RedHill Biopharma Ltd.

("RDHL")

Corporate Presentation
February 2025

Forward Looking Statement

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All forward-looking statements included in this presentation are made only as of the date of this presentation. We assume no obligation to update any written or oral forward-looking statement made by us or on our behalf as a result of new information, future events or other factors.

Corporate Highlights

An 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 with Multiple Near-Term Milestones

$2.6m	Streamlined	Talicia®	5 late-stage clinical assets	Advanced clinical pipeline
H1/24 Net revenues (ended 6/30/2024)	U.S. commercial organization	No. 1 branded U.S. Rx for *H. pylori*	Significantly de-risked with multiple U.S. Government and other collaborations and including 2 novel, broad-acting, NCEs	Addressing multiple indications incl.: GI, infectious diseases (incl. pandemic preparedness) and medical countermeasures

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

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

Commercial Product[ii]

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

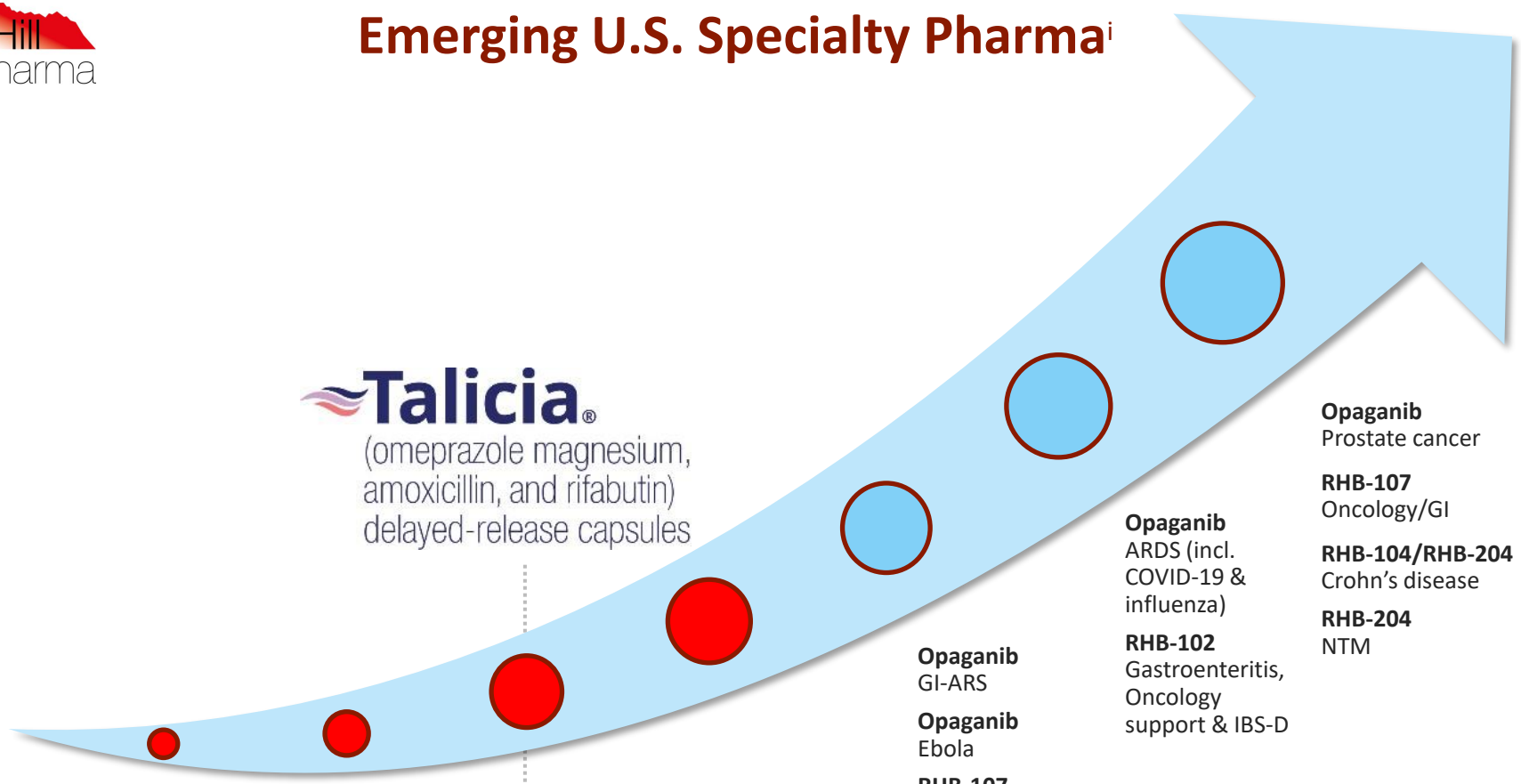
Talicia® (omeprazole magnesium, amoxicillin and rifabutin) - *H. pylori* infection in adults

Development Pipeline[iii]		Pre-Clinical	Phase 1/2	Phase 3	NDA
Opaganib • Anti-inflammatory • Antiviral • Anticancer	GI-ARS*(Radioprotection)	**U.S. Gov. collaborations** • NIH / BARDA funding • Pursuing FDA Animal Rule pathway			
	ARDS†(incl. COVID-19 & influenza)	**Phase 2/3 COVID-19 (ARDS)**			
	Oncology	**Phase 2 oncology programs** • Incl. an initiated Phase 2 study with opaganib in combination with Bayer's darolutamide in advanced prostate cancer			
	Ebola virus	**U.S. Gov. collaborations** • U.S. Army & BARDA funding			
RHB-107 (upamostat) • Antiviral	COVID-19, Oncology/GI	**Phase 2 COVID-19, GI & oncology indications** • Ongoing Phase 2 platform trial for early COVID-19 outpatient treatment (PROTECT study)			
	Ebola virus	**U.S. Army collaboration**			
RHB-102	Oncology support	**Comparative bioavailability studies** • UK MAA‡ in planning			
	Gastroenteritis	**Positive results from Phase 3 U.S. study**			
	IBS-D	**Positive results from Phase 2 U.S. study**			
RHB-204	NTM disease	**Phase 3-stage**			
RHB-104	Crohn's disease	**Positive results from Phase 3 MAP U.S. study**			

Broad-acting, host-directed antivirals

**GI-ARS: Gastrointestinal acute radiation syndrome; †ARDS: Acute respiratory distress syndrome; ‡MAA: Marketing Authorization Application. [i] Estimated timeline/indication in the pipeline is subject to changes in development plans and regulatory requirements/clarifications, including complementary /additional studies; [ii] Talicia®: www.talicia.com; [iii] Bekinda® (RHB-102) is a proposed tradename subject to FDA review and approval at the time of NDA filing.*

Emerging U.S. Specialty Pharma[i]



[i] Presented events are forward looking statements and estimates and are subject to uncertainties including, among others, clinical and regulatory outcomes, marketing approvals, financial resources and commercial viability; This slide and strategic plan is made for illustrative purposes only. Please see "Disclaimer and Forward-Looking Statements".

Financial Highlights[i]

RedHill Biopharma Ltd.
Nasdaq: RDHL

Market Cap (approx.)[i]	$7.6 million
American Depositary Shares (ADSs) (approx.)[ii]	1.3 million
Cash Balance as of June 30, 2024[iii]	$8.2 million
H1/24 Net Revenues	$2.6 million
H1/24 Gross Margin	45.4 %

[i] Financial information as of February 6, 2025, unless otherwise noted. [ii] Following a 25-to-1 reverse ADS split, effective August 20, 2024. [iii] Including cash, cash equivalents, short-term bank deposits and restricted cash.

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, Chief Operating Officer
MSc Neurology, MBE Cambridge, Sepal Pharma

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

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

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.

Eric Swenden
Alterphama nv, Lifeline Scientific

Kenneth Reed, MD
Dermatologist; Director Minerva Biotechnologies

Dr. Roni Mamluk, PhD
Ayala Pharmaceuticals, Chiasma

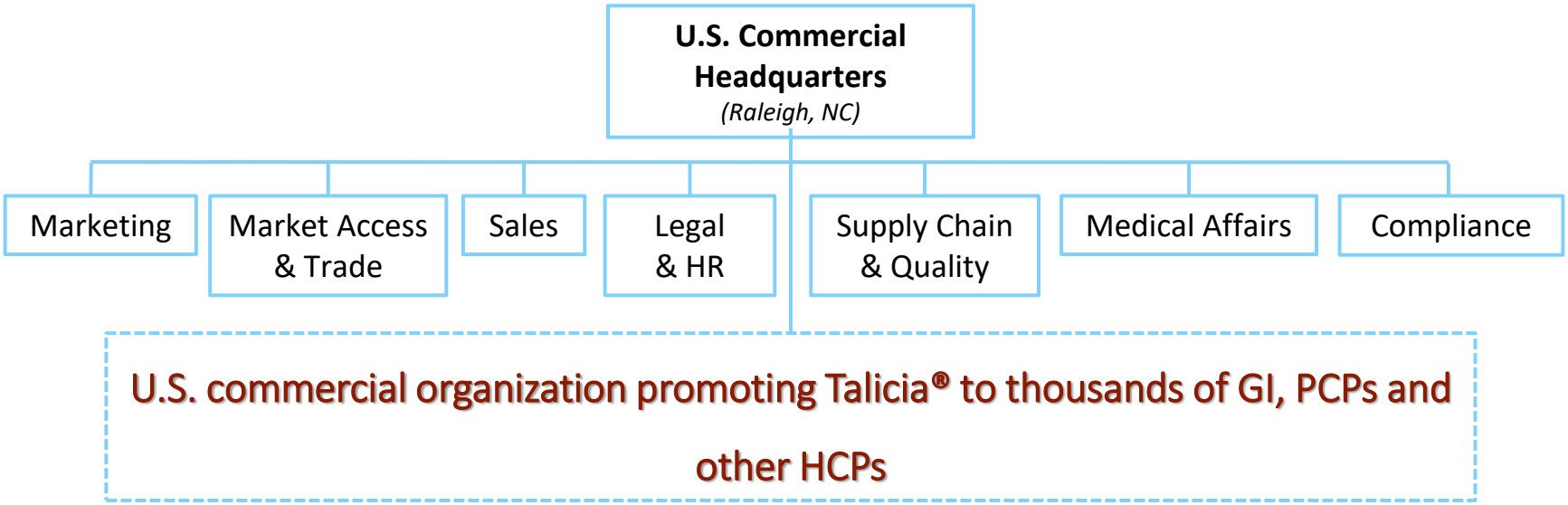
Shmuel Cabilly, PhD
Scientist, Director in several life-science companies

Rick D. Scruggs
Salix, Watson, Oclassen

Ofer Tsimchi
Danbar, Polysack, Director in several companies

* Includes select past positions

Streamlined U.S. Commercial Operations



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

Helicobacter pylori (*H. pylori*) infection
Launched Talicia® in Q1/2020

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 Positive Phase 3 Studies

Launched in the U.S. and UAE

Listed as First-Line Option for Treatment of H. pylori Infection in Newly Updated 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® (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

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]
Approved	– **NDA approved by U.S. FDA in November 2019 - launched in March 2020** – **Marketing approval received in United Arab Emirates (UAE) - launched in August 2024**
Key Attributes	✓ Zero-to-minimal[ii] *H. pylori* resistance to rifabutin and amoxicillin ✓ High rates of *H. pylori* eradication (>90%) achieved in Confirmed Adherent Population* ✓ Eradication rates remain high regardless of BMI or diabetes status[iii] ✓ Favorable tolerability and safety profile ✓ All-in-one formulation: supports ease of adherence, with a single co-pay
Market Exclusivity	– **FDA QIDP designation granted, providing eligibility for 8 years of market exclusivity** (initially 3 years, extended by 5 under QIDP) through 2027 – IP protecting Talicia®, with the latest patent to expire in 2042
Market Size	– **Affects over 50% of the world population, with ~2 million U.S. patients treated annually** – 2018 U.S. and global markets estimated at up to $1.4 billion and $4.8 billion respectively[iv] – **Rapid expansion of the prescriber base** – High levels of commercial (7/10 lives) and Government (6/10 lives) coverage

**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.[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] 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] 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.[iv] Foster Rosenblatt market analysis, October 2018.*

Talicia® Field Promotion Initiated July 2020

- ✓ RedHill's U.S. sales force promoting Talicia® to thousands of gastroenterologists, primary care physicians and other healthcare providers
- ✓ Rapid expansion in managed care coverage since launch

Talicia® is the Leading Branded *H. pylori* Therapy among U.S. Gastroenterologists[i]



Listed as First-Line Option for Treatment of H. pylori Infection in Newly Updated American College of Gastroenterology (ACG) Guideline[ii]

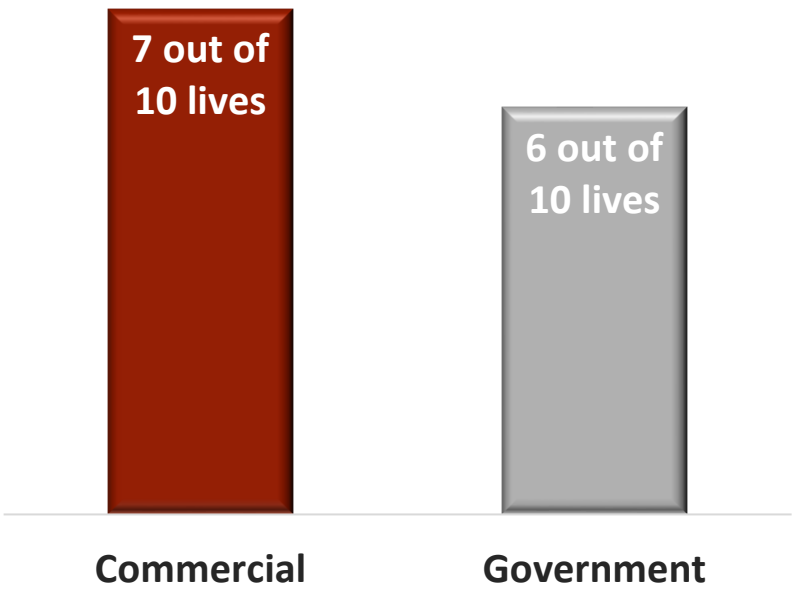
Now also commercially launched in UAE

[i] *IQVIA XPO data on file as of YTD 2024 (January - October).* [ii] *Chey WD, et al. ACG Clinical Guideline: Treatment of Helicobacter Pylori Infection. American Journal of Gastroenterology. 2024; 119(9): 1730-1753.*

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

Talicia® Coverage: 200 Million American Lives[i]

Talicia® Lives Covered[ii]



✓**Talicia now covered on Humana's Medicare Part D formularies.** Talicia® is the only Branded *H. pylori* therapy covered by Humana Part D without a Prior Authorization or Step Edit. Over 10M Medicare Part D lives now have formulary coverage of Talicia®

✓**Successful partnership established with major U.S. Retail Pharmacy chain** supporting patient access and affordability

✓**RedHill warranty program** supporting our conviction about the efficacy of Talicia®[iii] for commercial and cash patients

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

[i] Estimated coverage based on Managed Markets Insights & Technology (MMIT) as of December 31, 2024. [ii] Estimated coverage based on MMIT data for all payers as of December 31, 2024, coverage policies applied. [iii] Warranty commitment extends to commercially insured and non-insured Talicia® patients who completed the full 14-day treatment course and whose infection is not eradicated based on post-treatment confirmation testing.

H. pylori - Increasing Global Burden

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

- Chronic infection caused by *H. pylori*, a gram-negative bacterium that colonizes gastric mucosa, causes peptic ulcers and is the strongest risk factor for gastric cancer[i]:
  - Gastric cancer is the 4th most common cause of cancer related deaths worldwide, accounting for over 1 million new cases and approx. 800,000 deaths in 2020[ii]
  - Confirmed eradication of *H. pylori* infection leads to a ~75% decreased risk of gastric cancer[iii]
- *H. pylori* affects over 50% of the global population[i], with approx. 35% in the U.S.[iv] and 2 million patients treated annually[v]
- Commonly used therapies fail in approx. 25-40% of patients due to growing resistance of *H. pylori* to regimens containing antibiotics such as clarithromycin and metronidazole[vi]
- **2024 ACG* guideline was updated: No clarithromycin as a component to any therapy without prior resistance testing to confirm susceptibility[vii]**
- Failed antibiotic treatments may create newly-resistant bacteria[viii]

WHO and **FDA** identified clarithromycin-resistant *H. pylori* as a **priority for new drug development**

FDA recognized *H. pylori* as a pathogen with "**potential to pose a serious threat to public health**"

H. pylori added as a **human carcinogen** to the NTP's 2021 HHS Report on Carcinogens

**ACG: American College of Gastroenterology.* [i] *Lamb A, et al. Role of the Helicobacter pylori-induced inflammatory response in the development of gastric cancer. J Cell Biochem 2013 Mar;114(3):491-7.* [ii] *Morgan E, et al. The Current and Future Incidence and Mortality of Gastric Cancer in 185 Countries, 2020–40: A Population-Based Modelling Study. eClinicalMedicine, 2022, 47,101404.* [iii] *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).* [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, 2019;* [vi] *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.* [vii] *Chey WD, et al. ACG Clinical Guideline: Treatment of Helicobacter Pylori Infection. American Journal of Gastroenterology.2024; 119(9): 1730-1753.* [viii] *Nishizawa T, et al. Enhancement of Amoxicillin Resistance after Unsuccessful Helicobacter Pylori Eradication. Antimicrobial Agents and Chemotherapy. 2011;55(6):3012–3014.*

Positive Pivotal Phase 3 Study

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

Randomized, Double-Blind, Active Comparator, Two-Arm, Pivotal Phase 3 Study (ERADICATE Hp2), Comparing Talicia® Against a Regimen of Amoxicillin and Omeprazole Alone in the Treatment of Confirmed *H. pylori* Infection in Dyspepsia Patients, Regardless of Ulcer Status

Number of subjects	455 in the U.S.
Duration of Study Treatment	14 days
Primary Endpoint	The occurrence of *H. pylori* eradication in the Talicia® group compared to the active comparator group as confirmed via 13^C Urea Breath Test (UBT) testing 43-71 days after initiation of treatment

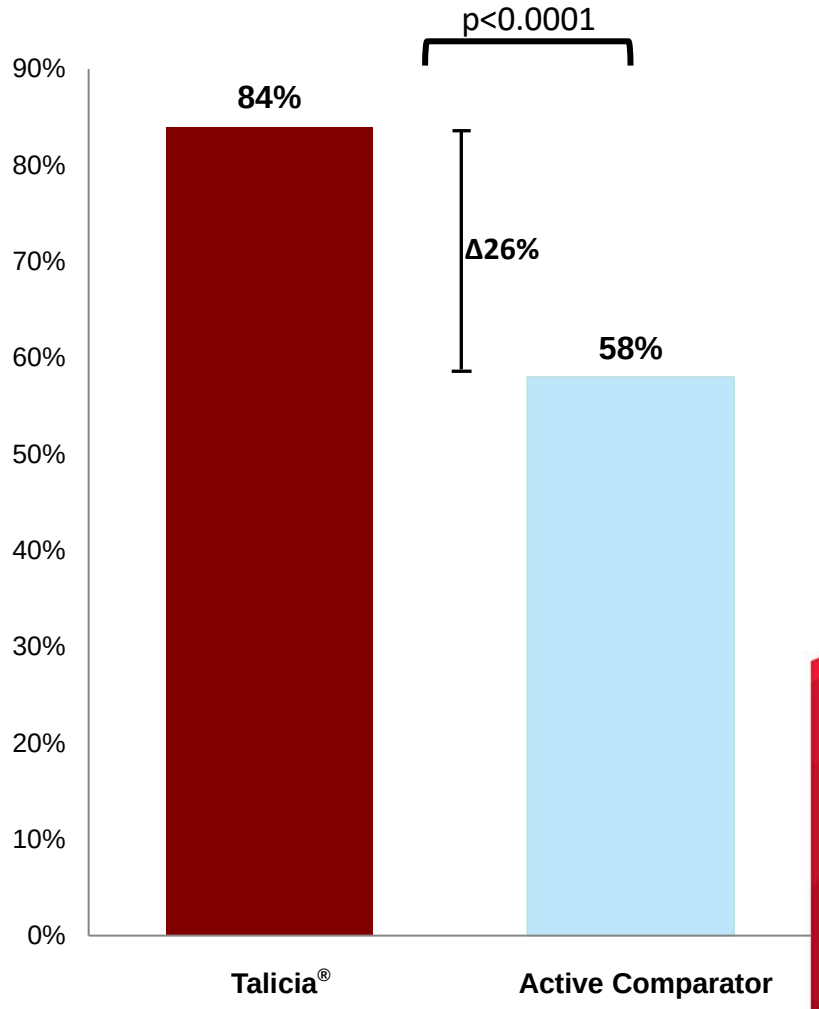
Positive Pivotal Phase 3 Study

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)

- Top-line results demonstrated 84% eradication of *H. pylori* with Talicia® vs. 58% in the active comparator arm (p<0.0001) (ITT)
- **90% eradication** based on adherence analysis (protocol defined subpopulation with evidence of drug exposure designated as Confirmed Adherent Population)
- No serious safety issues were reported in the study; Talicia® found to be well-tolerated

Analysis*	Phase 3 Results - Talicia® vs. Active Comparator	p-value
ITT Population	**84% vs. 58%**	**p<0.0001**
mITT Population	84% vs. 58%	p<0.0001
Confirmed Adherent Population (evidence of drug exposure)	**90% vs. 65%**	**P<0.0001**



[i] *ITT 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®

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 alternate antibiotics used in other therapies **vs.** zero to negligible resistance for the component antibiotics in Talicia®:

Alternate Antibiotics 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%)

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 - 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]** - **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** - 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.*

Strong Protection from Competition and Substitution

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

- FDA QIDP designation granted, providing eligibility for **8 years of market exclusivity** (initially 3 years, extended by 5 under QIDP) through 2027
- 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
- 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®- Clear Clinical Differentiation Provides Large Potential for Market Opportunity in the U.S. and WW

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

High Prevalence of *H. pylori*

Over 27M treatments annually WW[i]:
U.S.: 2M
5EU: up to 3.2M
Japan: up to 1.4M
China: up to 4.1M

Diminished Efficacy of commonly used therapies - Approx. 60%

Growing *H. pylori* resistance has led to diminished efficacy of commonly used therapies

Current Brand Medications Lack Clinical Differentiation

Talicia is the only branded agent employing a novel antibiotic (rifabutin) to eradicate *H. pylori*

$4.8B Global Market

Annual U.S. market for *H. pylori* therapies estimated at $1.4B[i]

Talicia®- Potential First-Line Therapy Targeting up to $1.4B U.S. Market

- **Efficacy** - demonstrated clinical activity with high statistical significance in eradicating *H. pylori* in two Phase 3 Trials (Pivotal and Supportive)
- **Addresses concerns of resistance** to clarithromycin and metronidazole
- **Attractive tolerability profile**
- **Potential to become preferred first-line treatment**
- **First all-in-one fixed-dose** - simple regimen potentially improves adherence and efficacy; Additional protection against generic substitution; Single co-pay

[i] Foster Rosenblatt. [ii] Fallone CA, et al. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults. Gastroenterology 2016;151:51–69.

RedHill Late-Stage R&D Pipeline

Late-Stage R&D Pipeline Overview[i]

Opaganib (ABC294640) *Broad-acting & host-directed antiviral*	
GI-ARS*	U.S. Gov. collaboration for evaluation as potential MCM[†] following FDA Animal Rule
Phosgene inhalation injury	Collaboration with Duke University School of Medicine for evaluation as potential MCM. FDA Animal Rule potential.
ARDS[‡] (incl. COVID-19 & influenza)	Phase 2/3 ready[ii]
Ebola virus disease	Preclinical-stage, in collaboration with the U.S. Gov. for evaluation as potential MCM
Influenza A H1N1	Preclinical-stage, in collaboration with NIAID
Inflammatory bowel disease	Phase 2 ready
Cholangiocarcinoma	Phase 2 study completed
Prostate cancer	• Phase 2 study with opaganib in combination with Bayer's darolutamide initiated • Prior investigator-sponsored Phase 2 study completed

RHB-107 (upamostat) *Broad-acting & host-directed antiviral*	
COVID-19 (symptomatic outpatients)	• Ongoing Phase 2 platform trial for early COVID-19 outpatient treatment (PROTECT study) • RedHill successfully completed a prior Phase 2 study
Ebola virus disease	Preclinical-stage
Pancreatic & breast cancer	Phase 2 PoC study completed

RHB-204	
Pulmonary nontuberculous Mycobacteria (NTM) disease	Phase 3 study terminated due to low enrollment rate

RHB-102	
Gastroenteritis & gastritis	Phase 3 study completed[iii]
Oncology support (in UK)	MAA[§] in planning
Diarrhea-predominant Irritable Bowel Syndrome (IBS-D)	Phase 3 ready

RHB-104	
Crohn's disease	First Phase 3 study completed[iv]
Multiple sclerosis	Phase 2a PoC study completed

**GI-ARS: Gastrointestinal acute radiation syndrome; †MCM: Medical countermeasure; ‡ ARDS: Acute respiratory distress syndrome. § MAA: Marketing Authorization Application. i Additional elaborated information can be found in this presentation and RedHill's ongoing public filings. [ii]Data obtained from the Phase 2/3 COVID-19 study to support the potential Phase 2/3 study ARDS. [iii] Confirmatory Phase 3 study is required and planned to support a potential NDA for RHB-102 (24 mg) for acute gastroenteritis and gastritis. iv Additional clinical studies are required to support an NDA for RHB-104 for Crohn's disease.*



Opaganib (ABC294640)[i]

Late-Stage Investigational New Drug

First-in-class, broad-acting, host-directed, orally administered sphingosine kinase-2 (SPHK2) inhibitor, targeting oncology indications, viral infection, nuclear/radioprotection and other inflammatory diseases

Gastrointestinal Acute Radiation Syndrome – U.S. Gov. collaboration; Development under FDA Animal Rule being pursued

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Data reported from global Phase 2/3 study in COVID-19; Ebola U.S. Gov. collaborations

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Phase 2 study in cholangiocarcinoma; Phase 2 study with opaganib in combination with Bayer's darolutamide initiated; Prior investigator-sponsored Phase 2 study in prostate cancer completed

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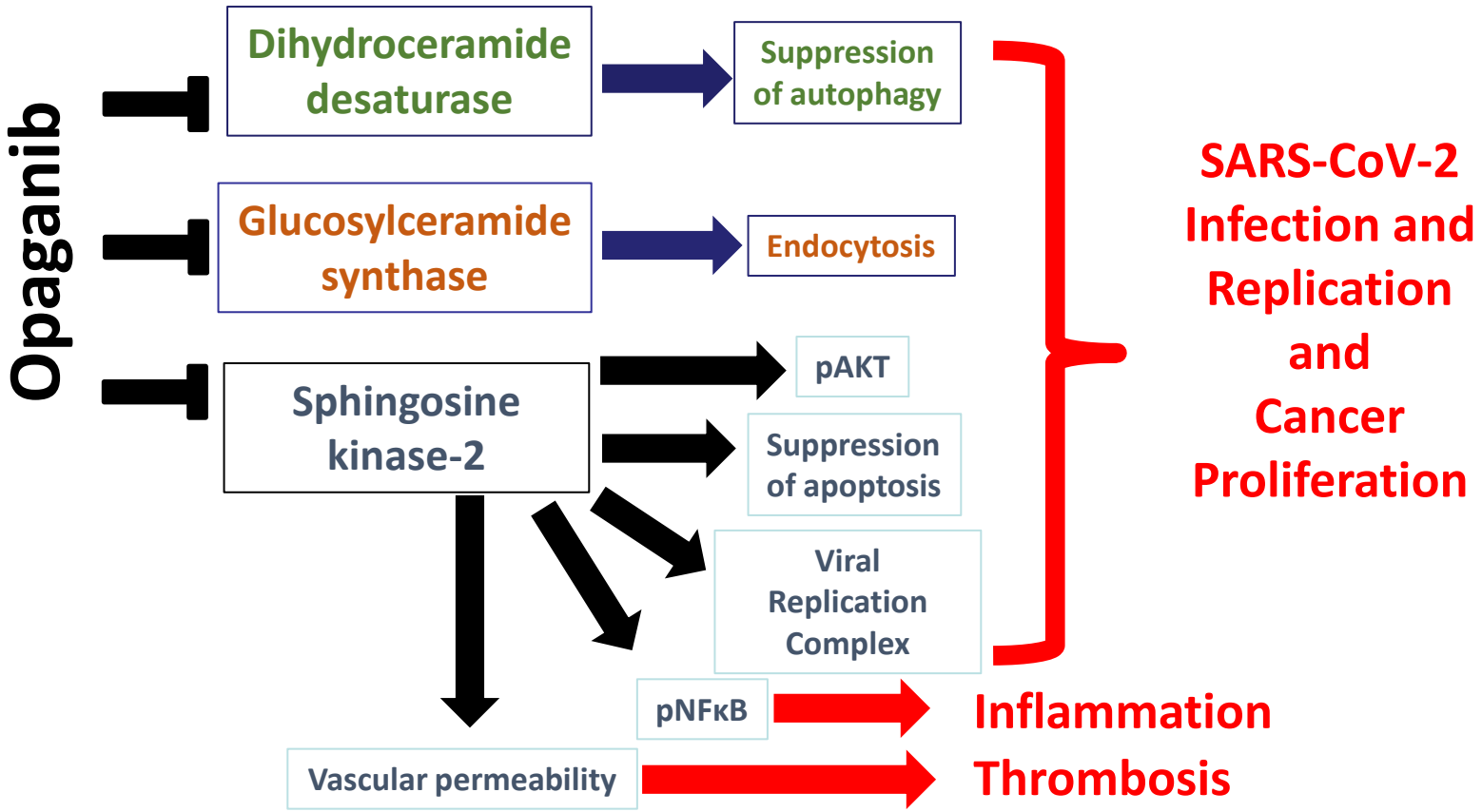
FDA Orphan Drug Designation granted for neuroblastoma

Opaganib – Broad-Acting, Host-Directed SPHK2 Inhibitor Targeting Inflammatory, Viral, GI, Metabolic and Oncological Diseases

The Product		- Potential **first-in-class, orally administered** sphingosine kinase-2 (SPHK2) inhibitor - **Broad-acting agent** targeting multiple potential diseases including COVID-19, acute respiratory distress syndrome (ARDS), gastrointestinal acute radiation syndrome (GI-ARS) and cholangiocarcinoma among others - **Host-directed and potent antiviral**, targeting a critical host factor and minimizing the potential development of drug resistance due to viral mutations - Demonstrated its **safety and tolerability** profile in more than 470 people in multiple clinical studies and expanded access use
Development Status	**Nuclear/Chemical Countermeasures, Inflammatory & GI**	- **Opaganib has been selected for evaluation as a potential medical countermeasure (MCM) against GI-ARS** by the U.S Gov's NIAID RNCP* for the nuclear MCM product development pipeline; RedHill announced positive preliminary results from new NIAID RNCP *in vivo* studies further confirming opaganib's protective activity in GI-ARS models in Dec 2024; Discussions are ongoing with NIAID regarding plans for next phase of development along the FDA Animal Rule pathway to approval - Additional collaboration discussions with U.S. and other governments are ongoing - RedHill ready to advance Phase 2 studies for **inflammatory bowel disease (IBD)**
	Viral diseases	- **Global Phase 2/3 COVID-19** study results demonstrated improved viral RNA clearance, faster time to recovery and reduced mortality in key subpopulations of moderate to severe hospitalized patients with COVID-19 - Results of **U.S. Army-funded *in vitro* and *in vivo* Ebola virus studies** showed that opaganib, delivered a statistically significant increase in survival time (at 150 mg/kg BID) in a U.S. Army-funded *in vivo* Ebola virus study, making it the first host-directed molecule to show activity in Ebola virus disease, and had previously showed *in vitro* that when combined with remdesivir**, opaganib demonstrated a synergistic effect, significantly improving potency while maintaining cell viability. BARDA collaboration ongoing - Preclinical development of opaganib in collaboration with the U.S. Army and NIAID for various antiviral indications is ongoing
	Oncology	- Phase 2a study for treatment of **cholangiocarcinoma** completed; FDA Orphan Drug Designation granted - Phase 2 study with opaganib in combination with Bayer's darolutamide in advanced ***prostate cancer*** has been initiated, and a prior investigator-sponsored Phase 2 study has been completed - Phase 1 study in cancer patients with ***advanced solid tumors*** completed - FDA Orphan Drug Designation granted in ***neuroblastoma***
	Metabolic disorders	- Positive results from multiple in vivo studies show the impact of sphingosine kinase-2 (SPHK2) inhibition in various models of ***metabolic disease***, supporting the potential of opaganib therapy for ***diabetes and obesity-related disorders***

**NIAID RNCP: National Institute of Allergy and Infectious Diseases Radiation and Nuclear Countermeasures Program. **Remdesivir, a leading COVID-19 therapy, is sold under the brand name Veklury® by Gilead Sciences, Inc. (Nasdaq: GILD).*

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.*

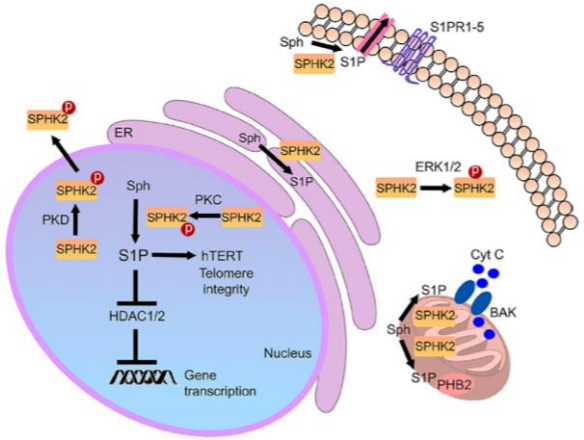
SPHK2 – Therapeutic Target for Metabolite Sphingosine-1-Phosphate (S1P) that has Pathological Roles in Various Diseases

- Sphingolipids regulate several important signaling transduction processes[i]
- Sphingosine Kinase 1 (SPHK1) and Sphingosine Kinase 2 (SPHK2) phosphorylate sphingosine to form Sphingosine-1-Phosphate (S1P)
- Many cells secrete S1P, which acts in an autocrine or paracrine manner, with most of the known actions of S1P being mediated by specific G protein-coupled receptors
- More recently, it was shown that S1P also has important intracellular targets involved in inflammation, cancer, infectious diseases and neurodegenerative diseases[ii, iii]

Intracellular Targets[iii]:

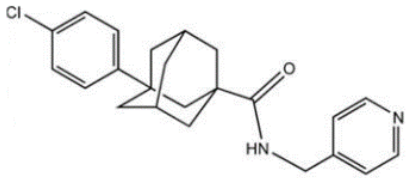
- In the nucleus, SPHK2 modulates gene expression and telomere integrity
- In the mitochondria, it may regulate prohibition 2 (PHB2) and Bax and Bak activation (BAK)
- In the ER it regulates cell death pathways
- In cancer, SPHK2 may be recruited to the plasma membrane, where it generates S1P

iv



[i] Kreitzburg KM, van Waardenburg RC, Yoon KJ. Sphingolipid metabolism and drug resistance in ovarian cancer. Cancer Drug Resistance. 2018;1. doi:10.20517/cdr.2018.06. [ii] Maceyka M, Harikumar KB, Milstien S, Spiegel S. Sphingosine-1-phosphate signaling and its role in disease. Trends in Cell Biology. 2012;22(1):50-60. doi:10.1016/j.tcb.2011.09.003. [iii, iv] Diaz Escarcega R, McCullough LD, Tsvetkov AS. The functional role of sphingosine kinase 2. Frontiers in Molecular Biosciences. 2021;8. doi:10.3389/fmolb.2021.683767.

Opaganib – A Potential Treatment for Gastrointestinal Acute Radiation Syndrome (GI-ARS)



- **Opaganib**, a novel, oral, small molecule, SPHK2 inhibitor, may offer a new therapeutic approach to mitigate GI-ARS
- **ARS** is an acute illness caused by irradiation of the body by a high dose of penetrating radiation in a short period of time; Can result from nuclear and radiological incidents (e.g., nuclear power plant accidents, detonations)
- Results from eight U.S. Government-funded *in vivo* studies and additional experiments indicate that opaganib is associated with:[i]
  - ✓ Protection of normal tissue, including gastrointestinal, from radiation damage due to ionizing radiation exposure or cancer radiotherapy
  - ✓ Improvement of antitumor activity, response to chemoradiation, and enhancement of tolerability and survival
- Additional collaboration discussions with U.S. and other governments are ongoing

[i] *Maines LW, et al. Opaganib Protects against Radiation Toxicity: Implications for Homeland Security and Antitumor Radiotherapy.-International Journal of Molecular Sciences. 2022;23(21):13191.*

U.S. Government Collaborations Aimed at Advancing the Development of Opaganib for ARS



RedHill, 2023:

- ✓ Opaganib selected by **National Institute of Allergy and Infectious Diseases (NIAID) Radiation and Nuclear Countermeasures Program (RNCP)** for testing via its radiation medical countermeasures Product Development Support contract as a potential treatment for ARS
- ✓ Opaganib awarded a further $1.7 million in U.S. Government funding via a **Small Business Innovation Research (SBIR) grant** awarded to RedHill's development partner, Apogee Biotechnology Corp. for development as a medical countermeasure for GI-ARS

Apogee Biotechnology Corp. (prior to the in-licensing of opaganib by RedHill in 2015):

- ✓ Contract received from the **U.S. Department of Health and Human Services' (HHS) Biomedical Advanced Research and Development Authority (BARDA)** to treat gastrointestinal (GI) tract injuries associated with ARS which was expanded by the Department of Defense (DOD)
- ✓ Contract received from the **National Cancer Institute (NCI)** to perform a proof-of-concept study to determine if opaganib reduces GI-ARS after abdominal or pelvic radiation in cell lines and mice

Opaganib Shows Promise as Radioprotectant in Animal Models and Safety in Humans

Opaganib:

- ✓ An advanced clinical stage orally administered; first-in-class patented novel sphingosine kinase 2 inhibitor; with over 5 years of stability shelf life
- ✓ Opaganib treatment was shown to be relatively safe and well-tolerated in clinical trials and in compassionate use indications in ~ 470 participants
- ✓ Substantially protects, *in vivo*, normal tissue from radiation damage that may occur through unintended exposure or cancer therapy
- ✓ Increases, *in vivo*, the antitumor activity of radiation (suppression of tumor growth and increased survival)
- ✓ Protects, *in vivo*, against radiation toxicity to GI tract
- ✓ Double allelic deletion of SK2 protects hematopoietic stem cells against radiation damage and improves survival of lethally irradiated mice
- ✓ This provides a mechanistic basis for SK2 inhibition as a potential therapeutic modality

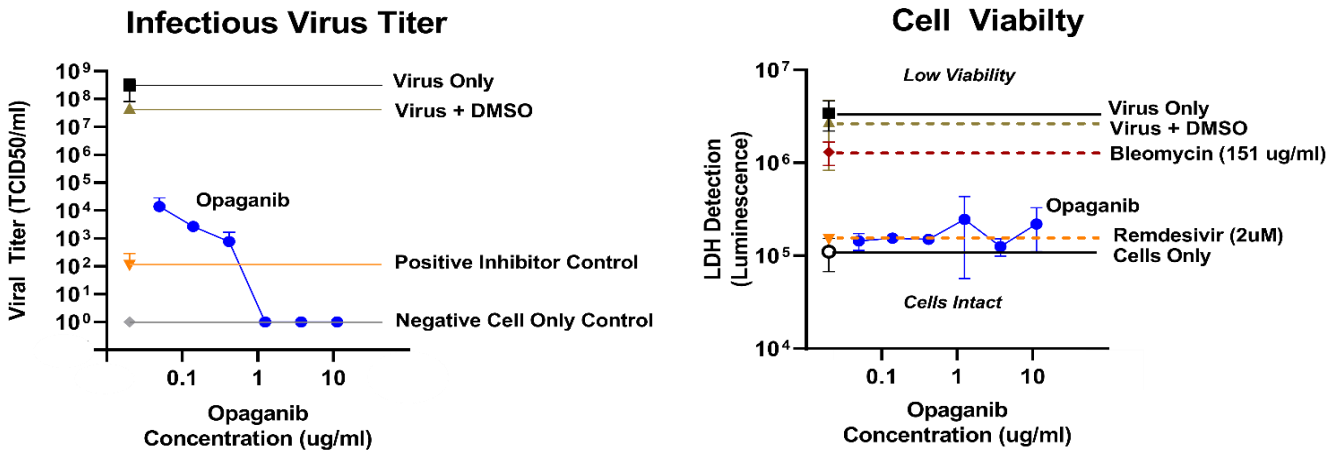
Opaganib COVID-19 Program: Overview

- ✓ **Novel oral drug candidate showing improved viral RNA clearance in patients with severe COVID-19 pneumonia**
- ✓ **Significant 70% mortality benefit when given on top of best SoC, as well as improved time to clinical recovery in a prespecified analysis of a Phase 2/3 study**
- ✓ **Demonstrated a 62% mortality reduction in a large subgroup of moderately severe hospitalized COVID-19 patients in a global Phase 2/3 post hoc analysis – data published in Microorganisms**[i]
- ✓ Successful preclinical model in human lung bronchial tissue showing complete inhibition of SARS-CoV-2 viral replication as measured after three days incubation
- ✓ Successful U.S. Phase 2 study (n=40) completed in hospitalized COVID-19 patients with promising safety and efficacy signals
- ✓ Over 470 subjects treated to date with a consistently favorable safety and tolerability profile
- ✓ Targets a host cell component, Sphingosine Kinase 2 (SPHK2), important for RNA virus replication, **irrespective of viral mutations** in the spike protein
- ✓ Independent anti-inflammatory activity
- ✓ Opaganib granted new USPTO patents protecting the administration of opaganib for the inhibition of a disease caused by a coronavirus in a subgroup population of patients requiring a fraction of inspired oxygen (FiO2) up to and including 60% at baseline, and covering the identification of a novel biomarker of coronavirus pneumonia (≤60% fraction of inspired oxygen (FiO2)) prognostic for potential opaganib efficacy in treating COVID-19

[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 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 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 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):
  - ✓ 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)
- ✓ **Opaganib is a novel oral drug candidate showing improved viral RNA clearance in patients with severe COVID-19 pneumonia**
- ✓ Provides clinical evidence supporting opaganib's potential antiviral activity
- ✓ Results 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 achieved in a severely ill hospitalized patient population with a median of 11-days from symptom onset

Opaganib Phase 2 COVID-19 Study - Positive Data

U.S. Phase 2 study of opaganib in patients hospitalized with COVID-19 pneumonia:

Non-powered study of 40 patients, randomized 1:1 to receive opaganib or placebo on top of standard-of-care. Follow up for up to 42 days post treatment initiation

Results demonstrated positive safety and efficacy signals:

- Opaganib found to be safe, with no material safety differences between the arms. Overall, fewer patients suffered from SAEs in the opaganib arm vs. placebo
- Opaganib arm demonstrated consistent trend of greater improvement in reducing oxygen requirement by end of treatment on Day 14 across key primary and secondary efficacy outcomes:
  - ✓ 50% of opaganib treated patients reached room air by Day 14 vs. 22% in the placebo group – benefit maintained regardless of whether patients received dexamethasone and/or remdesivir
  - ✓ 86.4% of opaganib treated patients were discharged from hospital by Day 14 vs. 55.6% of patients treated with placebo
  - ✓ Median time to discharge was 6 days for opaganib compared to 7.5 days for placebo
  - ✓ 81.8% of opaganib patients achieved a 2-point improvement in the WHO Ordinal Scale vs. 55.6% of patients in the placebo group – achieved in a median time of 6 days vs. 7.5 days, respectively
  - ✓ Greater reduction from baseline of the median total oxygen requirement (AUC) over 14 days (62% vs. 47%)

Opaganib – Novel, Host-Directed, Broad-Acting Agent Demonstrating Potent Antiviral Activity Against Multiple Viruses

- RedHill is working with the National Institute of Allergy and Infectious Diseases (NIAID) to evaluate opaganib's utility against a wide range of pathogens
- This work includes preclinical and translational research against additional viral infections, including Influenza, Chikungunya virus, RSV and Ebola
- **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

- **Results provide further evidence of opaganib's potential broad-acting antiviral effect**

SPHK2 as a Specific Target for Anti-cancer 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, 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
- SPHK2 also possesses a Pleckstrin Homology Domain allowing it to attach to membranes

Oncology Development Status

- ✓ 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
- ✓ Phase 2 study with opaganib in combination with Bayer's darolutamide in advanced prostate cancer initiated
- ✓ Prior investigator-sponsored Phase 2 study in prostate cancer completed - one study arm evaluated opaganib in combination with abiraterone; another study arm evaluated opaganib in combination with enzalutamide which showed activity but did not meet primary endpoint

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 - **Secondary endpoints:** to determine the PK and PD properties and to assess antitumor activity - 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 - 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 - Administration of opaganib resulted in a rapid and pronounced decrease in S1P levels - **One patient had a prolonged partial remission and several patients had prolonged stabilization of disease** - 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 - Phase 2a Study for Cholangiocarcinoma

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

Sites	Mayo Clinic, MD Anderson, Huntsman Cancer Institute, Emory University
Initiated	December 2017
Lead Investigator	Dr. Mitesh J. Borad, MD, Associate Professor of Medicine and Director of Phase I Drug Development at the Mayo Clinic Cancer Center in Arizona
Development status	- Enrollment completed for stand-alone arm (39 subjects) - preliminary data indicates efficacy signal in a number of subjects; data to be submitted for presentation - Second arm evaluating opaganib in combination with hydroxychloroquine, an anti-autophagy agent - Granted FDA Orphan Drug Designation for the treatment of cholangiocarcinoma - Compassionate use for cholangiocarcinoma under Expanded Access Program - **Phase 2 study completed**
Primary endpoint	- Response Rate - defined as CR+PR+SD of at least 4 months duration
Market Size	- Approximately 8,000 people are diagnosed with intrahepatic and extrahepatic bile duct cancers annually in the U.S.

Opaganib - Phase 2a Study for 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

Phase 2 Study: Opaganib in Combination with Bayer's Darolutamide 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 80 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 600mg bid + placebo (n=40) arm or the darolutamide 600 mg bid + opaganib 500 mg bid (n=40) arm
Primary Endpoint	- Improved 12-month radiographic progression-free survival (rPFS)
Development Status	- Study has been 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 - Phase 2 Study for Prostate Cancer

An investigator-sponsored Phase 2 Study evaluating the safety and efficacy of opaganib in metastatic castration-resistant prostate cancer (mCRPC) that is progressing during treatment with androgen-signaling blockers abiraterone or enzalutamide

Site	Medical University of South Carolina (Investigator Sponsored)
Dose	250 or 500 mg bid
Lead Investigator	Michael B. Lilly, MD, Professor at the Medical University of South Carolina Hollings Cancer Center
Development Status	- Study initiated in March 2020 - Cohort evaluating opaganib in combination with enzalutamide did not meet primary endpoint - Cohort evaluating opaganib in combination with abiraterone now complete
	- The study is supported by a grant from the NCI

Opaganib - Phase 2 Study for Prostate Cancer

Preliminary data from the investigator-sponsored Phase 2 study in metastatic castration-resistant prostate cancer (mCRPC) showed:

11 out of 66 patients (17%) achieved disease control, with all 66 patients completing enrollment:

3 in cohort 1a (abiraterone + opaganib 250 mg BID) 3 in cohort 1b (enzalutamide + opaganib 250 mg BID)	**3 patients achieved disease control**
26 in cohort 2 (abiraterone + opaganib 500 mg BID)	**4 patients achieved disease control (15%; 95% CI 4-35%)**
34 in cohort 3 (enzalutamide + opaganib 500 mg BID)	**4 patients achieved disease control (12%; 95% CI 3-27%)**

Data points to a distinct signal of activity, supporting testing of opaganib in selected populations and in possible combination therapies

Sphingosine Kinase-2 (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
- 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®)



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

--

Ongoing Phase 2 COVID-19 platform trial (PROTECT study)

--

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

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 - **Broad-acting** with potential to treat multiple viral infections, oncology and GI-inflammatory indications - **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 - 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	– **RHB-107 is being evaluated in the ongoing Phase 2 platform trial for early COVID-19 outpatient treatment (PROTECT study)** – **Successfully completed Phase 2 study in non-hospitalized patients with symptomatic COVID-19 in which the study met its primary endpoint showing good safety and tolerability; Highly promising efficacy results were also noted** – Demonstrated preliminary *in vitro* inhibition of *Omicron* BA.5 sub-variant – RHB-107, in combination with remdesivir (Veklury®)*, showed a distinct synergistic effect against Ebola in an *in vitro* study funded by the U.S. Army – RHB-107 is also the subject of several cooperative research projects with government and non-government bodies, evaluating RHB-107 against multiple viral targets, including influenza, amongst others
	– Demonstrated clinical safety profile from over 300 participants across 11 clinical studies
	– Phase 2 studies completed in locally advanced pancreatic cancer and metastatic breast cancer – FDA Orphan Drug Designation granted for treatment of pancreatic cancer – RHB-107 is planned to be evaluated in combination with opaganib in oncology
	– Based on mechanism of action and preliminary preclinical evidence, RHB-107 may represent a new class of drugs for IBS treatment

**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 – 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 – **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** – 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- Ongoing Phase 2 COVID-19 Platform Trial (PROTECT Study)

The PROTECT study, conducted by ACESO* and partner organizations, is an externally funded, 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). RHB-107 is the initial drug being evaluated in the early treatment arm of the study.

Sites	– Six sites across U.S., Thailand, South Africa and Uganda
Subjects	– Approximately 100 patients are expected to be fully enrolled out of the target patient population of 300 – The study will include 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	– Funding of the study by the JPEO-CBRND is subject to termination, requiring the study to cease enrolment on March 5th, 2025, prior to completion[i] – The study is being 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.* [i] *The reduction in number of patients randomized into the study may not allow for any conclusions to be reached regarding the efficacy of RHB-107 in this trial.*



RHB-102 (Bekinda®)[i]

Investigational new drug

Bimodal release, once-daily, oral tablet formulation of ondansetron

RHB-102 24 mg – UK MAA* in planning

RHB-102 24 mg – Positive Results from a U.S. Phase 3 Study for Gastroenteritis/Gastritis - Met Primary Endpoint

RHB-102 12 mg – Positive Results from a U.S. Phase 2 Study for IBS-D Met Primary Endpoint

**MAA: Marketing Authorisation Application.*

[i] Bekinda® is the proposed tradename for RHB-102, which is subject to review by the FDA at the time of NDA filing.

RHB-102 (Bekinda®) Highlights – Oncology Support, Gastroenteritis & IBS-D

The Drug	- A proprietary 24-hr bimodal release, once-daily, oral tablet formulation of the 5-HT3 antagonist ondansetron - a leading antiemetic drug
	- RHB-102 is in development for three indications: 1. Oncology support (24mg) – including for the management of chemotherapy and radiotherapy induced nausea and vomiting (CINV/RINV) 2. Gastroenteritis (24mg), and 3. IBS-D (12mg):
	– Oncology support uses PK bridging for efficacy to the existing label of Zofran® suppositories – Gastroenteritis and IBS-D are new indications for which ondansetron is not an approved treatment
Development Status	– **Oncology Support: MAA in planning** – Positive UK MHRA scientific advice meeting held in February 2023 deems RHB-102 data supportive of submission for approval for CINV/RINV
	– **Gastroenteritis & Gastritis:** Positive results from a first Phase 3 study
	– **IBS-D:** Positive results from a Phase 2 study
	– RHB-102 available for partnering in the U.S. and EX-U.S. – Patent granted by European Patent Office covering antiemetic extended-release solid dosage forms for the prevention of nausea and vomiting (CINV/RINV), providing potential for UK and EU protection of RHB-102 to March 2034

RHB-102 (Bekinda®) 24 mg: Oncology Support Development & Regulatory Status

RedHill developed BEKINDA® 24 mg for the management of nausea and vomiting in cancer patients undergoing chemotherapy or radiotherapy

Europe

- European Hybrid Marketing Authorization Application (MAA) for CINV and RINV indications, referencing Zofran® 16mg suppository, was previously withdrawn in February 2016
- Main gap was insufficient data to support the safety of RHB-102's bimodal release formulation
- Subsequently, RedHill successfully completed a Phase 3 study with RHB-102 in gastroenteritis patients, supporting the safety of Bekinda 24mg
- **A scientific advice meeting with UK's MHRA in February 2023, has 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)

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[i] 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. - Long-lasting (24H) oral treatment with the potential to reduce dehydration and hospital visits and stays
Market Size	- Approximately 179 million cases of acute gastroenteritis annually in the U.S., leading to an estimated 470,000 hospitalizations[ii] - Worldwide potential market could exceed $650 million annually[iii]
Development Status	- **Positive Phase 3 study results announced June 2017 - the study met primary endpoint** - **RedHill has designed a confirmatory Phase 3 study for acute gastroenteritis and gastritis**

[i] Bekinda® is a proposed tradename for RHB-102, which is subject to FDA review and approval. [ii] Scallan E, et al. Foodborne Illness Acquired in the United States - Unspecified Agents. Emerg Infect Dis. 2011;17(1):16-22. [iii] Graves NS. Acute gastroenteritis. Primary Care: Clinics in Office Practice. 2013;40(3):727–741 and Company analysis.

RHB-102 24 mg: Gastroenteritis & Gastritis Positive 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	- 10.6 million IBS diagnosed prevalent cases expected in the U.S. by 2026[i] - Total U.S. sales for IBS-D treatments are forecasted to reach ~$557 million in 2026[i]
Development Status	- **Positive top-line results announced Oct. 2017; Study successfully met primary endpoint** - **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] *GlobalData.*

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-204

Investigational new drug

Targeting pulmonary nontuberculous Mycobacteria (NTM) disease - with FDA Orphan Drug Designation, QIDP designation, including Fast-Track development status

U.S. Phase 3 Study – Terminated due to low enrollment rate

RHB-204 - Targeting First-Line Pulmonary NTM Disease

Planned Indication	- Pulmonary nontuberculous mycobacteria (NTM) disease caused by *Mycobacterium avium* Complex (MAC)
The Product	- Proprietary, stand-alone, oral treatment containing a fixed-dose, all-in-one combination of clarithromycin, clofazimine and rifabutin – three antibiotic drugs, each known to be active against NTM disease caused by MAC[i]
Key Attributes	- **A potential first-line treatment for a disease with no FDA-approved first-line therapy** - **A stand-alone, oral, fixed-dose therapy for a chronic disease requiring extended treatment** - Unique dosing combination – optimizing exposure for safety and efficacy while ensuring that intended combination of antibiotics is administered with each dose - Pre-clinical data indicates high efficacy and synergy against MAC that also maintains macrolide sensitivity (reduces emergence of resistance)
Market Size	- U.S. market potential estimated at approx. $938M in 2024[ii]
Development Status	- **Phase 3 study terminated due to low accrual rate, and shifting of Company resources to advance other late-stage development programs** - QIDP and Fast-Track Designation granted, providing eligibility for rolling NDA review, Priority Review and accelerated approval - Orphan Drug Designation granted by FDA and EMA, extending potential U.S. and EU post-approval market exclusivity to a total of 12 years and 10 years, respectively

[i] Wassilew et al, RESPIRATION 2021 [ii] Foster Rosenblatt/Company estimates.

RHB-204 for Pulmonary NTM - Background and Epidemiology



- **Difficult to treat infection with no FDA-approved first-line standard-of-care**
- NTM are a ubiquitous bacteria, mostly non-pathogenic but can cause human disease
  - Pulmonary manifestations account for 80-90% of NTM associated disease[i]
  - Approximately 80% of pulmonary NTM infections in the U.S. are associated with MAC[ii]
- Pulmonary NTM disease symptoms can include fever, weight loss, chronic or recurring cough, chest pain, blood in sputum and fatigue
- NTM have high levels of drug resistance and require long term dosing with three or more antibiotics[iii]
- An orphan disease - with an estimated 109,000 pulmonary NTM patients in the U.S. in 2022[iv]

[i] Wassilew N, et al. Pulmonary Disease Caused by Non-Tuberculous Mycobacteria. Respiration. 2016;91(5):386–402. [ii] Adjemian et al. Prevalence of Nontuberculous Mycobacterial Lung Disease in U.S. Medicare Beneficiaries. American Journal of Respiratory and Critical Care Medicine. 2012; 185(8), 881–886. [iii] Griffith et al. An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases. American Journal of Respiratory and Critical Care Medicine. 2007; 175(4), 367–416. [iv] Foster Rosenblatt/Company estimates.

RHB-204 - CleaR-MAC Phase 3 Study

A Phase 3 study intended to assess the efficacy and safety of RHB-204 as a first-line, stand-alone treatment for pulmonary NTM infections caused by MAC

Study Design	- Multi-center, randomized, double-blind, two-part, placebo-controlled, parallel-group Phase 3 study; 3:2 randomization - Up to 40 U.S. clinical sites; potential expansion to UK, Japan and additional territories - Two-part study: • Part one: placebo-controlled, subjects evaluated for primary endpoints at Month 6 • Part two: Open-label treatment with RHB-204 for 10 months, with follow-up 3 months post-treatment
Patient Population	- 125 subjects with symptomatic pulmonary MAC disease with nodular bronchiectasis - An interim sample size re-estimate is planned at approx. 50% enrollment
Endpoints	- Co-primary efficacy endpoints for Part one: - Sputum culture conversion (SCC) after 6 months of treatment (consecutive negative sputum cultures at Months 4,5,6) - Quality of Life questionnaire – Bronchiectasis (QoL-B) respiratory symptoms domain score from Baseline to Month 6 vs. placebo
Development Status	- U.S. Phase 3 study terminated in May 2023 due to a low accrual rate and shifting of Company resources to advance other late-stage development programs



RHB-104

Investigational new drug

Orally administered, combination therapy targeting MAP bacteria for treatment of Crohn's disease and potentially other autoimmune diseases*

Positive First Phase 3 Study in Crohn's Disease -
Study Successfully Met Its Primary Endpoint and Key Secondary Endpoints – results published in Antibiotics**

Potential MAP Diagnostic Progress May Enable Accelerated Clinical Development

**MAP: Mycobacterium avium subspecies paratuberculosis*
*** 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. https://doi.org/10.3390/antibiotics13080694*

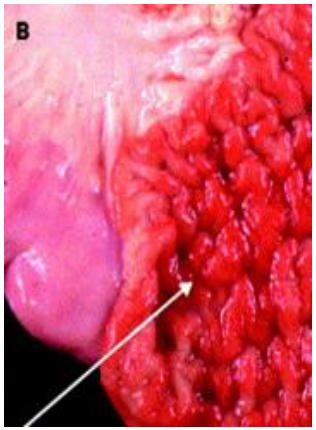
The Link between Crohn's Disease and MAP

Growing evidence that intracellular mycobacteria play a crucial role in Crohn's disease

- MAP (*mycobacterium avium subsp. paratuberculosis*) is the causative agent of Johne's disease, an infectious disease in cattle, clinically and pathologically similar 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 led to increasingly higher identification of MAP in Crohn's diseases patients
  - 92% (34/37 Crohn's disease patients by PCR) - Bull, J Clin Microbiol, 2003
  - 86% (52/60 Crohn's disease patients) - Shafran, Dig Dis Sci, 2002
- Crohn's disease is a multifactorial disease
  - Defective innate immunity to intracellular bacteria
  - Mutations in the NOD2 gene are strongly associated with Crohn's disease
- Mycobacterial infections in humans are difficult to treat; Effective anti-mycobacterial agents require intracellular activity
  - ATS/IDSA and WHO advise triple antibiotic therapy for non-tuberculosis mycobacterial disease*
- Antimicrobial therapy (RHB-104) directed against MAP resulted in significantly greater improvement in clinical and laboratory (FCP) measures of active Crohn's disease**



Crohn's disease



Johne's disease

*American Thoracic Society, Infectious Disease Society of America, World Health Organization

** 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. https://doi.org/10.3390/antibiotics13080694

RHB-104 for Crohn's - Product and Market Overview

Planned Indication	Treatment of Crohn's disease in adult patients
The product	Patent-protected combination of 3 antibiotics (clarithromycin, clofazimine and rifabutin) in a single oral capsule with potent intracellular, antimycobacterial and anti-inflammatory properties
Market Size	Worldwide market estimated to exceed $12.1 billion in 2029*
Positive First Phase 3 Results	Positive published results from the MAP US first Phase 3 study with RHB-104 in Crohn's disease - study successfully met its primary endpoint and key secondary endpoints**
Key Attributes	✓ Unique MoAs, including targeting the potential underlying cause of Crohn's ✓ Improved efficacy on top of standard-of-care ✓ Safety and tolerability enabling combining RHB-104 with standard-of-care ✓ Oral all-in-one capsule

**GlobalData Crohn's Disease Market Size and Forecast (8MM: U.S, UK, Canada, France, Germany, Italy, Japan & Spain), January 2023*

*** 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. https://doi.org/10.3390/antibiotics13080694*

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	Over 100 in the U.S., Canada, Europe, Australia, New Zealand and Israel
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 - Ongoing discussions with KOLs; FDA meeting planned to discuss design of confirmatory Phase 3 study and path to potential approval; Planned utilization of MAP Dx methods based on new literature for CD positive patients, subject to validation

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

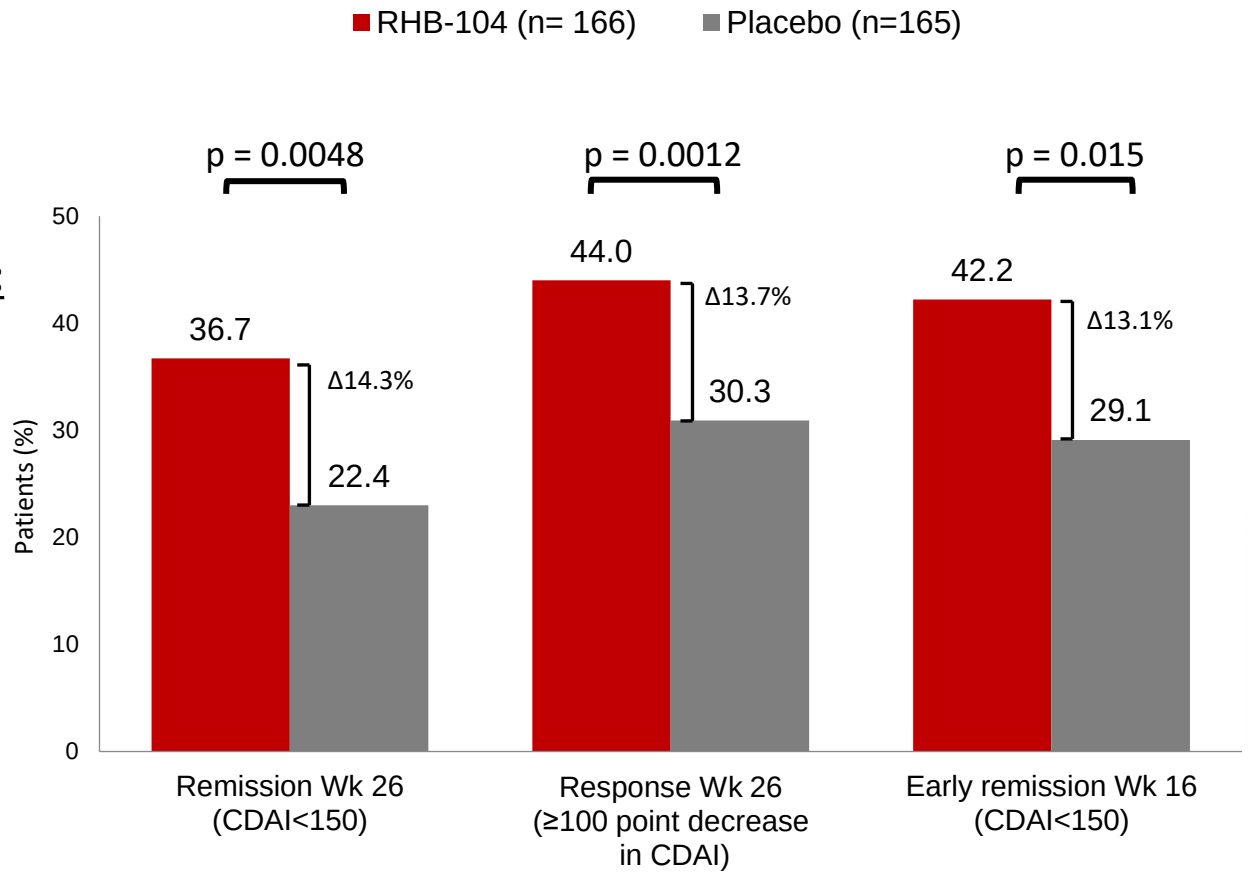
The MAP US Phase 3 study met its primary and key secondary endpoints, demonstrating meaningful, consistent and statistically significant clinical activity of orally administered RHB-104 as an add-on to standard-of-care treatments

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).*

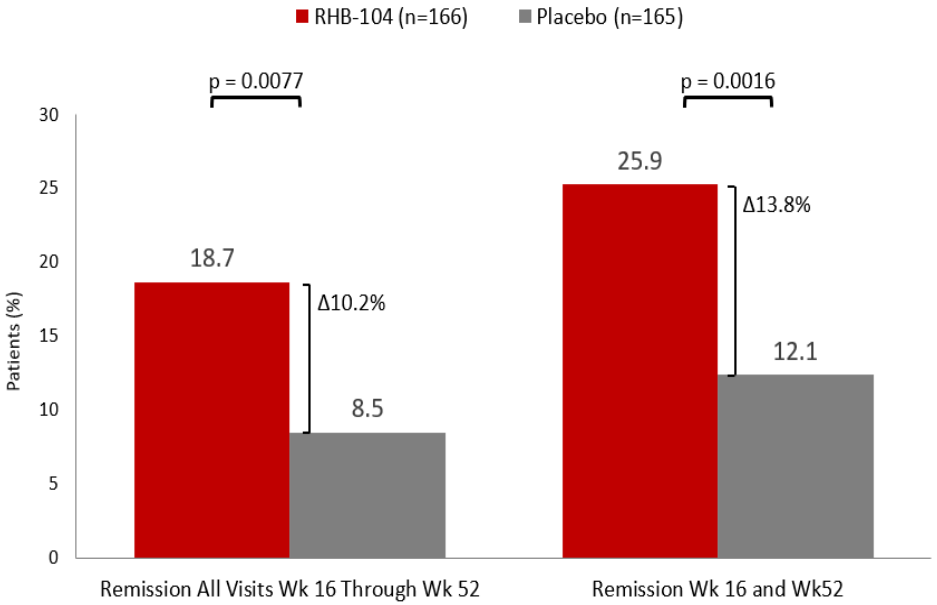
RHB-104 Crohn's Disease Phase 3 - Positive Results

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

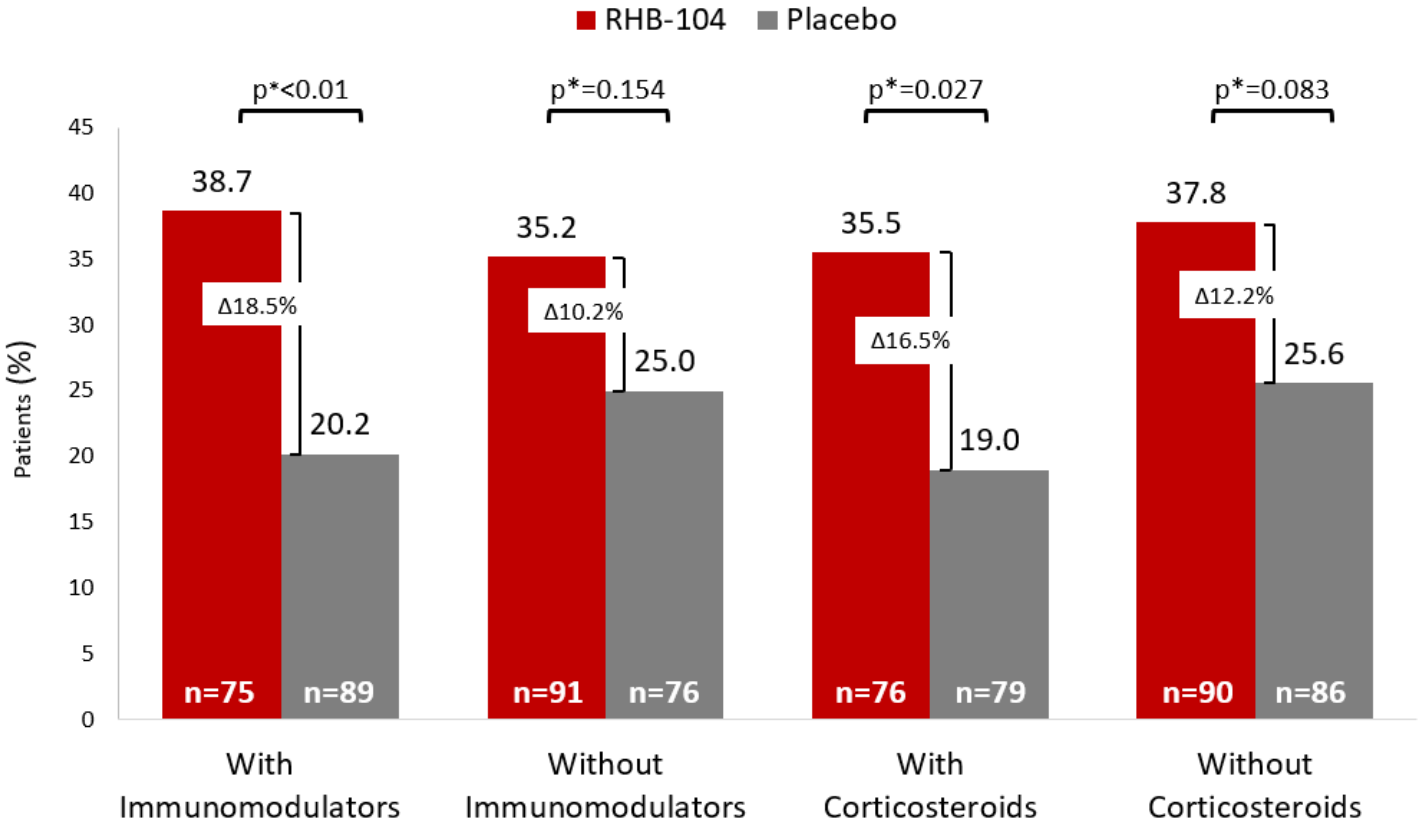


[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no);* [o] *Number of subjects reflects those subjects who have completed week 52 assessments and are no longer receiving blinded therapy.*

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

<u>Effects of concomitant immunomodulators and corticosteroids:</u> Remission at week 26 concomitant meds subgroup analyses demonstrated the impact of RHB-104 as an add-on therapy to a variety of standard-of-care agents despite not being prospectively powered

- ✓ Meaningful and statistically significant treatment effects were observed in patients using concomitant immunomodulators (38.7% vs. 20.2%, p<0.01) and corticosteroids (35.5% vs. 19.0%, p=0.027) throughout the trial

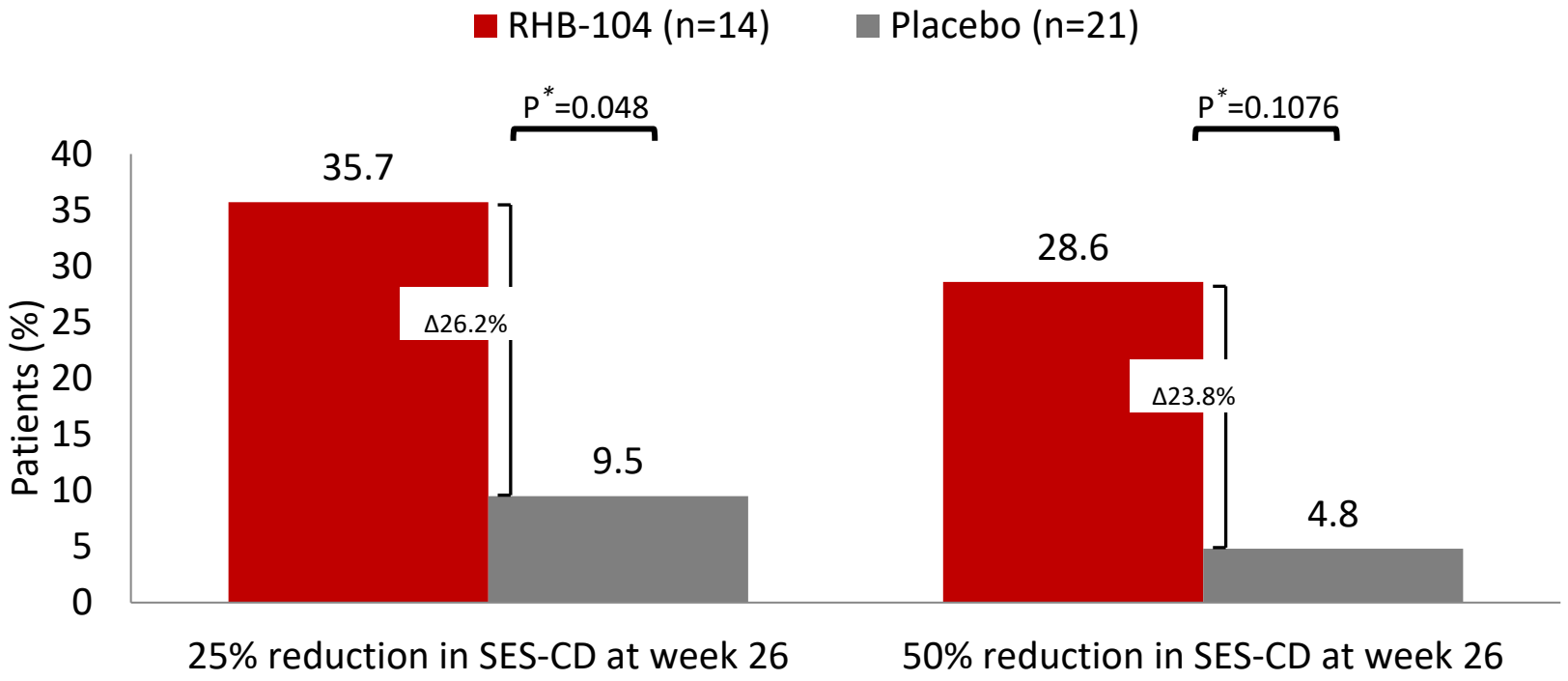


[i] Calculated with Cochran-Mantel-Haenszel (MH) chi-square test with stratification according to anti-TNF agent use (yes/no); [ϱ] Calculated with Mantel-Haenszel (MH) chi-square test.

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

Endoscopic response:

- ✓ Endoscopy was voluntary in the study
- ✓ In a small subset of patients (n=35) in whom endoscopy was performed, results showed meaningful improvement in endoscopic healing (Simple Endoscopic Score for Crohn's Disease (SES-CD)) at week 26 (statistically significant at 25% decrease with similar trend at 50% decrease)

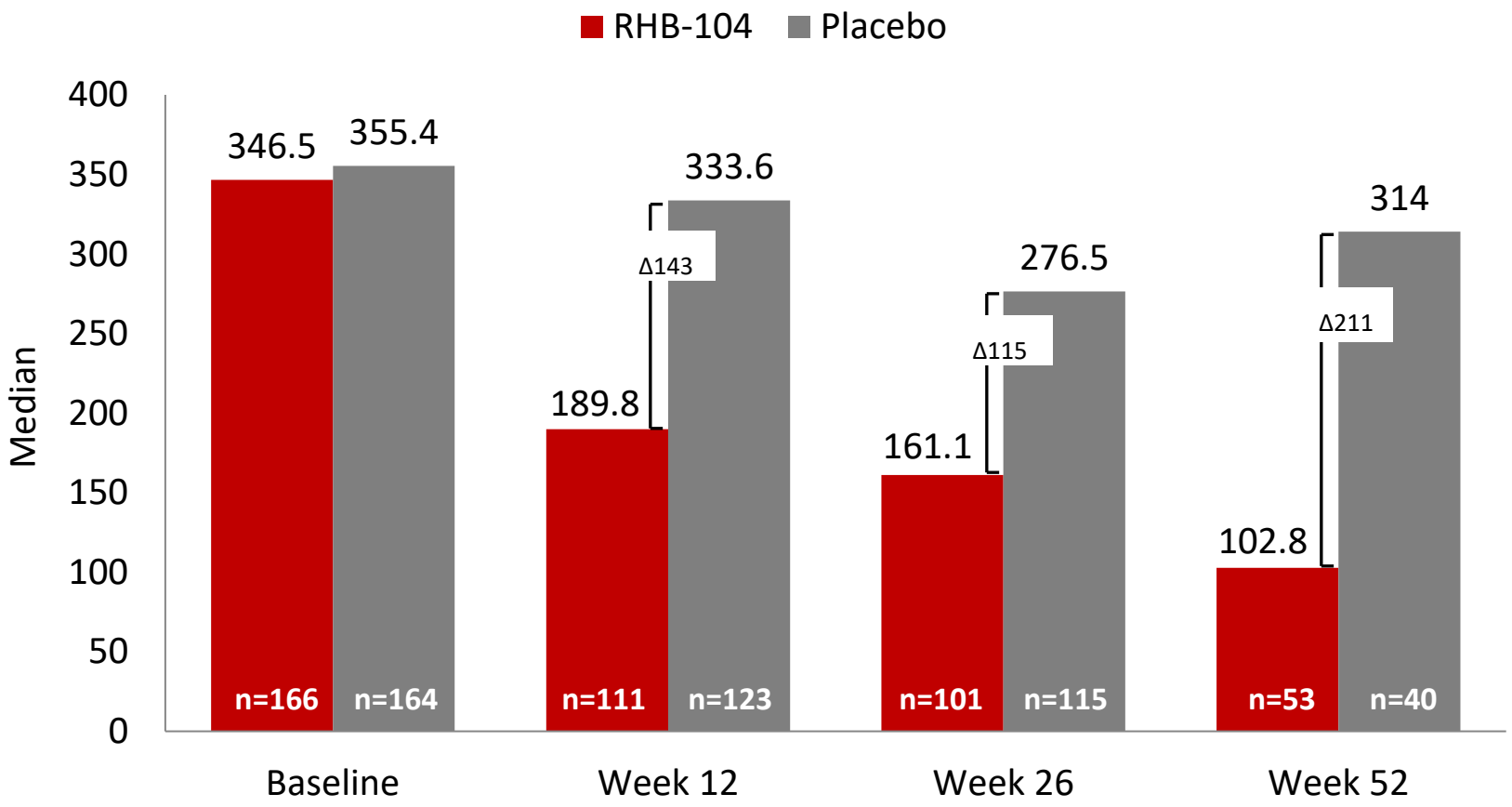


[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no).*

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

Median Fecal Calprotectin

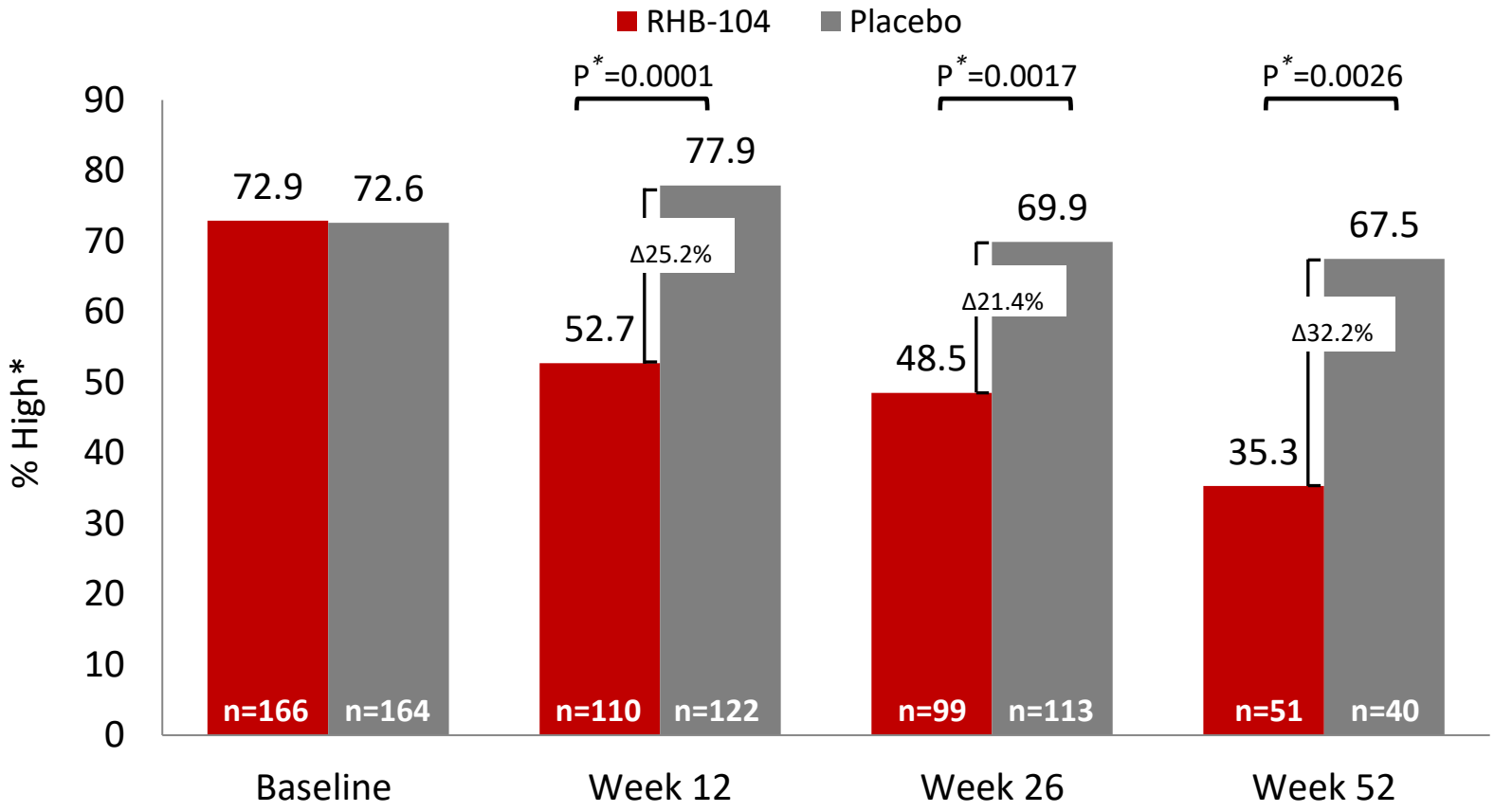
✓ Marked and continuous decline of calprotectin inflammatory marker in the RHB-104 active arm from baseline through week 52



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

% High Fecal Calprotectin**

- ✓ Proportion of high calprotectin declined significantly in the RHB-104 active arm from baseline through week 52 (weeks 12, 26 and 52)



[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no); ** High defined as > 162.9.*

RHB-104 - Multiple Barriers to Entry

- Global patent portfolio covering RHB-104, with additional claims being pursued
- Potential 3 years exclusivity for treatment of Crohn's disease
- 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-104 active components provide excellent synergistic anti-MAP growth activity compared to individual or dual combinations of the drugs[i]
- Oral, all-in-one capsule solution for patients and physicians (reduced co-pays, etc.)
- Potential PK synergies of APIs administered in the RHB-104 formulation that disappear when administered concomitantly
- APIs are not available in doses being used in RHB-104
- 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-104 and RHB-204 - Our Plans

We plan to evaluate RHB-104 and RHB-204 for moderate-severe Crohn's disease

Possible progress in MAP diagnostic technology may enable advancement towards a confirmatory study in MAP positive moderate-severe Crohn's disease patients with RHB-104

<u>Planned confirmatory trial design, pending regulatory input with RHB-104 and RHB-204:</u>

- Relatively small study in 10-20 MAP positive moderate-severe patients with active disease (inflammatory markers elevated)
- Randomized to active vs. placebo with primary endpoint to include mucosal healing
  - Potential correlation of the mucosal healing with MAP status (whether for eradication or suppression)

Thank You!

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