Press Release

RedHill Biopharma Announces Presentation of Positive Oral Opaganib Phase 2 Data in COVID-19

Positive U.S. Phase 2 safety and efficacy data for opaganib, a leading novel, oral, dual-mechanism drug candidate for moderate-to-severe COVID-19, presented at the World Microbe Forum

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Opaganib was associated with a reduction in the need for supplemental oxygen support, earlier time to discharge from hospital and was well tolerated

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Opaganib's global 475-patient Phase 2/3 study is fully enrolled, with study completion expected in the coming weeks

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Opaganib is host-targeted and expected to be effective against emerging viral variants

TEL AVIV, Israel and RALEIGH, NC, June 21, 2021, RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced presentation of the positive Phase 2 safety and efficacy data for oral opaganib (Yeliva®, ABC294640)[1] in hospitalized patients with COVID-19 pneumonia at the World Microbe Forum (WMF) 2021 (poster #: 5574).

Results and post hoc analyses of data from the 40-patient U.S. Phase 2 study were presented in a poster entitled, "*Opaganib, an Oral Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: A Randomized, Double-blind, Placebo-controlled Phase 2A Study, in Adult Subjects Hospitalized with SARS-CoV-2 Positive Pneumonia (NCT: 04414618)*"[2]. Patients in the study were randomized to receive either opaganib or placebo in addition to standard of care (SoC), predominantly including dexamethasone and/or remdesivir. Findings include:

- 50% of patients treated with opaganib (n=22) reached room air by Day 14 compared to 22% in the placebo group (n=18). The benefit of reaching room air by Day 14 for patients on

opaganib was maintained regardless of whether the patients were receiving dexamethasone and/or remdesivir

- 86.4% of patients treated with opaganib were discharged from hospital by Day 14 compared to 55.6% of patients treated with placebo
- Median time to discharge was 6 days for the opaganib group compared to 7.5 days for the placebo group
- 81.8% of opaganib patients achieved a 2-point improvement in the WHO Ordinal Scale compared to 55.6% of patients in the placebo group – achieved in a median time of 6 days versus 7.5 days, respectively
- No significant differences in safety-related measures between the two groups (with diarrhea being the main treatment-emergent difference in tolerability)

"The need for an effective oral therapy to treat COVID-19 is clear. Such a therapy would greatly improve our ability to manage this pandemic," **said Kevin Winthrop, MD, MPH, Professor of Infectious Diseases at Oregon Health & Science University, who presented the findings at WMF.** "These data, from this proof-of-concept clinical study of opaganib in patients with severe COVID-19, suggest a potential role of SK2 inhibition in combating the effects of this virus. With much more data on opaganib expected in the coming weeks, we could make some real progress toward having access to a much-needed oral therapy for patients who currently have a paucity of options available to them."

"Presentation of these positive data from our exploratory Phase 2 study support our growing confidence that opaganib could be the first novel, oral therapy to demonstrate efficacy in the treatment of COVID-19 in a large late-stage study. With the recent completion of enrollment of our 475-patient global Phase 2/3 study, we will have a clearer picture of that in the very near future," **said Mark L. Levitt, MD, Ph.D., Medical Director at RedHill**. "Opaganib acts on both the cause and effect of COVID-19 via a unique dual antiviral and anti-inflammatory mode of action. Being host-targeted, opaganib is also expected to maintain effect against the emerging SARS-CoV-2 variants, which continue to threaten the progress being made against the pandemic and underscore the urgent need for effective COVID-19 therapeutics."

The global 475-patient Phase 2/3 study of opaganib in severe COVID-19 has been approved in 10 countries and completed enrollment, through 57 participating sites, on June 6th. The primary endpoint of the study is the proportion of patients breathing room air without oxygen support by Day 14. Additional important outcome measures, such as time to discharge from hospital, improvement according to the World Health Organization Ordinal Scale for Clinical Improvement and incidence of intubation and mortality, will also be captured in the follow-up period of up to 6 weeks. The study received four independent DSMB recommendations to continue following unblinded safety reviews and a futility review. Additionally, an evaluation of the blinded blended intubation and mortality rates to date was encouraging as compared to reported rates of mortality from large platform studies such as RECOVERY, and other studies in similar patient populations[3].

About Opaganib (Yeliva®, 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, that is host-targeted and is therefore expected to be effective against emerging viral variants. Opaganib has also shown anticancer activity and 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, which recently completed enrollment, and has demonstrated positive safety and efficacy signals in preliminary top-line data from the 40-patient U.S. Phase 2 study.

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.

Opaganib demonstrated potent antiviral activity against SARS-CoV-2, the virus that causes COVID-19, completely 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 has shown decreased fatality rates from influenza virus infection and ameliorated *Pseudomonas aeruginosa*-induced lung injury by reducing the levels of IL-6 and TNF-alpha in bronchoalveolar lavage fluids[4].

The ongoing 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[5], **Talicia®** for the treatment of *Helicobacter pylori (H. pylori)* infection in adults[6], and **Aemcolo®** for the treatment of travelers' diarrhea in adults[7]. 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 (Yeliva®, ABC294640)**, a first-in-class SK2 selective inhibitor targeting multiple indications with positive Phase 2 COVID-19 data and an ongoing Phase 2/3 program for COVID-19 and Phase 2 studies for prostate cancer and cholangiocarcinoma ongoing; (iii) **RHB-107 (upamostat)**, a 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 (Bekinda®)**, 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 delay in last patient visit and 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] Opaganib, an Oral Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: A Randomized, Double-blind, Placebo-controlled Phase 2A Study, in Adult Subjects Hospitalized with SARS-CoV-2 Positive Pneumonia (NCT: 04414618). K. L. Winthrop, A. W. Skolnick, A. M. Rafiq, S. H. Beegle, J. Suszanski, G. Koehne, O.Barnett-Griness, A. Bibliowicz, R. Fathi, P. Anderson, G. Raday, G. Eagle, V. Katz Ben-Yair, H. S. Minkowitz, M. L. Levitt, M. S. Gordon
[3] 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.
[4] 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.
[5] Full prescribing information for Movantik® (naloxegol) is available at: www.Movantik.com.
[6] Full prescribing information for Talicia® (omeprazole magnesium, amoxicillin and rifabutin) is available at: www.Talicia.com.
[7] Full prescribing information for Aemcolo® (rifamycin) is available at: www.Aemcolo.com.