Phase III Randomized, Double Blind, Placebo-Controlled, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Add-On Fixed-Dose Anti-Mycobacterial Therapy (RHB-104) in Moderately to Severely Active Crohn's Disease (MAP US)

David Y. Graham, MD

Baylor College of Medicine, Houston TX, USA

Hardi R. MD[2], Welton T. MD[3], Krause R. MD[4], Levenson S. MD[5], Sarles H. MD[6], Sheikh A. MD[7], Epstein M. MD[8], Duvall G. MD[9], Freedland C. MD[10], Hebzda Z. MD[11], Arlukowicz T. MD[12], Kopon A. MD[13], Rydzewska G. MD[14], Zdravkovic N. MD[15], Svorcan P. MD[16], Zittan E. MD[17], Dugalic P. MD[18], Israeli E. MD[19], Anderson P.[20], Fehrmann C.[20], Bibliowicz A.[20], McLean P.[20], Fathi R.[20], Kalfus I. MD[20]

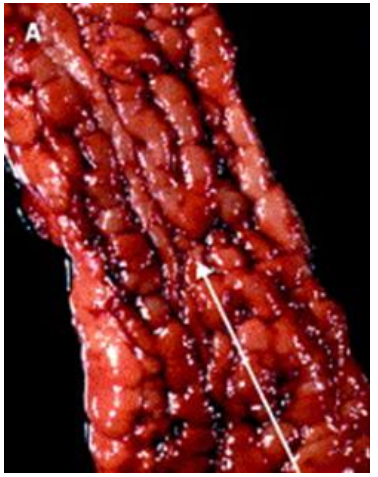
[2]Chevy Chase Clinical Research, Rockville, United States, [3]Cotton-O'Neil Clinical Research Center, Topeka, United States, [4]ClinSearch, Chatanooga, United States, [5]Digestive Care Associates, Inc., San Carlos, United States, [6]DHAT Research Institute / Digestive Health Associates of Texas, Richardson, United States, [7]Gastrointestinal Specialists of Georgia PC, Marietta, United States, [8]Investigative Clinical Research, Annapolis, United States, [9]Tyler Research Institute, Tyler, United States, [10]Advanced Research Institute Inc., New Port Richey, United States, [11]Unicardia, Krakow, Poland, [12]MEDICUM University of Warmia and Mazury, Olsztyn, Portugal, [13]Gastromed, Specialized Center of Gastrology and Endoscopy, Krakow, Poland, [14]Gastroenterology Dept, CSK MSWiA Warsaw, Faculty of Medicine and Health Sciences, UJK, Warsaw, Poland, [15]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia, [16]Zvezdara University Medical Center, Clinical Department of Gastroenterology and Hepatology, Belgrade, Serbia, [17]Emek Medical Center, Afula, Israel, Ellen and Pinchas Mamber Institute of Gastroenterology and Liver Diseases, and the IBD Unit, Afula, Israel, [18]Clinical Hospital Center Zemun, Department of Gastroenterology and Hepatology, Belgrade, Serbia, [19]Hadassah-Hebrew University, Institute of Gastroenterology and Liver Diseases, Jerusalem, Israel, [20]RedHill Biopharma Ltd., Tel-Aviv, Israel

Authors and Disclosures

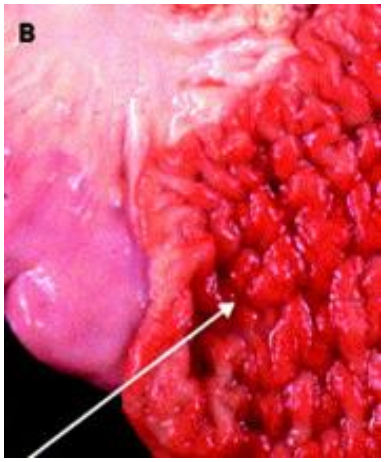
- David Y. Graham MD is a consultant to RedHill Biopharma and Takeda Pharmaceuticals
- Patricia Anderson, Clara Fehrmann, Patrick McLean and Ira N. Kalfus MD are consultants to RedHill Biopharma Ltd., the sponsor of this study

MAP and Crohn's Disease

- MAP can be cultured from peripheral blood mononuclear cells of Crohn's patients
  - Less commonly in healthy controls
- MAP has been considered as a possible cause of Crohn's disease since the disease was described in 1932
- Successful treatment of Crohn's disease with anti-MAP therapy would support causation
- This study is designed to test whether treating MAP improves remission in Crohn's disease compared to standard of care



Crohn's disease



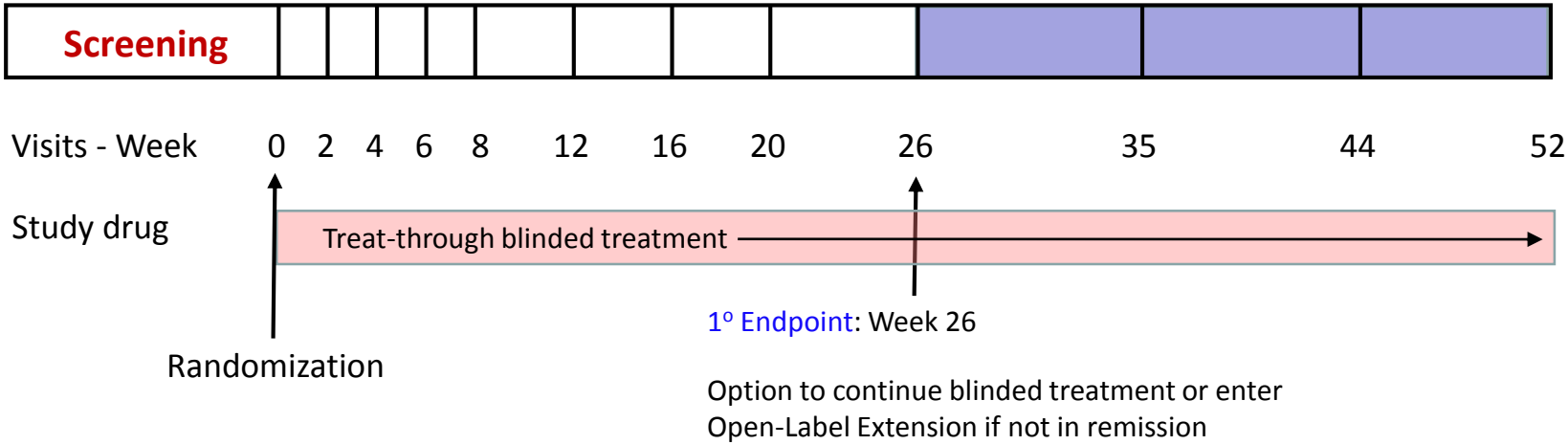
Johne's disease

Typical cobblestone appearance in Crohn's disease and JD

RHB-104 MAP US Study

- This is the first multinational randomized trial assessing efficacy and safety of anti-MAP therapy in Crohn's disease
- 52 week treat-through study of RHB-104 (a fixed dose oral combination of clarithromycin 95 mg, rifabutin 45 mg and clofazimine 10 mg) vs. placebo BID as add-on to standard-of-care, with primary endpoint at 26 weeks
- 331 Subjects randomized 1:1 to RHB-104 or placebo, stratified for concomitant use of anti-TNF agents
- Patients could opt for open-label treatment after 26 weeks of blinded study drug

RHB-104 MAP US Study Design



Procedures

MAP Testing (blood)		X		X		X	X	X	X	X	X	X
MAP Culture (blood)		X							X			X
CRP	X	X				X	X	X	X	X	X	X
Calprotectin	X	X				X			X			X
Colonoscopy† (optional)	(X)								(X)			

† *Study was designed before the routine use of endoscopy endpoints*

Key Inclusion/Exclusions

- Age: 18 to 75 years with active Crohn's disease
- Active Crohn's disease confirmed by one of following:
  - Endoscopy, CT/MRE, CRP or Fecal calprotectin >normal
- Disease of ileum and/or colon diagnosed at least 6 months prior to randomization
- CDAI score 220 to 450 inclusive
- Required continued treatment with at least one of the following standard of care medications:
  - Oral 5-aminosalicylic acid (5-ASA) compounds
  - Corticosteroids
    - Optional tapering after week 8
  - Azathioprine, 6-mercaptopurine (6-MP) or methotrexate
  - Infliximab or adalimumab

Study Endpoints

- Primary efficacy endpoint
  - Clinical remission: CDAI < 150 at week 26
- Secondary and other efficacy endpoints
  - Clinical response: ≥100 pt decrease in CDAI from baseline at week 26
  - Early clinical remission: CDAI <150 at week 16
  - Durable remission:
    - CDAI score < 150 from week 16 through week 52 at all study visits
    - CDAI score < 150 at week 16 and week 52
  - Steroid free remission:
    - CDAI <150 and off steroids for at least 3 weeks at week 52
- Additional SOC subgroup analyses of efficacy
- Safety

Statistical Analysis

- A sample size of 331 patients randomized 1:1 to RHB-104 or placebo was estimated to provide >80% power to detect a 15% treatment difference between RHB-104 and placebo at Week 26 at a nominal two-sided p-value of 0.05
- Endpoints beyond 26 weeks were included only for observational purposes to guide the design of maintenance of future remission trials, and the study was not powered for efficacy on this endpoint (or any of the secondary endpoints or subgroup analyses)

Patient Disposition

	RHB-104 n (%)	Placebo n (%)	Total
Total Screened			749
Screen Failures			418
Randomized	166 (100)	165 (100)	331
Completed study past week 26	85 (51.2)	88 (53.3)	175 (52.9)
Tx to Open Label Study			54
Discontinued from study	79 (47.6)	77 (46.7)	156 (47.1)
Withdrew Consent	25 (15.1)	26 (15.8)	51 (15.4)
Adverse Event(s)	22 (13.3)	21 (12.7)	43 (13.0)
Lost to Follow-up	6 (3.6)	7 (4.2)	13 (3.9)
Investigator decision	6 (3.6)	5 (3.0)	11 (3.3)
Intolerable Crohn's disease	5 (3.0)	5 (3.0)	10 (3.0)
Other	17 (10.2)	13 (7.9)	30 (9.1)

Demographics at Baseline

	RHB-104* (n=166)	Placebo* (n=165)
Gender		
Male, n (%)	91 (55)	98 (59)
Female, n (%)	75 (45)	67 (41)
Age (years), mean (SD)	39.0 (12.5)	39.3 (12.6)
BMI (kg/m^2), mean (SD)	25.9 (7.1)	26.2 (6.6)
Smoking		
Yes, n (%)	33 (20)	30 (18)
No, n (%)	133 (80)	135 (82)
CDAI Score, mean (SD)	298 (57.0)	293 (53.2)

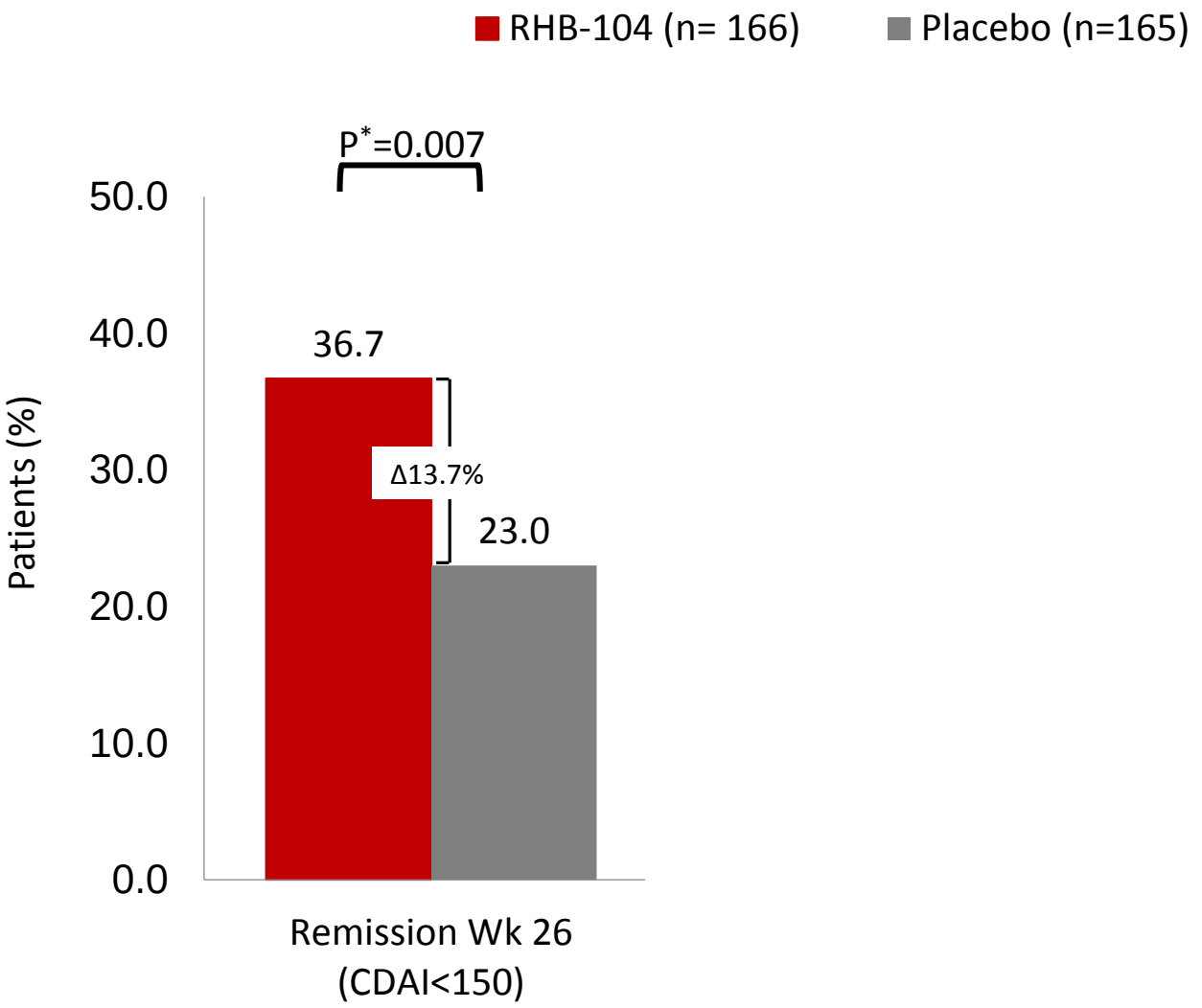
** RHB-104 and placebo as add-on to standard-of-care*

Demographics at Baseline

	RHB-104* (n=166)	Placebo* (n=165)
Time from Dx to MAP US, mean (SD)	10.4 (9.0)	10.8 (9.0)
< 2 years, n (%)	20 (12)	18 (11)
2-5 years, n (%)	36 (22)	37 (22)
> 5 years, n (%)	110 (66)	110 (67)
Site of primary Dx		
Ileum, n (%)	125 (75)	98 (59)
Colon, n (%)	93 (56)	106 (64)
Other, n (%)	12 (7)	8 (5)
CRP, mean (SD) Normal ≤ 0.999 mg/dL	1.34 (1.75)	1.38 (1.87)
Fecal calprotectin, mean (SD) Normal ≤ 162.9 mcg/g	543 (604)	668 (952)
Current immunomodulator use, n (%)	75 (45)	89 (54)
Current anti-TNF use (all patients were on immunomodulators as well), n (%)	31 (19)	36 (22)

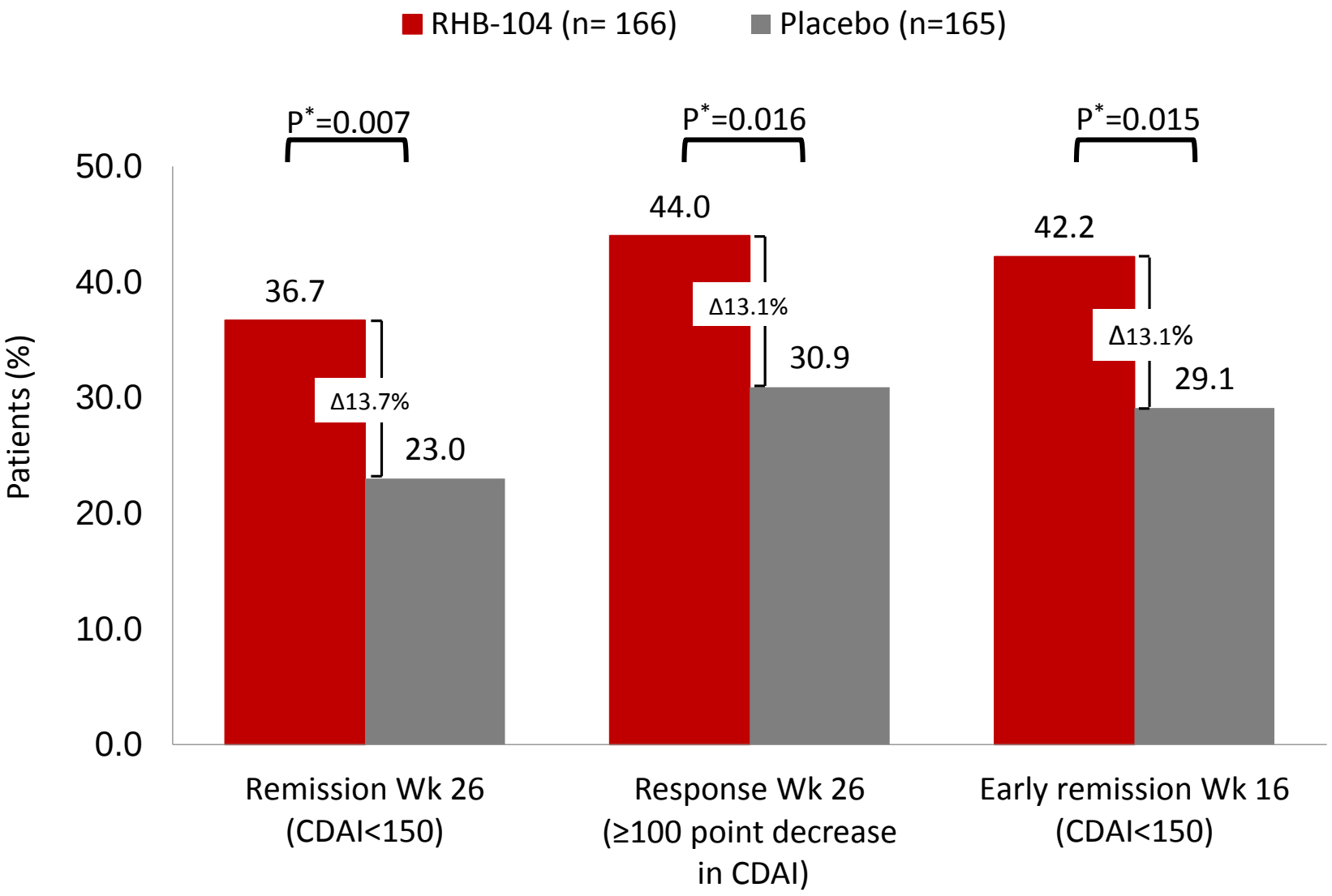
**RHB-104 and placebo as add-on to standard-of-care*

Primary and Secondary Endpoints



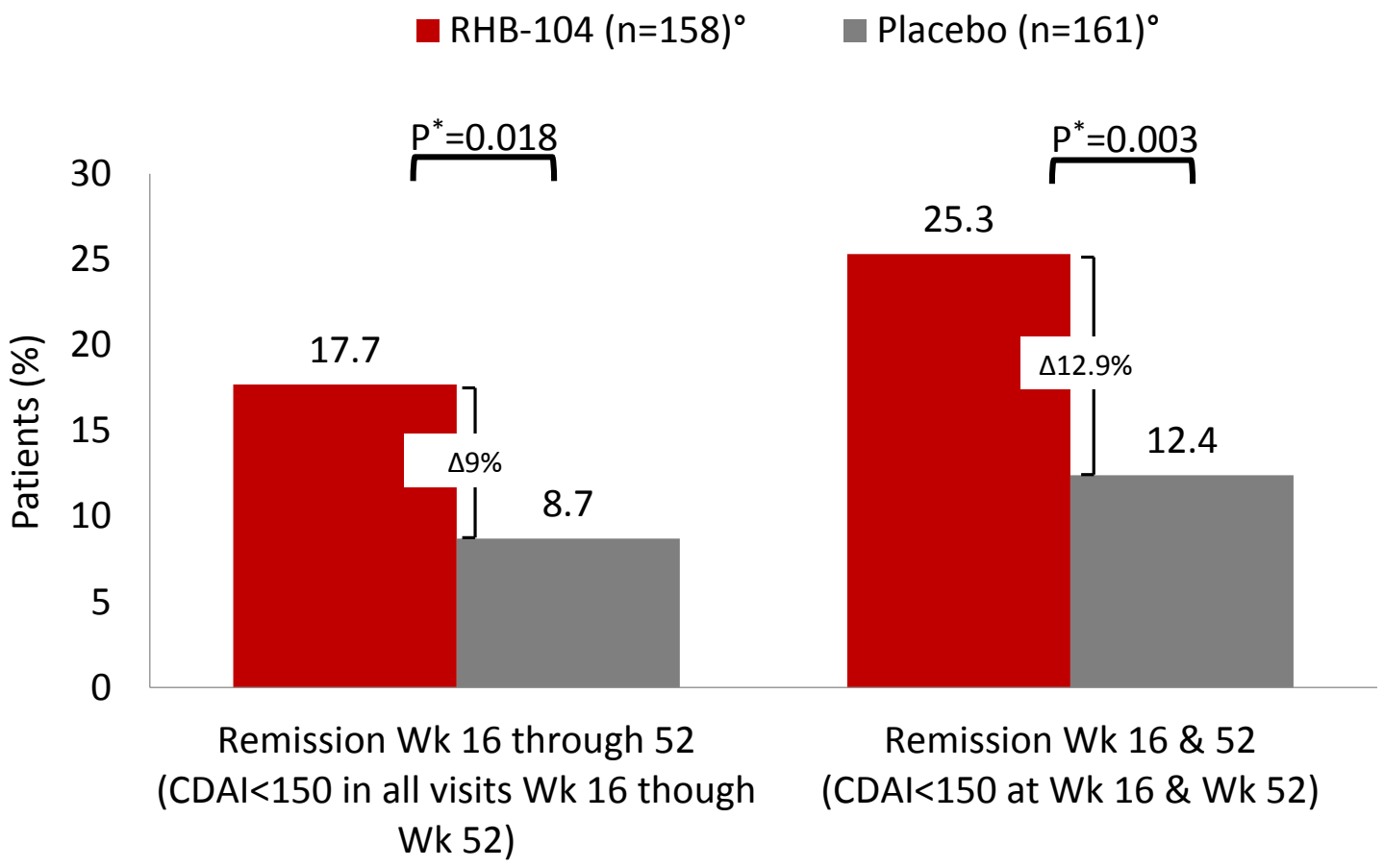
** Calculated with Cochran-Mantel-Haenszel (CMH) chi-square test with stratification according to anti-TNF agents use (yes/no)*

Primary and Secondary Endpoints



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

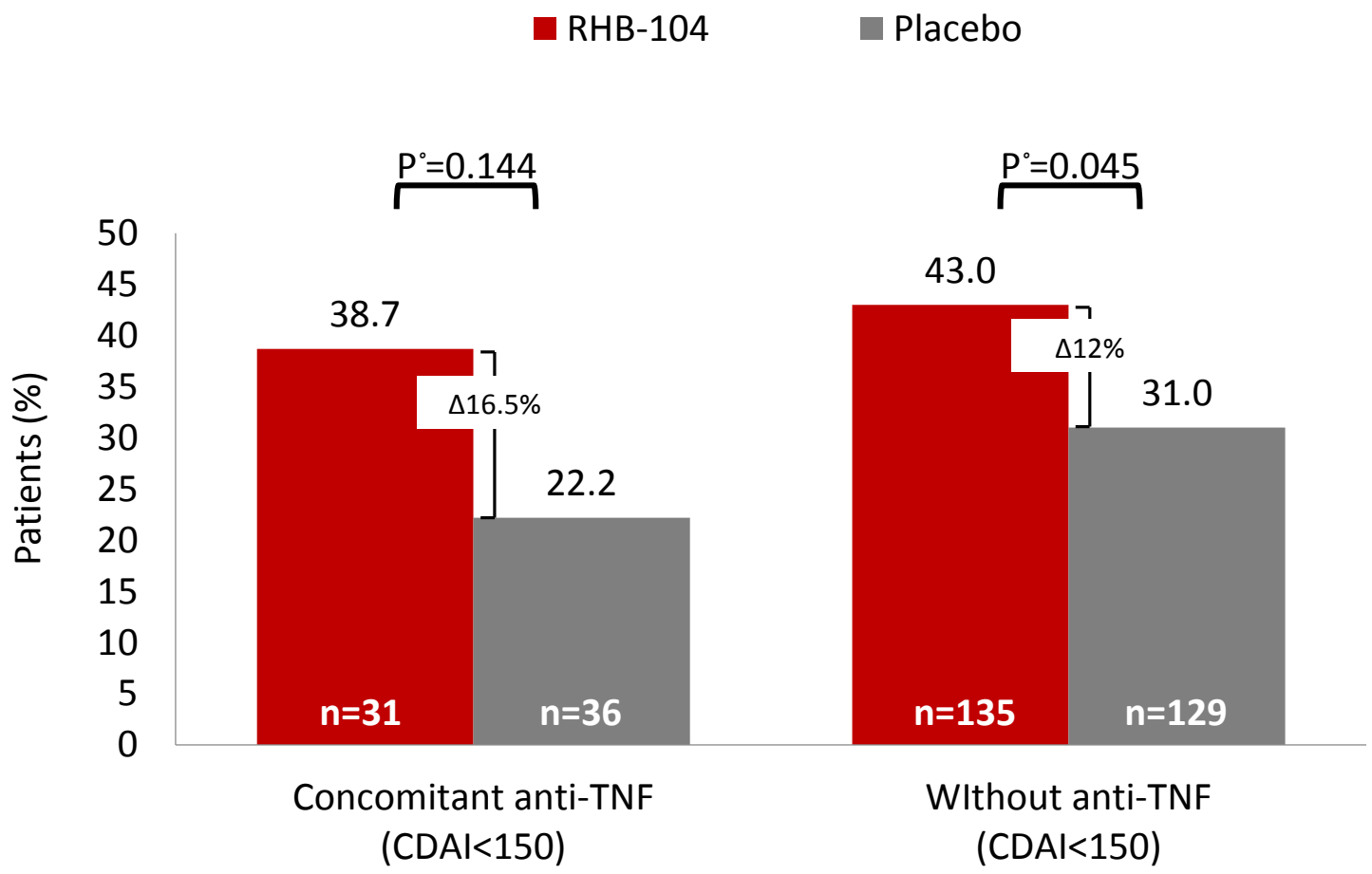
Durable Remission



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

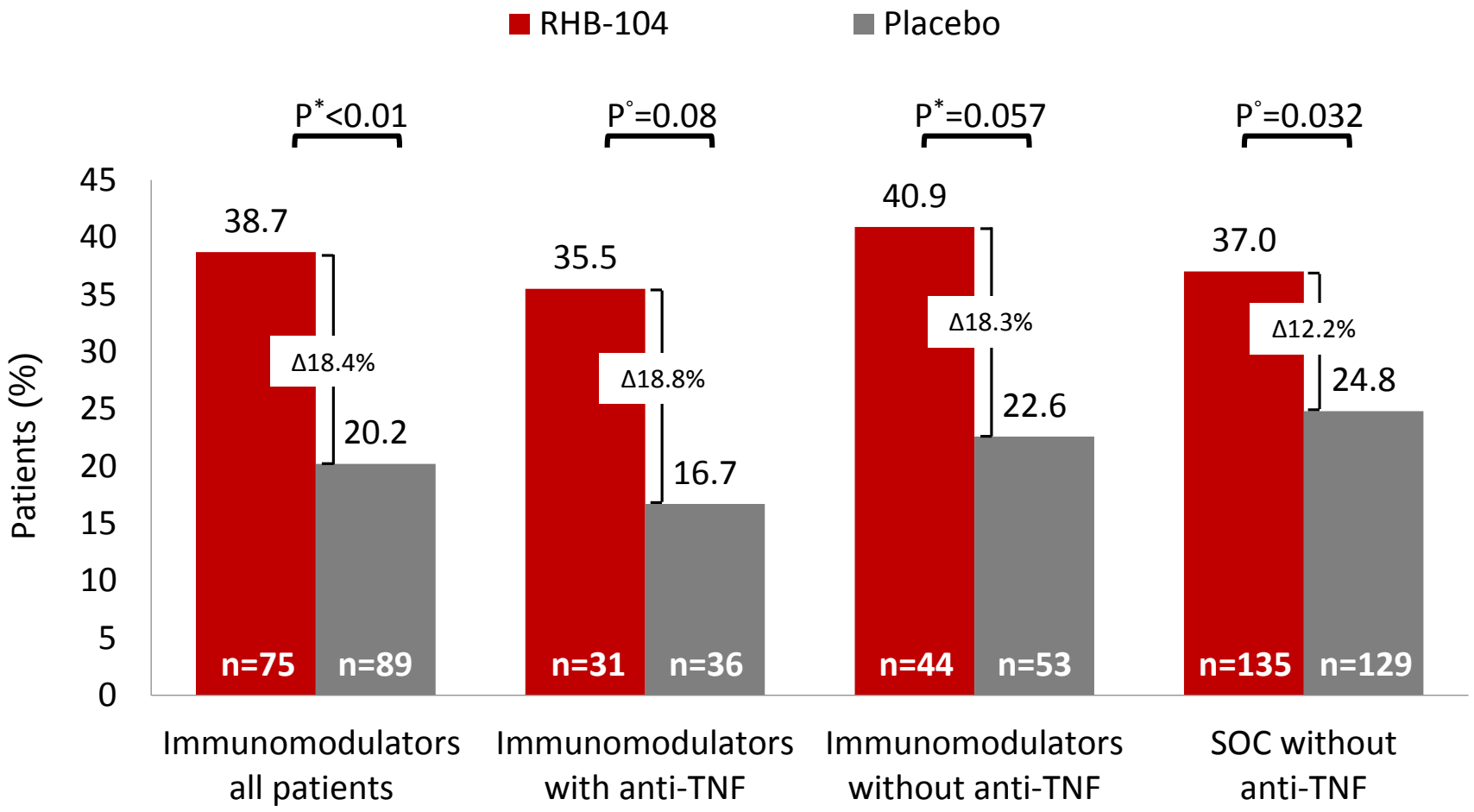
⁰ Number of subjects reflects those subjects who have completed week 52 assessments and are no longer receiving blinded therapy

Remission at Week 16 w/wout anti-TNF



°*Calculated with Mantel-Haenszel (MH) chi-square test*

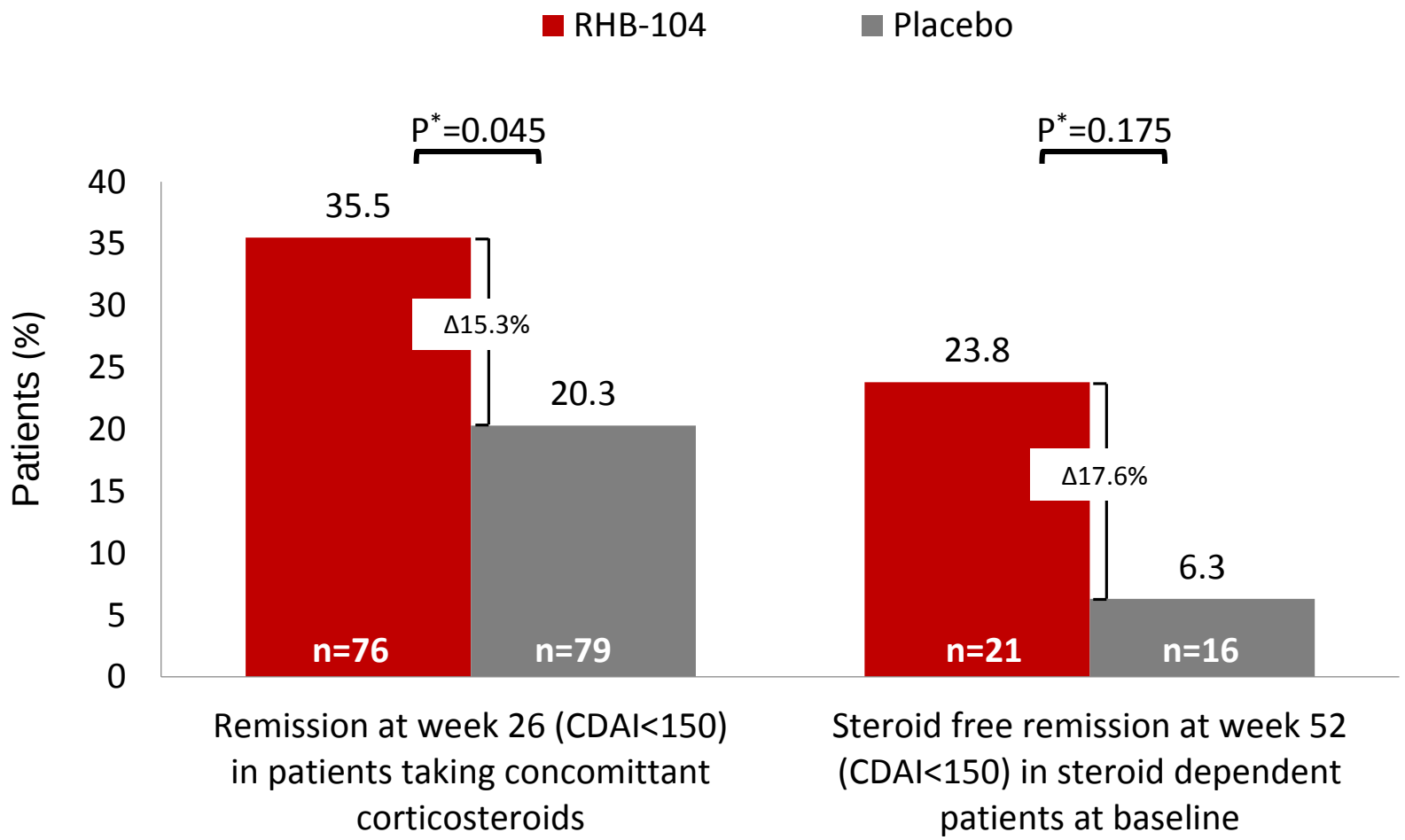
Remission at Week 26
Concomitant Meds Subgroup Analyses



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

° Calculated with Mantel-Haenszel (MH) chi-square test

Corticosteroid Remission



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

Common Adverse Events

	RHB-104 n (%)	Placebo n (%)	Total n (%)
Total subjects	166 (100)	165 (100)	331 (100)
Subjects with any adverse event†	115 (69.3)	90 (54.5)	205 (61.9)
Crohn's disease	21 (12.7)	25 (15.2)	46 (13.9)
Abdominal pain	24 (14.5)	19 (11.5)	43 (13.0)
Nausea	22 (13.3)	12 (7.3)	34 (10.3)
Diarrhoea	11 (6.6)	8 (4.8)	19 (5.7)
Vomiting	12 (7.2)	7 (4.2)	19 (5.7)
Headache	16 (9.6)	17 (10.3)	33 (10.0)
Arthralgia	16 (9.6)	7 (4.2)	23 (6.9)
Anaemia	10 (6.0)	6 (3.6)	16 (4.8)
Pyrexia	9 (5.4)	6 (3.6)	15 (4.5)
Clostridium difficile infection	3 (1.8)	12 (7.3)	15 (4.5)

† MedDRA preferred terms

Characterization of Adverse Events

Severity of Adverse Events comparable between treatment arms

Adverse Events (AEs)	RHB-104 n (%)	Placebo n (%)
Mild	65 (39)	58 (35)
Moderate	61 (37)	50 (30)
Severe	19 (11)	27 (16)
Serious AEs	31 (19)	29 (18)
AEs Leading to Study Drug Discontinuation	35 (21)	30 (18)
Death	0	0

Summary

- Clinically meaningful and statistically significant treatment effect with RHB-104 vs. placebo in:
  - **Primary endpoint of remission at week 26 (Δ14%)**
  - Secondary endpoints of early remission at week 16 (Δ13%), durable remission through week 52 (Δ9%) and additional endpoint of remission at weeks 16 and 52 (Δ13%)
- Consistent clinical benefit and treatment effect more strongly favoring RHB-104 in patients receiving concomitant anti-TNF agents (Δ19%), corticosteroids (Δ16%), or immunomodulators (Δ19%)
- Steroid-free remission in steroid dependent disease patients favored RHB-104 over placebo (Δ18%)
- Safe and well tolerated

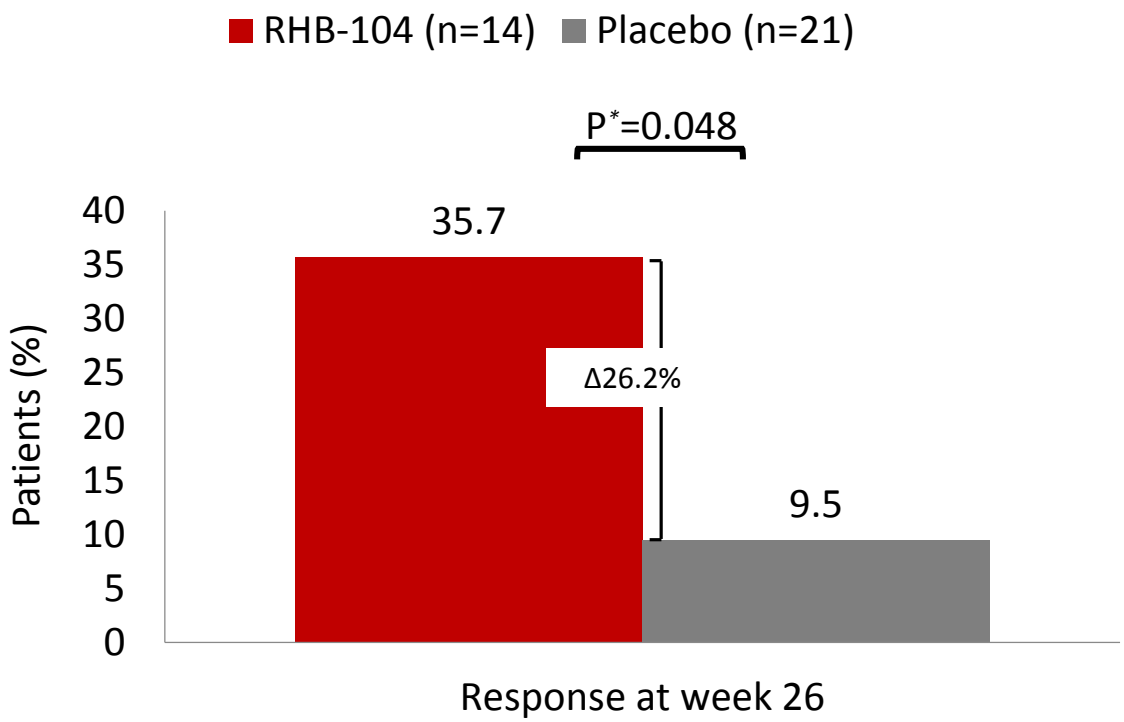
Conclusion

- RHB-104 is a promising new class of treatment for Crohn's disease
- Remission rates and safety data in patients with concomitant anti-TNF use indicates that it can be used effectively and safely as an adjunct treatment to other medications to enhance the response to medical treatment
- Despite the treat-through study design and the confounding effects of the post 26 week open-label option on patient retention, the data suggests that RHB-104 is effective through Week 52 as well as an effective long-term disease treatment
- This data provides further evidence for the role of MAP in the pathogenesis of Crohn's disease
- RHB-104 could provide a new oral antibiotic therapy for use across a broad spectrum of Crohn's disease patients

Thank You

Especially to the 100’s of patients, investigators and the investigative site personnel and to RedHill Biopharma

Endoscopic Response – 25% Decrease in SES-CD



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