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Fostamatinib Selected for NIH ACTIV-4 COVID-19 Clinical Trial

--ACTIV-4 Host Tissue Study will evaluate fostamatinib in ~300 hospitalized patients with COVID-19--

SOUTH SAN FRANCISCO, Calif., June 29, 2021 /PRNewswire/ -- Rigel Pharmaceuticals, Inc. (Nasdaq: RIGL), today announced that fostamatinib, the Company's novel oral spleen tyrosine kinase (SYK) inhibitor, has been selected for a National Institutes of Health (NIH) ACTIV-4 (Accelerating COVID-19 Therapeutic Interventions and Vaccines) trial in hospitalized patients with COVID-19.

The ACTIV-4 Host Tissue trial is a large, multi-site trial funded by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH and coordinated by Vanderbilt University Medical Center (VUMC). The trial is evaluating treatments, including fostamatinib, that aim to protect and heal host tissues in hospitalized patients with COVID-19.

This study follows a recently completed NHLBI/NIH-sponsored Phase 2 study (NCT04579393), with positive topline results, that evaluated fostamatinib in hospitalized adults with COVID-19. The study met its primary endpoint of safety and showed broad and consistent improvement in numerous efficacy endpoints including mortality, ordinal scale assessment, and number of days in the ICU. These data were submitted as part of a request for an emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) for fostamatinib in hospitalized patients diagnosed with COVID-19. These data have also been submitted for publication in a peer-reviewed medical journal.

"Despite welcome advances in some areas, COVID-19 and its variants will remain a real public health threat for the foreseeable future, particularly for those with pre-existing conditions," said Raul Rodriguez, Rigel's president and CEO. "The teams at the NIH and VUMC are ideally positioned to continue to advance clinical efforts for COVID-19 related lung injuries, including the study of fostamatinib's potential to treat and prevent conditions caused by an overactive immune system in COVID-19 patients," he added.

"Fostamatinib will be the fourth arm of our ACTIV-4 Host Tissue trial. The drugs tested on this platform offer an opportunity to better understand both the central pathways of disease progression and better ways to protect and heal the host tissues damaged by COVID-19," said Dr. Sean P. Collins, MD, MSc, ACTIV-4 Host Tissue Principal Investigator and

Professor of Emergency Medicine at VUMC.

ACTIV-4 Host Tissue Phase 3 Clinical Study Design
The Collaborative Network of Networks for Evaluating COVID-19 Therapeutic Strategies (CONNECTS) Master Protocol for Clinical Trials Targeting Macro-, Micro-immuno-thrombosis, Vascular Hyperinflammation, and Hypercoagulability and Renin-angiotensin-aldosterone System (RAAS) in Hospitalized Patients With COVID-19 (ACTIV-4 Host Tissue) is a multi-site, randomized, placebo-controlled trial of therapies, including fostamatinib, targeting the host response to COVID-19 in hospitalized patients. The Master Protocol is designed to be flexible in the number of study arms, the use of a single placebo group, and the stopping and adding of new therapies. Each active arm will include approximately 300 patients. Eligible participants will include patients hospitalized for COVID-19 with laboratory confirmed SARS-CoV-2 infection on oxygen therapy. The primary outcome is oxygen free days through day 28. Secondary outcomes include hospital mortality, use of mechanical ventilation, and WHO scale scores. More detail on the study can be found on clinicaltrials.gov: NCT04924660.

The study is part of Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), initiated and funded by the NHLBI, part of the NIH. ACTIV is a public-private partnership that unites partners from government, industry, academic and non-profit organizations to prioritize and speed development of the most promising COVID-19 treatments.

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 pro-inflammatory cytokine release by monocytes and macrophages, production of neutrophil extracellular traps (NETs) by neutrophils, and platelet aggregation.[3,4,5,6] Furthermore, SYK inhibition in neutrophils and platelets may lead to decreased thrombo-inflammation, alleviating organ dysfunction in critically ill patients with COVID-19.

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 (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)[7]; a Phase 3 clinical trial (NCT04629703) for the treatment of hospitalized high-risk patients with mild-to-moderate COVID-19[7]; and a Phase 2 clinical trial for the treatment of COVID-19 being conducted by Imperial College London. An NIH/NHLBI-sponsored Phase 2 clinical trial for the treatment of hospitalized patients with COVID-19, in collaboration with Inova Health System, was recently completed.

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.

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

Please see www.TAVALISSE.com for the full Prescribing Information.

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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 Hoepel W et al. *High titers and low fucosylation of early human anti–SARS-CoV-2 IgG promote inflammation by alveolar macrophages*. Science Translational Medicine 02 Jun 2021. DOI: https://www.doi.org/10.1126/scitranslmed.abf8654
3. Sung P-S and Hsieh S-L. *CLEC2 and CLEC5A: Pathogenic Host Factors in Acute Viral Infections*. Frontiers in Immunology December 6, 2019. DOI: https://doi.org/10.3389/fimmu.2019.02867 Strich J et al. *Fostamatinib Inhibits Neutrophils Extracellular Traps Induced by COVID-19 Patient Plasma: A Potential Therapeutic*. Journal of Infectious Disease March 15, 2021. DOI: https://doi.org/10.1093/infdis/jiaa789
4. Bye AP et al. *Aberrant glycosylation of anti-SARS-CoV-2 IgG is a pro-thrombotic stimulus for platelets*. BioRxiv March 26, 2021. DOI: https://doi.org/10.1101/2021.03.26.437014
5. *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 ability to further develop its clinical stage product candidates and fostamatinib's potential to treat and prevent conditions caused by COVID-19. 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 and uncertainties associated with the commercialization and marketing of TAVALISSE; risks that the FDA, EMA or other regulatory authorities may make adverse decisions regarding fostamatinib; risks that TAVALISSE 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 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 quarter ended March 31, 2021. In addition, the 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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