SYLLABUS & COURSE GUIDE

A Free, 90-Minute Live Activity
Premiere Date: Monday, October 28, 2024
7:30 PM - 9:00 PM ET

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Faculty:
Marla Dubinsky, MD (Moderator)
David P. Hudesman, MD, FACG, AGAF
Corey A. Siegel, MD, MS

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Information for Participants

Statement of Need

Cytokines, such as interleukin (IL)-23, are key drivers of intestinal inflammation in patients with inflammatory bowel disease. While all IL-23–targeted agents neutralize IL-23, differences in antibody structure can improve the ability of these agents to capture this inflammatory cytokine from a main source of production, namely CD64-positive myelocytes. As the treatment landscape of IL-23–targeted therapies continues to expand, it is crucial that gastroenterology clinicians understand the differentiating aspects of current and emerging treatments in order to develop an efficacious, lasting, and individualized treatment plan for each patient.

In this CME Outfitters livestream symposium, expert faculty will review the functions of Fc gamma receptors, CD64 and its connection with IL-23, the molecular attributes of anti–IL-23 therapies, in vivo data on expression of CD64 monocytes, and the most recent clinical trial data differentiating the anti–IL-23 agents. To demonstrate these concepts, animated 3-D models will be included in the educational program and available to attendees.

Learning Objectives

At the conclusion of this activity, learners will be able to better:

- Assess the role of pro-inflammatory cytokines in driving inflammation in the pathogenesis of IBD
- Classify the role of the IL-23/Th17 inflammatory axis in IBD pathogenesis
- 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

Financial Support

This activity is supported by an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.- both are Johnson & Johnson companies.

Target Audience

Gastroenterologists, gastroenterology fellows, physician associates (PAs), nurse practitioners (NPs), and nurses

Faculty

MARLA DUBINSKY, MD (MODERATOR)

Professor of Pediatrics and Medicine
Co-Director, Susan and Leonard Feinstein IBD Clinical Center
Director, Marie and Barry Lipman IBD Preconception and Pregnancy Clinic
Icahn School of Medicine, Mount Sinai New York
Chief, Division of Pediatric GI and Nutrition
Mount Sinai Kravis Children's Hospital
New York, NY

Marla C. Dubinsky, MD, is a Professor of Pediatrics and Medicine at the Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Dubinsky received her medical degree from Queen's University, Canada. She completed her pediatric residency at Alberta Children's Hospital, Calgary, Canada, and her clinical fellowship in gastroenterology and nutrition at Sainte-Justine Hospital at the University of Montreal, Canada. She completed her research fellowship in inflammatory bowel disease (IBD) at Cedars-Sinai Medical Center in Los Angeles, California, where she served as the Director of the Pediatric IBD Center before going to Mount Sinai as the Chief of Pediatric Gastroenterology and Nutrition at the Mount Sinai Kravis Children's Hospital and as Co-Director of the Susan and Leonard Feinstein IBD Clinical Center. Dr. Dubinsky is also Co-Director of the IBD Preconception and Pregnancy Planning Clinic at Mount Sinai. She is Co-Founder of Mi-Test Health as well as Cornerstones Health, a non-profit organization dedicated to enhancing and transforming communication between health care providers, patients, and industry partners through a creative, comprehensive, and expert-based educational program. She is also Co-Founder of Trellus Health, a resilience-driven, connected health solution for chronic conditions, leading with IBD. She is also a recipient of the 2022 Sherman Prize.

Dr. Dubinsky has been engaged in IBD clinical and translational research for over two decades. Her primary research focuses on developing predictive models and web-based decision support tools that integrate clinical markers and biomarkers to predict the natural history of IBD and response to therapy. She has a keen interest in personalized medicine in IBD, and her research uncovers predictors of rapid disease progression with the goal of preventing complications by altering treatment plans. Dr. Dubinsky is the principal investigator of multiple large longitudinal cohorts including the Road to Prevention Multiplex Family Program at Mount Sinai with over 700 enrolled participants, with a goal of using multi-omics data to predict the development of IBD in unaffected family members. She is co-investigator of the Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease (RISK) study and senior author on the manuscript presenting a model to predict the natural history of pediatric Crohn's disease. Dr. Dubinsky is very committed to women's reproductive health in IBD, and in addition to her research in this field she is Co-Founder of WECARE in IBD, an organization dedicated to the health of women with IBD. She is very committed to leading the next generation of female leaders in the field of gastroenterology. She has lectured widely, both nationally and internationally, and has published in more than 340 peer-reviewed journals, including *New England Journal of Medicine*, *Gastroenterology*, *Lancet*, *JAMA*, *The Journal of Pediatric Gastroenterology and Nutrition*, *The Journal of Crohn's and Colitis*, *Inflammatory Bowel Diseases*, and *The American Journal of Gastroenterology*.

Dr. Dubinsky reports the following financial relationships:

Advisory Board and Consultant: AbbVie Inc.; Abivax; AstraZeneca; Bristol Myers Squibb Company; Celltrion Inc.; Janssen Biotech, Inc.; Lilly; Merck & Co., Inc; Pfizer Inc.; Prometheus Biosciences; Spyre Therapeutics, Inc.; and Takeda Pharmaceuticals U.S.A., Inc.

Other financial or material support: (PI) Janssen Biotech, Inc. Road to Prevention; (Co-PI) Helmsley Foundation PK Dashboard Optimized Dosing of Infliximab Is Not Inferior to Standard Reactive Dosing: The OPTIMIZE Trial

DAVID P. HUDESMAN, MD, FACG, AGAF

Director, Inflammatory Bowel Disease Center at NYU Langone Health
Professor of Medicine, NYU Grossman School of Medicine
New York, NY

David P. Hudesman, MD, is Director of the Inflammatory Bowel Disease Center at NYU Langone Health and Professor of Medicine at the NYU School of Medicine. He specializes in the diagnosis and treatment of inflammatory bowel disease (IBD) and in the provision of integrated, seamless, patient-centered care. His research is focused on the development of biomarkers and evaluation and optimization of new medical therapies for the treatment of Crohn's disease and ulcerative colitis. Dr. Hudesman serves on the Educational Affairs Committee of the American College of Gastroenterology, the Professional Membership Committee of the Crohn's Colitis Foundation, and the Quality Committee of the American Gastroenterological Association.

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COREY A. SIEGEL, MD, MS
Director, Center for Digestive Health
Section Chief, Gastroenterology and Hepatology
Dartmouth Hitchcock Medical Center
Constantine and Joyce Hampers Professor of Medicine
Geisel School of Medicine at Dartmouth
Hanover, NH

Corey A. Siegel, MD, MS, is the Director of the Center for Digestive Health and Section Chief of Gastroenterology and Hepatology, Dartmouth Hitchcock Medical Center in Lebanon, New Hampshire. He is the Constantine and Joyce Hampers Professor of Medicine and a professor at The Dartmouth Institute for Health Policy and Clinical Practice at the Geisel School of Medicine at Dartmouth. Dr. Siegel attended college at Tufts University and then received his medical degree from Tufts University School of Medicine in Boston, Massachusetts. He completed his residency in internal medicine at the Dartmouth Hitchcock Medical Center where he also served as Chief Medical Resident. He then completed a fellowship in gastroenterology at Dartmouth Hitchcock followed by a fellowship in IBD at Massachusetts General Hospital in Boston.

Dr. Siegel's research interests include understanding risk-benefit tradeoffs in IBD, developing models to predict outcomes in Crohn's disease, creating tools to facilitate shared decision-making, expanding telemedicine services to patients with IBD living in rural locations, and improving the quality of care delivered to patients with IBD. He has been funded by the National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ), the Crohn's and Colitis Foundation, and the Leona M. and Harry B. Helmsley Charitable Trust for this work. Dr. Siegel has lectured nationally and internationally and published numerous journal articles and book chapters on this and other topics in IBD. He is the founder of the BRIDGe group, an international research collaboration of IBD investigators, and is currently the co-chair of the Crohn's and Colitis Foundation Quality of Care Program (IBD Qorus). Dr. Siegel was inducted into the International Organization for the Study of IBD (IOIBD) in 2013 and received the Sherman Prize in 2023. He lives in Hanover, New Hampshire with his wife and three boys.

Dr. Siegel reports the following financial relationships:

Advisory Board: AbbVie Inc.; Bristol Myers Squibb Company; Buhlmann; Janssen Pharmaceuticals, Inc.; Lilly; Napo Therapeutics; Pfizer Inc.; Prometheus Biosciences, Inc.; Roivant Sciences; Takeda Pharmaceuticals U.S.A., Inc.; and Trellus Health Inc.

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Other financial or material support: Dr. Corey Siegel is co-founder of MiTest Health, LLC (software company). Technology developed by MiTest Health, LLC has been licensed to Takeda.

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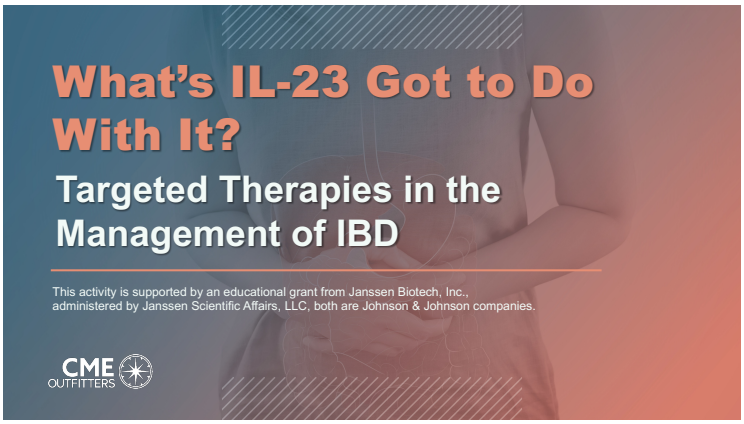
What's IL-23 Got to Do With It?
Targeted Therapies in the Management of IBD
This activity is supported by an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, both are Johnson & Johnson companies.
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LEARNING 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

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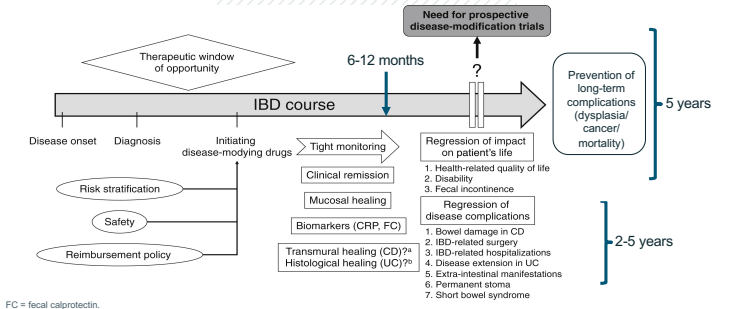
Section 1

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.

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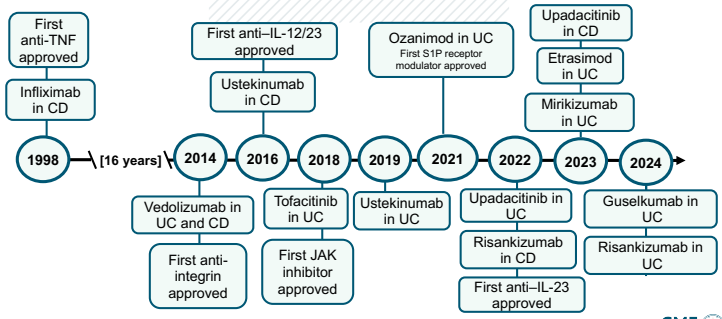
Evolution of IBD Treatment Landscape



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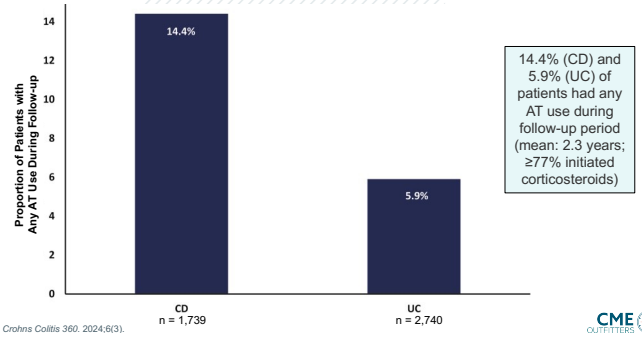
Advanced Treatment (AT) Uptake Is Low Within the First Few Years of IBD Diagnosis



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).

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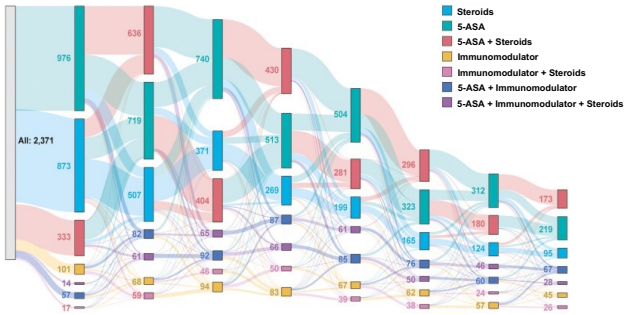
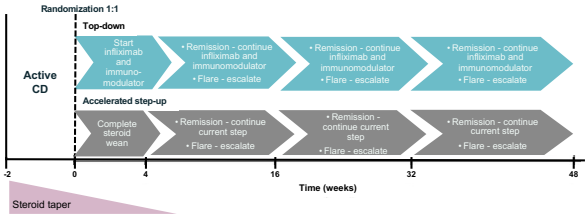
Patients with UC Are Treated with 5+ Rounds of Conventional Therapy Before They Receive an Advanced Therapy



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

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



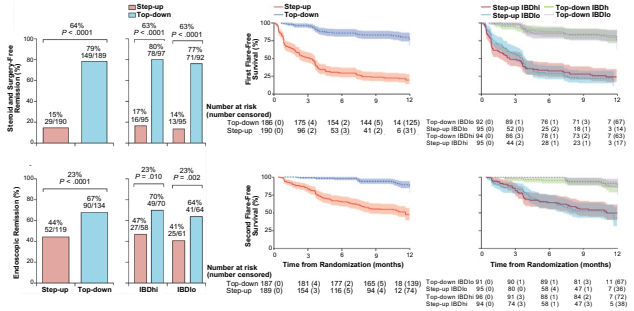
Primary endpoint
- Sustained surgery-free and steroid-free remission to week 48

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

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

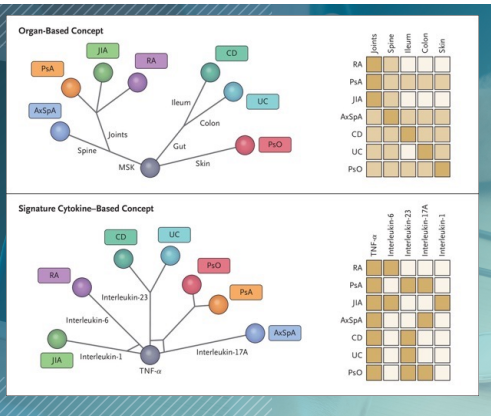
Early Effective Advanced Therapy (Not Biomarker Risk) Predicts CD Outcomes



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

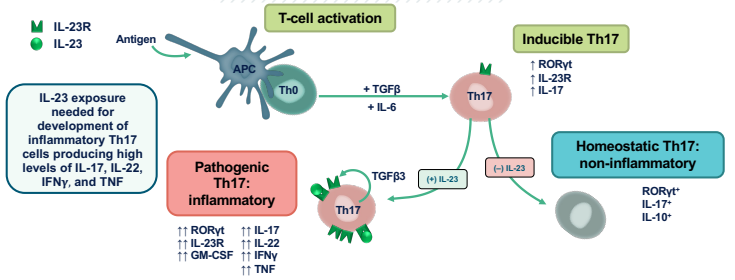
IQR = interquartile range. Noor V, et al. *Lancet Gastroenterol Hepatol*. 2024;9:415-427.

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.

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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.

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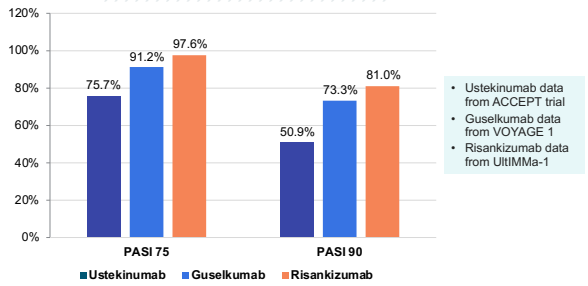
Efficacy of IL-23s in PsO: PASI Scores from Phase III Studies



- 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.

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FINAL THOUGHTS
Cytokines and Pathogenesis

Faculty Discussion

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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

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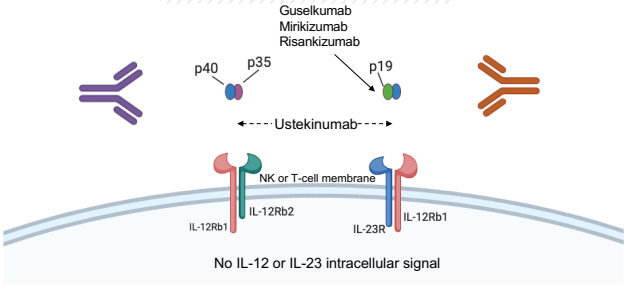
Anti-p40 (IL-12/23) and Anti-p19 (IL-23)



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.

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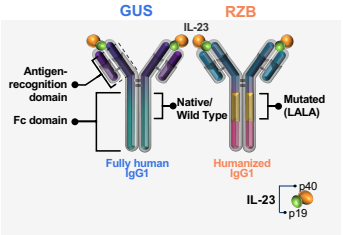
Clinically Relevant Differences Between Anti–IL-23 Therapeutic Antibodies May Be Related to Their Unique Molecular Attributes

- 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):i25-i26. 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.

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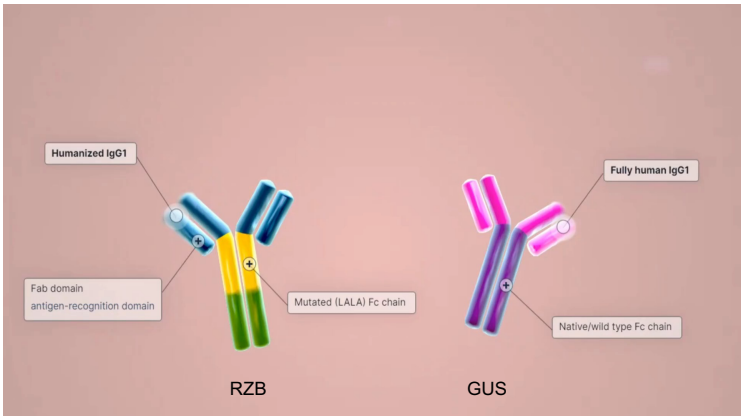
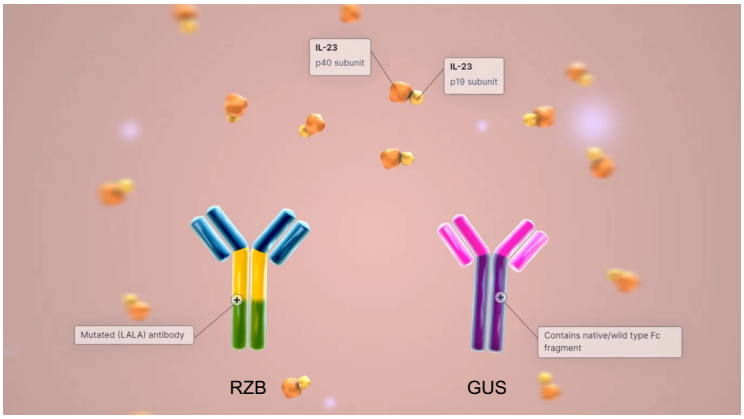
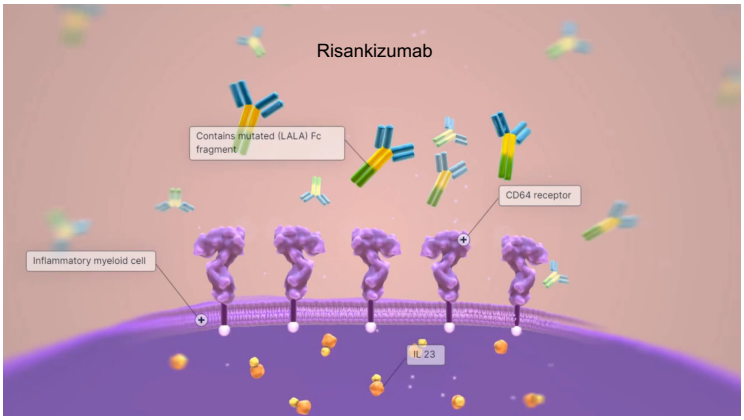
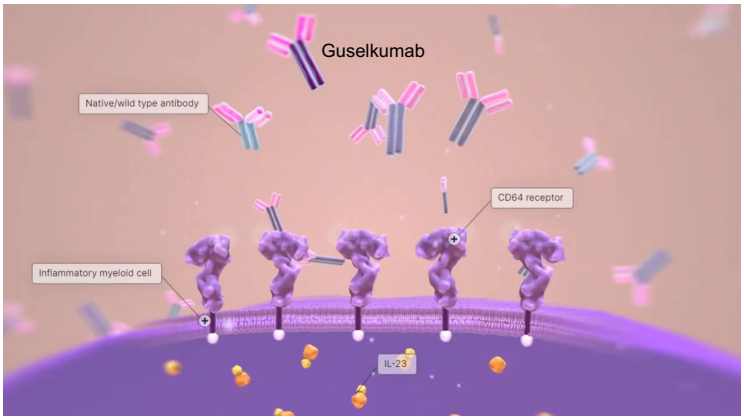

Humanized IgG1
Fab domain
antigen-recognition domain
Mutated (LALA) Fc chain
Fully human IgG1
Native/wild type Fc chain
RZB
GUS

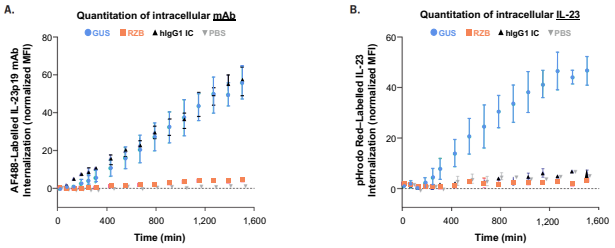

IL-23
p40 subunit
IL-23
p19 subunit
Mutated (LALA) antibody
Contains native/wild type Fc fragment
RZB
GUS


Risankizumab
Contains mutated (LALA) Fc fragment
CD64 receptor
Inflammatory myeloid cell
IL-23


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

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

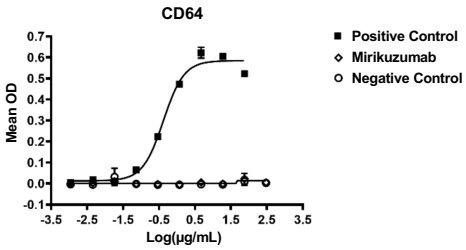
Quantitation of (A) mAb MFI and (B) IL-23 MFI in intracellular compartments of CD64+ inflammatory macrophages following treatment with IL-23p19 mAbs and IL-23



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

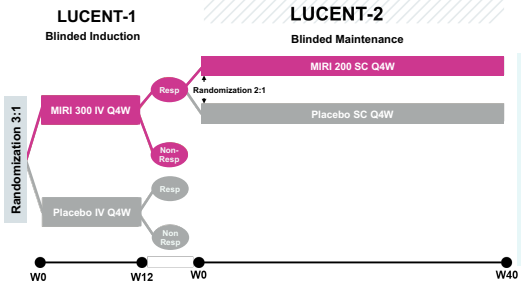
- All subjects who achieve response (i.e., clinical or endoscopic response) to active drug are **re-randomized** to active treatment or placebo

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

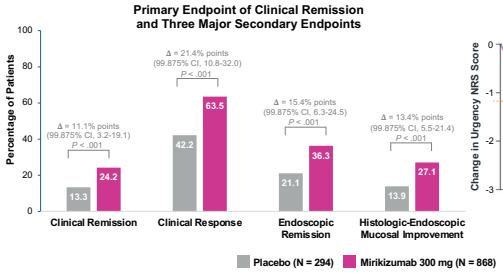


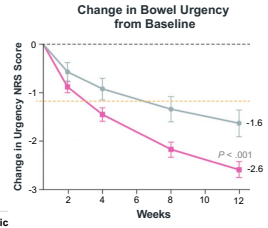
Induction: N = 1,281 adults with an incomplete response to, loss of response to, or inability to take conventional treatment, biologic therapy, or JAKi were assigned in a 3:1 ratio to receive MIRI (300 mg) or placebo IV every 4 weeks for 12 weeks

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.

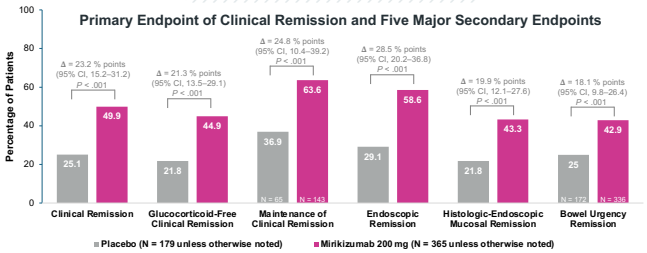
Mirikizumab in UC Induction: LUCENT-1





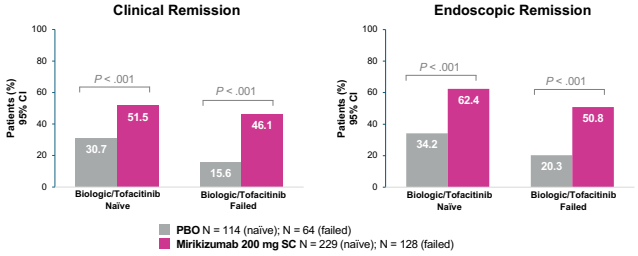
Mirikizumab is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients.
D'Haens G, et al. *N Engl J Med.* 2023;388:2444-2455.

Mirikizumab in UC Maintenance: LUCENT-2 Week 40 Endpoints



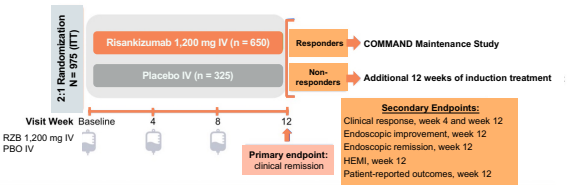
Clinical remission: stool frequency (SF) = 0, or SF = 1 with a ≥1-point decrease from baseline; rectal bleeding (RB) = 0; endoscopic subscore (ES) = 0 or 1 (excluding friability); endoscopic remission: ES = 0 or 1 (excluding friability), clinical remission at week 40, remission of symptoms at week 28, 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

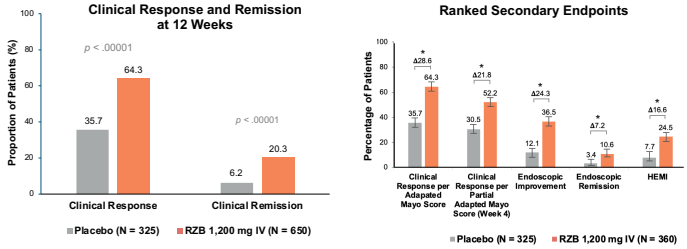


Key Inclusion Criteria:

- 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

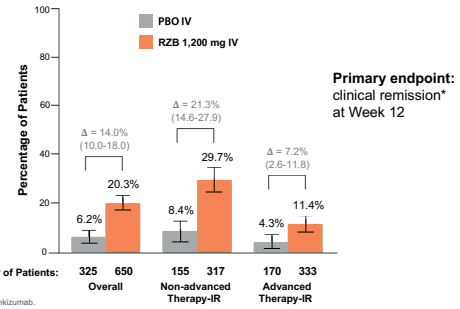
IV = intravenous
Louis E, et al. *JAMA*. 2024;332:881-897.

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.

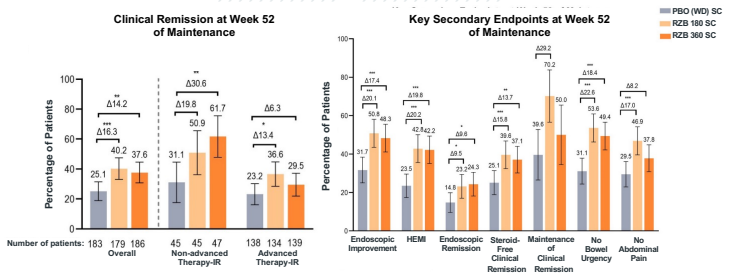
RZB in Treatment-Naïve and Treatment-Experienced Patients with UC: INSPIRE



Primary endpoint: clinical remission* at Week 12

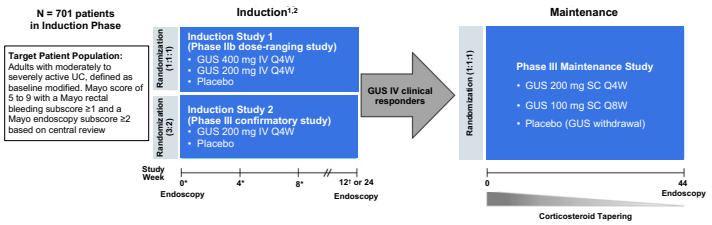
IR = inadequate responders; RZB = risankizumab.
*Clinical remission per adapted Mayo score: stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤1 without friability.
Risankizumab is indicated for patients with moderately to severely active UC.
Louis E, et al. *JAMA*. 2024;332:881-897.

Risankizumab Maintenance in UC: COMMAND



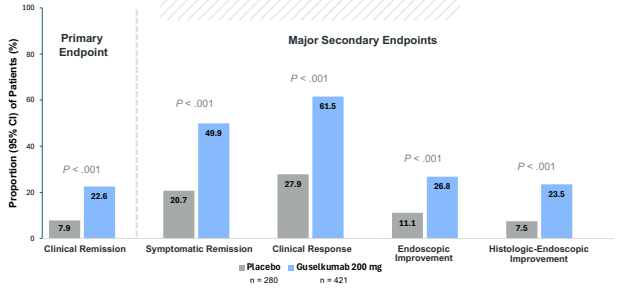
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$ versus PBO (WD) SC.
Risankizumab is indicated for the treatment of moderately to severely active ulcerative colitis and Crohn's disease in adult patients.
Louis E, et al. *J Crohns Colitis*. 2024;18(Suppl 1)i10-i12.

Guselkumab in UC: QUASAR



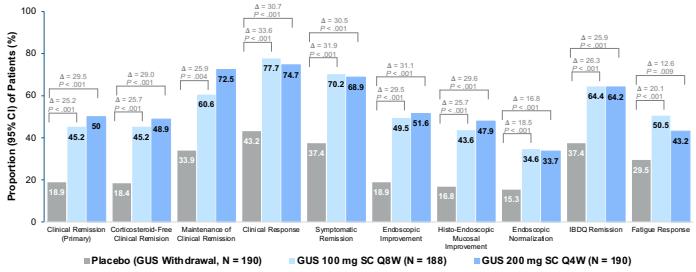
Q4W = every 4 weeks; Q8W = every 8 weeks.
*Study treatment administered; †Study treatment administered to Week 12 clinical non-responders.
GUS is indicated for adult patients with moderately to severely active ulcerative colitis.
1. Peyrin-Biroulet L, et al. *Gastroenterology*. 2023;165:1443-1457. 2.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

Guselkumab in UC Induction: QUASAR Phase III Week 12 Endpoints



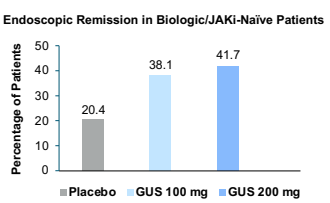
GUS is indicated for adult patients with moderately to severely active ulcerative colitis.
Clinical remission defined as a Mayo stool frequency subscore of 0 or 1 with no increase from baseline, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability.
Allegretti J. Abstract 913b presented at DDW 2023. *Gastroenterol Hepatol*. 2023;19:9-10.

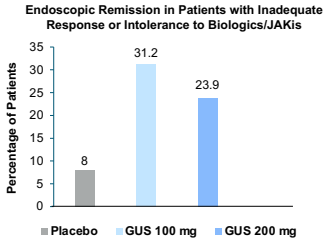
Guselkumab in UC Maintenance: QUASAR Week 44 Endpoints



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)

AEs = adverse events.
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 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(S1):i10-i12.

Guselkumab Safety in UC

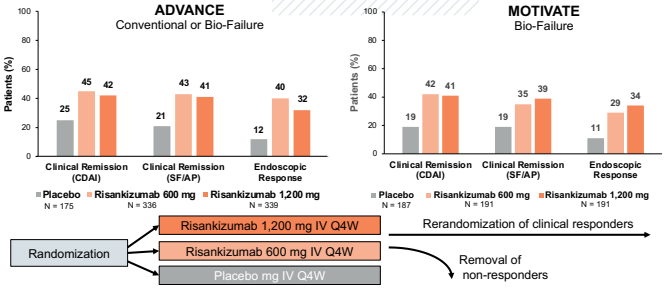
Outcome	Placebo (n = 105)	Guselkumab 200 mg IV (n = 101)	Guselkumab 400 mg IV (n = 107)	Combined (n = 208)
Any AE	59 (56.2)	45 (44.6)	53 (49.5)	98 (47.1)
AE within 1 hour of infusion	2 (1.9)	2 (2.0)	0	2 (1.0)
Serious AE	6 (5.7)	1 (1.0)	3 (2.8)	4 (1.9)
Death	0	0	0	0
Discontinuation for AE	3 (2.9)	1 (1.0)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

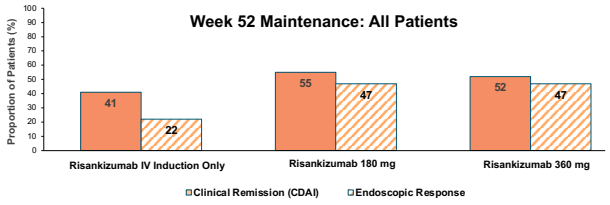
Corey Siegel, MD, MS

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; 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 ≤ CDAI <150.
D'Haens G, et al. *Lancet*. 2022;399(10340):2015-2030. Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046.

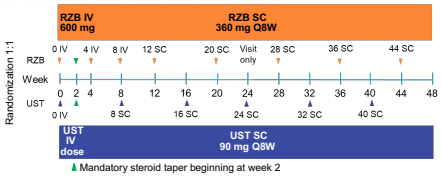
FORTIFY: Risankizumab Maintenance in CD



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)]



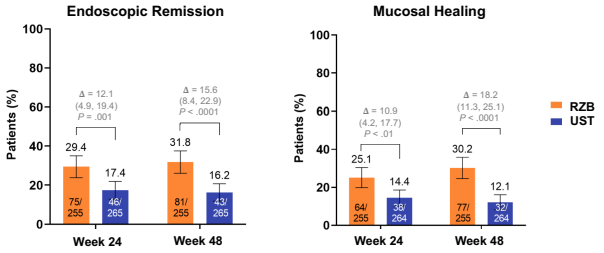
Key Eligibility Criteria:

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

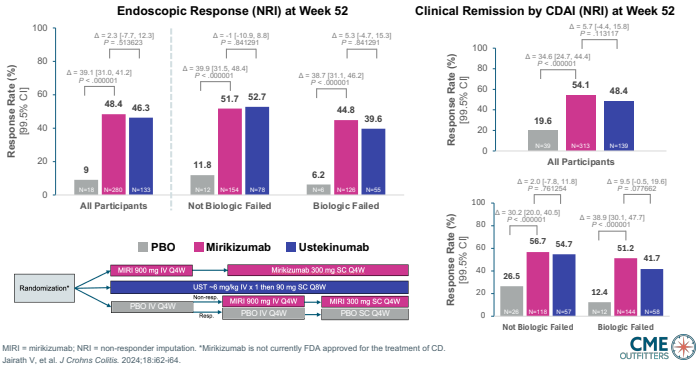
Peyrin-Biroulet L, et al. *N Engl J Med*. 2024;391:213-223.

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



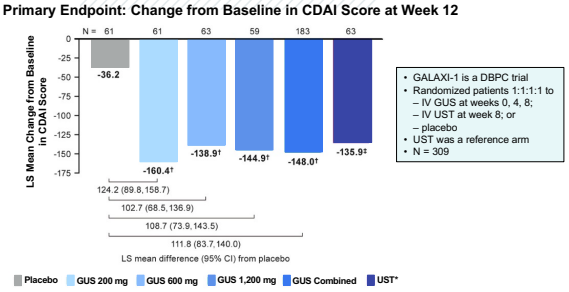
RZB = risankizumab; UST = ustekinumab.
Peyrin-Biroulet L, et al. *N Engl J Med*. 2024;391:213-223.

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



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.

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

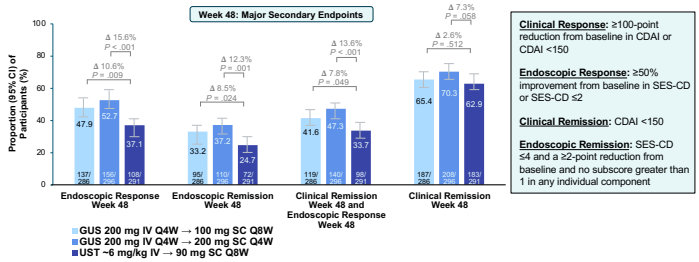


- GALAXI-1 is a DBPC trial
- Randomized patients 1:1:1:1 to
  - IV GUS at weeks 0, 4, 8;
  - IV UST at week 8; or
  - placebo
- UST was a reference arm
- N = 309

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

GUS* and 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. *Gueselkumab 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.

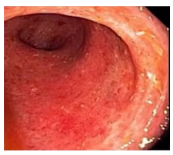
CME OUTFITTERS

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

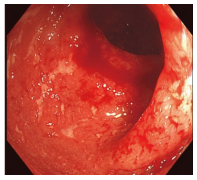
What would you do next?

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

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

Thank you for joining us.
Don't forget to collect your credit.

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In-Person

Livestream

Livestream: What’s IL-23 Got to Do With It? Targeted Therapies in the Management of IBD