2 SYNOPSIS

Name of Sponsor/Company: Rigel Pharmaceuticals, Inc./Astra Zeneca AB	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**
Name of Finished Product: R935788 Tablets/Fostamatinib Disodium	
Name of Active Ingredient: R935788 Sodium Hexahydrate	
Title of Study: A Phase II, Multi-Center, Simon Two-Stage Study of R935788 in Patients with Relapsed or Refractory T-Cell Lymphoma	
Publication (Reference): none	
Study Period (Years): 1 year	**Phase of Development:** 2

Objectives:

The primary objective was to assess the efficacy of R935788 (R788) 200 mg orally, twice daily (PO bid*)* in patients with relapsed or refractory T-cell lymphoma (TCL).

Secondary objectives were:

- To assess the safety and tolerability of R788 in patients with TCL
- To understand the pharmacokinetic (PK) profile of R788 in patients with TCL
- To study the role of Syk in the pathogenesis of TCL and to explore the biologic activity of R788 in patients with TCL.

The Data Safety Monitoring Committee (DSMC) for this study met on 22 March 2010. Based on the data reviewed, it was concluded that the study did not meet the criteria to continue into Stage 2. Therefore, an abbreviated clinical report of safety and primary efficacy is being submitted.

Methodology:

This was a phase 2, multi-center, Simon two-stage study of R788. Patients meeting specific inclusion and exclusion criteria were to be enrolled in two stages. All enrolled patients were treated with R788 200 mg PO bid until disease progression, unacceptable toxicity, or withdrawal.

In the initial stage (Stage 1) of the study, a total of 19 patients were planned for enrollment and treatment with R788 200 mg *PO* bid. According to the Simon design, if ≤ 3 of the 19 patients in Stage 1 had a response, the regimen was rejected. When ≥ 4 patients exhibited a response (complete response [CR], partial response [PR] or regressive stable disease [SD]) at Week 8 or later evaluation, the second stage (Stage 2) of 36 anticipated patients was to be opened for enrollment. The regimen was rejected at the end of Stage 2 if ≤ 12 of the total number of patients had a response. Otherwise, if at least 13 of the total number of patients had a response (CR, PR, or regressive SD), the regimen was acceptable for further development.

Stage 1 patients withdrawn prior to completion of 8 weeks of study participation for reasons other than disease progression, including noncompliance (defined as receiving less than 75% of the specified doses), were to be replaced. Patients withdrawn prior to completion of at least 2 weeks of R788 treatment due to disease

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Methodology (continued):

progression were also replaced. However, these patients were not included in the determination to proceed with Stage 2 of the study or in determining study success following Stage 2. These patients were included in the intent-to-treat (ITT) analysis of efficacy response rates at the completion of the study. No more than a total of 6 patients (Stage 1 and Stage 2) were to be replaced.

Dose interruption, adjustment or discontinuation due to adverse events (AEs) was done according to guidelines in the protocol. Dose reductions were decreased by 50 mg twice or 100 mg once daily (total daily reduction of 100 mg). Patients requiring > 3 consecutive weeks of study drug interruption or > 2 dose reductions were reviewed with the Medical Monitor.

Information collected at the scheduled visits included a review of AEs and other safety data, brief physical exams, vital signs, blood samples to analyze PK and pharmacodynamic (PD) parameters, and tumor assessments.

The DSMC monitored safety throughout the study.

Number of Patients (Planned and Analyzed):

Planned: Up to 61 patients, with at least 19 and 36 patients to be enrolled in Stage 1 and Stage 2, respectively.

Analyzed: A total of 18 patients received treatment in Stage 1; 0 patients received treatment in Stage 2. Data for 18 patients were analyzed.

Diagnosis and Main Criteria for Inclusion:
Patients were men and women at least 18 years of age with relapsed/refractory TCL, who had failed at least one prior treatment regimen and for whom no standard therapy existed. Sexually active female patients of childbearing potential must have had a negative serum pregnancy test, and must have agreed to use an effective method of birth control for the duration of the study and for 30 days thereafter.

Test Product, Dose and Mode of Administration, Lot Number: R788 was provided in 50 mg tablet strengths (lot numbers C8A00721 and C8G01751) and was administered orally at doses of 200 mg PO bid.

Duration of Treatment: The duration of study participation for each patient was approximately 3 months including a screening period of up to 28 days and a treatment period of 8 weeks. Patients continued treatment until disease progression, toxicity or withdrawal from the study. Enrollment in the study, from first patient enrolled to last patient enrolled, was expected to be approximately 14 months.

Reference Therapy, Dose and Mode of Administration, Batch Number: not applicable

Criteria for Evaluation:

Efficacy was assessed by overall regressive response rate (ORRR), overall response rate (ORR), and clinical benefit rate.

Safety was assessed by evaluating AEs, reviewing clinical laboratory values (chemistry, hematology), and evaluating physical examinations, vital signs, and Eastern Cooperative Oncology Group (ECOG) Performance Status results.

PK parameters of plasma R406 (the R788 metabolite) including maximum observed concentration (C_{max}) and area-under-the-concentration-time curve (AUC) were derived based on available R406 concentration data. Due to very low R788 plasma levels detected in previous R788 clinical studies, samples were not analyzed for R788 content.

PD assessments included comparison of activation of Syk and its downstream markers in tumor biopsy specimens before and after treatment with R788, and the correlation between baseline Syk activation in tumor biopsy specimens and response to therapy.

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Statistical Methods: All efficacy and safety analysis was based on the ITT population.

Efficacy: The number and percentage of patients who achieved a regressive response (best overall response of complete response [CR], partial response [PR] or regressive stable disease [RSD]), response (best overall response of CR or PR), and clinical benefit (best overall response of CR, PR, or SD) were presented; 95% confidence intervals for the best overall regressive response rate, response rate and the clinical benefit rate using the exact method were provided.

Stable disease assessments were categorized as either regressive or non-regressive. In general, a stable disease assessment where the sum of the products for the measurements at all target lesions was less than the sum of the products from the screening assessment were considered to be a RSD. A medical review was conducted to confirm the categorization of all stable disease assessments.

Safety: The incidence of treatment emergent adverse events (TEAEs) was displayed overall and by patient group by system organ class and preferred term. TEAEs were also summarized by severity and relationship to study drug. By patient incidence of serious adverse events (SAEs) was also displayed. AEs were categorized based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v 3.0) toxicity grades (ranging from 0 to 4). Changes from baseline to each post-baseline visit in vital signs were descriptively summarized. Hematology and chemistry laboratory parameters were summarized using descriptive statistics at baseline and each post-baseline time point. Changes from baseline were summarized. The most abnormal post-baseline toxicity grade for each available laboratory parameter were summarized relative to baseline (improved, no change, 1 grade increase, 2 grade increase and > 2 grade increase) using counts and percentages. Physical examinations and ECOG Performance status results were included in data listings only.

PK: The coefficient of variation (CV %) and geometric mean was provided for PK parameters (C_{max} and AUC). Graphic display of plasma R406 concentration vs. time was provided as either a linear or log-transformation scale. The coefficient of variation (CV %) and geometric mean was provided for R406 concentration data and C_{max} and AUC at each visit where data are available.

PD: Descriptive statistics including mean, median, standard deviation, and range were to be provided to summarize change in Syk expression in tumor tissue from baseline to post-treatment. Additional exploratory analyses may have been performed to assess the relationship between the activation of Syk pre- and post-treatment and disease response (These analyses have not been performed and are not presented in this CSR).

SUMMARY

All patients enrolled (ITT population) were included in the analysis of baseline characteristics and demographics (Section 14.1, Table 3). All enrolled patients received at least one dose of R788 and were included in the safety analyses. All patients that completed 8 weeks of therapy with R788 and/or had a follow-up tumor assessment were included in the analysis of efficacy.

Demographic and other Baseline Characteristics

A total of 18 patients were enrolled in Stage 1 of this study of which 10 (55.6%) were male. The median age was 68.5 years (range 44-78 years), and the majority (15/18; 83.3%) were white. Sixteen of 18 (88.8%) had an ECOG performance score of 0 or 1. At the most recent biopsy recorded 9/18 (50.0%) had peripheral TCL, unspecified; 7/18 (38.9%) had angioimmunoblastic TCL; and 1/18 (5.6%) each had transformed mycosis fungoides and “other” TCL. Eight of 18 patients had a “poor” International Prognostic Index (IPI) score at diagnosis. All patients had previously received systemic treatment; the median number of prior regimens was 2 (range 1 to 17).

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Efficacy Results: A total of 17/18 patients were evaluated for response. One patient died of Gram-negative sepsis on Day 56 and no response evaluation was performed. No CRs or PRs were observed, (ORR of 0). Five patients (3 patients had peripheral TCL, unspecified) had a best response of SD of which 4 had RSD (evidence of tumor regression was observed). The clinical benefit rate (CR + PR + SD) was 27.8%.

Safety Results:

Extent of Exposure

A total of 18 patients were enrolled and all 18 patients received study drug at a dose of 200 mg PO bid for a median (range) of 48.5 days (6 to 182 days). Study drug was interrupted in 15 patients (83.3%); interruption/missed dose was due to an AE in 11/15 patients. The median (range) number of missed doses was 17.5 (0 to 235). Five patients required a reduction in dose; all reductions were due to an AE. Dose reductions were undertaken for decreased absolute neutrophil count (ANC)/neutropenia, upper leg weakness, skin lesion infection, and diarrhea.

A total of 10 deaths were reported. Death was related to disease progression for 8/10 patients. One patient died due to Gram-negative sepsis considered related to underlying diabetes mellitus, shortly after withdrawal from the study; a second patient died of sepsis. Two additional SAEs with an outcome of death (hepatic failure and lobar pneumonia) were reported in patients with concomitant disease progression.

Eleven patients reported a total of 21 SAEs during the course of this study. SAEs considered possibly related to R788 administration included febrile neutropenia, neutropenia, pancytopenia, sepsis, pneumonia, superior vena cava clot, abdominal pain, diarrhea, and renal failure.

All 18 patients enrolled reported at least one AE during the course of treatment. Overall the most common AEs included: fatigue (61.1%), pyrexia and vomiting (44.4%), chills, diarrhea, nausea, neutropenia, and thrombocytopenia (38.9%), aspartate aminotransferase (AST) increased and anorexia (33.3%), dizziness, headache, and cough (27.8%), and peripheral edema, neutrophil count decreased, and hyponatremia (22.2%).

The safety profile of R788 in patients with TCL is comparable to the safety profile observed in patients with B-cell lymphomas treated at the same dose, 200 mg PO bid. Decreases in ANC,and increases in liver transaminases were observed, as were fatigue and GI symptoms such as vomiting, nausea and diarrhea. Hypertension was uncommonly seen in this population (2/18; 11%). There was no evidence of an increase in infections or opportunistic infections in this population of heavily pretreated patients.

Date of the Report: 27 May 2011