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¡Bienvenido!

Dr. Jesús Yamamoto-Furusho
Founder and Director of Inflammatory Bowel Disease Clinic (IBD)
National Institute of Medical Sciences and Nutrition in Mexico City.

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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

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ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 21 – Thursday, May 25, 2023
The Role of Non-Invasive Modalities in Colorectal Cancer Screening
Faculty: Douglas J. Robertson, MD, MPH
Moderator: T.R. Levin, MD, FACG
At Noon and 8pm Eastern

Week 22 – Thursday, June 1, 2023
Prior Authorization in GI: Tips from the ACG Prior Authorization Task Force
Faculty: Baharak Moshiree, MD, MSc, FACG, and Stephen T. Amann, MD, FACG
Moderators: Daniel J. Pambianco, MD, FACG, and Dayna S. Early, MD, FACG
At Noon and 8pm Eastern

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

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¡Bienvenido!

Dr. Maria Abreu

Dr. Fernando Velayos

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UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM
Crohn's and Colitis Center

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Positioning Medications in UC

Maria T. Abreu, MD
Director, Crohn's and Colitis Center
Professor of Medicine
Professor of Microbiology and Immunology
University of Miami Miller School of Medicine, Miami, FL
President-elect AGA

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Pharma Disclosures 2023

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- Consulting and/or speaking fees from AbbVie , Alimentiv, Amgen, Arena Pharmaceuticals, Bristol Myers Squibb, Celsius Therapeutics, Eli Lilly and Company, Gilead Sciences, Janssen Pharmaceuticals, Microba Life Sciences, Pfizer Pharmaceutical, Prometheus Biosciences, Takeda Pharmaceuticals, UCB Biopharma SRL, WebMD Global LLC.

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The Evolution of IBD Therapies

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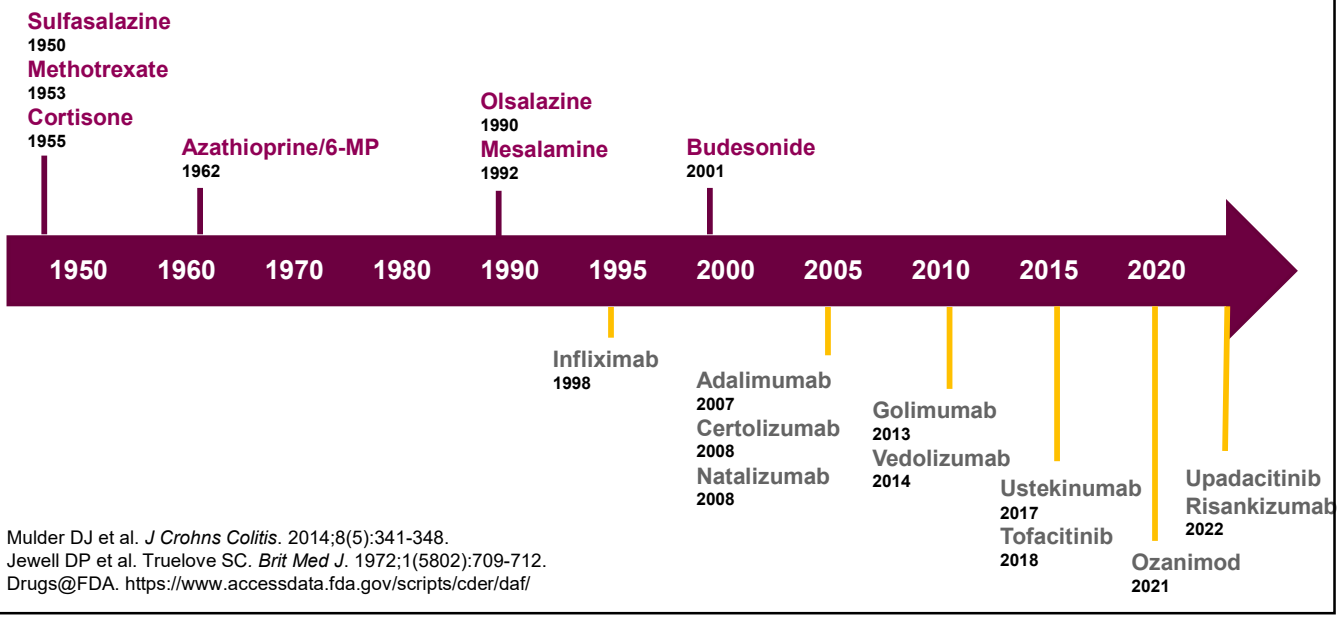

Mulder DJ et al. *J Crohns Colitis*. 2014;8(5):341-348.
Jewell DP et al. Truelove SC. *Brit Med J*. 1972;1(5802):709-712.
Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/

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Evolving Targets in IBD

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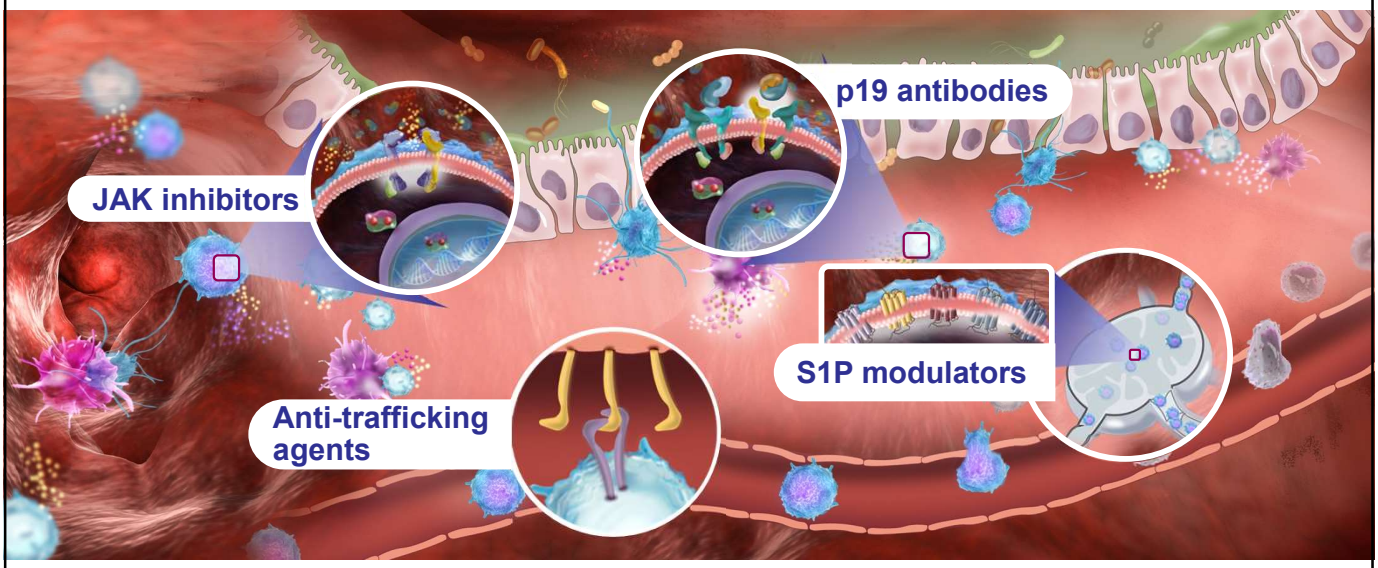

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Current and Emerging Strategies for IBD

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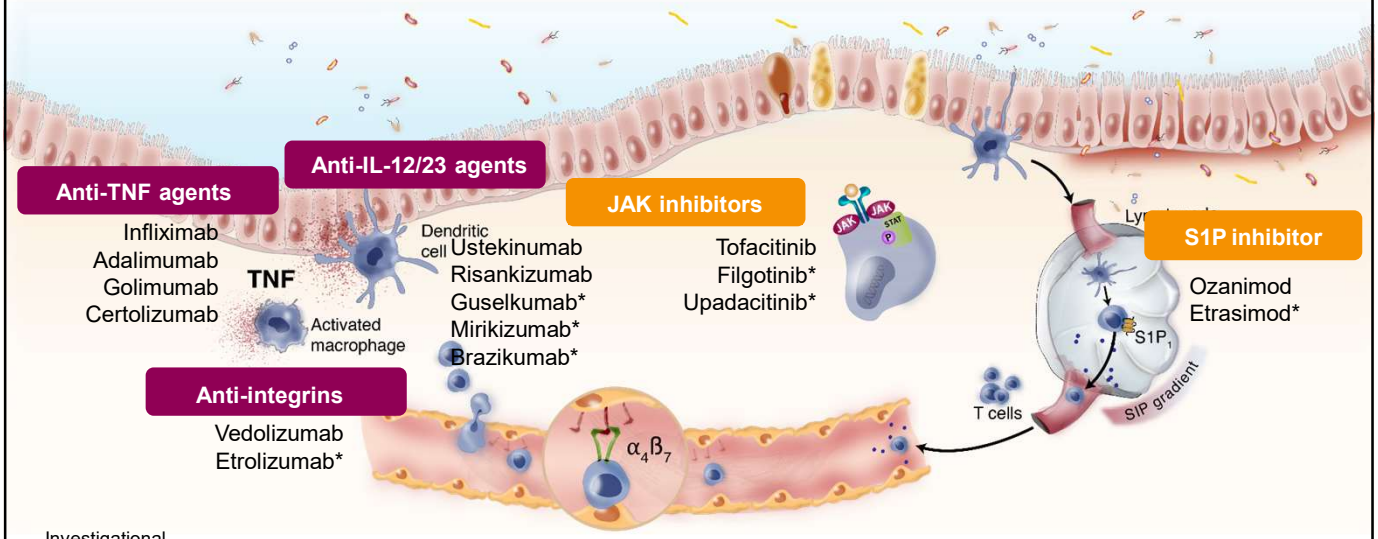

Investigational.
JAK = Janus kinase; TNF = tumor necrosis factor; S1P = sphingosine-1-phosphate.
Adapted from Coskun M et al. *Trends Pharmacol Sci.* 2017;38(2):127-142.

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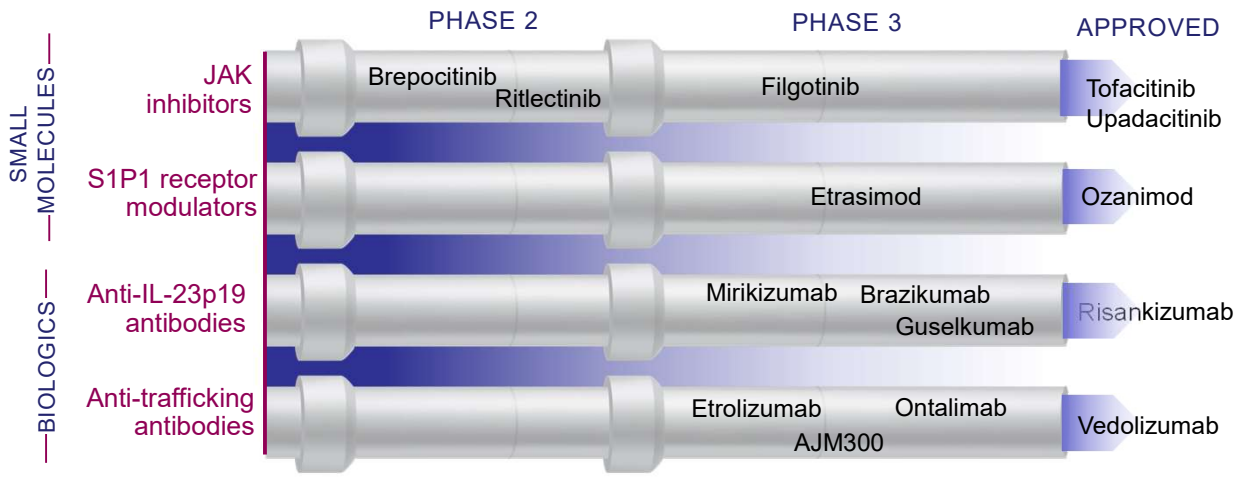
Key Classes in the IBD Pipeline



Ab = antibody; MAdCAM = mucosal addressin cell adhesion molecule.
Clinicaltrials.gov. https://clinicaltrials.gov. Accessed January 4, 2022.

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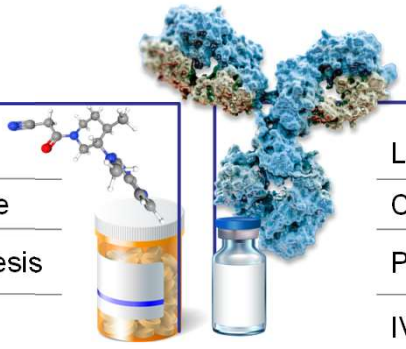
Small Molecules vs Biologics



Small molecules	Biologics
Small (single molecule)	Large (mixture)
Simple, well-defined structure	Complex heterogeneous structure
Produced by chemical synthesis	Produced in a living cell culture
Oral	IV to SC
Non-immunogenic	Immunogenic

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What do I take into account when choosing a medication for IBD?

- Patient factors:
  - Severity of the UC
    - Is this steroid-dependent disease? But they are going to work, functional
    - Is this steroid-refractory, sicker patient
    - We won't discuss hospitalized—infliximab or cyclo, there may be a role for upadacitinib
  - Phenotype of the CD
    - Inflammatory disease without a complication—almost anything is OK esp in biologic naïve
    - Transmural, penetrating disease—avoid steroids
    - Stricturing disease—do they need surgery?
    - Perianal CD

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What do I take into account when choosing a medication for IBD?

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- Patient factors:
  - Co-morbidities–e.g. cancer or cancer risk, infection risk
  - Age, childbearing
  - EIMs
  - Naïve patient versus previous biologic exposure
- Patient preference: IV, subq, oral
- Cost and/or insurance coverage

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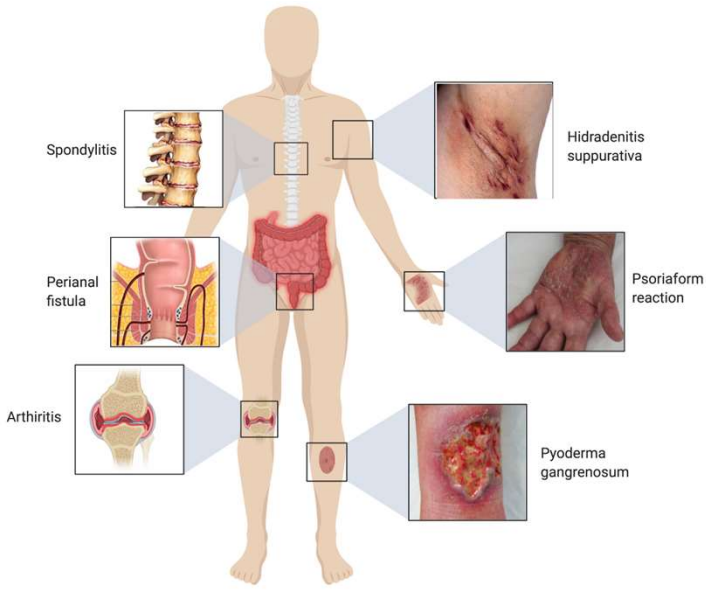
Need to Consider Diverse Manifestations of IBD When Choosing Therapy



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The steroid-dependent or chronically-active UC patient

- May be on low dose prednisone or budesonide
- Biologic-naïve
- Or could be on max mesalamine with ongoing symptoms

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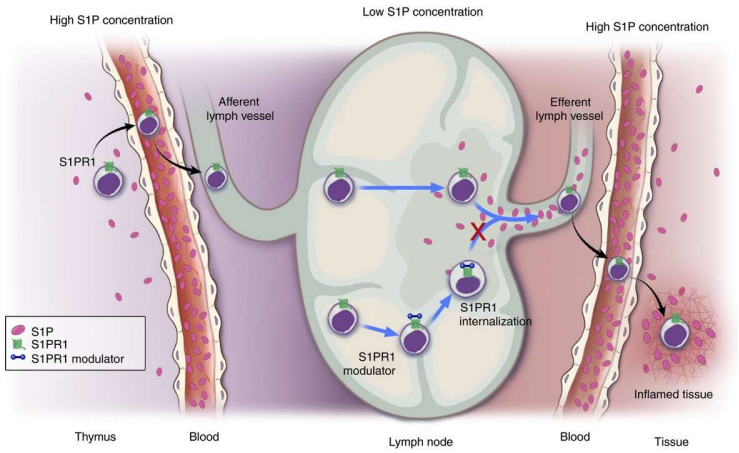
S1P Modulation

- S1P is a lipid metabolite that exerts its actions by engaging 5 G-protein-coupled receptors (S1PR1-S1PR5)
- S1P receptors are involved in several cellular and physiological events, including lymphocyte/ hematopoietic cell trafficking
- An S1P gradient (low in tissues, high in blood) regulates lymphocyte trafficking
- This S1P-S1PR pathway is involved in the pathogenesis of immune-mediated diseases



S1P, sphingosine-1-phosphate.
Wang J et al. *Aliment Pharmacol Ther*. 2021 Dec 21. doi: 10.1111/apt.16741. Online ahead of print.

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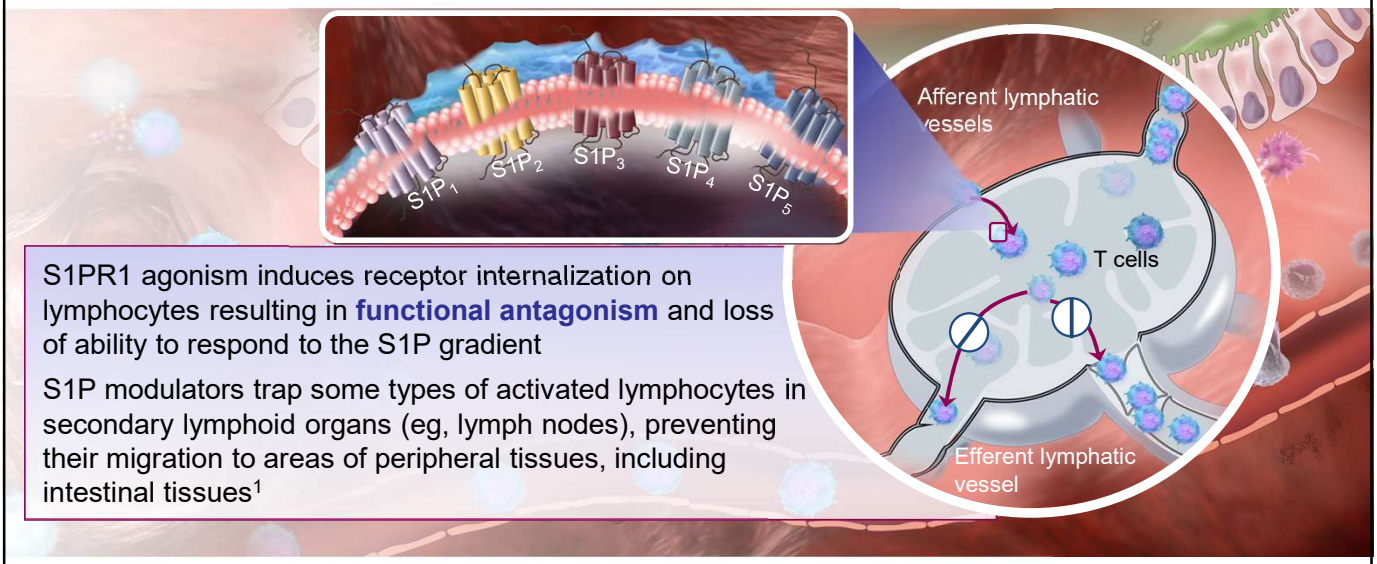
S1PR 1 Agonist Causes Sequestration of Lymphocytes in Lymph Nodes



S1PR1 agonism induces receptor internalization on lymphocytes resulting in **functional antagonism** and loss of ability to respond to the S1P gradient

S1P modulators trap some types of activated lymphocytes in secondary lymphoid organs (eg, lymph nodes), preventing their migration to areas of peripheral tissues, including intestinal tissues[1]

Danese S. *Gastroenterology*. 2020;158(3):467-470.

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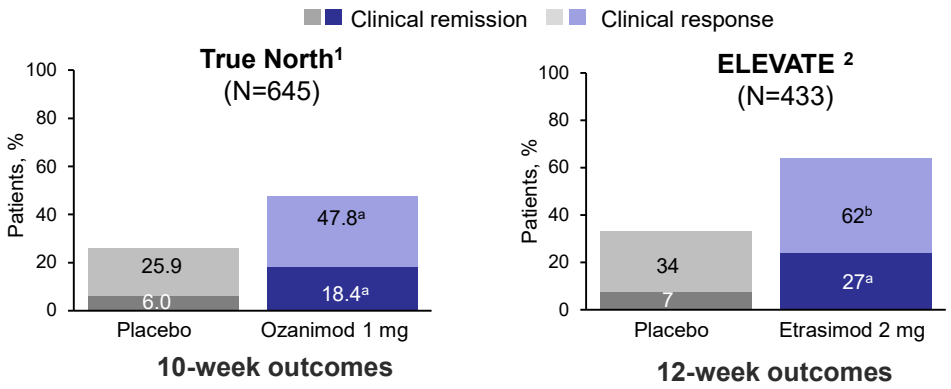
S1P Inhibitors for Induction Therapy in UC

OZANIMOD

ETRASIMOD



~39% previous biologic or JAK exposure

~30% previous biologic or JAK exposure

[a]*P*<0.0001; [a]*P*<0.0001.

1. Sandborn WJ et al. *N Engl J Med*. 2021;385:1280-1291. 2. Sandborn, W. et al. Lancet 2023; 401: 1159–71

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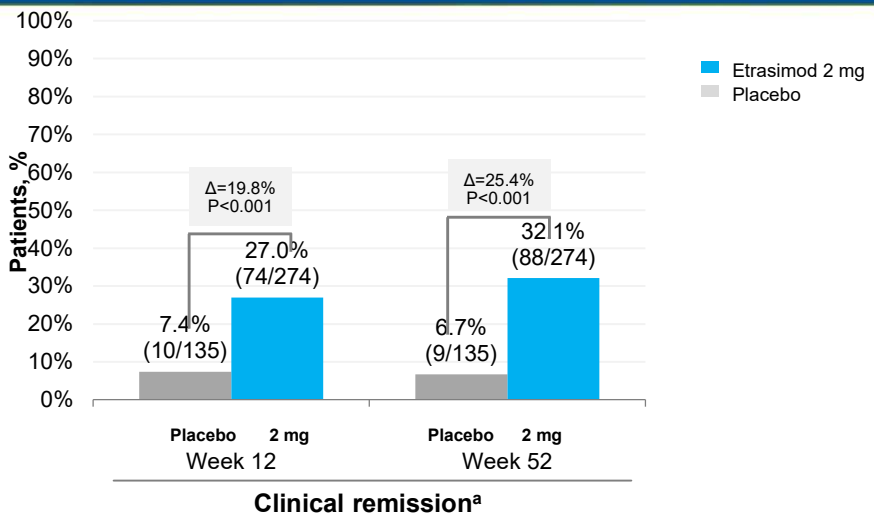
ELEVATE UC 52 coprimary endpoints

Baseline MMS 5 to 9 (N=409)

Clinical remission: RB=0, ES=0 or 1, SF=0 (or =1 with a ≥1-pt decrease)



Data were from reported randomized strata.[2] Percent of patients with clinical remission at Week 12 was derived from Cochran–Mantel–Haenszel analysis.[2] Endpoint in patients with baseline MMS 5–9 (n=409).[1]
[a]Clinical remission was defined as an SF subscore of 0 (or 1 with a ≥1-point decrease from baseline), RB subscore of 0, and ES ≤1 (excluding friability).[2]
ES, endoscopic score; MMS, Modified Mayo Score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Sandborn WJ et al. Lancet 2023 (Epub ahead of print).

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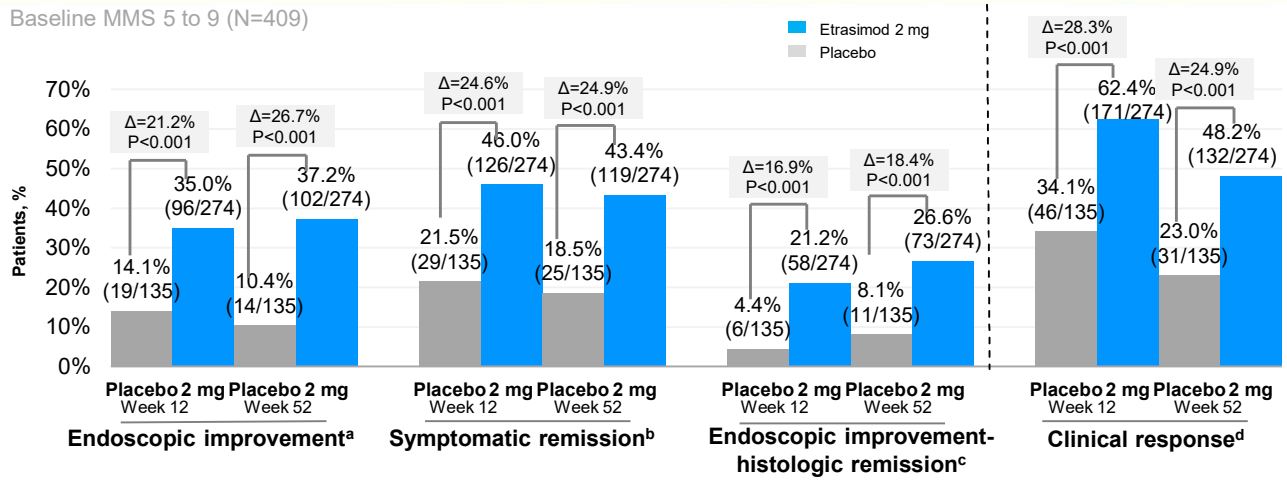
ELEVATE UC 52: key secondary endpoints

Key secondary endpoints | **Secondary endpoint**

Baseline MMS 5 to 9 (N=409)



[a]Endoscopic improvement was defined as ES ≤1 (excluding friability).[2] [b]Symptomatic remission was defined as SF subscore of 0 (or 1, with a ≥1-point decrease from baseline) and RB subscore of 0.[2] [c]Endoscopic improvement-histologic remission was defined as ES of ≤1 (excluding friability) with histologic remission measured by a Geboes score <2. This endpoint was designated in the protocol as 'mucosal healing' but referred to as endoscopic improvement-histologic remission in abstracts.[2] [d]Clinical response was defined as ≥2-point and ≥30% decrease from baseline in MMS, ≥1-point decrease from baseline in RB subscore, or an absolute RB subscore ≤1. Clinical response was not a key secondary endpoint.[2]
ES, endoscopic subscore; MMS, Modified Mayo Score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Sandborn WJ et al. Lancet 2023 (Epub ahead of print).

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ELEVATE UC 52 & UC 12 – Adverse events of special interest

Patients, n (EAIR)[1]	ELEVATE UC 52 & UC 12 Safety set (n=787) Placebo (n=260)	Etrasimod 2 mg (n=527)
Liver transaminases elevation	2 (0.02)	6 (0.02)
Bilirubin elevation	0	1 (<0.01)
Macular edema	1 (<0.01)	2 (<0.01)
Malignancies	0	0

- Two cases of macular edema were reported in patients receiving etrasimod – one of which was non-clinically significant and did not lead to drug interruption – and one case in patients receiving placebo[2]
- **No serious or severe hepatic injury** was reported in either treatment group in ELEVATE UC 52 or ELEVATE UC 12[2]
- **No malignancies** were reported in either trial[2]

EAIR is calculated as n divided by the total exposure in patient-years at risk for AE. AE, adverse event; EAIR, exposure-adjusted incidence rate; UC, ulcerative colitis.

Sandborn WJ et al. Lancet 2023 (Epub ahead of print) – Supplementary Appendix.

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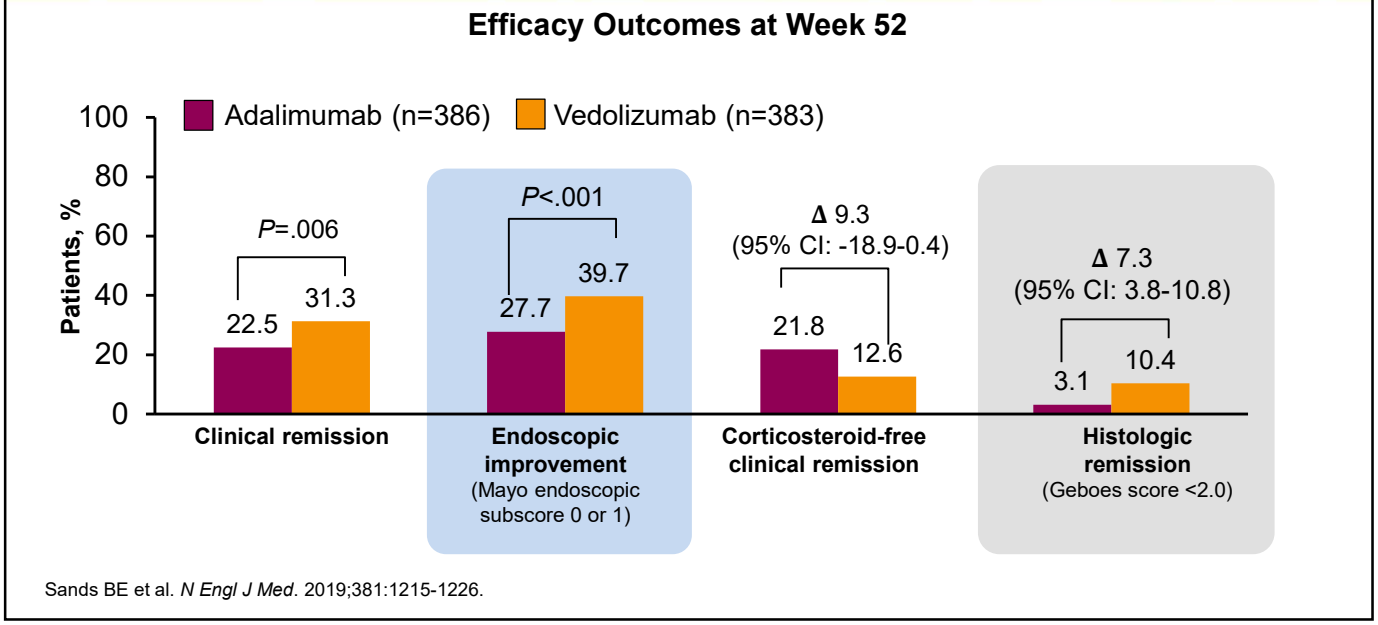
Vedolizumab Versus Adalimumab for Moderate-to-Severe UC: VARSITY Study



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

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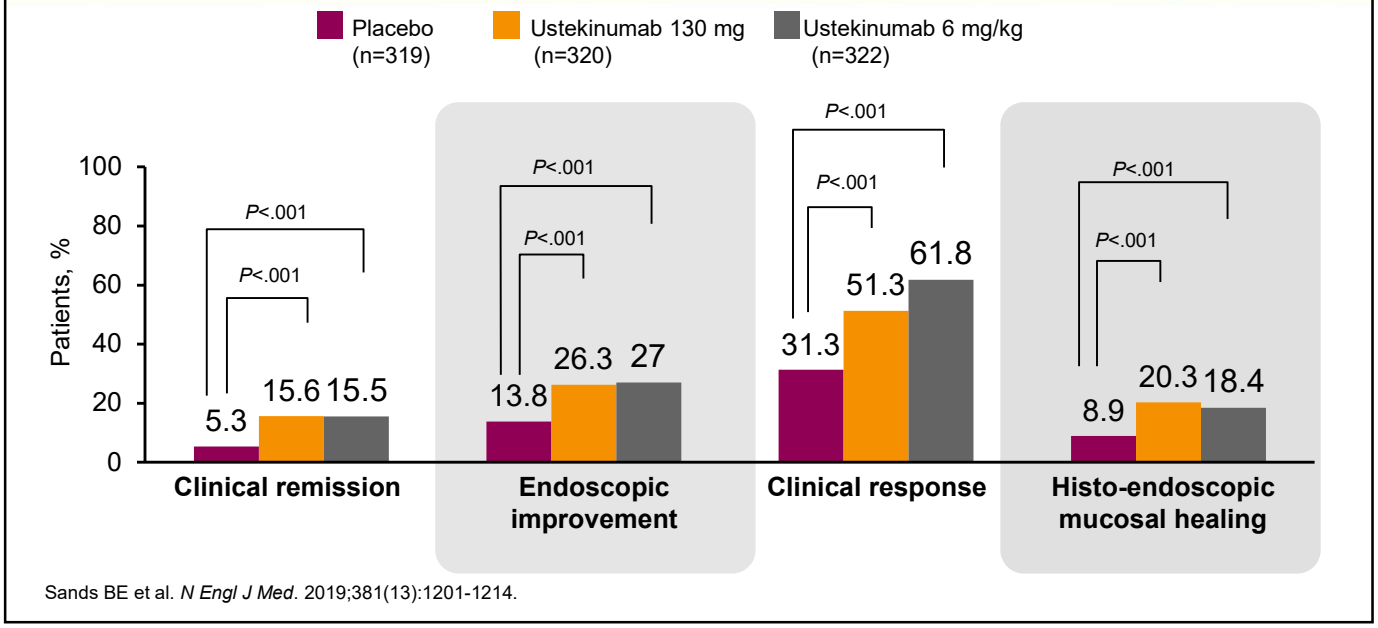
Ustekinumab Works in UC: Week 8 Outcomes



Sands BE et al. *N Engl J Med*. 2019;381(13):1201-1214.

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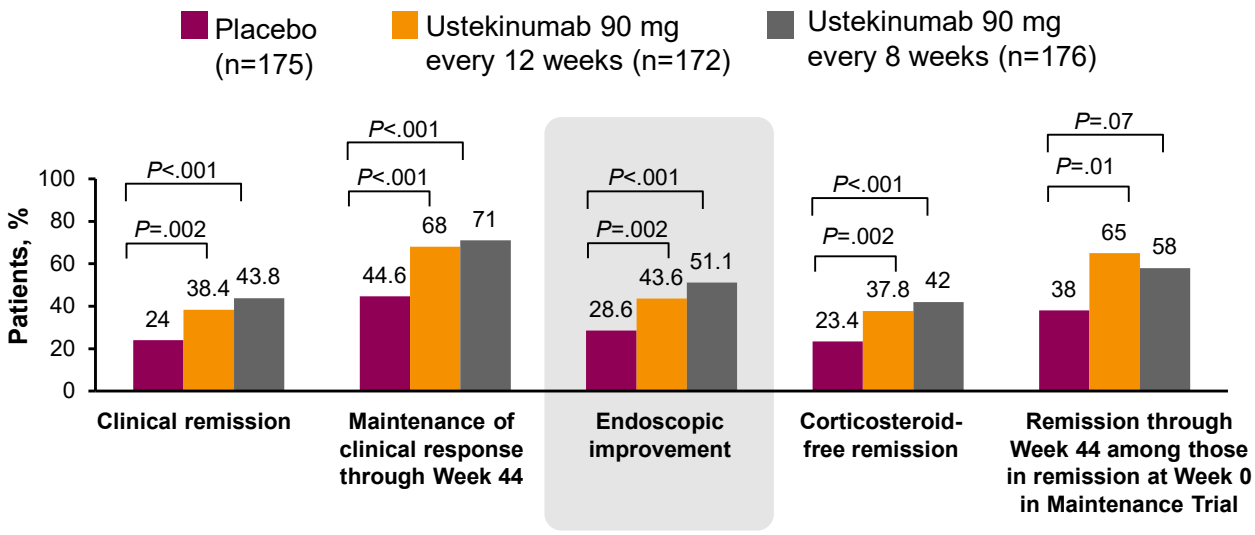
Ustekinumab Works in UC: Week 44 Outcomes



Sands BE et al. *N Engl J Med*. 2019;381(13):1201-1214.

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Deciding between these therapies in a biologic-naïve patient

- Oral versus IV or subq
- All safe
- Ozanimod unclear risk in pregnancy
- Consider EIMs although treating the colitis will often improve EIMs

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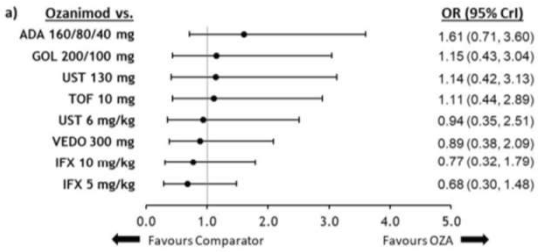
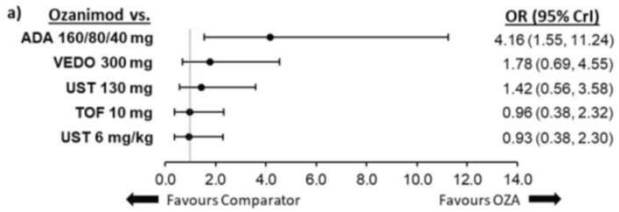
Network Analysis for Clinical Remission with Ozanimod

Clinical Remission in Biologic-Naïve Patients



Clinical Remission in Biologic-Experienced Patients



Eaton K et al. *J Crohns Colitis*. 2021;15(suppl_1):S103-S105.

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The steroid-dependent or chronically-active UC patient—failed first advanced therapy

- Depends on what they failed what you might do next
- Ozanimod failure—VDZ, IFX, ustekinumab
- VDZ failure—anti-TNFs, ustekinumab
- Anti-TNF failure-–JAK inhibitors or VDZ

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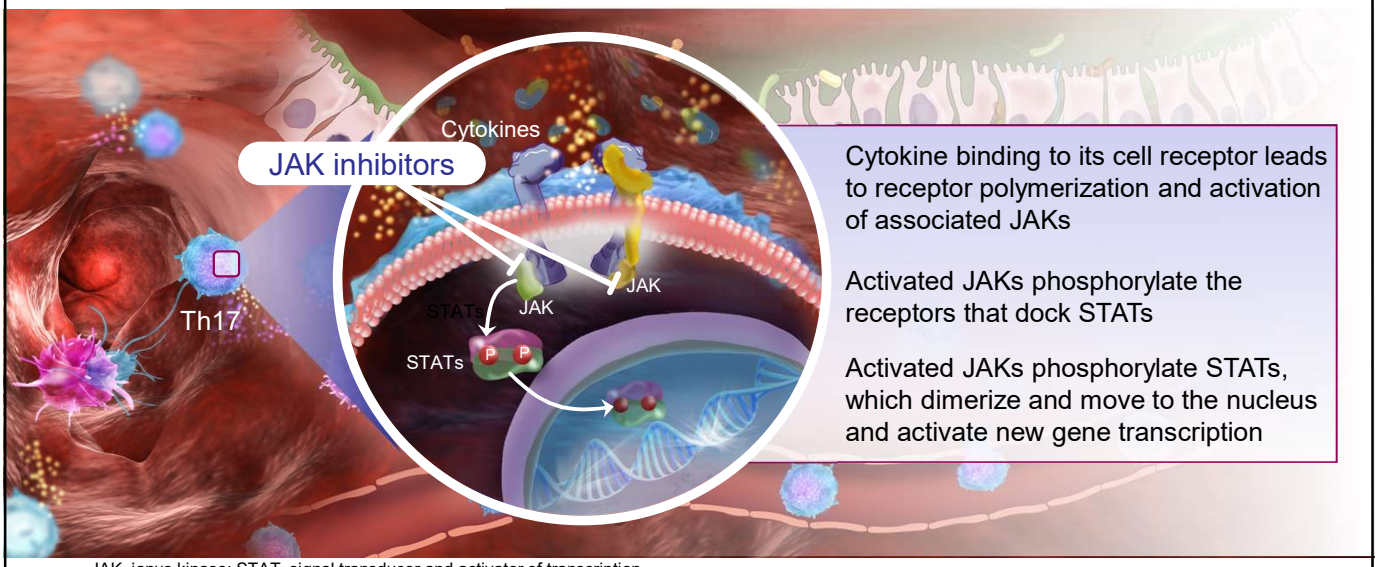
Binding of Cytokine Receptors by Cytokines Activates JAK Pathways Signaling



Cytokine binding to its cell receptor leads to receptor polymerization and activation of associated JAKs

Activated JAKs phosphorylate the receptors that dock STATs

Activated JAKs phosphorylate STATs, which dimerize and move to the nucleus and activate new gene transcription

JAK, janus kinase; STAT, signal transducer and activator of transcription.
Shukla T, Sands BE. *Curr Gastroenterol Rep.* 2019;21(5):22.

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Key Immunoregulatory Cytokines Linked TO JAK PATHWAY

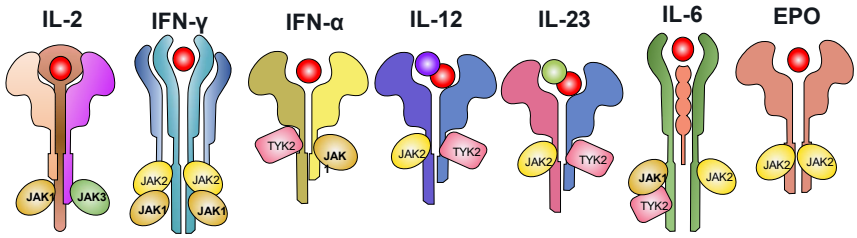
Different JAK inhibitors target several cytokines linked to UC inflammation

Tofacitinib (JAK1, JAK3)

Filgotinib
Upadacitinib (JAK1)

Peficitinib (JAK3)
Ritlecitinib

Brepocitinib (TYK2)
Deucravacitinib



INHIBITOR	IL-2	IFN-γ	IFN-α	IL-12	IL-23	IL-6	EPO
JAK1	+	+	+	-	-	+	-
JAK2	-	+	+	+	+	+	+
JAK3	+	-	-	-	-	-	-
TYK2	-	-	+	+	+	-	-

Abbreviations: EPO, erythropoietin; IFN, interferon.
O'Shea J, Plenge R. *Immunity.* 2012;36(4):542-550.

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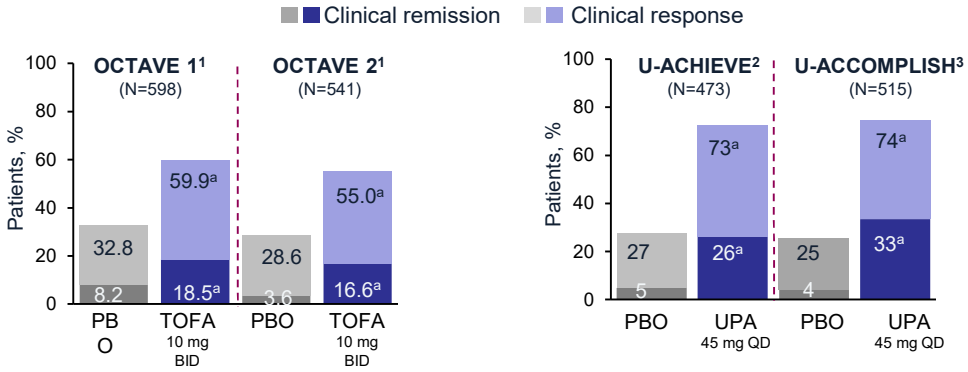
Pivotal Induction Studies of JAK Inhibitors in Moderate to Severe UC

TOFACITINIB

8-week outcomes

UPADACITINIB

8-week outcomes



[a]*P*<0.001 vs placebo; [b]*P*=0.01 vs placebo.
BID, twice daily; PBO, placebo; TOFA, tofacitinib; UPA, upadacitinib.
1. Sandborn WJ et al. *N Engl J Med*. 2017;376(18):1723-1736. 2. Danese, S. et al. *Lancet* 2022; 399: 2113–28

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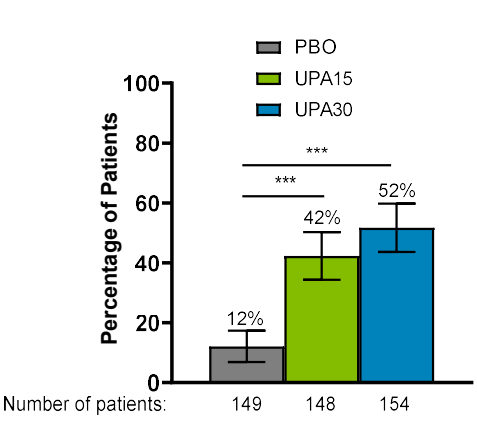
UPA15 and UPA30 Achieve Significance Compared to PBO for Clinical Remission at week 52

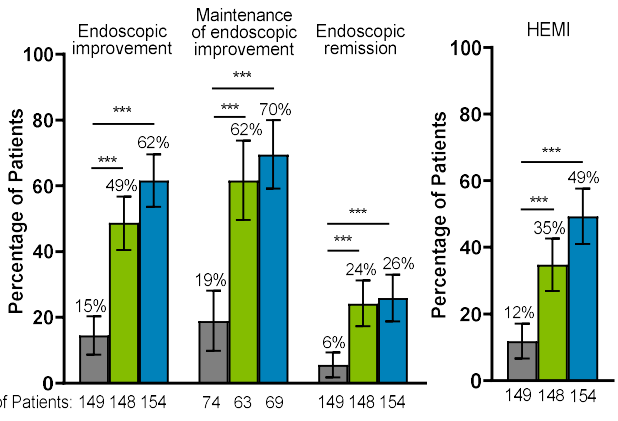
Primary Endpoint:

Clinical remission at 52 wk

Secondary Endpoints:

Endoscopic and histology





Danese, S. et al. *Lancet* 2022; 399: 2113–28

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Adverse Events of Special Interest: U-ACHIEVE Maintenance

Adverse Event	PBO N=149, (PYS =87.4)		UPA 15 mg QD N=148, (PYS= 119.3)		UPA 30 mg QD N=154, (PYS=135.1)	
	%	E/100 PY	%	E/100 PY	%	E/100 PY
Serious infection	4.0	6.9	3.4	4.2	2.6	3.0
Opportunistic infection excluding TB or herpes zoster	0	0	0.7	0.8	0	0
Herpes zoster	0	0	4.1	5.0	3.9	4.4
Any malignancy excluding NMSC	0.7	1.1	0.7	0.8	1.3	1.5
Any NMSC	0	0	0	0	1.3	1.5
Adjudicated VTE§	0	0	0	0	1.3	1.5
Adjudicated MACE‡	0.7	1.1	0	0	0	0
Adjudicated gastrointestinal perforation	0.7	2.3	0	0	0	0

No active tuberculosis or lymphoma were reported in the study.

Danese, S. et al. *Lancet* 2022; 399: 2113–28

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Tofacitinib/Upadacitinib: How and When to Use It

Advantages of tofacitinib

- Oral dosing
- Rapid onset of action
- Patients with poor PK for biologic
- Role in acute severe UC?
  - Tofacitinib 10mg PO TID/15mg BID
- Bridge to other biologic?
- Non-immunogenic
  - Patients with history of ADA
  - Patients at risk of interrupting medications

Limitations of tofacitinib

- Contraindicated during conception/pregnancy
- DVT/PE risk factors (eg, elderly, cancer)
- Herpes zoster (2- to 6-fold increase)
  - Key risk factors include age ≥65 years, diabetes mellitus, concomitant steroids, Asian race, and prior anti-TNF failure
- Increased total cholesterol, HDL and LDL (20% to 30%)
- Cardiovascular events
- No live vaccines
- All-cause mortality
  - RA literature; tofacitinib, 10mg BID

ADA, anti-drug antibodies; DVT, deep venous thrombosis; PE, pulmonary embolism; PK, pharmacokinetic.
Bernstein JA et al. *Clin Gastroenterol Hepatol.* 2019;17(5):988-990.

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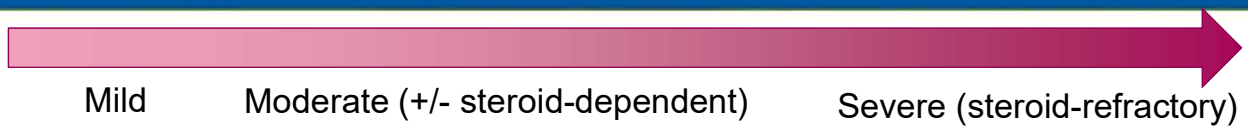
Synthesizing choices in UC treatment



Mild — Moderate (+/- steroid-dependent) — Severe (steroid-refractory)

	Mild	Moderate (+/- steroid-dependent)	Severe (steroid-refractory)
Naïve (mostly equipoised, patient preference important)		Ozanimod/etrasimod (proctitis)	Vedolizumab>adalimumab Ustekinumab Infliximab Infliximab Cyclo
Biologic-exposed		Change mechanism if did not work or lost mojo	JAKi (tofa, upadacitinib) if failed anti-TNFs (Avoid if CV/VTE risk factors)

Verdict out on S1P agonists and JAKi in pregnancy
I generally do not choose vedolizumab if dealing with EIMs

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New therapies for Crohn's disease

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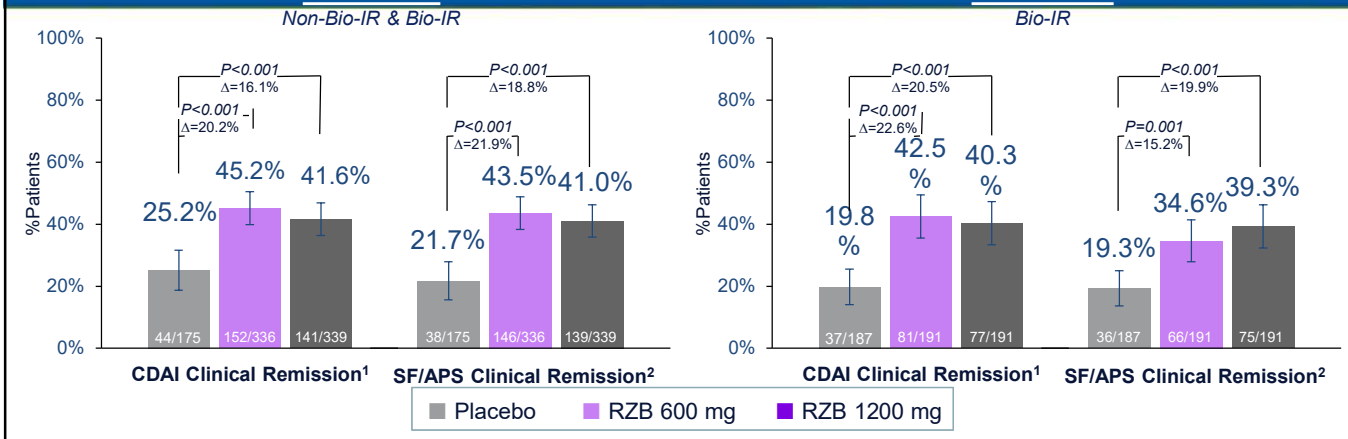
Risankizumab in Crohn's Disease Induction
Co-Primary Endpoint: Clinical Remission at Week 12



¹CDAI Clinical Remission: CDAI < 150
²SF/APS Clinical Remission: Average daily stool frequency (SF) ≤ 2.8 and not worse than baseline AND average daily abdominal pain score (APS) ≤ 1 and not worse than baseline
ITT population: Randomized subjects who received at least one dose of study drug who had baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease), excluding subjects from non-compliant site
Response rate (%) represents the synthesized results from NRI incorporating multiple imputation for missing data due to COVID-19
Statistical significance versus placebo was analyzed for the overall population with multiplicity adjustment for type I error control; P-value based on Cochran-Mantel-Haenszel (CMH) test adjusted for randomization stratification factors
Non-Bio-IR: Intolerance or inadequate response (IR) to prior conventional therapy; **Bio-IR**: Intolerance or inadequate response to prior biologic therapy.

D'Haens GR et al, Lancet 2022;399:2015-30.

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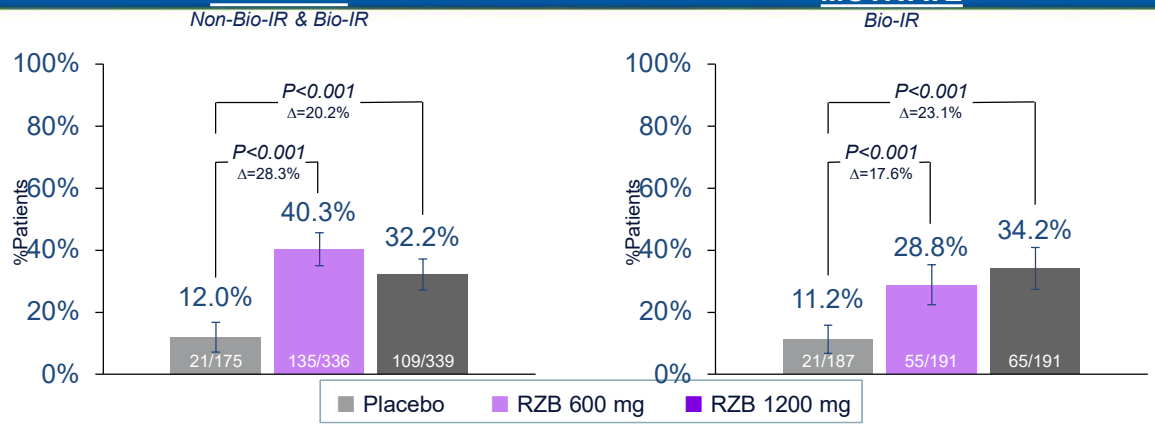
Risankizumab in Crohn's Disease Induction
Co-Primary Endpoint: Endoscopic Response at Week 12



Endoscopic Response: Decrease in SES-CD > 50% from baseline (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central readers
ITT population: Randomized subjects who received at least one dose of study drug who had baseline eligible SES-CD of ≥ 6 (≥ 4 for isolated ileal disease), excluding subjects from non-compliant site
Response rate (%) represents the synthesized results from NRI incorporating multiple imputation for missing data due to COVID-19
Statistical significance versus placebo was analyzed for the overall population with multiplicity adjustment for type I error control; P-value based on Cochran-Mantel-Haenszel (CMH) test adjusted for randomization stratification factors
Non-Bio-IR: Intolerance or inadequate response (IR) to prior conventional therapy; **Bio-IR**: Intolerance or inadequate response to prior biologic therapy.

D'Haens GR et al, Lancet 2022;399:2015-30.

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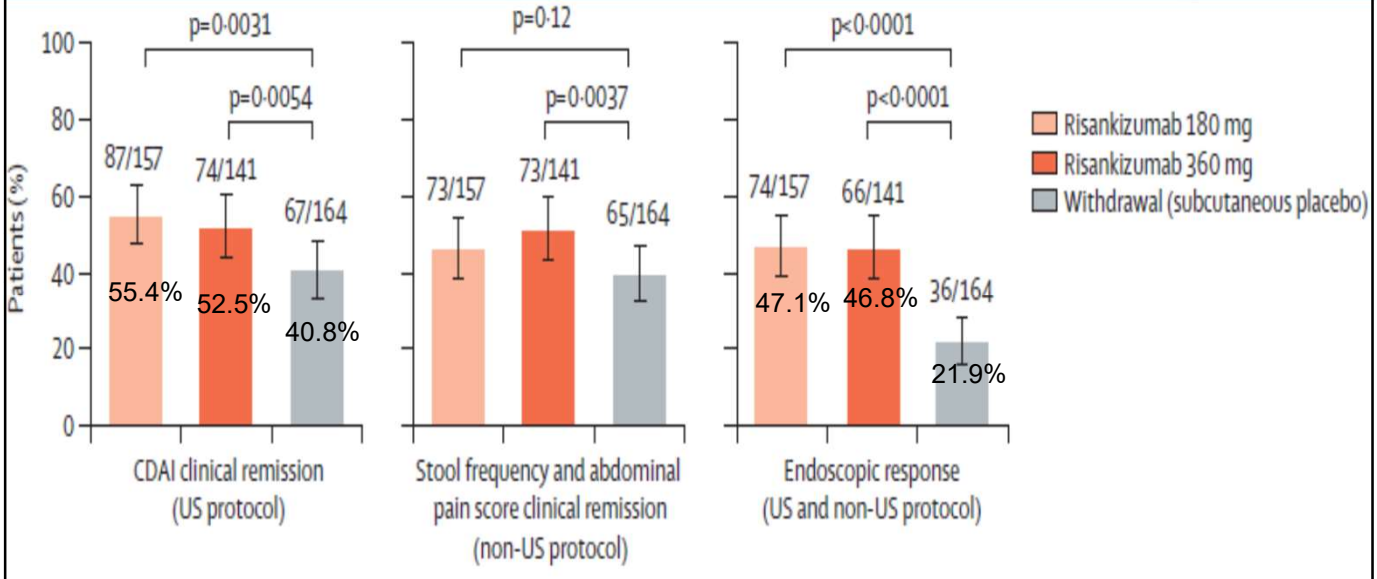
FORTIFY: Risankizumab Maintenance in Crohn's: Week 52



Ferrante M et al, Lancet 2022;399:2031-46.

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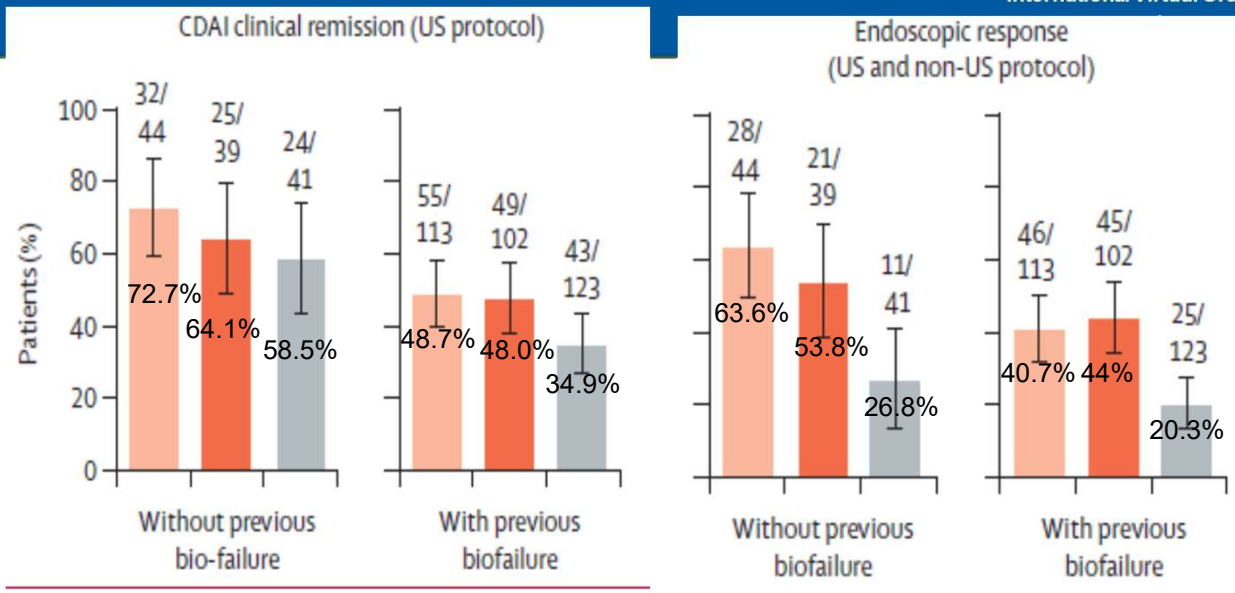
FORTIFY Results By Biologic Exposure, Wk 52



Ferrante M et al, Lancet 2022;399:2031-46.

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Risankizumab CD Maintenance study (FORTIFY) Adverse Events of Special Interest

	Withdrawal (PBO SC) (n=184) (PYs=160.4)	RZB 180 mg SC (n=179) (PYs=169.3)	RZB 360 mg SC (n=179) (PYs=166.4)
AE, exposure adjusted event rate		**Events (E/100 PYs)**	
CD	34 (21.2)	19 (11.2)	23 (13.8)
Serious infection	8 (5.0)	5 (3.0)	10 (6.0)
Opportunistic infection excluding TB or herpes zoster	0	1 (0.6)	1 (0.6)
Herpes zoster	1 (0.6)	2 (1.2)	0
Active TB	1 (0.6)	0	1 (0.6)
Adjudicated MACEs*	0	0	0
NMSC	1 (0.6)	0	0
Malignancies excluding NMSC	0	0	1 (0.6)
Serious hypersensitivity reactions	0	0	0
Adjudicated anaphylactic reaction	0	0	0
Hepatic events	4 (2.5)	8 (4.7)	9 (5.4)
Injection site reactions	15 (8.1)	16 (9.5)	23 (13.8)

The safety population includes patients excluded from efficacy from a non-compliant site, patients with lower SES-CD and patients that underwent 24 weeks of induction.
*MACE define as cardiovascular death, non-fatal myocardial infarction, and non-fatal myocardial infarction stroke.
AE, adverse event; CD, Crohn's disease; E, event; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient-year; RZB, risankizumab; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; TB, tuberculosis; TEAE, treatment-emergent adverse event.
Ferrante M, et al. Abstract presented at: UEGW, Virtual Meeting 4 October 2021. Abstract LB13.

Ferrante M et al, Lancet 2022;399:2031-46.

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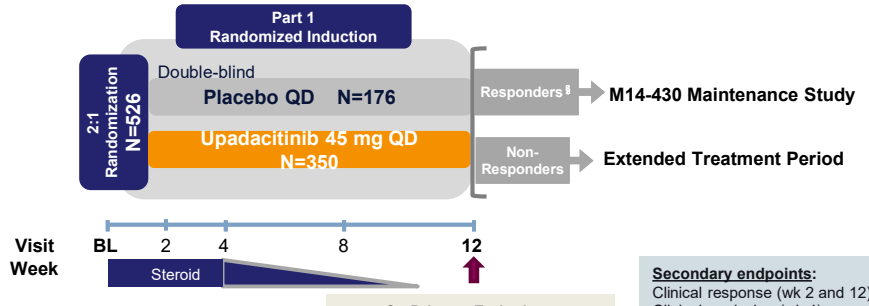
Upadacitinib in Crohn's: U-EXCEL Induction Study Design in Patients with Inadequate Response or Intolerance to Conventional or Biologic Therapy



Co-Primary Endpoints:
Clinical Remission at wk 12
Endoscopic Response at wk 12

Secondary endpoints:
Clinical response (wk 2 and 12)
Clinical remission (wk 4)
Corticosteroid-free clinical remission (wk 12)
Endoscopic remission (wk 12)

Main Inclusion Criteria:
- **18 to 75 years of age**
- **Moderately to severely active Crohn's disease (CD):**
  - Average daily liquid/very soft **stool frequency (SF) ≥ 4** and/or average daily **abdominal pain score (APS) ≥ 2**
  - Evidence of mucosal inflammation; **Simple Endoscopic Score for CD (SES-CD ≥ 6) (≥ 4** for patients with isolated ileal disease)
- **Intolerance or inadequate response to** one or more steroid, immunosuppressant or biologic therapy

§ Patients in U-EXCEL that achieved Clinical Response per SF/APS (defined as≥ 30% decrease in average daily SF and/or in average daily APS and both not greater than baseline) at week 12 or 24 were randomized to the Maintenance Study

Loftus E et al, United Eur Gastroenterol J 2022;10(S8):103-104. Abstract OP129.
Loftus EV et al, Am J Gastroenterol 2022;117(10S):e518. Abstract S736.

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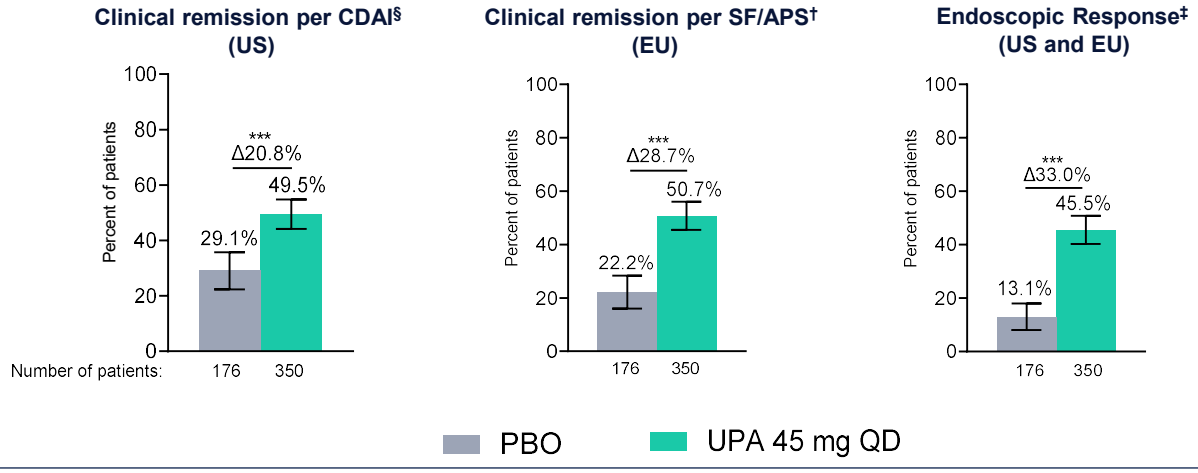
Patients Treated with UPA 45 mg QD Achieved a Significant Difference in Co-Primary Endpoints at Week 12 Compared to Placebo



§ **Clinical Remission per CDAI:** CDAI < 150
† **Clinical Remission per SF/APS:** Average daily SF ≤ 2.8 AND average daily APS ≤ 1 and neither worse than baseline
‡ **Endoscopic Response**: Decrease in SES-CD >50% from baseline (or SES-CD of 4), at least a 2-point reduction from baseline, scored by central reader.
95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE

Loftus E et al, United Eur Gastroenterol J 2022;10(S8):103-104. Abstract OP129.
Loftus EV et al, Am J Gastroenterol 2022;117(10S):e518. Abstract S736.

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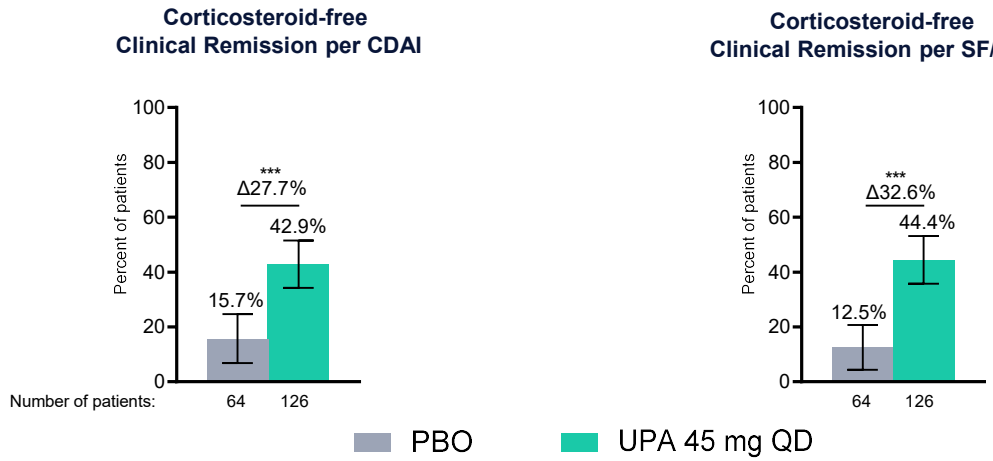
Patients on Corticosteroids at Baseline Treated with UPA 45 mg QD Achieved a Significant Difference in Corticosteroid-free Clinical Remission at Week 12



Corticosteroid-free Clinical Remission per CDAI or SF/APS: Discontinuation of corticosteroid and achievement of clinical remission (per CDAI or SF/APS), among subjects on steroids at baseline
95% CI for response rate is based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data. Point estimate and 95% CI for adjusted treatment difference are based on Cochran-Mantel

Loftus E et al, United Eur Gastroenterol J 2022;10(S8):103-104. Abstract OP129.
Loftus EV et al, Am J Gastroenterol 2022;117(10S):e518. Abstract S736.

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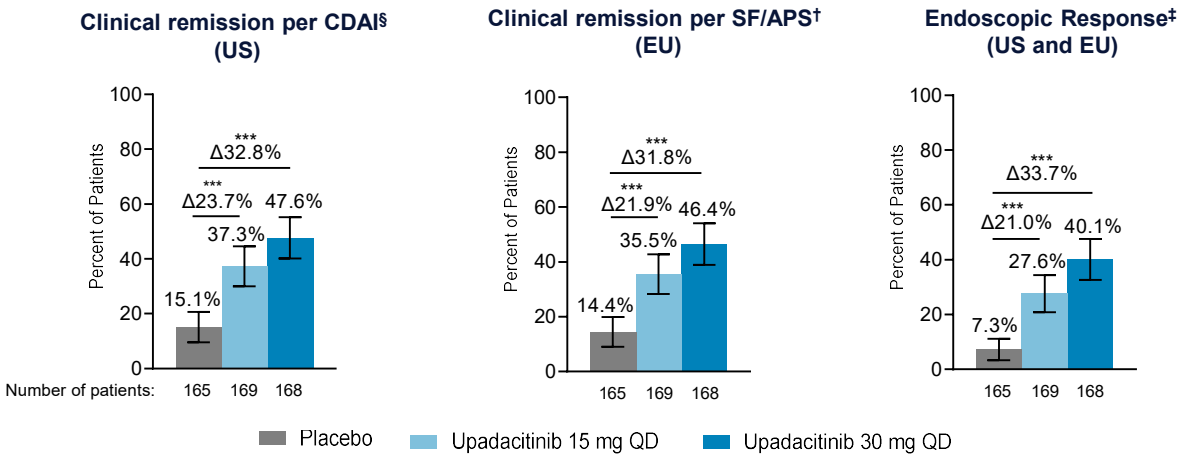
Patients Treated with UPA 15 mg or 30 mg Achieved Significant Differences in Co-Primary Endpoints at Week 52 Compared to Placebo



§ **Clinical Remission per CDAI:** CDAI < 150
† **Clinical Remission per SF/APS:** Average daily very soft or liquid SF ≤ 2.8 AND average daily APS ≤ 1 and neither worse than baseline
‡ **Endoscopic Response**: Decrease in SES-CD >50% from baseline (or SES-CD of 4, at least a 2-point reduction from baseline, scored by central reader
95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if t **Panes J, Loftus E Jr et al, Am J Gastroenterol 2022;117(S10). Abstract S37.**

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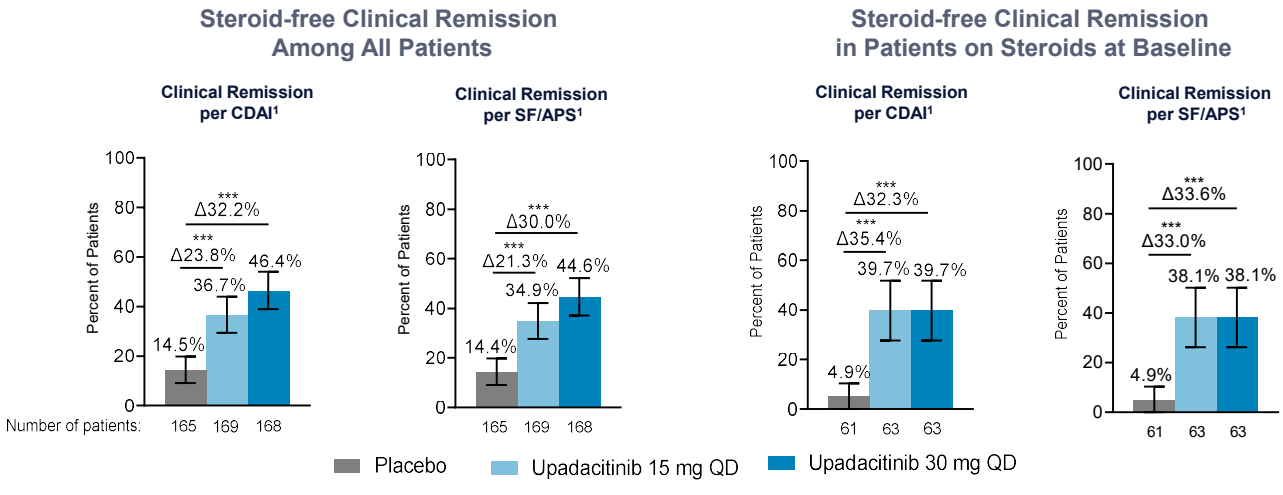
Steroid-free Clinical Remission at Week 52 was Achieved with UPA 15 mg or 30 mg Among All Patients and Those on Steroids at Baseline



1 **Steroid-free Clinical Remission per CDAI or SF/APS:** Without steroids for at least 90 days prior to study visit and achieved clinical remission (per CDAI or SF/APS)
95% CI for response rate is based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data. Point estimate and 95% CI for adjusted treatment difference are based on Cochran-Mantel-Haenszel test for adjusted strata f **Panes J, Loftus E Jr et al, Am J Gastroenterol 2022;117(S10). Abstract S37.**

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Treatment-Emergent Adverse Events

Adverse event (AE), Events (E/100 PY)	PBO N=223 PY= 107.0	UPA 15 mg QD N=221 PY=148.2	UPA 30 mg QD N=229 PY=166.5
Any AE	502 (469.2)	518 (349.5)	539 (323.7)
Severe AE	38 (35.5)	37 (25.0)	31 (18.6)
Serious AE	40 (37.4)	37 (25.0)	35 (21.0)
AE possibly related to study drug	135 (126.2)	135 (91.1)	139 (83.5)
AE leading to study drug discontinuation	8 (7.5)	19 (12.8)	14 (8.4)
AE related to COVID-19	11 (10.3)	12 (8.1)	18 (10.8)
All deaths	0	0	0

The safety population includes all patients who received at least one dose of the study drug during induction and maintenance periods. .
Events, E; Patient years, PY

Panes J, Loftus E Jr et al, Am J Gastroenterol 2022;117(S10). Abstract S37.

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Adverse Events of Special Interest

Adverse event, Events (E/100 PY)	PBO N=223; PY= 107.0	UPA 15 mg QD N=221; PY=148.2	UPA 30 mg QD N=229; PY=166.5
Serious infection	9 (8.4)	9 (6.1)	13 (7.8)
Opportunistic infection (excl Tuberculosis and Herpes zoster)	0	1 (0.7)	1 (0.6)
Herpes zoster	5 (4.7)	6 (4.0)	12 (7.2)
Anemia†	13 (12.2)	15 (10.1)	11 (6.6)
Lymphopenia	10 (9.3)	4 (2.7)	10 (6.0)
Neutropenia	1 (0.9)	3 (2.0)	5 (3.0)
Creatine phosphokinase elevation	3 (2.8)	5 (3.4)	8 (4.8)
Hepatic disorder‡	3 (2.8)	11 (7.4)	17 (10.2)
Renal disorder	2 (1.9)	0	0
Adjudicated gastrointestinal perforation	1 (0.9)	1 (0.7)	1 (0.6)
Adjudicated thromboembolic event*	0	0	1 (0.6)
Malignancies (all types)§	0	1 (0.7)	2 (1.2)

No tuberculosis, adjudicated cardiovascular, or non-melanoma skin cancer events were observed in any treatment group.

† Anemia (which includes other preferred terms, in addition to the preferred term "anaemia"), herpes zoster, neutropenia and lymphopenia were based on CMQ search. ‡ Hepatic disorder included transaminase elevations that were mild or moderate, asymptomatic, nonserious and uncommonly led to treatment discontinuation. *Hepatic vein thrombosis concurrent with an event of exacerbation of CD. § Metastatic ovarian cancer in a patient the upadacitinib 15 mg group; and colon cancer and invasive lobular breast cancer in one patient each in the upadacitinib 30 mg QD group.

Panes J, Loftus E Jr et al, Am J Gastroenterol 2022;117(S10). Abstract S37.

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How do these therapies compare to one another?

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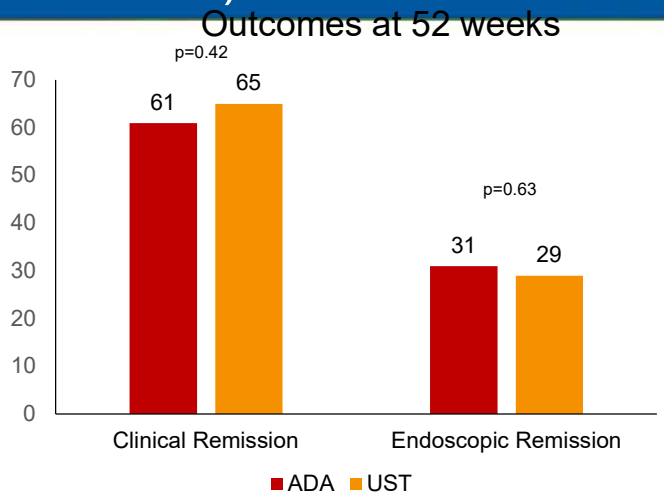
Comparative Effectiveness: SEAVUE Trial (UST vs. ADA)

International Virtual Grand Rounds
universe.gi.org

- Randomized controlled trial of mod-severe CD with at least one ulcer; 1:1 randomization to UST or ADA with assessment at week 52
- Primary outcome: clinical remission, secondary outcome of endoscopic remission
- 386 patients enrolled; 15% in UST group and 24% in ADA group discontinued prior to week 52
- SES-CD 9.8, 9.9 between groups, ~5 years disease duration
- Both therapies highly effective – no differences in safety outcomes



Sands BE, et al. Lancet. 2022 Jun 11;399(10342):2200-2211.

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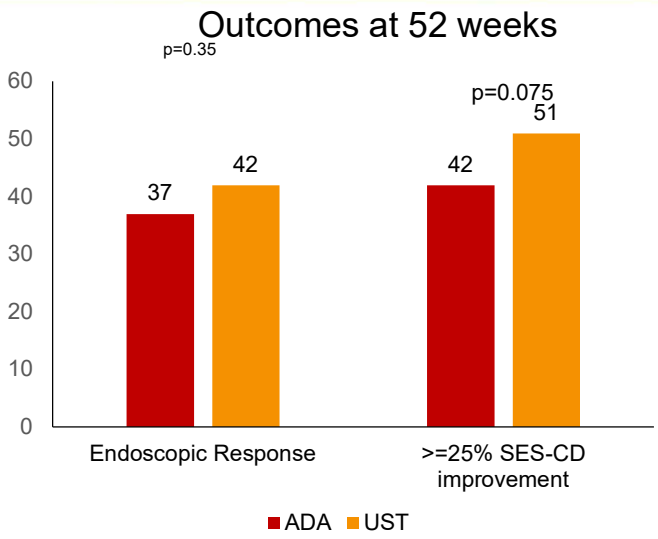
Comparative Effectiveness: SEAVUE Trial (UST vs. ADA)

- Median serum, trough at last dosing visit was 2.0 ug/ml for UST and 7.8 ug/ml for ADA
- At week 52, 2% of UST patients had antibodies; 75% of ADA patients with antibodies at one or more timepoints
- Most patients on ADA with antibodies (70%) had low titres
- However, no difference in clinical remission at week 52 for those with and without ADA antibodies
- With high rates of antibody formation; longer follow up is needed
- Optimization of ADA is likely needed



Sands BE, et al. Lancet. 2022 Jun 11;399(10342):2200-2211.

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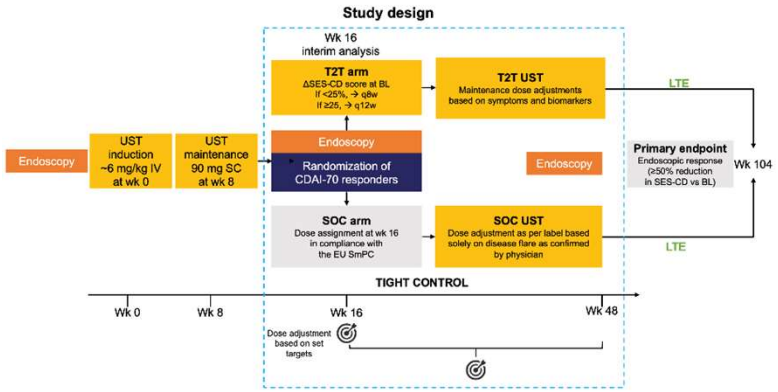
Optimization of Therapy: STARDUST Trial of UST Treat to Target

- Open label RCT of mod-severe CD with SES-CD ≥3; all received UST induction
- Responders at week 16 were randomly assigned to standard of care or treat to target
- Standard of care arm received q 12 or q 8 week dosing per European label
- T2T arm could escalate from q12 to q8 to q 4 weeks based on predefined targets
- Primary outcome: endoscopic response at week 48 (SES-CD ≥ 50% decrease)



Danese S, et al. Lancet Gastroenterol Hepatol. 2022 Apr;7(4):294-306.

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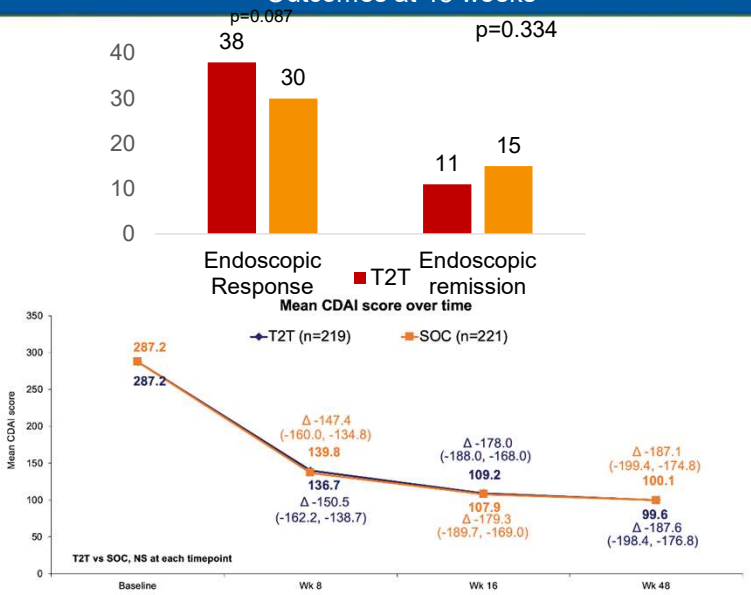
Optimization of Therapy: STARDUST

- Included 219 in T2T; 221 SoC
- Results similar between groups for endoscopic outcomes; steroid free outcomes, CDAI and biomarkers
- Timely escalation of UST for patients with CD based on endoscopy, clinical symptoms and biomarkers did not improve endoscopic outcomes at week 48



Danese S, et al. Lancet Gastroenterol Hepatol. 2022 Apr;7(4):294-306.

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Using network meta-analyses when we don't have head-to-head studies

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Clinical Remission, Endoscopic Improvement UC Network Meta-Analysis

Upadacitinib	2·70 (1·18–6·20)	4·49 (2·18–9·24)	6·15 (2·98–12·72)	2·84 (1·28–6·31)	4·91 (2·59–9·31)	2·92 (1·31–6·51)	3·56 (1·84–6·91)	3·00 (1·32–6·82)	4·64 (2·47–8·71)	2·70 (1·18–6·20)	9·54 (5·45–16·69)
3·01 (1·59–5·67)	Ozanimod	1·65 (0·77–3·55)	2·27 (1·05–4·89)	1·05 (0·45–2·41)	1·81 (0·91–3·60)	1·07 (0·46–2·49)	1·31 (0·65–2·67)	1·10 (0·47–2·61)	1·71 (0·87–3·37)	0·93 (0·47–1·85)	3·52 (1·91–6·49)
2·91 (1·19–7·10)	0·97 (0·39–2·39)	Filgotinib 200 mg	1·37 (0·71–2·62)	0·63 (0·30–1·31)	1·09 (0·63–1·89)	0·65 (0·31–1·35)	0·79 (0·44–1·41)	0·66 (0·31–1·42)	1·03 (0·60–1·77)	0·56 (0·32–0·97)	2·12 (1·34–3·35)
5·96 (2·35–15·14)	1·98 (0·77–5·09)	2·04 (0·66–6·33)	Filgotinib 100 mg	0·46 (0·22–0·95)	0·79 (0·45–1·39)	0·47 (0·22–0·99)	0·57 (0·32–1·03)	0·48 (0·22–1·03)	0·75 (0·43–1·30)	0·41 (0·23–0·71)	1·54 (0·97–2·45)
3·05 (1·68–5·51)	1·01 (0·55–1·86)	1·04 (0·43–2·50)	0·51 (0·20–1·27)	Tofacitinib	1·72 (0·90–3·29)	1·02 (0·45–2·30)	1·25 (0·64–2·45)	1·05 (0·46–2·41)	1·63 (0·86–3·08)	0·89 (0·46–1·69)	3·35 (1·90–5·91)
4·71 (2·83–7·83)	1·56 (0·92–2·66)	1·61 (0·71–3·65)	0·78 (0·33–1·86)	1·54 (0·96–2·48)	Etrolizumab	0·59 (0·31–1·14)	0·72 (0·48–1·08)	0·61 (0·31–1·21)	0·94 (0·69–1·29)	0·51 (0·36–0·72)	1·94 (1·42–2·64)
3·45 (1·90–6·24)	1·14 (0·62–2·11)	1·18 (0·49–2·83)	0·57 (0·23–1·44)	1·13 (0·64–1·99)	0·73 (0·45–1·18)	Ustekinumab	1·22 (0·62–2·39)	1·02 (0·44–2·35)	1·59 (0·83–3·02)	0·86 (0·45–1·66)	3·26 (1·83–5·79)
4·71 (2·68–8·28)	1·56 (0·87–2·81)	1·61 (0·68–3·79)	0·79 (0·32–1·93)	1·54 (0·90–2·63)	1·00 (0·64–1·55)	1·36 (0·79–2·33)	Vedolizumab	0·84 (0·41–1·68)	1·30 (0·96–1·74)	0·71 (0·45–1·10)	2·67 (1·87–3·80)
4·52 (2·55–8·01)	1·50 (0·83–2·72)	1·54 (0·65–3·65)	0·75 (0·30–1·86)	1·48 (0·86–2·55)	0·95 (0·61–1·51)	1·31 (0·76–2·26)	0·95 (0·57–1·60)	Golimumab	1·54 (0·79–3·01)	0·84 (0·43–1·65)	3·17 (1·74–5·79)
5·41 (3·30–8·86)	1·79 (1·07–3·01)	1·85 (0·82–4·15)	0·90 (0·38–2·12)	1·77 (1·11–2·81)	1·14 (0·88–1·49)	1·56 (0·98–2·48)	1·15 (0·75–1·75)	1·19 (0·77–1·84)	Adalimumab	0·54 (0·37–0·79)	2·05 (1·54–2·73)
2·75 (1·66–4·55)	0·91 (0·54–1·54)	0·94 (0·41–2·14)	0·46 (0·19–1·09)	0·90 (0·56–1·44)	0·58 (0·43–0·78)	0·79 (0·49–1·27)	0·58 (0·37–0·91)	0·60 (0·39–0·95)	0·51 (0·37–0·69)	Infliximab	3·76 (2·77–5·12)
8·23 (5·32–12·75)	2·74 (1·72–4·34)	2·82 (1·30–6·12)	1·38 (0·60–3·14)	2·71 (1·81–4·02)	1·74 (1·34–2·26)	1·74 (1·34–2·26)	1·74 (1·22–2·49)	1·82 (1·25–2·63)	1·52 (1·21–1·92)	3·00 (2·33–3·82)	Placebo

Endoscopic improvement

Clinical remission

Lasa Lancet Gastroenterol Hepatol 2022;7:161-70

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Network Meta-Analysis: Induction of Crohn's Clinical Remission/Clinical Response—Bio-Naïve

Induction of clinical remission

Induction of clinical response

Infliximab	0·61 (0·31–1·19)	1·50 (0·54–4·22)	2·65 (0·70–10·02)	1·72 (0·61–4·87)	2·07 (0·63–6·87)	2·28 (0·73–7·06)	4·53 (1·49–13·79)	6·17 (2·54–15·01)
0·56 (0·36–0·87)	Infliximab plus thiopurines	2·49 (0·73–8·52)	4·38 (0·99–19·45)	2·85 (0·83–9·82)	3·43 (0·87–13·54)	3·76 (1·01–14·03)	7·49 (2·04–27·49)	10·20 (3·34–31·10)
8·84 (1·95–40·03)	15·88 (3·29–76·64)	Adalimumab	1·76 (0·76–4·08)	1·15 (0·66–1·99)	1·38 (0·51–3·69)	1·51 (0·61–3·74)	3·01 (1·25–7·27)	4·10 (2·31–7·27)
..	..	..	Adalimumab plus thiopurines	0·65 (0·24–1·77)	0·78 (0·21–2·85)	0·86 (0·25–2·95)	1·71 (0·51–5·77)	2·33 (0·84–6·43)
7·90 (1·78–35·10)	14·18 (2·99–67·26)	0·89 (0·61–1·31)	..	Ustekinumab	0·83 (0·31–2·21)	1·32 (0·54–3·23)	2·63 (1·10–6·28)	3·58 (2·05–6·25)
..	..	..	..	..	Risankizumab	1·10 (0·38–3·19)	2·19 (0·77–6·21)	2·98 (1·33–6·64)
12·76 (2·76–59·08)	22·91 (4·64–113·02)	1·44 (0·75–2·80)	..	1·62 (0·87–3·00)	..	Vedolizumab	1·99 (0·75–5·26)	2·71 (1·34–5·48)
15·08 (3·46–65·83)	27·08 (5·81–126·25)	1·71 (1·02–2·84)	..	1·91 (1·21–3·00)	..	1·18 (0·67–2·10)	Certolizumab pegol	1·36 (0·70–2·66)
22·00 (5·17–93·56)	39·49 (8·68–179·61)	2·49 (1·62–3·82)	..	2·79 (1·94–3·99)	..	1·72 (1·04–2·85)	1·46 (1·11–1·92)	Placebo

(shaded/bolded are statistically significant)

Singh S et al, Lancet Gastroenterol Hepatol 2021;6:1002-14.

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Network Meta-Analysis: Induction of Crohn's Clinical Remission/Clinical Response—Bio-Exposed

Induction of clinical response	Induction of clinical remission				
	Risankizumab	1·34 (0·79–2·27)	0·74 (0·35–1·57)	**2·10 (1·12–3·92)**	**2·64 (1·89–3·68)**
	1·34 (0·62–2·90)	Ustekinumab	0·56 (0·25–1·22)	1·57 (0·80–3·06)	**1·97 (1·31–2·97)**
	1·51 (0·64–3·56)	1·13 (0·51–2·51)	Adalimumab	**2·82 (1·20–6·62)**	**3·55 (1·82–6·93)**
	1·87 (0·87–4·02)	1·40 (0·68–2·87)	1·24 (0·55–2·77)	Vedolizumab	1·26 (0·74–2·14)
	3·31 (1·86–5·90)	**2·47 (1·49–4·09)**	**2·19 (1·17–4·09)**	**1·77 (1·07–2·92)**	Placebo

(shaded/bolded are statistically significant)

Singh S et al, Lancet Gastroenterol Hepatol 2021;6:1002-14.

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Network Meta-Analysis: Maintenance of Crohn's Clinical Remission

	Maintenance of clinical remission							
Infliximab	0·68 (0·37–1·23)	0·86 (0·40–1·84)	0·97 (0·34–2·78)	1·13 (0·53–2·40)	1·69 (0·71–4·00)	1·44 (0·69–3·03)	1·32 (0·57–3·06)	**2·96 (1·60–5·49)**
	Infliximab plus thiopurines	1·27 (0·48–3·33)	1·43 (0·43–4·80)	1·67 (0·64–4·35)	2·49 (0·87–7·09)	2·12 (0·82–5·50)	1·94 (0·69–5·44)	**4·37 (1·85–10·29)**
		Adalimumab	1·13 (0·55–2·34)	1·31 (0·76–2·26)	1·96 (0·92–4·19)	1·68 (0·90–3·12)	1·53 (0·74–3·19)	**3·44 (2·17–5·46)**
			Adalimumab plus thiopurines	1·16 (0·47–2·88)	1·74 (0·61–4·97)	1·48 (0·57–3·86)	1·36 (0·48–3·81)	**3·05 (1·29–7·21)**
				Ustekinumab	1·49 (0·70–3·17)	1·27 (0·69–2·36)	1·17 (0·56–2·42)	**2·62 (1·66–4·13)**
					Risankizumab	0·85 (0·41–1·79)	0·78 (0·34–1·79)	1·75 (0·96–3·20)
						Vedolizumab	0·92 (0·45–1·87)	**2·06 (1·34–3·16)**
							Certolizumab pegol	**2·25 (1·27–3·97)**
								Placebo

(shaded/bolded are statistically significant)

Singh S et al, Lancet Gastroenterol Hepatol 2021;6:1002-14.

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Network Meta-Analysis: Crohn's Safety in Maintenance Trials (Serious Adverse Events, Infections)

Risk of infection	Risk of serious adverse events						
	Infliximab	1·77 (1·03–3·05)	1·51 (0·83–2·77)	1·28 (0·64–2·53)	0·96 (0·51–1·80)	1·13 (0·45–2·81)	0·94 (0·60–1·47)
	1·18 (0·77–1·81)	Infliximab plus thiopurine	0·85 (0·38–1·93)	0·72 (0·30–1·73)	0·54 (0·24–1·25)	0·64 (0·22–1·84)	0·53 (0·26–1·07)
	0·54 (0·33–0·90)	0·46 (0·24–0·89)	Adalimumab	0·84 (0·53–1·36)	0·64 (0·35–1·17)	0·75 (0·31–1·83)	0·62 (0·41–0·94)
	0·79 (0·45–1·36)	0·67 (0·33–1·33)	1·45 (1·03–2·02)	Ustekinumab	0·75 (0·38–1·49)	0·88 (0·34–2·29)	0·74 (0·44–1·24)
	0·70 (0·39–1·25)	0·59 (0·29–1·22)	1·29 (0·79–2·09)	0·89 (0·52–1·52)	Vedolizumab	1·17 (0·47–2·92)	0·98 (0·63–1·52)
	0·28 (0·05–1·47)	0·24 (0·04–1·32)	0·51 (0·10–2·63)	0·35 (0·07–1·85)	0·40 (0·08–2·10)	Certolizumab pegol	0·83 (0·38–1·84)
	0·84 (0·55–1·27)	0·71 (0·39–1·29)	1·54 (1·17–2·01)	1·06 (0·75–1·51)	1·19 (0·80–1·78)	3·00 (0·60–15·03)	Placebo

(shaded/bolded are statistically significant)

Singh S et al, Lancet Gastroenterol Hepatol 2021;6:1002-14.

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Synthesizing choices in CD treatment

	Mild	Moderate	Severe or Fistulizing disease
Naïve (mostly equipoised, patient preference important)		Adalimumab Vedolizumab Ustekinumab Risankizumab	Infliximab Ustekinumab Risankizumab
Biologic-exposed		Depends on initial MoA Risankizumab Upadacitinib	JAKi (upadacitinib) if failed anti-TNFs Works in fistulizing disease Works quickly

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Unanswered Questions

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- Best sequence of biologics
  - Ideally biomarker-based
  - Insurance decides (sorry to burst your bubble)
- Take into account the full picture:
  - Severity of inflammation at induction—how quickly do you need it to work?
  - Extraintestinal manifestations, fistulizing disease
  - Age and comorbidities

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How to follow a patient on biologic therapy

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American College of Gastroenterology y Asociación Mexicana de Gastroenterología

Fernando Velayos MD MPH
Regional Lead- Kaiser Permanente Northern California IBD Program
Chief of Gastroenterology and Hepatology-KP San Francisco Medical Center
Professor of Medicine, UCSF

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Screening and monitoring patients on biologics is key for making treatment decisions

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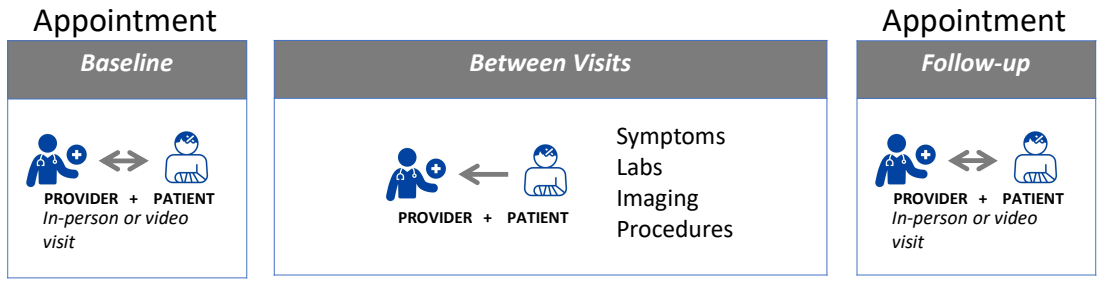

- Decide to start biologic/ small molecule based on disease activity and past testing
- Discuss potential risks and side effects
- Screen history and send labs/ tests before starting

- Review labs/tests/ past history and if appropriate start biologic/small molecule
- Monitor disease activity/ response/ side effects of new therapy

- Review recent labs/tests
- Assess disease activity/ response/ side effects to new therapy
- Adjust or change medication

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Screening and monitoring patients on biologics is key for making treatment decisions

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- Explain why important and provide a road map of what to expect and what you will do with this information
- Consider having written "scripts" that can be used in the medical record and sent to patients so they can also be aware of what to expect

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Objectives

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- Review how to start and monitor patients starting on current biologic/small molecule therapies
  - Vaccinations
  - Labs/tests at baseline and at follow-up
  - Screening for contraindications and warnings/precautions
- Discuss how to measure disease activity and how frequently to monitor after starting therapy

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All patients starting a biologic/small molecule should be considered for the following vaccine preventable illnesses

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Vaccine	Recommendation	Frequency
Influenza	- All patients, Avoid live (intranasal) version of vaccine	Annually
Tetanus,diptheria & pertussis (TDaP)	- TDaP once as adult, Tetanus (TD) booster every 10 years thereafter	Every 10 years
Hepatitis A	- Adults if serology shows patient is susceptible - May be given combined with Hepatitis B	2-dose series at Month 0 & 6
Hepatitis B	- Adults if serology shows patient is susceptible - May be given combined with Hepatitis A	3-dose series at Month 0, 1, 6
Pneumococcal (PCV13)	- Adults (doses given before age 18 count) - May give PCV13 $\geq$ 1 year after last PPSV23 dose	Max lifetime: Once
Pneumococcal (PPSV23)	- Adults, may give PPSV23 at least 8 weeks after PCV13 dose	1st dose, Booster #1 at Year 5, Booster #2 at age $\geq$ 65 years

Live vaccines are contraindicated for all patients on IMM, biologics, and/or small molecule inhibitor therapy

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All patients should have following baseline and follow-up labs when on a biologic/small molecule

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Baseline	Follow-up
Standing labs if not completed past 3 months (standing labs) - CBC - Liver tests - Creatinine	CBC, liver function: after induction (4-12 weeks) and then every 3-4 months Creatinine: after induction and then yearly
If not completed past 6 months - Hepatitis A, B screening - TB screening - Stool tests (if diarrhea) - TPMT (if planning AZA. 6MP)	Consider confirming Hep B antibody response after vaccination Annually: TB testing

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Special screening and monitoring with anti-TNF therapies

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Therapy	Label Contra-indications	Conditions to Screen and Monitor For	Other considerations
Infliximab Adalimumab Certolizumab Golimumab	• None	• Infection • Latent TB/ Hepatitis B • Moderate-severe heart failure • Demyelinating disorder, optic neuritis • Cytopenia's • Lymphoma, malignancy • Lupus-like syndrome • Increase Liver function tests	

FDA Label

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Special screening and monitoring with vedolizumab

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Therapy	Label Contra-indications	Conditions to Screen and Monitor For	Other considerations
Vedolizumab	• Hyper-sensitive	• Infection • Progressive Multifocal Leukoencephalopathy (PML) (theoretical) • Liver Injury	JCV testing is not needed

FDA Label

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Special screening and monitoring with ustekinumab

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Therapy	Label Contra-indications	Conditions to Screen and Monitor For	Other considerations
Ustekinumab	• Hyper-sensitive	• Infection • Latent TB • Malignancy • Posterior Reversible Encephalopathic Syndrome • Interstitial Pneumonia	

FDA Label

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Special screening and monitoring with risankizumab

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Therapy	Label Contra-indications	Conditions to Screen and Monitor For	Other considerations
Risankizumab	• Hyper-sensitive	• Infection • Latent TB	

FDA Label

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Special screening and monitoring with tofacitinib, upadacitinib (Janus kinase inhibitors)

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Label Contra-indications	Conditions to Screen and Monitor For	Other considerations
• Hyper-sensitive	• Infection leading to hospitalization/death including TB • All-cause mortality including sudden cardiac death vs TNF blockers in RA patients • Malignancy (lymphoma/lung cancer) • MACE (cardiovascular death, myocardial infarction, stroke) • Thrombosis (PE, venous and arterial) vs TNF • Gastrointestinal perforations • Neutropenia, anemia, liver enzymes, lipids • Fetal harm (ustekinumab) • Hepatitis reactivation (including C)	• Lipid panel at 4-6 weeks and then annually • Vaccinate against zoster • Check serum creatinine phosphokinase if muscle ache/ weakness • Screen hepatitis C

FDA Label

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Special screening and monitoring with ozanimod

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Label Contraindications	Conditions to Screen and Monitor For	Other considerations
• Prior 6 months- unstable angina, myocardial infarction, heart failure, transient ischemic attack • Mobitz Type II second degree or third-degree heart block, sick sinus syndrome • Severe untreated sleep apnea • Concomitant use monoamine oxidase inhibitor	• Infection (reduction lymphocyte count by 45%) • Bradyarrhythmia and atrioventricular conduction delays • Liver injury • Possible fetal risk • Increased blood pressure* • Decline in pulmonary function • Macular edema • Disease rebound when stopping	See next slide

* Especially high tyramine foods-aged cheese, cured or processed meats, fermented alcohol, citrus/tropical fruits, fermented vegetables)

FDA Label

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Special screening and monitoring with ozanimod

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Therapy	Baseline	Follow-up
Ozanimod	• BP + heart rate • ECG to rule out QTc prolongation, heart block, sick sinus • Eye exam if history diabetes, macular edema, uveitis • Varicella antibody titer if no vaccination or confirmed history chicken pox • Pregnancy test	• Week 4 and annual blood pressure • Eye exam if vision changes • Pulmonary function tests if any shortness or breath or reduced exercise capacity

FDA Label

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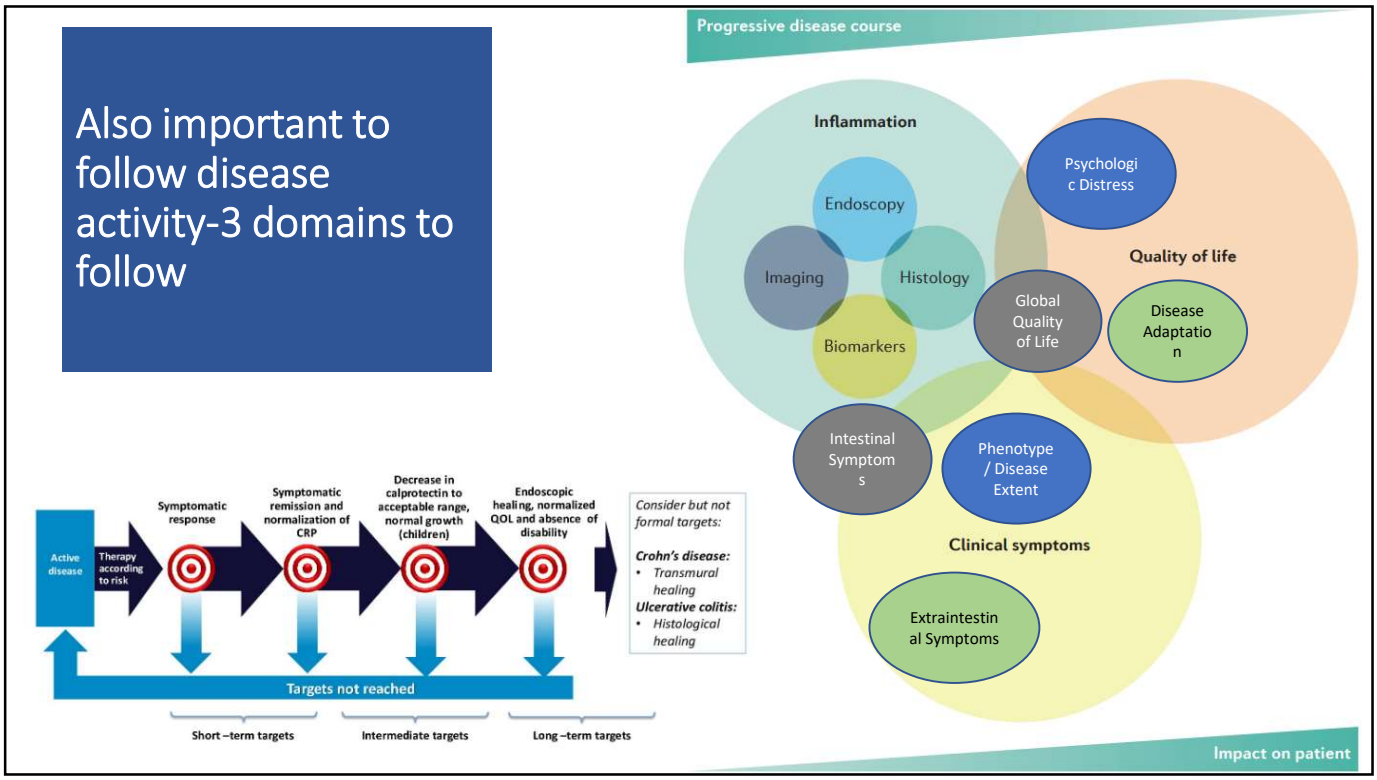
Also important to follow disease activity-3 domains to follow



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How to Measure and how Frequently to Measure Disease Activity in IBD?

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Table 1. Domains of Disease Activity

Domain	Measures	Clinically accessible Indices
Inflammation	Endoscopy	UCEIS, Mayo score, SES-CD, Rutgeerts post-operative score
	Imaging	MRI/MRE, CTE
	Biomarkers	CRP, fecal calprotectin
Quality of life	Psychological distress	PHQ-9, Hospital Anxiety and Depression Scale
	Disease adaptation	Brief Illness Perception Questionnaire
	Global quality of life	Short Inflammatory Bowel Disease Questionnaire
Clinical symptoms	Phenotype/Disease Extent	Montreal Classification
	Intestinal and extra-intestinal symptoms	HBI, SCCAI

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Monitoring Symptoms-Harvey Bradshaw Index for Crohn's Disease

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Descriptor	Description	Score
General well-being	Very well	0
	Slightly below par	1
	Poor	2
	Very poor	3
	Terrible	4
Abdominal pain	None	0
	Mild	1
	Moderate	2
	Severe	3
Liquid stools daily	1 per occurrence	_
Abdominal mass	None	0
	Dubious	1
	Definite	2
	Definite and tender	3

Complications	1 per item	_
	Arthralgia	
	Uveitis	
	Erythema Nodosum	
	Apthous ulcer	
	Pyoderma gangrenosum	
	Anal fissure	
	New fistula	
	Abscess	
	Total (out of 19)	

- >16-severe
- -8-16 moderate
- 5-7 mild
- Response
  - > 3 points
- Not best way to follow perianal disease

- *At baseline, during induction, right after induction, and then at least every 3-4 months if improving*
- *Every 6-12 months when stable/ in remission*

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Monitoring Symptoms- Simple C linical Colitis Activity Index for UC

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Descriptor	Description	Score
Bowel frequency (day)	0-3	0
	4-6	1
	7-9	2
	>9	3
Bowel frequency (night)	0	0
	1-3	1
	4-6	2
Urgency to defecate	none	0
	hurry	1
	immediately	2
	incontinent	3
Blood in stool	none	0
	trace	1
	occasionally frank	2
	usually frank (>50%)	3

General well-being	very well	0
	slightly below par	1
	poor	2
	very poor	3
	terrible	4
Extracolonic Features	Arthritis	
	yes	1
	no	0
	Uveitis	
	yes	1
	no	0
	Erythema nodosum	
	yes	1
	no	0
	Pyoderma gangrenosum	
	yes	1
	no	0
	Total (out of 19)	

- >5 active disease
- <=2 remission
- Can follow change

- *At baseline, during induction, right after induction, and then at least every 3-4 months if improving*
- *Every 6-12 months when stable/ in remission*

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Which biomarkers should be followed and how frequently should they be obtained

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Baseline	Follow-up
Inflammatory markers if not completed past 3 months- CRP, calprotectin	After induction and every 3-6 months until stable Can consider every 6-12 months if in remission

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Monitoring Endoscopic Inflammation- UC Endoscopic Activity Index and Mayo Score

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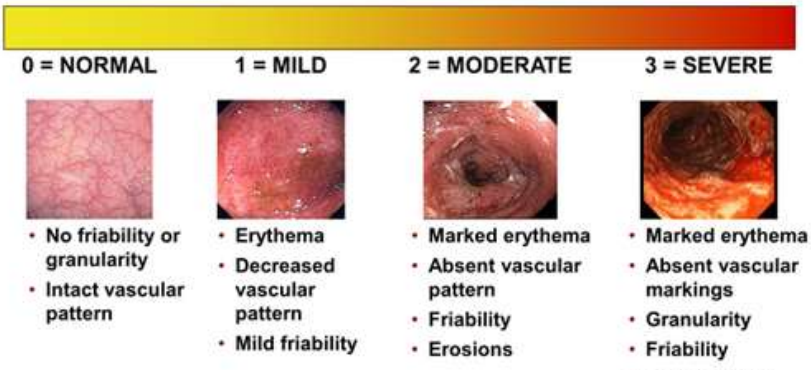
Most Severely Affected Area on Endoscopy	Score
Vascular pattern	
0 = Normal	
1 = Patchy obliteration	
2 = Obliterated	
Bleeding	
0 = None	
1 = Mucosal	
2 = Luminal, mild	
3 = Luminal, moderate or severe	
Erosions and Ulcers	
0 = None	
1 = Erosions	
2 = Superficial ulcer	
3 = Deep Ulcer	
Sum	



- *Consider colonoscopy or flexible sigmoidoscopy if no evaluation past 1-2 years*
- *Perform 6 months after starting therapy*

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Monitoring Endoscopic Inflammation- Simple Endoscopic Score for Crohn's

Size of Ulcers, cm	Ileum	R colon	TV colon	L colon	Rectum	Total
0 = none						
1 = apthous						
2 = large (0.5-2)						
3 = very large (>2)						
Ulcerated Surface, %						
0 = none						
1 = <10						
2 = 10 - 30						
3 = >30						
Affected Surface, %						
0 = unaffected						
1 = <50						
2 = 50 - 75						
3 = >75						
Presence of Narrowing						
0 = none						
1 = single, passable						
2 = multiple, passable						
3 = cannot be passed						
						SES-CD

- *Consider colonoscopy or cross-sectional imaging if no evaluation past 1-2 years*
- *Perform 9-12 months after starting therapy*

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Monitoring Post-Operative Inflammation- Rutgeerts Score

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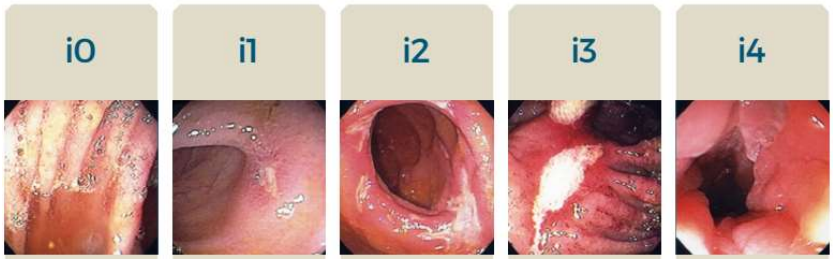
Rutgeerts Grade	Endoscopic Finding	Risk of Recurrence at 5 Years
i0	No lesions in distal ileum	6%
i1	No more than 5 apthous ulcers in distal ileum	6%
i2	More than 5 apthous ulcers with normal mucosa between lesions or skip areas of larger lesions up to 1 cm confied to the anastamosis	27%
i3	Diffuse apthous ileitis with diffusely inflamed intervening mucosa	63%
i4	Diffuse inflammation with large lesions, large ulcers and/or nodules and/or narrowing/stenosis	100%

- *Perform 6-9 months after surgery/ starting therapy*



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How to measure Quality of Life: Short IBD-Q

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1. How often has the feeling of fatigue or being tired and worn out been a problem for you during the past 2 weeks?
2. How often during the last 2 weeks have you delayed or canceled a social engagement because of your bowel problem?
3. As a result of your bowel problems, how much difficulty did you experience doing leisure or sports activities during the past 2 weeks?
4. How often during the past 2 weeks have you been troubled by pain in the abdomen?
5. How often during the past 2 weeks have you felt depressed or discouraged?
6. Overall, in the past 2 weeks, how much of a problem have you had with passing large amounts of gas?
7. Overall, in the past 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?
8. How often during the past 2 weeks have you felt relaxed and free of tension?
9. How much of the time during the past 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?
10. How often during the past 2 weeks have you felt angry as a result of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

- *4 domains: social, bowel, emotional, and systemic*
- *Each question scored on 7-point Likert scale (1-severe, 7 no problem)*
- *Range 10 (poor) to 70 (optimal QOL)*
- *<50 is poor QOL*
- *Responsive over time*

- *Check at baseline, every 3-4 months if improving*
- *Every 6-12 months when stable/ in remission*
- *More of a tool to also understand impact and discuss important topics brought up in questionnaire*

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Summary: How to screen and monitor p atients on a biologic/small molecule

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- Inform patients on risks and side effects of biologics/small molecules and why it is important to have regular follow-up when on a biologic/small molecule: Do not hide or omit this part of treatment
- Provide a road map of what to expect and what you will do with this information
- Consider having written “scripts” that can be used in the medical record and sent to patients so they can also be aware of what to expect

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Summary: How to screen and monitor patients on a biologic/small molecule

- ***Patients should expect***
  - Getting non-live virus vaccines for vaccine preventable infections if eligible
  - Screening for hepatitis and TB even if mechanistically unlikely
  - Blood work during induction and quarterly to assess for medication side effects
  - Some additional testing before starting ozanimod
  - Regular assessment of response and medication side effects
    - Symptoms: During induction and every 3-6 months
    - Biomarkers: During induction and every 3 months until normalized
    - Colonoscopy/ cross-sectional imaging: 3-6 months (UC), 6-9 months (Crohn's) after starting therapy
    - Quality of Life Assessment: Every 3-4 months while improving, every 6-12 months once stable

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