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Rigel's Fostamatinib Being Studied by National Institute of Health in Patients with Sickle Cell Disease

First patient enrolled in NIH/NHLBI-sponsored Phase 1 Study of fostamatinib, Rigel's oral SYK inhibitor

SOUTH SAN FRANCISCO, Calif., Jan. 22, 2025 /PRNewswire/ -- Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL) today announced the first patient has been enrolled in a Phase 1 study evaluating the safety and tolerability of escalating doses of fostamatinib, the company's oral spleen tyrosine kinase (SYK) inhibitor, in patients with sickle cell disease (SCD). The study is being sponsored by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institute of Health (NIH). Fostamatinib, marketed in the U.S. as TAVALISSE® (fostamatinib disodium hexahydrate) tablets, is approved for the treatment of adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

"Our Phase 1 study evaluating fostamatinib in patients with sickle cell disease is an opportunity to explore a potential new treatment option for a disease that is associated with a high degree of recurrent acute pain events and other acute and chronic potentially life-threatening complications," stated Richard Childs, M.D., scientific director of the NHLBI. "Preclinical research conducted by NIH/NHLBI investigators lead us to believe that SYK inhibition may have the potential to reduce complications related to red cell sickling and thrombo-inflammation in this patient population."

"We are excited to support another important study conducted by the NIH/NHLBI for fostamatinib, as they investigate SYK inhibition and its potential to benefit patients with sickle cell disease, a devasting, lifelong condition," said Raul Rodriguez, Rigel's president and CEO. "The study focuses on an area of critical unmet need and contributes to Rigel's mission to improve the lives of patients with hematologic disorders and cancer."

This open label Phase 1 dose-escalation study is expected to enroll approximately 20 patients with SCD (NCT05904093). The trial is led by principal investigator Swee Lay Thein, M.D., senior investigator and chief of the Sickle Cell Branch at the NHLBI. Patients will receive oral fostamatinib at a dose of 100 mg twice daily for 14 days, which will be escalated to 150 mg twice daily for an additional 28 days if tolerated. The primary objective of the study is to evaluate the safety and tolerability of fostamatinib. The secondary and exploratory

objectives are to assess the mechanism of action of fostamatinib in SCD and mechanistic effects of fostamatinib mediated SYK inhibition on red blood cell membrane integrity and deformability, rate of sickling kinetics, platelet activation and aggregation, and neutrophil activation and neutrophil extracellular trap (NET) formation. The clinical study is being conducted at the NIH Clinical Center in Bethesda, Maryland and is being funded and sponsored by the NIH/NHLBI, with study material provided by Rigel.

About SCD & SYK Inhibition

Sickle cell disease (SCD) is a genetic hemoglobinopathy that leads to the production of abnormal hemoglobin, the protein that carries oxygen through the body. Normally, red blood cells are disc-shaped and flexible enough to move easily through the blood vessels. In sickle cell disease, red blood cells become rigid and crescent – or "sickle" – shaped, leading to strokes, infections, vaso-occlusive crises (VOC), and multi-organ dysfunction. The condition affects more than 100,000 people in the United States[1] and an estimated 7-8 million people worldwide.[2]

In preclinical studies, R406, the active metabolite of fostamatinib, was shown to inhibit production of neutrophil extracellular traps (NETs) by neutrophils *in vitro*.[3] In a humanized SCD mouse model, R406 treatment significantly decreased platelet ATP secretion and aggregation in response to collagen without a significant effect on bleeding time.[4] Fostamatinib could potentially ameliorate SCD-related prothrombic state without an increase in bleeding, addressing an important unmet need. Furthermore, tyrosine phosphorylation of red blood cell (RBC) Band 3 (the anion exchanger 1, of the *SLC4A1* gene) compromises the RBC's integrity, leading to shedding of red cell derived microparticles and release of hemoglobin and mitochondrial DNA, key contributors to thrombo-inflammation pathophysiology. By impacting phosphorylation of RBC Band 3 protein, fostamatinib offers the potential for enhanced RBC membrane stability and reduced sickling of RBCs.[5]

About TAVALISSE®

Indication

TAVALISSE (fostamatinib disodium hexahydrate) tablets is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Important Safety Information

Warnings and Precautions

- Hypertension can occur with TAVALISSE treatment. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects. Monitor blood pressure every 2 weeks until stable, then monthly, and adjust or initiate antihypertensive therapy for blood pressure control maintenance during therapy. If increased blood pressure persists, TAVALISSE interruption, reduction, or discontinuation may be required.
- Elevated liver function tests (LFTs), mainly ALT and AST, can occur with TAVALISSE. Monitor LFTs monthly during treatment. If ALT or AST increase to ≥3 x upper limit of normal, manage hepatotoxicity using TAVALISSE interruption, reduction, or discontinuation.

- Diarrhea occurred in 31% of patients and severe diarrhea occurred in 1% of patients treated with TAVALISSE. Monitor patients for the development of diarrhea and manage using supportive care measures early after the onset of symptoms. If diarrhea becomes severe (≥Grade 3), interrupt, reduce dose or discontinue TAVALISSE.
- Neutropenia occurred in 6% of patients treated with TAVALISSE; febrile neutropenia occurred in 1% of patients. Monitor the ANC monthly and for infection during treatment. Manage toxicity with TAVALISSE interruption, reduction, or discontinuation.
- TAVALISSE can cause fetal harm when administered to pregnant women. Advise pregnant women the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. Verify pregnancy status prior to initiating TAVALISSE. It is unknown if TAVALISSE or its metabolite is present in human milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during TAVALISSE treatment and for at least 1 month after the last dose.

Drug Interactions

- Concomitant use of TAVALISSE with strong CYP3A4 inhibitors increases exposure to the major active metabolite of TAVALISSE (R406), which may increase the risk of adverse reactions. Monitor for toxicities that may require a reduction in TAVALISSE dose.
- It is not recommended to use TAVALISSE with strong CYP3A4 inducers, as concomitant use reduces exposure to R406.
- Concomitant use of TAVALISSE may increase concentrations of some CYP3A4 substrate drugs and may require a dose reduction of the CYP3A4 substrate drug.
- Concomitant use of TAVALISSE may increase concentrations of BCRP substrate drugs (eg, rosuvastatin) and P-Glycoprotein (P-gp) substrate drugs (eg, digoxin), which may require a dose reduction of the BCRP and P-gp substrate drug.

Adverse Reactions

- Serious adverse drug reactions in the ITP double-blind studies were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis, which occurred in 1% of TAVALISSE patients. In addition, severe adverse reactions occurred including dyspnea and hypertension (both 2%), neutropenia, arthralgia, chest pain, diarrhea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope, and hypoxia (all 1%).
- Common adverse reactions (≥5% and more common than placebo) from FIT-1 and FIT-2 included: diarrhea, hypertension, nausea, dizziness, ALT and AST increased, respiratory infection, rash, abdominal pain, fatigue, chest pain, and neutropenia.

Please see www.TAVALISSEUSPI.com **for Full Prescribing Information.**

To report side effects of prescription drugs to the FDA, visit www.fda.gov/medwatch or call 1-800-FDA-1088 (800-332-1088).

TAVALISSE is a registered trademark of Rigel Pharmaceuticals, Inc.

Disclaimer
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

About Rigel

Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL) is a biotechnology company dedicated to discovering, developing and providing novel therapies that significantly improve the lives of patients with hematologic disorders and cancer. Founded in 1996, Rigel is based in South San Francisco, California. For more information on Rigel, the Company's marketed products and pipeline of potential products, visit www.rigel.com.

1. National Heart, Lung, and Blood Institute. *Sickle Cell Disease | What Is Sickle Cell Disease?* Accessed January 3, 2025. https://www.nhlbi.nih.gov/health/sickle-cell-disease
2. G. B. D. S. C. D. Collaborators. *Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: a systematic analysis from the Global Burden of Disease Study 2021.* Lancet Haematol. 2023 Aug;10(8):e585-e599. doi: 10.1016/S2352-3026(23)00118-7. Epub 2023 Jun 15.
3. Strich JR, Ramos-Benitez MJ, Randazzo D, Stein SR, Babyak A, Davey RT, Suffredini AF, Childs RW, Chertow DS. *Fostamatinib Inhibits Neutrophils Extracellular Traps Induced by COVID-19 Patient Plasma: A Potential Therapeutic*. J Infect Dis. 2021 Mar 29;223(6):981-984.
4. Vogel S, Kamimura S, Smith ML, et al. *SYK inhibition suppresses NLRP3 inflammasome activation in platelets from sickle cell mice leading to decreased platelet secretion, aggregation, spreading, and in vitro thrombus formation*. Thromb Res. 2024;237:18-22
5. Noomuna P, Risinger M, Zhou S, et al. *Inhibition of Band 3 tyrosine phosphorylation: a new mechanism for treatment of sickle cell disease*. Br J Haematol. 2020;190(4):599-609.

Forward Looking Statements

This press release contains forward-looking statements relating to, among other things, evaluating fostamatinib in patients with sickle cell disease and the potential of SYK inhibition to reduce complications related to red cell sickling and thrombo-inflammation. Any statements contained in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Forward-looking statements can be identified by words such as "explore", "potential", "may", "expected", "will" and similar expressions in reference to future periods. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on Rigel's current beliefs, expectations, and assumptions and hence they inherently involve significant risks, uncertainties and changes in circumstances that are difficult to predict and many of which are outside of our control. Therefore, you should not rely on any of these forward-looking statements. 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 and uncertainties associated with the development and commercialization of fostamatinib; risks that the FDA, European Medicines Agency, PMDA 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 Annual Report on Form 10-K for the year ended December 31, 2023 and subsequent filings. Any forward-looking statement

made by us in this press release is based only on information currently available to us and speaks only as of the date on which it is made. Rigel does not undertake any obligation to update forward-looking statements, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise, 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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