Histologic Remission as a Treatment Target in Ulcerative Colitis: Is It Ready for Prime Time?

PRE – READING INFORMATION

Recognized

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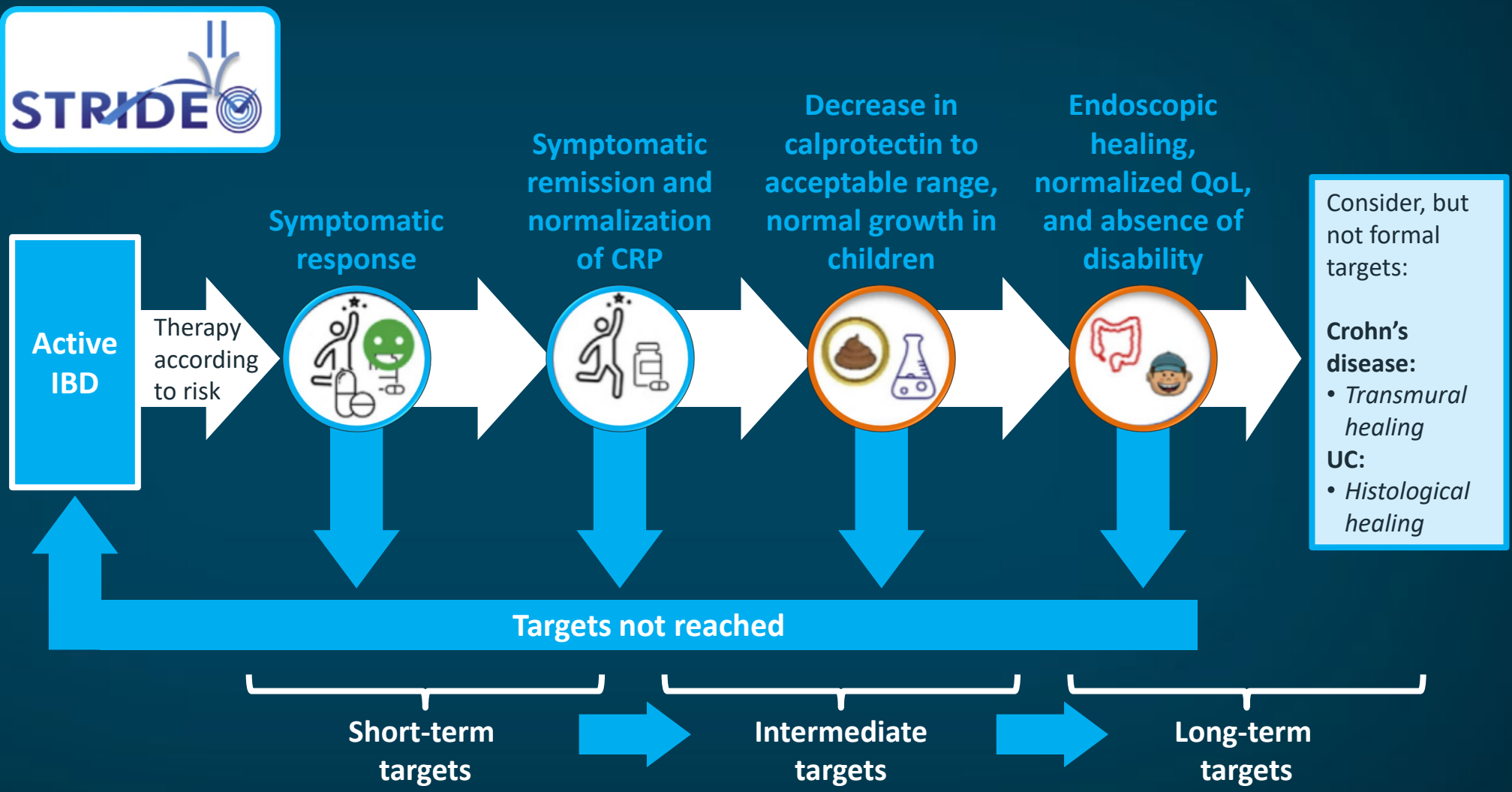
STRIDE II: Treatment Targets for UC

Management goals for UC have shifted in recent years toward achieving clinical remission combined with mucosal healing (deep remission)



CRP = C-reactive protein; IBD = irritable bowel disease; QoL = quality of life.

Turner D, et al. *Gastroenterology*. 2021;160:1570-1583.

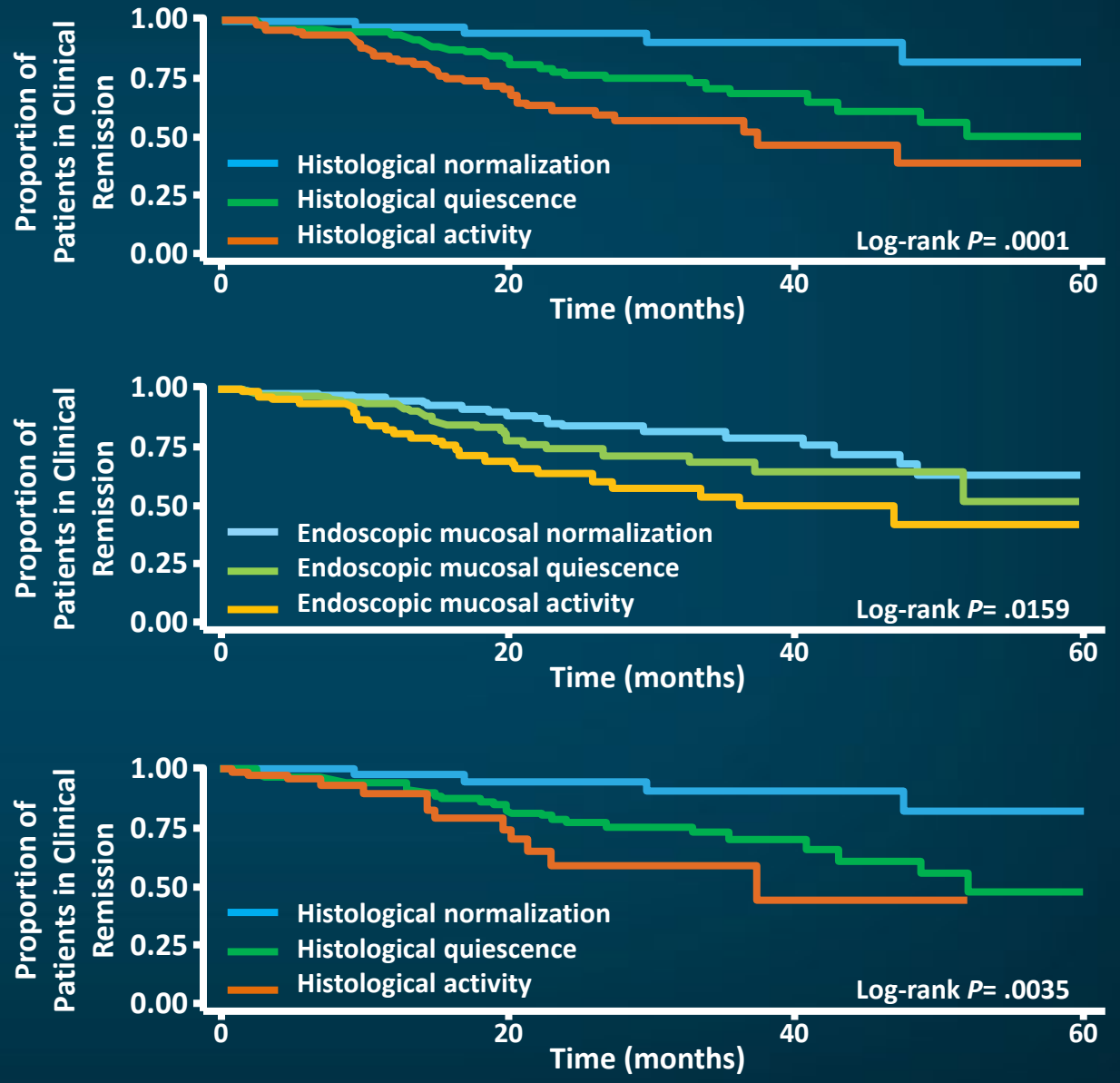
Why Care About Histologic Remission?

I. Analysis of effect of endoscopic mucosal and histologic activity on clinical relapse-free survival

   A. Clinical relapse-free survival vs histologic healing

   B. Clinical relapse-free survival vs endoscopic mucosal healing

   C. Clinical relapse-free survival vs histologic healing in patients with endoscopic mucosal healing



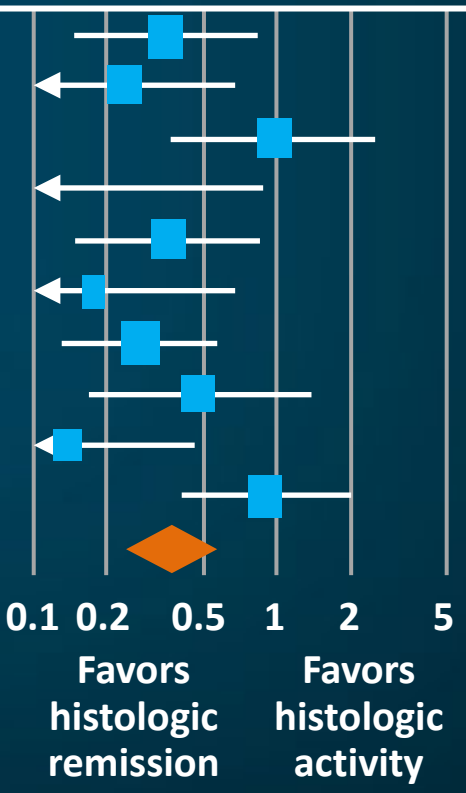
Christensen B, et al. *Clin Gastroenterol Hepatol*. 2017;15:1557-1564.e1.

Benefit of Achieving Endoscopic and Histologic Remission: Meta-Analysis

- Patients achieving more rigorous treatment endpoints (endoscopic and histologic remission) have a substantially lower risk of clinical relapse compared with patients achieving clinical remission

Risk of clinical relapse in patients in endoscopic remission (MES 0) achieving histologic remission vs persistent histologic activity

Study Name	Risk Ratio	Lower Limit	Upper Limit
Nishio 2006	0.35	0.15	0.84
Bessissow 2012	0.24	0.09	0.69
Jauregui-Amezaga 2014	0.99	0.38	2.60
Nishiyama 2015	0.05	0.00	0.90
Theede 2016	0.36	0.15	0.87
Frieri 2017	0.18	0.05	0.70
Takeuchi 2017	0.28	0.13	0.58
Lobaton 2018	0.48	0.17	1.39
Cushing 2019	0.14	0.04	0.46
Jangi 2019	0.91	0.41	2.00
Total	0.37	0.24	0.56



Yoon H, et al. *Gastroenterology*. 2020;159:1262-1275.e7.

Important Histologic Targets

Histologic Category	Proposed Definition	Geboes Score	RHI	NI
Histologic healing	Complete normalization of the mucosa	0.0, 1.0, 2A.0, 2B.0, 3.0, 4.0, and 5.0	Cannot be determined	Cannot be determined
Histologic remission (quiescent colitis)	Persistent architectural abnormalities with or without basal plasmacytosis and without active (neutrophilic) inflammation	<2B.0	≤3 as long as lamina propria neutrophils score = 0 and neutrophil in epithelium score = 0	≤1
Histologic remission without basal plasmacytosis	As above plus absence of basal plasma cells separating the base of the crypts from the muscularis mucosae	0.0-0.3, 1.0-1.1, 2A.0-2A.3, 2B.0, 3.0, 4.0, and 5.0	≤1	Cannot be determined
Histologic remission without basal plasmacytosis or increased mucosal eosinophils	As above plus absence of increased lamina propria eosinophils	0.0-0.3, 1.0-1.1, 2A.0, 2B.0, 3.0, 4.0, and 5.0	Cannot be determined	Cannot be determined
Histologic near remission	Persistent architectural abnormalities without basal plasmacytosis and only minimal active (neutrophilic) inflammation	0.0-0.3, 1.0-1.1, 2A.0-2A.3, 2B.1, and/or 3.1, 4.0, 5.0	2-6 with score 0-1 for chronic inflammatory cell infiltrate + score of 1 for lamina propria neutrophils and/or neutrophils in epithelium	Cannot be determined

NI = Nancy Index.

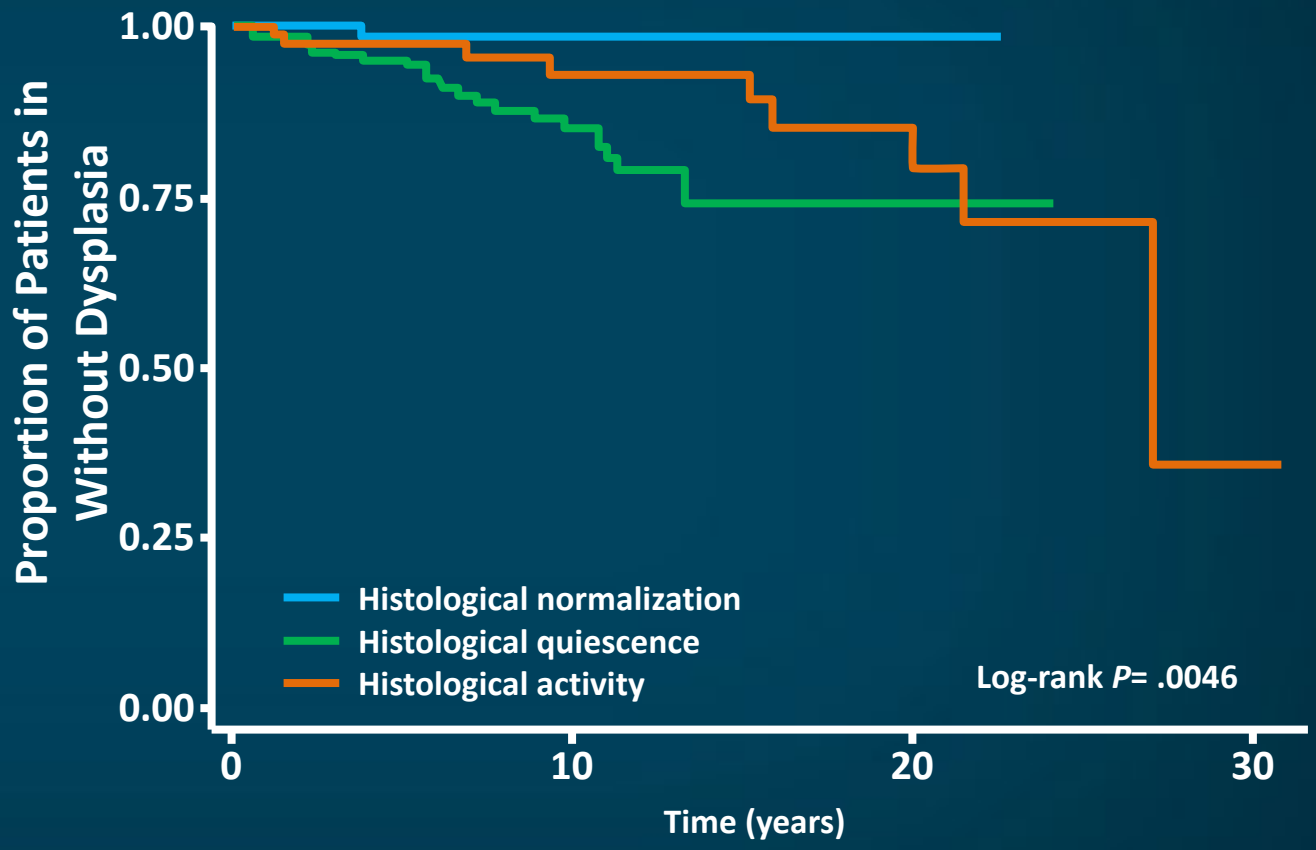
RHI = Robarts Histology Index.

Pai R, et al. *Gastrointest Endosc*. 2018;88:887-898.

Achieving Histologic Normalization in UC Is Associated With a Reduced Risk of Subsequent Dysplasia (continued)

I. Results

A. In multivariate analysis dysplasia development was statistically lower in those with histologic normalization (aHR = 0.32) but not in those with histologic quiescence (aHR = 0.52; 95% CI: 0.25, 1.10)



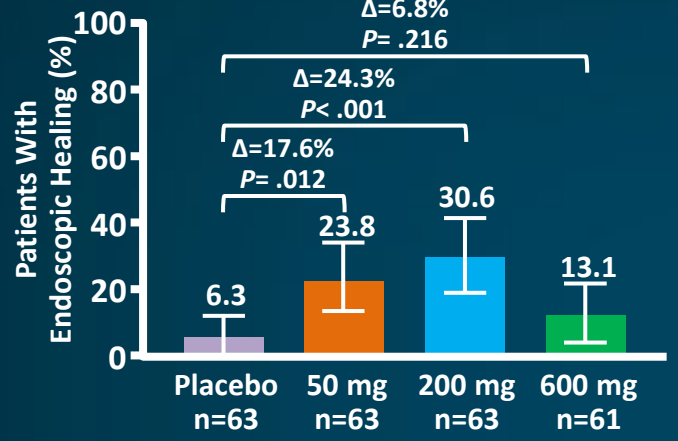
Kaplan-Meier curve of dysplasia-free survival once patients have either achieved histologic normalization or histologic quiescence or have persistent inflammation.

aHR = adjusted hazard ratio.

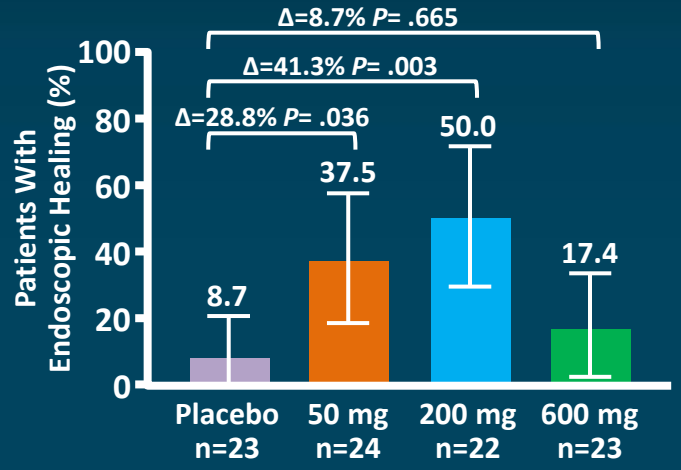
Shaffer S, et al. *Inflamm Bowel Dis.* 2022;28:553-559.

Mirikizumab in UC: Results

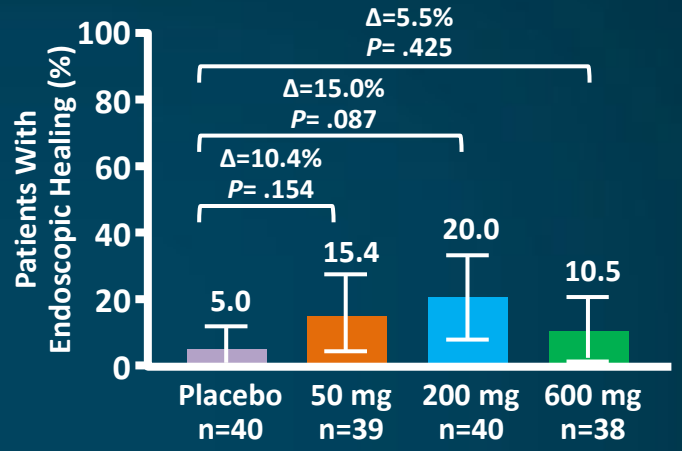
Endoscopic improvement



Endoscopic improvement
Biologic Naive



Endoscopic improvement
Biologic Experienced



Week 52 efficacy results

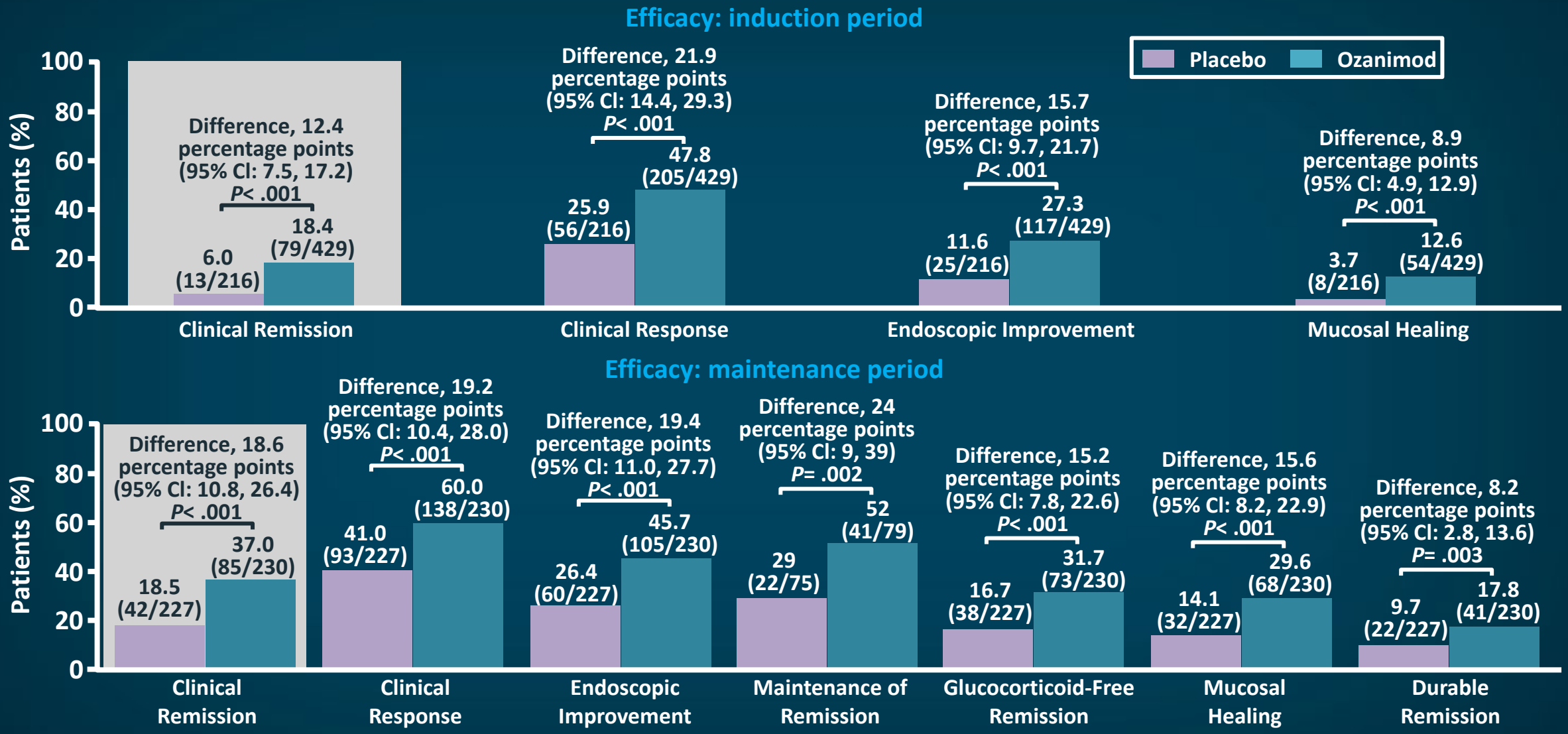
Results	Mirikizumab SC Q4W 200 mg (n=47)	Mirikizumab SC Q12W 200 mg (n=46)	Placebo SC Q4W (n=13)
Clinical remission, n (%)	22 (46.8)	17 (37.0)	1 (7.7)
Clinical response, n (%)	38 (80.9)	35 (76.1)	7 (53.8)
Endoscopic remission, n (%)	7 (14.9)	13 (28.3)	1 (7.7)
Endoscopic improvement, n (%)	27 (57.4)	22 (47.8)	2 (15.4)
Symptomatic remission, n (%)	36 (76.6)	30 (65.2)	7 (53.8)
Histologic remission, n (%)	31 (66.0)	17 (37.0)	5 (38.5)
Change from baseline IBDQ total score, mean ± SD	61.7 ± 30.8	49.4 ± 32.3	70.8 ± 23.80
Clinical remission durability, n/N (%)	11/18 (61.1)	5/13 (38.5)	0/3 (0.0)
Clinical response durability, n/N (%)	38/47 (80.9)	33/44 (75.0)	7/13 (53.8)
Clinical response week 12 to remission week 52, n/N (%)	11/29 (37.9)	12/33 (36.4)	—
CRP, median (range), mg/L	2.55 (0.23-20.10); n=41	1.55 (0.10-22.70); n=43	1.48 (0.10-14.0); n=9
Fecal calprotectin, median (range), mg/kg	103 (15-1,753); n=41	232 (15-2,502); n=36	342 (50-2,100); n=8

- **Histologic remission by Geboes**

IBDQ = Inflammatory Bowel Disease Questionnaire.

Sandborn WJ, et al. *Gastroenterology*. 2020;158:537-549.e10.

Ozanimod in UC: Results

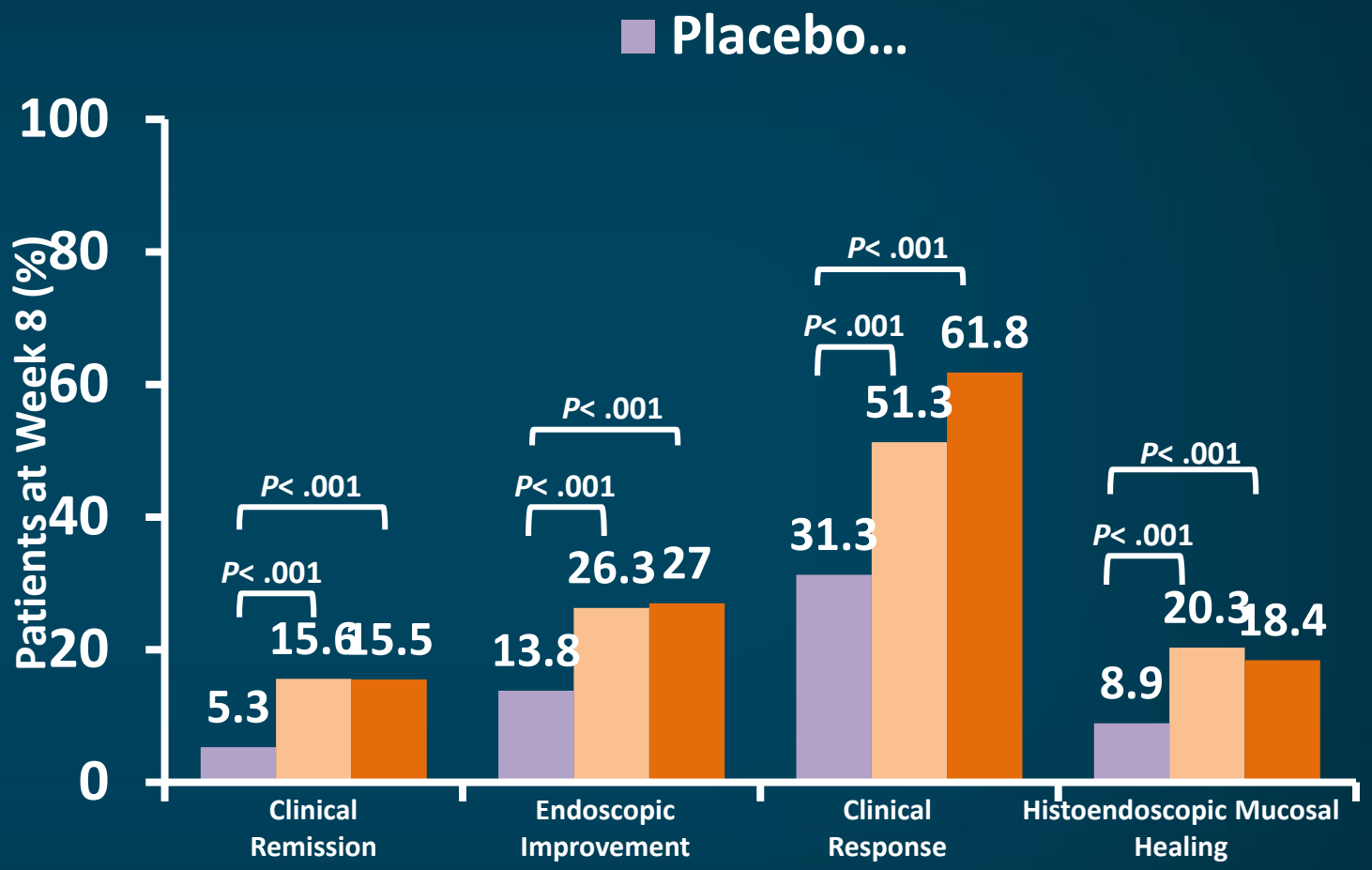


- These data support sphingosine-1-phosphate receptor modulators as a new class of oral therapy

Sandborn WJ, et al. *N Engl J Med*. 2021;385:1280-1291.

Patients Outcomes at Week 8 in the Induction Trial: Ustekinumab

- The percentages of patients who met major secondary endpoints or had histoendoscopic mucosal healing were significantly higher in both ustekinumab groups than in the placebo group



Sands B, et al. *N Engl J Med*. 2019;381:1201-1214.

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