NEWS RELEASE

RedHill Biopharma: Concerning Rates of Clarithromycin Prescribing for H. pylori, Despite Increasing Antibiotic Resistance, Uncovered in New Digestive Diseases & Sciences Publication

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Despite increasing resistance to, and suboptimal H. pylori eradication rates with, clarithromycin, a new study, published in Digestive Diseases and Sciences, indicates that over 80% of all prescriptions for H. pylori infection contain clarithromycin

In addition, this analysis highlighted a nearly 40% failure rate for clarithromycin-based triple therapies in treatment-naïve patients; Study also showed a more than 80% failure rate in CYP2C19 rapid metabolizers, accounting for approximately 30% of Americans

Talicia, an FDA-approved therapy, is intended for first-line H. pylori eradication therapy

RALEIGH, N.C. and TEL-AVIV, Israel, Dec. 9, 2021 /PRNewswire/ -- **RedHill Biopharma Ltd.** (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced the publication in the journal Digestive Diseases and Sciences of a new study entitled "**Pitfalls of Physician-Directed Treatment of Helicobacter pylori: Results from Two Phase 3 Clinical Trials and Real-World Prescribing Data**", revealing concerning rates of widespread, physician-directed prescribing of clarithromycin-based regimens for patients with persistent H. pylori infection despite rising rates of antibiotic resistance and prior patient macrolide use.

"The failure rate of clarithromycin-based therapy is alarming enough on its own. More alarming still is that more

than 80% of all prescriptions for H. pylori infection are clarithromycin-based therapies – despite clear ACG recommendations to avoid clarithromycin triple therapy in patients with any prior macrolide use or in regions where the resistance rate is known to be 15% or above (or where resistance levels are not known)," **said Dr. Colin W. Howden, MD, Professor Emeritus, Chief of the Division of Gastroenterology, University of Tennessee Health Science Center.** "Such failure rates and resistance have not been seen with Talicia. Since it does not contain clarithromycin, Talicia can be prescribed first-line without having to be concerned about local clarithromycin resistance, prior macrolide use, or patient CYP2C19 status."

This study assessed prescribing patterns and associated cure rates of physician-directed therapy for subjects with persistent H. pylori infection after participation in either of two Phase 3 clinical trials (ERADICATE Hp and ERADICATE Hp2). The study also conducted CYP2C19 genotype analysis of subjects who were prescribed clarithromycin-based triple therapy. The most frequently selected treatments for physician-directed therapy from ERADICATE Hp and Hp2 were clarithromycin-based triple regimens (71.7%). Clarithromycin-based triple therapies across these studies showed eradication rates of approximately 60%, while rapid CYP2C19 metabolizers had eradication rates of less than 20%. This is clinically relevant because roughly one third of Americans have either rapid or ultra-rapid CYP2C19 metabolizer status[1]. Additionally, the study analyzed real world H. pylori retail prescription data, which revealed that the most frequently selected treatments for physician-directed therapy were clarithromycin-based triple regimens, accounting for more than 80% of prescriptions.

"This study highlights the need for a change in prescribing habits for H. pylori given rising resistance and the suboptimal eradication rates seen with clarithromycin-based regimens. This study demonstrated an approximately 60% eradication rate for clarithromycin-based therapies in treatment naïve patients[2], which is consistent with recently published eradication rates[3]," **said Dr. June Almenoff, MD, Ph.D., RedHill's Chief Medical Officer.** "Conversely, efficacy data from the two Phase 3 studies demonstrated eradication rates of approximately 89% in the ERADICATE Hp mITT population and 90% in the ERADICATE Hp2 adherent population for Talicia in treatment-naïve subjects, identified no primary or acquired resistance to rifabutin and found that cure rates were largely unaffected by CYP2C19 metabolic status."

About Talicia®

Talicia® is the only rifabutin-based therapy approved for the treatment of H. pylori infection and is designed to address the high resistance of H. pylori bacteria seen with other antibiotics. The high rates of H. pylori resistance to clarithromycin have led to significant rates of treatment failure with clarithromycin-based therapies and are a strong public health concern, as highlighted by the ACG, FDA and the World Health Organization (WHO) in recent years.

Talicia® is a novel, fixed-dose, all-in-one oral capsule combination of two antibiotics (amoxicillin and rifabutin) and a

proton pump inhibitor (PPI) (omeprazole). In November 2019, Talicia® was approved by the U.S. FDA for the treatment of H. pylori infection in adults. In the pivotal Phase 3 study, Talicia® demonstrated 84% eradication of H. pylori infection in the intent-to-treat (ITT) group vs. 58% in the active comparator arm ($p<0.0001$). Minimal to zero resistance to rifabutin, a key component of Talicia®, was detected in RedHill's pivotal Phase 3 study. Further, in an analysis of data from this study, it was observed that subjects who were confirmed adherent[4] to their therapy had response rates of 90.3% in the Talicia® arm vs. 64.7% in the active comparator arm[5].

Talicia® is eligible for a total of eight years of U.S. market exclusivity under its Qualified Infectious Disease Product (QIDP) designation and is also covered by U.S. patents which extend patent protection until 2034 with additional patents and applications pending and granted in various territories worldwide.

About H. pylori

H. pylori is a bacterial infection that affects approximately 35%[6] of the U.S. population, with an estimated two million patients treated annually[7]. Worldwide, more than 50% of the population has H. pylori infection, which is classified by the WHO as a Group 1 carcinogen. It remains the strongest known risk factor for gastric cancer[8] and a major risk factor for peptic ulcer disease[9] and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[10]. More than 27,000 Americans are diagnosed with gastric cancer annually[11]. Eradication of H. pylori is becoming increasingly difficult, with current therapies failing in approximately 25-40% of patients who remain H. pylori-positive due to high resistance of H. pylori to antibiotics – especially clarithromycin – which is still commonly used in standard combination therapies[12].

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[13], **Talicia®** for the treatment of Helicobacter pylori (H. pylori) infection in adults[14], and **Aemcolo®** for the treatment of travelers' diarrhea in adults[15]. 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 COVID-19 and Phase 2 studies for prostate cancer and cholangiocarcinoma ongoing; (iii) **RHB-107** (**upamostat**), an oral serine protease inhibitor in a U.S. Phase 2/3 study as treatment for 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; (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; and (vi) **RHB-106**, an encapsulated bowel preparation. More information about the Company is available at **www.redhillbio.com** / **https://twitter.com/RedHillBio**.

About Talicia® (omeprazole magnesium, amoxicillin and rifabutin)

INDICATION AND USAGE

Talicia is a three-drug combination of omeprazole, a proton pump inhibitor, amoxicillin, a penicillin-class antibacterial, and rifabutin, a rifamycin antibacterial, indicated for the treatment of Helicobacter pylori infection in adults.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Talicia and other antibacterial drugs, Talicia should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

IMPORTANT SAFETY INFORMATION

Talicia contains omeprazole, a proton pump inhibitor (PPI), amoxicillin, a penicillin-class antibacterial and rifabutin, a rifamycin antibacterial. It is contraindicated in patients with known hypersensitivity to any of these medications, any other components of the formulation, any other beta-lactams or any other rifamycin.

Talicia is contraindicated in patients receiving rilpivirine-containing products.

Talicia is contraindicated in patients receiving delavirdine or voriconazole.

Serious and occasionally fatal hypersensitivity reactions have been reported with omeprazole, amoxicillin and rifabutin.

Severe cutaneous adverse reactions (SCAR) (e.g. Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)) have been reported with rifabutin, amoxicillin, and omeprazole. Additionally, drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with rifabutin.

Acute Tubulointerstitial Nephritis has been observed in patients taking PPIs and penicillins.

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents and may range from mild diarrhea to fatal colitis.
Talicia may cause fetal harm. Talicia is not recommended for use in pregnancy. Talicia may reduce the efficacy of hormonal contraceptives. An additional non-hormonal method of contraception is recommended when taking Talicia.

Talicia should not be used in patients with hepatic impairment or severe renal impairment.

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and exacerbation of existing autoimmune disease.

The most common adverse reactions (≥1%) were diarrhea, headache, nausea, abdominal pain, chromaturia, rash, dyspepsia, oropharyngeal pain, vomiting, and vulvovaginal candidiasis.

To report SUSPECTED ADVERSE REACTIONS, contact RedHill Biopharma INC. at 1-833-ADRHILL (1-833-237-4455) or FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**.

Full prescribing information for Talicia is available at **www.Talicia.com**

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 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® and Movantik®; (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 March 18, 2021. 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

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[2] mITT population who failed placebo as primary treatment, who entered into physician directed care phase

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[4] Defined as the PK population which included those subjects in the ITT population who had demonstrated presence of any component of investigational drug at visit 3 (approx. day 13) or had undetected levels drawn >250 hours after the last dose.

[5] The pivotal Phase 3 study with Talicia® demonstrated 84% eradication of H. pylori infection with Talicia® vs. 58% in the active comparator arm (ITT analysis, p<0.0001).

[6] Hooi JKY et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology 2017; 153:420-429.

[7] IQVIA Custom Study for RedHill Biopharma, 2019

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[11] National Cancer Institute, Surveillance, Epidemiology, and End Results Program (SEER).

[12] Malfertheiner P. et al. Management of Helicobacter pylori infection - the Maastricht IV/ Florence Consensus Report, Gut 2012;61:646-664; O'Connor A. et al. Treatment of Helicobacter pylori Infection 2015, Helicobacter 20

(S1) 54-61; Venerito M. et al. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of Helicobacter pylori infection. Digestion 2013;88(1):33-45.

[13] Full prescribing information for Movantik® (naloxegol) is available at: **www.Movantik.com**.

[14] Full prescribing information for Talicia® (omeprazole magnesium, amoxicillin and rifabutin) is available at: **www.Talicia.com**.

[15] Full prescribing information for Aemcolo® (rifamycin) is available at: **www.Aemcolo.com**.

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