RedHill Biopharma Ltd.

("RDHL")

Corporate Presentation
November 2021

Forward Looking Statement

This presentation does not constitute an offer or invitation to sell or issue, or any solicitation of an offer to subscribe for or acquire any of the Company's securities or to participate in any investment in the Company.

No representation or warranty is made to the accuracy or completeness of this presentation. You must make your own investigation and assessment of the matters contained herein. In particular, no representation or warranty is given, and the Company has no responsibility, as to the achievement or reasonableness of any forecasts, estimates, or statements as to prospects contained or referred to in this presentation.

Statements in this presentation that are not historical facts (including statements containing "believes," "anticipates," "plans," "expects," "may," "will," "would," "intends," "estimates" and similar expressions) are forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. These statements are not guarantees of future performance, are based on current expectations of future events and are subject to risks and uncertainties that could cause actual activities or timing to differ materially from those expressed or implied by such statements, including risks that we will not have sufficient working capital, the effect of COVID-19 on the business of the Company, that the products we promote in the U.S. may not generate sufficient revenues, that there will be delays in the initiation and progress of our studies, trials or other therapeutic candidate development efforts or delays in obtaining, or we will be unable to obtain, FDA or other regulatory approvals for our products, unable to establish collaborations, that our therapeutic candidates will not be commercially viable, that our pursuit of treatments for SARS-CoV-2 will not be successful or we won't have sufficient resources for manufacturing scale-up and large-scale deployment, and risks relating to our Expanded Access Policy (EAP) among other risks. Additional information about the risk factors that may affect the realization of forward-looking statements is set forth in the Company's filings with Securities and Exchange Commission, including the Company's Annual Report on Form 20-F filed on March 18, 2021. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. You should not place undue reliance on forward-looking statements as a prediction of actual results.

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 and infectious diseases

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

Promoting Three FDA-Approved Drugs

Multiple Phase 3 and Phase 2 Programs

movantik® (naloxegol) 25 mg tablets

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

Aemcolo® (rifamycin) delayed release tablets

[i] *Movantik® is a registered trademark of AstraZeneca*

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

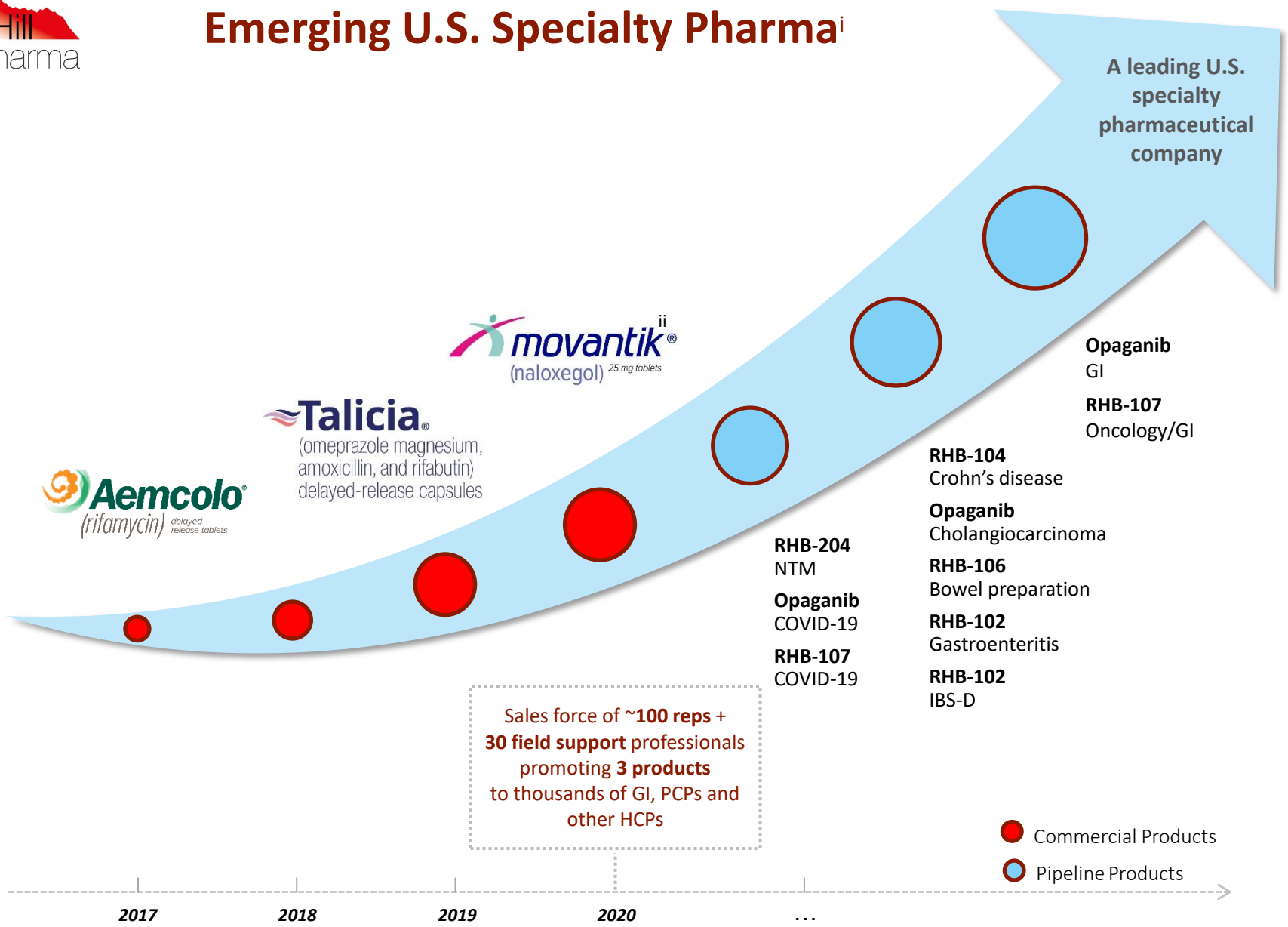
Commercial Products[ii]

- **Talicia®** (omeprazole magnesium, amoxicillin and rifabutin) delayed-release capsules — Talicia® (omeprazole magnesium, amoxicillin and rifabutin) - *H. pylori* infection in adults
- **movantik®** (naloxegol) 25 mg tablets — Movantik® (naloxegol) - Opioid induced constipation (OIC) in adults with chronic non-cancer pain[iii]
- **Aemcolo®** (rifamycin) delayed release tablets — Aemcolo® (rifamycin) - Travelers' diarrhea caused by noninvasive strains of *E. coli* in adults

Development Pipeline[iv]		Pre-Clinical / Phase 1/2 / Phase 3 / NDA
RHB-204	NTM disease	Phase 3 U.S. study ongoing
RHB-104	Crohn's disease	Positive results from Phase 3 MAP US study
RHB-102	Gastroenteritis	Positive results from Phase 3 U.S. study
	IBS-D	Positive results from Phase 2 U.S. study
RHB-106	Bowel cleanser	Phase 2/3 studies planned
Opaganib	Oncology Indications + COVID-19	Phase 2/3 COVID-19 & Phase 2 oncology program
RHB-107 (upamostat)	Oncology/GI + COVID-19	Ongoing Phase 2/3 COVID-19, GI & oncology indications

[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; Movantik®: www.movantik.com ; [iii] Movantik® is a registered trademark of AstraZeneca; [iv] 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".*

[ii] *Movantik® is a registered trademark of AstraZeneca.*

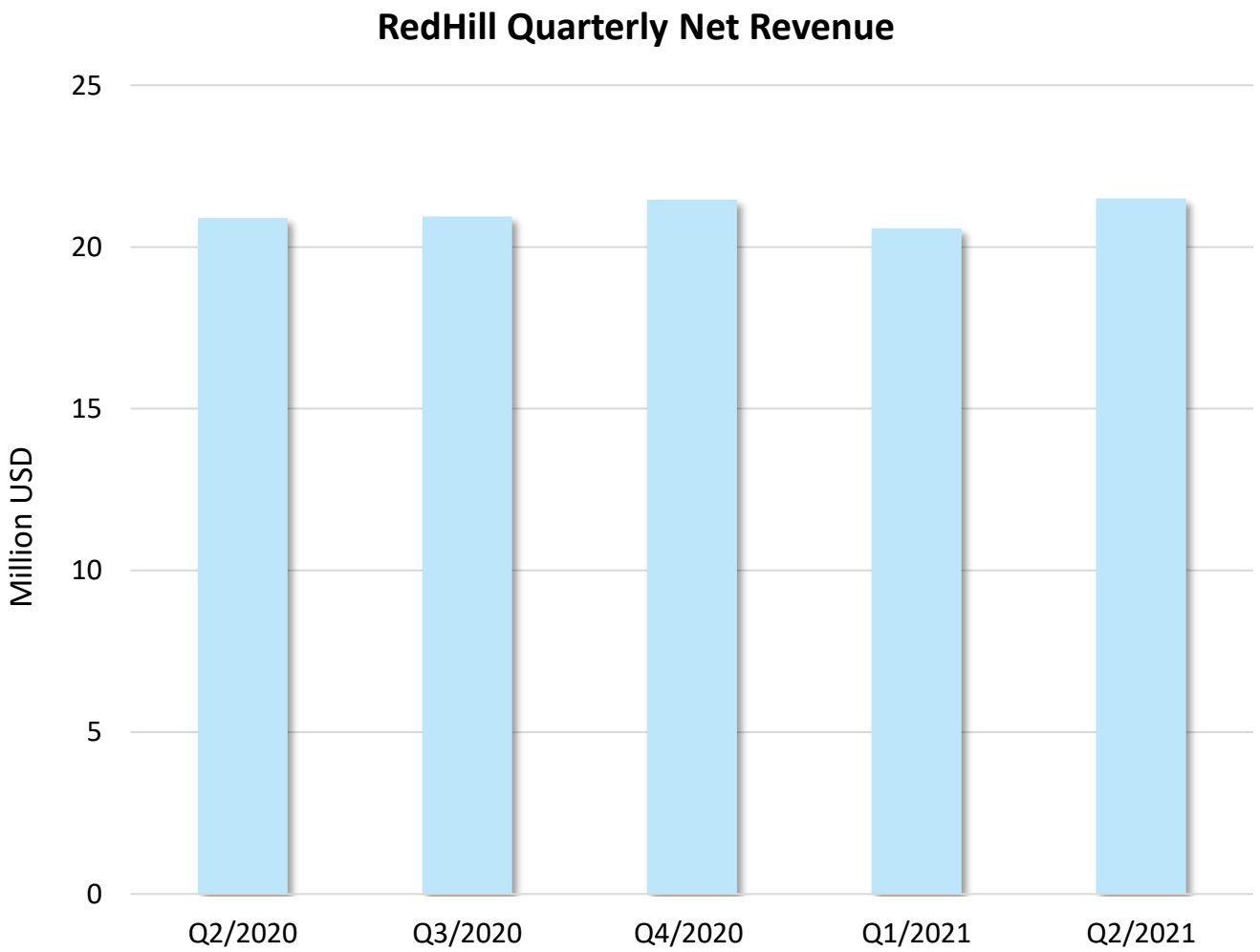
Financial Highlights[i]

RedHill Biopharma Ltd.
Nasdaq: RDHL

Market Cap (approx.)	$212 million
American Depositary Shares (ADSs)	46.9 million (Representing 468.8 million ordinary shares outstanding)
Cash Balance as of September 30, 2021[ii]	Approx. $51.5 million

[i] *Financial information as of November 15, 2021, unless otherwise noted ii cash, cash equivalent, bank deposits and restricted cash.*

Revenue Growth Despite Challenging Pandemic Conditions



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

Micha Ben Chorin, Chief Financial Officer
GVT, Pyramid Analytics, Starhome B.V.

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

David Wasserman, Senior VP Alliance & Project Management
Salix, Watson Pharmaceuticals, Glaxo PLC

Rob Jackson, Senior VP Sales & Marketing
Salix, Vicuron, Merck & Co.

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

Steven Thomasian, VP Supply Chain
Salix, Kala Pharmaceuticals, Cempra Pharmaceuticals

Aida Bibliowicz, VP Clinical Affairs Europe
MSc Technion, MBA TAU, Cato Research Israel

Todd Krzyzaniak, VP Finance US Operations
Salix Pharmaceuticals, BioDelivery Sciences International

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

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

Rick D. Scruggs, Chief Commercial Officer, Head of US Operations
Salix, Watson, Oclassen

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

Bob J. Gilkin, Senior VP Market Access & Trade Relations
Synergy Pharmaceuticals, AstraZeneca

Reginald Williams, VP Quality
Salix, Amgen, Eli Lilly and Merck & Co

Danielle Abramson, PhD, Senior VP Global Head of IP
Brown University, Greenberg Traurig

Craig Miller, VP Trade Channel
Salix, Oclassen Pharmaceuticals, Watson Pharmaceuticals

Michelle Snelling, VP Human Resources
Salix Pharmaceuticals, INC Research

Ben Martie, VP Legal Affairs
ViiV Healthcare (GSK), Chimerix Inc.

Board of Directors and Advisory Board

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

Alessandro Della Chà
Cosmo Pharma, Acacia Pharma Group plc

Rick D. Scruggs
Salix, Watson, Oclassen

Ofer Tsimchi
Danbar, Polysack, Director in several companies

Alla Felder
Neuroderm, PwC

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

Advisory Board

Jeff Leighton, PhD
Glaxo, Exogen, Genesis, Inspire

Werner Tschollar, MD
Past SVP for Worldwide R&D, Novartis

Scott Harris, MD
Lyric, Avaxia, Ocera, Napo

Prof. Ran Oren, MD
Digestive and Liver expert, Hadassah

Prof. Chezy Barenholz, PhD
Prof., Hebrew University of Jerusalem, Co-inventor of Doxil®

Abe Schwartz
Covalon Tech., CEO Cedara Software

Prof. Colin Blakemore, PhD
Oxford, Past CEO - UK Medical Research Council

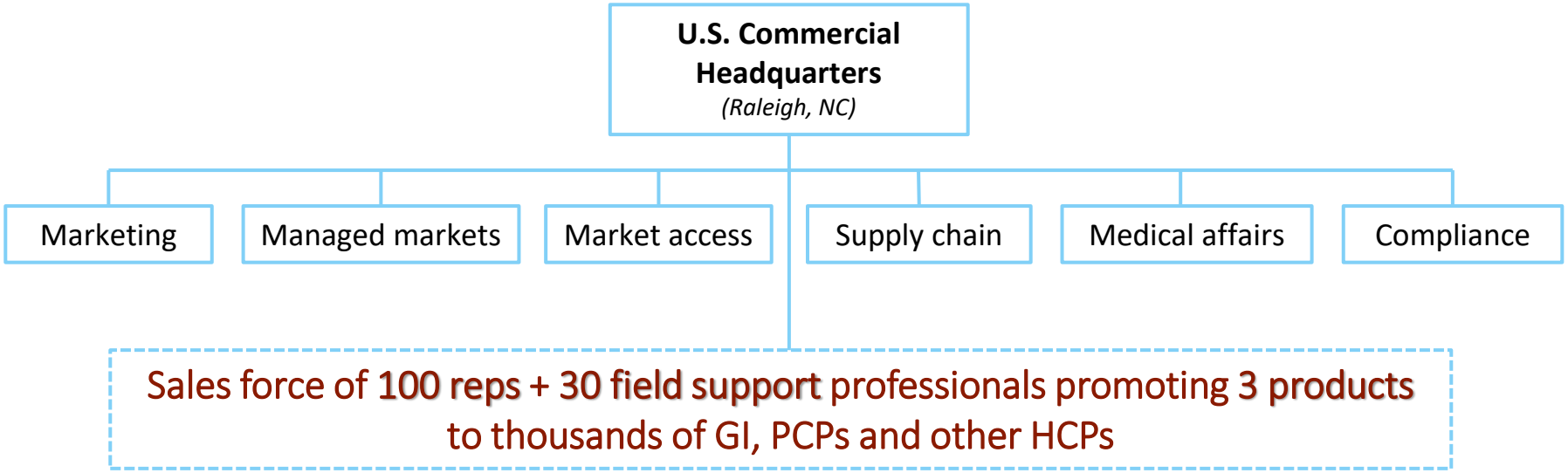
Ira Kalfus, MD
Lev pharma, Aetna/US Healthcare

Prof. Thomas Borody, MD
Founder Centre for Digestive Diseases

Jerry Rosenblatt, PhD
Foster Rosenblatt Consulting, IMS Health

Commercial Operations - Strong U.S. Presence

Launched Aemcolo® in Q4/2019, Talicia® in Q1/20 and promoting Movantik® since April 2020



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

movantik®[i]
(naloxegol) 25 mg tablets

Aemcolo®
(rifamycin) delayed release tablets

[i] *Movantik® is a registered trademark of AstraZeneca*

RedHill Biopharma



Indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain

[1] *Movantik® is a registered trademark of AstraZeneca*

MOVANTIK® (naloxegol) Important Safety Information

IMPORTANT SAFETY INFORMATION

- **MOVANTIK may cause serious side effects, including:**
  - Opioid withdrawal. You may have symptoms of opioid withdrawal during treatment with MOVANTIK, including sweating, chills, diarrhea, stomach pain, anxiety, irritability, and yawning. Patients taking methadone to treat their pain may be more likely to experience stomach pain and diarrhea. Tell your doctor if you have any of these symptoms
  - Severe Stomach Pain and/or Diarrhea. This can happen within a few days of starting MOVANTIK and can lead to hospitalization. If either of these side effects occurs, stop taking MOVANTIK and call your doctor immediately
  - Tear in your stomach or intestinal wall (perforation). Stomach pain that is severe can be a sign of a serious medical condition. If you get stomach pain that gets worse or does not go away, stop taking MOVANTIK and get emergency medical help right away
- **Do not take MOVANTIK if you:**
  - Have a bowel blockage (intestinal obstruction) or have a history of bowel blockage
  - Are allergic to MOVANTIK or any of the ingredients in MOVANTIK
- MOVANTIK can interact with other medicines and cause side effects, including opioid withdrawal symptoms (see symptoms above). Tell your doctor or pharmacist before you start or stop any medicines during treatment with MOVANTIK
- **Before you take MOVANTIK, tell your doctor about all of your medical conditions, including if you:**
  - Have any stomach, bowel (intestines) problems, including inflammation in parts of the large intestine (diverticulitis), or inflammation and injury of the intestines caused by reduced blood flow (ischemic colitis)
  - Have had recent surgery on the stomach or intestines
  - Have any kidney, or liver problems
  - Are pregnant or plan to become pregnant. Taking MOVANTIK during pregnancy may cause opioid withdrawal symptoms in you or your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with MOVANTIK
  - Are breastfeeding or plan to breastfeed. It is not known if MOVANTIK passes into your breast milk. Taking MOVANTIK while you are breastfeeding may cause opioid withdrawal in your baby. You and your healthcare provider should decide if you will take MOVANTIK or breastfeed. You should not breastfeed if you take MOVANTIK
- **Tell your doctor about all of the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. Other medicines may affect the way MOVANTIK works
- **If you stop taking your opioid pain medicine, stop taking MOVANTIK and tell your doctor**
- Avoid eating grapefruit or drinking grapefruit juice during treatment with MOVANTIK
- **The most common side effects of MOVANTIK include:** Stomach (abdomen) pain, diarrhea, nausea, gas, vomiting, headache, and excessive sweating

APPROVED USE FOR MOVANTIK

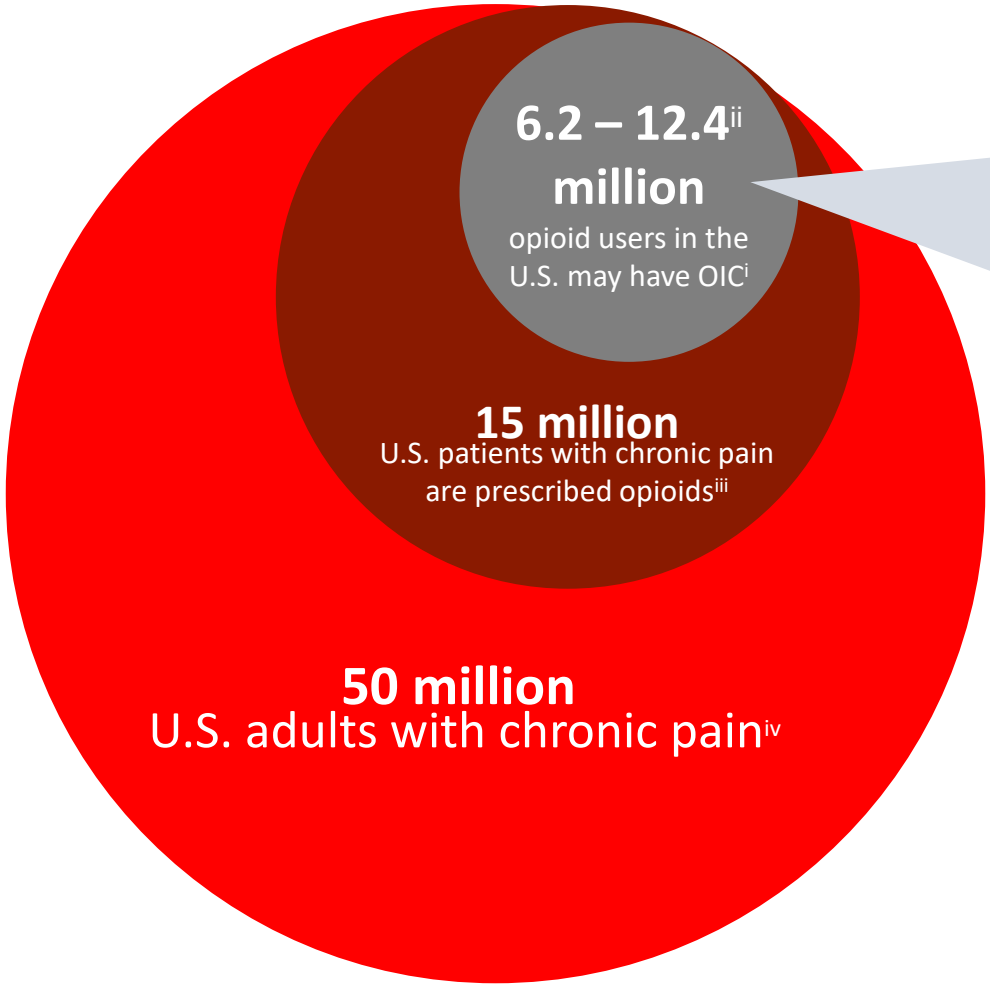
MOVANTIK is a prescription medicine used to treat constipation that is caused by prescription pain medicines called opioids, in adults with long-lasting (chronic) pain that is not caused by active cancer.

See full prescribing information for Movantik®: www.movantik.com

Movantik®- FDA-Approved for Treatment of Opioid-Induced Constipation

Approved Indication	Treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain
Drug	Oral naloxegol tablets available in 12.5mg and 25mg dosage strengths
Approved	Approved in the U.S. in 2014 - launched in 2015 by AstraZeneca and Daiichi Sankyo
Key Attributes	✓ Specifically designed for opioid-induced constipation ✓ Favorable tolerability and safety profile ✓ Available in two doses ✓ Strong reimbursement coverage
Market Exclusivity	Patent protection extending until at least 2028

OIC is a Large and Underserved Market[i]

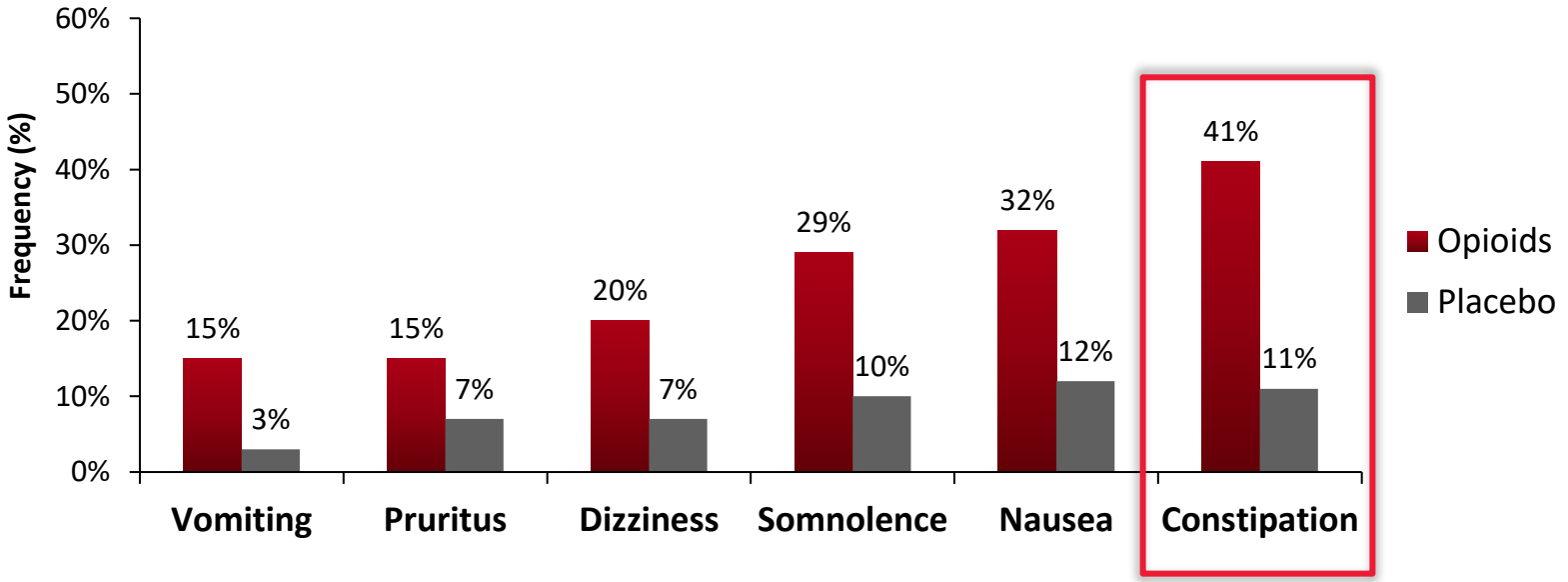


71% of patients with OIC report little to no benefit from constipation treatments[iii]

[i] *Bell TJ et al. Pain Med. 2009;10(1):35-42. Dahlhamer J, Lucas J, Zelaya C et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults – United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67:1001-1006. Accessed September 29, 2020. https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6736a2-H.pdf.* [ii] *30.7% of patients with chronic noncancer pain are prescribed opioids. Prevalence of OIC is estimated at between 40% to 81% in patients with chronic noncancer pain. Mathieson S et al. J Int Med. 2020;287:458-474.* [iii] *Constipation treatments included OTC laxatives (stool softeners, osmotics, stimulants, salines, and rectal options), prescription laxatives, and behavioral therapies (fiber supplements, increased fluids and exercise, and dietary changes). Coyne KS et al. Clinicoecon Outcomes Res. 2014;6:269-281.* [iv] *Vegia AR et al. Pain Res Treat. 2018. doi: 10.1155/2018/5704627 5. Coyne KS et al. Clinicoecon Outcomes Res. 2014;6:269-281.*

Constipation is One of the Most Common Side Effects of Opioid Therapy[i]

Results from a meta-analysis that included randomized controlled trials of opioid therapy in patients with chronic non-cancer pain:[ii]



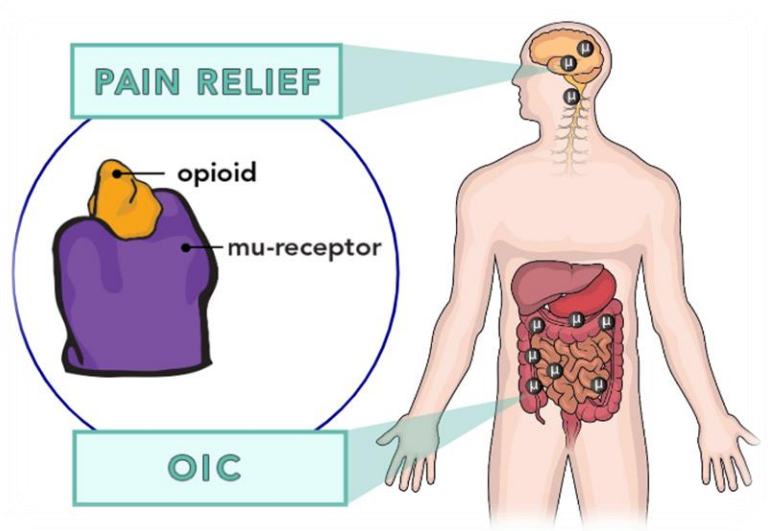
OIC Can Occur with Initiation of Opioid Therapy and May Persist for the Duration of Treatment[i]

[i] *Panchal SJ et al. Int J Clin Pract. 2007;61:1181-1187. Becker G et al. Lancet. 2009;373:1198-1206.*
[ii] *Kalso E et al. Pain. 2004;112:372-380.*

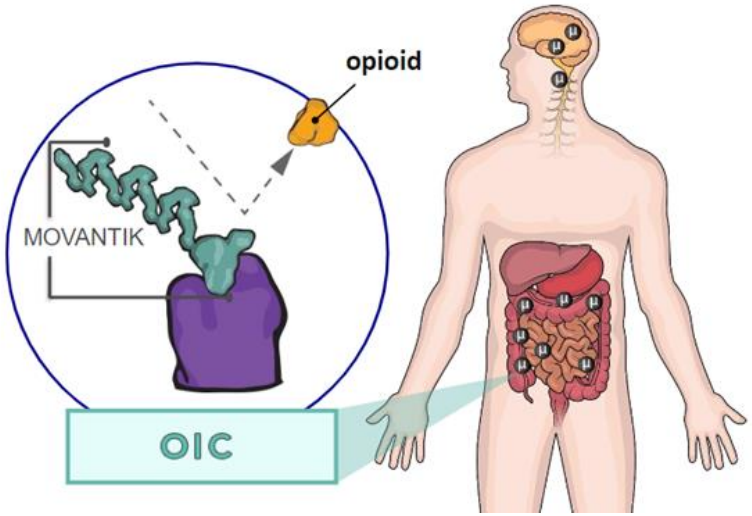
Movantik® is a Once-Daily Oral Therapy Specifically Designed to Treat OIC

Movantik functions as a peripherally acting mu-opioid receptor antagonist (PAMORA) in tissues such as the bowel, thereby decreasing the constipating effect of opioids while limiting the potential for interference with centrally mediated opioid analgesia.

OIC is caused by opioid binding to mu-receptors in the GI tract



*Movantik antagonizes opioid binding at the mu-receptor**



Movantik is a PEGylated derivative of naloxone, limiting central effect[i]

[i] *Movantik Prescribing Information. Raleigh, NC: RedHill Biopharma; Version 07/2020.*

Movantik - the #1 Prescribed Oral PAMORA[i]

Over **2,000,000** prescriptions written since 2015[ii]

The **#1 prescribed** oral PAMORA specifically designed to treat OIC[ii]

The American Gastroenterological Association recommends the use of Movantik as one of the prescription options for management of OIC[iii]

Movantik is covered or preferred without prior authorization for the majority of commercial and Medicare Part D patients in the U.S.[iv]

[i] Data on file. Prescription data. RedHill Biopharma; 2020. [ii] Since Jan 2017. Data on file. MOVANTIK CVA. RedHill Biopharma; 2019. [iii] Crockett SD et al. Gastroenterology. 2019;156:218-226. [iv] "Covered or preferred without prior authorization" means that additional information is not required to be provided to the health plan in order for MOVANTIK to be covered. Step edits and quantity limits may apply. "Patients" means covered lives (Commercial, Employer, Fed Prog, FEHBP, Municipal Plan, PBM, Union, EGWP, Medicare MA, Medicare PDP, Medicare SN, Medi-Medi, PACE) on all Tiers in the Nation, as calculated by MMIT as of January 11, 2021.

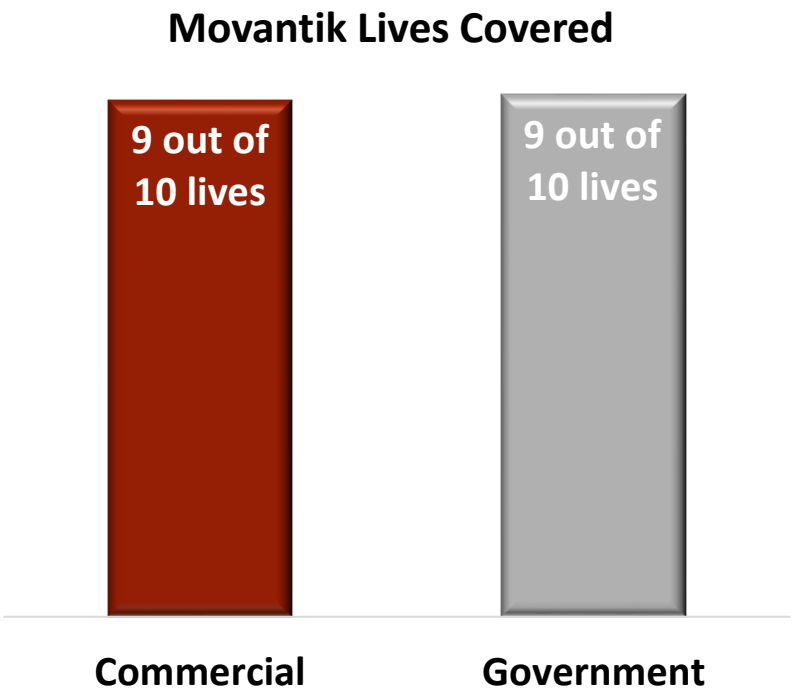
Movantik Acquisition - A Transformative Event for RedHill

RedHill acquired the global rights to Movantik[i] (excluding Europe and Canada) from AstraZeneca in April 2020

- RedHill benefits from the large investment made by AstraZeneca to make Movantik a brand leader
  - First oral PAMORA approved in the U.S. for the treatment of OIC
- **RedHill is enhancing focus to grow this product**
  - Movantik prescription (TRx) growth led by RedHill promotion, reversing the trend of prescription decline prior to RedHill acquisition
  - RedHill's sales force is enlarging promotional footprint
  - Targeting gastroenterologists, primary care physicians and additional specialists

[i] *Full prescribing information for MOVANTIK® is available at: www.movantik.com; MOVANTIK® is a registered trademark of AstraZeneca*

Continued Best Coverage in PAMORA Class



- ✓ Best coverage without restrictions in the PAMORA class for both Commercial and Government segments
- ✓ Improved both Commercial and Medicare Part D coverage since acquiring Movantik
- ✓ Continue to identify opportunities to increase or enhance coverage

Source: Estimated coverage based on MMIT data for all payers as of 7.2.2021; Commercial lives with policies applied and exclude HIX (health insurance exchange); Government lives include Medicaid (State and Managed) and Medicare Part D

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 omeprazole, amoxicillin and rifabutin.

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.

Talicia®- Approved by U.S. FDA 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**
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] – **Approximately 300% quarter-over-quarter prescription growth** and rapid expansion of the prescriber base – **National coverage for 167 million lives**, with additional coverage expected

[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

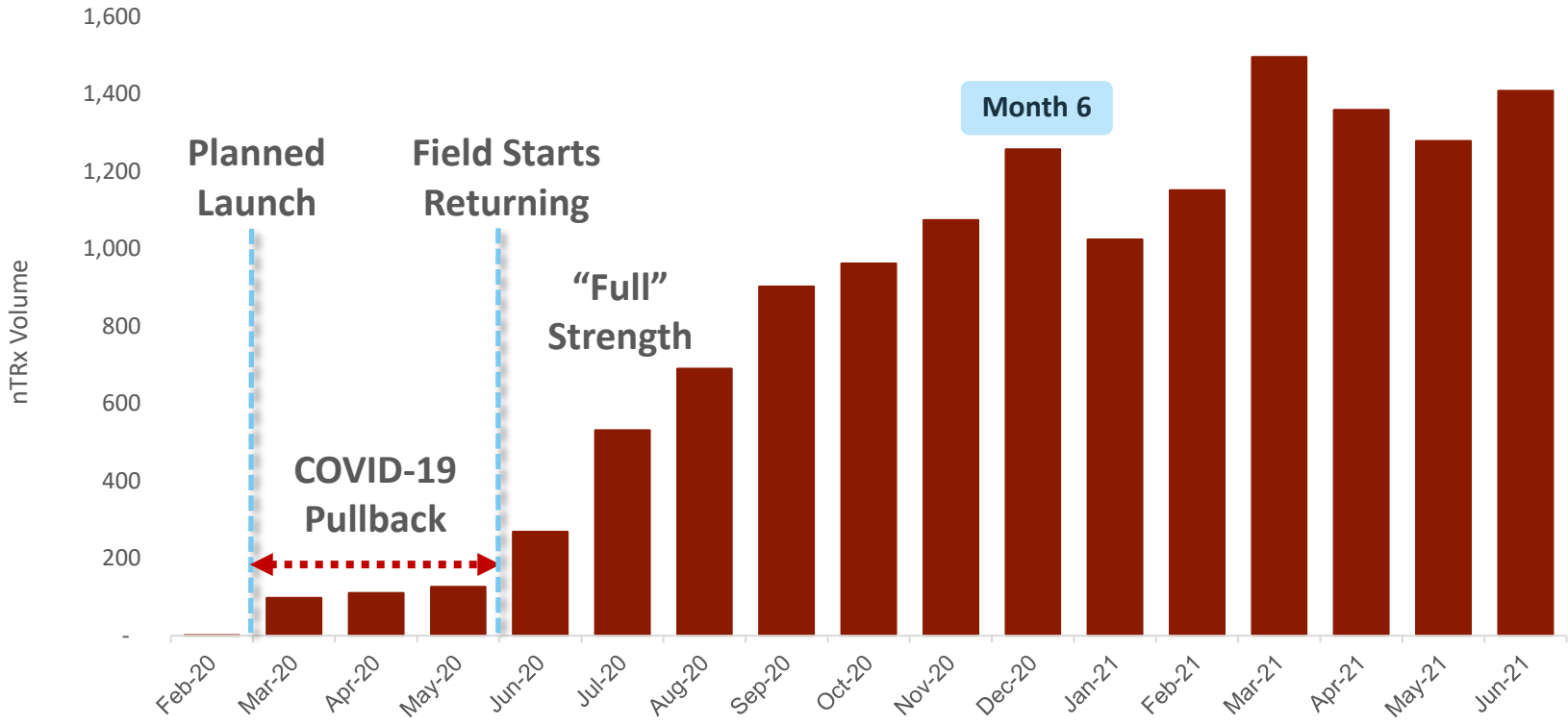
RedHill's U.S. sales force promoting Talicia® to approx. 25,000 gastroenterologists, primary care physicians and other healthcare providers
Rapid expansion in managed care coverage since launch



Talicia Delivered >10% Growth in Q2/21

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

Talicia nTRx Growth

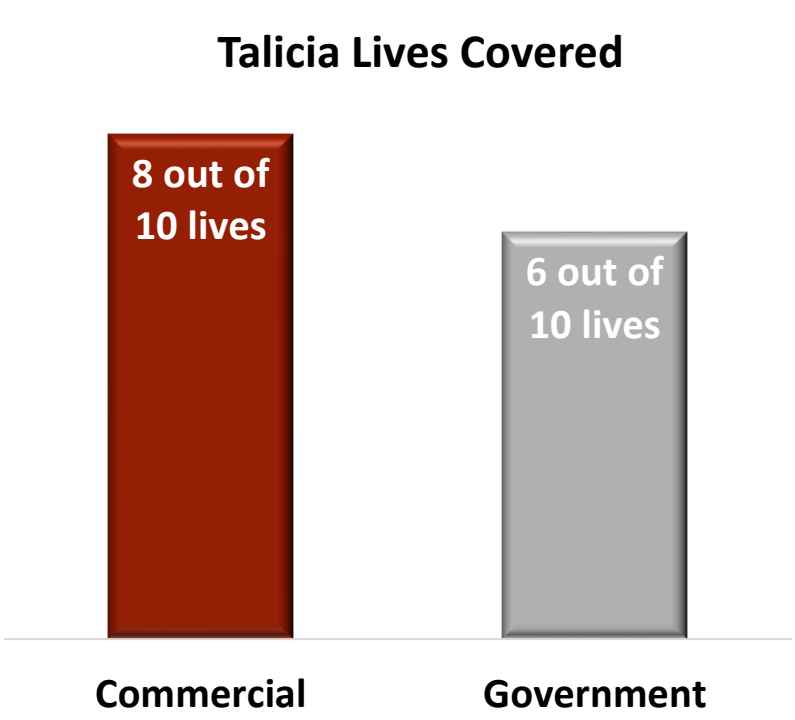


Talicia continues to achieve launch milestones with over 10% Q/Q growth in Q2/21 and strong commercial coverage

Data from IQVIA Xponent nTRx (normalized TRx)

Talicia Commercial Coverage Continues to Improve and Now Covers 8 out of 10 lives

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



- ✓ Talicia Commercial coverage continues to grow; Majority of Commercially insured patients can now access Talicia with no restrictions
- ✓ 8 out of 10 Commercially insured patients can access Talicia, with most having access without restrictions
- ✓ Payer strategy continues to support expanding coverage

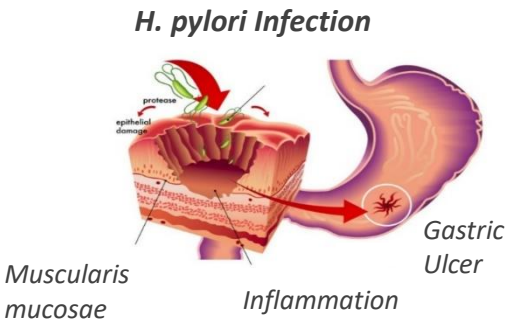
Source: Estimated coverage based on MMIT data for all payers as of 7.2.2021; Commercial lives with policies applied and exclude HIX (health insurance exchange) and Tricare; Government lives include Medicaid (State and Managed) and Medicare Part D

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

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

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

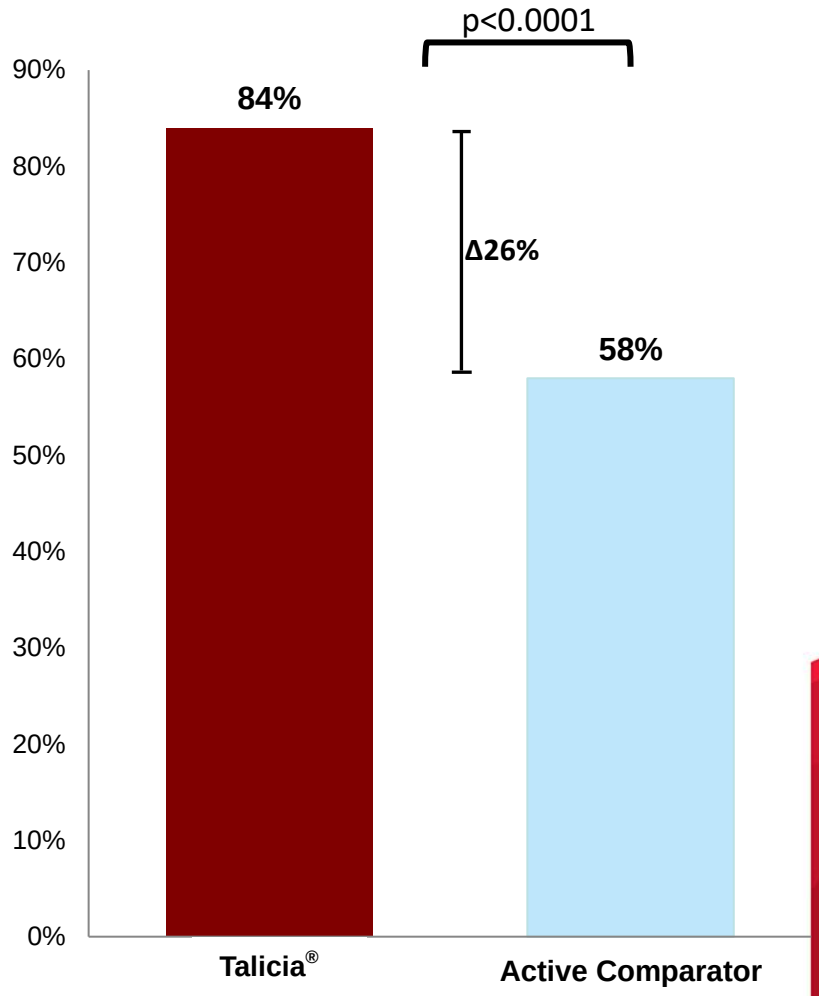
Positive Pivotal Phase 3 Study

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

- 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
- Acute use with low sensitivity for price differences → low incentive for substitution
- 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

Current brands provide only modest convenience improvement vs. generics

$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
- Robust U.S. patent portfolio and FDA QIDP designation, with U.S. marketing exclusivity through 2028

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



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

Travelers' diarrhea is a significant market:

- Approximately **93 million** Americans travel 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;*



Opaganib (ABC294640)[i]

Investigational new drug

First-in-class, orally-administered sphingosine kinase-2 (SK2) inhibitor targeting multiple oncology, inflammatory and GI indications

Top-line results reported from global Phase 2/3 study for COVID-19

--

Positive top-line data from U.S. Phase 2 study for COVID-19

--

Phase 2 studies in cholangiocarcinoma and prostate cancer ongoing

[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 - SK2 Inhibitor for COVID-19 and Oncology, Gastrointestinal and Inflammatory Diseases

The Product	- Potential first-in-class, orally-administered sphingosine kinase-2 (SK2) inhibitor - with anti-cancer, anti-inflammatory activities, targeting multiple oncology, inflammatory and GI indications - **Potent anti-viral activity, targeting a critical host factor - minimizing potential development of resistance due to viral mutations**
Market	- Significant market potential - multiple indications with an unmet need
Development Status	- Completed numerous successful pre-clinical studies in oncology, GI-Inflammation and radioprotection models, as well as food effect and toxicology studies
	- Phase 1 study in cancer patients with advanced solid tumors successfully met primary and secondary endpoints

	- **Phase 2a study for treatment of cholangiocarcinoma ongoing**
	  - Orphan Drug Designation for the treatment of cholangiocarcinoma
	  - Compassionate use for cholangiocarcinoma under Expanded Access Program

	- Investigator-sponsored Phase 2 study in prostate cancer ongoing
	- **Post-hoc analysis of global Phase 2/3 data showed statistically significant reduction in mortality and reaching room air by Day 14 (primary endpoint) in moderately severe patients** - **Positive top-line safety and efficacy data from U.S. Phase 2 study in patients hospitalized with COVID-19 pneumonia**

[i] *Based on a preliminary review of partial unaudited data; patient accrual, treatment and analysis ongoing*

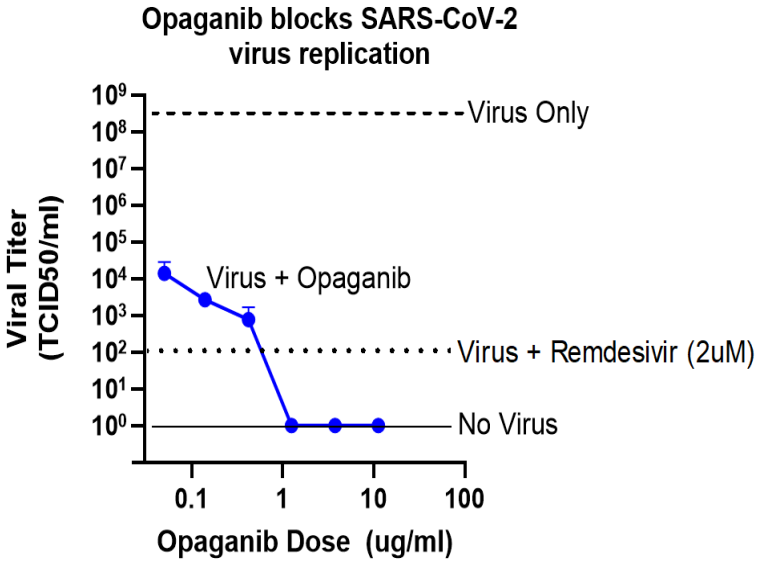
Opaganib - Complete Inhibition of SARS-CoV-2

Opaganib's unique MoA combines potent antiviral and anti-inflammatory activities, targeting a host cell component and minimizing likelihood of resistance

Potent Anti-SARS-CoV-2 Activity:

Opaganib evaluated in *in vitro* model of human lung bronchial tissue (EpiAirway™), including positive control of remdesivir:

- Opaganib completely inhibited SARS-CoV-2 viral replication as measured after three days incubation
- Opaganib demonstrated the most potent activity vs. all compounds tested, including remdesivir
- Dose-dependent inhibition of virus production without compromising cell membrane integrity
- Opaganib further demonstrated potent inhibition *of Delta* (India), *Beta* (South African) and *Gamma* (Brazilian) COVID-19 variants in preclinical study at non-cytotoxic doses



Opaganib - COVID-19 Studies

Global Phase 2/3 Study - Potential meaningful benefit to moderately severe patients

Randomized, double-blind, parallel-arm, placebo-controlled global Phase 2/3 study

- 475 subjects enrolled with severe COVID-19 pneumonia; study approved in 10 countries
- Top-line data of study efficacy endpoints showed consistent trends in favor of the opaganib despite not achieving statistical significance
- Post-hoc analysis of 54% of study patients hospitalized with moderately severe disease demonstrated statistically significant reduction in mortality, time to room air and time to hospital discharge
- Data packages submitted to regulators ahead of planned regulatory advice

U.S. Phase 2 Study - Positive data announced

U.S. randomized, double-blind, placebo-controlled Phase 2 study

- Positive top-line safety and efficacy data
- Small sample size of 40 hospitalized patients with COVID-19 pneumonia
- Focused on safety and initial efficacy signals; not powered for statistical significance

Preliminary Top-Line Data from Opaganib Phase 2/3 Study in Severe COVID-19 Pneumonia

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: the proportion of patients breathing room air without oxygen support by Day 14

Preliminary 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 group 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 days 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 Phase 2 COVID-19 Study - Positive Top-Line 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 received opaganib or placebo on top of standard-of-care. Follow up for up to 42 days post treatment initiation

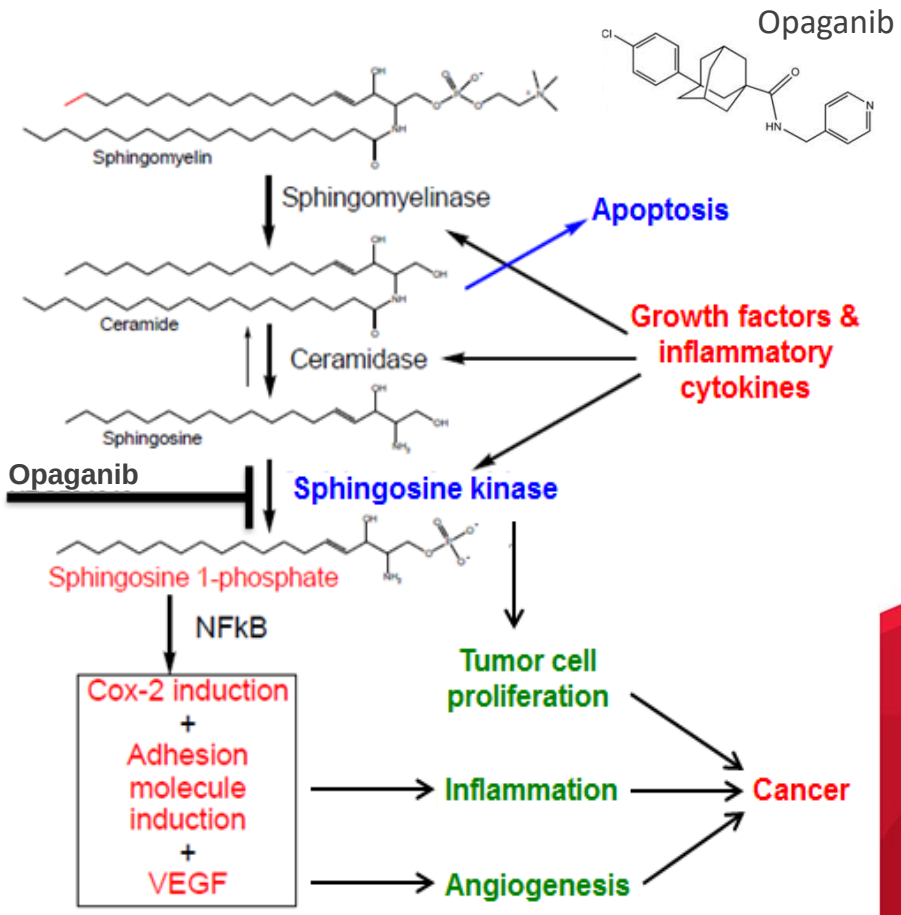
Results demonstrated positive safety and efficacy signals:

- 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 (62.0% vs. 47%)

Opaganib - Novel SK2 Inhibitor with Anti-Cancer, Anti-Inflammatory and Anti-Viral Activities

Opaganib selectively inhibits SK2, a lipid kinase with multiple cellular functions - potentially inhibiting tumor growth, pathological inflammation, and viral replication

- Sphingosine kinase-2 (SK2) impacts tumor growth and proliferation, pathological inflammation and cytokine production, including TNFα and IL-6
- SK2 is a critical component of the replication-transcription complex of many viruses. Blocking it may play a role in inhibiting viral replication
- Opaganib demonstrated potent anti-viral activity, targeting a host cell component and minimizing likelihood of resistance



Opaganib - Positive Phase 1 Study

Phase 1 Clinical study of opaganib in 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 - 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 demonstrated to be safe and well tolerated and was shown to be safely administered to cancer patients 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 Ongoing

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 - Recruitment initiated for second arm evaluating opaganib in combination with hydroxychloroquine, an anti-autophagy agent
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)

Investigational new drug

Potential first-in-class small molecule targeting oncology, inflammatory lung diseases and GI indications

U.S. Phase 2/3 COVID-19 ongoing in non-hospitalized patients

47

RHB-107 - S1 Serine Protease Inhibitor with Ongoing Phase 2/3 COVID-19 Study in Non-Hospitalized Patients

The Drug	First-in-class, orally-administered inhibitor of S1 family of trypsin-like serine proteases with potential for use in the treatment of cancer, inflammatory lung diseases, irritable bowel syndrome, inflammatory bowel disease and pancreatitis
	RHB-107 is a specific and potent inhibitor of human trypsin-3 (Ki ~ 20nM), trypsin-2 (Ki ~ 75nM), trypsin-6 (~100nM), trypsin-1 (Ki ~ 190nM) and matriptase-1 (~200nM) RHB-107 also inhibits a specific inhibitor of a number of members of the type II transmembrane serine proteases (TTSPs), some of which are important factors in the spread of infectious disease, including, matriptase, TMPRSS11, HAT-like 5 (HATL5), HAT, TMPRSS2 and hepsin
	Licensed worldwide rights from Heidelberg Pharma (formerly Wilex), excluding China, Taiwan, Macao and Hong Kong
Development Status	– **Phase 2/3 study in non-hospitalized patients with symptomatic COVID-19 ongoing in U.S. and South Africa; Recruitment completed for part A of the study – top-line data expected Q1/22 with Part B to follow**
	– Demonstrated clinical safety profile from approx. 200 patients across 10 clinical studies, including Phase 2 studies in locally advanced pancreatic cancer and metastatic breast cancer
	– FDA Orphan Drug Designation awarded for treatment of pancreatic cancer
	– RHB-107 planned to be evaluated in combination with opaganib in an ongoing Phase 2a study in cholangiocarcinoma

48

RHB-107 - Ongoing Phase 2/3 COVID-19 Study

Ongoing Phase 2/3 study with RHB-107 in non-hospitalized patients with symptomatic COVID-19 not requiring supplemental oxygen

- ✓ **Study design**: 310 patients to be enrolled in a 2-part, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2/3 study
- ✓ **Innovative use of home-based monitoring technologies** with home nursing support allowing patients participate from home
- ✓ **Primary endpoint**: time to sustained recovery
- ✓ Patients will be tested for specific viral strain
- ✓ Conducted in U.S. and South Africa

RHB-107 expected to be effective against emerging viral variants with mutations in the spike protein

- ✓ Once-daily orally-administered treatment early in course of disease, with demonstrated clinical safety
- ✓ Targets serine proteases - human cell factors involved in viral entry
- ✓ Demonstrated potent inhibition of SARS-CoV-2 viral replication in pre-clinical model of human bronchial tissue



RHB-204

Investigational new drug

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

U.S. Phase 3 Study Ongoing

RHB-204 - Targeting First-Line Pulmonary NTM Disease

Planned Indication	- Pulmonary Mycobacterium avium Complex (MAC) disease in adults with nodular bronchiectasis
The Product	- Patent-protected, oral all-in-one combination of three antibiotic drugs (clarithromycin, clofazimine and rifabutin) each known to be active against NTM disease caused by MAC[i]
Key Attributes	- **Targeting first-line treatment - potential new standard-of-care for a disease with no FDA-approved first-line therapy** - **Convenient stand-alone oral therapy for a chronic disease requiring extended treatment** - Unique dosing combination - optimizing exposure for safety and efficacy
Market Size	- U.S. market potential estimated at approx. $530M in 2021[ii]
Development Status	- **Phase 3 study ongoing** - QIDP and Fast-Track Designation granted, providing eligibility for rolling NDA review, Priority Review and accelerated approval - Orphan Drug designation extends potential U.S. market exclusivity to a total of 12 years post-approval

[i] *Wassilew et al, RESPIRATION 2021* [ii] *Foster Rosenblatt*

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[ii]
  - Approximately 80% of pulmonary NTM infections in the U.S. are associated with Mycobacterium avium complex (MAC)[iii]
- Pulmonary NTM disease symptoms can include fever, weight loss, chronic or recurring cough, chest pain, blood in sputum and fatigue[iv]
- NTM have high levels of drug resistance and require long term dosing with three or more antibiotics[ii]
- An orphan disease - with an estimated 110,000 pulmonary NTM patients in the U.S. in 2017[v]

[i] *Wassilew et al, RESPIRATION 2016* [ii] *Griffith DE, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases Am J Respir Crit Care Med. 2007;175(4):367-416; 3 American Thoracic Society;* [iii] *Prevots DR et al, Am J Respir Crit Care Med 2010;* [iv] *Daley et al CHEST 2017;* [v] *Foster Rosenblatt/Company estimates*

52

RHB-204 - CleaR-MAC Phase 3 Study Ongoing

A Phase 3 study to assess RHB-204 as a first-line treatment for the Treatment of pulmonary Mycobacterium avium Complex (MAC) disease in adults with nodular bronchiectasis

Study Initiated	- November 2020
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 - 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% enrolment
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



RHB-104

Investigational new drug

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

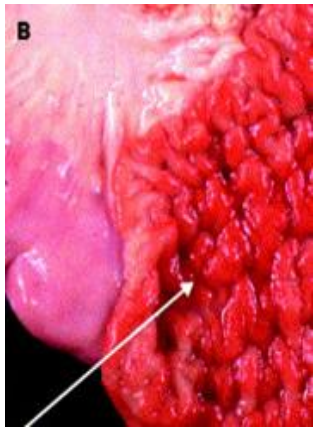
The Link between Crohn's Disease and MAP

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 $12.8 billion in 2022[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 Global Forecast , September 2017*

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

[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

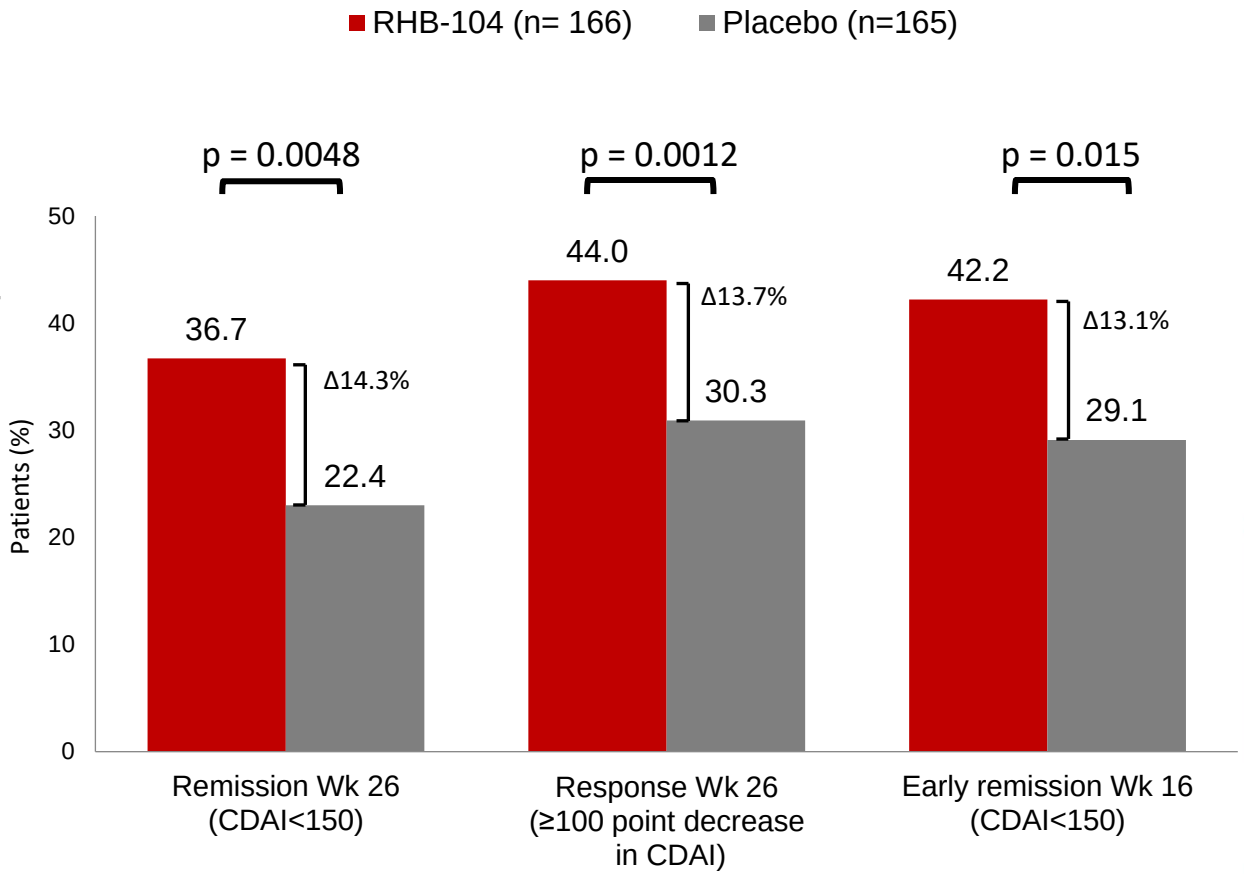
The MAP US Phase 3 study met its primary and key secondary endpoints, demonstrating meaningful, consistent and statistically significant clinical activity of orally-administered RHB-104 as an add-on to standard-of-care treatments

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)*

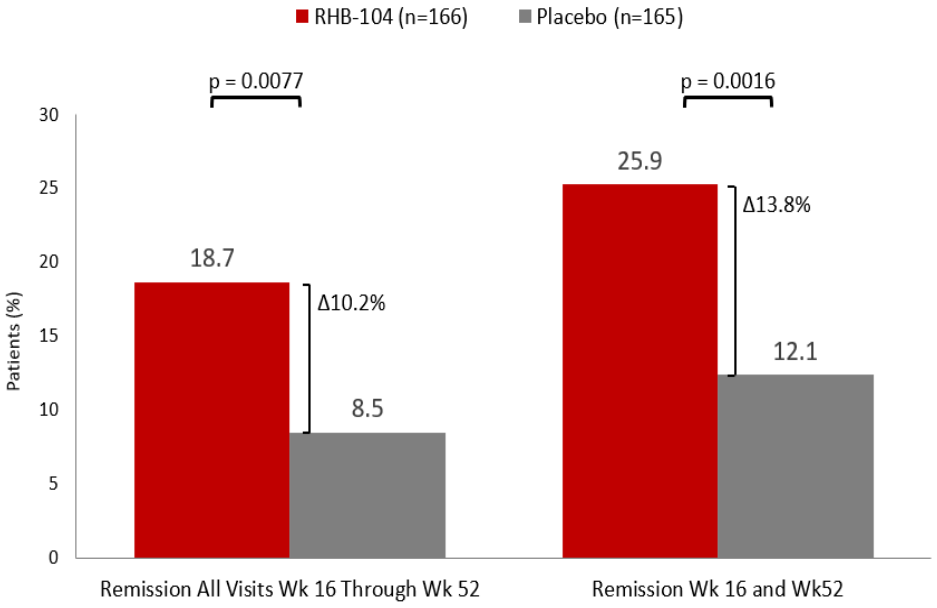
RHB-104 Crohn's Disease Phase 3 - Positive Results

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

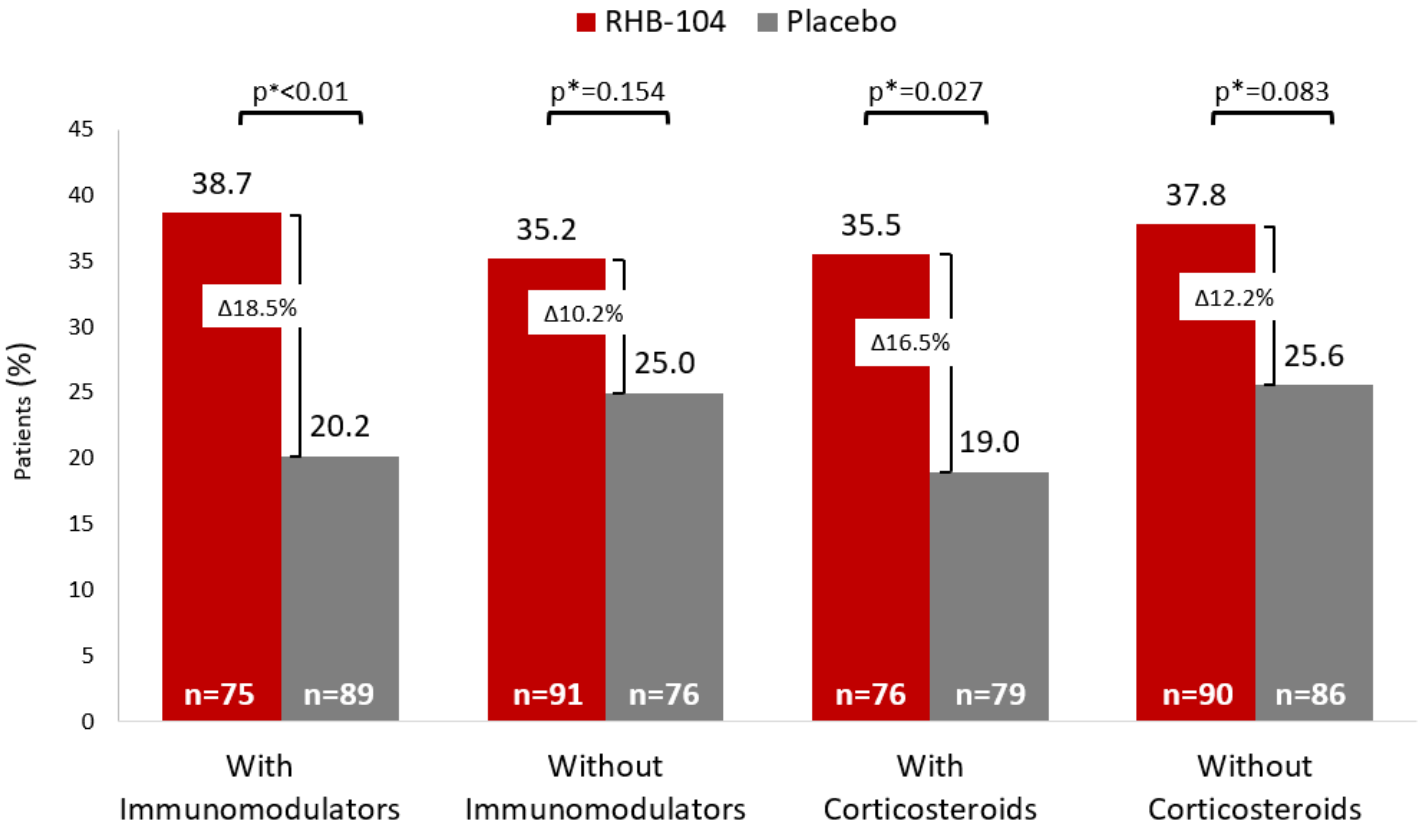


[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no); [ρ] Number of subjects reflects those subjects who have completed week 52 assessments and are no longer receiving blinded therapy*

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

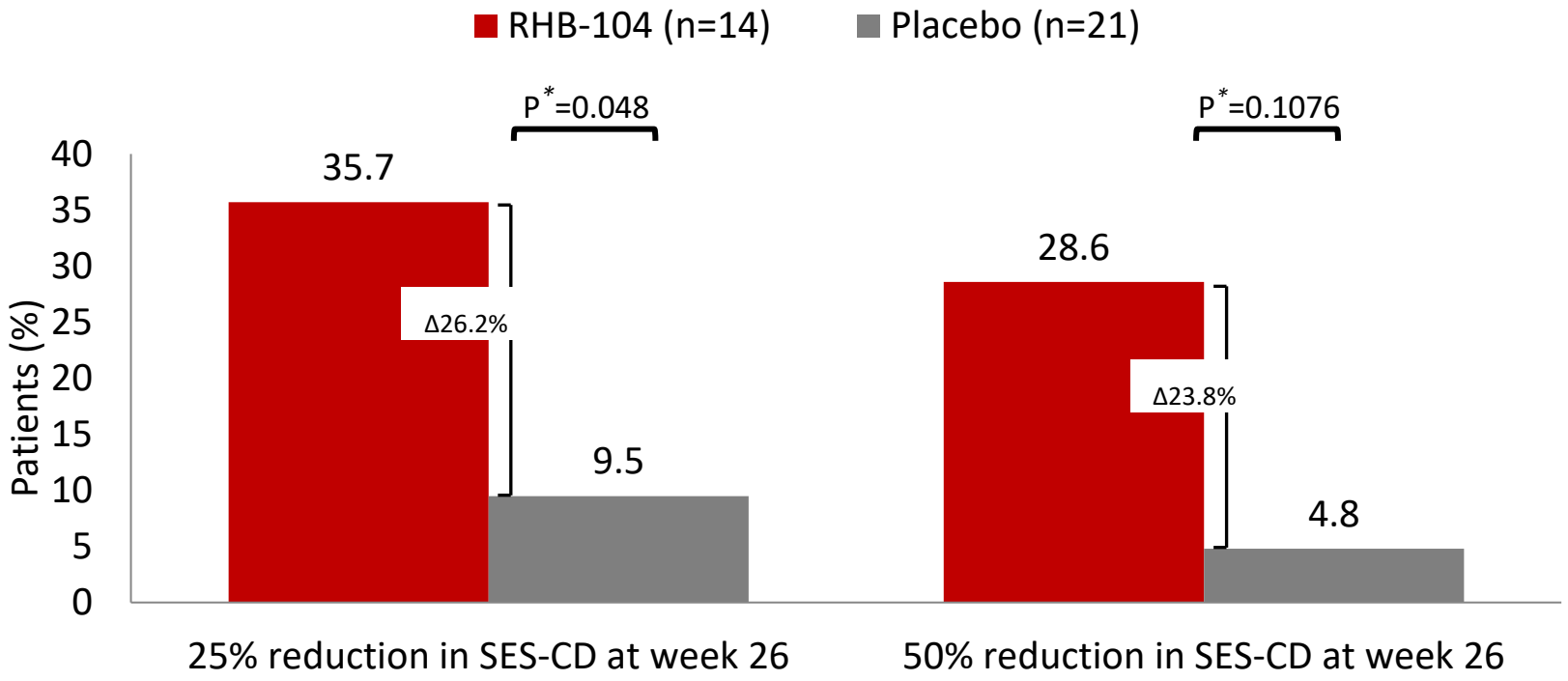


[i] *Calculated with Cochran-Mantel-Haenszel (MH) chi-square test with stratification according to anti-TNF agent use (yes/no); [ρ] Calculated with Mantel-Haenszel (MH) chi-square test*

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)

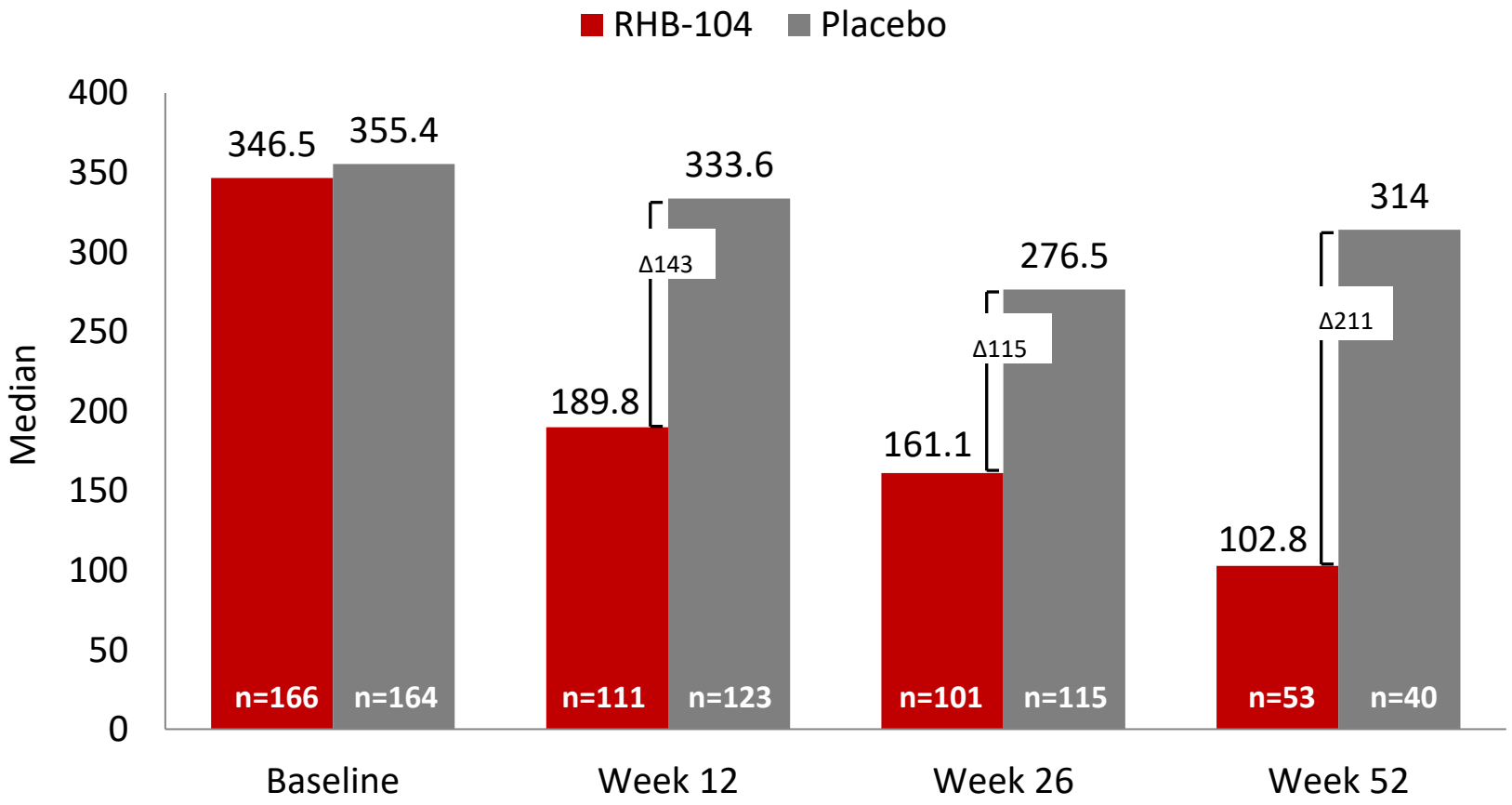


[i] *Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no)*

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

Median Fecal Calprotectin

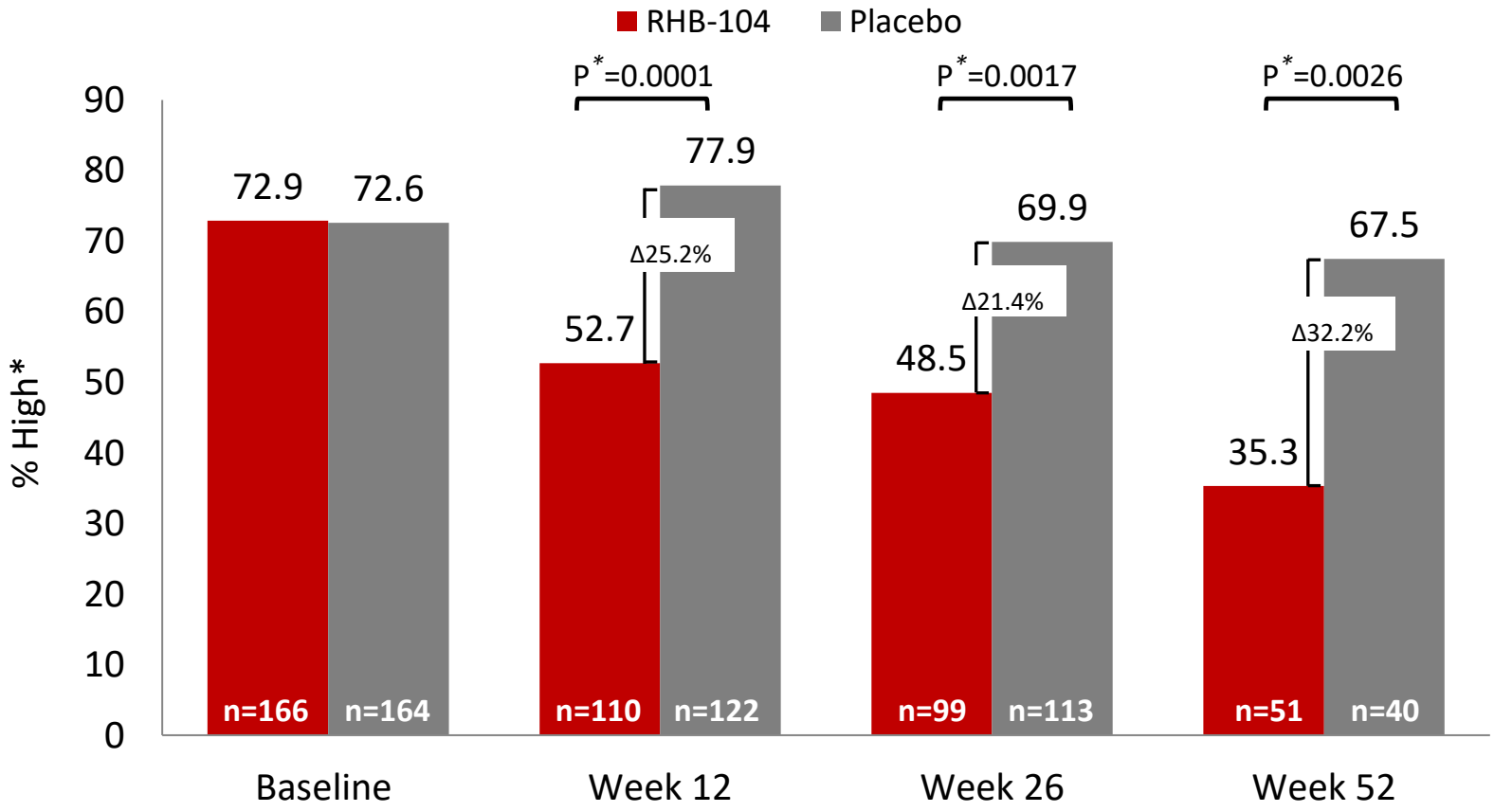
✓ Marked and continuous decline of calprotectin inflammatory marker in the RHB-104 active arm from baseline through week 52



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]
- 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-102[i] *Investigational new drug*

A bi-modal extended release, once-daily, ondansetron

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

[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 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 designing 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-106

Investigational new drug

Proprietary Encapsulated Formulation for Bowel Preparation

70

RHB-106 - Encapsulated Bowel Preparation

Planned Indication	Preparation of the gastrointestinal tract prior to abdominal procedures/surgeries, such as colonoscopy
The Product	– Proprietary, flavorless, odorless, solid oral encapsulated formulation for bowel preparation – Caplet formulation composed of sodium picosulfate, magnesium oxide, ascorbic acid and simethicone, mannitol and other excipients
Potential Advantages	– Improved safety over existing encapsulated preparations – Convenient, easy, taste free, and odorless – Can be taken with water
Potential Market Size	– Approx. 19 million colonoscopies performed annually in the U.S[i] – 2019 U.S. sales of bowel preparations estimated at approximately $580 million[ii]
Development Status	– Phase 2/3 studies planned – Phase 2a with a previous formulation of RHB-106 conducted in 62 patients in Australia[iii] demonstrating significantly improved patient response and comparable bowel cleansing

[i] *IDATA Research, August 2018;* [ii] *Foster-Rosenblatt, December 2019;* [iii] *Ramrakha SR et al. Investigating the tolerability of four bowel preparations – the taste test, J Gastroenterol Hepatol, 2006; 21 (Suppl;4): A286-A299*

Thank You!

RedHill Biopharma Ltd.
21 Ha'arba'a St.
Tel-Aviv, 6473921, Israel
Website: www.RedHillbio.com
Email: info@redhillbio.com
Tel: +972-3-541-3131