NEWS RELEASE

RedHill's Opaganib Protects Against Radiation-Induced Lung Inflammation and Fibrosis - New Publication

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The data, published in the International Journal of Molecular Sciences, demonstrate that opaganib significantly improved long-term survival in an in vivo model of lung damage following exposure to ionizing radiation

Opaganib is the first selective sphingosine kinase-2 (SPHK2) inhibitor investigational drug targeting sphingolipid metabolism for the treatment of radiation-induced inflammation

Opaganib, a novel oral, small molecule pill with a five-year shelf-life, is easy to administer and distribute, supporting potential central government stockpiling for use as radioprotection therapy in mass casualty radiological or nuclear incidents, if approved by the FDA

Opaganib is being tested as a potential treatment for Acute Radiation Syndrome (ARS) following selection by the U.S government National Institutes of Health's (NIH) Radiation and Nuclear Countermeasures Program (RNCP) for its radiation medical countermeasures Product Development Program

Opaganib is being developed for multiple additional indications, including COVID-19, acute respiratory distress syndrome (ARDS), filoviruses (including Ebola) and oncology

TEL AVIV, Israel and RALEIGH, N.C., Feb. 20, 2024 /PRNewswire/ -- **RedHill Biopharma Ltd.** (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced a new publication of data from multiple experiments in the **International Journal of Molecular Sciences**[1]. The published data shows that opaganib[2] protects against radiation-induced lung inflammation and fibrosis in an in vivo mouse model of lung damage following exposure to ionizing radiation, demonstrating its potential use as a medical countermeasure against nuclear irradiation and in cancer radiotherapy.

Radiation-induced inflammation is known to occur in two phases – in an initial inflammatory response immediately after irradiation and in a delayed response that can occur weeks later. As such, one of the experiments looked specifically at longer-term survival with two treatment windows: 1-3 days post-radiation and 31-45 days post-radiation. The opaganib group treated both during the initial and delayed phases of inflammation demonstrated a highly statistically significant improvement in survival at Day 180 (60% survival compared with 10% for controls, p=0.008). Thus, treating with opaganib during both initial and delayed phases of inflammation provided the greatest improvement in survival.

"The data, when looked at collectively across multiple experiments, demonstrate that opaganib significantly improved long-term survival associated with reduced lung fibrosis, suppression of granulocyte infiltration, and reduced expression of IL-6 and TNFα in an in vivo model of lung damage following exposure to ionizing radiation," **said Dr. Lynn W. Maines, lead author of the publication and VP of Research at Apogee Biotechnology Corporation, RedHill's development partner for opaganib**. "These data further demonstrate that sphingolipid metabolism is a critical regulator of fibrogenesis, and specifically show that opaganib suppresses radiation-induced pulmonary inflammation and fibrosis."

Opaganib is being tested as a potential treatment for Acute Radiation Syndrome (ARS), following selection by the U.S government National Institutes of Health's (NIH) Radiation and Nuclear Countermeasures Program (RNCP) for its radiation medical countermeasures Product Development Program. Opaganib was also recently selected for inclusion into the BARDA/NIH Chemical Countermeasures screening program for Sulfur Mustard exposure. Opaganib, a novel, oral, small molecule pill with a five-year shelf-life, is easy to administer and distribute, supporting potential central government stockpiling for use as a medical countermeasure in the event of mass casualty nuclear radiation incidents or Sulfur Mustard attack, if approved by the U.S. Food and Drug Administration (FDA).

About Lung Inflammation, Fibrosis and Acute Radiation Syndrome (ARS)

ARS, sometimes known as radiation toxicity or radiation sickness, is generally rare; however, public health emergencies, such as a nuclear power plant accident or detonation of a nuclear device, could affect large numbers of people. ARS is an acute illness caused by irradiation of the body by a high dose of penetrating radiation in a short

period of time. Much of the damage caused by ARS is caused by inflammation secondary to the direct effects of ionizing radiation itself. The inflammation can occur throughout the body, but specifically, inflammation in the lungs can cause the tissue around the air sacs of the lungs (alveoli) to become damaged, thickened, and scarred – this is known as pulmonary fibrosis. As the lungs scar and stiffen, breathing becomes more difficult, and the amount of oxygen entering the blood system becomes reduced.

Current treatments for ARS are supportive care, including blood transfusions, antibiotics, etc., as well as the availability of four approved products (three growth factors to address neutropenia and one to mitigate thrombocytopenia*). However, other radiation-induced clinical manifestations that have been observed in natural history studies and remain unaddressed with the current treatments include GI-ARS, cutaneous injury, and late effects in the lung, heart, and kidneys. Opaganib, an SPHK2 inhibitor, may offer a new therapeutic approach to mitigate both hematopoietic-ARS and GI-ARS. It has also been reported in the literature that inhibition of SPHK2 promotes the viability and robustness of hematopoietic stem cells, even in the face of radiation damage, supporting increased survival.

* The agents are filgrastim, PEGylated filgrastim and romiplostim (Neupogen®, Neulasta® and Nplate®, all Amgen Inc., NasdaqGS: **AMGN**), sargramostim (Leukine®, **Partner Therapeutics Inc**.).

About Opaganib (ABC294640)

Opaganib, a proprietary investigational host-directed and potentially broad-acting drug, is a first-in-class, orally administered sphingosine kinase-2 (SPHK2) selective inhibitor with anticancer, anti-inflammatory and antiviral activity, targeting multiple potential diseases, including gastrointestinal acute radiation syndrome (GI-ARS), COVID-19, other viruses as part of pandemic preparedness, and cholangiocarcinoma (bile duct cancer).

Opaganib's host-directed action is thought to work through the inhibition of multiple pathways, the induction of autophagy and apoptosis, and disruption of viral replication, through simultaneous inhibition of three sphingolipid-metabolizing enzymes in human cells (SPHK2, DES1 and GCS).

Opaganib was selected by the U.S. government's Radiation and Nuclear Countermeasures Program (RNCP), led by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, for the nuclear medical countermeasures product development pipeline as a potential treatment for Acute Radiation Syndrome (ARS).

Opaganib has demonstrated antiviral activity against SARS-CoV-2, multiple variants, and several other viruses, such as Influenza A. Opaganib also recently demonstrated a distinct synergistic effect when combined individually with remdesivir (Veklury®, Gilead Sciences Inc., Nasdaq: **GILD**), significantly improving potency while maintaining cell

viability, in a U.S. Army-funded and conducted in vitro Ebola virus study.

Being host-targeted, and based on data accumulated to date, opaganib is expected to maintain effect against emerging viral variants. In prespecified analyses of Phase 2/3 clinical data in hospitalized patients with moderate to severe COVID-19, oral opaganib 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. Opaganib has demonstrated its safety and tolerability profile in more than 470 people in multiple clinical studies and expanded access use. Data from the opaganib global Phase 2/3 study was published in **medRxiv**.

Opaganib has received Orphan Drug designation from the FDA for the treatment of cholangiocarcinoma and has undergone studies in advanced cholangiocarcinoma (Phase 2a) and prostate cancer. Opaganib also has a Phase 1 chemoradiotherapy study protocol ready for FDA-IND submission.

Opaganib has also shown positive preclinical results in renal fibrosis, and has the potential to target multiple oncology, radioprotection, viral, inflammatory, and gastrointestinal 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 **Talicia®**, for the treatment of Helicobacter pylori (H. pylori) infection in adults[3], and **Aemcolo®**, for the treatment of travelers' diarrhea in adults[4]. RedHill's key clinical late-stage development programs include: (i) **opaganib (ABC294640)**, a first-in-class oral broad-acting, host-directed SPHK2 selective inhibitor with potential for pandemic preparedness, targeting multiple indications with a U.S. government collaboration for development for Acute Radiation Syndrome (ARS), a Phase 2/3 program for hospitalized COVID-19, and a Phase 2 program in oncology; (ii) **RHB-107** (**upamostat**), an oral broad-acting, host-directed, serine protease inhibitor with potential for pandemic preparedness is in late-stage development as a treatment for non-hospitalized symptomatic COVID-19, with non-dilutive external funding covering the entirety of the RHB-107 arm of the 300-patient Phase 2 adaptive platform trial, and is also targeting multiple other cancer and inflammatory gastrointestinal diseases; (iii) **RHB-102**, with potential UK submission for chemotherapy and radiotherapy induced nausea and vomiting, positive results from a Phase 3 study for acute gastroenteritis and gastritis and positive results from a Phase 2 study for IBS-D; (iv) **RHB-104**, with positive results from a first Phase 3 study for Crohn's disease; and (v) **RHB-204**, a Phase 3-stage program for pulmonary nontuberculous mycobacteria (NTM) disease.

RedHill is open to opportunities to acquire revenue generating assets in various indications, aligned to our strategic direction. Trading in RedHill's shares, ADSs and Warrants is regulated by the Securities and Exchange Commission (SEC), and the Company is committed to work in compliance with all relevant SEC and FDA regulations and

requirements.

More information about the Company is available at **www.redhillbio.com** / **twitter.com/RedHillBio**.

Forward Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 and may discuss investment opportunities, stock analysis, financial performance, investor relations, and market trends. Such statements, including, but not limited to, statements regarding the intended use of net proceeds from the offering, 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 risk that the Company will not comply with the listing requirements of the Nasdaq Capital Market ("Nasdaq") to remain listed for trading on Nasdaq, the addition of new revenue generating products, out-licensing of the Company's development pipeline assets, timing of opaganib's development for Acute Radiation Syndrome, non-dilutive development funding from RHB-107 and its inclusion in a key platform study. 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, market and other conditions, the risk that the addition of new revenue generating products or out-licensing transactions will not occur; the risk that acceptance onto the RNCP Product Development Pipeline will not guarantee ongoing development or that any such development will not be completed or successful; the risk that the FDA does not agree with the Company's proposed development plans for opaganib for any indication, the risk that observations from preclinical studies are not indicative or predictive of results in clinical trials; the risk that the FDA pre-study requirements will not be met and/or that the Phase 3 study of RHB-107 in COVID-19 outpatients will not be approved to commence or if approved, will not be completed or, should that be the case, that we will not be successful in obtaining alternative non-dilutive development funding for RHB-107, the risk that HB-107's late-stage development for non-hospitalized COVID-19 will not benefit from the resources redirected from the terminated RHB-204 Phase 3 study, that the Phase 2/3 COVID-19 study for RHB-107 may not be successful and, even if successful, such studies and results may not be sufficient for regulatory applications, including emergency use or marketing applications, and that additional COVID-19 studies for opaganib and RHB-107 are likely to be required, as well as risks and uncertainties associated with the risk that the Company will not successfully commercialize its products; as well as risks and uncertainties associated with (i) the initiation, timing, progress and results of the Company's research, manufacturing, pre-clinical 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 pre-clinical studies or clinical

trials or the development of a commercial companion diagnostic for the detection of MAP; (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 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 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, pre-clinical 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 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 experiences using investigative drugs under the Company's Expanded Access Program; (xiv) competition from other companies and technologies within the Company's industry; and (xv) the hiring and employment commencement date of executive managers. 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 April 28, 2023. 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: Financials

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[1] Maines LW, Keller SN, Smith RA, Green CL, Smith CD. The Sphingolipid-Modulating Drug Opaganib Protects

against Radiation-Induced Lung Inflammation and Fibrosis: Potential Uses as a Medical Countermeasure and in Cancer Radiotherapy. International Journal of Molecular Sciences. 2024; 25(4):2322. **https://doi.org/10.3390/ijms25042322**

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

[3] 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**.

[4] 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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