2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Rigel Pharmaceuticals, Inc.</td><td rowspan="2">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="2">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Not applicable</td></tr>
<tr><td>Name of Active Ingredient:
Fostamatinib Disodium Hexahydrate</td><td></td><td></td></tr>
<tr><td colspan="3">Title of Study: A Phase 3 Open-Label Extension Study of Fostamatinib Disodium in the Treatment of Warm Antibody Autoimmune Hemolytic Anemia</td></tr>
<tr><td colspan="3">Investigators: Data on file</td></tr>
<tr><td colspan="3">Study Center(s): This was a multicenter study conducted in 19 countries. A total of 40 centers enrolled and treated at least 1 subject.</td></tr>
<tr><td colspan="3">Publications (reference): None.</td></tr>
<tr><td colspan="2">Studied Period (years):
Date first subject enrolled: 30 October 2019 (first subject’s informed consent date)
Study completion date: 20 December 2022 (last subject’s last visit date)
Database lock: 23 February 2023 (the study was terminated earlier than planned)</td><td>Phase of Development:
Phase 3 open-label extension</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of this study was to evaluate the long-term safety of fostamatinib in subjects with warm antibody autoimmune hemolytic anemia (wAIHA).
The secondary objectives of this study were the following:
To compare the proportion of subjects with wAIHA who achieved a durable hemoglobin response between those who had been randomized to either fostamatinib or placebo in the parent study (C-935788-057).
To estimate the durability of response in subjects who received fostamatinib for wAIHA.
To assess steroid use in subjects with wAIHA treated with fostamatinib.</td></tr>
<tr><td colspan="3">Methodology:
Study C-935788-058 was a Phase 3 multi-center, open-label extension study to evaluate the long-term safety and efficacy of fostamatinib (R788) in subjects with wAIHA who had previously failed at least one prior wAIHA treatment regimen and completed 24 weeks of participation in Study C-935788-057. The planned duration of study treatment for subjects enrolled in this extension study was up to 2 years.
All subjects received open-label fostamatinib. The starting dose of fostamatinib in the extension study was based on subject’s responses at the Week 22 visit in the parent study (C-935788-057). Subjects who had achieved a hemoglobin response at any time during the parent study continued to receive treatment in C-935788-058 at the dose and regimen from the Week 22 visit in the C-935788-057 study. Hemoglobin response during C-935788-057 was defined as a hemoglobin level ≥ 10 g/dL with an increase from baseline in hemoglobin of ≥ 2 g/dL, in which the hemoglobin measurement was made outside a Rescue Treatment Visit Exclusion Period.
All other subjects who entered the extension study initially received fostamatinib at 100 mg orally (PO) twice daily (bid). Starting at Week 4, the initial fostamatinib dose of 100 mg PO bid was increased to</td></tr>
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fostamatinib 150 mg PO bid in subjects who adequately tolerated the study drug, based on the Investigator's judgment.

All subjects remained blinded to their treatment assignment in study C-935788-057 (active or placebo).

The subject's dose of study drug could be reduced at any time during the extension study to a dose as low as fostamatinib 100 mg PO once daily (qd) if dose limiting adverse events (AEs) were observed per the dose adjustment schedule below:

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3	Dose Level -4
100 mg PO bid	150 mg PO qd	100 mg PO qd	discontinue	–
150 mg PO bid	100 mg PO bid	150 mg PO qd	100 mg PO qd	discontinue

Abbreviations: bid = twice daily; PO = oral; qd = once daily

Over the course of the study, subjects were expected to visit the clinic approximately 25 times. Safety assessments were performed, and hemoglobin levels were assessed at each visit to evaluate the safety and efficacy of fostamatinib and to determine if a dose adjustment was required. After Week 104, subjects returned 2 weeks later for a follow up visit.

Allowed wAIHA Therapies

Subjects continued concurrent other wAIHA therapy (maximum of 2 therapies). Doses and regimens of concurrent wAIHA therapies, including Promacta, did not need to remain constant during the study. Temporary steroid dose increases could be undertaken as rescue therapy.

Disallowed wAIHA Therapies

Splenectomy and any investigational agents were not allowed during study treatment. Other medications when prescribed for wAIHA (e.g., cyclosporine, rituximab or other anti-CD20 monoclonal antibody, chemotherapy agents [e.g., cyclophosphamide, vincristine, etc.]) were not allowed during study treatment; such medications were allowed if prescribed prior to and continued in the parent study C-935788-057 for non-wAIHA indications and must have remained at a stable dose during the course of study drug treatment in Study C-935788-058.

Concurrent Medications Adjustment Criteria

Prior to any decrease of concurrent wAIHA therapies, subjects must have achieved a durable response followed by 2 consecutive hemoglobin assessments showing continued response in Study C-935788-057 or C-935788-058. Adjustment of other concurrent therapies were undertaken cautiously and according to standard clinical practice.

Steroid Taper Protocol

A steroid taper was considered for subjects who reached Week 12, achieved a durable response, and had ≥ 2 subsequent scheduled visits with hemoglobin assessments showing continued response.

Rescue Protocol

Use of rescue medications (including increases in steroid doses) were to be avoided for the duration of the study unless medically necessary. Rescue medications were given following a decrease in hemoglobin of > 1.5 g/dL from baseline or new or worsening symptoms of anemia, so long as urgent treatment was required, in the judgment of the Investigator.

Number of Subjects (Planned and Analyzed):

A total of 71 subjects who completed 24 weeks of participation in study C-935788-057 were enrolled in extension study C-935788-058, including 38 [53.5%] subjects who had been randomized to fostamatinib and 33 [46.5%] subjects who had been randomized to placebo.

The term "subject" refers to patients with wAIHA participating in this extension study. The "fostamatinib at onset" group refers to subjects who had been randomized to fostamatinib in the parent study, C-935788-057, and the "fostamatinib after placebo" group refers to subjects who had been randomized to placebo in the parent study, C-935788-057. All subjects received open-label fostamatinib in this extension study. At the time of database lock,

one subject in the fostamatinib at onset group who signed the informed consent form for participation never received study drug in this extension study. As such, 70 subjects were treated as of the database lock date.
Diagnosis and Main Criteria for Inclusion: All subjects must have completed all 24 weeks of participation in study C-935788-057 to be eligible for the extension study, C-935788-058. **Exclusion Criteria:** Any subject who discontinued participation in Study C-935788-057 prior to Week 24 was excluded from participation in study C-935788-058.
Test Product, Dose and Mode of Administration, Batch Number: Fostamatinib was provided as 100 mg and 150 mg orange film-coated tablets administered orally. The manufacturing lot numbers for fostamatinib used in this study were CBYFV, CCMFC, CCNDS, CBYFK, CCMFF, and CCNDT.
Duration of Treatment: Treatment was planned for up to 2 years; however, the study was terminated early based on a discussion between Rigel and the US Food and Drug Administration (FDA) that deemed a filing for regulatory approval with fostamatinib in the treatment of wAIHA would not be feasible.
Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.
Criteria for Evaluation: <u>Safety</u> Safety was assessed by examination of treatment-emergent adverse events (TEAEs), extent of exposure, and changes from baseline over time in selected laboratory values (e.g., absolute neutrophil count, liver function tests [LFTs], alkaline phosphatase, lactate dehydrogenase, leukocytes, and other selected laboratory tests). Furthermore, changes in vital sign measurements of pulse, blood pressure, temperature, and body weight were monitored. Clinically significant changes in laboratory parameters or vital signs were reported as TEAEs. All AEs recorded as occurring before study treatment administration in this study were considered baseline conditions. Treatment-emergent adverse events of interest include hypertension, neutropenia, diarrhea, infection, and hepatotoxicity. <u>Efficacy</u> Hemoglobin response assessments were used to evaluate the efficacy of fostamatinib and to determine if a dose adjustment was required. The secondary efficacy endpoints evaluated the achievement of a durable hemoglobin response during the study and the corresponding duration of response, the maintained hemoglobin response and the corresponding duration of a maintained response, and the use of permitted rescue medications. Other efficacy endpoints included achievement of a prednisone-equivalent level of total daily steroid dose of < 10 mg/day in subjects on ≥ 10 mg/day at study entry, decreasing concomitant wAIHA therapy dose or frequency among subjects who ever achieved a durable hemoglobin response, change in corticosteroid dose (prednisone-equivalent), change in reticulocyte count, lactate dehydrogenase (LDH), and haptoglobin over time, and incidence of hospitalization related to autoimmune hemolytic anemia (AIHA).
Statistical Methods: <u>Determination of Sample Size:</u> No formal statistical power calculations were conducted to determine the sample size. The sample size was based upon the number of subjects in the C-935788-057 study who completed 24 weeks of participation and who chose to participate and were eligible to participate in this extension study.

General Considerations:

With the exception of within-subject comparisons among placebo subjects, analyses presented by treatment assignment in C-935788-057 are descriptive only and no hypothesis testing was conducted.

Analysis Populations:

- *Safety Analysis Population*: The Safety Analysis Population consisted of all subjects who received any amount of fostamatinib during the extension study.
- *Efficacy Analysis Population*: The Efficacy Population included all subjects who received any amount of study drug (both fostamatinib and placebo) during either the C-935788-057 study or the extension study and had at least one post-baseline efficacy assessment in the extension study.

Safety Analysis

Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1, summarized by system organ class (SOC) and preferred term (PT), and presented by subject incidence and event frequency. For vital signs and quantitative laboratory tests (hematology, serum chemistry, and LFTs), descriptive statistics were presented by visit for the actual values and the changes from baseline.

Efficacy Analysis:

The number and percentage of subjects who achieved a hemoglobin response and maintained a response are presented for the overall population and according to the treatment assignment in the C-935788-057 study. The confidence intervals (CI) were calculated using the exact Clopper-Pearson 95% CI for proportions.

Descriptive statistics were used to summarize total duration of response for subjects who achieved different type of hemoglobin response and for the other duration variables. Descriptive statistics were also used to summarize changes from baseline in hemoglobin values, reticulocyte count, LDH, and haptoglobin over time for the overall population and each treatment group (fostamatinib at onset and fostamatinib after placebo).

Exact Clopper Pearson 95% CIs for the proportion of subjects using permitted rescue medications, the number and percentage of subjects who achieved a level of total daily steroid dose < 10 mg/day, and the proportion of subjects hospitalized related to AIHA are presented for the overall population and according to the treatment assignment in the C-935788-057 study.

Each endpoint was summarized for the treatment period (exposure from Day 1 through Week 104) and within 24 weeks of treatment (exposure from Day 1 through Week 24) unless specified in the endpoints.

RESULTS:

Disposition, Demographics, and Baseline Characteristics:

Seventy-one subjects were enrolled in Study C-935788-058, including 38 (53.5%) subjects previously randomized to fostamatinib in the C-935788-057 study (the fostamatinib at onset group) and 33 (46.5%) subjects previously randomized to placebo in the C-935788-057 study (the fostamatinib after placebo group). At the time of database lock 16 (22.5%) subjects had completed the extension study and 55 (77.5%) subjects had discontinued the study. One subject who enrolled in the study never received study treatment.

Of the 70 subjects treated in Study C-935788-058, 17 (24.3%) subjects were from US/Canada/Australia, 22 (31.4%) were from Western Europe, and 31 (44.3%) were from Eastern Europe.

The median subject age at screening was lower in the fostamatinib at onset group (median 58.0 years; range 29 – 84) than in the fostamatinib after placebo group (median 65.0 years; range 26 – 87). The majority of subjects were female (43 subjects [61.4%] overall) and white (64 subjects [91.4%] overall).

The median duration of wAIHA in subjects was lower in the fostamatinib at onset group compared with the fostamatinib after placebo group (2.6 years vs 3.5 years, respectively).

Baseline mean hemoglobin was 10.3 g/dL for each treatment group. The baseline mean haptoglobin was 38.0 mg/dL (normal range: 40 – 240 mg/dL), the mean reticulocyte count was 7.84% (normal range: 0.2 – 2.3%), and mean LDH was 365.1 U/L (normal range: 120 – 246 U/L). Baseline hemoglobin was defined as the last

non-missing value obtained prior to administration of the first dose of study drug in study C-935788-058, provided that the value was not collected during a rescue treatment visit exclusion period. Baseline values for other measurements were defined as the last available values obtained prior to administration of first dose of study drug.

Safety Results:

- The mean treatment duration in the fostamatinib after placebo group was 53.4 weeks versus 60.5 weeks [which was in addition to 24 weeks of fostamatinib exposure in the parent study (C-935788-057)] in the fostamatinib at onset group. The median duration of exposure (range) in the fostamatinib at onset group versus the fostamatinib after placebo group, respectively, was: 64.0 (2.14, 106.86) weeks versus 46.0 (8.14, 106.43) weeks. The total daily dose (mean dose intensity) of fostamatinib was lower for subjects in the fostamatinib at onset group than in the fostamatinib after placebo group: 256.7 mg/day versus 266.1 mg/day, respectively.
- TEAEs were reported in 94.3% of subjects in the study, with a lower proportion of subjects who had prior exposure to fostamatinib reporting at least 1 TEAE compared with subjects who had no prior exposure: 89.2% of subjects in the fostamatinib at onset group versus 100.0% in the fostamatinib after placebo group.
- The most commonly reported TEAEs for ≥ 10% of total subjects in the fostamatinib at onset group and the fostamatinib after placebo group, respectively, were diarrhea (18.9% vs 36.4%), COVID-19 (24.3% vs 18.2%), neutropenia (13. 5% vs 15.2%), hypertension (13.5% vs 27.3%), decreased hemoglobin (16.2% vs 12.1%), warm type hemolytic anemia due to exacerbation of underlying disease (10.8% vs 27.3%), and fatigue (10.8% vs 9.1%).
- TEAEs ≥ Grade 3 were reported in 37.8% of subjects in the fostamatinib at onset group and 48.5% of subjects in the fostamatinib after placebo group. Neutropenia and warm type hemolytic anemia were the only severe TEAEs reported in ≥ 5% subjects.
- Treatment-emergent serious adverse events (TESAEs) were reported in a lower proportion of subjects in the fostamatinib at onset group than in the fostamatinib after placebo group: 27.0% versus 39.4%, respectively. The most frequently reported TESAEs (≥ 2 subjects overall) included: warm type hemolytic anemia (4 [5.7%]), pneumonia (3 [4.3%]), COVID-19 pneumonia (2 [2.9%]), and COVID-19 (2 [2.9%]), and dyspnea (2 [2.9%]). Only one TESAE, severe neutropenia, reported in the fostamatinib at onset group, was considered related to treatment with fostamatinib.
- There were 8 deaths in the study, 3 in the fostamatinib at onset group and 5 in the fostamatinib after placebo group. None of the deaths were considered related to treatment with fostamatinib. Two of the deaths were COVID-19 related (1 in each of the treatment groups). In the fostamatinib at onset group, 1 subject died due to myocardial infarction, 1 subject died due to COVID-19 pneumonia, and one subject died due to dyspnea. In the placebo group, 2 subjects died due to cardiac failure, 1 subject died due to COVID-19 infection, 1 subject died due to pneumonia, and 1 subject died due to acute leukemia.
- The most frequently reported (≥ 5%) TEAEs considered related to treatment in the fostamatinib at onset group or the fostamatinib after placebo group, respectively, included diarrhea (16.2% vs 27.3%), hypertension (8.1% vs 18.2%), and neutropenia (10.8% vs 9.1%).
- TEAEs that led to study discontinuation were reported in a lower number of subjects in the fostamatinib at onset group versus the fostamatinib after placebo group (5 vs 11 subjects), and included diarrhea, COVID-19 pneumonia, dyspnea, neutropenia, and neutrophil count decreased in the fostamatinib at onset group; and diarrhea, ulcerative colitis, acute cardiac failure, acute leukemia, asthenia, lymphoproliferative disorder, Evans syndrome, warm type hemolytic anemia, hemoglobin decreased, and fatigue in the fostamatinib after placebo group.
- TEAEs that led to study drug interruptions, dose reductions, and treatment discontinuations were also reported in a lower number of subjects in the fostamatinib at onset group than in the fostamatinib after placebo group (12 vs 20 subjects). Diarrhea was the most commonly reported TEAE that led to study treatment withdrawal.

- Adverse events of interest (AEOI) were reported in a lower proportion of subjects in the fostamatinib at onset group versus the fostamatinib after placebo group (64.9% vs 81.8%, respectively), with infection (51.4% vs 36.4%) as the most frequently reported AEOI. AEOI reported in ≥ 10% of subjects in either group included diarrhea (18.9% vs 36.4%), hypertension (13.5% vs 30.3%), neutropenia (16.2% vs 15.2%), and hepatoxicity (10.8% vs 9.1%).
- Hepatoxicity events were reported in a similar percentage of subjects in each treatment group (10.8% in the fostamatinib at onset group and 9.1% in the fostamatinib after placebo group. Hepatotoxicity AEs included ALT increased, blood bilirubin increased, jaundice, LFT increased, hepatic enzyme increased, AST increased, and transaminases increased.
- No subjects experienced elevations in transaminase laboratory values meeting the criteria for Hy's law.
- Blood pressure shift tables showed lower incidence of worsening blood pressure (by worst post-baseline value) and better control of worsening blood pressure (by last post-baseline value) in the fostamatinib at onset group versus fostamatinib after placebo. There were no occurrences of hypertensive crisis.

Efficacy Results:

Analyses of secondary efficacy endpoints showed similar outcomes between the two study arms. The durable hemoglobin response rate was 44.7% for the fostamatinib at onset group, 42.4% for the fostamatinib after placebo group and average duration of durable response was 52.6% (35.8%, 69.0%) versus 60.6% (42.1%, 77.1%) for the fostamatinib at onset group and the fostamatinib after placebo group, respectively. Rescue medication was used by 41 (58.6%) subjects during the study; 21 (56.8%) in the fostamatinib at onset group and 20 (60.6%) in the fostamatinib after placebo group. The most commonly used permitted rescue medications included corticosteroids for systemic use (in 18 [48.6%] subjects in fostamatinib at onset versus 17 [51.5%] subjects in fostamatinib after placebo).

CONCLUSIONS:

To date, there are no disease-targeted therapies approved for wAIHA. Fostamatinib is approved for ITP with a safety database of almost 5000 subjects treated.

The achievement of durable response rates was similar between treatment groups, and the average duration of response suggested that the fostamatinib benefit seemed durable. The duration of responses is well maintained in the extension study (C-935788-058) and have similar rate as C-935788-057 fostamatinib group. Similar results were observed in several efficacy endpoints in the extension study treatment groups compared to the fostamatinib treatment group in the parent study (C-935788-057). The results indicate that efficacy in wAIHA subjects from fostamatinib appears to be maintained in the extension study.

The long-term safety profile for fostamatinib observed in subjects with wAIHA support and expand the safety profile established in the primary Phase 3 studies in ITP, in prior studies in subjects with RA, and in the parent Phase 3 study C-935788-057 in the same subjects with wAIHA (24 weeks exposure). There were no new safety findings with up to 106 weeks exposure to fostamatinib as high as 150 mg po bid. Overall, the results of this Phase 3 open-label extension study support the long-term safety of fostamatinib administered at 100-150 mg BID in subjects with wAIHA.

Date of the report: 16 June 2023 (Final)