

THIRD ANNUAL

GI ReConnect

June 1-3, 2023

Hyatt Regency Huntington Beach Resort
Huntington Beach, California

Provided by:





Value of Endoscopic-Histologic Healing

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Disclosure Statement

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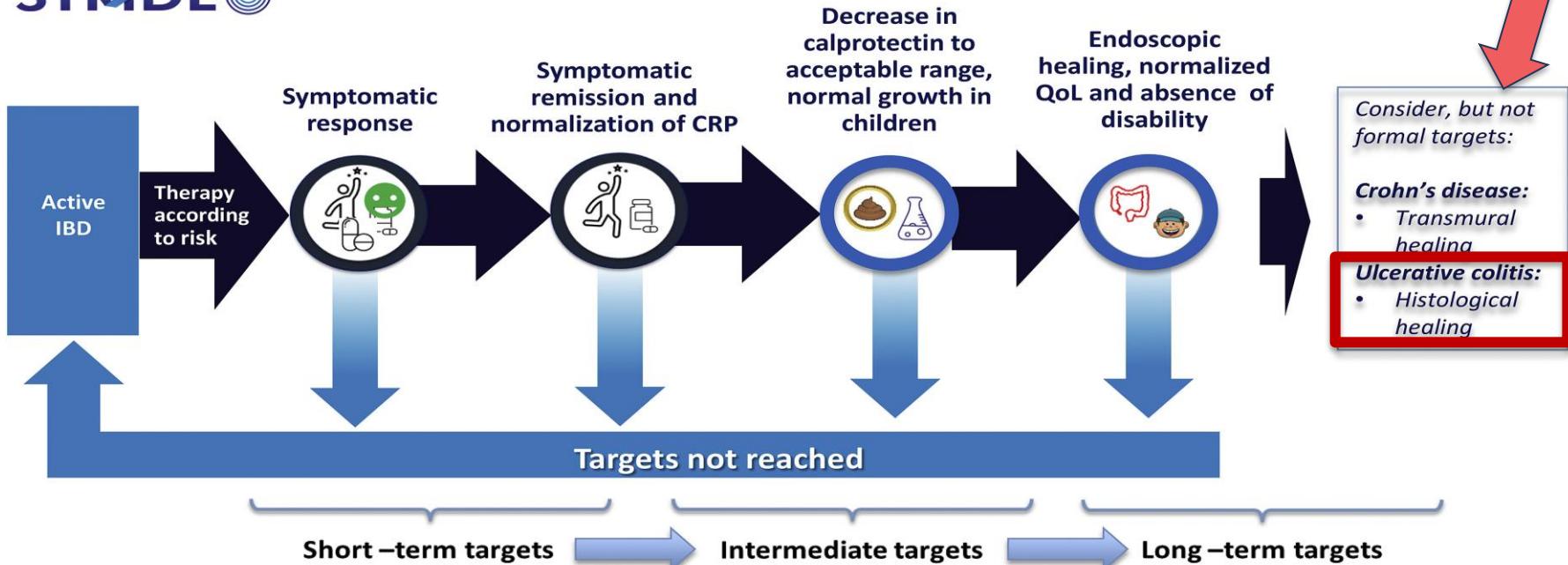
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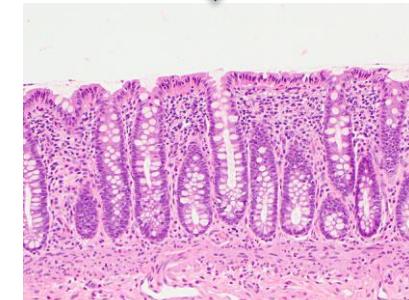
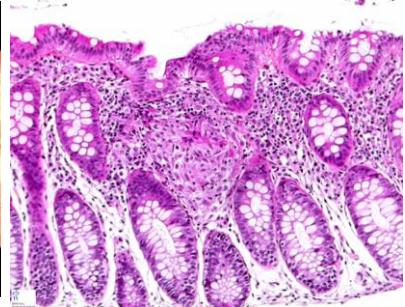
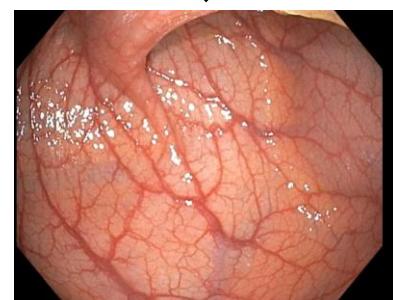
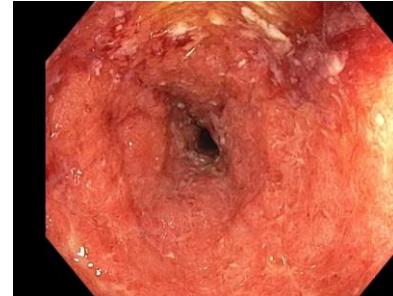
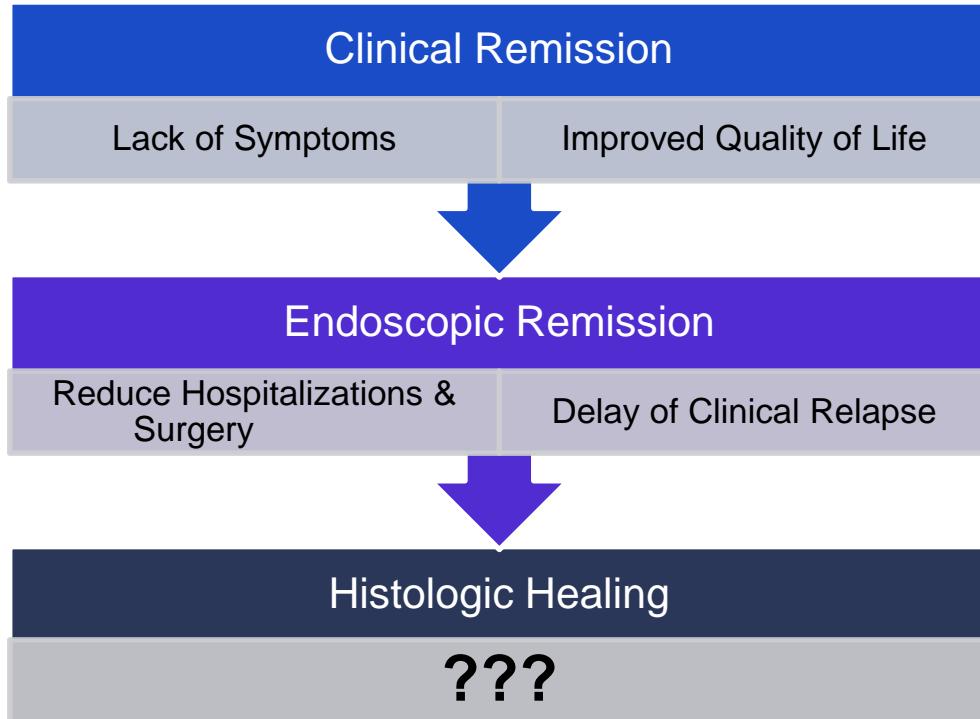
- Consultant/Speaker: Abbvie, BMS, Janssen, Pfizer, Lilly
- Consultant: Pfizer, Samsung bioepis, Fresenius Kabi, Celltrion, Medtronic

STRIDE Guidelines

STRIDE-II: An Update on Selecting Therapeutic Targets in IBD (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD



Can Endo-Histologic Healing Provide Additional Value?



Most Common Histologic Scoring Systems

<u>Robarts Histopathology Index Score (RHI)</u>	<u>Geboes Score (GS)</u>	<u>Nancy histological index: (UC)</u>	<u>Truelove & Richards' index (1st, 1956, UC)</u>
4-item measurement: <ul style="list-style-type: none">• Inflammation• Epithelial changes and/or• Erosions/Ulcers	7-items: <ul style="list-style-type: none">• Structural changes• Signs of inflammation• Epithelial changes and/or• Erosions/Ulcers	<ul style="list-style-type: none">• Neutrophil infiltration• Crypt destruction• Epithelial regeneration	3-grade scale <ul style="list-style-type: none">• no inflammation• mild to moderate• severe inflammation
0 (remission) to 33 (severe)	0 (remission) to 5.4 (severe)	0 (remission) to 6 (severe)	1 (remission) to 3 (severe)

1. Pai RK et al. *Gastrointest Endosc.* 2018;88(6):887-898.

3. Mosli MH et al. *Cochrane Database Syst Rev.* 2017;5:CD011256.

5. Geboes K et al. *Gut.* 2000;47(3):404-409.

7. Peyrin-Biroulet L et al. *Gastroenterology.* 2021;161(4):1156-1167.

2. Peyrin-Biroulet L et al. *Am J Gastroenterol.* 2015;110(9):1324-1338.

4. Mosli MH et al. *Gut.* 2017;66(1):50-58.

6. Sands BE et al. *N Engl J Med.* 2019;381(13):1215-1226.

Additional Scoring Systems

Reference	Histologic Index without Cut-offs	Reference	Histologic index	Cut-off
Agnholt 2003	Agnholt Score			Stage 0 (score 0): no increase in inflammation stage 1 (1-3): chronic, non-active inflammation stage 2 (4-6): mild active inflammation stage 3 (7-9): moderate active inflammation stage 4 (10-14): severe active inflammation
D'Haens 1999	Global Histological Activity Score	Drews 2009	Drews Score	Maximum score: 24.
Geboes 2005	Colonic Global Histological Activity Score	Gomes 1986	Gomes Score	1 (no activity) to 13
Geboes 2005	Ileal Global Histological Activity Score	Laharie 2011	Laharie Score	Probability of chronic ileitis (max. score = 10) low 0-2 moderate 3-4 high 5-10 Probability of chronic colitis (max. score =17) low 0-3 moderate 4-8 high 9-17
Mantzaris 2009	Average Histologic Score	Naini 2012	Naini and Cortina Score	inactive: 0 mildly active: 1-5 moderately active: 6-10 severely active: 11-14
Sipponen 2008	Sipponen Score	Requeiro 2009	Requeiro Score	Maximum score: 10
Smith 2010a	Dieleman Score	Ward 1977	Ward Score	0-1 - Grade 0 (none inflammation) 2-4 - Grade 1 (mild inflammation) 5-8 - Grade 2 (moderate inflammation) 9-12 - Grade 3 (severe inflammation) Histologic healing defined as grade of 0 Histologic improvement = decrease of at least 1 grade
		Yamamoto 2005	Savermuttu Index	

Evidence Supporting Histologic Healing: Prospective Study

- Prospective longitudinal UK study - 91 UC patients; Follow-up ~6 years
- 24% histologic inflammation despite endoscopic remission

Assessment	Remission Rate
Simple Clinical Colitis Activity Index	41%
Mucosal healing (Baron scoring)	62%
Histology (Truelove & Richards' index)	52%
Clinical + endoscopy + histology remission	29%

Histological remission patients:

- Less likely to require second corticosteroids course or escalate therapy to IMM/ biologics ($HR=0.42, P=0.02$)
- Less likely for hospitalization ($HR=0.21, P=0.02$)

Evidence Supporting Histologic Healing: UC

UC patients in histologic remission had:

- significantly lower rates of relapse & hospitalization compared to those without histologic remission¹
- reduced risk of colorectal cancer²

¹ Mosli MH, et al. Gut. 2017;66(1):50-58.

² Wanders LK, et al. Inflamm Bowel Dis. 2017;23(8):1491-1497.

Evidence Supporting Histologic Healing: CD

Histologic remission in CD patients showed:

- lower rates of clinical relapse & surgical intervention in 2 years follow-up.¹
- reduced risk of disease progression & need for surgery.²

¹Colombel JF, et al. J Crohns Colitis. 2017;11(8):886-893. (147 patients on adalimumab)

² Lobatón T, et al. Aliment Pharmacol Ther. 2015;42(4):441-451.

Key Concerns:

Histologic Remission in IBD Systematic Review

- 120 studies
- 22 different histological scoring systems for IBD
- None fully validated.
- 16-100% had histologic activity despite endoscopic remission.

Histological remission:

- may predict risk of complications in ulcerative colitis
- data more scarce in Crohn's disease

Achieving Endo-Histologic Remission

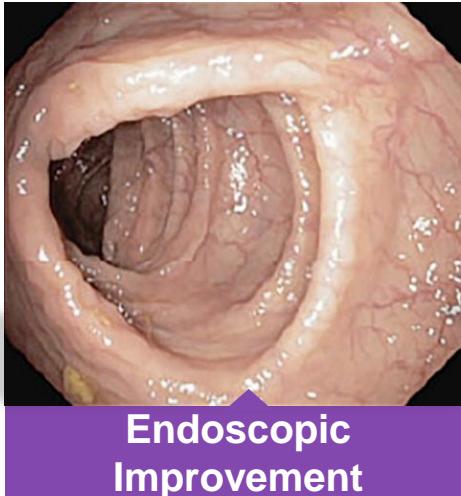
What is the current clinical trial data?

Ustekinumab
Adalimumab
Vedolizumab

Ozanimod
Upadacitinib

Ustekinumab:

First Clinical Trial Assessment of Histo-Endoscopic Mucosal Improvement



Endoscopic
Improvement

Mayo endoscopy subscore
of 0 or 1



Histologic
Improvement

Neutrophil infiltration <5% of
crypts, no crypt destruction,
and no erosions, ulcerations,
or granulation tissue

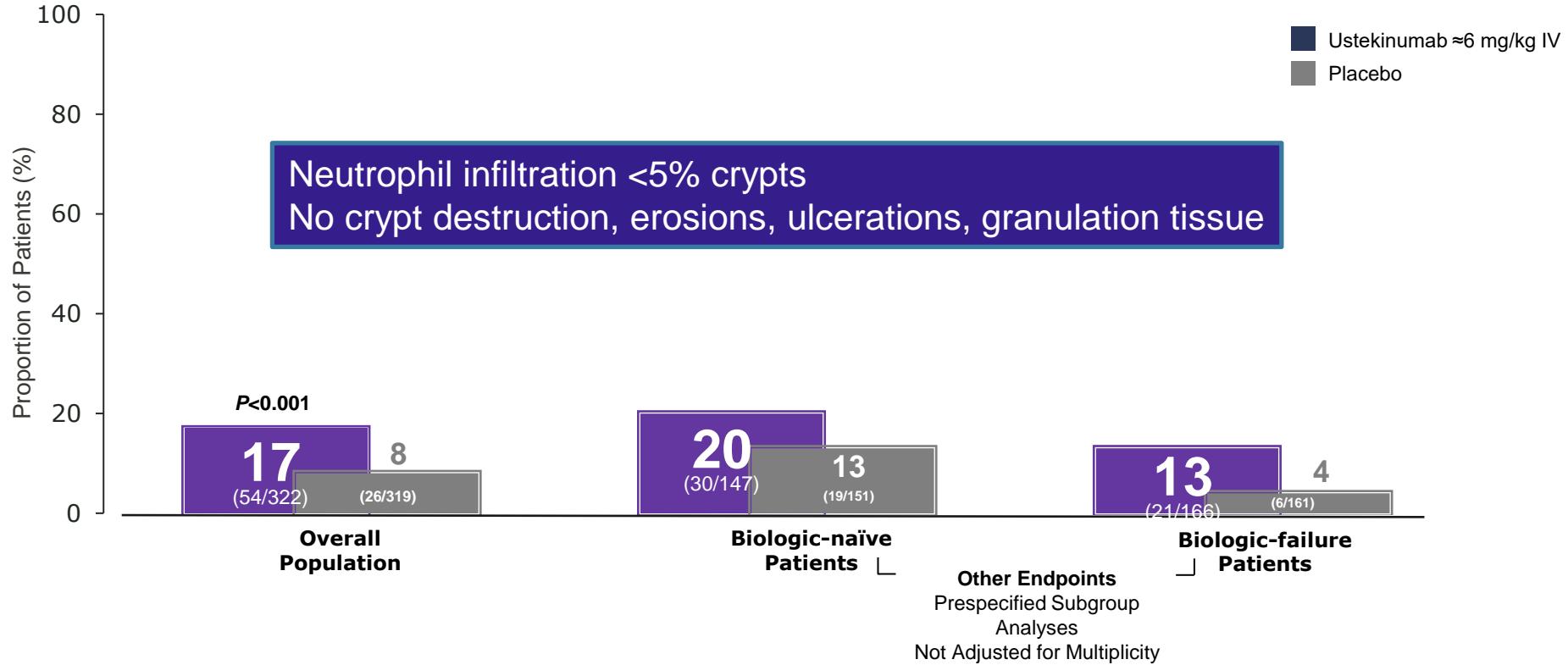
Geboes

Histo-
Endoscopic
Mucosal
Improvement

Ustekinumab: Histo-Endoscopic Mucosal Improvement:

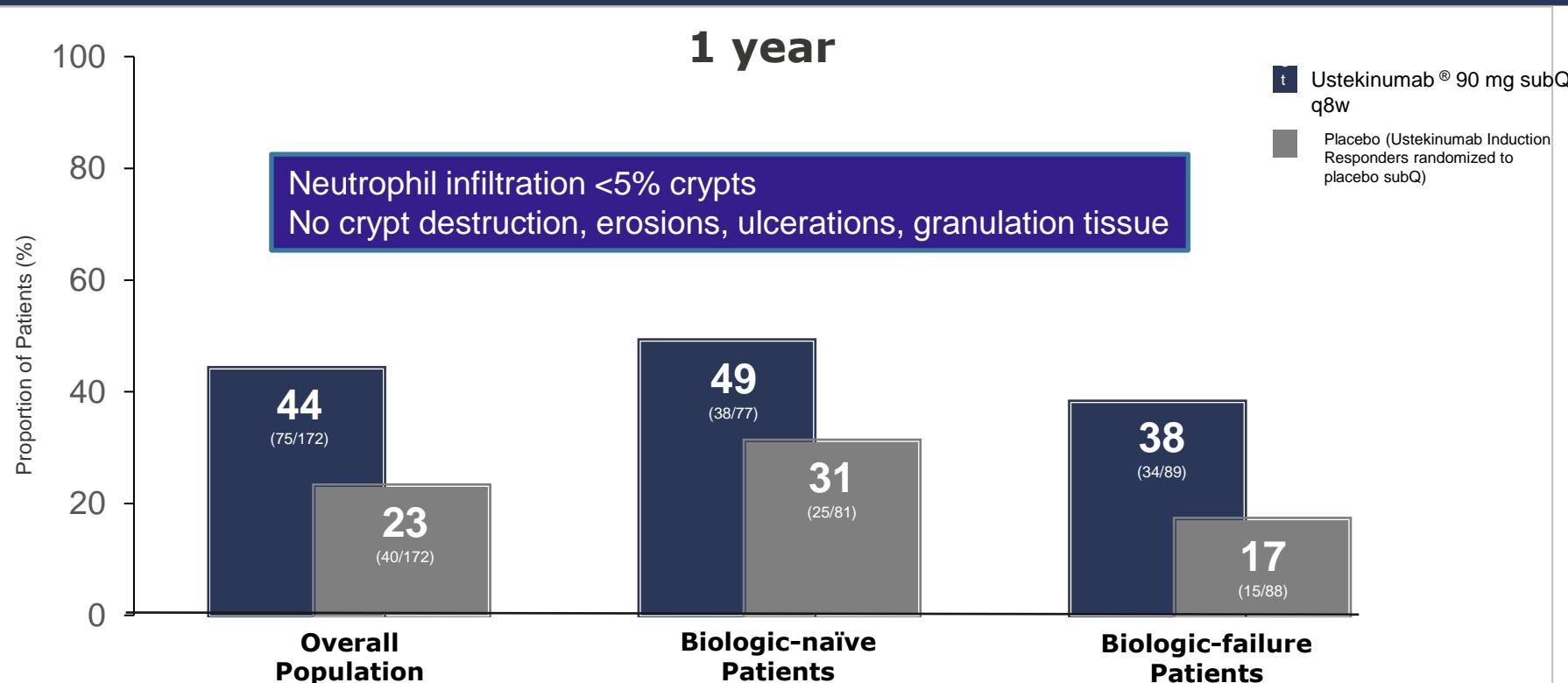
Mayo Endoscopy 0 or 1 and Geboes Score ≤ 3.1

Week 8



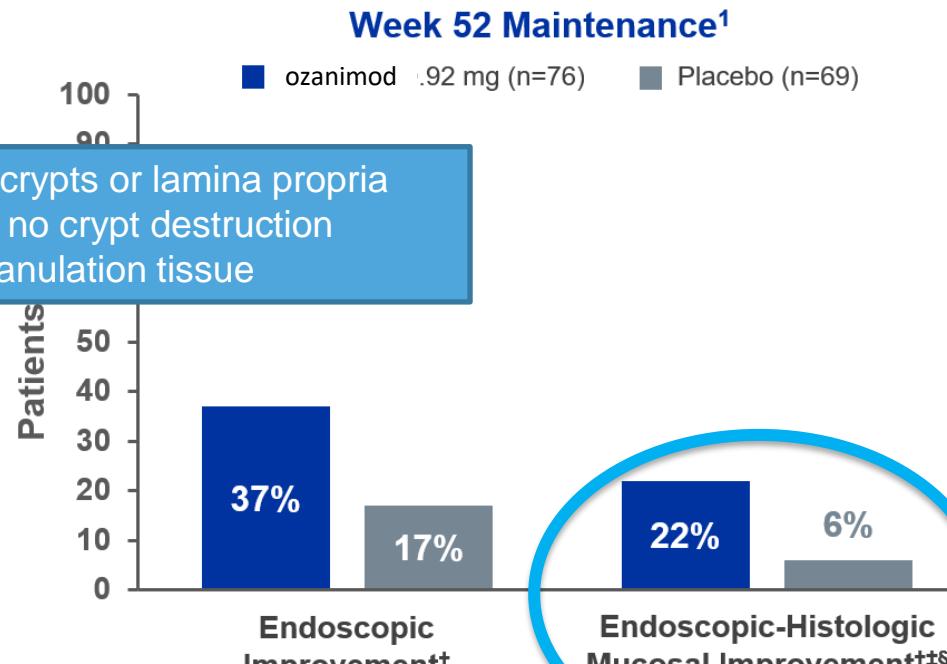
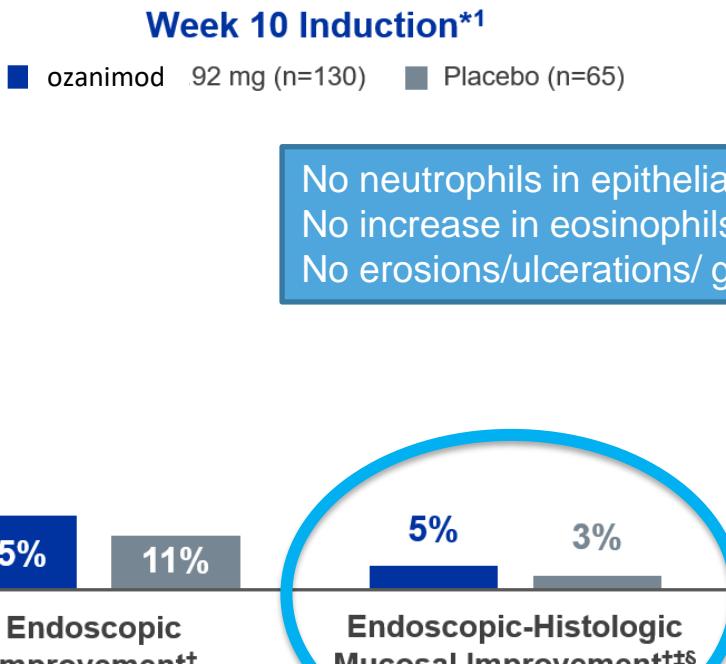
Ustekinumab: Histo-Endoscopic Mucosal Improvement:

Mayo Endoscopy 0 or 1 and Geboes <3.1



Ozanimod: Endo-Histologic Improvement: (Geboes <2.0)

Prior antiTNFs exposed



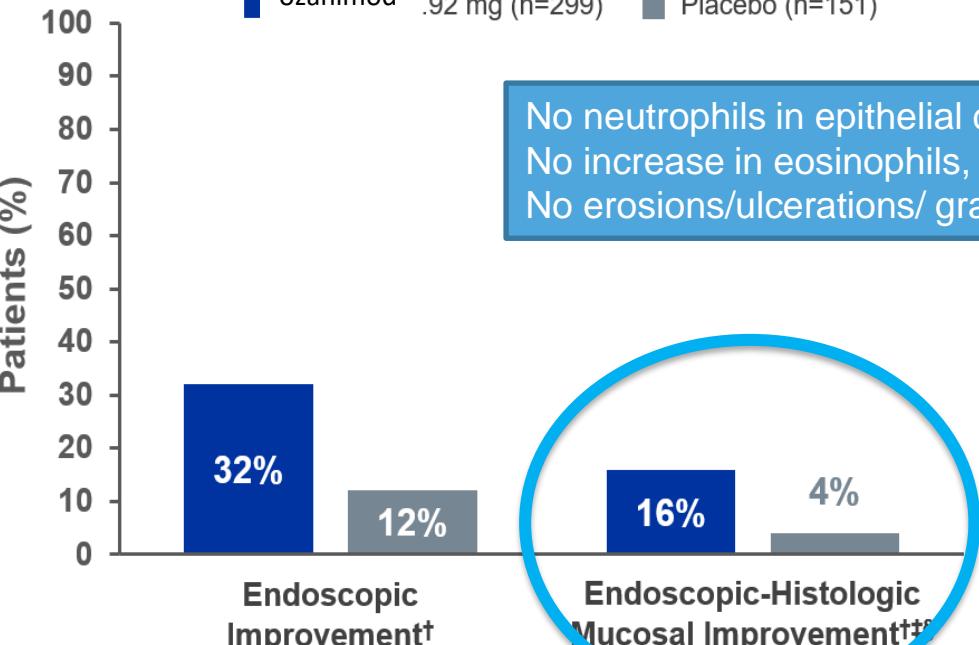
No neutrophils in epithelial crypts or lamina propria
No increase in eosinophils, no crypt destruction
No erosions/ulcerations/ granulation tissue

Ozanimod: Endo-Histologic Improvement: (Geboes <2.0)

AntiTNFs Naive

Week 10 Induction^{*1}

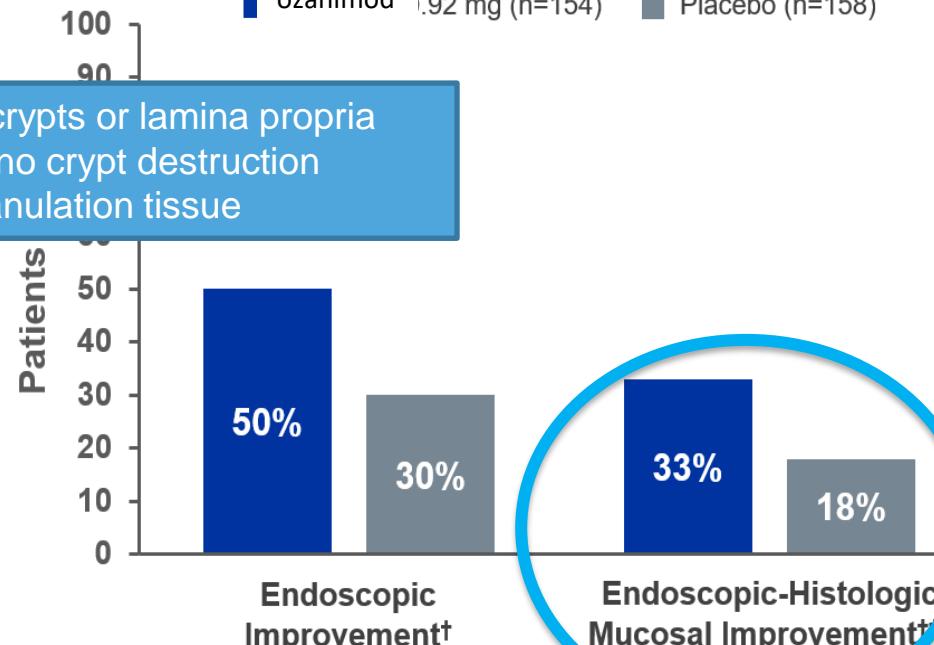
ozanimod .92 mg (n=299) Placebo (n=151)



No neutrophils in epithelial crypts or lamina propria
No increase in eosinophils, no crypt destruction
No erosions/ulcerations/ granulation tissue

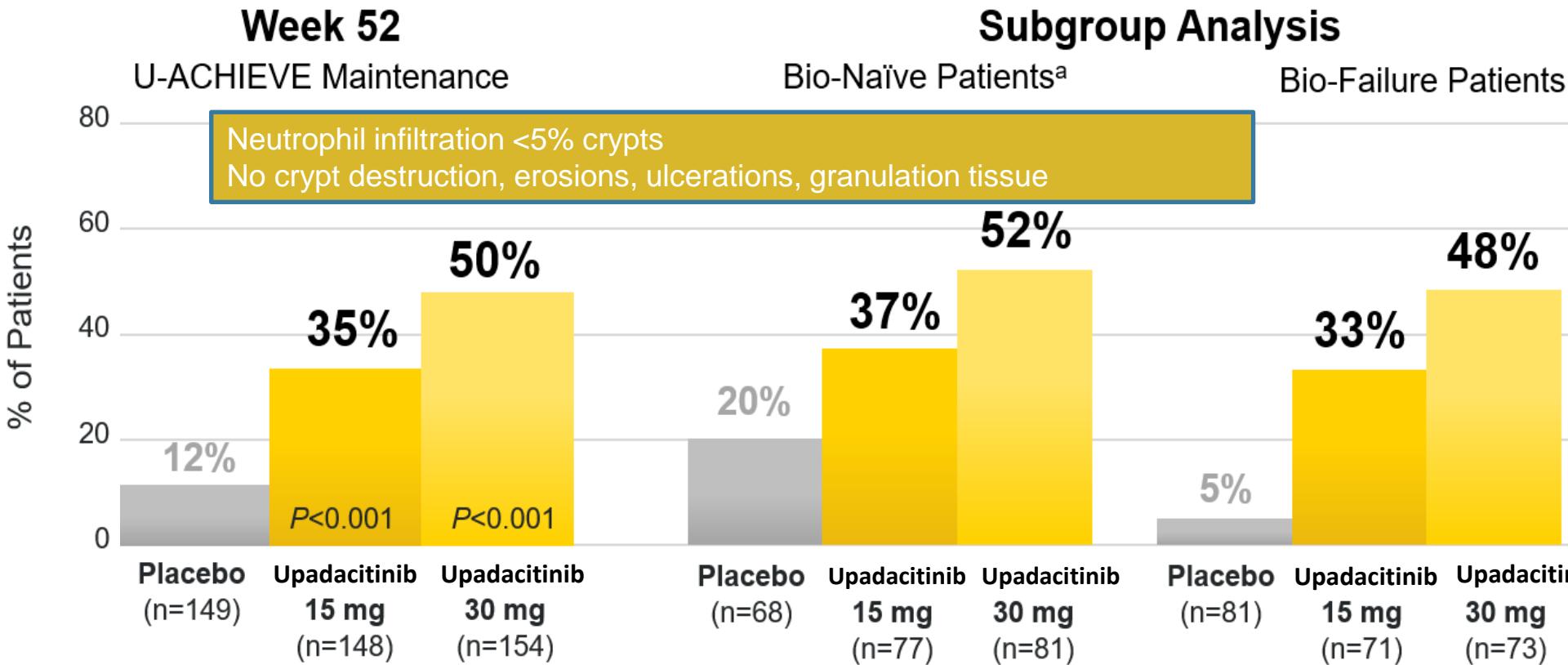
Week 52 Maintenance¹

ozanimod .92 mg (n=154) Placebo (n=158)



Upadacitinib: HEMI Week 52:

Mayo Endoscopy 0 or 1 and Geboes Score ≤ 3.1



VARSITY Trial End Points

Robarts Histopathology Index (RHI)

Geboes Score (GS)

Endpoint Definitions

Histologic remission	RHI as <3 ⁶	GS as <2 ⁶
Composite endoscopic improvement + histologic remission	RHI as ≤2 ⁷	GS as <2 ⁷
Composite endoscopic improvement +minimal histologic disease	RHI as ≤4 ⁷	GS as ≤3.1 ⁷

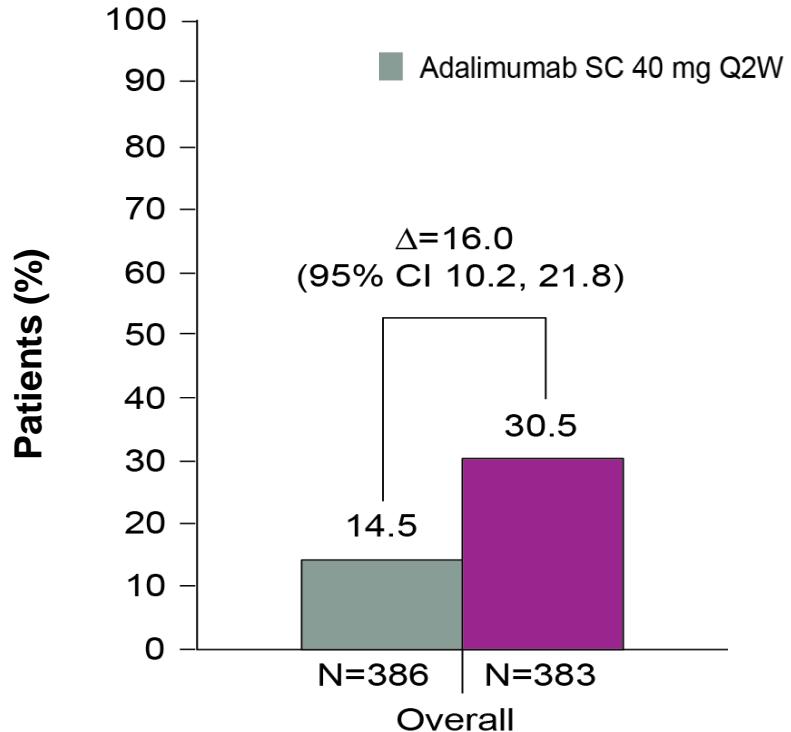
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5. Geboes K et al. *Gut.* 2000;47(3):404-409. 6. Sands BE et al. *N Engl J Med.* 2019;381(13):1215-1226. 7. Peyrin-Biroulet L et al. *Gastroenterology.* 2021;161(4):1156-1167.

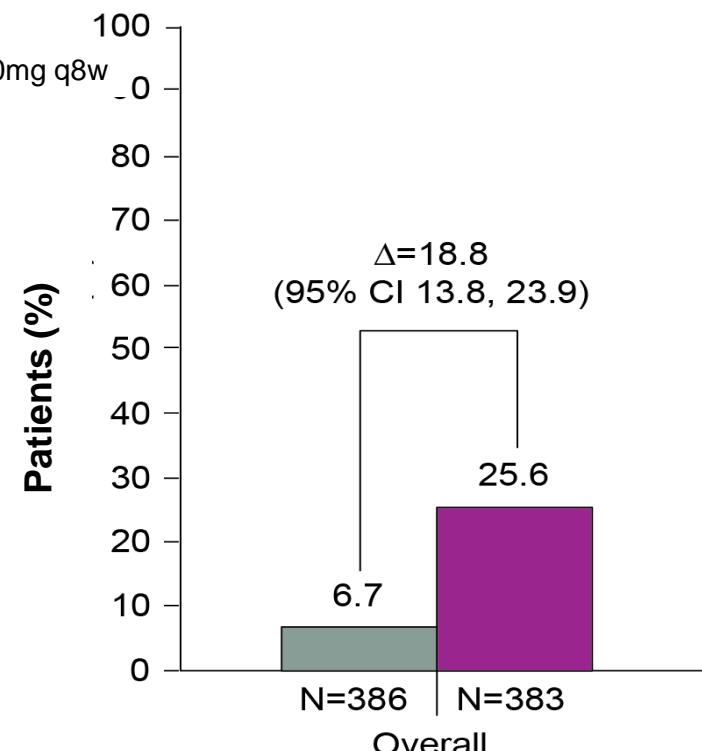
VARSITY: (Week 52)

Histologic Remission Plus Endoscopic Improvement

Robarts Histopathology Index (RHI) Score $\leq 2^{\dagger}$

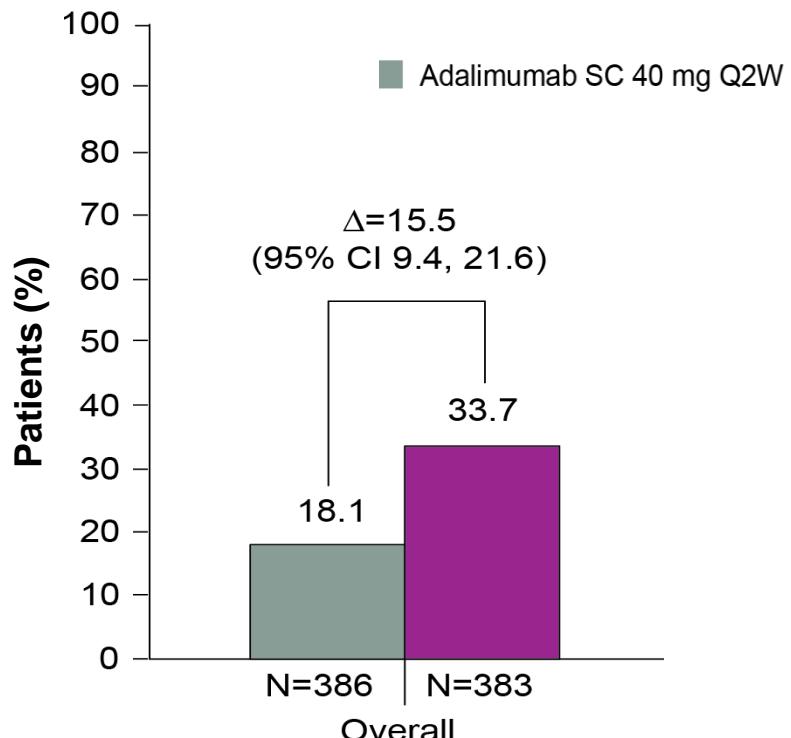


Geboes Score $< 2^{\ddagger}$

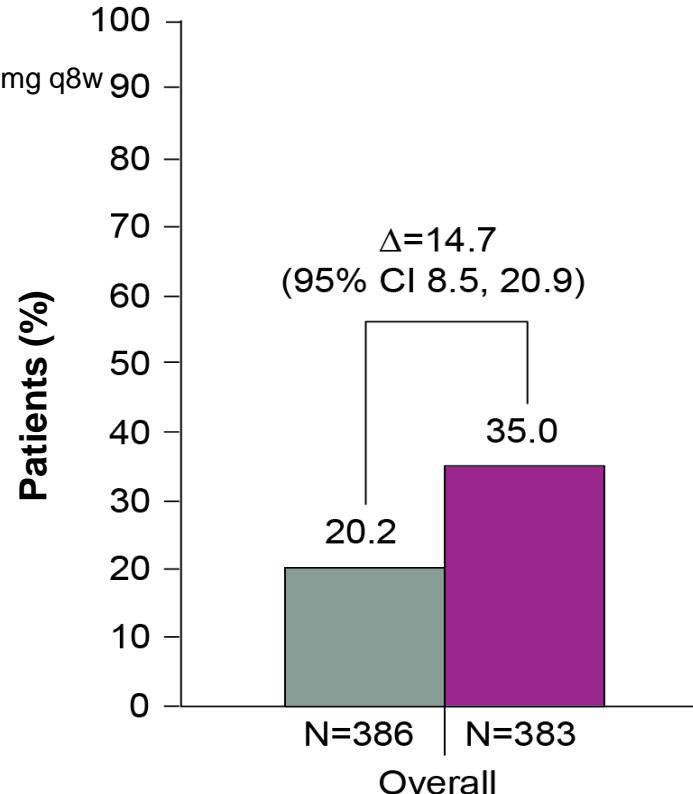


VARSITY: (Week 52) Minimal Histologic Disease Activity Plus Endoscopic Improvement

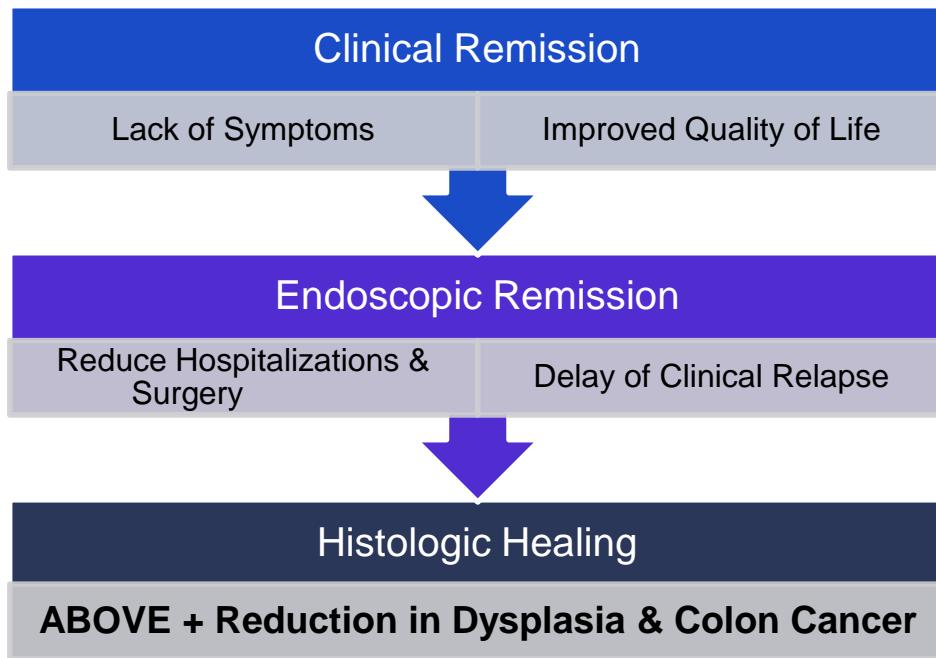
Robarts Histopathology Index (RHI) Score $\leq 4^{\dagger}$



Geboes Score $< 3.1^{\ddagger}$



Evidence Supporting Endo-Histologic Healing



Histologic remission is achievable in UC!

Limitations

- **No validated definition of histologic remission in IBD**
- **Scoring systems variable across different trials**
- **Sampling errors**
- **Interpretation can vary between institutions & pathologists**

Incorporating Endo-Histologic Healing into Practice: *Unanswered Questions*

- Will this be our new goal? STRIDE III guidelines!!?
- What if we cannot achieve Endo-Histologic Remission?
 - Should we switch therapies?
 - Do we need longer duration studies to achieve this? 2? 5 years?
 - Should we modify monitoring schedules?
- Could we change practice guidelines? Colon cancer surveillance every 5 years?

Prospective data still needed

The Future: Beyond Endo-Histo Remission?

Gastroenterology 2023;164:241–255

Intestinal Barrier Healing Is Superior to Endoscopic and Histologic Remission for Predicting Major Adverse Outcomes in Inflammatory Bowel Disease: The Prospective ERICA Trial

Timo Rath,¹ Raja Atreya,¹ Julia Bodenschatz,¹ Wolfgang Uter,² Carol E. Geppert,³ Francesco Vitali,¹ Sarah Fischer,¹ Maximilian J. Waldner,¹ Jean-Frédéric Colombel,⁴ Arndt Hartmann,³ and Markus F. Neurath^{1,5}



¹Department of Gastroenterology, Ludwig Demling Endoscopy Center of Excellence, University Hospital Erlangen, Medical Clinic 1, Friedrich-Alexander University Erlangen-Nuernberg, Erlangen, Germany; ²Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander University Erlangen-Nuernberg, Erlangen, Germany; ³Institute for Pathology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuernberg, Erlangen, Germany; ⁴Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York, and ⁵Deutsches Zentrum für Immuntherapie (DZI), Friedrich-Alexander University Erlangen-Nuernberg, Erlangen, Germany

Intestinal Barrier Healing

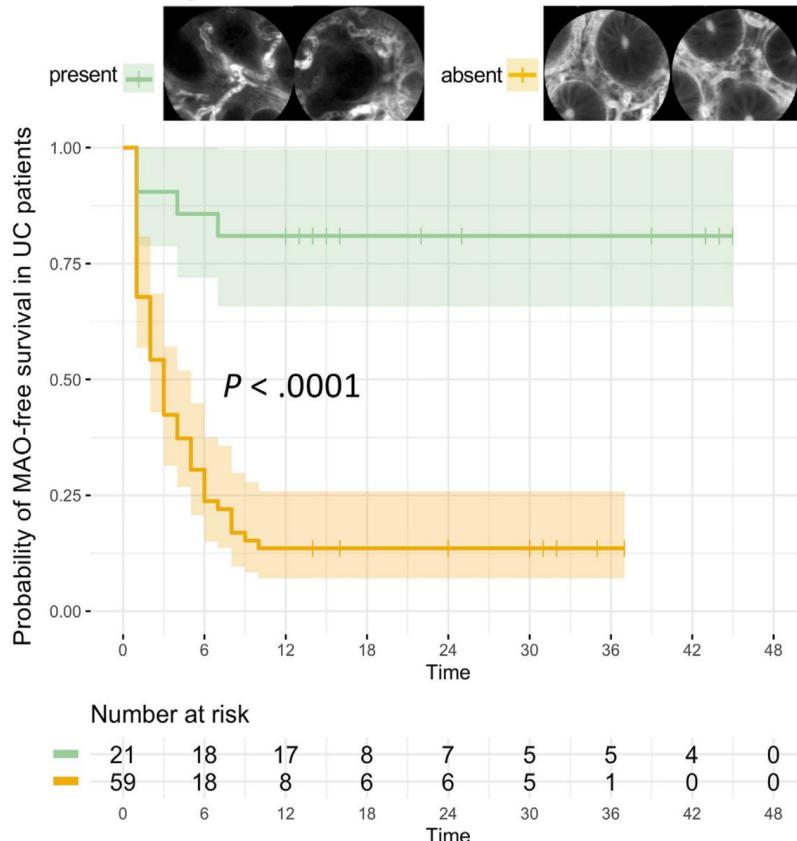
- 181 patients (100 CD, 81 UC) in clinical remission
- → ileo-colonoscopy + confocal endomicroscopy
- Followed for median 35 (CD) & 25 (UC) months
- Major Adverse Events:
 - disease flares
 - IBD-hospitalization or surgery
 - start/ dose escalation of steroids, immunomodulators, biologics, small molecules.



Histologic remission predicted AE-free survival in UC not CD

Intestinal Barrier Healing

Barrier Healing Colon



Barrier healing on endomicroscopy superior to endoscopic & histologic remission for:

- predicting AE-free survival
- decreased risk of UC & CD progression

Questions?



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