What's IL-23 Got to Do With It?

Targeted Therapies in the Management of IBD

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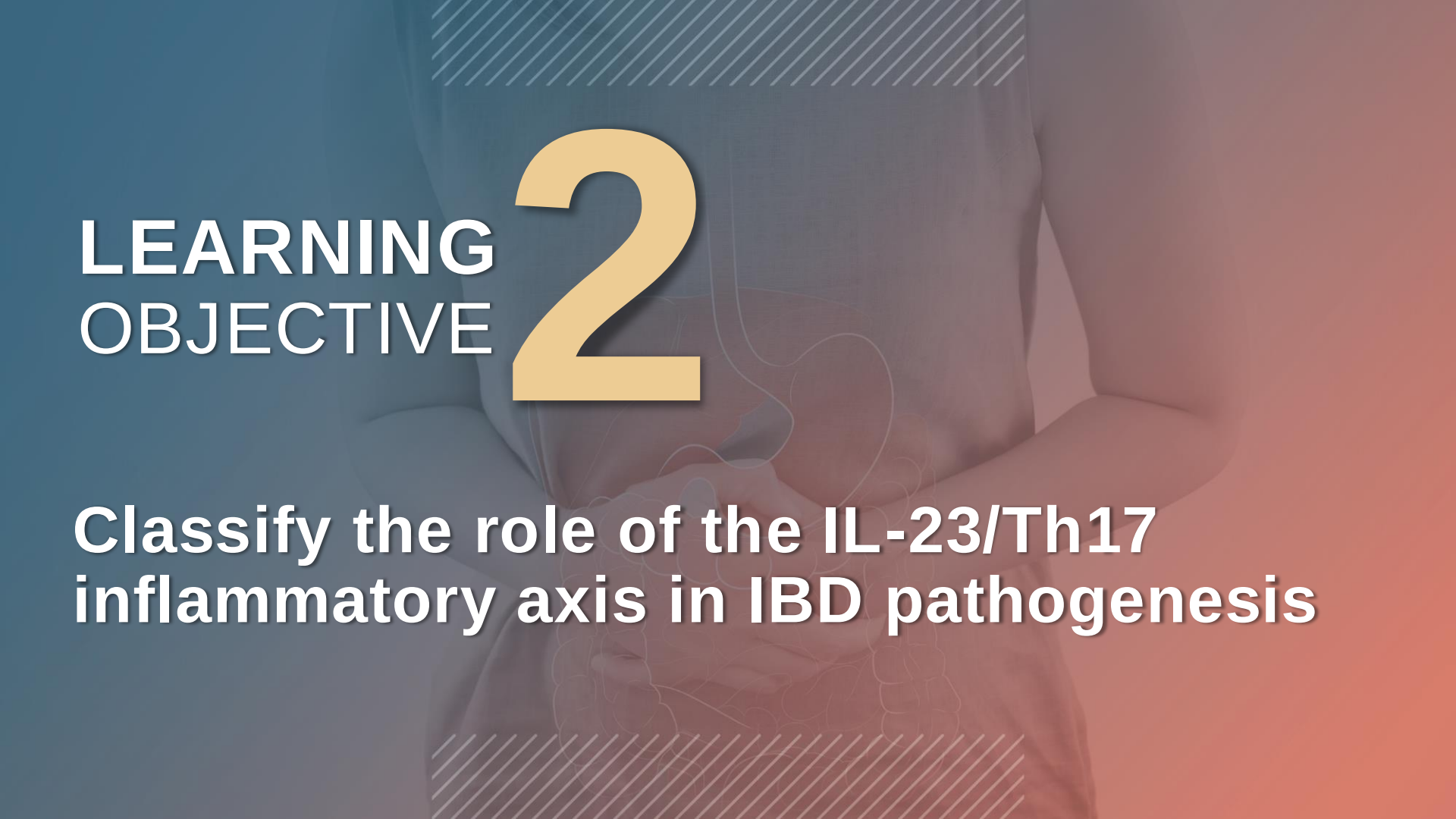
LEARNING OBJECTIVE 1

Assess the role of pro-inflammatory cytokines in driving inflammation in the pathogenesis of IBD



LEARNING OBJECTIVE 2

Classify the role of the IL-23/Th17 inflammatory axis in IBD pathogenesis

LEARNING OBJECTIVE 3

Evaluate the clinical implications of anti–IL-23 agents used in the treatment of IBD to bind to CD64 receptors on IL-23–producing cells

Audience Response - Icebreaker

What is the most difficult aspect of patient care for IBD? (pick your top 3)

A. Knowledge of drugs
B. Prior authorizations
C. Drug positioning
D. Loss of response
E. Lack of time with patients
F. Staffing challenges

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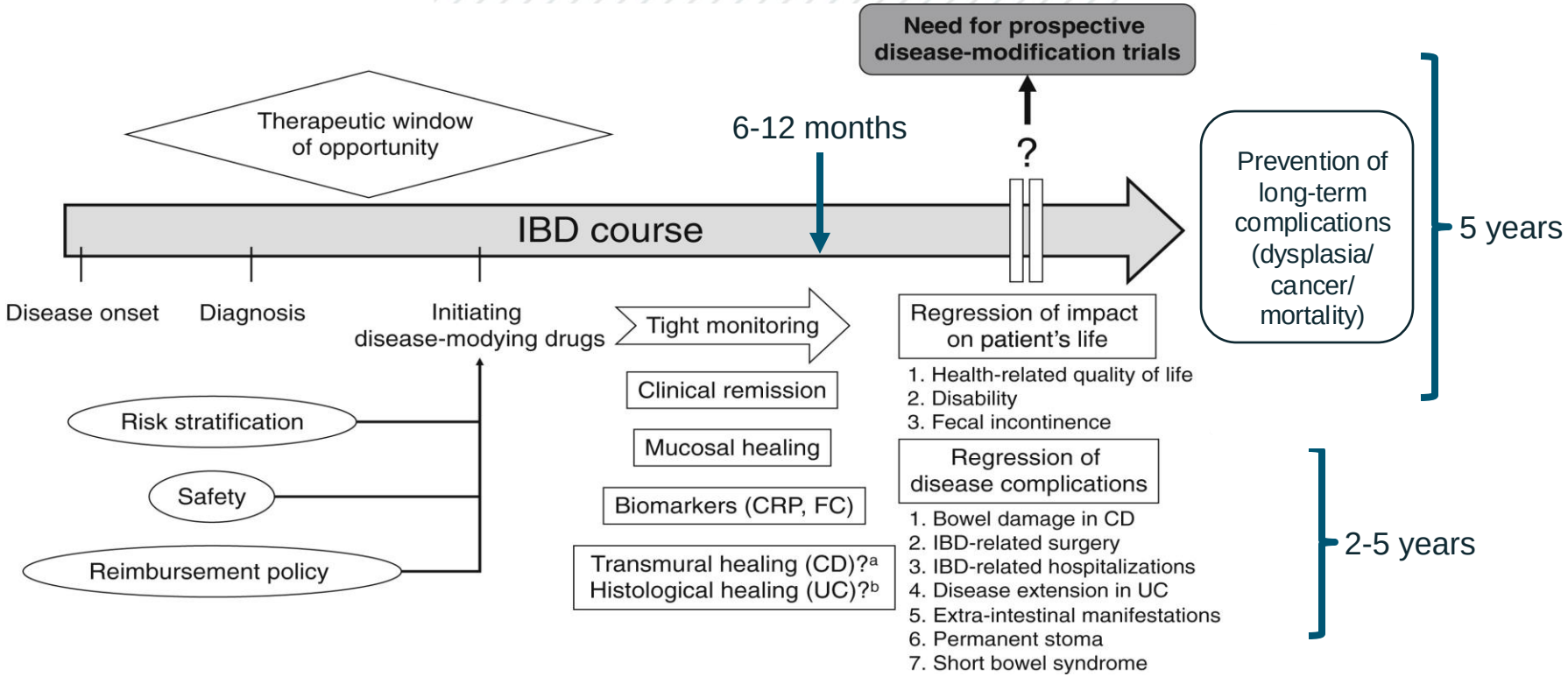
What is the most difficult aspect of caring for patients with IBD?

Faculty Discussion of ARS

Section 1

Marla Dubinsky, MD

Defining Goals for Treatment

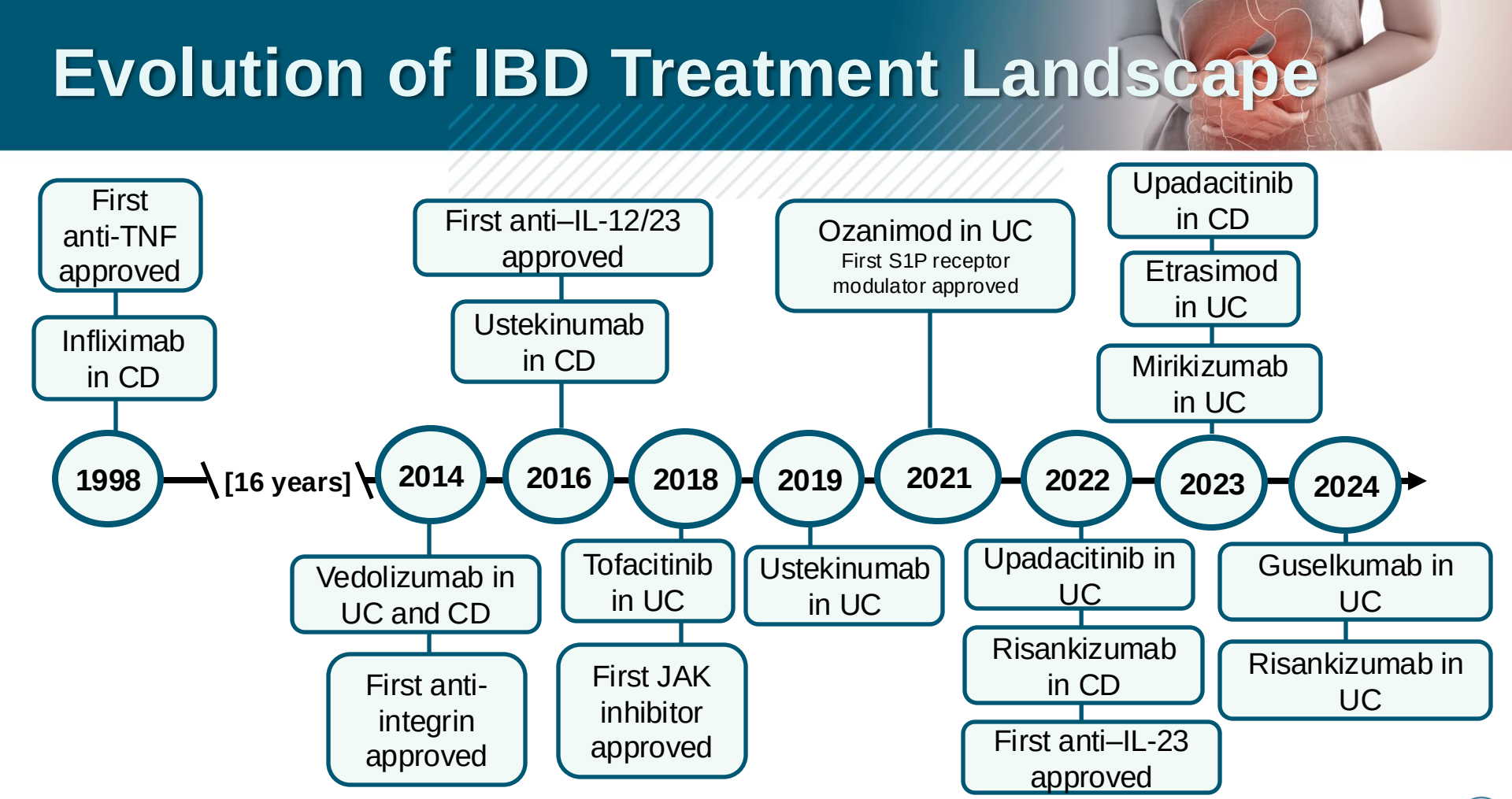


FC = fecal calprotectin.

[a]Transmural healing may be the ultimate therapeutic goal in CD; [b]Histologic healing may be the ultimate therapeutic goal in UC.

Le Berre C, et al. *Gastroenterology*. 2022;162(5):1424-1438.

Evolution of IBD Treatment Landscape



CD = Crohn's disease; IBD = inflammatory bowel disease; IL = interleukin; JAK = Janus kinase; TNF = tumor necrosis factor; UC = ulcerative colitis.
Modified from Pouillon L, et al. *Nat Rev Gastroenterol Hepatol.* 2021;18(2):143.

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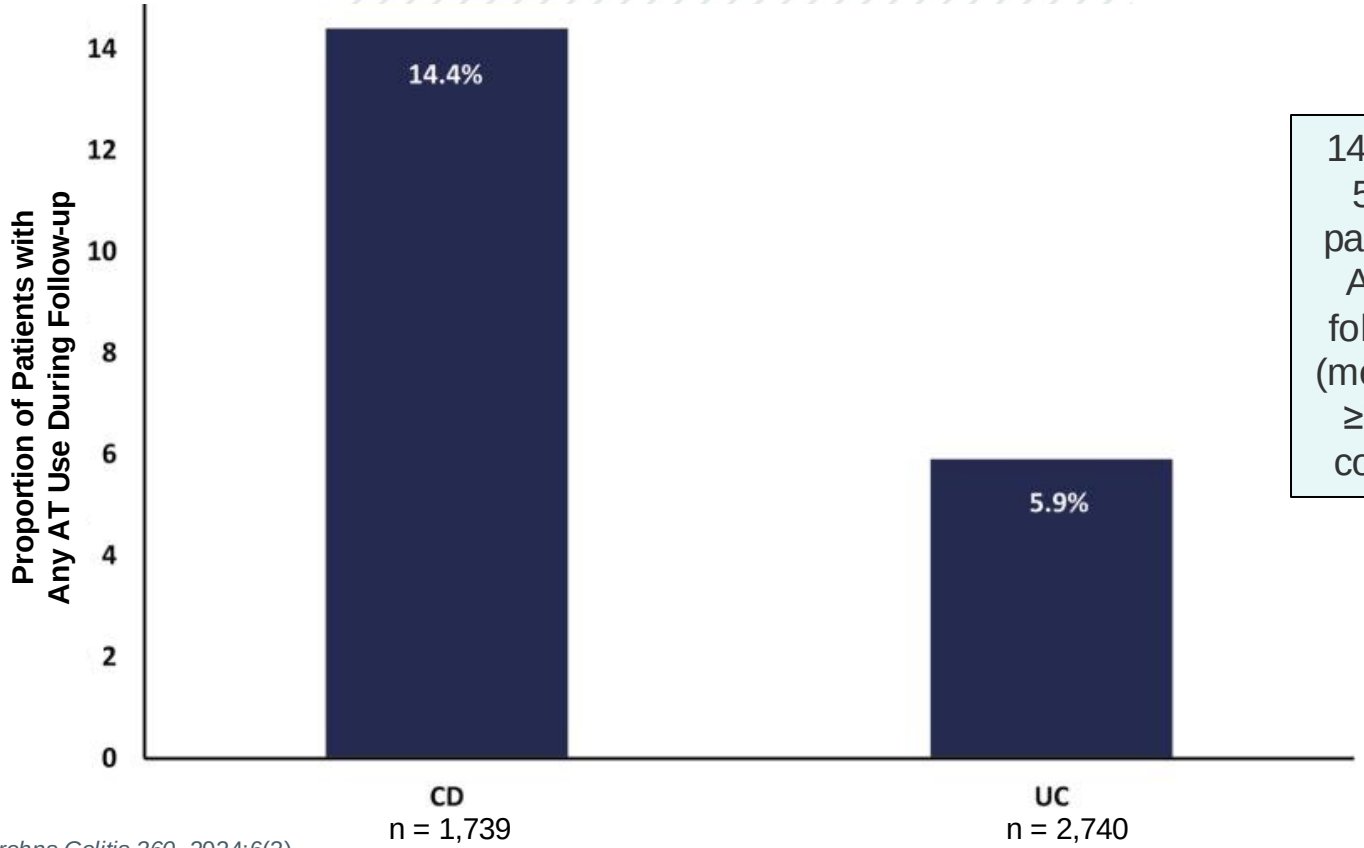
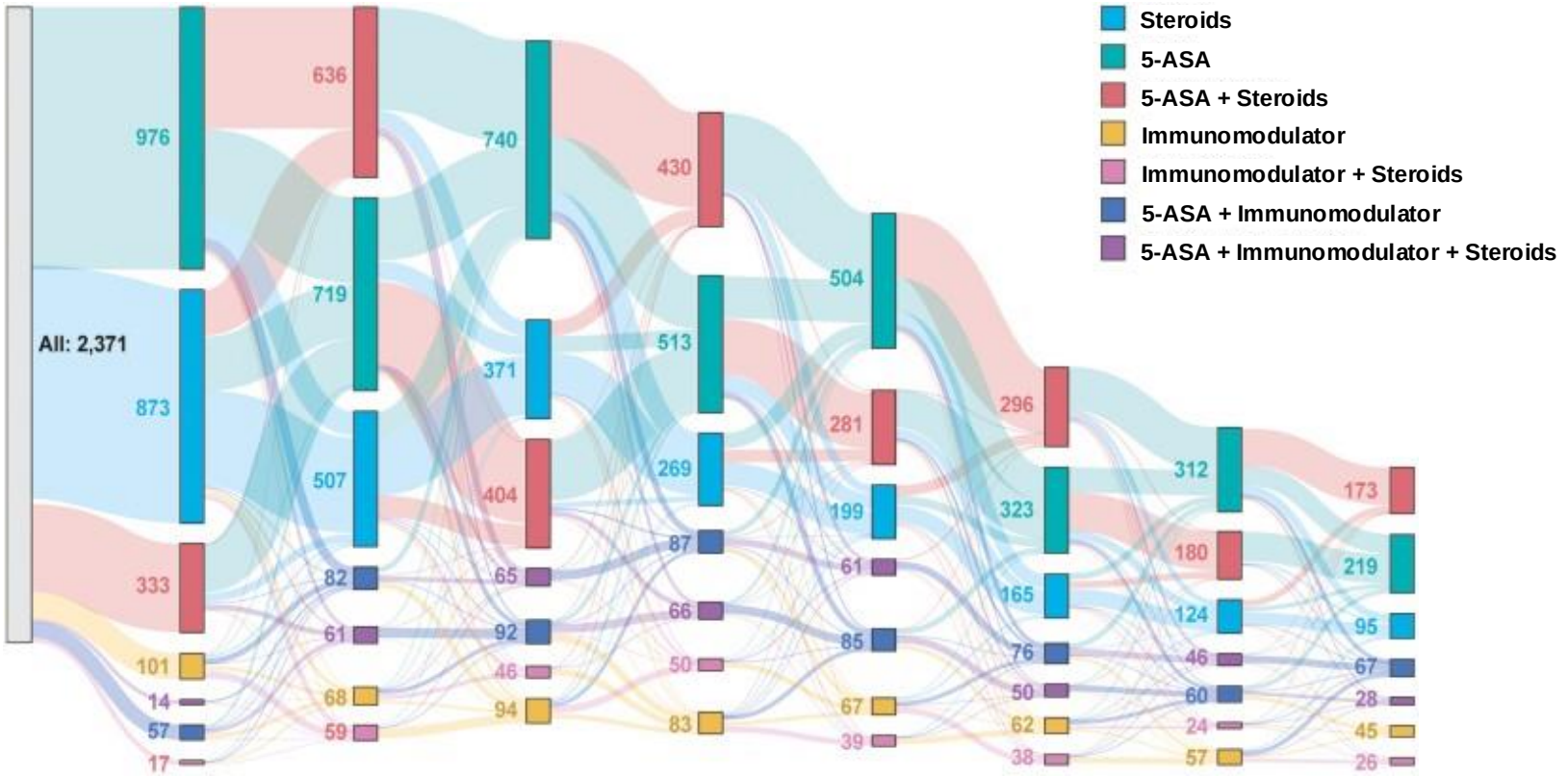
Advanced Treatment (AT) Uptake Is Low Within the First Few Years of IBD Diagnosis



14.4% (CD) and 5.9% (UC) of patients had any AT use during follow-up period (mean: 2.3 years; ≥77% initiated corticosteroids)

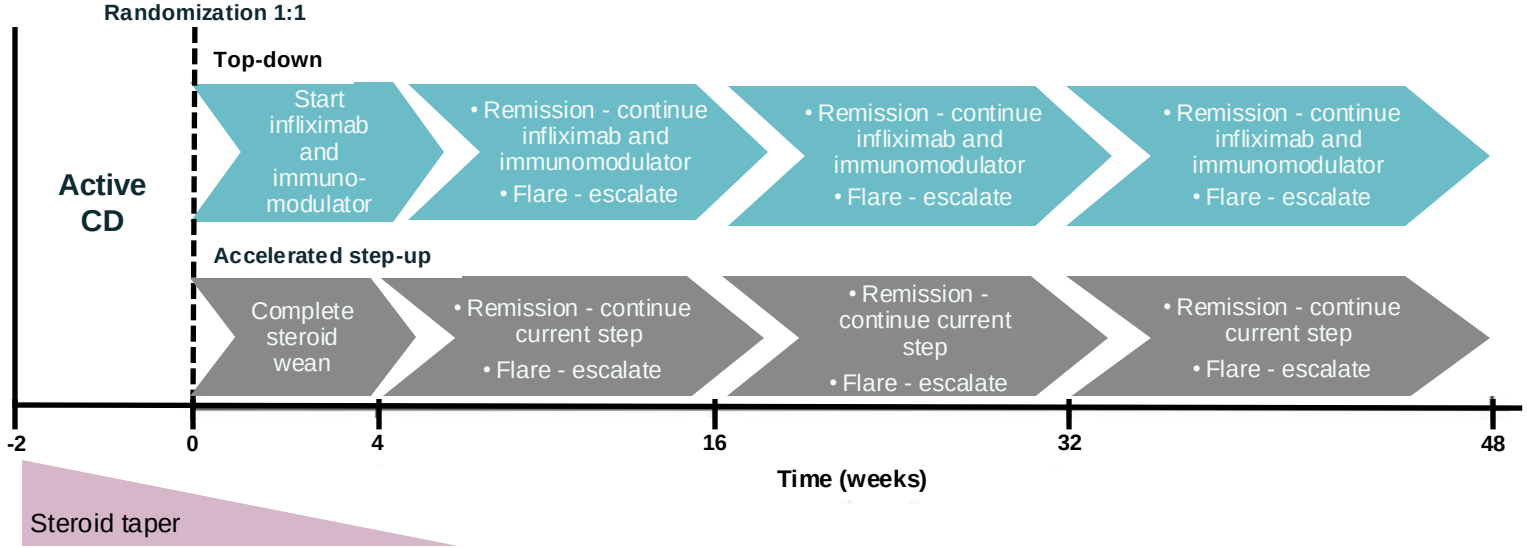
Siegel CA, et al. *Crohns Colitis 360*. 2024;6(3).

Patients with UC Are Treated with 5+ Rounds of Conventional Therapy Before They Receive an Advanced Therapy



Siegel CA, et al. *Crohns Colitis 360.* 2024;6(3):otae040.

The Profile Study: Step-Up Therapy Put to Bed Once and for All



Primary endpoint

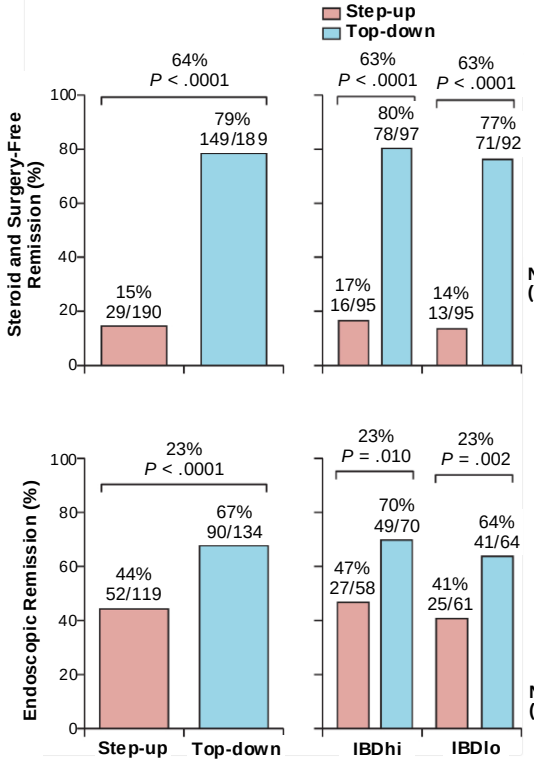
- Sustained surgery-free and steroid-free remission to week 48

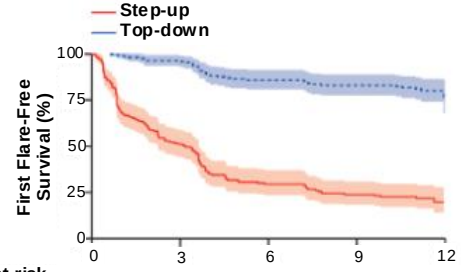
Secondary endpoints

- Endoscopic remission
- Quality of life
- Surgeries and hospitalizations
- Disease flares
- Steroid courses

Trial visit	Accelerated step-up	Top-down
Week -2 (screening)	Start steroid induction for active CD	Start steroid induction for active CD
Week 0 (randomization)	Following randomization, continue steroid taper	Following randomization, start infliximab and immunomodulator and continue steroid taper
Week 4, 16, 32, 48 (after randomization)	Remission - continue on current step of treatment Flare 1 - start steroids and immunomodulator Flare 2 - start infliximab alongside immunomodulator	Remission - continue infliximab and immunomodulator Flare 1 - additional course of steroid medication Flare 2 - consider non-response and trial withdrawal

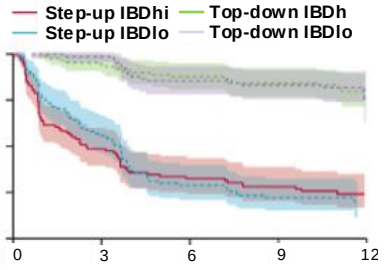
Early Effective Advanced Therapy (Not Biomarker Risk) Predicts CD Outcomes



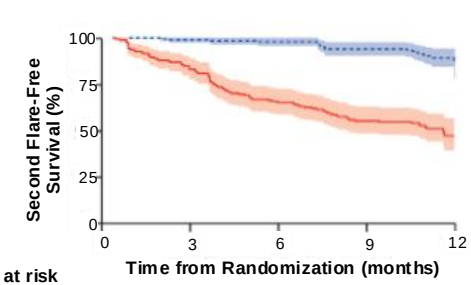


Number at risk (number censored)

Top-down	186 (0)	175 (4)	154 (2)	144 (5)	14 (125)
Step-up	190 (0)	96 (2)	53 (3)	41 (2)	6 (31)

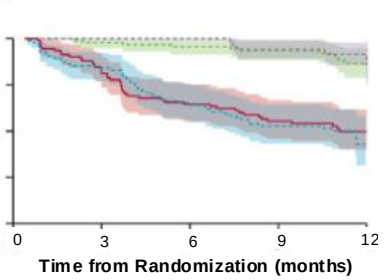


Top-down IBDlo	92 (0)	89 (1)	76 (1)	71 (3)	7 (67)
Step-up IBDlo	95 (0)	52 (0)	25 (2)	18 (1)	3 (14)
Top-down IBDhi	94 (0)	86 (3)	78 (1)	73 (2)	7 (63)
Step-up IBDhi	95 (0)	44 (2)	28 (1)	23 (1)	3 (17)



Number at risk (number censored)

Top-down	187 (0)	181 (4)	177 (2)	165 (5)	18 (139)
Step-up	189 (0)	154 (3)	116 (5)	94 (4)	12 (74)

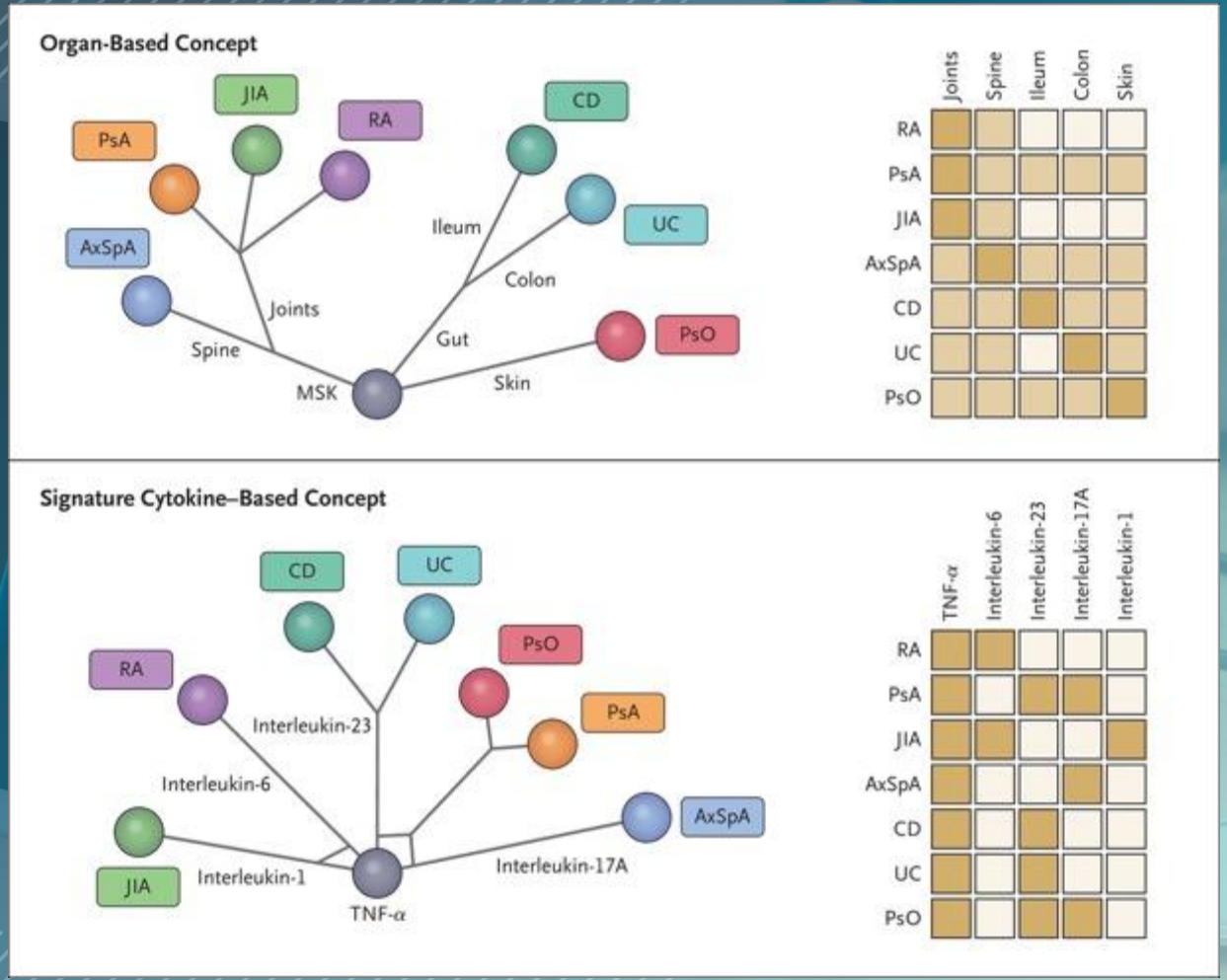


Top-down IBDlo	91 (0)	90 (1)	89 (1)	81 (3)	11 (67)
Step-up IBDlo	95 (0)	80 (0)	58 (4)	47 (1)	7 (36)
Top-down IBDhi	96 (0)	91 (3)	88 (1)	84 (2)	7 (72)
Step-up IBDhi	94 (0)	74 (3)	58 (1)	47 (3)	5 (38)

Median of 12 [IQR 0-191] days from time of diagnosis to enrollment and start GCC (-2 weeks to randomized)
Median of 15 [IQR 13-20] days from time of randomization and 1st dose of infliximab

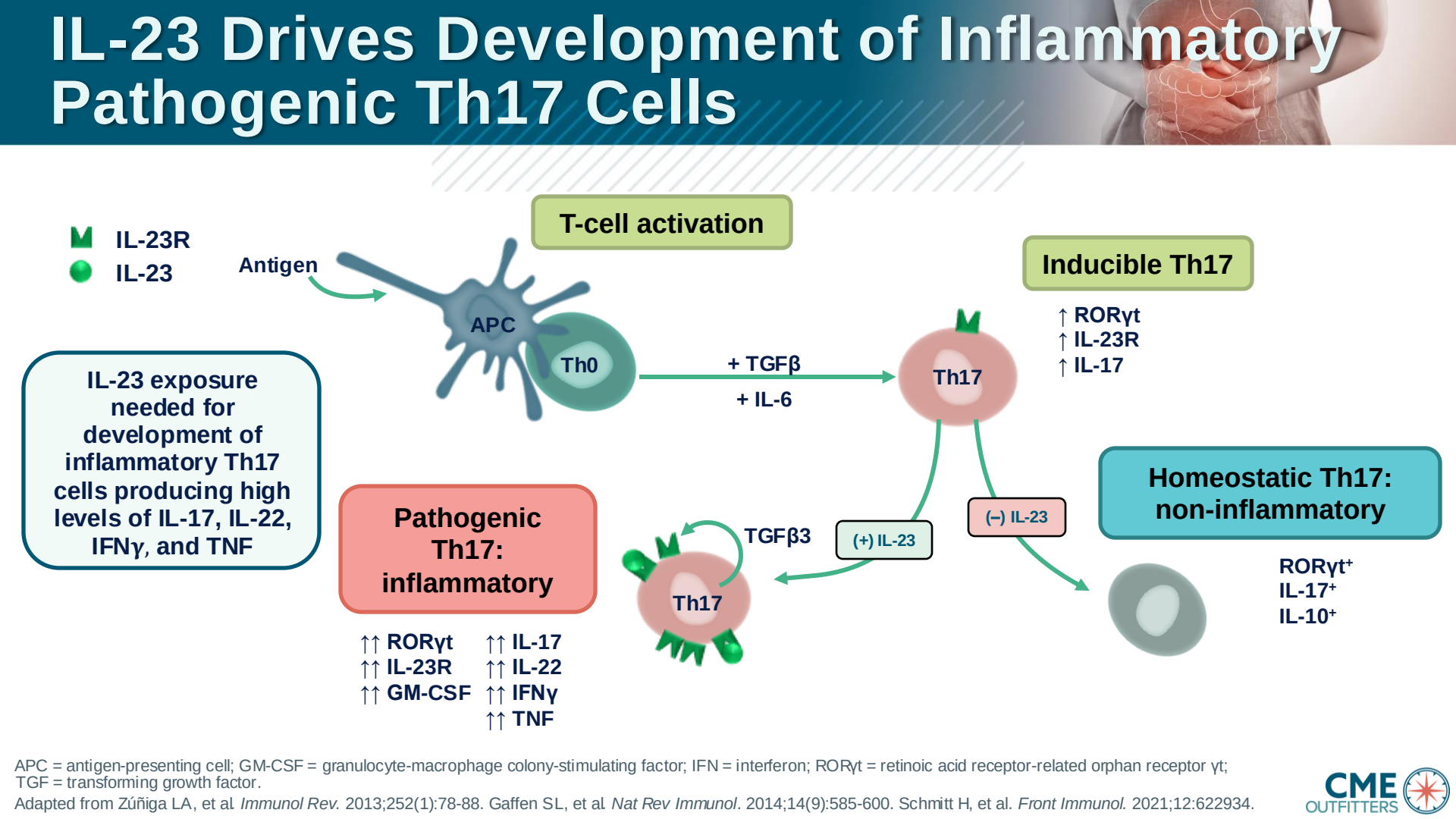
IQR = interquartile range. Noor V, et al. *Lancet Gastroenterol Hepatol.* 2024;9:415-427.

Cytokine Connections in Immune-Mediated Inflammatory Diseases



Schett G, et al. *N Engl J Med*, 2021;385(7):628-639.

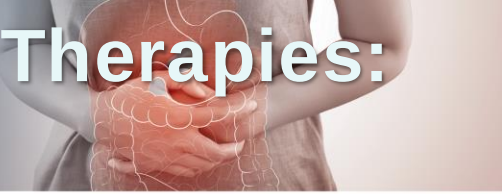
IL-23 Drives Development of Inflammatory Pathogenic Th17 Cells



APC = antigen-presenting cell; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; RORγt = retinoic acid receptor-related orphan receptor γt; TGF = transforming growth factor.

Adapted from Zúñiga LA, et al. *Immunol Rev.* 2013;252(1):78-88. Gaffen SL, et al. *Nat Rev Immunol.* 2014;14(9):585-600. Schmitt H, et al. *Front Immunol.* 2021;12:622934.

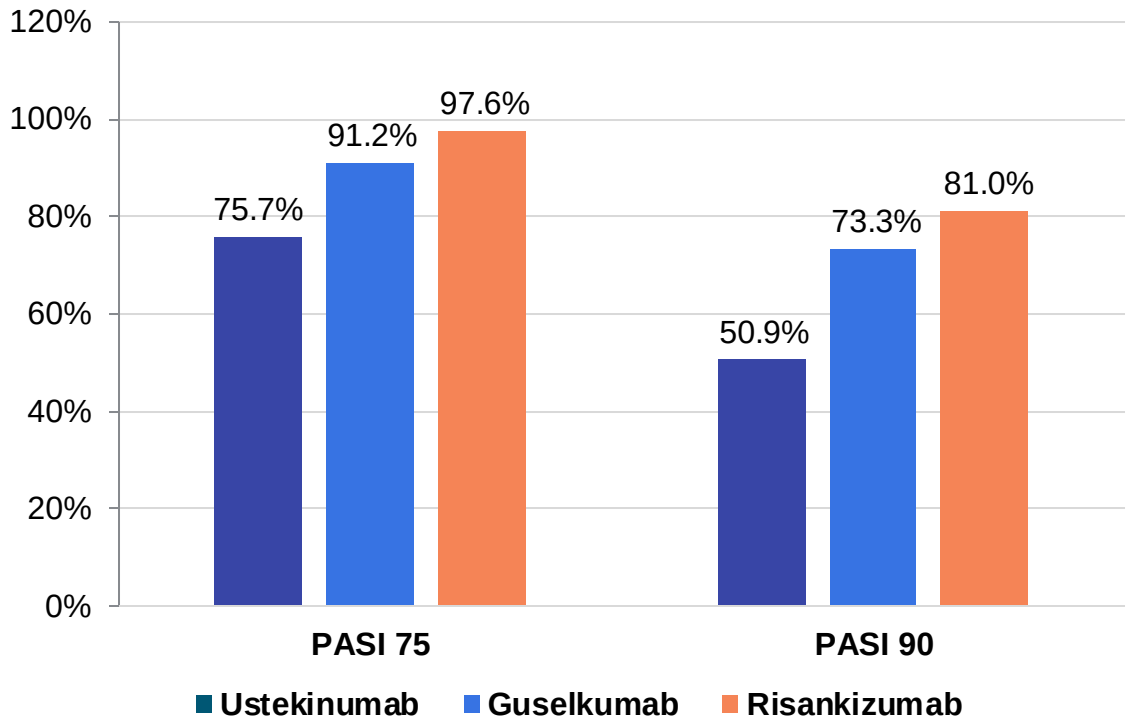
IL-12/23–Targeted vs IL-23–Targeted Therapies: Lessons from Dermatology Practice



- Dermatology practice is moving toward increasing use of IL-23–targeted therapies
- Higher rates of response in psoriasis with IL-23–targeted agents vs ustekinumab
- Patients with persistent disease while on ustekinumab show improvement after switching to an IL-23–targeted agent

Erichetti E, et al. *Acta Derm Venereol*. 2024;104:adv41053. Augustin M, et al. *Dermatol.* 2020;156(12):1344-1353.

Efficacy of IL-23s in PsO: PASI Scores from Phase III Studies



- Ustekinumab data from ACCEPT trial
- Guselkumab data from VOYAGE 1
- Risankizumab data from UltIMMa-1

PASI = Psoriasis Area and Severity Index (PASI) score.

Yang K, et al. *Am J Clin Dermatol*. 2021;22:173-192.

FINAL THOUGHTS
Cytokines and Pathogenesis

Faculty Discussion

Section 2

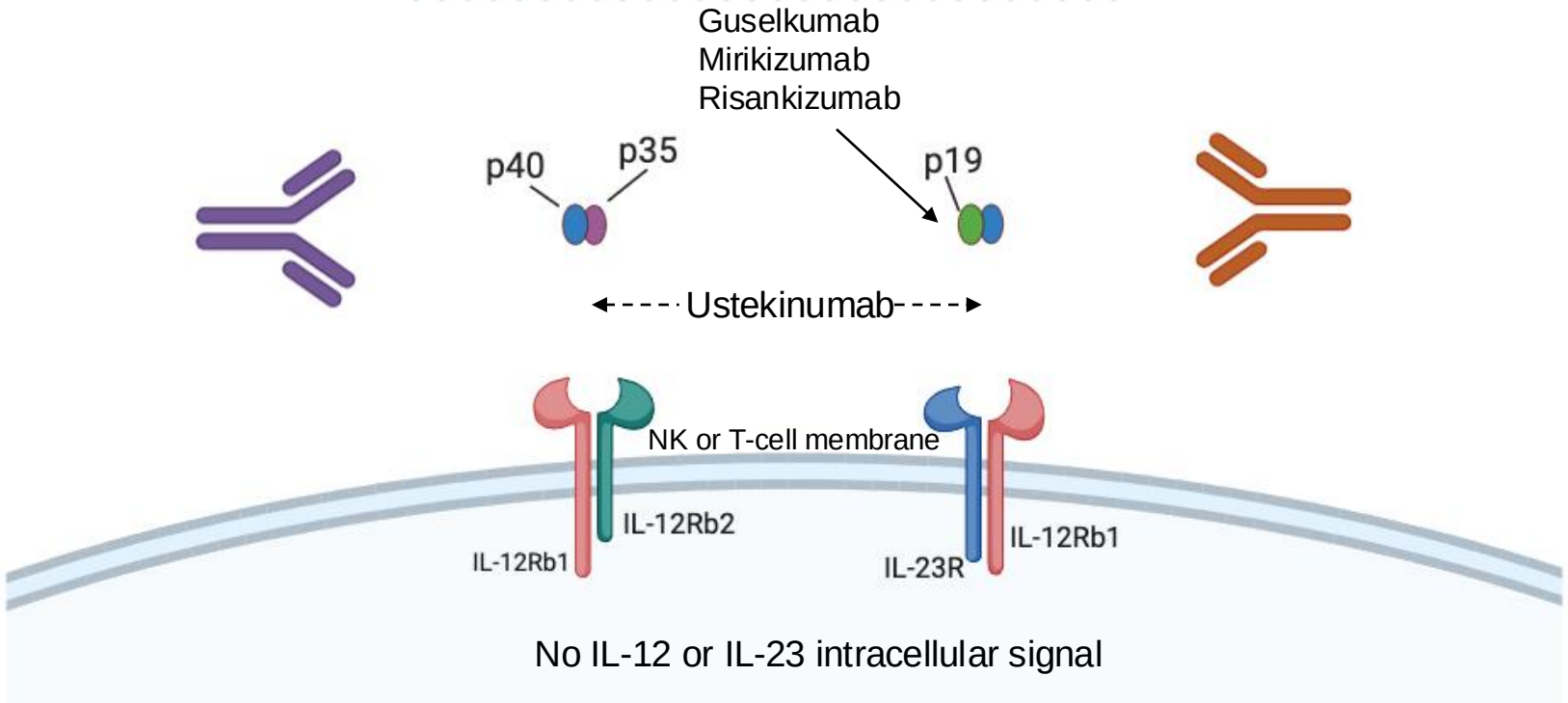
Corey Siegel, MD, MS

Audience Response

Which of the following is true regarding binding affinity of IL-23 inhibitors to CD64 receptors?

A. Binding of CD64 occurs with only risankizumab
B. Binding of CD64 occurs with only guselkumab
C. Binding of CD64 occurs with only mirikizumab
D. Binding of CD64 occurs with risankizumab, guselkumab, and mirikizumab
E. I don’t know

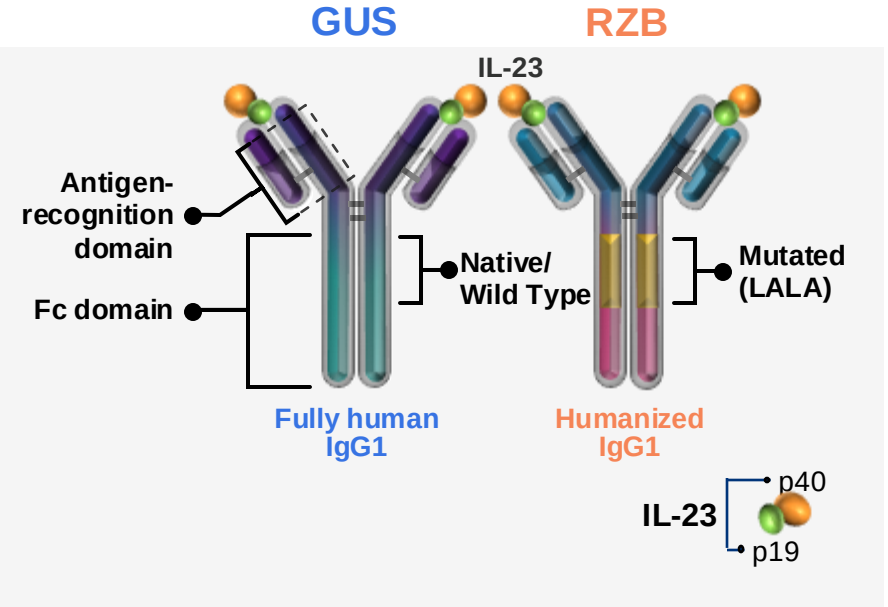
Anti-p40 (IL-12/23) and Anti-p19 (IL-23)



Adapted from Gately MK, et al. *Annu Rev Immunol*. 1998;16:495-521. Wilson NJ, et al. *Nat Immunol*. 2007;8(9):950-957. Nickoloff BJ, et al. *J Clin Invest*. 2004;113(12):1664-1675. Nestle FO, et al. *J Invest Dermatol*. 2004;123(6):xiv-xv. Created with Biorender.

Clinically Relevant Differences Between Anti–IL-23 Therapeutic Antibodies May Be Related to Their Unique Molecular Attributes

- Guselkumab (GUS) and risankizumab (RZB) are mAbs that selectively target the p19 subunit of IL-23
- GUS and RZB have shown efficacy in the treatment of inflammatory bowel diseases*
- Potential differences in the therapeutic profiles may be related to their unique molecular attributes
- GUS and RZB have differences in the Fc region that affect binding to Fc-gamma receptors

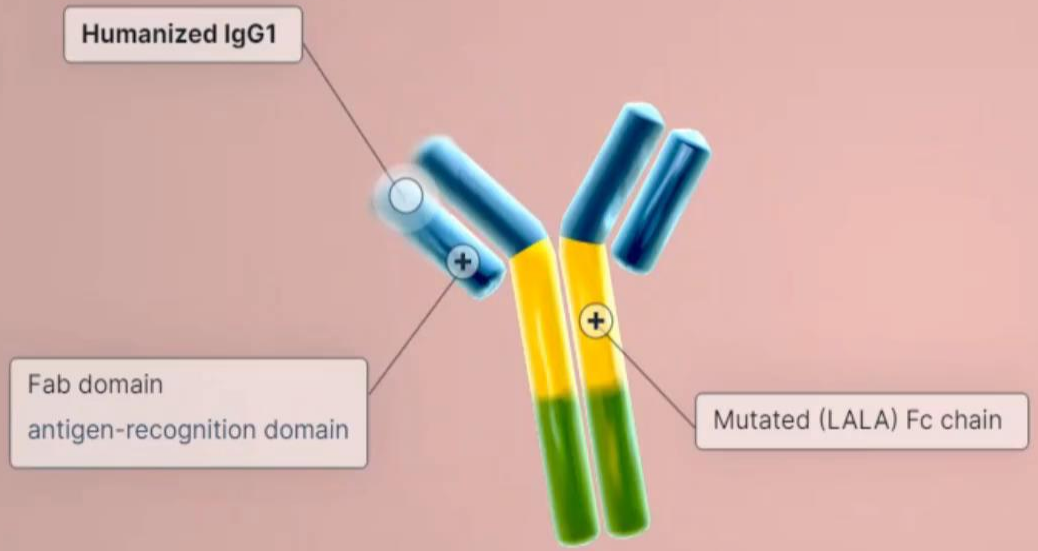


Objective: Examine the binding and functional characteristics of the antigen-binding and Fc regions of GUS and RZB

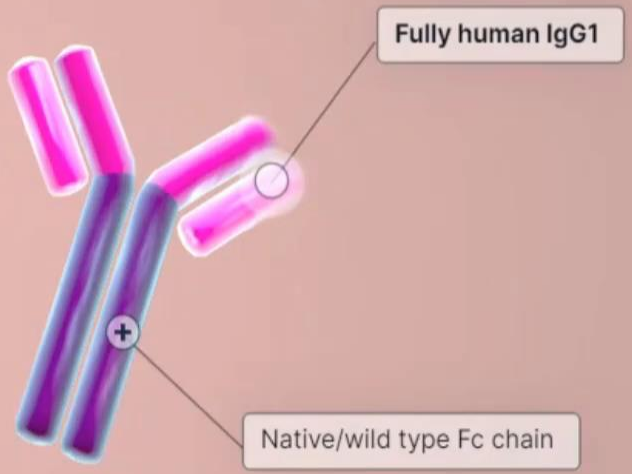
Fc = fragment crystallizable; IgG = immunoglobulin G; LALA = leucine to alanine substitutions at positions 234 and 235; mAbs = monoclonal antibodies.

*GUS is indicated for the treatment of adults with moderately to severely active ulcerative colitis; RZB is indicated for the treatment of adults with moderately to severely active Crohn's disease and treatment of adults with moderately to severely active ulcerative colitis.

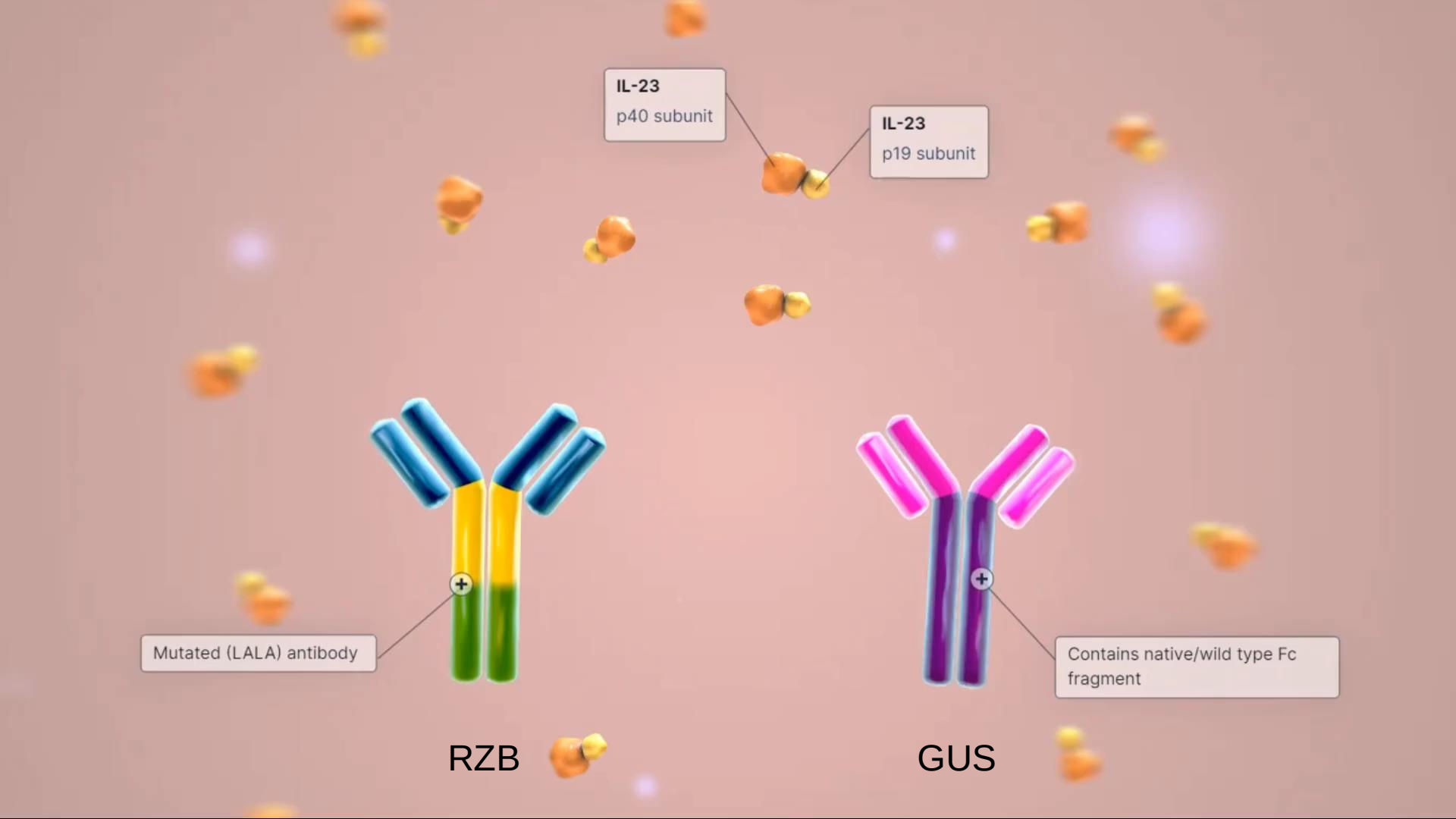
D'Haens G, et al. *Lancet*. 2022;399(10340):2015-2030. Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046. Sandborn WJ, et al. *Gastroenterology*. 2022;162(6):1650-1664. Dignass A, et al. *J Crohns Colitis*. 2022;16(Suppl 1):i025-i026. Louis E, et al. *Aliment Pharmacol Ther*. 2004;19(5):511-519. Vos AC, et al. *Gastroenterology*. 2011;140(1):221-230. Wojtal KA, et al. *PLoS One*. 2012;7(8):e43361.


Humanized IgG1
Fab domain
antigen-recognition domain
Mutated (LALA) Fc chain

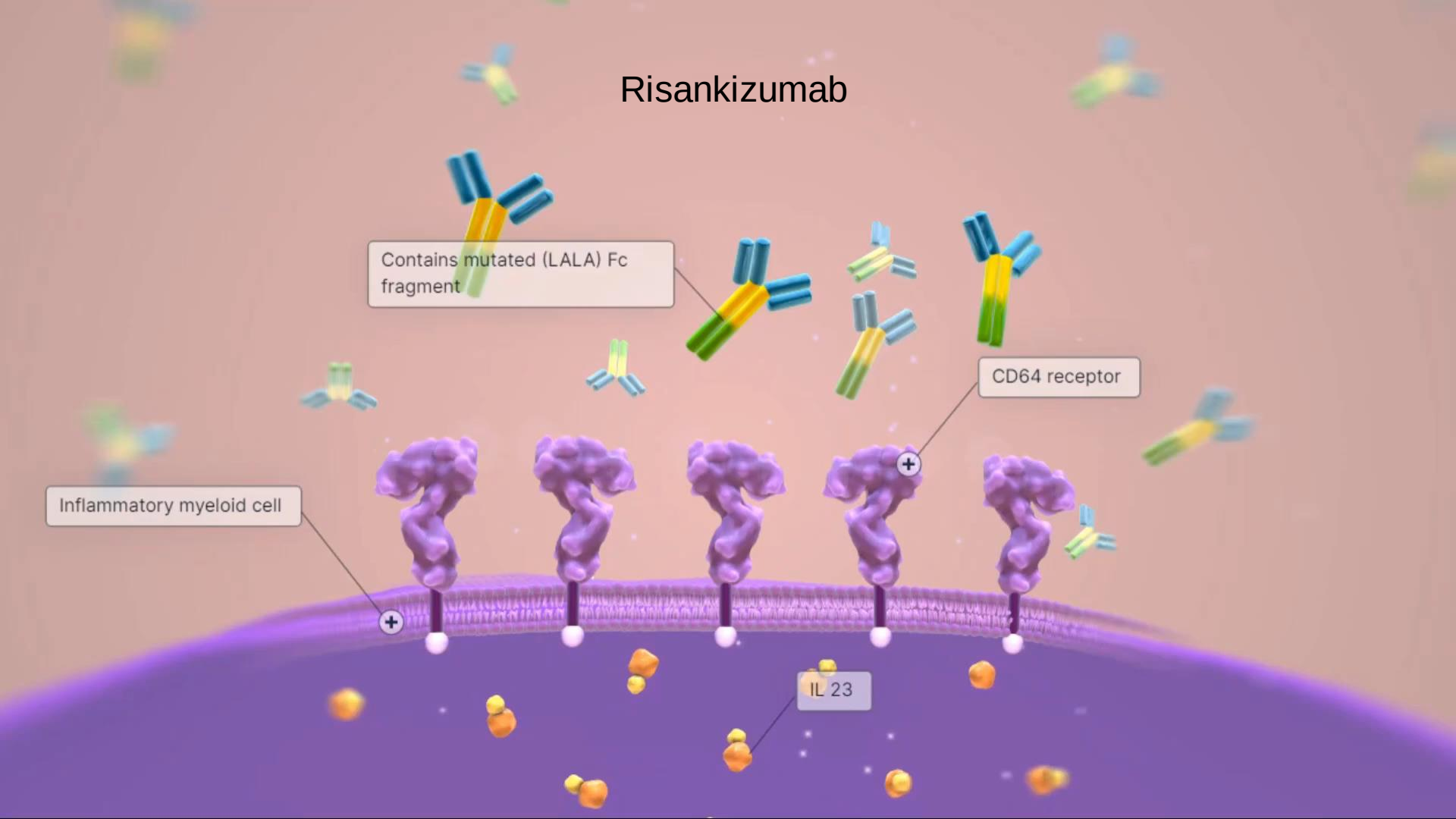
RZB


Fully human IgG1
Native/wild type Fc chain

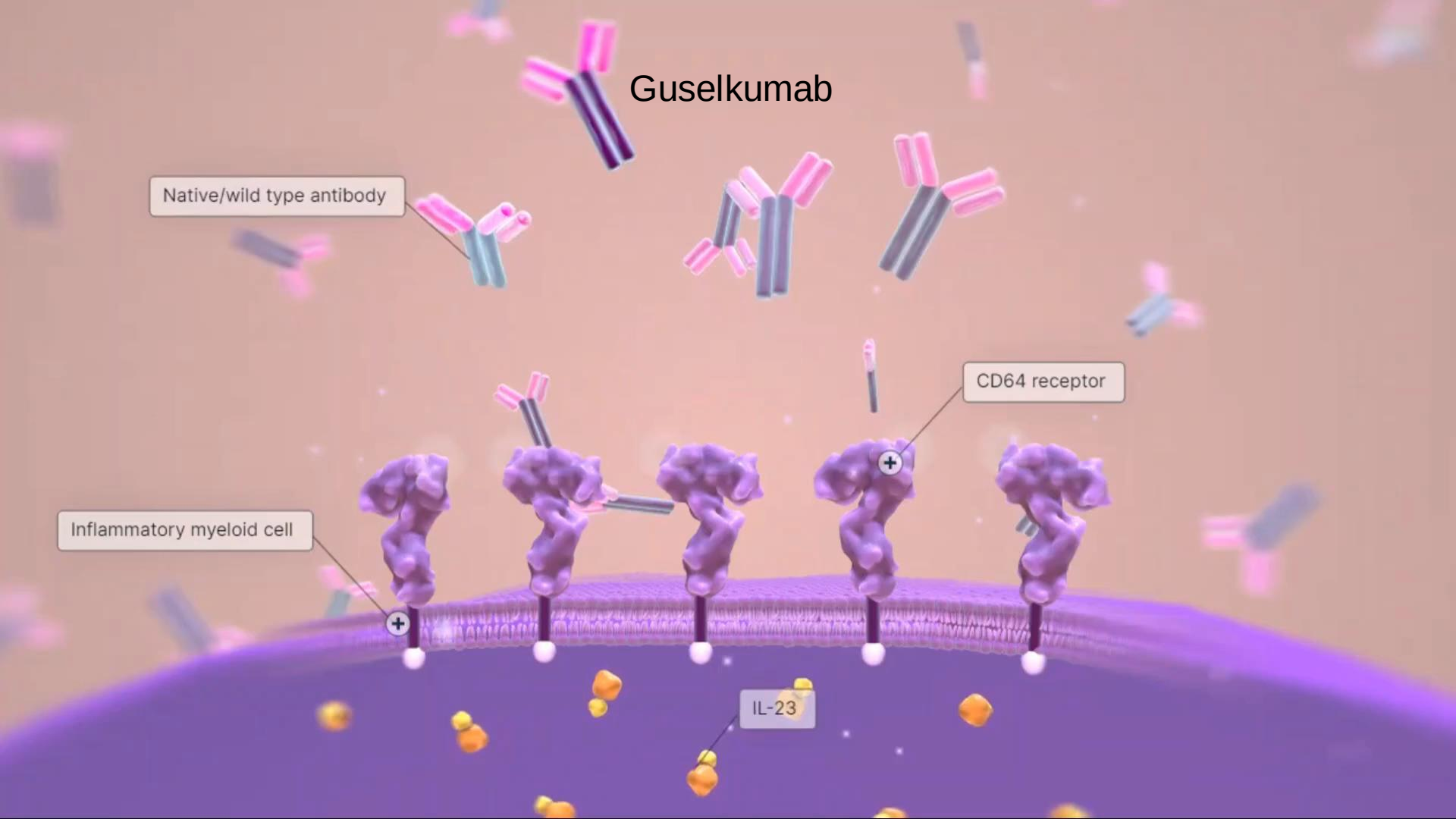
GUS


IL-23
p40 subunit
IL-23
p19 subunit
Mutated (LALA) antibody
Contains native/wild type Fc fragment
RZB
GUS

Risankizumab

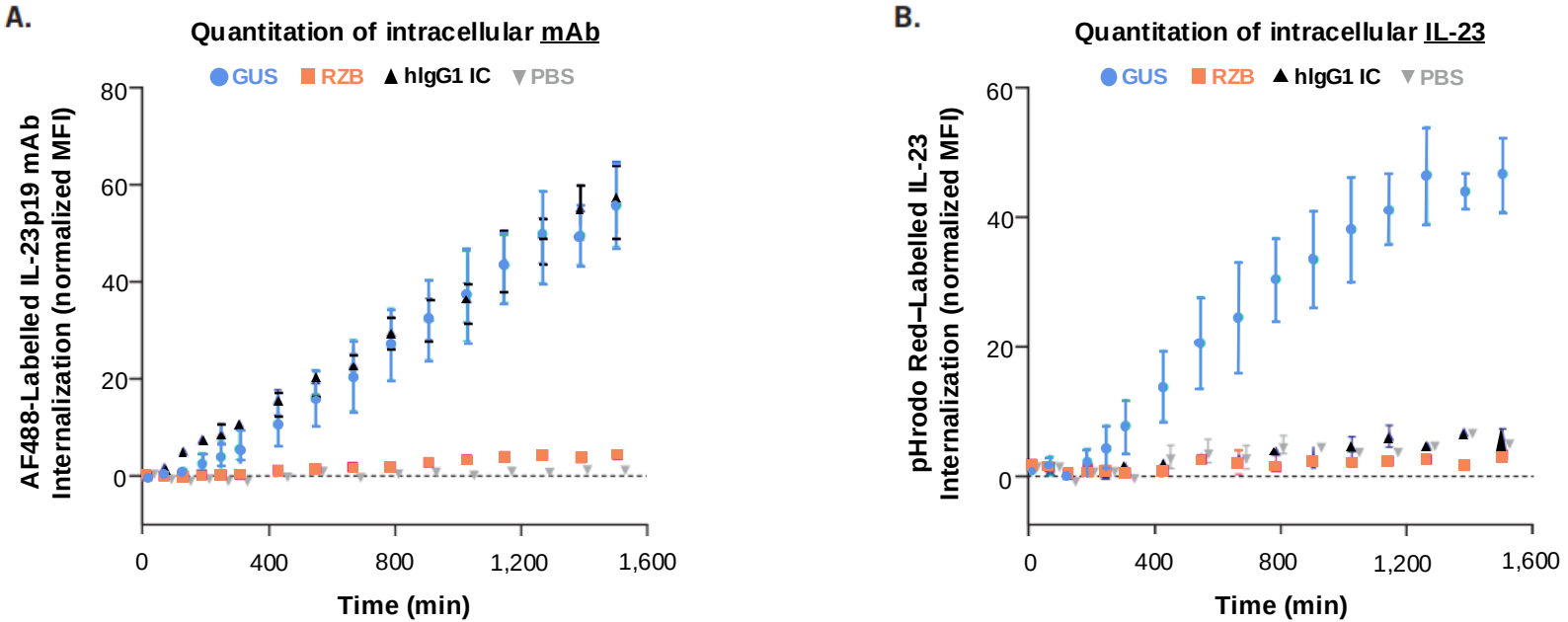


Guselkumab


Native/wild type antibody
CD64 receptor
Inflammatory myeloid cell
IL-23

In Vitro Evaluations of CD64 and IL-23 Binding: GUS and RZB

Quantitation of (A) mAb MFI and (B) IL-23 MFI in intracellular compartments of CD64+ inflammatory macrophages following treatment with IL-23p19 mAbs and IL-23

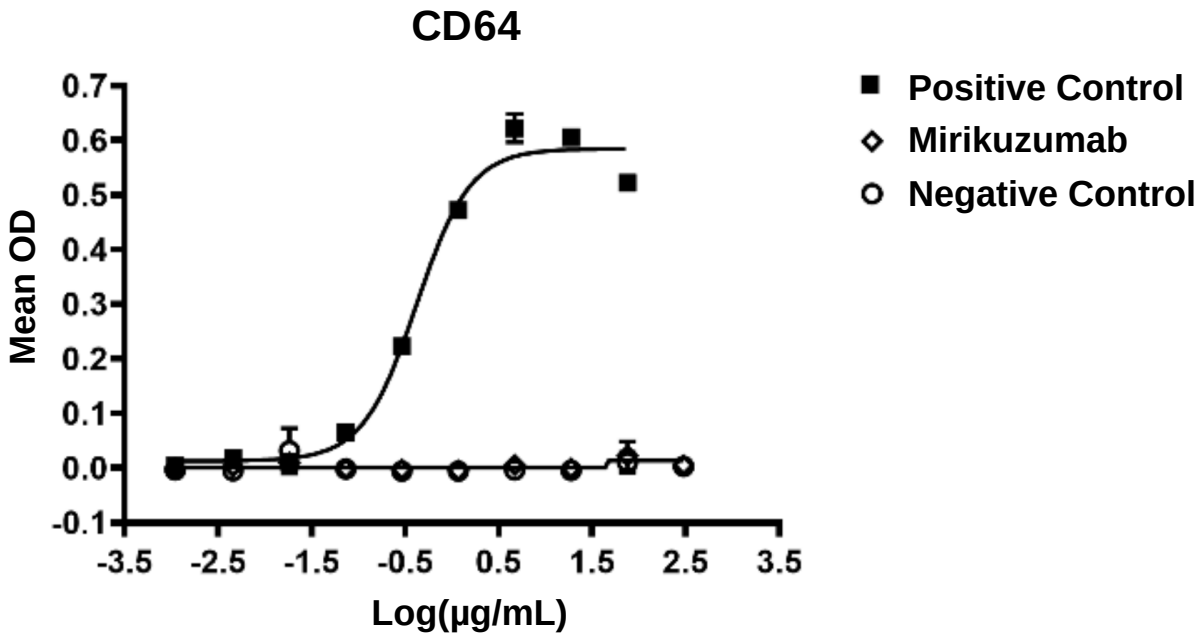


MFI = mean fluorescence intensity.

Atreya R, et al. *J Crohns Colitis*. 2024;18(Suppl 1):i470.

In Vitro Evaluations of CD64 and IL-23 Binding: Mirikizumab

Assessment of Fc Receptor Activation and Complement Binding



Data are mean + standard deviation (SD) of duplicate wells.

Steere B, et al. *J Pharmacol Exp Ther*. 2023;387(2):180-187.

Audience Response

Which of the following is true regarding binding affinity of IL-23 inhibitors to CD64 receptors?

A. Binding of CD64 occurs with only risankizumab
B. Binding of CD64 occurs with only guselkumab
C. Binding of CD64 occurs with only mirikizumab
D. Binding of CD64 occurs with risankizumab, guselkumab, and mirikizumab

Section 3

David P. Hudesman, MD, FACG, AGAF

Study Designs in IBD

Induction followed by randomized withdrawal maintenance

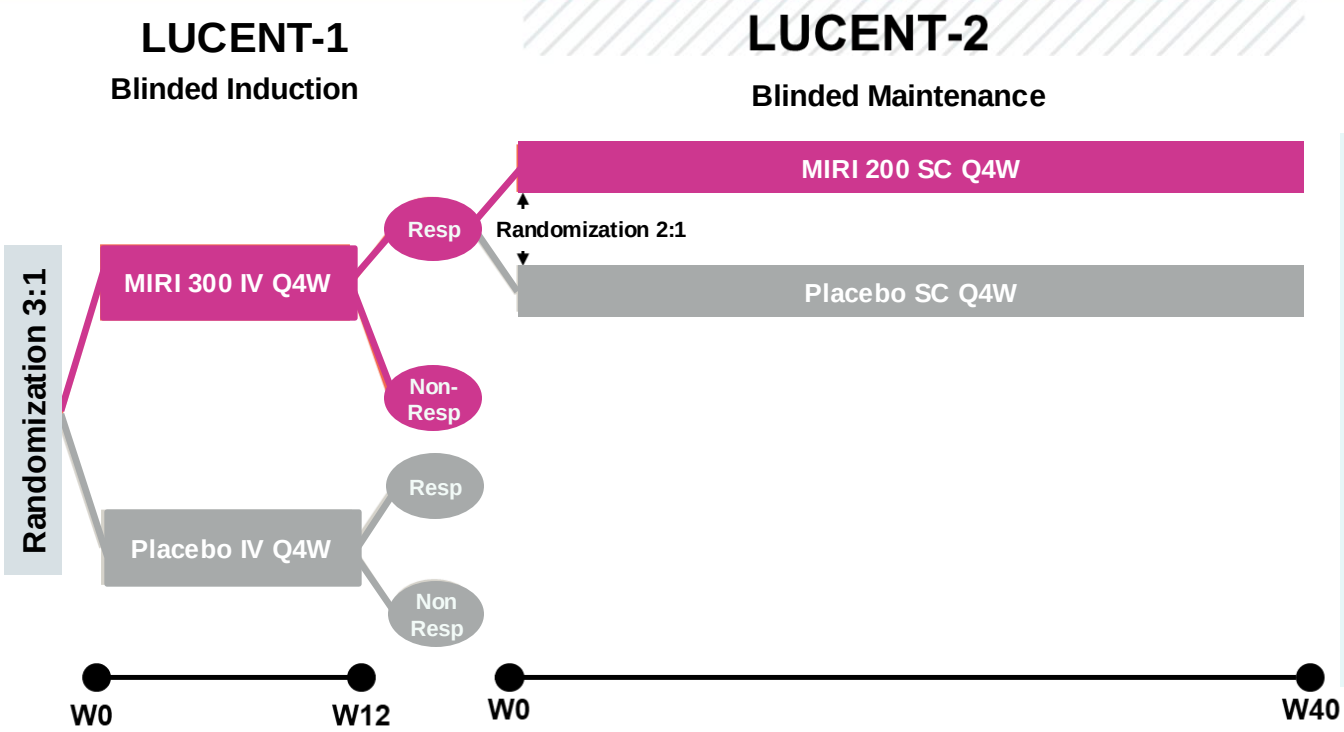
- All subjects who achieve response (i.e., clinical or endoscopic response) to active drug are **re-randomized** to active treatment or placebo

Treat-through design

- Randomize subjects once at the start of the trial to one of the treatment arms (i.e., dosing regimen or placebo) and subjects are **treated continuously without rerandomization** through 52 weeks

U.S. Department of Health and Human Services Food and Drug Administration. Crohn's Disease: Developing Drugs for Treatment Guidance for Industry. 2022.

Mirikizumab in UC: LUCENT-1 and LUCENT-2



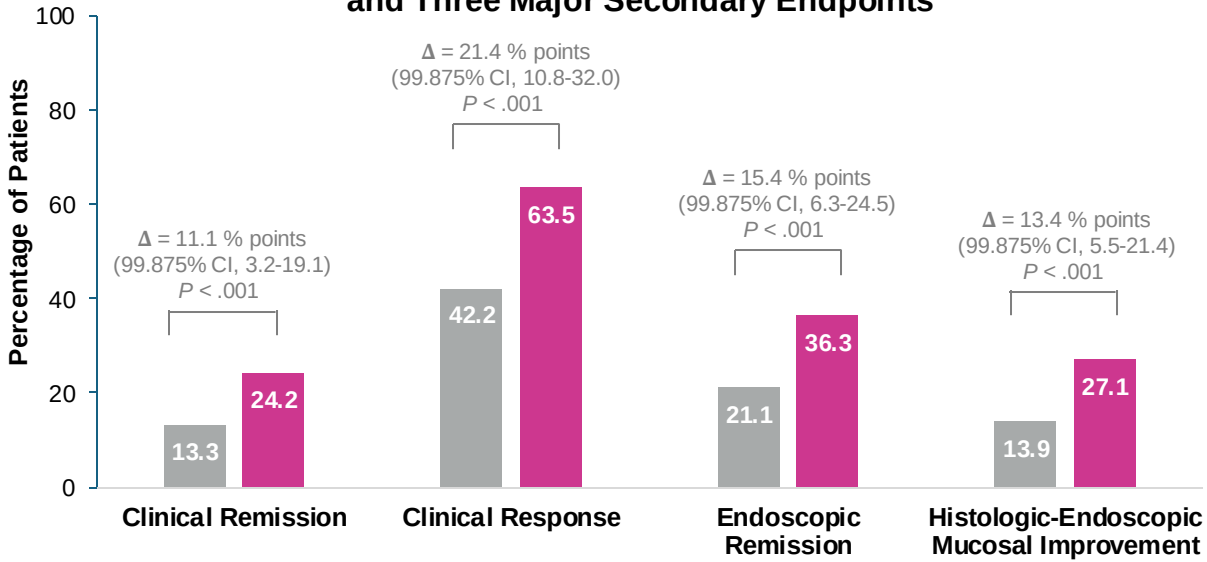
Induction: N = 1,281 adults with an incomplete response to, loss of response to, or inability to take conventional treatment, biologic therapy, or JAKi were assigned in a 3:1 ratio to receive MIRI (300 mg) or placebo IV every 4 weeks for 12 weeks

Maintenance: N = 544 adults with a clinical response to MIRI at week 12 were reassigned in a 2:1 ratio to receive MIRI (200 mg) or placebo SC every 4 weeks for 40 weeks

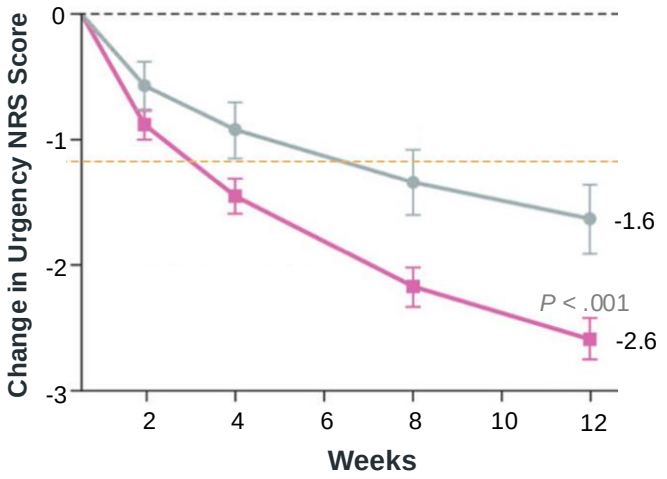
Non-Resp = non-responders; Resp = responders; SC = subcutaneous.
Clinical response: ≥2-point and ≥30% decrease in the modified Mayo score (MMS) from baseline with RB = 0 or 1, or ≥1-point decrease from baseline.
Maintenance randomization was stratified by induction remission status, biologic failure status, baseline corticosteroid use, and world region.
Mirikizumab is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients.
D'Haens G, et al. *N Engl J Med*. 2023;388:2444-2455.

Mirikizumab in UC Induction: LUCENT-1

Primary Endpoint of Clinical Remission and Three Major Secondary Endpoints



Change in Bowel Urgency from Baseline



Placebo (N = 294) Mirikizumab 300 mg (N = 868)

Mirikizumab is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients.

D'Haens G, et al. *N Engl J Med*. 2023;388:2444-2455.

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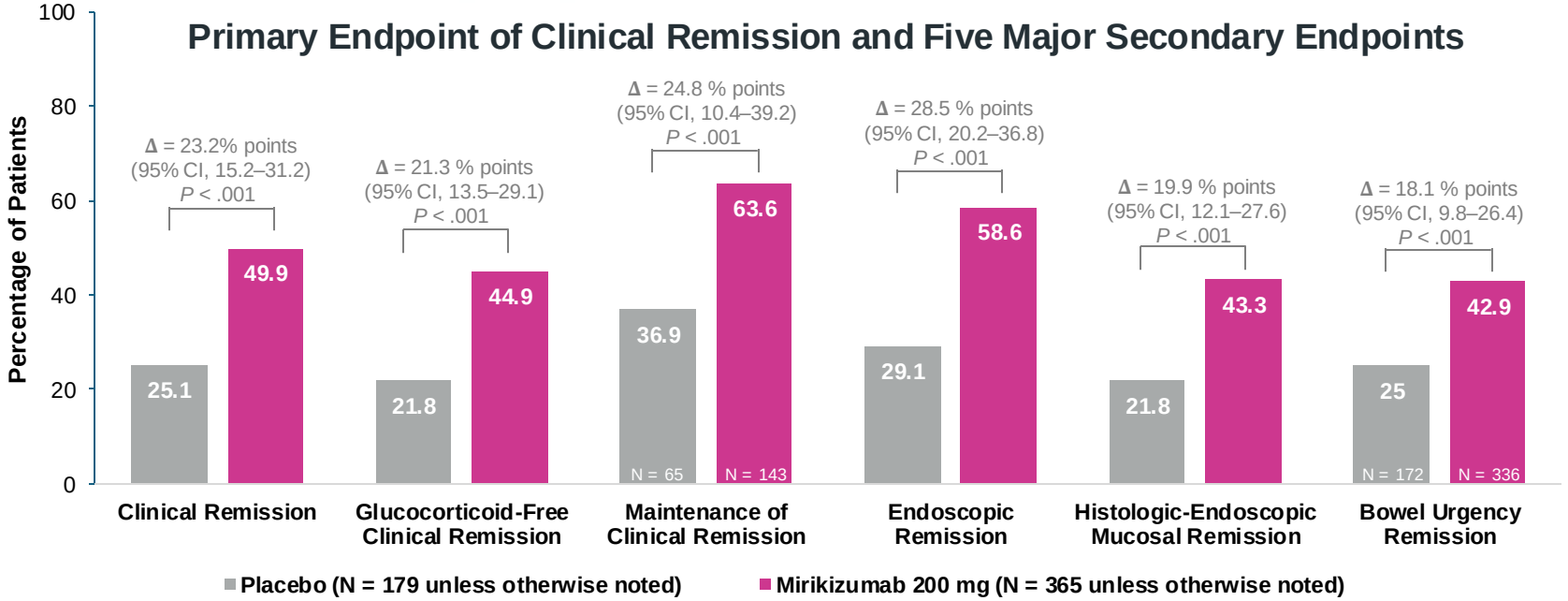
Mirikizumab in UC Maintenance: LUCENT-2 Week 40 Endpoints

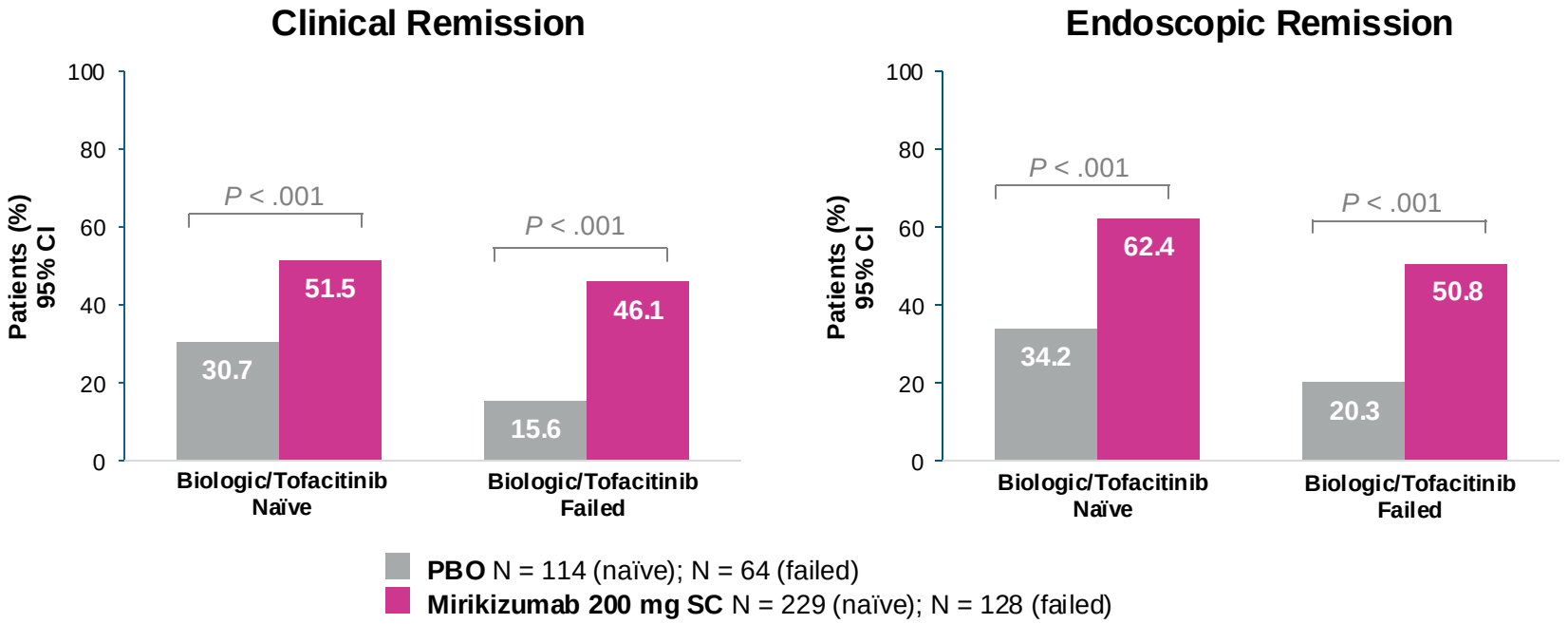


Clinical remission: stool frequency (SF) = 0, or SF = 1 with a ≥1-point decrease from baseline; rectal bleeding (RB) = 0; endoscopic subscore (ES) = 0 or 1 (excluding friability); endoscopic remission: ES = 0 or 1 (excluding friability), clinical remission at week 40, remission of symptoms at week 28, and no glucocorticoid use for ≥12 weeks before week 40.

Mirikizumab is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients.

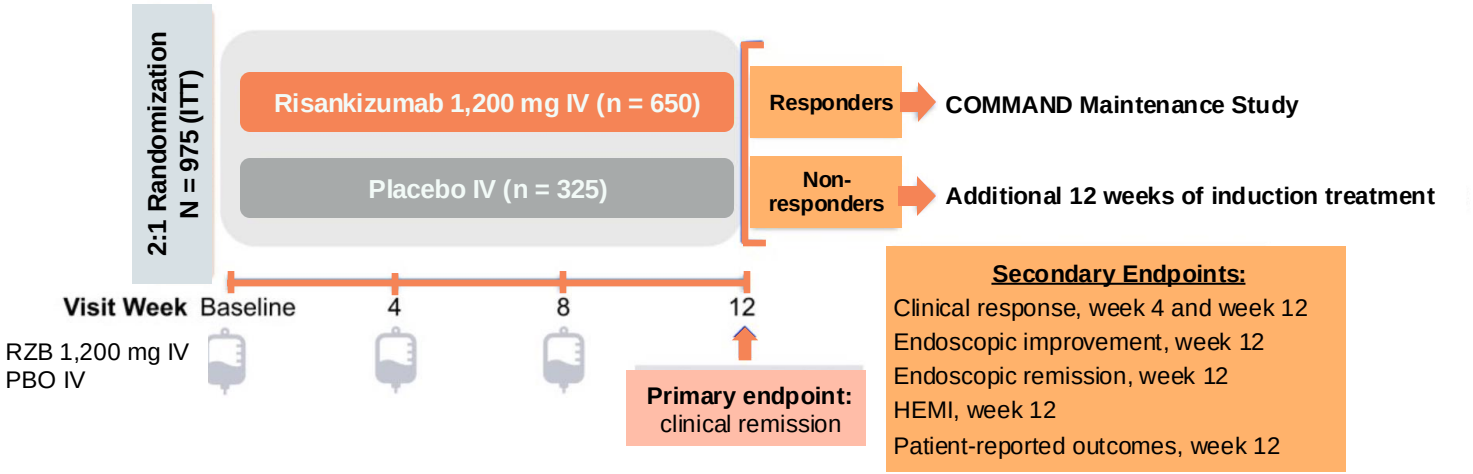
D'Haens G, et al. *N Engl J Med*. 2023;388:2444-2455.

MIRI in Treatment-Naïve and Treatment-Experienced Patients with UC: LUCENT-2



PBO = placebo.
Mirikizumab is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients.
D'Haens G, et al. *N Engl J Med.* 2023;388:2444-2455.

Risankizumab in UC: INSPIRE/COMMAND



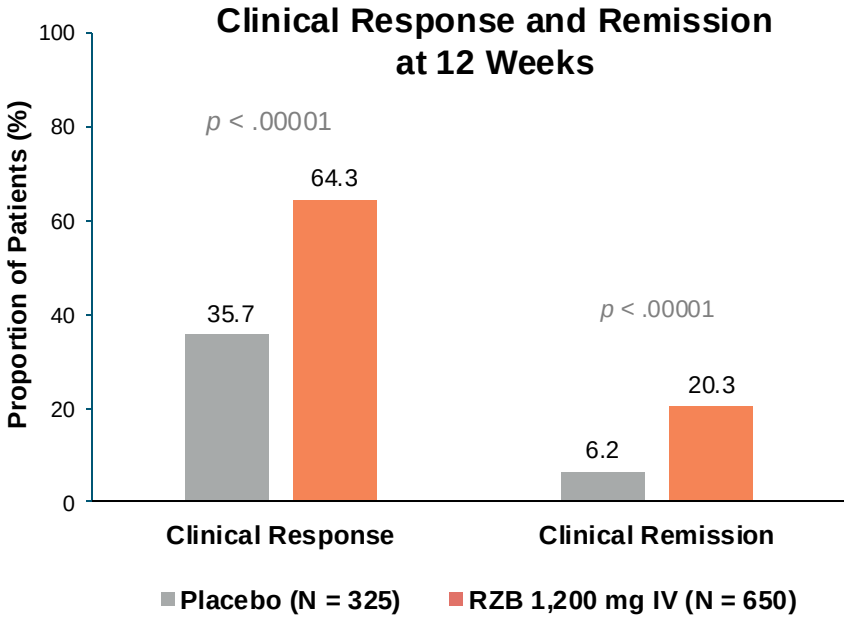
Key Inclusion Criteria:

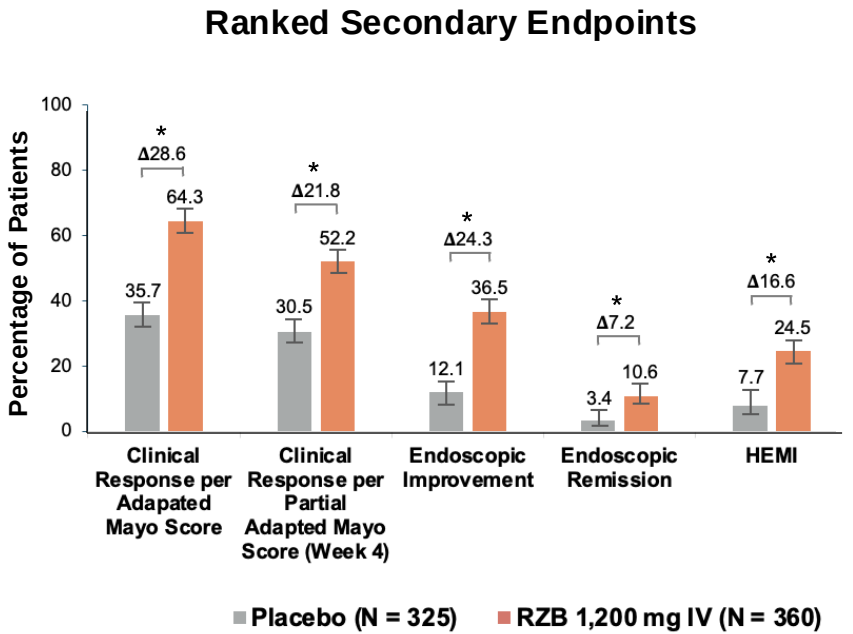
- Age 18 to 80
- **Moderately to severely active UC:** Adapted Mayo score of 5-9 and endoscopic subscore of 2-3 (central review) with biopsy-confirmed diagnosis at least 3 months prior to baseline
- **Intolerance or inadequate response to conventional (non-advanced) and/or advanced therapies** (biologics, JAK inhibitors, and S1P receptor modulators)
- No prior exposure to ustekinumab or IL-23 inhibitors was permitted

IV = intravenous

Louis E, et al. *JAMA*. 2024;332:881-897.

Risankizumab Induction in UC: INSPIRE





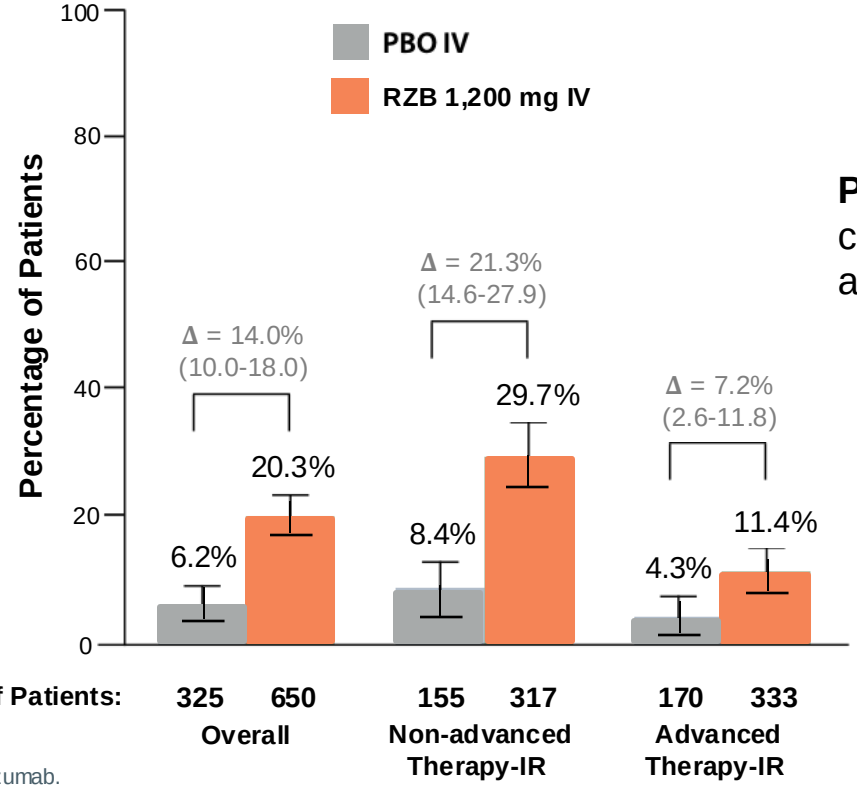
*P value < .00001 vs PBO.

Risankizumab is indicated for adults with moderately to severely active UC.

Clinical remission per Adapted Mayo Score is defined as stool frequency subscore (SFS) ≤1 and not greater than baseline, rectal bleeding subscore (RBS) of 0 and endoscopic subscore ≤1 without friability. Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1.

Louis E, et al. *Am J Gastroenterol.* 2023;118(10S):S624-S625.

RZB in Treatment-Naïve and Treatment-Experienced Patients with UC: INSPIRE



Primary endpoint:
clinical remission*
at Week 12

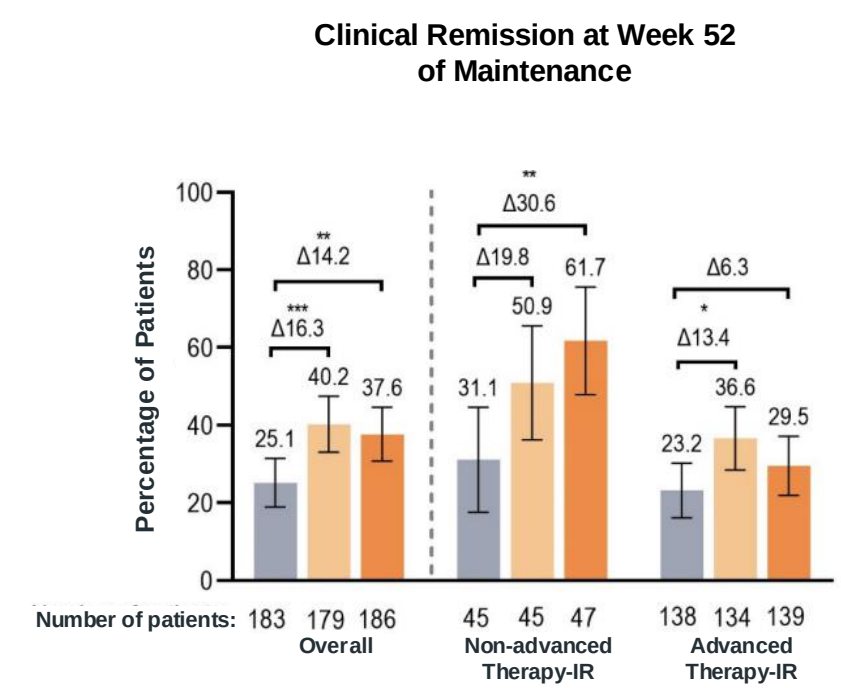
IR = inadequate responders; RZB = risankizumab.

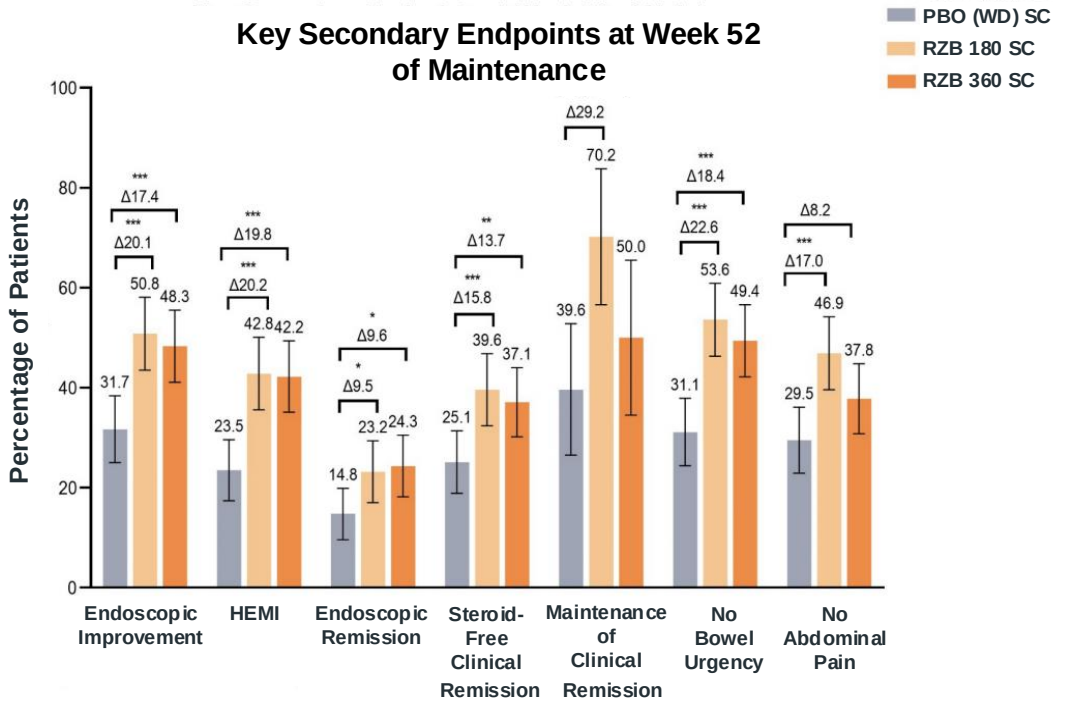
*Clinical remission per adapted Mayo score: stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤1 without friability.

Risankizumab is indicated for patients with moderately to severely active UC.

Louis E, et al. *JAMA*. 2024;332:881-897.

Risankizumab Maintenance in UC: COMMAND





*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$ versus PBO (WD) SC.

Risankizumab is indicated for the treatment of moderately to severely active ulcerative colitis and Crohn's disease in adult patients.

Louis E, et al. *J Crohns Colitis*. 2024;18(Suppl 1)i10-i12.

Guselkumab in UC: QUASAR

N = 701 patients in Induction Phase

Target Patient Population:
Adults with moderately to severely active UC, defined as baseline modified. Mayo score of 5 to 9 with a Mayo rectal bleeding subscore ≥1 and a Mayo endoscopy subscore ≥2 based on central review

Induction[1,2]

Randomization (1:1:1)

Induction Study 1
(Phase IIb dose-ranging study)
- GUS 400 mg IV Q4W
- GUS 200 mg IV Q4W
- Placebo

Randomization (3:2)

Induction Study 2
(Phase III confirmatory study)
- GUS 200 mg IV Q4W
- Placebo

GUS IV clinical responders

Study Week: 0* | 4* | 8* | 12† or 24

Endoscopy: 0* | 12† or 24

Maintenance

Randomization (1:1:1)

Phase III Maintenance Study
- GUS 200 mg SC Q4W
- GUS 100 mg SC Q8W
- Placebo (GUS withdrawal)

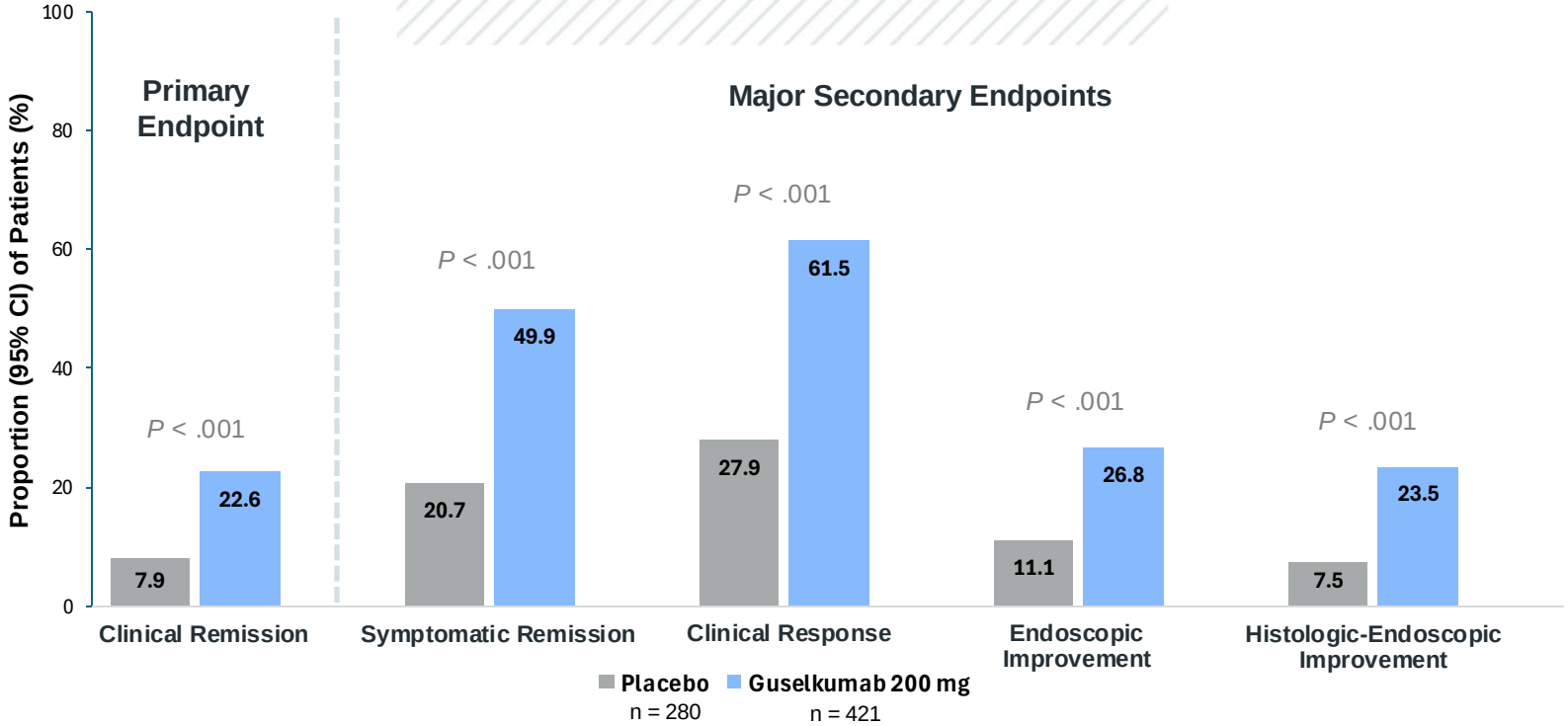
0 | 44

Endoscopy: 0 | 44

Corticosteroid Tapering

Q4W = every 4 weeks; Q8W = every 8 weeks.
*Study treatment administered; †Study treatment administered to Week 12 clinical non-responders.
GUS is indicated for adult patients with moderately to severely active ulcerative colitis.
1. Peyrin-Biroulet L, et al. *Gastroenterology*. 2023;165:1443-1457. 2. Allegretti JR, et al. *Gastroenterology*. 2023;164:S-1572.

Guselkumab in UC Induction: QUASAR Phase III Week 12 Endpoints



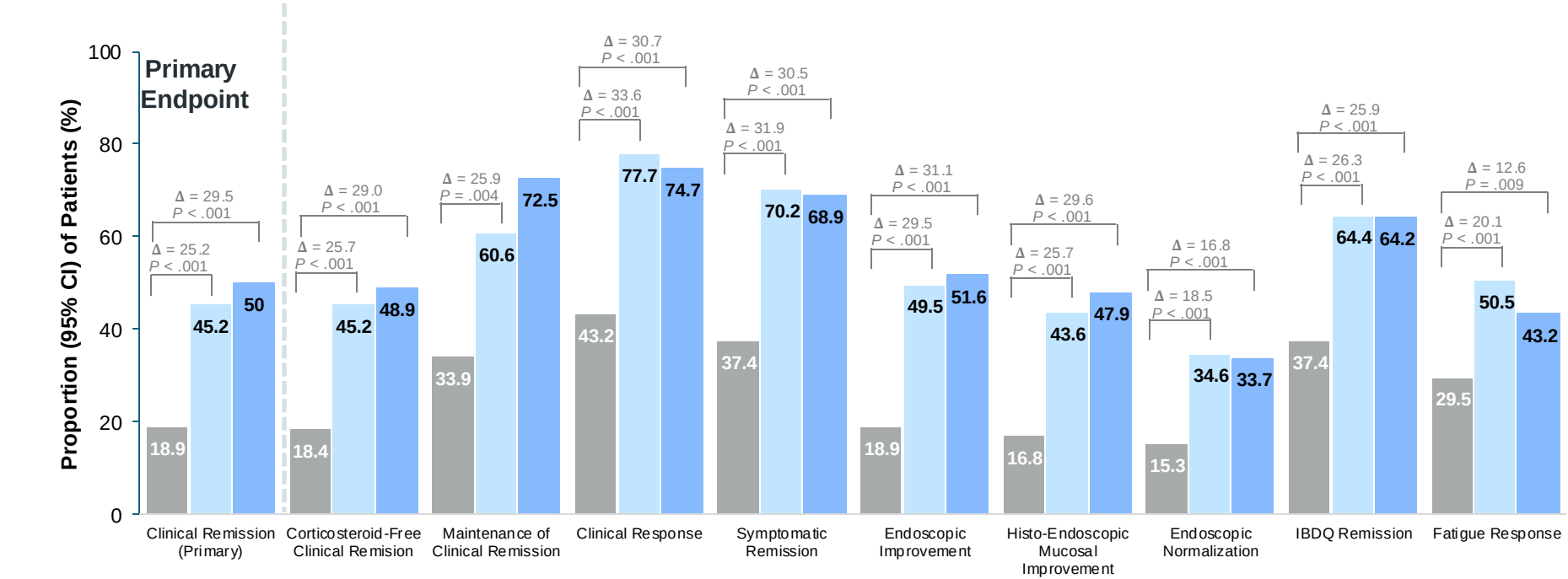
GUS is indicated for adult patients with moderately to severely active ulcerative colitis.

Clinical remission defined as a Mayo stool frequency subscore of 0 or 1 with no increase from baseline, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability.

Allegretti J. Abstract 913b presented at DDW 2023. *Gastroenterol Hepatol.* 2023;19:9-10.

CME OUTFITTERS

Guselkumab in UC Maintenance: QUASAR Phase III Week 44 Endpoints

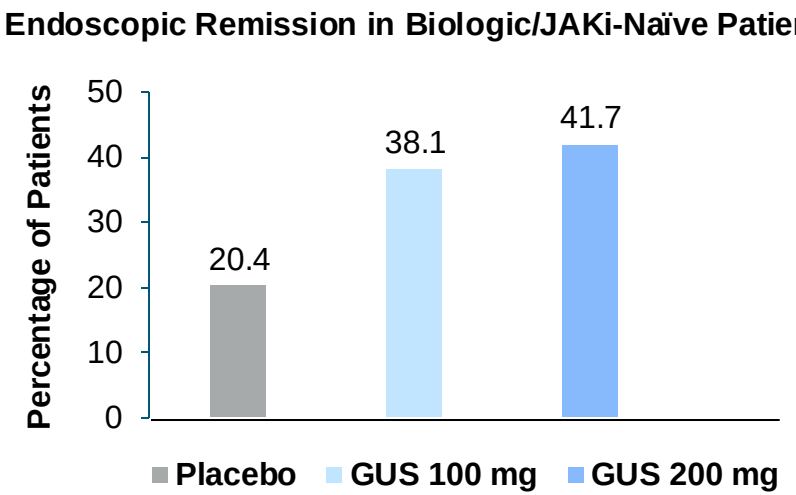


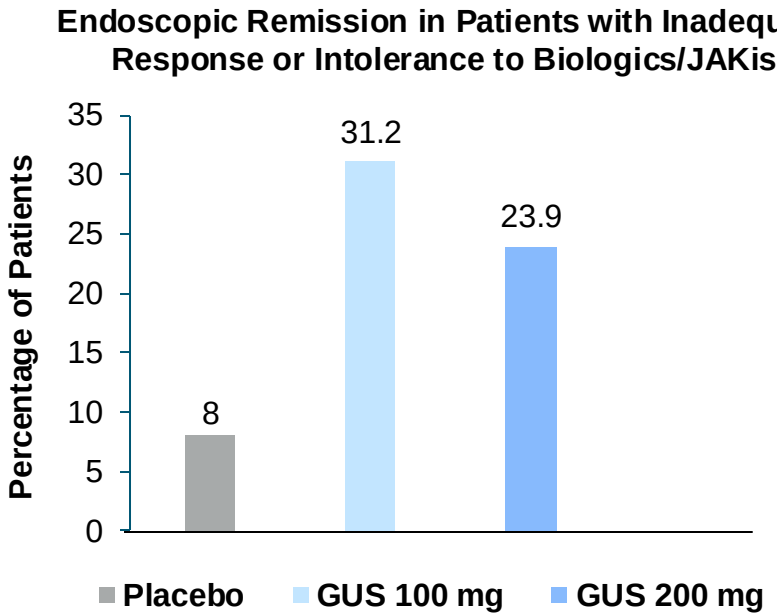
Primary analysis population: randomized patients with a modified Mayo score of 5-9 at induction who received at least one maintenance study treatment dose.

GUS is indicated for adult patients with moderately to severely active ulcerative colitis.

Rubin DT. Digestive Disease Week (DDW) 2024. Abstract 759. https://ddw.digitellinc.com/p/s/the-efficacy-and-safety-of-guselkumab-as-maintenance-therapy-in-patients-with-moderately-to-severely-active-ulcerative-colitis-results-from-the-phase-3-quasar-maintenance-study-5792.

GUS in Treatment-Naïve and Treatment-Experienced Patients with UC at Week 44: QUASAR





JAKi = JAK inhibitor.

Allegretti JR, et al. United European Gastroenterology Week (UEGW) 2024. Abstract OP082. https://www.nxtbook.com/ueg/UEG/ueg-journal-abstracts-2024/index.php#/p/74.

Mirikizumab Safety in UC

Outcome, n (%)	200 mg Mirikizumab Q4W SC (n = 289)
TEAEs	184 (63.7)
AEs of special interest:	
Infections (all)	87 (30.1)
Infections (serious)	3 (1.0)
Cerebrocardiovascular events	2 (0.7)
Malignancies	0 (0)
Immediate hypersensitivity reaction	4 (1.4)
Injection site reactions	16 (5.5)
Death	0 (0)
Discontinuation due to AE	8 (2.8)

AE = adverse event.

Sands BE, et al. *Inflamm Bowel Dis*. 2024 Mar 9:izae024. [Epub ahead of print.]

Rizankizumab Safety in UC

Treatment-Emergent AEs Among Safety Population Through Week 52[a]			
Events/100 Patient Years	**PBO (WD) SC n = 196; PY = 174.9**	**RZB 180 mg SC n = 193; PY = 185.4**	**RZB 360 mg SC n = 195; PY = 173.5**
Any AE	399 (228.1)	399 (215.2)	406 (234.0)
AE related to COVID-19	28 (16.0)	21 (11.3)	29 (16.7)
AE with reasonable possibility of being drug-related[b]	75 (42.9)	85 (45.9)	61 (35.2)
Severe AE	14 (8.0)	3 (1.6)	7 (4.0)
Serious AE	20 (11.4)	11 (5.9)	11 (6.3)
AE leading to discontinuation of study drug	4 (2.3)	5 (2.7)	5 (2.9)
All deaths	0	0	1 (0.6)[c]
Serious infections[d]	4 (2.3)	2 (1.1)	1 (0.6)
Infusion/Injection site reactions[e]	3 (1.7)	14 (7.6)	10 (5.8)

COVID-19 = coronavirus disease 2019; PBO = placebo; PY = patient-years; WD = withdrawal.

[a]The safety population included all patients who clinically responded to IV RZB at 12 or 24 weeks, were randomized to COMMANDat maintenance week 0 and received at least one dose of study drug during 52-week maintenance period; [b]As assessed by the investigator; [c]One death was reported in the RZB 360 mg arm in a patient diagnosed with colon adenocarcinoma, which was retrospectively found in the screening biopsy tissue; [d]Serious infections in RZB-treated patients included COVID-19, COVID-19 pneumonia, abscess limb, and pneumonia; [e]All infusion/injection site reaction events were nonserious and did not lead to study discontinuation.

Louis E, et al. *J Crohns Colitis.* 2024;18(S1):i10-i12.

Guselkumab Safety in UC

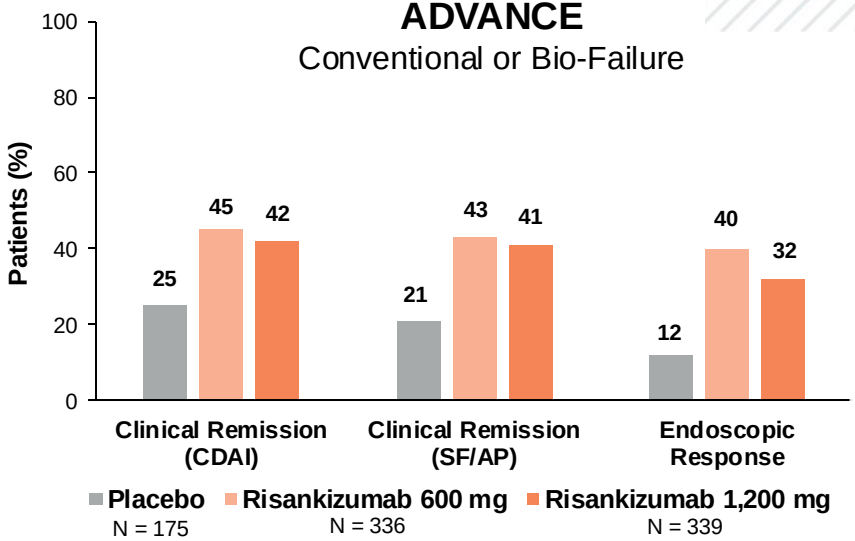
Outcome	Placebo (n = 105)	Guselkumab 200 mg IV (n = 101)	Guselkumab 400 mg IV (n = 107)	Combined (n = 208)
Any AE	59 (56.2)	45 (44.6)	53 (49.5)	98 (47.1)
AE within 1 hour of infusion	2 (1.9)	2 (2.0)	0	2 (1.0)
Serious AE	6 (5.7)	1 (1.0)	3 (2.8)	4 (1.9)
Death	0	0	0	0
Discontinuation for AE	3 (2.9)	1 (1.0)	0	1 (0.5)
Malignancy	0	0	0	0
Infection	13 (12.4)	14 (13.9)	10 (9.3)	24 (11.5)
Serious Infection	2 (1.9)	0	0	0

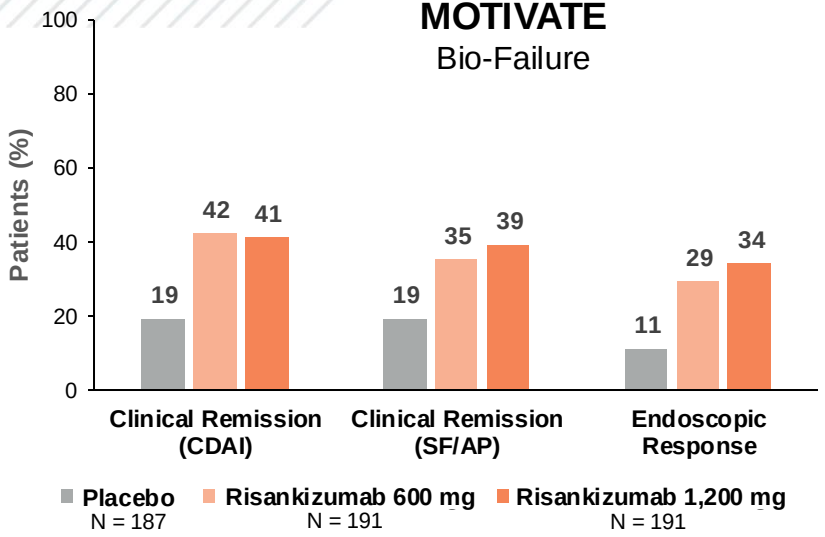
Peyrin-Biroulet L, et al. *Gastroenterology* 2023;165(6):1443-1457.

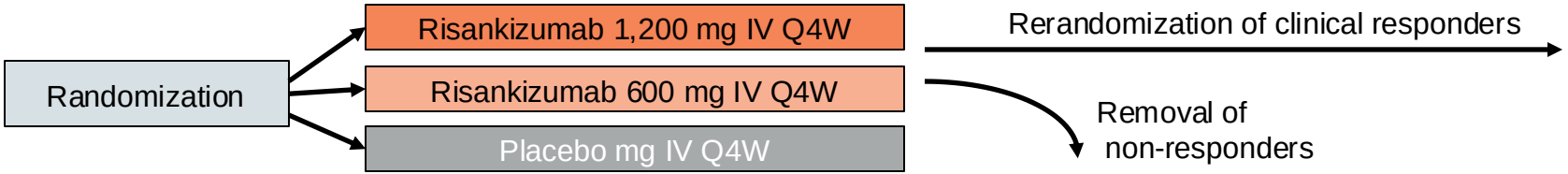
Overview of Data in CD

Corey Siegel, MD, MS

ADVANCE and MOTIVATE: Risankizumab Induction in CD





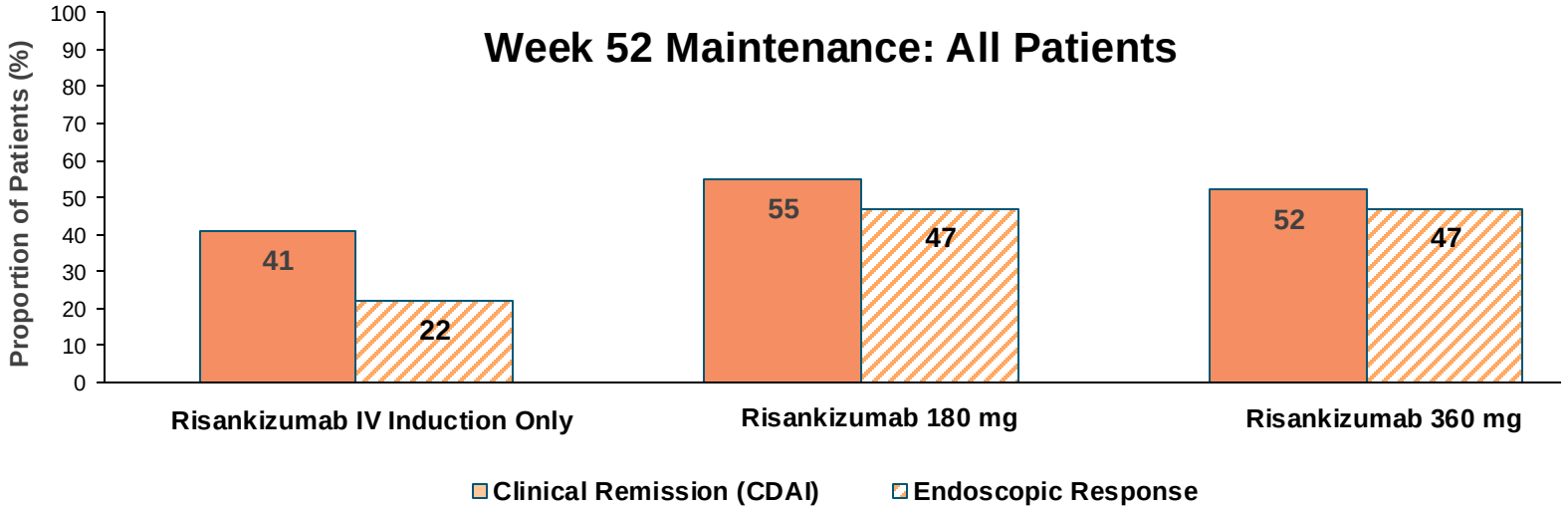


CDAI = Crohn's disease activity index; SF/AP = stool frequency/abdominal pain.

Clinical responders defined as ≥30% decrease in average daily stool frequency or APS and not worse than baseline; endoscopicresponse defined as >50% decline in SES-CD vs baseline by central reviewer (or in patients with SES-CD of 4 at baseline, ≥2-point decrease vs baseline); CDAI clinical remission a CDAI <150.

D'Haens G, et al. *Lancet*. 2022;399(10340):2015-2030. Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046.

FORTIFY: Risankizumab Maintenance in CD



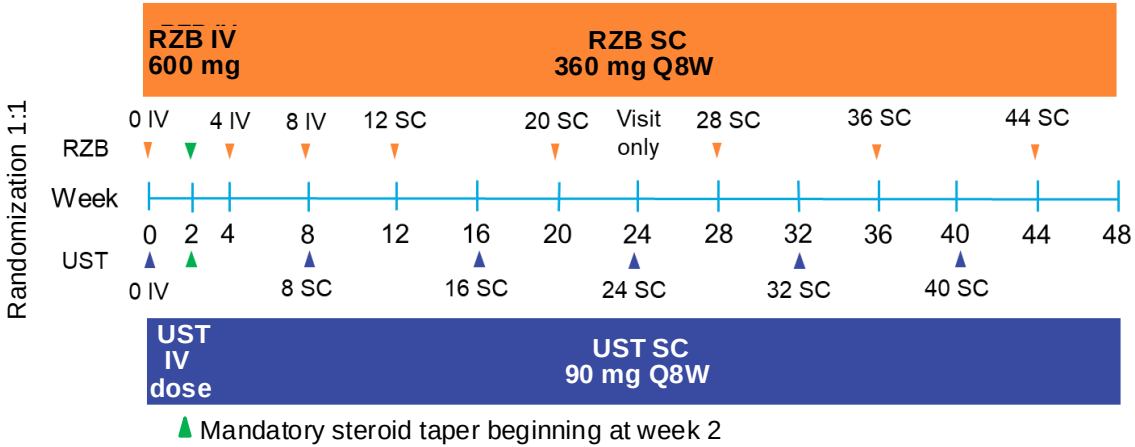
Endoscopic response defined as >50% decline in SES-CD vs baseline by central reviewer (or in patients with SES-CD of 4 at baseline, ≥2-point decrease vs baseline); CDAI clinical remission a CDAI <150.

Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046.

RZB vs UST in Patients with CD: Phase IIIb SEQUENCE Trial

Stratification Factors:

- Number of prior anti-TNF failure (1, > 1)
- Corticosteroid use at baseline (yes or no)]



Key Eligibility Criteria:

Moderate to severe CD: CDAI 220-450

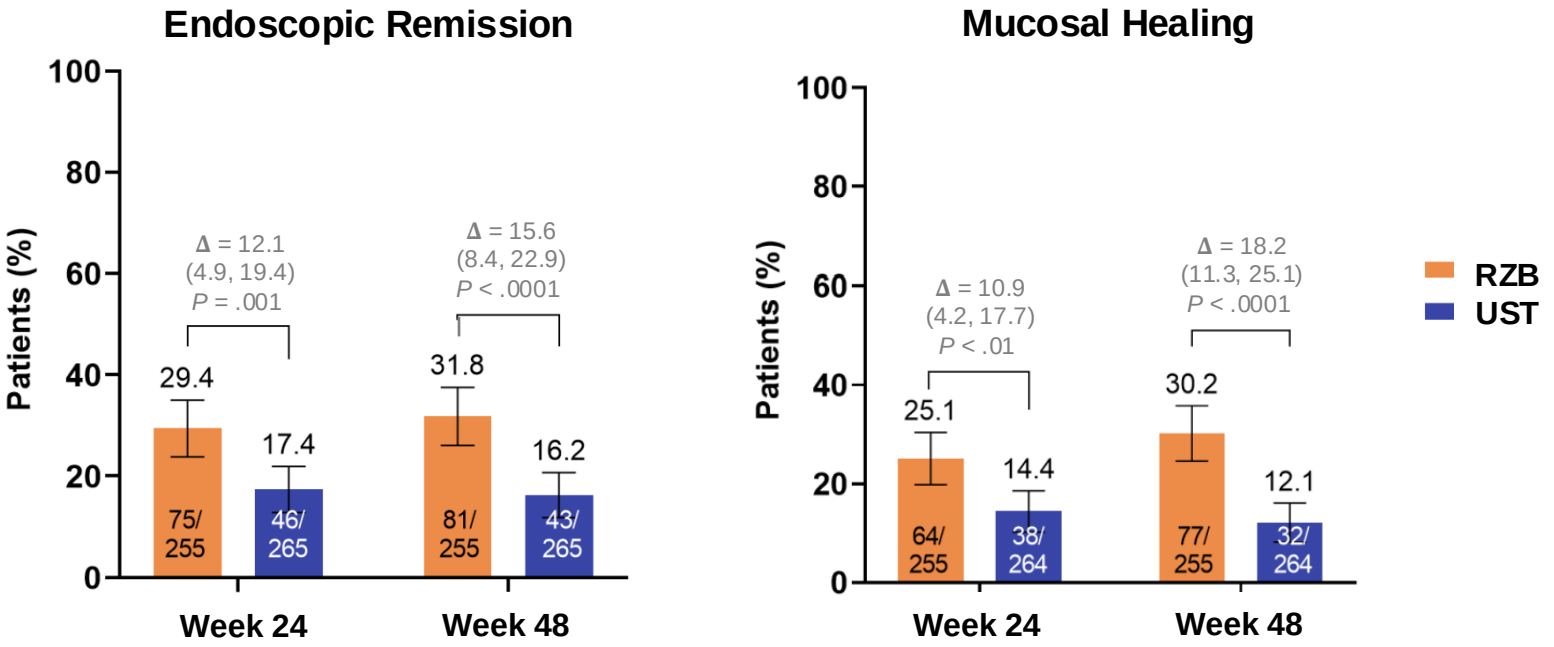
- Average daily SF ≥4 and/or average daily APS ≥2
- SES-CD, excluding the narrowing component, ≥6 (≥4 for isolated ileal disease), as scored by the site Investigator and confirmed by a central reader

Prior failure of ≥1 anti-TNF therapies

- Prior biologic therapy that could potentially influence the therapeutic impact on CD was exclusionary, including vedolizumab

Peyrin-Biroulet L, et al. *N Engl J Med*. 2024;391:213-223.

RZB vs UST in Patients with CD: Phase IIIb SEQUENCE Trial

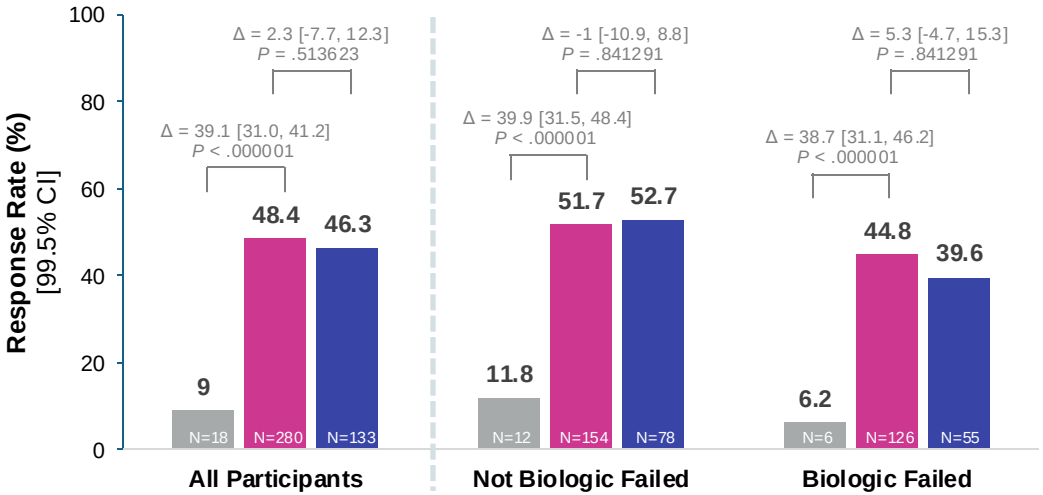


RZB = risankizumab; UST = ustekinumab.

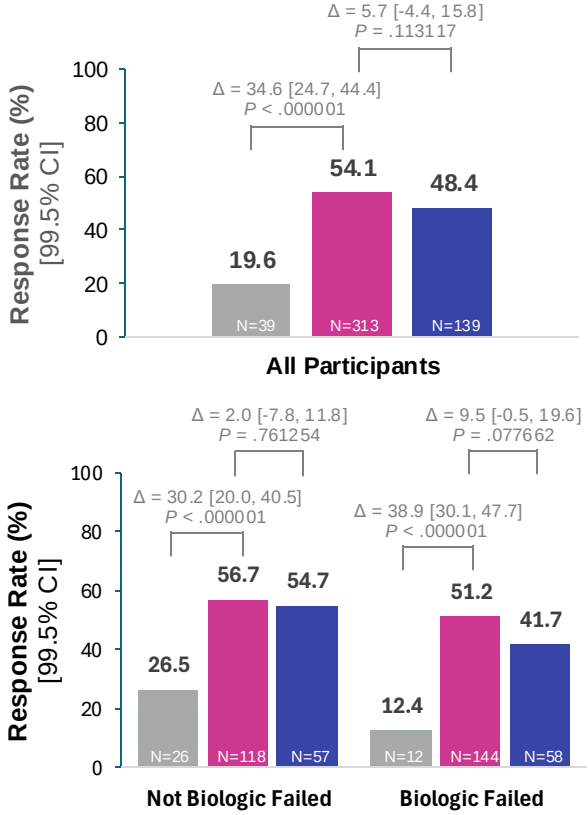
Peyrin-Biroulet L, et al. *N Engl J Med*. 2024;391:213-223.

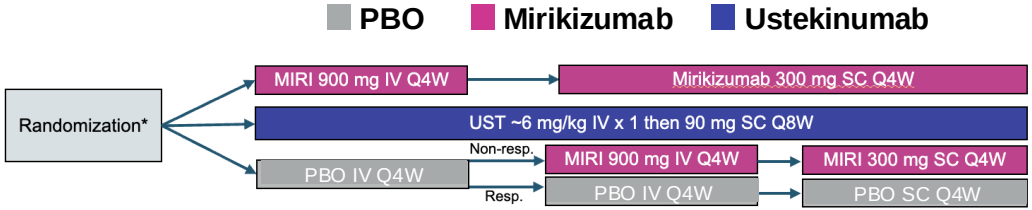
VIVID-1: MIRI* vs UST in Moderate-to-Severe CD

Endoscopic Response (NRI) at Week 52



Clinical Remission by CDAI (NRI) at Week 52

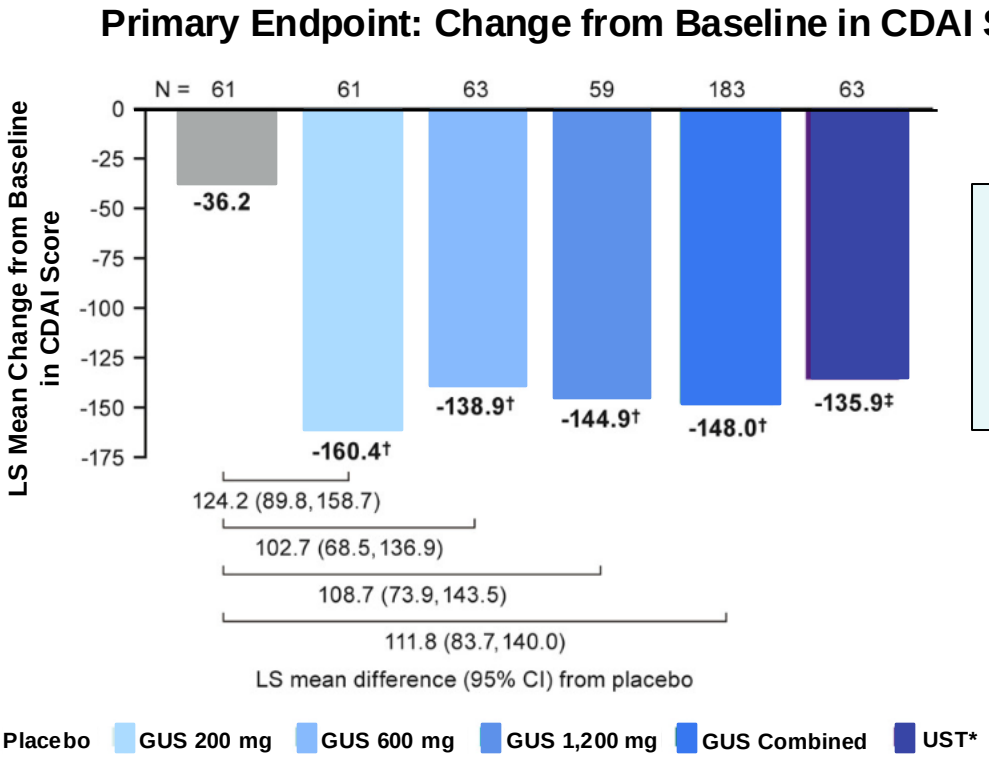




MIRI = mirikizumab; NRI = non-responder imputation.
*Mirikizumab is not currently FDA approved for the treatment of CD.
Jairath V, et al. *J Crohns Colitis.* 2024;18:i62-i64.

CME OUTFITTERS

GUS* vs UST in CD at 12 Weeks: GALAXI-1

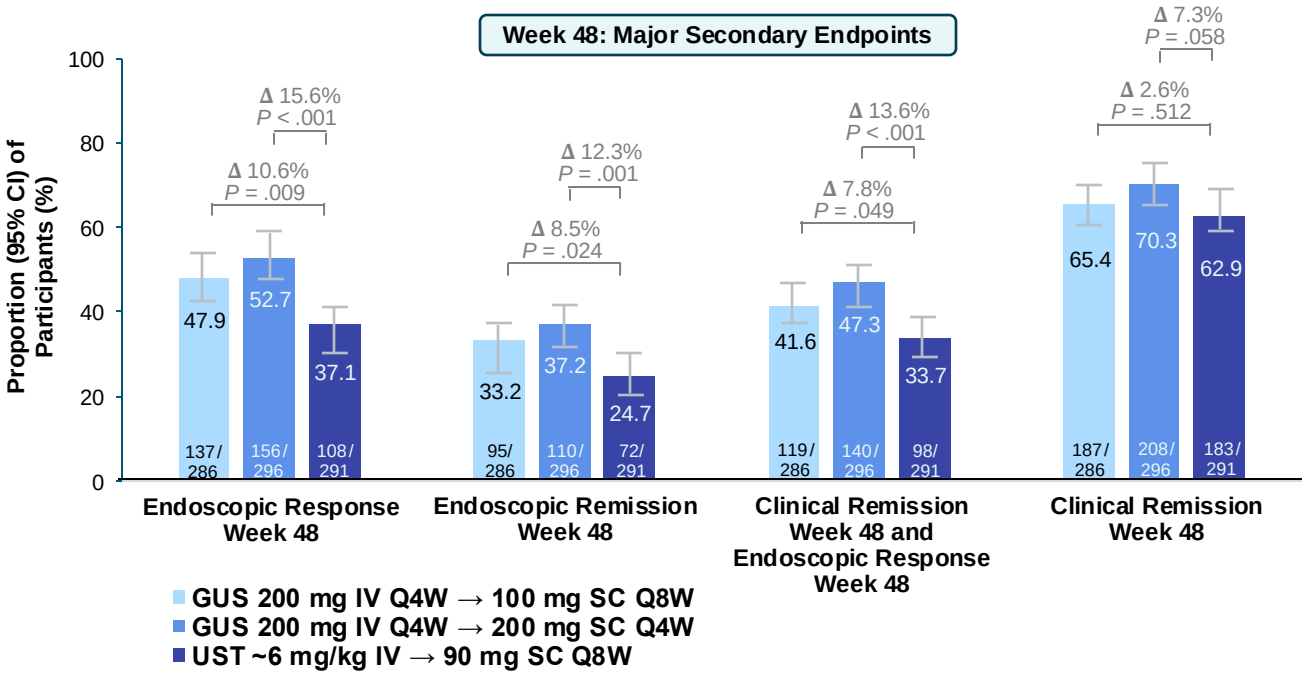


- GALAXI-1 is a DBPC trial
- Randomized patients 1:1:1:1 to
  - IV GUS at weeks 0, 4, 8;
  - IV UST at week 8; or
  - placebo
- UST was a reference arm
- N = 309

CDAI = Crohn's Disease Activity Index; DBPC = double-blind placebo controlled; LS = least squares.
*UST 6 mg/kg IV → 90 mg SC; †*P* value < .05 for GUS vs placebo; ‡Nominal *P* value < .05 from post hoc analysis of UST vs placebo.
Guselkumab is not currently FDA approved for CD.
Sandborn W, et al. *Gastroenterology*. 2002;162:1650-1664.e8.

GUS* vs UST in CD at 48 Weeks: GALAXI 2 and 3

GALAXI 2 and 3 are identical 48-week, randomized, double-blind, double-dummy, placebo, and active-comparator (UST) treat-through trials assessing the efficacy and safety of guselkumab in patients with moderately to severely active CD



Clinical Response: ≥100-point reduction from baseline in CDAI or CDAI <150

Endoscopic Response: ≥50% improvement from baseline in SES-CD or SES-CD ≤2

Clinical Remission: CDAI <150

Endoscopic Remission: SES-CD ≤4 and a ≥2-point reduction from baseline and no subscore greater than 1 in any individual component

GUS = guselkumab; UST = ustekinumab. *Guselkumab is not currently FDA approved for CD.

Panaccione R, et al. Digestive Disease Week (DDW) 2024. Abstract 1057b. https://acrabstracts.org/abstract/efficacy-and-safety-of-guselkumab-therapy-in-patients-with-moderately-to-severely-active-crohns-disease-results-of-the-galaxi-2-3-phase-3-studies/.

Final Points About IL-23s

IL-23is and Improvements in Fatigue, Bowel Urgency, and Abdominal Pain

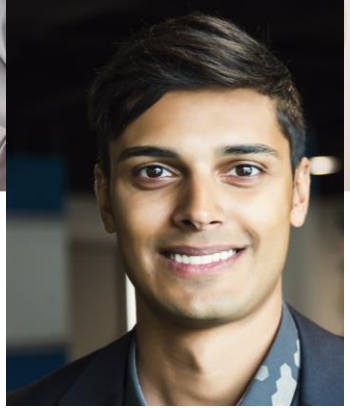
Disease Subtype	Study	Symptom	Conclusions
UC	QUASAR[1]	Fatigue (PROMIS-Fatigue-SF7a) Bowel Urgency and Abd Pain (IBD Questionnaire)	GUS induction group showed greater improvement in patient-reported symptoms of fatigue at week 12 vs PBO GUS induction group showed improvements in abdominal pain and bowel urgency and symptoms of urgency at week 12
UC	LUCENT-1 and LUCENT-2[2,3]	Fatigue (NRS) and Bowel Urgency (UNRS)	MIRI induction group showed improvement in fatigue that was sustained in maintenance therapy (week 40) MIRI patients achieved sustained bowel urgency improvement vs PBO at week 12 and week 52
CD	MOTIVATE, ADVANCE and FORTIFY [4,5]	Fatigue (FACIT-F), stool frequency and abdominal pain scores	RZB induction group showed improvements in fatigue that were sustained in maintenance therapy (week 52) Stool frequency and abdominal pain score clinical remission was reached in 73 (52%) of patients on RZB vs 65 (40%) of patients on PBO

GUS = guselkumab; IL-23is = IL-23 inhibitors; MIRI = mirikizumab; RZB = risankizumab.

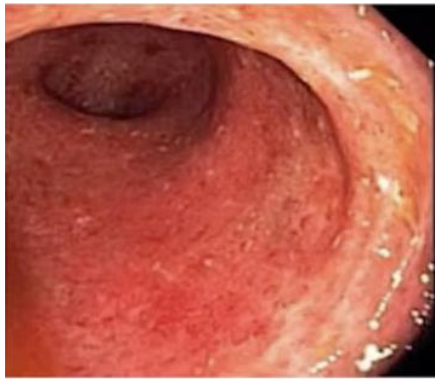
1. Dignass A, et al. *J Crohns Colitis*. 2024;18(Suppl 1):i166-i167. 2. Rubin D, et al. *J Crohns Colitis*. 2024;18(Suppl 1):i1825-i1826. 3. Tinoco da Silva Torres J, et al. *J Crohns Colitis*. 2024;18(Suppl 1):i214-i215. 4. Peyrin-Biroulet L, et al. *Aliment Pharmacol Ther*. 2023;57:496-508. 5. Ferrante M, et al. *Lancet*. 2022;399:2031-2046.

Patient Cases

Patient Case: Gavin M.



- 28-year-old man
- Diagnosed 8 months ago with left-sided UC
- Patient is reluctant to discuss symptoms
- Weight: 65 kg, height: 180 cm (71 in)
- Current symptoms:
  - 6-month history of abdominal cramping and "multiple" loose stools/day; rectal bleeding reported
- Diagnosis:
  - Moderately active (Mayo 2) UC, confirmed on colonoscopy
- Medications:
  - Prednisone taper and 5-ASA; had improvement but unable to wean without his symptoms returning
- No history of treatment with biologic agents



Audience Response

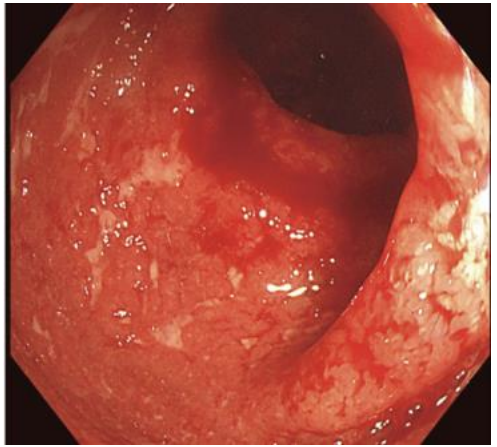
What would you do next?

A. Increase dose of prednisone and re-evaluate in 8 weeks
B. Start vedolizumab
C. Start S1P receptor modulator
D. Start anti-TNF
E. Start IL-23 inhibitor
F. I’m not sure

CME OUTFITTERS

Patient Case: Sheila H.

- 32-year-old woman with 4-month history of UC
- Currently being treated with adalimumab every 2 weeks
- Having symptom recurrence after 9 months of therapy
- Current symptoms:
  - 6-8 stools per day, urgency and rectal bleeding
- Colonoscopy:
  - Active disease up to 60 cm, Mayo 3
- Labs:
  - Calprotectin 1,250 µg/mg
- CRP 3.7
- C-diff and infectious workup negative



Audience Response

What would you do next?

A. Change adalimumab dosing to weekly
B. Switch to infliximab
C. Switch to vedolizumab
D. Switch to ustekinumab
E. Switch to IL-23 inhibitor
F. Switch to S1P modulator
G. Switch to JAK inhibitor
H. I’m not sure

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Consider the underlying mechanisms behind the inflammatory pathways implicated in IBD, such as those impacting IL-23 and Th17 pathways, when considering treatment options
- Differentiate between IL-23–targeted therapies and their unique characteristics to individualize and optimize patient treatment
- Integrate the latest evidence into your positioning of IL-23 therapies in IBD management

Additional Resources

To learn more, click on the *Materials* and *Resources* tabs to access additional resources, including an interactive 3D digital animation.

QUESTIONS & ANSWERS

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In-Person

Livestream