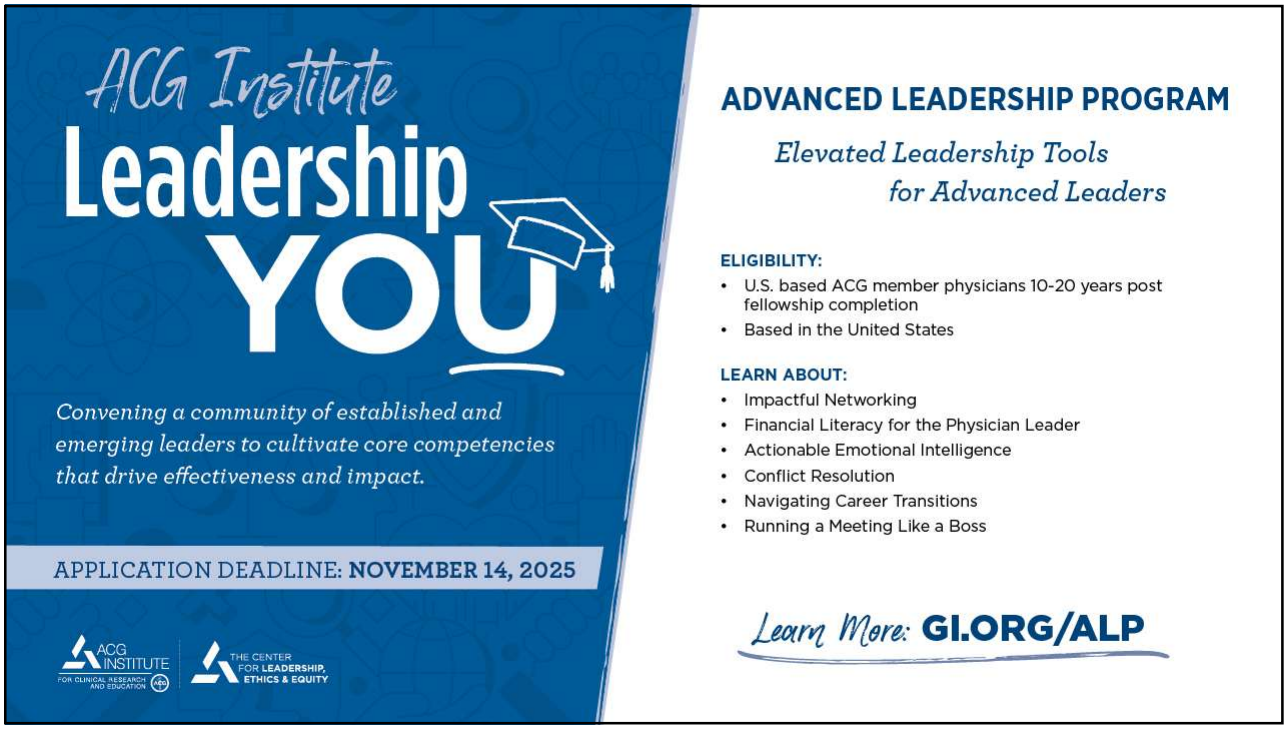
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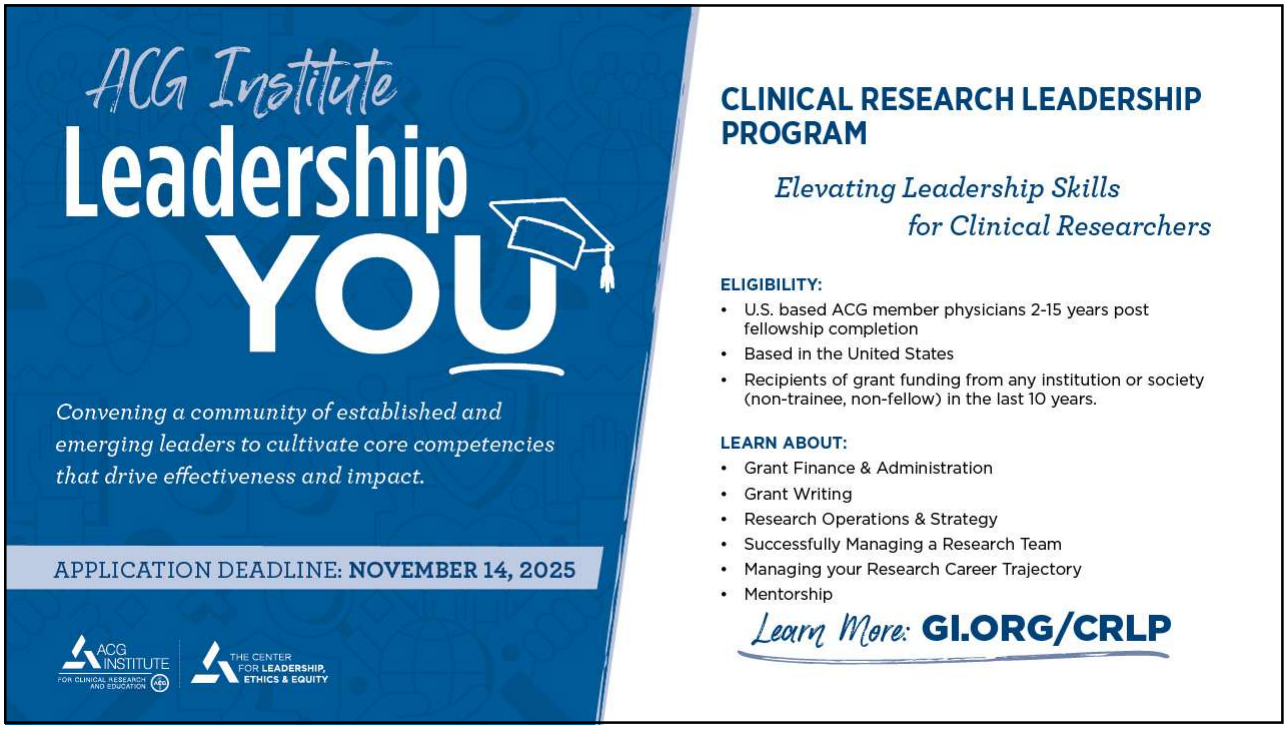
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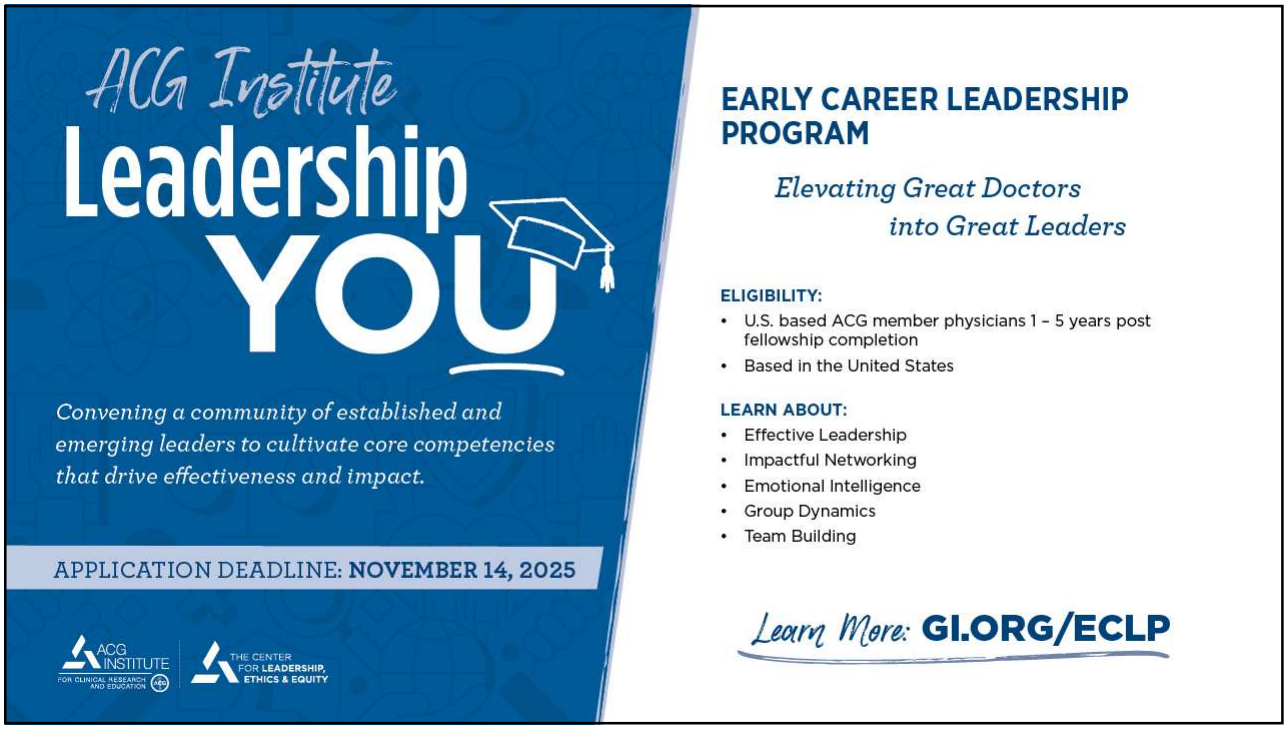
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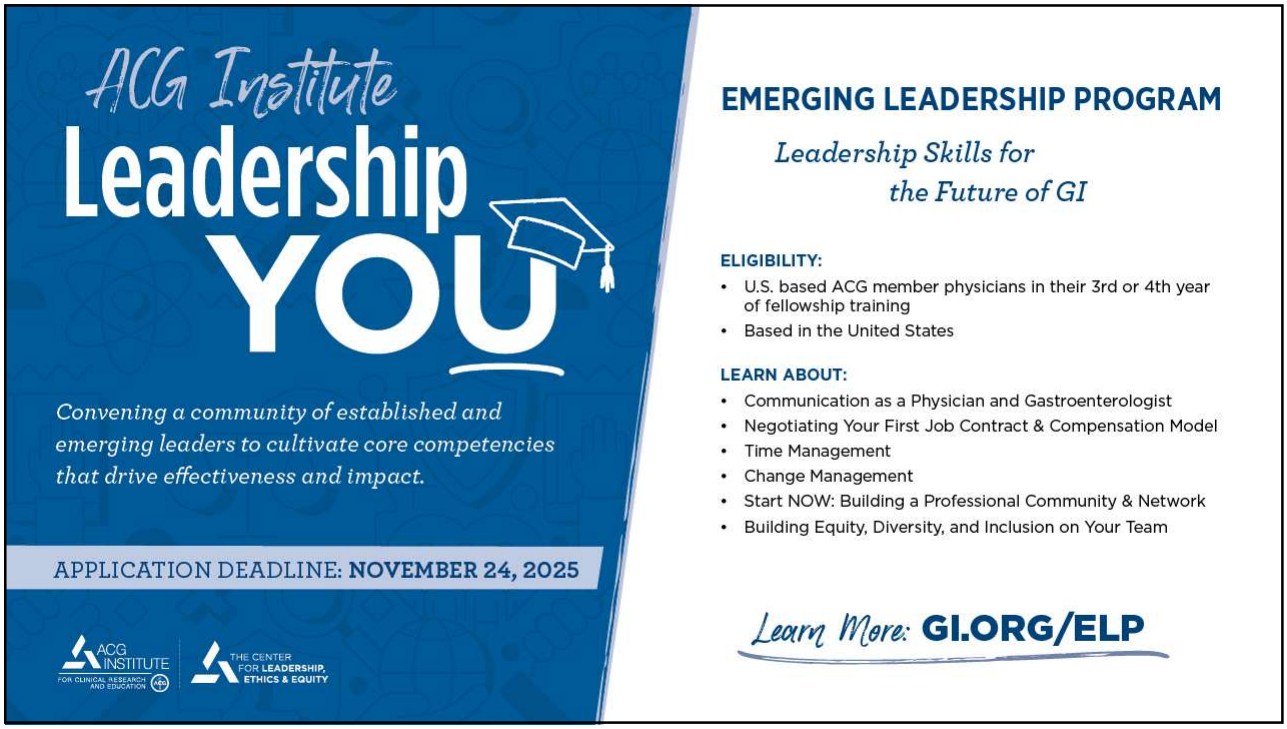
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NOTE: Must complete Prequalification Form (bit.ly/33guW6k) by November 3rd

6

ACG/ASGE Epidemiologic Research Award in Gastrointestinal Endoscopy

$50k/ 1- or 2-year award

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- **Request a Letter of Support from GIQuIC by November 3**
  - Email: research@giquic.org

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- **Visit gi.org/research-awards** to learn more about the 8 grant categories & apply
- **New! Grant Writing Resources -** gi.org/grant-writing-resources
  - for grant tips, videos, and written resources

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Virtual Grand Rounds

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Participating in the Webinar

All attendees will be muted and will remain in "Listen Only Mode"

Type your questions here so that the moderator can see them.
Not all questions will be answered but we will get to as many as possible.

A handout with the slides and room to take notes can be downloaded from your control panel.

Exit

Moderator:
Edward V. Loftus, Jr., MD, FACG

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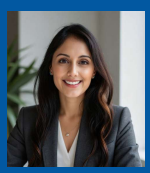
ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 42 – Thursday October 16, 2025
The Role of Social Determinants of Health in Gastroenterology Care
Faculty: Costas H. Kefalas, MD, MMM, MS-PopH, FACG
Moderator: Sonali Paul, MD, FACG
At Noon and 8pm Eastern

There will be No Virtual Grand Rounds October 23rd and 30th for the ACG 2025 Annual Meeting
We hope you will join us in Phoenix or Online!



Week 45 – Thursday, November 6, 2025
Quality Indicators for Upper GI Endoscopy
Faculty: Rena H. Yadlapati, MD, MSHS, FACG
Moderator: Dayna S. Early, MD, FACG
At Noon and 8pm Eastern

Visit **gi.org/ACGVGR** to Register

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ACG Virtual Grand Rounds

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Disclosures

Gary R. Lichtenstein MD, FACG

AbbVie: Consultant, Speakers Bureau; American Regent: Consultant, Speakers Bureau; Bausch Health: Speakers Bureau; Bristol Meyers Squibb / Celgene: Consultant, Research Grant; Celltrion: Consultant; Eli Lilly: Consultant, Data Safety Monitoring Board, Speakers Bureau; Focus Medical Communications: Speakers Bureau; Johnson and Johnson: Consultant, Speakers Bureau, Research Grant, University of PA IBD Fellowship Support; Kabi Fresenius: Consultant; MedEd Consultants: Consultant; Merck: Consultant; Pharmacosmos: Consultant; Physician Education Resource: Speakers Bureau; Pfizer Pharmaceuticals: Consultant; Takeda: Consultant; UCB: Consultant, Research Grant; Vindico: Speakers Bureau

Edward V. Loftus, Jr., MD, FACG

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**All of the relevant financial relationships listed for these individuals have been mitigated*

Off label discussion of: Azathioprine, 6-Mercaptopurine, Methotrexate, and Mesalamine

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Updated Guidelines for the Management of Crohn's Disease: 2025

Gary R. Lichtenstein, MD, FACG
Professor of Medicine
Raymond and Ruth Perelman School of Medicine of the University of Pennsylvania
Vice Chief, Division of Gastroenterology and Hepatology
Development and Philanthropy
Director Emeritus, Program for Inflammatory Bowel Disease
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

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Agents Not FDA Approved will be discussed

- Azathioprine
- 6-Mercaptopurine
- Methotrexate
- Mesalamine

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Learning Objectives

- Incorporate a goal-based management plan for IBD into your practice
- Treat effectively early
- Interpret the available data for comparative efficacy of available treatments in Crohn's disease
- Develop a rational strategy for treatment selection and optimization in patients with Crohn's disease

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What's New in Crohn's Disease?

- **Evolving approach to management and monitoring**
  - Treat to target
  - Persistent Unmet need
  - Intestinal ultrasound
  - AGA Guideline on monitoring
- **New treatments approved by FDA**
  - Risankizumab (p19IL23 antibody)
  - Guselkumab (p19IL23 antibody)
  - Mirikizumab (p19IL23 antibody)
  - Upadacitinib (selective JAK-1)
  - Infliximab SC
  - Vedolizumab SC
  - Biosimilars - Infliximab, Adalimumab and Ustekinumab
- **Novel risk stratification approach**
- **Considerations for positioning therapies**

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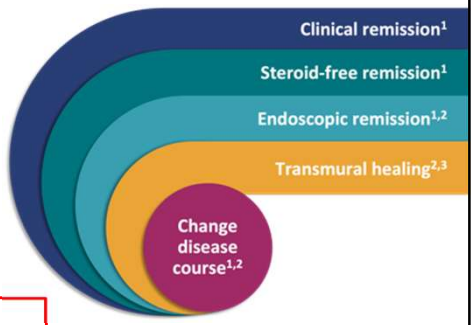
Types of Remission in IBD

- Clinical/Symptomatic remission
- Deep remission (objective bowel and inflammation control)
- Functional remission (addresses other co-morbid problems)
- Goal: meaningful functional remission that lasts



Ultimate Goal: Sustained functional remission

[1]Peyrin-Biroulet L et al. *Am J Gastroenterol*. 2015;110:1324-38; [2]Sandborn WJ et al. *J Crohns Colitis*. 2014;8:927-35; [3]Castiglione F et al. *Aliment Pharmacol Ther*. 2019;49:1026-39; Rubin DT et al. *Am J Gastroenterol Suppl*. 2016;3:4-7.

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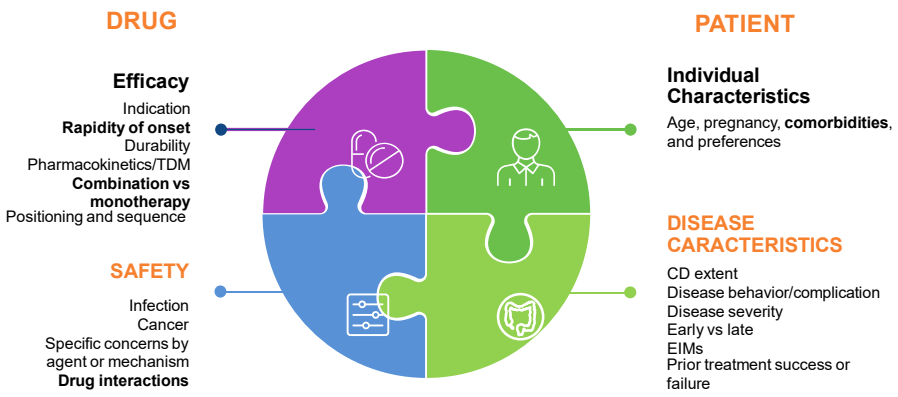
Pieces of the Therapy Choice Puzzle in IBD



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Prognosis and Assessing Disease Severity in Crohn's Disease

Crohn's Disease

Low Risk

- Age at initial diagnosis > 30 years
- Limited anatomic involvement
- No perianal and/or severe rectal disease
- Superficial ulcers
- No prior surgical resection
- No stricturing and/or penetrating behavior

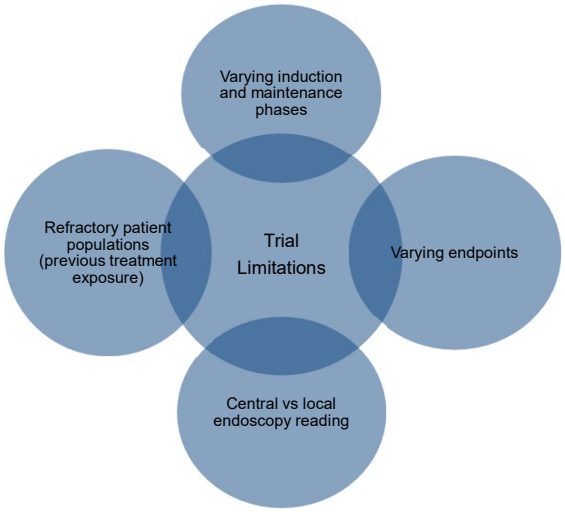
Moderate/High Risk

- Age at initial diagnosis < 30 years
- Extensive anatomic involvement
- Perianal and/or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Stricturing and/or penetrating behavior

Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264
Sandborn WJ. *Gastroenterology*. 2014;147(3):702-703.

Clinical Trial Considerations

- Failing to account for differences in trial designs may be misleading to interpretation
- When evaluating efficacy outcomes across trials, consider:
  - Placebo-adjusted response rates
  - Numbers needed to treat
  - Risk ratios



Sands BE et al. *J Crohns Colitis.* 2019;13:1217-1226.

Evaluation of Head-To-Head Trials

Strengths and weaknesses of different comparative approaches

Approach	Strengths	Weaknesses
Meta-analysis	• Provides context that individual studies cannot provide • Outcomes might include more precise estimate of treatment effects or risk factors for disease than individual studies • Reduces the need for repeated research studies	• Included studies should be similar enough to be pooled • Potential research and publication bias • Erroneous or poorly conducted studies can adversely affect results of entire meta-analysis • Needs appropriate comparison methods to adjust for trial differences
Real-world evidence	• Bridges the gap between clinical trials and practice • Provides information on a population-based level from a wide variety of sources • Captures long-term data about effectiveness and safety, including rare events, in heterogeneous populations • Complements randomized controlled trails	• Data completeness, accuracy and consistency may not be uniform (potential selection bias, information bias, recall bias and detection bias) • Study populations are unselected, which limits treatment comparisons
Head-to-head trials	• Gold standard: compare therapies in the same population and setting • Increasingly required by regulatory authorities	• Expensive • Long timelines • Eligible participants do not always reflect real-world patients owing to strict inclusion and exclusion criteria • Require careful study design and selection of appropriate comparator and end points

Pouillon L et al. *Nature Review Gastroenterology Hepatology*. 2020; 17: 365-376.

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What's New in Crohn's Disease?

Evolving approach to management and monitoring

- Persistent unmet needs
- Treat-to-target strategy
- Intestinal ultrasound
- AGA Guideline on monitoring
- **Novel risk stratification approach**
- **Considerations for positioning therapies**

New treatments approved by FDA

- Anti-IL-23 (p19) antibodies
  - Risankizumab
  - Guselkumab
  - Mirikizumab
- JAK-1 inhibitors
  - Upadacitinib
- Subcutaneous therapies
  - Infliximab SC
  - Vedolizumab SC
- Biosimilars - Infliximab, Adalimumab and Ustekinumab

AGA = American Gastroenterological Association; IL = interleukin; JAK = Janus kinase; SC = subcutaneous.
Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264

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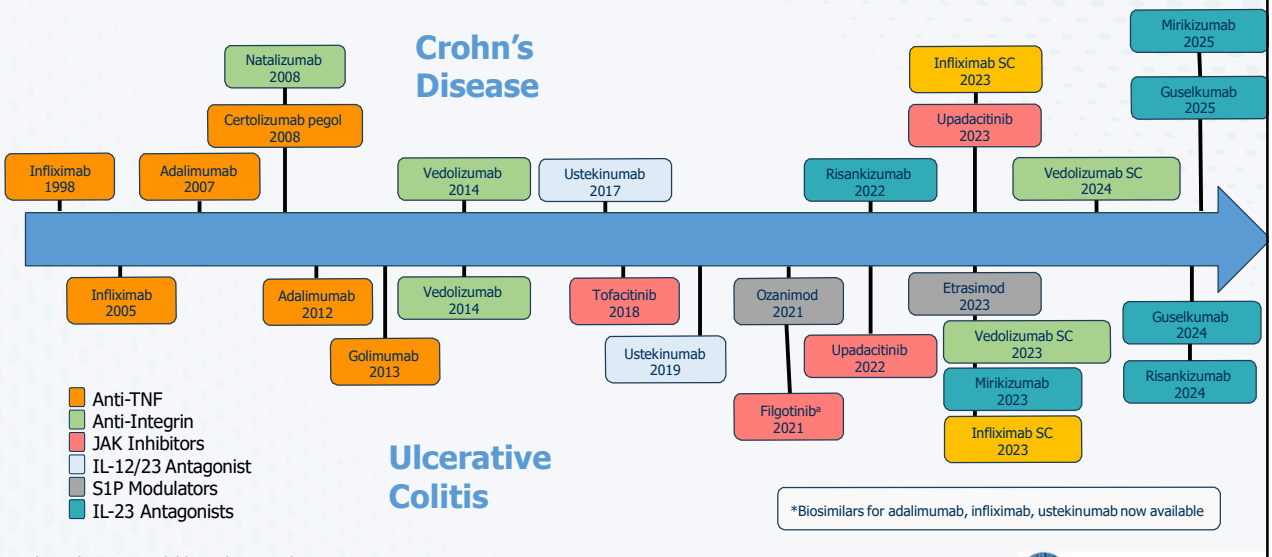
2025: Advanced IBD Therapies for IBD



[a]Filgotinib is not available in the United States.
Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264; Rubin DT, et al. *Am J Gastroenterol.* 2025;120(6):1187-1224.

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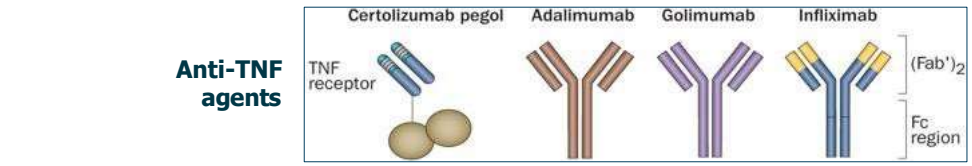
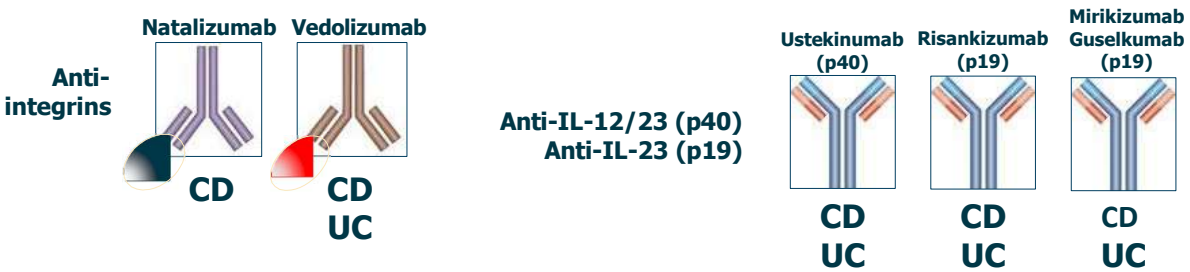
Biologic Therapies for IBD





Fab = fragment antigen-binding; Fc = fragment crystallizable.
Modified from: van Schouwenburg PA, et al. *Nat Rev Rheumatol.* 2013;9(3):164-172.

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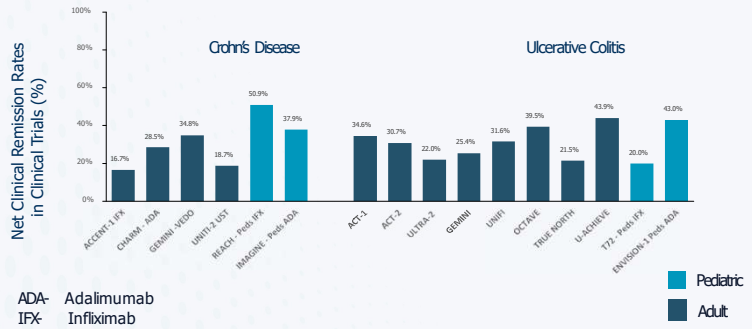
Persistent Unmet Needs in IBD Management Despite Treatment Advances

The "Ceiling Effect"



ADA- Adalimumab
IFX- Infliximab
UST- Ustekinumab
VEDO- Vedolizumab

Current tactics for therapy choice led to remission in <u>less than 50%</u> of patients with their first therapeutic choice.

Significant Room for Improvement

ADA = adalimumab; IFX = infliximab; UST = ustekinumab; VEDO = vedolizumab.
Kayal M, et al. *Clin Gastroenterol Hepatol.* 2022;S1542-3565(22)00201-4; Kayal M, et al. *Clin Gastroenterol Hepatol.*2023;S1542-3565(23)00035-6.

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We Need Additional Tools To Manage IBD More Effectively

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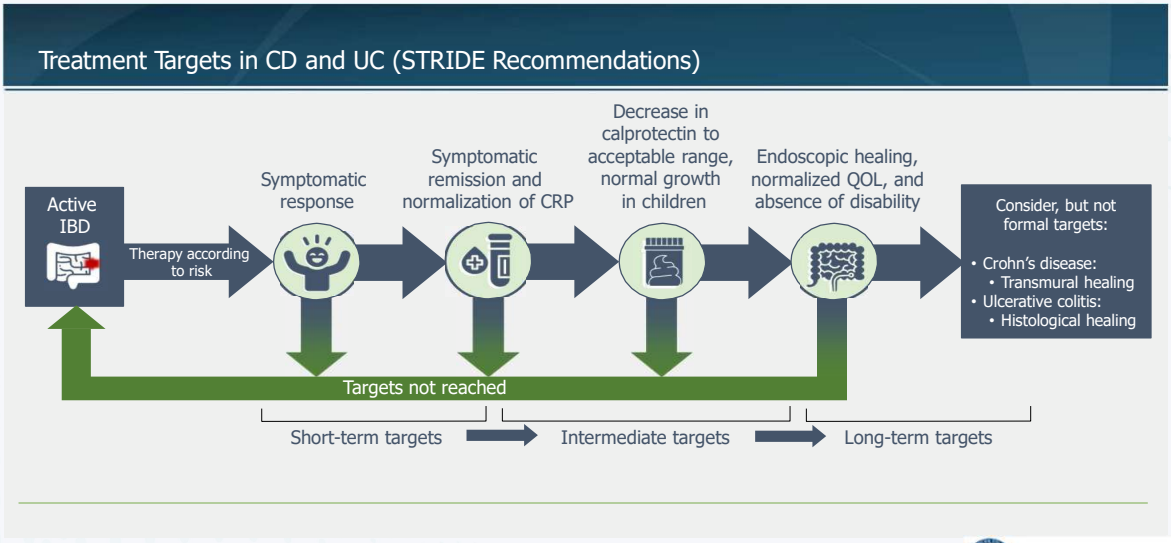
Objectives



QOL = quality of life; UC = ulcerative colitis.
Turner D, et al. *Gastroenterology*. 2021;160(5):1570-1583.

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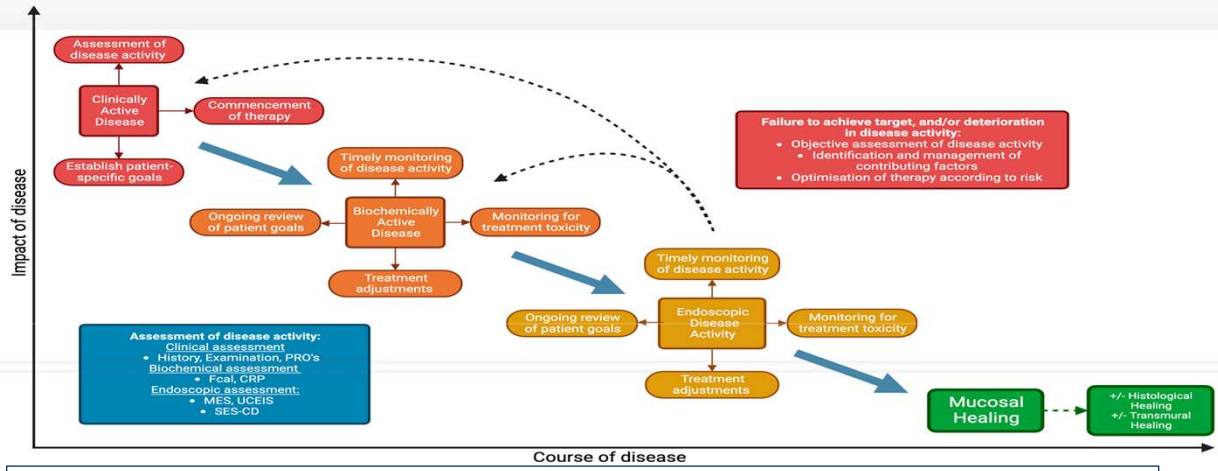
Use Treat-to-Target



Composite Targets in IBD:

- CD: No abdominal pain, no irregular bowels, endoscopic/radiologic healing
- UC: No bleeding, normal stool frequency, endoscopic healing

West J, et al. *J Clin Med*. 2023;12(19):6292.

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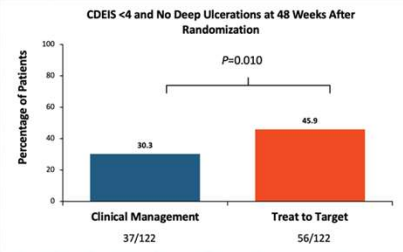
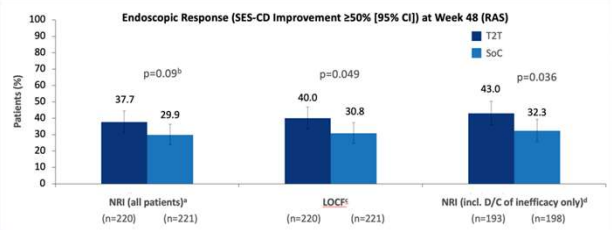
Treat-to-Target Studies in Crohn's Disease

CALM
- Adalimumab +/- azathioprine
- CDAI, prednisone
- CRP, fecal CalPro

STARDUST
- Ustekinumab
- Endoscopic response





CalPro = calprotectin; CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; CRP = C-reactive protein; D/C = discontinuation; LOCF = last-observation carried forward; NRI = non-responder imputation; RAS = randomized analysis set; SES-CD = Simple Endoscopic Score in Crohn's Disease; SoC = standard of care; T2T = treat-to-target.

Colombel JF, et al. *Lancet.* 2018;390(10114):2779-2789; Danese S, et al. *Lancet Gastroenterol Hepatol.* 2022;7(4):294-306.

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Intestinal Ultrasound

Characteristics:
- Bowel wall thickness
  - (Normal < 3 mm in small bowel and colon)
- Bowel wall hyperemia by color doppler imaging
- Bowel wall layer stratification
- Presence of inflammatory/mesenteric fat
- Lymphadenopathy
- Complications (stricture, abscess, fistula)

Limitations:
- Limited visualization of the stomach, esophagus, and rectum
- No ability for interventional procedure
- - Exam may be limited by body habitus and overlying bowel gas

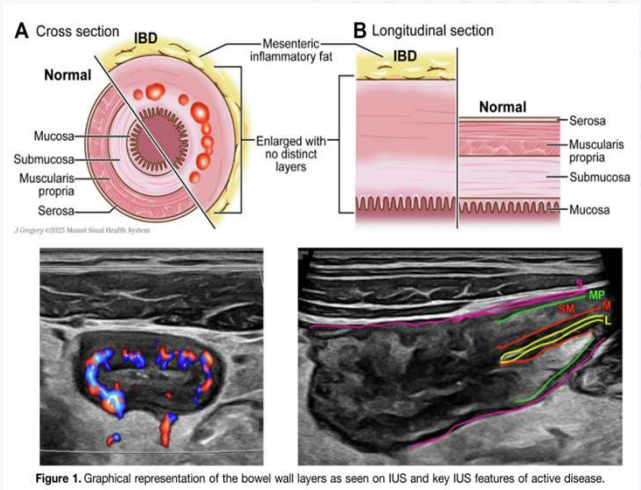

Figure 1. Graphical representation of the bowel wall layers as seen on IUS and key IUS features of active disease.

IUS =intestinal ultrasound.

Chavannes M, et al. *Clin Gastroenterol Hepatol.* 2024;22:1790–1795.

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Biomarkers for Crohn's Disease

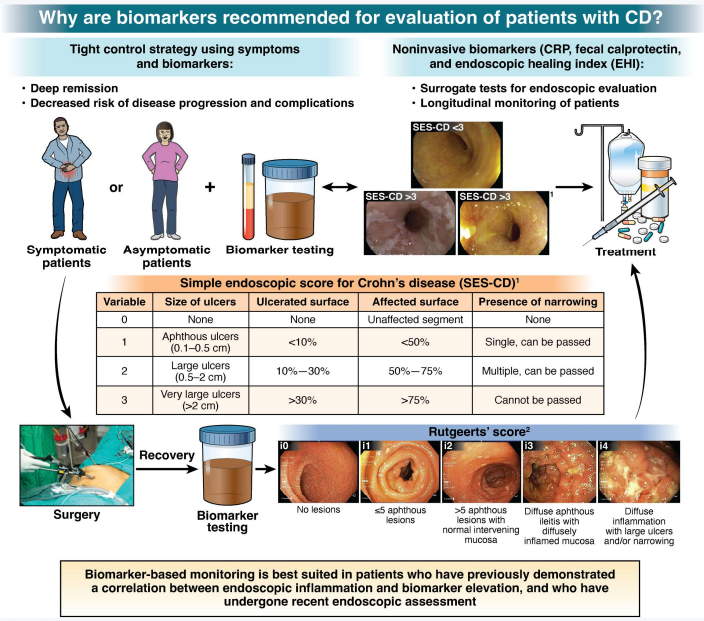
- Endoscopy
  - SES-CD
  - Rutgeert's Score
- CRP
- Calprotectin
- Radiology
  - MRE
  - CTE
  - Abdominal ultrasound


Gastroenterology 2023;165:1367–1399

GUIDELINES

AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Crohn's Disease

Ashwin N. Ananthakrishnan,[1,*] Jeremy Adler,[2,3,*] Karen A. Chachu,[4,*] Nghia H. Nguyen,[5] Shazia M. Siddique,[6,7] Jennifer M. Weiss,[8] Shahnaz Sultan,[9] Fernando S. Velayos,[10] Benjamin L. Cohen,[11] and Siddharth Singh,[12,13] on behalf of the AGA Clinical Guidelines Committee*



CTE = computed tomography enterography;
MRE = magnetic resonance enterography.
Ananthakrishnan AN et al. *Gastroenterology*. 2023;165(6):1367-1399

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Develop Tailored Monitoring Strategies

- **Understand phase of management**
  - Induction
  - Maintenance
  - Recapture
- **Don't rely on symptoms**
- **Determine benchmarked biomarker**
  - Based on target
  - Sensitivity/reliability for monitoring
  - Availability (patient willingness/test availability/cost)
- **Consider endoscopic confirmation before treatment adjustment**
- **Determine cadence for monitoring**
  - Low risk, stable remission
  - High risk, stable remission
  - Result of last test
  - Sensitivity of the test for detecting meaningful change in disease status


Gastroenterology 2023;165:1367–1399

GUIDELINES

AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Crohn's Disease

Ashwin N. Ananthakrishnan,[1,*] Jeremy Adler,[2,3,*] Karen A. Chachu,[4,*] Nghia H. Nguyen,[5] Shazia M. Siddique,[6,7] Jennifer M. Weiss,[8] Shahnaz Sultan,[9] Fernando S. Velayos,[10] Benjamin L. Cohen,[11] and Siddharth Singh,[12,13] on behalf of the AGA Clinical Guidelines Committee*

Ananthakrishnan AN, et al. *Gastroenterology*. 2023;165(6):1367-1399.

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Choice of Therapy Is Based on Data and on Benefits and Risks

RISK

Risk: Benefit tolerance changes with acuity of illness and risk of poor outcomes

CDPATH

System dynamics analysis

- Clinical phenotype (SB, perianal)
- ASCA
- ANCA

Siegel CA et al. *Aliment Pharmacol Ther*. 2016;43: 262-271.

37

Crohn's Disease: Treat Effectively Early

CD patients treated with anti-TNF earlier in disease course (< 2 years) were 2-3 times more likely to be in clinical remission at 6-12 months

Study or subgroup	Early treatment biologics Events	Total	Remission rate	Control Events	Total	Remission rate	Weight	Odd ratio M-H, random, 95% CI
1.1.1 Adult								
D'Haens 2008	39	65	60.0%	23	64	35.9%	11.0%	2.67 (1.31, 5.45)
Schreiber 2010	24	39	61.5%	79	176	44.9%	11.1%	1.96 (0.97, 4.00)
Colombel 2015	105	134	78.4%	31	54	57.4%	12.1%	2.69 (1.36, 5.29)
Panaccione 2016	84	174	48.3%	418	1190	35.1%	50.9%	1.72 (1.25, 2.37)
Subtotal (95% CI)	**252**	**412**	**61.2%**	**551**	**1484**	**37.1%**	**85.2%**	**1.97 (1.53, 2.53)**
Total events	252			551				
Heterogeneity: Tau²=0.00; Chi²=2.18, df=3 (p=0.54); I²=0%								
Test for overall effect: Z=5.28 (p<0.00001)								
1.1.2 Paediatric								
Kim 2011	15	18	83.3%	5	11	45.5%	1.9%	6.00 (1.08, 33.38)
Hyams 2009	16	26	61.5%	13	26	50.0%	4.7%	1.60 (0.53, 4.82)
Walter 2014	58	68	85.3%	41	68	50.3%	8.2%	3.82 (1.67, 8.75)
Subtotal (95% CI)	**89**	**112**	**79.5%**	**59**	**105**	**56.2%**	**14.8%**	**3.07 (1.59, 5.94)**
Total events	89			59				
Heterogeneity: Tau²=0.03; Chi²=2.20. df=2 (p=0.33); I²=9%								
Test for overall effect: Z=3.33 (p=0.00009)								
Total (95% CI)	**341**	**524**		**610**	**1589**	**38.4%**	**100.0%**	**2.11 (1.66, 2.68)**
Heterogeneity: Tau²=0.00; Chi²=6.12. df=6 (p=0.41); I²=2%								
Test for overall effect: Z=6.13 (p<0.00001)								
Test for subgroup differences: Chi²=1.53, df=1 (p=0.22), I²=34.7%								

Ungaro RC et al. *Aliment Pharmacol Ther*. 2020;51(9):831-842.

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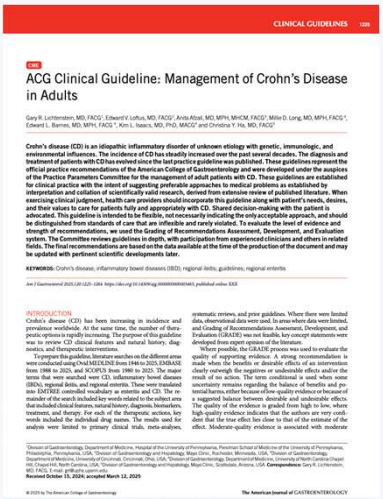
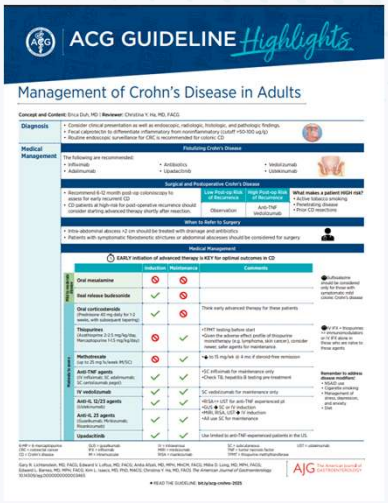
Updated ACG Guideline Highlights


CLINICAL GUIDELINES

ACG Clinical Guideline: Management of Crohn's Disease in Adults



Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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ACG Crohn's Disease Guidelines: Highlighted Statements

Diagnosis

- We recommend the use of fecal calprotectin (cutoff > 50 – 100 ug/g) to differentiate inflammatory from non-inflammatory disease of the colon (Strong recommendation; moderate level of evidence)

Therapy Initiation

- We suggest against requiring failure of conventional therapy prior to initiation of advanced therapy for the management of Crohn's disease (Conditional recommendation, low level of evidence)

Mild to Moderate CD

- We recommend against the use of oral mesalamine for induction or maintenance in patients with mildly to moderately active Crohn's disease (strong recommendation, moderate level of evidence)

ACG = American College of Gastroenterology.
Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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ACG Crohn's Disease Guidelines: Highlighted Statements

Moderate to Severe Crohn's Disease

- We recommend the use of Risankizumab as compared to Ustekinumab in patients with moderate to severe Crohn's disease and prior exposure to anti-TNF therapy. (Conditional recommendation; low level of evidence)
- Strong/Moderate recommendations for all of the IL-23 agents in Crohn's disease (Risankizumab, Mirikizumab and Guselkumab); for Guselkumab both SQ and IV load for induction

Perianal Crohn's Disease

- We recommend infliximab for induction of remission of perianal fistulizing Crohn's disease (strong recommendation, moderate level of evidence)

Post-Operative Crohn's Disease

- In patients with surgically induced remission of CD, we suggest postoperative endoscopic assessment at 6-12 months over no monitoring (conditional recommendation, moderate level of evidence)
- In Crohn's disease patients with low-risk recurrence of postoperative disease, we suggest continued observation as compared to immediate initiation of medical therapy for Crohn's disease (conditional recommendation, very low level of evidence)
- In high-risk Crohn's disease patients, we recommend anti-TNF therapy in order to prevent postoperative endoscopic recurrence (strong recommendation, moderate level of evidence)

IV = intravenous; SQ = subcutaneous; TNF = tumor necrosis factor.
Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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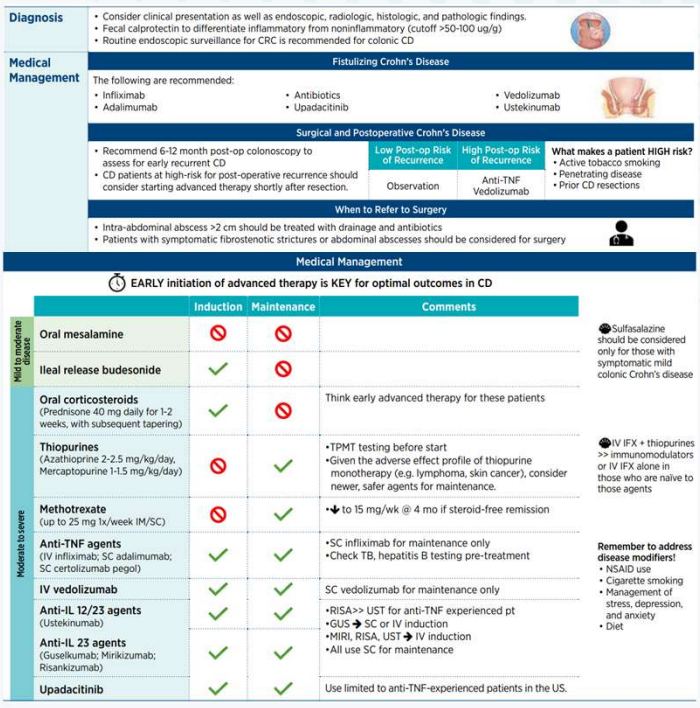
ACG Crohn's Disease Guidelines: Highlighted Statements



Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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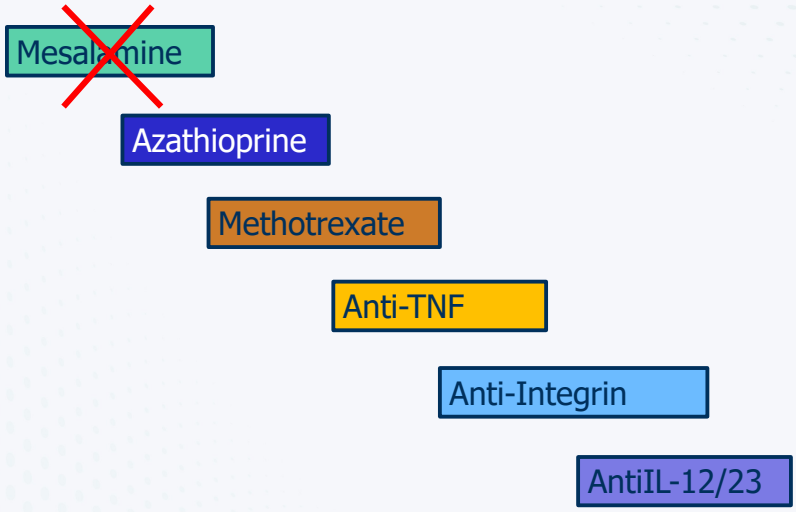
Prior Conventional Treatments: Crohn's Disease



sq = subcutaneous.
Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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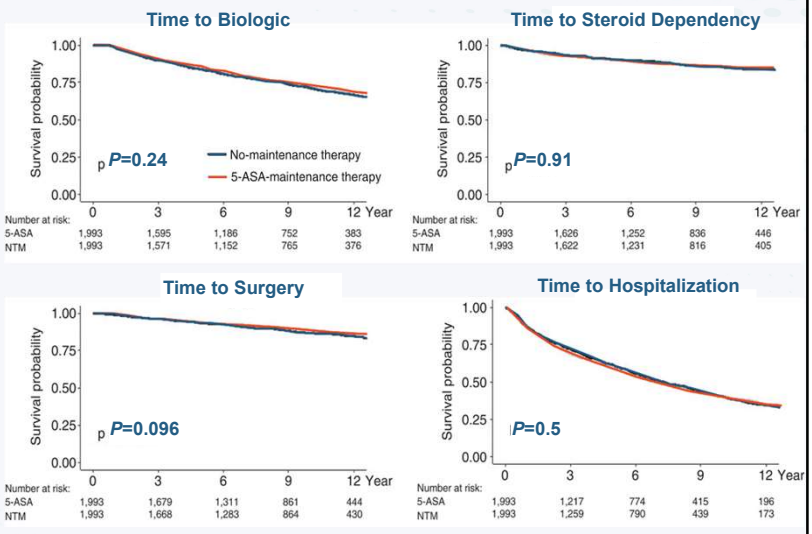
5-ASA Therapy Is *NOT* Superior to No Therapy in Patients With Mild CD

- Epi-IIRN dataset searched for all patients diagnosed with CD (n=19264) in Israel between 2005-2020
- Propensity score matching
- 3027 (26%) received 1st line 5-ASA and 5583 (29%) no therapy



Atia O et al. *Aliment Pharmacol Ther.* 2023 May;57(9):1004-1013.

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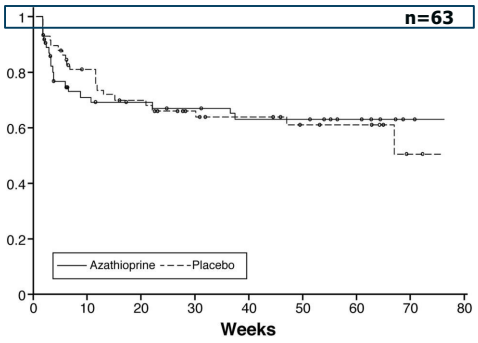
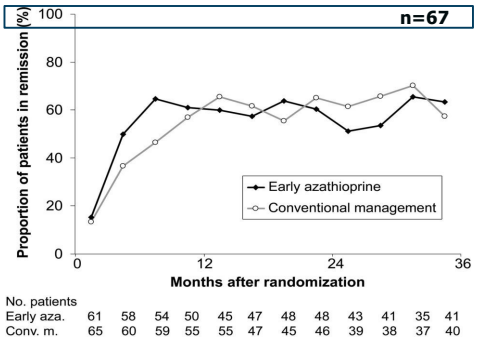
Early AZA Therapy is not More Effective than Placebo or Conventional Therapy for CD



Actuarial probability of survival free relapse. Defined as CDAI >175 in patients treated with azathioprine and placebo.[1]



Proportion of patients in **corticosteroid-free remission** per trimester over time. Concomitant proportions were significantly different only at trimester 3 (P<.05).[2]

aza = azathioprine; CDAI = Crohn's Disease activity index; Conv. m. = conventional management.
1. Panés J, et al. *Gastroenterology.* 2013;145(4):766-774; 2. Cosnes J, et al. *Gastroenterology.* 2013;145(4):758-765.

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Prior Conventional Treatments: Crohn's Disease

Azathioprine / 6-Mercaptopurine:

Because of their relatively slow onset of action of 8–12 weeks, thiopurines are not effective agents for induction of remission among patients with active, symptomatic disease

There are 3 scenarios by which a thiopurine is used after corticosteroid induction of remission.
1.) to initiate the thiopurine at the time of the first course of corticosteroid,
2.) after repeated courses of corticosteroids or in patients who are corticosteroid-dependent (i.e., unable to taper the steroid without CD relapse), and
3.) as a concomitant medication with an anti-TNF agent to reduce the risk of development of antibodies and improve pharmacokinetic parameters.

Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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Prior Conventional Treatments: Crohn's Disease

Recommendations for Management of Crohn's Disease

8. We recommend against azathioprine (at doses of 1.5–2.5 mg/kg/d) and 6-mercaptopurine (at doses of 0.75–1.5 mg/kg/d) for induction of remission in moderately to severely active CD (strong recommendation, moderate level of evidence).

9. We suggest azathioprine (at doses of 1.5–2.5 mg/kg/d) and 6-mercaptopurine (at doses of 0.75–1.5 mg/kg/d) for maintenance of remission in patients with moderately to severely active CD who had induction of remission with corticosteroids (conditional recommendation, low level of evidence).

11. We suggest methotrexate (up to 25mg once weekly intramuscular or subcutaneous) for maintenance of remission in patients with moderately to severely active CD who had induction of remission with corticosteroids (conditional recommendation, moderate level of evidence)

Key concepts

43. Azathioprine, 6-mercaptopurine, or methotrexate may be used in treatment of active CD and as adjunctive therapy for reducing immunogenicity associated with anti-tumor necrosis factor (TNF) therapy

Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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Meta Analysis: Risk of Lymphoma with AZA / 6-MP Use

- **18 studies (among 4383 citations) met inclusion criteria.**
- **The SIR for lymphoma was**
  - Overall- 4.92 (95% CI, 3.10–7.78),
  - 2.80 (95% CI, 3.10–7.78) in 8 population studies
  - 9.24 (95% CI, 4.69–18.2) in 10 referral studies.
- **Population studies demonstrated an**
  - Increased risk among current users (SIR=5.71; 95% CI, 3.72–10.1) but
  - No increased risk in former users (SIR=1.42; 95% CI, 0.86–2.34).

Kotlyar D, et al, Clinical Gastroenterology and Hepatology 2015;13:847–858.

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Meta Analysis: Risk of Lymphoma with AZA / 6-MP Use

- **Risk Became Significant after One year of exposure**
- **Sex***
  - Men have a greater risk than women (RR = 1.98; P < .05)
  - Both sexes were at increased risk for lymphoma
  - Men: SIR for men = 4.50 (95% CI 3.71–5.40)
  - Women: SIR for women = 2.29 (95% CI 1.69–3.05)
- **Age**
  - Age 30-59: 1 lymphoma per 2000 pt-yrs of followup
  - Patients < 30 years had the highest RR
    - SIR=6.99 (CI, 95% CI,2.99–16.4)
    - Younger men had the highest risk: Men < 30 : SIR~ 9
  - The absolute risk was highest in patients > 50 years 1:354 cases per patient–year RR=4.78

*- subanalysis of 2 studies

Kotlyar D, et al, Clinical Gastroenterology and Hepatology 2015;13:847–858.

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Methotrexate

- Effective for induction and maintenance of Crohn's disease[1]
- **NOT Primary therapy for UC** (METEOR and MERIT-UC trials negative)[4,5]
- Effective for prevention of anti-drug antibodies
- Limited by toxicity/side effects[2]
- Relatively contraindicated in menstruating females
- May impact sperm genetic integrity (n=4)[3]
- No data for its use as salvage therapy after failing anti-TNF therapy

Methotrexate Side Effects

- Rash
- Nausea, mucositis, diarrhea
- Bone marrow suppression
- Hypersensitivity pneumonitis
- Increased liver enzymes
- Hepatic fibrosis/cirrhosis

1. Feagan BG, et al. *N Engl J Med.* 1995;332(5):292-297; 2. Patel V, et al. *Cochrane Database Syst Rev.* 2014;2014(8):CD006884;
3. Ley D, et al. *Gastroenterology.* 2018;154(8):2064-2067; 4. Carbonnel F, et al. *Gastroenterology.* 2016;150(2):380-388;
5. Herfath H, et al. *J Crohns Colitis.* 2018;12(S1):S300-S301.

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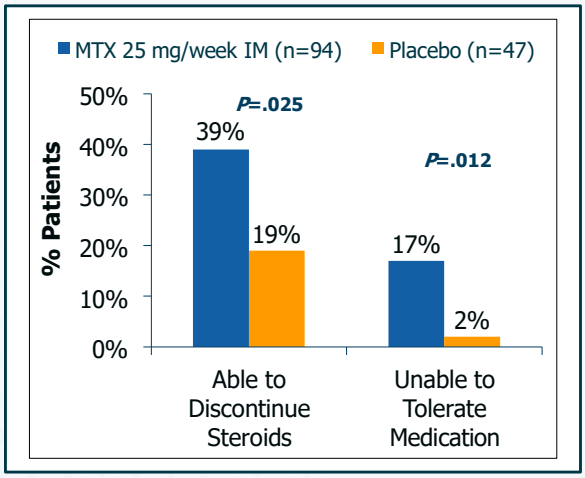
Induction and Maintenance of Remission With Methotrexate in Crohn's Disease



1

MTX 15 mg/week IM[2]

- After 40 weeks, the proportion of patients who remained in remission was higher in the methotrexate group than in the placebo group (26 of 40 [65%] vs 14 of 36 [39%]:
  - Unadjusted *P*=.04;
  - After adjustment for the route of entry into the trial and study center, *P*=.01
  - Absolute reduction in the risk of relapse, 26.1%; 95% CI, 4.4%-47.8%

IM = intramuscular; MTX = metheotrexate;
1. Feagan BG, et al. *N Engl J Med.* 1995;332(5):292-297.
2. Feagan BG, et al. *N Engl J Med.* 2000;342(22):1627-1632.

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Novel Treatments: Crohn's Disease 2025

- Guselkumab
- Mirikizumab
- Risankizumab
- Upadacitinib
- Vedolizumab sq
- Infliximab sq

sq = subcutaneous.
Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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Biologic therapy: Anti-IL-12/23 antibodies

Agents targeting IL-12/23 (anti-p40 antibody) and IL-23 (anti-p19 antibody)
Recommendation

17. We recommend ustekinumab in patients with moderate-to-severe CD for induction and maintenance of remission (strong recommendation, moderate level of evidence).

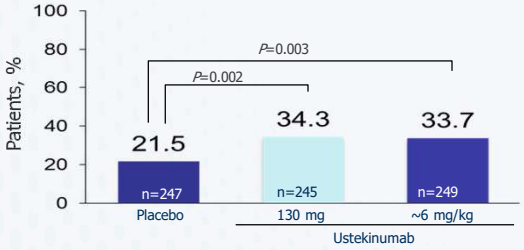
Key concept

46. Biologic therapy (including anti-IL-12/23 therapy, anti-TNF therapy, and anti-integrin therapy) dose optimization may be considered for patients with inadequate or loss of response to that specific biologic agent's induction and maintenance.

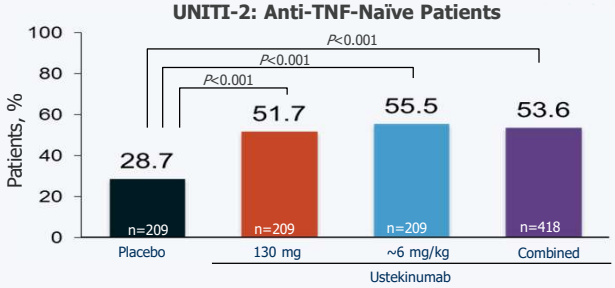
Ustekinumab

- Primary endpoint – clinical response at week 6 (≥100-point CDAI reduction)

UNITI-1: Patients Failing Anti-TNF Therapy



UNITI-2: Anti-TNF-Naïve Patients



CDAI = Crohn's Disease Activity Index.
Feagan BG, et al. *N Engl J Med.* 2016;375(20):1946-1960; Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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Biologic Therapy: Anti-IL-23 (p19) antibodies

Agents targeting IL-12/23 (anti-p40 antibody) and IL-23 (anti-p19 antibody)
Recommendation

17. We recommend ustekinumab in patients with moderate-to-severe CD for induction and maintenance of remission (strong recommendation, moderate level of evidence).

Key concept

46. Biologic therapy (including anti-IL-12/23 therapy, anti-TNF therapy, and anti-integrin therapy) dose optimization may be considered for patients with inadequate or loss of response to that specific biologic agent's induction and maintenance.

Guselkumab

- Superior to placebo in achieving clinical response at Week 12 and achieving clinical remission and endoscopic response at Week 48[1]
- Superior to ustekinumab in achieving endoscopic response and remission, but not clinical remission, at Week 48[1]
- Subcutaneous delivery safe, efficacious, and superior to placebo in achieving clinical remission and endoscopic response at Week 12[2]

Recommendation

20. We recommend the use of mirikizumab for induction and maintenance of remission in patients with moderate to severely active CD (strong recommendation, moderate level of evidence).
21. We recommend the use of intravenous guselkumab for induction followed by subcutaneous guselkumab for maintenance of remission in patients with moderate to severely active Crohn's disease (strong recommendation, moderate level of evidence).
22. We recommend the use of subcutaneous guselkumab for induction and maintenance of remission in patients with moderate to severely active Crohn's disease (strong recommendation, moderate level of evidence).

1. Panaccione R, et al. *Lancet Gastroenterol.* 2025;406(10501):358-375; 2. Hart A, et al. *Gastroenterol.* 2025 Mar 18:S0016-5085(25)00522-0;
3. Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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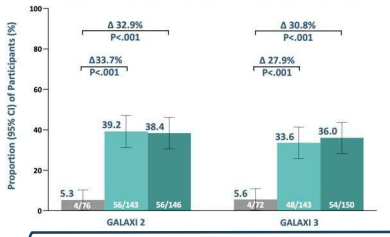
Guselkumab is More Effective Than Placebo in Moderately to Severely Active Crohn's Disease: Phase 3 GALAXI 2 & 3

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

Results:

Wk12 Clinical Response & Wk48 Endoscopic Response



Wk12 Clinical Response & Wk48 Clinical Remission

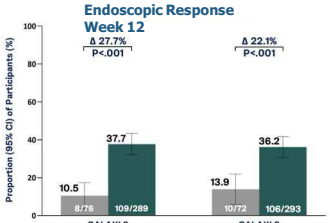
Placebo | GUS 200 mg IV q4w → 100 mg SC q8w | GUS 200 mg IV q4w → 200 mg SC q4w

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

Conclusion: The GALAXI 2 & 3 studies independently established short- and long-term efficacy of guselkumab in moderate-to-severely active CD

Major Secondary Endpoint: Efficacy of Guselkumab

Endoscopic Response Week 12



Placebo IV
Combined GUS 200 mg IV

GUS = guselkumab; q#w = every # weeks; Wk = week.
Panaccione R, et al. *Lancet Gastroenterol.* 2025;406(10501):358-375.

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GRAVITI: Phase 3 Study of SC Induction and Maintenance in CD

Subcutaneous Guselkumab Induction and Maintenance is Efficacious and Safe in Crohn's Disease: Phase 3 GRAVITI Study

FULLY SUBCUTANEOUS DOSING REGIMEN

POPULATION

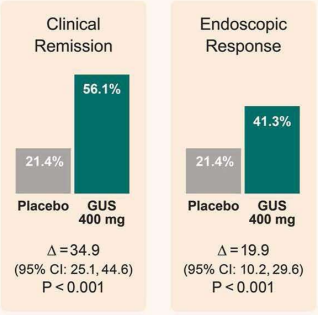
347 participants with moderately to severely active **Crohn's disease**

STUDY DESIGN

Phase 3
Randomized 1:1:1

- Placebo SC (n=117)
- Guselkumab 400 mg SC q4w → 100 mg SC q8w (n=115)
- Guselkumab 400 mg SC q4w → 200 mg SC q4w (n=115)

CO-PRIMARY ENDPOINTS AT WEEK 12



All multiplicity-controlled clinical and endoscopic endpoints through week 48 were met

Safety findings were consistent with other approved indications

Hart A, et al. *Gastroenterol.* 2025;169(2):308-325.

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Biologic Therapy: Anti-IL-23 (p19) antibodies

Mirikizumab

- Superior to placebo in achieving clinical response at Week 12 and achieving clinical remission and endoscopic response at Week 52[1]
- Non-inferior to ustekinumab in achieving clinical remission, but not endoscopic response, at Week 52[1]
- Demonstrated efficacy in achieving endoscopic response among ustekinumab-treated patients who switched to mirikizumab[2]

Agents targeting IL-12/23 (anti-p40 antibody) and IL-23 (anti-p19 antibody)

Recommendation

17. We recommend ustekinumab in patients with moderate-to-severe CD for induction and maintenance of remission (strong recommendation, moderate level of evidence).

Key concept

46. Biologic therapy (including anti-IL-12/23 therapy, anti-TNF therapy, and anti-integrin therapy) dose optimization may be considered for patients with inadequate or loss of response to that specific biologic agent's induction and maintenance.

Recommendation

20. We recommend the use of mirikizumab for induction and maintenance of remission in patients with moderate to severely active CD (strong recommendation, moderate level of evidence).
21. We recommend the use of intravenous guselkumab for induction followed by subcutaneous guselkumab for maintenance of remission in patients with moderate to severely active Crohn's disease (strong recommendation, moderate level of evidence).
22. We recommend the use of subcutaneous guselkumab for induction and maintenance of remission in patients with moderate to severely active Crohn's disease (strong recommendation, moderate level of evidence).

1. Ferrante M, et al. *Lancet*. 2024;404(10470):2423-2436; 2. D'Haens, G et al. *J Crohn's and Colitis*. 2025;19(S1):i173-i174.
3. Lichtenstein GR, et al. *Am J Gastroenterol*. 2025;120(6):1225-1264.

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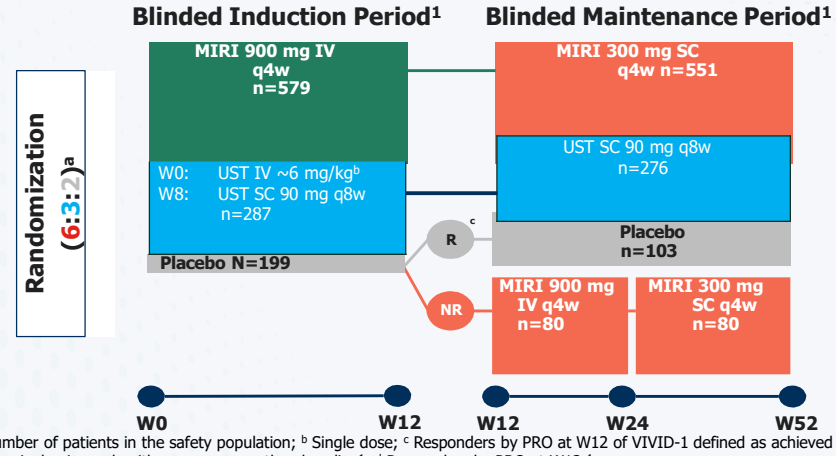
Crohn's Disease

Phase III

Mirikizumab: Trial Design
VIVID-1 Trial



[a] Number of patients in the safety population; [b] Single dose; [c] Responders by PRO at W12 of VIVID-1 defined as achieved ≥30% decrease in loose stool frequency and/or abdominal pain, and neither score worse than baseline[1]; [d] Responders by PRO at W12.[4]

MIRI = Mirikizumab-mrkz; NR = nonresponder; PRO = patient-reported outcome; R = responder.

Ferrante M, et al. *Lancet*. 2024;404(10470):2423-2436; 2. ClinicalTrials.gov. Updated December 27, 2024. Accessed August 5, 2025. https://clinicaltrials.gov/ct2/show/NCT03926130; 3. ClinicalTrials.gov. Updated April 18, 2025. Accessed August 5, 2025. https://classic.clinicaltrials.gov/ct2/show/NCT04232553; 4. Mirikizumab-mrkz. Prescribing information. Eli Lilly and Company; January 2025.

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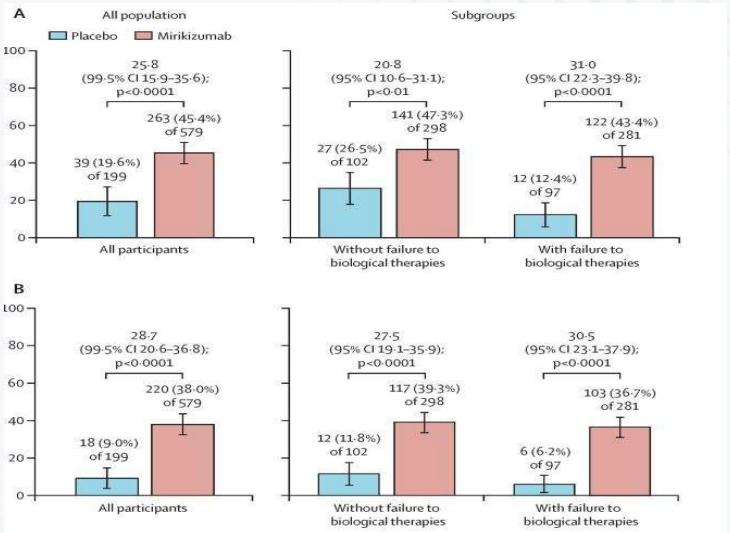
Mirikizumab in CD (VIVID-1): Phase 3 RCT

- Mirikizumab vs ustekinumab vs placebo (6:3:2)
- Co-primary endpoints:
  - PRO clinical response at week 12 and CDAI clinical remission week 52 [A]
  - PRO clinical response at week 12 and endoscopic response week 52 [B]

Week-12 Data



A. Clinical response by PRO at week 12 and clinical remission by CDAI at week 52 (NRI).

B. Clinical Response by PRO at week 12 and endoscopic response at week 52 (NRI).

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

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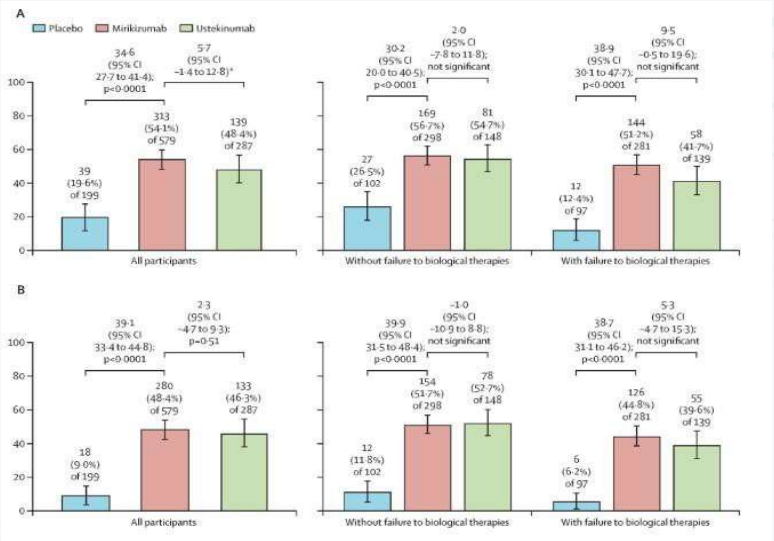
Mirikizumab in CD (VIVID-1): Phase 3 RCT

- Mirikizumab vs ustekinumab vs placebo (6:3:2)
- Co-primary endpoints:
  - PRO clinical response at week 12 and CDAI clinical remission week 52 [A]
  - PRO clinical response at week 12 and endoscopic response week 52 [B]

Week-52 Data



A. Clinical remission by CDAI (NRI) at week 52

B. Endoscopic response (NRI) at week 52

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

60

Mirikizumab vs Placebo and Mirikizumab vs Ustekinumab in Crohn's Disease (VIVID-1): Phase 3 RCT

- Mirikizumab was safe and effective as induction and maintenance treatment for patients with moderately-to-severely active Crohn's Disease who had intolerance, inadequate response, or loss of response to standard therapy.
- Mirikizumab demonstrated non-inferiority to ustekinumab in clinical remission but not in endoscopic response at week 52.
- Mirikizumab also demonstrated a greater improvement in histologic response compared to ustekinumab, particularly in patients who had previously failed on biologic therapies.

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

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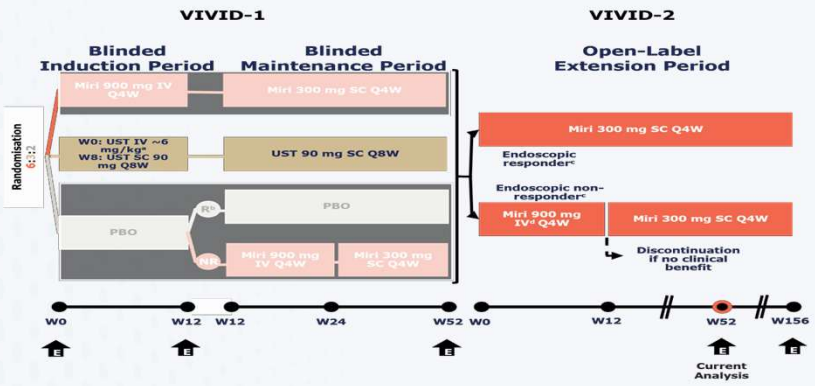
Study Design and Methods



- Data from VIVID-1 patients assigned to UST:
  - Week 52 endoscopic responders received Miri SC
  - Week 52 endoscopic non-responders received Miri IV-SC
- Efficacy after 52 weeks of treatment in VIVID-2 in patients with baseline SES-CD ≥7 (≥4 for isolated ileal disease)
- Safety assessed during the first year of VIVID-2
- Cutoff date: 2 August 2024[e]

[a] Single dose; [b] Responders by PRO at W12 of VIVID-1 defined as achieved ≥30% decrease in loose stool frequency and/or abdominal pain, and neither score worse than baseline; [c] Endoscopic responder and endoscopic non-responder based on VIVID-1 week-52 endoscopy (response defined as ≥50% reduction from baseline in SES-CD total score); [d] Miri 900 mg IV induction for 3 doses, then continue with Miri 300 mg SC Q4W. Discontinuation from study if no clinical benefit observed by investigator at week 12; [e] Patients who entered VIVID-2 after 1 August 2023 were not included in this interim analysis.
E = endoscopy; PBO = placebo.
D'Haens G, et al. Presented at: European Crohn's and Colitis Organisation (ECCO) 2025 Congress; February 19-22, 2025, Berlin, Germany.

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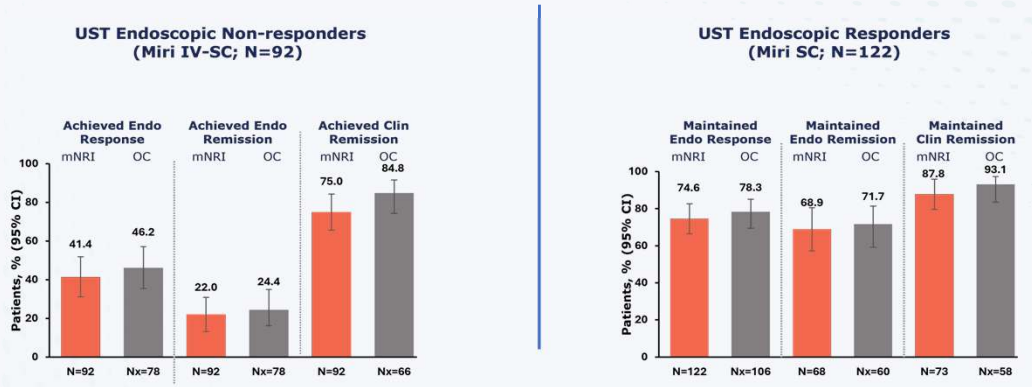
Efficacy of Mirikizumab at W52 in VIVID-2
Ustekinumab-Treated Patients Who Switched to Mirikizumab



Notes: Endoscopic responder and endoscopic non-responder based on VIVID-1 week 52 endoscopy (response defined as ≥50% reduction from baseline in SES-CD total score). Maintenance was assessed based on the response or remission status at week 52 in VIVID-1. Discontinuations or missing data handled using mNRI and OC; mNRI used a hybrid imputation method: Sporadically missing data and data from patients who discontinued treatment due to extraordinary circumstances were imputed by multiple imputation. Patients who discontinued for other reasons were treated as non-responders. Endoscopic remission: SES-CD ≤4 and ≥2-point reduction from baseline, with no subscore >1 in any individual variable. Clinical remission: CDAI <150.
Clin = clinical; Endo = endoscopic; mNRI = modified non-responder imputation; N = number of patients in the analysis population; Nx=number of patients with non-missing values; OC = observed case.
D'Haens G, et al. Presented at: ECCO 2025 Congress; February 19-22, 2025, Berlin, Germany.

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Efficacy of Mirikizumab at Week 52 in VIVID-2:
Ustekinumab-Treated Patients Who Switched to Mirikizumab

Efficacy of mirikizumab in patients with CD previously exposed to ustekinumab:

- **>40% of ustekinumab endoscopic non-responders achieved endoscopic response** after 1 year of mirikizumab treatment.
- **High maintenance rates were observed for ustekinumab endoscopic responders** switched to mirikizumab SC.
- **Safety data consistent** with known safety profile of mirikizumab.

D'Haens G, et al. Presented at: ECCO 2025 Congress; February 19-22, 2025, Berlin, Germany.

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Biologic Therapy: Anti-IL-23 (p19) antibodies

Risankizumab

- Superior to placebo in achieving clinical remission and endoscopic response at Week 12 and at Week 52[1]
- Superior to ustekinumab in achieving clinical remission at Week 24 and endoscopic remission at Week 48[2]

Agents targeting IL-12/23 (anti-p40 antibody) and IL-23 (anti-p19 antibody)

Recommendation

17. We recommend ustekinumab in patients with moderate-to-severe CD for induction and maintenance of remission (strong recommendation, moderate level of evidence).

Key concept

46. Biologic therapy (including anti-IL-12/23 therapy, anti-TNF therapy, and anti-integrin therapy) dose optimization may be considered for patients with inadequate or loss of response to that specific biologic agent's induction and maintenance.

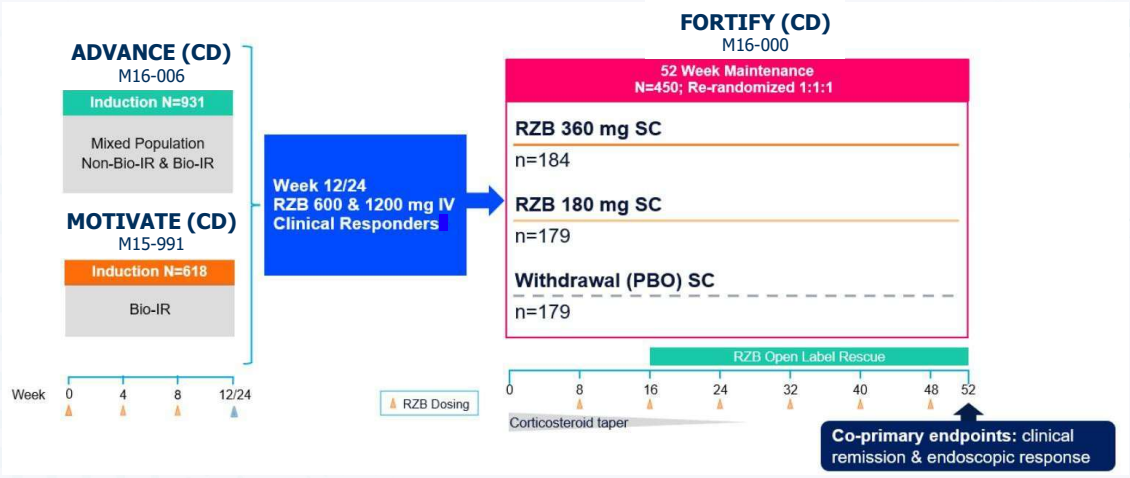
Recommendation

18. We recommend the use of risankizumab for induction and maintenance of remission in patients with moderate to severely active CD (strong recommendation, moderate level of evidence).
19. We recommend the use of risankizumab as compared with ustekinumab in patients with moderate-to-severe CD and prior exposure to anti-TNF therapy (conditional recommendation low level of evidence).

1. D'Haens G, et al. *Lancet.* 2022;399(10340):2015-2030; 2. Ferrante M, et al. *Lancet.* 2022;399(10340):2031-2046;
3. Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

65

Risankizumab for Crohn's Disease

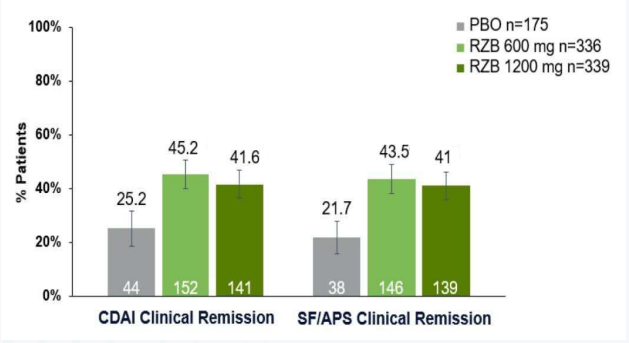


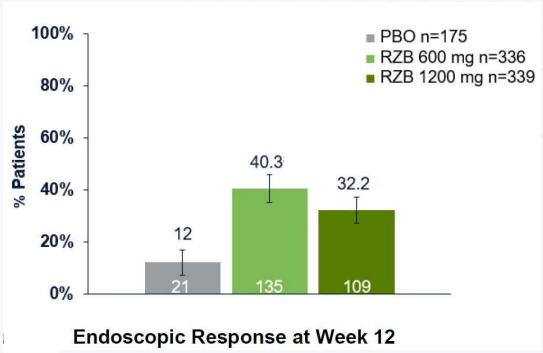
IR = inadequate response; RZB = risankizumab.
D'Haens G, et al. *Lancet.* 2022;399(10340):2015-2030.

66

Risankizumab: ADVANCE (Naïve and Exposed)

Co-primary endpoints





SF/APS = Stool Frequency/Abdominal Pain Score.
D'Haens G, et al. *Lancet*. 2022;399(10340):2015-2030.

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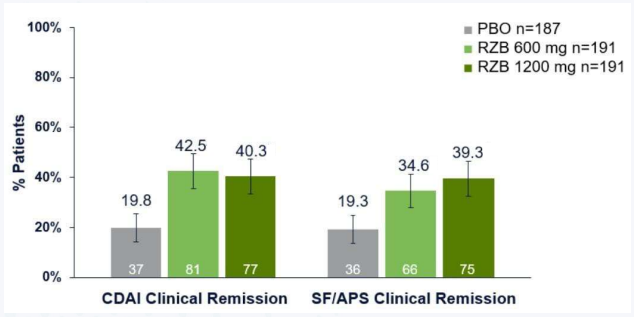
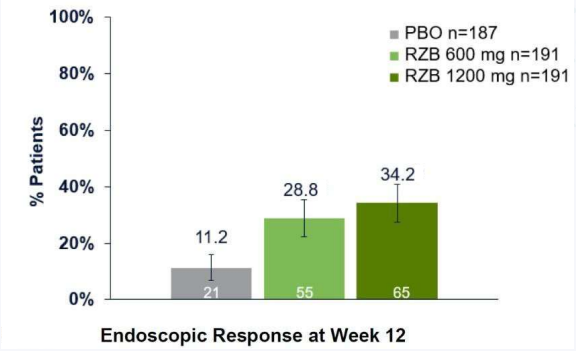
Risankizumab: MOTIVATE (Bio-Exposed)

Co-primary endpoints





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

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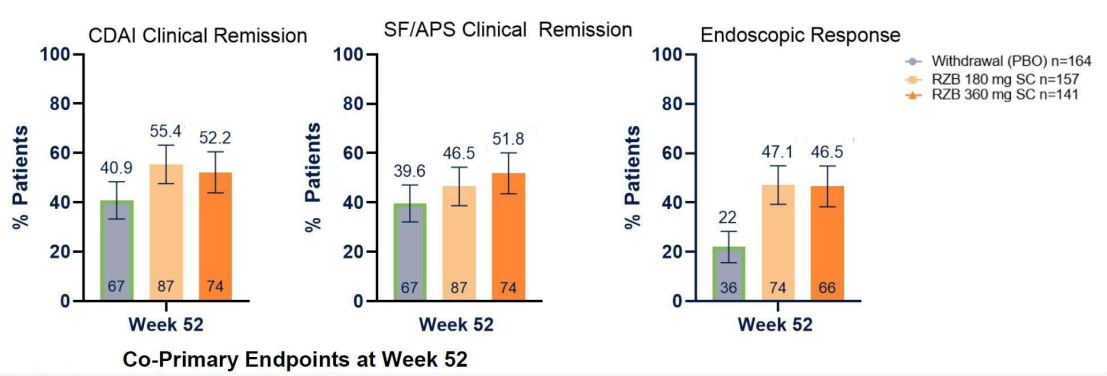
Risankizumab: FORTIFY(Maintenance)

Responders: 52-week follow-up



No safety signals identified vs placebo

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

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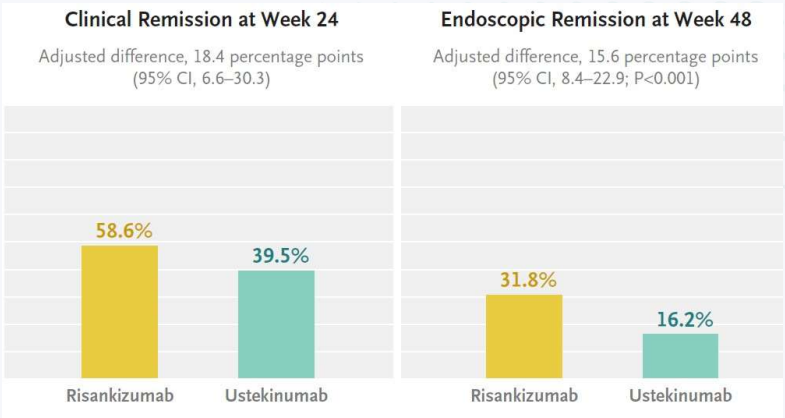
Head-to-Head: SEQUENCE Study of UST vs RISA in TNF exposed CD

- 527 patients with moderate-to-severe CD
- Failed at least 1 anti-TNF (approximately 77% 1, and 23% had failed >1)
- No other biologic- or AT-failures
- Randomized to usual doses of UST or RZB (no dose escalation)
- **Open-label—patients and providers were not blinded (central endoscopy readers were blinded)**
- Clinical remission: CDAI ≤150
- Endoscopic remission: SES-CD ≤4, no individual subscore >1



RZB not inferior to UST

RZB superior to UST

AT = anti-TNF.
Peyrin-Biroulet L, et al. *N Engl J Med*. 2024;391(3):213-223.

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Subcutaneous Biologic Therapy

Infliximab (anti-TNF agent)[1]

- Subcutaneous infliximab as maintenance demonstrates superiority to placebo in achieving clinical remission, endoscopic response, endoscopic remission, and corticosteroid-free remission at Week 54 in both Crohn's disease and ulcerative colitis

Vedolizumab (anti-integrin agent)[2]

- Vedolizumab demonstrates superiority to placebo in achieving clinical remission at Week 52

Anti-TNF agents recommendations

12. We recommend anti-TNF agents (intravenous infliximab, subcutaneous adalimumab, subcutaneous certolizumab pegol) for induction and maintenance of remission for moderately to severely active CD (strong recommendation, moderate level of evidence).
13. We recommend combination therapy of intravenous infliximab with immunomodulators (thiopurines) as compared with treatment with either immunomodulators alone or intravenous infliximab alone in patients with CD who are naive to those agents (strong recommendation, moderate level of evidence).
14. We recommend subcutaneous infliximab as an option for maintenance of remission in patients with moderately to severely active CD who respond to intravenous induction with infliximab (strong recommendation, moderate level of evidence).

Agents targeting leukocyte trafficking
Recommendation

15. We recommend intravenous vedolizumab for induction and maintenance of symptomatic remission in patients with moderately to severely active CD (strong recommendation, moderate level of evidence).
16. We recommend subcutaneous vedolizumab as an option for maintenance of remission in patients with moderately to severely active CD who respond to 2 intravenous induction doses of vedolizumab (strong recommendation, moderate level of evidence).

1. Little RD et al. J. Clin. Med. 2022, 11(20), 6173; 2. Vermeire S, et al. J Crohn's Colitis. 2022;16:27-38;
3. Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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Subcutaneous Infliximab for Maintenance Is Effective in UC and CD: LIBERTY-CD and LIBERTY-UC[1]

Week 54 efficacy in CD, n (%)[2]	SC IFX CD n=231	Placebo CD n=112	*P* value
Clinical remission	144 (62.3%)	32 (32.1%)	**<.0001**
Endoscopic response	118 (51.1%)	20 (17.9%)	**<.0001**
Endoscopic remission	80 (34.6%)	12 (10.7%)	**<.0001**
Corticosteroid free remission	39/98 (39.8%)	10/44 (22.7%)	**.0434**

Week 54 efficacy in UC, n (%)[3]	SC IFX UC n=294	Placebo UC n=144	*P* value
Clinical remission	127 (43.2%)	30 (20.8%)	<.0001
Clinical response	158 (53.7%)	45 (31.3%)	<.0001
Endoscopic-histologic mucosal improvement	105 (35.7%)	24 (16.7%)	<.0001
Corticosteroid free remission	44/120 (36.7%)	11/61 (18%)	.0127

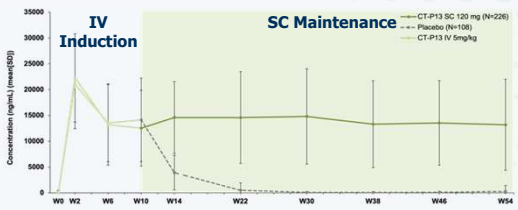
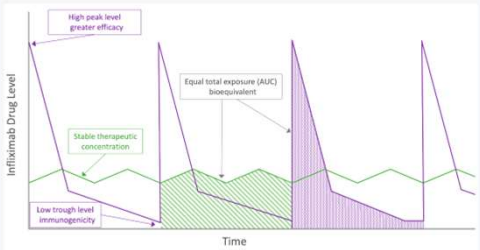


Figure 2. Visual representation of proposed theoretical pharmacokinetic advantages and disadvantages between intravenous (purple) and subcutaneous (green) infliximab. AUC = area under the curve.



1. Little RD, et al. *J Clin Med.* 2022;11(20):6173.
2. Hanauer SB, et al. Presented at: Digestive Disease Week (DDW) 2023; May 6-9, 2023; Chicago, IL. #1028.
3. Sandborn WJ, et al. Presented at: DDW 2023; May 6-9, 2023; Chicago, IL. #Tu1701.

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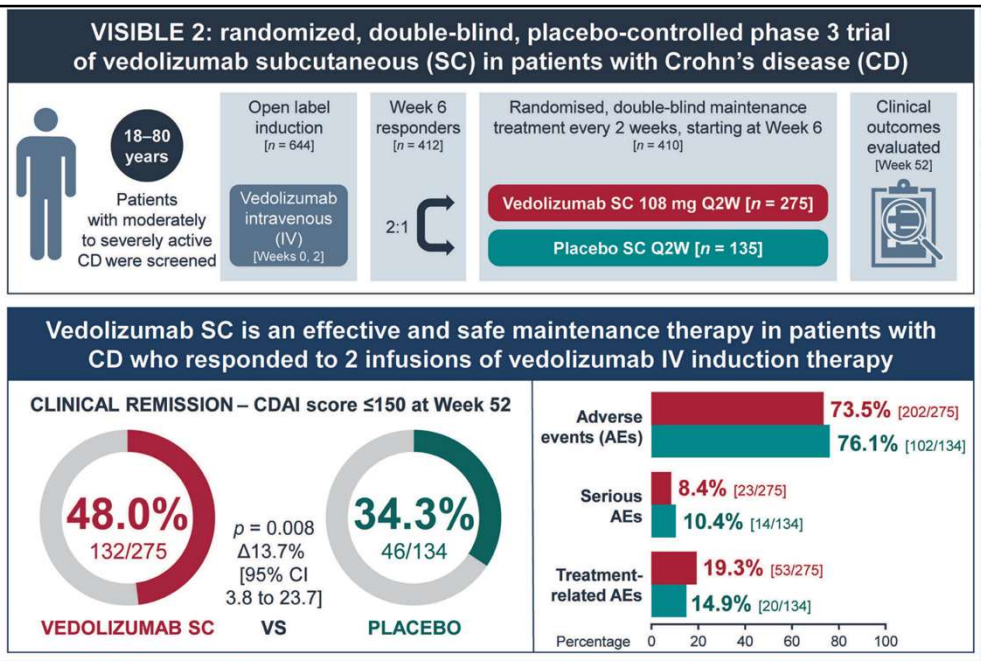

Vermeire S, et al. *J Crohns Colitis*. 2022;16(1):27-38.

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JAK Inhibition

Upadacitinib

- Upadacitinib significantly reduced disease symptoms within 1 week of initiation, including among patients with prior biologic failure[1]
- Upadacitinib superior to placebo in achieving clinical remission and endoscopic response at Week 52[2]
- Upadacitinib superior to placebo achieving resolution of drainage at Week 12 and closure of external openings of perianal fistulas at Week 12 and Week 52[3]

Agents targeting JAK inhibitor

Recommendation

23. We recommend upadacitinib for induction and maintenance of remission for patients with moderately to severely CD who have previously been exposed to anti-TNF agents (strong recommendation, moderate level of evidence).

1. 1. Colombel JF, et al. *Clin Gastroenterol Hepatol*. 2024 Aug;22(8):1668-1677; 2. Loftus EV et al. *N Engl J Med*. 2023; 388:1966-1980;
3. Colombel JF et al. *Clin Gastroenterol Hepatol*. 2025 May;23(6):1019-1029; 4. Lichtenstein GR, et al. *Am J Gastroenterol*. 2025;120(6):1225

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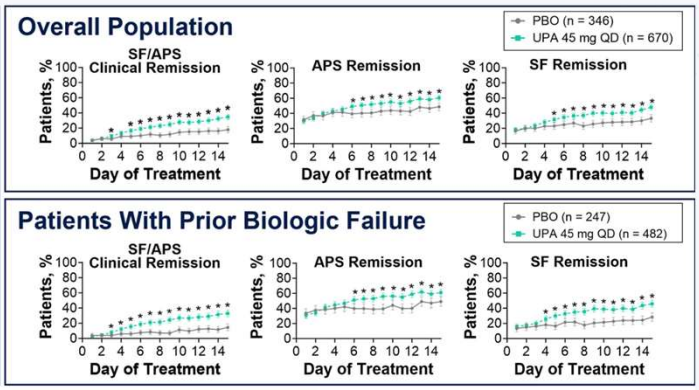
Upadacitinib (UPA) Onset of Action in CD

- Post hoc analysis of U-EXCEL and U-EXCEED induction, U-ENDURE maintenance of upadacitinib in CD
- Daily diary scores for first 15 days for outcomes of SF and abdominal pain

Upadacitinib rapidly improved stool frequency (SF) and abdominal pain score (APS) within the first week of treatment in patients with moderately to severely active Crohn's disease, including those with prior biologic failure



Error bars represent 95% confidence intervals.
*Nominal $P < .05$ vs PBO.

Colombel JF, et al. *Clin Gastroenterol Hepatol.* 2024;22(8):1668-1677.

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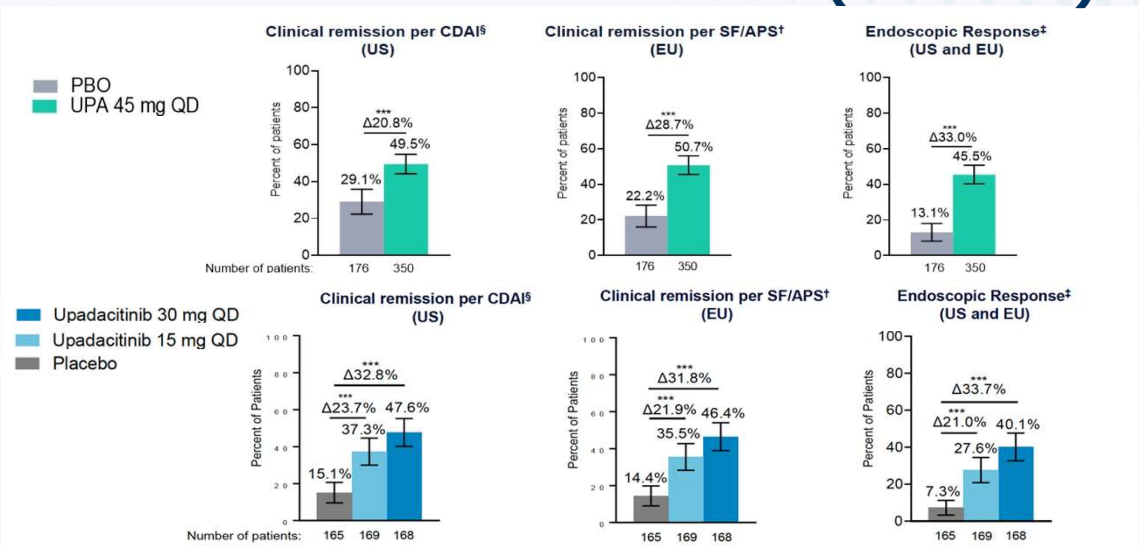
Upadacitinib in Moderate-to-Severe Crohn's Disease Weeks 12 and 52 (Phase 3)



Loftus EV, et al. *N Engl J Med.* 2023;388(21):1966-1980.

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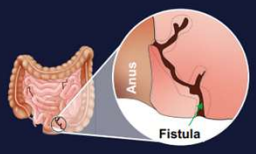
Crohn's Disease: Upadacitinib for Perianal Disease Post hoc Phase 3 U-EXCEL, U-EXCEED, U-ENDURE

Post hoc analysis of patients with fistulizing Crohn's disease from the phase 3 U-EXCEL, U-EXCEED, and U-ENDURE studies

Resolution of drainage and closure of external openings of perianal fistulas was observed with once daily upadacitinib treatment



12-week induction

Placebo n = 47

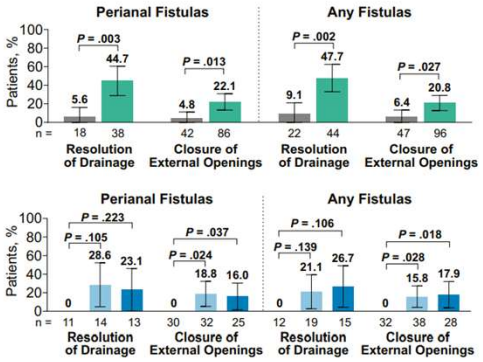
Upadacitinib 45 mg n = 96

52-week maintenance
(among responders to induction)

Placebo n = 32

Upadacitinib 15 mg n = 38

Upadacitinib 30 mg n = 28



Colombel JF, et al. *Clin Gastroenterol Hepatol.* 2025;23(6):1019-1029.

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JAK Inhibition for Crohn's Disease

General Considerations

- Induction and maintenance dosing
  - Tofacitinib[1] – effective in UC; ineffective in CD
  - Upadacitinib[2] 45 mg QD (8 weeks UC/12 weeks CD) → 30 mg or 15 mg QD
- Better in bio-naïve patients, but work quite well after biologics too
- Excellent for joints too
- Works in perianal disease as well (upadacitinib)
- JAK inhibition affects lipid transport in some patients
- Not usually clinically relevant
- Dose-related risk of herpes zoster: VACCINATE
- Dose-related follicular acne

1. Sandborn WJ et al. N Engl J Med. 2017;376(18):1723-1736; 2. Danese S et al. Lancet. 2022;399(10341):2113-2128;
3. Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264.

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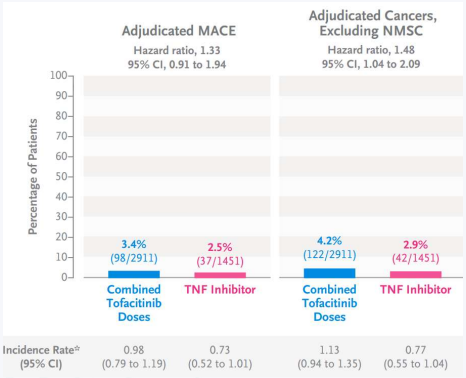
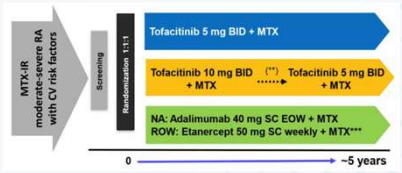
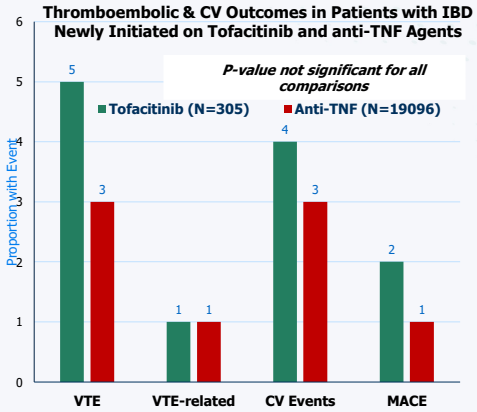
Phase 4 ORAL Surveillance Study of Tofacitinib in Rheumatoid Arthritis



Ytterberg S, et al. *N Engl J Med.* 2022;286(4):316-26.





FDA Label Changes in the U.S.:

- **Position JAKinibs after anti-TNF**
- **Screen for risk of VTE and CV disease**
- **Dose reduce in maintenance when possible**

Rubin DT, et al. *Aliment Pharmacol Ther.* 2022;55:302–310; Kochar BD, et al. *Dig Dis Sci.* 2022;67(11):5206-5212.

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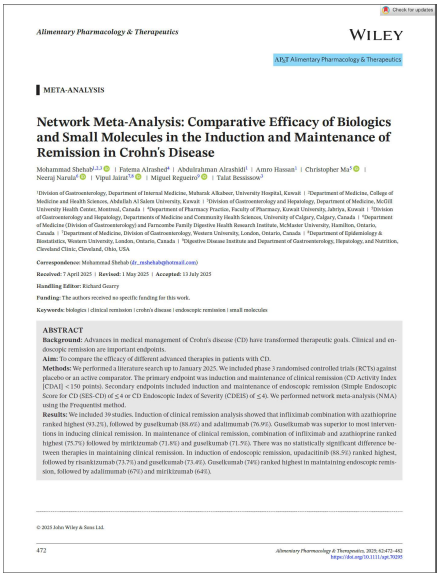
Recent NMA Assessing Disease Therapies



Alimentary Pharmacology & Therapeutics WILEY

META-ANALYSIS

Network Meta-Analysis: Comparative Efficacy of Biologics and Small Molecules in the Induction and Maintenance of Remission in Crohn's Disease

ABSTRACT

Background: Advances in medical management of Crohn's disease (CD) have transformed therapeutic goals. Clinical and endoscopic remission are important endpoints.

Aim: To compare the efficacy of different advanced therapies in patients with CD.

Methods: We performed a literature search up to January 2025. We included phase 3 randomised controlled trials (RCTs) against placebo or an active comparator. The primary endpoint was induction and maintenance of clinical remission (CD Activity Index [CDAI] <150 points). Secondary endpoints included induction and maintenance of endoscopic remission (Simple Endoscopic Score for CD (SES-CD) of ≤4 or CD Endoscopic Index of Severity (CDEIS) of ≤4). We performed network meta-analysis (NMA) using the Frequentist method.

Results: We included 39 studies. Induction of clinical remission analysis showed that infliximab combination with azathioprine ranked highest (93.2%), followed by guselkumab (88.6%) and adalimumab (76.9%). Guselkumab was superior to most interventions in inducing clinical remission. In maintenance of clinical remission, combination of infliximab and azathioprine ranked highest (75.7%) followed by mirikizumab (71.8%) and guselkumab (71.5%). There was no statistically significant difference between therapies in maintaining clinical remission. In induction of endoscopic remission, upadacitinib (88.5%) ranked highest, followed by risankizumab (73.7%) and guselkumab (73.4%). Guselkumab (74%) ranked highest in maintaining endoscopic remission, followed by adalimumab (67%) and mirikizumab (64%).

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472 *Alimentary Pharmacology & Therapeutics*, 2025; 62:472–482

Conclusion: "Novel IL-23 inhibitors (such as mirikizumab, risankizumab and guselkumab) and anti-TNFs (such as infliximab and adalimumab) ranked high in the induction of clinical and endoscopic remission. This highlights the potential of novel advanced therapies for CD."

Treatment	SUCRA (%)
Infliximab AZA	93.28
Guselkumab	88.63
Adalimumab	76.95
Infliximab	74.30
Risankizumab	66.55
Ustekinumab	57.04
Upadacitinib	56.89
Azathioprine	55.99
Vedolizumab	42.30
Mirikizumab	37.37
Filgotinib	35.95
Adalimumab AZA	31.41
Certolizumab	19.53
Etrolizumab	8.21
Placebo	5.61

SUCRA table showing comparative efficacy of biologics / small molecules for induction of clinical remission.

Treatment	SUCRA (%)
Infliximab AZA	75.75
Mirikizumab	71.88
Guselkumab	71.57
Adalimumab	71.07
Upadacitinib	70.48
Adalimumab AZA	61.02
Risankizumab	59.87
Infliximab	54.81
Ustekinumab	47.95
Vedolizumab	34.87
Cerolizumab	33.61
Filgotinib	22.49
Etrolizumab	19.94
Placebo	4.68

SUCRA table showing comparative efficacy of biologics / small molecules for maintenance of clinical remission.

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Dietary Treatments in Crohn's Disease

Key concept

42. For adult patients with mild CD and low risk of progression, diet-based strategies along with careful monitoring for inadequate symptom relief, worsening inflammation, or disease progression may be considered.

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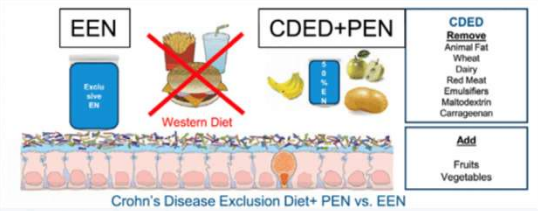
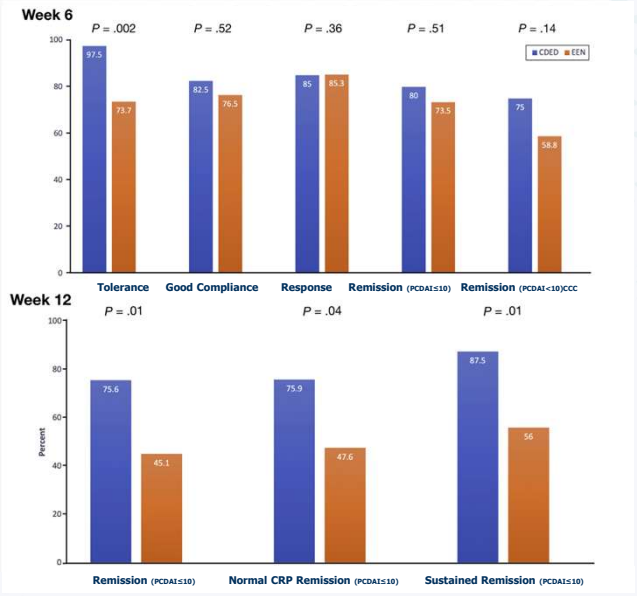
Exclusion Diet & Partial Enteral vs Exclusive Enteral



Crohn's Disease Exclusion Diet+ PEN vs. EEN

GROUP 1
Stage 1: CDED plus 50% of calories from formula for 6w
Stage 2: CDED with 25% PEN from 7-12w

GROUP 2
Stage 1: EEN for 6w
Stage 2: Free diet with 25% PEN from 7-12w



6w = 6 weeks; 7-12w = 7 to 12 weeks; CDED = CD exclusion diet; EEN = exclusive enteral nutrition; PEN = partial enteral nutrition.
Levine A, et al. *Gastroenterol.* 2019;157(2):440-450.

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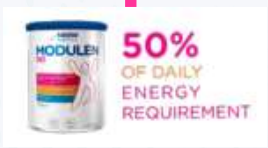
Crohn's Disease Exclusion Diet

3-phase, whole-food diet
Avoidance of dietary components that adversely effect the microbiome & intestinal barrier



Levine A et al. *Gastroenterol.* 2019;157:440-450.

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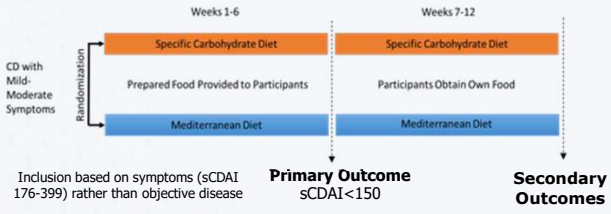
Specific Carbohydrate and Mediterranean Diet Achieve Similar Clinical Remission Rates, but Not Inflammation Control in CD

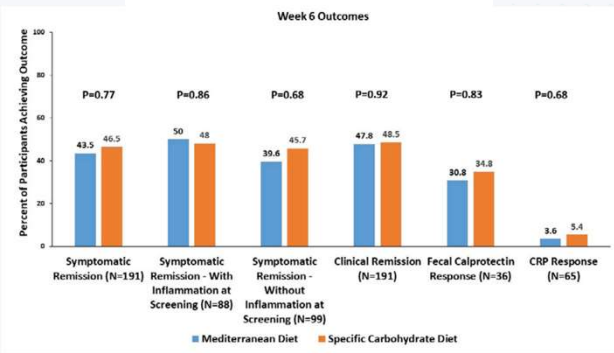


Inclusion based on symptoms (sCDAI 176-399) rather than objective disease

Primary Outcome
sCDAI<150

Secondary Outcomes

	SCD	Mediterranean diet
High intake	Unprocessed meats, poultry, fish, eggs Most vegetables, fruits and nuts	Olive oil Fruits and vegetables Nuts and cereals
Avoid or limit	Grains and dairy Sweeteners other than honey	Red/processed meat Sweets



SCD = Specific Carbohydrate Diet; sCDAI = short Crohn's Disease Activity Index.
Lewis JD, et al. *Gastroenterology.* 2021;160(S-157):Abstract 781.

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Other Treatments in Crohn's Disease

Biosimilars

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NC2

FDA-Approved Infliximab and Adalimumab Biosimilar Products

Humira (adalimumab)

Biosimilar Name	Approval Date
Amjevita (adalimumab -atto)	September 2016
Cyltezo[a] (adalimumab-adbm)	August 2017
Hyrimoz[b] (adalimumab-adaz)	October 2018
Hadlima[b] (adalimumab-bwwd)	July 2019
Abrilada (adalimumab-afzb)	November 2019
Hulio (adalimumab-fkjp)	July 2020
Yusimry (adalimumab-aqvh)	December 2021
Idacio (adalimumab-aacf)	December 2022
Yuflyma (adalimumab-aaty)	May 2023

Remicade (infliximab)

Biosimilar Name	Approval Date
Inflectra (infliximab-dyyb)	April 2016
Renflexis (infliximab-abda)	May 2017
Ixifi (infliximab-qbtx)	December 2017
Avsola (infliximab-axxq)	December 2019

Biosimilars Position Statement for the Crohn's & Colitis Foundation (2024)

[a]Interchangeable; [b]Contains citrate.

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Slide 86

NC1 CHECK ADA biosimilars?
Choi, Natalie [BSD], 2024-01-29T14:12:22.978

NC2 Update qr to 2024 statement
Choi, Natalie [BSD], 2024-01-29T14:19:54.453

Currently FDA Approved Ustekinumab Biosimilars

The table outlines major biosimilar products, their manufacturers, and approval years.

PRODUCT	MANUFACTURER	APPROVAL YEAR
Wezlana® (ustekinumab-auub)	**Amgen**	**2021**
Pyzchiva® (ustekinumab-ttwe)	**Samsung Bioepis/Sandoz**	**2022**
Selarsdi™ (ustekinumab-aekn)	**Teva/Alvotech**	**2023**
Otulfi™ (ustekinumab-aauz)	**Formycon/Fresenius Kabi**	**2023**
Imuldosa™ (ustekinumab-srlf)	**Accord BioPharma**	**2023**
Yesintek™ (ustekinumab-kfce)	**Biocon Biologics**	**2022**
Steqeyma® (ustekinumab-stba)	**Celltrion**	**2021**

Source: https://www.fda.gov/drugs/biosimilars/biosimilar-product-information [a]Interchangeable [b]Contains citrate

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Choosing Therapies: Who's on First? What's on Second?

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Current Challenges in Sequencing Treatments for IBD

- **Heterogeneity of disease types**
- **Primary non-response/Secondary non-response (loss of response)**
- **Challenges interpreting available data:**
  - Clinical trials design
  - Selection bias: separating biological resistance from mechanism vs. complicated progressive disease
- **Which treatment is first?**
- **How do I know it is working?**
- **What treatment is next?**
- **Where does surgery fit into the sequencing?**

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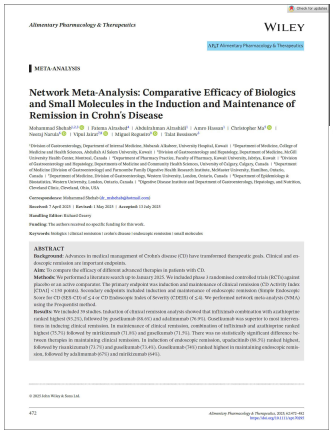
Crohn's Disease
Recent NMA Assessing Disease Therapies



Alimentary Pharmacology & Therapeutics

WILEY

META-ANALYSIS

Network Meta-Analysis: Comparative Efficacy of Biologics and Small Molecules in the Induction and Maintenance of Remission in Crohn's Disease

ABSTRACT

Background: Advances in medical management of Crohn's disease (CD) have transformed therapeutic goals. Clinical and endoscopic remission are important endpoints.

Aim: To compare the efficacy of different advanced therapies in patients with CD.

Methods: We performed a literature search up to January 2025. We included phase 3 randomised controlled trials (RCTs) against placebo or an active comparator. The primary endpoint was induction and maintenance of clinical remission (CD Activity Index [CDAI] < 150 points). Secondary endpoints included induction and maintenance of endoscopic remission (Simple Endoscopic Score for CD (SES-CD) of ≤ 4 or CD Endoscopic Index of Severity (CDEIS) of ≤ 6). We performed network meta-analysis (NMA) using the Frequentist method.

Results: We included 59 studies. Induction of clinical remission analysis showed that infliximab combination with azathioprine ranked highest (93.2%), followed by guselkumab (88.6%) and adalimumab (76.9%). Guselkumab was superior to most interventions in inducing clinical remission. In maintenance of clinical remission, combination of infliximab and azathioprine ranked highest (75.7%) followed by mirikizumab (71.8%) and guselkumab (71.5%). There was no statistically significant difference between therapies in maintaining clinical remission. In induction of endoscopic remission, upadacitinib (60.3%) ranked highest, followed by risankizumab (71.7%) and guselkumab (71.4%). Guselkumab (74%) ranked highest in maintaining endoscopic remission, followed by adalimumab (67%) and mirikizumab (64%).

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472 Alimentary Pharmacology & Therapeutics. 2025;62:472–482. https://doi.org/10.1111/apt.18282

Conclusion: "Novel IL-23 inhibitors (such as mirikizumab, risankizumab and guselkumab) and anti-TNFs (such as infliximab and adalimumab) ranked high in the induction of clinical and endoscopic remission. This highlights the potential of novel advanced therapies for CD."

Treatment	SUCRA (%)
Infliximab AZA	93.28
Guselkumab	88.63
Adalimumab	76.95
Infliximab	74.30
Risankizumab	66.55
Ustekinumab	57.04
Upadacitinib	56.89
Azathioprine	55.99
Vedolizumab	42.30
Mirikizumab	37.37
Filgotinib	35.95
Adalimumab AZA	31.41
Certolizumab	19.53
Etrolizumab	8.21
Placebo	5.61

SUCRA table showing comparative efficacy of biologics / small molecules for induction of clinical remission.

Treatment	SUCRA (%)
Infliximab AZA	75.75
Mirikizumab	71.88
Guselkumab	71.57
Adalimumab	71.07
Upadacitinib	70.48
Adalimumab AZA	61.02
Risankizumab	59.87
Infliximab	54.81
Ustekinumab	47.95
Vedolizumab	34.87
Cerolizumab	33.61
Filgotinib	22.49
Etrolizumab	19.94
Placebo	4.68

SUCRA table showing comparative efficacy of biologics / small molecules for maintenance of clinical remission.

Shehab M, et al. *Alimentary Pharmacology and Therapeutics* 2025 Sep;62(5):472-482.

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Crohn's Disease First Line: Ustekinumab = Adalimumab
SEAVUE

- Randomized, double-blinded, parallel-group, active-controlled study
- Biologic-naïve patients
- N=386; 191 UST, 195 ADA
- Tolerability favored ustekinumab

Figure 1: Primary Endpoint
Clinical Remission (CDAI<150) at week 52

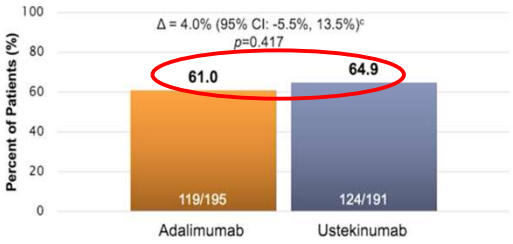
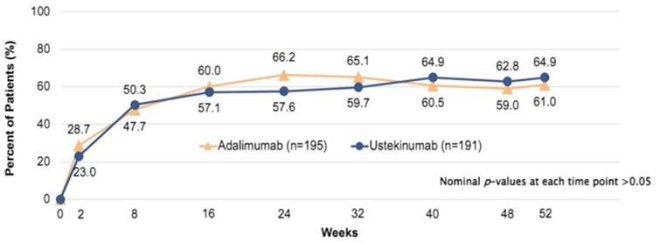


Figure 2: Clinical Remission (CDAI <150) Through Week 52



Sands BE et al. *Lancet*. 2022;399(10342):2200-2211.

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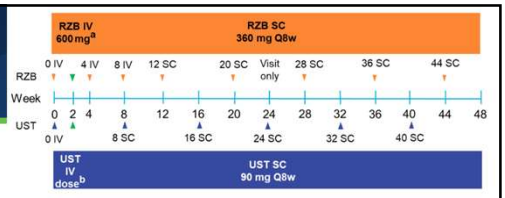
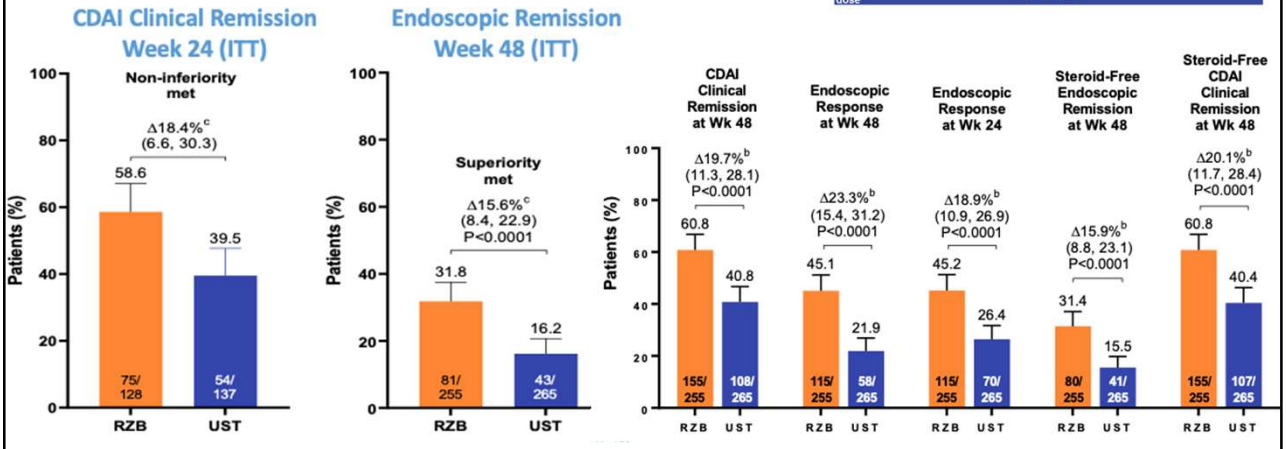
Crohn's Disease Second Line After Anti-TNF: Risankizumab > Ustekinumab SEQUENCE





Peyrin-Biroulet L et al. Presented at UEGW. October 2023. LB01.

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Concepts Involved with Positioning of Therapies

Disease Prognosis

- **Mild Disease:** No Therapy, close monitoring (with biomarkers, endoscopy and imaging)
- **Aggressive Disease:** Advanced Therapies e.g. Biologic Therapy or JAK (prior TNF use)

Access to Treatment

- All medical options should be available based on physician recommendations.
- Step therapy and third-party payer restrictions should not interfere with clinical decision-making.

Treatment Sequencing

- First-line therapies offer higher remission rates than subsequent treatments after prior failures.
- With prior biologics- JAK (Upa) or IL-23 are best

Response Types

- Differentiating **primary non-response** vs **secondary non-response** is essential for guiding next treatment steps.

Data Interpretation

- **Network Meta Analysis:** Subgroup/meta-analyses offer hypothesis-generating insights but are not sufficient for individual treatment decisions.

Preferred Anti-TNF Agent

- **Infliximab is preferred** among anti-TNF agents for moderately to severely active CD and for perineal CD.

Risk-Based Therapy

- Higher infection risk patients may benefit from **vedolizumab** or **anti-IL-23** strategies over broadly immunosuppressive agents.
- **Prior malignancy:** Consider anti-IL23 or vedolizumab
- **Elderly:** Consider anti-IL23 or vedolizumab

Extra-intestinal Manifestations

- Therapy choice may be guided by extra-intestinal symptoms (eg, joints, skin).
- Arthropathy- AntiTNF, AntiIL-23, Upadicitinib,
- Skin (Psoriasis

Lichtenstein GR, et al. *Am J Gastroenterol.* 2025;120(6):1225-1264;
Rubin DT, et al. *Am J Gastroenterol.* 2025;120(6):1187-1224.

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Commit Patients to Effective Management Early

- Don't make your patients "earn" the appropriate therapy by failing other treatments first!
- Based on prognosis, use advanced therapies at time of diagnosis
- Employ/embrace/encourage STEROID AVOIDANCE strategies
- Early treatment with effective therapy:
  - More likely to respond (esp Crohn's)
  - More likely to have disease modification (including disability)
  - More likely to have cost effective therapy
  - Allows considerations for de-intensification later (testable hypotheses)

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Summary: Update on Management of Crohn's Disease in 2025

- Treat with advanced therapies based on activity and severity at time of presentation
- Avoid steroids when possible (more often!)
- Phase of management and first therapies matter!
- Employ treat to target strategies to achieve objective endpoints for control
- Consider co-existing immune conditions and relative contraindications for therapies

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Questions

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**All of the relevant financial relationships listed for these individuals have been mitigated*

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