June 8, 2022

Rigel Announces Top-line Results from FORWARD Phase 3 Clinical Trial of Fostamatinib in Patients with Warm Autoimmune Hemolytic Anemia

Conference call and webcast to be held today at 8:00 a.m. Eastern Time

SOUTH SAN FRANCISCO, Calif., June 8, 2022 /PRNewswire/ -- Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL) today announced top-line efficacy and safety data from the FORWARD Phase 3 clinical trial, a global, multi-center, randomized, double-blind, placebo-controlled trial of fostamatinib in patients with warm autoimmune hemolytic anemia (wAIHA). The trial did not demonstrate statistical significance in the primary efficacy endpoint of durable hemoglobin response in the overall study population. In a post-hoc regional analysis of U.S., Canadian, Australian, and Western European trial sites, patients treated with fostamatinib had a favorable durable hemoglobin response compared to placebo, whereas in the Eastern European trial sites patients did not. Rigel plans to continue analyzing the data to understand the geographical differences in patient disease characteristics and outcomes and discuss these findings with the U.S. Food and Drug Administration (FDA).

The safety and tolerability profile in the FORWARD trial was consistent with the existing fostamatinib safety database.

Efficacy Results:
The trial includes 90 patients in three pre-specified geographic regions, 14 sites in the U.S., Canada, and Australia; 16 sites in Western Europe (Austria, Germany, Spain, France, Italy, Belgium, U.K., Netherlands, Norway); and 16 sites in Eastern Europe (Bulgaria, Czech Republic, Russia, Ukraine, Georgia, Belarus, Serbia). Patients were randomized 1:1 to receive fostamatinib or matching placebo twice daily for 24 weeks. The primary efficacy endpoint of durable hemoglobin (Hgb) response was defined as achieving a Hgb ≥10 g/dL with an increase from baseline ≥2 g/dL on three consecutive available visits during the 24-week treatment period. The data from the primary endpoint are as follows:

Primary Endpoint Results						
Regions	**Overall**		**U.S., Canada and Australia and Western Europe***		**Eastern Europe**	
Treatment Group	Fostamatinib (n=45)	Placebo (n=45)	Fostamatinib (n=25)	Placebo (n=28)	Fostamatinib (n=20)	Placebo (n=17)
Durable hemoglobin response rate n (%)	16 (35.6%)	12 (26.7%)	9 (36.0%)	3 (10.7%)	7 (35.0%)	9 (52.9%)
P-Value	P=0.398		P=0.03		P=0.304	

*Post-hoc analysis

The trial also included key secondary endpoints, including hemoglobin response on at least one visit, change in Hgb from baseline of ≥2 g/dL, use of permitted rescue therapy after week 4, change in Hgb from baseline to end of treatment and change from baseline to week 24 in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale. The data from the secondary endpoints are as follows:

Secondary Endpoint Results						
	Overall		**U.S., Canada and Australia and Western Europe***		**Eastern Europe**	
	Fostamatinib (n=45)	Placebo (n=45)	Fostamatinib (n=25)	Placebo (n=28)	Fostamatinib (n=20)	Placebo (n=17)
Number of subjects with hemoglobin response on at least one visit n (%)	21 (46.7%)	16 (35.6%)	13 (52.0%)	5 (17.9%)	8 (40.0%)	11 (64.7%)
Number of subjects with change in Hgb from baseline of ≥2 g/dL n (%)	22 (48.9%)	16 (35.6%)	14 (56.0%)	5 (17.9%)	8 (40.0%)	11 (64.7%)
Change in mean Hgb from baseline to end of treatment LS Mean (95% CI)	1.8 (1.06, 2.54)	1.85 (1.07, 2.63)	2.25 (1.19, 3.31)	1.27 (0.12, 2.41)	1.28 (-0.07, 2.64)	2.27 (0.88, 3.66)
Number of subjects free (no use) of rescue therapy after Week 4 n (%)	18 (40.0%)	18 (40.0%)	12 (48.0%)	8 (28.6%)	6 (30.0%)	10 (58.8%)
Change from baseline to Week 24 in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale LS Mean (95% CI)	2.9 (-0.70, 6.50)	1.9 (-1.85, 5.69)	7.0 (2.05, 11.88)	0.7 (-4.25, 5.74)	-0.7 (-6.28, 4.86)	4.7 (-1.33, 10.73)

*Post-hoc analysis

Safety Results:

Across the trial's overall patient population, fostamatinib was generally well-tolerated. The safety profile of the product was consistent with prior clinical experience and no new safety issues were discovered. The most common adverse events (≥10%) with fostamatinib and placebo were diarrhea (26.7% and 6.7%), hypertension (24.4% and 17.8%), fatigue (15.6% and 11.1%), pyrexia (13.3% and 6.7%), nausea (13.3% and 8.9%), and dyspnea (13.3% and 11.1%). There were five deaths on the study (2 with fostamatinib and 3 with placebo), all of which were determined to be unrelated to study drug. The safety results were consistent with the overall safety profile data collected to date, which includes more than 3,900 patients across multiple diseases. Safety results are as follows:

Safety Results						
	Overall		U.S., Canada and Australia, and Western Europe*		Eastern Europe	
	Fostamatinib (n=45)	Placebo (n=45)	Fostamatinib (n=25)	Placebo (n=28)	Fostamatinib (n=20)	Placebo (n=17)
Patients with at least 1 Adverse Event (AE) *n (%)*	42 (93.3%)	40 (88.9%)	25 (100.0%)	28 (100.0%)	17 (85.0%)	12 (70.6%)
Patients with at least 1 Serious Adverse Event (SAE) *n (%)*	15 (33.3%)	17 (37.8%)	8 (32.0%)	13 (46.4%)	7 (35.0%)	4 (23.5%)
Patients with Treatment-related SAEs *n (%)*	3 (6.7%)	2 (4.4%)	2 (8.0%)	1 (3.6%)	1 (5.0%)	1 (5.8%)
Patients with an AE ≥ grade 3 *n (%)*	24 (53.3%)	19 (42.2%)	15 (60.0%)	16 (57.1%)	9 (45.0%)	3 (17.6%)
Patients with at least one Treatment-related AE *n (%)*	24 (53.3%)	12 (26.7%)	16 (64.0%)	10 (35.7%)	8 (40.0%)	2 (11.7%)
Patients who discontinued from study due to AEs *n (%)*	4 (8.9%)	6 (13.3%)	2 (8.0%)	5 (17.9%)	2 (10.0%)	1 (5.8%)

*Post-hoc analysis

"While we are disappointed in the overall results, which were impacted by a large placebo response rate from Eastern European clinical sites, we are encouraged by the top-line results from the U.S., Canada, Australia, and Western Europe. We continue to believe fostamatinib has the potential to benefit patients with wAIHA, a population with a serious unmet medical need," said Raul Rodriguez, President and Chief Executive Officer of Rigel Pharmaceuticals. "We will continue to analyze the data and look forward to discussing our findings with the FDA. On behalf of the entire Rigel team, we are grateful to the patients, their caregivers, and the healthcare professionals who participated in the trial."

"There are currently no approved therapies specifically indicated for wAIHA and the treatments that are currently used have shortcomings related to efficacy, safety, and quality of life," said David Kuter, M.D., D.Phil., Director of Clinical Hematology at Massachusetts General Hospital, Professor of Medicine at Harvard Medical School, and Lead Investigator. "On balance, the findings from the U.S., Canadian, Australian, and Western European trial sites are supportive of fostamatinib for the treatment of wAIHA, however, the confounding results from the Eastern European trial sites require further analysis of the data from this trial. I look forward to working with Rigel to better understand these data."

Of the 90 patients that completed the FORWARD Phase 3 study, 71 (79%) enrolled in the open-label extension study. Data from this study will be reported later.

Conference Call and Webcast Today at 8:00 a.m. Eastern Time

Rigel will hold a live conference call and webcast today at 8:00 a.m. Eastern Time (5:00 a.m. Pacific Time).

Participants can access the live conference call by dialing (877) 407-3088 (domestic) or (201) 389-0927 (international). The conference call will also be webcast live and can be accessed from the Investor Relations section of the company's website at www.rigel.com. The webcast will be archived and available for replay after the call via the Rigel website.

About AIHA

Autoimmune hemolytic anemia (AIHA) is a rare, serious blood disorder in which the immune system produces antibodies that lead to the destruction of the body's own red blood cells.

Warm antibody AIHA (wAIHA), which is the most common form of AIHA, is characterized by the presence of antibodies that react with the red blood cell surface at body temperature. wAIHA affects approximately 36,000 adult patients in the U.S.[1] and can be a severe, debilitating disease. To date, there are no disease-targeted therapies approved for wAIHA, despite the unmet medical need that exists for these patients.

About the FORWARD Phase 3 Study

Fostamatinib is currently being evaluated in a Phase 3 randomized, double-blind, placebo-controlled clinical study in 90 patients with wAIHA who have failed at least one prior treatment. The study will evaluate the efficacy of fostamatinib versus placebo in achieving a durable hemoglobin response, defined as a hemoglobin level ≥ 10 g/dL, with an increase from baseline level of ≥ 2 g/dL, with the response not being attributed to rescue therapy, and durability measure in hemoglobin on three consecutive available visits during the 24-week treatment period. Secondary endpoints include other measures of hemoglobin response, use of rescue medication, and safety.

The FDA has granted fostamatinib Orphan Drug and Fast Track designations for the treatment of patients with wAIHA.

Fostamatinib, commercially available in the U.S. under the brand name TAVALISSE® (fostamatinib disodium hexahydrate) tablets, is the first and only FDA-approved SYK inhibitor indicated for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment.

About Rigel

Rigel Pharmaceuticals, Inc., is a biotechnology company dedicated to discovering, developing and providing novel small molecule drugs that significantly improve the lives of patients with hematologic disorders, cancer and rare immune diseases. Rigel's pioneering research focuses on signaling pathways that are critical to disease mechanisms. The company's first FDA approved product is TAVALISSE® (fostamatinib disodium hexahydrate) tablets, the only oral spleen tyrosine kinase (SYK) inhibitor for the treatment of adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment. The product is also commercially available in Europe, the United Kingdom (TAVLESSE) and Canada (TAVALISSE) for the treatment of chronic immune thrombocytopenia in adult patients.

Fostamatinib is currently being studied in a Phase 3 clinical trial (NCT03764618) for the treatment of warm autoimmune hemolytic anemia (wAIHA)[2]; a Phase 3 clinical trial (NCT04629703) for the treatment of hospitalized high-risk patients with COVID-19[2]; and an NIH/NHLBI-sponsored Phase 3 clinical trial (ACTIV-4 Host Tissue Trial, NCT04924660) for the treatment of COVID-19 in hospitalized patients.

Rigel's other clinical programs include its interleukin receptor-associated kinase (IRAK) inhibitor program, and a receptor-interacting serine/threonine-protein kinase (RIPK) inhibitor program in clinical development with partner Eli Lilly and Company. In addition, Rigel has product candidates in development with partners BerGenBio ASA and Daiichi Sankyo.

For further information, visit www.rigel.com or follow us on Twitter or LinkedIn.

1. Prevalence: A. Zanella, et al, *haematologica* 2014; 99(10); % Warm AIHA: T. Kalfa; Hematology Am Soc Hematol Educ Program. 2016 Dec 2; 2016(1): 690–697
2. *The product for this use or indication is investigational and has not been proven safe or effective by any regulatory authority.*

Forward Looking Statements

This release contains forward-looking statements relating to, among other things, the topline data from the FORWARD trial in patients with wAIHA and our expectations related to the potential and market opportunity for fostamatinib as therapeutic for, among other things, wAIHA. Any statements contained in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Words such as "potential", "may", "expects", and similar expressions are intended to identify these forward-looking statements. These forward-looking statements are based on Rigel's current expectations and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward looking statements as a result of these risks and uncertainties, which include, without limitation, risks that the FDA, EMA or other regulatory authorities may make adverse decisions regarding fostamatinib; risks that clinical trials may not be predictive of real-world results or of results in subsequent clinical trials; risks that fostamatinib may have unintended side effects, adverse reactions or incidents of misuses; the availability of resources to develop Rigel's product candidates; market competition; as well as other risks detailed from time to time in Rigel's reports filed with the Securities and Exchange Commission, including its Quarterly Report on Form 10-Q for the period ended March 31, 2022 and subsequent filings. Rigel does not undertake any obligation to update forward-looking statements and expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein, except as required by law.

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