RedHill Announces Unanimous DSMB Recommendation to Continue Phase 2/3 COVID-19 Study with Opaganib

November 19, 2020

Pre-scheduled independent Data and Safety Monitoring Board (DSMB) unanimously recommends continuation of the global Phase 2/3 study of orally administered opaganib in severe COVID-19 pneumonia

Enrollment in the 270-patient global Phase 2/3 COVID-19 study with opaganib is more than 50% complete

Enrollment completed in the parallel U.S. Phase 2 study evaluating opaganib's safety and initial efficacy signal in 40 hospitalized patients with severe COVID-19 pneumonia - data expected in the coming weeks

Emergency use authorization applications planned as early as Q1/2021

Opaganib's mechanism of action potentially minimizes likelihood of resistance due to viral mutations

TEL AVIV, Israel and RALEIGH, N.C., Nov. 19, 2020 /PRNewswire/ -- RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced that the global Phase 2/3 study with opaganib (Yeliva®, ABC294640)[1] in patients hospitalized with severe COVID-19 pneumonia has received a unanimous recommendation to continue, following a pre-scheduled safety review by an independent Data and Safety Monitoring Board (DSMB). The DSMB's recommendation is based on an unblinded analysis of safety data from the first 70 patients treated for 14 days.

"With each review of unblinded safety data, by independent reviewers, as part of our development program, our confidence in the safety profile of opaganib increases further," **said Mark L. Levitt, M.D., Ph.D., Medical Director at RedHill**. "We are fast compiling a robust and extensive safety data set with opaganib, giving us good reason to look forward to the rapid conclusion of this study which, if positive, is expected to provide the necessary efficacy data to support the next step of emergency use applications in the first quarter of 2020."

Enrollment in the 270-patient global Phase 2/3 study with opaganib in patients with severe COVID-19 pneumonia (NCT04467840) is more than 50% complete. The study, approved in six countries and rapidly enrolling across 22 study sites, is on track to deliver top line data in the first quarter of 2021. This study is focused on and powered for efficacy evaluation. A prescheduled, unblinded futility interim analysis will be conducted by the DSMB in the coming weeks, evaluating data from the first 135 subjects that have reached the primary endpoint.

The parallel U.S. Phase 2 study with opaganib (NCT04414618) has completed enrollment of all 40 subjects, with topline data expected in the coming weeks. This study is not powered for efficacy and is focused on safety evaluation and identification of efficacy signals.

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

About Opaganib (ABC294640, Yeliva®)

Opaganib, a new chemical entity, is a proprietary, first-in-class, orally administered, sphingosine kinase-2 (SK2) selective inhibitor with demonstrated dual anti-inflammatory and antiviral activity 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 also being evaluated in a global Phase 2/3 study and a U.S. Phase 2 study for the treatment of severe COVID-19. 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[2] 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[3]. Analysis of treatment outcomes suggested 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 with non-cancer pain[4], **Talicia®** for the treatment of *Helicobacter pylori (H. pylori)* infection in adults[5], and **Aemcolo®** for the treatment of travelers' diarrhea in adults[6]. RedHill's key clinical late-stage investigational development programs include: (i) **RHB-204**, with a planned Phase 3 study for pulmonary nontuberculous mycobacteria (NTM) infections; (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 first-in-class, serine protease inhibitor, targeting cancer and inflammatory gastrointestinal diseases and is also being evaluated for COVID-19 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, the timing of potential emergency use applications of opaganib and reporting of topline data, safety analysis and of unblinded futility interim analysis for 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 successful; the risk of a delay in receiving data to support emergency use applications or in making such 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 the Company will not initiate the Phase 2/3 study for opaganib in certain geographies, will not expand this study to additional countries and that it will not be successful and that enrollment, reporting of topline data, safety analysis and/or unblinded futility interim analysis will be delayed; the risk that other COVID-19 patients treated with opaganib will not show any 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, 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 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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[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] Kurd R, Ben-Chetrit E, Karameh H, Bar-Meir M, Compassionate Use of Opaganib For Patients with Severe COVID-19. medRxiv 2020.06.20.20099010; doi: https://doi.org/10.1101/2020.06.20.20099010

[4] Full prescribing information for Movantik® (naloxegol) is available at: www.Movantik.com.

[5] Full prescribing information for Talicia® (omeprazole magnesium, amoxicillin and rifabutin) is available at: www.Talicia.com.

[6] Full prescribing information for Aemcolo® (rifamycin) is available at: www.Aemcolo.com.