NEWS RELEASE

RedHill Biopharma's Positive Opaganib Results Indicate Reduction in Venetoclax Resistant Cells

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Resistance to venetoclax (Venclexta® and Venclyxto®, Abbvie / Genentech), the $2.5 billion blockbuster Chronic Lymphocytic Leukemia (CLL) therapy, is emerging as a therapeutic challenge, with leukemic cells persisting over time, even with combination therapy[1]

Studies show that sphingosine kinase 2 (SPHK2) is overexpressed in venetoclax-resistant cancer cells and that SPHK2 inhibition may reduce T-cell-induced activation and proliferation of venetoclax-resistant CLL cancer cells and resensitize previously resistant CLL cells[2,3]

New in vivo study shows adding opaganib, a potent SPHK2 inhibitor, to venetoclax reduces CLL cell ($CD19^+$, $CD5^+$) counts by 50% compared to controls and lowered $CD3^+$, $CD4^+$ and $CD8^+$ T cell counts compared to controls with lowered PD1 expression ($CD8^+$)[4]

Data shows opaganib's venetoclax combination potential in CLL; builds on multiple preclinical studies demonstrating opaganib's therapeutic add-on potential in oncology; further clinical evaluation ongoing in a Phase 2 study of opaganib + darolutamide in advanced prostate cancer

Opaganib has a safety and tolerability profile shown in more than 470 clinical trials / expanded access participants. It targets multiple oncology, virology, inflammation, diabetes and obesity indications, with several U.S. government partnerships, including BARDA funding, in place

TEL-AVIV, Israel and RALEIGH, N.C., Dec. 15, 2025 /PRNewswire/ -- RedHill Biopharma Ltd. (NASDAQ: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced positive in vivo results, indicating that opaganib combined with venetoclax reduces Chronic Lymphocytic Leukemia (CLL) cells by half compared to controls, and further demonstrates opaganib's potential as an add-on therapy to venetoclax in venetoclax-resistant CLL.

"Understanding mechanisms of resistance to targeted therapies such as the BCL-2 inhibitor venetoclax is essential to improve current treatment strategies and may provide key insights to personalize treatment for chronic lymphocytic leukemia (CLL) patients," **said Romina Gamberale, PhD, Independent Researcher at CONICET from the Institute of Experimental Medicine (IMEX, CONICET-National Academy of Medicine) in Buenos Aires, Argentina, who led the study.** "Our previous ex vivo work has shown that sphingosine kinase 2 (SPHK2) is overexpressed in venetoclax-resistant CLL cells and that inhibiting SPHK2 may reduce T-cell-induced resistance and resensitize previously resistant cells. The results of this in vivo study in mice indicate that adding opaganib, a potent SPHK2 inhibitor, to venetoclax reduced CLL cell counts by 50% compared to controls, showing that opaganib may have a significant role to play in mitigating BCL-2 inhibitor resistance."

Dr. Mark Levitt, Chief Scientific Officer at RedHill, said: "Venetoclax is a key CLL therapy and finding ways to maintain its effectiveness, and to reduce the potential for resistance-related treatment failure, could represent a breakthrough in the ability to treat CLL patients. This promising data supports the hypothesis that opaganib, as a potent inhibitor of SPHK2, provides a potential route to maintaining venetoclax effects in treating CLL. Opaganib has shown potential as add-on therapy in several preclinical oncology models and is currently undergoing a Phase 2 clinical trial in combination with darolutamide in advanced prostate cancer. This new data now adds CLL to the list of potential cancer indications where opaganib has shown potential to bring additive therapeutic value."

Opaganib has a safety and tolerability profile shown in more than 470 clinical trials / expanded access participants. It targets multiple oncology, virology, inflammation, medical countermeasures, diabetes and obesity indications, with several U.S. government partnerships, including BARDA funding, in place.

Approved by the FDA in 2016, venetoclax (Venclexta® and Venclyxto®, Abbvie / Genentech), is a first-in-class BCL-2 inhibitor that has become a mainstay of CLL therapy, achieving sales of approximately $2.5 billion in 2024. Venetoclax works by blocking a protein called BCL-2, which is often overproduced in certain cancer cells and prevents the process of apoptosis (programmed cell death) – helping to keep the cancer cells alive and growing. By binding to, and inhibiting, the BCL-2 protein, venetoclax enables the cancer cells to undergo apoptosis and die.

About Chronic Lymphocytic Leukemia (CLL)

CLL is a slow-growing blood and bone marrow cancer that affects a type of white blood cell called lymphocytes. It is the most common type of leukemia in adults and has a highly variable clinical course. It is generally not considered to be curable.

About Opaganib (ABC294640)

Opaganib is a first-in-class, proprietary investigational host-directed and potentially broad-acting orally administered drug with anticancer, anti-inflammatory and antiviral activity. Opaganib is targeted at multiple potential oncology, radioprotection, viral, inflammatory, and gastrointestinal indications, including several cancers, diabetes and obesity-related disorders, gastrointestinal acute radiation syndrome (GI-ARS), COVID-19, Ebola and other viruses as part of pandemic preparedness. Opaganib has also shown positive preclinical results in renal fibrosis.

Opaganib has received orphan-drug designations from the FDA in cholangiocarcinoma and neuroblastoma. It is currently undergoing a Phase 2 clinical trial in combination with darolutamide in advanced prostate cancer and has previously undergone studies in advanced cholangiocarcinoma (Phase 2a). Opaganib also has a Phase 1 chemoradiotherapy study protocol ready for FDA-IND submission.

Opaganib 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).

Several U.S. government medical countermeasures and pandemic preparedness programs have selected opaganib for evaluation for multiple indications, including GI-ARS, Ebola virus disease and others. Funding bodies include the Radiation and Nuclear Countermeasures Program (RNCP), led by the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. government Department of Health & Human Services' National Institutes of Health, and the Administration for Strategic Preparedness and Response's (ASPR) Center for Biomedical Advanced Research and Development Authority (BARDA).

Opaganib has demonstrated antiviral activity against SARS-CoV-2, multiple variants, and several other viruses, such as Influenza A and Ebola. Opaganib delivered a statistically significant increase in survival time when given at 150 mg/kg twice a day (BID) in a United States Army Medical Research Institute of Infectious Diseases (USAMRIID) in vivo Ebola virus study, making it the first host-directed molecule to show activity in Ebola virus disease. Opaganib also recently demonstrated a distinct synergistic effect when combined individually with remdesivir (Veklury®, Gilead Sciences Inc.), 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 **Microorganisms**.

About RedHill Biopharma

RedHill Biopharma Ltd. (Nasdaq: RDHL) is a specialty biopharmaceutical company primarily focused on U.S. development and commercialization of drugs for gastrointestinal diseases, infectious diseases and oncology. RedHill promotes the FDA-approved gastrointestinal drug **Talicia®,** for the treatment of Helicobacter pylori (H. pylori) infection in adults[5], with a recent co-commercialization agreement in the U.S. with Cumberland Pharmaceuticals. RedHill's key clinical late-stage development programs include: (i) **opaganib (ABC294640)**, a first-in-class, orally administered sphingosine kinase-2 (SPHK2) selective inhibitor with anti-inflammatory, antiviral, and anticancer activity, targeting multiple indications with U.S. government and academic collaborations for development for medical countermeasures including radiation and chemical exposure indications such as GI-Acute Radiation Syndrome (GI-ARS), a Phase 2/3 program for hospitalized COVID-19, and a Phase 2 study in prostate cancer in combination with darolutamide; (ii) **RHB-204**, a next-generation optimized formulation of RHB-104, with a planned Phase 2 study for Crohn's disease (based on RHB-104's positive Phase 3 Crohn's disease study results) and Phase 3-stage for pulmonary nontuberculous mycobacteria (NTM) disease; (iii) **RHB-102**, with positive results from a U.S. Phase 3 study for acute gastroenteritis and gastritis, positive results from a U.S. Phase 2 study for IBS-D and potential UK submission for chemotherapy and radiotherapy induced nausea and vomiting. RHB-102 is partnered with Hyloris Pharma (EBR: HYL) for worldwide development and commercialization outside North America; and (iv) **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 and is also targeting multiple other cancer and inflammatory gastrointestinal diseases.

More information about the Company is available at **www.redhillbio.com** / **X.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 may be preceded by the words "intends," "may," "will," "plans," "expects," "anticipates," "projects," "predicts," "estimates," "aims," "believes," "hopes," "potential" or similar words, and include, among others, statements regarding the potential impact of Talicia. 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 opaganib may not replicate its potential to mitigate resistance in CLL therapy; the risk that the strategic transaction with Cumberland will not bring the currently anticipated benefits to RedHill's global Talicia business or to RedHill's financial position, costs or its broader strategic objectives; the risk regarding the Company's ability to maintain compliance with Nasdaq's listing requirements, including the minimum stockholders' equity requirement; the risk that the addition of new revenue generating products or out-licensing transactions will not occur; the risk of current uncertainty regarding U.S. government research and development funding and that the U.S. government is under no obligation to continue to support development of our products and can cease such support at any time; the risk that acceptance onto the RNCP Product Development Pipeline or other governmental and non-governmental development programs 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 its programs; the risk that the Company's development programs and studies 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 studies may be required; 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 any necessary commercial companion diagnostics; (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®; (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 10, 2025. 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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[4] Unpublished results - data on file

[5] 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**.

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