AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00029
Edition Number	1
Date	29 October 2013

(OSKIRA-Asia-1X): A Long-term Study to Assess the Safety of Fostamatinib in the Treatment of Rheumatoid Arthritis in Asia

Study dates: First subject enrolled: 19 July 2012
Last subject last visit: 23 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 (CSR) has been prepared.

[redacted]

Publications

None.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Primary objectives:	**Primary outcome variables:**
Evaluate the long-term safety and tolerability of fostamatinib in patients with active RA.	Adverse events (AEs), serious infective events (SIEs), laboratory safety data, vital signs, electrocardiograms and physical examination.
Secondary objectives:	**Secondary outcome variables:**
Assess the signs and symptoms of RA, as measured by components of the American College of Rheumatology (ACR) response criteria and Disease Activity Score based on a 28 joint count (DAS28) score.	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); DAS28 score.
Assess physical function status of patients after administration of fostamatinib using the HAQ-DI.	HAQ-DI score.
Assess health-related quality of life using the 36-item Short Form Health Survey (SF-36) questionnaire.	SF-36 physical and mental component scores, 8 individual domain scores.

Given the early termination of the study, only the primary objective is addressed in this synoptic CSR.

Study design

This was an open-label extension study to investigate the long-term safety of fostamatinib in patients who had completed the OSKIRA-Asia-1 (D4300C00008) Phase II dose finding study. There was no randomisation for this study; all patients received fostamatinib 100 mg once daily (*qd*).

No fostamatinib doses higher than 100 mg *qd* were allowed for long-term treatment, except for the short-term management of a disease flare, when doses of fostamatinib of 150 mg *qd* were allowed in patients who had not previously had a dose reduction due to increased blood pressure in study D4300C00008, up to a maximum treatment duration of 4 weeks. Patients were required to return to the 100 mg *qd* dose once the disease had been brought under control.

All patients were on stable background methotrexate (7.5 to 25 mg per week) during the study. An experienced independent joint assessor, blinded to other study assessments, was used at each site to perform the assessment of swollen and tender joint counts. A Safety

Review Committee reviewed the accumulating safety data, and a Cardiovascular Adjudication Committee (CVAC) reviewed pre-defined AEs of potential cardiovascular (CV) nature.

Target subject population and sample size

Male and female patients aged ≥18 years with active RA despite current treatment with methotrexate, who had successfully completed D4300C00008 and whose disease was adequately controlled, in the opinion of the investigator.

Since the objective of this study was to assess the long-term safety of fostamatinib, all eligible patients from study D4300C00008 could be recruited; there was neither a minimum nor a maximum number of patients required.

The study was terminated early due to programme closure (data cut-off 19 August 2103). Of the 115 patients enrolled into this extension study, 109 (94.8%) patients were ongoing treatment when the study was stopped.

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

Fostamatinib blue, film-coated, 50 mg tablets were taken orally, *qd*. Tablets could be taken with or without food, but not with food/drink known to inhibit cytochrome P450 3A4. Dose increase to 150 mg *qd* for short-term management of disease flares was permitted. [Fostamatinib batch numbers: 11666.2/1, 11666.4/1.]

If necessary, to control symptoms of RA, patients could have intramuscular, intravenous or intra-articular corticosteroid injections. The dose of NSAIDs could also be re-initiated up to the previous dose level (ie, the dose level prior to the patient achieving sustained stable RA disease activity) in the event of a disease flare.

Duration of treatment

Treatment was intended to continue until fostamatinib was commercially licensed for the treatment of RA, (or sooner if the development programme for fostamatinib was discontinued), unless any discontinuation criteria were met.

Statistical methods

The full analysis set was the primary population for reporting efficacy and safety data, and comprised all patients who received at least 1 dose of investigational product.

No formal statistical analysis was to be carried out in this study. All data were listed and selected variables were summarised.

Subject population

A total of 115 patients were enrolled in the study, with 109 (94.8%) patients still on treatment when the study was stopped. Six (5.2%) patients discontinued treatment before the study was stopped; 2 (1.7%) patients discontinued the study due to an AE, 3 (2.6%) patients due to a

lack of therapeutic response and 1 (0.9%) patient due to development of study-specific discontinuation criteria.

Median age of the study population was 54 years (range: 28 to 73 years), 87.8% were female, and all were Asian. Age, age group and sex distribution were as expected for the intended patient population. In total, 18 (15.7%) patients were aged 65 years or above.

Summary of efficacy results

Efficacy results have been listed only.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

Total exposure to fostamatinib was 52.29 treatment-years. Mean duration of exposure was 166 days. In total, 8 (7.0%) patients had at least one dose interruption (with 7 patients interrupting due to an AE) and 14 (12.2%) had a dose increase due to a protocol-specified dose change in order to control an RA flare. Median duration of dose interruption was 9 days, with 1 (0.9%) patient having an interruption of more than 28 days.

A total of 72 (62.6%) patients experienced an AE. No patients died. The overall numbers of patients with serious AEs (SAEs) and AEs leading to discontinuation of investigational product (DAEs) were low (SAE: 4 [3.5%] patients; DAEs: 3 [2.6%] patients).

Most common AEs were nasopharyngitis (14 [12.2%] patients), hypertension (7 [6.1%] patients), RA (7 [6.1%] patients) and neutropenia (6 [5.2%] patients). The SAEs reported were seborrhoeic keratosis, pancreatitis acute, osteonecrosis and road traffic accident. The DAEs reported were seborrhoeic keratosis, neutropenia and headache.

One patient experienced an event of seborrhoeic keratosis that was coded to the Medical Dictionary for Regulatory Activities System Organ Class ‘neoplasms benign, malignant and unspecified (incl. cysts and polyps)’; biopsy found intraepithelial carcinoma arising from seborrhoeic keratosis with malignant change.

Three days after completing treatment 1 patient reported an AE of herpes zoster; the event was local, not disseminated. No other opportunistic infections were observed.

No AEs were adjudicated as CV events.

No absolute neutrophil counts were reported $<0.5 \times 10^9$/L. Two patients experienced SIEs (ie, infections fulfilling criteria for SAE or requiring intravenous antimicrobials); 1 event of pneumonia and 1 urinary tract infection. The pneumonia patient had low neutrophil counts pre-treatment. The urinary tract infection patient had neutrophils within the normal range throughout the study. Both SIEs resolved.

No patients met the clinical chemistry criteria of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN) and total bilirubin ≥2xULN for potential drug-induced liver injury.