2 SYNOPSIS

Name of Sponsor/Company: Rigel Pharmaceuticals, Inc.	**Individual Study Table Referring to part of the Dossier** **Volume:**
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Title of Study: A Phase I/II Multi-Center, Open Label Trial of the Safety and Efficacy of R935788 in Patients with Relapsed/Refractory B-Cell Lymphoma

Investigators: A list of investigators is provided in Appendix 16.1.4

Study Centers: 11 centers

Publications (reference): Friedberg et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin's lymphoma and chronic lymphocytic leukemia Blood November 17, 2009; DOI 10.1182/blood-2009-08-236471

Study Period: 22 March 2007 – 4 February 2009* * One patient ongoing – to be reported in an addendum after completion	**Phase:** I/II

Study Objectives:

The primary objective was to assess the safety and tolerability of R935788 (R788) in patients with relapsed/refractory B-cell lymphoma.

Secondary objectives were:

- To determine the optimal biologic dose of R788 in patients with relapsed/refractory B-cell lymphoma
- To evaluate the efficacy of R788 in patients with relapsed refractory B-cell lymphoma
- To understand the pharmacokinetic (PK) profile of R788 in patients with B-cell lymphoma
- To explore the pharmacodynamic effects of R788 in patients with B-cell lymphoma

Methodology:

This was a multi-center, open label, study of R788 conducted in two phases. Phase I of the study was an open label, dose escalation study to determine the optimal dose for Phase II. Phase II was an open label safety and efficacy study in three distinct sub-groups of B-cell lymphoma.

In Phase I, two cohorts of 6 patients each were to be sequentially assigned to receive 200 mg (Cohort 1) and 250 mg (Cohort 2) R788 orally, twice daily (*PO bid).* The criteria for enrolling into Cohort 2 were based on the occurrence of dose limiting toxicity (DLT) in ≤ 1/6 patients in Cohort 1 during the initial 28 day treatment period. Patients in Phase I who did not experience DLT or disease progression were permitted to continue treatment at the assigned dose level until disease progression, toxicity or withdrawal. Patients who experienced DLT resumed treatment at a lower dose level when the toxicity grade decreased to ≤ 1. Once all patients in Phase I completed 28 days of treatment, the optimal dose of R788 was determined based on safety and anti-tumor activity.

In Phase II, three groups of 16 patients each were to receive R788 at the optimal biologic dose *bid* until disease progression, limiting toxicity or withdrawal. Group 1 consisted of patients with diffuse large B-cell lymphoma (DLBCL), Group 2 consisted of patients with follicular lymphoma, and Group 3 consisted of

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patients with mantle cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphomas, small lymphocytic lymphomas (SLL), and chronic lymphocytic leukemia (CLL).

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

Number of Patients (Planned and Analyzed):

A total of 12 and 48 patients were to be enrolled in Phase I and Phase II, respectively. A total of 13 patients received treatment in Phase I, 68 patients received treatment in Phase II. A total of 76 patients were analyzed for efficacy and 81 patients were analyzed for safety.

Diagnosis and Main Criteria for Inclusion:

Patients were men and women at least 18 years of age with relapsed/refractory B-cell malignancy, (DLBCL, follicular lymphoma, mantle cell lymphoma, MALT lymphoma, marginal zone lymphoma, CLL or SLL), who had failed at least one prior treatment regimen and for whom no standard therapy existed; who were intolerant of such standard therapy or who were not candidates for such standard therapy; who had measurable disease, defined as at least one lesion $\geq$ 1.5 cm in its longest dimension. Male patients, if sexually active, must have agreed to use at least one medically acceptable form of birth control for the duration of the study and for 30 days thereafter. Sexually active female patients of childbearing potential must have had a negative serum pregnancy test, and must have agreed to use two independent methods of birth control for the duration of the study and for 30 days thereafter.

Test Product, Dose and Mode of Administration, and Batch Numbers:

R788 was provided in two tablet strengths (25 mg [Lots C610019, C7F0021, and C8A00701] and 100 mg [Lots C1145001, C610066, and C7K0010]) and was administered orally at doses of 200 mg *bid* and 250 mg *bid*.

Duration of Treatment:

The duration of study participation for each patient was approximately 3 months including a screening period of up to 21 days, and a treatment period of 8 weeks following which patients were allowed to continue treatment until disease progression, toxicity or withdrawal from the study. The median duration of treatment for patients in Phase I was 182 days [range 57-372 days]. The median duration of treatment for patients in Phase II was 43, 92, and 112 days for Groups 1, 2, and 3, respectively [range 3 - 511 days]. During the treatment periods, study drug was self administered by the patient. Enrollment of the study, from first patient enrolled to last patient enrolled was expected to be approximately 14 months.

Reference Therapy, Dose and Mode of Administration, and Batch Number:

Not applicable.

Criteria for Evaluation:

Efficacy was to be assessed by response rate, clinical benefit rate, time to first response and duration of response, progression free survival (PFS) and overall survival.

Safety was to be assessed by evaluating AEs, identifying DLTs (if any), reviewing clinical laboratory values (chemistry, hematology), and evaluating serial physical examinations, vital signs, Karnofsky Performance

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Scores (KPS) and electrocardiograms (ECGs).

The pharmacokinetic profile was to be assessed by group for plasma R406 concentration vs. time, maximum observed concentration (C_{max}) and area-under-the-concentration-time curve (AUC).

Pharmacodynamic effect was to be assessed, by group and overall, for change from baseline to each visit, for CD14+ cells and change in phospho-Syk (Y525, Y348 and Y352) expression in tumor tissue from baseline to post-treatment.

Statistical Methods:

Efficacy:

Primary efficacy analyses: The number and percentage of patients who achieved a response were to be presented for each patient group and overall for patients entering the study in Phase II based on both the intent-to-treat (ITT) population and the per-protocol (PP) population.

Statistical Methods (continued):

Secondary efficacy analyses:

- Clinical Benefit Rate
- Time to First Response and Duration of Response
- Progression Free Survival
- Overall Survival

Safety: The incidence of AEs was to be displayed overall and by patient group by system organ class and preferred term. AEs were also to be summarized by severity and relationship to study drug. By patient incidence of serious AEs (SAEs) was also to be displayed. Adverse events were to be categorized based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v 3.0) toxicity grades (ranging from 0 to 4).

Samples for PK/pharmacodynamic analysis were collected at specified time points. Plasma concentration was summarized descriptively by R788 treatments and time point at which data were collected. Pharmacodynamic data will be presented, analyzed, and summarized in a separate report.

SUMMARY - CONCLUSIONS

Efficacy Results:

Evidence of anti-tumor efficacy was observed in virtually all of the lymphoma subtypes studied, but particularly in CLL/SLL (ORR, 54.5%) and DLBCL (ORR, 22%). This activity is consistent with the importance of syk to B-cell receptor (BCR) signaling and the presumed importance of BCR signaling to these two lymphoma subtypes.

Responses were generally brief, particularly in DLBCL, and consistent with the aggressiveness of disease in

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this subgroup and with expectations in these groups of heavily pretreated patients.

Safety Results:

Adverse events with an incidence of ≥ 20% overall included fatigue, diarrhea, neutropenia, nausea, anemia, thrombocytopenia, headache, hypertension, cough, dyspnea, pyrexia, vomiting, and dizziness.

The events most commonly considered potentially related to study drug treatment included: diarrhea (46.9%), fatigue (40.7%), neutropenia (29.6%), anemia (25.9%), hypertension (24.7%), thrombocytopenia (22.2%), headache (16.0%), leukopenia and AST increased each (14.8%).

Grade 1 or 2 adverse events were reported by 33.4% of patients. Events of Grade 3 severity were reported for 43.2% of patients. Grade 4 and 5 adverse events were reported for 12 and 6 patients respectively (14.8 and 7.4%).

Events resulting in death included: acute respiratory distress syndrome, sepsis, cardiac failure, cardio-respiratory arrest (2 pts due to disease progression), and cardiac arrest (1 pt due to disease progression).

Grade 3/4 events reported most commonly included: neutropenia (20 pts, 24.7%), anemia (10 pts, 12.3%), leukopenia (7 pts, 11.1%), thrombocytopenia, hypertension (6 pts ea. 7.4%), and febrile neutropenia (4 pts, 4.9%).

PK Results:

The pharmacokinetics of R788 was not assessed in this study because previous studies had shown very low and sporadic plasma levels of R788, due to the conversion to its active metabolite, R940406 (R406). Following multiple administrations of 200 mg R788 *bid* and 250 mg R788 *bid*, R406 steady-state exposure was approximately two-three fold higher than levels observed on Day 1 of dosing. The plasma exposure of R406 in this study is consistent with that observed previously in normal volunteer studies.

Date of Report: 29 March 2010