2022 SCSG GI SYMPOSIUM

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Best of DDW 2022: Inflammatory Bowel Disease

Jenny Sauk, MD
Associate Professor of Medicine
Vatche and Tamar Manoukian Division of Digestive Diseases at David Geffen School of Medicine at UCLA

Parambir Dulai, MD
Associate Professor of Medicine
Director of GI Clinical Trials and Precision Medicine
Division of Gastroenterology, Northwestern University

Disclosures

Parambir Dulai, MD

- Research Support: Takeda, Pfizer
- Consulting: Johnson and Johnson, Gilead, Lily, BMS, Novartis, Pfizer, Takeda
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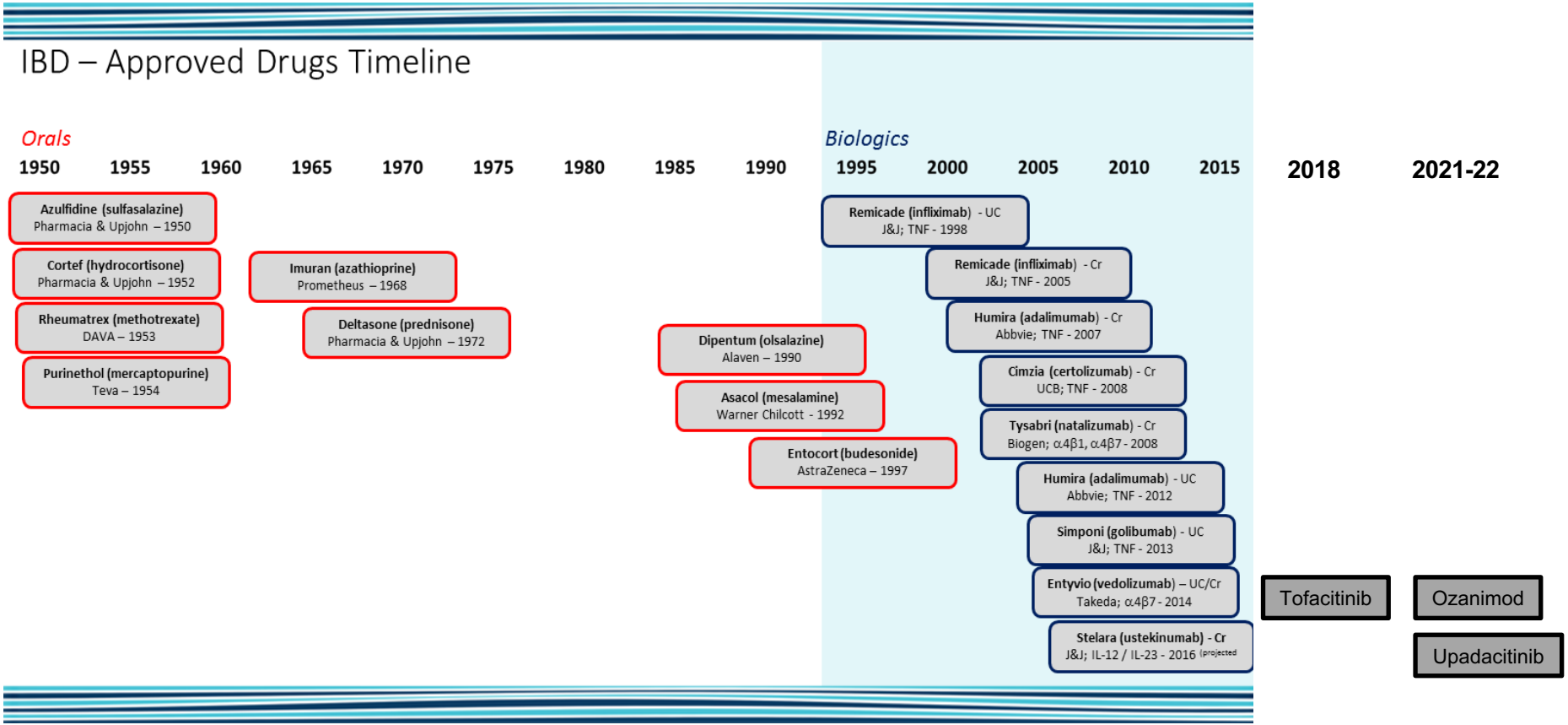
Jenny Sauk, MD

- Speaker's Bureau: Abbvie
- Consultant: CorEvitas
- Advisory Board: Prometheus

- Acknowledgements: Andres Yarur; Bruce Sands; Bharati Kochar

IBD: FDA Approved Medications



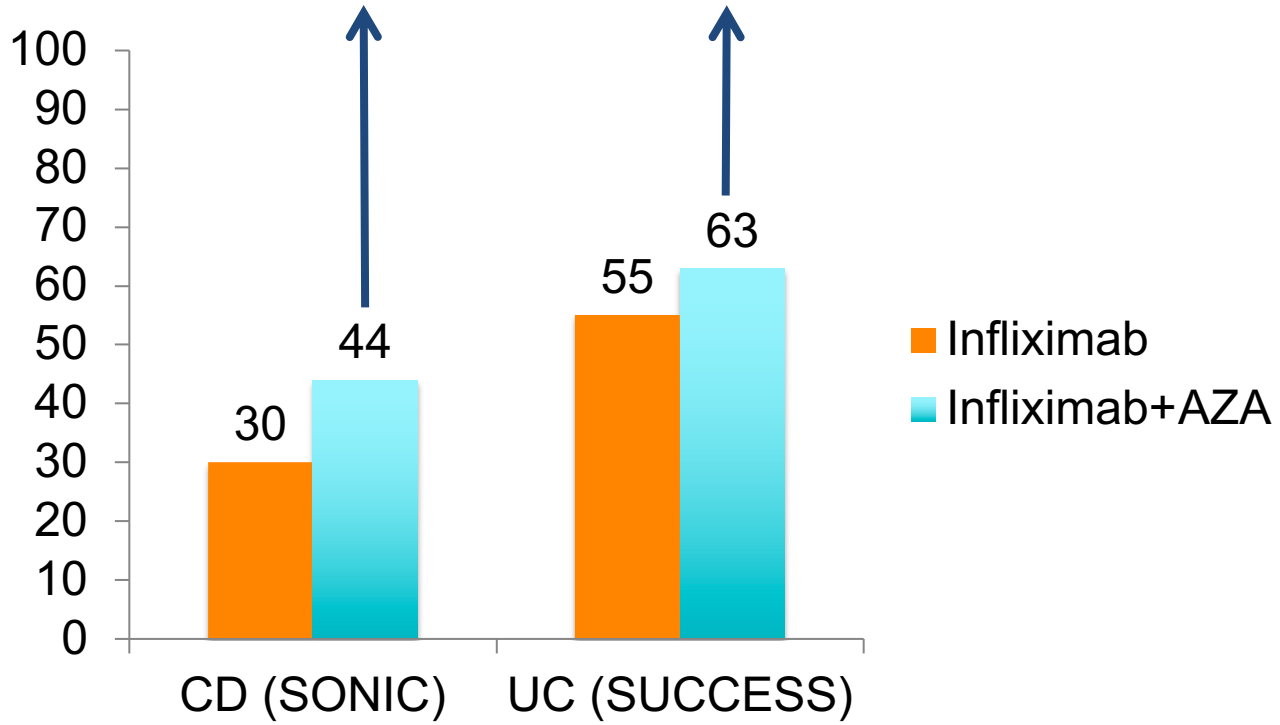
Current Biologic Therapies in Crohn's Disease: Room for Improvement

	Clinical Response	Week	Overall Remission	Week
CHARM - Adalimumab	60%	4	25.2%	54
ACCENT I- Infliximab	58.5%	2	16.7%	54
GEMINI II- Vedolizumab	37.5%	6	17.7%	52
UNITI II- Ustekinumab	58%	8	36.3%	50

UC Large Registry Trials: Effect Sizes Clinical Remission

Therapy Arm	Placebo Arm	Effect Size	Trial
38.8%	14.9%	**23.9%**	ACT 1- Infliximab
33.9%	5.7%	**28.2%**	ACT 2- Infliximab
16.5%	9.3%	**7.2%**	ULTRA 2- Adalimumab
17.8%	6.4%	**11.4%**	PURSUIT SC- Golimumab
16.9%	5.4%	**11.5%**	GEMINI- Vedolizumab
15.5%	5.3%	**10.2%**	UNIFI- Ustekinumab
18.5%	8.2%	**10.3%**	OCTAVE 1- Tofacitinib
16.6%	3.6%	**13%**	OCTAVE 2- Tofacitinib
18.4%	6%	**12.4%**	TRUE NORTH- Ozanimod

Unmet need: Mucosal Healing with anti-TNFα +/-immunomodulator



Colombel JF *et al. N Engl J Med*. 2010 Apr 15;362(15):1383-95
Panaccione R *et al.* Gastroenterol 2014 Feb;146(2):392-400.e3.

Therapeutic Ceiling in IBD

Overcome Treatment Plateau

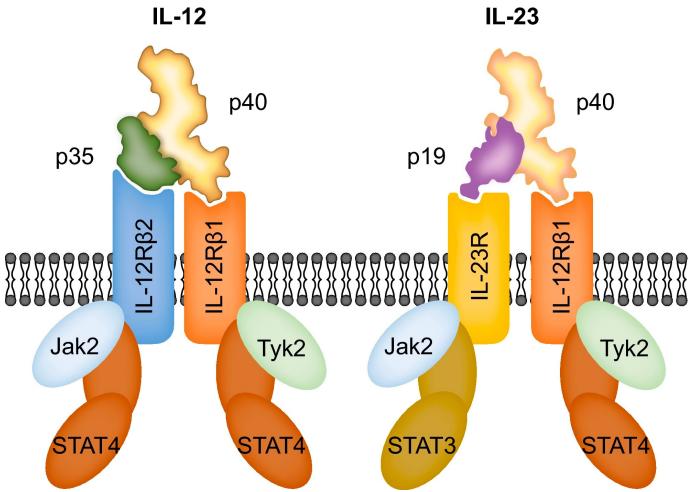
- Therapeutics: Novel Mechanisms of Action
- Longer Induction Period?
- Optimizing Drug Levels: Therapeutic Drug Monitoring
- Combination Biologic Therapies?

Safety Considerations

- Treatment Withdrawal
- IBD Therapeutics in Elderly

Therapeutics: Novel Mechanisms of Action

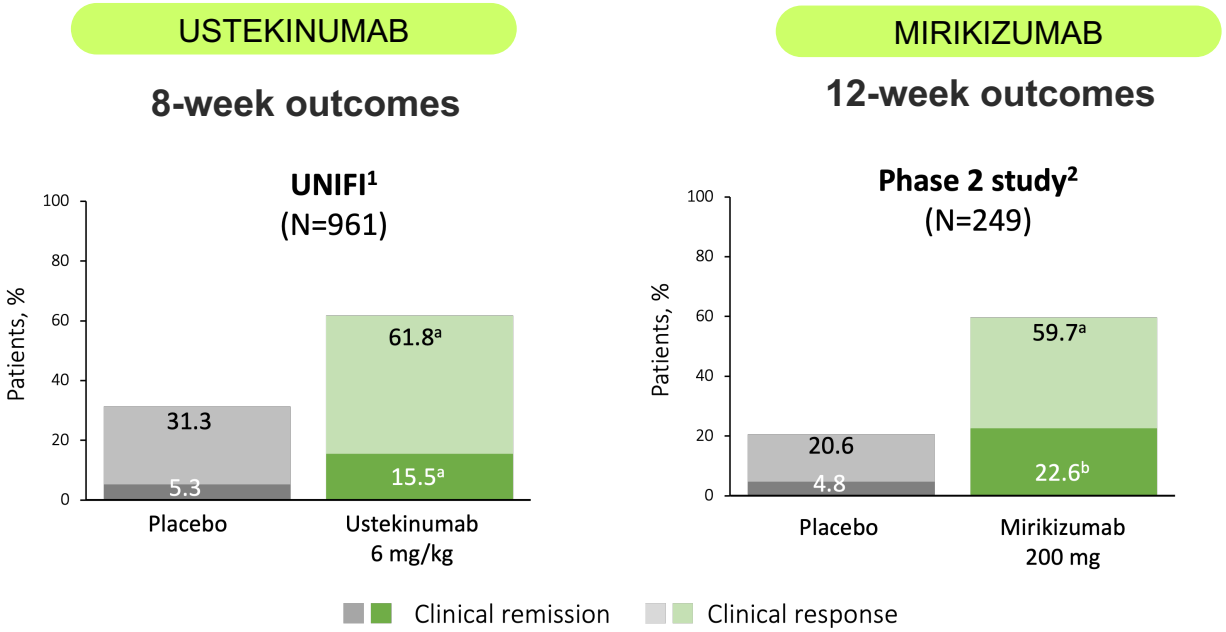
IL-23 Inhibitors Mechanism and p19 Antibodies in Development for UC and CD



Agent	Development phase			
	1	2	3	Approved
Risankizumab	UC, CD			Psoriasis
Guselkumab	UC, CD			Psoriasis, PsA
Brazikumab	UC, CD			
Mirikizumab	UC, CD			

1. ClinicalTrials.gov. www.clinicaltrials.gov. Accessed January 10, 2022. 2. D'Haens G et al. *J Crohns Colitis*. 2021 Nov 10;jjab201. doi: 10.1093/ecco-jcc/jjab201. Online ahead of print.3. Danese S et al. J Crohns Colitis. 2018;S578-S686.

Induction Studies in UC With IL-12/23 and IL-23 Inhibitors



[a]*P*<0.001 vs placebo; [b]*P*=0.004 vs placebo.

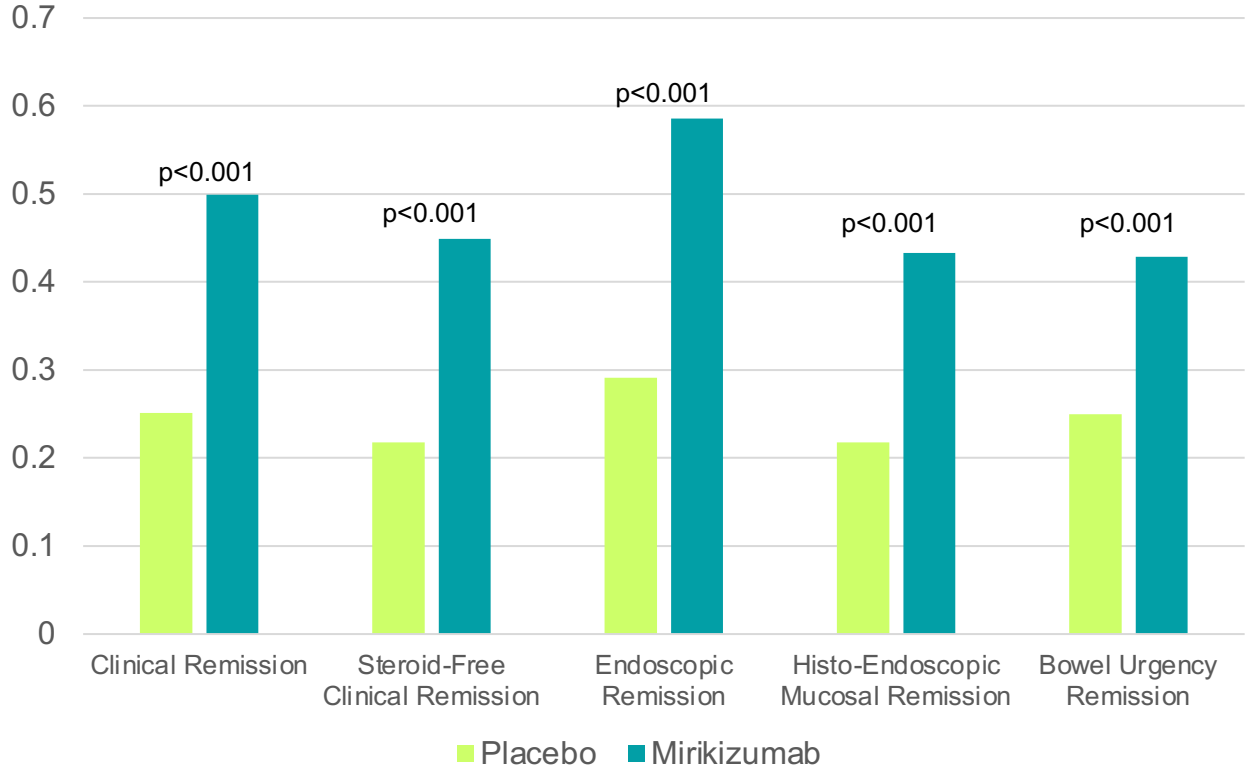
1. Sands BE et al. *N Engl J Med.* 2019;381(13):1201-1214. 2. Sandborn WJ et al. *Gastroenterology*. 2020;158(3):537-549.

Efficacy and Safety of Mirikizumab as Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis (Dubinsky MC. Et al.) – Phase 3 trial

- Mirikizumab is a humanized IgG4 monoclonal Ab against p19
- LUCENT-1 phase 3 induction study superiority of Mirikizumab to placebo for induction of clinical remission and other clinical, endoscopic, and histologic endpoints in moderate to severe UC[1]
  - Given as 300mg IV infusion every 4 weeks for 12 weeks
- LUCENT-2 is a maintenance study in which responders to induction re-randomized 2:1 to Mirikizumab or Placebo (PBO)
  - Miri dosing 200mg SC every 4 weeks for 40 weeks

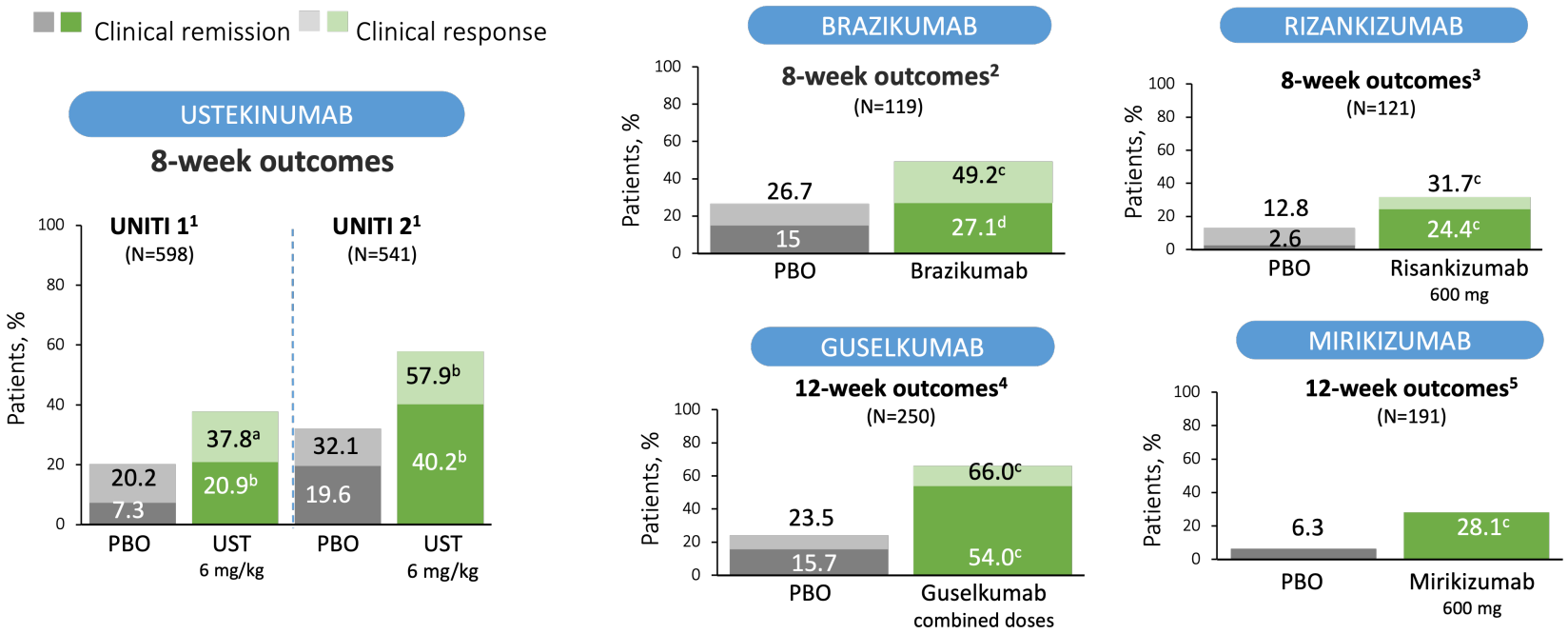
1. D'Haens et al. ECCO 2022

Maintenance Efficacy



Clinical remission: Stool frequency = 0 with a >1 point decrease from baseline, and Rectal bleeding = 0; Endoscopic remission: Mayo endoscopic sub-score of 0 or 1; HEMR: Geboes < 2b and endoscopic remission

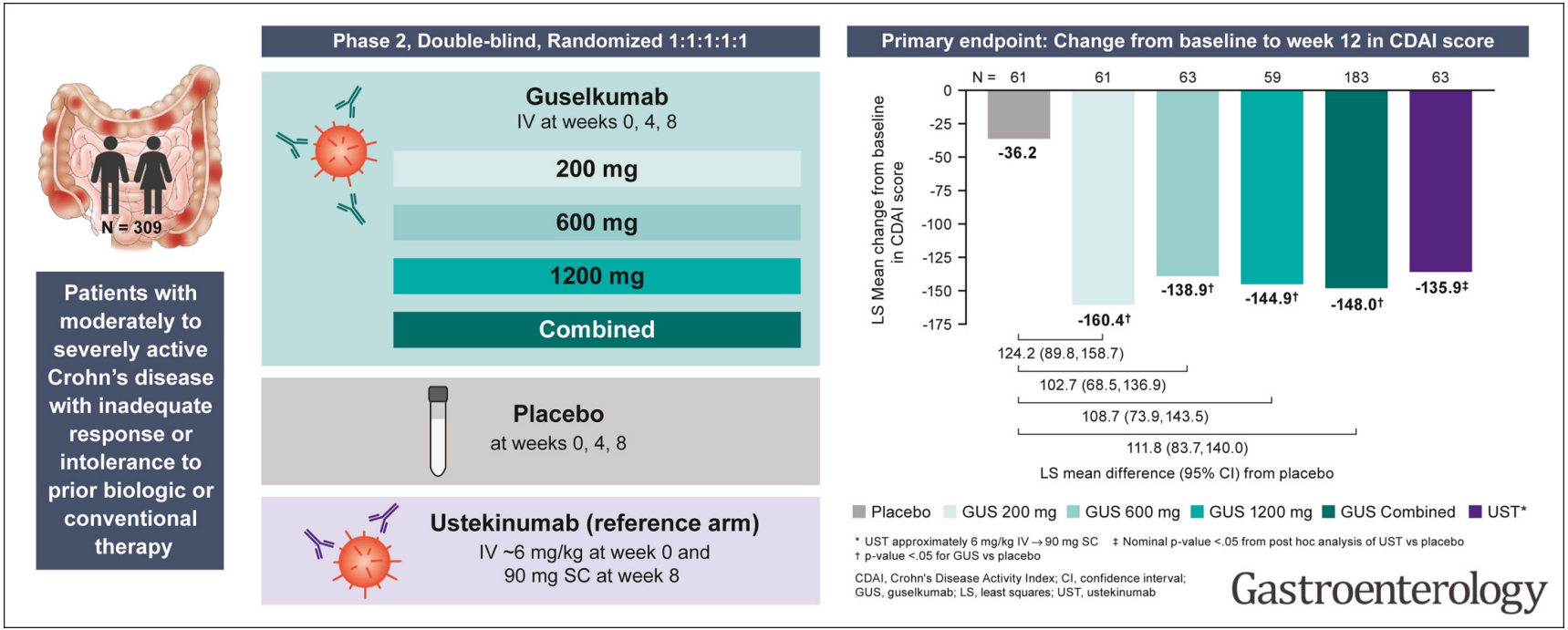
Phase 2 Induction Studies in CD With IL-23 Inhibitors



[a]*P*=0.001 vs placebo; [b]*P*<0.001 vs placebo; [c]*P*=0.05; [d]*P*=NS.
BID, twice daily; FIL, filgotinib; PBO, placebo; TOFA, tofacitinib; UPA, upadacitinib.
1. Feagan BG, et al. *N Engl J Med*. 2016;375(20):1946-1960. 2. Sands BE, et al. *Gastroenterology*. 2017;153(1):77-86.e6. 3.Feagan BG et al. *Lancet*. 2017;389(10080):1699-1709. 4. Danese 5. Sands BE et al. Presented at: Digestive Disease Week 2019; May 18-21, 2019; San Diego, CA. Abstract 1003.

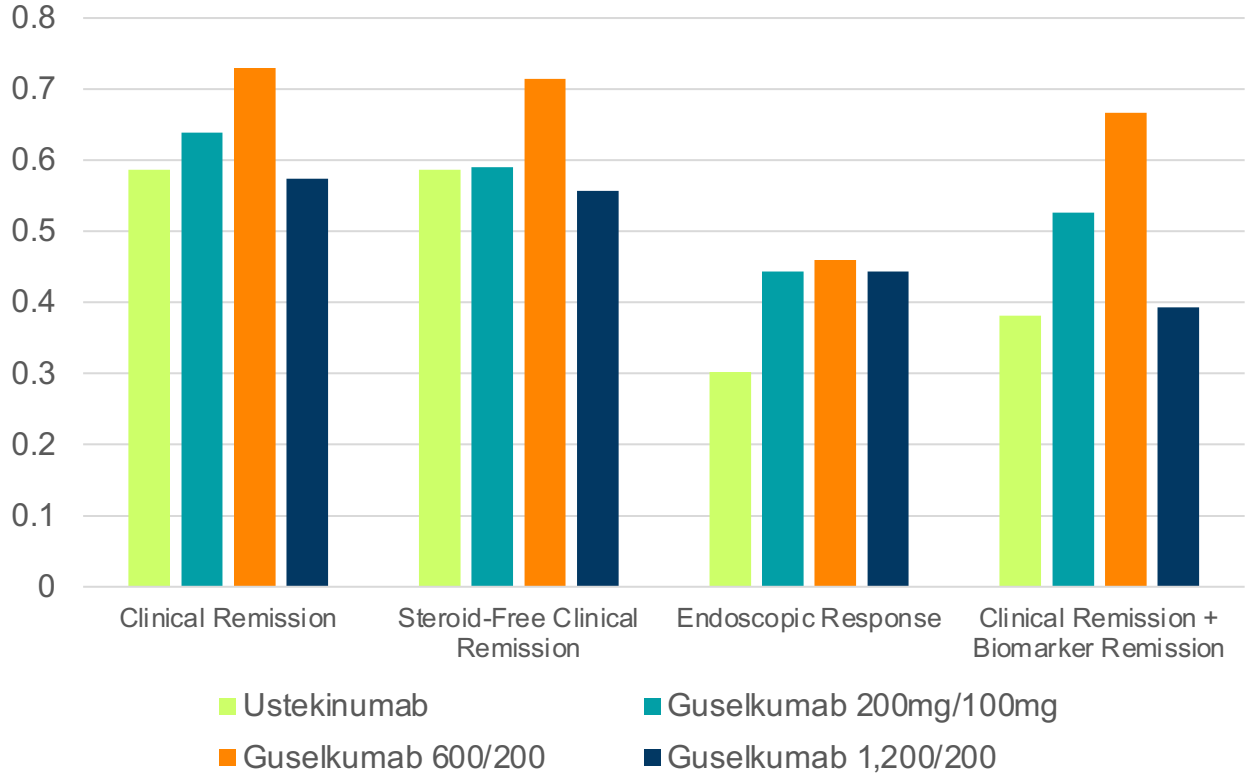
Efficacy and Safety of Guselkumab Maintenance Therapy in Patients with Moderate to Severe Crohn's Disease (Panaccione R. et al.) – Phase 2 trial

- Guselkumab is a humanized monoclonal IgG1 Ab directed against p19



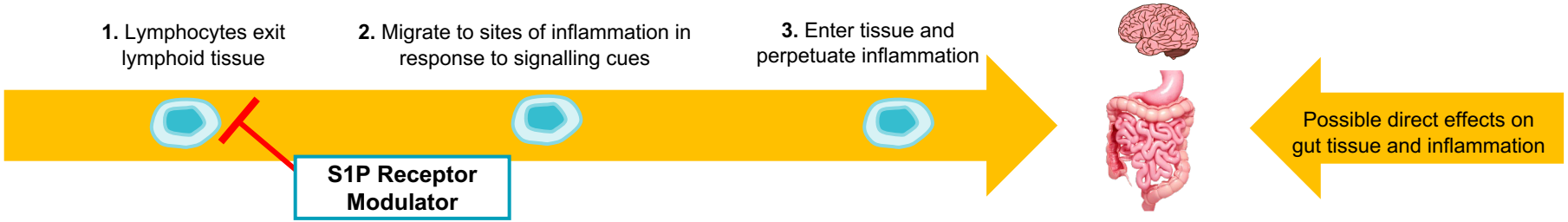
Sandborn et al. Gastroenterology 2022

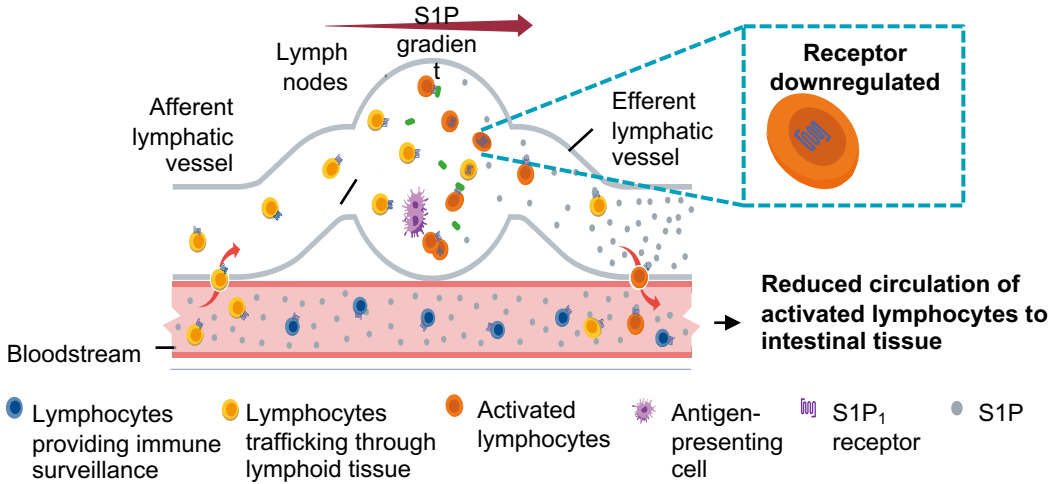
Maintenance Efficacy – week 48



Clinical Remission: CDAI < 150; Endoscopic Response: > 50% improvement in SES-CD from baseline; Biomarker Remission: CRP < 3 or Fcal < 250

S1P Receptor Modulator Mechanism of Action

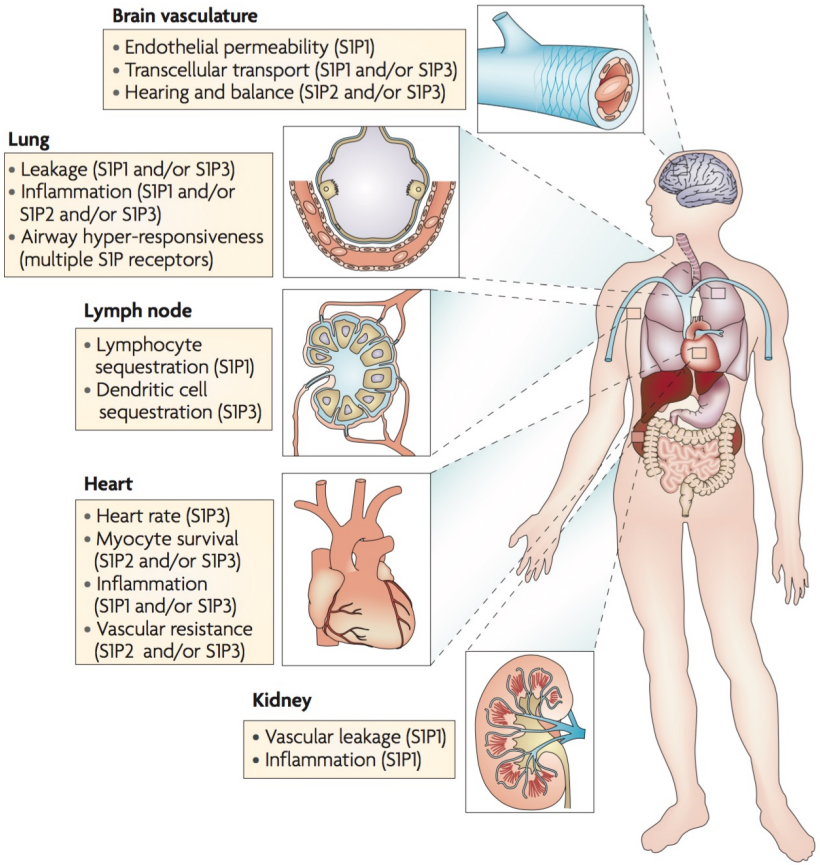




- Under physiological conditions, about 2% of the total lymphocyte pool in the human body located in the circulation.[1]
- S1P regulates lymphocyte migration from lymphoid tissue to sites of inflammation.[2]
- Cells involved in immune surveillance (eg, monocytes and NK cells) are not negatively affected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

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

Sphingosine-1-phosphate receptors: S1P1-5



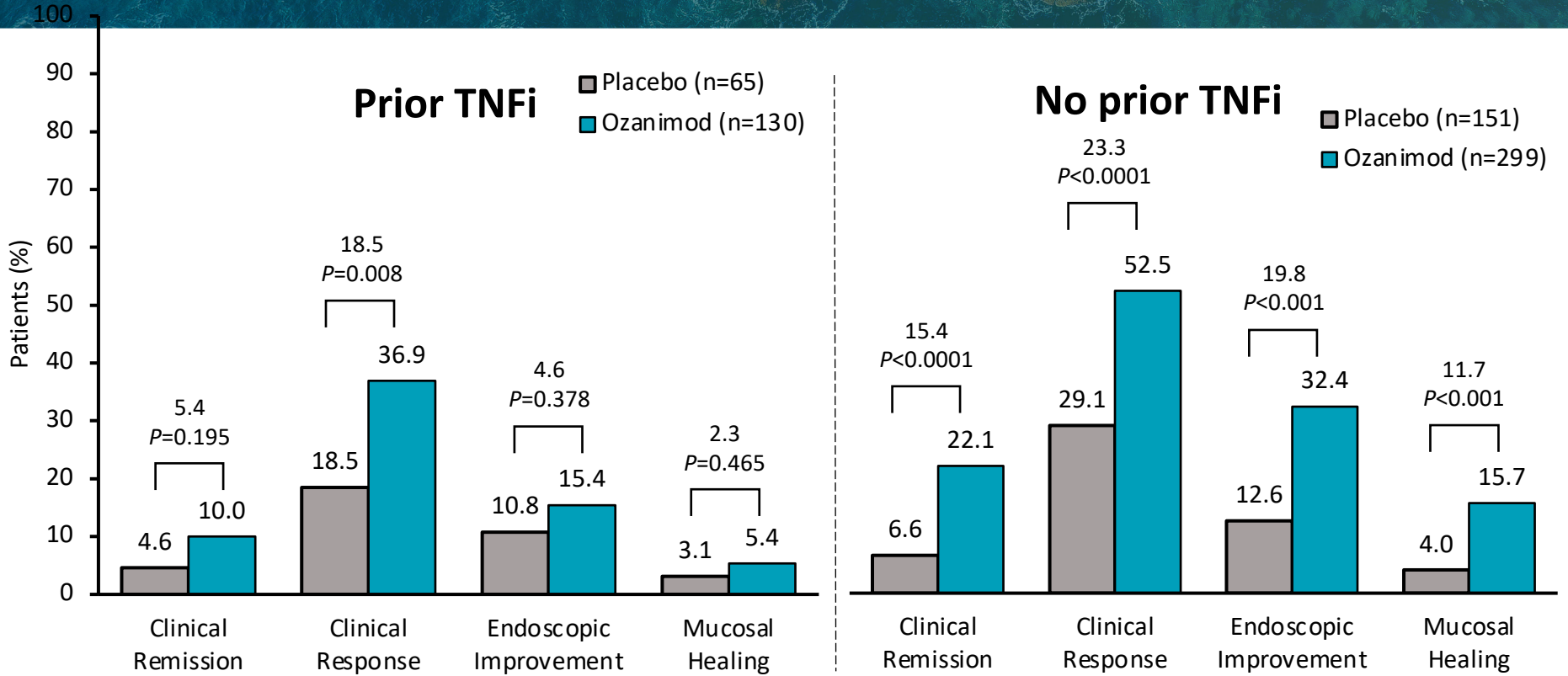
Fingolimod: Nonselective S1P1 to S1P5 receptor modulator[2,3]

Ozanimod: Selective S1P1 and S1P5 receptor modulator[4,5]

Etrasimod: Selective S1P1, S1P4, and S1P5 receptor modulator[2]

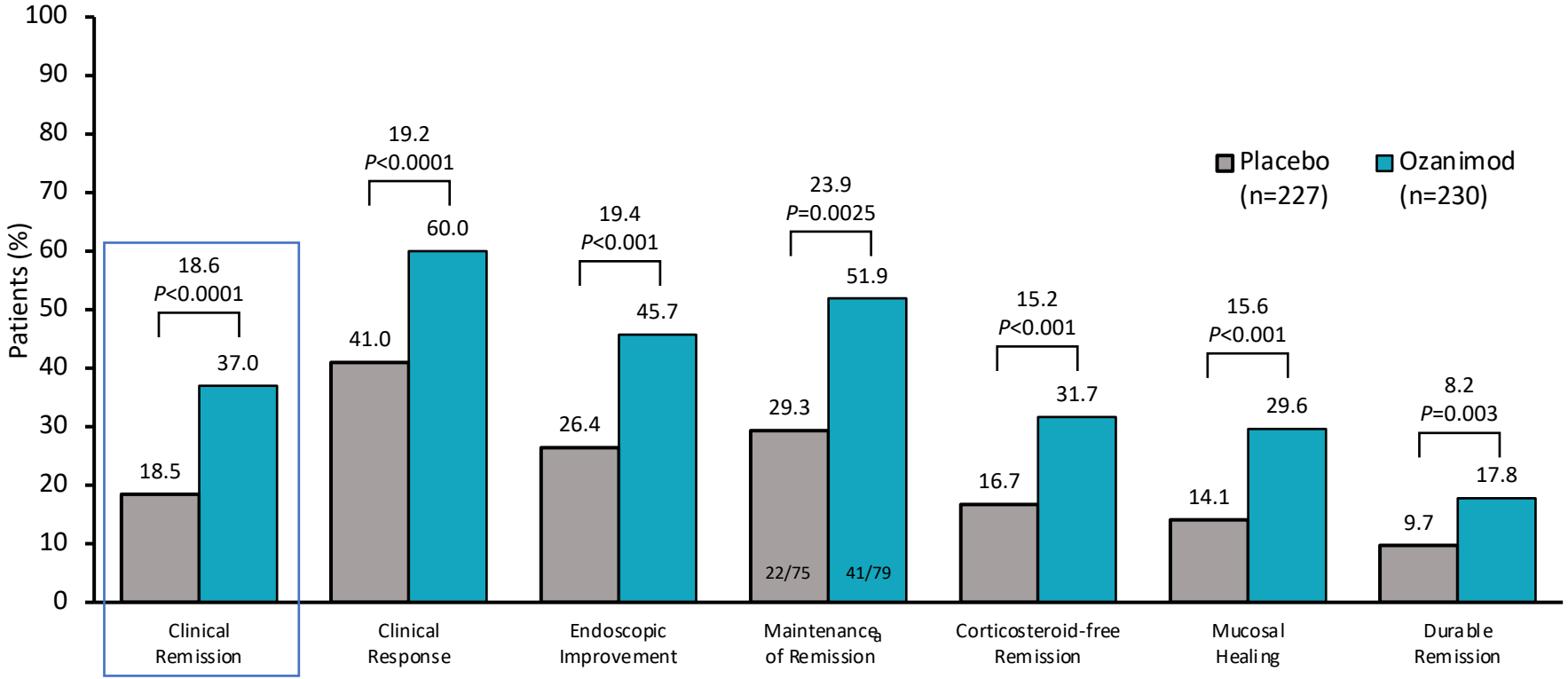
1. Peyrin-Biroulet L, et al. *Autoimmun Rev*. 2017;16(5):495-503.
2. Sandborn WJ, et al. *Gastroenterology*. 2020;158(3):550-561.
3. Scott FL, et al. *Br J Pharmacol*. 2016;173(11):1778-1792.
4. Sabino J, et al. *Therap Adv Gastroenterol*. 2019;(12):1-14.
5. Tran JQ, et al. *J Clin Pharmacol*. 2017;57(8):988-996.

Efficacy of Ozanimod in Moderate-to-Severe UC by Prior TNF Inhibitor Use at Week 10 – True North Study



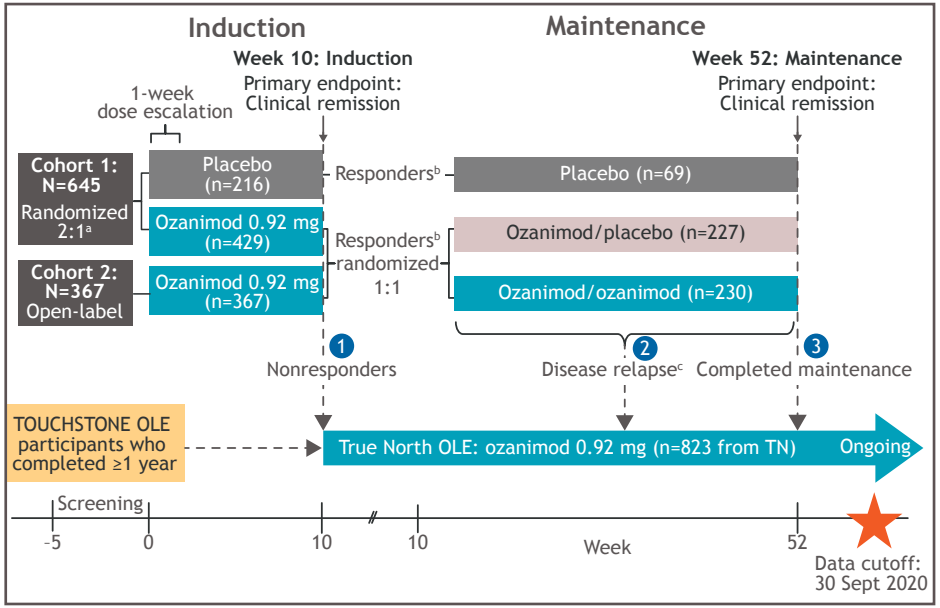
Sandborn WJ, et al. New Engl J Med 2021.

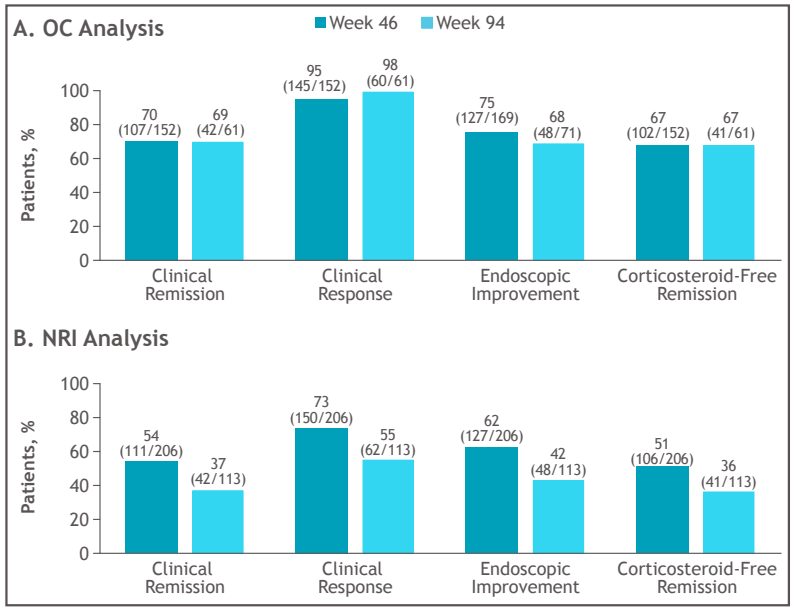
Efficacy of Ozanimod in Moderate-to-Severe UC at Week 52 (Maintenance, ITT) – True North Study



Sandborn WJ, et al. New Engl J Med 2021.

Long-Term Use of Ozanimod in Patients with Moderate to Severe UC (Wolf DC. Et al.)





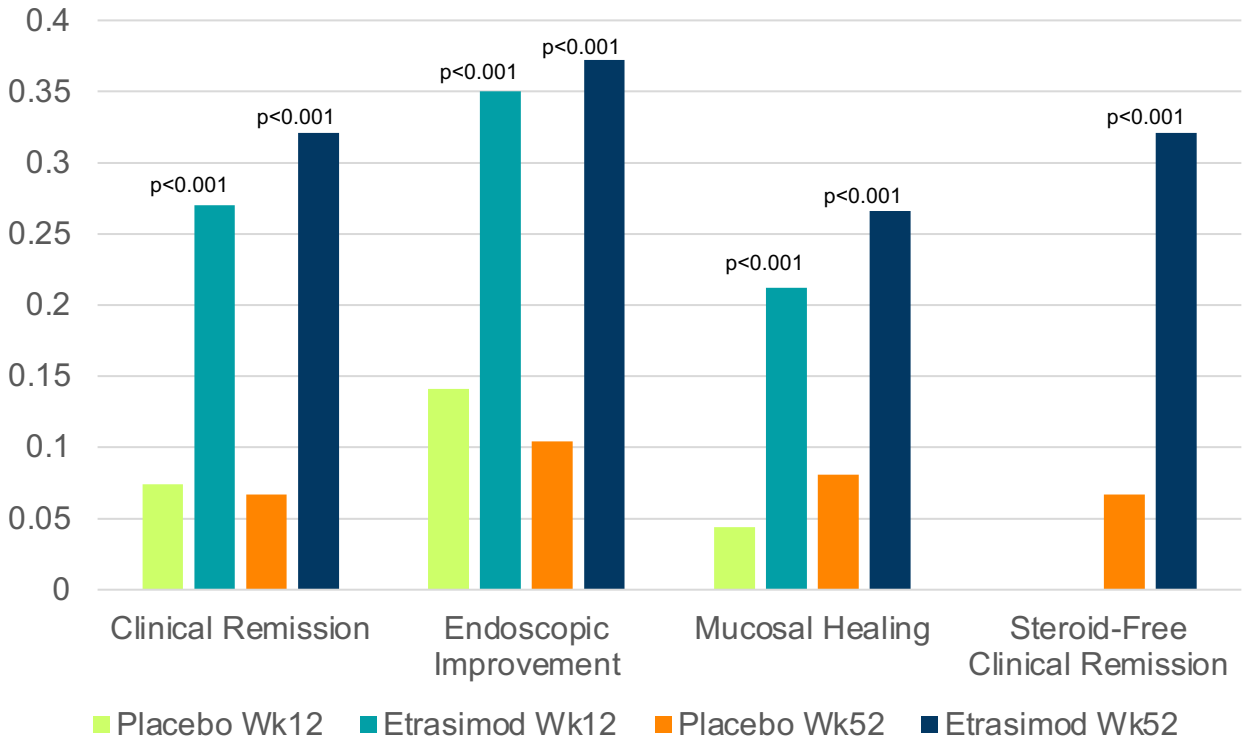
Nearly 60% of those losing response after ozanimod withdrawal were recaptured

Etrasimod 2mg once daily for Moderate to Severe UC (Sandborn et al.) – Phase 3

- Etrasimod is oral once daily SIP receptor 1, 4, 5 receptor modulator
- Elevate UC 12 was a 12-week induction study of moderate to severe UC on Etrasimod or placebo
- Elevate UC 52 treat through design in which patients that had done 12 weeks of induction continued treatment or placebo. If they had no response or worsened, could go to open lab extension study

	Expression	Biologic Outcomes	Clinical Relevance
S1P1	Broad, including B, T, and dendritic cells, endothelium, cardiac tissue, and neurons	Lymphocyte migration, dendritic cell migration, vascular barrier function, bradycardia, nociception, proliferation	Autoimmune 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**	**Inhibition of effector cytokines, secretion of IL-10**	**Autoimmune modulation**
S1P5	Restricted; natural killer cells, endothelial cells, oligodendrocytes	Natural killer cell migration, blood-brain barrier integrity, oligodendrocyte function	Autoimmune modulation, myelination

Induction and Maintenance Efficacy



Longer Induction Period?

Efficacy and Safety of Extended Induction Treatment with Upadacitinib in Patients with Moderate-Severe UC (Vermeire et al.)

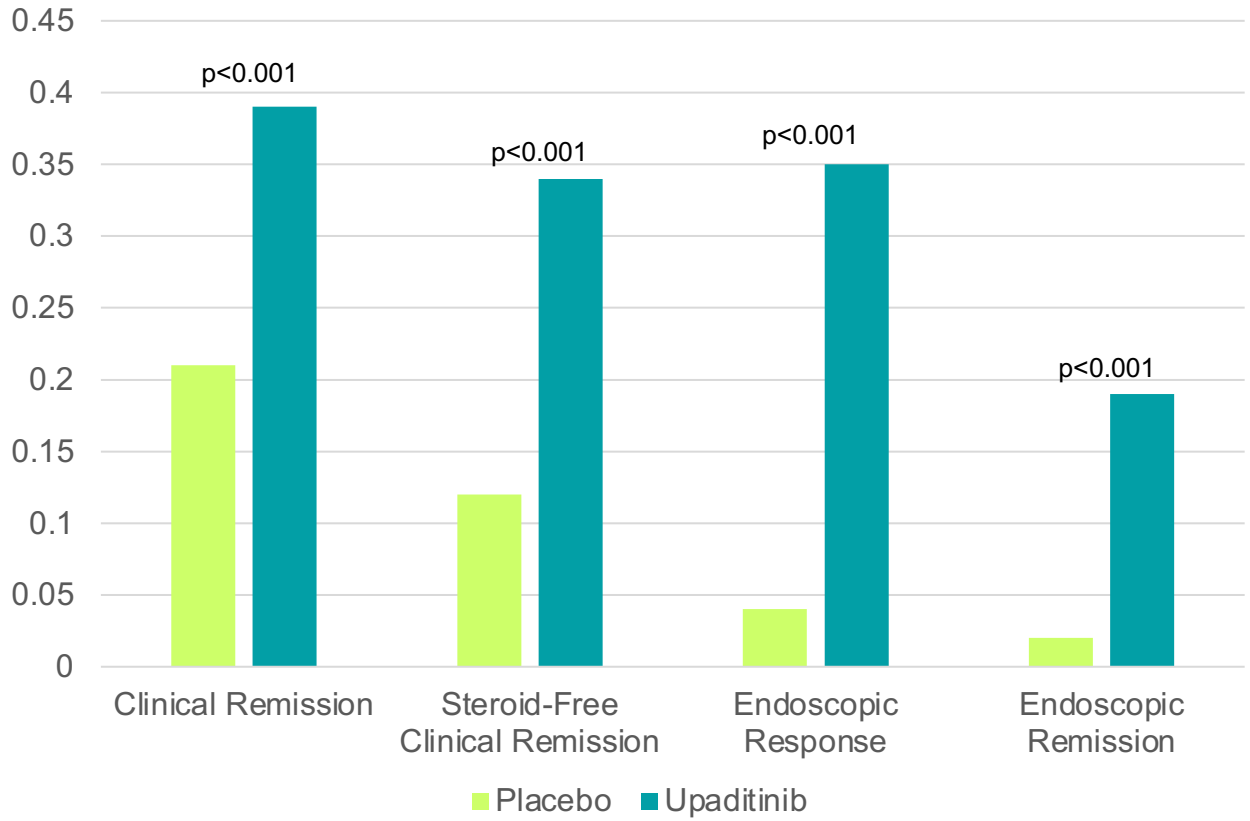
- Background:
  - Upadacitinib is a selective Janus kinase inhibitor and has been shown to be safe and effective when administered at a dose of 45 mg once daily as 8-week induction therapy in moderate-severe UC
    - Significantly improves UC symptoms as early as day 1
    - Patients who achieve early symptom improvement are more likely to attain clinical remission or response at week 8
- Aim:
  - To evaluate the outcomes following extended induction (45 mg once daily for 16 weeks) followed by maintenance (15 or 30 mg once daily) treatment with upadacitinib in patients with UC who did not achieve a response after 8 weeks

Efficacy and Safety of Extended Induction Treatment with Upadacitinib in Patients with Moderate-Severe UC

- Results:
  - 125 patients who failed to achieve a clinical response after 8 weeks of induction treatment received open-label upadacitinib 45 mg daily for an additional 8 weeks
  - 48.3% achieved a clinical response at week 16 and were re-randomized to upadacitinib 30 or 15 mg
  - Among responders at week 16, upadacitinib 30 mg vs 15 mg achieved the following endpoints at week 52:
    - Clinical remission – 33.3% vs 19.0%
    - Maintenance of clinical response – 66.7% vs 35.7%
    - Endoscopic improvement – 37.5% vs 23.8%

- Conclusions:
  - Prolonged induction treatment for a total of 16 weeks was beneficial in almost half of patients with UC who failed to achieve a clinical response after 8 weeks induction with upadacitinib 45 mg daily
  - Benefit of maintenance therapy in delayed responders was further demonstrated with upadacitinib 30 mg daily providing greater benefit than upadacitinib 15 mg daily

Efficacy and Safety of Upadacitinib 12-week Induction for Moderate-Severe Crohn's Disease (Colombel et al.)



Conclusion

- Novel IL-23, S1P, and JAK1 inhibitors
- IL-23 class with significant improvements and possibly superior to IL12/23 (Ustekinumab)
- S1P with durable response
- JAK1 inhibitors with robust induction and maintenance

Optimizing Therapeutic Drug Levels in IBD

CONCENTRATIONS OF 6-TGN AND METHOTREXATE CORRELATE WITH PHARMACOKINETICS OF INFLIXIMAB, BUT NOT VEDOLIZUMAB OR USTEKINUMAB: RESULTS OF THE COMBO-IBD STUDY

Andres Yarur, Alexandra Bruss, Poonam Beniwal, Parakkal Deepak, Dermot McGovern, Maria Abreu, Marla Dubinsky, Gil Melmed

Presentation Number: 236

Background

- Previous data suggest improvement in pharmacokinetics of infliximab (IFX) combined with thiopurines (Active metabolite: 6-TGN) and methotrexate (MTX)
- The effect of combination therapy (thiopurine or methotrexate) on vedolizumab (VDZ) and ustekinumab (UST) pharmacokinetics are not known

Aims:

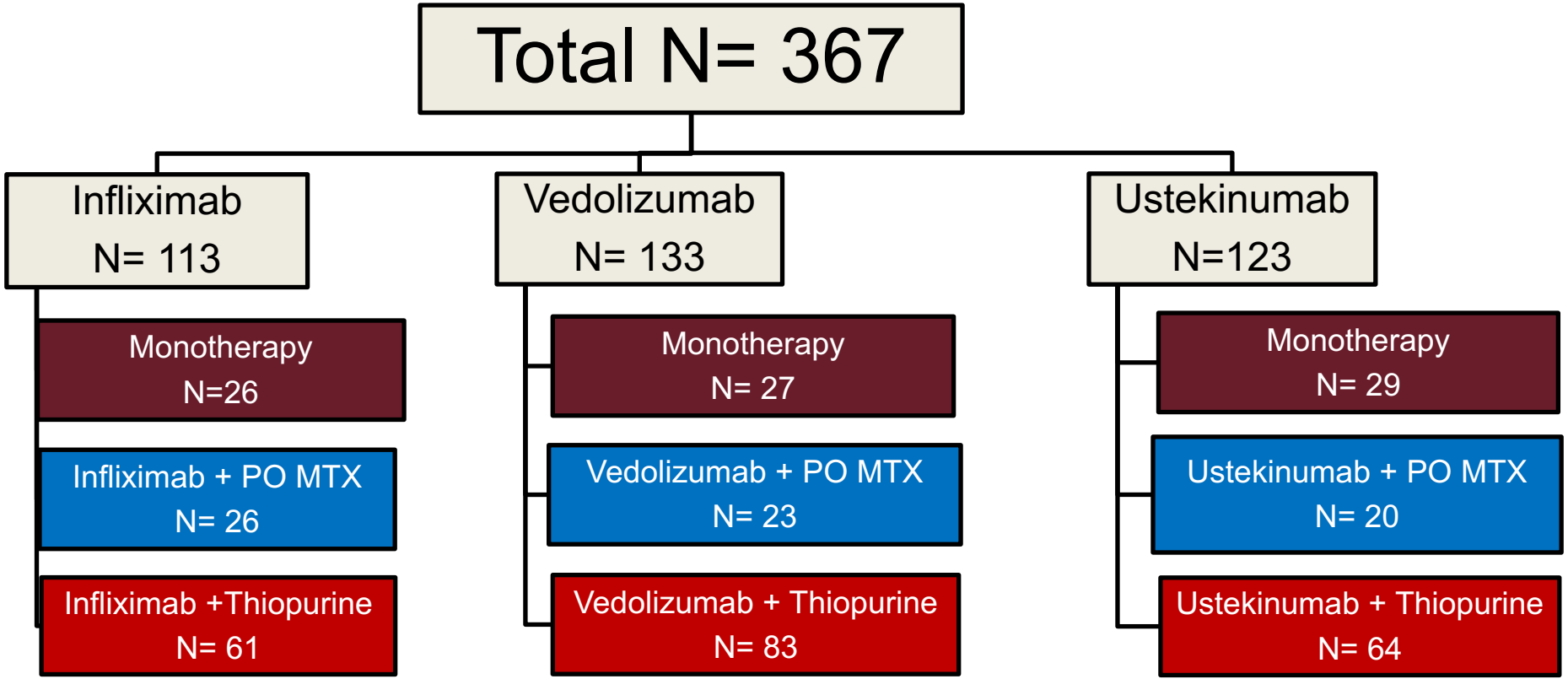
- To assess the correlation between thiopurines, 6-thioguanine and use of oral methotrexate with:
  - Trough concentrations: IFX, VDZ and UST
  - Anti-drug antibodies (ADA)
  - Clinical/endoscopic outcomes

Methods: Design

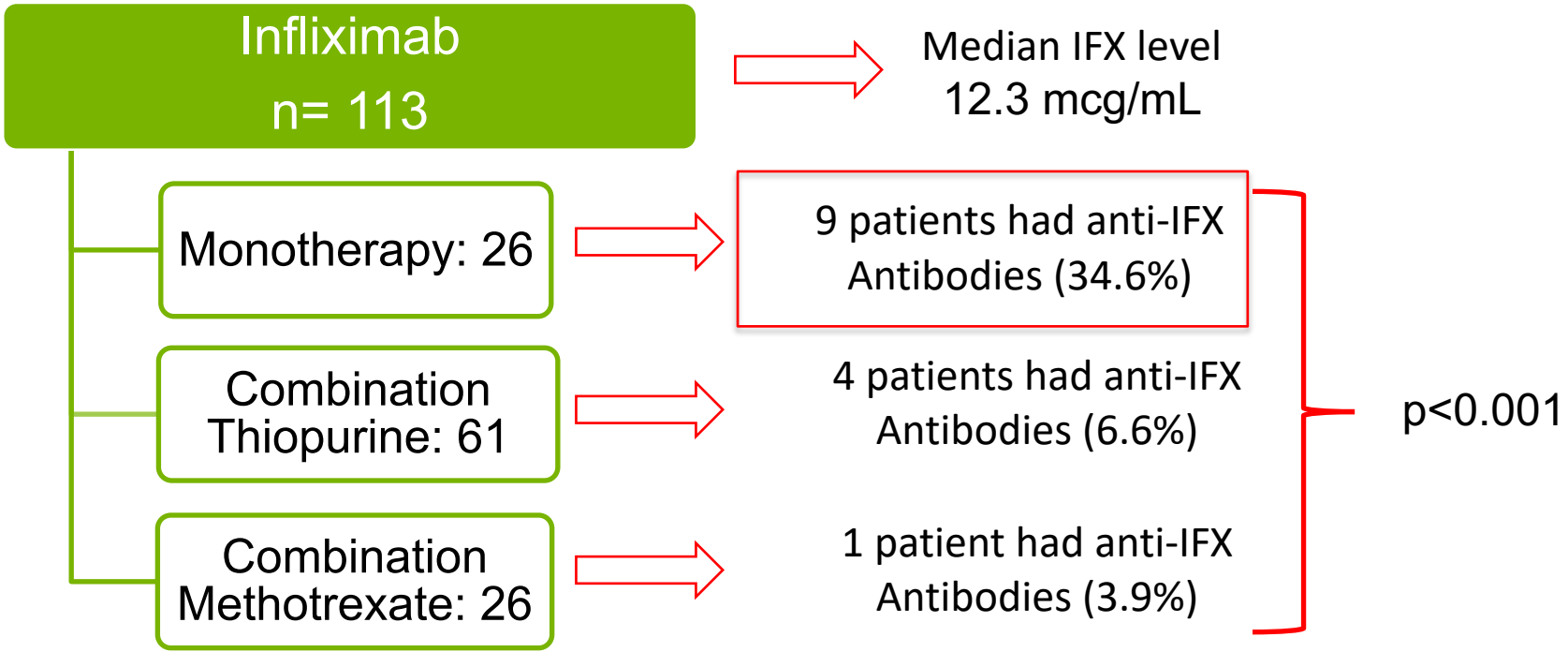
- **Study Design**: Prospective, cohort study
- Enrollment: May of 2017 → September of 2021 (Medical College of Wisconsin)
- **Inclusion Criteria:**
  - Crohn's disease or Ulcerative Colitis
  - On standard maintenance doses of:
    - Infliximab or Vedolizumab or Ustekinumab for ≥ 30 weeks (≥32 for UST)
  - On monotherapy or combination therapy with either:
    - PO Methotrexate 12.5 or 15 mg weekly or
    - Thiopurine (6-mercaptopurine or azathioprine)

- **Primary Outcome:** Drug level; Anti-drug antibodies for IFX, VDZ, UST
- **Secondary Outcome:**
  - Steroid-free deep remission
    - CD: Harvey-Bradshaw Index <5 + CRP normal + fecal calprotectin normal + no steroids
    - UC: Partial Mayo score<2 + CRP normal + normal fecal calprotectin + no steroids
  - Endoscopic remission
    - SES-CD ≤ 2
    - Endoscopic Mayo score ≤ 1

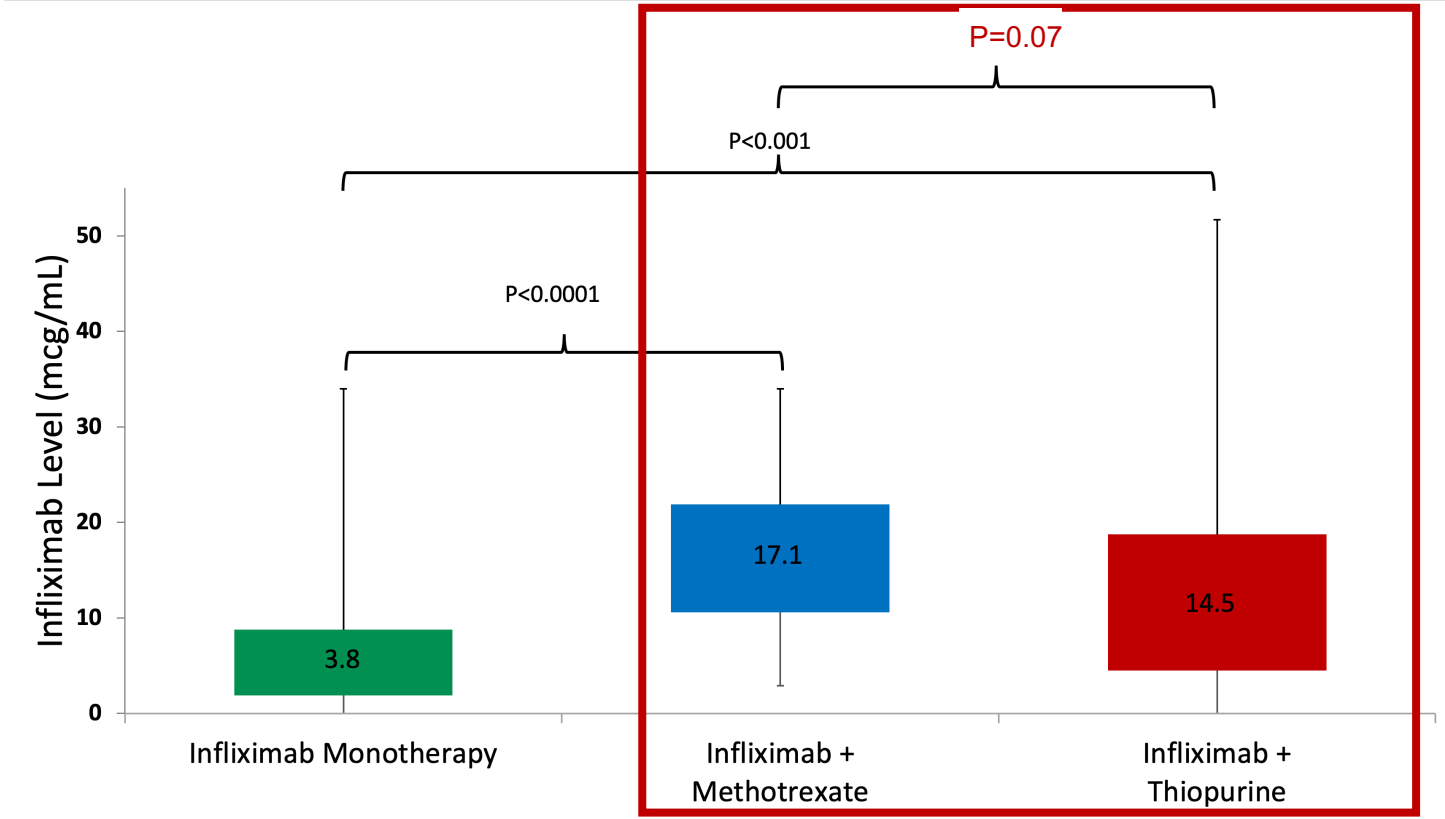
Results Overview



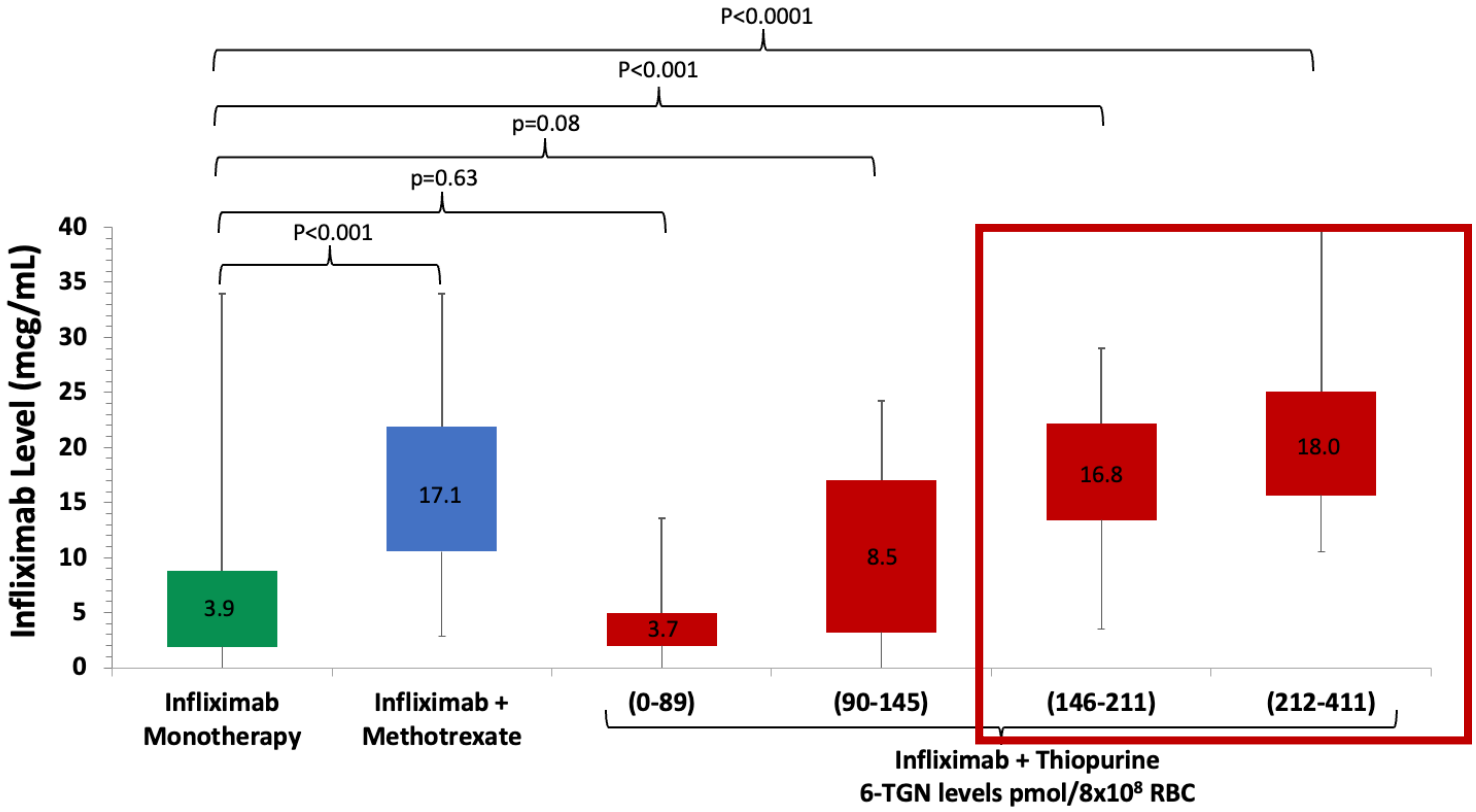
Results: Infliximab



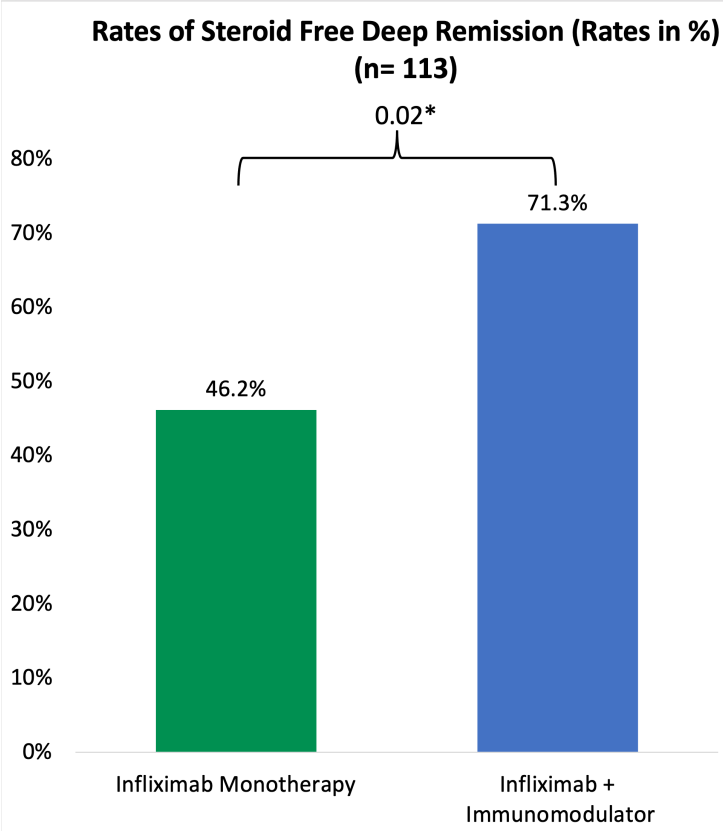
RESULTS: Infliximab Trough Levels Mono vs Combination Therapy

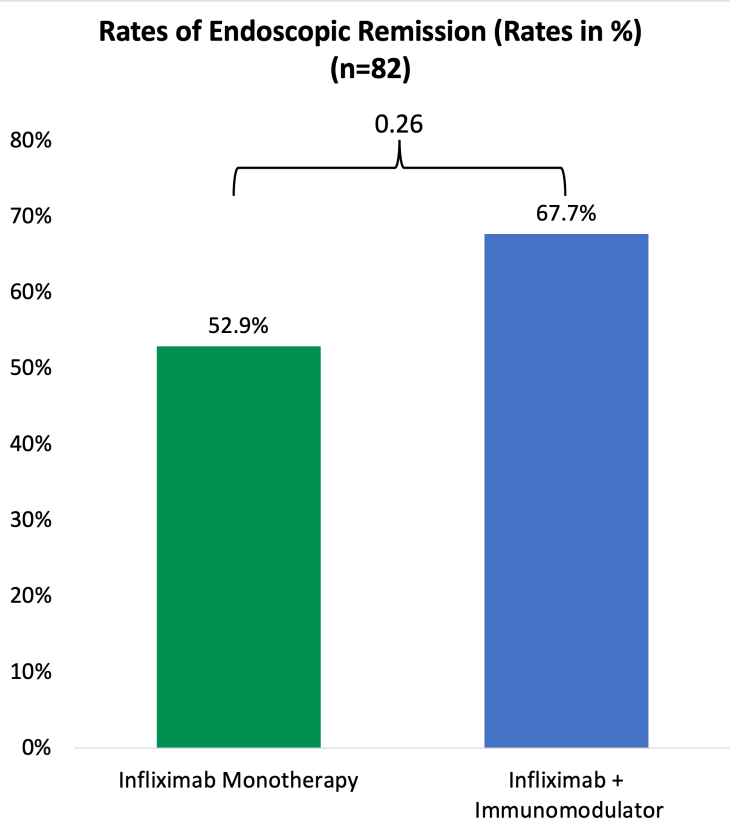


RESULTS: Infliximab Trough Levels Mono vs Combination Therapy

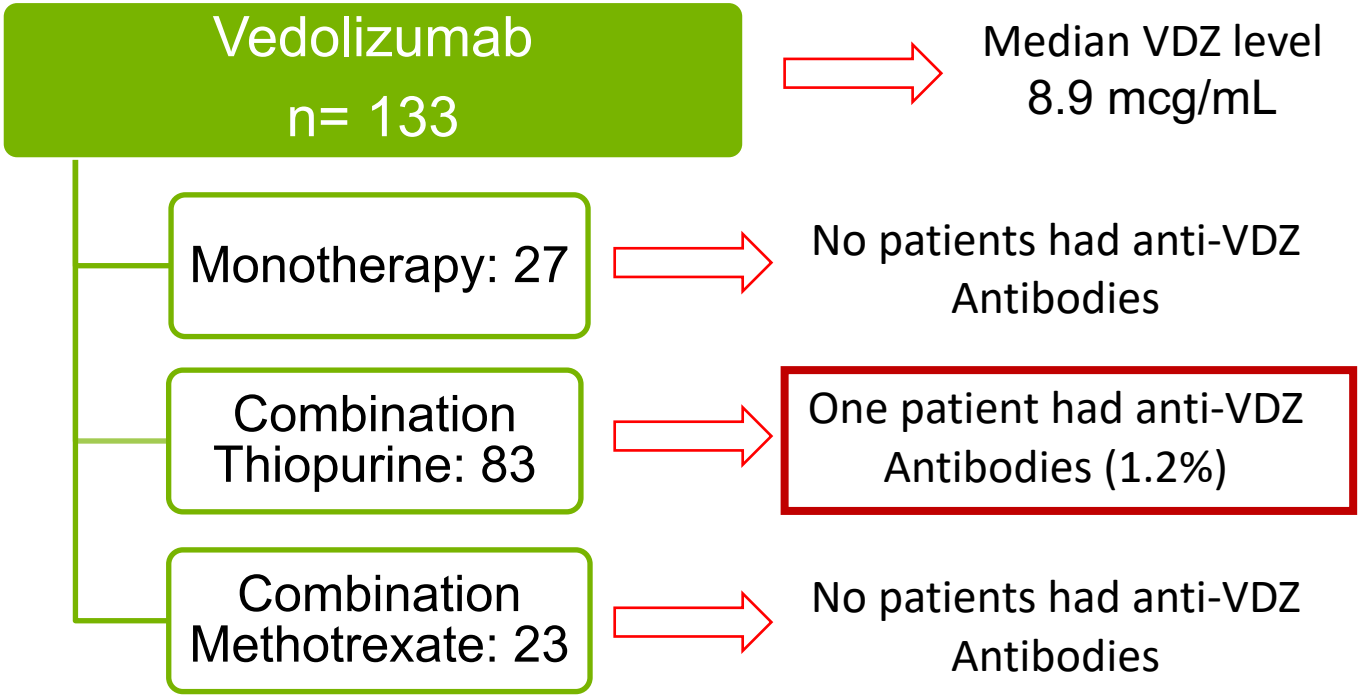


RESULTS: Infliximab Efficacy Mono vs Combination Therapy

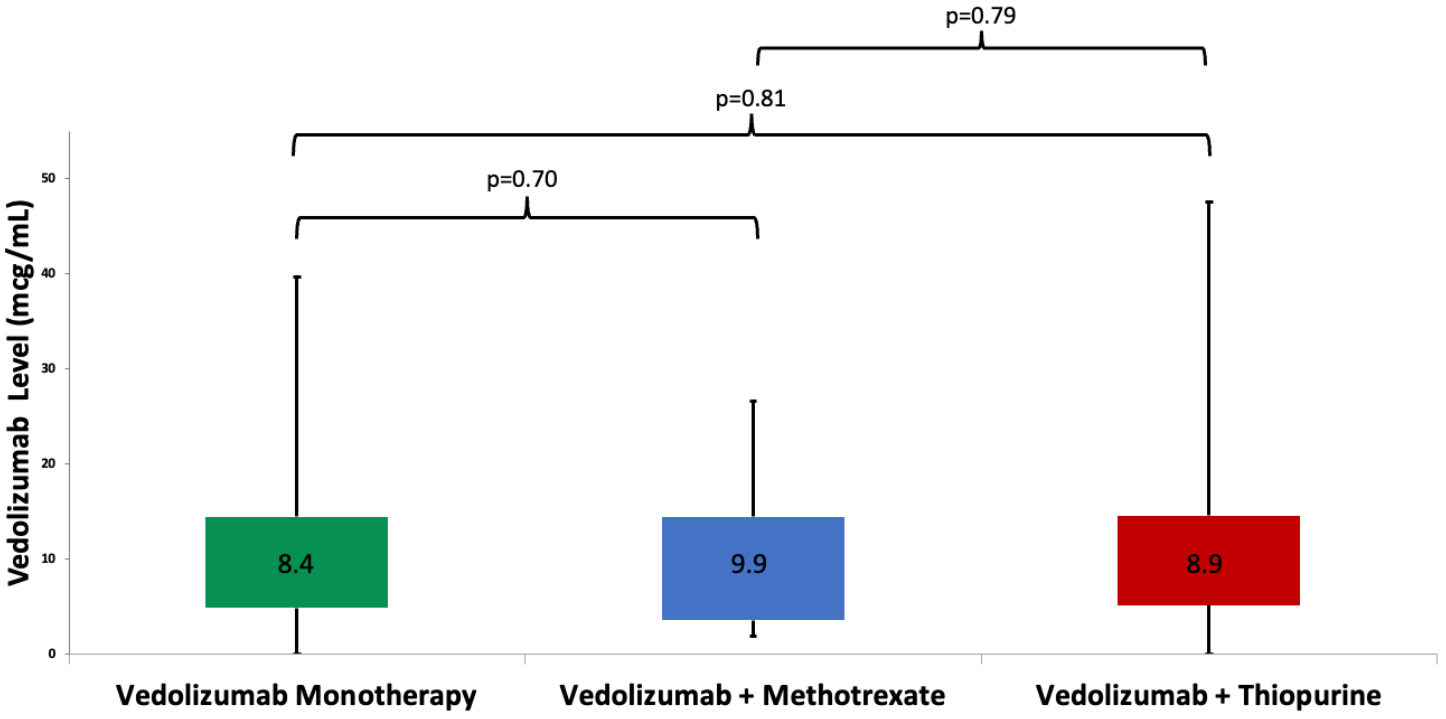




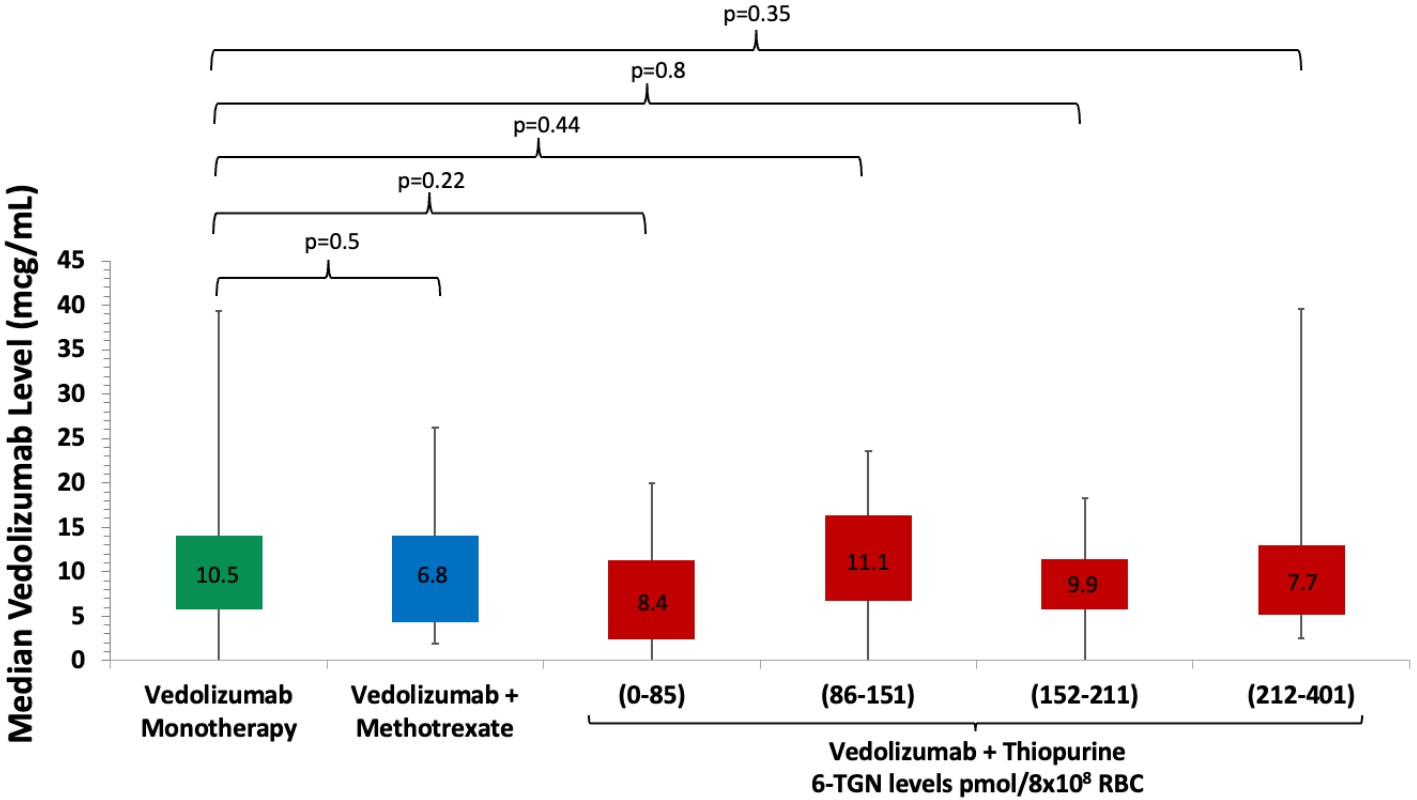
RESULTS: Vedolizumab



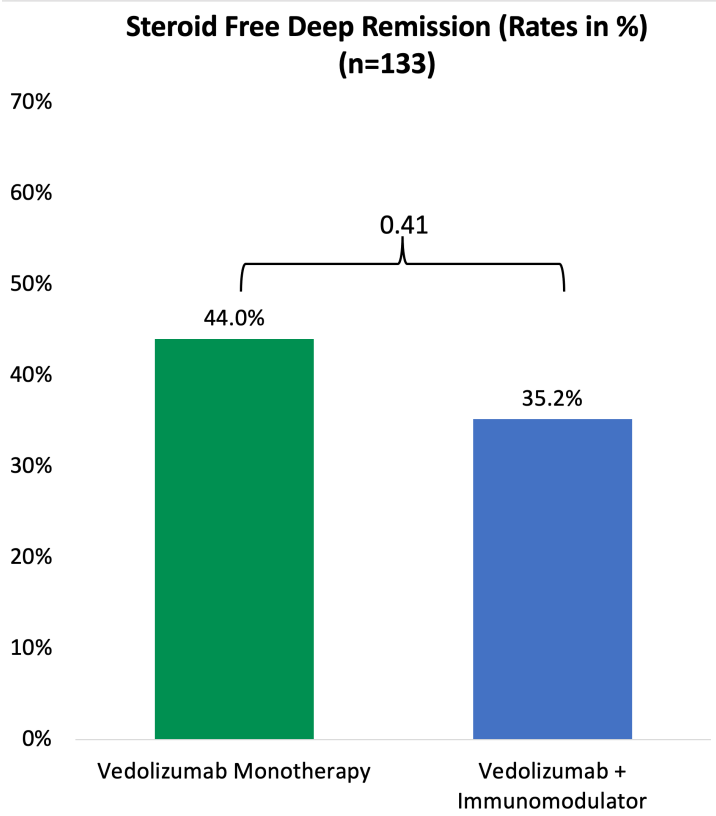
RESULTS: Vedolizumab Trough Levels Monotherapy vs Combination

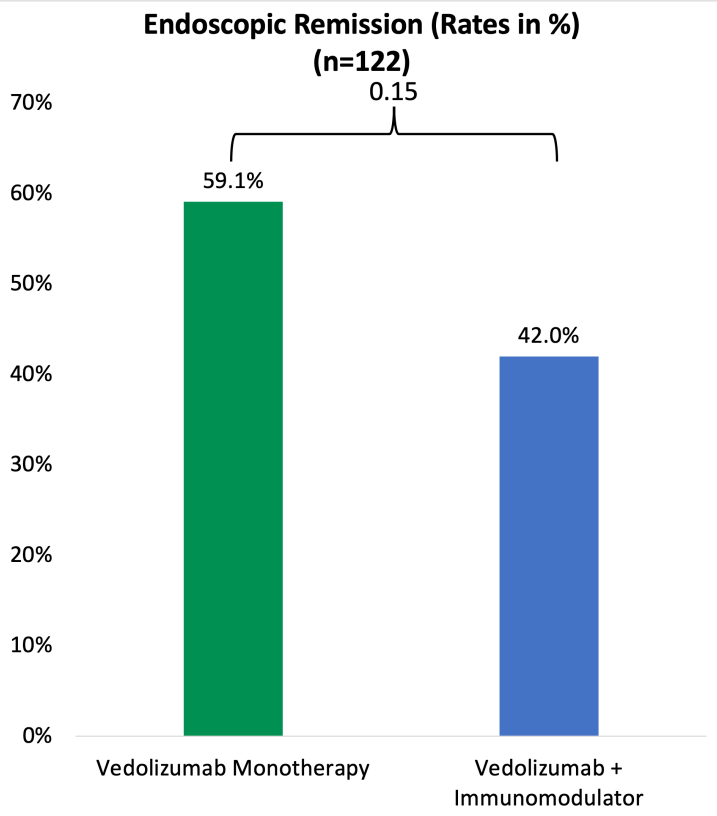


RESULTS: Vedolizumab Trough Levels by Combination Group

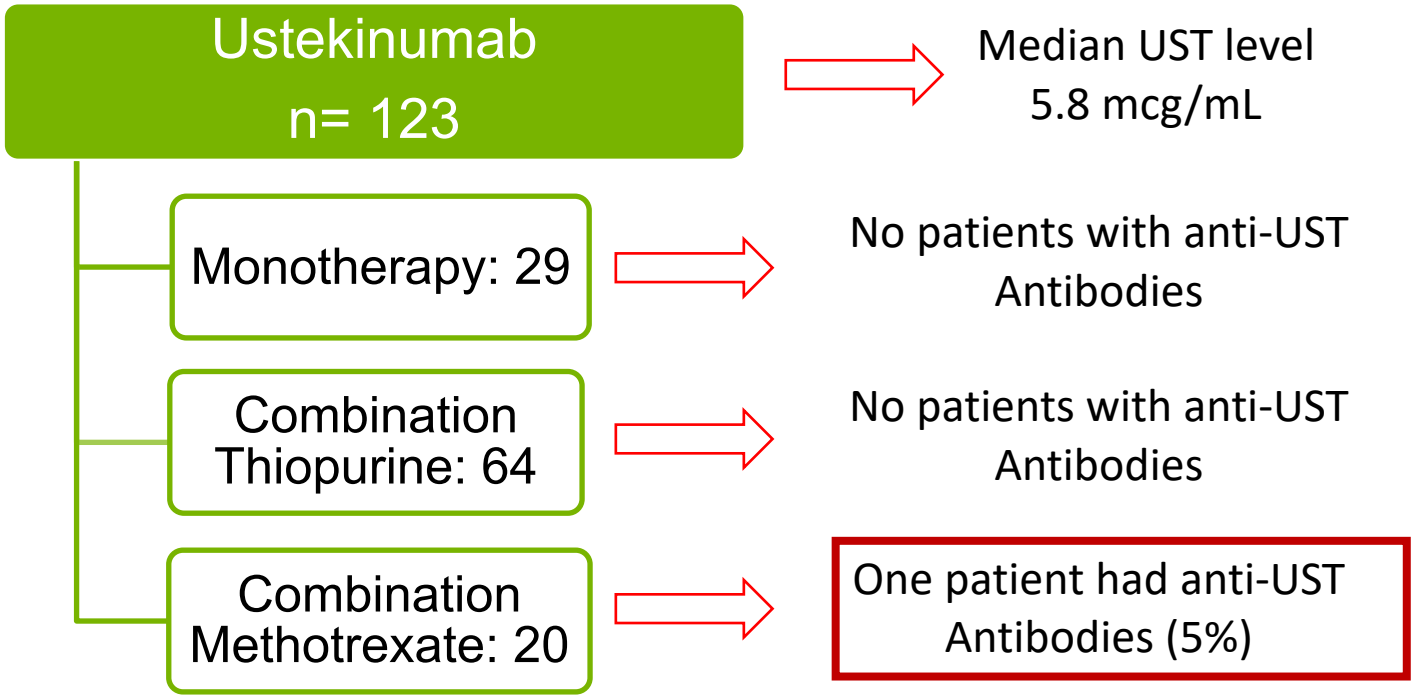


RESULTS: Vedolizumab Efficacy Mono vs Combination Therapy

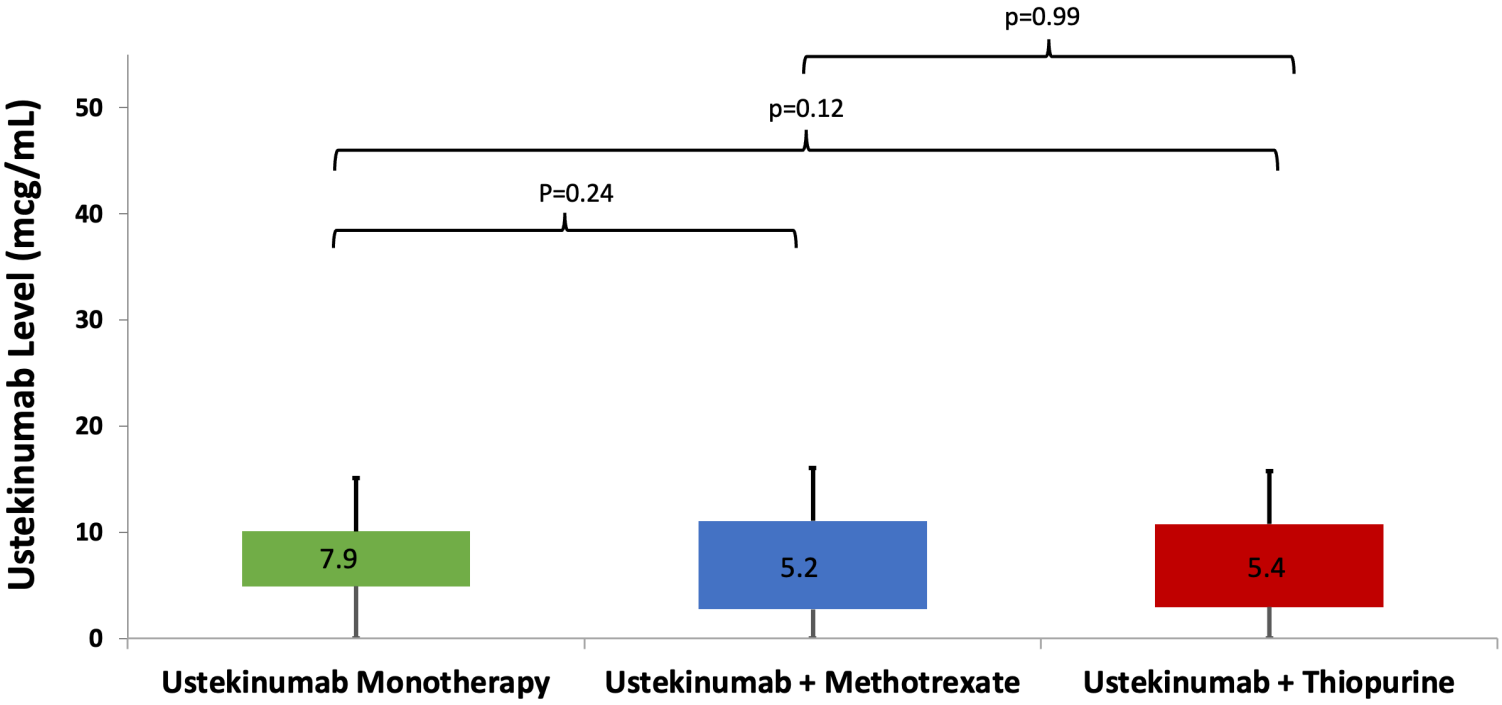




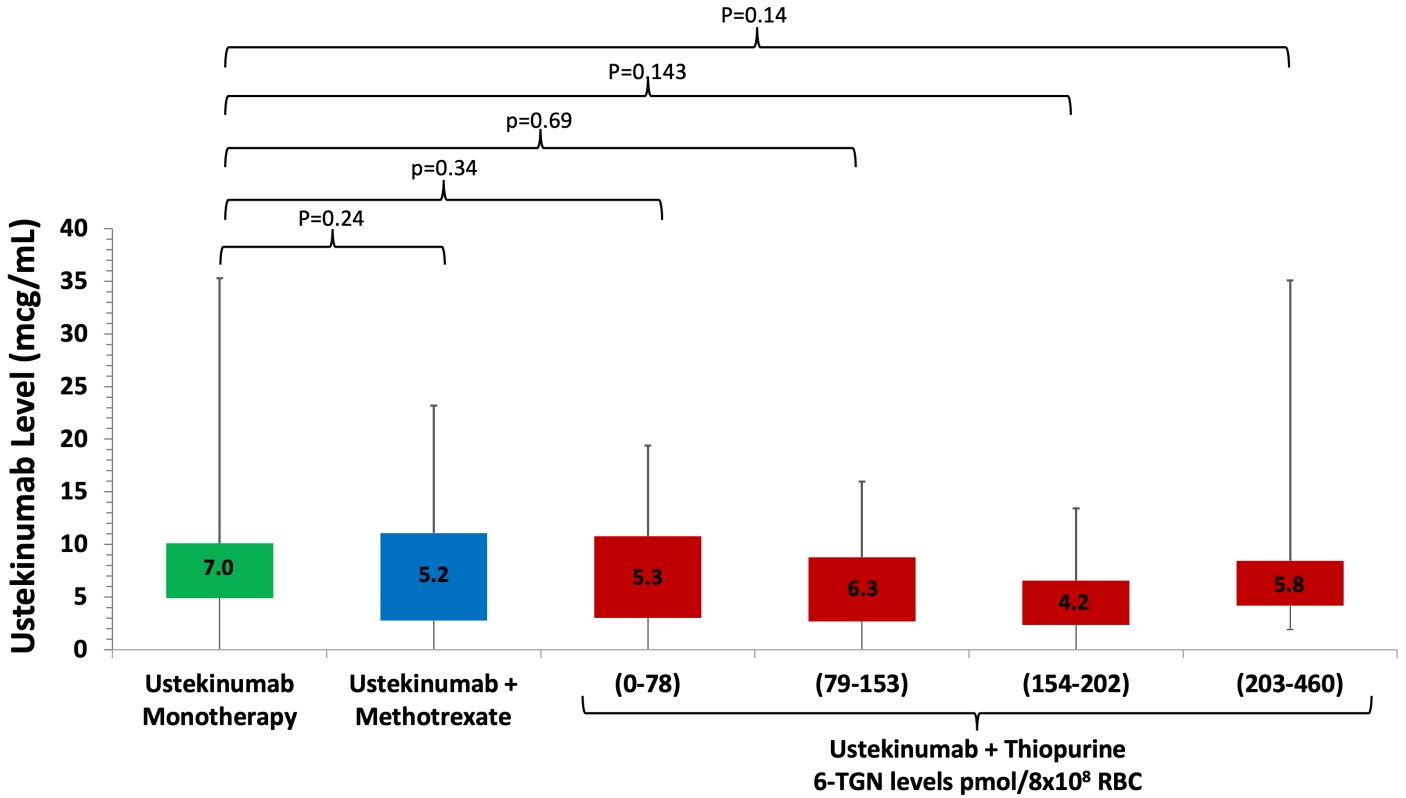
RESULTS: Ustekinumab



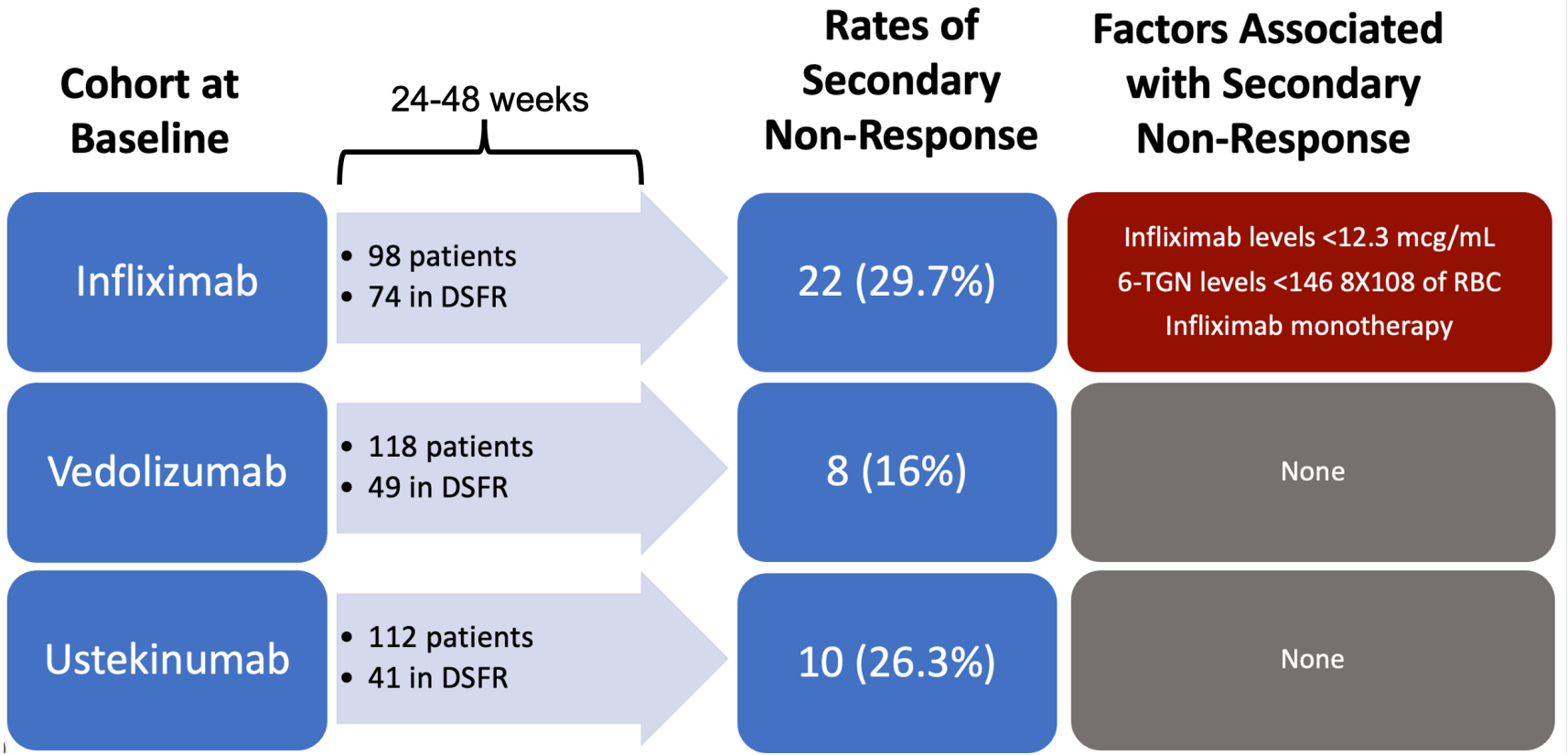
RESULTS: No Differences in UST Trough Levels Among Therapeutic Groups



RESULTS: Ustekinumab Trough Levels by Combination Group



Results: Long-Term Outcomes



Conclusion

- Combination therapy of IFX and PO MTX or a thiopurine with 6-TGN optimization should be highly considered
- Oral MTX is a viable alternative to thiopurines
- First prospective study to show that combination therapy to improve pharmacokinetics of VDZ or UST is not warranted

Combination Biologic Therapies?

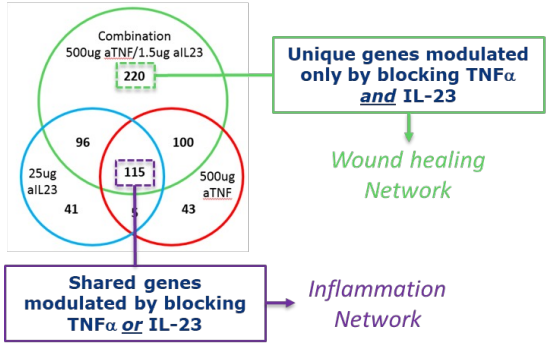
EFFICACY AND SAFETY OF COMBINATION INDUCTION THERAPY WITH GUSELKUMAB AND GOLIMUMAB IN PARTICIPANTS WITH MODERATELY-TO-SEVERELY ACTIVE ULCERATIVE COLITIS: RESULTS THROUGH WEEK 12 OF A PHASE 2a RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, PARALLEL-GROUP, MULTICENTER, PROOF-OF-CONCEPT STUDY (VEGA)

BG Feagan, BE Sands, WJ Sandborn, N Shipitofsky, M Marko, S Sheng, J Johanns, M Germinaro, M Vetter, J Panés

Presentation Number: 886

Background

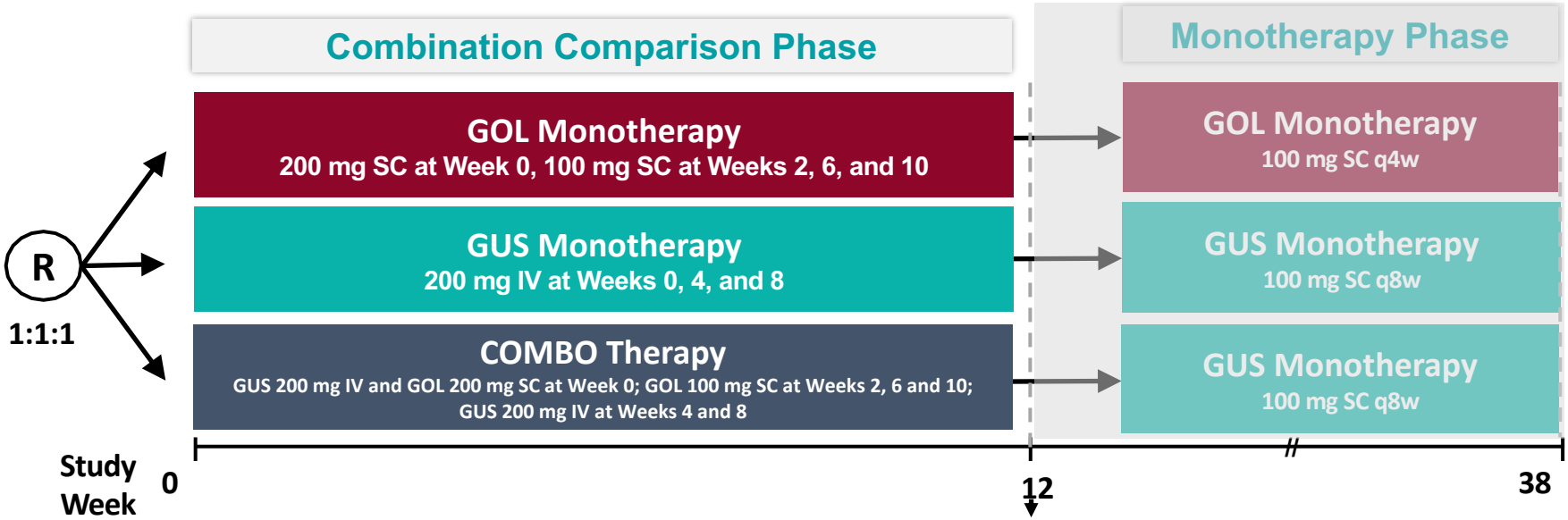
- Guselkumab, IL-23p19 subunit antagonist
- Golimumab, TNFα antagonist



- Can combination therapy with guselkumab and golimumab increase treatment response?

- Phase 2a, proof-of-concept study evaluating safety and efficacy of combination therapy through week 12 of guselkumab + golimumab vs. guselkumab or golimumab monotherapy in moderate-to-severe ulcerative colitis

Study Design



Primary Endpoint: Clinical response
Major Secondary Endpoint: Clinical remission based on full Mayo score

Patient Population

- Moderately-to-severely active UC (Mayo score 6-12, inclusive, and an endoscopy subscore ≥2 by central review)
- Naïve to TNFα antagonists and have had an inadequate response or intolerance to conventional therapy (immunosuppressants [AZA, 6-MP] and/or corticosteroids)
- Immunosuppressants must have been discontinued prior to randomization
- Corticosteroids up to a dose of prednisone (or equivalent) of 20 mg/day permitted with mandatory tapering beginning at Week 6

R=Randomization; GUS=Guselkumab; GOL=Golimumab; COMBO=Combination Guselkumab + Golimumab

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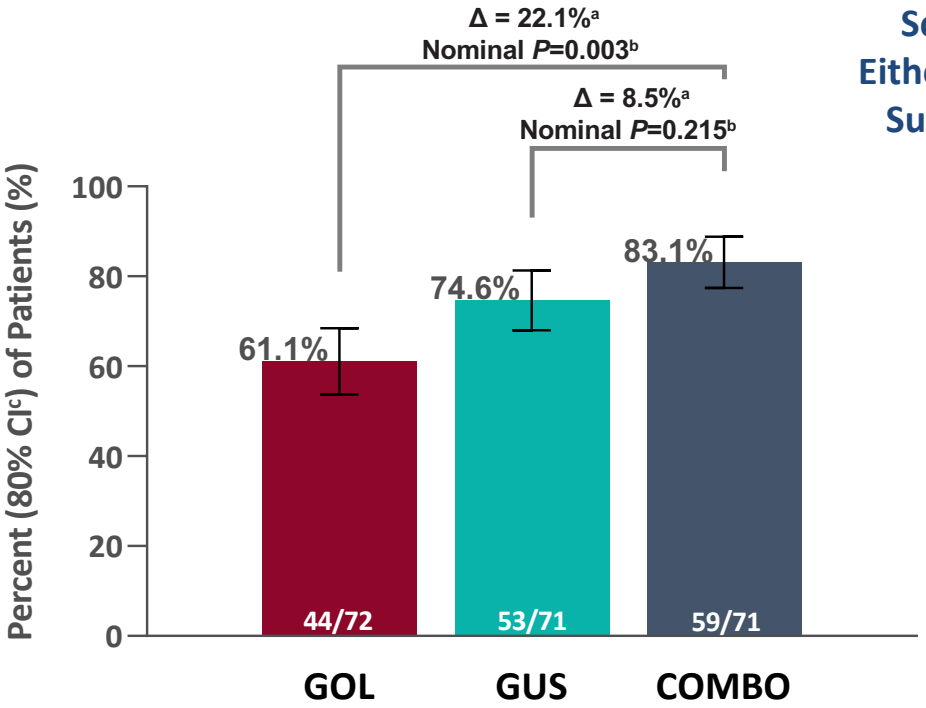
Baseline Patient Characteristics

	Golimumab	Guselkumab	COMBO (Golimumab + Guselkumab)	Total
Number of Patients	72	71	71	214
Mean age (SD), years	38.1 (10.47)	39.1 (13.67)	37.8 (11.69)	38.4 (11.96)
Male, n (%)	42 (58.3%)	40 (56.3%)	34 (47.9%)	116 (54.2%)
UC duration, years, mean (SD)	4.7 (4.48)	5.4 (5.70)	4.6 (4.61)	4.9 (4.94)
Disease limited to left side of colon, n (%)	38 (52.8)	36 (50.7)	50 (70.4)	124 (57.9)
Full Mayo score (0-12), mean (SD)	8.7 (1.44)	8.9 (1.33)	8.8 (1.37)	8.8 (1.38)
Endoscopy subscore (0-3), n (%)				
Subscore of 2 (moderate)	35 (48.6)	24 (33.8)	28 (39.4)	87 (40.7)
Subscore of 3 (severe)	37 (51.4)	47 (66.2)	43 (60.6)	127 (59.3)
Patients with prior use of immunosuppressants, n (%)	24 (33.3)	28 (39.4)	37 (52.1)	89 (41.6)
Patients receiving corticosteroids at baseline, n (%)	31 (43.1)	28 (39.4)	29 (40.8)	88 (41.1)

Primary Endpoint: Clinical Response at Week 12

Decrease from Baseline in the Mayo Score ≥30% and ≥3 Points with Either a Decrease in Rectal Bleeding Subscore ≥1 or a Rectal Bleeding Subscore of 0 or 1



[a]The adjusted treatment difference between the combination therapy vs. the monotherapy groups were based on the Wald statistic with the CMH weight.
[b]The p-value was based on the CMH chi-square test, stratified by corticosteroid use at baseline (Yes, No).
[c]The 80% confidence intervals (CIs) for response rates were based on the Wald statistic.

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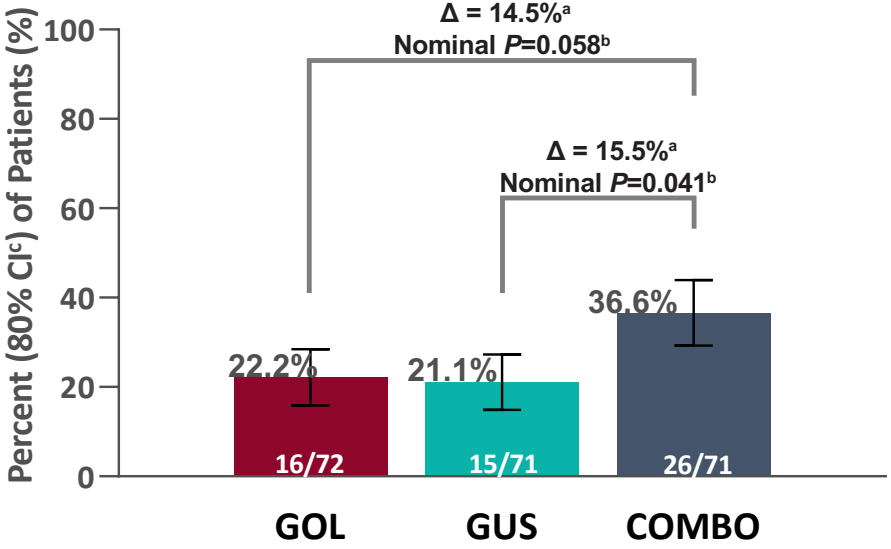
Clinical Remission at Week 12

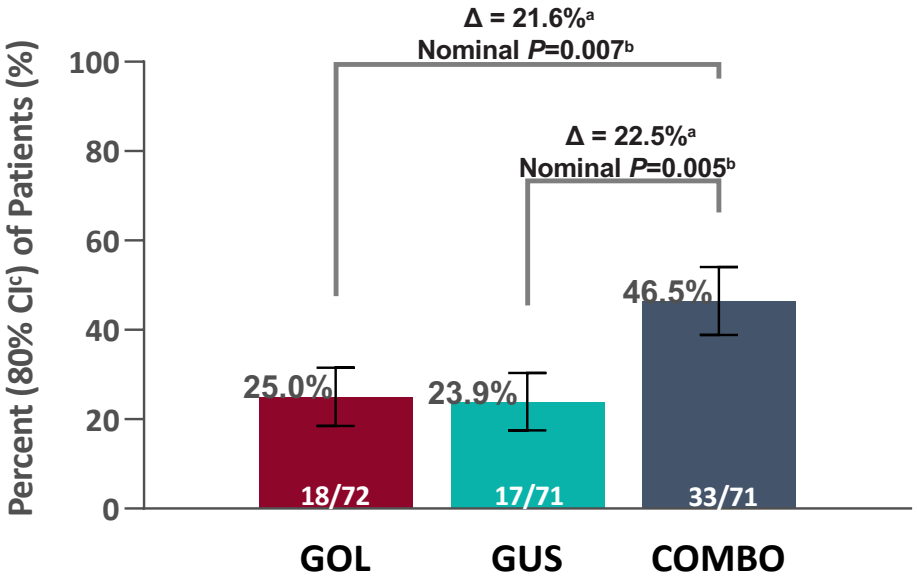
Major Secondary Endpoint:

Mayo Score ≤2 with No Individual Subscore >1



Modified Mayo Score:

Mayo Stool Frequency Subscore of 0 or 1 and Not Increased from Baseline, a Rectal Bleeding Subscore of 0, and an Endoscopy Subscore of 0 or 1 with No Friability Present on the Endoscopy



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[c]The 80% confidence intervals (CIs) for response rates were based on the Wald statistic.

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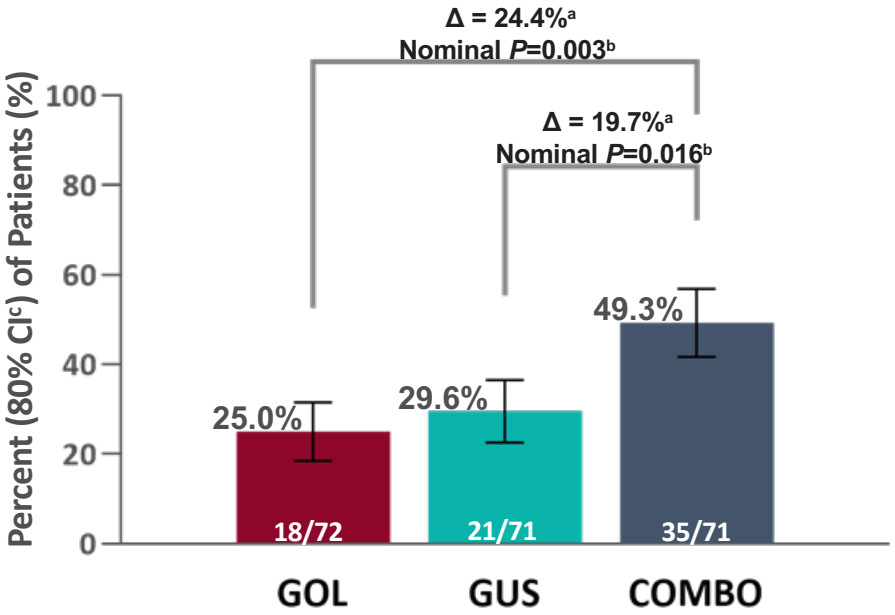
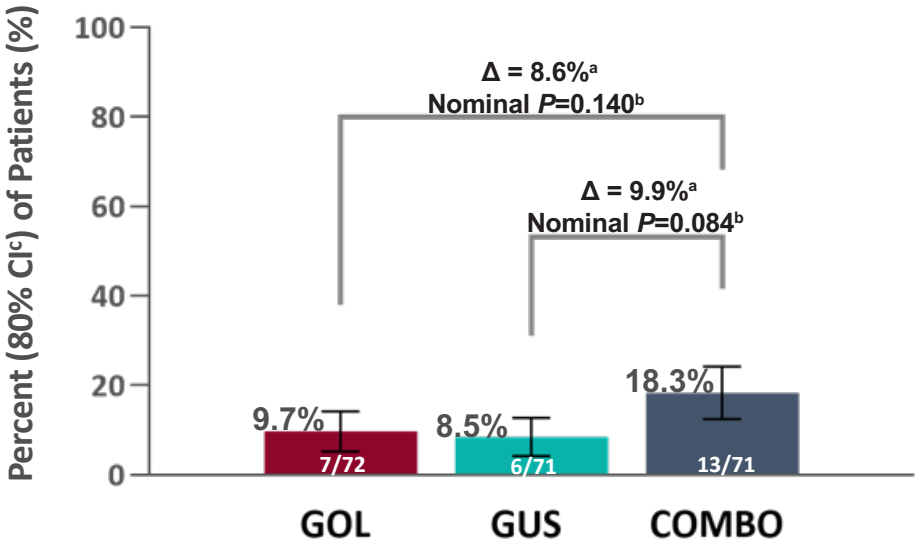
Endoscopic Improvement at Week 12

Endoscopy Subscore of 0 or 1 with No Friability Present on the Endoscopy



Endoscopic Normalization at Week 12

Endoscopy Subscore of 0 with No Friability Present on the Endoscopy



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[c]The 80% confidence intervals (CIs) for response rates were based on the Wald statistic.

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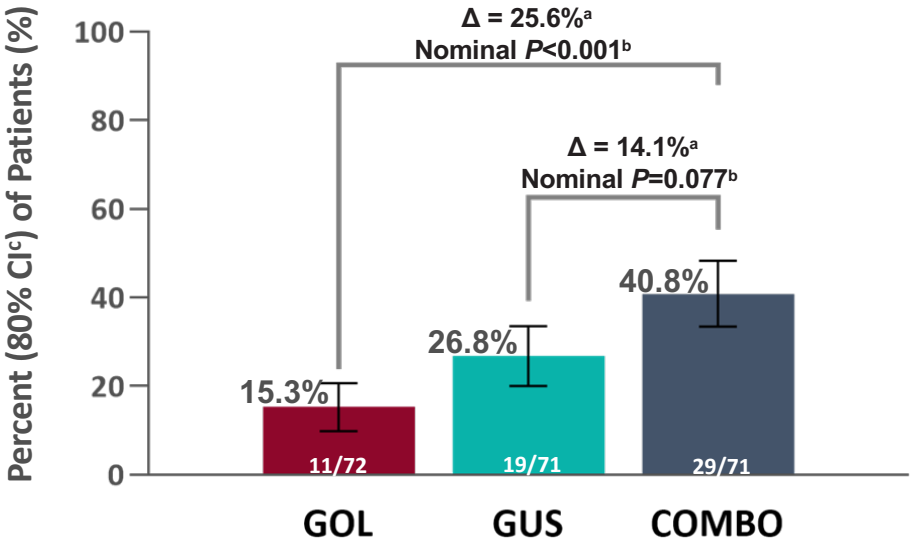
Composite Endpoint of Histologic Remission and Endoscopic Improvement at Week 12



Histologic Remission: absence of neutrophils from the mucosa (both lamina propria and epithelium), no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system

Endoscopic Improvement: Endoscopy subscore of 0 or 1 with no friability present on the endoscopy

[a]The adjusted treatment difference between the combination therapy vs. the monotherapy groups were based on the Wald statistic with the CMH weight.
[b]The p-value was based on the CMH chi-square test, stratified by corticosteroid use at baseline (Yes, No).
[c]The 80% confidence intervals (CIs) for response rates were based on the Wald statistic.

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Key Safety Findings Through Week 12

	Golimumab	Guselkumab	COMBO (Golimumab + Guselkumab)
Number of Patients	72	71	71
Patients with ≥1, n (%)			
Adverse events (AEs)	38 (52.8)	31 (43.7)	29 (40.8)
Serious AEs	1 (1.4)	2 (2.8)	1 (1.4)
AEs leading to discontinuation of study agent	3 (4.2)	1 (1.4)	2 (2.8)
Infection[a]	16 (22.2)	10 (14.1)	10 (14.1)
Serious infection[a]	0	0	1 (1.4)

- One patient receiving combination therapy experienced two concurrent serious infections of influenza and sepsis
- No deaths, malignancies, or opportunistic infections (including cases of TB) were reported through Week 12

[a]As assessed by the investigator.

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Serious Adverse Events Through Week 12

	Golimumab	Guselkumab	COMBO (Golimumab + Guselkumab)
Number of Patients	72	71	71
Patients with ≥1 SAE n (%)	1 (1.4)	2 (2.8)	1 (1.4)
Infections and infestations[a]	0	0	1 (1.4)
Influenza[b]	0	0	1 (1.4)
Sepsis[b]	0	0	1 (1.4)
Cardiac disorders	0	1 (1.4)	0
Atrial fibrillation	0	1 (1.4)	0
Gastrointestinal disorders	1 (1.4)	1 (1.4)	0
Ulcerative colitis	1 (1.4)	0	0
Small intestinal obstruction	0	1 (1.4)	0

[a] As assessed by the investigator
[b] Concurrent serious infections occurred in the same patient
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Conclusion

- Combination induction treatment with guselkumab and golimumab resulted in greater proportions of patients achieving the following endpoints at Week 12 than either guselkumab or golimumab monotherapy:
  - Clinical response
  - Clinical remission
  - Endoscopic improvement and endoscopic normalization
  - Composite endpoint of histologic remission and endoscopic improvement

- Adverse event rates were comparable among the treatment groups

Withdrawal of Therapy

WITHDRAWAL OF INFLIXIMAB OR CONCOMITANT IMMUNOSUPPRESSANT THERAPY IN CROHN'S DISEASE PATIENTS ON COMBINATION THERAPY: A RANDOMIZED CONTROLLED TRIAL (SPARE)

Edouard Louis, Mattieu Resche-Rigon, David Laharie, Jack Satsangi, Nik Ding, Jan Preiss, Geert D' Haens, Laurence Picon, Peter Bossuyt, Lucine Vuitton, Peter Irving, Yoram Bouhnik, Stephanie Viennot, Christopher Lamb, Richard Pollok, Filip Baert, Maria Nachury, Mathurin Fumery, Cyrielle Gilletta, Shomron Ben-Horin, Jean-Frederic Colombel, Erik Hertervig, GETAID and SPARE-BIOCYCLE consortium

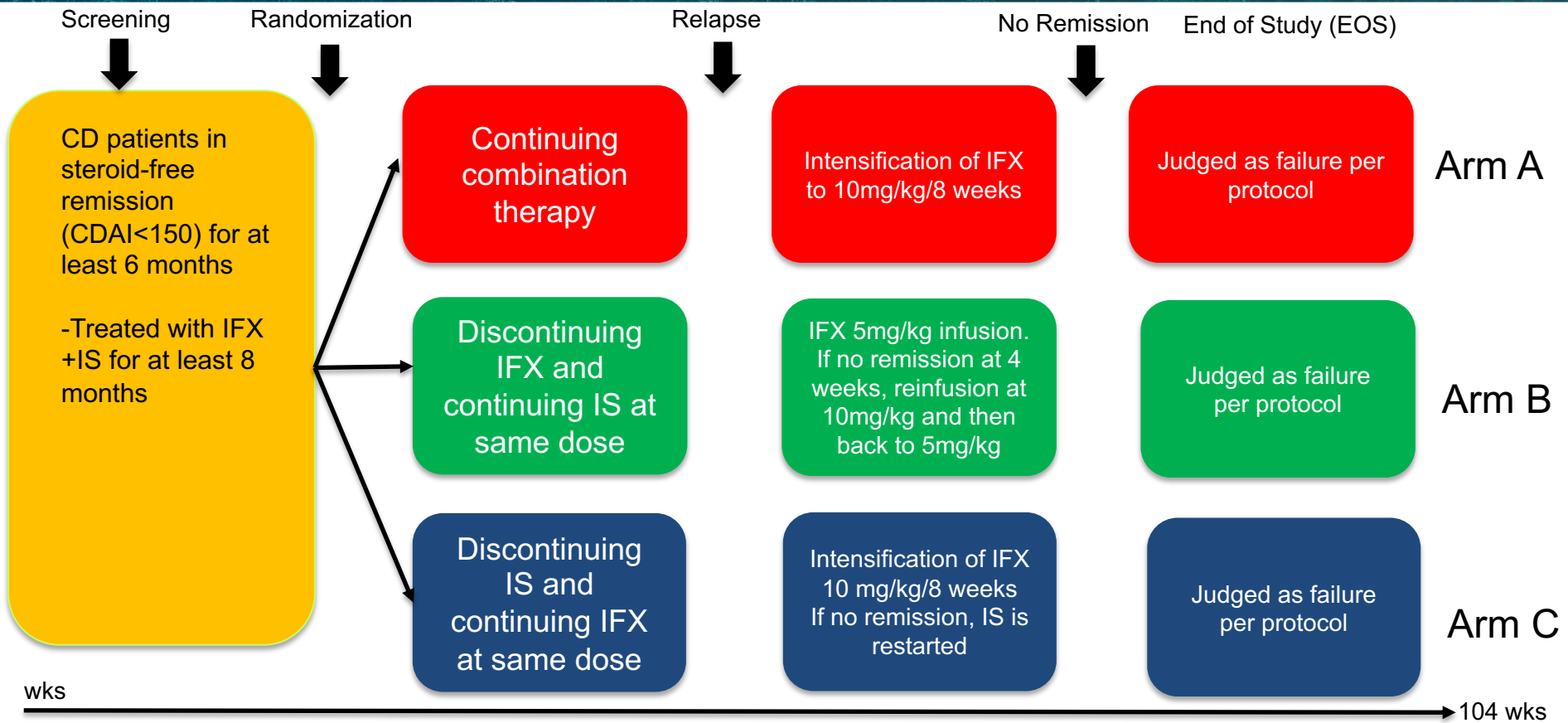
Presentation Number: 5115

De-Escalation of Treatment

- Combination therapy with infliximab (IFX) and an immunosuppressant (IS) is a standard of care option, especially for treatment-naïve moderate-severe Crohn's disease and ulcerative colitis
- Once in established remission, few controlled data exist to guide de-escalation

- Randomized, open-label controlled trial over 2 years comparing the clinical outcomes in Crohn's disease patients
  - Continuing combination therapy
  - Discontinuing IFX but continuing IS
  - Discontinuing IS but continuing IFX

Study Schema



Baseline Demographics

Parameters	Arm A (n=67) Combo	Arm B (n=71) Stop IFX	Arm C (n=69) Stop IS
Age (yrs)	36 (27-45.5)	32 (25-42.5)	31(26-44)
Female (n, %)	30(44.8)	28 (39.4)	31(44.9)
Disease duration (yrs; med, IQR)	6.4 (3.2-12.7)	6.7 (3.3-10.7)	6.8 (2.9-12.6)
Anti-TNF started <2 yrs after dx (n, %)	32(47.8)	38 (53.5)	33(47.8)
IS failure prior to anti-TNF	22(32.8)	23(32.4)	19 (27.5)
Thiopurine (n, %)	62 (93)	69 (97)	65(91)
CRP (mg/L)(med, IQR)	1.3 (0.5-2.9)	1.3 (0.6-2.8)	1.2 (0.5-2.6)
Fecal calprotectin (ug/g) (med, IQR)	95 (23-425)	95 (28-305)	61(22-195)
Ulcers at endoscopy (n, %)	9 (11.9)	8 (11.3)	6 (8.7)
CDEIS (med IQR)	0 (0-0)	0 (0-0)	0 (0-0)

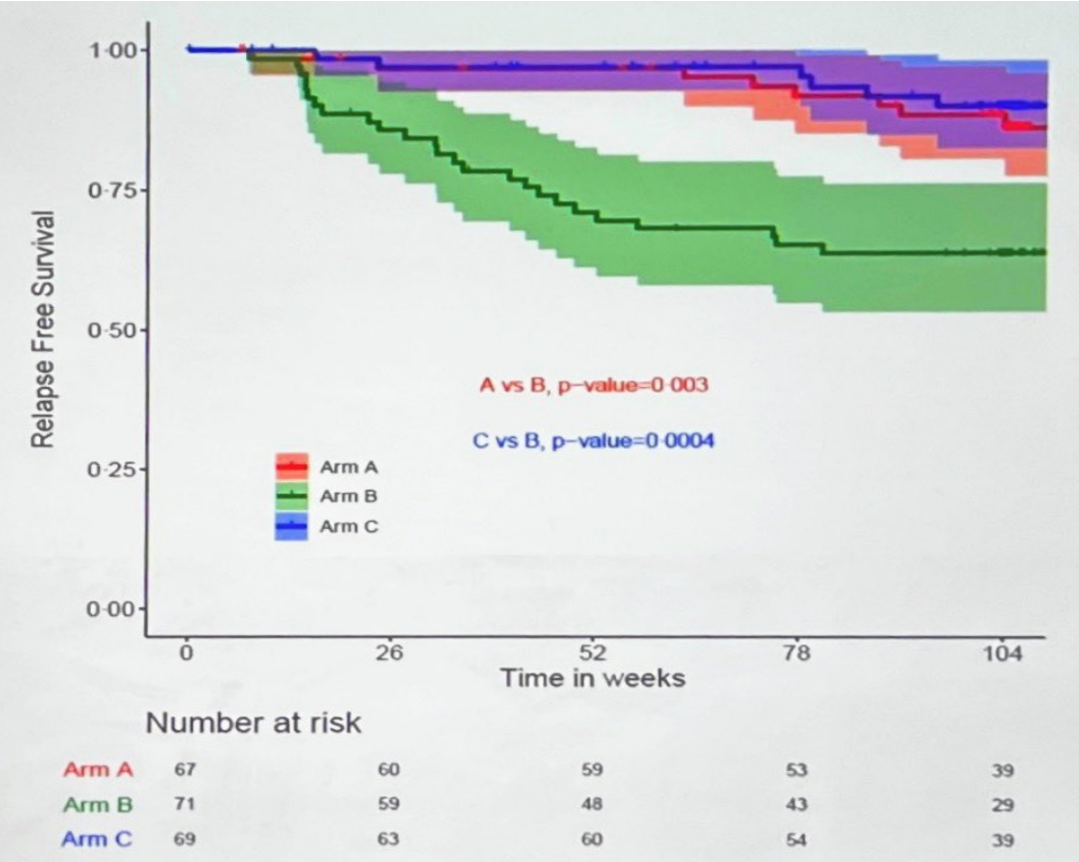
First Co-Primary Endpoints

- **Relapse rate over two years**
  - Relapse
    - CDAI $\geq$ 250 at any visit between 150 and 250 with an increase in at least 70 points, over two consecutive visits one week apart, with a CRP >5mg/L or a fecal calprotectin >250 µg/g
    - New opening perianal or entero-cutaneous fistula
    - Intra-abdominal abscess (size at least 3 cm) or perianal abscess (size at least 2 cm)
    - Episode of intestinal obstruction confirmed by abdominal imaging and requiring hospitalization

Second Co-Primary Endpoints

- **Mean Time Spent in Remission over Two Years**
  - For patients who relapsed, the time was computed from day 1 until relapse, and added to time spent in first and subsequent regained remission

First Co-Primary Endpoint: Relapse Rate Over Time



arm C
arm A

arm B

At week 104, relapse rate:

14%(4-23) in arm A (combo)
36% (24-47) in arm B (stop IFX)
10% (2-18) in arm C (stop IS)

Second Co-Primary Endpoint: Mean Time Spent in Remission Over Two Years

Arm A vs Arm B = **6 days** (95%CI: -33 - **44** days)
Arm C vs Arm B = **14 days** (95%CI: -21 - **69** days)

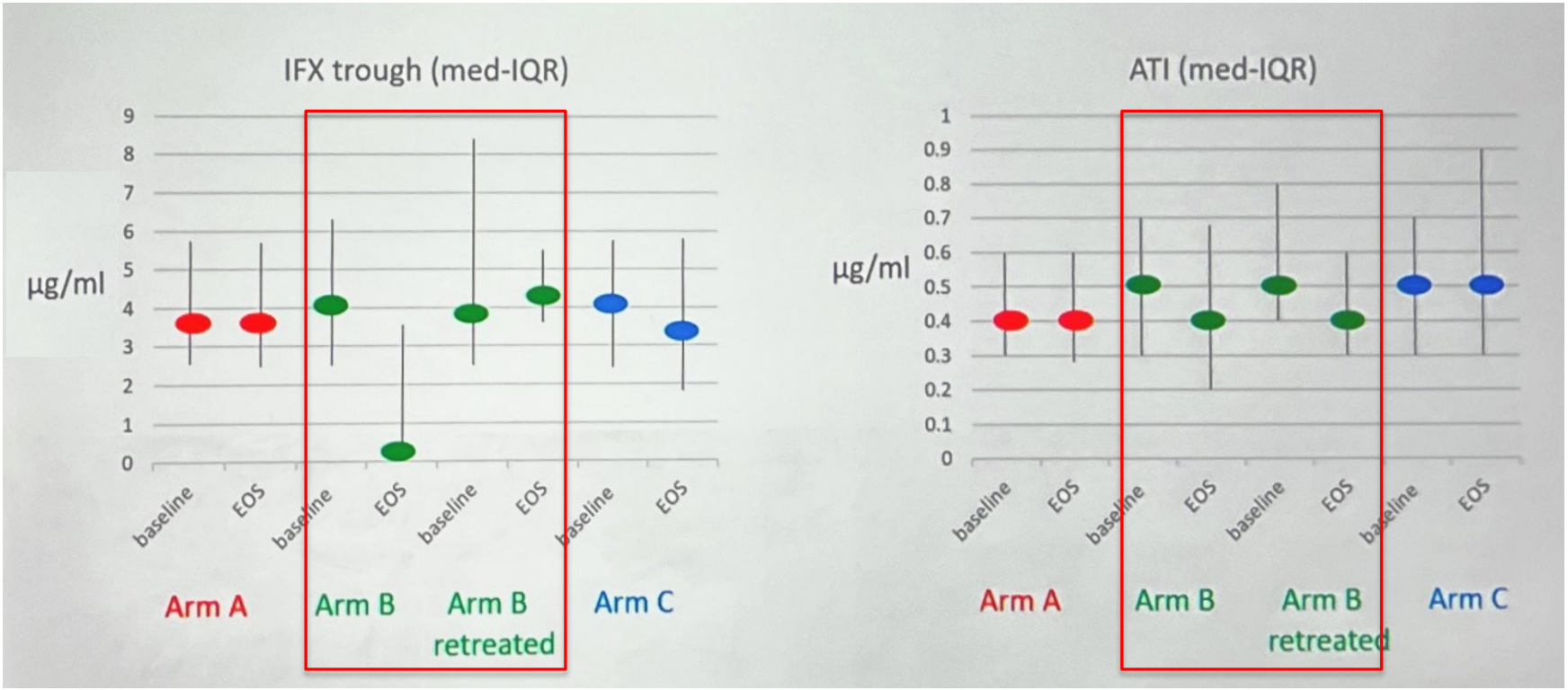
Prespecified non-inferiority threshold was 34 days.
As the 95% CI overlapped the threshold, the hypothesis was rejected

Outcomes of Relapsers

- Out of 39 relapsers, 28 were retreated/optimized
  (7 were treatment failures; 4 protocol deviation)

- Remission was achieved in 25/28 **(89%)**
  - 1/ 2 retreated patient in arm A (Combo)
  - 22/ 23 in arm B (Stop IFX)
  - 2/ 3 in arm C (stop IS)

Evolution of IFX Trough Levels and ATI between Baseline and End of Study (EOS)



Predictors of Relapse: Multivariable Analysis

	HR	95% CI	*p*
Arm B vs. Arm A	6.67	2.17-20	0.001
Arm B vs. Arm C	6.25	2-20	0.002
Age at dx <17 yrs	3.34	1.43-7.81	0.005
hsCRP at baseline	1.1	1-1.2	0.039
Fecal calprotectin >300µg/g at baseline	2.62	1.11-6.18	0.028
CDEIS at baseline	1.2	1.02-1.42	0.029

Multivariable analysis in patients stopping IFX (arm B):
6-TGN at baseline>300 pmol/ 9 x 10^8 (HR 0.23; 95% CI; 0.07-0.69; 0-0.009)

Conclusions

- **IFX withdrawal,** but not IS withdrawal, associated with a **higher relapse rate** than continuation of combination therapy; and a reduced time in remission (14 days over 2 years)
- **Almost all patients who stopped IFX achieved remission when resuming treatment** and overall failure rates were similar across groups
- Younger age at onset and evidence of inflammation at baseline were associated with clinical relapse in all treatment groups
- Low 6-TGN predicted clinical relapse in patients stopping IFX
- Presence or development of strictures and baseline CRP elevation predicted treatment failure in all groups
- Smoking predicted treatment failure in those stopping IFX

Safety: IBD and the Elderly

COMORBIDITY INFLUENCES THE COMPARATIVE SAFETY OF BIOLOGIC THERAPIES IN OLDER ADULTS WITH INFLAMMATORY BOWEL DISEASES

Bharati Kochar, David Cheng, Tianxi Cai, Ashwin Ananthakrishnan
Presentation Number: 3445

Background: IBD and the Elderly

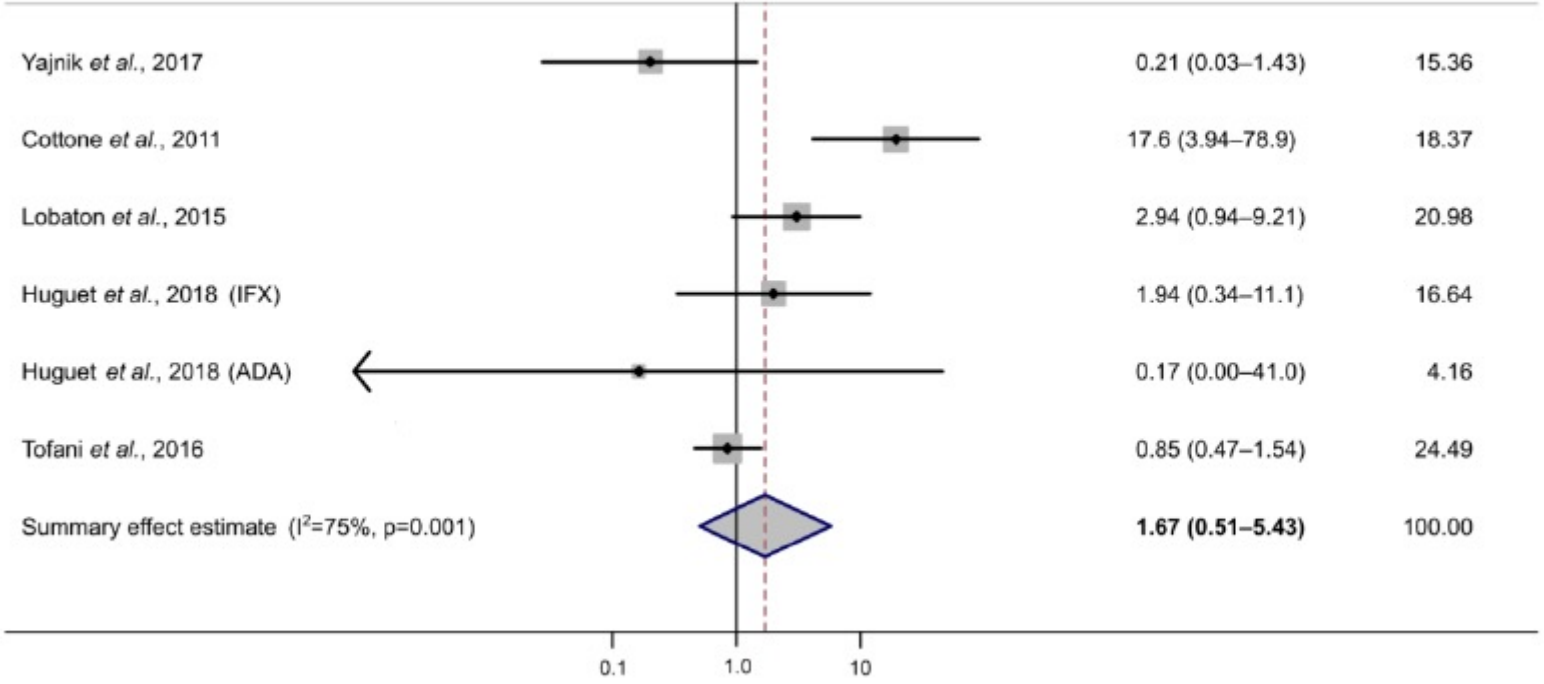
- Number of older adults requiring immunosuppressive therapy for the treatment of IBD is rapidly rising

- Older adults have a higher baseline risk for infection compared to younger adults
  - Older adults are a heterogeneous population with differential risks
  - Serious comorbidity is an important risk factor for infections

- **Study Aim:** To assess comparative safety of anti-TNF agents, vedolizumab, and ustekinumab in older adults with IBD accounting for the contribution of comorbidity

Background

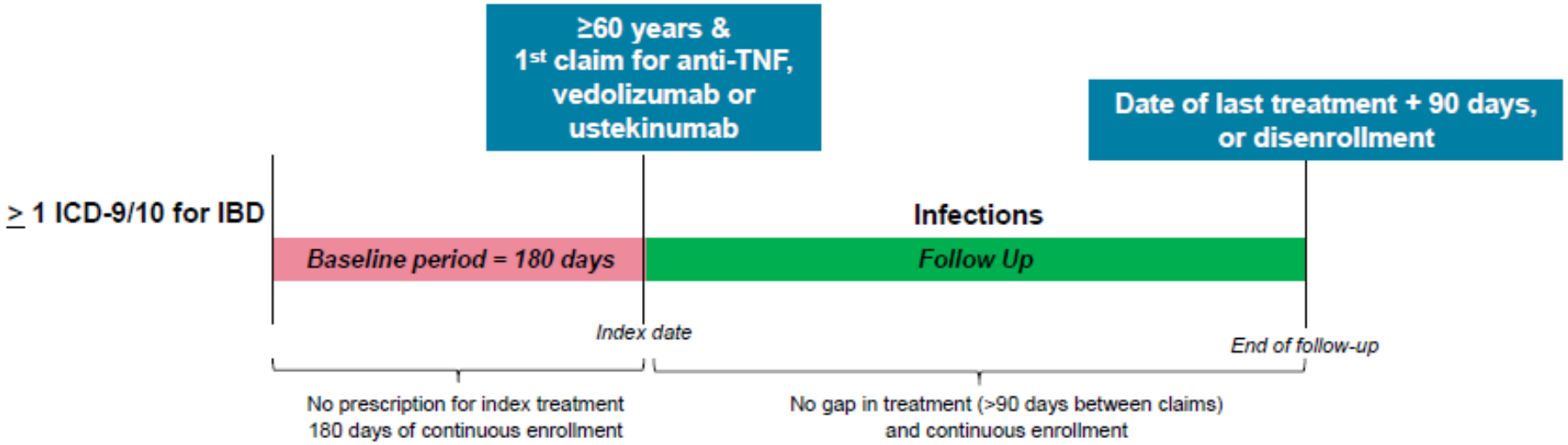
Current studies are inconclusive about risk of infections with biologic agents in older adults



Piovani *et al APT* 2020

Methods

Observational cohort study using unidentifiable claims data from 2008 to 2019 in a commercial U.S. health insurance plan from every U.S. state, Puerto Rico, Virgin Islands and Washington, D.C.



Methods

- US nationwide commercial insurance plan database
- 3,693 patients with IBD
  - Mean age: 67-68 years
  - Initiated treatment with:
    - Anti-TNF (n=2,369)
    - Vedolizumab (n=972)
    - Ustekinumab (n=352)
  - Adjusted for comorbidity with Charlson Comorbidity Index (CCI)
- **Outcomes:**
  - Primary: Time from treatment initiation to infection-related hospitalizations (serious infection)
  - Secondary: Time from treatment initiation to any infection

Baseline Characteristics

	Anti-TNF	Vedolizumab	Ustekinumab
n	2369	972	352
Mean age* in years (SD)	67 (±6)	68 (±7)	67 (±6)
% Female	54	49	68
% Crohn's disease	55	44	84
% Prior IBD hospitalization	16	18	20
% Corticosteroid use^	38	35	36
% Immunomodulator use^	12	6	10
Mean Charlson comorbidity index	1.3	1.5	1.6
Mean follow up in days (SD)	366 (±320)	307 (±300)	167 (±155)

TNF: Tumor Necrosis Factor
*at treatment initiation
SD: Standard Deviation
^at baseline, the 180-day period prior to biologic initiation

Results

- Compared with anti-TNF, the risk for infection-related hospitalization overall:
  - Vedolizumab (HR=0.94; 95%CI: 0.84-1.04)
  - Ustekinumab (HR= 0.92; 95% CI: 0.74-1.16)

- Compared to anti-TNF, for **patients with CCI >1**, risk for infection-related hospitalization:
  - Vedolizumab (HR=0.78; 95% CI:0.65-0.94)
  - Ustekinumab (HR=0.66; 95% CI:0.46- 0.91)

Secondary Outcome: Any Infection

Any Infection	Hazard Ratio	95% Confidence Interval	p-interaction
Vedolizumab vs anti-TNF agents	0.86	0.66 – 1.07	
Charlson comorbidity index ≤1	0.81	0.51 – 1.15	0.65
Charlson comorbidity index >1	0.90	0.65 – 1.22	
Ustekinumab vs anti-TNF agents	0.82	0.43 – 1.32	
Charlson comorbidity index ≤1	0.94	0.31 – 1.82	0.59
Charlson comorbidity index >1	0.71	0.29 – 1.26	

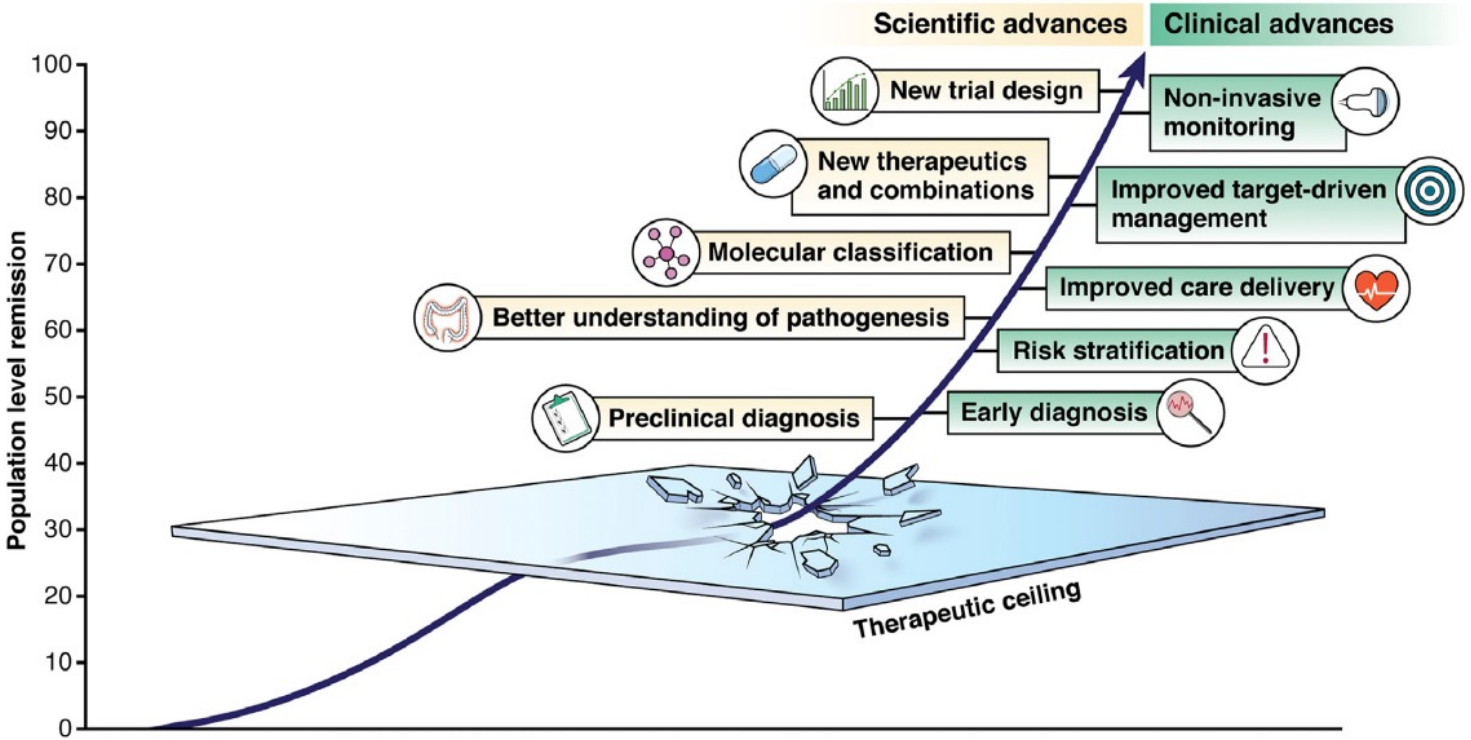
Conclusion

- For older adults **with greater comorbidity**, vedolizumab and ustekinumab confer a lower risk for infection-related hospitalization compared to anti-TNF therapies

- Overall, there were no overall differences in the rate of serious infections for older adults treated with anti-TNF, vedolizumab, and ustekinumab

- Advanced age, frailty, comorbidity need to be better understood in the older adult IBD patient to improve access to modern therapies

Breaking Therapeutic Ceiling



Raine T, Danese S *Gastroenterol* 2022; 162:1507-1511