Press Release

RedHill Biopharma's Opaganib Demonstrates Significant Decrease of Kidney Fibrosis

COVID-19 and long COVID patients are at increased risk of developing kidney damage

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Opaganib significantly decreased kidney fibrosis in a preclinical in vivo model

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Renal fibrosis is a progressive process which occurs in patients with chronic kidney disease (CKD) and can ultimately lead to end-stage renal failure

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Opaganib is a novel, late clinical-stage oral pill drug candidate with dual anti-inflammatory and antiviral activity and has already demonstrated strong inhibition against variants of concern, including Delta

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The global 475-patient Phase 2/3 study with opaganib oral pill in hospitalized COVID-19 patients has completed treatment and follow up phase, with top-line results upcoming

TEL AVIV, Israel and RALEIGH, NC, September 7, 2021, RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced results of a new preclinical study demonstrating opaganib's (ABC294640)[1] efficacy in significantly decreasing renal fibrosis in a unilateral ureteral obstruction-induced renal interstitial fibrosis model. Reports suggest that over 20% of hospitalized COVID-19 patients experience acute renal failure[2].

Kidney fibrosis generally leads to loss of tissue function and subsequent organ failure, with high mortality rate. New therapeutic small molecules to modulate fibrosis are urgently needed. The aim of the *in vivo* efficacy study was to verify the effect of opaganib on kidney inflammation and fibrosis in a unilateral ureteral obstruction (UUO) model – a well characterized model for renal fibrosis. Results from the study showed that opaganib significantly decreased renal fibrosis.

"A final, common pathway in chronic kidney disease is fibrosis, the formation of internal scar tissue, which can cause devastating effects and can ultimately lead to end-stage kidney failure. This new preclinical data, demonstrating opaganib's ability to decrease kidney fibrosis, along with its observed anti-inflammatory properties, positions opaganib as a potential novel therapy for the millions of patients suffering from chronic kidney disease and potentially extends to COVID-19 patients with Acute Kidney Injury (AKI) who are at risk of developing renal fibrosis," **said Reza Fathi, PhD., RedHill's Senior VP, R&D**. "Kidney injury and its associated progression to fibrosis is an important facet in both the acute phase of COVID-19 and in long COVID. Recent research has shown that after acute kidney injury, which we know can be a result of COVID-19 infection, the kidneys often fail to repair themselves properly and that sphingosine kinase-2 (SK2), which is inhibited by opaganib, is part of this process. These findings provide further support for the extensive work we are doing with opaganib in COVID-19. With the upcoming readout, we expect to learn more about kidney outcomes from hospitalized COVID-19 patients treated with opaganib in our global Phase 2/3 study."

Renal fibrosis, a common outcome of chronic kidney disease (CKD), is characterized by an excessive accumulation and deposition of extracellular matrix (ECM) components and fibrous tissue. Renal fibrosis may ultimately lead to end-stage renal failure, a devastating disorder that requires dialysis or kidney transplantation. CKD is a very common disease, affecting 15% of U.S. adults[3].

Recent studies have found that patients infected with SARS-CoV-2 are at increased risk of developing kidney damage, as well as chronic and end-stage kidney disease., associated with morbidity and mortality in these patients. Findings have suggested that beyond the acute phase of the disease, COVID-19 survivors, even those who did not require hospitalization, exhibit an increased risk of developing major adverse kidney disease such as CKD. In addition, data suggests that approximately 10% of people infected with COVID-19 may experience long COVID (post-acute sequalae), potentially involving acute kidney-related outcomes[4].

Opaganib, a leading novel small molecule investigational oral pill in development for the treatment of COVID-19, is a unique host targeted, dual antiviral and anti-inflammatory drug that acts on the cause and effect of COVID-19. It is believed to exert its antiviral effect by selectively inhibiting SK2, a key enzyme produced in human cells that may be recruited by the virus to support its replication. Opaganib's global 475-patient Phase 2/3 study in hospitalized patients with COVID-19 has completed its treatment and follow up phase, and study top-line results are upcoming.

Evaluations of blinded blended intubation and mortality rates from the Phase 2/3 study have been encouraging compared to reported rates of mortality from large platform studies such as RECOVERY, and other studies in similar patient populations[5]. Furthermore, the opaganib Phase 2/3 study has also passed four Data Safety Monitoring Board reviews, as well as a futility review, extending the total opaganib safety database to more than 460 patients and healthy subjects. Opaganib previously delivered positive U.S. Phase 2 data in patients with severe COVID-19, has been recently published

in medRxiv. Additionally, encouraging use of opaganib under compassionate use exemption has been experienced in Israel and Switzerland.

About Opaganib (ABC294640)

Opaganib, a new chemical entity, is a proprietary, first-in-class, orally-administered, sphingosine kinase-2 (SK2) selective inhibitor, with dual anti-inflammatory and antiviral activity. Opaganib is host-targeted and is expected to be effective against emerging viral variants, having already demonstrated strong inhibition against variants of concern, including *Delta*. Opaganib has also shown anticancer activity and positive preclinical results in renal fibrosis, and also has the potential to target multiple oncology, viral, inflammatory, and gastrointestinal indications.

Opaganib is being evaluated as a treatment for COVID-19 pneumonia in a global Phase 2/3 study that has completed patient treatment and follow-up, with top-line results upcoming. Opaganib previously delivered positive U.S. Phase 2 data in patients with severe COVID-19, recently published in medRxiv.

Opaganib has also received Orphan Drug designation from the U.S. FDA for the treatment of cholangiocarcinoma and is being evaluated in a Phase 2a study in advanced cholangiocarcinoma and in a Phase 2 study in prostate cancer. Based on a preliminary review of partial unaudited data, the ongoing study in prostate cancer has met its primary endpoint. Patient accrual, treatment and analysis in this study are ongoing.

Opaganib demonstrated potent antiviral activity against SARS-CoV-2, the virus that causes COVID-19, inhibiting viral replication in an *in vitro* model of human lung bronchial tissue. Additionally, preclinical *in vivo* studies have demonstrated opaganib's potential to ameliorate inflammatory lung disorders, such as pneumonia, and have shown decreased fatality rates from influenza virus infection and amelioration of *Pseudomonas aeruginosa*-induced lung injury by reducing the levels of IL-6 and TNF-alpha in bronchoalveolar lavage fluids[6].

The ongoing clinical studies with opaganib are registered on www.ClinicalTrials.gov, a web-based service by the U.S. National Institute of Health, which provides public access to information on publicly and privately supported clinical studies.

About RedHill Biopharma

RedHill Biopharma Ltd. (Nasdaq: RDHL) is a specialty biopharmaceutical company primarily focused on gastrointestinal and infectious diseases. RedHill promotes the gastrointestinal drugs, **Movantik**® for opioid-induced constipation in adults, **Talicia**® for the treatment of *Helicobacter pylori (H. pylori)* infection in adults, and **Aemcolo**® for the treatment of travelers' diarrhea in adults. RedHill's key clinical late-stage development programs include: (i) **RHB-204**, with an ongoing Phase 3 study for pulmonary nontuberculous mycobacteria (NTM) disease; (ii) **opaganib (ABC294640)**, a first-in-class oral SK2 selective inhibitor targeting multiple indications with a Phase 2/3 program for

COVID-19 and Phase 2 studies for prostate cancer and cholangiocarcinoma ongoing; (iii) **RHB-107** (**upamostat**), an oral serine protease inhibitor in a U.S. Phase 2/3 study as treatment for symptomatic COVID-19, and targeting multiple other cancer and inflammatory gastrointestinal diseases; (iv) **RHB-104**, with positive results from a first Phase 3 study for Crohn's disease; (v) **RHB-102** , with positive results from a Phase 3 study for acute gastroenteritis and gastritis and positive results from a Phase 2 study for IBS-D; and (vi) **RHB-106**, an encapsulated bowel preparation. More information about the Company is available at www.redhillbio.com / https://twitter.com/RedHillBio.

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements may be preceded by the words "intends," "may," "will," "plans," "expects," "anticipates," "projects," "predicts," "estimates," "aims," "believes," "hopes," "potential" or similar words. Forward-looking statements are based on certain assumptions and are subject to various known and unknown risks and uncertainties, many of which are beyond the Company's control and cannot be predicted or quantified, and consequently, actual results may differ materially from those expressed or implied by such forward-looking statements. Such risks and uncertainties include the risk that in the next studies opaganib will not be found effective in decreasing renal fibrosis, the delay in top-line data from the Phase 2/3 COVID-19 study for opaganib, that the Phase 2/3 COVID-19 study for opaganib may not be successful and, even if successful, such study and results may not be sufficient for regulatory applications, including emergency use or marketing applications, and that additional COVID-19 studies for opaganib are likely to be required by regulatory authorities to support such potential applications and the use or marketing of opaganib for COVID-19 patients, that opaganib will not be effective against emerging viral variants, as well as risks and uncertainties associated with (i) the initiation, timing, progress and results of the Company's research, manufacturing, preclinical studies, clinical trials, and other therapeutic candidate development efforts, and the timing of the commercial launch of its commercial products and ones it may acquire or develop in the future; (ii) the Company's ability to advance its therapeutic candidates into clinical trials or to successfully complete its preclinical studies or clinical trials (iii) the extent and number and type of additional studies that the Company may be required to conduct and the Company's receipt of regulatory approvals for its therapeutic candidates, and the timing of other regulatory filings, approvals and feedback; (iv) the manufacturing, clinical development, commercialization, and market acceptance of the Company's therapeutic candidates and Talicia®; (v) the Company's ability to successfully commercialize and promote Movantik®, Talicia® and Aemcolo®; (vi) the Company's ability to establish and maintain corporate collaborations; (vii) the Company's ability to acquire products approved for marketing in the U.S. that achieve commercial success and build and sustain its own marketing and commercialization capabilities; (viii) the interpretation of the properties and characteristics of the Company's therapeutic candidates and the results obtained with its therapeutic candidates in research, preclinical studies or clinical trials; (ix) the implementation of the Company's business model, strategic plans for its business and therapeutic candidates; (x) the scope of protection the Company is able to establish and maintain for intellectual property rights covering its therapeutic candidates and commercial products and its ability to operate its business

without infringing the intellectual property rights of others; (xi) parties from whom the Company licenses its intellectual property defaulting in their obligations to the Company; (xii) estimates of the Company's expenses, future revenues, capital requirements and needs for additional financing; (xiii) the effect of patients suffering adverse events using investigative drugs under the Company's Expanded Access Program; and (xiv) competition from other companies and technologies within the Company's industry. More detailed information about the Company and the risk factors that may affect the realization of forward-looking statements is set forth in the Company's filings with the Securities and Exchange Commission (SEC), including the Company's Annual Report on Form 20-F filed with the SEC on March 18, 2021. All forward-looking statements included in this press release are made only as of the date of this press release. The Company assumes no obligation to update any written or oral forward-looking statement, whether as a result of new information, future events or otherwise unless required by law.

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[1] Opaganib is an investigational new drug, not available for commercial distribution.
[2] Nadim, M.K., Forni, L.G., Mehta, R.L. et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 16, 747–764 (2020).
[3] Centers for Disease Control and Prevention – Chronic Kidney Disease in the United States, 2021
[4] Bowe B, Xie Y, Xu E, Al-Aly Z, Kidney Outcomes in Long COVID. JASN Sep 2021
[5] Based on preliminary blinded blended data from 463 patients. The Company did not conduct a head-to-head comparison study in the same patient population. The theoretical comparison between the global Phase 2/3 study with opaganib and reported rates of mortality from large platform studies such as RECOVERY, and other studies in similar patient populations, serves as a general benchmark and should not be construed as a direct and/or applicable comparison as if the Company conducted a head-to-head comparison study.
[6] Xia C. et al. Transient inhibition of sphingosine kinases confers protection to influenza A virus infected mice. Antiviral Res. 2018 Oct; 158:171-177. Ebenezer DL et al. Pseudomonas aeruginosa stimulates nuclear sphingosine-1-phosphate generation and epigenetic regulation of lung inflammatory injury. Thorax. 2019 Jun;74(6):579-591.