# RedHill Biopharma Ltd.

## ("RDHL")

Corporate Presentation
May 2026

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# Corporate Highlights

Emerging U.S. specialty biopharmaceutical company (Nasdaq: RDHL), primarily focused on U.S. commercialization and development of drugs for gastrointestinal (GI) diseases, infectious diseases and oncology

## Strong U.S. Commercial Footprint and Robust Development Pipeline

**Net Revenues FY 2025**

$7.8M*

**Late-Clinical-Stage Pipeline**

Multiple de-risked programs and successfully completed Phase 3 studies

**Strengthened U.S. Commercial Organization**

Partnered with Cumberland Pharma for the co-commercialization of Talicia®

Talicia®
(omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

**#1 branded *H. pylori* Rx among U.S. Gastroenterologists**

** Includes continuing and discontinued operations.*

# Emerging U.S. Specialty Pharma: Select Programs[i]

## Commercial Product[ii]

**Talicia®** (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

**Talicia® (*H. pylori* infection in adults) |** *U.S. Co-Commercialization Partnership with Cumberland Pharma.* | CUMBERLAND PHARMACEUTICALS

## Development Pipeline

| | | Preclinical | Phase 1/2 | Phase 3 | NDA |
|---|---|---|---|---|---|
| **Opaganib** (ABC294640)<br>• Anticancer<br>• Antiviral<br>• Anti-inflammatory<br>• Metabolic disorders | Oncology | **Phase 2 oncology programs** | | | |
| | Virus-induced ARDS* | **Phase 2/3 COVID-19 (ARDS)** | | | |
| | Ebola virus | **Preclinical stage** | | | |
| | Diabetes and obesity | **Preclinical stage** | | | |
| | GI-ARS† (Radioprotection) | **Preclinical stage** | Pursuing FDA Animal Rule pathway | | |
| **RHB-102** (Bekinda®)[iii] | GLP-1/GIP-associated GI Intolerance | **Planned Phase 2 proof-of-concept** | | | |
| | Gastroenteritis | **Positive results from a first U.S. Phase 3 study** | | | |
| | IBS-D | **Positive results from U.S. Phase 2 study** | | | |
| | Oncology support | **UK MAA‡ planned** | | | |
| **RHB-204** | Crohn's disease | **Phase 2-stage** | | | |
| | Pulmonary NTM§ disease | **Phase 3-stage** | | | |
| **RHB-107** (upamostat)<br>• Antiviral | COVID-19, Oncology/GI | **Phase 2 COVID-19, GI & oncology indications** | | | |

Includes the **DARO LIPID Trial** | ongoing Phase 2 combination study with **Bayer's darolutamide** in prostate cancer

BAYER · ANZUP · Chris O'Brien Lifehouse · Ramsay Hospital Research Foundation

In partnership with Hyloris Pharma. (ex-North America)

Hyloris PHARMACEUTICALS

** ARDS: Acute respiratory distress syndrome; †GI-ARS: Gastrointestinal acute radiation syndrome; ‡ MAA: Marketing Authorisation Application; § NTM: Nontuberculous mycobacteria. ǂ Estimated timeline/indication in the pipeline is subject to changes in development plans and regulatory requirements/clarifications, including complementary /additional studies; # For full Talicia® prescribing information, see: www.talicia.com; ### Bekinda® (RHB-102) is the proposed tradename which is subject to FDA review and approval at the time of NDA filing.*

# Financial Highlights[i]

**RedHill Biopharma Ltd.**
**Nasdaq: RDHL**

| | |
|---|---|
| Market Cap (approx.)[i] | $5.2 million |
| American Depositary Shares (ADSs) (approx.) | 5.2 million |
| **FY 2025 (Fiscal Year Ended Dec 31, 2025):** | |
| Cash Balance[ii] | $4.1 million |
| Net Revenues[iii] | $7.8 million |
| Gross Margin[iii] | 74.6% |
| Equity Financing Capacity[iv] | $31.7 million |

*[i] Financial information as of May 8, 2026, unless otherwise noted. [ii] Including cash, cash equivalents, short-term bank deposits and restricted cash. [iii] Includes continuing and discontinued operations. [iv] "Any Market Purchase Agreement", announced in June 2025; SEPA (Standby Equity Purchase Agreement), announced in December 2025.*

# Highly Experienced Senior Leadership

**Dror Ben-Asher,** Chief Executive Officer
P.C.M.I. Ltd.

**Razi Ingber,** Chief Financial Officer
PwC

**Adi Frish,** Chief Corporate & Business Development Officer
Y. Ben-Dror, MediGus

**Gilead Raday, MSc, Mphil,** Chief Operating Officer
Sepal Pharma, Charles Street Securities LLP

**Rick D. Scruggs,** President, RedHill Biopharma Inc. & Chief Commercial Officer
Salix, Watson, Oclassen

**Guy Goldberg,** Chief Business Officer
Eagle Pharma, ProQuest, McKinsey

**Mark L. Levitt, MD, PhD,** Chief Scientific Officer
NCI, Teva, Inotek, Immune Pharma

**Reza Fathi, PhD,** Senior VP R&D
XTL, PharmaGenics, Harvard Inst. of Chem. & Cell Biology

**Patricia Anderson,** Senior VP Regulatory Affairs
MAPI Group, OptumInsight, Bayer, Novopharm

# Board of Directors*

**Dror Ben-Asher, CEO**
P.C.M.I. Ltd.

**Kenneth Reed, MD**
Dermatologist; Director Minerva Biotechnologies

**Dr. Roni Mamluk, PhD**
Ayala Pharmaceuticals, Chiasma

**Shmuel Cabilly, PhD**
Scientist, Director in several life-science companies

**Rick D. Scruggs**
Salix, Watson, Oclassen

**Ofer Tsimchi**
Danbar, Polysack, Director in several companies

* Includes select past positions

# Significantly Strengthened U.S. Commercial Operations in Partnership with Cumberland Pharmaceuticals*†

**U.S. Co-Commercialization Partnership Designed to:**

- Accelerate Talicia sales growth
- Leverage Cumberland's expanded national GI sales promotion and marketing support
- Deliver significant efficiencies through shared operational responsibility

**"A strong growth opportunity for both companies"**

A.J. Kazimi, CEO

CUMBERLAND® PHARMACEUTICALS

Combined U.S. commercial operations focused on commercialization to thousands of gastroenterologists (GIs), advanced practice providers (APPs), and primary care providers (PCPs)

**Talicia®**
(omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

Indicated for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults

U.S. launch in Q1/20

Leading Branded *H. pylori* Therapy among U.S. Gastroenterologists[i]

**RedHill announced on Oct 20, 2025, a strategic partnership with Cumberland Pharmaceuticals Inc., incl. $4 million strategic investment for a 30% ownership stake in RedHill's global Talicia business and co-commercialization agreement for Talicia (See PR here); Restructuring of the commercial operations is currently ongoing. † On April 23, 2026, Cumberland and Apotex, a Canadian-based global health company, announced their planned strategic transaction to integrate Cumberland's U.S branded business into Apotex.*

*[i] IQVIA XPonent Plantrak 12 months ending September 2025*

RedHill Biopharma

# Talicia®

## (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

**Indicated for the treatment of *Helicobacter pylori* infection in adults**

***Approved for Marketing by U.S. FDA Following Two Phase 3 Studies***

***Launched in the U.S. and the United Arab Emirates (UAE)***

***Listed as First-Line Option for Treatment of H. pylori Infection in the 2024 American College of Gastroenterology (ACG) Guideline****




*Chey WD, et al. ACG Clinical Guideline: Treatment of Helicobacter Pylori Infection. American Journal of Gastroenterology. 2024; 119(9): 1730-1753.

# Talicia®- FDA-Approved for Treatment of *H. pylori* Infection in Adults

Talicia® (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

| | |
|---|---|
| **Approved Indication** | Treatment of *H. pylori* infection in adults |
| **Drug** | Omeprazole magnesium, amoxicillin and rifabutin 10.3 mg/ 250 mg/ 12.5 mg delayed-release capsules[i] |
| **Regulatory Status** | – **U.S. FDA approved (2019); United Arab Emirates (UAE) approved (2024); UK MAA* planned** |
| **Key Attributes** | ✓ High rates of *H. pylori* eradication (>90%) achieved in confirmed adherent population[i]<br>✓ Zero to minimal *H. pylori* resistance to rifabutin and amoxicillin reported[ii]<br>✓ Simple regimen (all-in-one oral capsule) with a single prescription<br>✓ Flexible dosing schedule (4 capsules TID at least 4 hours apart for 14 days)<br>✓ Generic rifabutin is commercially available only as 150 mg capsules in the U.S. and is not therapeutically equivalent to the low-dose formulation of rifabutin found in Talicia (50 mg, TID)[iii] |
| **Market Exclusivity** | – U.S. patent protection until 2042<br>– **FDA QIDP designation granted, providing 8 years of market exclusivity** (initially 3 years, extended by 5 under QIDP) through 2027 |
| **Market Size** | – **Affects over 50% of the world population[iv], with ~1.6 million U.S. patients treated annually[v]**<br>– High levels of government (7/10 lives) and commercial (6/10 lives) coverage |

*.[i] Each delayed-release capsule contains omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium), amoxicillin 250 mg, and rifabutin 12.5 mg. [ii] Confirmed adherent population 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. [ii] Resistance rates as determined by in vitro testing of 345 H. pylori isolates collected at baseline from patients enrolled in the Talicia pivotal trial. [iii] Talicia 50 mg, three times daily (TID), had higher intragastric exposure times than 150 mg once daily or twice daily, or 300 mg once daily generic rifabutin; Howden CW, et al. Physiologically-based Pharmacokinetic Modelling to Predict Intragastric Rifabutin Concentrations in the Treatment of Helicobacter Pylori Infection. Alimentary Pharmacology & Therapeutics. 2023;58(2):159–167. [iv] Hooi JKY et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology 2017; 153:420-429. [v] IQVIA Custom Study for RedHill Biopharma, 2021.*

# *H. pylori* Overview and Increasing Global Burden

Talicia® (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

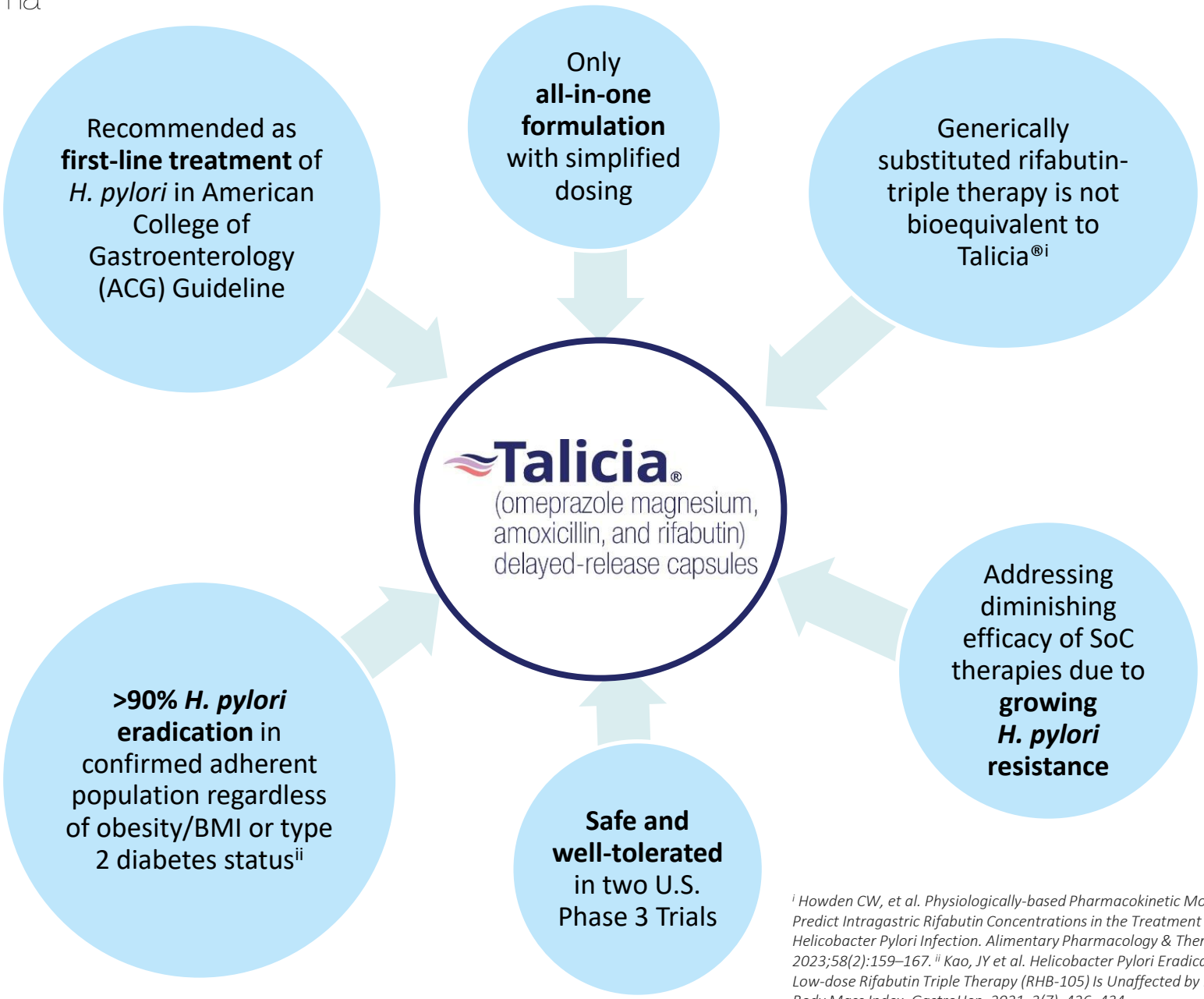
| | | | |
|---|---|---|---|
| **FDA** recognizes *H. pylori* as a **potential serious public health threat**[i] | **IARC*/(WHO)** classifies *H. pylori* as a Group 1 carcinogen | *H. pylori* is listed **as a human carcinogen in the HHS NTP 2021 HHS Report on Carcinogens** | **WHO** identifies antimicrobial resistance (AMR) as **one of the top global public health and development threats**[ii] |

- *H. pylori* is a gram-negative bacterium that colonizes gastric mucosa
- Infection with *H. pylori* is the most common chronic bacterial infection in humans[iii]:
  - It affects over 50% of the global population; In the U.S., approx. 35% of the population are affected[iv], with around 1.6 million patients treated annually[v]
- Chronic *H. pylori* infection is the strongest known risk factor for gastric cancer, the 5th leading cause of cancer related deaths worldwide, accounting for almost 1 million new cases and over 1.3 million deaths in 2022[vi]

  → **Confirmed eradication of *H. pylori* leads to a ~75% decreased risk of gastric cancer[vii]**
- Infection is also associated with other conditions, including dyspepsia, peptic ulcer disease, primary gastric B-cell lymphoma, vitamin B12 deficiency, iron deficiency anemia and mucosa-associated lymphoid tissue (MALT) lymphoma[viii]
- Commonly used therapies fail in approx. 25% to 40% of patients due to growing antimicrobial resistance of *H. pylori* to regimens containing antibiotics such as clarithromycin and metronidazole[ix]

*IARS: International Agency for Research on Cancer, the specialized cancer research agency of the World Health Organization (WHO). [i] FDA, Department of Health and Human Services. 21 CFR Part 317: Qualifying Pathogens That Have the Potential To Pose a Serious Threat to Public Health. eCFR. Available at: https://www.ecfr.gov/current/title-21/part-317. Accessed March 2025. [ii] World Health Organization. Antimicrobial Resistance. Fact Sheet, 21 Nov. 2023. World Health Organization, WHO, 2023. [iii] Chey WD, et al. ACG Clinical Guideline: Treatment of Helicobacter Pylori Infection. American Journal of Gastroenterology. 2024; 119(9): 1730-1753. [iv] Hooi JKY, et al. Global Prevalence of Helicobacter Pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology. 2017;153(2):420–429. [v] IQVIA Custom Study for RedHill Biopharma, 2021. [vi] World Cancer Research Fund. Stomach Cancer Statistics. WCRF, accessed 3 Dec. 2025. [vii] Kumar S, et al. Risk Factors and Incidence of Gastric Cancer After Detection of Helicobacter pylori Infection: A Large Cohort Study. Gastroenterology. 2020;158(3).[viii] Vakil N, et al. Physiologically Based Pharmacokinetic Modeling and Simulation to Support a Change in the FDA-Labeled Dosing Frequency of RHB-105 Low-Dose Rifabutin Triple Therapy for Helicobacter pylori Eradication. J Clin Pharmacol. 2025; Malfertheiner et al. Nat Rev Dis Primers. 2024; National Toxicology Program. Report on Carcinogens, 15th ed. U.S. Dep. of Health and Human Services. 2021. Helicobacter pylori (Chronic Infection). [ix] Malfertheiner P. et al. Management of Helicobacter pylori infection - the Maastricht IV/ Florence Consensus Report. Gut. 2012;61(5):646–664; O'Connor A, et al. Treatment of Helicobacter Pylori Infection 2015. Helicobacter. 2015;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.*

# Talicia® - A Rational and Effective Choice for *H. pylori* Therapy




[i] *Howden CW, et al. Physiologically-based Pharmacokinetic Modelling to Predict Intragastric Rifabutin Concentrations in the Treatment of Helicobacter Pylori Infection. Alimentary Pharmacology & Therapeutics. 2023;58(2):159–167.* [ii] *Kao, JY et al. Helicobacter Pylori Eradication by Low-dose Rifabutin Triple Therapy (RHB-105) Is Unaffected by High Body Mass Index. GastroHep, 2021, 3(7), 426–434.*

# 1st Line Use of Talicia® in Peer-Reviewed Literature and 2024 ACG Guideline[i]

**Talicia®: Listed as empiric first-line option by >15 peer-reviewed publications including the 2024 American College of Gastroenterology (ACG) *H. pylori* Treatment Guideline**


1730 CLINICAL GUIDELINES

ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection

William D. Chey, MD, FACG[1], Colin W. Howden, MD, FACG[2], Steven F. Moss, MD, FACG[3], Douglas R. Morgan, MD, MPH, FACG[4], Katarina B. Greer, MD, MSEpi[5], Shilpa Grover, MD, MPH[6] and Shailja C. Shah, MD, MPH[7]

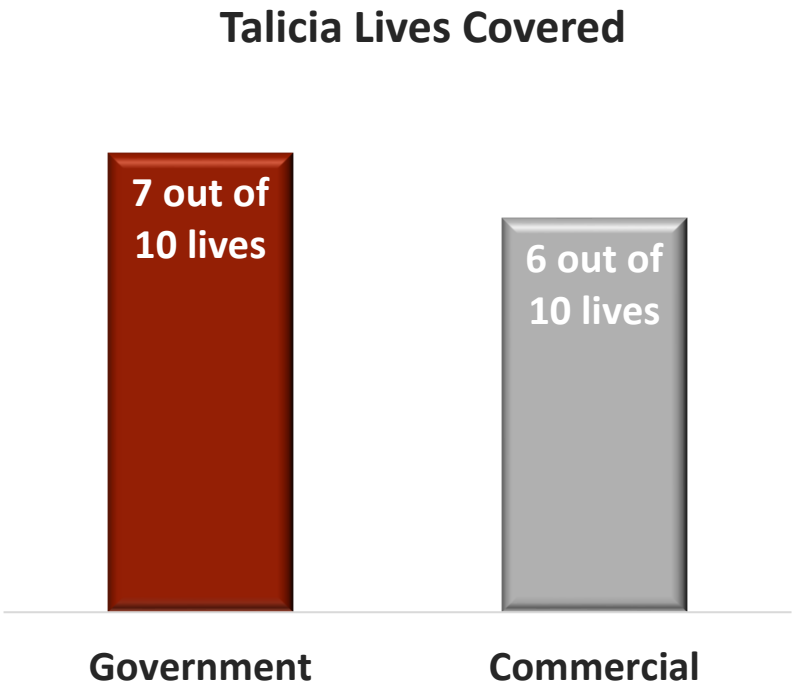
- Furthermore, the 2024 ACG Guideline recommends **against** the use of clarithromycin as part of any treatment regimen without prior susceptibility testing[i]
- Since Talicia® does not contain clarithromycin, there is no risk of possible clarithromycin resistance, eliminating the need for antimicrobial sensitivity testing prior to treatment

Talicia®
(omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

[i] *Chey WO, Howden CW, Moss SF, et al. ACG Clinical Guideline: treatment of Helicobacter pylori infection. Am) Gastroenterol. 2024;1 12(9): 1730 -1753.*

# Talicia® Continues to Have Broad U.S. Managed Care Coverage

**Talicia Access: More than 200 Million American Lives have Formulary Coverage[i]**




- **Talicia is Preferred on Aetna, OptumRx, and Express Scripts Commercial Formularies**
- **Talicia is covered on Medi-Cal, California's Medicaid Program, with no PA/ST or restrictions and a $0 copay**
- **Talicia is now covered on Humana's Medicare Part D Formulary, the VA National Formulary, and Preferred on TennCare**

Talicia®
(omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

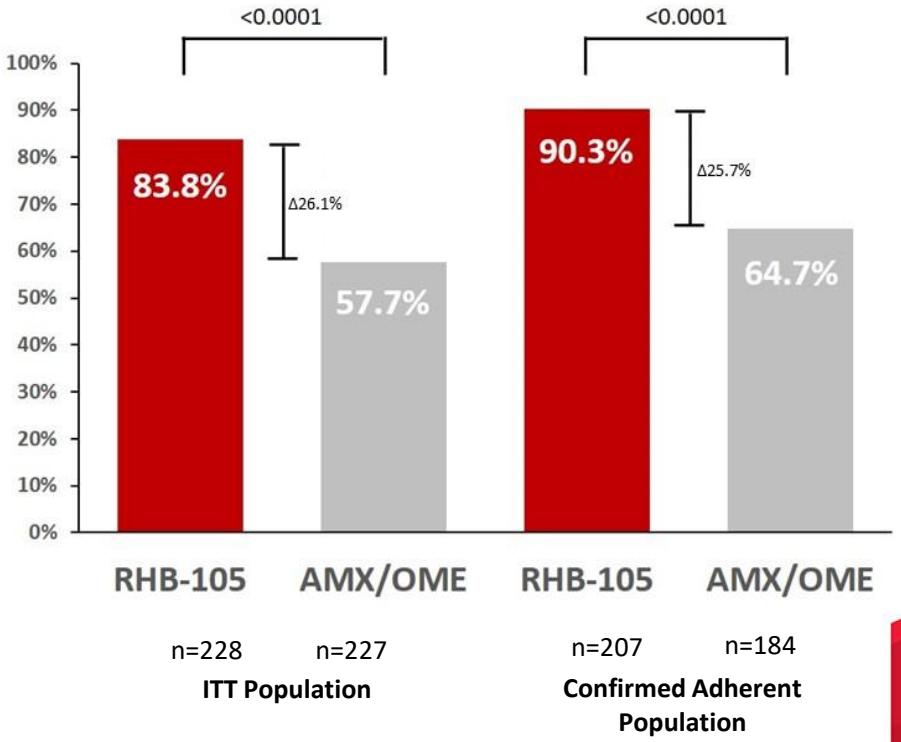
[i] *Estimated coverage based on Clarivate® Fingertip Formulary as of April 1, 2026.*

# ERADICATE Hp 2 Study: Positive Results

Talicia® (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

**The ERADICATE Hp2 study met its primary endpoint with a high degree of statistical significance (p<0.0001)**

- **Primary endpoint:** $^{13}$C UBT at 43-71 days post treatment ITT analysis
- **Number of subjects:** 455 in the U.S.
- Eradication rate of 83.8% in the ITT population receiving Talicia vs. 57.5% with active comparator (Δ26.1%); p-value<0.0001
- **90% eradication** based on adherence analysis (confirmed adherent population*) using protocol-defined population with evidence of drug ); p-value<0.0001
- No safety signals reported
- No AEs related to myelotoxicity
- Well tolerated




*IIT population included all randomized patients who received at least one dose of study drug; Confirmed adherent population 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.*

# Resistance Patterns in Pivotal Study Demonstrate Zero to Negligible Resistance For Component Antibiotics in Talicia®[i]

Talicia® (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

- 345 *H. pylori* isolates were collected at baseline from treatment naïve patients across 20 U.S. states and tested for antibiotic resistance
- Results confirmed high resistance of *H. pylori* to antibiotics commonly used in other therapies **vs.** zero to negligible resistance for the component antibiotics in Talicia®:

**Antibiotics Commonly Used in Other Therapies**

| Antibiotic | *H. Pylori* Resistance Rate |
|---|---|
| Clarithromycin (n=345) | 60 (17.4%) |
| Metronidazole (n=344) | 150 (43.6%) |

**Antibiotics Contained in Talicia®**

| Antibiotic | *H. Pylori* Resistance Rate |
|---|---|
| Rifabutin (n=345) | **0 (0%)** |
| Amoxicillin (n=345) | 22 (6.4%) |

[i] *Hulten, K. G., et al. National and regional US antibiotic resistance to Helicobacter pylori: Lessons from a clinical trial. Gastroenterology. 2021.161(1), 342–344.e1.*

# Positive Supportive First Phase 3 Study

Talicia® (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

A Randomized Placebo-Controlled Phase 3 Study (ERADICATE Hp) to Assess the Safety and Efficacy of Talicia® in the Treatment of Confirmed *H. pylori* Infection in Dyspepsia Patients, Regardless of Ulcer Status

| | |
|---|---|
| **Number of Subjects** | 118 in the U.S. |
| **Treatment Duration** | 14 days |
| **Primary Endpoints** | - The occurrence of *H. pylori* eradication as confirmed via 13C UBT testing 28-35 days after completion of treatment<br>- Greater eradication of *H. pylori* infection over historical standard of care efficacy levels of 70% effectiveness |
| **Positive Phase 3 Results** | - **Study met protocol-defined primary endpoint - demonstrating 89.4% efficacy in eradicating *H. pylori* infection (p< 0.001) in the mITT population[i]**<br>- **63% eradication rate demonstrated in open-label treatment of treatment naïve placebo-arm patients with physician choice therapy (mostly clarithromycin triple therapy) for persistent *H. pylori* infection**<br>- No serious adverse events related to the drug were noted in the study |

[i] *mITT Population included those subjects who completed the study and returned for a follow-up test of cure.*

# IP - Strong Protection from Competition and Substitution

Talicia® (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules

- Talicia® is covered by a portfolio of U.S. patents, including those for its unique 'all-in-one' capsule formulation and distinct PK profile, among others, with the latest patent set to expire in 2042; Additional patents have been granted and more applications are pending in various territories worldwide
- FDA QIDP designation granted, providing **8 years of market exclusivity** (initially 3 years, extended by 5 under QIDP) through 2027
- Generically substituted rifabutin-triple therapy is not bioequivalent to Talicia®[i]
  - Unique low-dose (50 mg TID) rifabutin formulation is not commercially available and cannot be replicated by prescribers
- Indication allowing unique labeling, marketing and promotional opportunity
- 'All-in-one' easy to use regimen with single co-pay preferred over more cumbersome regimens

[i] *Howden CW, et al. Physiologically-based Pharmacokinetic Modelling to Predict Intragastric Rifabutin Concentrations in the Treatment of Helicobacter Pylori Infection. Alimentary Pharmacology & Therapeutics. 2023;58(2):159–167.*

# Talicia® (omeprazole magnesium, amoxicillin and rifabutin) - 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 rifamycins.

Talicia® is contraindicated in patients receiving delavirdine, voriconazole or rilpivirine-containing products.

Serious and occasionally fatal hypersensitivity reactions have been reported with the components of Talicia®: omeprazole, amoxicillin and rifabutin.

Severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the components of Talicia®: rifabutin, amoxicillin, and omeprazole.

Drug-induced enterocolitis syndrome (DIES) has been reported with use of amoxicillin, a component of Talicia.

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

*Clostridioides difficile* - associated diarrhea has been reported with use of nearly all antibacterial agents and may range from mild diarrhea to fatal colitis.

Talicia® may cause fetal harm and is not recommended for use in pregnancy. It may also 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 and systemic lupus erythematosus 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.

Please also see complete Prescribing Information

# R&D Pipeline Overview[i]

| RHB-102 (Bekinda®) – In partnership with Hyloris Pharma (ex-North America) | |
|---|---|
| **GLP-1/GIP-associated GI Intolerance** | Planned Phase 2 proof-of-concept (PoC) study |
| **Gastroenteritis & gastritis** | First U.S. Phase 3 study successfully completed[ii] |
| **Irritable bowel syndrome with diarrhea (IBS-D)** | U.S. Phase 2 study successfully completed; Phase 3 ready |
| **Oncology support** | UK MAA* planned |

| RHB-204 | |
|---|---|
| **Crohn's disease** | Phase 2 study planned |
| **Pulmonary nontuberculous mycobacterial (NTM) disease** | Phase 3-stage |

| Opaganib (ABC294640) | |
|---|---|
| **Prostate cancer** | Ongoing Phase 2 study evaluating opaganib **in combination with Bayer's darolutamide** |
| **Cholangiocarcinoma** | Phase 2a study completed |
| **Neuroblastoma and chronic lymphocytic leukemia** | Preclinical data support potential as an add on therapy; neuroblastoma: Phase 2 ready |
| **Virus-induced ARDS† (incl. COVID-19 & influenza)** | Phase 2/3 ready[iii]; Phase 2/3 study in hospitalized COVID-19 patients completed |
| **Ebola virus disease and other viral infections** | • Preclinical stage<br>• Additional preclinical evaluation ongoing with NIAID for various antiviral indications |
| **Metabolic disorders (diabetes and obesity)** | Preclinical stage |
| **GI-ARS‡** | Preclinical stage, with development under FDA Animal Rule |
| **Inflammatory bowel disease** | Phase 2 ready |

| RHB-107 (upamostat) | |
|---|---|
| **COVID-19 (symptomatic outpatients)** | • Phase 2a study successfully completed<br>• Included in a separate U.S. Gov.-supported Phase 2 platform trial for early COVID-19 outpatient treatment (PROTECT study) – study terminated |
| **Influenza** | Preclinical stage |
| **Pancreatic & breast cancer** | Phase 2 PoC study completed |

**MAA: Marketing Authorisation Application. † ARDS: Acute respiratory distress syndrome; ‡ GI-ARS: Gastrointestinal acute radiation syndrome.*

*[i] Additional elaborated information can be found in this presentation and RedHill's ongoing public filings. [ii] Confirmatory Phase 3 study is required and planned to support a potential NDA for RHB-102 (24 mg) for acute gastroenteritis and gastritis. [iii]Data obtained from the Phase 2/3 COVID-19 study to support the potential Phase 2/3 study ARDS.*




# RHB-102 (Bekinda®)[i]

*Investigational new drug*

*Proprietary, bimodal extended-release, once-daily, oral tablet formulation of ondansetron*

***--***

***RHB-102 – GLP-1/GIP Receptor Agonist Therapy-Associated GI Intolerance - Planned Phase 2 Proof-of-Concept Study***

***--***

***RHB-102 (24 mg) – Gastroenteritis/Gastritis - Positive Results from a First U.S. Phase 3 Study***

***--***

***RHB-102 (12 mg) – IBS-D - Positive Results from a U.S. Phase 2 Study***

***--***

***RHB-102 (24 mg) – Oncology Support - UK MAA* planned***

# RHB-102 (Bekinda®) Highlights

| | |
|---|---|
| **The Drug** | A proprietary bimodal immediate and extended-release, once-daily, oral tablet formulation of ondansetron, a 5-HT3 antagonist |
| **Development Status** | – **GLP-1/GIP-associated GI Intolerance:** Planned Phase 2 proof-of-concept study |
| | – **Gastroenteritis & Gastritis (24 mg):** Positive results from a first U.S. Phase 3 study<br>– Results publication: JAMA Network Open[i] |
| | – **IBS-D (12 mg):** Positive results from a U.S. Phase 2 study<br>– Results publication: The American Journal of Gastroenterology[ii] |
| | – **Oncology Support (24 mg):** UK MAA* planned<br>– Positive UK MHRA scientific advice meeting held in February 2023 deems RHB-102 data supportive of submission for approval for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy<br>– Uses PK bridging for efficacy to the existing label of Zofran® suppositories |
| **IP** | – Patent protected until at least 2034 in the U.S. and 2035 outside the U.S. |
| **Partnering Status** | – Available for partnering in the U.S., Canada and Mexico<br>– Out licensed worldwide (excluding the territories mentioned above) to Hyloris Pharmaceuticals SA (Euronext Brussels: HYL) for all indications |

➢ **RHB-102 is positioned to capture a large cross-indication market share of the growing multi-billion market for various GI indications at competitive pricing**

**MAA: Marketing Authorisation Application.*

*[i] Silverman RA, House SL, Meltzer AC, et al. Bimodal Release Ondansetron for Acute Gastroenteritis Among Adolescents and Adults: A Randomized Clinical Trial. JAMA Netw Open. 2019;2(11):e1914988. doi:10.1001/jamanetworkopen.2019.14988. [ii] Plasse TF, Barton G, Davidson E, et al. Bimodal release ondansetron improves stool consistency and symptomatology in diarrhea-predominant irritable bowel syndrome: A randomized, double-blind trial. Am J Gastroenterol 2020;115:1466-73.*

# U.S. Ondansetron Market Overview

- Ondansetron is FDA-approved for the prevention of nausea and vomiting associated with chemotherapy, radiotherapy, and postoperative nausea and vomiting (PONV)

- 5-$HT_3$ receptor antagonists (e.g., ondansetron) are recommended as components of first-line antiemetic regimens in major U.S. clinical practice guidelines (e.g., NCCN and ASCO)

- Ondansetron is widely used off-label across U.S. emergency, inpatient, and outpatient settings (e.g., acute gastroenteritis and other nausea-related presentations)

- The U.S. market is high-volume and largely generic, with extensive utilization across care setting
  - Ondansetron accounts for approx. 23 million administrations or discharge prescriptions in U.S. emergency departments alone in 2021[i]

[i] *Cairns C, Kang K. National Hospital Ambulatory Medical Care Survey: 2021 emergency department summary tables. Available from: https://www.cdc.gov/nchs/data/nhamcs/web_tables/2021-nhamcs-ed-web-tables-508.pdf.*

# RHB-102 - Strategic Considerations for Adoption and Pricing

- ✓ **High-volume ondansetron utilization creates a clear and familiar pathway for RHB-102 adoption**
- ✓ **Attractive COGS profile and payer-aligned pricing make RHB-102, a convenient once-daily therapy, a competitive solution in a large established market**



# Exclusive Worldwide Licensing Agreement with Hyloris Pharmaceuticals for RHB-102 (ex. North America)

**About Hyloris Pharmaceuticals SA:**

- Hyloris (EBR: HYL) is a specialty biopharma company focused on innovating, reinventing, and optimizing existing medications to address important healthcare needs and deliver relevant improvements for patients, healthcare professionals and payors

**Exclusive Worldwide Licensing Agreement (Excluding North America):**

- An exclusive global development and commercialization agreement with Hyloris for RHB-102
- Excludes U.S., Canada and Mexico where the rights remain with RedHill
- RedHill intends to continue development of RHB-102 for FDA approval in the U.S., if granted
- Hyloris will be responsible for all development, regulatory and commercialization activities related to RHB-102 in its territories across all indications

**Key Terms of the Agreement:**

- Upfront payment
- Up to $60 million in potential milestone payments*
- Royalties up to mid-20s percent on net revenues**, with minimum annual payments

** Contingent upon achieving specified commercial targets.*
***Subject to certain cost recoupments.*




# GLP-1/GIP Receptor Agonist Therapy-Associated Gastrointestinal (GI) Intolerance

→ ***Proprietary, once-daily oral pill, addressing the most common treatment-limiting GI adverse events associated with existing and next-generation GLP-1/GIP therapies:***

- ✓ ***Nausea***
- ✓ ***Vomiting***
- ✓ ***Diarrhea***

# RHB-102 (Bekinda®) Partnering Value Proposition

- ✓ **Differentiated, once-daily oral GI-intolerance solution**
  - ✓ Only **once-daily oral ondansetron** combining **immediate and extended-release** coverage, supporting adherence with a single oral tablet
  - ✓ Aligned to **improve titration success** and **reduce early discontinuation** of GLP-1/GIP therapies by addressing treatment-limiting GI adverse events
- ✓ **Clinically and mechanistically de-risked**
  - ✓ Shown to be effective, safe and well-tolerated as an antiemetic in a **positive U.S. Phase 3 study** in gastroenteritis/gastritis (24mg) and a **positive U.S. Phase 2 study** in IBS-D (12mg), as well as a positive **comparative PK clinical study** as part of the oncology support (CINV/RINV) program
  - ✓ Leverages **decades of widely used ondansetron across U.S. Emergency Departments as a first-line treatment for acute nausea and vomiting**
- ✓ **Efficient development and regulatory pathway**
  - ✓ **Accelerated FDA 505(b)(2) pathway**, enabling a rapid and cost-effective route to approval

➢ **RHB-102 presents a de-risked, once-daily adjunct therapy designed to improve GLP-1/GIP tolerability, support dose escalation, and enhance long-term treatment persistence**

# RHB-102 and GLP-1/GIP Agonists - Commercial Opportunity

- **Significant & Rapidly Expanding Patient Population**
  - The total GLP-1 agonist market was valued at approximately $53.7 billion in 2024 and is projected to reach around $182 billion in 2031 with the launch of new candidates[i]
  - **>2% of the U.S. adult patients taking a GLP-1 drug**[ii] translating into several million patients on therapy
  - High incidence of GI intolerance across GLP-1/GIP therapies creates a substantial and growing commercial opportunity for targeted supportive care
- **Enhanced Tolerability**
  - Increased tolerability leads to improved adherence and outcomes; Discontinuation is heavily driven by GI AEs
- **Underserved Care Market**
  - Management of GLP-1/GIP-related GI side effects remains largely empirical, underscoring the unmet need for dedicated, evidence-based supportive therapy
  - Competitor PoC studies, including NG101[iii] and tradipitant[iv] provide models of potential development and validate the commercial need for effective antiemetic solutions, reinforcing the potential market opportunity for RHB-102 in this space
- **Rapid Path to approval via 505(b)(2) route**
  - Leveraging extensive ondansetron and RHB-102 safety experience and existing clinical data

*[i] GlobalData. GLP-1R Agonists – Label Extensions/Drug Repurposing: Market Overview. April 2025. [ii] FAIR Health. Obesity and GLP-1 Drugs: A Claims-Based Analysis. FAIR Health White Paper; May 27, 2025. [iii] Neurogastrx, Inc. press release, 7 Oct 2025. [iv] Vanda Pharmaceuticals Inc. press release, 25 Sept 2025.*

# RHB-102 and GLP-1/GIP Agonists - Potential Benefits

- **Improved titration success:**
  - Enabling patients to reach target GLP-1 doses faster and stay there
- **Reduced discontinuations/switching:**
  - Even modest symptom control can prevent abandonment
- **Better quality of life early on:**

  The first 4–12 weeks are the danger zone for dropout
- **Potential cost offsets:**
  - Fewer GI-driven visits/calls/ER trips[i]

- **Differentiated long-acting antiemetic addressing the leading side effect driving GLP-1 discontinuation, with a clinically validated and de-risked mechanism of action**

# RHB-102 (24 mg): Gastroenteritis & Gastritis - Positive First Phase 3 Results

A Randomized, Double-Blind, Placebo Controlled, Parallel Group Phase 3 Study (GUARD study) to Assess the Safety and Efficacy of RHB-102 (24 mg) for the Treatment of Acute Gastroenteritis & Gastritis

| | |
|---|---|
| **The Product** | Patent-protected, once-daily extended-release oral tablet ondansetron (24 mg) |
| **Number of Subjects** | 321 adults and children over the age of 12 |
| **Sites** | 21 in the U.S. |
| **Primary Endpoint** | The absence of vomiting, without rescue medication and intravenous hydration, from 30 minutes post first dose of the study drug until 24 hours post dose |
| **Potential Advantages** | - If approved by FDA, RHB-102 could become the first 5-HT3 antiemetic drug indicated for the treatment of acute gastroenteritis or gastritis in the U.S.<br>- Long-lasting (24H) oral treatment with the potential to reduce dehydration and hospital visits and stays |
| **Market Size** | - Acute gastroenteritis is estimated to account for approx. 179 million cases annually in the U.S., resulting in roughly 900,000 hospitalizations each year[i]<br>- Global market for gastroenteritis is projected to reach $7.23 billion by 2029, representing a CAGR of 4.37% from 2024 to 2029[ii] |
| **Development Status** | - **Positive Phase 3 study results announced June 2017 - the study met primary endpoint**<br>- **RedHill has designed a confirmatory Phase 3 study for acute gastroenteritis and gastritis** |

*[i] Schmidt MA et al., Emerging Infectious Diseases (CDC), 2022;28(11):2234–2242. [ii] Mordor Intelligence, Gastrointestinal Therapeutics Market (2024–2029), 2024.*

# RHB-102 (24 mg): Gastroenteritis & Gastritis - Positive First Phase 3 Results

A Randomized, Double-Blind, Placebo Controlled, Parallel Group Phase 3 Study ("GUARD") to Assess Safety and Efficacy of RHB-102 (24 mg) for Treatment of Acute Gastroenteritis & Gastritis

**Results**

- **The Phase 3 GUARD study successfully met its primary endpoint in the Intent to Treat (ITT) population (p = 0.04)**
- **ITT:** RHB-102 (24 mg) improved the efficacy outcome by 21%; 65.6% of RHB-102 (24 mg) treated patients as compared to 54.3% of placebo patients (p = 0.04; n=192 in the RHB-102 group and n=129 in the placebo group)
- **PP:** In patients who met all protocol entry criteria and for which the diagnosis of gastroenteritis was confirmed (n=177 in the RHB-102 group and n=122 in the placebo group), RHB-102 (24 mg) improved the efficacy outcome by 27%; 69.5% of patients in the RHB-102 (24 mg) group vs. 54.9% in the placebo group, (p = 0.01)
- RHB-102 (24 mg) was demonstrated to be safe and well-tolerated; electrocardiogram results showed no adverse changes with treatment

# RHB-102 (12 mg): IBS-D – Positive Phase 2 Results

A Randomized, Double-Blind, Placebo-Controlled, 2-Arm Parallel Group Phase 2 Clinical Study Designed to Evaluate the Safety and Efficacy of RHB-102 (12 mg) in Patients Suffering from Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D)

| | |
|---|---|
| **The Product** | Patent-protected, once-daily extended-release oral tablet ondansetron (12 mg) |
| **Number of Subjects** | 126 patients |
| **Sites** | 16 in the U.S. |
| **Primary Endpoint** | Response in stool consistency compared to baseline, per FDA guidance definition |
| **Market Size** | It is estimated that approximately 5% of the U.S. adult population have IBS-D[i] |
| **Development Status** | - **Positive top-line results announced Oct. 2017; Study successfully met primary endpoint**<br>- **Positive End-of-Phase 2/Pre-Phase 3 FDA meeting announced Sep. 2018 - design of two pivotal Phase 3 studies with RHB-102 to be finalized and partnership discussions accelerated** |

[i] *Grundmann O et al. J Gastroenterol Hepatol. 2010;25(4):691-699.*

# RHB-102 (12 mg): IBS-D – Positive Phase 2 Results

A Randomized, Double-Blind, Placebo-Controlled, 2-Arm Parallel Group Phase 2 Clinical Study Designed to Evaluate the Safety and Efficacy of RHB-102 (12 mg) in Patients Suffering from Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D)

**Results**

- **Primary endpoint:** The Phase 2 study met its primary endpoint, improving the primary efficacy outcome of stool consistency response (per FDA guidance definition) by an absolute difference of 20.7% (p=0.036)
    - 56.0% responders of subjects treated with RHB-102 (n=75) vs. 35.3% responders of the placebo subjects (n=51)
- **Secondary endpoints:** While not powered for statistical significance of the secondary efficacy endpoints, the study suggested clinically meaningful improvement in both abdominal pain response and overall response (combined stool consistency and abdominal pain response)
- **Safety:** RHB-102 (12 mg) was demonstrated to be safe and well-tolerated

# RHB-102 (24 mg): Oncology Support

- **An MAA for RHB-102 (24 mg) is planned in the UK for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy**
- **Development is being advanced by our partner, Hyloris Pharmaceuticals, holder of the worldwide rights excluding North America**
- **Historical development and regulatory pathway leading to current status in Europe:**
- RedHill submitted a European Hybrid Marketing Authorisation Application (MAA) for this indication in 2014, referencing Zofran® 16 mg suppository
- The review outcome was that there was insufficient data to support the safety of RHB-102's bimodal release formulation at the time
- Since then, RedHill completed comparative PK studies against ondansetron 8 mg BID, showing 24h coverage above Cmin, with no midday troughs
- Subsequently, RedHill successfully completed a U.S. Phase 3 study with RHB-102 in gastroenteritis patients, supporting the safety of RHB-102 (24 mg)
- **In 2023, a scientific advice meeting with UK's MHRA confirmed that the added safety data seems to complete the clinical requirements to support the Hybrid MAA in the UK**
- Other countries (EU and WW) in which Zofran® suppositories are approved can be followed up with using the same strategy (U.S. has not approved Zofran® suppositories, hence this regulatory strategy doesn't apply there)




# Opaganib (ABC294640)

*Late-Stage Investigational New Drug*

*First-in-class, broad-acting, host-directed, orally administered sphingosine kinase-2 (SPHK2) inhibitor, targeting inflammatory, viral, oncological and metabolic diseases*

***Oncology – Ongoing Phase 2 study evaluating opaganib in combination with Bayer's darolutamide; Phase 2a study in cholangiocarcinoma completed; positive preclinical results reported and FDA Orphan Drug Designation granted for neuroblastoma***

***--***

***COVID-19 – Data reported from global Phase 2/3 study***

***--***

***Ebola – Preclinical stage***

***--***

***Metabolic disorders (diabetes and obesity) – Positive results reported from multiple in vivo studies***

***--***

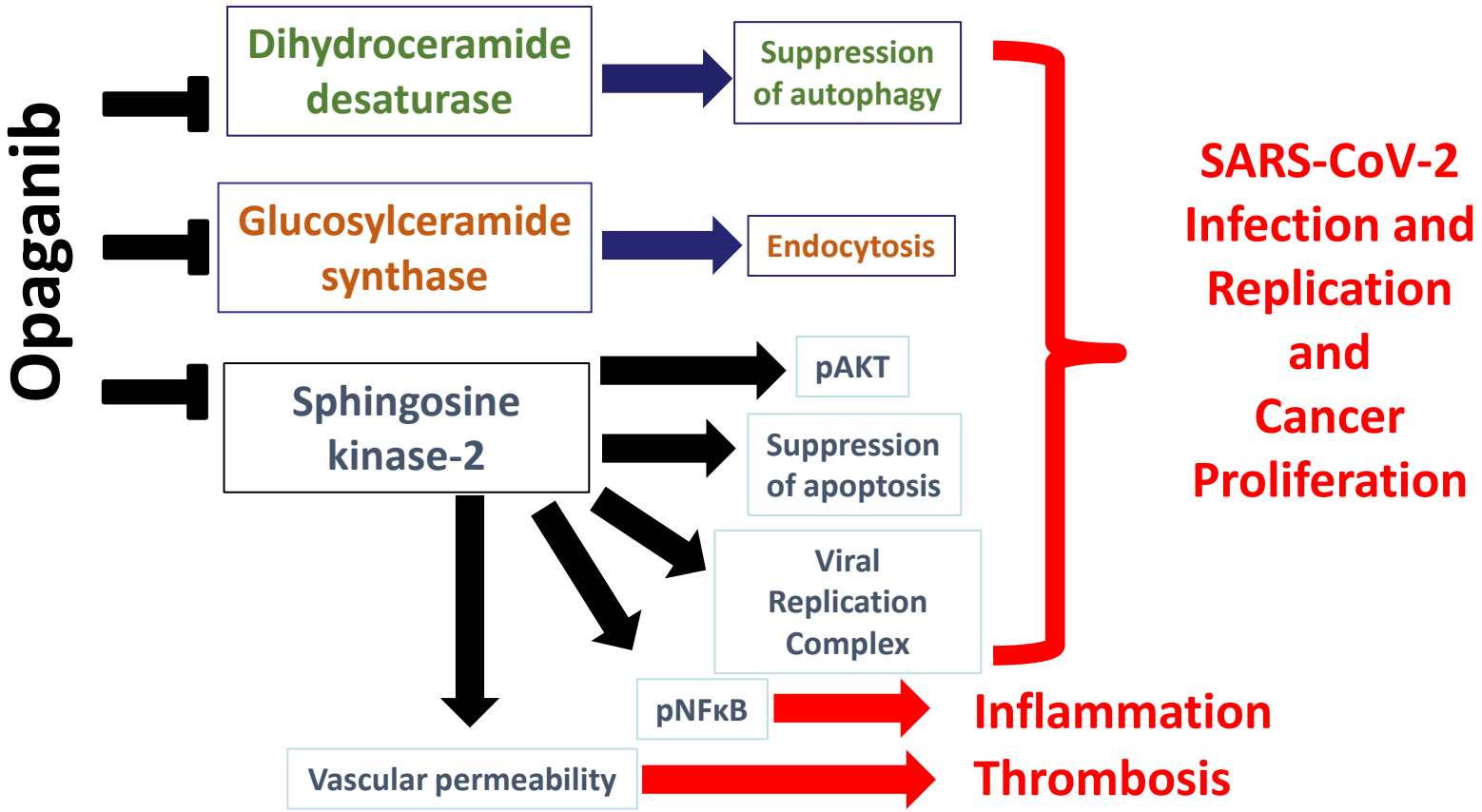
***Gastrointestinal Acute Radiation Syndrome (GI-ARS) – Preclinical stage; development under FDA Animal Rule***

# Opaganib – Broad-Acting Sphingosine kinase-2 (SPHK2) Inhibitor with Multi-Indication Potential

- **Opaganib is a proprietary, first-in-class, orally administered small molecule sphingosine kinase-2 (SPHK2) selective inhibitor drug**
- **Potentially broad-acting, it is in development for multiple oncology, viral, inflammatory, metabolic (diabetes and obesity) and additional indications**
- Demonstrated its **safety and tolerability profile in > 470 participants** across multiple clinical studies and expanded access use
- In addition to potential regulatory exclusivities, opaganib is covered by a portfolio of patents with the latest patent set to expire in 2041

| Oncology | Viral diseases<br>Host-directed antiviral | Inflammatory diseases | Metabolic disorders | Additional Indications |
|---|---|---|---|---|
| - **Prostate cancer:** Ongoing Phase 2 study in combination with **Bayer's darolutamide** in prostate cancer<br>- **Cholangiocarcinoma:** Phase 2a study completed; FDA Orphan Drug Designation granted<br>- **Preclinical data support opaganib's potential as add on therapy in:**<br>- **Neuroblastoma:** Positive preclinical results reported; Phase 2 ready; FDA Orphan Drug Designation granted**;** Potential PRV*<br>- **Chronic lymphocytic leukemia (CLL):** Combination with venetoclax showed reduction in resistant cells | - **COVID-19:** Global Phase 2/3 study completed in hospitalized patients with severe COVID-19 pneumonia<br>- **Virus-induced ARDS caused by COVID-19 and influenza:** Phase 2/3 study being explored<br>- **Ebola and other viral infections**: Preclinical stage<br>- Additional preclinical evaluation ongoing with NIAID for other antiviral indications | - **Inflammatory bowel disease:** Phase 2 ready<br>- **Pulmonary and renal fibrosis and acute kidney injury:** Phase 2 ready | - **Diabetes and obesity-related disorders:** Preclinical stage<br>- Positive results from multiple *in vivo* studies announced | **Radioprotection:**<br>- **Gastrointestinal acute radiation syndrome (GI-ARS):** Preclinical stage<br>- FDA Animal Rule pathway<br>- Additional studies planned in non-human primates<br>- **Radiotherapy protection of normal tissue:** Phase 2 ready<br>**PRV: Priority Review Voucher.* |

# Opaganib Simultaneously Inhibits Three Sphingolipid-Metabolizing Enzymes in Human Cells[i]




[i]Smith CD, et al. Recent Progress in the Development of Opaganib for the Treatment of Covid-19. Drug Design, Development and Therapy. 2022;Volume 16:2199–2211.

# SPHK2 as a Specific Target for Anticancer Drugs

## Why SPHK2 for Anticancer Therapy?

- SPHK2 is an innovative molecular target for anticancer therapy because of its critical role in catalyzing the formation of intracellular S1P, known to regulate cell proliferation and activation of inflammatory pathways
- SPHK2, unlike SPHK1:
  - Has a nuclear localization signal
  - Possesses a Pleckstrin Homology Domain allowing it to attach to membranes including the endoplasmic reticulum and mitochondria
  - Contains a pro-apoptotic BH3 binding domain which may promote apoptosis under certain conditions.
- Down-regulation of the kinase function of SPHK2 inhibits the proliferation of tumor cells

## Oncology Development Status

- ✓ Ongoing Phase 2 study evaluating opaganib in combination with Bayer's darolutamide in advanced prostate cancer
- ✓ Completed numerous successful pre-clinical studies in various oncology indications
- ✓ Phase 1 study in cancer patients with advanced solid tumors successfully met primary and secondary endpoints
- ✓ Phase 2a study for treatment of cholangiocarcinoma completed
- ✓ Prior investigator-sponsored Phase 2 study evaluating opaganib with abiraterone or enzalutamide in prostate cancer completed

# Opaganib and Bayer's Darolutamide - Phase 2 Combination Study in Advanced Prostate Cancer

**A double-blind, placebo-controlled randomized Phase 2 trial, financially supported by Bayer (ETR: BAYN) and the Ramsay Hospital Foundation, evaluating the efficacy of opaganib in combination with Bayer's darolutamide in men with metastatic castrate-resistant prostate cancer (mCRPC), testing the potentially enhancing effect of opaganib in patients with a poor prognosis**

| | |
|---|---|
| **Lead Investigator** | - Professor Lisa Horvath from Chris O'Brien Lifehouse and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) |
| **Subjects** | - The study will enroll 60 male patients who have had no treatment with newer, potent androgen receptor signaling inhibitors (incl. darolutamide, enzalutamide, apalutamide, or abiraterone) and will utilize a companion lipid biomarker test (PCPro) to select mCRPC patients who have a poor prognosis due to standard of care treatment |
| **Study Arms** | - Patients who are PCPro-positive will be randomized on a 1:1 ratio to either the darolutamide 600 mg BID + placebo (n=30) arm or the darolutamide 600 mg BID + opaganib 500 mg BID (n=30) arm |
| **Primary Endpoint** | - Improved 12-month radiographic progression-free survival (rPFS) |
| **Development Status** | - Recruitment initiated |
| **Market Size** | - The prostate cancer market is valued at approximately $12 billion[i] |

[i] *GlobalData database: 2024 Prostate Cancer Market Size in 8MM (Accessed February 2025).*

# Opaganib - Positive Phase 1 Study

## Phase 1 Clinical study of opaganib in Cancer Patients with Advanced Solid Tumors

| | |
|---|---|
| **Study Design** | - Open-label, dose-escalation, PK and PD, first-in-human Phase I study with opaganib |
| **Site** | - Medical University of South Carolina |
| **Subjects** | - 21 patients with advanced solid tumors, the majority of which were GI cancer patients |
| **Endpoints** | - **Primary endpoints:** to identify the maximum tolerated dose (MTD) and the dose limiting toxicities (DLTs) and to evaluate the safety of opaganib<br>- **Secondary endpoints:** to determine the PK and PD properties and to assess antitumor activity<br>- The study included the first-ever longitudinal analyses of plasma S1P levels as a potential PD biomarker for activity of a sphingolipid-targeted drug |
| **Positive Phase 1 Results (June 2016)** | - The study met its primary and secondary endpoints<br>- Opaganib was found to be safe and well tolerated as well as safely administered to cancer patients over a prolonged period at doses that provide circulating drug levels that are predicted to have therapeutic activity<br>- Administration of opaganib resulted in a rapid and pronounced decrease in S1P levels<br>- **One patient had a prolonged partial remission and several patients had prolonged stabilization of disease**<br>- Of the three patients with cholangiocarcinoma, one had a partial response and the other two stable disease, one which lasted for over a year |

# Opaganib – Completed Phase 2a Study for Cholangiocarcinoma

- Granted FDA Orphan Drug Designation for the treatment of cholangiocarcinoma
- Compassionate use for cholangiocarcinoma under Expanded Access Program

**Single-arm Phase 2a clinical study evaluating opaganib in patients with advanced, unresectable, intra-hepatic, perihilar and extra-hepatic cholangiocarcinoma**

**Study Part 1 – Treatment with opaganib:**

- Completed enrollment of the full cohort of 39 patients evaluable for efficacy in the first cohort
- Preliminary data indicated 6 of 39 patients evaluable for efficacy achieved the primary endpoint of stable disease or better for at least 4 months, with good safety and tolerability in heavily pretreated subjects with advanced cholangiocarcinoma
  - Preliminary data indicated a signal of activity in a number of subjects with advanced cholangiocarcinoma
  - Data to be submitted for presentation at upcoming scientific meeting

**Study Part 2 – Cotreatment of opaganib and hydroxychloroquine sulfate (HCQ), an anti-autophagy agent:**

- This expansion cohort was opened in light of the Part 1 preliminary data, positive data from a preclinical program evaluating opaganib in combination with additional compounds, and KOL input
- RedHill closed enrollment to the second dose tier of Stage 1 In May 2022, due to COVID-19 pandemic-related enrollment slowdown
- **Of the 7 patients enrolled (4 evaluable for efficacy), one subject demonstrated durable stable disease for 10 months and transitioned to a Single Patient IND**
- RedHill is exploring combination therapies and selection biomarkers to establish a development pathway in this indication

# Opaganib - Promising Preclinical Efficacy in Neuroblastoma

- Positive data indicate opaganib may enhance the therapeutic efficacy of the oxaliplatin + doxorubicin (OXDOX) chemotherapy combination in high-risk neuroblastoma
- Data showed opaganib directly destabilized n-Myc, a key oncogenic driver of neuroblastoma and other solid tumors
- n-Myc regulates cell proliferation, differentiation, and apoptosis during embryonic development and is a critical factor driving poor outcomes
- **Findings support opaganib's potential as an add-on therapy in high-risk neuroblastoma**

*Studies conducted by Penn State (Jeremy Hengst, PhD) and our partner, Apogee Biotechnology; funded by the Beat Childhood Cancer Foundation and Four Diamonds*

# Opaganib COVID-19 Global Phase 2/3 Program Overview

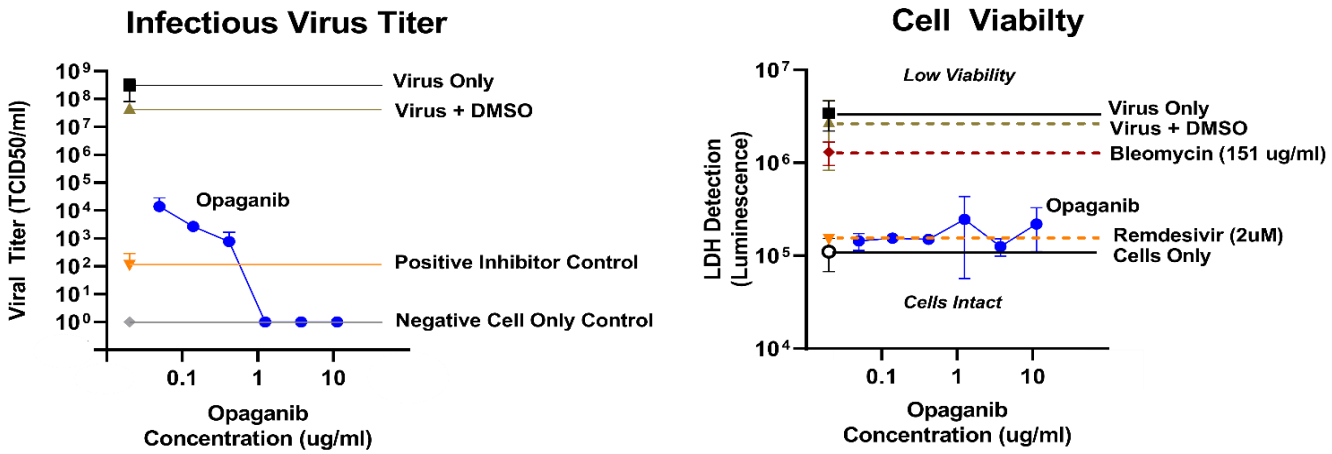
- ✓ Opaganib completed a 463-patient global Phase 2/3 study in hospitalized patients with severe COVID-19 pneumonia (NCT04467840)
- ✓ Key findings for opaganib included:
  - ✓ **Improved viral RNA clearance, reducing the median time to clearance by at least 4 days in patients with severe COVID-19 pneumonia (prespecified Phase 2/3 analysis)**
  - ✓ **A 70.2% mortality benefit when added to the best available SoC* in hospitalized patients, and a significant 34% benefit in time to recovery (prespecified Phase 2/3 analysis)**
  - ✓ **A 62% mortality reduction in a large subgroup of moderately severe hospitalized COVID-19 patients (post hoc Phase 2/3 analysis)[i]**
- ✓ The proposed mechanism of action is host-directed and potentially broad-acting – opaganib targets a host cell component, SPHK2, important for RNA virus replication, making it likely to remain effective against emerging viral variants[ii]
- ✓ Opaganib is under evaluation for its potential to treat virus-induced acute respiratory distress syndrome (ARDS) caused by COVID-19 and influenza
  - ✓ Data from the global Phase 2/3 COVID-19 study provide a strong rationale for further evaluating opaganib's potential in treating virus-induced ARDS, potentially supporting a Phase 2/3 study in this indication

** SoC: standard of care; in this study, SoC included treatment with remdesivir and corticosteroids.*

*[i] Neuenschwander FC, et al. Effect of Opaganib on Supplemental Oxygen and Mortality in Patients with Severe SARS-CoV-2 Based upon FIO2 Requirements. Microorganisms. 2024; 12(9):1767. [ii] Smith CD, et al. Recent Progress in the Development of Opaganib for the Treatment of Covid-19. Drug Design, Development and Therapy. 2022;Volume 16:2199–2211.*

# Opaganib Demonstrated Potent Antiviral Activity Against SARS-CoV-2 Variants

- Opaganib was evaluated in *in vitro* model of human lung bronchial tissue (EpiAirway™), including positive control of remdesivir:
  - Opaganib inhibited infectious virus production of SARS-CoV-2 (WA1/2020) in a dose-dependent manner at pharmacologically relevant concentrations, **with complete inhibition seen starting at 1 µg/ml**, without cytotoxicity
  - Dose-dependent inhibition of virus production shown without compromising cell membrane integrity




- Opaganib further demonstrated potent inhibition *of Delta*, *Beta* and *Gamma* SARS-CoV-2 variants in a preclinical study at non-cytotoxic doses
- Opaganib further demonstrated *in vitro* inhibition of *Omicron*, including sub-variant BA.5 adding to previous variant-agnostic efficacy data

# Opaganib Global Phase 2/3 Study in Severe COVID-19

## Global Phase 2/3 study in patients hospitalized with severe COVID-19 pneumonia

- Randomized, double-blind, parallel-arm, placebo-controlled global Phase 2/3 study
- 475 Patients randomized 1:1 to receive opaganib or placebo on top of standard-of-care
- Primary endpoint: proportion of patients reaching room air by Day 14

## Top-line data demonstrated positive trends:

- Despite not meeting the primary endpoint, analysis of the study efficacy endpoints showed trends in favor of the opaganib arm vs. placebo across multiple endpoints, including the primary endpoint, despite not achieving statistical significance

## Post hoc analysis demonstrated a statistically significant benefit to moderately severe patients, supporting potential use in earlier stages of disease[i]:

- Analysis of 251 hospitalized, moderately severe COVID-19 patients requiring a Fraction of inspired Oxygen (FiO2) up to 60% (54% of study participants) showed:
  - ✓ 62% statistically significant reduction in mortality (7/117 in opaganib arm vs. 21/134 for placebo; nominal p-value=0.019, Relative Risk 2.6)
  - ✓ 21% statistically significant efficacy benefit in reaching room air by day 14 (77% of opaganib patients vs. 63.5% for placebo; nominal p-value=0.033)
  - ✓ 4-day earlier hospital discharge (10 days for opaganib vs. 14 for placebo) resulting in a total saving of 524 cumulative hospitalization days across the group by Day 42 (nominal p-value=0.0195)
  - ✓ Overall adverse events balanced between the groups, suggesting good safety

[i] *Neuenschwander FC, et al. Effect of Opaganib on Supplemental Oxygen and Mortality in Patients with Severe SARS-CoV-2 Based upon FIO2 Requirements. Microorganisms. 2024; 12(9):1767.*

# Opaganib Global Phase 2/3 Study in Severe COVID-19 - Significant Improvement in Viral Clearance

- ✓ In a prespecified analysis of all Phase 2/3 study patients with positive PCR at screening, opaganib improved median time to viral RNA clearance by at least 4 days
    - Median of 10 days for viral clearance in the opaganib arm vs. clearance median not reached by end of 14-day treatment in placebo arm (Hazard Ratio 1.34; nominal p-value=0.043, n=437/463)
- ✓ Results were achieved in a severely ill hospitalized patient population with a median of 11-days from onset of symptoms - a patient population much further advanced than mild-moderate outpatients with less than 5 days from symptom onset, for which oral anti-viral medications have recently been approved

# Opaganib Global Phase 2/3 Study in Severe COVID-19 - 70% Mortality Benefit in Opaganib + SoC Subgroup

- ✓ A prespecified analysis of Phase 2/3 data in severe COVID-19 patients showed a **significant 70.2% mortality benefit** with opaganib by Day 42 when given on top of the best available SoC, remdesivir and corticosteroids
  - Mortality rate of 6.98% for the opaganib + SoC arm (n=3/43) vs. 23.4% for placebo + SoC arm (n=11/47) (nominal p-value=0.034)
- ✓ A second prespecified analysis showed opaganib delivered a **significant 34% benefit in time to recovery**, defined as achieving a score of 1 or less on the WHO Ordinal Scale by Day 14
  - 37.4% of opaganib +SoC arm (n=86/230) reached this event vs. 27.9% of placebo + SoC arm (n=65/233) (nominal p-value=0.013, Hazard Ratio 1.49)
- Results were achieved in a severely ill hospitalized patient population with a median of 11-days from symptom onset

# Opaganib Activity Against Ebola and Additional Viruses

- RedHill reported preclinical data from multiple studies evaluating opaganib's potential against Ebola and influenza in collaboration with U.S. Government agencies:

| | |
|---|---|
| **Ebola virus disease** | • U.S. Army Medical Research Institute of Infectious Diseases (USAMIIRD) funded *in vivo* Ebola viral infection studies show that opaganib may increase survival (at 150 mg/kg BID)<br>• Opaganib, in combination with remdesivir (Veklury®) also showed a distinct synergistic effect against Ebola in a separate *in vitro* study |
| **Influenza** | • National Institute of Allergy and Infectious Diseases (NIAID) study results demonstrated opaganib's potent *in vitro* inhibition of influenza A H1N1, at low concentrations and with no evidence of toxicity at these levels* |

| Opaganib Concentration | $EC_{90}$ | $CC_{50}$ | $SI_{90}$ |
|---|---|---|---|
| 0.05-3 µg/ml | <0.05 | >3 | >60 |

**Utilizing preclinical services from the NIAID, part of the National Institutes of Health (NIH)*

*The results were obtained in Normal Human Bronchial Epithelial Cells (NHBE) assay, the natural human target of the virus, making it a realistic model*

- RedHill is seeking ongoing collaborations for further development of opaganib in Ebola
- Additional preclinical evaluation ongoing with NIAID for various antiviral indications

# SPHK2 Inhibition in Metabolic Disease - Potential of Opaganib Therapy for Diabetes and Obesity-Related Disorders

- Positive results from multiple *in vivo* studies show the impact of SPHK2 inhibition in various models of metabolic disease, supporting the potential of opaganib therapy for diabetes and obesity-related disorders, alone or combined with semaglutide[i]
- Sphingolipid metabolism is implicated in insulin resistance, β-cell disruption, adipocyte function, inflammation and immune regulation, vascular complications and energy metabolism – all significant components of obesity, diabetes and their associated complications
- Opaganib's ability to modulate multiple signaling pathways through simultaneous inhibition of three sphingolipid-metabolizing enzymes in human cells provides a strong rationale for evaluation of opaganib in obesity-related disorders
- Global obesity-diabetes drugs market is projected to be worth around $100 billion by 2034 – largely driven by Glucagon-like peptide-1 (GLP-1) inhibitors (Ozempic®, Wegovy®, Trulicity® and Mounjaro®) and sodium glucose cotransporter-2 (SGLT2) inhibitors (Jardiance®)

[i] *Maines, L et al. Opaganib Promotes Weight Loss and Suppresses High-Fat Diet-Induced Obesity and Glucose Intolerance. Diabetes, Metabolic Syndrome and Obesity. 2025; 16: 969–83. https://doi.org/10.2147/dmso.s514548.*




# RHB-204

*Investigational new drug*

*Proprietary, fixed-dose oral antibiotic combination therapies in development for the treatment of moderate to severe Crohn's disease in Mycobacterium avium subspecies paratuberculosis-positive (MAP+) patients*

***RHB-204: Crohn's Disease – Phase 2 Study Planned, supported by positive RHB-104 Phase 3 study results with RHB-104; Positive FDA feedback on pathway to approval received***

***Pulmonary NTM disease – Phase 3-Stage; Granted FDA Orphan Drug Designation and QIDP Designation, Including Fast-Track Development Status***

# RHB-204 for Crohn's Disease – Next-Generation Formulation of RedHill's RHB-104

| | |
|---|---|
| **Planned Indication** | - Moderate to severe Crohn's disease (CD) in *Mycobacterium avium subspecies paratuberculosis* -positive (MAP+) patients |
| **Additional Potential Indication** | - Potential first-line therapy in Phase-3 stage development for pulmonary nontuberculous mycobacterial (NTM) disease caused by *Mycobacterium avium* complex (MAC), where no FDA-approved first-line therapies exist |
| **The Product** | - Proprietary, fixed-dose, oral capsule containing a combination of three antibiotics, incl. clarithromycin, rifabutin and clofazimine, with potent intracellular, anti-mycobacterial and anti-inflammatory properties |
| **Key Attributes** | - Novel next-generation formulation of Phase 3-stage RHB-104 designed to support enhanced tolerability, safety and adherence<br>- Supports a differentiated therapeutic approach targeting both the suspected underlying cause and symptoms of the disease<br>- Supported by positive RHB-104 Phase 3 results in CD |
| **Market Size** | - CD market expected to grow from $13.6 Bn to $19.1 Bn across the U.S., Japan, and EU5 over 2024-2033 at a CAGR of 3.87%[i] |
| **Development Status** | - **Phase 2 study planned in MAP+ moderate to severe CD patients; Positive FDA feedback on pathway to approval received** |
| **IP** | - Patent protected until at least 2041 |

[i] *DataMonitor - Disease Analysis: Crohn's Disease, September 2024.*

# RHB-204: Next-Generation Formulation of Phase 3-Stage RHB-104 for Crohn's Disease

- **RHB-204** is a proprietary, oral fixed-dose-combination of antibiotics (clarithromycin, rifabutin and clofazimine) targeting *Mycobacterium avium subspecies paratuberculosis* (MAP)-positive Crohn's Disease (CD)
- RHB-204 contains the same antibiotic components as RHB-104, with an optimized dosing profile designed to enhance tolerability, safety and patient adherence
  - Components include antimicrobial agents with potent intracellular, anti-mycobacterial and anti-inflammatory properties
- A Phase 2 study of RHB-204 in MAP-positive patients is planned - positive feedback and guidance on pathway to approval was received following a Type C meeting with FDA
- **This study introduces a novel approach by addressing the root cause of CD, which is suspected to be caused by MAP**
- **If approved, RHB-204 has the potential to shift the treatment paradigm by addressing the suspected underlying cause and symptoms of CD**
- RHB-204 is supported by a strong foundation of clinical data from the positive safety and efficacy results achieved in the RHB-104 Phase 3 study
- Strong patent protection until at least 2041



# Crohn's Disease and the Potential Role of *Mycobacterium avium subspecies paratuberculosis* (MAP)

- **Crohn's disease** causes inflammation of the digestive tract which can be both painful and debilitating, and may lead to life-threatening complications
- Most likely a result of a combination of inherited genetic traits, environmental stimuli, and overzealous immune and inflammatory responses
- MAP has been implicated as a potential infectious cause of Crohn's disease[i]
- MAP causes Johne's disease in cattle, an intestinal condition with clinical and pathological similarities to Crohn's disease:
  - An intracellular pathogen that proliferates in monocytes/macrophages
  - Extremely slow growing and widely pervasive in the environment
- Advances in diagnostic technology have enabled higher detection of MAP in Crohn's diseases patients
  - 92% (34/37 Crohn's disease patients by PCR)[ii]
  - 86% (52/60 Crohn's disease patients)[iii]
- Phase 3 data support the anti-MAP approach: RHB-104 showed higher remission (36.7% vs. 22.4%; p=0.0048), superior response (p=0.0042), and improved fecal calprotectin vs. placebo[iv]

*[i] Greenstein RJ, The Lancet Infectious Diseases, 2003. [ii] Bull, J Clin Microbiol, 2003. [iii] Shafran, Dig Dis Sci, 2002. [iv] Graham DY, Naser SA, Borody T, Hebzda Z, Sarles H, Levenson S, Hardi R, Arłukowicz T, Svorcan P, Fathi R, et al. Randomized, Double-Blind, Placebo-Controlled Study of Anti-Mycobacterial Therapy (RHB-104) in Active Crohn's Disease. Antibiotics. 2024; 13(8):694.*

# RHB-204: Next-Generation Formulation of RHB-104 - Rationale

✓ **Enhanced safety and tolerability:**

| Antibiotic | RHB-204 Daily Dose | RHB-104 Daily Dose | Rationale for Dose Selection (RHB-204) |
|---|---|---|---|
| **Clofazimine** | 80 mg | 100 mg | Reduced dose to minimize risk of QT prolongation |
| **Rifabutin** | 240 mg | 450 mg | Reduced dose to reduce risk of myelotoxicity, uveitis and drug interaction effects on clarithromycin |
| **Clarithromycin** | 950 mg | | Key antimycobacterial agent maintained at the same dose, with the addition of two antibiotics to mitigate development of antibiotic resistance |

- *In vitro data show RHB-204 is comparable to RHB-104 in MAP-killing efficacy (spot and phage assays across multiple MAP strains), achieved at the lower doses of the two actives – suggesting potential for reduced toxicity and side effects*

✓ **Reduced pill burden:** Dosing of 3 capsules BID (6 pills per day) instead-of the prior 5 capsules BID (10 pills per day), reducing pill burden by 40% and potentially leading to improved patient adherence

✓ **Extended IP protection:** Composition of matter patent extending to at least 2041 as well as regulatory protection

✓ **Strong clinical foundation:** RHB-204 is supported by a strong foundation of clinical data from the positive safety and efficacy results achieved in the RHB-104 Phase 3 study in CD (“MAP US” study)

# RHB-204 - Development Plans for Crohn's Disease (CD)[i]

## Planned Phase 2 Study:

- 40-80 patients with MAP-positive, active (i.e., inflammatory markers elevated) moderate-to-severe CD will be selected using digital PCR evaluation of MAP tissues[ii] and randomized to receive active treatment or placebo in addition to standard of care
- **Expected Primary Endpoints per FDA Guidance:**
  - Mucosal healing - considered by FDA as a new gold standard in efficacy evaluation in CD
  - MAP status
  - Clinical remission

  - ➢ The planned study will be the first ever clinical study in specifically defined MAP-positive CD patients
  - ➢ RedHill initiated two new collaborations with leading academic centers utilizing cutting-edge rapid and accurate MAP detection diagnostics – the lack of which has previously been a major barrier to advancing the Company's novel anti-MAP CD program
  - ➢ The innovative study design enables a smaller sample size allowing for lower study costs and faster time to completion
  - ➢ Clinical study material has already been manufactured and is in place ready for study implementation

*[i] Additional FDA guidance on the potential path to approval of RHB-204 is to be obtained prior to initiation of further clinical studies.[ii] Subject to potential further validation.*

# RHB-104 Positive First Phase 3 Study in Crohn's - Met Primary Endpoint and Key Secondary Endpoints

Multi-center, randomized, double-blind, placebo-controlled, parallel group study (MAP US study) to assess efficacy and safety of orally administered, fixed-dose combination RHB-104 in subjects with moderately to severely active Crohn's disease, on-top of baseline background SoC medications

| | |
|---|---|
| **Number of Subjects** | 331 |
| **Sites** | 92 sites across the U.S., Canada, Europe, Australia, New Zealand and Israel |
| **Treatment Groups** | Patients randomized 1:1 to RHB-104 vs. placebo BID as add-on to standard-of-care, stratified for concomitant use of anti-TNF agents |
| **Primary Endpoint** | State of remission at week 26 |
| **Previous Studies** | - Several PK, Phase 1, 2 and 3 clinical studies conducted |
| **Phase 3 MAP US Development Status** | - Positive Phase 3 results - study met its primary endpoint and key secondary endpoints |

# RHB-104 Crohn's Disease Phase 3 - Positive Results

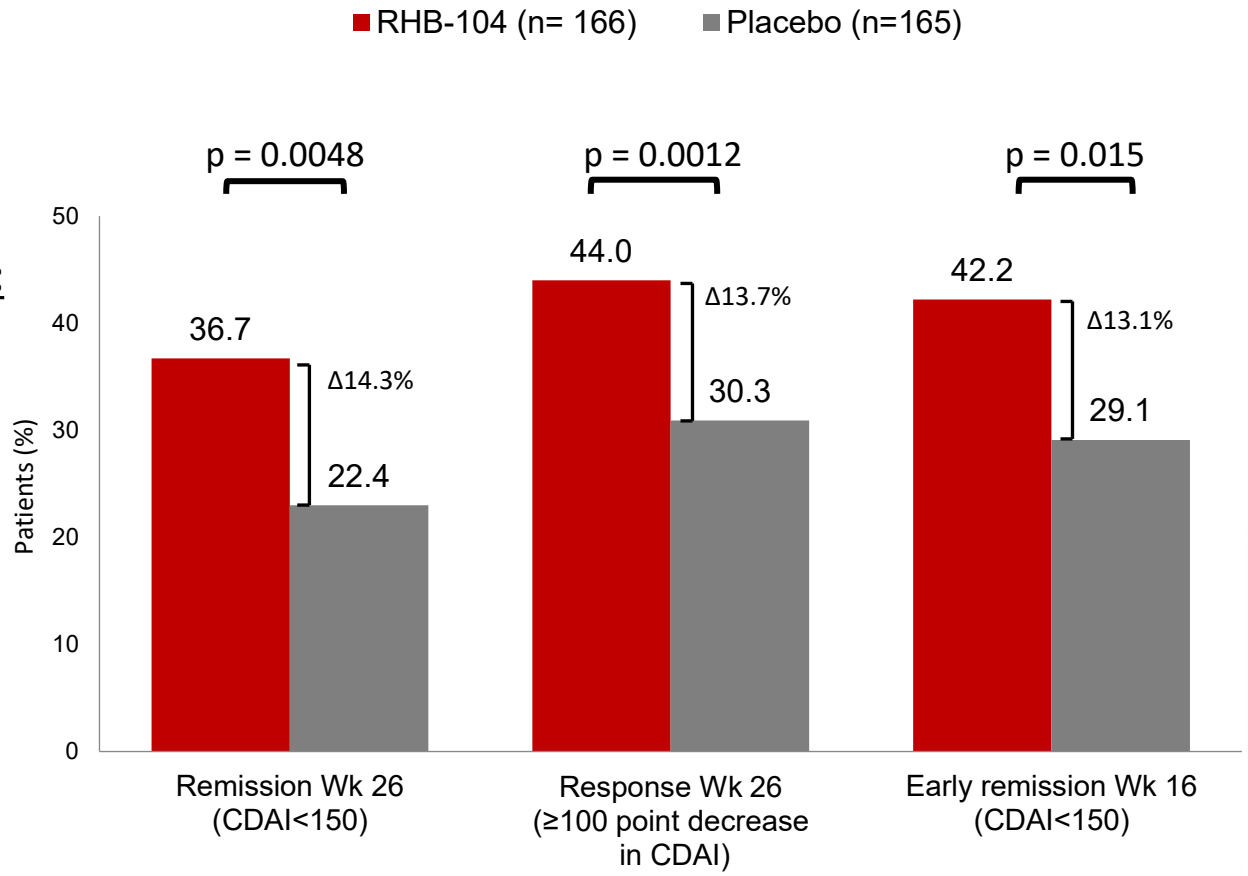
**The MAP US Phase 3 study met its primary and key secondary endpoints, demonstrating meaningful, consistent and statistically significant clinical activity of orally administered RHB-104 as an add-on to standard-of-care treatments**

**Primary Endpoint Met:**

- ✓ Remission at week 26

**Secondary Endpoints Met:**

- ✓ Response at week 26
- ✓ Early remission at week 16




[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no).*

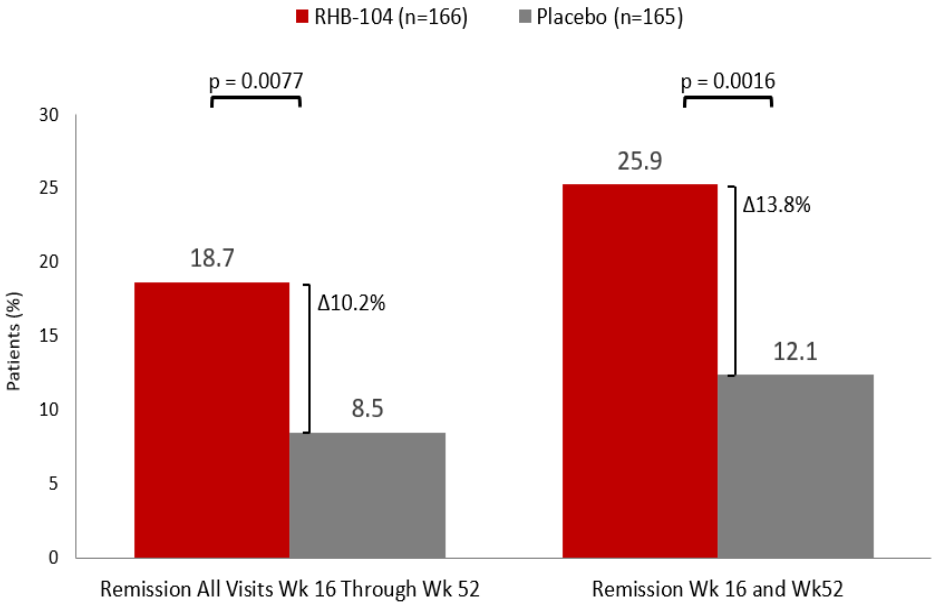
# RHB-104 Crohn's Disease Phase 3 - Positive Results

## Additional Endpoints Met:

- ✓ **Durable remission weeks 16-52:** statistically significant benefit in durable remission on all visits, weeks 16-52, demonstrating an improvement of 100% over placebo
- ✓ **Maintenance of remission:** analysis of maintenance of remission at week 52 in subjects noted to be in remission at week 16 demonstrated statistically significant benefit with RHB-104 over placebo

## Safety:

- ✓ **RHB-104 was demonstrated to be generally safe and well-tolerated** similar TAEs, SAEs and AEs leading to study drug discontinuation between treatment groups
- ✓ ECG monitoring report demonstrated evidence of progressive prolongation of the QTcF interval across visits; None of these QT abnormalities resulted in adverse cardiac events




[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no);* [o] *Number of subjects reflects those subjects who have completed week 52 assessments and are no longer receiving blinded therapy.*

# RHB-204 for Crohn's Disease - Multiple Barriers to Entry

- Global patent portfolio, with additional claims being pursued
- Potential 3 years exclusivity for treatment of Crohn's disease under the FDA 505(b)(2) regulatory pathway
- Oral, all-in-one capsule solutions for patients and physicians (reduced co-pays, etc.)
- Limited commercial availability of clofazimine in the U.S., often requiring participation in an Expanded Access Program (EAP) or a name-based individual import permit
- Lower concentrations of the triple combination of RHB-204 active components provide excellent synergistic anti-MAP growth activity compared to individual or dual combinations of the drugs[i]
- Potential PK synergies of drug substances used in both formulations disappear when drug substances are administered concomitantly
- Generic alternatives for the antibiotic components of RHB-204 are not available at the dosages used in these products
- Physicians' potential liability exposure and complicated ramp-up period

[i] *Alcedo KP, et al. RHB-104 Triple Antibiotics Combination in Culture Is Bactericidal and Should Be Effective for Treatment of Crohn's Disease Associated with Mycobacterium Paratuberculosis. Gut Pathogens. 2016;8(1).*

# RHB-204 for Pulmonary Nontuberculous Mycobacterial (NTM)

| | |
|---|---|
| **Planned Indications** | - Pulmonary nontuberculous mycobacterial (NTM) disease caused by *Mycobacterium avium* complex (MAC) |
| **The Product** | - Proprietary, fixed-dose, oral capsule containing a combination of three antibiotics, incl. clarithromycin, rifabutin and clofazimine, with potent intracellular, anti-mycobacterial and anti-inflammatory properties |
| **Key Attributes** | - A potential first-line treatment for a disease with no FDA-approved first-line therapy<br>- Oral, fixed-dose combination product |
| **Development Status** | - U.S. Phase 3 study was terminated due to a low accrual rate |
| **IP** | - Patent protected until at least 2041<br>- Granted FDA QIDP and Fast-Track Designation for NTM disease, and Orphan Drug Designation by FDA and EMA, extending potential U.S. and EU post-approval market exclusivity to a total of 12 years and 10 years, respectively for NTM disease |

[i] *Foster Rosenblatt/Company estimates.*




# RHB-107 (upamostat)

*Late-Stage Investigational New Drug*

*First-in-class, broad-acting, host-directed serine protease inhibitor targeting COVID-19, oncological, GI and inflammatory lung diseases*

*Orally administered, once-daily, small molecule drug*

***Phase 2 study for COVID-19 in non-hospitalized patients - Positive Phase 2 data reported***

***--***

***Included in a separate U.S. Gov.-supported Phase 2 COVID-19 platform trial (PROTECT study) study terminated***

# RHB-107 - Broad-Acting, Host-Directed S1 Serine Protease Inhibitor Targeting Viral Infections, Oncology and GI Indications

| | |
|---|---|
| **The Drug** | - First-in-class, once-daily, oral, small molecule inhibitor of the S1 family of serine proteases<br>- **Broad-acting** with potential to treat multiple viral infections, oncology and GI-inflammatory indications<br>- **Host-directed antiviral** – RHB-107 targets host cell factors rather than viral factors, suggesting it will remain effective against emerging variants |
| | - RHB-107 is a potent inhibitor of multiple serine proteases, including human trypsin-3, trypsin-2, trypsin-6, trypsin-1 and matriptase-1<br>- RHB-107 also inhibits multiple type II transmembrane serine proteases (TTSPs), some of which are important factors in viral diseases |
| | - Licensed worldwide rights from Heidelberg Pharma (formerly Wilex), excluding China, Taiwan, Macao and Hong Kong |
| **Development Status** | – **Successfully completed a Phase 2 study in non-hospitalized patients with symptomatic COVID-19, meeting its primary endpoint of safety and tolerability; Highly promising efficacy results were also noted**<br>– **Included in a separate U.S. Gov.-supported Phase 2 platform trial for early COVID-19 outpatient treatment (PROTECT study) - the trial was terminated due to challenges to enrollment and U.S. Government funding limitations; While a benefit in time to resolution of symptoms and time to viral clearance were observed regarding the efficacy of RHB-107 in this study, it did not reach statistical significance**<br>– RHB-107 demonstrated a robust synergistic effect against Ebola when combined with remdesivir (Veklury®)* in an *in vitro* study funded by the U.S. Army<br>– Evaluation is planned for influenza |
| | – Demonstrated clinical safety profile from approx. 300 participants across 9 clinical studies |
| | – Phase 2 studies completed in locally advanced pancreatic cancer and metastatic breast cancer<br>– FDA Orphan Drug Designation granted for treatment of pancreatic cancer |
| | – Based on mechanism of action and preliminary preclinical evidence, RHB-107 may represent a new class of drugs for IBS treatment |
| **IP** | – Patent protected until at least 2041 |

**Remdesivir, a leading COVID-19 therapy, is sold under the brand name Veklury® by Gilead Sciences, Inc. (Nasdaq: GILD).*

# RHB-107- Positive Phase 2 COVID-19 Study

## Phase 2 study of RHB-107 in non-hospitalized patients with symptomatic COVID-19

| | |
|---|---|
| **Study Design** | – Patients randomized[i] on a 1:1:1 basis to receive placebo or one of two dose levels of RHB-107 (200 mg or 400 mg) for 14 days |
| **Sites** | – Six sites across the U.S. and one in South Africa |
| **Subjects** | – 61 patients participated in the study<br>– Patients required to have ≥2 moderate or severe symptoms at baseline |
| **Endpoints** | – **Primary endpoint:** Determination of the safety and tolerability of two dose levels and selection of a dose to be used in the pivotal efficacy study<br>– **Main secondary endpoint:** Time to sustained recovery from symptomatic illness |
| **Development Status** | – **RHB-107 successfully met the primary endpoint of safety and tolerability and delivered promising efficacy results, despite the small number of patients in each treatment group, including faster recovery from severe COVID-19 symptoms and 100% reduction in hospitalization due to COVID-19**<br>– Discussions ongoing for external non-dilutive funding for additional late-stage COVID-19 development |

[i] *Study arms were well balanced with respect to baseline disease severity, risk factors and vaccination status.*

# RHB-107 – Positive Phase 2 COVID-19 Study

**The primary endpoint was met** – RHB-107 was found to be safe and well-tolerated at both dose levels (200 mg and 400 mg) in COVID-19 outpatients

**Evaluation of secondary endpoints demonstrated preliminary evidence of efficacy, including:**

- **100% reduction in hospitalization due to worsening COVID-19:** Zero patients (0/41) on the RHB-107 arms vs. 15% (3/20) hospitalized on the placebo-controlled arm (nominal p-value=0.0317)

- **87.8% reduction in new severe COVID-19 symptoms after treatment initiation:** Only one patient in the RHB-107 treated group, 2.4%, (1/41) vs. 20% (4/20) of patients in the placebo-controlled arm (nominal p-value=0.036)

- **Days to sustained recovery, median (interquartile):**

| Placebo | RHB-107 (200 mg) | RHB-107 (400 mg) |
|---|---|---|
| 8 (4-26) days | 4 (2-6) days | 3 (2-6) days |

- The most common variant was *Delta*

# RHB-107- Phase 2 COVID-19 Platform Trial (PROTECT Study)

**The PROTECT study, conducted by ACESO* and partner organizations, was a U.S. Gov.-supported, adaptive, randomized, double blind, multi-site Phase 2 platform trial, comparing investigational products to control, in standard-risk, non-hospitalized adult SARS-CoV-2 infected participants (NCT05954286).**

| | |
|---|---|
| **Sites** | – Five sites across U.S., Thailand and South Africa |
| **Subjects** | – The study included standard-risk, non-hospitalized adult SARS-CoV-2 infected participants with at least two moderate-severe symptoms at baseline |
| **Primary Endpoint** | – Time to sustained alleviation or resolution of COVID-19 symptoms |
| **Development Status** | – The trial was terminated due to challenges to enrollment and U.S. Government funding limitations after a total of 92 of the planned 300 participants were enrolled<br>– While a benefit in time to resolution of symptoms and time to viral clearance were observed, it did not reach statistical significance<br>– Whether the lack of significant results were due to true lack of efficacy or accrual of fewer than one third of the planned number of patients is unknown<br>– The study was conducted by researchers from ACESO* and partner organizations and administered by the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF) |

**ACESO: Austere environments Consortium for Enhanced Sepsis Outcomes.*

# Thank You!

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