A Randomized Double Blind Placebo Controlled Phase III Study to Assess the Safety and Efficacy of Rifabutin Triple Therapy (RHB-105) for *Helicobacter pylori* (*H. pylori*) Infection in Dyspepsia Patients

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Financial and Other Disclosures

- **Data from IRB-approved human research is presented**

I have the following financial interests or relationships to disclose:	Disclosure code
RedHill Biopharma Ltd.	Consultant, Medical Director and Shareholder

Indication

- ***H. pylori* is an infectious disease[1] (Kyoto)**
  - Irrespective symptoms and stage of disease
- **A test-and-treat strategy is appropriate for uninvestigated dyspepsia[2] (Maastricht V)**
- ***H. pylori* infected individuals should be offered eradication therapy with caveats**
  - Age, alarm symptoms and *H. pylori* prevalence/susceptibility
- ***"the only good H. pylori is a dead H. pylori[3]***

[1]Gut 2015;64:1353-1367
[2]Malfertheiner P, et al. Gut 2017;66:6–30
[3]Graham D., Lancet, Vol 350 • July 5, 1997

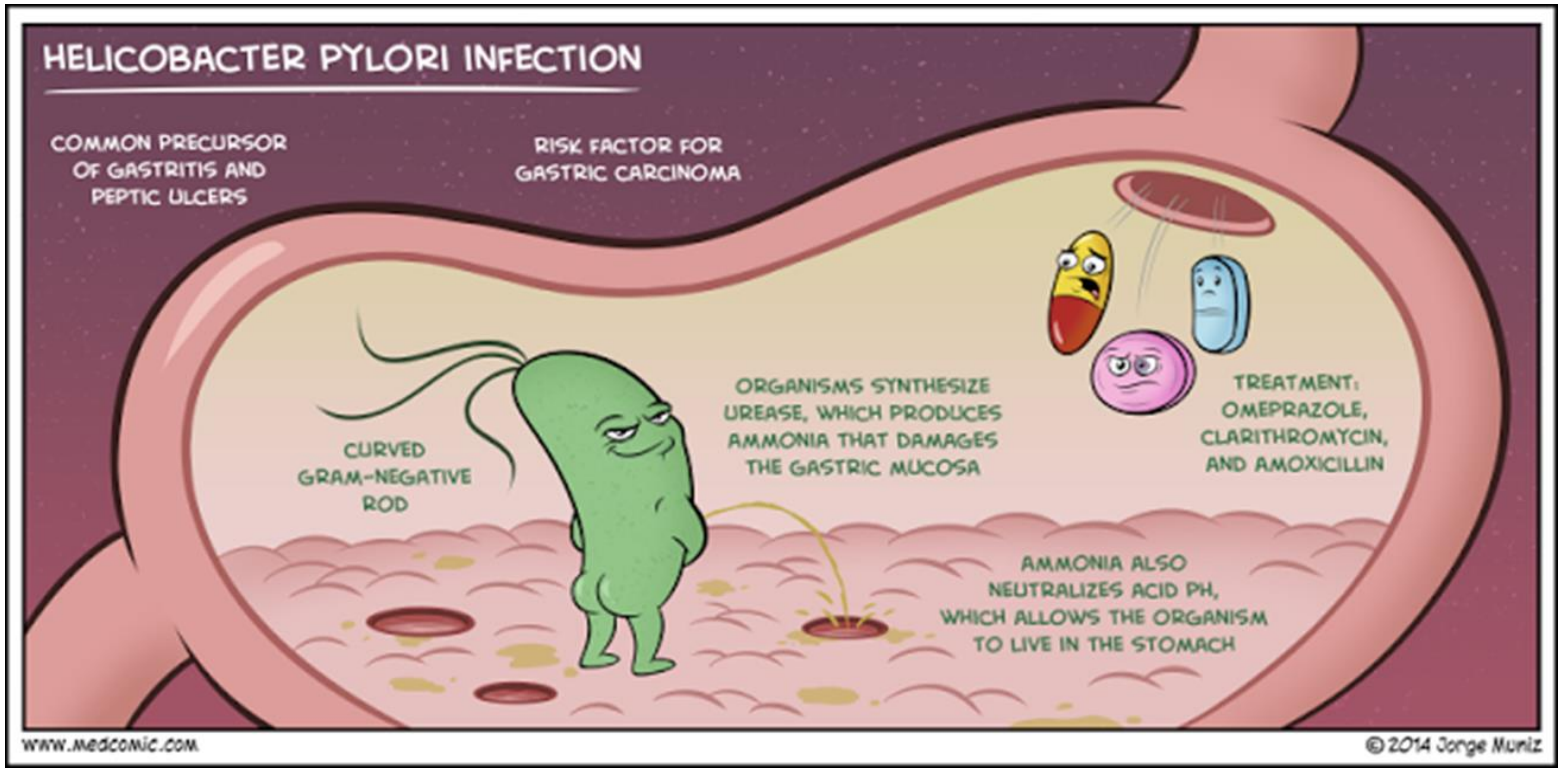
H. pylori – A Global Issue

- **~50% of world's population is infected**
  - 30-40% in US with 60-70% sub-populations[1]
  - 60% in Israel[2]
- **First course of tx offers**
  - Greatest chance at eradication
  - Reduced risk of gastritis, PUD and gastric cancer[3]
- **Treatment failure associated with increased risk of antibiotic resistance**

[1]Epplein et al., Cancer Epidemiol Biomarkers Prev. 2011;20:826–34
[3] Helicobacter Pylori: A Worldwide Perspective 2014. Shmuely and Niv,Helicobacter pylori in IEpidemiology, Pathophysiology, Diagnosis, Management and Resistance to Therapy, pp 169-182, 2016
[3]Gut 2015;64:1353-1367

The Problem

- Up to 30% failure to eradicate with standard triple therapy
- ↑resistance to clarithromycin & metronidazole



The Solution

- **RHB-105**
  - **"All-in one" capsule formulation**
  - **4 capsules tid**
    - Amoxicillin 1000 mg tid → 3 gm daily
    - Rifabutin 50 mg tid → 150 mg daily
    - Omeprazole 40 mg tid → 120 mg daily
  - **>90% efficacy in AMX/RIF/PPI single site SOC failed tx study[1]**
  - **Minimal resistance noted to AMX/RIF**

[1]Borody et al., Aliment Pharmacol Therapy. 2006, 23, 481-488

Randomized DBPC Phase III Study (ERADICATE Hp)

- **Assess the Safety and Efficacy of RHB-105 in the Treatment of Confirmed *Helicobacter pylori* Infection in Dyspepsia Patients**
  - Negative ^{13}C UBT 28-35 days post tx
- **118 Subjects**
- **2:1 Randomization**
  - RHB-105:Placebo – 77:41
  - 63% Female:37% Male
  - 92% White and Hispanic
  - 9 active sites
- **Treatment failures received investigator directed therapy with f/u test of cure post therapy**

Major Inclusion/Exclusion Criteria

- **Inclusion Criteria**
  - Aged 18 – 65 years
  - Positive for *H. pylori* by ^{13}C UBT and fecal antigen test or gastric biopsy within 6 weeks
  - Dyspeptic symptoms for at least 2 weeks – recurrent pain/discomfort in upper abdomen
- **Exclusion Criteria**
  - Alarm symptoms/signs
  - Antibiotics 4 weeks prior
  - Bismuth or PPI 2 weeks prior
  - Hx. prior *H. pylori* eradication therapy

Assumptions and Endpoints

- **RHB-105 at least 20% more effective than 70% historical control**
- **90% power, 0.025 one sided**
- **Primary endpoint – mITT population**
  - RHB-105 success rate vs 70% reported effectiveness of SOC triple therapy
  - Comparison vs placebo would not be informative
- **Secondary endpoint**
  - Safety

Protocol Defined Populations

- **Intent-to-Treat (ITT), n=77**
  - At least one dose of RHB-105 drug
- **Modified Intent-to-Treat (mITT), n=66**
  - At least one dose of RHB-105 and ^{13}C UBT day 28-35
    - 5 subjects withdrawn due to poor compliance (<75%)
    - 5 subjects lost to follow up
    - 1 subject with AE of nausea discontinued study drug
- **Per Protocol (PP), n=63**
  - At least one dose of RHB-105, ^{13}C UBT day 28-35 and no major protocol violations
    - 3 subjects withdrawn due to premature test of cure at days 20, 24, and 27

Disposition of All Subjects

	RHB-105 N = 77	Placebo N = 41	Total (N = 118)
Completed main study	63 (81.8%)	30 (73.2%)	93 (78.8%)
Discontinued from main study	14 (18.2%)	11 (26.8%)	25 (21.2%)
Reason for early termination:			
Lost to follow-up	6 (7.8%)	7 (17.1%)	13 (11.0%)
<75% compliance with drug	5 (6.5%)	0	5 (4.2%)
Withdrawal of informed consent	2 (2.6%)	3 (7.3%)	5 (4.2%)
Safety issue with inability to continue on study drug (Anemia)	0	1 (2.4%)	1 (0.8%)
AE Nausea with d/c study drug	1 (1.3%)	0	1 (0.8%)

Efficacy Results

- **Primary endpoint**
  - mITT RHB -105 success rate 89.4% (59/66 subjects), p-value<0.001
- **Sensitivity Analyses**
  - PP success rate 88.9% (56/63), p-value<0.001
  - ITT success rate 76.6% (59/77), p-value=0.085
  - SOC eradication rate of 63% (17/27 subjects)

SOC Success Rate Post Tx

H. pylori Eradication by Population	Treatment Group	Success	Failure	P-value
mITT	RHB-105	59 (89.4%)	7 (10.6%)	0.006
	SOC tx naive	17 (63.0%)	10 (37.0%)	
ITT	RHB-105	59 (76.6%)	18(23.3%)	0.009
	SOC tx naive	17 (52.0%)	16 (50.0%)	

Placebo Comparator Not Informative

mITT	RHB-105 N = 66	Placebo N = 37	Total
Success	59 (89.4%)	1 (2.7%)	60
Failure	7 (10.6%)	36 (97.3%)	43
P-value	< 0.001		
PP	N = 63	N = 36	
Success	56 (88.9%)	1 (2.8%)	57
Failure	7 (11.1%)	35 (97.2%)	42
P-value	< 0.001		
ITT	N = 77	N = 41	
Success	59 (76.6%)	1 (2.4%)	60
Failure	18 (23.4%)	40 (97.6%)	58
P-value	0.085		

Safety

- **151 AEs in 55 of 118 subjects**
  - 103 AEs in RHB-105 arm:48 AEs in placebo arm
- **55 TEAEs**
  - 31 mild
  - 20 moderate
  - 4 severe
    - RHB-105: Rash / diarrhea
    - Placebo: Anemia / perirectal abscess
    - 1 Additional anemia noted at baseline in RHB-105 subject

Summary of Treatment-Emergent Adverse Events (>5% Safety Population)

	RHB-105 N = 77		Placebo N = 41		Total N = 118	
Category	**# Pts (%)**	**# AEs**	**# Pts (%)**	**#AEs**	**# Pts (%)**	**# AEs**
All System Organ Classes	38 (49.4%)	103	17 (41.5%)	48	55 (46.6%)	151
Diarrhea	11 (14.3%)	14	4 (9.8%)	4	15 (12.7%)	18
Abdominal tenderness	5 (6.5%)	5	3 (7.3%)	3	8 (6.8%)	8
Headache	10 (13.0%)	13	4 (9.8%)	4	14 (11.9%)	17
Dizziness	3 (3.9%)	4	3 (7.3%)	3	6 (5.1%)	7
Chromaturia	**10 (13.0%)**	**10**	**1 (2.4%)**	**1**	**11 (9.3%)**	**11**

Summary of Treatment-Related TEAEs (>5% Safety Population)

	RHB-105 N = 77		Placebo N = 41		Total N = 118	
Category	**#Pts (%)**	**# AEs**	**#Pts (%)**	**#AEs**	**#Pts (%)**	**# AEs**
All System Organ Classes	38 (49.4%)	103	17 (41.5%)	48	55 (46.6%)	151
Related	23 (29.9%)	40	8 (19.5%)	23	31 (26.3%)	63
Not Related	15 (19.5%)	63	9 (22.0%)	25	24 (20.3%)	88
Diarrhea	9 (11.7%)	9	4 (9.8%)	4	13 (11.0%)	13
Headache	4 (5.2%)	5	3 (7.3%)	3	7 (5.9%)	8
Chromaturia	**9 (11.7%)**	**9**	**1 (2.4%)**	**1**	**10 (8.5%)**	**10**

Related = Possibly, Probably, or Definitely Related. Unrelated = Unlikely, Unrelated.

Treatment emergent AEs are defined as those beginning on or after the first dose of study treatment.

Safety

- **2 SAEs unrelated to study drug**
  - Anemia noted at screening – subject completed study (RHB-105 arm)
  - Perirectal abscess 18 days after completing study drug (placebo arm)
- **2 Early discontinuations in RHB-105 Arm**
  - Pharyngitis with poor compliance
  - Nausea with poor compliance

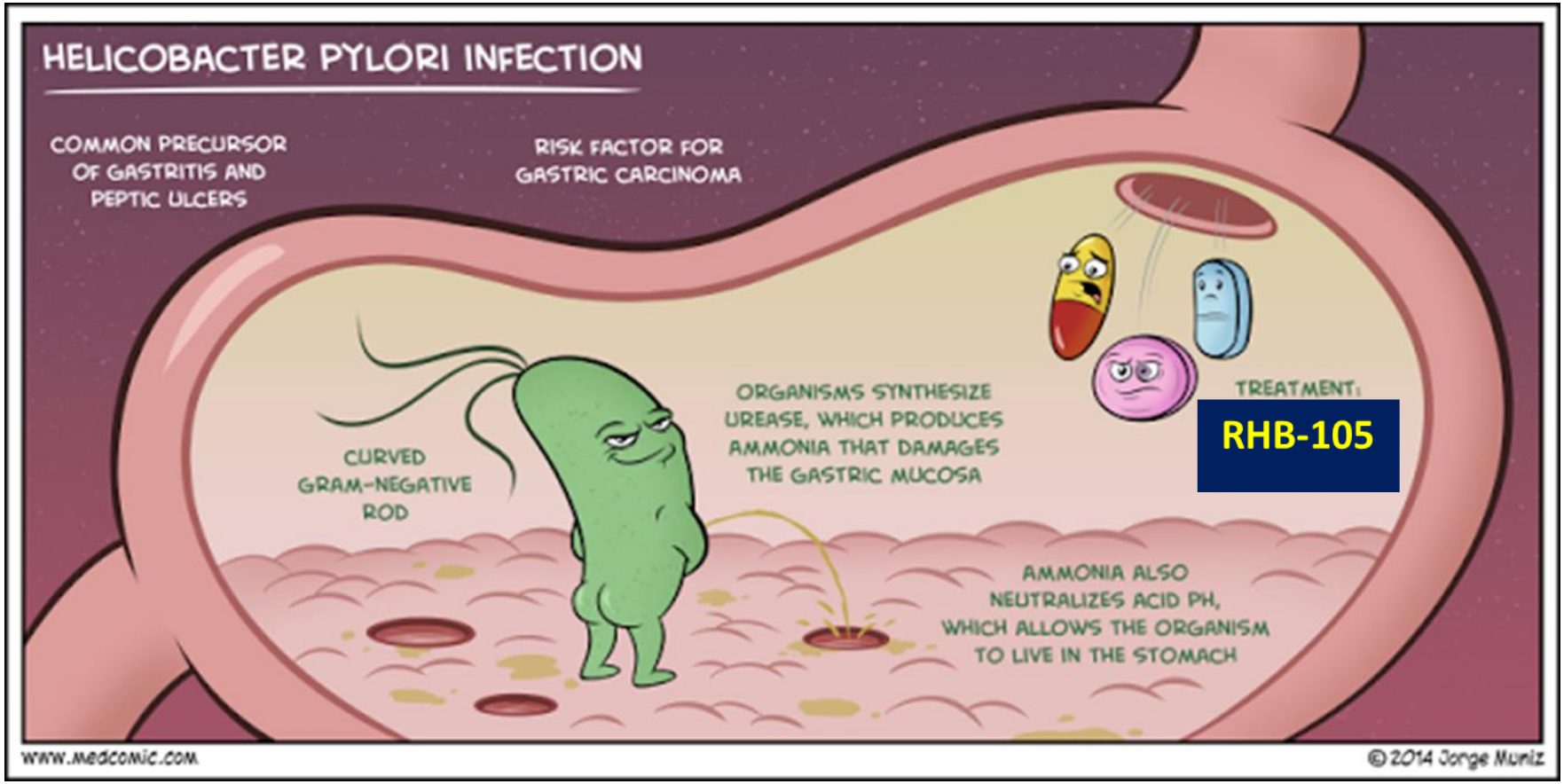
RHB-105 Study Conclusions

- A novel “3 in 1” potential new therapy
- Safe, well tolerated and more effective than historical or physician selected SOC treatment
- Confirmatory Phase III study planned
- Subject compliance and retention essential

Thank You

- Subjects and Study Site personnel who participated and supported this study
- David Graham and other PIs
- Special thanks to Dennis Riff, lead enroller

Thank You


HELICOBACTER PYLORI INFECTION
COMMON PRECURSOR OF GASTRITIS AND PEPTIC ULCERS
RISK FACTOR FOR GASTRIC CARCINOMA
CURVED GRAM-NEGATIVE ROD
ORGANISMS SYNTHESIZE UREASE, WHICH PRODUCES AMMONIA THAT DAMAGES THE GASTRIC MUCOSA
AMMONIA ALSO NEUTRALIZES ACID PH, WHICH ALLOWS THE ORGANISM TO LIVE IN THE STOMACH
TREATMENT:
RHB-105
www.medcomic.com
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