AstraZeneca

**Abbreviated Clinical Study Report Synopsis**

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| Drug Substance | Fostamatinib |
| Study Code | D4302C00001 |
| Edition Number | 1 |
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# A Phase II Trial to Evaluate the Efficacy of Fostamatinib in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

**Study dates:**

First patient enrolled: 18 January 2012
Last patient last visit: 3 patients are ongoing
Data cut-off for this report: 30 October 2013

**Phase of development:**

II

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

## Introduction

This study is being submitted as an abbreviated clinical study report (aCSR), because AstraZeneca (AZ) returned the rights to fostamatinib to Rigel Pharmaceuticals, who decided not to progress development in diffuse large B-cell lymphoma (DLBCL). The decision to stop development of fostamatinib was not due to any clinical safety reason. Patient enrolment was completed on 14 June 2013. However three patients, considered by the Investigator to still be receiving clinical benefit, continue to receive fostamatinib 200 mg bid.

This report presents the data of the 68 patients with DLBCL treated with fostamatinib.

### Study centres

This study was conducted at 23 study centres in the United States and 2 study centres in the United Kingdom.

### Publications

There were no publications at the time of writing this report.

### Objectives and criteria for evaluation (amended)

Primary objective:

- To evaluate the efficacy of fostamatinib (200 mg bid) in patients with relapsed or refractory DLBCL, by assessing the overall response rate (ORR).

Secondary objectives:

- To evaluate ORR and durable response rate (DRR) of patients with two distinct molecular subtypes of relapsed or refractory DLBCL; B-cell receptor activation positive (BCA+) and B-cell receptor activation negative (BCA-). Several BCA signatures may be considered and selected signature(s) will be evaluated in a further study.

- To further evaluate the efficacy of fostamatinib (200 mg bid) in patients with relapsed or refractory DLBCL, by assessing duration of response (DoR), and progression-free survival (PFS).

- To further evaluate the safety and tolerability of fostamatinib (200 mg bid) in the treatment of patients with relapsed or refractory DLBCL.

- To characterise the pharmacokinetics (PK) of R940406 (R406), the active metabolite of fostamatinib.

Exploratory Objectives:

- To explore the correlation between patient response to fostamatinib and the mutational status of key B-cell receptor pathway genes.
- To collect information about the prevalence of BCA+ and BCA- patients.
- To collect and store DNA, RNA, and/or tissue for future exploratory research into genetic and proteomic variation that may influence response and/or resistance to fostamatinib or susceptibility to DLBCL.
- To evaluate the pharmacodynamic (PD) effects of fostamatinib on SYK target inhibition and downstream tumour-derived markers of pathway activity.
- To explore the relationship between R406 PK parameters and PD endpoints (biomarker levels, response, and any predominant AEs).

**Study design**

This study was originally designed as a randomised, two-arm double-blind, multi-centre study of two doses of fostamatinib, 100 mg and 200 mg bid, in patients with relapsed or refractory DLBCL. Anti-tumour activity had been observed in patients with DLBCL when given 200 mg bid fostamatinib in a previous study by Rigel Pharmaceuticals (C935788-009). Since the 100 mg bid dose was felt likely to be better tolerated for long-term administration, and had not been previously tested in lymphoma trials, the lower dose was included in the initial design of this study. The aim of the study was to evaluate the efficacy and tolerability of both doses of fostamatinib, and to select a dose for further study. With the implementation of Protocol Amendment 1, treatment with lower dose fostamatinib (100 mg bid) was stopped and the higher dose of fostamatinib (200 mg bid) was given to enrolling patients. Treatment assignment was no longer blinded. Thirty additional patient who were biologically evaluable (defined as patients with adequate fresh tumour biopsy material) were planned for this portion of the study.

The primary objective of this study was to evaluate the efficacy of fostamatinib in patients with relapsed or refractory DLBCL by assessing the overall response rate (ORR). In addition, patients in whom fostamatinib was thought to demonstrate efficacy (both frequency and duration of response [DoR]) were explored by sub-classification into B-cell receptor activation positive and negative (BCA +/-) segments. The hypothesis explored was that patients whose tumours demonstrated B-cell signalling were more likely to respond, or would respond for longer duration, to fostamatinib.

In order to adequately assess the relevance of responses in the study (and responses in BCA+ and BCA- patient subgroups), the durable response rate (DRR) had to be assessed (defined as the number [%] of patients having complete remission [CR] or partial remission [PR] with a DoR of at least 24 weeks), and the DoR for patients.

Consent was obtained from patients to provide a sample of archival tumour biopsy material for molecular analysis, and one fresh pre-treatment excisional tumour biopsy in this study, to: a) support generation of BCA+ and BCA- signatures for future selection of responding patients, b) confirm pathway inhibition by analysis of relevant biomarkers, and c) help inform the dose selection for future studies. In addition, optional tumour biopsies were requested from consenting patients at progression.

Blood samples for pharmacogenetic (PGx) analysis, for the determination of *UGT1A1* genotype and for other exploratory analyses, were collected during the study.

The CSP was amended because of a lack of an objective response in the first 35 patients evaluated. Toxicity profiles of both doses were reviewed in a blinded fashion and were found to be acceptable and similar to those reported in the previous Rigel Pharmaceuticals, Inc Phase II study. The lower fostamatinib dose (100 mg bid) was omitted from the study, and all subsequent patients received the higher dose (200 mg bid). In addition, patients previously randomised and receiving blinded treatment were unblinded, and if assigned 100 mg bid, were offered dose escalation. The two patients still on study at the time of the amendment were unblinded; the first patient's dose was escalated to 200 mg bid, and it was determined that the second patient had been assigned to the 200 mg bid dose at study entry.

**Target subject population and sample size**

The target subject population of this study included patients with DLBCL who had progressed following therapy with an anthracycline-containing regimen (i.e., R-CHOP) and high-dose chemotherapy with stem-cell rescue, or who were ineligible for high-dose chemotherapy with stem-cell rescue.

**Investigational product and comparator(s): dosage, mode of administration and batch numbers**

Fostamatinib and placebo for oral administration were supplied as oval blue, film-coated tablets containing 50 mg or excipient, respectively. Doses of 100 mg or 200 mg, twice daily, were planned. Following the approval of Protocol Amendment 1, only the 200 mg dose, twice daily, was administered.

**Duration of treatment**

Patients were allowed to continue on therapy as long as they had no limiting toxicity or disease progression, did not withdraw from the study, and were considered, by the investigator, to still be receiving clinical benefit (patients were allowed to continue on therapy after progression criteria was met only if they were considered to be receiving clinical benefit).

**Statistical methods**

There were 4 analysis sets defined for this study:

- The full analysis set consisted of all randomised or dosed patients on the basis of randomised or assigned treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment were included in the full analysis set.

- The safety analysis set consisted of all patients who received at least 1 dose of randomised study treatment irrespective of follow-up.

- The pharmacokinetic (PK) analysis set consisted of patients who received at least one dose of fostamatinib and who had at least one plasma concentration variable above the lower limit of quantitation (results presented in a separate report).

- The personalised healthcare (PHC) biomarkers analysis set consisted of patients from whom a pre-treatment fresh tumour biopsy and/or archival tumour biopsy were obtained. These samples had to have passed appropriate quality control (QC) checks to generate valid gene expression data. The results were not analysed for this aCSR.

**Subject population**

All patients entering this study had relapsed or refractory DLBCL and had received previous chemotherapy. The majority of patients had received 2 or 3 (30.9% and 27.9%, respectively) previous chemotherapy treatments with R-CHOP or an equivalent chemo-immunotherapy.

Most patients were Caucasian (91.2%) and male (69.1%). The mean age (±standard deviation [StD]) was 63.6 ±12.6 years. The youngest patient was 29 years-of-age and the oldest was 86 years-of-age. The majority of patients were ≥50 and <75 years of age.

**Summary of efficacy results**

The primary objective of this study was to evaluate the efficacy of fostamatinib in patients with relapsed or refractory DLBCL by assessing the ORR.

The best overall tumour response during the study was one patient (4.8%) with a complete response and one patient (4.8%) with a partial response, both in the 100 mg fostamatinib group. In addition, stable disease was demonstrated by 2 patients (9.5%) in the 100 mg group and 5 patients (10.6%) in the 200 mg group. Response assessments were performed at scheduled time points throughout the study as detailed in the study plan.

Patients were assessed using the revised response criteria for malignant lymphoma. Patients were assessed for response, with CT and FDG-PET scans at 8 weeks, then every 12 weeks until radiological progression by clinical CT. The ORR rates observed were 9.52% (95% confidence intervals [CIs]: 1.17, 30.38) in the 100 mg group and 0.00% (95% CIs: 0.00,7.55) in the 200 mg group.

**Summary of pharmacokinetic results**

The results of the PK analyses are reported outside of this aCSR.

**Summary of pharmacodynamic results**

Overall patient response to fostamatinib was limited, precluding biomarker development.

**Summary of safety results**

There were a total number of 18 deaths during the study, 16 of which were related to the disease under investigation. Two SAEs had an outcome of death. In addition, 13 patients experienced SAEs that did not lead to death, and 3 patients experienced AEs and 2 patients experienced SAEs leading to discontinuations due to fostamatinib. Every patient in the 100 mg group experienced at least 1 AE and 93.6% of patients in the 200 mg group experienced at least 1 AE. The majority of patients experienced AEs in the gastrointestinal disorders SOC. At least 40% of total patients experienced AEs in each of the general disorders, investigations, and blood and lymphatic system disorders SOCs.