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Rigel Announces Completion of Patient Enrollment for NIH/NHLBI-Sponsored Phase 2 Trial of Fostamatinib in Hospitalized COVID-19 Patients

Topline data expected in April 2021

SOUTH SAN FRANCISCO, Calif., March 11, 2021 /PRNewswire/ -- Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL) today announced the completion of patient enrollment in a multi-center Phase 2 clinical trial to evaluate the safety of fostamatinib, Rigel's oral spleen tyrosine kinase (SYK) inhibitor, for the treatment of hospitalized COVID-19 patients. The study is sponsored by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health (NIH), in collaboration with Inova Health System. Fostamatinib is marketed in the U.S. as TAVALISSE® (fostamatinib disodium hexahydrate) tablets, and is approved in the U.S., Europe, and Canada as a treatment for adult chronic immune thrombocytopenia (ITP).

The Phase 2 clinical trial is being conducted at the NIH Clinical Center in Bethesda, Maryland, the nation's largest hospital devoted entirely to clinical research, and Inova Fairfax Hospital.

This is a double-blind, placebo-controlled Phase 2 clinical trial that randomly assigned fostamatinib plus standard of care (SOC) or matched placebo plus SOC (1:1) to 58 evaluable patients who are a 5 to 7 on the 8-point ordinal scale (requiring supplemental oxygen via nasal canula or non-invasive ventilation, requiring mechanical ventilation or extracorporeal membrane oxygenation). Treatment will be administered orally twice daily for 14 days. There will be a follow-up period to day 60. The primary endpoint of this study is cumulative incidence of serious adverse events (SAE) through day 29, with multiple secondary endpoints designed to assess the early efficacy and clinically relevant endpoints of disease course as well as in vitro biological correlatives evaluating the effects of the drug on pathways involved in the pathophysiology of COVID-19, including NETosis. The NHLBI and Rigel expect to report topline data from this clinical trial in April 2021.

About COVID-19 & SYK Inhibition

COVID-19 is the infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). SARS-CoV-2 primarily infects the upper and lower

respiratory tract and can lead to acute respiratory distress syndrome (ARDS). Additionally, some patients develop other organ dysfunction including myocardial injury, acute kidney injury, shock resulting in endothelial dysfunction and subsequently micro and macrovascular thrombosis.[1] Much of the underlying pathology of SARS-CoV-2 is thought to be secondary to a hyperinflammatory immune response associated with increased risk of thrombosis.[2]

SYK is involved in the intracellular signaling pathways of many different immune cells. Therefore, SYK inhibition may improve outcomes in patients with COVID-19 via inhibition of key Fc gamma receptor (FcγR) and c-type lectin receptor (CLR) mediated drivers of pathology, such as inflammatory cytokine release by monocytes and macrophages, production of neutrophil extracellular traps (NETs) by neutrophils, and platelet aggregation.[3,4,5] Furthermore, SYK inhibition in neutrophils and platelets may lead to decreased thromboinflammation, alleviating organ dysfunction in critically ill patients with COVID-19.

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.TAVALISSE.com for full Prescribing Information.

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

TAVALISSE and TAVLESSE are registered trademarks of Rigel Pharmaceuticals, Inc.

About Rigel (www.rigel.com)
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 (TAVLESSE) and Canada (TAVALISSE) for the treatment of chronic immune thrombocytopenia in adult patients.

Fostamatinib is currently being studied in a Phase 3 trial for the treatment of warm autoimmune hemolytic anemia (wAIHA)[6]; an NIH/NHLBI-sponsored Phase 2 trial for the treatment of hospitalized COVID-19[6] patients, in collaboration with Inova Health System; and a Phase 2 trial for the treatment of COVID-19 being conducted by Imperial College London. Additionally, Rigel has launched a Phase 3 clinical trial of fostamatinib for the treatment of hospitalized COVID-19 patients.

Rigel's other clinical programs include its interleukin receptor-associated kinase (IRAK) inhibitor program, and a receptor-interacting serine/threonine-protein kinase (RIP1) inhibitor program in clinical development with partner Eli Lilly and Company. In addition, Rigel has product candidates in development with partners AstraZeneca, BerGenBio ASA, and Daiichi Sankyo.

1. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020
2. Becker RC. COVID-19 Update: COVID-19 associated coagulopathy. Journal of Thrombosis and Thrombolysis May 15, 2020. DOI: https://doi.org/10.1007/s11239-020-02134-3
3. Hoepel W. et al. Anti-SARS-CoV-2 IgG from severely ill COVID-19 patients promotes macrophage hyper-inflammatory responses. bioRxiv July 13, 2020. DOI: https://doi.org/10.1101/2020.07.13.190140
4. Sung P-S and Hsieh S-L (2019) CLEC2 and CLEC5A: Pathogenic Host Factors in Acute Viral Infections. Front. Immunol. 10:2867. DOI: https://doi.org/10.3389/fimmu.2019.02867
5. Behnen M. Immobilized Immune Complexes Induce Neutrophil Extracellular Trap Release by Human Neutrophil Granulocytes via Fcγ RIIIB and Mac-1. The Journal of Immunology July 2014. DOI: https://doi.org/10.4049/jimmunol.1400478
6. *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, Rigel's expectations on timing to report topline data from the Phase 2 trial, and the potential clinical benefit of fostamatinib for the treatment of hospitalized COVID-19 patients and the role of SYK inhibition in potentially improving outcomes for COVID-19 patients, including by alleviating thromboinflammation. 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," "could," "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, unforeseen and foreseen delays in Rigel's ongoing clinical trials; risks that the FDA, EMA or other regulatory authorities may make adverse decisions regarding fostamatinib or any other of Rigel's products and product candidates; risks that clinical trials may not be predictive of real-world results, or of results in subsequent clinical trials; risks that TAVALISSE may have unintended side effects, adverse reactions or incidents of misuse; 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, 2020 . In addition, the ongoing COVID-19 pandemic may result in further delays in Rigel's studies, trials and sales, or impact Rigel's ability to obtain supply of TAVALISSE. 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.

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