# Press Release

## RedHill Biopharma Reports Top-Line Data from Opaganib Phase 2/3 Study in Severe COVID-19 Patients

*While preliminary top-line data of the study efficacy endpoints showed consistent trends in favor of the opaganib arm, the study endpoints did not achieve statistical significance*

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*Analysis of the top-line data is ongoing, including regarding the potential for increased benefit of opaganib in patients at earlier stages of the disease on low flow oxygen support*

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*Top-line safety data shows good tolerability with balanced adverse events between the study arms*

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*Additional data will be presented upon further analysis and will be discussed with U.S. and non-U.S. regulators to help determine next steps*

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*RedHill plans to hold a conference call to discuss the results in greater detail following further data analysis*

**TEL AVIV, Israel and RALEIGH, NC, September 14, 2021,** RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced preliminary top-line data from the 475-patient global Phase 2/3 study with opaganib (ABC294640)[1] in hospitalized patients with severe COVID-19 pneumonia.

Preliminary top-line data showed that the study did not meet its primary endpoint. Analysis of the study efficacy endpoints did show trends in favor of the opaganib arm vs. placebo across multiple endpoints, including the primary endpoint, despite not achieving statistical significance.

Top-line safety data showed good tolerability of opaganib, with balanced adverse events between the study arms. These findings, together with preliminary analysis pointing to increased benefit in a subset of patients requiring less oxygen, could support the potential utilization of opaganib in earlier stages

of the disease and are in line with the previously announced results from the U.S. Phase 2 study and the previously observed antiviral activity of opaganib.

“We would like to thank the patients, physicians and supporting medical staff who took part in this important study. While we are disappointed with the data not reaching statistical significance, we do see a trend that needs to be investigated that opaganib may provide benefit to patients earlier in the course of the disease. This correlates with what we know about opaganib’s strong antiviral mechanism and effect against variants, as well as its mechanism of action and previously announced results from the Phase 2 U.S. study with opaganib,” **said Dror Ben Asher, RedHill CEO**. “In parallel, we continue to make progress with our Phase 2/3 study with another novel, orally-administered drug candidate, RHB-107 (upamostat) in non-hospitalized symptomatic COVID-19 patients, with the recent approval of the study in South Africa and its expansion within the United States. We are determined to continue our efforts to advance potential treatments to address COVID-19 and its overwhelming impact worldwide.”

The multi-center, randomized, double-blind, parallel-arm, placebo-controlled Phase 2/3 study enrolled 475 subjects with severe COVID-19 pneumonia requiring hospitalization and treatment with supplemental oxygen. Subjects were randomized at a 1:1 ratio to receive either opaganib or placebo, on top of standard-of-care therapy. The primary endpoint of the study is the proportion of patients breathing room air without oxygen support by Day 14.

Analysis of the top-line data is ongoing, including an analysis of the potential for increased benefit of treatment with opaganib in patients at earlier stages of disease. RedHill intends to discuss the data with regulators, including U.S. FDA and foreign regulators, to help determine next steps.

The top-line results from the Company's Phase 2/3 study with opaganib are preliminary in nature, as they are based solely on top-line information provided to the Company by an independent third-party contractor. The Company intends to examine the data from this study in greater detail, along with all of the information gathered during this study, including all safety, and secondary outcome measures. Such analysis may result in findings inconsistent with the top-line data disclosed in this release. As such, investors should not rely on the top-line results reported in this release as the final definitive results of the study.

Opaganib is a novel small molecule investigational drug in oral pill form. Opaganib has a unique dual antiviral and anti-inflammatory mechanism of action that acts on the viral cause and inflammatory 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.

**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 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 of all SARS-CoV-2 variants tested to date 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, have demonstrated opaganib's potential to decrease renal fibrosis 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[2].

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[3], **Talicia®** for the treatment of *Helicobacter pylori (H. pylori)* infection in adults[4], and **Aemcolo®** for the treatment of travelers' diarrhea in adults[5]. 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; that further analysis of the top-line results of the Phase 2/3 COVID-19 study for opaganib results in findings inconsistent with the top-line data disclosed in this release; that no further COVID-19 studies for opaganib will be commenced, and if commenced, may not be successful, including with respect to patients in earlier stages of COVID-19 on low flow oxygen support; that the Phase 2/3 study for RHB-107 in COVID-9 patients may not be successful; that any additional studies for opaganib and the Phase 2/3 study for RHB-107 in COVID-19 patients, even if successful, will not be sufficient for regulatory applications, including emergency use or marketing applications, and that additional COVID-19 studies for opaganib and RHB-107 will be required by regulatory authorities to support such potential applications and the use or marketing of opaganib or RHB-107 for COVID-19 patients, that opaganib and RHB-107 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] 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.
[3] Full prescribing information for Movantik® (naloxegol) is available at: www.Movantik.com.
[4] Full prescribing information for Talicia® (omeprazole magnesium, amoxicillin and rifabutin) is available at: www.Talicia.com.
[5] Full prescribing information for Aemcolo® (rifamycin) is available at: www.Aemcolo.com.