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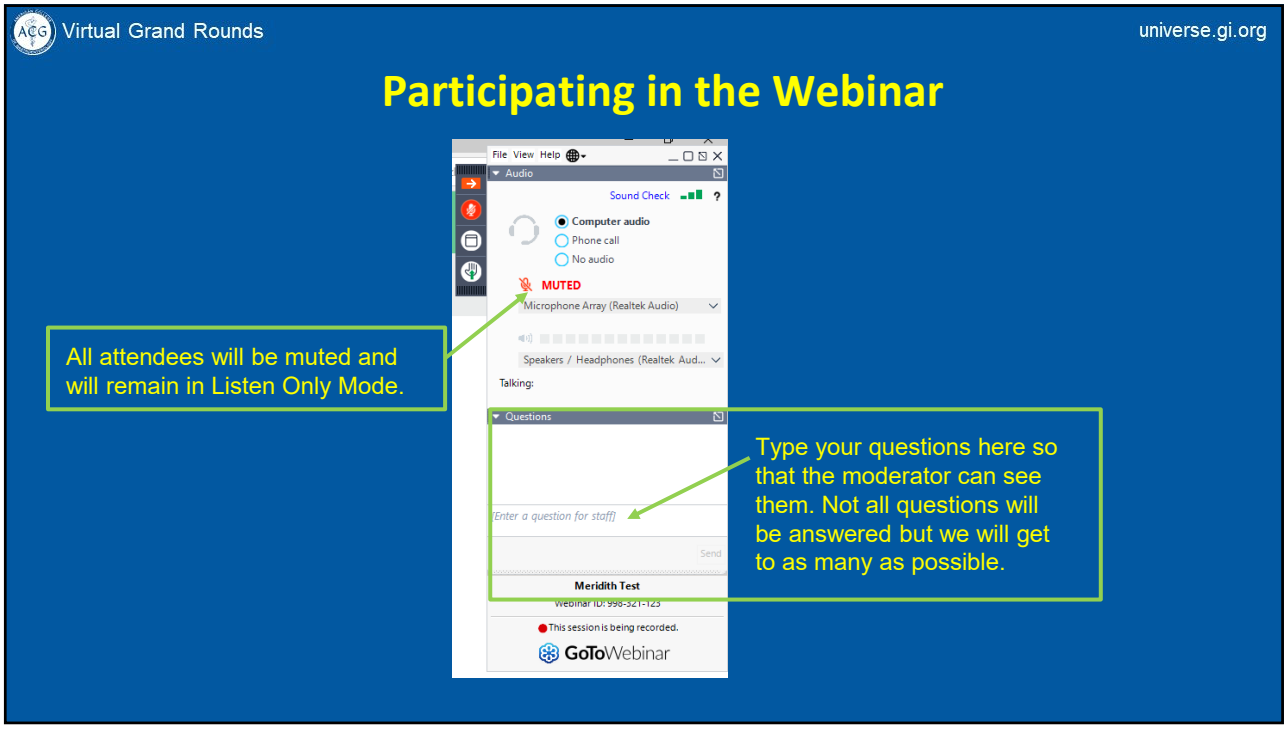
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How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

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MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

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ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

There will be NO Virtual Grand Rounds until January 5, 2023.
Have a wonderful holiday season and a happy New Year!




Week 1 –Thursday, January 5, 2023
AI in GI
Faculty: Seth A. Gross, MD, FACG
Moderator: Nasim Parsa, MD
At Noon Eastern and NEW! **8pm Eastern!**

Week 2 – Thursday, January 12, 2023
How Can We Close the Screening Disparity Gaps in Our Population?
Faculty: Renee L. Williams, MD, MHPE, FACG
Moderator: Loren G. Rabinowitz, MD
At Noon Eastern and NEW! **8pm Eastern!**

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

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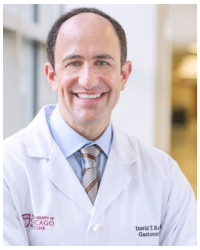

David T. Rubin, MD, FACG **(update Dec 2022 represents last 36 months)**

Consultant/Advisor	Abbvie, Altrubio, Aslan Pharmaceuticals, Athos Therapeutics, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Ltd., Bristol-Myers Squibb, Celgene Chronicles, Corp/Syneos, ClostraBio, Connect BioPharma, Eco R1, Genentech/Roche, Gilead Sciences, Iterative Health, Janssen Pharmaceuticals, Kaleido Biosciences, Lilly, Pfizer, Prometheus Biosciences, Reistone, Seres Therapeutics, Takeda, Target RWE, Trellus Health
Grant Support	Takeda, Helmsley Charitable Trust, GastroIntestinal Research Foundation
Board of Trustees	Crohn's & Colitis Foundation, GastroIntestinal Research Foundation, Cornerstones Health, Inc
Stock Options	Alike Health, Altrubio, Datos Health, Iterative Health

Samir A. Shah, MD, FACG

Dr. Shah has no relevant financial relationships with ineligible companies.

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

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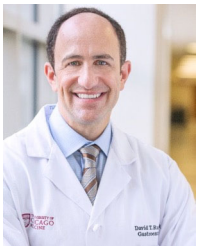
Optimal Positioning of Small Molecule Treatment Options in IBD



David T. Rubin, MD, FACG
Joseph B. Kirsner Professor of Medicine
Professor of Pathology
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@IBDMD
RubinLab.uchicago.edu

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Learning Objectives

- Understand the need and benefit of novel small molecule therapy in IBD.
- Incorporate JAK inhibitors and S1P receptor modulator therapy in the management of patients with IBD.
- Interpret the safety data for the novel targeted small molecule therapies for patients with IBD.

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Medical Treatment Options for IBD

Treatment	Induction	Maintenance	
Dietary treatment (PEN/EEN)	CD	CD	Conventional Therapies (traditional)
5-ASA	UC	UC	
Steroids (budesonide and prednisone equivalents)	✓	X	
Antibiotics	?	?	
Thiopurines	X	✓	Conventional Therapies (Immunomodulators)
Methotrexate	CD	CD	
Anti-integrin (natalizumab, vedolizumab)	✓	✓	Biological Therapies
Anti-p40 (ustekinumab) Anti-p19 (risankizumab)	✓	✓	
Anti-TNF (adalimumab, certolizumab pegol, golimumab, infliximab)	✓	✓	
JAKinibs (tofacitinib, upadacitinib)	UC	UC	Targeted synthetic Small molecules
S1P receptor mod (ozanimod)	UC	UC	

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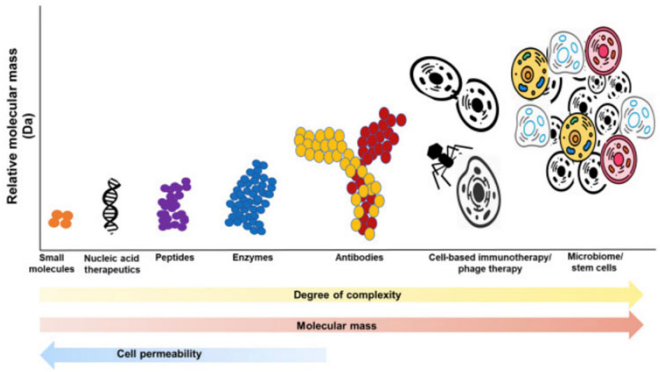
What is A Small Molecule?

- Small enough to get absorbed through the lining of the small intestine
- Conventional synthetic small molecules (azathioprine, methotrexate, cyclosporine)
- Targeted synthetic small molecules (JAKinibs, S1Ps, others)



Chhabra, M. *Translational Biotechnology.* 2021.

15

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Why Do We Need Novel Small Molecule Therapies in IBD?

- Unmet needs in IBD
- Novel mechanisms
- Convenience of delivery (oral)
- Avoids monoclonal antibody challenges
  - Immunogenicity
  - Protein leakage (dose:exposure challenges)

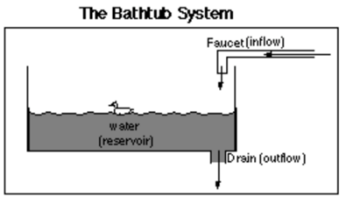

Figure 2.2. The Bathtub system is an open system with three components, an inflow, an outflow, and a reservoir; it is an open system since we do not keep track of the ultimate source and sink for water — we are only concerned with the water withinthe confines of the system portrayed in this drawing.

Fig from Dave Bice, Penn State, psu.edu

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JAK Inhibitors:
Tofacitinib, Upadacitinib, Filgotinib

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Intracellular Signaling Through the JAK/STAT Pathway Is Integral for Many Cytokines

STAT: Signal Transducer and Activator of Transcription

Cytokines that signal through JAK/STAT combinations

JAKs are involved in lipid metabolism too

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JAK Inhibitors Approved and Under Investigation in IBD

Name	Target	Studied Indication
Filgotinib	JAK 1 selective	Crohn's disease Ulcerative colitis
Upadaticinib	JAK 1 selective	Ulcerative colitis (FDA Approved 2022) Crohn's disease (NCT02782663) Rheumatoid arthritis (FDA Approved 2019) Atopic Dermatitis (FDA Approved 2022)
SHR0302	JAK 1 selective	UC
Tofacitinib	Non-selective (JAK 1, 2, 3)	Ulcerative colitis (FDA Approved 2018) Rheumatoid arthritis (FDA Approved 2012) Psoriatic arthritis (FDA Approved 2017) Ankylosing spondylitis (FDA Approved 2021)
TD-1473	Non-selective (JAK 1, 2, 3) Intestinally-restricted	Ulcerative colitis (Phase 1b)
BMS-986165	Tyrosine kinase 2 (TKY2) inhibitor	Plaque psoriasis LATTICE UC phase 2 negative LATTICE CD phase 2 ongoing
Baricitinib	Non-selective (JAK 1, 2)	Rheumatoid arthritis Alopecia areata COVID (FDA Emergency Authorization May 2022)

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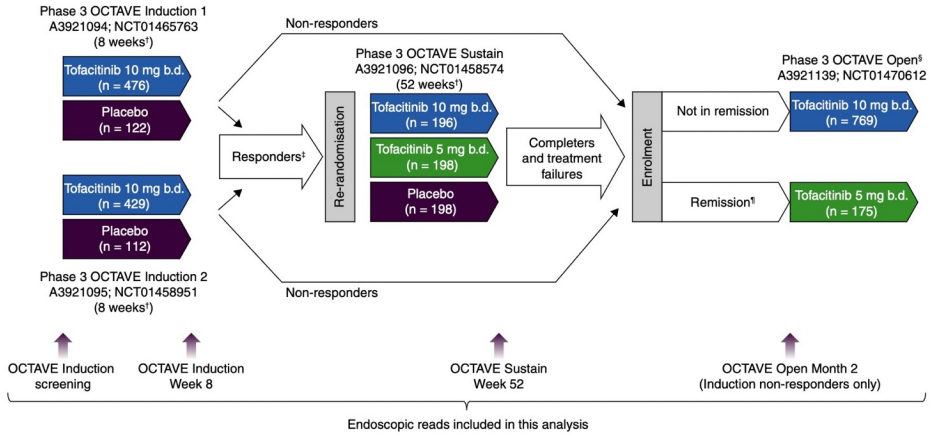
Tofacitinib (JAK1-3 inhibitor) for Patients with Moderate-to-Severe Ulcerative Colitis: Phase 3 OCTAVE Program



Sandborn WJ, et al. N Engl J Med. 2017; 376(18):1723-1736.

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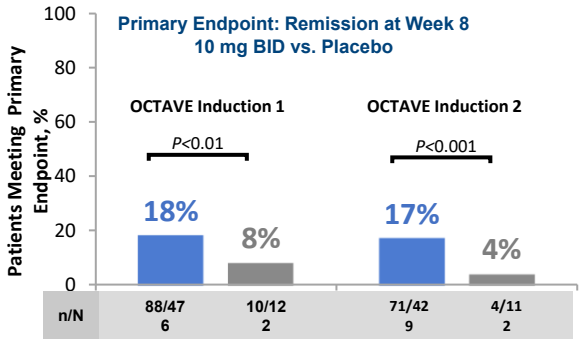
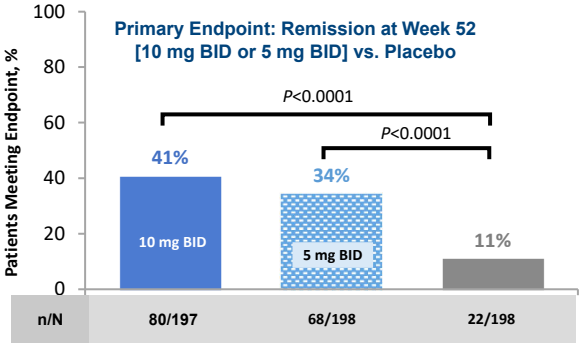
Tofacitinib for Induction and Maintenance of Moderately to Severely Active Ulcerative Colitis (OCTAVE 1 and 2)



~50% of patients in OCTAVE Induction had failed or were intolerant to prior TNF blocker therapy



Corticosteroid tapering was required upon entrance to maintenance study for patients receiving corticosteroids at baseline

Remission defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0

Sandborn WJ, et al. *N Engl J Med.* 2017;376(18):1723-1736.

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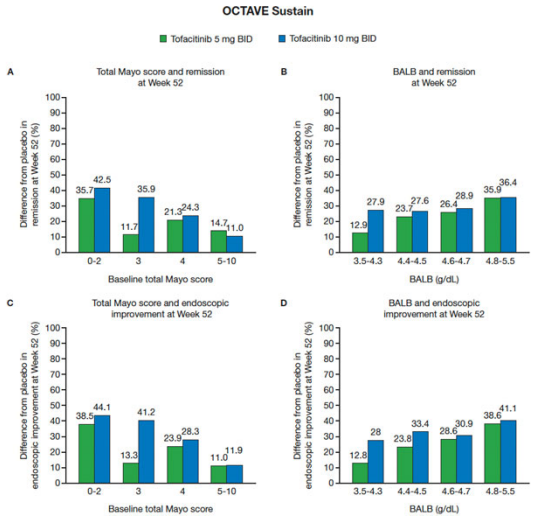
Baseline Albumin Does Not Predict Response to Tofacitinib in Patients with Ulcerative Colitis



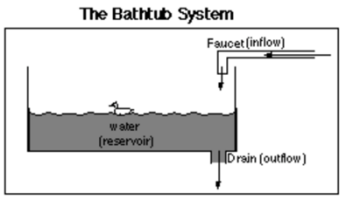


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Fig from Dave Bice, Penn State, psu.edu

Lichtenstein G, et al. *Am J Gastroenterol.* 2018;113:pS354-S355.

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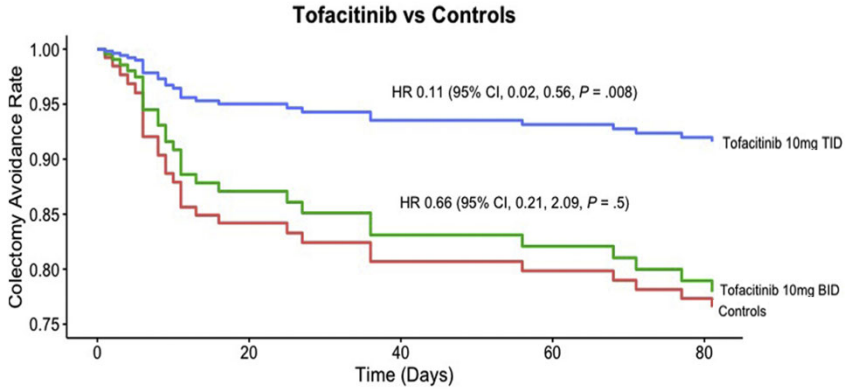
Tofacitinib Compared with Standard Care for Acute Severe UC (Hospitalized)



Berinstein JA, Sheehan JL, et al. Clin Gastroenterol Hepatol. 2021 Oct;19(10):2112-2120.e1.

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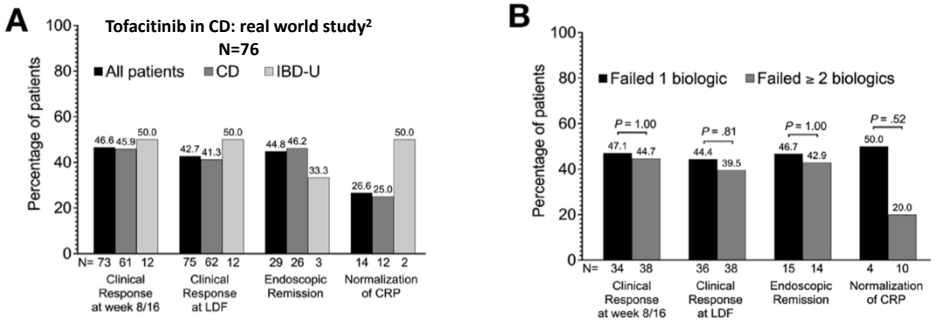
What About Tofacitinib in Crohn's Disease?

- **Tofacitinib: two phase 2b studies negative[1]**
  - Induction clinical remission week 8: N.S. (placebo 36.7% v tofa 5 BID 43.5% v tofa 10 BID 43.0%)
  - Maintenance Response 100 or remission week 26: N.S. (PBO 38.1% v tofa 5 BID 39.5% v tofa 10 BID 55.8%)
- **Real world multi-center experience: positive, favor Crohn's colitis[2]**



[1]Panés J, et al. *Gut.* 2017;66:1049-1059.
[2]Fenster M, et al. *Clin Gastroenterol Hepatol*. 2021 Oct;19(10):2207-2209.e3. Epub 2020 Oct 14.

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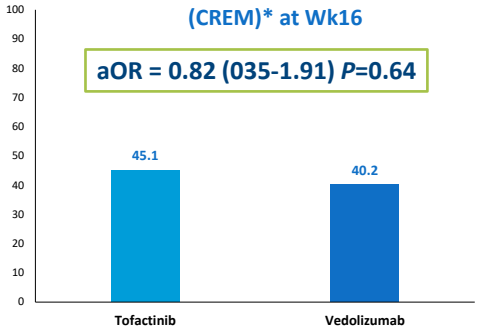
Tofacitinib or Vedolizumab in UC Patients After ≥ 1 Biologic Therapy

Multi-center retrospective study (tofacitinib n=126, vedolizumab n=178)

Corticosteroid-free Clinical Remission (CREM)* at Wk16

aOR = 0.82 (035-1.91) *P*=0.64



Corticosteroid-free Clinical Remission = Partial Mayo Score ≤2 and no use of steroids at Wk16

VEDOLIZUMAB:

Predictors of vedolizumab failure:
- Partial Mayo >6
- CRP >30 g/L
- ≥1 Primary Failure to Biologics

TOFACITINIB:

No predictors of tofacitinib failure

Tofacitinib more effective in cases of primary failure to anti-TNFs and multiple therapeutic failures

Buisson, A, *et al*. Presented at DDW. May 2022. Su1503.

25

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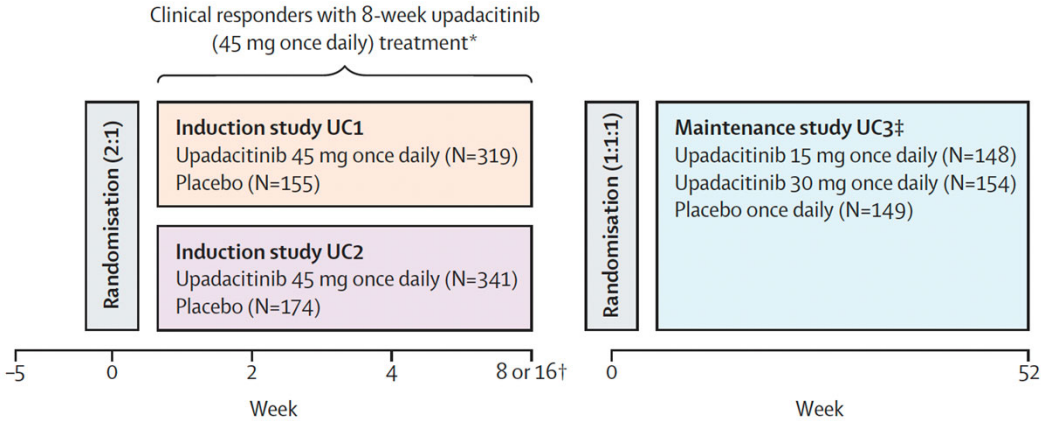
Upadacitinib (selective JAK-1 inhibitor) in Moderate-to-Severe UC Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Program



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

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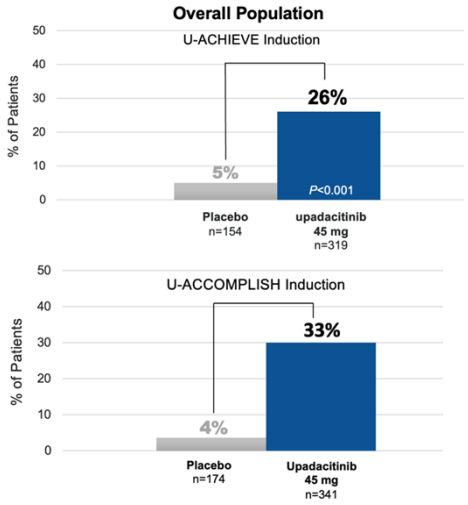
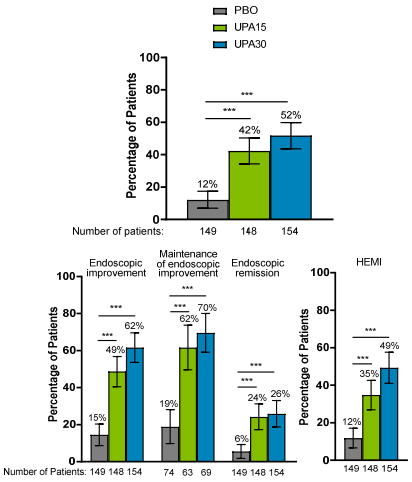
Upadacitinib in Induction and Maintenance in Patients with UC

Induction Clinical Remission at Week 8

Clinical remission was defined as stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤1 without friability.



Maintenance Primary Endpoint: Clinical remission at Week 52



Secondary Endpoints: Endoscopy and histology

Danese S, et al. *Lancet.* 2022;399(10341):2113-2128.
Panaccione R, et al. Presented at UEGW 2021.

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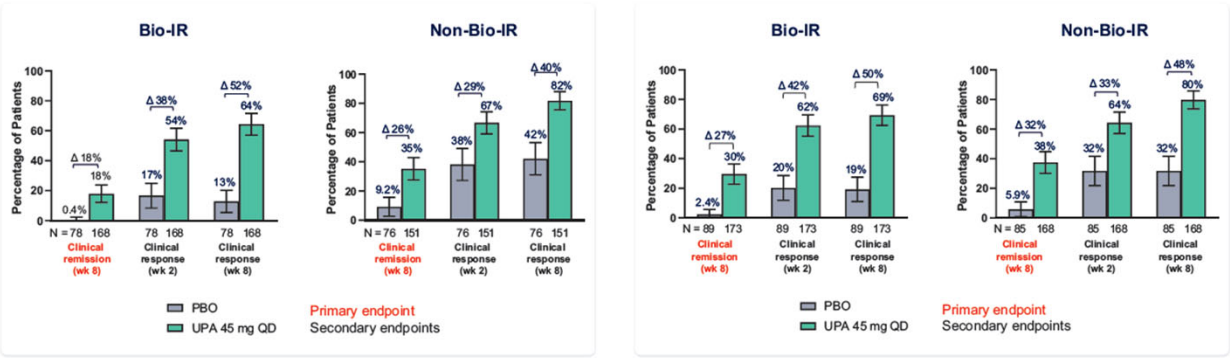
Upadacitinib in Induction by Bio-IR Status
(U-ACHIEVE and U-ACCOMPLISH Phase 3 Induction Trials)



Bio-IR: experienced previous biologic failure (inadequate response, loss of response, or intolerance)

Vermiere S, et al. Presented at ACG 2021.

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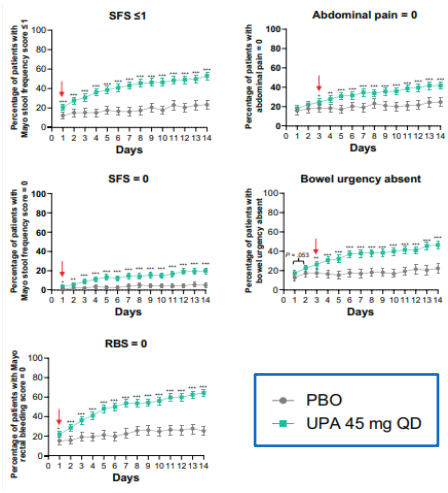
Upadacitinib Timing of Response in UC

- **Methods**
  - U-ACHIEVE and U-ACCOMPLISH multicenter, double-blind, PBO-controlled trials with randomization to UPA 45 mg QD or PBO (2:1)
- **Results**
  - N=998
  - Day 7 SFS ≤1 were more likely co-achieve clinical remission at week 8 (OR 2.53, 95% CI 1.59-4.00)
- **Conclusion**
  - UPA 45 mg QD significantly improved symptoms as early as day 1
  - Patients with early improvement were more likely to achieve clinical remission at week 8

Change in Daily Symptoms UPA 45 mg vs. PBO



UPA, Upadacitinib; PBO, placebo

Vermeire, S, *et al*. Presented at DDW. May 2022. 967.

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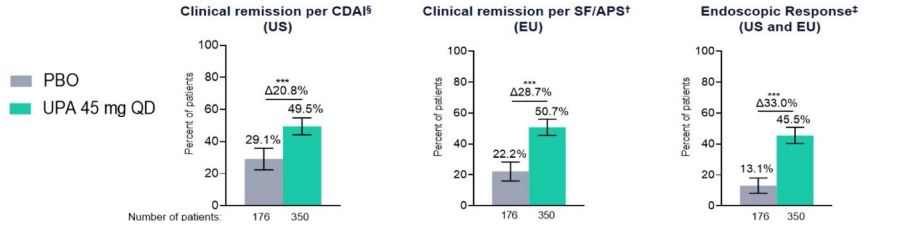
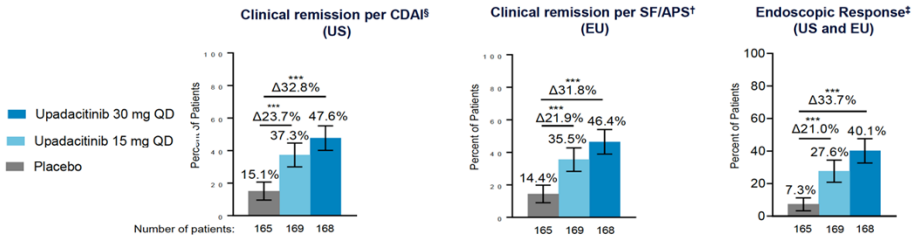
Upadacitinib in Moderate-to-Severe Crohn's Disease weeks 12 and 52 (Phase 3)



Loftus, EV, et al. *United European Gastroenterol J.* 2022;10(s8).



Panes J, et al. *Am. J. Gastroenterol.* 2022;17(s8).

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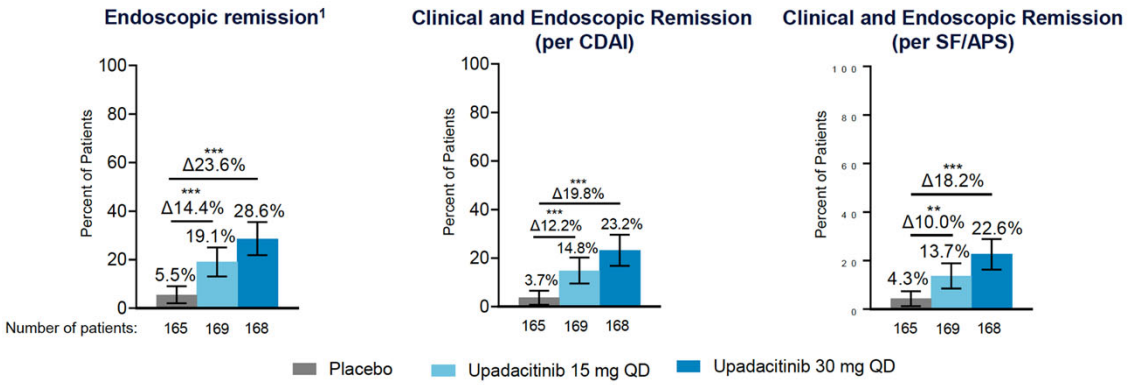
Upadacitinib for Moderate-to-Severe Crohn's Disease: Phase 3 Secondary Endpoints



1 Endoscopic Remission: SES-CD ≤ 4, at least a 2-point reduction versus baseline and no subscore >1 in any individual variable, as scored by a central reviewer
95% CI for response rate is the synthetic result 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 due to COVID-19. Point estimate and 95% CI for adjusted treatment difference are based on Cochran-Mantel-Haenszel test for adjusted strata for categorical endpoints. Non-responder imputation incorporating multiple imputation was used to handle missing data due to COVID-19; ***P < .0001 vs PBO; **P < .001 vs PBO

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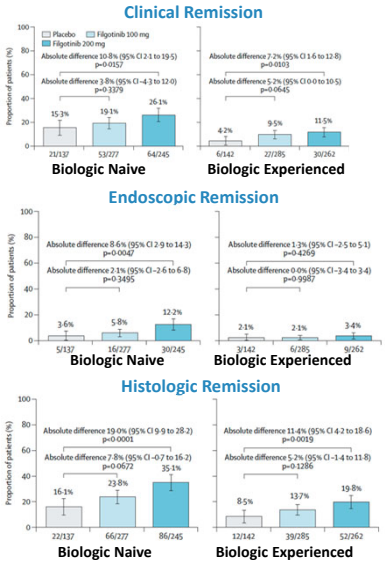
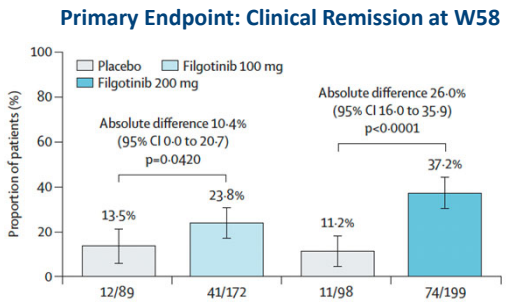
Filgotinib (JAK-1 inhibitor) SELECTION Trial: Phase 2b/3 Induction and Maintenance

Primary Endpoint at W10

Key Secondary Endpoints W10





Feagan BG, *et al. Lancet*. 2021;397(10292):2372-2384.

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Safety of JAKinibs in IBD

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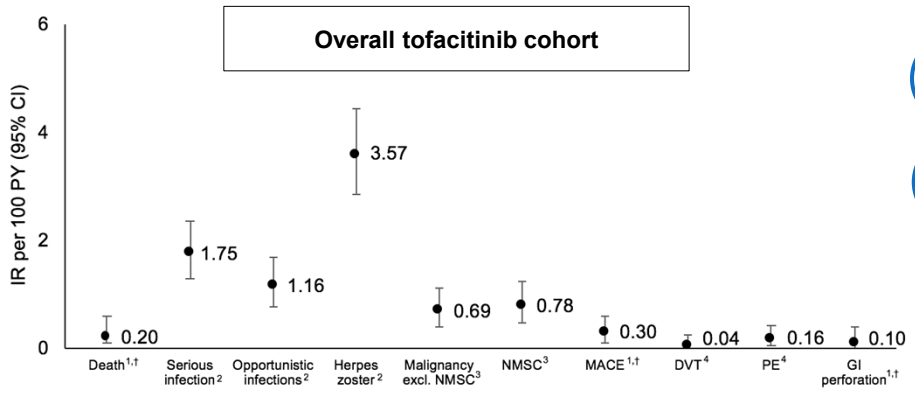
Incidence Rates of Adverse Events in the OCTAVE Clinical Program



N=1157
2403.6 PY exposure

Treatment duration
≤6.1 years
(median: 623 days)

Most patients
(n=960; 83%)
received 10 mg BID
predominant dose

Figure created from Sandborn WJ, et al. 2019[1], Winthrop KL, et al. 2019[2], Lichtenstein GR, et al. 2019[3], and Sandborn WJ, et al. 2019[4].
Data as of September 2018 data-cut for all AEs unless otherwise indicated.
[†]For death, MACE, and GI perforation, data as of November 2017 data-cut.
AE=adverse event; BID=twice daily; CI=confidence interval; DVT=deep vein thrombosis; GI=gastrointestinal; IR=incidence rate;
MACE=major adverse cardiovascular event; N=total number of patients; n=number of patients in subpopulation;
NMSC=non-melanoma skin cancer; PE=pulmonary embolism; PY=patient-years.

1. Sandborn WJ, et al. Abstract P466 presented at the 14th Congress of the ECCO; 6-9 March 2019. Copenhagen, Denmark;
2. Winthrop KL, et al. Abstract 0P007 presented at UEG Week; 19-23 October 2019. Barcelona, Spain;
3. Lichtenstein GR, et al. Abstract P0393 presented at UEG Week; 19-23 October 2019. Barcelona, Spain;
4. Sandborn WJ, et al. *Aliment Pharmacol Ther*. 2019; 50(10): 1068–1076.

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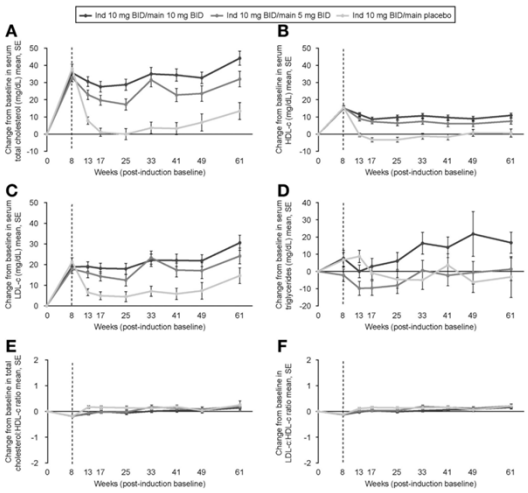
Tofacitinib and Upadacitinib Affect Lipids

Tofacitinib

- Total cholesterol, LDL-c and HDL-c all moderately increased from baseline for both 5 and 10 mg maintenance doses
- Lipid ratios predictive of CV risk remained relatively stable during both induction and maintenance

Upadacitinib

- Demonstrated to increase lipid levels in patients with rheumatoid arthritis



Sands BE, *et al. Inflamm Bowel Dis*. 2021 Jun;27(6):797-808.
Sands BE, *et al. Clin Gastroentol Hepatol*. 2020 Jan;18(1):123-132.
Charles-Schoeman C, *et al.* Presented at ACR Convergence. Nov 2020. Abstract 1211.

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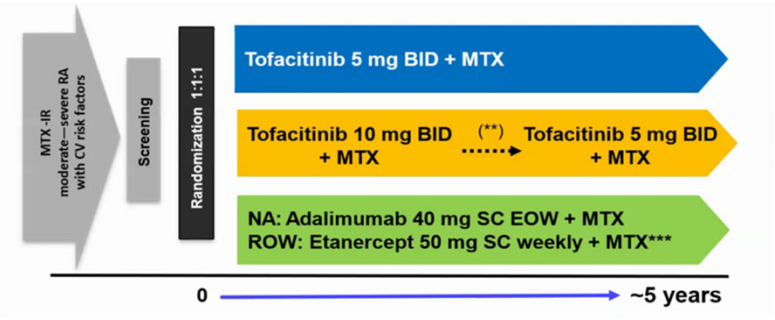
ORAL Surveillance Study A3921133

Methods:

- **Randomized, open-label, non-inferiority safety end-point study of tofacitinib vs anti-TNF**
- **Subjects: active RA despite MTX, age >50, 1 cardiovascular risk factor**
- **Randomized tofa 5 mg BID(n=1455), 10 mg BID (n=1456), or TNF inhibitor (n=1451)**
- **(ALL with MTX)**



**patients in 10 mg BID arm discontinued treatment in Feb 2019; patients had option to switch to 5 mg BID

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

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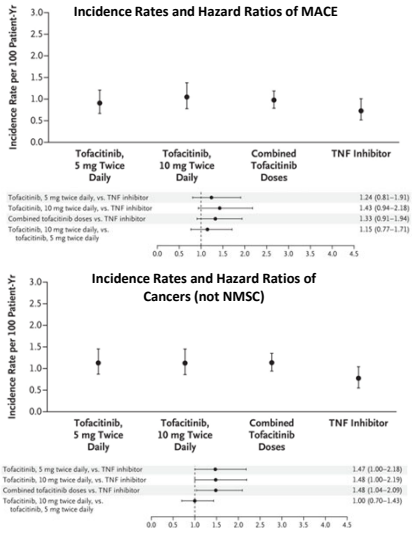
Adverse Events with Tofacitinib in Patients with Rheumatoid Arthritis

Event	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)
Adverse event — no. (%)	1333 (91.6)	1344 (92.3)	1308 (90.1)
Serious adverse event — no. (%)	351 (24.1)	390 (26.8)	306 (21.1)
Discontinuation of trial treatment due to adverse event — no. (%)			
Permanent discontinuation‡	210 (14.4)	304 (20.9)	210 (14.5)
Temporary discontinuation§	665 (45.7)	736 (50.5)	576 (39.7)
Adverse events of special interest			
Serious infection — no. (%)	141 (9.7)	169 (11.6)	119 (8.2)
Hazard ratio vs. TNF inhibitor (95% CI)	1.17 (0.92–1.50)	1.48 (1.17–1.87)	Referent
Adjudicated opportunistic infection — no. (%)¶	39 (2.7)	44 (3.0)	21 (1.4)
Hazard ratio vs. TNF inhibitor (95% CI)	1.82 (1.07–3.09)	2.17 (1.29–3.66)	Referent
All herpes zoster, serious and nonserious — no. (%)‖	180 (12.4)	178 (12.2)	58 (4.0)
Hazard ratio vs. TNF inhibitor (95% CI)	3.28 (2.44–4.41)	3.39 (2.52–4.55)	Referent
Adjudicated hepatic event — no. (%)	46 (3.2)	72 (4.9)	35 (2.4)
Hazard ratio vs. TNF inhibitor (95% CI)	1.29 (0.83–2.00)	2.14 (1.43–3.21)	Referent
Adjudicated NMSC — no. (%)	31 (2.1)	33 (2.3)	16 (1.1)
Hazard ratio vs. TNF inhibitor (95% CI)	1.90 (1.04–3.47)	2.16 (1.19–3.92)	Referent
Adjudicated pulmonary embolism — no. (%)	9 (0.6)	24 (1.6)	3 (0.2)
Hazard ratio vs. TNF inhibitor (95% CI)	2.93 (0.79–10.83)	8.26 (2.49–27.43)	Referent
Adjudicated DVT — no. (%)	11 (0.8)	15 (1.0)	7 (0.5)
Hazard ratio vs. TNF inhibitor (95% CI)	1.54 (0.60–3.97)	2.21 (0.90–5.43)	Referent
Adjudicated VTE — no. (%)	17 (1.2)	34 (2.3)	10 (0.7)
Hazard ratio vs. TNF inhibitor (95% CI)	1.66 (0.76–3.63)	3.52 (1.74–7.12)	Referent
Adjudicated death from any cause — no. (%)	26 (1.8)	39 (2.7)	17 (1.2)
Hazard ratio vs. TNF inhibitor (95% CI)	1.49 (0.81–2.74)	2.37 (1.34–4.18)	Referent



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

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Impact of ORAL Surveillance Study on Regulatory Labels for JAKinibs

- **Position JAKinibs after anti-TNF**
- **Screen for risk of VTE and MACE**
- **Dose reduce when possible**
  - **NOTE: that with tofacitinib and upadacitinib in UC, patients with "refractory" disease do better with higher dose in maintenance (Tofa 10 BID, Upa 30 QD)**

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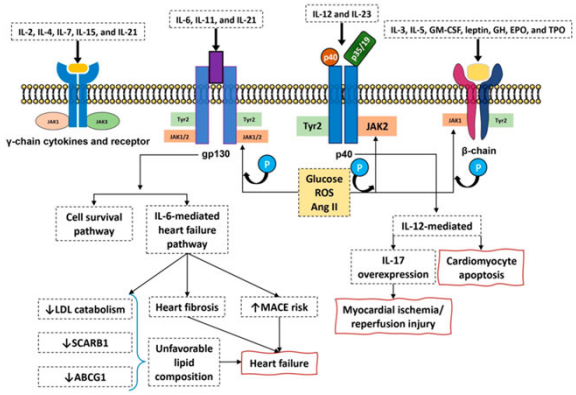
Mechanistic Considerations for JAKinibs and VTE or MACE

- **Unclear!**
  - **Tox studies did not see any markers.**
  - **No signal in the UC/RA/PsA pivotal trials or real world studies**
  - **IBD (especially colonic) is associated with increased VTE and MACE. Expected that if JAKinib was pro-thrombotic there would be a strong signal**
- **The role of JAK-STAT signaling in clotting cascades or cellular interactions related to that is not well characterized.**
- **IL-6 is associated with atherosclerotic heart disease, and JAKinib inhibits IL-6**



Przemyslae JK, et al. *Int J Mol Sci.* 2020;21(19):7390.

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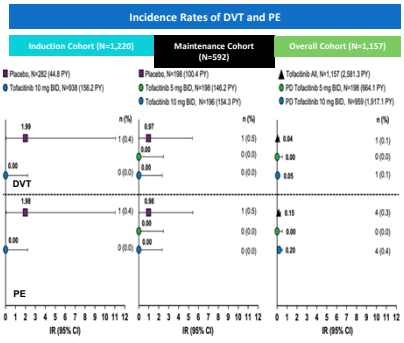
Rare Incidence of Venous Thromboembolic Events in Patients With UC on Tofacitinib



IRs of Adverse Events of Special Interest in the Maintenance and Overall Cohorts

	Maintenance Cohort			Overall cohort (induction + maintenance + OLE)
	Placebo (n=198)	Tofacitinib 5 mg BID (n=198)	Tofacitinib 10 mg BID (n=196)	Tofacitinib all (n=1157)
	n (%) | IR (95% CI)	n (%) | IR (95% CI)	n (%) | IR (95% CI)	n (%) | IR (95% CI)
Serious infection event	2 (1.0) | 1.9 (0.2-7.0)	2 (1.0) | 1.4 (0.2-4.9)	1 (0.5) | 0.6 (0.0-3.5)	33 (2.9) | 2.0 (1.4-2.8)
Herpes Zoster (HZ)	1 (0.5) | 1.0 (0.0-5.4)	3 (1.5) | 2.1 (0.4-6.0)	10 (5.1) | 6.6 (3.2-12.2)	65 (5.6) | 4.1 (3.1-5.2)
Opportunistic Infection[a]	1 (0.5) | 1.0 (0.0-5.4)	2 (1.0) | 1.4 (0.2-4.9)	4 (2.0) | 2.6 (0.7-6.7)	21 (1.9) | 1.3 (0.8-2.0)
Opportunistic Infection (excluding HZ)[a]	0 (0.0) | 0 (0.0-3.6)	0 (0.0) | 0.0 (0.0-2.5)	0 (0) | 0.0 (0.0-2.4)	4 (0.4) | 0.2 (0.1-0.6)
Malignancy (excluding NMSC)[a]	1 (0.5) | 1.0 (0.0-5.4)	0 (0.0) | 0.0 (0.0-2.5)	0 (0) | 0.0 (0.0-2.4)	11 (1.0) | 0.7 (0.3-1.2)
NMSC[a]	1 (0.5) | 1.0 (0.0-5.4)	0 (0.0) | 0.0 (0.0-2.5)	3 (1.5) | 1.9 (0.4-5.6)	11 (1.0) | 0.7 (0.3-1.2)
MACE[a]	0 (0.0) | 0 (0.0-3.6)	1 (0.5) | 0.7 (0.0-3.8)	1 (0.5) | 0.6 (0.0-3.5)	4 (0.4) | 0.2 (0.1-0.6)
GI perforations[a]	1 (0.5) | 1.0 (0.0-5.4)	0 (0.0) | 0.0 (0.0-2.5)	0 (0) | 0.0 (0.0-2.4)	3 (0.3) | 0.2 (0.0-0.5)

NOTE: With the exception of malignancy (excluding NMSC), NMSC, and MACE, IRs presented in the table exclude events that occurred >28 days after the last dose of the study drug.
CI, confidence interval; IR, incidence rate, patients with >=1 event per year per 100 patient-years; OLE, open-label, long-term extension study; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular event; GI, gastrointestinal; [a]Adjudicated data do not include data from Study A3921063

Sandborn WJ, *et al. Aliment Pharmacol Ther*. 2019 Nov;50(10):1068-1076.
Sandborn WJ, et al. Clin Gastroenterol Hepatol. 2019 Jul;17(8):1541-1550.

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Tofacitinib: Incidence Rates for Selected Adverse Events of Special Interest Across Studies and Indications

Table 3 IRs (95% CI) for AEs of special interest

	RA (N=7964)	PsA (N=783)	UC (N=1157)	PsO (N=3663)
Total tofacitinib exposure, patient-years	23 497	2038	2581	8950
Serious infections, IR (95% CI) (n)	2.5 (2.3 to 2.7) (592)	1.2 (0.7 to 1.7) (24)	1.7 (1.2 to 2.3) (45)	1.3 (1.1 to 1.5) (119)
All HZ (non-serious and serious), IR (95% CI) (n)	3.6 (3.3 to 3.8) (795)	1.8 (1.2 to 2.4) (36)	3.5 (2.8 to 4.3) (87)	2.4 (2.0 to 2.7) (209)
Adjudicated OIs excluding tuberculosis, IR (95% CI) (n)	0.4 (0.3 to 0.5) (95)	0.3 (0.1 to 0.7) (7)	1.6 (1.1 to 2.1) (40)*	0.3 (0.2 to 0.5) (29)
Adjudicated tuberculosis, IR (95% CI) (n)	0.2 (0.1 to 0.2) (38)	0.0 (0.0 to 0.2) (0)	0.0 (0.0 to 0.1) (0)*	0.0 (0.0 to 0.1) (1)
Adjudicated malignancies excluding all NMSC, IR (95% CI) (n) n1 (%)	0.7 (0.6 to 0.9) (179) 211 (2.6)	0.7 (0.4 to 1.2) (15) 18 (2.3)	0.6 (0.3 to 1.0) (16)* 20 (1.8)*	0.7 (0.5 to 0.8) (60) 74 (2.0)
Adjudicated NMSC, IR (95% CI) (n) n1 (%)	0.6 (0.5 to 0.7) (133) 135 (1.7)	0.8 (0.4 to 1.3) (16) 16 (2.0)	0.7 (0.4 to 1.1) (19)* 19 (1.7)*	0.7 (0.5 to 0.9) (63) 67 (1.8)
Adjudicated melanoma, IR (95% CI) (n) n1 (%)	0.1 (0.0 to 0.1) (14) 14 (0.2)	0.0 (0.0 to 0.2) (0) 0 (0.0)	0.1 (0.0 to 0.3) (2)* 2 (0.2)*	0.1 (0.0 to 0.1) (5) 5 (0.1)
Adjudicated lymphoma/lymphoproliferative disorders, IR (95% CI) (n) n1 (%)	0.1 (0.0 to 0.1) (12) 19 (0.2)	0.1 (0.0 to 0.3) (1) 1 (0.1)	0.1 (0.0 to 0.3) (2)* 2 (0.2)*	0.02 (0.0 to 0.1) (2) 4 (0.1)
Adjudicated gastrointestinal perforation, IR (95% CI) (n)	0.1 (0.1 to 0.2) (27)	0.1 (0.0 to 0.3)(1)	0.2 (0.1 to 0.5) (6)*	0.1 (0.0 to 0.2) (7)
Adjudicated MACE,† IR (95% CI) (n)	0.4 (0.3 to 0.5) (85)‡	0.3 (0.1 to 0.6) (6)	0.3 (0.1 to 0.5) (7)*	0.3 (0.2 to 0.4) (23)
DVT,§ IR (95% CI) (n)	0.2 (0.1 to 0.2) (37)	0.1 (0.0 to 0.3) (1)	0.0 (0.0 to 0.2) (1)	0.1 (0.0 to 0.1) (6)
PE,§ IR (95% CI) (n)	0.1 (0.1 to 0.2) (31)	0.1 (0.0 to 0.3) (1)	0.2 (0.0 to 0.4) (4)	0.1 (0.0 to 0.2) (9)

*N=1124.
†Composite MACE defined as any myocardial infarction, stroke or cardiovascular death.
‡N=7311.
§Previously reported in Mease *et al*[40] (excludes Study A3921133) and Sandborn *et al*.[44]
AE, adverse event; DVT, deep vein thrombosis; HZ, herpes zoster; IR, incidence rate (unique patients with events per 100 patient-years); MACE, major adverse cardiovascular events; N, number of patients in the disease cohort; n, unique number of patients with event (events are counted up to 28 days beyond the last dose or to the data cut-off date, and are included in the calculation of IR); n1, all events, including those occurring outside the 28-day risk period; NMSC, non-melanoma skin cancer; OI, opportunistic infection; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

Burmester GR, et al. *RMD Open*. 2021;7:e001595.

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Tofacitinib Real-World Safety and Efficacy in Ulcerative Colitis Comparable to Registration Trials

Rates of Clinical, Endoscopic and Histological Remission in Different Trials for Tofacitinib in Ulcerative Colitis

Abstract Reference	Study design	N	Prior TNF	Clinical remission*	Endoscopic remission	Histological remission	Discontinued	Colectomy
1	Retrospective observational Chicago	91	97%	-	64% (9/14)	36% (5/14)	-	-
2	Prospective observation Belgium	40	98%	33%	28%	25%	63%	30%
3	Systematic review 11 articles/8 abstracts	2,013		36%	-	-	-	-
4	Systematic review 7 observational studies	715		28%	-	-	35%	13%

*Clinical remission rates between week 16 and 26

Serious infections occurred in 4%,[4] abnormal lipids 12%,[4] zoster infection in 3%[4] and thromboembolic events in 0.3%[3]

[1]Cohen NA, et al. *Dig Dis Sci*. 2022 Oct 15. Epub ahead of print.
[2]Verstockt B, et al. *Journal of Crohn's and Colitis*. 2021;15(S_1) S456–S457..
[3]Taneja V, et al. *J Clin Gastroenterol*. 2021 Sep 9. Epub ahead of print.
[4]Lucaciu L, et al. *Therap Adv Gastroenterol*. 2021 Dec 23;14:17562848211064004.

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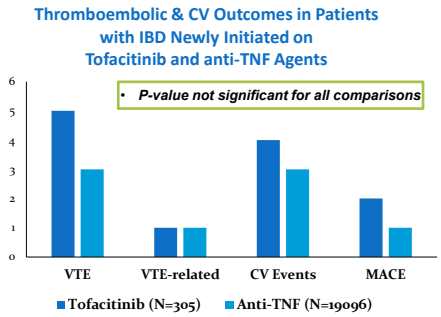
Tofacitinib *NOT* Associated with Increased Risk of VTE when Compared to Anti-TNF Agents in Patients with IBD

Methods

- Retrospective cohort study in a large U.S. claims database
- Identified patients with IBD by ICD-codes
- Primary outcomes were ICD-codes for VTE and cardiovascular (CV)-events
- Fitted propensity score (PS)-weighted Cox proportional hazard models



Kochar B, *et al*. Presented at DDW. May 2022. Tu1435.

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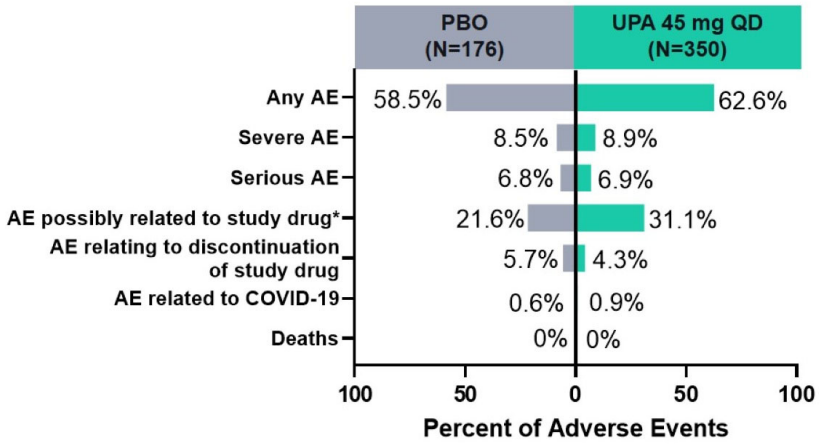
Upadacitinib: Treatment-Emergent Adverse Events



Loftus, EV, et al. *United European Gastroenterol J.* 2022;10(s8).

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Upadacitinib: Adverse Events of Special Interest Ulcerative Colitis Program

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.

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Practical Approach to Tofacitinib and Upadacitinib

- **Moderately to severely active UC, After anti-TNF, monotherapy**
- **Baseline labs including lipid panel, screen for VTE risk (personal/family history, obesity, immobility)**
- **Dosing:**
  - **Tofa: 10 mg BID for 8-16 weeks, then 10 or 5 mg BID in maintenance**
    - **Consider dose reduction (to 5 mg BID) in maintenance if deep remission[1]**
  - **Upa: 45 mg QD for 8 (-16) weeks, then 30 or 15 mg QD in maintenance**
- **Vaccinate for herpes zoster, can be after starting therapy- use attenuated vaccine (now FDA approved for ≥18 yo)**
- **Assess efficacy early: 2 weeks symptom assessment; 4-6 weeks FCP, repeat lipid panel**

Lab	At initiation	4-8 weeks	Every 3-6 months
Lymphocytes	✓	✓	✓
Neutrophils	✓	✓	✓
Hemoglobin	✓	✓	✓
Lipids	(✓)	✓	
Liver enzymes	✓	✓	✓

[1]Vermeire S, et al. *Gut.* 2021;15(7):1130-1141.

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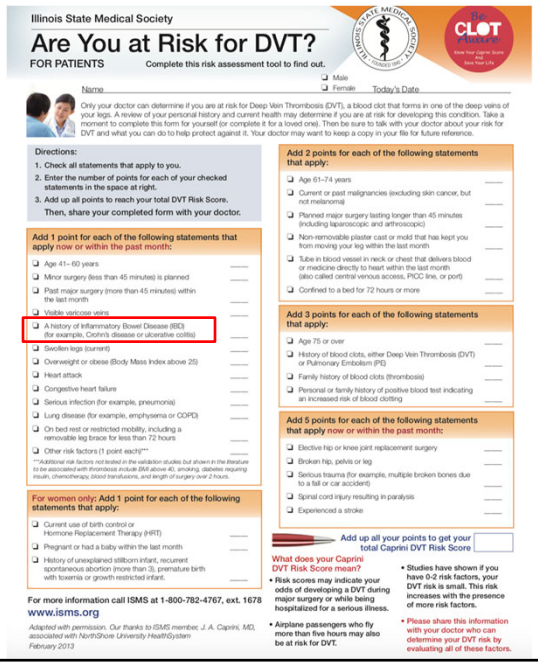
How To Screen People for Risk of DVT: The Caprini Score



Illinois State Medical Society

Are You at Risk for DVT?

FOR PATIENTS Complete this risk assessment tool to find out.

Name ☐ Male ☐ Female Today's Date

Only your doctor can determine if you are at risk for Deep Vein Thrombosis (DVT), a blood clot that forms in one of the deep veins of your legs. A review of your personal history and current health may determine if you are at risk for developing this condition. Take a moment to complete this form for yourself (or complete it for a loved one). Then be sure to talk with your doctor about your risk for DVT and what you can do to help protect against it. Your doctor may want to keep a copy in your file for future reference.

Directions:
1. Check all statements that apply to you.
2. Enter the number of points for each of your checked statements in the space at right.
3. Add up all points to reach your total DVT Risk Score.

Then, share your completed form with your doctor.

Add 1 point for each of the following statements that apply now or within the past month:
- ☐ Age 41–60 years
- ☐ Minor surgery (less than 45 minutes) is planned
- ☐ Past major surgery (more than 45 minutes) within the last month
- ☐ Visible varicose veins
- ☐ A history of Inflammatory Bowel Disease (IBD) (for example, Crohn's disease or ulcerative colitis)
- ☐ Swollen legs (current)
- ☐ Overweight or obese (Body Mass Index above 25)
- ☐ Heart attack
- ☐ Congestive heart failure
- ☐ Serious infection (for example, pneumonia)
- ☐ Lung disease (for example, emphysema or COPD)
- ☐ On bed rest or restricted mobility, including a removable leg brace for less than 72 hours
- ☐ Other risk factors (1 point each)***

*** Additional risk factors not tested in the validation studies but shown in the literature to be associated with thrombosis include BMI above 40, smoking, diabetes requiring insulin, chemotherapy, blood transfusions, and length of surgery over 2 hours.

For women only: Add 1 point for each of the following statements that apply:
- ☐ Current use of birth control or Hormone Replacement Therapy (HRT)
- ☐ Pregnant or had a baby within the last month
- ☐ History of unexplained stillborn infant, recurrent spontaneous abortion (more than 3), premature birth with toxemia or growth restricted infant.

Add 2 points for each of the following statements that apply:
- ☐ Age 61–74 years
- ☐ Current or past malignancies (excluding skin cancer, but not melanoma)
- ☐ Planned major surgery lasting longer than 45 minutes (including laparoscopic and arthroscopic)
- ☐ Non-removable plaster cast or mold that has kept you from moving your leg within the last month
- ☐ Tube in blood vessel in neck or chest that delivers blood or medicine directly to heart within the last month (also called central venous access, PICC line, or port)
- ☐ Confined to a bed for 72 hours or more

Add 3 points for each of the following statements that apply:
- ☐ Age 75 or over
- ☐ History of blood clots, either Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE)
- ☐ Family history of blood clots (thrombosis)
- ☐ Personal or family history of positive blood test indicating an increased risk of blood clotting

Add 5 points for each of the following statements that apply now or within the past month:
- ☐ Elective hip or knee joint replacement surgery
- ☐ Broken hip, pelvis or leg
- ☐ Serious trauma (for example, multiple broken bones due to a fall or car accident)
- ☐ Spinal cord injury resulting in paralysis
- ☐ Experienced a stroke

Add up all your points to get your total Caprini DVT Risk Score ☐

What does your Caprini DVT Risk Score mean?
- Risk scores may indicate your odds of developing a DVT during major surgery or while being hospitalized for a serious illness.
- Airplane passengers who fly more than five hours may also be at risk for DVT.
- Studies have shown if you have 0-2 risk factors, your DVT risk is small. This risk increases with the presence of more risk factors.
- Please share this information with your doctor who can determine your DVT risk by evaluating all of these factors.

For more information call ISMS at 1-800-782-4767, ext. 1678
www.isms.org

Adapted with permission. Our thanks to ISMS member, J. A. Caprini, MD, associated with NorthShore University HealthSystem
February 2013

Cronin M, et al. *Clin Appl Thromb.* 2019.

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S1P Receptor Modulators:
Ozanimod, Etrasimod

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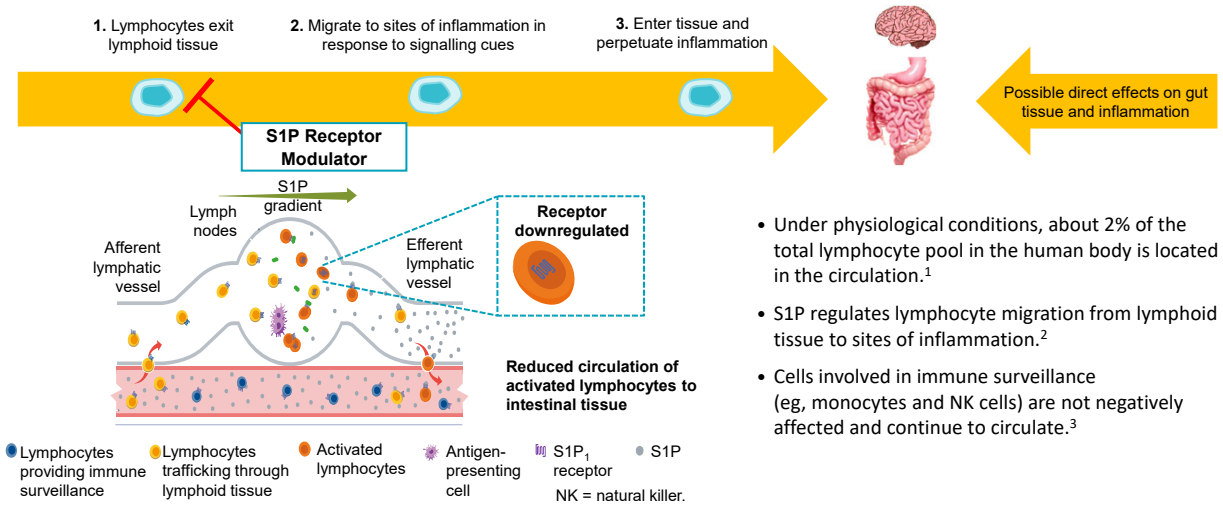
S1P Receptor Modulator Mechanism of Action



- Under physiological conditions, about 2% of the total lymphocyte pool in the human body is located in the circulation.[1]
- S1P regulates lymphocyte migration from lymphoid tissue to sites of inflammation.[2]
- Cells involved in immune surveillance (eg, monocytes and NK cells) are not negatively affected and continue to circulate.[3]

Scott FL, et al. *Br J Pharmacol*. 2016;173(11):1778-1792; Danese S, et al. *J Crohns Colitis*. 2018;12(suppl_2):S678-S686; Harris S et al. *Neurol Neuroimunol Neuroinflamm*. 2020;7(5):e839.

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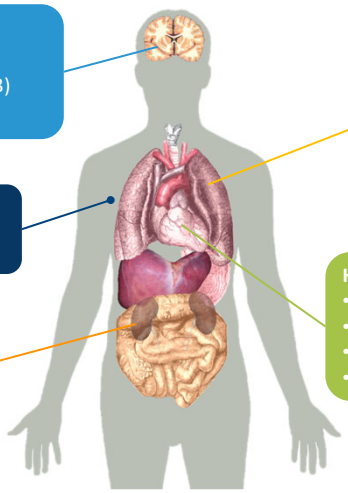
Sphingosine-1-Phosphate Receptors: $S1P_{1-5}$ (Ozanimod is S1P1, P5; Etrasimod is S1P1, P4, P5)

Brain vasculature
- Endothelial permeability (S1P1)
- Transcellular transport (S1P1 and/or S1P3)
- Hearing and balance (S1P2 and/or S1P3)

Lymph nodes
- Lymphocyte sequestration (S1P1)
- Dendritic cell sequestration (S1P3

Kidneys
- Vascular leakage (S1P1)
- Inflammation (S1P1)



Lungs
- Leakage (S1P1 and/or S1P3)
- Inflammation (S1P1 and/or S1P2 and/or S1P3)
- Airway hyper-responsiveness (multiple S1P receptors)

Heart
- Heart rate (S1P3)
- Myocyte survival (S1P2 and/or S1P3)
- Inflammation (S1P1 and/or S1P3)
- Vascular resistance (S1P2 and/or S1P3)

Adapted from Marsolais D, Rosen H. *Nat Rev Drug Discov*. 2009;8(4):297-307; Rivera J, et al. *Nat Rev Immunol*. 2008;8(10):753-763.

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Differentiation of S1P Modulators

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
First-dose monitoring	No	?

Ozanimod:
- Reduces lymphocytes: Level normalizes within 3 days to 3 months of cessation (healthy and MS populations)[1,2]
- Half-life: ~20 hours (metabolite ~11 days)[1,2]
- Has first-dose heart rate reduction; mitigated with dose escalation[1]

Etrasimod:
- Reduces lymphocytes: Level normalizes within 7 days of cessation[4]
- Half-life: ~33 hours[3]
- Has modest first-dose HR reduction; titration does not alter cardiovascular effects[6]

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.

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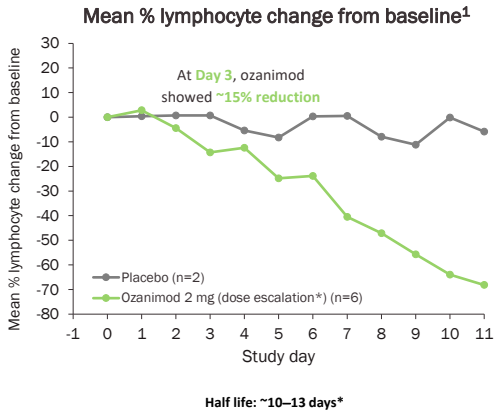
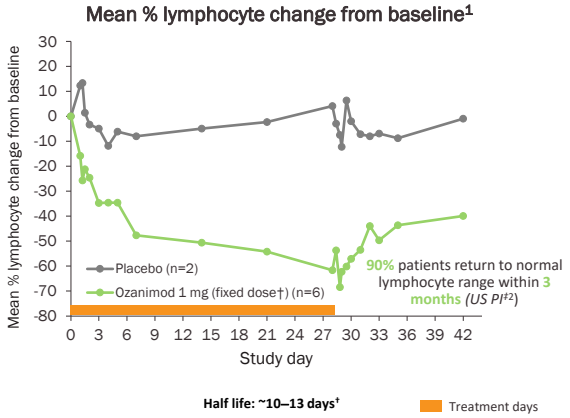
Ozanimod Phase 1 Data (Healthy Volunteers): Lymphocyte Reduction





[1]Tran JQ et al, *J Clin Pharmacol*. 2017;57:988–996.

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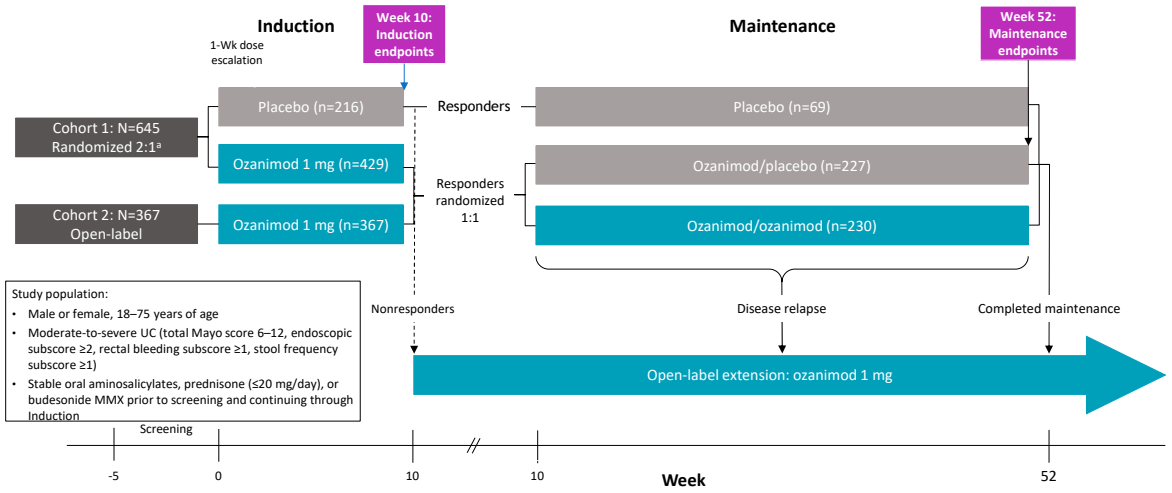
Ozanimod in Moderate-to-Severe UC
Phase 3, Randomized, Double-Blind, Placebo-Controlled True North Study



Danese S, et al. UEGW 2020. October 2020. Presentation LB10.
Sandborn WJ, et al. UEGW 2020. October 2020. Presentation LB5.
Sandborn WJ, et al. UEGW 2020. October 2020. Presentation LB02.

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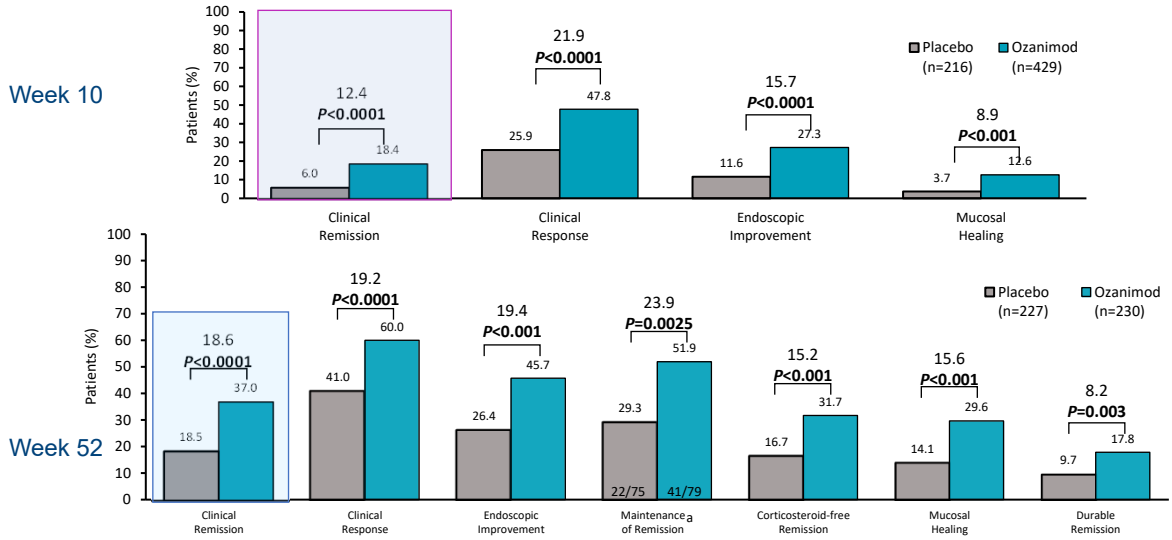
Ozanimod (S1P1,P5)for Induction and Maintenance of Moderately to Severely Active UC: TRUE NORTH Study



Sandborn WJ, et al. *N Engl J Med.* 2021 Sep 30;385(14):1280-1291.

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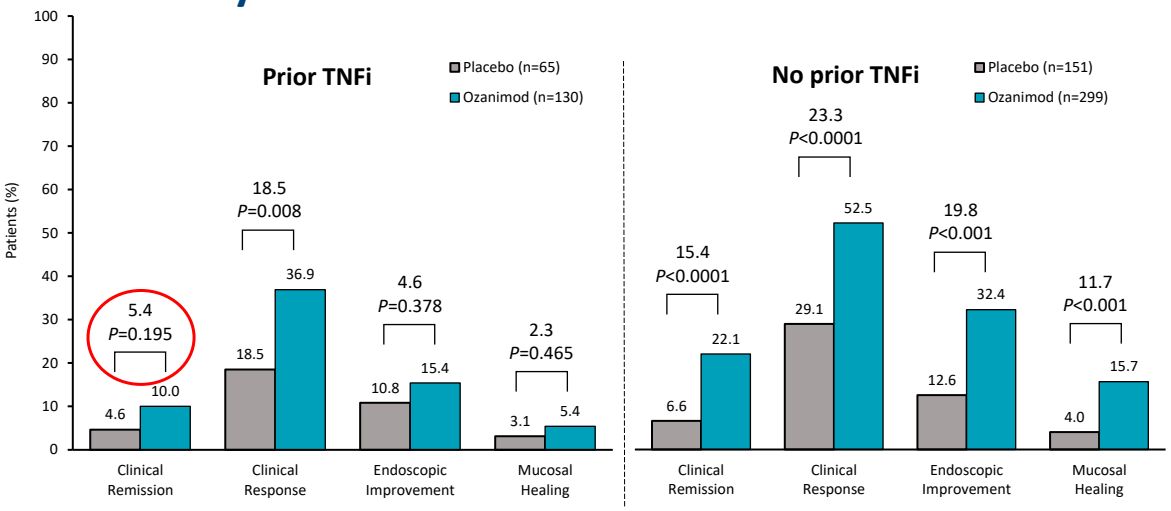
Ozanimod for Induction of UC by Prior TNF Inhibitor Use at Week 10



Sandborn WJ, et al. *N Engl J Med.* 2021 Sep 30;385(14):1280-1291.

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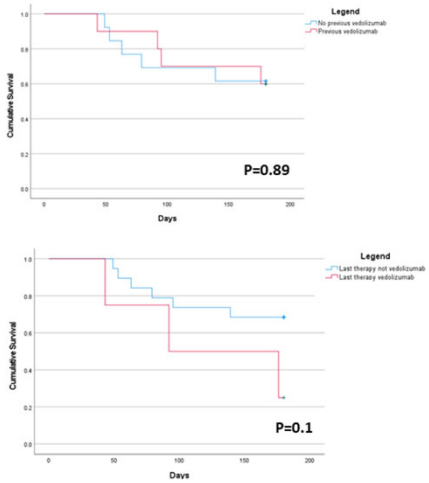
Ozanimod in the Treatment of Ulcerative Colitis: Initial Real-World Data from A Large Tertiary Center

Ozanimod is Equally Effective in Patients with Prior Vedolizumab Exposure (n=15)



Safety Profile

Patient	Week of event	Event	Outcome	Cessation of ozanimod
1	3	Acute gastroenteritis - son had similar illness	Resolved	No
2	2	Fatigue	Resolved	No
3	1	Nausea	Resolved	No
4	1	Mild liver derangement	Remained mild	No
5	4	Chest pain, stopped medication for 1 day, investigations normal	Resolved	No
6	3	Hypertensive urgency	Continued hypertension	Yes
7	1	Fatigue and headache	Improved upon stopping therapy	Yes

Cohen NA, et al. *Clin Gastroenterol Hepatol.* [Epub ahead of print April 2, 2022].

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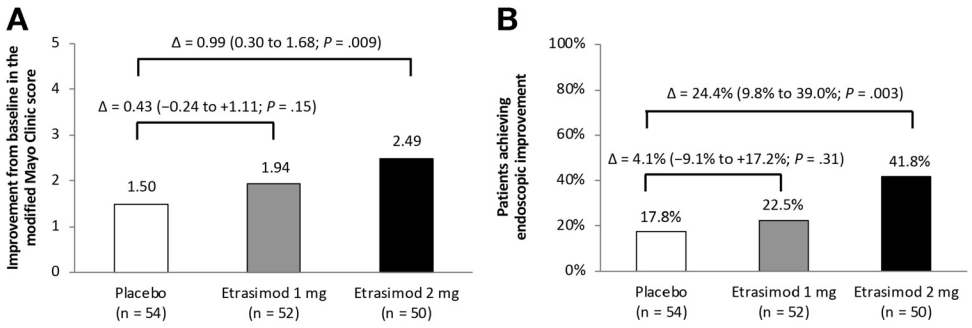
Etrasimod (S1P1,P4,P5) for Moderate-to-Severe UC Phase 2 Week 12



Sandborn WJ, et al. *Gastroenterology.* 2020;158(3):550-561.

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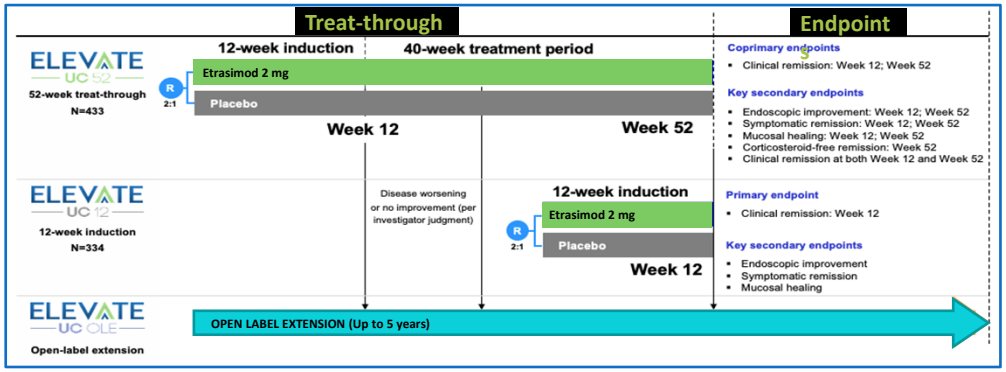
Etrasimod is Effective in Induction and Maintenance in UC ELEVATE UC 12 & 52: Trial Design

Methods

- ELEVATE UC 12 & 52: Phase 3 randomized, double-blinded, placebo-controlled trials evaluating etrasimod 2 mg daily in adults with UC
- Study population: Moderate-severe UC (16-80 years, Baseline Modified Mayo Score 4-9)



Sandborn, W, *et al*. Presented at DDW. May 2022. 968a

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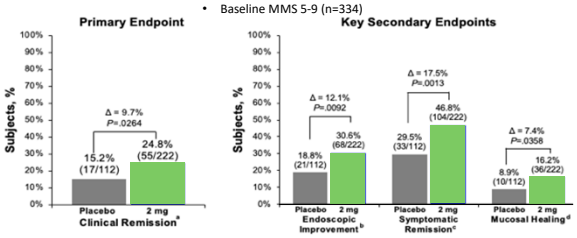
Etrasimod is Effective in Induction and Maintenance in UC
ELEVATE UC 12 & 52: Results

Results ELEVATE UC 12:

- N=354 randomized (Etrasimod 2mg N=238, Placebo N=116)
- N= 316 completed week 12

Figure 1: Primary and Key Secondary Efficacy Endpoints at Week 12

- Baseline MMS 5-9 (n=334)



Results ELEVATE UC 52:

- N = 433 (Etrasimod 2mg N=289, Placebo N=144)
- N = 207 completed week 52

Figure 2: Primary Endpoint Clinical Remission at week 12 and 52

- Baseline MMS 5-9 (n=409)

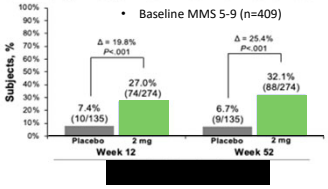
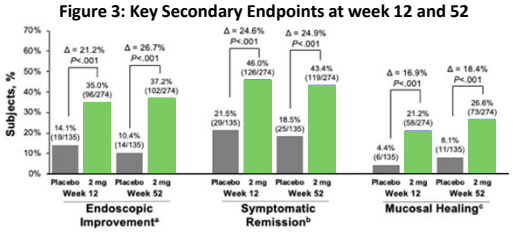


Figure 3: Key Secondary Endpoints at week 12 and 52



Sandborn, W, *et al*. Presented at DDW. May 2022. 968a.

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Safety of S1P Receptor Modulators in IBD

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Safety of Ozanimod in Moderate-to-Severe UC

	Induction Period (Week 10)		Maintenance Period (Week 52)	
	Placebo (n=216)	Ozanimod (n=429)	Placebo (n=227)	Ozanimod (n=230)
Any treatment-emergent adverse event (TEAE)	82 (38.0)	172 (40.1)	83 (36.6)	113 (49.1)
Common TEAEs (≥3% in any group)				
Anemia	12 (5.6)	18 (4.2)	4 (1.8)	3 (1.3)
Nasopharyngitis	3 (1.4)	15 (3.5)	4 (1.8)	7 (3.0)
Headache	4 (1.9)	14 (3.3)	1 (0.4)	8 (3.5)
Alanine aminotransferase increased	0	11 (2.6)	1 (0.4)	11 (4.8)
Gamma glutamyl transferase increased	0	5 (1.2)	1 (0.4)	7 (3.0)
Arthralgia	3 (1.4)	10 (2.3)	6 (2.6)	7 (3.0)
Serious TEAEs	7 (3.2)	17 (4.0)	18 (7.9)	12 (5.2)
UC exacerbation[a]	4 (1.9)	6 (1.4)	9 (4.0)	1 (0.4)
Anemia[a]	0	4 (0.9)	0	1 (0.4)
Appendicitis/Complicated appendicitis[a]	0	1 (0.2)	3 (1.2)	0
Severe TEAEs	4 (1.9)	14 (3.3)	9 (4.0)	9 (3.9)
TEAEs leading to treatment discontinuation	7 (3.2)	14 (3.3)	6 (2.6)	3 (1.3)

[a]Occurring in ≥2 patients in any group.

Sandborn WJ, et al. *N Engl J Med.* 2021 Sep 30;385(14):1280-1291.

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Etrasimod Safety in Moderate-to-Severe UC

	Placebo (n = 54)	Etrasimod 1 mg (n = 52)	Etrasimod 2 mg (n = 50
Patients with any TEAE, n (%)	27 (50.0)	31 (59.6)	28 (56.0)
Number of TEAEs, n	64	66	78
Patients with TEAEs leading to death, n	0	0	0
Patients discontinued due to ≥1 TEAE, n (%) [number of events]	0	3 (5.8) [5]	4 (8.0) [4]
Patients with serious TEAEs, n (%) [number of events]	6 (11.1) [7]	3 (5.8) [3]	0
TEAE relation to study drug, n (%) [no. of events]			
Not related	27 (50.0) [57]	30 (57.7) [61]	26 (52.0) [71]
Related	3 (5.6) [6]	4 (7.7) [5]	5 (10.0) [7]
Treatment-related TEAEs of special interest, n (%) [e]			
Atrioventricular block, second degree (type 1)	0	0	1 (2.0) [f]
Heart rate lowering	0	0	1 (2.0) [f]
TEAEs reported by ≥2 patients in any treatment group, n (%)			
UC—worsening	4 (7.4)	5 (9.6)	2 (4.0)
Upper respiratory tract infection	2 (3.7)	4 (7.7)	2 (4.0)
Nasopharyngitis	4 (7.4)	2 (3.8)	1 (2.0)
Anemia [g]	2 (3.7)	2 (3.8)	3 (6.0)
Urinary tract infection	0	2 (3.8)	2 (4.0)
Abdominal pain	2 (3.7)	2 (3.8)	0
Headache	1 (1.9)	0	3 (6.0)
Nausea	2 (3.7)	1 (1.9)	1 (2.0)
Fecal calprotectin increased	2 (3.7)	1 (1.9)	1 (2.0)
Arthralgia	2 (3.7)	1 (1.9)	1 (2.0)
Blood creatine phosphokinase increased	0	1 (1.9)	2 (4.0)
γ-Glutamyl transferase increased	0	1 (1.9)	2 (4.0)
Sinusitis	0	1 (1.9)	2 (4.0)
Fever	1 (1.9)	0	2 (4.0)
Anal fissure	2 (3.7)	0	0
Hyperlipasemia	0	0	2 (4.0)
Neutrophil count increased [h]	0	2 (3.8)	0

Modified from Sandborn WJ, et al. *Gastroenterology.* 2020;158(3):550-561.

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Etrasimod Safety in Moderate-to-Severe UC

	Placebo (n = 54)	Etrasimod 1 mg (n = 52)	Etrasimod 2 mg (n = 50
Patients with any TEAE, n (%)	27 (50.0)	31 (59.6)	28 (56.0)
Number of TEAEs, n	64	66	78
Patients with TEAEs leading to death, n	0	0	0
Patients discontinued due to ≥1 TEAE, n (%) [number of events]	0	3 (5.8) [5]	4 (8.0) [4]
Patients with serious TEAEs, n (%) [number of events]	6 (11.1) [7]	3 (5.8) [3]	0
TEAE relation to study drug, n (%) [no. of events]			
Not related	27 (50.0) [57]	30 (57.7) [61]	26 (52.0) [71]
Related	3 (5.6) [6]	4 (7.7) [5]	5 (10.0) [7]
Treatment-related TEAEs of special interest, n (%) [e]			
Atrioventricular block, second degree (type 1)	0	0	1 (2.0) [f]
Heart rate lowering	0	0	1 (2.0) [f]
TEAEs reported by ≥2 patients in any treatment group, n (%)			
UC—worsening	4 (7.4)	5 (9.6)	2 (4.0)
Upper respiratory tract infection	2 (3.7)	4 (7.7)	2 (4.0)
Nasopharyngitis	4 (7.4)	2 (3.8)	1 (2.0)
Anemia [g]	2 (3.7)	2 (3.8)	3 (6.0)
Urinary tract infection	0	2 (3.8)	2 (4.0)
Abdominal pain	2 (3.7)	2 (3.8)	0
Headache	1 (1.9)	0	3 (6.0)
Nausea	2 (3.7)	1 (1.9)	1 (2.0)
Fecal calprotectin increased	2 (3.7)	1 (1.9)	1 (2.0)
Arthralgia	2 (3.7)	1 (1.9)	1 (2.0)
Blood creatine phosphokinase increased	0	1 (1.9)	2 (4.0)
γ-Glutamyl transferase increased	0	1 (1.9)	2 (4.0)
Sinusitis	0	1 (1.9)	2 (4.0)
Fever	1 (1.9)	0	2 (4.0)
Anal fissure	2 (3.7)	0	0
Hyperlipasemia	0	0	2 (4.0)
Neutrophil count increased [h]	0	2 (3.8)	0

Modified from Sandborn WJ, et al. *Gastroenterology.* 2020;158(3):550-561.

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Practical Approach to Ozanimod

- **Moderately to severely active UC, monotherapy**
- **Baseline labs, ECG, eye exam (only in patients with diabetes or uveitis**
- **Dosing:**
  - **0.23 mg BID for 1-4 days, then 0.46 mg for day 5-7, 0.92 mg on day 8 and after**
- **Vaccinate for varicella zoster, 4-6 weeks prior to starting therapy**
- **Assess efficacy early: 2 weeks symptom assessment; 4-6 weeks FCP, repeat lipid panel**

Lab	At initiation	4-8 weeks	Every 3-6 months
Lymphocytes	✓	✓	✓
Neutrophils	✓	✓	✓
Hemoglobin	✓	✓	✓
Liver enzymes	✓	✓	✓

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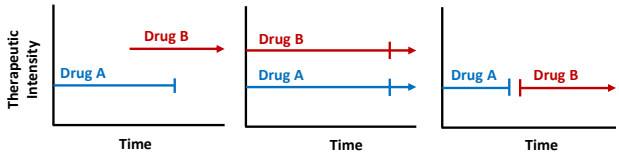
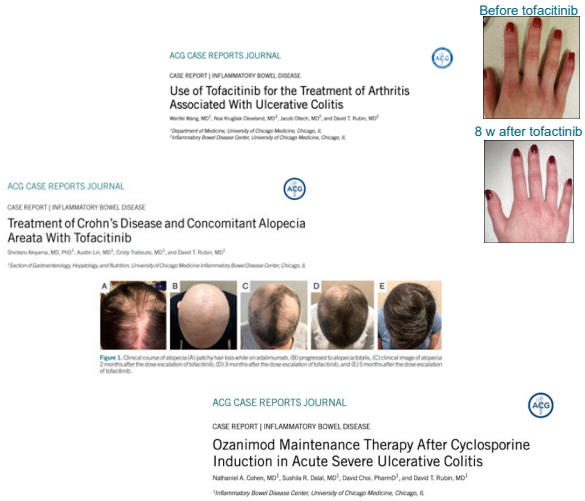
Novel Considerations for Small Molecules

- Intermittent (pulse) therapy?
- Induction, followed by different strategy for maintenance
- Combination therapy
- What else?





Wang W, et al. *ACG Case Rep J.* 2019;6(9):e00226.
Akiyama S, et al. *ACG Case Rep J.* 2021;8(11):e00690.
Cohen NA, et al. *ACG Case Rep J.* 2022;9(7):e00832.

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Case Examples

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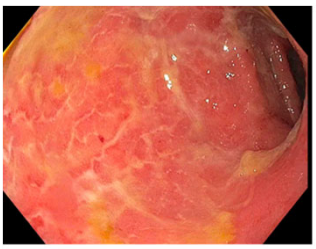
Case Example: 32 yo Medical Resident with Resistant UC

- 32 yo medical resident with left-sided ulcerative colitis at age 9
- Previous therapy with mesalamine, infliximab, adalimumab, vedolizumab, ustekinumab, tofacitinib
- Presented with urge incontinence 2/month and 6-8 stools per day with bleeding (SCCAI=9)
- Current meds: golimumab and budesonide foam



- Started on upadacitinib 45 mg daily (stopped golimumab and budesonide)
- Improved symptoms within 2 weeks

	CRP (mg/L)	FCP (ug/g)	Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL Cholesterol (mg/dL)	Hemoglobin	Albumin
Baseline Labs	4	680	167	63	61	92	14.9 g	4.6 g/dL
Week 4 Labs								
Week 12 Labs								

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Case Example: 32 yo Medical Resident with Resistant UC

- Continued to feel well
- Seen for follow-up labs and in clinical remission
- Repeat flexible sigmoidoscopy performed

	CRP (mg/L)	FCP (ug/g)	Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL Cholesterol (mg/dL)	Hemoglobin	Albumin
Baseline Labs	4	680	167	63	61	92	14.9 g	4.6 g/dL
Week 4 Labs	2.2	5.27	182	81	39	93		
Week 10 Labs	0.6	-	-	-	-	-	13.5 g	4.2 g/dL

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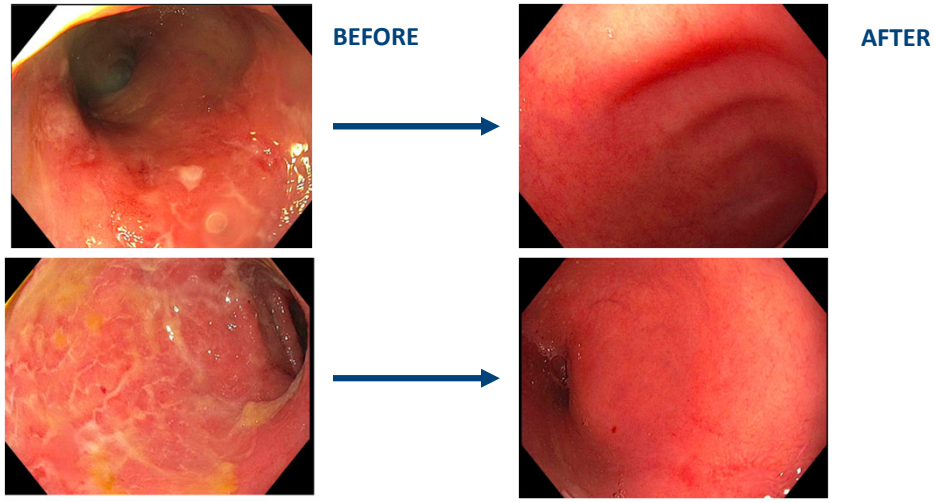
Case: Endoscopic Improvement on Upadacitinib at 13wks



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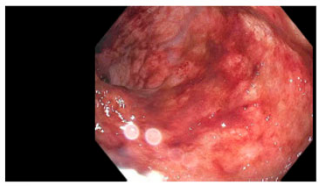
Case: Undergraduate Student with Ulcerative Proctitis

- 20 yo undergraduate student diagnosed with UP diagnosed 9 months prior
- Previous therapy with mesalamine suppositories and enemas, steroid suppositories, and oral mesalamine
- Presented with urgency, rectal bleeding, 4 BM/day, no incontinence (SCCAI=7)
- Current meds: oral mesalamine and steroid suppositories

- Started on ozanimod 1 mg daily (stopped mesalamine and steroid supp)
- Improved symptoms within 12 weeks, biochemical makers



	CRP (mg/L)	FCP (mcg/g)	Absolute Lymphocytes Interface External (cells/uL)	Lymphocytes Interface External (%)
Baseline Labs	1.4	1100	1800	27.6
Week 6 Labs	31.1	1145	776	19.9
Week 20	<1.0	38	900	18

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Summary of Small Molecules in IBD 2022

Clinical Scenario	JAK1-3 Inhibitor	JAK1 Inhibitor		S1P Receptor Modulator	
	Tofacitinib (IR: 10 mg BID, 5 mg BID) (ER: 11, 22 mg QD)	Upadacitinib (45 mg PO QD for 8 weeks, then 15 mg or 30 mg QD)	Filgotinib (200 mg daily)	Ozanimod (titration in week 1, then 1 mg daily)	Etrasimod (2mg daily)
New UC, failing 5-ASA	X	X	Not available in the U.S.	✓	In development
Moderate to severe UC, failing anti-TNF	✓	✓		✓	
Low albumin	✓	✓		probably	
Concomitant MS and UC	X	X		✓	
Peripheral arthropathy	✓	✓		probably	
Axial spondyloarthropathy	✓	✓		unknown	
Inpatient acute severe UC	maybe	unknown		unknown	
History of heart disease	Not if atherosclerotic	Not if atherosclerotic		Not if type 2 heart block	
History of eye disease, specifically uveitis or DM-related	✓	✓		Not recommended	

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Questions?

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Samir A. Shah, MD, FACG

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ACG Hepatology Circle
ACG Functional GI Health and Nutrition Circle
ACG GI Circle
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