NEWS RELEASE

RedHill Biopharma Advances its Groundbreaking Late-Stage Crohn's Disease Program Building on Statistically Significant Positive RHB-104 Phase 3 Results

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The planned innovative Phase 2 study of RHB-204[1] will be the first ever clinical study in Crohn's Disease (CD) patients who are all MAP-positive, and will correlate mucosal healing with MAP[2] infection eradication utilizing novel endpoints and imaging, pending Type C discussions on path to FDA approval, with FDA guidance expected in Q2/25

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Patent protected until 2041, RHB-204 is a next generation anti-MAP therapy derivative of RHB-104[3] which successfully met its groundbreaking Phase 3 study primary and secondary endpoints demonstrating a statistically significant 64% improvement in efficacy versus SoC and showed compelling mucosal healing data in CD patients who underwent colonoscopy. The inclusion of MAP-positive only patients in the planned study with RHB-204 is anticipated to demonstrate a more consistent benefit in the study population across all efficacy outcomes

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Based on insights from RHB-104's statistically significant positive Phase 3 study results, the improved formulation RHB-204 is designed to reduce pill burden and further enhance tolerability, safety and adherence, and along with

the uniquely defined patient population (MAP-positive), allows for a study design with a small sample size and decisive endpoints, entailing lower study costs and expedited timeframe

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The role of MAP as a cause of CD, to be tested in this study, supports a paradigm-shifting new therapeutic approach for CD – focused on addressing the actual cause of the disease, not the symptoms

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The multibillion-dollar Crohn's disease market is expected to expand significantly, with sales in the key markets growing from $13.6 billion in 2024 to over $19 billion in 2033, presenting significant commercial potential for a new FDA approved therapy

RALEIGH, N.C. and TEL-AVIV, Israel, March 12, 2025 /PRNewswire/ -- **RedHill Biopharma Ltd.** (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced plans to advance its groundbreaking late-stage program for Crohn's disease (CD) with initiation of an innovative Phase 2 study of RHB-204 in Mycobacterium avium subspecies paratuberculosis-positive (MAP+) moderate to severe CD, utilizing novel endpoints and the new gold standard in imaging techniques, pending Type C discussions on path to FDA approval with guidance from FDA anticipated next quarter.

Patent protected until 2041, and with an expected pediatric orphan designation (subject to FDA approval to transfer from RHB-104), RHB-204, is a novel next generation improved formulation of Phase 3-stage RHB-104, designed to support enhanced tolerability, safety and adherence, with a 40% pill burden reduction, and thus potential better outcomes. In its groundbreaking positive Phase 3 study which met primary and secondary endpoints, RHB-104 demonstrated a 64% increase in efficacy versus SoC, superior remission as early as week 16, improving further at week 26 and continuing through week 52, and also showed compelling mucosal healing data in those patients who underwent colonoscopy.

The Phase 2 study is expected to have primary endpoints of mucosal healing (considered a new gold standard in efficacy evaluation in Crohn's disease), MAP status and clinical remission, per FDA guidance following the positive Phase 3 CD study results with RHB-104. The RHB-204 study will be the first ever clinical trial in CD patients who are all MAP-positive, and will correlate mucosal healing with MAP eradication.

Based on the successful RHB-104 Phase 3 study insights and specified endpoints, it is expected that the RHB-204 study could be efficiently conducted with a clearly defined and relatively small patient population, precise and decisive endpoints, and an expedited timeframe (with early efficacy indications potentially at just 16 weeks),

reducing substantially the anticipated program costs. Clinical study material has already been manufactured and is in place ready for study implementation.

The CD market is expected to expand significantly over the 2024–2033 forecast period, with sales in the United States, Japan, and five major European markets, growing from $13.6 billion to $19.1 billion at a compound annual growth rate (CAGR) of 3.87%[4]. With significant numbers of treatment failures and approximately 1.6 million diagnosed prevalent cases of CD diagnosed globally last year[4], there is a strong need for effective new CD therapies. Where applicable, the Company intends to explore the potential for additional regulatory process designations, such as breakthrough therapy designation and fast track designations that may provide additional exclusivity or potential for priority review vouchers, where applicable.

Dr. David Y. Graham, Professor of Medicine and Molecular Virology and Microbiology at Baylor College of Medicine, said: "Up to 40% of patients fail to respond to anti-TNF treatment, and over time up to 50% of responders lose response and have disease flare-ups. In addition to the unmet medical need for alternative therapeutic approaches, most of the existing drugs for CD are both expensive and are intravenously administered, further adding to the treatment cost burden. Moreover, several of these existing therapies have known safety issues, including Black Box Warnings, so we believe a safe and effective orally administered therapy would be a very convenient and welcome addition. Based on the safety and efficacy data with concomitant anti-TNFs, immunomodulators and steroids demonstrated in RedHill's initial RHB-104 Phase 3 U.S. study, the development of RHB-204 may provide an expedited route to a safe, oral, stand-alone or combination therapy."

"Advances in diagnostic technology have led to increasingly higher identification of MAP in Crohn's diseases patients[5]," **said Gilead Raday, Chief Operating Officer and Head of R&D at RedHill**. "Utilizing gold standard imaging technology to provide clear and unambiguous efficacy results, the study is designed to include only MAP positive CD patients and is expected to increase the study's power, potentially allowing to demonstrate the benefits of RHB-204 anti-MAP therapy in a relatively small sample size, over and above the promising efficacy observed in the positive Phase 3 study results of RHB-104's in all-comer CD patients. RedHill is actively pursuing partnering and collaborations for this program, including ongoing discussions with non-dilutive external funding sources, which may pave the way to a much-needed new therapeutic modality for CD, focused on addressing a suspected cause of the disease, as opposed to just its symptoms."

The randomized, double-blind, placebo-controlled 331-patient Phase 3 study of RHB-104 in active Crohn's disease met its primary and secondary endpoints, showing RHB-104 standard of care (SoC) to be 64% more effective than SoC alone, was published in the peer-reviewed journal, **Antibiotics**[6]. In the global study, conducted across 92 sites, a total of 166 patients were randomized to receive RHB-104 plus SoC and 165 to placebo plus SoC. Data for the primary endpoint, clinical remission at week 26, shows, with high statistical significance, that 36.7% (61/166) of RHB-

104 patients achieved clinical remission at week 26 vs. 22.4% (37/165) of placebo patients (p = 0.0048). In the secondary endpoint of mucosal healing, endoscopy was performed in a group of 35 patients who volunteered to undergo colonoscopy, with results showing meaningful improvement in endoscopic healing (Simple Endoscopic Score for Crohn's Disease (SES-CD)) at week 26 (statistically significant at 25% decrease with similar trend at 50% decrease), despite the small sample size. Further corroborating these results was the statistically significantly marked and continuous decline of inflammatory marker, fecal calprotectin (FCP) - an accepted surrogate for mucosal healing - in the RHB-104 active arm from baseline through week 52 in patients with high calprotectin at baseline. RHB-104 was found to be generally safe and well tolerated, with adverse event reporting similar to placebo. Full results are available in the publication.

About Crohn's Disease:

Crohn's disease (CD) is a form of Inflammatory Bowel Disease (IBD) causing inflammation of digestive tract tissue that can lead to abdominal pain, severe diarrhea, fatigue, weight loss and malnutrition. CD can be highly debilitating and remains a serious burden for both patients and healthcare systems: destroying quality of life and even leading to life-threatening complications. There is no known cure for Crohn's disease. According to the Cleveland Clinic, experts estimate that more than three-quarters of a million Americans and approximately 6-8 million people globally have Crohn's disease

Commonly used FDA approved therapies in the treatment of CD include: Abbvie's Humira® (adalimumab), Janssen's Remicade® (infliximab) and Stelara® (Ustekinumab), BMS's Zeposia® (ozanimod) and Pfizer's Xeljanz® (tofacitinib).

About RHB-204

RHB-204 is a proprietary, fixed-dose oral capsule containing a combination of clarithromycin, rifabutin and clofazimine, at specific doses designed to safely and effectively treat MAP+-related Crohn's disease.

Patent protected until at least 2041, and with an expected pediatric orphan designation (subject to FDA approval to transfer from RHB-104), RHB-204 is a next-generation formulation of RHB-104 with an optimized formulation for the treatment of CD. It contains the same three antimicrobial agents with potent intracellular, anti-mycobacterial and anti-inflammatory properties, and with an optimized dosing profile, RHB-204 provides the potential for enhanced tolerability, safety and compliance with a 40% pill burden reduction. RHB-204 is supported by a strong foundation of clinical data from the positive safety and efficacy results achieved in the Phase 3 study of RHB-104 in CD, with its potential further demonstrated using mucosal healing imaging, considered to be the gold standard for efficacy evaluation in CD.

Originally developed for the treatment of pulmonary NTM disease caused by MAC, RHB-204 was granted FDA Fast Track and Orphan Drug Designation, in addition to QIDP Designation under the Generating Antibiotic Incentives Now Act (GAIN Act), extending U.S. post-approval U.S. market exclusivity to a potential total of 12 years. RHB-204

has additionally been granted EU Orphan Designation, providing eligibility for 10 years EU post-approval market exclusivity. RedHill has protection for RHB-204, and its use in treating pulmonary MAC disease, until 2041.

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[7]. RedHill's key clinical late-stage development programs include: (i) **RHB-204** with a planned Phase 2 study for Crohn's disease and Phase 3-stage for pulmonary nontuberculous mycobacteria (NTM) disease; (ii) **RHB-104**, with positive results from a first Phase 3 study for Crohn's disease; (iii) **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 program study in prostate cancer in combination with Bayer's darolutamide; (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; and (v) **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. 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 and include, among others, statements regarding the potential development of RHB-204 for Crohn's disease. 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 development of RHB-204 for Crohn's disease may not be completed and if completed may not be successful; the risk that the Company will not benefit from its agreement with Hyloris as currently anticipated; the Company's ability to 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 observations from preclinical studies are not indicative or predictive of results in clinical trials; 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 8, 2024. 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-204 is an investigational new drug, not available for commercial distribution in the United States.
[2] Mycobacterium avium subspecies paratuberculosis
[3] RHB-104 is an investigational new drug, not available for commercial distribution in the United States.
[4] DataMonitor - Disease Analysis: Crohn's Disease, September 2024
[5] Bull, J Clin Microbiol, 2003 and Shafran, Dig Dis Sci, 2002
[6] Graham DY, et al. Randomized, Double-Blind, Placebo-Controlled Study of Anti-Mycobacterial Therapy (RHB-104) in Active Crohn's Disease. Antibiotics (Basel). 2024 Jul 25;13(8):694. doi: 10.3390/antibiotics13080694. PMID: 39199994; PMCID: PMC11350828.
[7] 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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