RedHill Biopharma Announces Positive Top-Line Safety and Efficacy Data from Phase 2 COVID-19 Study of Opaganib

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- **Preliminary data from the non-powered U.S. Phase 2 study of 40 hospitalized patients shows that orally-administered opaganib was safe, with no material safety differences between opaganib and control arms**
- **Consistent trends demonstrate greater improvement in reducing oxygen requirement by end of treatment at Day 14 in the opaganib-treated arm across key primary and secondary efficacy outcomes, correlating with clinical improvement as defined by the World Health Organization (WHO) ordinal scale**
- **The opaganib-treated arm demonstrated a greater improvement in reaching room air within 14 days (52.6% vs. 22.2%); greater improvement in reduction to 50% supplemental oxygen by Day 14 (89.5% vs. 66.7%); a higher proportion of patients discharged by Day 14 (73.7% vs. 55.6%) and a greater reduction in the median total oxygen requirement (AUC) over 14 days (68.0% vs. 46.7%)**
- **Top-line data from the global Phase 2/3 COVID-19 study in 270 hospitalized patients expected Q1/2021 and an interim DSMB futility analysis is expected in the coming weeks**
- **Opaganib targets a human cell component involved in viral replication, potentially minimizing the likelihood for resistance due to viral mutations**

TEL AVIV, Israel and RALEIGH, N.C., Dec. 31, 2020 /PRNewswire/ -- RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced that preliminary top-line data from its U.S. Phase 2 study with orally-administered opaganib (Yeliva®, ABC294640)[1] in patients hospitalized with COVID-19 pneumonia demonstrated positive safety and efficacy signals.

The randomized, double-blind, placebo-controlled U.S. Phase 2 proof-of-concept study with opaganib (NCT04414618) enrolled 40 patients requiring oxygen support. The study was not powered for statistical significance and aimed to evaluate safety and identify preliminary signs of activity. Patients in the study were randomized at a 1:1 ratio to receive either opaganib or placebo on top of standard-of-care (SoC) and were followed up for up to 42 days post treatment initiation.

- Top-line results from the study found opaganib to be safe, with no material safety differences between the opaganib and placebo treatment arms. Overall, fewer patients suffered from serious adverse events (SAEs) in the opaganib treatment arm than in the placebo arm. In this small sample size, there were few events of intubation or fatality and these were balanced between the two arms.
- The opaganib-treated arm demonstrated a consistent trend of greater improvement in reducing oxygen requirement by end of treatment on Day 14 across key primary and secondary efficacy outcomes, correlating with clinical improvement as defined by the World Health Organization (WHO) ordinal scale:
  - A greater improvement in the proportion of patients reaching room air and no longer requiring oxygen support by Day 14 vs. the control arm (52.6% vs. 22.2%).
  - A greater improvement in the proportion of patients with 50% reduction in supplemental oxygen by day 14 vs. the control arm (89.5% vs. 66.7%).
  - A higher proportion of patients discharged by Day 14 vs. the control arm (73.7% vs. 55.6%).

- A greater reduction from baseline of the median total oxygen requirement (AUC) over 14 days vs. the control arm (68.0% vs. 46.7%).

Full analysis of the data, including viral and inflammatory biomarker analyses, baseline risk factors and SoC background therapy stratifications, is expected in the coming weeks. The Company will provide the data for peer review when available.

"We are pleased with these encouraging top-line results from our exploratory Phase 2 study which confirm opaganib's safety and demonstrate promising signals of activity when treating patients with COVID-19 and who require oxygen support. These preliminary results support our ongoing global Phase 2/3 study in severe COVID-19 pneumonia, which is expected to read out in Q1/2021. We continue to work diligently to compile a robust data set to support potential filing of global emergency use applications," **said Mark L. Levitt, MD, Ph.D., Medical Director at RedHill**.

Gilead Raday, RedHill's Chief Operating Officer, added: "Opaganib has a unique dual mode of action that is both anti-inflammatory and antiviral – acting on both the cause and the effects of COVID-19. Opaganib targets sphingosine kinase-2, a human cell component involved in viral replication and not the virus itself. The mounting evidence of new SARS-CoV-2 mutations emerging globally underscores the importance of this unique mechanism, which potentially minimizes the risk of viral resistance to therapy. The trends of patient improvement shown by the preliminary top-line data support the ongoing Phase 2/3 study with opaganib, which will provide a more in-depth understanding of opaganib's activity."

The efficacy of opaganib in severe COVID-19 pneumonia is being further explored in an ongoing global Phase 2/3 study and is expected to report top-line data in the first quarter of 2021. This study (NCT04467840) is being conducted across approximately 30 clinical sites in several countries and is on track to enroll up to 270 patients. The study has undergone two unblinded reviews of safety data by an independent Data and Safety Monitoring Board (DSMB), with unanimous recommendations to continue the study. An interim DSMB futility analysis will be conducted in the coming weeks, evaluating data from the first 135 subjects that have reached the primary endpoint.

The top-line results from the U.S. Phase 2 study of opaganib in patients hospitalized with COVID-19 pneumonia 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 studies.

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 of viral replication, potentially minimizing the likelihood of viral resistance. Opaganib has also shown anticancer activity and has the potential to target multiple oncology, viral, inflammatory, and gastrointestinal indications.

Opaganib 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 is also being evaluated as a treatment for COVID-19 pneumonia in a global Phase 2/3 study and has demonstrated positive safety and efficacy signals in preliminary top-line data from a U.S. Phase 2 study.

Preclinical data have demonstrated both anti-inflammatory and antiviral activities of opaganib, with the potential to ameliorate 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.

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[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 investigational development programs include: (i) **RHB-204**, with an ongoing 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**, 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 includes statements regarding the timing of the reporting of a full analysis of the data from the U.S. Phase 2 trial evaluating opaganib, the timing of potential emergency use applications for opaganib and the timing of reporting of top-line 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 top-line data from the Phase 2/2 study and in receiving data to support emergency use applications or in making such emergency use applications, if at all; the risk that the full analysis of data from the U.S. Phase 2 clinical study evaluating opaganib will be delayed or will differ from the preliminary data; 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 top-line 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. 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.

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