RedHill Biopharma Ltd.

("RDHL")

Corporate Presentation
September 2023

Forward Looking Statement

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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 and infectious diseases

Strong U.S. Commercial Footprint and Robust Development Pipeline with Multiple Near-Term Milestones

$5.4m	~60	2	5
Net revenues 6 mo. ended 6/30/2023	U.S. commercial organization team members	FDA-approved drugs	Clinical late-stage assets Multiple **Phase 3** programs including 2 novel, broad-acting, host-directed antivirals

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

Aemcolo®
(rifamycin) delayed release tablets

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

Commercial Products[ii]

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

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

Aemcolo® (rifamycin) delayed release tablets

- **Aemcolo® (rifamycin) - Travelers' diarrhea caused by noninvasive strains of *E. coli* in adults**

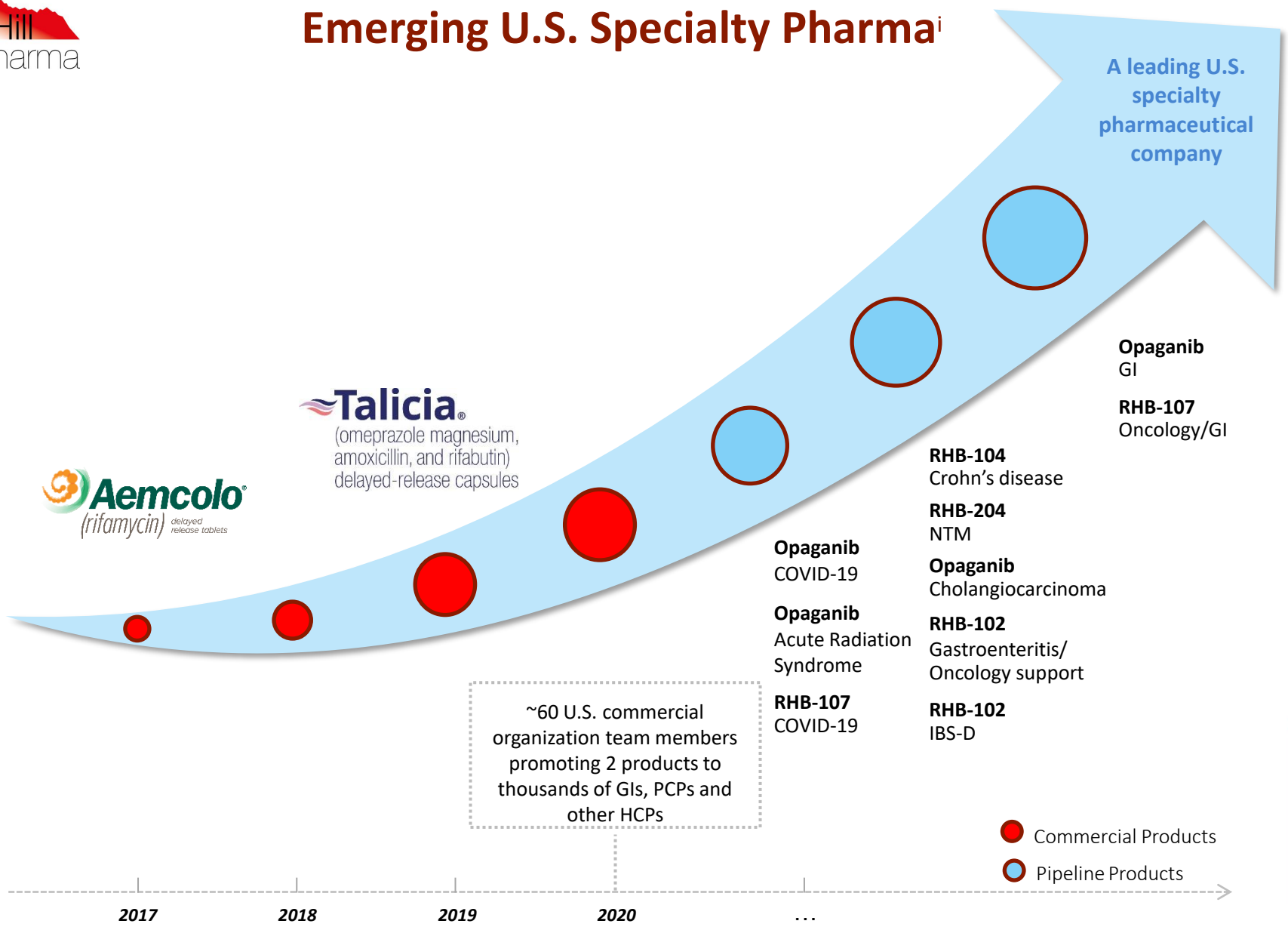
Development Pipeline[iii]

		Pre-Clinical	Phase 1/2	Phase 3	NDA
Opaganib • Anti-inflammatory • Antiviral	Acute Radiation Syndrome	**U.S. Gov. collaboration**	• U.S. Gov. collaboration - NIAID Radiation and Nuclear Countermeasures Program • Pursuing FDA Animal Rule pathway		
	ARDS* (incl. COVID-19), Oncology	**Phase 2/3 COVID-19 (ARDS) & Phase 2 oncology program**			
RHB-107 (upamostat) • Antiviral	COVID-19, Oncology/GI	**Phase 2 COVID-19, GI & oncology indications**		Broad-acting, host-directed antivirals	• U.S. Gov. - supported COVID-19 platform trial (ACESO** PROTECT) expected to start in Q3/23 (cleared for initiation by FDA)
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**			

**ARDS: Acute respiratory distress syndrome. ** ACESO: Austere environments Consortium for Enhanced Sepsis Outcomes. ***MAA: Marketing Authorisation Application.*

[i] Estimated timeline/indication in the pipeline is subject to changes in development plans and regulatory requirements/clarifications, including complementary /additional studies; [ii] For full prescribing information see: Aemcolo®: www.Aemcolo.com; Talicia®: www.talicia.com; [iii] Bekinda® (RHB-102) and Yeliva® (opaganib) are proposed tradenames which are 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.)	$5.03 million
American Depositary Shares (ADSs)[ii]	5.85 million
Cash Balance as of June 30, 2023[iii]	$16.3 million
H1/23 Net Revenues	$5.4 million
H1/23 Gross Margin	55.2%

[i] Financial information as of August 30, 2023, unless otherwise noted. [ii] Following a one-to-forty reverse ADS split, effective March 23, 2023. [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.

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

Razi Ingber, Chief Financial Officer
PwC

June S. Almenoff, MD, PhD, Chief Medical Officer
Furiex, GSK, Tigenix

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

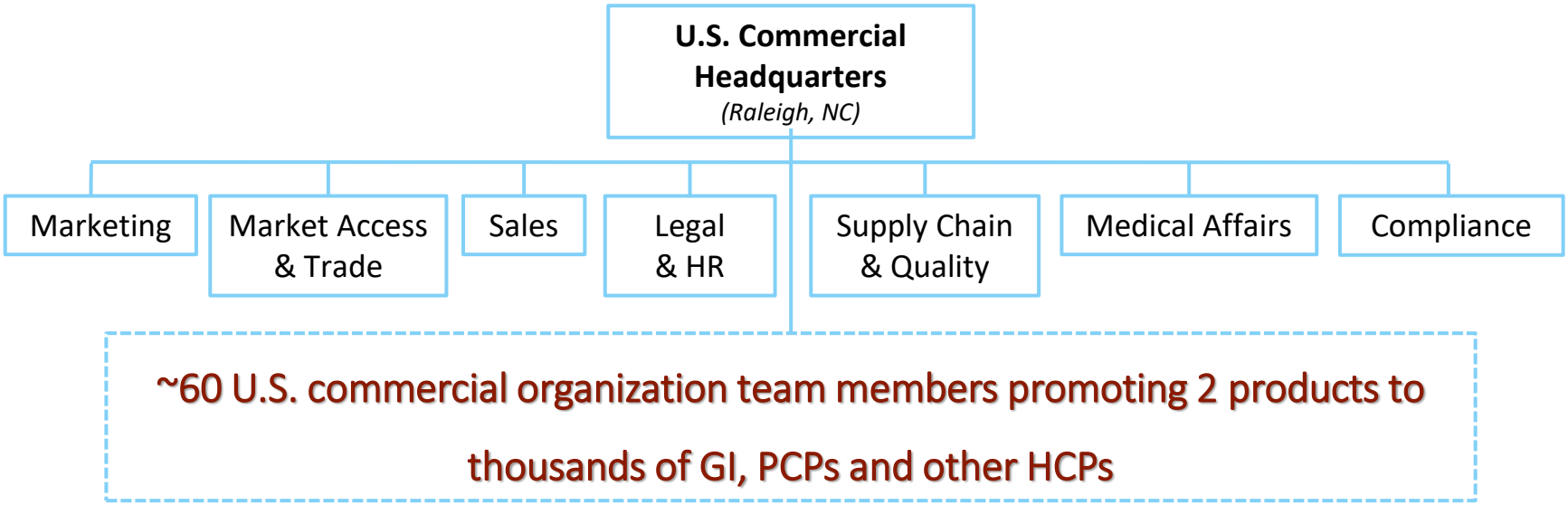
Shmuel Cabilly, PhD
Scientist, Director in several life-science companies

Rick D. Scruggs
Salix, Watson, Oclassen

Ofer Tsimchi
Danbar, Polysack, Director in several companies

Alla Felder
Neuroderm, PwC

Commercial Operations - Strong U.S. Presence



Promoting Two FDA-Approved Drugs:

Talicia® (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules	Aemcolo® (rifamycin) delayed release tablets
Helicobacter pylori (*H. pylori*) infection	Travelers' diarrhea caused by noninvasive *E. coli*
Launched Talicia® in Q1/2020 and Aemcolo® in Q4/2019	

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.



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.

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 mg[i]/ 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 also received from United Arab Emirates (UAE) Ministry of Health**
Key Attributes	✓ Addresses concerns of resistance to clarithromycin and metronidazole ✓ Favorable tolerability and safety profile ✓ Aims to become the new first-line standard-of-care with broader indication ✓ All-in-one capsule: supports ease of adherence and compliance, with a single co-pay
Market Exclusivity	– **Eligible for extended market exclusivity for total of 8 years** under QIDP designation – Patent protection extending until at least 2034
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[ii] – **Rapid expansion of the prescriber base** – High levels of commercial (7/10 lives) and Government (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] 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]



Talicia® has been suggested as a first-line treatment in numerous peer-reviewed publications including The Medical Letter®*[ii]

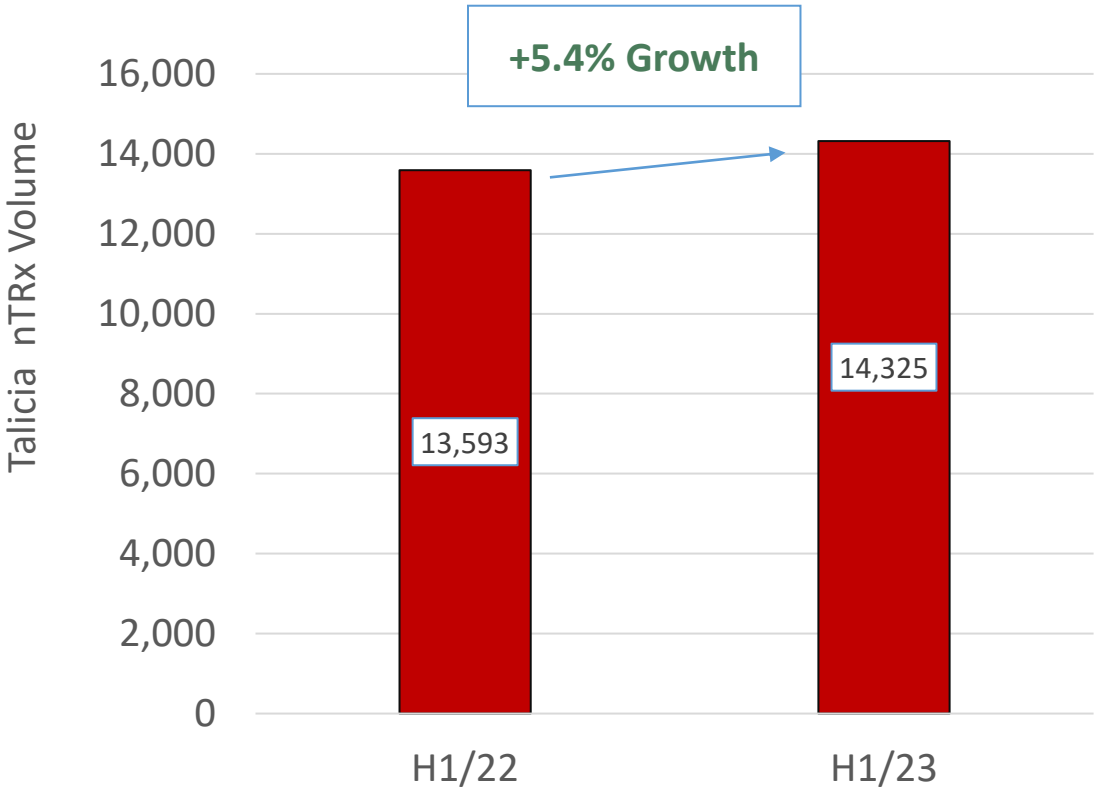
**The Medical Letter, Inc. is a nonprofit organization that publishes critical appraisals of new prescription drugs and comparative reviews of drugs for common diseases in its newsletter.*

[i] IQVIA XPO Data on file (as of June 30, 2023). [ii] "Two Vonoprazan Combinations (Voquezna) for H. pylori". The Medical Letter on Drugs and Therapeutics, October 31, 2022, Volume 64; Issue No. 1772. pp. 169-173. For further citation information contact medinfo@redhillus.com.

Talicia® Delivered 5.4% Prescription Growth in H1/22 vs. H1/23

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

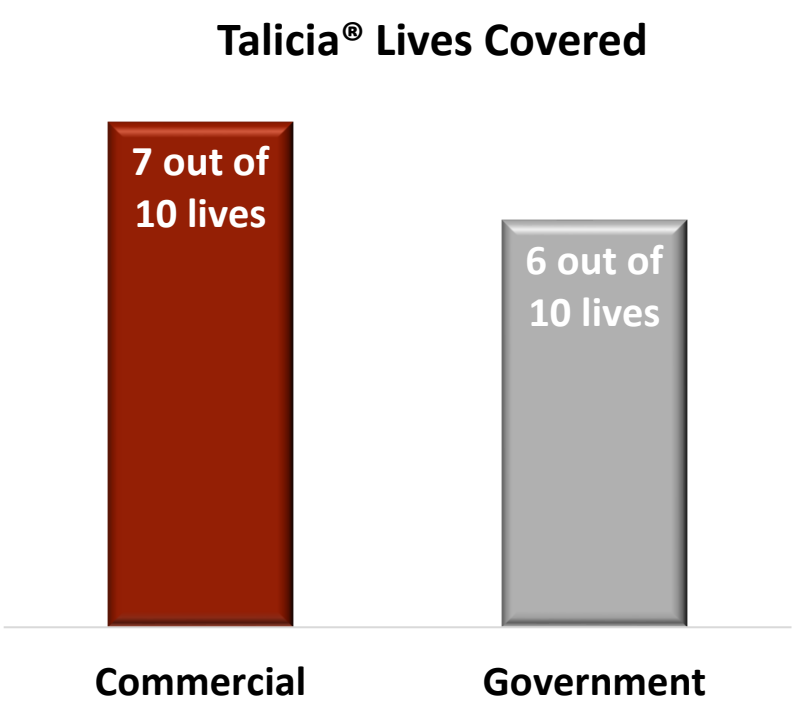
Talicia® nTRx Growth



IQVIA Xponent Data (as of June 30, 2023)

Talicia® Coverage Continues to Expand[i]

Talicia® Coverage: Over 202 Million American Lives[ii]



✓An additional 1.9 million Medicare Part D lives gained coverage in May 2022

✓Commercial PBM* win improved coverage to "preferred" for up to 58 million lives starting July 2022

✓RedHill community-setting warranty program established to refund Talicia® non-responders in March 2023[iii]

✓Continued strategies are underway to expand Medicare Part D Coverage

✓We continue to execute our coverage strategy for Talicia®

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

*PBM=Pharmacy Benefit Management

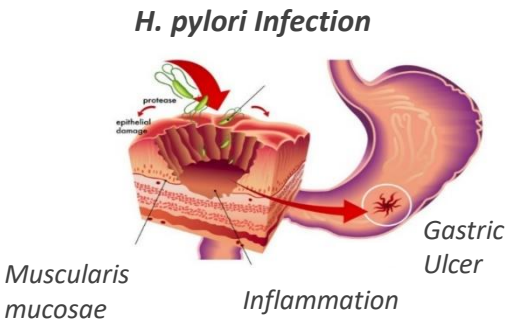
[i] *Estimated coverage based on Managed Markets Insights & Technology data for all payers (as of June 30, 2023); Commercial lives with policies applied and exclude HIX (health insurance exchange) and Tricare; Government lives include Medicaid (State and Managed) and Medicare Part D.* [ii] *Data accurate as of June 30, 2023.* [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 Disease

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

***H. pylori* infection → Progressive gastro-duodenal damage**

- *H. pylori* - a Group I carcinogen and the strongest risk factor for gastric cancer[i] and peptic ulcer disease; Also associated with iron deficiency, B12 deficiency and drug malabsorption
  - Gastric cancer - a leading cause of cancer mortality worldwide, accounting for ~700K deaths annually
  - Eradication of *H. pylori* infection reduces gastric cancer risk[ii] by about 75%
- U.S. *H. pylori* prevalence estimated at approx. 35% of the population - over 100 million people[iii], with an estimated 2 million patients treated annually[iv]
- SoC fails in approximately 25-40% of patients due to growing resistance to clarithromycin and metronidazole - antibiotics commonly used in standard combination therapies[v]
- **American College of Gastroenterology (ACG) guidelines generally exclude the majority of U.S. population from treatment with SoC -** recommending against clarithromycin-based triple SoC therapies in cases of prior macrolide exposure (most of the U.S. population), in regions with unknown clarithromycin resistance (most U.S. regions) or regions with ≥ 15% clarithromycin resistance[vi]
  - Failed antibiotic treatments create newly-resistant bacteria[vii]



[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] *Kumar S et al. Risk Factors and Incidence of Gastric Cancer After Detection of Helicobacter pylori Infection: A Large Cohort Study, Gastroenterology 2019.* [iii] *Hooi JKY et al. Global Prevalence of Helicobacter pylori Infection:Systematic Review and Meta-Analysis. Gastroenterology 2017;153:420-429;* [iv] *IQVIA Custom Study for RedHill Biopharma, 2019;* [v] *Malfertheiner P. et al. Management of Helicobacter pylori infection - the Maastricht IV/ Florence Consensus Report, Gut 2012;61:646-664; O'Connor A. et al. Treatment of Helicobacter pylori Infection 2015, Helicobacter 20 (S1) 54-61; Venerito M. et al. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of Helicobacter pylori infection. Digestion 2013;88(1):33-4;* [vi] *Chey, WD et al. Am. J. Gastroenterol 2017; 112: 212-38. vii Nishizawa T et al. Enhancement of Amoxicillin Resistance after Unsuccessful Helicobacter pylori Eradication. Antimicrob. Agents Chemother. 2011, p. 3012–3014.*

H. pylori Resistance - An Important Public Health Concern

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

WHO: *H. pylori* ranked as pathogen with "high priority" need for new treatments

- February 2017 - WHO publishes global priority pathogen list
- Intended to identify the most important resistant bacteria at a global level for which there is an urgent need for new treatments
- *H. pylori* (clarithromycin-resistant) categorized as a pathogen for which there is a High Priority need to develop new treatments
- *H. pylori* added as a known human carcinogen to the 2021 HHS Report on Carcinogens[i]

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

FDA: *H. pylori* identified under the GAIN Act as pathogen posing serious threat to public health

- Talicia® received FDA QIDP designation under the GAIN Act for serious or life-threatening infections
- Priority Review
- Extended market exclusivity for a total of 8 years

The three new qualifying pathogens are:

Coccidioides species

Cryptococcus species

Helicobacter pylori

All 18 of the original draft pathogens remain on the list

[i] *NTP (National Toxicology Program). 2021. Report on Carcinogens, Fifteenth Edition.; U.S. Department of Health and Human Services, Public Health Service. https://ntp.niehs.nih.gov/go/roc15*

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

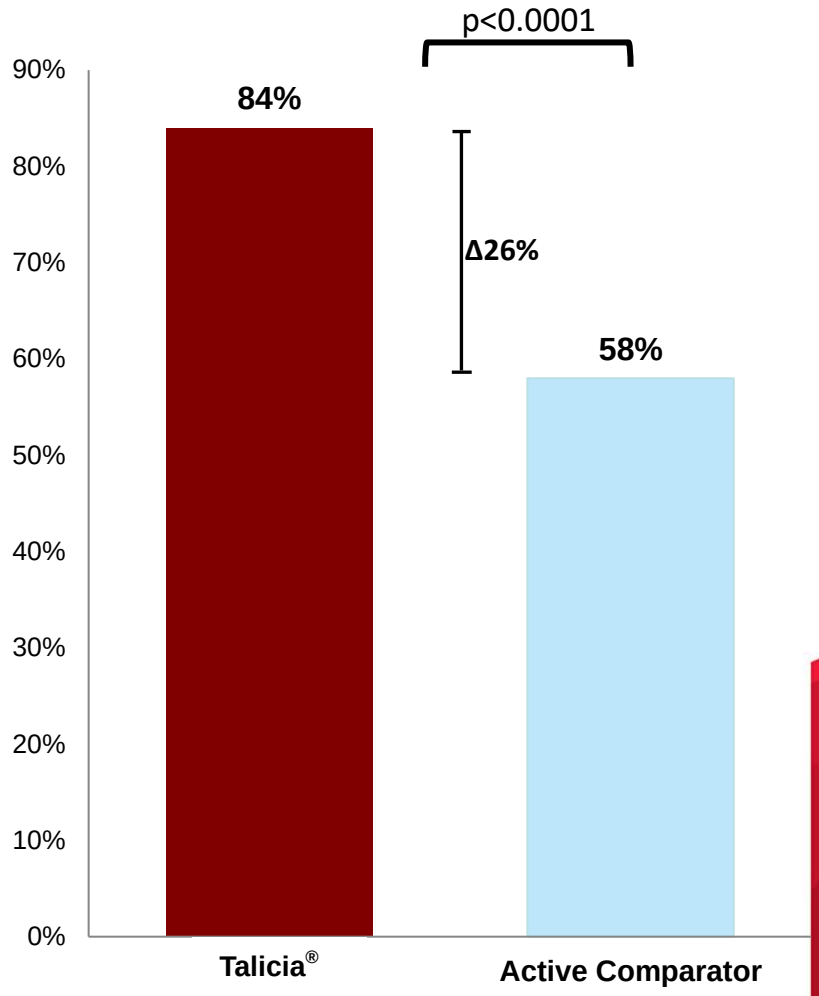
Positive Pivotal Phase 3 Study

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 PK 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
PK 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; PK 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

***H. pylori* Resistance to Standard-of-Care**

- *H. pylori* culture results from patients across 20 U.S. states supported the high resistance of *H. pylori* to the antibiotics most commonly used for treatment -

Antibiotic	*H. pylori* Resistance Rate
Metronidazole	44%
Clarithromycin	17%
Amoxicillin	6%
Rifabutin	**0%**

- Consistent with the literature[i] describing the diminished efficacy of standard-of-care therapies, open-label part of the study showed 53% eradication of *H. pylori* with standard-of-care[ii]

- Consistent 21-29% treatment benefit of Talicia® vs. the active comparator across all *H. pylori* culture susceptibility and resistance subgroups

[i] *Fallone CA et al. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults. Gastroenterology 2016;151:51–69.*
[ii] *N=90; therapy in open-label part with patients who failed eradication was determined by the treating physician*

Positive 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 - Superiority in 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)** - **63% eradication rate demonstrated in open-label treatment of treatment naïve placebo-arm patients with physician choice therapy (mostly standard of care (SoC)) for persistent *H. pylori* infection –** supporting the potential superior efficacy of Talicia® - No serious adverse events related to the drug were noted in the study

Strong Protection from Competition and Substitution

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

- FDA QIDP designation providing eligibility for a total of **8 years of market exclusivity**
- Talicia® is covered by U.S. patents covering the unique 'all-in-one' capsule formulation and distinct PK profile, **extending until at least 2034**, with additional pending patents and applications in various territories worldwide
- Clear dosing differentiation versus available commercial options; rifabutin dosing (50mg tid) 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

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 Standard-of-Care - Approx. 60%

Growing *H. pylori* resistance has led to diminished efficacy of current standard-of-care

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 U.S. pivotal Phase 3 study
- **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 compliance 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 Biopharma

Aemcolo® (rifamycin) delayed release tablets

Indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *E. coli* in adults

Approved for Marketing by U.S. FDA
Launched in the U.S. by RedHill - December 2019



Aemcolo® (rifamycin) - Important Safety Information

INDICATION AND IMPORTANT SAFETY INFORMATION
Aemcolo® is indicated for the treatment of travelers' diarrhea caused by noninvasive strains of Escherichia coli (E. coli) in adults.

Limitations of Use
Aemcolo® is not indicated in patients with diarrhea complicated by fever or bloody stool or due to pathogens other than noninvasive strains of E. coli.

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

CONTRAINDICATION
Aemcolo® is contraindicated in patients with a known hypersensitivity to rifamycin, any of the other rifamycin class antimicrobial agents, or any of the components in Aemcolo®.

WARNINGS AND PRECAUTIONS
Risk of Persistent or Worsening Diarrhea Complicated by Fever and/or Bloody Stool
Aemcolo® was not shown to be effective in patients with diarrhea complicated by fever and/or bloody stool or diarrhea caused by pathogens other than E. coli and is not recommended for use in such patients.

Discontinue Aemcolo® if diarrhea gets worse or persists more than 48 hours and consider alternative antibacterial therapy.

Clostridium difficile - Associated Diarrhea (CDAD)
CDAD has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis.

Consider CDAD in all patients who present with diarrhea following antibacterial drug use. Careful
medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Development of Drug-Resistant Bacteria
Prescribing Aemcolo® in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS
Discontinuation of Aemcolo® due to adverse reactions occurred in 1% of patients. The most frequent adverse reactions were abdominal pain (0.5%) and pyrexia (0.3%).

Adverse reactions that occurred in at least 2% of Aemcolo®-treated patients and with a higher incidence than in the placebo or ciprofloxacin groups were constipation 3.5% and headache 3.3%, respectively.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on AEMCOLO use in pregnant women to inform any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes.
Lactation
There is no information regarding the presence of AEMCOLO in human milk, the effects on the breastfed infant, or the effects on milk production.
Pediatric Use
The safety and effectiveness of AEMCOLO has not been established in pediatric patients <18 years of age.

See Full prescribing information for Aemcolo® is available at www.aemcolo.com

RedHill Biopharma

Aemcolo® (rifamycin) delayed release tablets

Launched by RedHill in the U.S. - December 2019

- A rifamycin antibacterial approved by U.S. FDA in Nov. 2018 for the treatment of travelers' diarrhea caused by noninvasive strains of *E. coli* in adults
- In-licensed U.S. rights from Cosmo Pharmaceuticals N.V. in Oct. 2019
- FDA QIDP designation granted, providing five years of exclusivity, in addition to five years of data exclusivity granted as a new chemical entity (NCE), extending regulatory exclusivity through 2028

- ✓ Minimally absorbed
- ✓ Targeted delivery system
- ✓ Proven efficacy against *E. coli*
- ✓ Reliable safety and tolerability
- ✓ Simple BID dosing



** We and Cosmo are in discussions with respect to the potential amendment/termination of our license to Aemcolo*

High Travel Spending Per Person in the U.S. Points to Significant Commercial Opportunity

Travelers' diarrhea is a significant market:

- Approximately **93 million** Americans traveled abroad in 2018, of which **60 million** traveled to medium to high risk regions[i]
- Travelers' diarrhea may affect up to **70%** of travelers depending on destination and season of travel[ii]
- **> 1/3** of those travelers are seeking health advice prior to leaving[iii]
- **52%** of travelers travel with OTC meds for gastro ailments and **28%** travel with a prescription antibiotic[iv]
- The International Society of Travel Medicine (ISTM) recommends **traveling with an antibiotic for self-treatment** when visiting developing regions[iii]

[i] *https://travel.trade.gov/view/m-2018-O-001/index.html;* [ii] *CDC Yellow Book;* [iii] *"Travel Health, Knowledge, Attitudes and Practices among United States Travelers." J Travel Med 2004; 11:23–26; iv Aemcolo survey market research, Aries Sep. 2019;*

Late-Stage Development Pipeline



Opaganib

Acute Radiation Syndrome	Development under **FDA Animal Rule** being pursued
Severe COVID-19 pneumonia (ARDS*)	Phase 2/3
Cholangiocarcinoma	Phase 2 study analysis anticipated
Prostate cancer	Phase 2 enrollment completed
Inflammatory diseases[i]	Phase 2 ready
Influenza A H1N1, Ebola and RSV	Phase 2 ready



RHB-107

COVID-19 (symptomatic outpatients) **(and additional viral indications under investigation in earlier phase studies)**	Phase 2 ACESO** PROTECT multinational platform trial - expected to start in Q3/23
	Phase 2 completed by RedHill
Oncology	Phase 2

Broad-acting, host-directed antivirals

▼

Pandemic Preparedness

"It Ain't Over Till It's Over…but It's Never Over"

– Anthony S. Fauci, M.D.[ii]



RHB-102

Acute gastroenteritis & gastritis/Oncology support	Phase 3
IBS-D	Phase 3 ready



RHB-204

Pulmonary nontuberculous Mycobacteria (NTM) disease	Phase 3 terminated due to low enrollment rate



RHB-104

Crohn's disease	Phase 3
Multiple sclerosis	Phase 2

**ARDS: Acute respiratory distress syndrome. **ACESO: Austere environments Consortium for Enhanced Sepsis Outcomes.*

[i] Including ulcerative colitis and Crohn's disease. [ii] Fauci, A. S. (2022). It Ain't Over Till It's Over. . .but It's Never Over - Emerging and Reemerging Infectious Diseases. The New England Journal of Medicine, 387(22), 2009–2011.



Opaganib (ABC294640)[i]

Late-Stage Investigational New Drug

First-in-class, broad-acting, host-directed, orally-administered sphingosine kinase-2 (SPHK2) inhibitor, targeting viral (incl. COVID-19), inflammatory (incl. Acute Radiation Syndrome) and oncological diseases

Acute Radiation Syndrome (ARS) – U.S. Gov. collaboration (NIAID RNCP); Development under FDA Animal Rule being pursued

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

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Phase 2 study in cholangiocarcinoma – study analysis anticipated; Phase 2 study in prostate cancer - enrollment completed

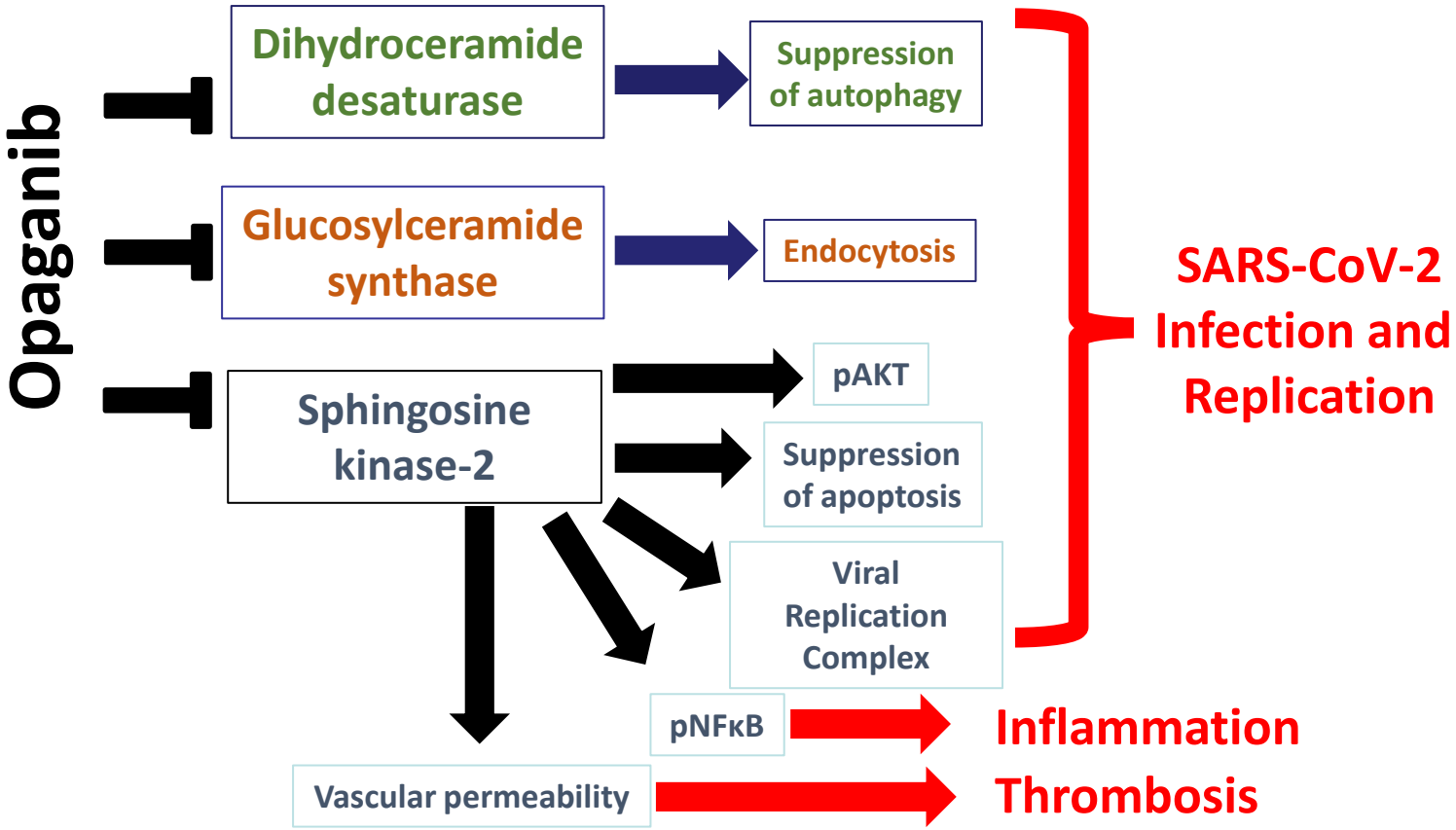
[i] *Yeliva® is the proposed tradename for the drug product containing opaganib, which is subject to review by the FDA at the time of NDA filing*

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

The Product	- Potential first-in-class, orally-administered sphingosine kinase-2 (SPHK2) inhibitor - **Broad-acting agent** targeting viral (incl. COVID-19), inflammatory (incl. Acute Radiation Syndrome (ARS)) and oncological diseases (incl. cholangiocarcinoma and prostate cancer) - **Host-directed and potent antiviral**, targeting a critical host factor and minimizing the potential development of drug resistance due to viral mutations
Development Status	- Opaganib has demonstrated its safety and tolerability profile in more than 470 people in multiple clinical studies and expanded access use
	- **Opaganib selected by NIAID RNCP* for the nuclear medical countermeasures product development pipeline as a potential ARS treatment** - **Positive FDA Type B meeting held for ARS** – FDA provided guidance on opaganib's developmental pathway to potential approval under the Animal Rule - Additional collaboration discussions with U.S. and other governments are ongoing - RedHill ready to advance Phase 2 studies for IBD
	- **Opaganib demonstrated antiviral activity in several *in vitro* and *in vivo* viral infection models, including SARS-CoV-2, Influenza and Ebola** - 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 - Ongoing preclinical development of opaganib in collaboration with the US Army and NIAID for various antiviral indications
	- Phase 1 study in cancer patients with advanced solid tumors
	- **Phase 2a study for treatment of cholangiocarcinoma – study analysis anticipated** - Orphan Drug Designation for the treatment of cholangiocarcinoma
	- Investigator-sponsored Phase 2 study in prostate cancer

**NIAID RNCP: National Institute of Allergy and Infectious Diseases, Radiation and Nuclear Countermeasures Program*

Opaganib's Host-Directed Mechanism of Action Inhibits Three Enzymes Contributing to Its Broad Antiviral Effect in Addition to Its Anti-Inflammatory and Anti-Thrombotic Effects[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) 16:2199-2211.

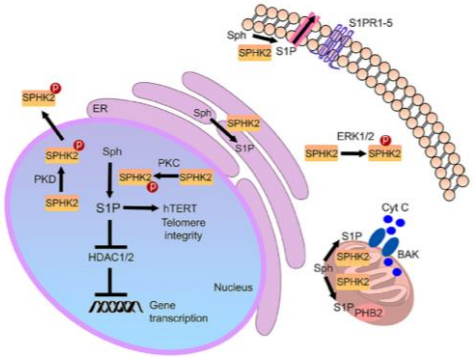
SPHK2 – Therapeutic Target for Metabolite Sphingosine-1-Phosphate (S1P) that has Pathological Roles in Various Diseases

- Sphingolipids regulate several important signaling transduction processes[i]
- Sphingosine Kinase 1 (SK1) 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, neurodegenerative diseases and infectious diseases[ii, iii]
- Opaganib elevates ceramides and reduces S1P in cells, conditions that increase the antitumor efficacy of radiation while concomitantly suppressing inflammatory damage to normal tissue
- Therefore, opaganib may suppress toxicity from unintended IR exposure and improve patient response to chemoradiation

Intracellular Targets[iii]:

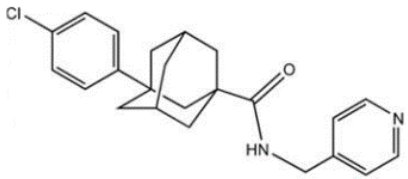
- In the nucleus, SPHK2 modulates gene expression and telomere integrity
- In the mitochondria, it may regulate prohibition 2 (PHB2) and Bax and Bak activation (BAK)
- In the ER it regulates cell death pathways
- In cancer, SPHK2 may be recruited to the plasma membrane, where it generates S1P

iv



[i]Kreitzburg K et al., Sphingolipid metabolism and drug resistance in ovarian cancer. Cancer Drug Resist. 2018;1:181-97. [ii] Maceyka M et al., Sphingosine-1-phosphate signaling and its role in disease. Trends Cell Biol. 2012 Jan;22(1):50-60. [iii, iv] Diaz E et al., The functional role of sphingosine kinase 2. Frontiers in Molecular Biosciences. 2021 May;8:1-7.[iv] (https://creativecommons.org/licenses/by/4.0/legalcode)

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



- **Opaganib**, a novel, oral, small molecule, SPHK2 inhibitor, may offer a new therapeutic approach to mitigate gastrointestinal-ARS (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, Lynn W., et al. "Opaganib Protects against Radiation Toxicity: Implications for Homeland Security and Antitumor Radiotherapy." International Journal of Molecular Sciences, vol. 23, no. 21, Oct. 2022, p. 13191. Crossref, https://doi.org/10.3390/ijms232113191.*

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:

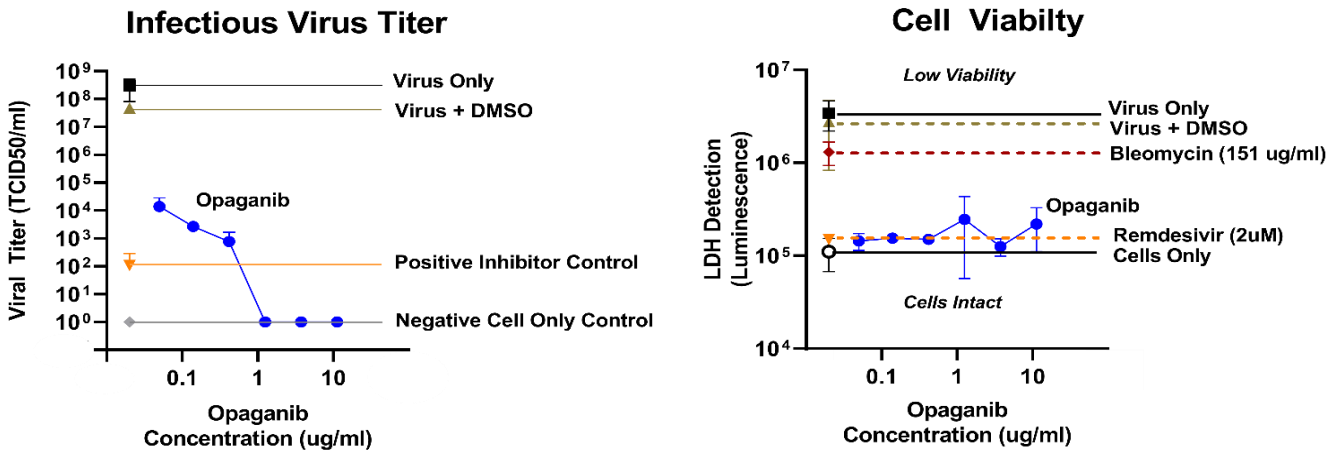
- ✓ An advanced clinical stage orally administered; first-in-class patented novel sphingosine kinase 2 inhibitor; with over 5 years of stability shelf life
- ✓ Safe in humans, as confirmed in clinical trials and in compassionate use indications in ~ 470 participants
- ✓ Substantially protects, *in vivo*, 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**
- ✓ 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 method of use patent that protects 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 by United States Patent and Trademark Office (USPTO)

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:

- 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

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 – study analysis anticipated
- ✓ Investigator-sponsored Phase 2 study in prostate cancer - Enrollment completed and patient follow-up ongoing in study arm evaluating combination with abiraterone; arm evaluating opaganib in combination with enzalutamide 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 Orphan Drug designation for the treatment of cholangiocarcinoma - Compassionate use for cholangiocarcinoma under Expanded Access Program - **Phase 2 study analysis anticipated**
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.



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

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U.S. Gov. -supported COVID-19 platform trial (ACESO PROTECT) cleared for initiation by FDA and expected to start in Q3/23

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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	– **Accepted for inclusion in ACESO's PROTECT adaptive platform trial for early COVID-19 outpatient treatment – cleared for initiation by FDA and expected to start in Q3/23** – **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 – Discussions ongoing for external non-dilutive funding for additional late-stage COVID-19 clinical development – 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 mechanisms of action and preliminary clinical evidence, RHB-107 may be active against IBS

RHB-107 – Accepted for Inclusion in U.S. Government-Supported COVID-19 Platform Trial

- RHB-107 has been accepted for inclusion in the **ACESO* PROTECT study,** an adaptive, randomized, double-blind, multi-site Phase 2 platform trial for early COVID-19 outpatient treatment
- Study received FDA clearance to start (enrollment is expected to begin in Q3/23) and is estimated to be completed by end of 2024
- The 300-patient study will be conducted in U.S., Thailand, Ivory Coast and South Africa
- Predominantly funded by U.S. Government Department of Defense's JPEO-CBRND**, conducted by researchers from ACESO and partner organizations and administered by Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF)
- Investigational products (IPs) will be compared to control, in standard-risk, non-hospitalized adult SARS-CoV-2 infected participants with at least two moderate-severe symptoms at baseline
- RHB-107 is the initial drug being evaluated in the early treatment arm of the study; The primary efficacy assessment in the early treatment indication will be time to sustained alleviation or resolution of COVID-19 symptoms[i]
- IPs were selected for inclusion based on review of preclinical and early clinical data, evaluating, safety, tolerability, efficacy of the IP, route of administration and product availability, with oral, subcutaneous, and intramuscular delivery modes prioritized due to acceptability and feasibility of administration

**ACESO: Austere environments Consortium for Enhanced Sepsis Outcomes. ** JPEO-CBRND: Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense.*

[i] Participants will be followed for a period of up to 12 weeks.

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-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®) - 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, Griffin PM, Angulo FJ, Tauxe RV, Hoekstra RM. Foodborne Illness Acquired in the United States - Unspecified Agents. Emerg Infect Dis. 2011;17(1):16-22*

[iii] *Graves S. Nancy, Acute Gastroenteritis, Prim Care Clin Office Pract 40 (2013) 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	- It is estimated that at least 30 million Americans may suffer from IBS, of which approximately 40% are of the IBS-D subtype[i] - 8.3 million diagnosed prevalent cases in 2018 in the U.S[ii] - 2019 potential U.S. market for IBS-D treatments estimated to reach ~ $980M
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] *Lovell RM, Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis, Clin Gastroenterol Hepatol (2012), 10(7)712-721; Saito YA et al, The epidemiology of irritable bowel syndrome in North America: a systemic review, Am J Gastroenterol (2002), 97(8): 1910-5;* [ii] *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 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[i]
  - 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[iii]
- NTM have high levels of drug resistance and require long term dosing with three or more antibiotics[iv]
- An orphan disease - with an estimated 109,000 pulmonary NTM patients in the U.S. in 2022[v]

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

Potential MAP[i] Diagnostic Progress May Enable Accelerated Clinical Development

[i] *Mycobacterium avium subspecies paratuberculosis*

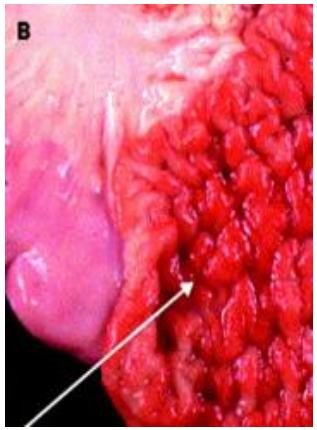
The Link between Crohn's Disease and MAP

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[i] and WHO advise triple antibiotic therapy for non-tuberculosis mycobacterial disease



Crohn's disease



Johne's disease

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

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[i]
Positive First Phase 3 Top-Line Results	Positive 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

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

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

[i] *Results were provided by independent third party prior to database lock and are not final*

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

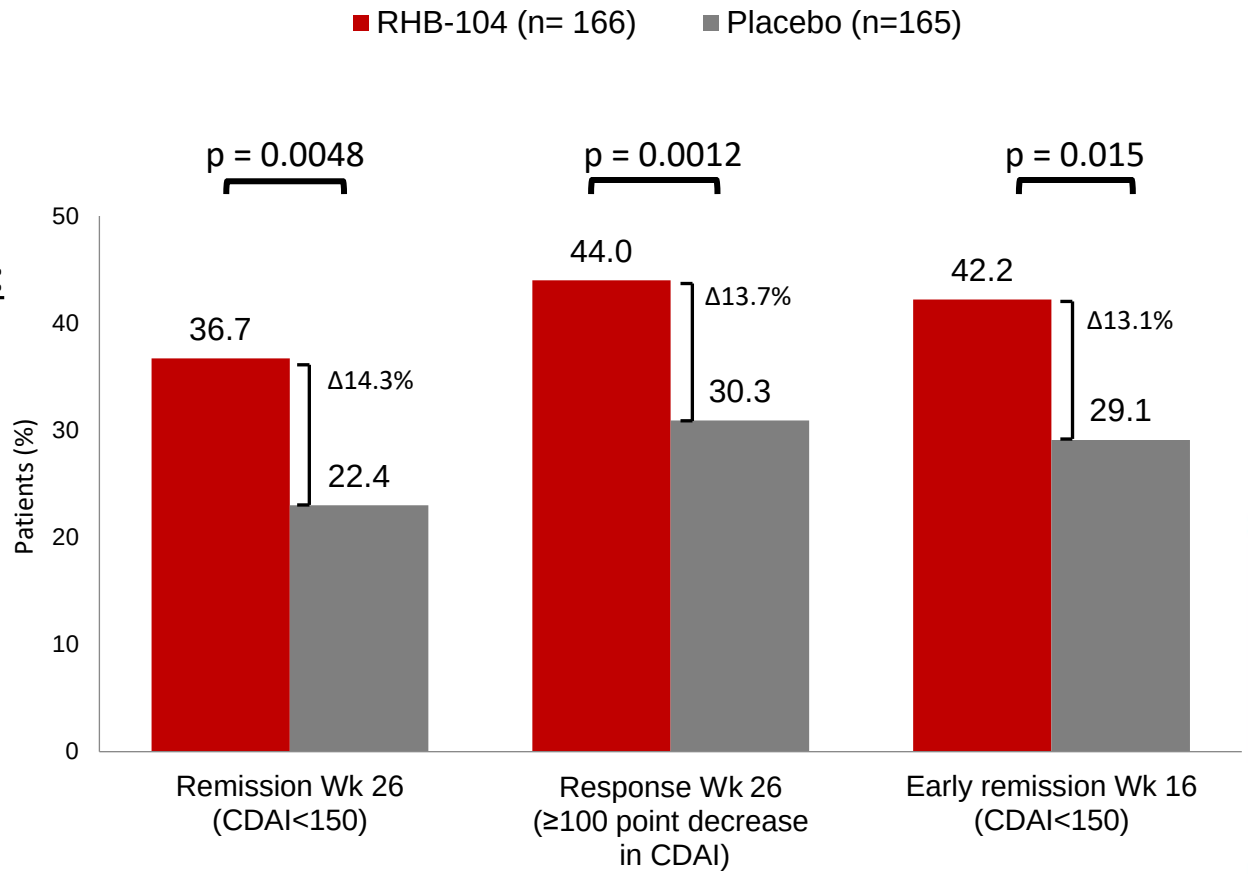
The MAP US Phase 3 study met its primary and key secondary endpoints, demonstrating meaningful, consistent and statistically significant clinical activity of orally-administered RHB-104 as an add-on to standard-of-care treatments

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)*

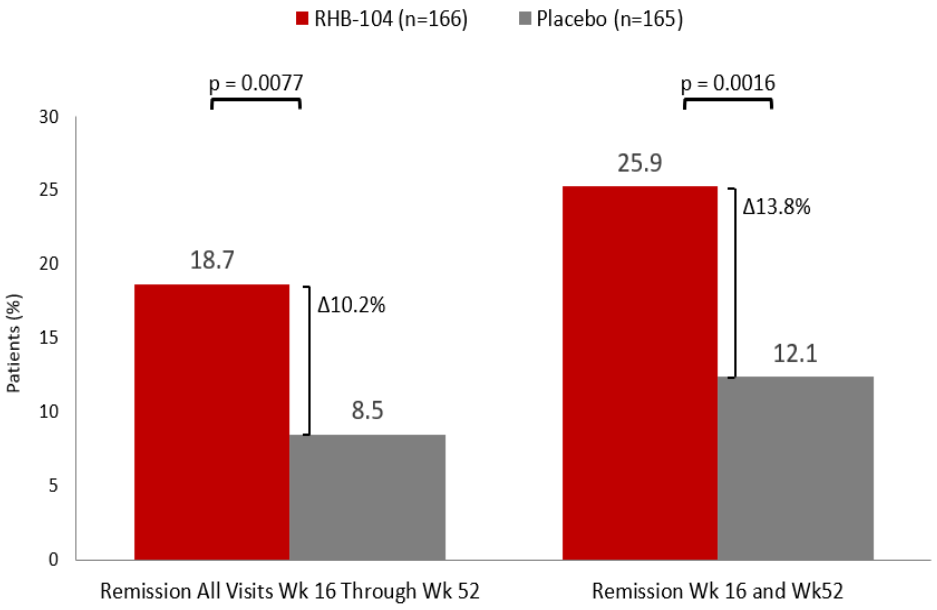
RHB-104 Crohn's Disease Phase 3 - Positive Results

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

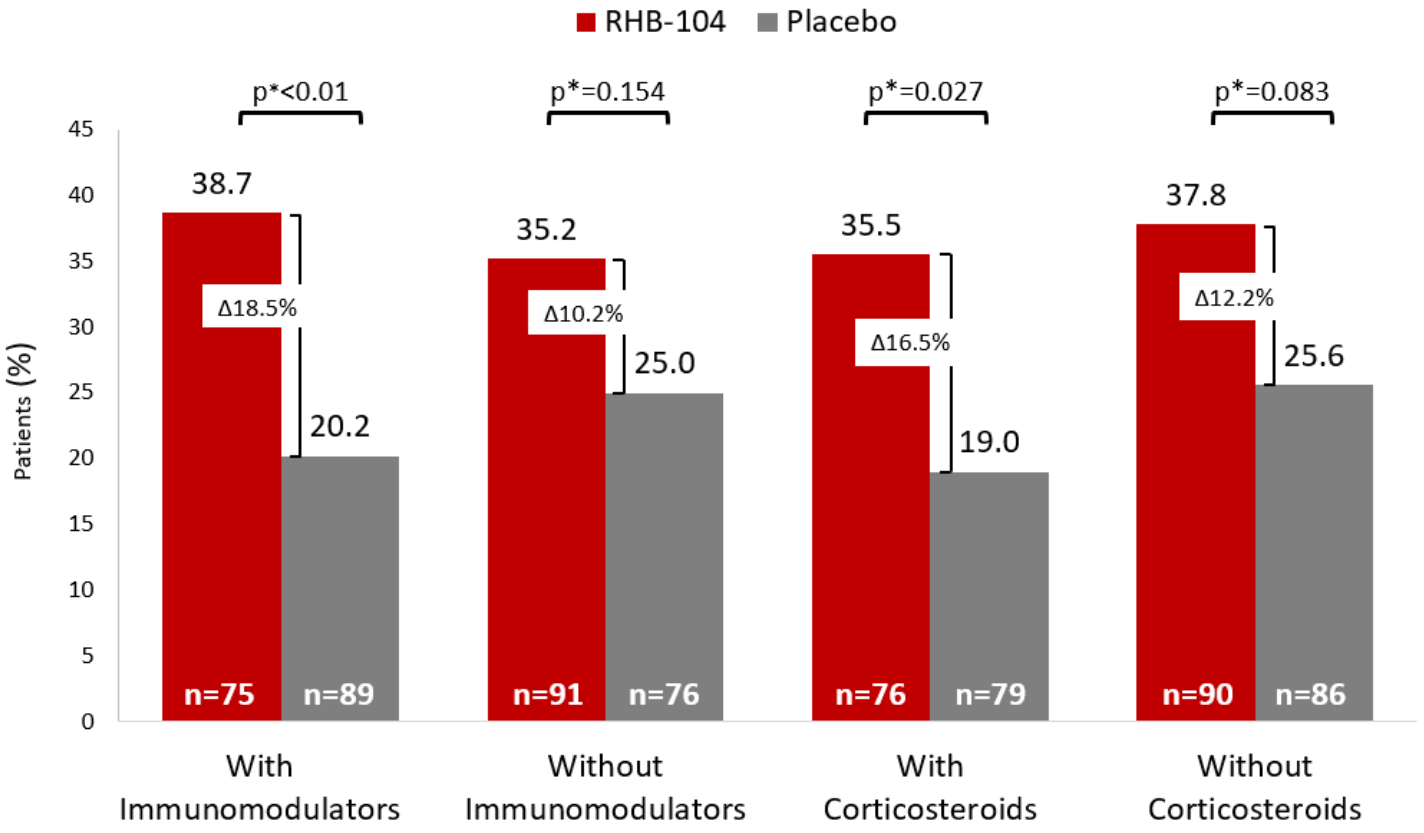


[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no); [ø] Number of subjects reflects those subjects who have completed week 52 assessments and are no longer receiving blinded therapy*

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

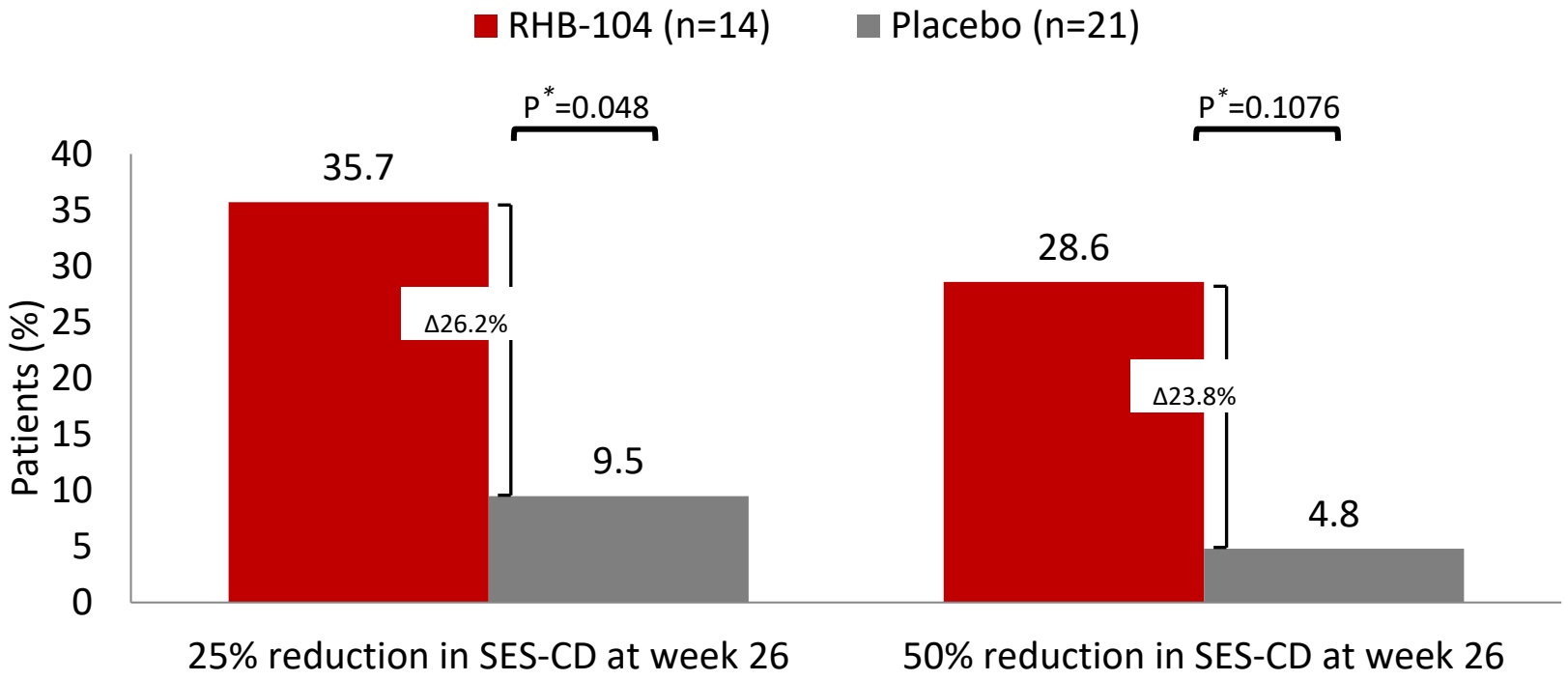


[i] *Calculated with Cochran-Mantel-Haenszel (MH) chi-square test with stratification according to anti-TNF agent use (yes/no); [ρ] Calculated with Mantel-Haenszel (MH) chi-square test*

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)

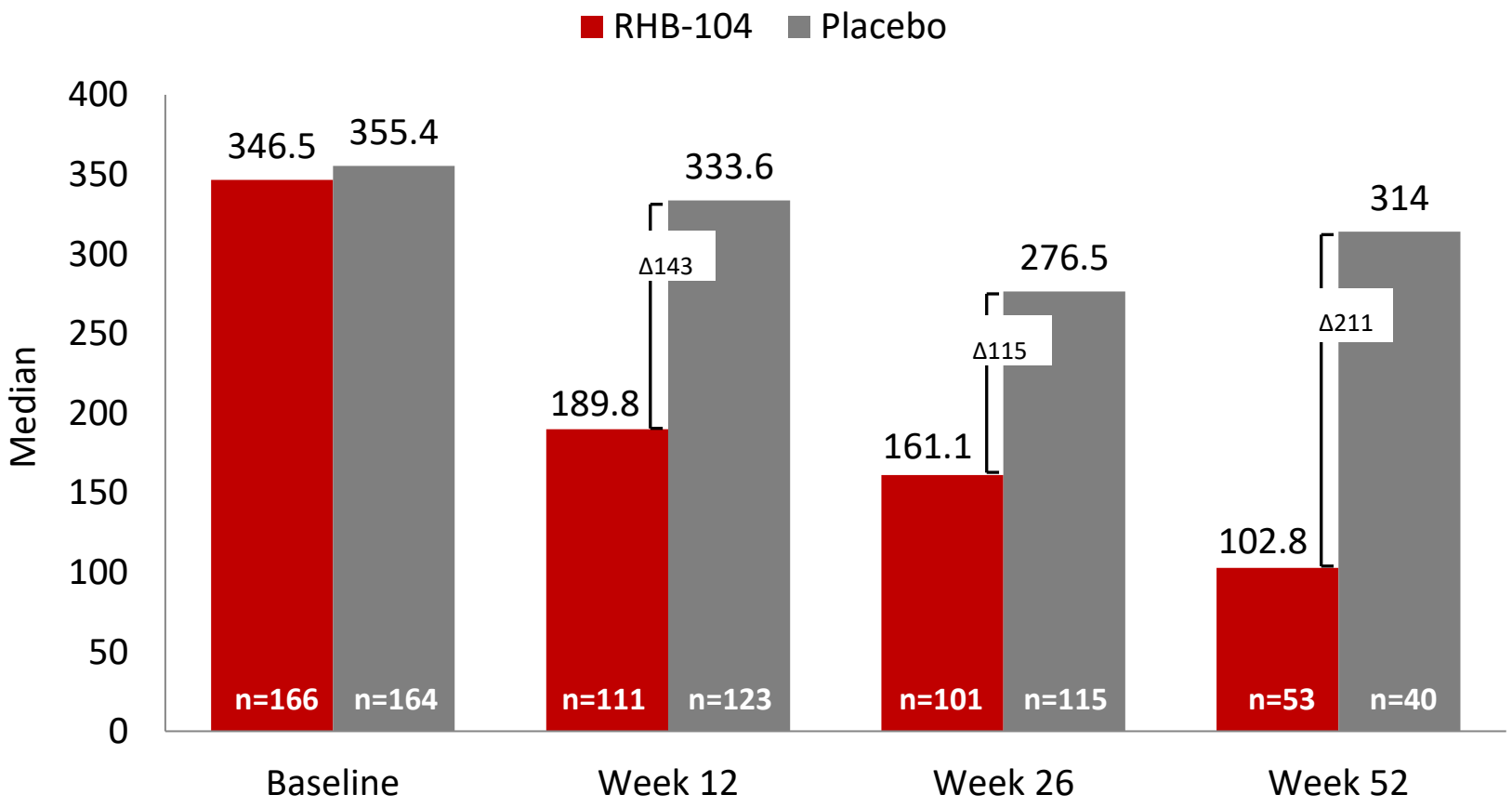


[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no)*

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

Median Fecal Calprotectin

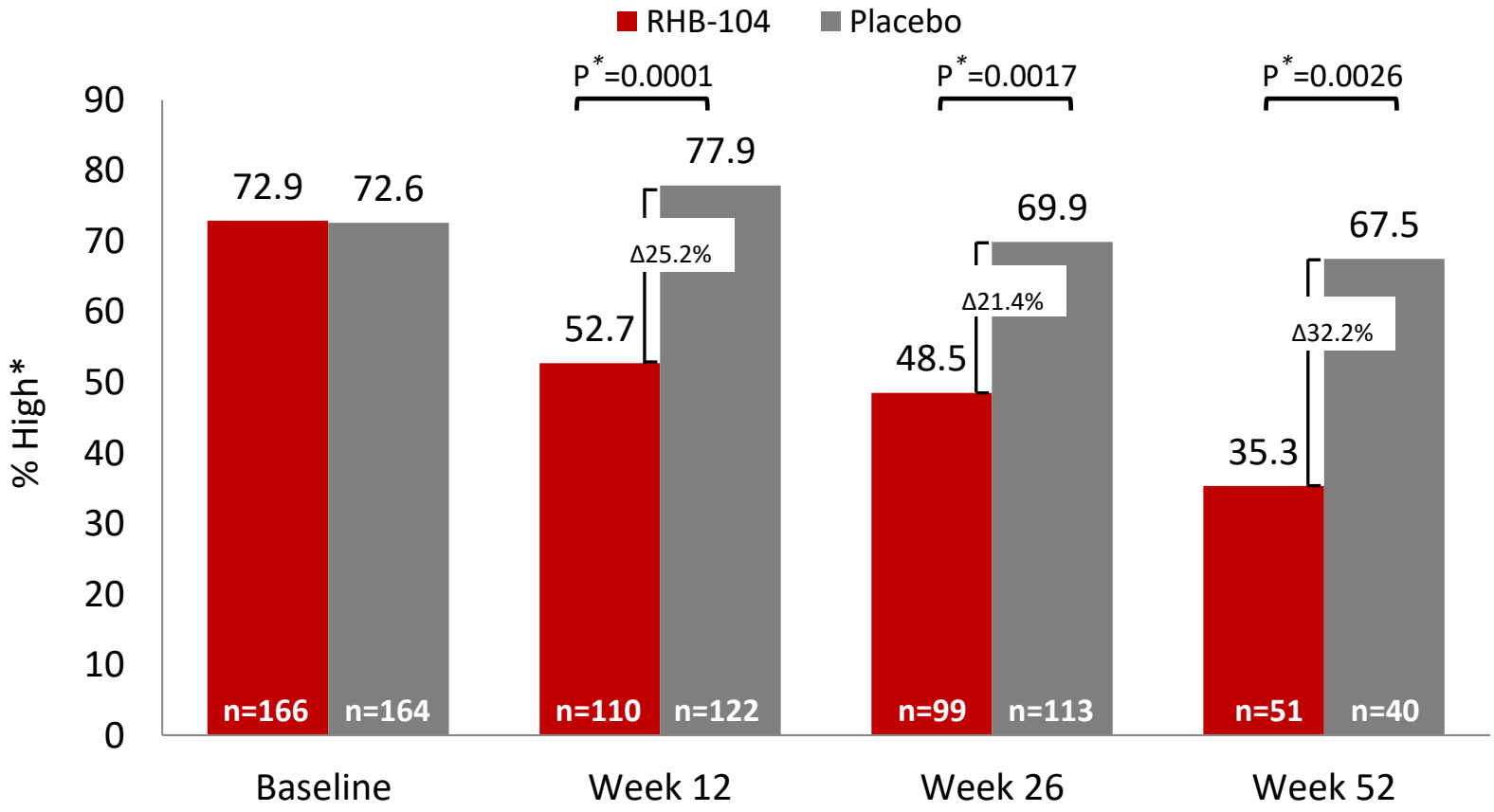
✓ Marked and continuous decline of calprotectin inflammatory marker in the RHB-104 active arm from baseline through week 52



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

- Robust global patent portfolio covering RHB-104, with additional claims being pursued
- Potential 3 years exclusivity for treatment of Crohn's disease
- Limited availability of clofazimine (distributed by the World Health Organization (WHO) and Novartis) and generally requires name based individual import permit or Expanded Access Program (EAP) process for use
- 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, Thanigachalam S, Naser SA. 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, 8:32.*

RHB-104 - Our Plans

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

<u>Planned confirmatory trial design, pending regulatory input:</u>

- Relatively small study in 100-150 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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