RedHill's Phase 2/3 COVID-19 Candidate Opaganib Reduces ARDS-Related Blood Clotting in Preclinical Model

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- **Acute respiratory distress syndrome (ARDS)-induced thrombosis (blood clotting) may occur in up to one-third of COVID-19 patients requiring ICU admission and is a contributing cause of mortality**
- **Opaganib demonstrated reduced thrombosis in a preclinical model of ARDS**
- **Opaganib has also been shown to inhibit SARS-CoV-2 viral replication as well as pro-inflammatory markers in relevant preclinical models**
- **Top-line data from the U.S. Phase 2 study of orally administered opaganib in patients with severe COVID-19, evaluating safety and potential efficacy signals, is expected later this month following the last patient's last dose administered on November 26**
- **Top-line data from a global Phase 2/3 study of opaganib in patients with severe COVID-19, currently more than 60% enrolled, is expected in Q1/2021 with potential global emergency use applications to follow**

TEL AVIV, Israel and RALEIGH, N.C., Dec. 15, 2020 /PRNewswire/ -- RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced promising preliminary results from a preclinical study within which opaganib, a novel, orally administered sphingosine kinase 2 (SK2) selective inhibitor, (administered at 250mg/kg,) demonstrating a reduction of thrombosis (blood clotting) in an acute respiratory distress syndrome (ARDS) – a preclinical animal model designed to measure thrombotic (blood clot) risks.

This latest finding points towards another important potential benefit of opaganib to COVID-19 patients – in addition to the already established inhibition of SARS-CoV-2 replication and the potential reduction in hyper immune-response by opaganib. Following these preliminary findings, additional work is being planned to evaluate the range of potential physiologically and pharmacologically relevant opaganib doses with respect to thrombosis reduction.

"Acute Respiratory Distress Syndrome (ARDS) is one of the most dangerous outcomes of COVID-19 disease, putting severely ill COVID-19 patients at an increased risk of potentially fatal venous thrombosis and pulmonary embolism. There are currently very limited options available to physicians that have been shown to be effective against ARDS, and specifically against ARDS-induced thrombosis," **said Reza Fathi, PhD., RedHill's Senior VP, R&D**. "Results from our study show opaganib 250 mg/kg reduced blood clot length, weight and total thrombus score in a preclinical model of ARDS. This adds to the known antiviral and anti-inflammatory activities of opaganib and provides the potential for a unique triple-action effect on the pathophysiological processes associated with COVID-19 disease. Opaganib, which targets a host cell component, potentially minimizes the likelihood for resistance due to viral mutations. Before the end of this month, we expect topline clinical data insights into the safety and potential efficacy signals of opaganib from the non-powered U.S. Phase 2 study in which the last patient has been given their last dose on November 26, followed in Q1/2021 by top-line data from the larger global Phase 2/3 study, which is powered for efficacy and already more than 60% enrolled."

"The ARDS thrombosis model we used to conduct this work is validated and highly predictive, and the results we saw with opaganib are impressive and provide reason for promise," **said Sebastien Labbe, Ph.D., Director, Translational Research at IPS Therapeutique Inc.**, who carried out the study. "The results provide insight into a highly desirable potential effect of opaganib for use in managing patients with severe COVID-19, whose prognosis can be very poor."

ARDS-induced thrombosis may occur in up to one-third of COVID-19 patients requiring Intensive Care Unit (ICU) admission and up to 9% of all

hospitalized patients[1] and is associated with a poor prognosis. The preclinical study was designed to assess the efficacy of opaganib in reducing the incidence of adverse thromboembolic events in situ in the lipopolysaccharide (LPS)-induced model of pulmonary inflammation, a reliable model of ARDS that can mimic COVID-19 inflammation[2].

The results from the preclinical study of opaganib are preliminary and were provided to the Company by an independent third-party following an initial independent analysis and remain subject to additional review and analysis. Such review and analysis may result in findings inconsistent with the results disclosed in this release and may not be replicated in future preclinical or clinical studies.

Opaganib is a novel, orally administered, sphingosine kinase-2 (SK2) selective inhibitor with demonstrated dual anti-inflammatory and antiviral activity that acts on both the cause and the effects of COVID-19 disease, targeting a host cell component involved in viral replication, potentially minimizing likelihood of resistance due to viral mutations.

A U.S. Phase 2 study with opaganib in patients with severe COVID-19 pneumonia (NCT04414618) has completed enrollment of all 40 subjects, and the last patient has been given their last dose – top-line data is expected later this month. This Phase 2 study is not powered for efficacy and is focused on safety evaluation and identification of efficacy signals.

In parallel, enrollment in the 270-patient global Phase 2/3 study with opaganib in patients with severe COVID-19 pneumonia (NCT04467840) is over 60% complete. The study is approved in six countries and is on track to deliver topline data in the first quarter of 2021. This study is focused on and powered for efficacy evaluation, and recently received a unanimous recommendation to continue by an independent Data and Safety Monitoring Board (DSMB), following a pre-scheduled safety review of the first 70 patients to have been treated for 14 days. The DSMB is scheduled to conduct a second pre-planned safety review this month of the first 135 patients who have reached the primary endpoint, and this will later be followed by a prescheduled, unblinded futility interim analysis of efficacy data from the same patients. The Company will remain blinded to this data.

About Opaganib (ABC294640, Yeliva®)

Opaganib, a new chemical entity, is a proprietary, first-in-class, orally administered, sphingosine kinase-2 (SK2) selective inhibitor with a demonstrated unique triple-action effect on the pathophysiological processes associated with COVID-19 disease, that targets a host cell component, potentially minimizing the likelihood for resistance due to viral mutations. Opaganib has also shown anticancer activity and has the potential to target multiple oncology, viral, inflammatory and gastrointestinal indications.

Opaganib is being evaluated in a global Phase 2/3 study and a U.S. Phase 2 study for the treatment of severe COVID-19 pneumonia. Opaganib 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.

Preclinical data have demonstrated both anti-inflammatory and antiviral activities of opaganib, with the potential to reduce inflammatory lung disorders, such as pneumonia, and mitigate pulmonary fibrotic damage. 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[3] have demonstrated that opaganib 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.

Opaganib was originally developed by U.S.-based Apogee Biotechnology Corp. and completed multiple successful preclinical studies in oncology, inflammation, GI, and radioprotection models, as well as a Phase 1 clinical study in cancer patients with advanced solid tumors and an additional Phase 1 study in multiple myeloma.

Under a compassionate use program, patients with severe COVID-19 (as classified by the WHO ordinal scale) were treated with opaganib in a leading hospital in Israel. Data from the treatment of these first patients with severe COVID-19 with opaganib have been published[4]. Analysis of treatment outcomes suggests substantial benefit to patients treated with opaganib under compassionate use in both clinical outcomes and inflammatory markers as compared to a retrospective matched case-control group from the same hospital. All patients in the opaganib-treated group were discharged from hospital on room air without requiring intubation and mechanical ventilation, whereas 33% of the matched case-control group required intubation and mechanical ventilation. Median time to weaning from high-flow nasal cannula was reduced to 10 days in the opaganib-treated group, as compared to 15 days in the matched case-control group.

The development of opaganib has been supported by grants and contracts from U.S. federal and state government agencies awarded to Apogee Biotechnology Corp., including from the NCI, BARDA, the U.S. Department of Defense and the FDA Office of Orphan Products Development.

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®)**, a first-in-class 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-104**, with positive results from a first Phase 3 study for Crohn's disease; (iv) **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; (v) **RHB-107** (**upamostat**), a Phase 2-stage serine protease inhibitor with a planned Phase 2/3 study in symptomatic COVID-19 and targeting multiple other cancer and inflammatory gastrointestinal diseases; and (vi) **RHB-106**, an encapsulated bowel preparation. More information about the Company is available at www.redhillbio.com.

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 and include statements regarding the timing of the reporting of data from the U.S. Phase 2 trial evaluating opaganib, and

the timing, if at all, of potential emergency use applications of opaganib and reporting of data, from the global Phase 2/3 study with opaganib. 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, without limitation, the risk that the Company's Phase 2/3 study evaluating opaganib will not be completed or successful; the risk of a delay in receiving data from the Phase 2/3 study with opaganib or delay in making emergency use applications, if at all; the risk that the U.S. Phase 2 clinical study evaluating opaganib will not be successful and the risk that the reporting of data from this clinical study will be delayed, if at all; the risk that other COVID-19 patients treated with opaganib will not show any or insufficient clinical improvement; the development risks of early-stage discovery efforts for a disease that is still little understood, including difficulty in assessing the efficacy of opaganib for the treatment of COVID-19, if at all; intense competition from other companies developing potential treatments and vaccines for COVID-19; the effect of a potential occurrence of patients suffering serious adverse events using opaganib under compassionate use programs; the risk that the ongoing Phase 3 study for pulmonary nontuberculous mycobacteria (NTM) disease will be delayed, not be completed, or will not be successful, 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 lack of sufficient financial resources which may result in material adverse impact on the Company's research, manufacturing, preclinical studies, clinical trials, and other therapeutic candidate development activities including delay or termination of preclinical or clinical activities or of any other such activities (iii) the Company's ability to advance its therapeutic candidates into clinical trials or to successfully complete its preclinical studies or clinical trials (iv) 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; (v) the manufacturing, clinical development, commercialization, and market acceptance of the Company's therapeutic candidates and Talicia®; (vi) the Company's ability to successfully commercialize and promote Movantik®, Talicia® and Aemcolo®; (vii) the Company's ability to establish and maintain corporate collaborations; (viii) 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; (ix) 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; (x) the implementation of the Company's business model, strategic plans for its business and therapeutic candidates; (xi) 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; (xii) parties from whom the Company licenses its intellectual property defaulting in their obligations to the Company; (xiii) estimates of the Company's expenses, future revenues, capital requirements and needs for additional financing; (xiv) the effect of patients suffering adverse events using investigative drugs under the Company's Expanded Access Program; and (xv) 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 4, 2020. 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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[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.

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