CLINICAL STUDY REPORT SYNOPSIS

NAME OF SPONSOR/COMPANY: AstraZeneca AB NAME OF FINISHED PRODUCT: Fostamatinib (R935788) NAME OF ACTIVE INGREDIENT(S): R940406 (R406)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol Number: C-935788-012/AstraZeneca AB Study Code: D4300C00021

Title of Study: An Open-Label, Multicenter Extension Study to Evaluate the Safety of R935788 in Patients with Rheumatoid Arthritis Who Have Completed the Treatment Phase of a Rigel-Sponsored R935788 Study

Investigators: [redacted]

Study Center(s): [redacted]

Publication (Reference): Not applicable

Study Period: Study Initiation Date: 07 June 2008 Interim Cutoff Date: 15 January 2013	**Phase of development:** 2b

Objectives:

The primary objective of this study was to investigate the long-term safety of fostamatinib in patients with rheumatoid arthritis (RA) who completed the treatment phase of Study C-935788-006X (C-788-006X), C-935788-010 (C-788-010), or C-935788-011 (C-788-011).

The secondary objective of this study was to investigate the long-term efficacy of fostamatinib in patients with RA who completed the treatment phase of Study C-788-006X, C-788-010, or C-788-011.

Methodology:

This study was an open-label, long-term extension for patients who completed the treatment phase of Study C-788-006X (open-label extension study) or C-788-010 or C-788-011 (randomized, controlled studies). There was no randomization to treatment in this trial. Patients that continued to meet the inclusion/exclusion criteria were offered the opportunity to receive open-label fostamatinib treatment. The majority of patients (63.5%) who were originally treated with placebo were switched to open-label fostamatinib 100 mg twice daily (BID). Exceptions to this were patients who received placebo once daily (QD) in C-788-010 (they were switched to open-label fostamatinib 150 mg QD), patients who had a dose reduction in studies C-788-010 or C-788-011 (they were switched to open-label fostamatinib 100 mg QD), and patients who received open-label fostamatinib 50 mg BID, 100 mg QD, or 150 mg QD in C-788-006X (who then continued to receive these doses).

Patients had to agree to the visit schedule. In addition, the patients could not have had any clinically significant adverse clinical or laboratory effects while participating in C-788-006X, C-788-010, or C-788-011. Patients remained blinded to their treatment assignment from the previous study (active or placebo) and could have continued to receive their regular maintenance RA medications. A baseline visit was required for patients who did not receive a dose of study drug within 14 days prior to enrollment.

Number of Patients (planned and analyzed): Approximately 800 male and female patients were planned to be recruited; 624 patients were enrolled in this study.

Diagnosis and Main Criteria for Inclusion:

Patients with RA who:

- Were treated in Study C-788-006X.
- Completed Study C-788-010 or C-788-011 and did not withdraw due to adverse events (AE).
- Withdrew from Study C-788-010 at Month 4 or Month 5 because of a predefined lack of efficacy.

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Test Product, Dose, Mode of Administration, and Batch Number: All patients self-administered fostamatinib (R935788 or R788) orally. Patients treated with fostamatinib in the previous studies received 50 mg BID, 100 mg BID, 100 mg QD, or 150 mg QD doses. Patients originally treated with placebo in the previous studies received 100 mg QD, 150 mg QD, or 100 mg BID doses.

Fostamatinib was supplied as a blue film-coated oval tablet containing either 50 mg (Batch Numbers: DKWF, DKWG, C8A0072, C8G0176, DNNF, DNNT) or 100 mg (Batch Numbers: C7K0010, C8G0180, C9I2282, C9I2283, C9I2284) of active ingredient.

Reference Product, Dose, Mode of Administration, and Batch Number: Not Applicable

Duration of Treatment: Open-label study is ongoing.

Criteria for Evaluation:

Efficacy:

The primary efficacy parameter was Disease Activity Score 28 modified to include the 28 joint counts (DAS28)-C-reactive protein (CRP).

The secondary parameters were:

- Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, and changes from baseline in HAQ-DI scores
- Swollen joint counts (SJCs) and changes from baseline in swollen joints
- Tender joint counts (TJCs) and changes from baseline in tender joints
- CRP (mg/L) and changes from baseline in CRP (mg/L)
- Patient's disease activity assessment on a visual analog scale (VAS), and changes from baseline in the patient's disease activity assessment

Each of these efficacy parameters were collected at all quarterly post-baseline visits (3 months, 6 months, 9 months, 12 months, etc).

Safety:

The primary safety assessments were:

- AEs
- Vital signs
- Complete blood counts (CBCs)
- Serum chemistry
- Pregnancy tests
- 12-lead electrocardiograms (ECGs)

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Statistical Methods: This was an open-label extension study of the C-788-006X, C-788-010, and C-788-011 clinical studies; therefore, a sample size calculation was not needed. The full analysis set (FAS) included all patients who entered this extension study and received at least 1 dose of the study drug. The FAS was used for all safety and efficacy analyses.

The primary objective was to investigate the long-term safety of fostamatinib. Safety measures, including AEs, clinical laboratory evaluations, physical examination, vital signs, and ECGs were summarized using descriptive statistics and listings. Treatment-emergent adverse events (TEAEs) were tabulated by treatment groups. Changes from baseline in each vital sign were tabulated and summarized descriptively by treatment and scheduled time point. The number and proportion of patients with lab abnormalities were summarized by treatment group. A frequency analysis of the overall status of normality in ECG by time point and treatment was presented. Descriptive statistics (number of patients, mean, standard deviation [SD], minimum, maximum, and median) of each interval were calculated at each visit by treatment, and changes from baseline were summarized with descriptive statistics by treatment.

The secondary objective was to investigate the long-term efficacy of fostamatinib. The primary efficacy parameter was DAS28-CRP. The DAS28 consisted of a composite score of the following variables: TJC, SJC, CRP, and patient global score. The secondary efficacy parameters were the observed values, decreases from baseline in efficacy parameters, and percent decrease from baseline in HAQ-DI, SJCs, and TJCs. Descriptive statistics were summarized at each quarter by treatment groups where data were collected, including number of observations (n), mean, SD, median, and range for each continuous variable.

Summary - Conclusions

Demographics and Baseline Characteristics:

The majority of the patients in this study were female (535 patients, 85.7%), and either Hispanic (307 patients, 49.2%) or Caucasian (290 patients, 46.5%). The overall mean (SD) age of the patients at the first dispensation of study drug was 53.0 years (12.58), and ranged from 18 years to 87 years. The overall mean (SD) RA duration was 10.46 years (8.667), with a range of 1.0 year to 56.0 years.

Efficacy Results:

The primary efficacy parameter used to investigate the long-term efficacy of fostamatinib was DAS28-CRP, which indicated the maintained effectiveness in patients who were able to continue long-term fostamatinib treatment. Consistent with DAS28-CRP, the long-term treatment effect of fostamatinib was also maintained for all secondary efficacy parameters: HAQ-DI, TJC, SJC, CRP, and patient disease activity assessment.

Safety Results:

- The most commonly reported AEs (reported in > 10% of patients) were diarrhea, urinary tract infection, hypertension, and upper respiratory tract infection. Overall, these were generally mild to moderate.
- There were 13 deaths (2.1% of patients) during the study reporting period. There was an additional patient who died of an event that started shortly after the 28 day follow-up period after their last dose. The majority of deaths (9 patients [1.4%]) were events within the infections and cardiac disorders *Medical Dictionary for Regulatory Activities* (MedDRA) system organ classes (SOCs). The remaining deaths were single events in a variety of MedDRA SOCs.
- In this study, 17.3% of patients experienced a treatment-emergent serious AE (SAE).
- One female patient in the 100-mg BID treatment group was a potential Hy's Law patient (met the clinical chemistry criteria of alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 3 × upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN) for potential drug induced liver injury). While the patient was participating in study C-788-012, she had ALT values > 3 × ULN on 6 occasions (Days 50, 56, 176, 478, 486, and 490). She had a single occasion of bilirubin = 2 × ULN (Day 328), which was not contemporaneous with the occasions when her ALT was raised within a 5 month difference in time between the elevations in ALT/AST and the bilirubin rise. This patient did not have clinically evident hepatic injury.
- In this study, 0.5% of patients had an ALT value of > 10 × ULN. These elevations did not result in clinically evident hepatic injury. An additional 2.6% of patients had at least 1 occurrence of ALT > 5 × ULN and 7.5% had at least 1 occurrence of ALT > 3 × ULN. Overall, 1.9% of patients discontinued study drug due to reported TEAEs of increased transaminases and 4.2% of patients required a change in study drug due to a reported TEAE of transaminases increased.
- Consistent with the previous fostamatinib Phase 2 studies, fostamatinib was associated with elevations in systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension (15.5% of patients) was 1 of the most commonly occurring TEAEs by PT and all cases were reported as mild or moderate in intensity. In the study, 2 patients (0.3%) reported an SAE of hypertensive crisis; both events were adjudicated as hypertensive events of a serious nature by the independent adjudication committee. At any occurrence postbaseline, 44.3% of patients had a SBP increase ≥ 20 mmHg and 1.6% of patients had a SBP of ≥ 180 mmHg at some time during the study. In addition, 58.9% of patients had a DBP increase ≥ 10 mmHg and 17.8% of patients had a DBP reading ≥ 160/110 mmHg.

Conclusion:

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