostamatinib 150 mg *qd*; Fostamatinib 100 mg *qd*

Mean age of the study population was 53 years (range: 19 to 85 years), 82.5% were female, and most were White (79.2%). At entry to the extension study, overall mean DAS28-CRP was 4.27. Demographic and baseline disease characteristics were as expected for this RA population, given the mixed population. Due to the designs of the qualifying studies, the 100 mg *bid* group included patients who had tolerated 100 mg *bid* treatment for the duration of the qualifying study as well as patients who received 100 mg *bid* for the first time in the extension study (i.e., patients who received placebo in the qualifying study, patients who entered the extension study as non-responders at Week 12 of the qualifying study and patients who received adalimumab in the qualifying study).

Summary of efficacy results

Mean DAS28-CRP scores were 4.5, 3.8 and 3.9 in the 100 mg *bid*, 150 mg *qd* and 100 mg *qd* groups, respectively, at entry to the extension study (Week 0). The DAS28-CRP scores were maintained throughout the study with similar values to Week 0 observed at the later visits for all 3 treatment groups in those patients who remained on study treatment. Mean DAS28-CRP scores were higher at the termination visit (5.2, 5.0 and 4.5 in the 100 mg *bid*, 150 mg *qd* and 100 mg *qd* groups, respectively) compared to Week 0. These results were as expected as approximately one third of the patients who had prematurely discontinued IP had discontinued from the study due to a lack of therapeutic response.

Likewise, for the mTSS, JSN and ES, HAQ-DI and patient reported outcome endpoints, scores were maintained throughout the study with similar values at entry to the extension study observed at the later visits for all 3 treatment groups in those patients who remained on study treatment.

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 with polymorphisms in the gene encoding UGT1A1, or in this study as a whole, had alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and bilirubin levels that met the clinical chemistry criteria for potential drug induced liver injury.

Two patients had an indirect bilirubin concentration >2x the upper limit of normal (ULN) and one patient had a direct bilirubin concentration >2xULN: all were in the 100 mg *bid* group and were *28/*28. There was no evidence of clinical consequence for any genotype group on fostamatinib treatment.

Summary of safety results

Total exposure in treatment years, from entry in this extension study up to data cut-off, was 975.34, 234.15 and 125.90 years in the 100 mg *bid*, 150 mg *qd* and 100 mg *qd* groups, respectively. This was reflective of the number of patients per treatment group.

The proportions of patients who had at least 1 dose interruption were 18.2%, 14.6% and 19.0% in the 100 mg *bid*, 150 mg *qd* and 100 mg *qd* groups, respectively, and the proportions with dose reductions were 10.8%, 5.9% and 1.9%, respectively.

Table S2 Adverse events in any category

	Number (%) of patients [a], Event rate (per 100 pt years)[b]		
	--ENTRY TO DATA CUT-OFF--		
AE Category	**Fostamatinib 100 mg bid (n=1310) - (tot. dur=999.6) -**	**Fostamatinib 150 mg qd (n=357) - (tot. dur=237.2) -**	**Fostamatinib 100 mg qd (n=211) - (tot. dur=129.3) -**
Any AE	926 (70.7) 92.6	226 (63.3) 95.3	132 (62.6) 102.1
Any AE with outcome = death	5 (0.4) 0.5	1 (0.3) 0.4	0 (0.0) 0.0
Any SAE (including events with outcome = death)	120 (9.2) 12.0	24 (6.7) 10.1	8 (3.8) 6.2
Any AE leading to discontinuation of IP	121 (9.2) 12.1	17 (4.8) 7.2	16 (7.6) 12.4
Any AE leading to dose reduction of IP[c]	101 (7.7) 10.1	18 (5.0) 7.6	6 (2.8) 4.6

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

b Number of patients with AEs divided by the tot.dur (total duration of exposure in years) across all patients in the full analysis set within each treatment group and period, multiplied by 100.

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

The most commonly reported AEs were diarrhoea (14.1% [18.5 events per 100 patient years], 10.4% [15.6 events per 100 patient years] and 11.8% [19.3 events per 100 patient years] of patients in the 100 mg *bid*, 150 mg *qd* and 100 mg *qd* groups, respectively) and hypertension

(11.5% [15.0 events per 100 patient years], 4.8% [7.2 events per 100 patient years] and 5.7% [9.3 events per 100 patient years], respectively). Rheumatoid arthritis and nasopharyngitis were the only other AEs reported in >5% of patients in any treatment group.

Overall, 9.2% (12.0 events per 100 patient years), 6.7% (10.1 events per 100 patient years) and 3.8% (6.2 events per 100 patient years) of patients, respectively, had a serious adverse event (SAE) and 9.2% (12.1 events per 100 patient years), 4.8% (7.2 events per 100 patient years) and 7.6% (12.4 events per 100 patient years) of patients, respectively, had a discontinuation of IP due to an AE (DAE). There were 6 AEs with an outcome of death reported during the study: 5 (0.4%) patients in the 100 mg *bid* group and 1 (0.3%) patient in the 150 mg *qd* group. In addition, 1 patient in the 100 mg *bid* group died of an event that started post-treatment.

Overall, the incidence of adjudicated CV events, including major adverse CV events (MACE), was low. From entry in this extension study up to data cut-off, 18 (1.4%), 2 (0.6%) and 2 (0.9%) patients had a SAE adjudicated to be a CV event. The event rates per 100 patient years were 1.8, 0.8 and 1.5, respectively. There were 5 MACE events (all in the 100 mg *bid* group): 1 fatal CV event, 1 non-fatal stroke and 3 non-fatal myocardial infarctions. In addition, there was 1 patient in the 100 mg *bid* group who had a fatal event that was adjudicated to be a death due to undetermined cause and 1 patient in the 100 mg *bid* group had a fatal CV event that occurred post-treatment.

Mean systolic and diastolic BP remained relatively constant throughout the study with similar values to Week 0 observed at the later visits for all 3 treatment groups in those patients who remained on study treatment. Five patients (all in the 100 mg *bid* group), had a DAE related to increased BP: 4 (0.3%) patients had hypertension and 1 (0.1%) patient had BP increased.

The incidence of serious infective events (SIEs, ie, infections fulfilling criteria for SAE or requiring intravenous antimicrobials) was low: 37 (2.8%), 5 (1.4%) and 3 (1.4%) patients in the 100 mg *bid*, 150 mg *qd* and 100 mg *qd* groups, respectively. One death was attributed to a SIE (liver abscess, 100 mg *bid* group) from entry in this extension study up to data cut-off. There was evidence of neutropenia (absolute neutrophil count [ANC] <1.0 x 10^9) prior to the event in 1 of the patients with SIEs during the study: Patient E7822301 in the 100 mg *bid* group had an ANC of 0.93 x 10^9/L at Week 0 (Day -1) prior to an SIE of osteomyelitis on Day 23. Four patients (3 [0.2%] in the 100 mg *bid* group and 1 [0.3%] in the 150 mg *qd* group) had an ANC <0.5 x 10^9/L at at least one visit from entry in this extension study up to data cut-off.

Increases in ALT or AST >10x ULN were reported for 3 patients (all in the 100 mg *bid* group); review of the individual cases showed that all had returned to within normal limits at the follow-up visit. Eighteen patients had either ALT and/or AST ≥5 to <10x ULN from entry in the extension study up to data cut-off (17, 0 and 1 patient in the 100 mg *bid*, 150 mg *qd* and 100 mg *qd* groups, respectively). No patients met the clinical chemistry criteria of ALT or AST ≥3x ULN and total bilirubin ≥2x ULN for potential drug induced liver injury from entry into the extension study up to data cut-off.

[redacted]