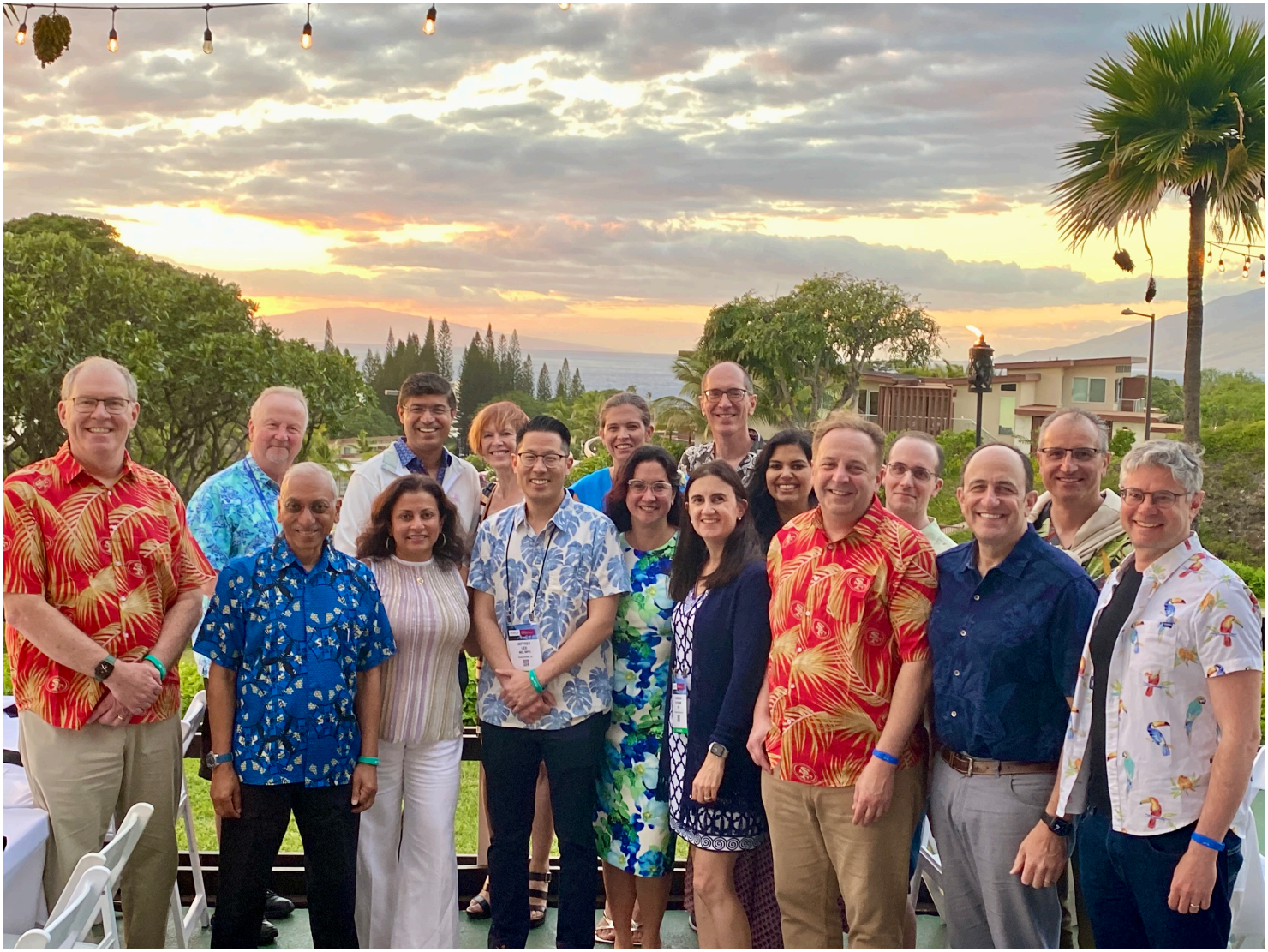

Winners of the
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Gastroenterology Updates • IBD • Liver Disease

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FEBRUARY 18–21, 2024
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Year in Review: Ulcerative Colitis

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Relevant Disclosures

DTR

Consultant and/or Grant Support

- Abbvie
- Boehringer Ingelheim, Ltd.
- Bristol-Myers Squibb
- Iterative Health
- Image Analysis Group
- Janssen Pharmaceuticals
- Lilly
- Pfizer
- Prometheus Biosciences
- Takeda
- Target RWE
- Trellus Health

FSV

None

Objectives

- Overview key UC papers and abstracts you should know from 2023
  - Important
  - Interesting
  - Innovative
- 5 domains
  - Impact of UC on Society and Patients
  - Causative Role of Diet and Environment in UC
  - Promising Diagnostics
  - Helpful Guidelines for Practice Management
  - Therapeutics
- Our goal: 1 key clinical take home (if possible)

Impact of UC on Society and Patients

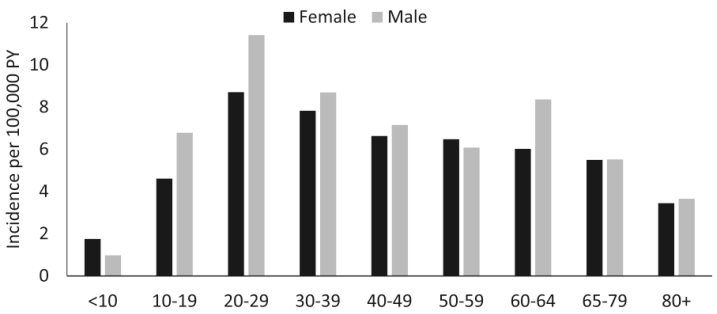
Updated incidence, prevalence, and racial-ethnic distribution of UC in the USA

- 4 Administrative Datasets
  - Medicare
  - Medicaid (FL, NY, PA, OH, CA)
  - Anthem
  - Optum

IBD
0.7% US pop

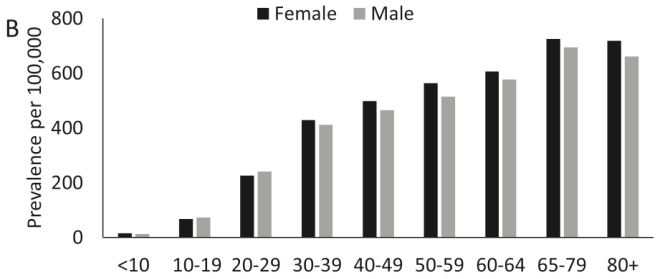
2.39 million IBD
1.253 million UC

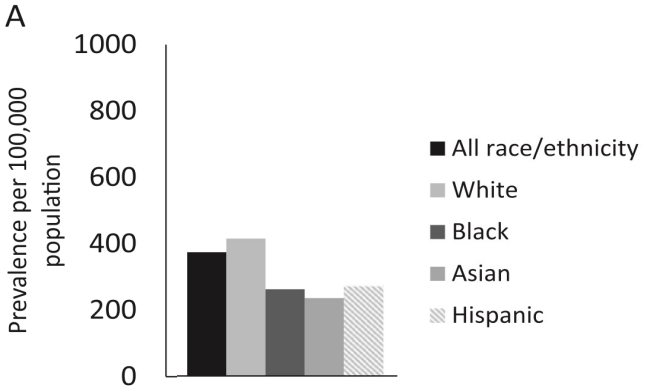
Incidence



- Peaks 20- 30's then steady
- Incidence 6.3 per 100,000
- Prevalence 378 per 100,000
  - Highest in Caucasians

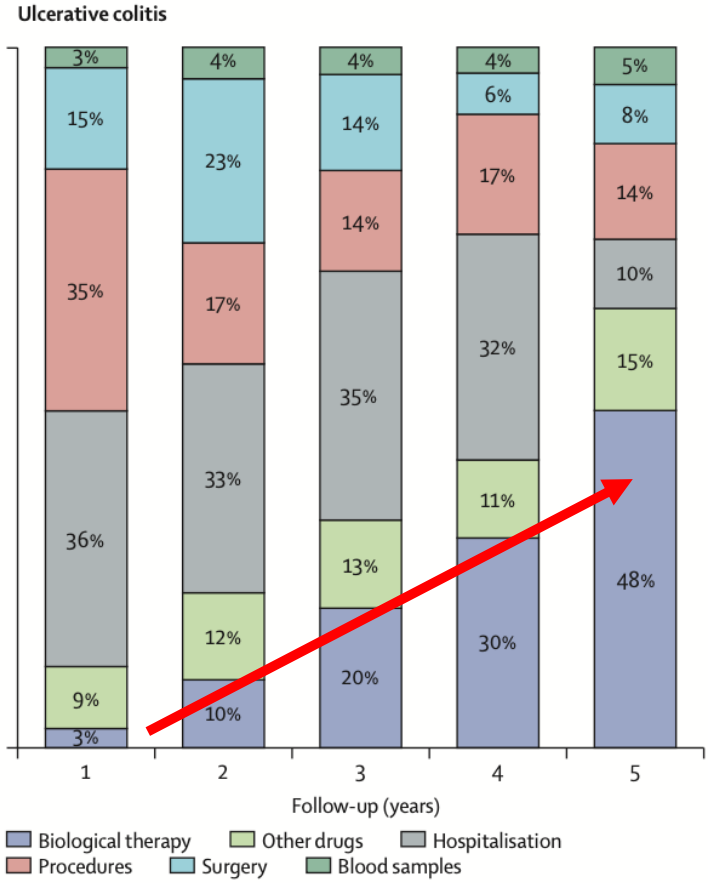
Prevalence





Lewis JD, et al. *J Gastroenterol*. 2023;10:1053

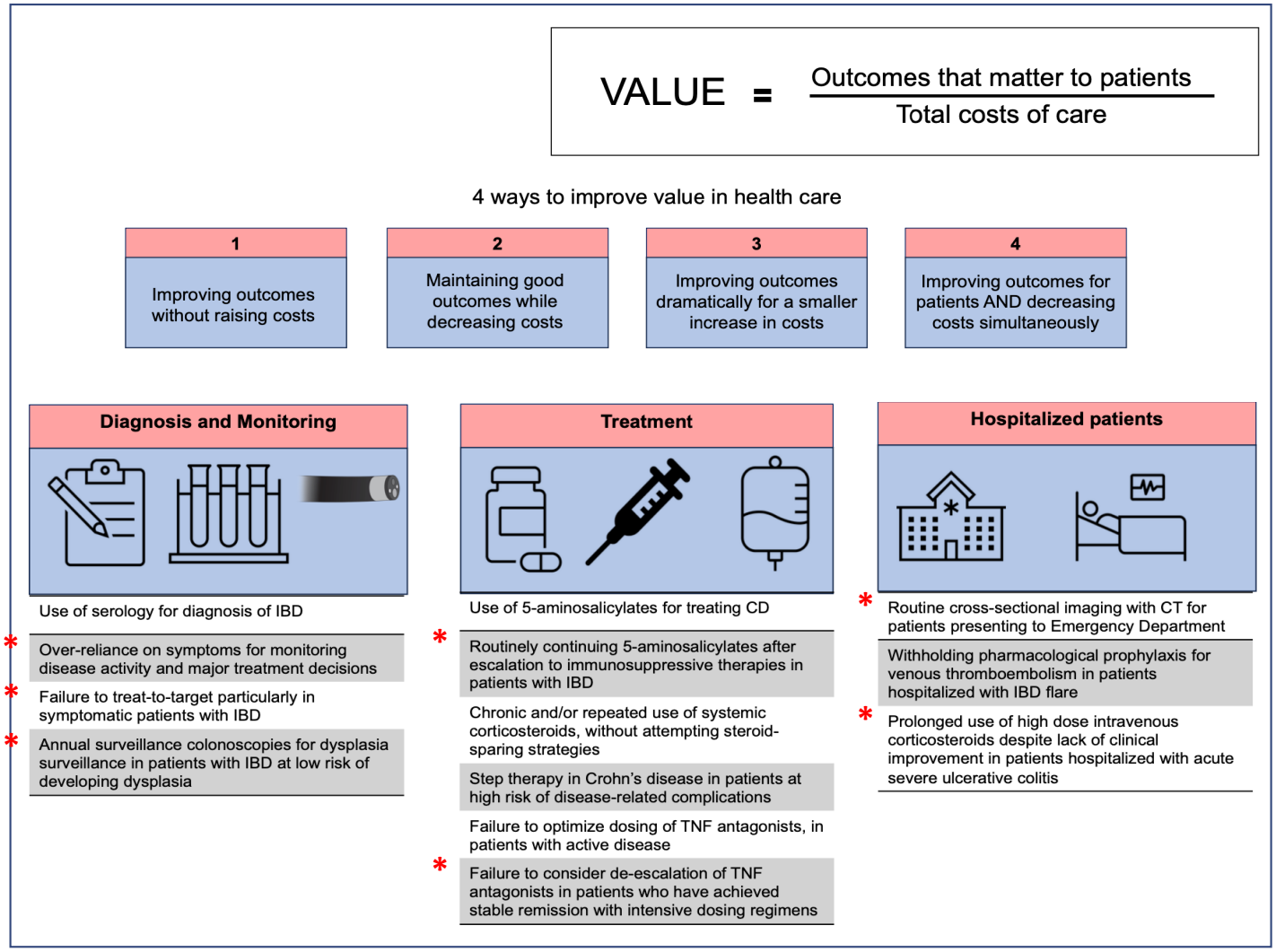
The cost of inflammatory bowel disease in high-income settings: a Lancet Gastroenterology & Hepatology Commission



- These data are important for assessing patterns of care and often used for reducing costs but not informing care
- Unanswered questions- Do we know
  - The correct cost proportions (modifiable)
  - What are actual and indirect costs (not just relative costs)
  - Proportion of patients
    - in control and disease effectively monitored
    - % developed disability and complications of disease
    - Quality of life
  - Value of care delivered

Burisch J, et al. *Lancet Gastroenterol Hepatol.* 2023;8(5):458-492.

Common low-value practices in IBD

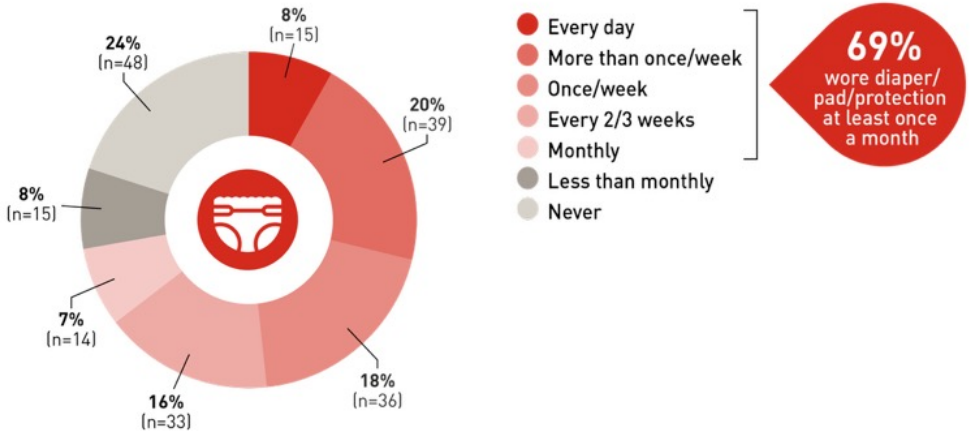


Singh S, Velayos F, Rubin DT Clin Gastro Hep Oct 2023

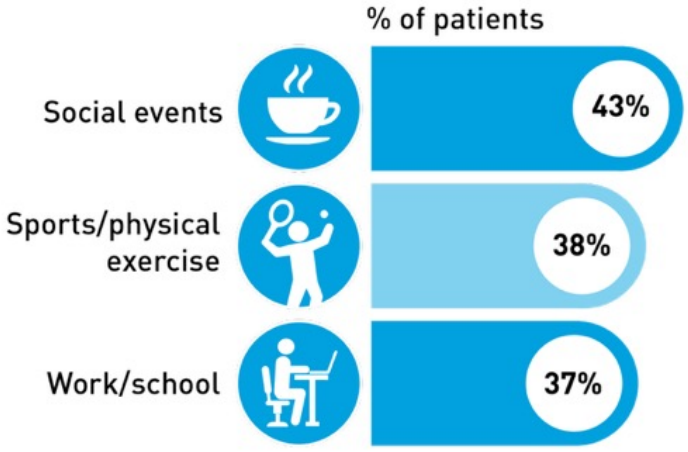
Bowel urgency- renewed interest in a very impactful symptom- CONFIDE Study

Cross-sectional survey study completed by 200 US and 556 European patients and 200 US and 503 European HCPs

Use of diapers, pads or other protection in the last three months due to fever/anticipation of bowel-urgency related accident



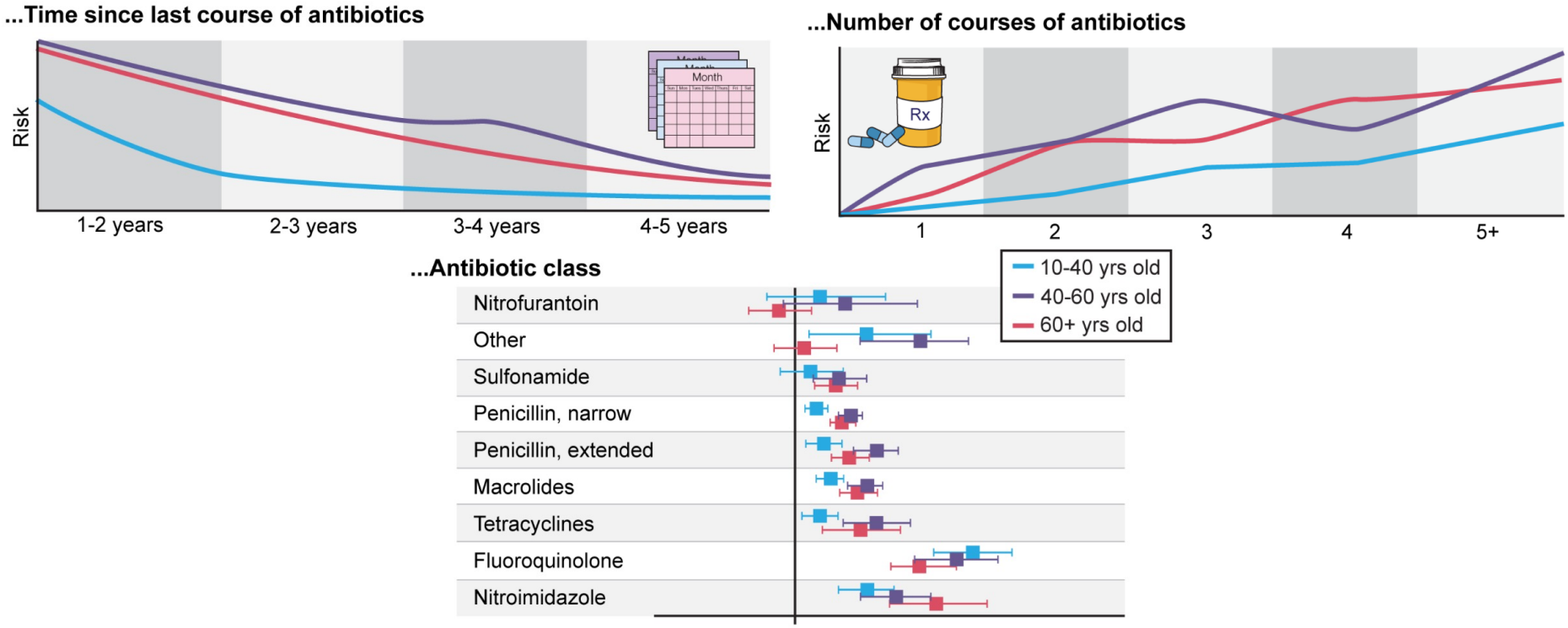
Patients who declined participation in activites in the past 3 months due to bowel urgency



Tavis S, Rubin DT et al I*nflammatory Bowel Diseases*, 2023
https://medical.lilly.com/us/diseases/disease-education-resources/gastroenterology/inflammatory-bowel-disease/education-resources/symptom-impact-and-experience

Causative Role of Diet and Environment in UC

Antibiotic use as a risk factor for inflammatory bowel disease across the ages: a population-based cohort study



Faye AS, et al. *Gut*. 2023;72(4):663-670.

Medication use and risk of UC (PURE study)

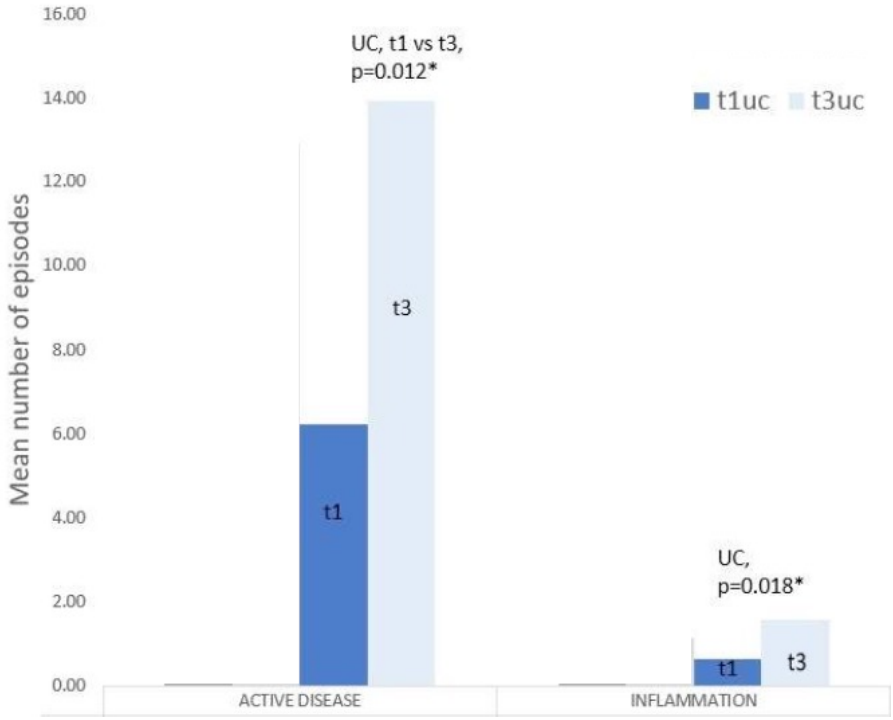
- Prospective cohort of 133,137 adults without IBD from 24 countries
- Follow-up every 3 years for development of IBD
- Mean follow-up of 11 years
- 428 incident cases UC

Medication	Adj OR (95:CI)
Long term NSAIDs	5.7 (2.1-15.6)
Hormonal Medications	4.2 (1.5-11.6)
Antibiotics	3.1 (1.8-5.4)

Narula N et al Clinical Gastroenterology and Hepatology 2023;21:2649–2659

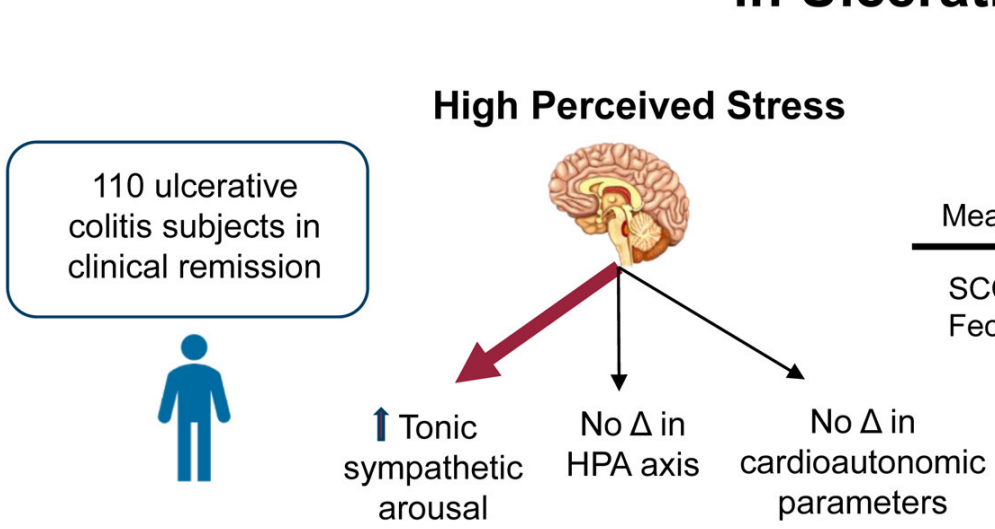
Ultra-processed foods increase risk of active UC (Manitoba Living with IBD Study)

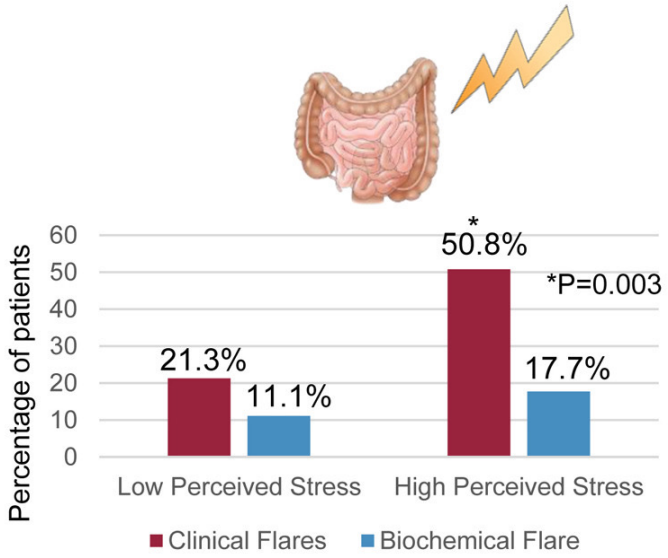
- Prospective study
- Patients with confirmed IBD with symptoms in prior 2 years
- Filled online survey every 2 weeks
  - Symptoms
  - Harvard Food Frequency Questionnaire →calculated % calories ultra processed food by tertile
- Serial measurement calprotectin
- Compared 3rd (high) vs 1st tertile UPF consumption



Vagianos K et al American Journal of Gastroenterology 2024 epub

High Stress Perception and Increased Risk of Clinical Flares in Ulcerative Colitis





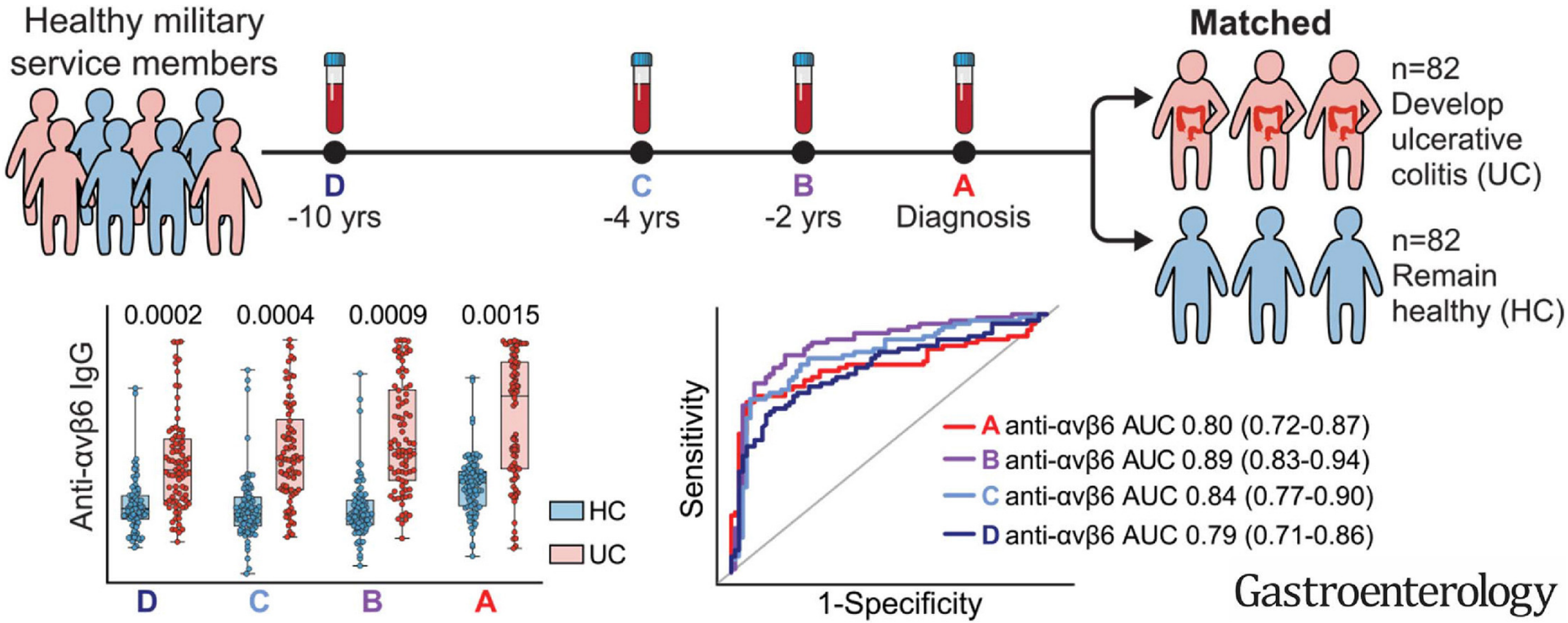
Outcomes:
Clinical Flares: SCCAI ≥5
Biochemical Flares: SCCAI ≥5 +fecal calprotectin ≥ 250µg/g

Clinical Gastroenterology and Hepatology

Sauk J, et al. *CGH.* 2023;21(3):P741-749.E3.

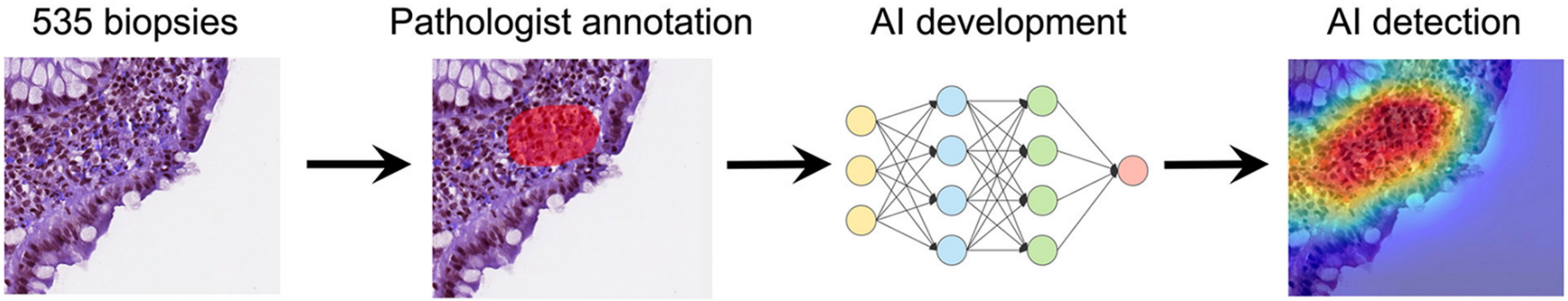
Promising Diagnostics

Anti-Integrin αvβ6 Autoantibodies Are a Novel Biomarker that Antedate Ulcerative Colitis



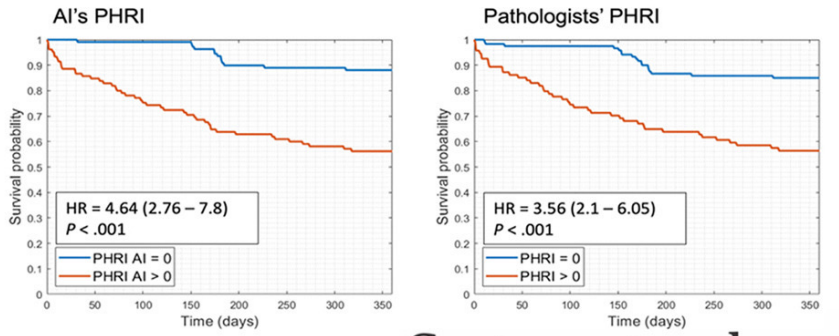
Livanos A, et al. *Gastroenterology.* 2023;164(4):619-629.

Artificial Intelligence Enabled Histological Prediction of Remission or Activity and Clinical Outcomes in Ulcerative Colitis



AI assessment of histological remission/activity			
	PHRI >0	**RHI > 3**	**NHI > 1**
	N=375	**N=374**	**N=374**
Sensitivity	0.89 (0.82-0.94)	0.94 (0.87-0.98)	0.89 (0.81-0.94)
Specificity	0.85 (0.80-0.89)	0.76 (0.71-0.81)	0.79 (0.73-0.83)

Risk of flare stratification



Gastroenterology

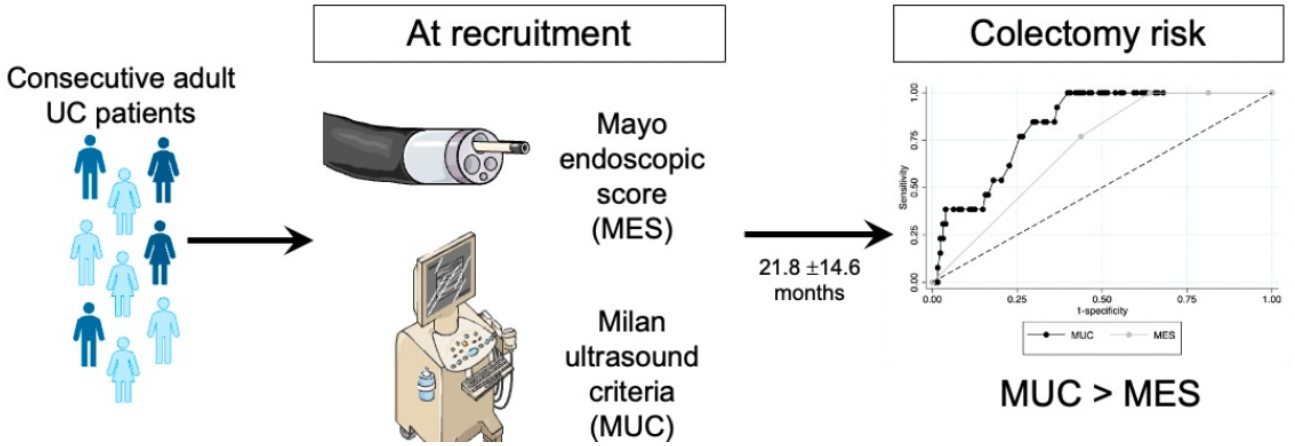
Iacucci M, et al. *Gastroenterology.* 2023;164(7):P118—1188.E2.

Transmural Severity Is A Superior Predictor of Colectomy Risk Compared to Endoscopic Severity

- **n=141 pts**
- **13 colectomies**
- **MUC independently associated with colectomy risk at median 3.5 months**

- **OR: 1.53 (1.03-2.27)**
- OR: 1.5 (95% CI, 1.0–2.3) in the subgroup of patients with clinically active disease (PMS≥2)

- **BWT and BWF were not independently better than MES**



MUC > MES

MUC = 1.4 × Bowel Wall Thickness (mm) + 2 × Bowel Wall Flow

Piazza N, et al. *J Crohn's Colitis*. 2023; jjad152.

Helpful Guidelines for Practice Management

AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis

Background:

- Biomarkers are used frequently for noninvasive monitoring and treatment decision making

- Evidence synthesis on the clinical performance of serum C-reactive protein (CRP), fecal calprotectin, and fecal lactoferrin in patients with established UC in symptomatic remission or with active symptoms

Use Biomarkers and Symptoms over Biomarkers Alone

Biomarkers Enough for Medical Decision Making*

1. Symptomatic Remission, calprotectin <150 and/or nl CRP
2. Mod-Severe Symptoms, calprotectin >150 and/or ⬆ CRP

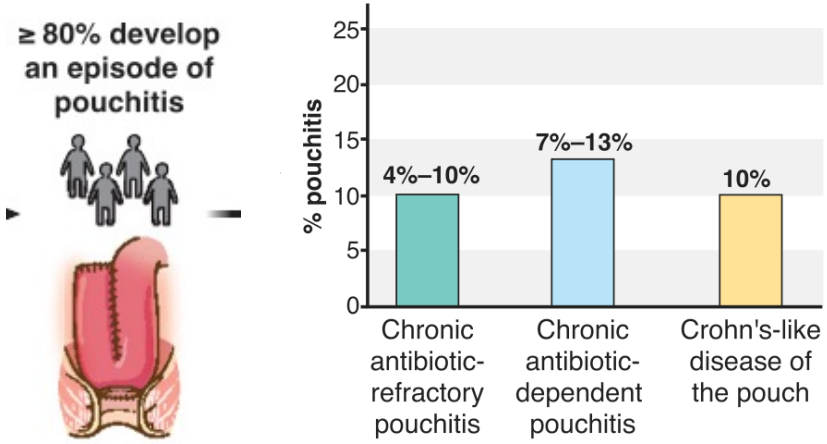
Proceed with Endoscopic Assessment of Activity for Medical Decision Making

1. Symptomatic Remission, ⬆ calprotectin and/or CRP
2. Mod-Severe Symptoms, normal calprotectin and/or CRP
3. Mild symptoms, regardless of biomarkers

Singh S, Velayos F, et al. *Gastroenterology.* 2023;164(3):344-372.

** Colonoscopy within 3 years*

AGA Clinical Practice Guideline for Pouchitis and Inflammatory Disorders of Pouch



Pouchitis: Cipro +/- metronidazole 2-4 weeks

Abx Dependent

- Lowest effective dose chronic antibiotics
- *Advanced therapies if concern about risk of chronic antibiotics*

Abx Refractory or Crohn's like disease

- Ileal release budesonide
- *Advanced therapies (even ones failed prior to colectomy)*

AGA Clinical Practice Update on Managing Ostomies

Table 1. Treatment Strategies for High Ostomy Output

Type of treatment	Examples
Bulking agents	Psyllium fiber Guar gum Marshmallows[9]
Antimotility agents	Loperamide Diphenoxylate and atropine Codeine Tincture of opium
Antisecretory agents	Proton pump inhibitors/ H2 agonists Somatostatin analogues (ie, octreotide)
Anti-inflammatory agents (if resulting from recurrent Crohn's disease)	Consultation with IBD specialist
Adaptation-promoting agents	GLP-2 analogues (teduglutide, elsiglutide, glepaglutide, apraglutide)
Surgical	Reversal of the ostomy with restoration of intestinal continuity when possible

GLP-2, glucagon-like peptide 2; IBD, inflammatory bowel disease.

Review plus Tips

- Derm issues
- Leakage
- Retraction
- Hernia
- Prolapse

Resources

Therapeutics

Current Medications for Ulcerative Colitis

5-ASA	Sulfasalazine Mesalamine Oral/Enema/suppository
Corticosteroids	Prednisone Budesonide MMX Foams/Enemas/suppository
Conventional Synthetic Small Molecules	Azathioprine/6-MP Cyclosporine/Tacrolimus
Biologics	Infliximab (IV/SC)/Adalimumab/Golimumab (incl biosimilars) Vedolizumab (IV/SC) Ustekinumab Mirikizumab Guselkumab
Targeted Synthetic Small Molecules	Tofacitinib Ozanimod Etrasimod Upadacitinib
Other	Curcumin/CurQD Lactobacillus

Current Medications for Ulcerative Colitis

5-ASA	Sulfasalazine Mesalamine Oral/Enema/suppository
Corticosteroids	Prednisone Budesonide MMX Foams/Enemas/suppository
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Targeted Synthetic Small Molecules	Tofacitinib Ozanimod Etrasimod Upadacitinib
Other	Curcumin/CurQD Lactobacillus

Established Therapies → Novel Indications

Vedolizumab Effective for Chronic Pouchitis: EARNEST RCT

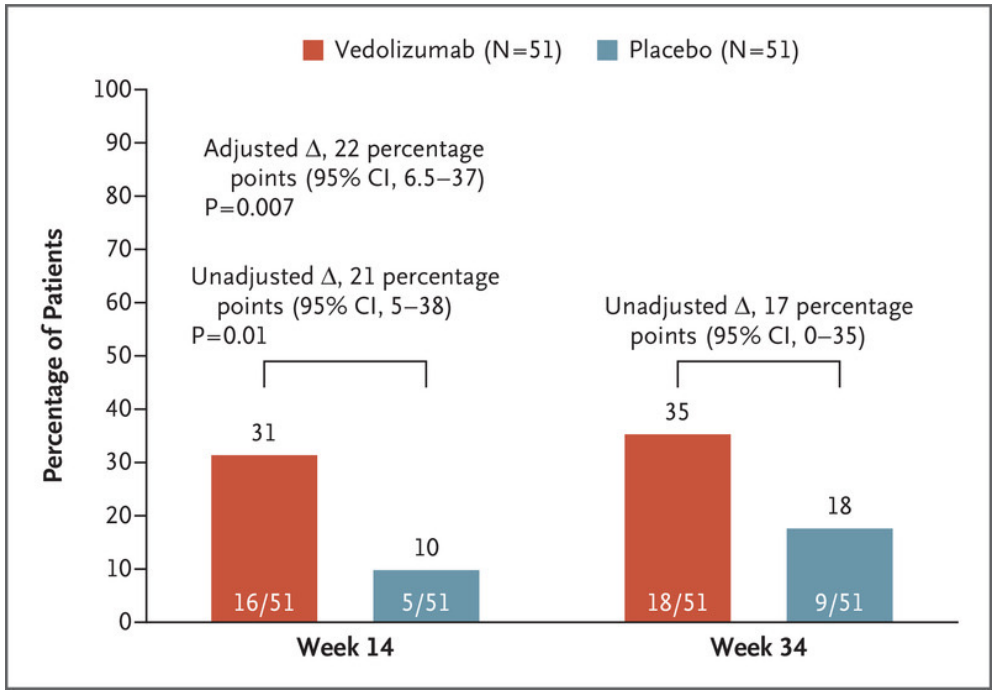
Methods:

- Phase 4 randomized trial
- Chronic pouchitis after IPAA
  - At least 3 episodes in past year
  - Prior anti-TNF OK
- 1: 1 Vedo vs PBO after 4 weeks Cipro
  - No Abx permitted weeks 4-14
  - 10% VDZ, 16% PBO steroids baseline
- Primary outcome: clinical and endoscopic remission (mPDAI <4 and reduction >=2 points) at week 14
- Secondary endpoint: week 34

Of note- higher antibiotic use in vedolizumab group after week 4

Approved in EU for pouchitis

AGA Pouchitis guideline does not specify vedolizumab first line



Travis S, et al. *NEJM.* 2023;338:1191-1200.

Tofacitinib is Effective for Acute Severe Ulcerative Colitis (TACOS RCT)

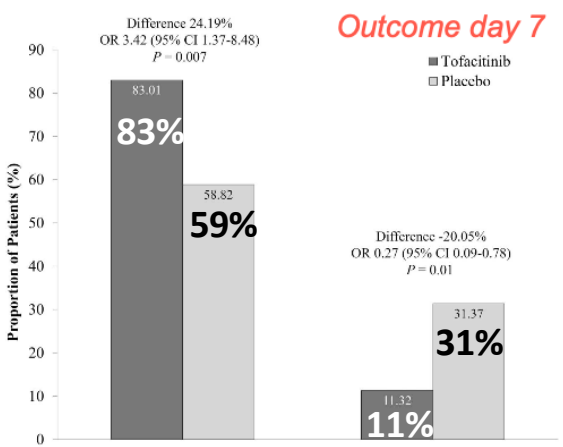
N= 53 Tofa vs n=51 PBO

Methods:

- RCT single center India
- ASUC defined Truelove Witts
- Excluded pts IV steroids or tofa in 4 weeks prior, VTE, significant health issues

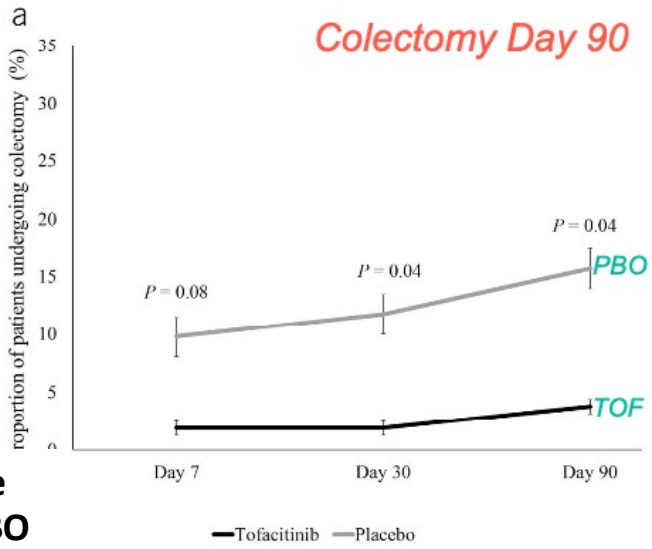
Protocol:

- 100 mg IV hydrocortisone q6h
- Tofa 10 mg tid x 7 days v PBO
- Outcome: response (decline Lichtiger by >3 and absolute score <10 for at least 2 consecutive days
- Responders: 40 mg prednisone (12-week taper); tofa 10 bid vs 5ASA/AZA (PBO group)



Response

Need for rescue
IFX n=5 T/11 PBO
Surg n=1 T/5 PBO

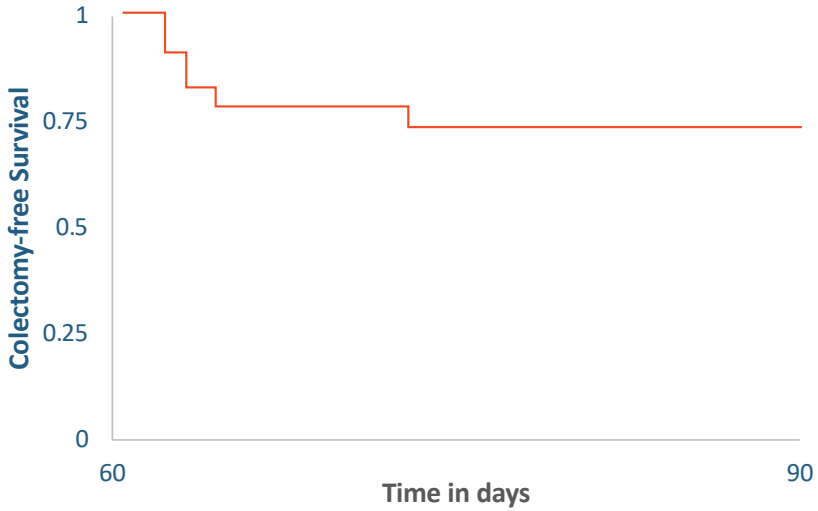


Conclusion: In patients with ASUC, combination of tofacitinib and corticosteroids improved treatment responsiveness and decreased the need for rescue therapy.

Singh A, et al. *AJG* 2024

Off-Label, High Intensity Upadacitinib Can Be Considered for the Treatment of Hospitalized Patients With Acute Severe UC

- Methods
  - Retrospective multicenter case series
  - 25 Patients who failed IV corticosteroids
  - Treated with UPA 30mg BID (n=18) or UPA 45qd (n=7)
    - Duration to end of admission or CRP normalization
- Results
  - 19/25 pancolitis, 6/25 left sided
  - 21/25 (76%) prior advanced therapy, 4 prior tofa
  - 90-day colectomy 24%
  - Steroid-free remission: 15/18 (83%)
  - 1 each (4%) venous thromboembolism (post-op after colectomy), COVID-19, and bacteremia



CONCLUSION

- First case series of off-label high intensity upadacitinib for acute severe UC
- Prospective trials are needed to evaluate safety and optimal dose/duration

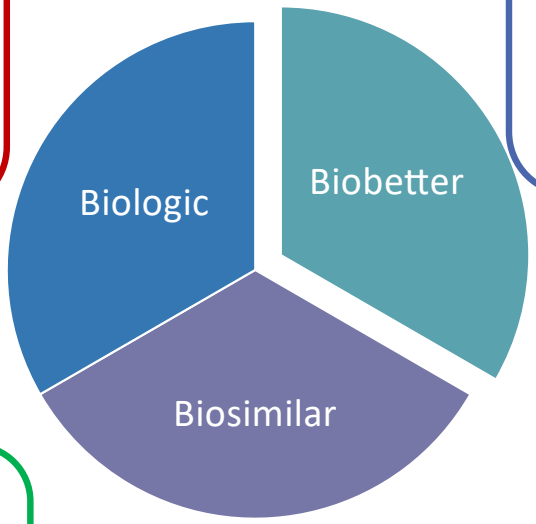
Berinstein J, *et al*. American J Gastro 2024 epub.

UPA, upadacitinib, tofa, tofacitinib

Modifications of Established Therapies

Subcutaneous IFX and Biobetters

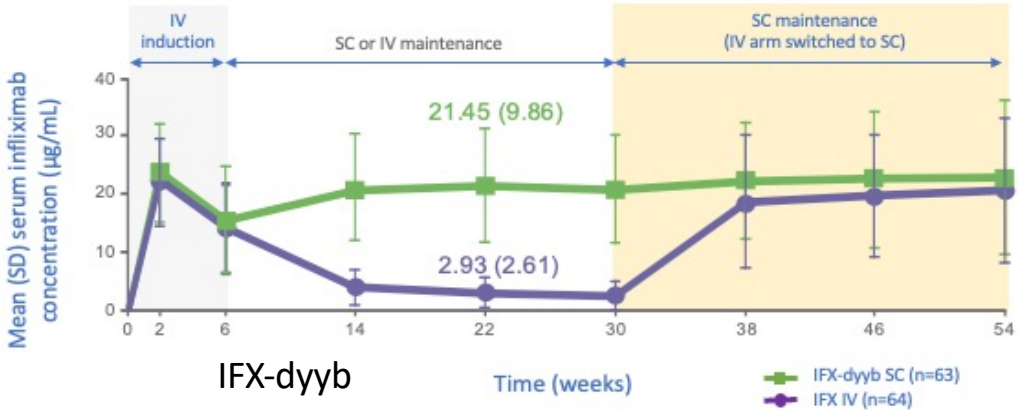
- ✓ Novel therapeutic
- ✓ Originates from biotech
- ✓ Patentable
- ✓ Reference Price



- ✓ Intentional modification of drug structure to improve drug safety, efficacy, immunogenicity, manufacturing attributes, or other performance measure
- ✓ Typically, cannot go through biosimilar approval process
- ✓ Not lower price

- ✓ Similar to originator
- ✓ Not patentable
- ✓ Lower price
- ✓ Special biosimilar approval process

Torres-Obreque KM et al Drug Disc Today 2022; 2. Alten R et al Clin Drug Invest 2022; 3.Schreiber S et al. *Gastroenterology.* 2021



IFX-dyyb

Comparable outcomes Wk 30/54 remission, safety, immunogenicity

Liberty UC RCT: IV IFX-dyyb Induction Followed by Subcutaneous IFX-dyyb Maintenance is Effective in UC

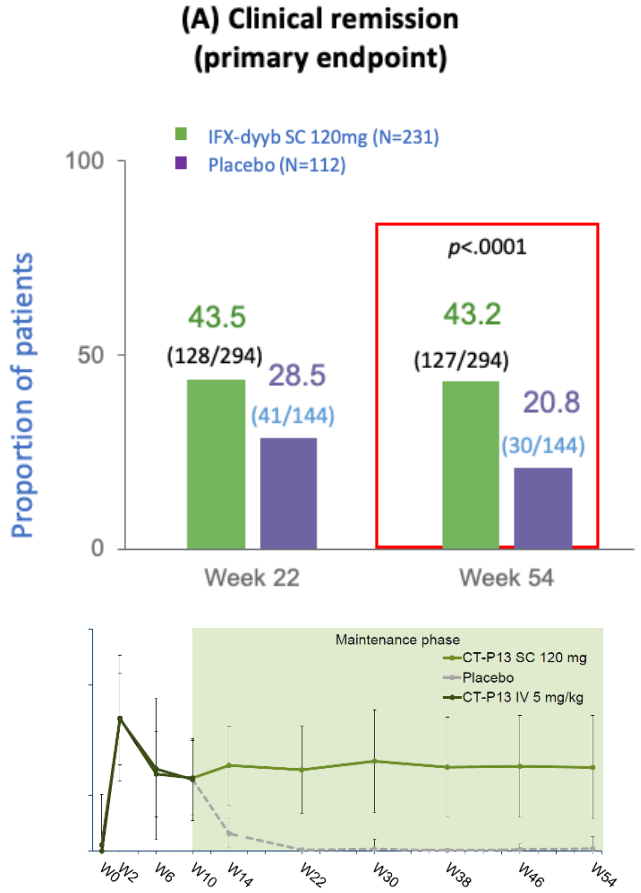
- *FDA Approved October 2023*

Methods:

- 498 pts moderate-severe UC received IV IFX-dyyb at W0, W2, and W6
- W10 2:1 randomization to sc IFX-dyyb 120 mg eow vs PBO if clinical response
- Increase to 240 mg permitted after W22

Results:

- Primary endpoint clinical remission
- Safety profiles comparable between sc IFX and PBO



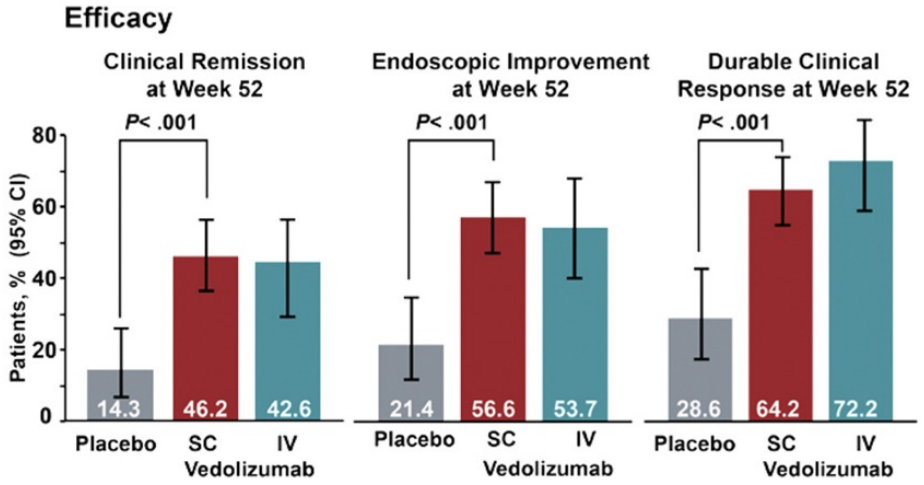
Sands BE et al., J Crohns Colitis. 2023;17(Supplement 1):i623–i624. [ECCO 2023, Presentation number P492]; Sands BE et al., [DDW 2023, Presentation number Tu1701].

Subcutaneous Vedolizumab is Effective in UC (VISIBLE 1 trial)

- *FDA Approved September 2023*

Methods

- Moderate-severe UC open label IV VDZ W0, W2, W6
- W6 responders randomized sc VDZ 108 mg w2 weeks vs PBO
- Primary endpoint clinical remission W52



- Approved as maintenance after IV(2 doses) induction in UC only (Crohn's under review)
- Pre-filled pen (108 mg)
- Dosing every 2 weeks at week 6 after first 2 IV doses
- New drug application

Sandborn WJ et al Gastroenterology 2020

Janus kinase Inhibitors

Upadacitinib is Effective in Tofacitinib-Experienced UC Patients

Study 1

- Retrospective multi-center cohort in 11 U.S. centers; n=100 (98 UC, 2 IBD-U); 32% exposed to tofacitinib
- **Outcomes:** Clinical response, Wk8 & 16 clinical remission (symptom resolution), 6mo endoscopic remission (Endoscopic Mayo≤1)

Study 1				
	Bio-naïve n/N (%)	**Exposed to 1-2 therapies n/N (%)**	**Exposed to 3-4 therapies n/N (%)**	**P value**
Clinical Remission (Week 16)	23/27 (85.2)	10/14 (71.4)	5/6 (83.3)	0.47
Endoscopic Healing (6 months)	23/29 (79.3)	5/9 (55.6)	2/8 (25.0)	0.02

Study 2

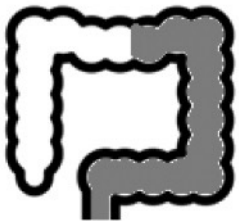
- Prospective single-center cohort of tofacitinib-experienced patients; n=26
- **Outcomes:** SCCAI, HBI, calprotectin

Study 2			
	Week 2 N=10	**Week 4 N=8**	**Week 8 N=8**
Clinical response, n (%)	6 (60)	7 (87.5)	**8 (100)**
Clinical remission, n (%)	4 (40)	7 (87.5)	**7 (87.5)**
SF remission, n (%)	1 (25)	6 (85.7)	**7 (100)**
Δ calprotectin from baseline, ug/g (SD)	-	-649.2 (772.7)	**-180 (721.8)**
Calprotectin <150ug/g, n (%)	-	2 (66.7)	**4 (80)**

Deepak P, *et al*. Presented at DDW. May 2023. Tu1806.
Friedberg S, *et al. Clin Gastroenterol Hepatol.* 2023 Jul;21(7):1913-1923.

REMIT-UC: Real World Effectiveness and Safety of Tofacitinib in Ulcerative Colitis

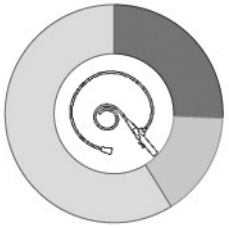
8-center Canadian IBD Research Consortium cohort study

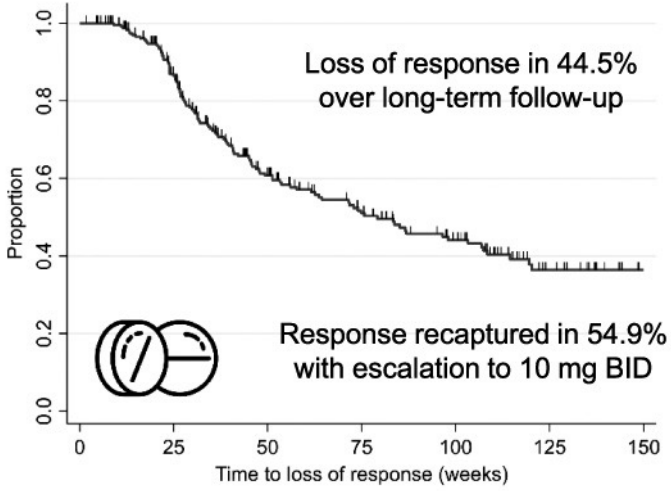


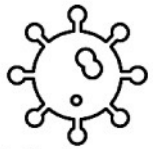
334 adult UC patients
375 patient-years of follow-up

12 month
Clinical remission 35.2%
Clinical response 45.1%

Endoscopic remission 25.7%
Endoscopic response 41.2%







Serious infections
2.1/100 patient-years

Zoster
0.5/100-PY

VTE
1.1/100-PY

Cancer
0.8/100-PY

Ma C, et al. *Am J Gastroenterol.* 2023;118(5):p861-871.

Anti p-19 (IL-23) biologics

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

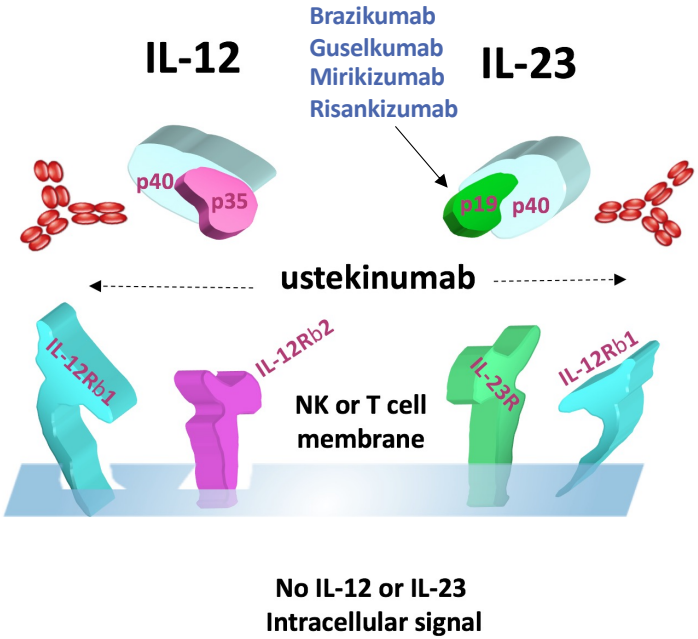


Figure adapted from de Gately MK, et al. 1998[1], Wilson NJ, et al. 2007[2], Nickoloff BJ et al, 2004[3], Nestle FO et al. J 2004[4]

	p40	p19			
Approved	**Ustekinumab**	**Risankizumab**	**Mirikizumab**	**Guselkumab**	**Brazikumab**
Moderate to Severe Plaque Psoriasis	2009[5]	2019[5]	--	2017[5]	--
Active Psoriatic Arthritis	2013[5]	2019[5]	--	2020[5]	--
Moderate to Severely Active Crohn's Disease	2016[6]	2023[7]	In development	In development	In development
Moderate to Severely Active Ulcerative Colitis	2019[6]	In development	2023[8]	In development	In development

1. Gately MK, et al. *Annu Rev Immunol*. 1998;16:495-521.
2. Wilson NJ, et al. *Nat Immunol*. 2007;8(9):950-7.
3. Nickoloff BJ, Nestle FO. *J Clin Invest.* 2004;113(12):1664-75.
4. Nestle FO et al. *J Invest Dermatol*. 2004; 123:xiv-xxv
5. Yang K, et al. AM J Clin Dermatol. 2021;22(2):173-192.
6. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761044s003lbl.pdf. Accessed on May 1, 2023.
7. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761262s000lbl.pdf. Accessed on May 1, 2023.
8. https://investor.lilly.com/news-releases/news-release-details/fda-approves-lillys-omvohtm-mirikizumab-mrkz-first-class. Accessed on Jan 9, 2024.

Mirikizumab is Effective as Induction and Maintenance Therapy for UC

- *FDA Approved October 2023*

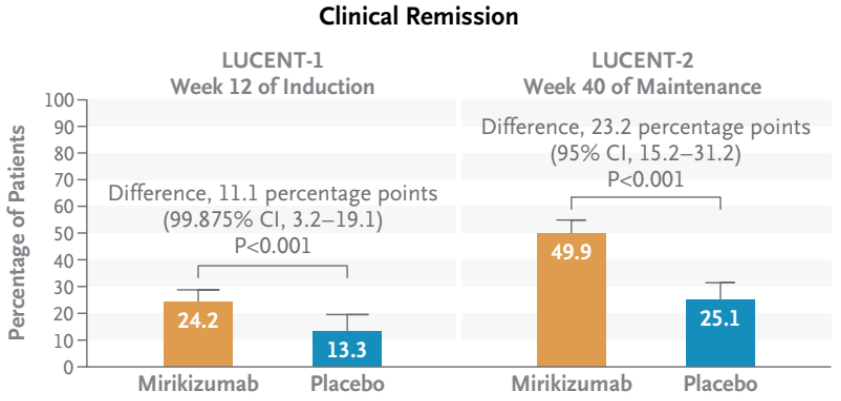
Methods:

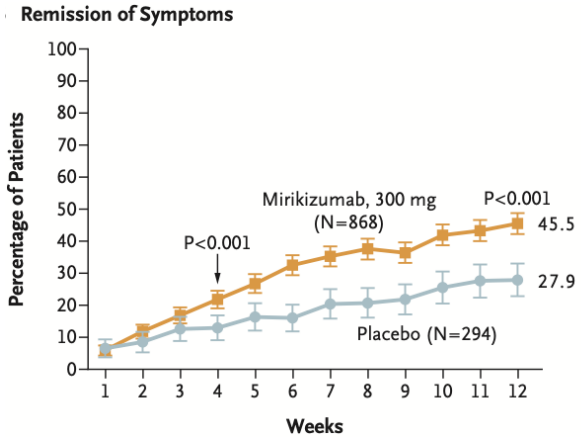
- 1281 Pts moderate-severe UC randomized 3:1 to mirankizumab (300 mg) IV every 4 weeks for 12 weeks or PBO
- Responders randomized 2:1 mirankizumab (200 mg) or PBO sc every 4 weeks for 40 weeks

Results:

- Difference in remission seen beginning W4
- Nasopharyngitis and arthralgias more common with mirankizumab
- OI (zoster) or cancer occurred in small number MKZ treated patients

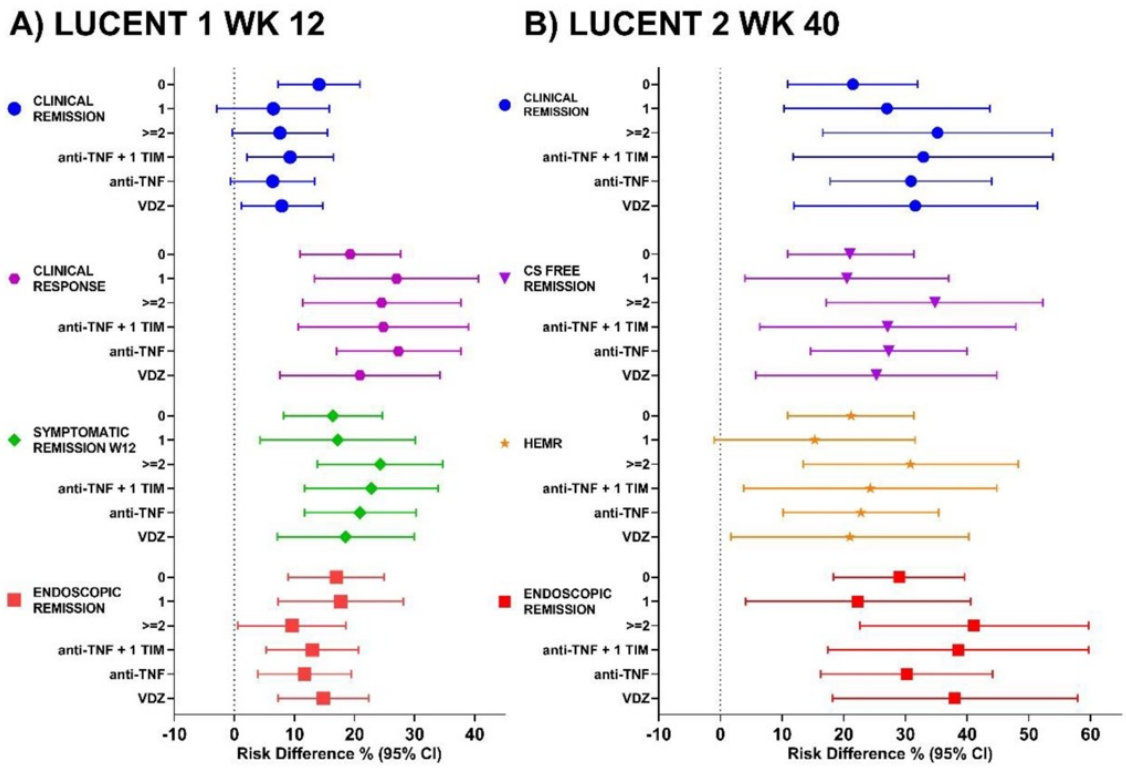
Conclusion: Mirankizumab was more effective than PBO for inducing and maintaining remission in UC





D'Haens, G et al. N Engl J Med. 2023 Jun 29;388(26):2444-2455.

Mirikizumab Is Effective for Induction and Maintenance in UC Regardless of Exposure to Prior Therapy



Navabi S, *et al.* Presented at DDW. May 2023. Tu1712.

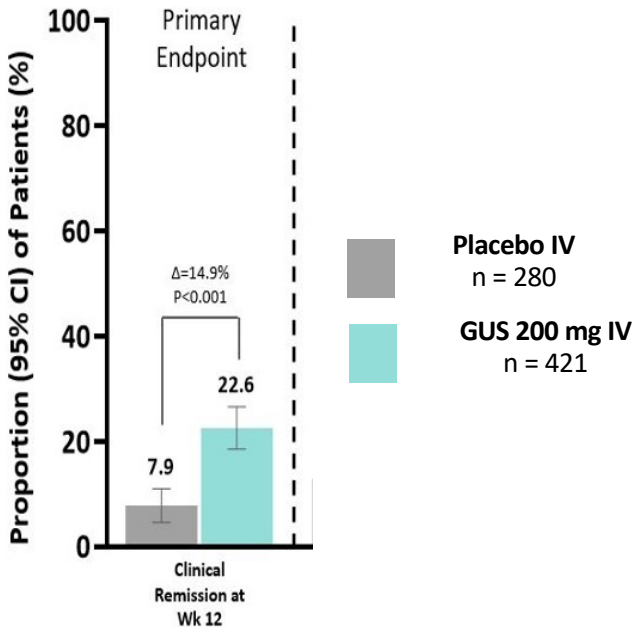
MIRI, mirikizumab; VDZ, vedolizumab; tofa, tofacitinib; TIM, targeted immune modulator

Guselkumab Induction Is Effective in Moderately-to-Severely Active Ulcerative Colitis: QUASAR Phase 3 DB-RCT

- *FDA Approved plaque psoriasis (2017) & psoriatic arthritis (2020)*

Methods

- Pts moderate-severe UC randomized 3:2 to IV GUS 200mg or placebo at W0, 4, 8
- Primary endpoint was clinical remission at W12



Results

- N=701 (49% failed ≥1 advanced therapy, 43% on steroids, 68% Mayo endoscopy subscore 3)
- Symptomatic improvement by W2, symptomatic remission by W4
- Adverse events in the GUS group were similar to placebo
- 1.5% of ADA at W12, none with neutralizing ADA

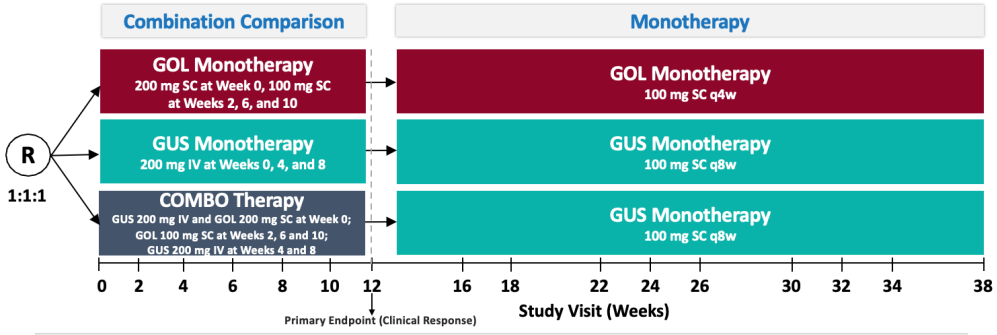
Conclusion

- Guselkumab induction appeared safe and effective in the treatment of moderate-to-severely active UC

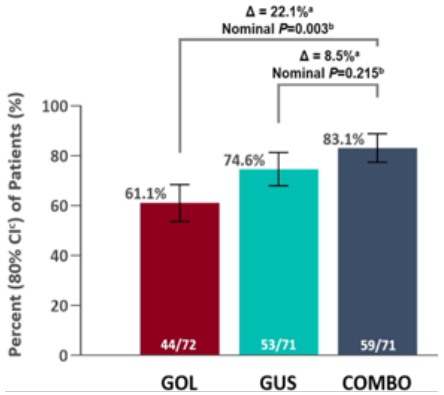
Allegretti JR, *et al.* Presented at DDW. May 2023. 913b.

IV, intravenous; GUS, guselkumab; UC, ulcerative colitis; ADA, anti-drug antibodies

Combination Therapy With Guselkumab and Golimumab in Ulcerative Colitis (VEGA)

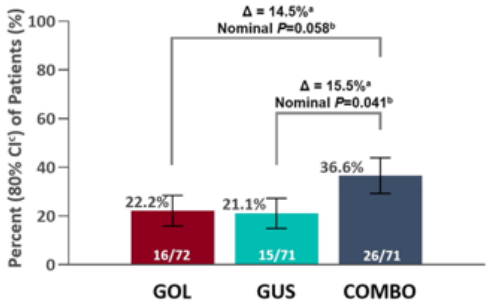


Clinical response* at Week 12 (primary endpoint)

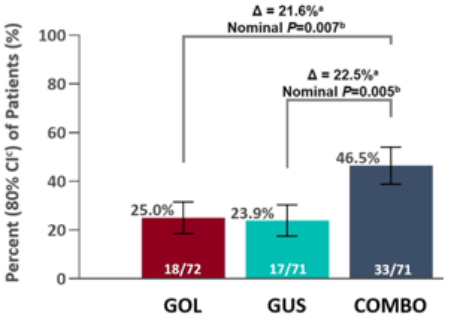


Clinical remission* at Week 12

Mayo score ≤2 with no individual subscore >1 (major secondary endpoint)



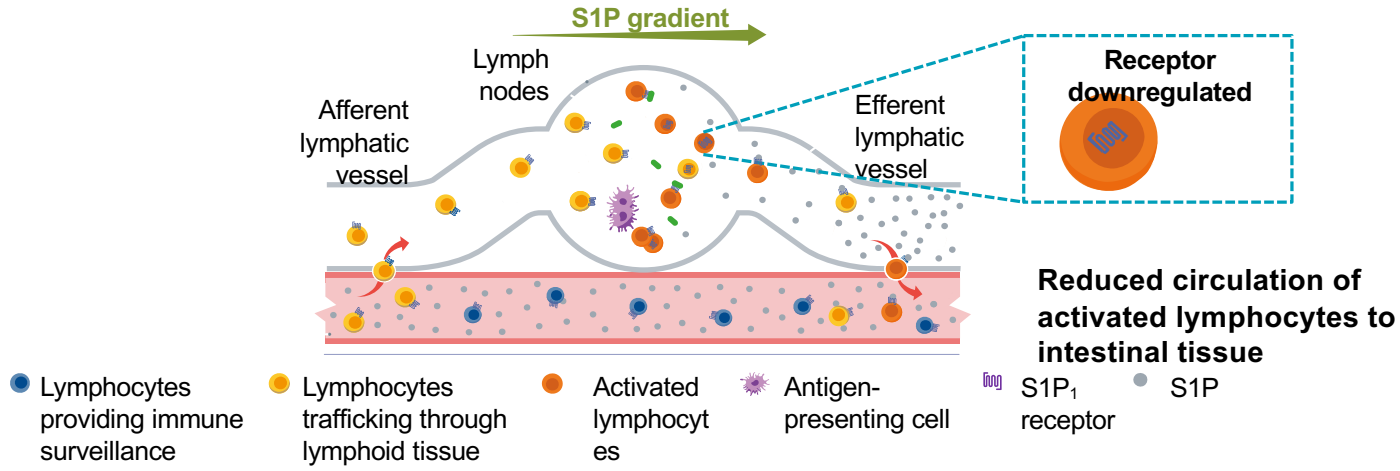
Modified Mayo score

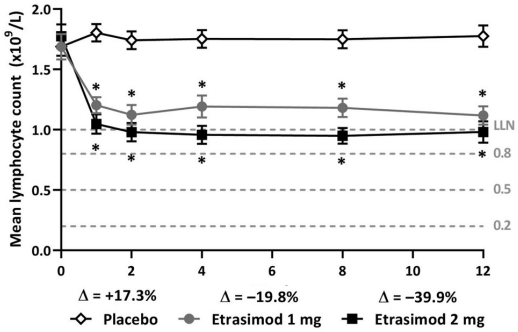


Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2023;8(4):307-320.

S1P Receptor Modulators

S1P Receptor Modulator Mechanism of Action





Danese S, et al. *J Crohns Colitis.* 2018;12(suppl_2):S678-S686
Sandborn WJ, et al. *Gastroenterology.* 2020;158(3):550-561.

S1P Differentiation

	Expression[1]	Biologic Outcomes[1]	Clinical Relevance[1]
S1P1	Broad, including B, T, and dendritic cells, endothelium, cardiac tissue, and neurons	Lymphocyte migration, dendritic cell migration, vascular barrier function, bradycardia, nociception, proliferation	Immune modulation, bradycardia, tumor maintenance
S1P2	Broad, including vascular smooth muscle, endothelium, cardiac tissue, lung fibroblasts, and tumor cells	Vasoconstriction, inflammation, fibrosis, inhibition of B-cell survival, proliferation	Renal injury, fibroblast contraction, tumor maintenance
S1P3	Broad, including vascular smooth muscle, endothelium, cardiac tissue, and lung fibroblasts	Vasoconstriction, fibrosis, proliferation	Hypertension, tumor maintenance
S1P4	Restricted; T cells, dendritic cells, breast cancer cells	Inhibition of effector cytokines, secretion of IL-10	Immune modulation
S1P5	Restricted; natural killer cells, endothelial cells, oligodendrocytes	Natural killer cell migration, blood-brain barrier integrity, oligodendrocyte function	Immune modulation, myelination

Medication	Target	Indication
Fingolimod	Nonselective **S1P1-5** receptor modulator[2,3]	MS (FDA 2010)
Ozanimod	Selective **S1P1 and S1P5** receptor modulator[4,5]	UC (FDA 2021)
Etrasimod	Selective **S1P1, S1P4, and S1P5** receptor modulator[2]	UC (FDA 2022) CD (Phase 3, NCT04173273)
Amiselimod	Selective **S1P1** receptor modulator	CD (Phase 2, NCT02389790)

1. Peyrin-Biroulet L, et al. *Autoimmun Rev*. 2017;16(5):495-503.
2. Sandborn WJ, et al. *Gastroenterology*. 2020;158(3):550-561.
3. Scott FL, et al. *Br J Pharmacol*. 2016;173(11):1778-1792.
4. Sabino J, et al. *Therap Adv Gastroenterol*. 2019;(12):1-14.
5. Tran JQ, et al. *J Clin Pharmacol*. 2017;57(8):988-996.

Etrasimod is Effective for Induction and Maintenance in UC- ELEVATE UC 12 and ELEVATE UC52

- *FDA Approved October 2023*

Methods

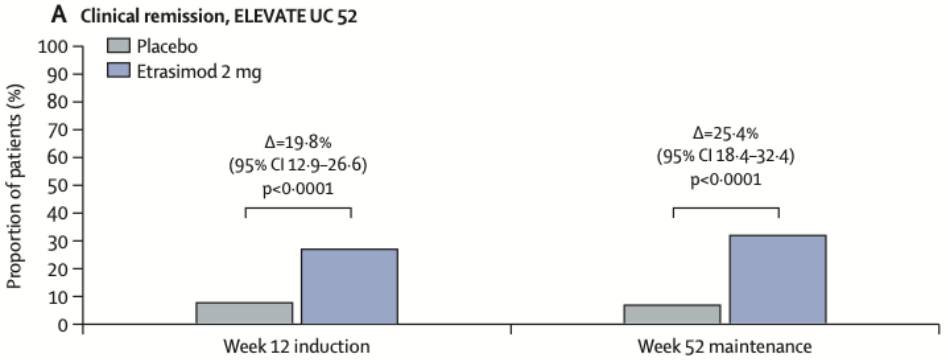
- Pts moderate-severe UC randomized 2:1 to po etrasimod (2 mg) or PBO
- Primary endpoint was clinical remission at W12 and W52

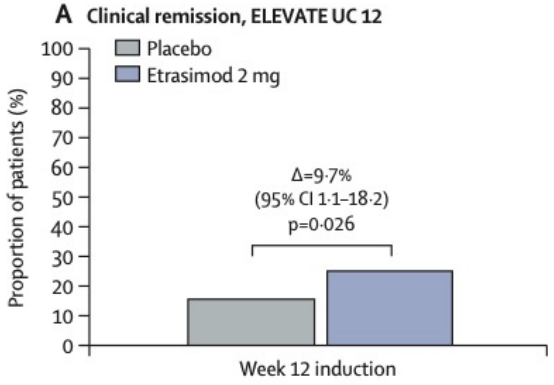
Results

- N=433 (E52), N=354 (E12)
- Adverse events
  - 71% etrasimod and 56% PBO (E52)
  - 47% etrasimod and 47% PBO (E12)
- No deaths or malignancy

Conclusion

- Etrasimod appeared safe and effective for induction and maintenance of moderate-to-severely active UC





Sandborn WJ et al Lancet Apr 2023.

IV, intravenous; GUS, guselkumab; UC, ulcerative colitis; ADA, anti-drug antibodies

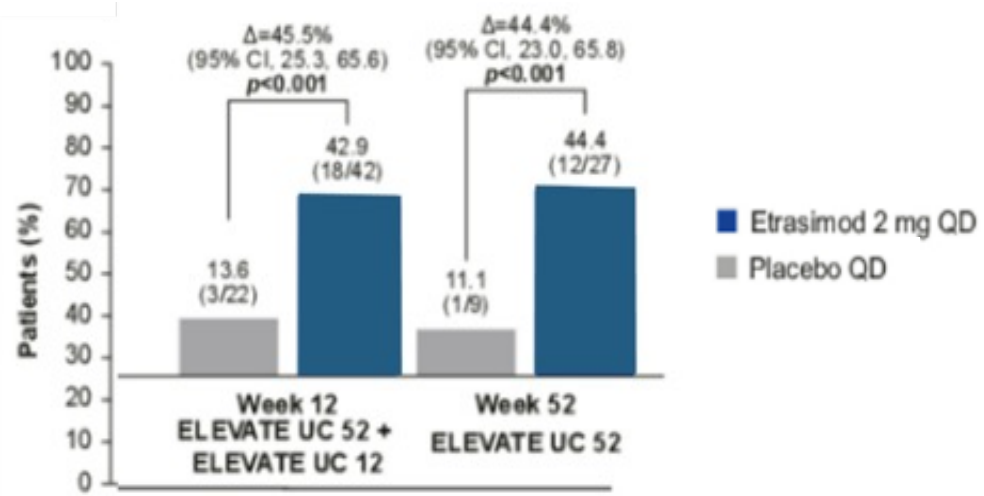
Etrasimod (S1P) is Effective in Isolated Proctitis: Post-Hoc of Phase 3 Trial

Methods:

- Subgroup analysis of ELEVATE UC 12/52 patients with isolated proctitis (<10cm of active rectal involvement)

Results:

- n=64 (42 Etrasimod and 22 PBO)
- Clinical remission, endoscopic improvement, and symptomatic/EIHR at Wk12 and clinical remission at Wk52



Dubinsky M, *et al*. Presented at DDW. May 2023. Tu1708.

Distinguishing Ozanimod and Etrasimod

Differentiating Parameter	Ozanimod[1-3]	Etrasimod[4-7]
Receptor selectivity	**S1P1, S1P5**	**S1P1, S1P4, S1P5**
Lymphocyte suppression in healthy volunteers	1 mg: ~65%	2 mg: 69%
Lymphocyte suppression in disease (MS, UC, CD)	1 mg: 50%	2 mg: 40%
CYP450 interactions	Yes	No
Liver enzyme elevations	Yes	No
Active metabolites	Yes	No
Half-life	21 hours; metabolite 11 days	~33 hours
Fast lymphocyte recovery time	No	Yes
First-dose HR reduction	Yes	Yes (modest)
Dose titration required	Yes	No

1. Tran JQ, et al. *J Clin Pharmacol*. 2017;57(8):988-996. 2. US National Library of Medicine. Ozanimod hydrochloride package insert. Updated September 1, 2020. Accessed April 9, 2021. https://dailymed.nlm.nih.gov/dailymed/. 3. Sandborn WJ, et al. *N Engl J Med.* 2016;374(18):1754-1762. 4. Schreiber S, et al. Poster presented at: 2016 Advances in Inflammatory Bowel Diseases, Crohn's and Colitis Foundation's Clinical and Research Conference; December 8-10, 2016; Lake Buena Vista, Florida. Poster P-180. 5. Peyrin-Biroulet L, et al. Poster presented at: 12th Congress of European Crohn's and Colitis Organisation; February 15-18, 2017; Barcelona, Spain. Poster P369. 6. Peyrin-Biroulet L, et al. Poster presented at: 13th Congress of European Crohn's and Colitis Organisation; February 14-17, 2018; Vienna, Austria. Poster P573. 7. Sandborn WJ, et al. *Gastroenterology*. 2020;158(3):550-561.

Potpourri

Anti-TNF-Like Ligand 1a (TL1A) Is Effective Induction Therapy for Moderate-Severe UC: ARTEMIS-UC Phase 2 Trial for PRA023 (now MK-7240)

- Background
  - TNF-like ligand 1A (TL1A) is a member of the TNF superfamily linked to multiple autoinflammatory & fibrotic diseases
  - PRA023 is an investigational anti-TL1A monoclonal antibody
- Methods

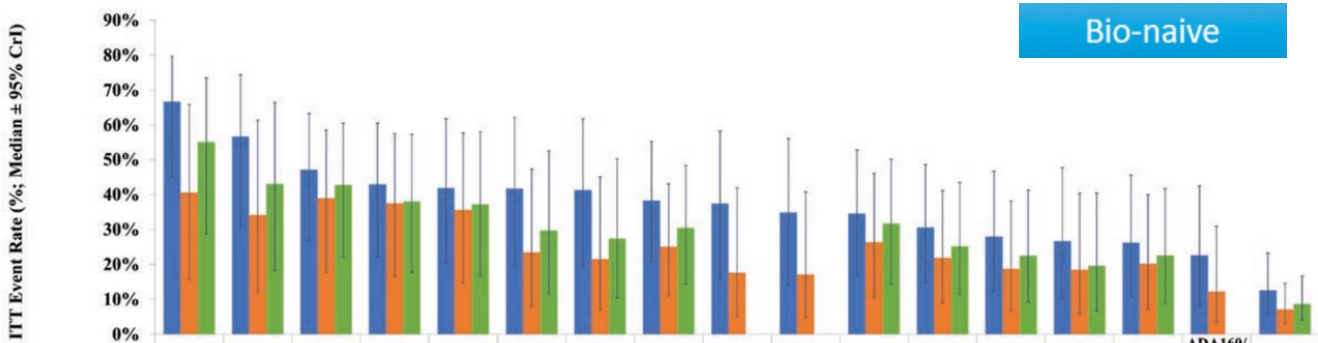
- Results

Baseline demographics	Placebo (n=67)	PRA023 (n=68)
Duration of disease, years, mean (SD)	6.3 (6.2)	6.7 (6.4)
Proctosigmoiditis; Left-sided colitis; Pancolitis	7 (10%), 28 (42%), 32 (48%)	2 (3%), 35 (51%), 31 (46%)
Modified Mayo Score, mean (SD)	7.1 (1.1)	6.9 (1.2)
Fecal Calprotectin (µg/g)	1395.4 (1430.6)	1219.1 (1381.5)
Concomitant immunosuppressant use, n (%)	11 (16%)	7 (10%)
Concomitant corticosteroid use, n (%)	39 (58%)	35 (52%)
Number of prior advanced therapies exposed, n (%)		
0	35 (52%)	36 (53%)
1	8 (12%)	12 (18%)
2	12 (18%)	14 (21%)
≥3	12 (18%)	6 (9%)

Sands B, *et al.* Presented at DDW. May 2023. 477a.

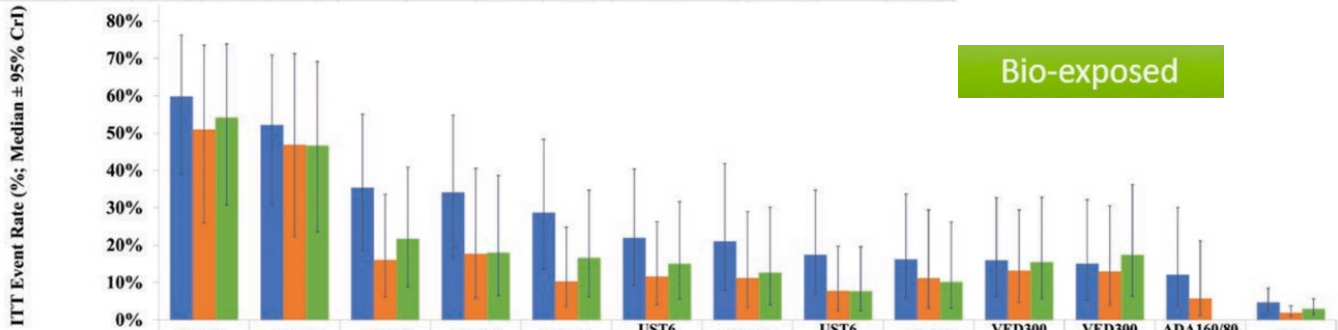
Ulcerative Colitis:
Network Meta-Analysis of Treat Through Clinical Response

Bio-naive



	UPA45 xUPA30	UPA45 xUPA15	TOF10 xTOF10	TOF10 xTOF5	FIL200 xFIL200	UST6 xUST90 Q8W	UST6 xUST90 Q12W	VED300 xVED300 Q8W	INF10 xINF10	INF5 xINF5	VED300 xVED300 Q4W	GOL200/ 100 xGOL100	GOL200/ 100 xGOL50	FIL100 xFIL100	OZA0.92 xOZA 0.92	ADA160/ 80 xADA40 Q2W	PBO xPBO
Clinical Response	66.7%	56.6%	47.1%	43.0%	41.9%	41.7%	41.3%	38.3%	37.4%	34.9%	34.6%	30.6%	28.0%	26.7%	26.2%	22.6%	12.7%
Clinical Remission	40.6%	34.1%	39.0%	37.5%	35.6%	23.5%	21.5%	25.0%	17.7%	17.2%	26.4%	21.9%	18.8%	18.5%	20.2%	12.2%	7.2%
Endoscopic Improvement	55.0%	43.1%	42.7%	38.0%	37.2%	29.7%	27.4%	30.5%			31.7%	25.2%	22.5%	19.7%	22.6%		8.7%

Bio-exposed



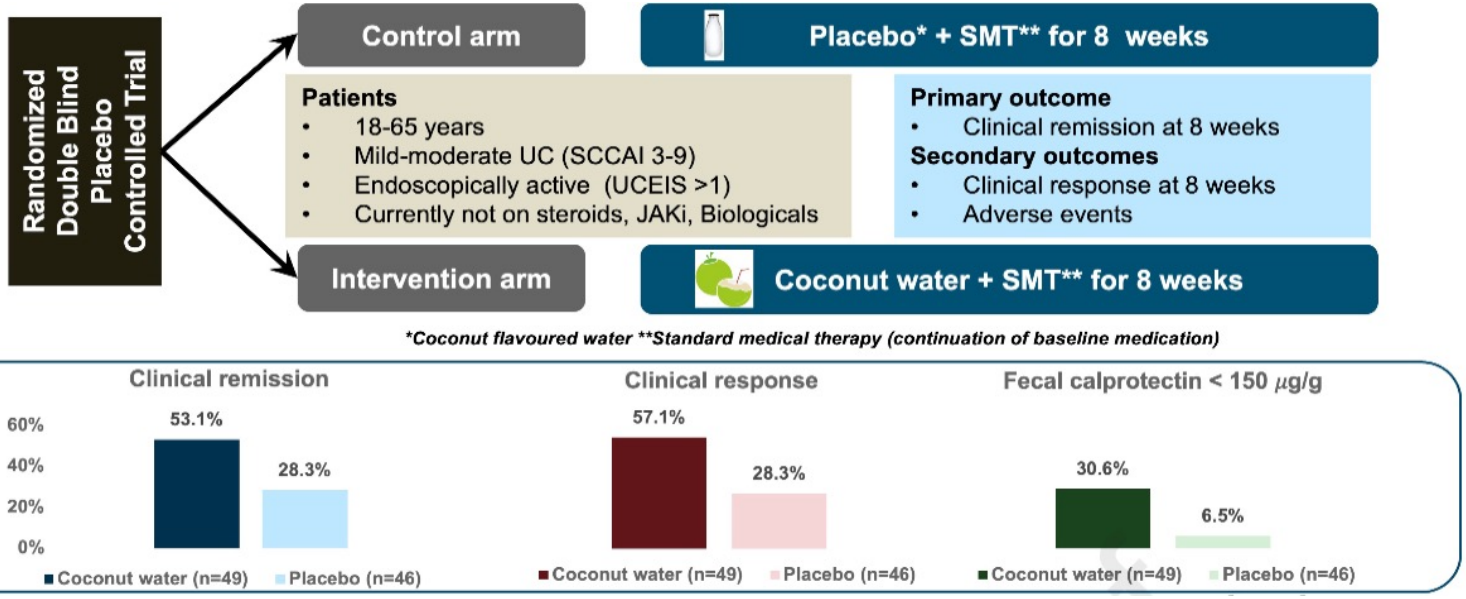
	UPA45 xUPA30	UPA45 xUPA15	TOF10 xTOF10	FIL200 xFIL200	TOF10 xTOF5	UST6 xUST90 Q8W	OZA0.92 xOZA0.92	UST6 xUST90 Q12W	FIL100 xFIL100	VED300 xVED300 Q8W	VED300 xVED300 Q4W	ADA160/80 xADA40 Q2W	PBO xPBO
Clinical Response	59.8%	52.2%	35.4%	34.1%	28.7%	22.0%	21.0%	17.5%	16.2%	16.0%	15.0%	12.1%	4.7%
Clinical Remission	51.0%	46.9%	16.1%	17.7%	10.3%	11.6%	11.2%	7.8%	11.2%	13.2%	12.9%	5.8%	1.9%
Endoscopic Improvement	54.1%	46.6%	21.7%	18.0%	16.6%	15.0%	12.6%	7.7%	10.2%	15.4%	17.4%		2.9%

Panaccione R, et al. *Crohns Colitis 360*. 2023;5(2):otad009. Published 2023 Mar 1.

Coconut water induces clinical remission in mild-moderate UC

Why coconut water

- anti-inflammatory due to presence of cytokinins, phytohormones, and vitamins
- Antibacterial, antifungal, antiviral, and anti-oxidant actions
-Anti-microbial peptides which can influence the gut microbiome
- Rich source of dietary potassium, which has been linked with inflammation.



Kedia S et al. Clinical Gastroenterology and Hepatology (2024)

Summary: Year in Review Ulcerative Colitis

- Exciting ongoing research into pre-disease states and environmental influences
- Multiple new FDA-approved drugs are available and safe and effective in moderate-to-severe UC management
- Novel uses of advanced therapies in ASUC and pouchitis appear promising
- Disease Monitoring is a critical part of management of UC
  - Updated guidelines on biomarkers including calprotectin
  - Newer Disease monitoring tools are emerging including IUS
  - Application of AI for monitoring
- Stay away from antibiotics and chips and other UPF (when possible); Enjoy a coconut or two while in Maui, and de-stress