NEWS RELEASE

RedHill Biopharma Announces Recruitment Initiated into Expanded Phase 2 Opaganib/Darolutamide Combination Study in Advanced Prostate Cancer

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Recruitment initiated into the Phase 2 opaganib plus darolutamide study in patients with advanced prostate cancer, sponsored by ANZUP, and supported by Bayer and Ramsay Hospital Research Foundation

Precision medicine approach: The 60-patient Phase 2 study uses the PCPro™ lipid biomarker test to identify patients with poor prognosis most likely to benefit from the combination

Led by Professor Lisa Horvath, the study is expected to recruit people at sites across Australia and New Zealand

Prostate cancer is the second most diagnosed cancer in the world with around 1.5 million new cases per year, causing almost 400,000 deaths[1]. Prostate cancer market is approximately $12 billion[2]

This study marks a key step in RedHill's development of opaganib in oncology, complementing its U.S. Government-supported medical countermeasures and infectious diseases programs

TEL AVIV, Israel and RALEIGH, N.C., July 1, 2025 /PRNewswire/ -- RedHill Biopharma Ltd. (NASDAQ: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced the initiation of patient recruitment into the Phase 2 study evaluating the efficacy of opaganib[3] in combination with darolutamide[4] in men with

metastatic castrate-resistant prostate cancer (mCRPC), sponsored by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group Ltd. (ANZUP) in Australia, and supported by Bayer (ETR: BAYN) and Ramsay Hospital Research Foundation. The Company also announced the study will recruit people across at least 10 sites across Australia and New Zealand.

Led by Professor Lisa Horvath, from Sydney's Chris O'Brien Lifehouse, and ANZUP, the innovative 60-participant placebo-controlled randomized study is designed to test the potentially enhancing effect of opaganib in overcoming resistance to standard of care androgen receptor pathway inhibition (ARPI) treatment.

The unique study will utilize a companion lipid biomarker test (PCPro[5]) to select mCRPC patients who have poor prognosis to standard of care treatment, and who may benefit from an opaganib + darolutamide combination approach to treatment. The study's primary endpoint is improved 12-month radiographic progression-free survival (rPFS). Several secondary and exploratory endpoints will also be evaluated.

Cancer cells can block apoptosis (programmed cell death), an important cell-level process designed to help the body get rid of unneeded or abnormal/unhealthy cells, which are critical in fighting the spread of cancer. Prior research shows that opaganib enhances androgen receptor signaling inhibitor efficacy in vitro[6], through simultaneous inhibition of three sphingolipid-metabolizing enzymes in human cells (SPHK2, DES1 and GCS), and may potentially provide the key to overcoming darolutamide resistance in men with mCRPC.

Prostate cancer is the second most diagnosed cancer in the world with around 1.5 million new cases per year, causing almost 400,000 deaths every year, while millions more people are living with prostate cancer resulting in a significant burden of disease.[7] The global prostate cancer market was worth approximately $12 billion in 2023.[8]

About the Study

The study is a double-blind, placebo-controlled randomized Phase 2 trial, adding opaganib to darolutamide in people with mCRPC and poor prognosis (as defined by plasma lipid signature, PCPro). The target population of the study is people with mCRPC who have had no treatment with newer, potent AR signaling inhibitors including darolutamide, enzalutamide, apalutamide, or abiraterone. 200 people with prostate cancer who are identified as potentially eligible will have a 5-ml plasma sample taken for PCPro testing. Those who are PCPro-positive (estimated 40% of patients) and agree to enter the study will be randomized on a 1:1 ratio to either the darolutamide 600mg bid + placebo (n=30) arm or the darolutamide 600 mg bid + opaganib 500 mg bid (n=30) arm. The study is registered on **clinicaltrials.gov** (NCT04207255).

About Prostate Cancer

Prostate cancer is the second most diagnosed cancer in the world with around 1.5 million new cases annually – causing around 400,000 deaths, with millions more people living with prostate cancer, resulting in a significant burden of disease. Globally, the number of cases of prostate cancer increased by almost 120% from 1990 to 2019[9].

When prostate cancer spreads outside of the prostate to other parts of the body (such as the lymph nodes or bones) it is classified as advanced or metastatic prostate cancer[10]. Five-year survival rates for prostate cancer diagnosed at Stage 1 is 100%; this drops to just 28% for people with Stage 4 (advanced) disease[11].

About Androgen Receptor Pathway Inhibitors (ARPI)

ARPI is a key therapeutic strategy in treating prostate cancer, particularly castration-resistant prostate cancer. These treatments work by blocking the activity of male hormones such as testosterone (androgens), which are implicated in the growth of prostate cancer cells. By disrupting the AR signaling pathway, these therapies aim to slow tumor progression and improve patient outcomes. Key therapeutic options include darolutamide, enzalutamide, (Xtandi®, Pfizer / Astellas) and apalutamide (Erleada®, Johnson and Johnson).

About Opaganib (ABC294640)

Opaganib, a first-of-its-kind proprietary investigational host-directed and potentially broad-acting orally administered drug with anticancer, anti-inflammatory and antiviral activity, targeting multiple potential indications, including several cancers, diabetes and obesity-related disorders, gastrointestinal acute radiation syndrome (GI-ARS), chemical exposure indications, COVID-19, Ebola and other viruses as part of pandemic preparedness.

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).

Several U.S. government countermeasures and pandemic preparedness programs have selected opaganib for evaluation for multiple indications, including Acute Radiation Syndrome (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**.

Opaganib has received several orphan-drug designations from the FDA in oncology and other diseases 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 ANZUP

ANZUP is the leading cancer-cooperative clinical trials group that brings together all of the professional disciplines and groups involved in researching and treating urogenital cancers and conduct high quality cancer research. ANZUP's mission is to improve the lives of people affected by bladder, kidney, testicular, penile and prostate cancers towards our vision of living life without fear of cancer. ANZUP identifies gaps in evidence and areas of clinical need, collaborates with the best clinicians and researchers in genitourinary cancer and communicates frequently and effectively with the broader community along the way. ANZUP receives valuable infrastructure support from the Australian Government through Cancer Australia.

About Chris O'Brien Lifehouse and Ramsay Hospital Research Foundation

Chris O'Brien Lifehouse is a world-class not-for-profit, comprehensive cancer hospital based in Sydney, Australia. From screening to prevention, diagnosis, treatment and wellness, Chris O'Brien Lifehouse treats all types of cancer, specializing in those that are complex and rare, offering patients every service and therapy they need under one roof.

Ramsay Hospital Research Foundation was established in 2017 to enhance healthcare delivery and improve patient

outcomes in Australia, guided by a mission to provide better outcomes for its patients, to investigate the diseases and illnesses which affect them and to progress the learning and development of those who care for them.

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[12]. 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 anticancer, anti-inflammatory and antiviral activity, targeting multiple indications with U.S. government and academic collaborations for development for 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-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; and (iv) **RHB-102**, with potential UK submission for chemotherapy and radiotherapy induced nausea and vomiting, positive results from a U.S. Phase 3 study for acute gastroenteritis and gastritis and positive results from a U.S. Phase 2 study for IBS-D. RHB-102 is partnered with Hyloris Pharma (EBR: HYL) for worldwide development and commercialization outside North America.

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. 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 Company's ability to regain and maintain compliance with the Nasdaq Capital Market's listing requirements; 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 of market and other conditions and 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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[1] Bray et al: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. **https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21834**

[2] Global market data provided by GlobalData

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

[4] Darolutamide (Nubeqa®) tablets [**Prescribing Information**]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, October 2023.

[5] PCPro is a proprietary lipid biomarker assay from Chris O'Brien Lifehouse, a not-for-profit comprehensive cancer hospital

[6] ANZUP – Data on File

[7] Bray et al: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. **https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21834**

[8] Market data provided by GlobalData

[9] Weiyu Zhang et al: Global Burden of Prostate Cancer and Association with Socioeconomic Status, 1990–2019: A Systematic Analysis from the Global Burden of Disease Study. **J Epidemiol Glob Health.** 13: 407–421 (2023).

[10] Cancer Council NSW. Advanced Prostate Cancer. 2023

[11] **https://www.hopkinsmedicine.org/health/conditions-and-diseases/prostate-cancer/prostate-cancer-prognosis#:~:text=Stage%20IV%20Prostate%20Cancer%20Prognosis,regional%20cancers%20of%20the%20prostate**.

[12] 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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