NEWS RELEASE

RedHill's Oral Broad-Acting Antivirals, Opaganib and RHB-107, Inhibit Dominant Omicron Sub-Variant BA.5

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Novel, oral, host-targeted, broad-acting antivirals, once-daily RHB-107 (upamostat) and twice-daily opaganib, demonstrated in vitro inhibition of the COVID-19-causing SARS-Cov-2 Omicron BA.5 sub-variant in testing conducted by University of Tennessee Health Sciences Center

Results add to previous variant-agnostic efficacy data for both investigational drugs against COVID-19 disease and several other viral diseases, highlighting their promising profile as broad acting, host-directed candidate therapies for pandemic preparedness

Development of both opaganib for hospitalized patients and RHB-107 for non-hospitalized patients is ongoing, including ongoing and planned pandemic preparedness research collaborations with US governmental agencies, pivotal Phase 3 trial design and regulatory clearances, and securing of external non-dilutive funding

TEL AVIV, Israel and RALEIGH, N.C., Oct. 3, 2022 /PRNewswire/ -- **RedHill Biopharma Ltd.** (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced study results showing in vitro efficacy against the currently dominant Omicron COVID-19 sub-variant BA.5, by both of RedHill's novel, oral, host-directed and broad-acting investigational antivirals, once-daily RHB-107 (upamostat)[1] and twice-daily opaganib[2]. These results build on previously reported data on the inhibition of COVID-19, variants of concern and other viruses, and further support their broad-acting, host-directed mechanisms of action.

The study was done in collaboration with renowned virologist, **Dr. Colleen B. Jonsson, Harriet Van Vleet Professor of Virology, Director of the Regional Biocontainment Laboratory (RBL), and Director of the Institute for the Study of Host-Pathogen Systems at the University of Tennessee Health Sciences Center (UTHSC), who remarked:** "We tested RHB-107 and opaganib using a primary human nasal epithelial cell culture model of Omicron BA.5, which was specifically selected due to the high level of SARS-CoV-2 entry factor expression in these cells. The results of our work show that both RHB-107 and opaganib inhibit Omicron sub-variant BA.5 viral replication, which is indicative of antiviral activity. Of further interest is the hypothesis that, compared to Delta, Omicron replication is increased as compared to primary epithelial lung cell cultures - hinting at a different possible mechanism of cell entry via membrane fusion and the endocytic pathway. Although we may be potentially dealing with different methods of viral cell entry, these new data suggest that it does not prevent either RHB-107 or opaganib from exerting their viral inhibition capabilities."

"Almost three years after SARS-CoV-2 hit the headlines, we have seen extensive mutation and the emergence of many variants and sub-variants. Consequently, these results, showing viral inhibition of Omicron sub-variant BA.5 by both RHB-107 and opaganib, are especially encouraging. They add to the weight of data in support of their variant-agnostic capabilities, and further support their potential as easily administered, low-pill burden, oral options for treating non-hospitalized and hospitalized patients with COVID-19," **said Reza Fathi, PhD., RedHill's Senior VP, R&D.** "There has been a recent shift in international and governmental policy, research, and funding focus to address the urgent need to develop broad-spectrum antivirals to prevent future viral pandemics. The ideal drugs would likely be broad-acting, with activity against a range of viruses, that target the host-pathways and cellular proteins used by such viruses to infect and replicate. RedHill's two novel, broad-acting, host-directed antivirals, opaganib and RHB-107, have both shown, despite three years of continual viral mutation, encouraging signs of their potential against the COVID-19-causing SARS-CoV-2 variants, as well as there being additional data suggesting their potential against various other viruses including influenza A."

RHB-107 recently reported positive results from the Phase 2 part of Phase 2/3 study in symptomatic non-hospitalized COVID-19, successfully meeting the study's primary endpoint showing good safety and tolerability and highly promising efficacy results including faster recovery from severe COVID-19 symptoms and reduced rates of hospitalization (**NCT04723527**).

Opaganib has previously demonstrated a 70% reduction in mortality in key hospitalized patient sub-populations, as well as improved viral RNA clearance and faster time to recovery, in its Phase 3 study in hospitalized patients with moderate to severe COVID-19 (**NCT04467840**). Opaganib's suggested host-directed mechanism of action was recently described in a manuscript entitled "**Recent Progress in the Development of Opaganib for the Treatment**

of COVID-19" published in the journal **Drug Design, Development and Therapy** in July 2022. The paper outlines opaganib's multi-faceted potential to: inhibit multiple pathways, induce autophagy and apoptosis, and disrupt the viral RTC (replication-transcription complex) through simultaneous inhibition of three sphingolipid-metabolizing enzymes in human cells (SK2, DES1 and GCS). These mechanisms support the hypothesis of broad antiviral effect and attenuation of multi-organ dysfunction in COVID-19 patients. Moreover, because of its host-directed targeting, opaganib is unlikely to encounter viral resistance due to mutation, which may be a problem for direct-acting antivirals.

Late-stage development of both opaganib and RHB-107 is ongoing pending Phase 3 trial design regulatory approvals and securing of external funding.

The ongoing clinical studies with RHB-107 and 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 Opaganib (ABC294640)

Opaganib, a new chemical entity, is a proprietary, first-in-class, orally-administered, investigational sphingosine kinase-2 (SK2) selective inhibitor, with suggested dual anti-inflammatory and antiviral activity. Opaganib is host-targeted and, based on data accumulated to date, is expected to maintain effect against emerging viral variants, having already shown in vitro inhibition against variants of concern, including Omicron and Delta. Opaganib has also shown anticancer activity and positive preclinical results in renal fibrosis, and has the potential to target multiple oncology, viral, inflammatory, and gastrointestinal indications.

In prespecified analyses of Phase 2/3 clinical data, oral opaganib has demonstrated improved viral RNA clearance, faster time to recovery and significant mortality reduction in key patient subpopulations versus placebo on top of standard of care. Data from the opaganib global Phase 2/3 study has been submitted for peer review and recently published in **medRxiv**. Opaganib previously delivered promising U.S. Phase 2 data in patients with moderate to severe COVID-19, published in **Open Forum Infectious Diseases**.

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. Patient accrual, treatment and analysis in the prostate cancer study are ongoing.

Opaganib demonstrated potent antiviral activity against SARS-CoV-2, the virus that causes COVID-19, inhibiting viral replication of the original SARS-CoV-2 and 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 decrease renal fibrosis, have shown decreased fatality rates from influenza virus infection, and amelioration of bacteria-induced

pneumonia lung injury with reduced levels of IL-6 and TNF-alpha in bronchoalveolar lavage fluids.

About RHB-107 (upamostat)

RHB-107 is a proprietary, first-in-class, once-daily orally-administered investigational antiviral, that targets human serine proteases involved in preparing the spike protein for viral entry into target cells. Because it is host-cell targeted, RHB-107 is expected to also be effective against emerging viral variants with mutations in the spike protein.

Top-line results from Part A of the Phase 2/3 study (**NCT04723527**) evaluating treatment with RHB-107 in non-hospitalized patients with symptomatic COVID-19 early in the course of the disease, showed a 100% reduction in hospitalization due to COVID-19, with zero patients (0/41) on the RHB-107 arms versus 15% (3/20) hospitalized on the placebo-controlled arm. The study also showed an approx. 88% reduction in reported new severe COVID-19 symptoms after treatment initiation, with only one patient in the RHB-107 treated group 2.4%, (1/41) versus 20% (4/20) of patients in the placebo-controlled arm. Further analysis showed faster recovery from severe COVID-19 symptoms with a median of 3 days to recovery with upamostat vs. 8 days with placebo.

In addition, RHB-107 inhibits several proteases targeting cancer and inflammatory gastrointestinal disease. RHB-107 has undergone several Phase 1 studies and two Phase 2 studies, demonstrating its clinical safety profile in approximately 200 patients.

RedHill acquired the exclusive worldwide rights to RHB-107, excluding China, Hong Kong, Taiwan and Macao, from Germany's Heidelberg Pharmaceuticals (FSE: HPHA) (formerly WILEX AG) for all indications.

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 hospitalized COVID-19 and Phase 2 studies for prostate cancer and cholangiocarcinoma ongoing; (iii) **RHB-107** (**upamostat**), an oral serine protease inhibitor in a Phase 3-stage study as treatment for non-hospitalized 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; and (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. More information about the Company is available at **www.redhillbio.com**/ **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 RHB-107 and opaganib will not be shown to be broad acting, host-directed candidate therapies for pandemic preparedness, the risk that a pivotal Phase 3 trial for RHB-107 and/or opaganib will not be initiated or that such trial 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 17, 2022. 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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Category: R&D

[1] RHB-107 is an investigational new drug, not available for commercial distribution.

[2] Opaganib is an investigational new drug, not available for commercial distribution.

[3] Movantik® (naloxegol) is indicated for opioid-induced constipation (OIC). Full prescribing information see: **www.movantik.com**

[4] Talicia® (omeprazole magnesium, amoxicillin and rifabutin) is indicated for the treatment of H. pylori infection in adults. For full prescribing information see: **www.Talicia.com** .

[5] Aemcolo® (rifamycin) is indicated for the treatment of travelers' diarrhea caused by noninvasive strains of Escherichia coli in adults. For full prescribing information see: **www.aemcolo.com** .

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