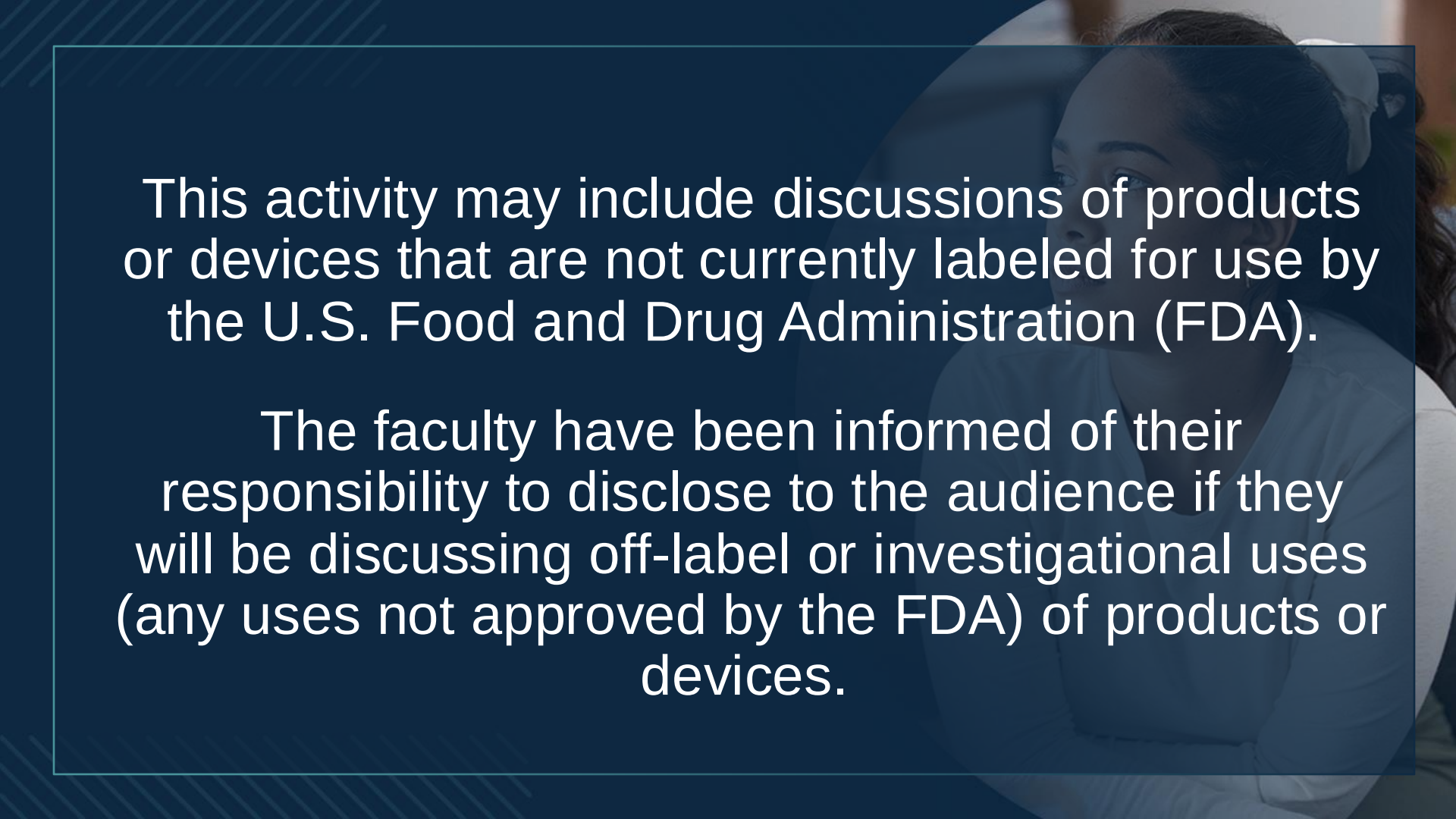
CME OUTFITTERS

IBD, IL-23, and Inflammation, Oh My!

Following the Yellow Brick Road in Using IL-23 Targeted Therapies in Managing IBD

This activity is supported by an educational grant from Janssen Biotech Inc., administered by Janssen Scientific Affairs LLC.



This activity may include discussions of products or devices that are not currently labeled for use by the U.S. Food and Drug Administration (FDA).

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices.

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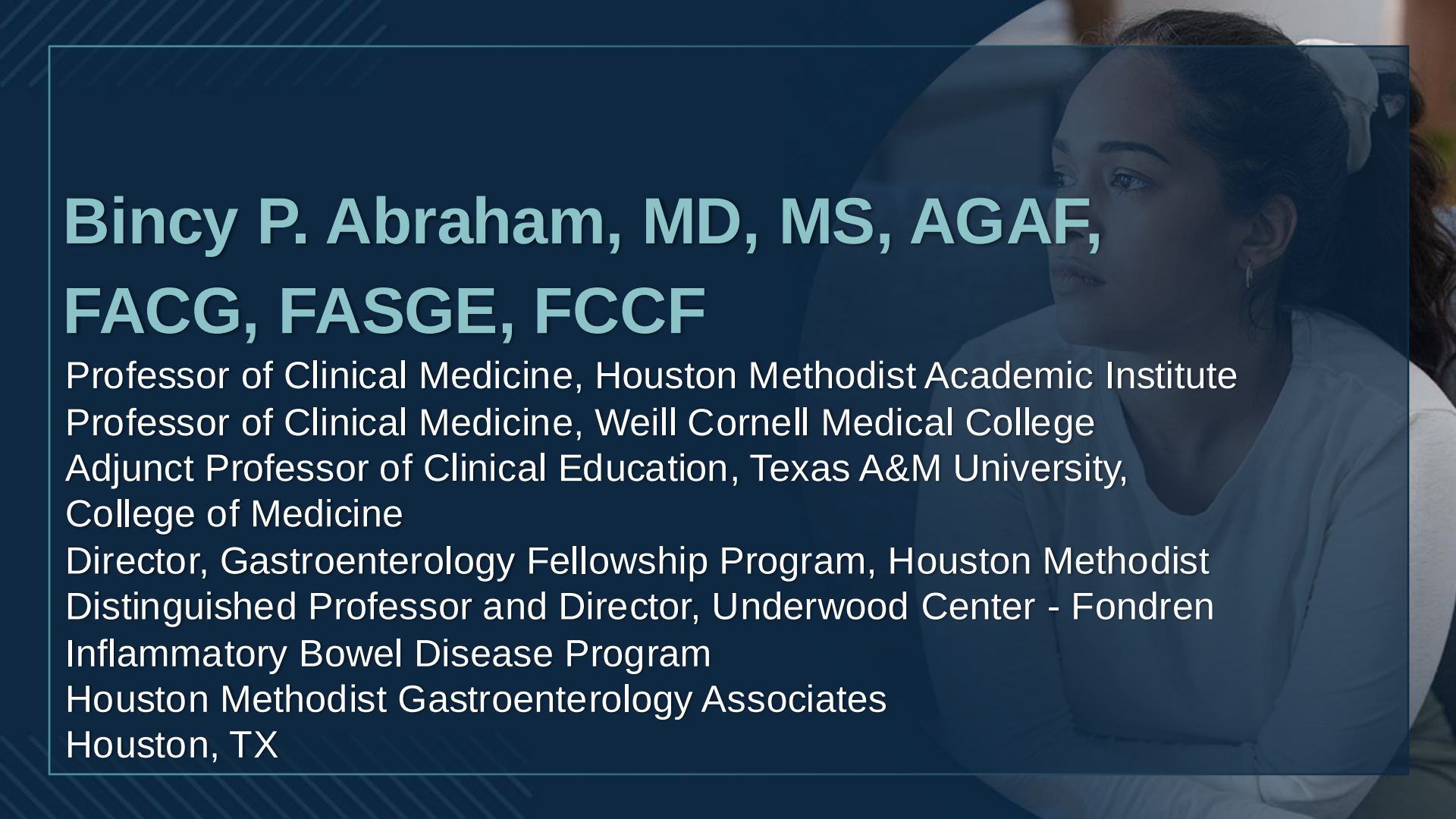

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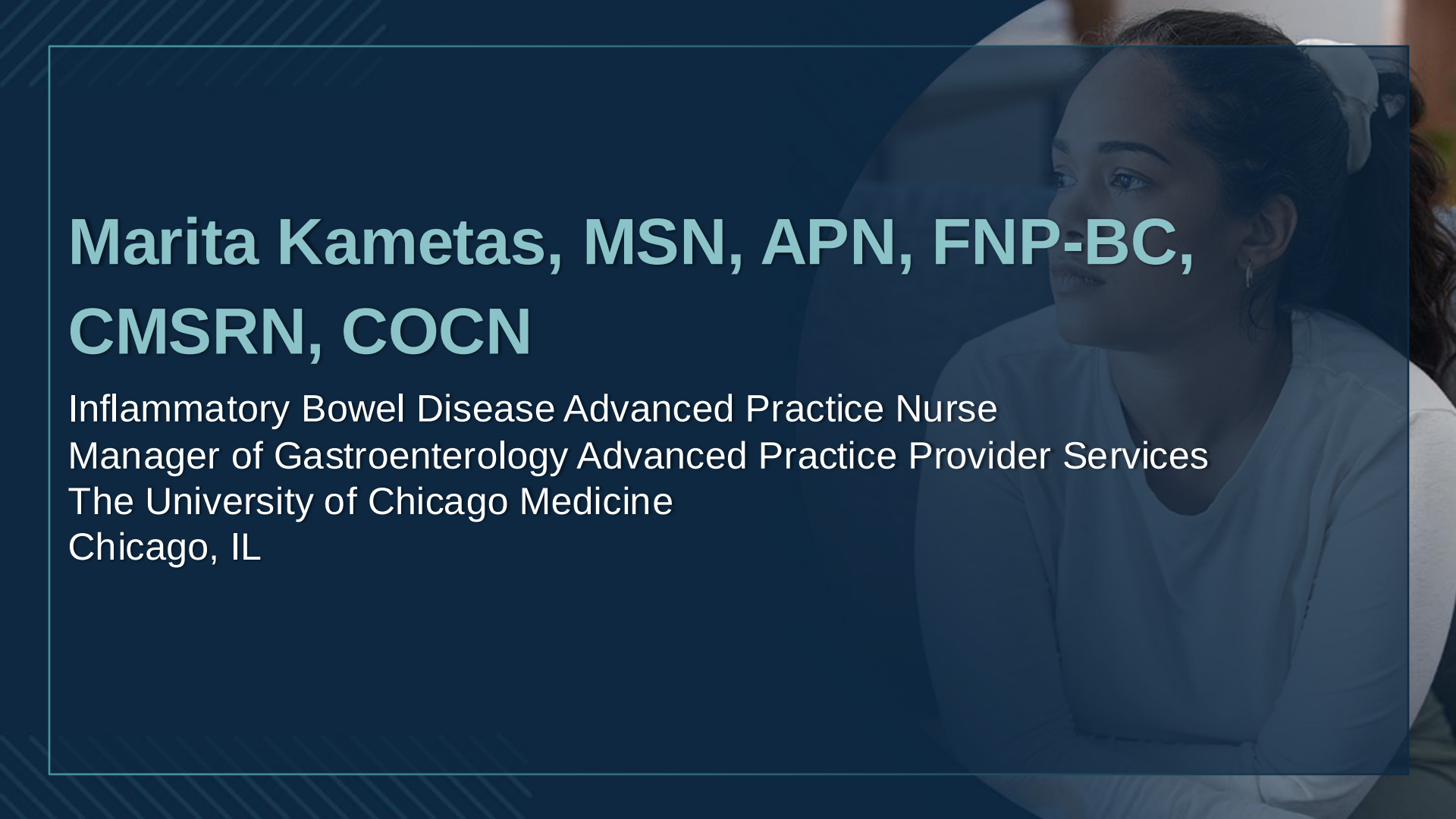

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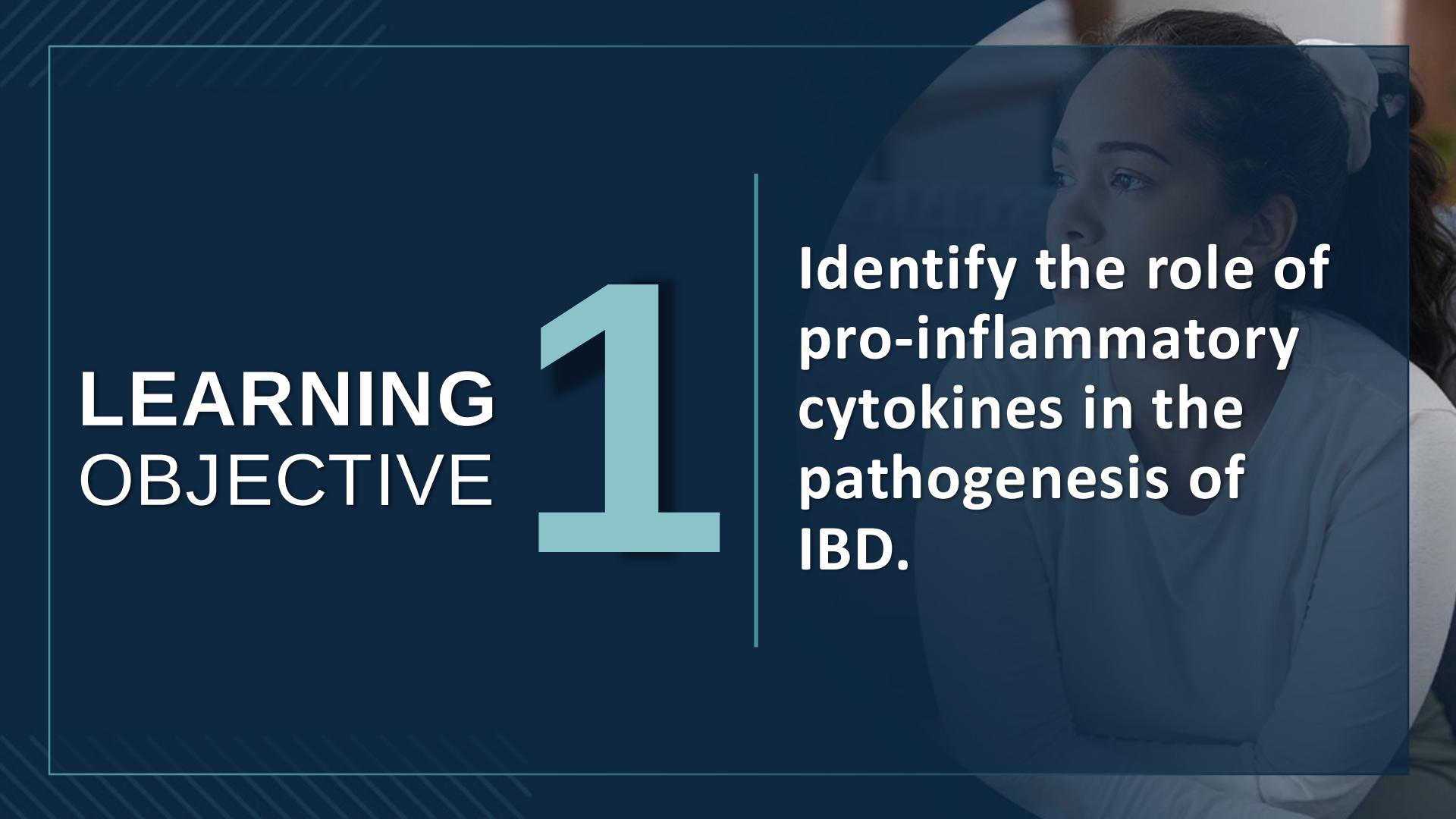
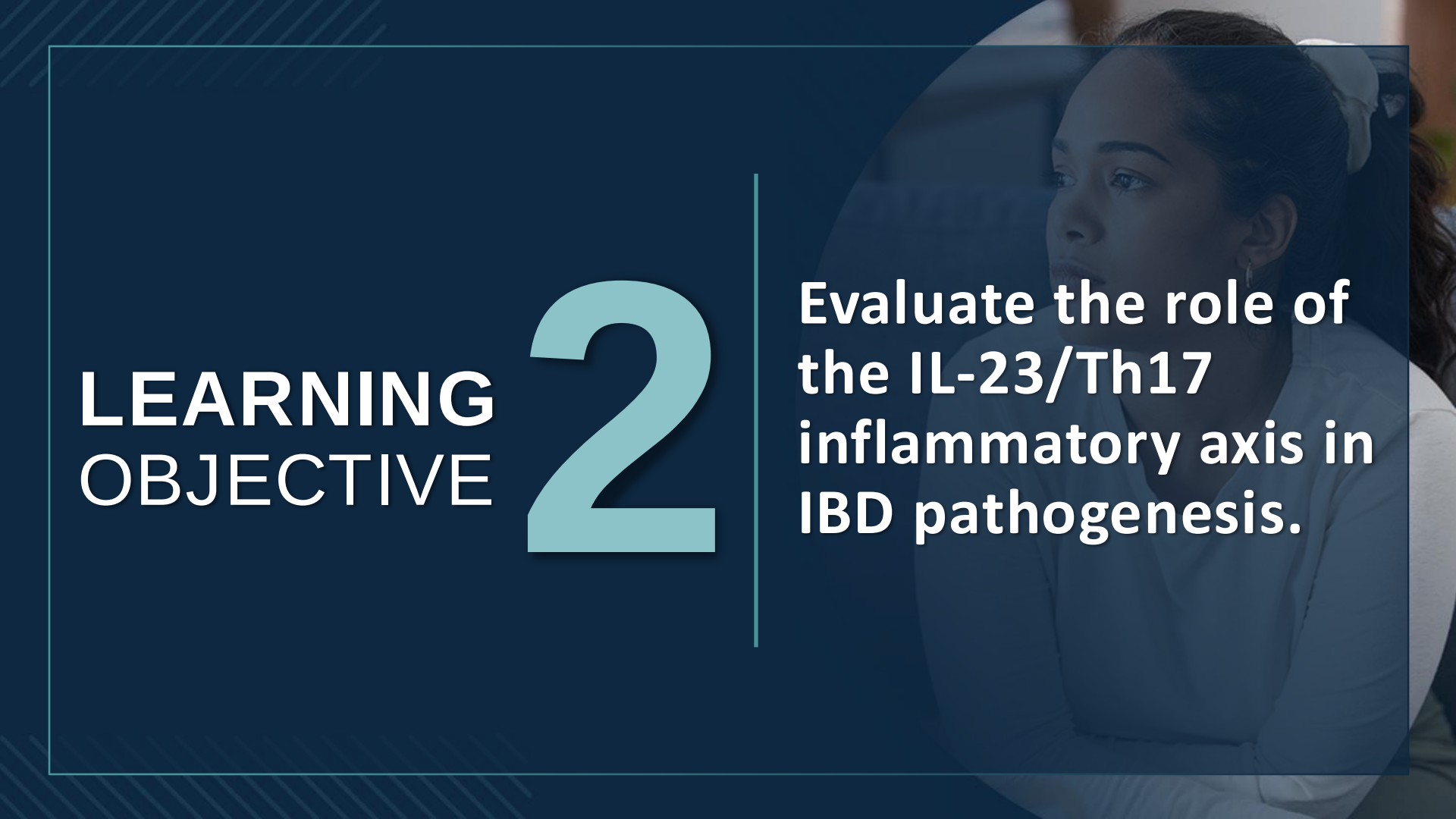


LEARNING OBJECTIVE 1

Identify the role of pro-inflammatory cytokines in the pathogenesis of IBD.

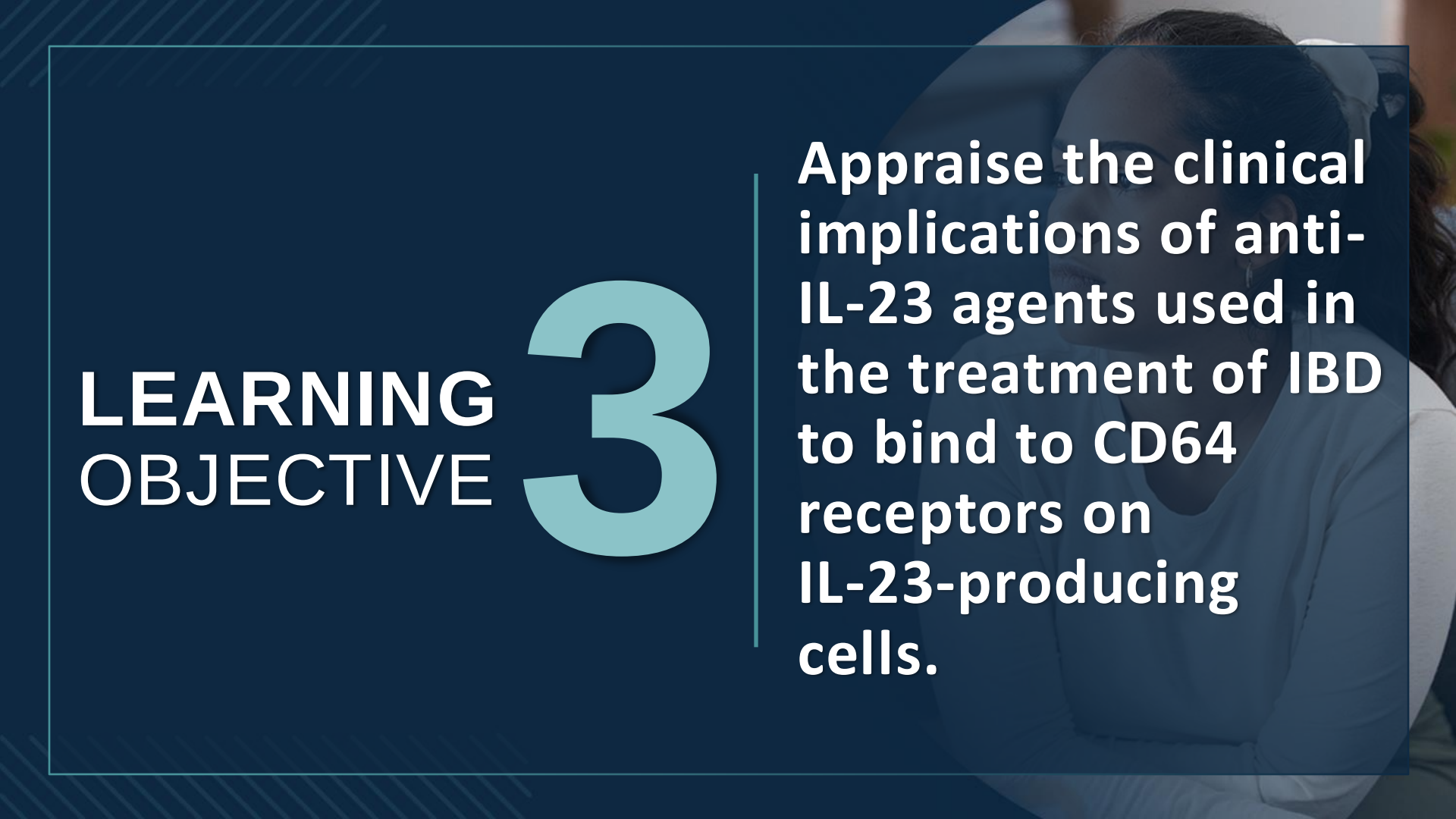
LEARNING OBJECTIVE 2

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



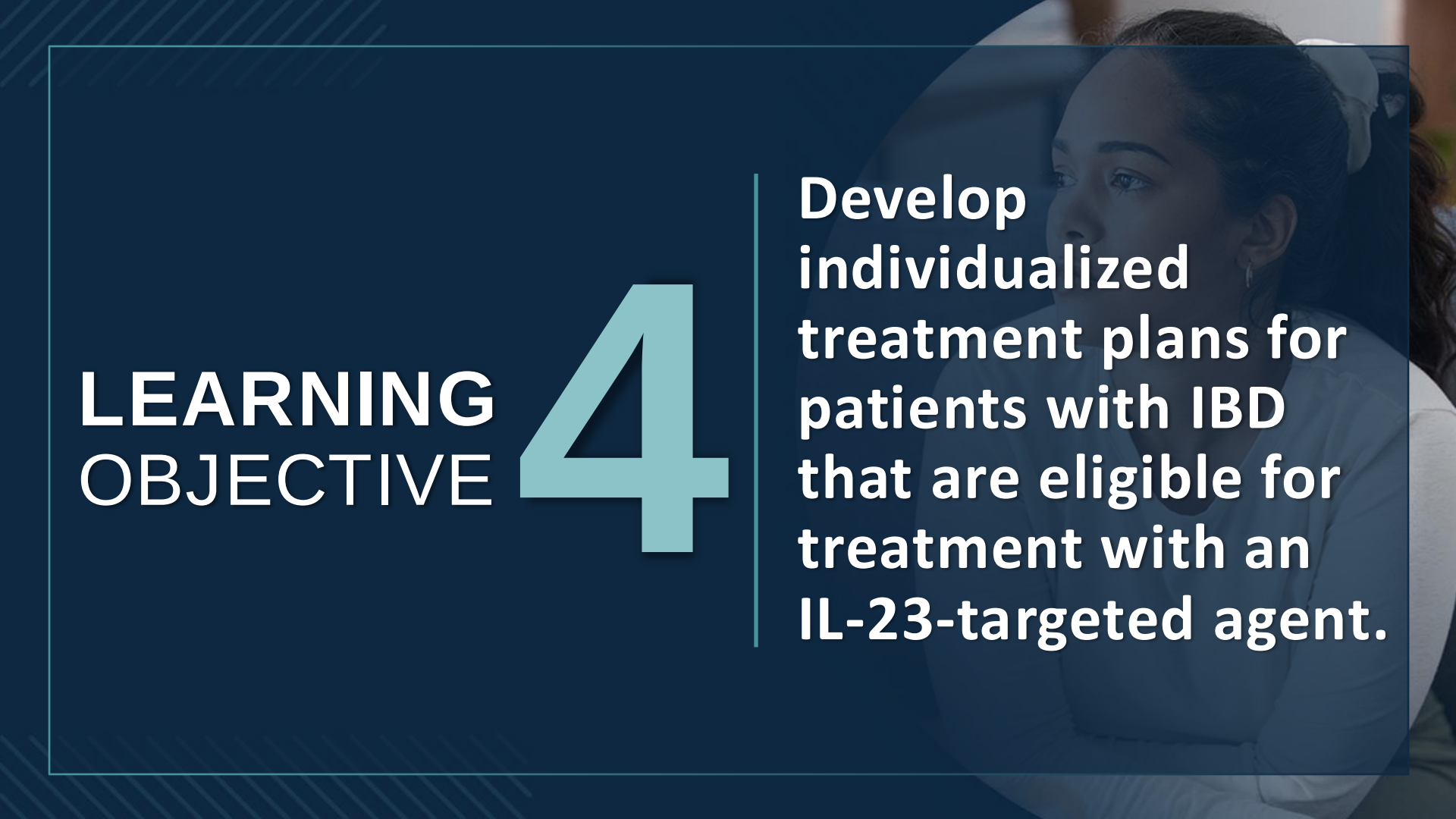
LEARNING OBJECTIVE 3

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



LEARNING OBJECTIVE 4

Develop individualized treatment plans for patients with IBD that are eligible for treatment with an IL-23-targeted agent.

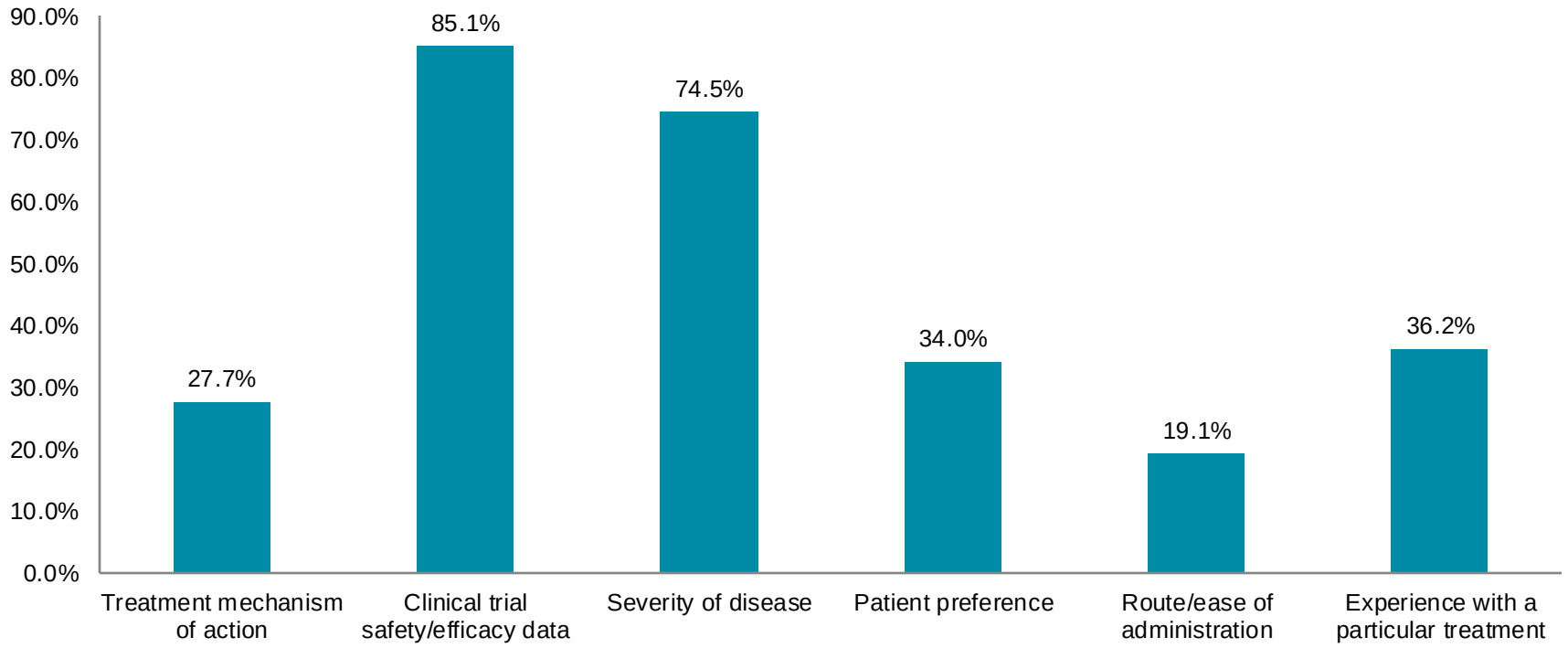


Audience Response - Icebreaker

What factors most heavily influence your selection of therapy for IBD? Pick your top 3.

A. Treatment mechanism of action
B. Clinical trial safety/efficacy data
C. Severity of disease
D. Patient preference
E. Route/ease of administration
F. Experience with a particular treatment

What factors most heavily influence your selection of therapy for IBD? Pick your top 3.



Results recorded on Feb 6, 2025.

CME OUTFITTERS

Illuminating Pathways: IL-23/Th17 Axis and Optimizing IL-23 Inhibition

Uma Mahadevan, MD

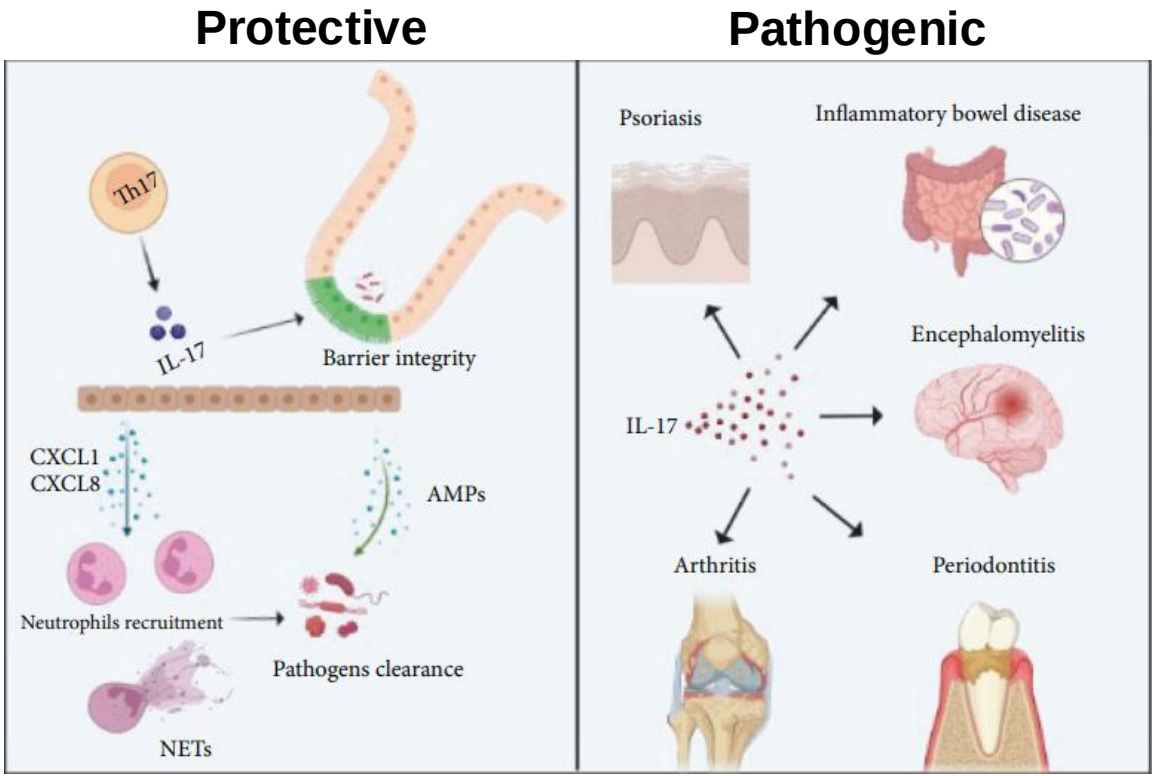
Why Target IL-23 in IBD?

- Inhibition of IL-23
  - Decreases mucosal inflammation
  - Improves epithelial barrier integrity
  - Suppresses gut inflammation in T-cell mediated colitis
- Anti-IL-23 therapy preserves protective IL-17 gut functions
  - Animal models of IL-17 blockade - mixed results
  - Trials of anti-IL-17A/IL-17A receptor antagonists in IBD resulted in worse outcomes vs placebo

IBD = inflammatory bowel disease.

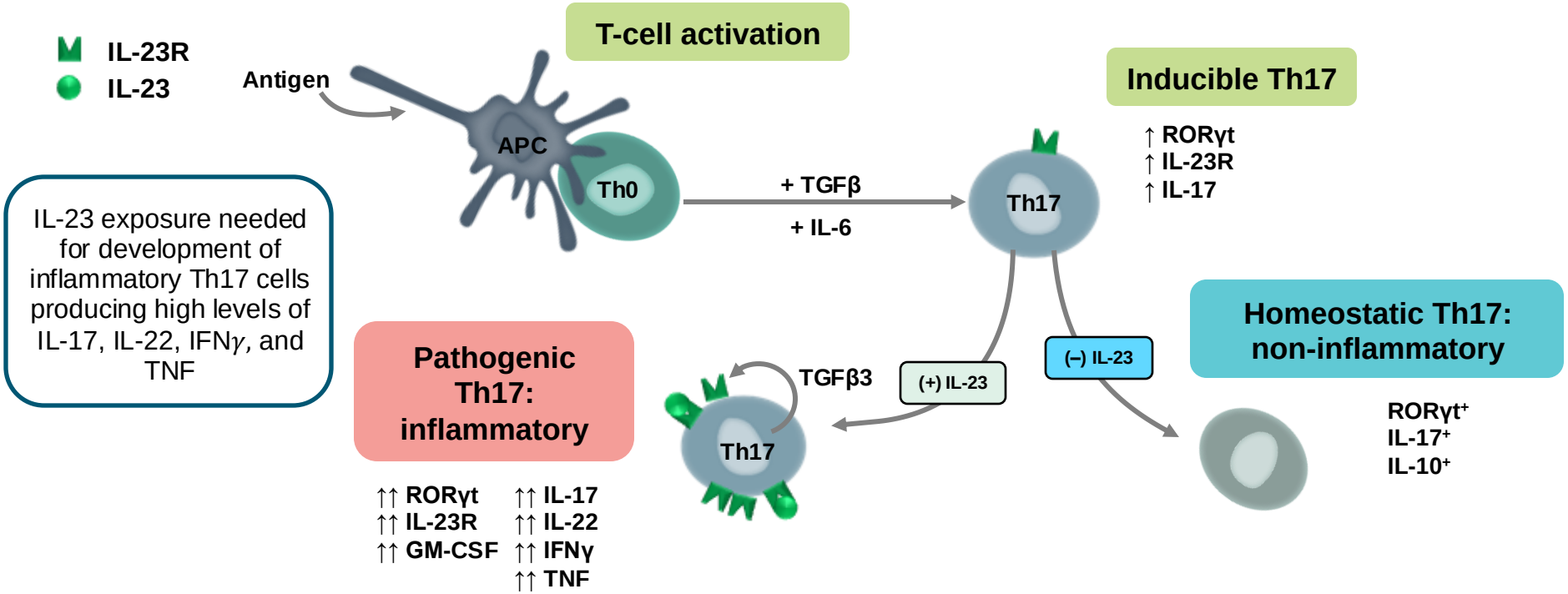
Hohenberger M, et al. *J Dermatolog Treat.* 2018;29(1):13-18. Vuyuru SK, et al. *Drugs*. 2023;83(10):873-891. Wallace KL, et al. *World J. Gastroenterol.* 2014;20(1):6-21.

Role of IL-17: Pathogenic and Protective Immunity



AMPs = antimicrobial peptides; NETs = neutrophil extracellular traps; Th = T helper cell.
Sun L, et al. *J Immunol Res.* 2023;1:3360310.

IL-23 Drives Development of Inflammatory Pathogenic Th17 Cells

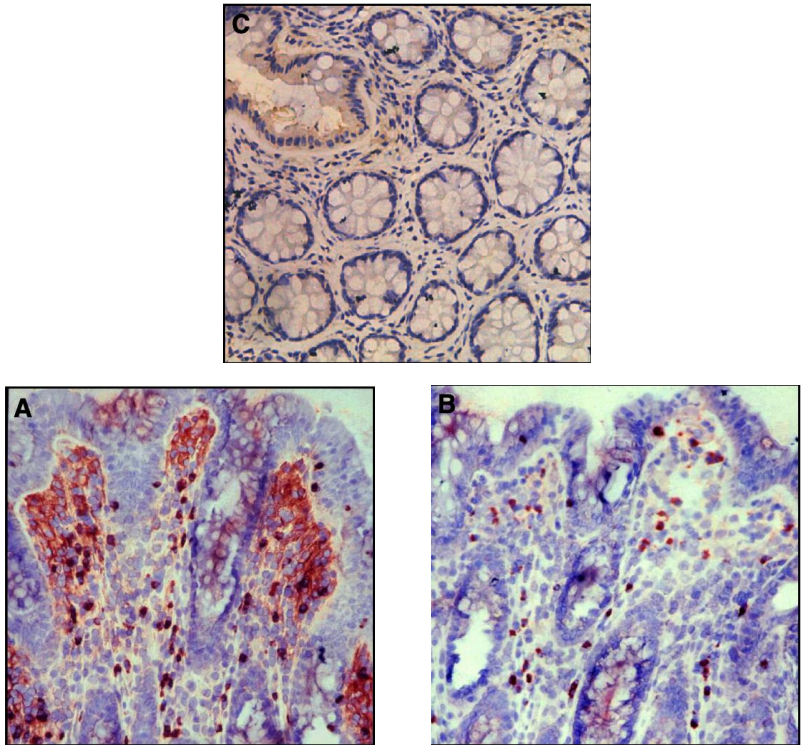


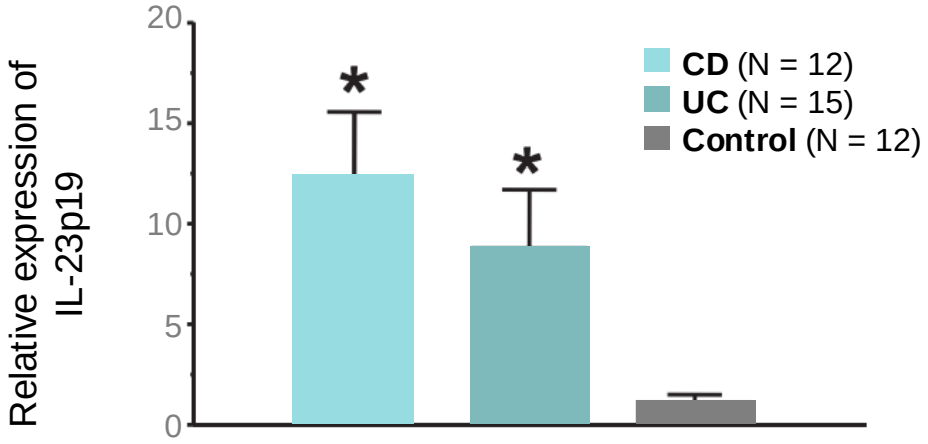
APC = antigen-presenting cell; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; RORγt = retinoic acid receptor-related orphan receptor gamma t; TGF = transforming growth factor; TNF = tumor necrosis factor.

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.

Animation

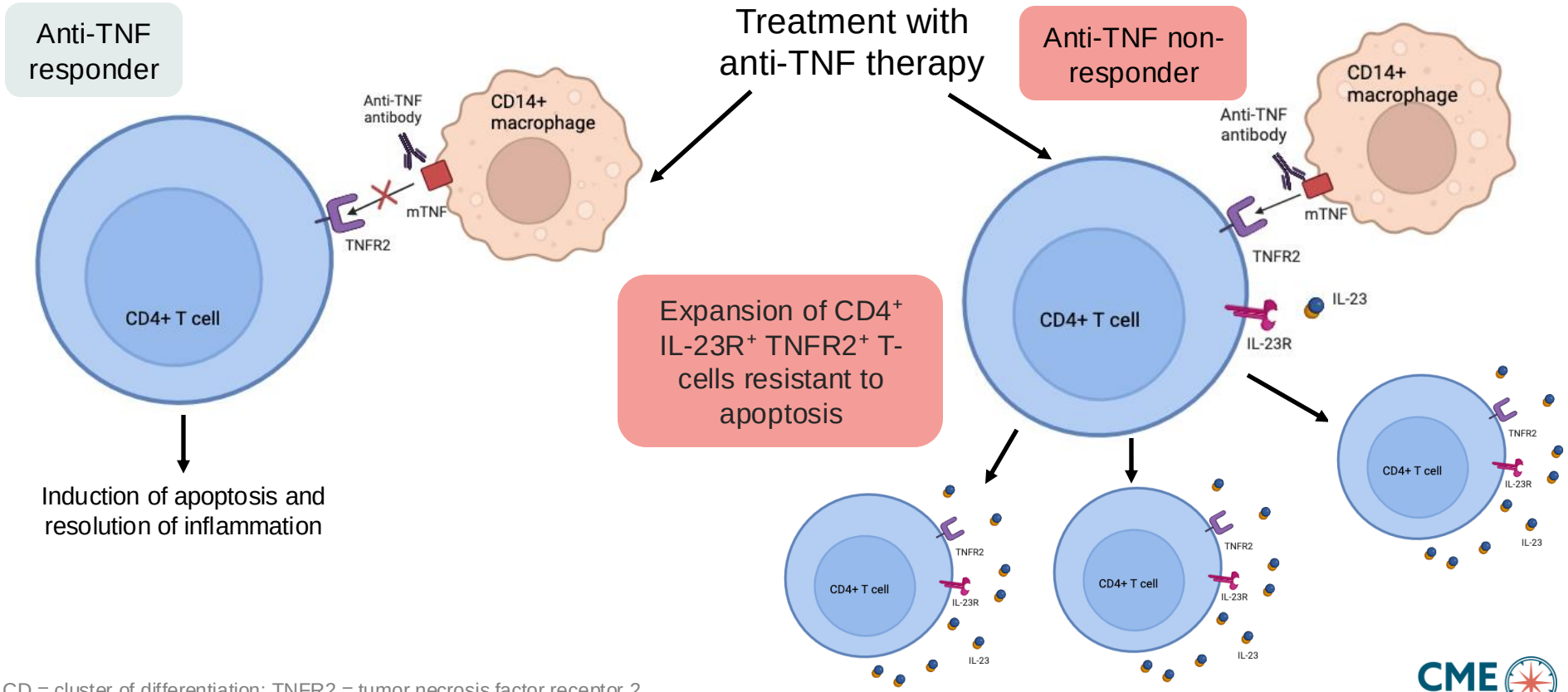
IL-23 Expression in Patients with IBD





CD = Crohn's disease; UC = ulcerative colitis. *P= 0.05 versus control.
Liu Z, et al. *J Leukoc Biol*. 2011;89(4):597-606.

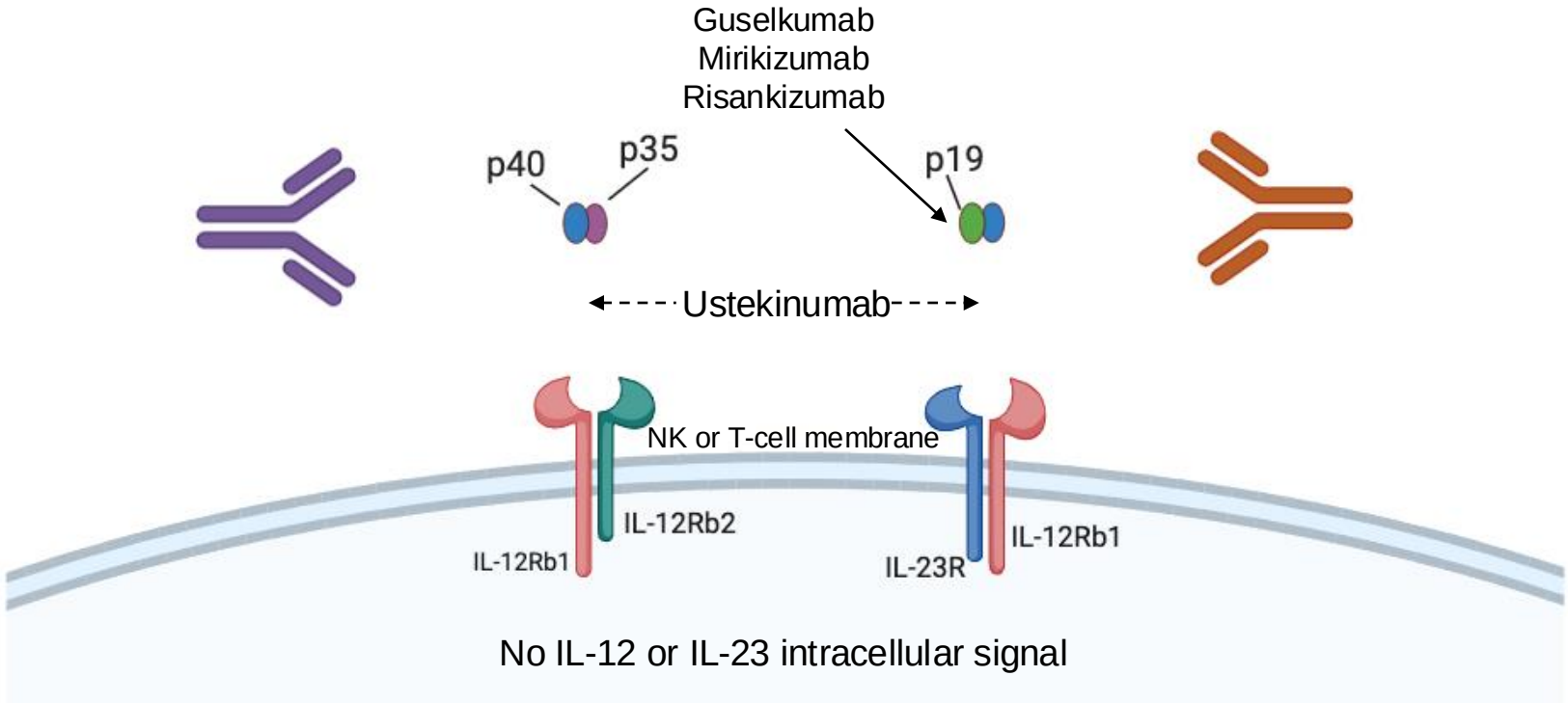
IL-23 Mediated Resistance to Anti-TNF



CD = cluster of differentiation; TNFR2 = tumor necrosis factor receptor 2.

Adapted from Schmitt H, et al. *Semin Immunopathol*. 2019;41(6):737-746. Schmitt H, et al. *Gut*. 2019;68(5):814-828.

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

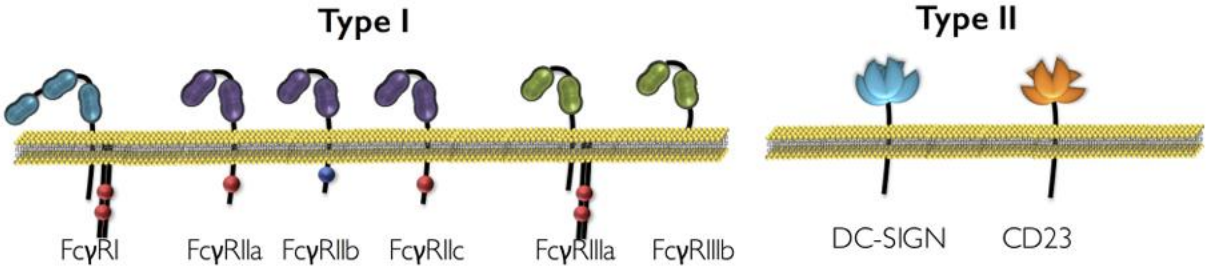


NK = natural killer cell.

Adapted from Gately MK, et al. *Annu Rev Immunol*. 1998;16(1):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.

Importance of Fcγ Receptors and CD64 Receptors

- Fcγ receptors: surface receptors on immune cells that recognize the Fc portion of IgG
- CD64 (FcγRI) is the only Fcγ receptor with high affinity for IgG1
- CD64+ cells are the primary cellular source of IL-23 in IBD



	Type I						Type II	
	FcγRI	FcγRIIa	FcγRIIb	FcγRIIc	FcγRIIIa	FcγRIIIb	DC-SIGN	CD23
Neutrophils	#	+	+	-	-	+	-	#
Eosinophils	#	+	+	-	-	#	-	#
Basophils	#	+	+	-	-	+/-	-	#
Monocytes	+	+	+	-	+/-	-	-	#
Macrophages	+/-	+	+	-	+/-	-	+/-	#
Dendritic cells	-/#	+	+	-	-/#	-	+	-
Platelets	-	+	-	-	-	-	-	-

\+ Constitutive expression
\- No expression
\# Inducible expression

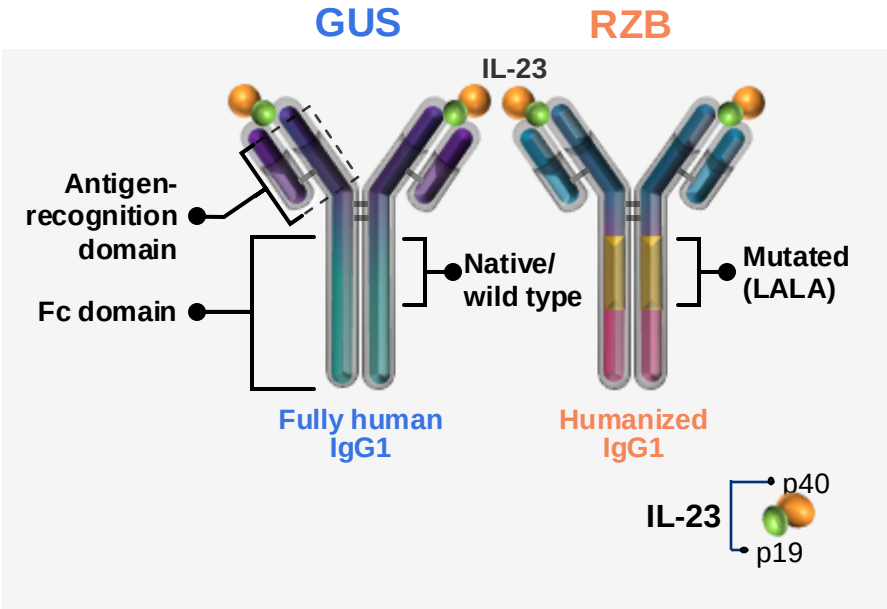
IgG = immunoglobulin G.

Bournazos S, et al. *Microbiol Spectr*. 2016;4(6):10.

CME OUTFITTERS

Differences Between GUS and RZB 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; LALA = leucine to alanine substitutions at positions 234 and 235; mAbs = monoclonal antibodies.

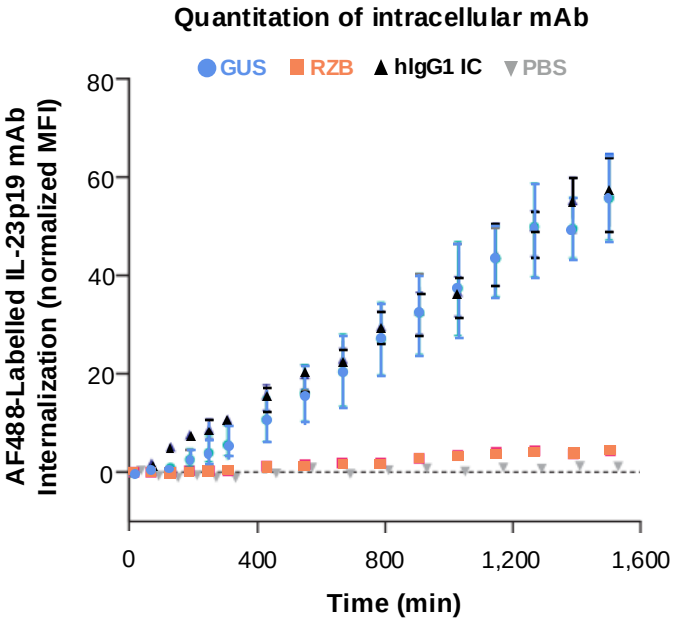
Guselkumab is indicated for the treatment of adults with moderately to severely active UC. Risankizumab is indicated for the treatment of adults with moderately to severely active CD and treatment of adults with moderately to severely active UC.

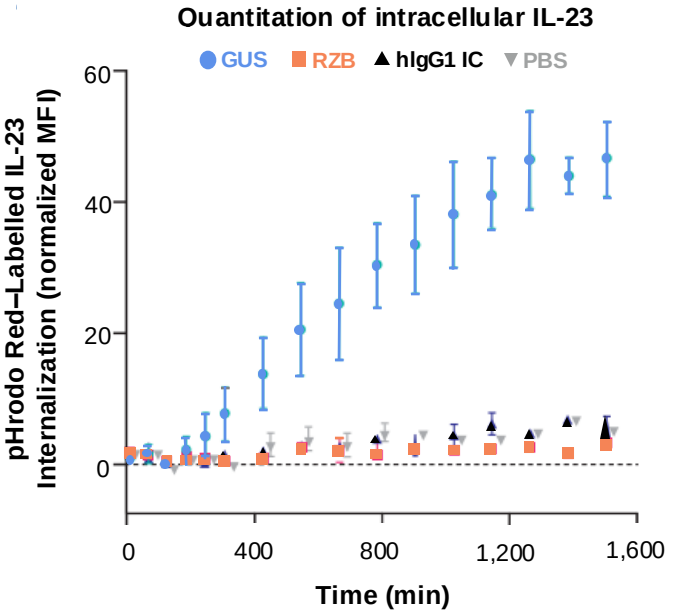
D'Haens G, et al. *Lancet*. 2022;399(10340):2015-2030. Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046. Sandborn WJ, et al. *Gastroenterology*. 2022;162(6):1650-1664. Dignass A, et al. *J Crohns Colitis*. 2022;16(Suppl 1):i025-i026. Louis E, et al. *Aliment Pharmacol Ther*. 2004;19(5):511-519.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

Animation

In Vitro Evaluations of CD64 and IL-23 Binding: Guselkumab and Risankizumab

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





MFI = mean fluorescence intensity; PBS = phosphate buffered saline.

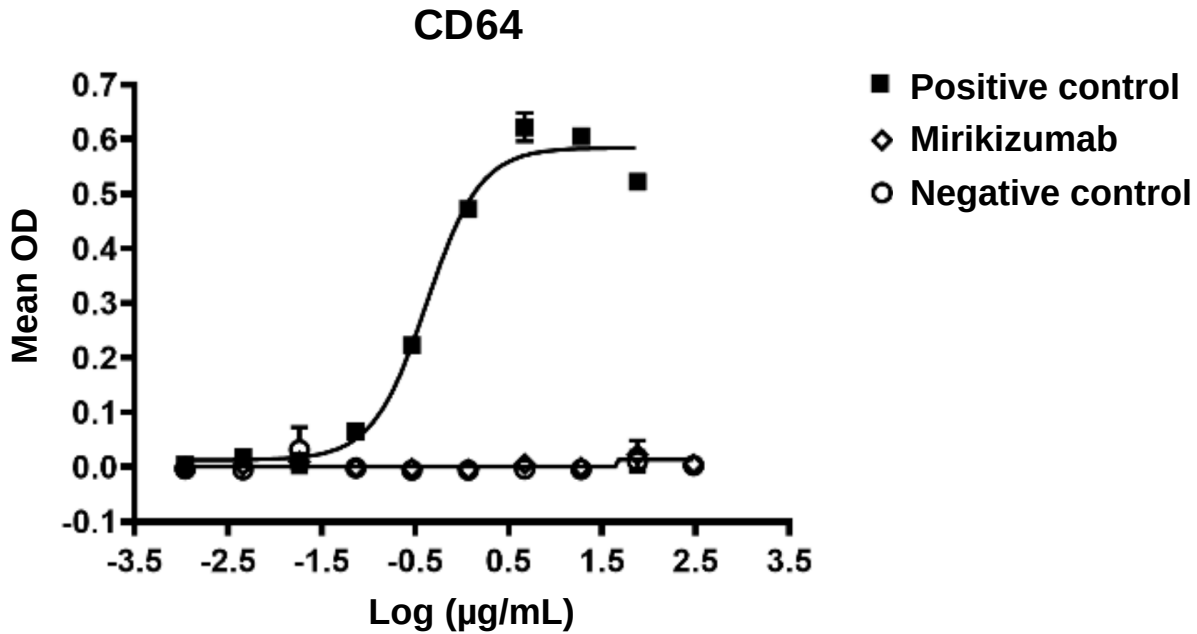
Guselkumab is indicated for the treatment of adults with moderately to severely active UC. Risankizumab is indicated for the treatment of adults with moderately to severely active CD and treatment of adults with moderately to severely active UC.

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

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

Assessment of Fc Receptor Activation and Complement Binding

Mirikizumab is a humanized IgG4 anti-human IL-23p19 monoclonal antibody



Data are mean + standard deviation (SD) of duplicate wells.
Mirikizumab is indicated for the treatment of adults with moderately to severely active UC.
Steere B, et al. *J Pharmacol Exp Ther*. 2023;387(2):180-187.

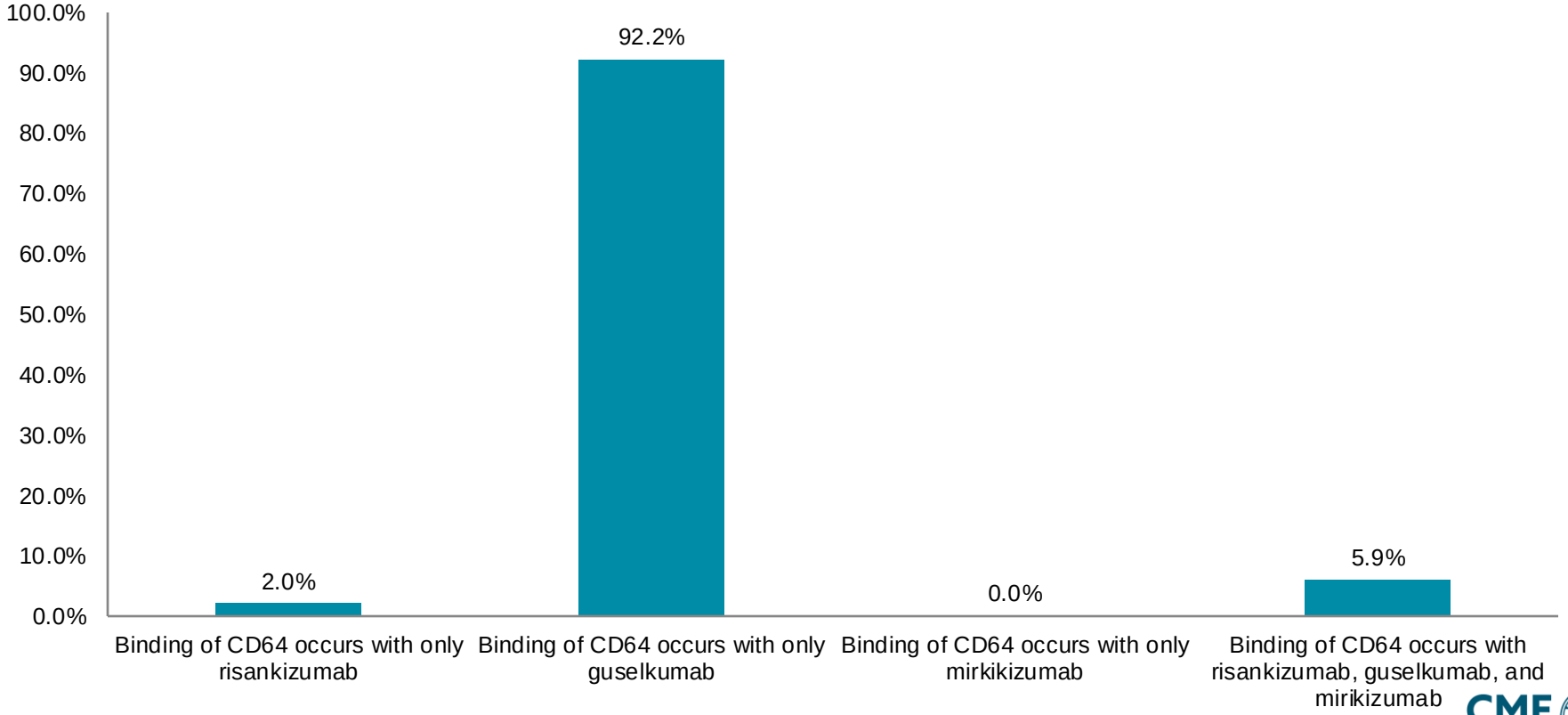
CME OUTFITTERS

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

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



Results recorded on Feb 6, 2025.

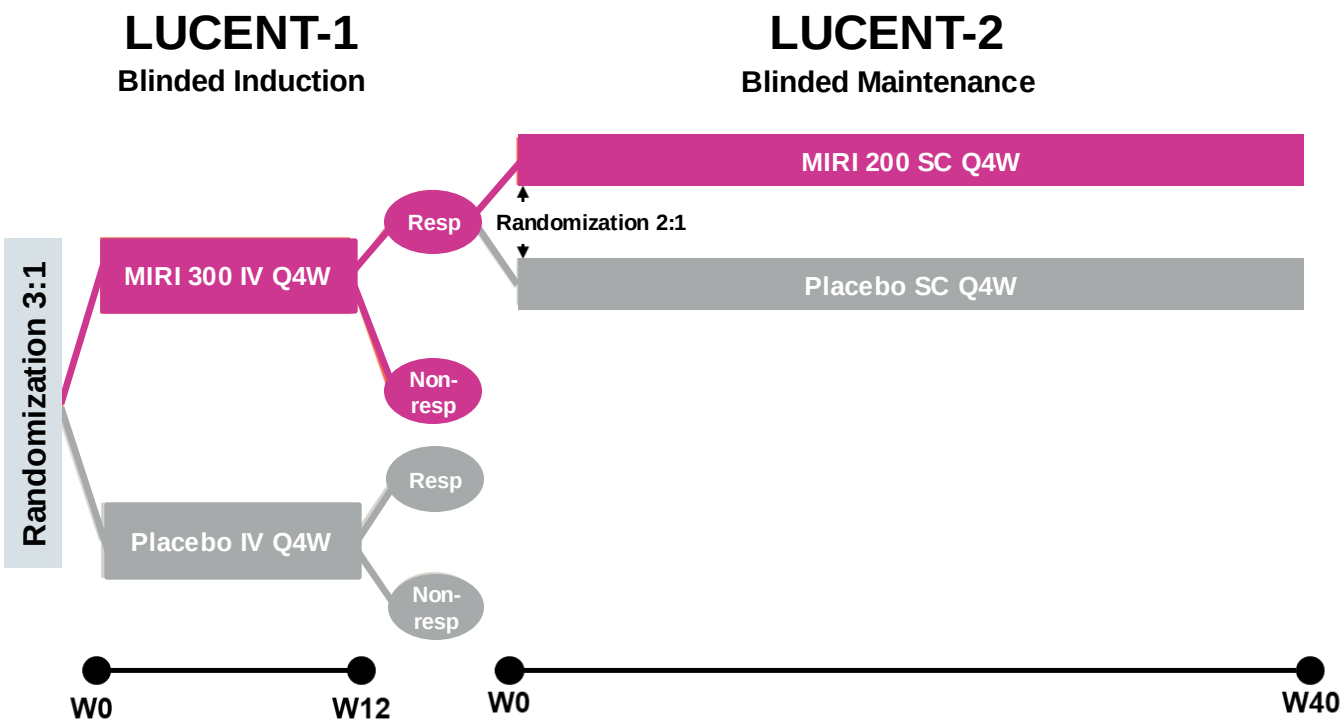
CME OUTFITTERS

Data With IL-23 Inhibitors

Bincy P. Abraham, MD, MS, AGAF, FACG, FASGE, FCCF

Ulcerative Colitis

Mirikizumab in UC: LUCENT-1 and LUCENT-2



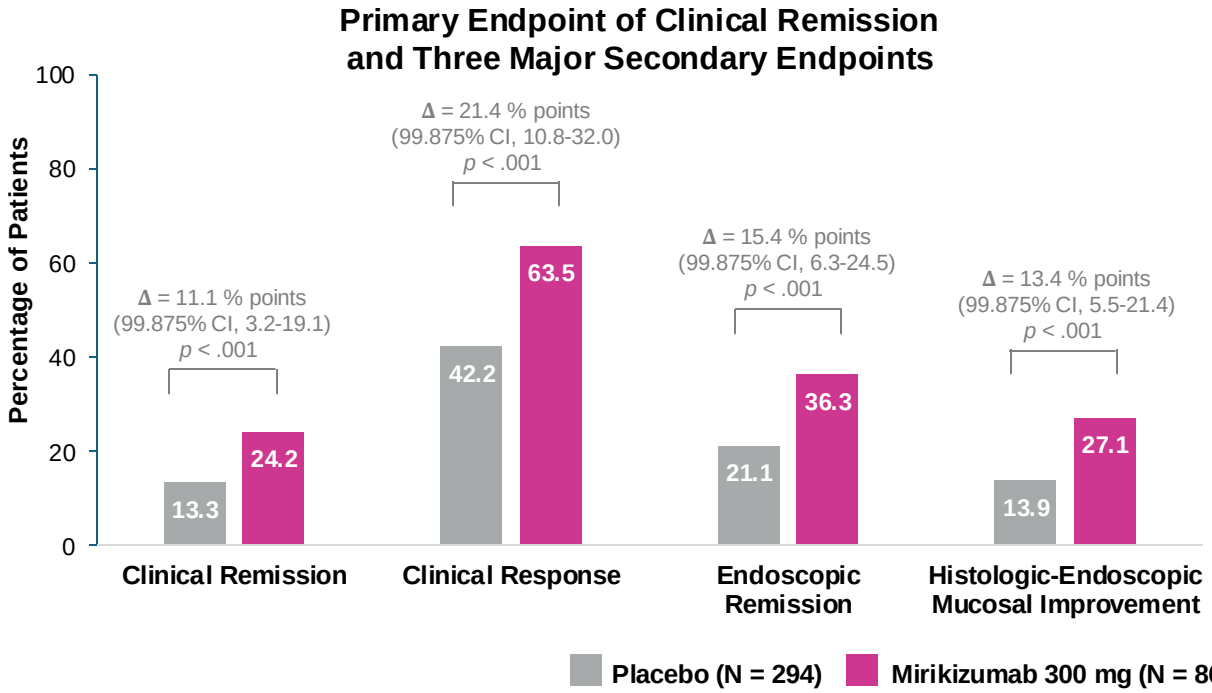
Induction: N = 1,281 adults with an incomplete response to, loss of response to, or inability to take conventional treatment, biologic therapy, or JAKis were assigned in a 3:1 ratio to receive MIRI (300 mg) or placebo IV every 4 weeks for 12 weeks

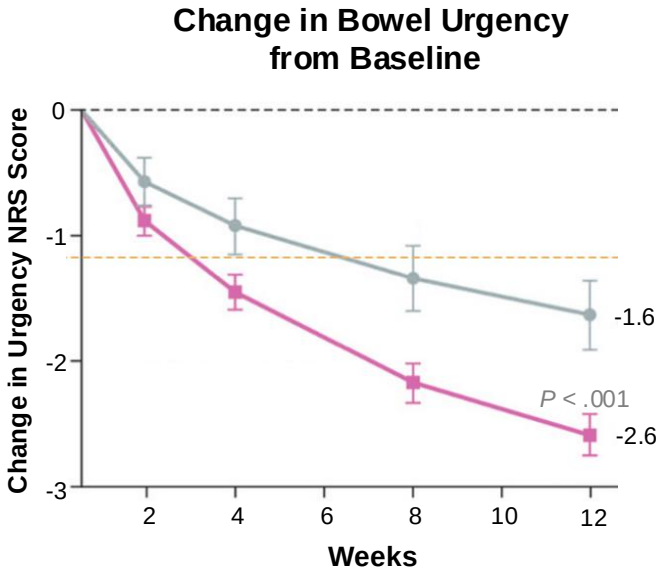
Maintenance: N = 544 adults with a clinical response to MIRI at week 12 were reassigned in a 2:1 ratio to receive MIRI (200 mg) or placebo SC every 4 weeks for 40 weeks

Non-resp = non-responders; Resp = responders; IV = intravenous; SC = subcutaneous; JAKi = Janus kinase inhibitor.
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 adults with moderately to severely active UC.
D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444-2455.

CME OUTFITTERS

Mirikizumab in UC Induction: LUCENT-1

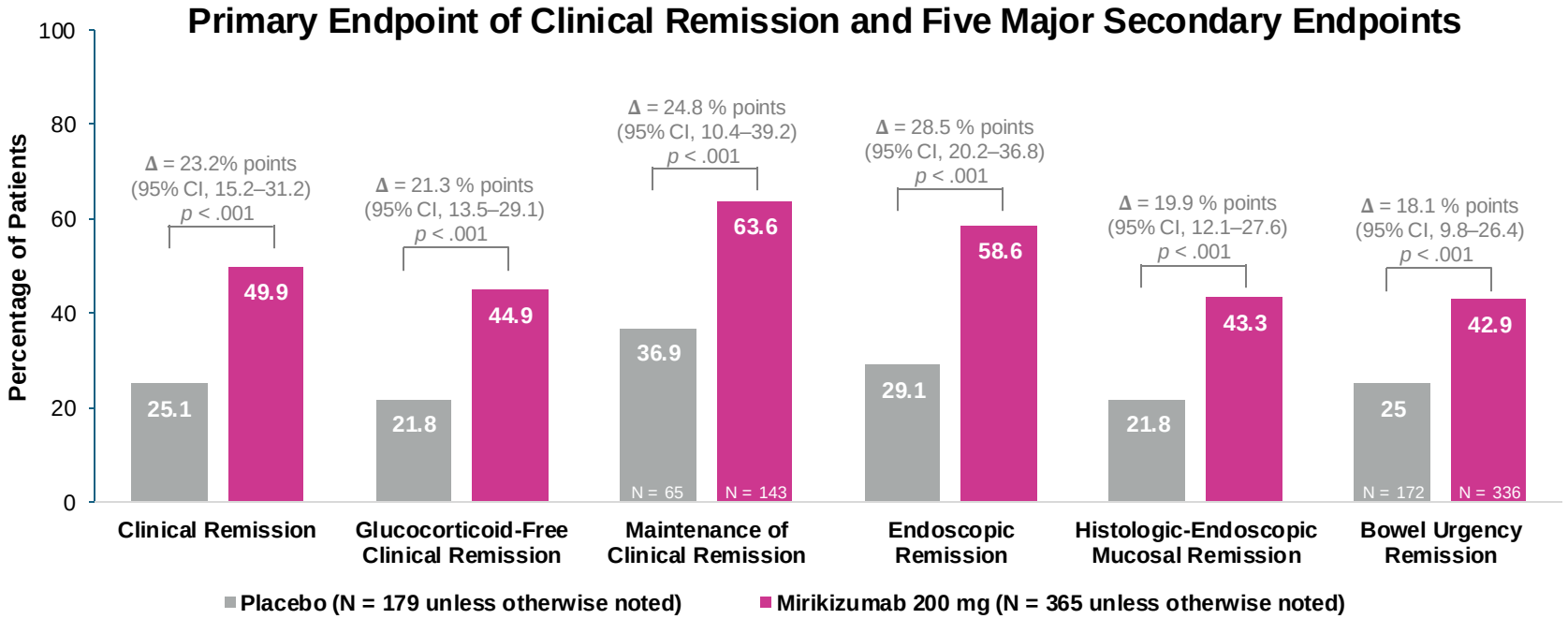




NRS = numeric rating scale.
Mirikizumab is indicated for the treatment of adults with moderately to severely active UC.
D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444-2455.

CME OUTFITTERS

Mirikizumab in UC Maintenance: LUCENT-2 Week 40 Endpoints



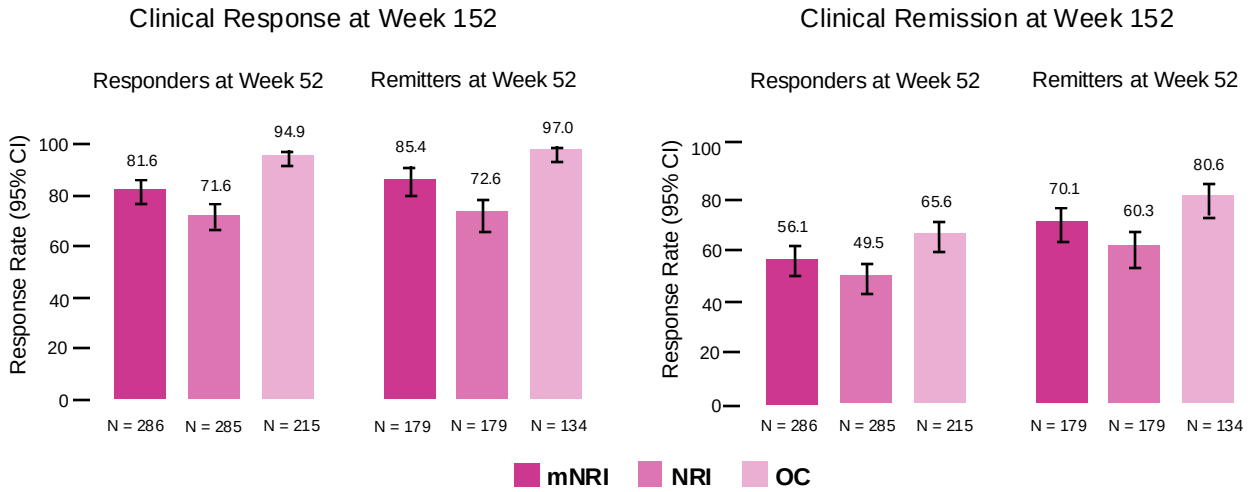
Clinical remission: stool frequency (SF) = 0, or SF = 1 with a ≥ 1-point decrease from baseline; rectal bleeding (RB) = 0; endoscopic subscore (ES) = 0 or 1 (excluding friability); endoscopic remission: ES = 0 or 1 (excluding friability), clinical remission at week 40, remission of symptoms at week 28,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

Mirikizumab is indicated for the treatment of adults with moderately to severely active UC.

D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444-2455.

Mirikizumab Maintenance in UC: Long-Term Follow-Up from LUCENT-3

LUCENT-3 open-label extension study of patients completing 52 weeks of maintenance treatment in LUCENT-2



NRI = non-responder imputation; mNRI = modified NRI; OC = observed case.

Clinical remission: SF = 0 or 1 with ≥ 1-point decrease in modified Mayo score (MMS) from baseline, RB = 0, and ES = 0 or 1 (excluding friability).

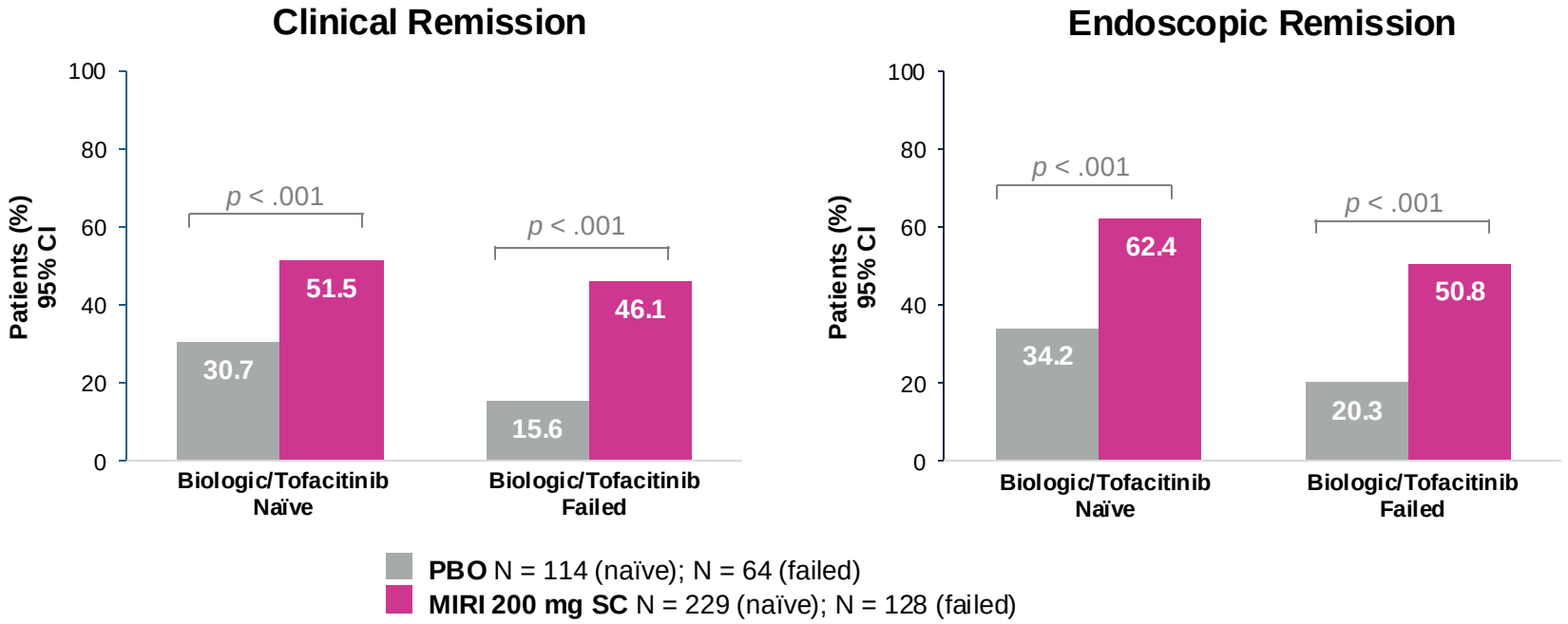
Clinical response: ≥ 2-point and ≥ 30% decrease in the MMS from baseline, RB = 0 or 1, or RB ≥ 1-point decrease from baseline.

Mirikizumab is indicated for the treatment of adults with moderately to severely active UC.

Sands BE, et al. *Inflamm Bowel Dis*. 2024:izae253.

CME OUTFITTERS

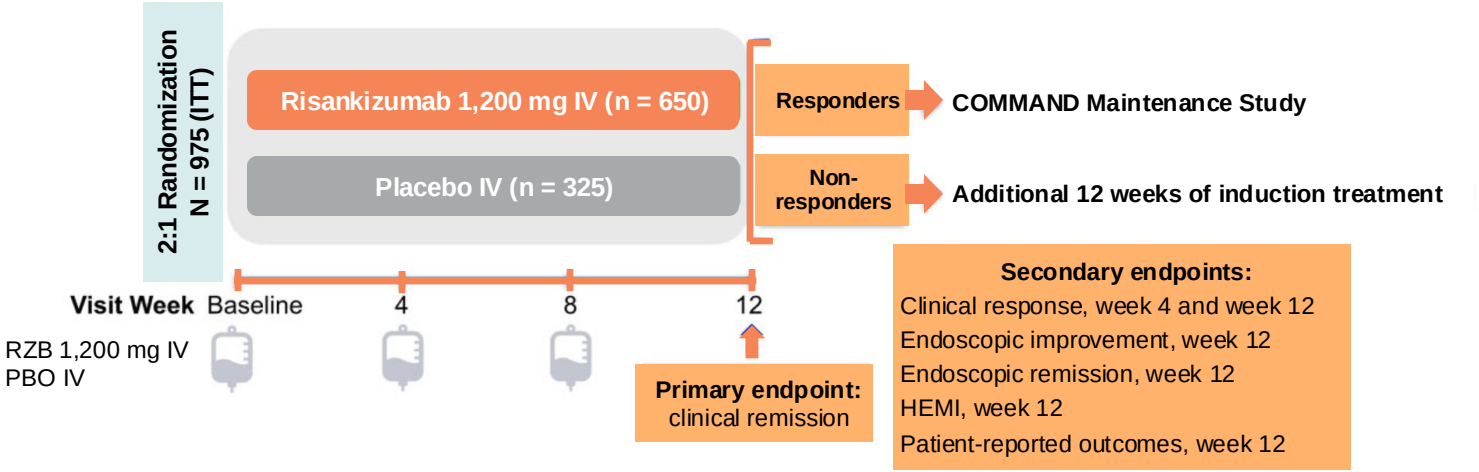
Mirikizumab in Treatment-Naïve and Treatment-Experienced Patients with UC: LUCENT-2



PBO = placebo.
Mirikizumab is indicated for the treatment of adults with moderately to severely active UC.
D'Haens G, et al. *N Engl J Med.* 2023;388(26):2444-2455.

CME OUTFITTERS

Risankizumab in UC: INSPIRE/COMMAND



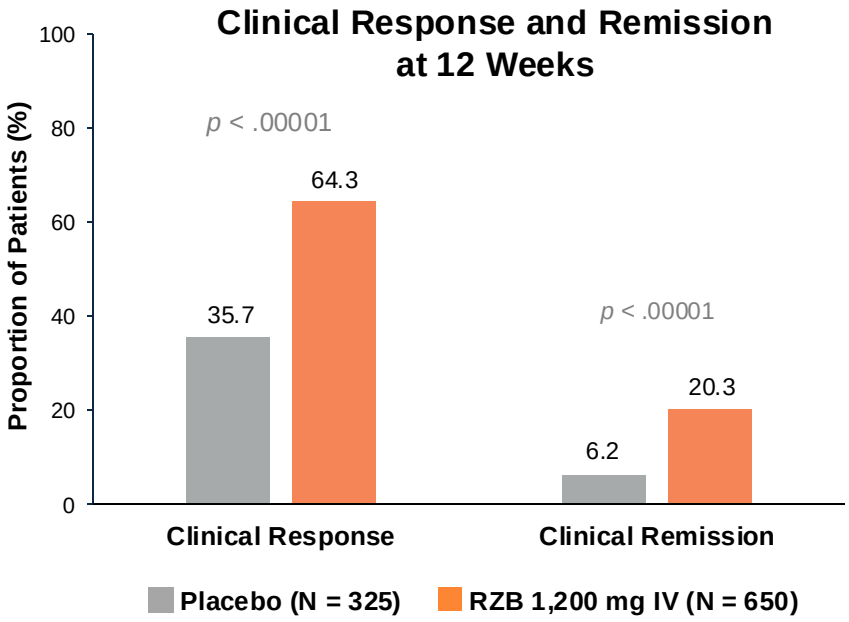
Key Inclusion Criteria:

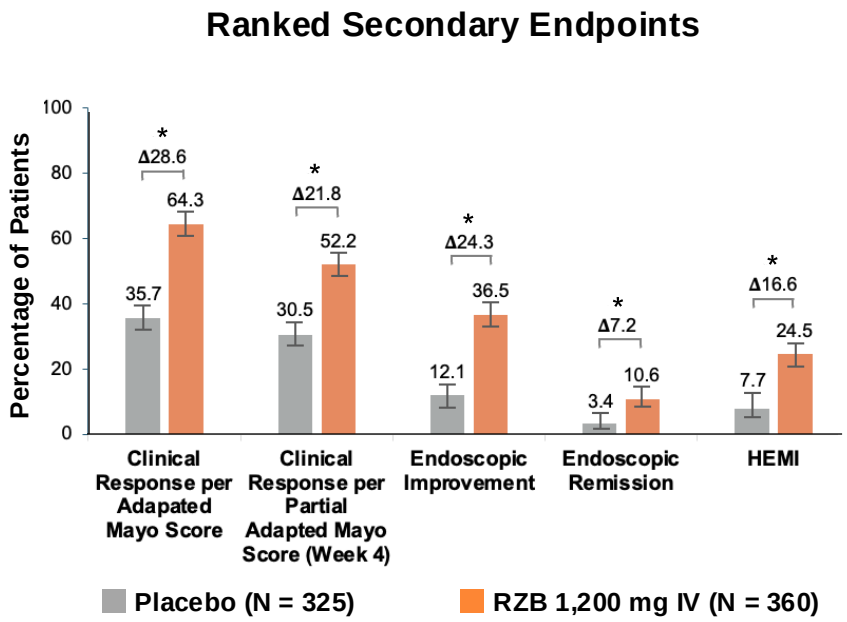
- Age 18 to 80
- **Moderately to severely active UC:** Adapted Mayo score of 5-9 and endoscopic subscore of 2-3 (central review) with biopsy-confirmed diagnosis at least 3 months prior to baseline
- **Intolerance or inadequate response to conventional (non-advanced) and/or advanced therapies** (biologics,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

HEMI = histologic-endoscopic mucosal improvement.

Louis E, et al. *JAMA.* 2024;332(11):881-897.

Risankizumab Induction in UC: INSPIRE





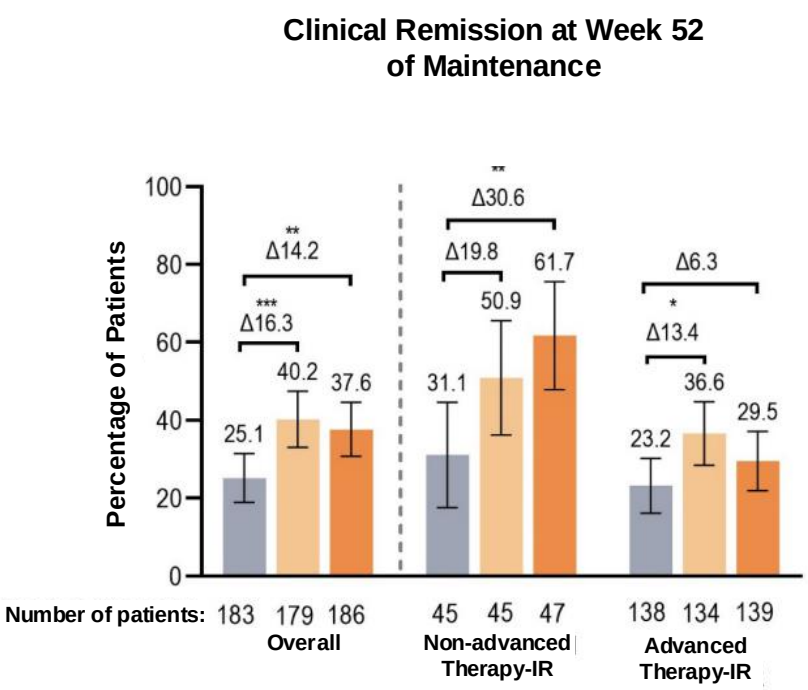
*p value < .00001 vs PBO.

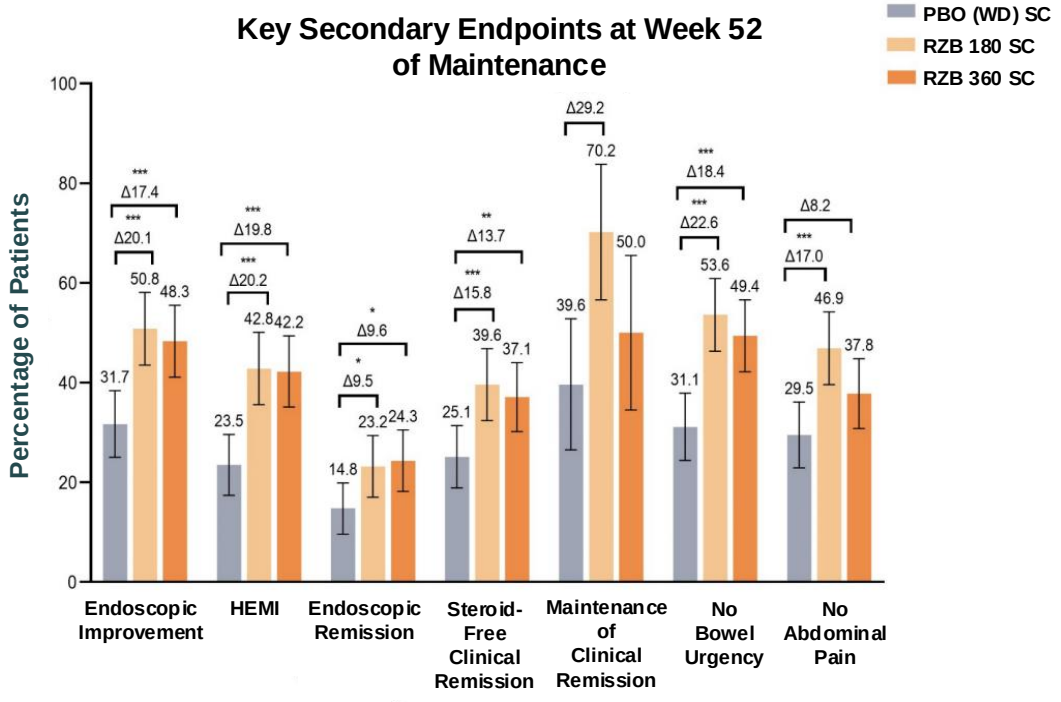
Clinical remission per Adapted Mayo Score is defined as stool frequency subscore (SFS) ≤ 1 and not greater than baseline, rectal bleeding subscore (RBS) of 0 and endoscopic subscore ≤ 1 without friability. Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and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

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

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

Risankizumab Maintenance in UC: COMMAND





PBO (WD) = placebo-controlled withdrawal.

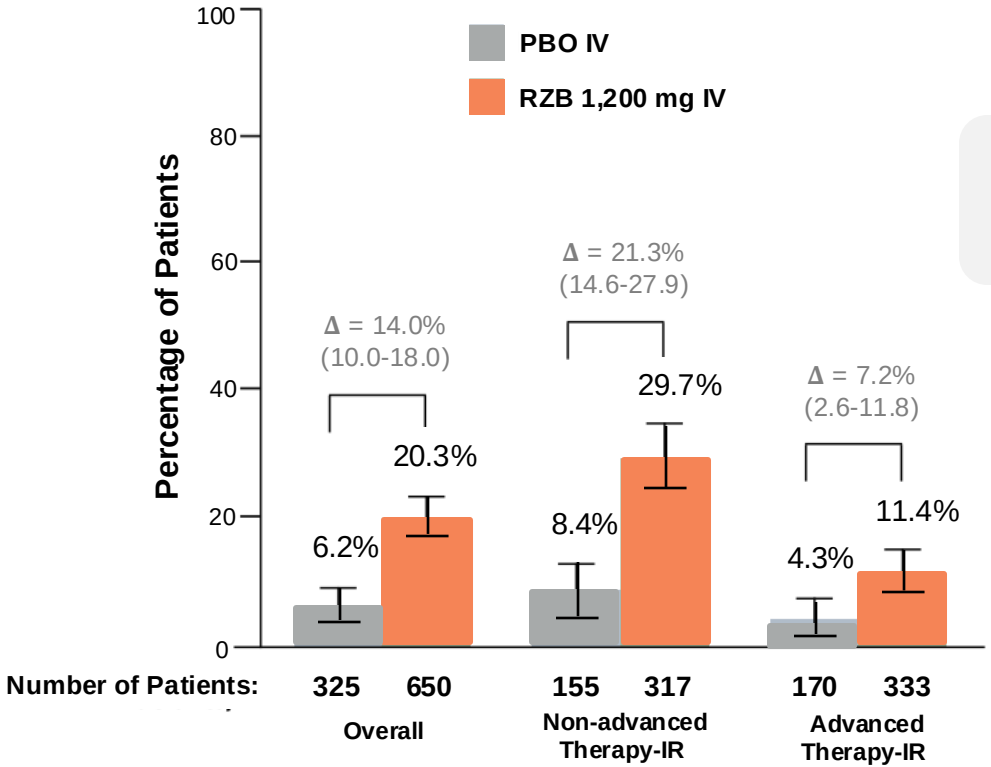
*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$ versus PBO (WD) SC.

Risankizumab is indicated for the treatment of adults with moderately to severely active UC and CD.

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

CME OUTFITTERS

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



Primary endpoint: clinical remission* at week 12

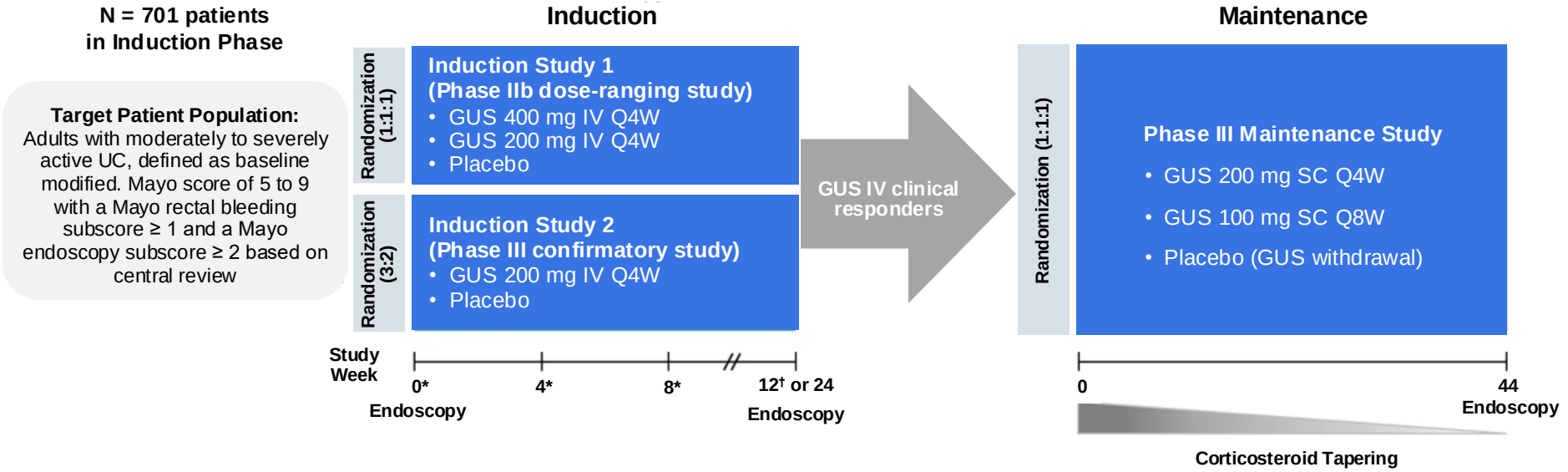
IR = inadequate responders.

*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 the treatment of patients with moderately to severely active UC.

Louis E, et al. *JAMA*. 2024;332(11):881-897.

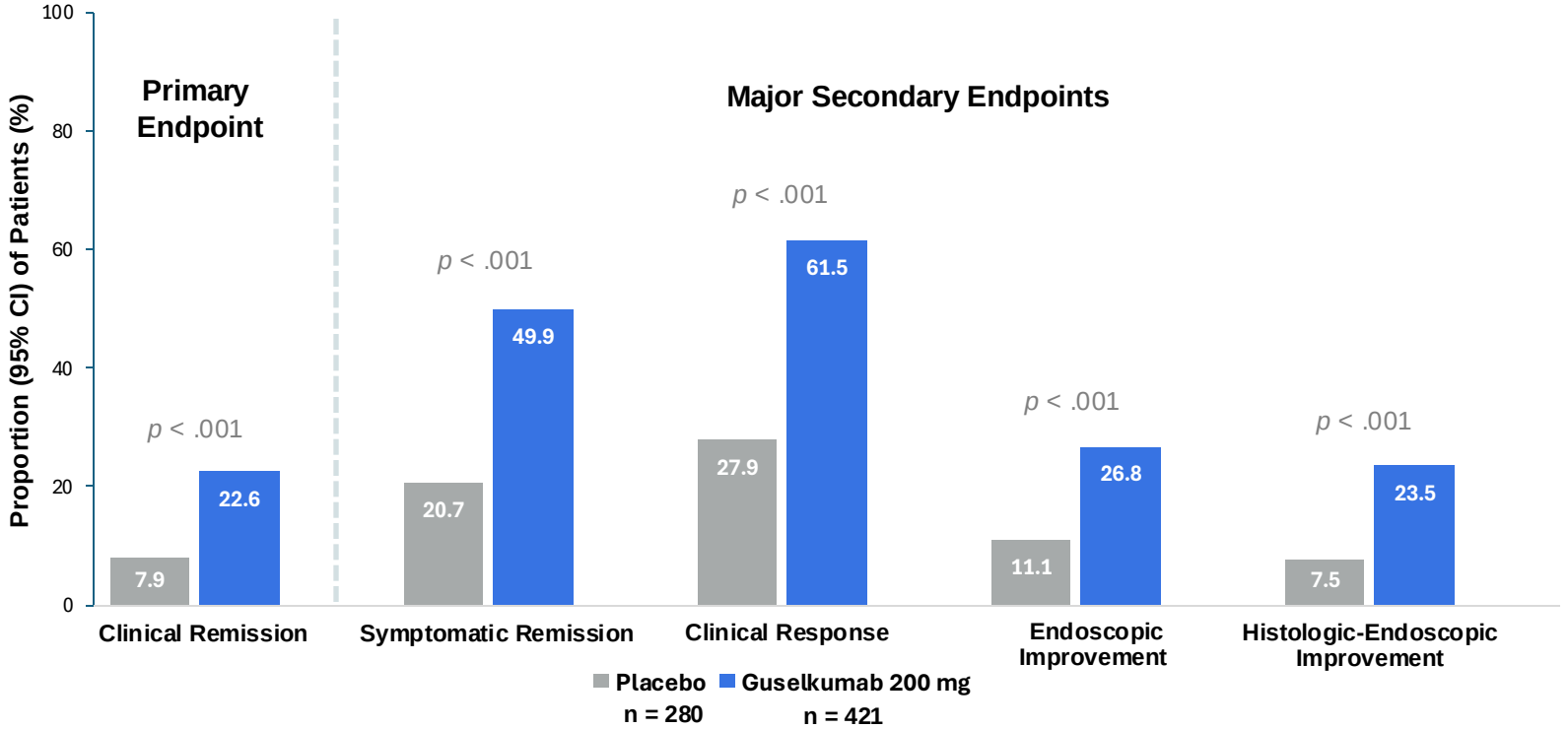
Guselkumab in UC: QUASAR



Q4W = every 4 weeks; Q8W = every 8 weeks.
*Study treatment administered. †Study treatment administered to week 12 clinical non-responders.
Guselkumab is indicated for the treatment of adults with moderately to severely active UC.
Peyrin-Biroulet L, et al. *Gastroenterology*. 2023;165(6):1443-1457. Allegretti JR, et al. *Gastroenterology*. 2023;164(6):S-1572.

CME OUTFITTERS

Guselkumab in UC Induction: QUASAR Phase III Week 12 Endpoints

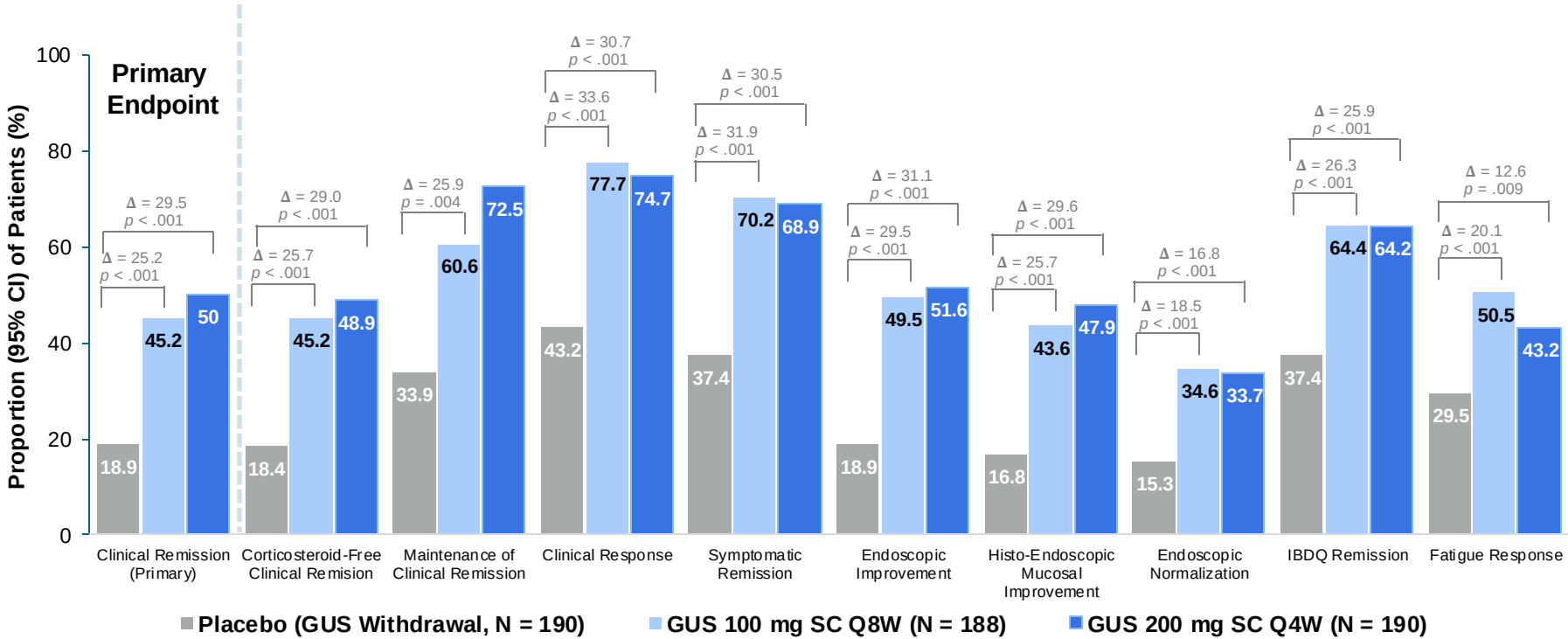


Clinical remission defined as a Mayo stool frequency subscore of 0 or 1 with no increase from baseline, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability.

Guselkumab is indicated for the treatment of adults with moderately to severely active UC.

Allegretti J. Digestive Disease Week [DDW]; 2023. Abstract No. 913b. *Gastroenterol Hepatol.* 2023;19(7 Suppl 3):9-10. https://pmc.ncbi.nlm.nih.gov/articles/PMC10910368/.

Guselkumab in UC Maintenance: QUASAR Phase III Week 44 Endpoints



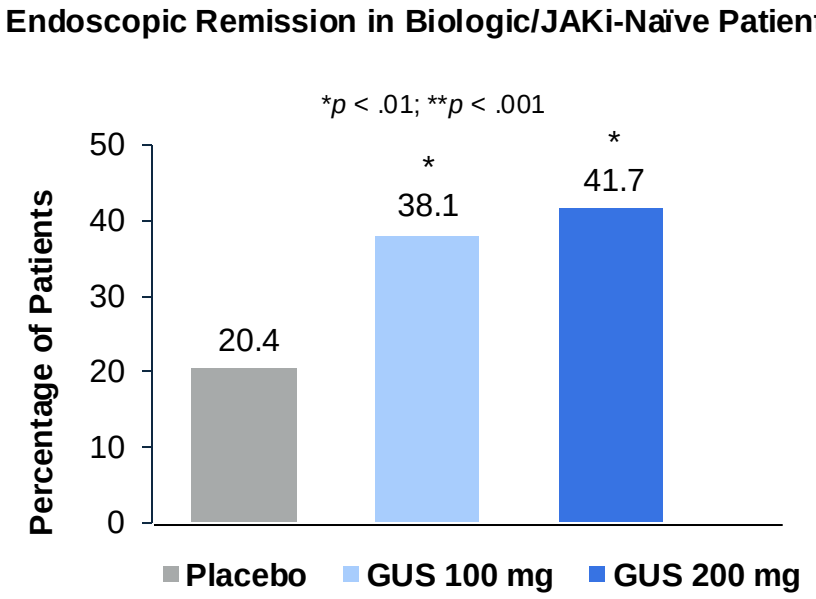
IBDQ = IBD questionnaire.

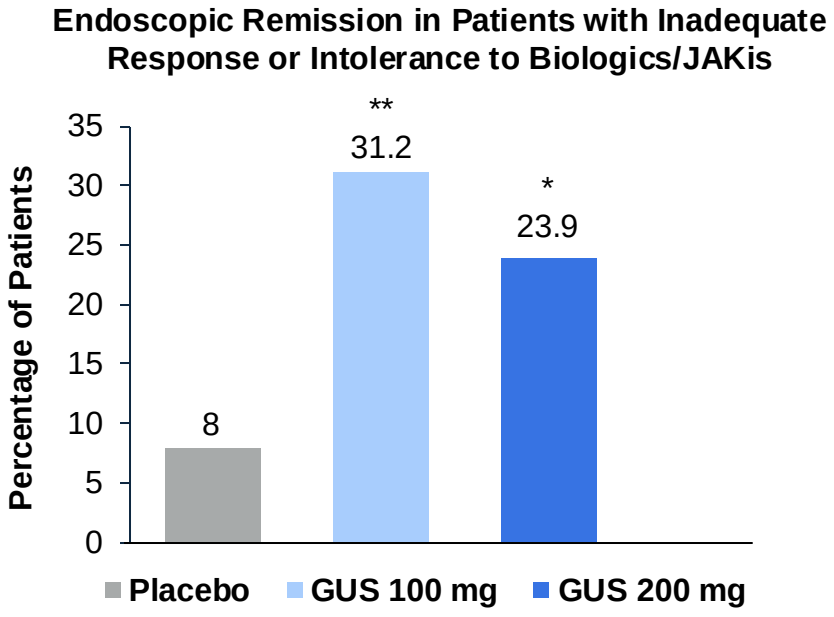
Primary analysis population: randomized patients with a modified Mayo score of 5-9 at induction who received at least one maintenance study treatment dose.

Guselkumab is indicated for the treatment of adults with moderately to severely active UC.

Rubin DT. DDW; 2024. Abstract No. 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





BIO = biologic.

Guselkumab is indicated for the treatment of adults with moderately to severely active UC.

Allegretti JR, et al. United European Gastroenterology Week [UEGW]; 2024. Abstract No. 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;30(12):2245-2258.

Risankizumab 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)

PY = patient years.

[a]The safety population included all patients who clinically responded to IV RZB at 12 or 24 weeks, were randomized to COMMAND at 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(Suppl 1):i10-i12.

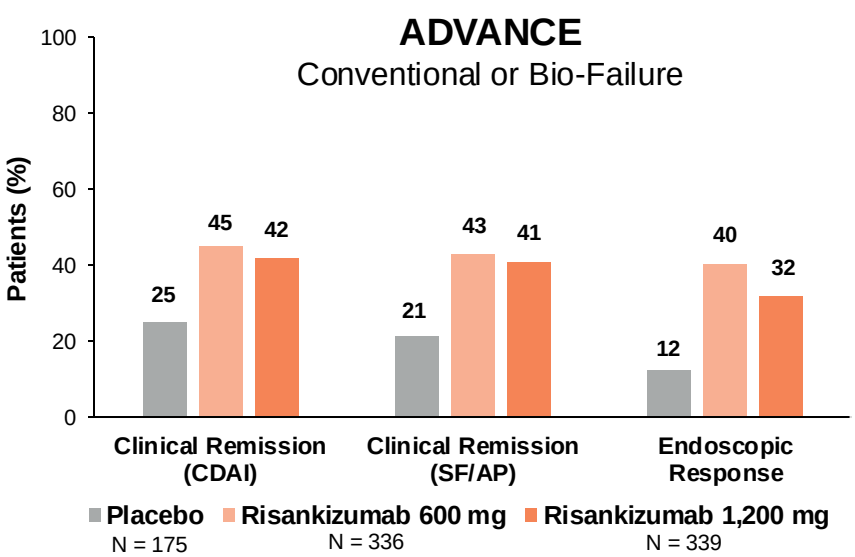
Guselkumab Safety in UC

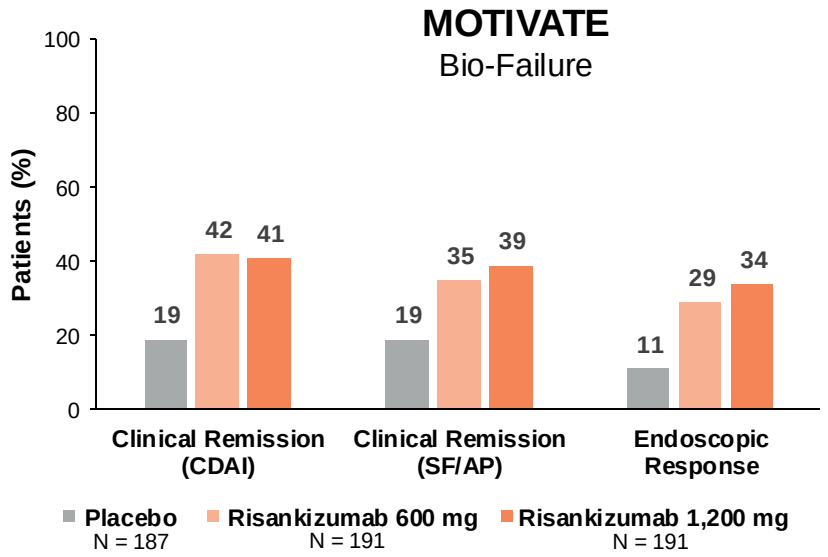
Outcome	Placebo (n = 105)	Guselkumab 200 mg IV (n = 101)	Guselkumab 400 mg IV (n = 107)	Combined (n = 208)
Any AE	59 (56.2)	45 (44.6)	53 (49.5)	98 (47.1)
AE within 1 hour of infusion	2 (1.9)	2 (2.0)	0	2 (1.0)
Serious AE	6 (5.7)	1 (1.0)	3 (2.8)	4 (1.9)
Death	0	0	0	0
Discontinuation for AE	3 (2.9)	1 (1.0)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

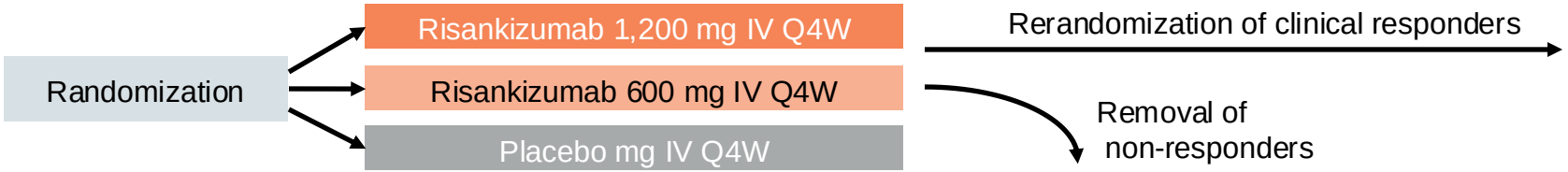
Peyrin-Biroulet L, et al. *Gastroenterology*. 2023;165(6):1443-1457.

Crohn’s Disease

ADVANCE and MOTIVATE: Risankizumab Induction in CD







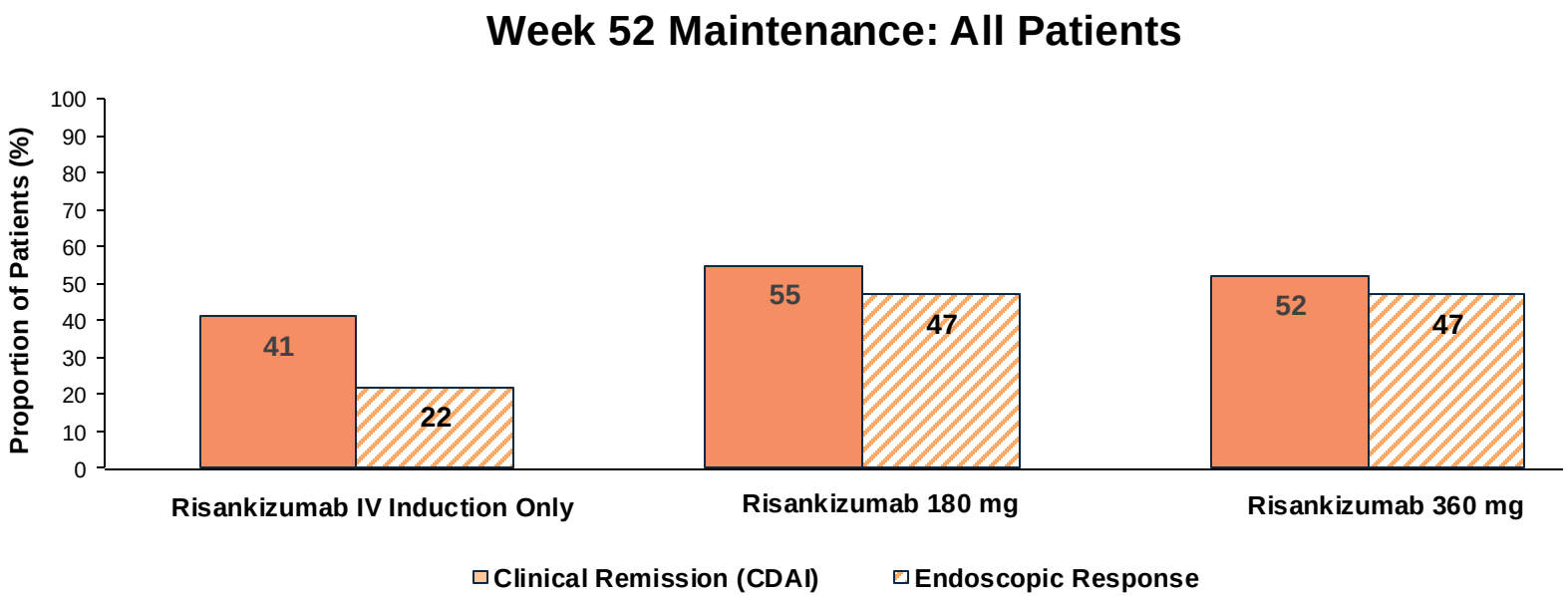
CDAI = Crohn's disease activity index; SF/AP = stool frequency/abdominal pain.

Clinical responders defined as ≥ 30% decrease in average daily stool frequency or abdominal pain score (APS) and not worse than baseline; endoscopic response defined as > 50% decline in simple endoscopic score (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.

Risankizumab is approved for the treatment of adults with moderately to severely active CD.

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.

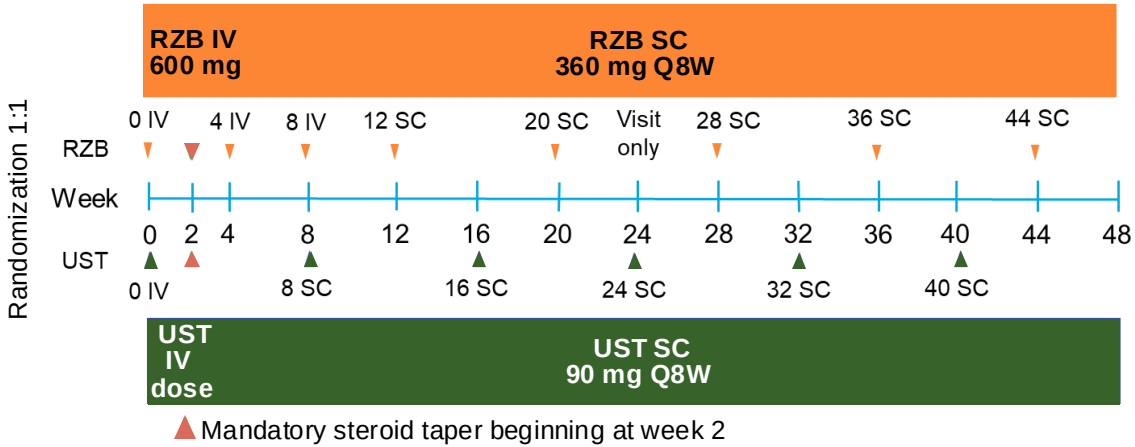
Risankizumab is approved for the treatment of adults with moderately to severely active CD.

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

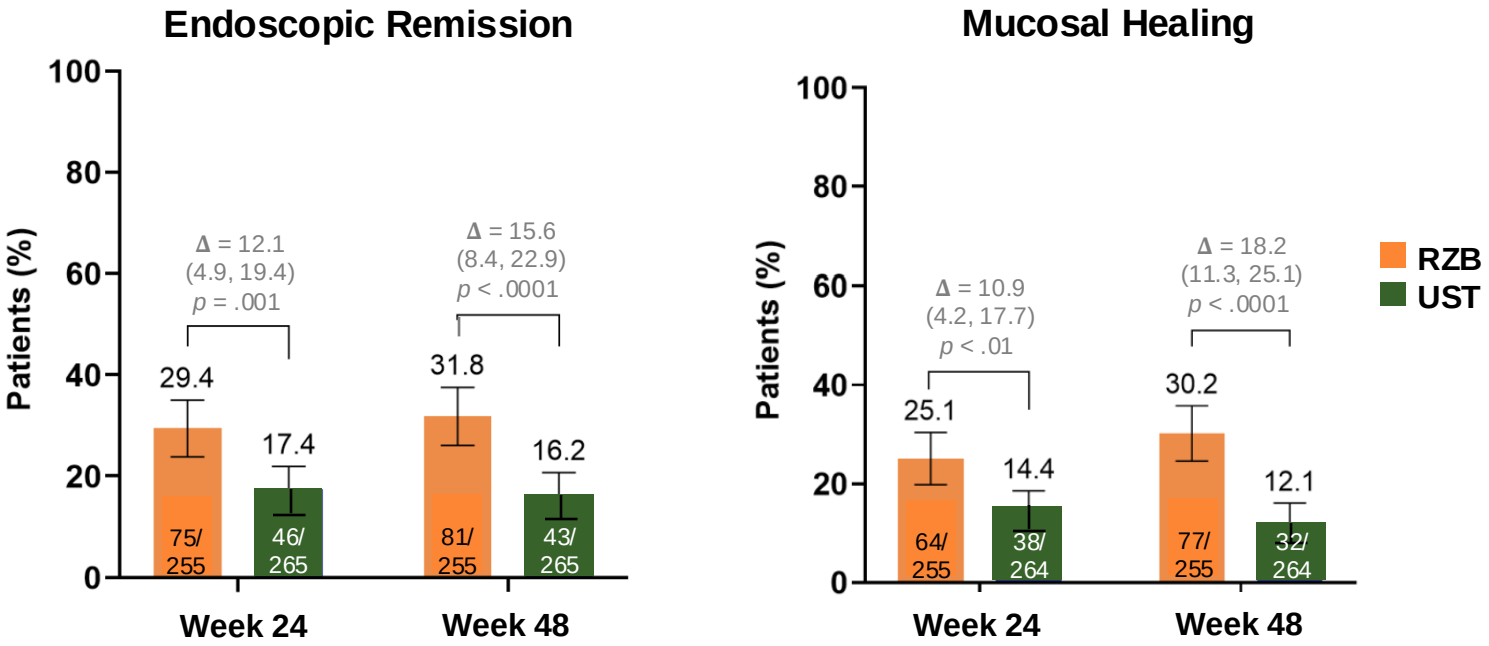
Prior failure of ≥1 anti-TNF therapies

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

Risankizumab and ustekinumab are approved for the treatment of adults with moderately to severely active CD.

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

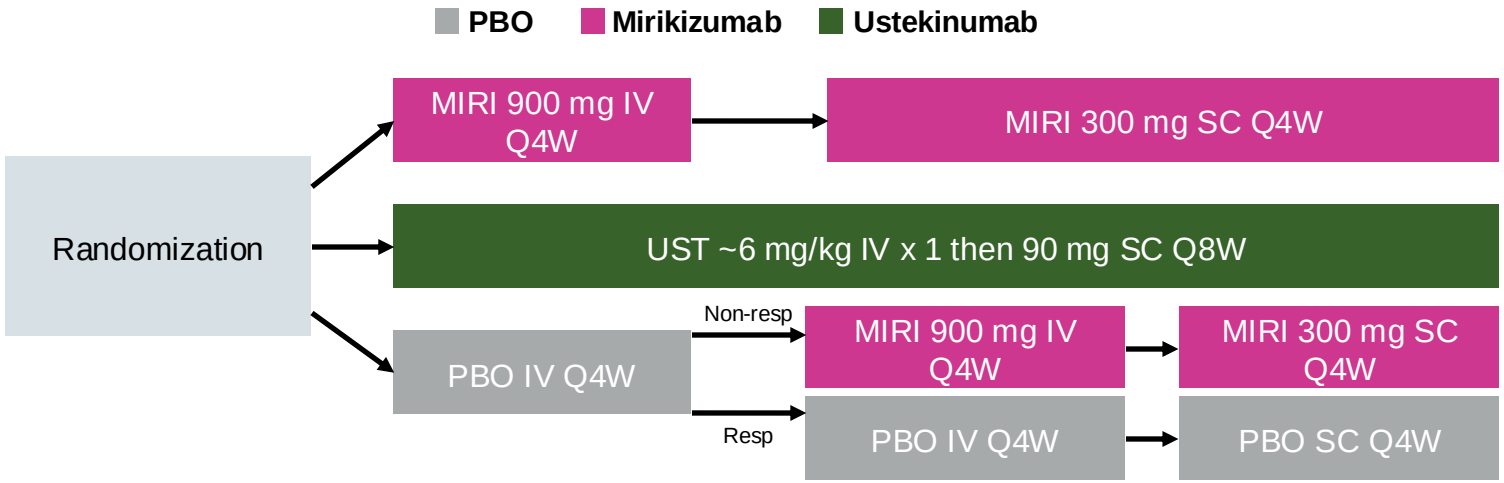
RZB vs UST in Patients with CD: Phase IIIb SEQUENCE Trial



Risankizumab and ustekinumab are approved for the treatment of adults with moderately to severely active CD.

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

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

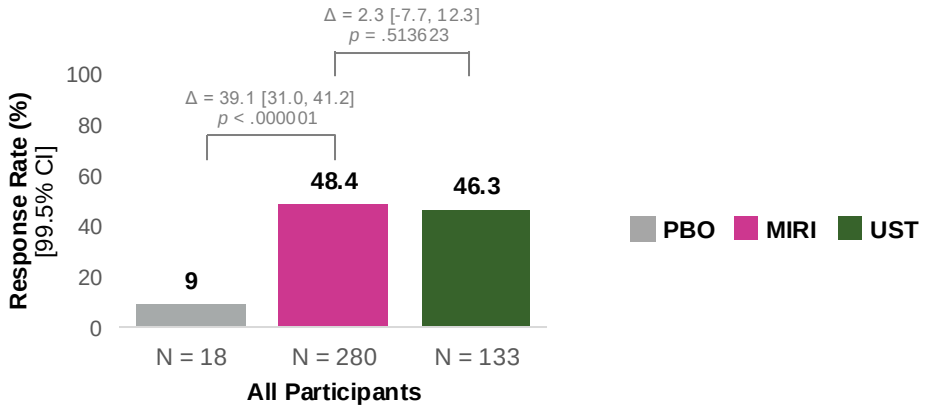


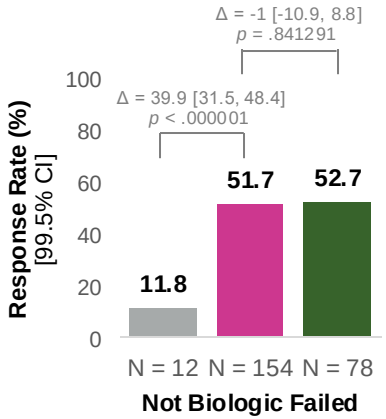
Mirikizumab is approved for the treatment of adults with moderately to severely active CD.

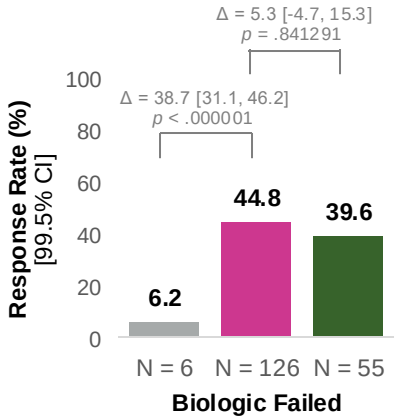
Ferrante M, et al. *Lancet.* 2024;404(10470):2423-2436.

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

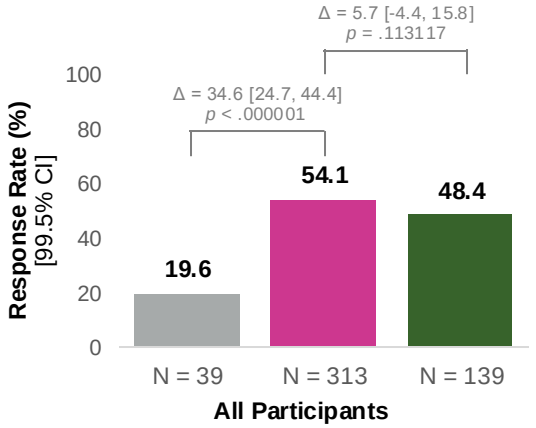
Endoscopic Response (NRI) at Week 52

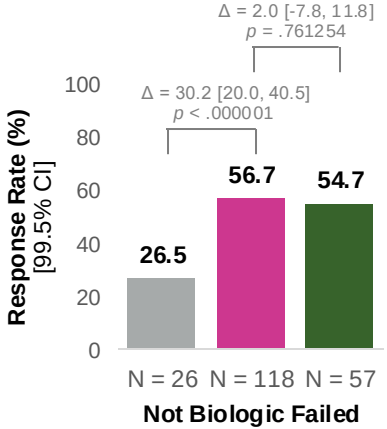


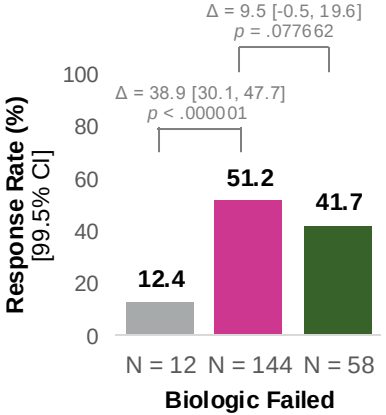




Clinical Remission by CDAI (NRI) at Week 52





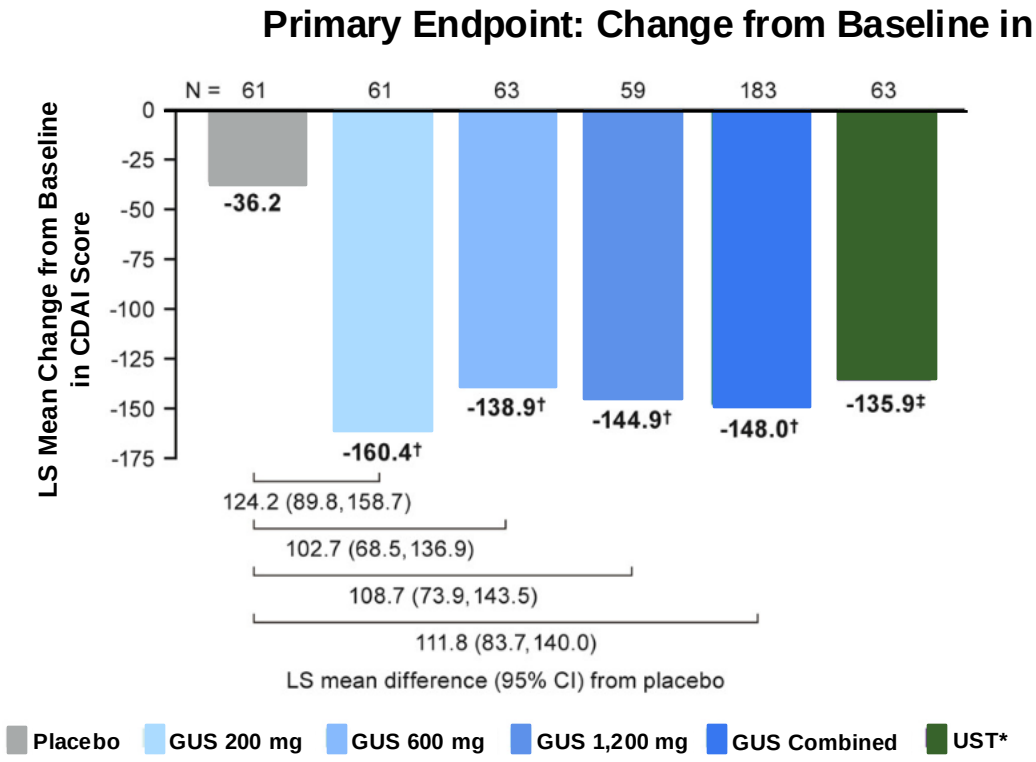


Mirikizumab is approved for the treatment of adults with moderately to severely active CD.

Ferrante M, et al. *Lancet.* 2024;404(10470):2423-2436.

CME OUTFITTERS

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



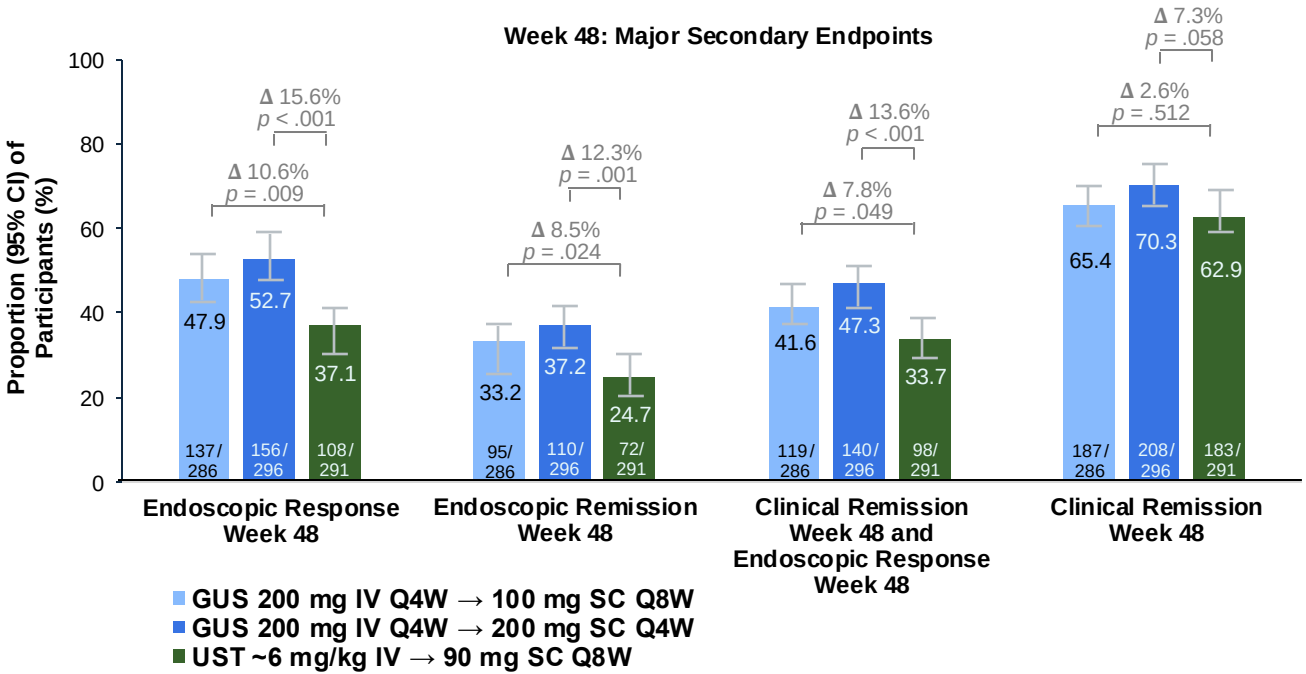
- GALAXI-1 is a DBPC trial
- Randomized patients 1:1:1:1 to
  - IV GUS at weeks 0, 4, 8
  - IV UST at week 8
  - Placebo
- UST was a reference arm
- N = 309

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*. 2022;162(6):1650-1664.

CME OUTFITTERS

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 GUS 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

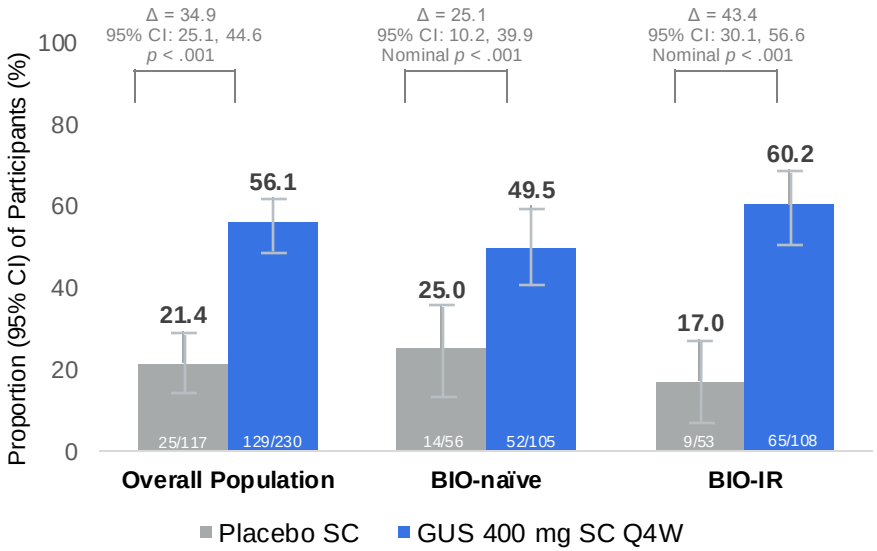
Endoscopic Remission: SES-CD ≤ 4 and a ≥ 2-point reduction from baseline and no subscore greater than 1 in any individual component

Guselkumab is not currently FDA-approved for CD.

Panaccione R, et al. DDW; 2024. Abstract No. 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/.

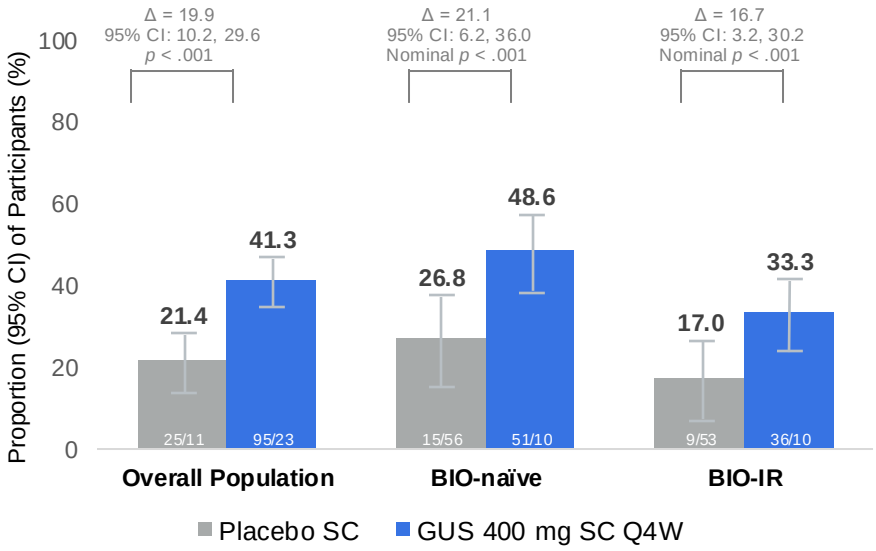
Subcutaneous GUS in CD: Phase III GRAVITI Study Responses at Week 12

Clinical Remission



Clinical remission: CDAI score < 150

Endoscopic Response



Endoscopic response: ≥ 50% improvement from baseline in SES-CD score

Guselkumab is not FDA-approved for use in CD.

Panaccione R, et al. American College of Gastroenterology [ACG] Annual Scientific Meeting; 2024. Abstract No. S1052. https://journals.lww.com/ajg/fulltext/2024/10001/s1052_efficacy_and_safety_of_subcutaneous.1053.aspx.

Safety of IL-23 Inhibitors in CD

Adverse Event	Guselkumab N = 595	Mirikizumab N = 630	Risankizumab N = 373
AEs	458 (77.0%)	495 (78.6%)	210 (56%)
Serious AEs	53 (8.9%)	65 (11.5%)	27 (7%)
Discontinuation due to AE	40 (6.7%)	32 (5.1)	9 (2%)
Serious Infections	4 (0.6%)	14 (2.2%)	0

D'Haens G, et al. *Lancet.* 2022;399(10340):2015-2030. Ferrante M, et al. *Lancet.* 2024;404(10470):2423-2436. Panaccione R, et al. DDW; 2024. Abstract No. 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/.

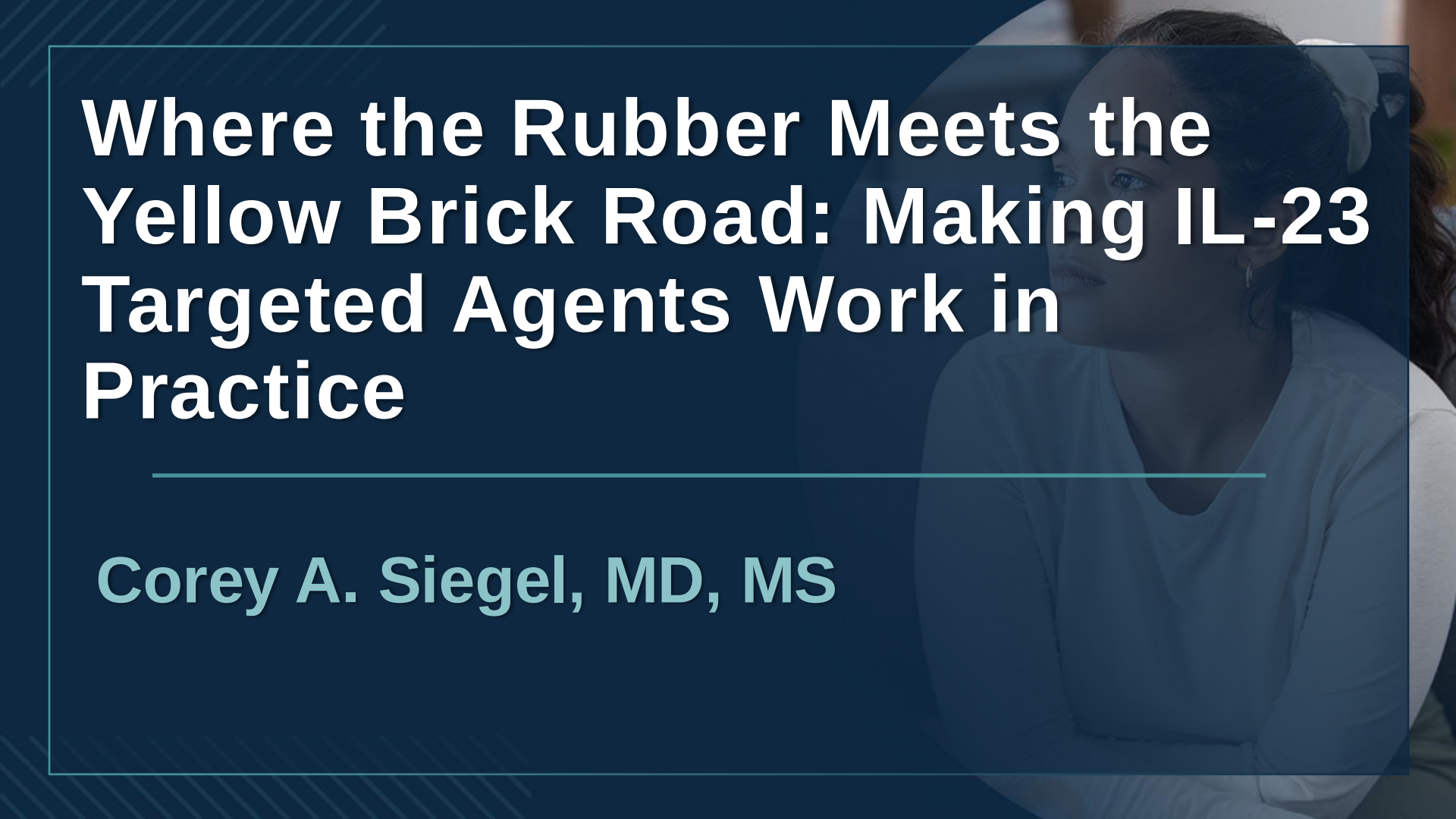
Dosing of IL-23 Inhibitors in IBD

Agent	UC Dose		CD Dose	
	Induction	Maintenance	Induction	Maintenance
Guselkumab	200 mg IV at week 0, 4, and 8	100 mg SC at week 16 and every 8 weeks thereafter **OR** 200 mg SC at week 12 and every 4 weeks thereafter	Not currently FDA approved for CD	-
Mirikizumab	300 mg at week 0, 4, and 8	200 mg SC at week 12 and every 4 weeks thereafter	900 mg IV at week 0, 4, and 8	300 mg SC at week 12 and every 4 weeks thereafter
Risankizumab	1200 mg IV at week 0, 4, and 8	180 or 360 mg SC at week 12 and every 8 weeks thereafter	600 mg IV at week 0, 4, and 8	180 or 360 mg SC at week 12 and every 8 weeks thereafter

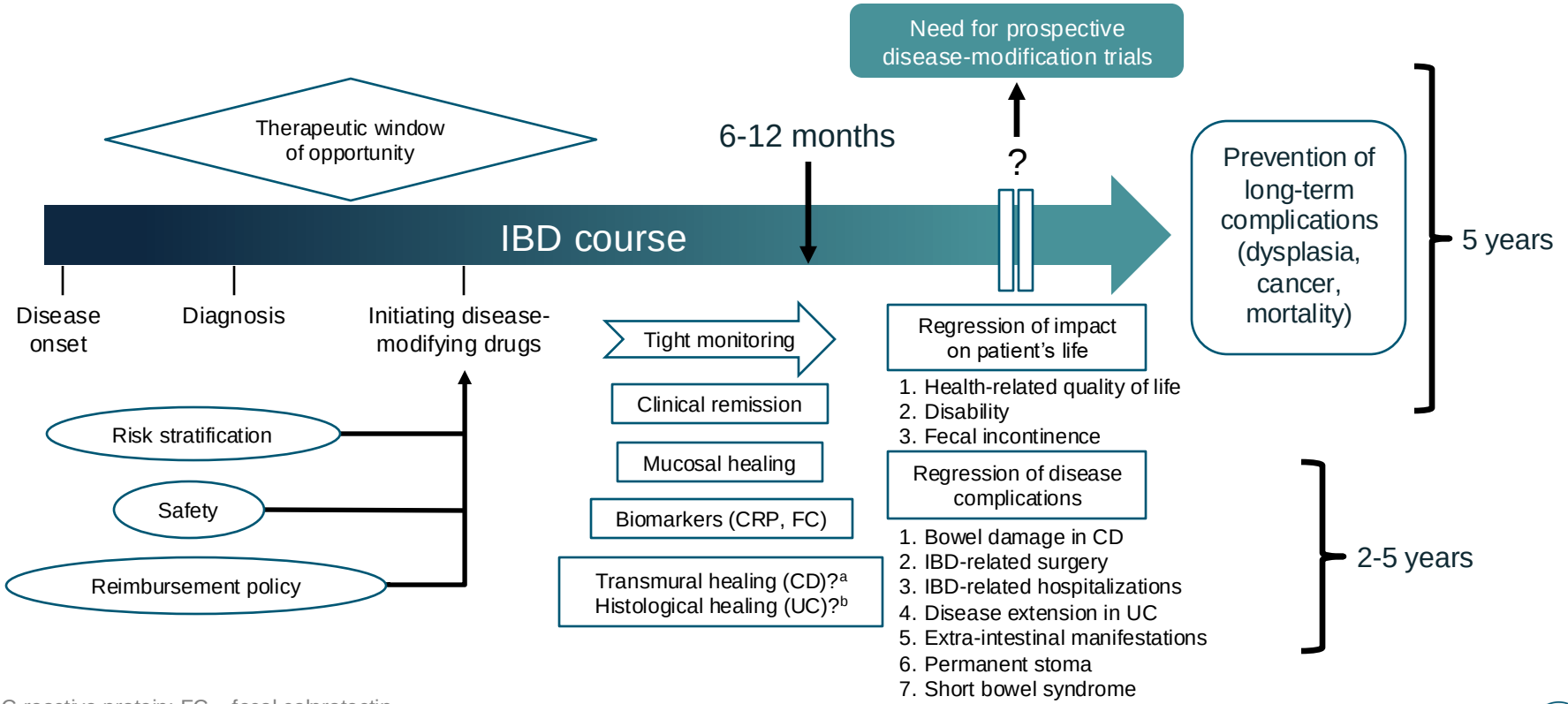
Guselkumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761061s000lbl.pdf. Mirikizumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761279s000lbl.pdf. Risankizumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761105s000lbl.pdf.

Where the Rubber Meets the Yellow Brick Road: Making IL-23 Targeted Agents Work in Practice

Corey A. Siegel, MD, MS



Defining Goals for Treatment

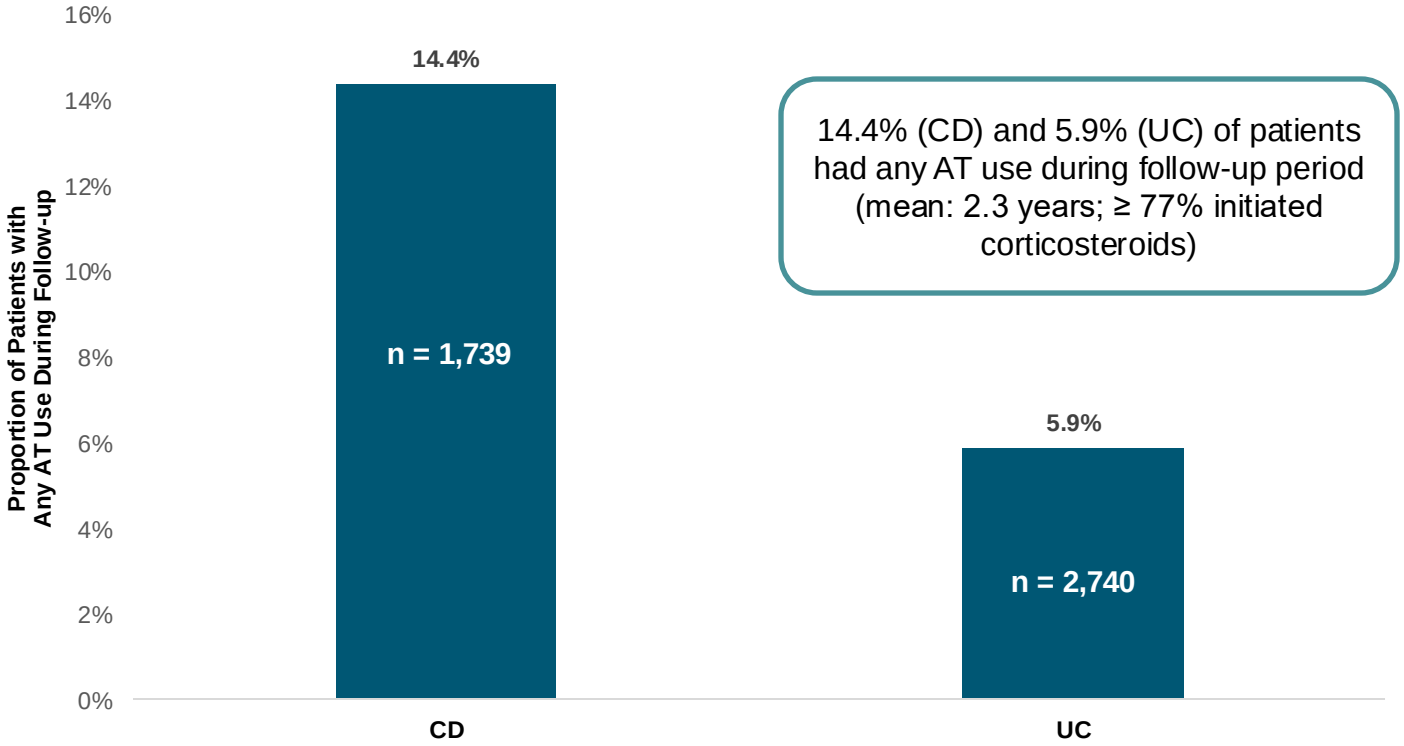


CRP = C-reactive protein; FC = fecal calprotectin.

[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.

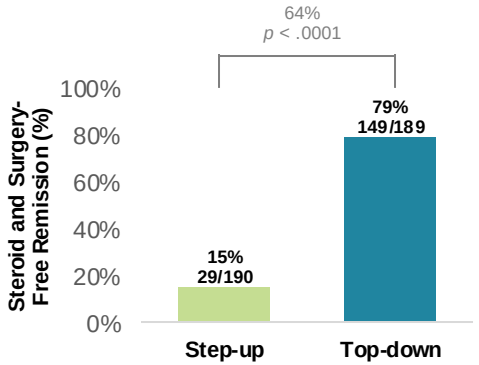
Advanced Treatment (AT) Uptake Is Low Within the First Two Years of IBD Diagnosis

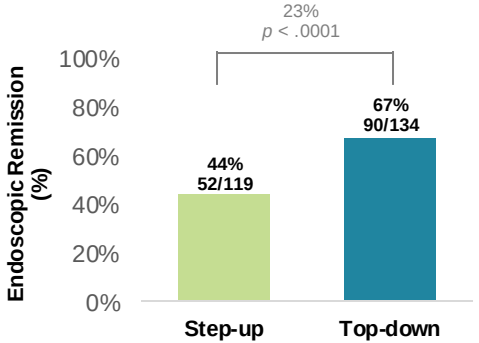


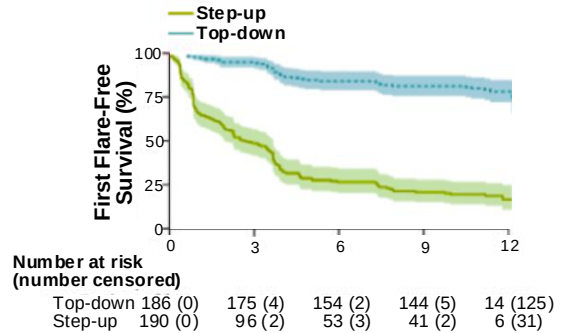
14.4% (CD) and 5.9% (UC) of patients had any AT use during follow-up period (mean: 2.3 years; ≥ 77% initiated corticosteroids)

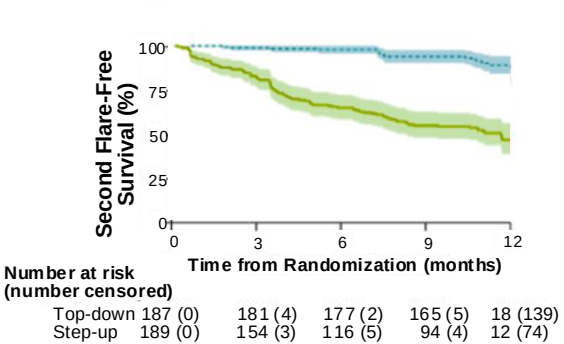
Siegel CA, et al. *Crohns Colitis 360*. 2024;6(3):otae040.

Early Effective Advanced Therapy Predicts CD Outcomes









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, GCC = glucocorticoids.

Noor V, et al. *Lancet Gastroenterol Hepatol.* 2024;9(5):415-427.

How Do We Put Together the Puzzle of Therapy Selection?

DRUG

Efficacy

Indication
Rapidity of onset
Durability
Pharmacokinetics/TDM
Combination vs monotherapy
Positioning and sequence

Safety

Infection
Cancer
Specific concerns by agent or mechanism

PATIENT

Individual Characteristics

Age
Stages of disease
Comorbidities and other inflammatory conditions
Preferences
Access to treatment

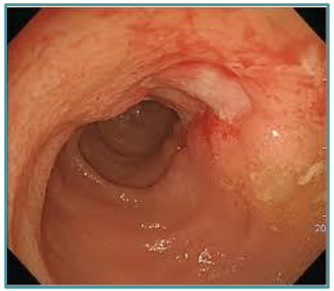
Disease Characteristics

CD vs UC
Disease behavior/complication
Disease severity
Early vs late
EIMs
Treatment history

TDM = therapeutic drug monitoring; EIM = extraintestinal manifestation.

Patient Case: Jordan F.

- 19-year-old college student
- Concerned about changes in bathroom habits
- Weight: 89 kg, height: 191 cm (75 in)
- Current symptoms:
  - 3-month history of abdominal cramping
  - Approximately 3-4 loose stools/day
  - Unexplained weight loss (~10 pounds)
- Diagnosis:
  - Moderately active ileal Crohn’s disease
- Medications:
  - Self-treatment with loperamide over the counter prior to diagnosis
  - No history of treatment with biologic agents or steroids

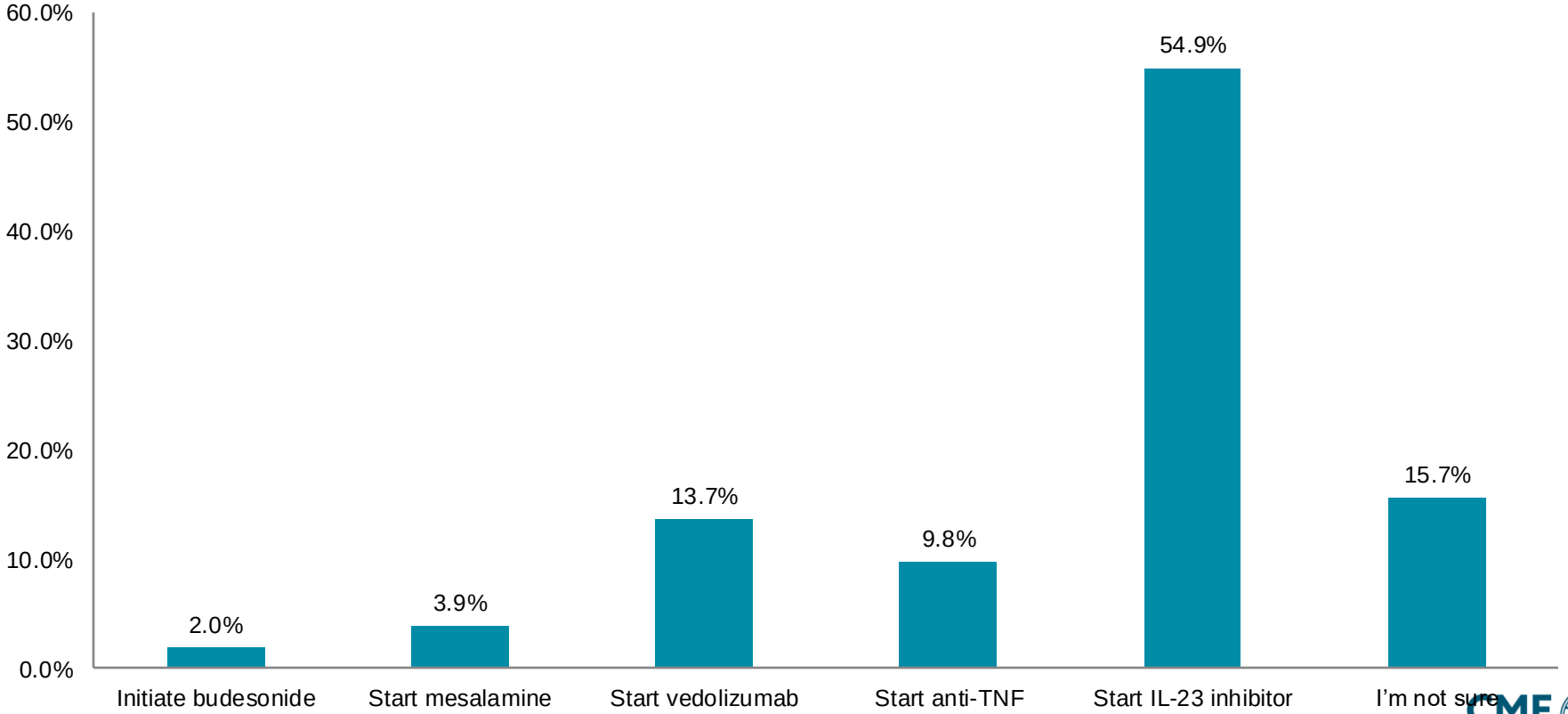


Audience Response

How would you treat this patient?

A. Initiate budesonide
B. Start mesalamine
C. Start vedolizumab
D. Start anti-TNF
E. Start IL-23 inhibitor
F. I’m not sure

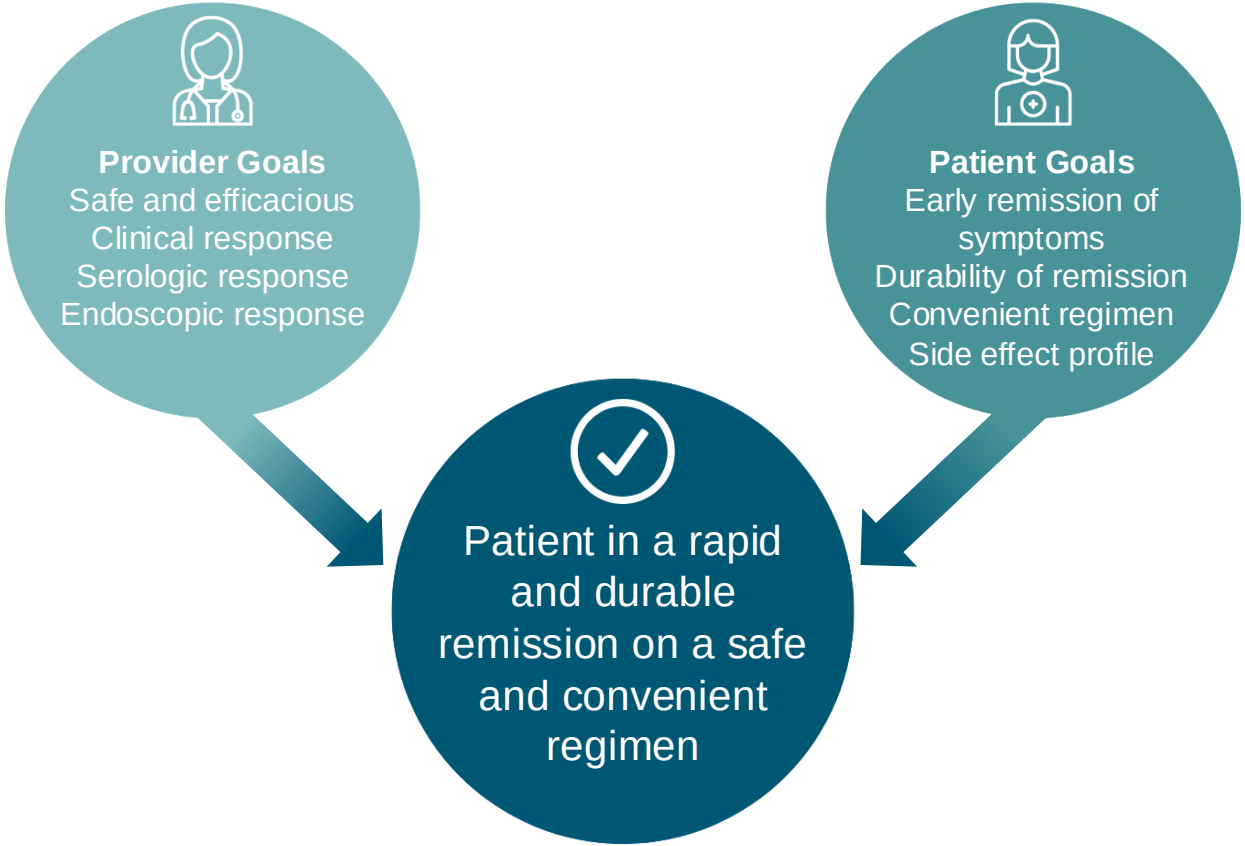
How would you treat this patient?



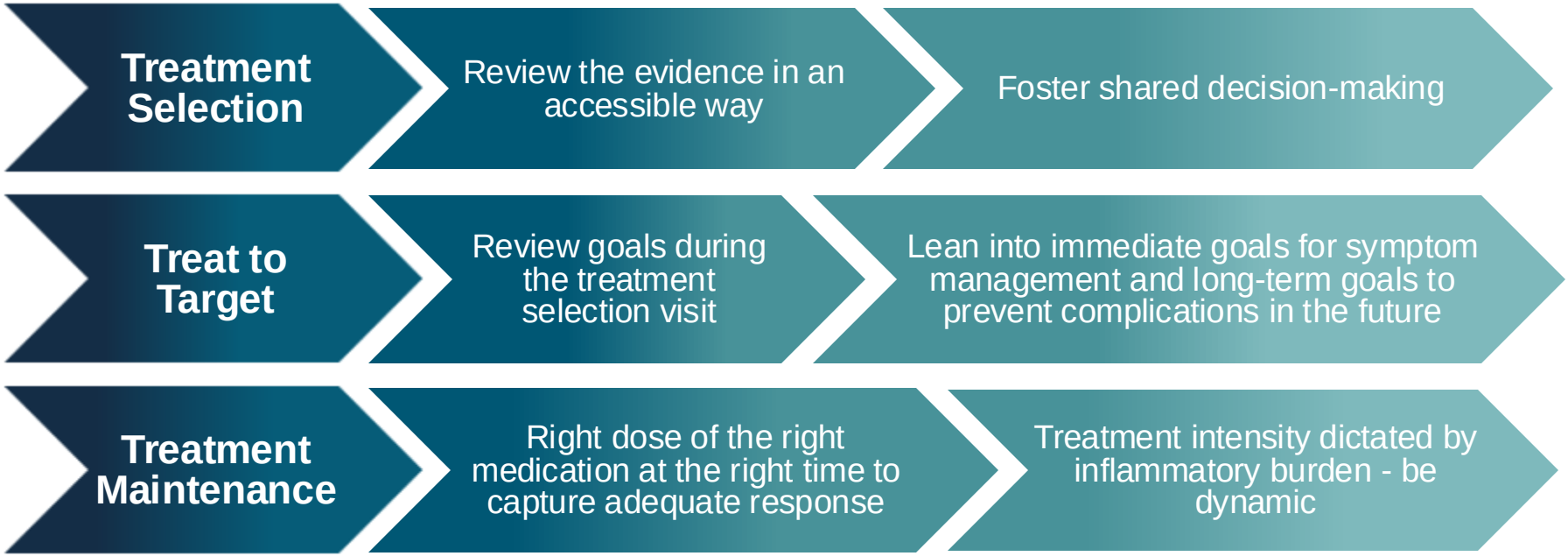
Results recorded on Feb 6, 2025.

CME OUTFITTERS

Aligning on Treatment Goals with Patients

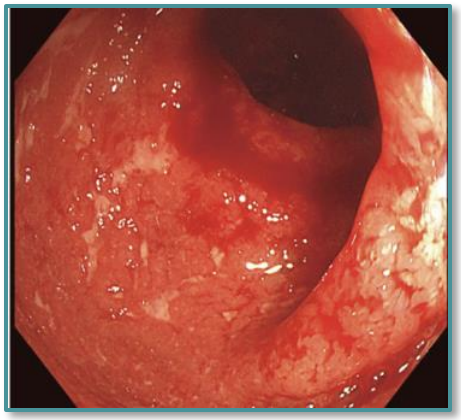


Education to Ensure Alignment



Patient Case: Hailey J.

- 38-year-old woman with 2-year history of UC
- Currently being treated with adalimumab every 2 weeks
- Annual review of treatment plan
  - Concern for poor control of inflammation
- Current symptoms:
  - 5-8 stools per day, urgency and rectal bleeding
- Colonoscopy:
  - Active disease up to 65 cm, Mayo 2
- Labs:
  - Calprotectin 950 µg/mg
- CRP 3.9
- *C. diff* and infectious workup negative

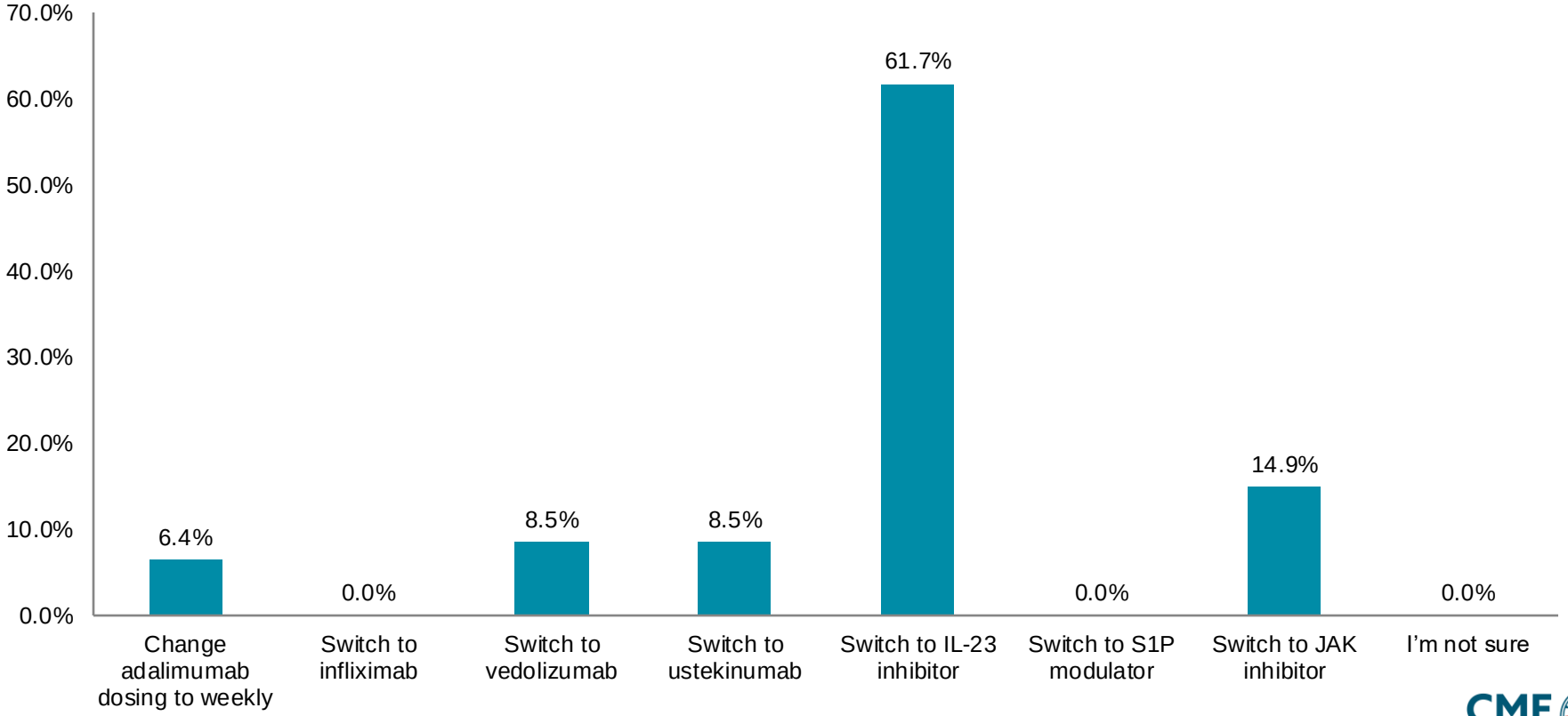


Audience Response

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

What would you do next?



Results recorded on Feb 6, 2025.

CME OUTFITTERS

New AGA Living Guidelines on Treatment of Moderate to Severe UC

ADVANCED THERAPY-NAÏVE PATIENTS (FIRST-LINE THERAPY)

SUGGEST using a **HIGHER** efficacy or **INTERMEDIATE** efficacy medication rather than a lower efficacy medication.
(Conditional recommendation, low certainty of evidence)

HIGHER EFFICACY MEDICATIONS: Infliximab, Vedolizumab, Ozanimod, Etrasimod, Upadacitinub*, Risankizumab, Guselkumab
INTERMEDIATE EFFICACY MEDICATIONS: Golimumab, Ustekinumab, Tofacitinib*, Filgotinib*, Mirikizumab
LOWER EFFICACY MEDICATIONS: Adalimumab

PRIOR EXPOSURE TO ONE OR MORE ADVANCED THERAPIES, PARTICULARLY TNF ANTAGONISTS

SUGGEST using a **HIGHER** efficacy or **INTERMEDIATE** efficacy medication rather than a lower efficacy medication.
(Conditional recommendation, low certainty of evidence)

HIGHER EFFICACY MEDICATIONS: Tofacitinib, Upadacitinub, Ustekinumab
INTERMEDIATE EFFICACY MEDICATIONS: Filgotinib, Mirikizumab, Risankizumab, Guselkumab
LOWER EFFICACY MEDICATIONS: Adalimumab, Vedolizumab, Ozanimod, Etrasimod

*The FDA label recommends the use of JAKis only in patients with prior failure or intolerance to TNF antagonists.
Filgotinib is not available for use in the United States.

Singh S, et al. *Gastroenterology.* 2024;167(7):1307-1343.

SMART Goals
Specific, Measurable, Attainable, Relevant, Timely

- Appreciate the role of the IL-23/Th17 axis in driving the inflammatory pathogenesis of IBD
- Differentiate between IL-23 targeted therapies based on their unique characteristics to individualize and optimize patient treatment
- Consider early use of IL-23 therapies in appropriate patients based on the latest evidence and recommendations
- Collaborate with your patients to identify the best treatment option for their goals

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