2nd Annual

GI ReConnect

June 10-11, 2022

HILTON SANTA FE BUFFALO THUNDER
SANTA FE, NEW MEXICO

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GI ReConnect

IBD: Controlled Clinical Trials

Bruce E. Sands, MD, MS
Chief of the Dr. Henry D. Janowitz Division of Gastroenterology
Dr. Burrill B. Crohn Professor of Medicine
Icahn School of Medicine at Mount Sinai
Mount Sinai Hospital
Mount Sinai Health System
New York, USA

Disclosure Statement

Disclosure Statement

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Faculty Disclosures

- Consultant: Abbvie, Amgen, AstraZeneca, Arena Pharmaceuticals, Boehringer-Ingelheim, BMS, Celltrion Healthcare, Glaxo SmithKline, Janssen, Eli Lilly, Merck & Co., Pfizer, Sun Pharma, Takeda, Teva
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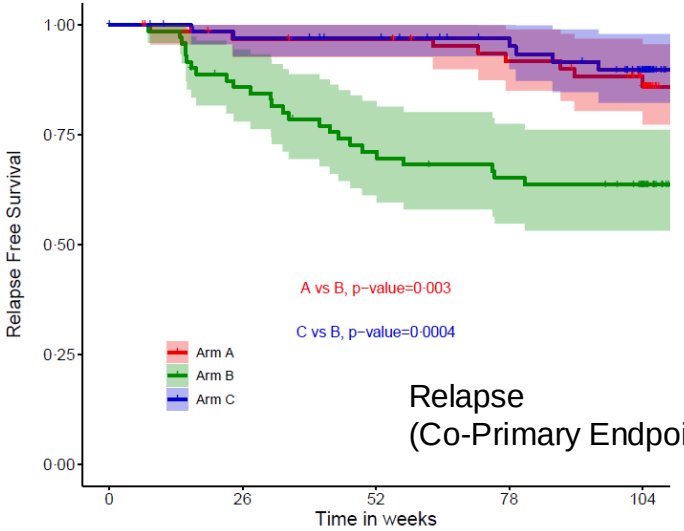
Stock Options	Ventyx Biosciences

SPARE: RCT of Withdrawal of Infliximab or Concomitant Immunosuppressant Therapy in CD Patients on Combination Therapy

- 204 CD patients in steroid-free remission (CDAI <150) for at least 6 mo and treated with IFX and IS combination therapy for at least 1 year (IFX at 5 mg/kg every 8 wk for at least 6 mo)
- Randomized to continue combination therapy; or to stop IFX; or to stop IS, followed for 2 yr
- On relapse
  - Arm A (Continued Combo): IFX increased to 10 mg/kg every 8 wk
  - Arm B (Stopping IFX): IFX 5 mg/kg infusion. If no remission at 4 wk, infusion at 10 mg/kg and then back to 5 mg/kg. If further relapse, 10 mg/kg every 8 wk
  - Arm C (Stopping IS): IFX intensification IFX to 10 mg/Kg/8 wk. If no remission, IS restarted
- **2nd Co-Primary Endpoint (mean time in remission over 2 yr): non-inferiority rejected at prespecified threshold of 34 d**



Arm C stopping IS

Arm A continuing combo

Arm B stopping IFX

Relapse
(Co-Primary Endpoint)

39 relapsers, 28 retreated/optimized

Remission achieved

1/2 in **arm A** (Combo)

22/23 in **arm B** (Stop IFX)

2/3 in **arm C** (Stop IS)

Louis E et al. Digestive Disease Week 2022, San Diego, CA. Abstract 887.

SPARE: Practical Implications

- Most patients in durable steroid-free remission on combination therapy of infliximab and immunosuppressant may stop immunosuppressant
- If stopping infliximab, check that 6TGN levels ≥300
- Even if there is relapse on stopping infliximab, the majority (but not all) can re-achieve remission: weigh risk-benefit for your patient

Louis E et al. Digestive Disease Week 2022, San Diego, CA. Abstract 887.

ENTERPRET: Randomized Trial of Vedolizumab Dose Optimization in Patients With Moderate to Severe UC With Early Non-response and High Drug Clearance

N = 170

Induction Dosing
VDZ 300 mg IV wk 0, 2, 6

No clinical response* at wk 6 and serum VDZ conc <50 mcg/mL at wk 5

Week 6

n = 108 (64%)
1:1

Standard VDZ Dosing
(n=53)

300 mg Q8W

Dose-Optimized VDZ
(n=55)

Regimen A:
VDZc ≥30 to <50 mcg/mL
600 mg at WK6, then 300 mg Q4W

or

Regimen B:
VDZc <30 mcg/mL
600 mg at WK6, then 600 mg Q4W

*≥2 points or ≥25% reduction in partial Mayo score

Osterman M et al. Digestive Disease Week 2022, San Diego, CA. Abstract 791.

ENTERPRET: Randomized Trial of Vedolizumab Dose Optimization in Patients With Moderate to Severe UC With Early Non-response and High Drug Clearance

	Standard VDZ Dosing (N=53)	Dose-Optimized VDZ (N=55)	Regimen A (N=28)	Regimen B (N=27)
Primary Endpoint				
Endoscopic mucosal healing[1], wk 30, n (%)	10 (18.9)	8 (14.5)	4 (14.3)	4 (14.8)
Secondary Endpoints				
Clinical remission[2], wk 30, n (%)	5 (9.4)	5 (9.1)	2 (7.1)	3 (11.1)
Clinical response[3], wk 30, n (%)	17 (32.1)	17 (30.9)	8 (28.6)	9 (33.3)
Clinical response[4], wk 14, n (%)	18 (34.0)	22 (40.0)	12 (42.9)	10 (37.0)
Durable clinical response[5]	12 (22.6)	17 (30.9)	8 (28.6)	9 (33.3)

[1]MES≤1; [2]Complete Mayo Score ≤2, no subscore >1; [3]Reduction in complete Mayo Score ≥3 and ≥30 from BL with decrease in RB score ≥1; [4]Reduction in partial Mayo Score ≥2 and ≥25% from BL with decresase in RB ≥1 or RB=≤1 at week 14; 5 Clinical response at weeks 14 and 30 based on partial Mayo score

Osterman M et al. Digestive Disease Week 2022, San Diego, CA. Abstract 791.

ENTERPRET: Practical Implications

- Dose intensification not effective for UC patients who do not respond to standard vedolizumab induction and who have low serum vedolizumab levels: yet another negative TDM study!
- Is trough level (C_{min}) the correct parameter? Prior work suggests C_{avg} more strongly associated with response in CD and UC[1]

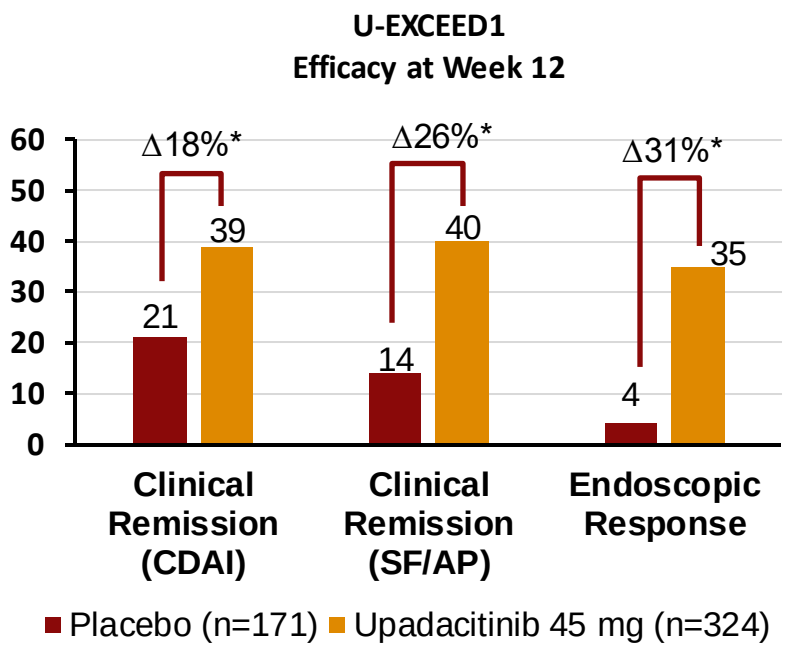
[1]Rosario M et al. *J Crohns Colitis*. 2017;1;11:921-929.

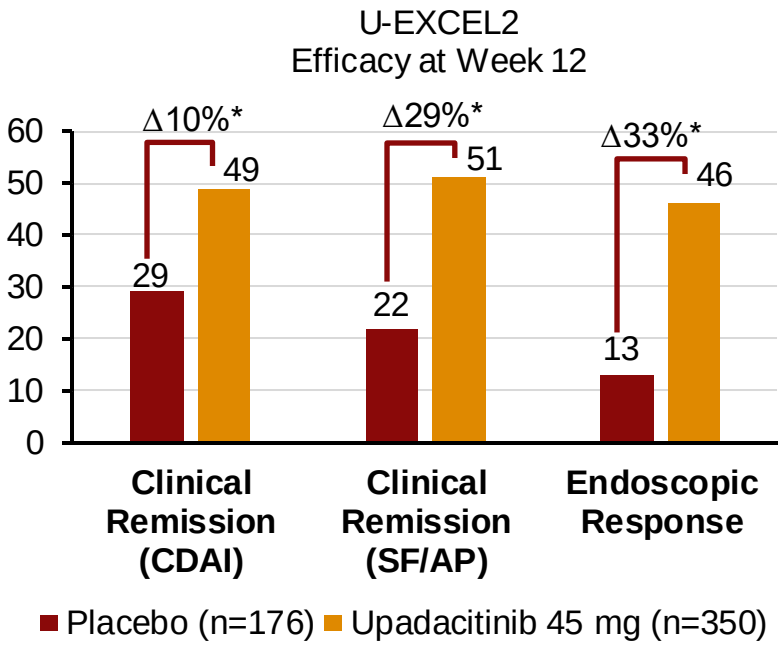
Updacitinib in UC: Efficacy

- Most effective agent we have yet seen in UC
  - At week 8, 73-74% in clinical response, 26-33% in clinical remission, 36-44% with endoscopic improvement, 30-37% with histo-endoscopic mucosal improvement
  - High rates of corticosteroid-free remission
  - Works very quickly: significant improvement in rectal bleeding and stool frequency in just one day
  - Excellent maintenance effect with both 15 and 30 mg doses

Danese S et al. *Lancet*. Published Online May 26, 2022 https://doi.org/10.1016/ S0140-6736(22)00581-5;
Vermeire S et al. Digestive Disease Week 2022, San Diego, CA, Abstract 967.

U-EXCEED & U-EXCEL: Ph3 Induction Studies of Upadacitinib in Crohn's Disease





*p<0.0001

[1]Colombel JF et al. Digestive Disease Week 2022, San Diego, CA, Presentation 867f;
[2]https://news.abbvie.com/article_print.cfm?article_id=12406.

Adverse Events of Special Interest in U-ACHIEVE Maintenance

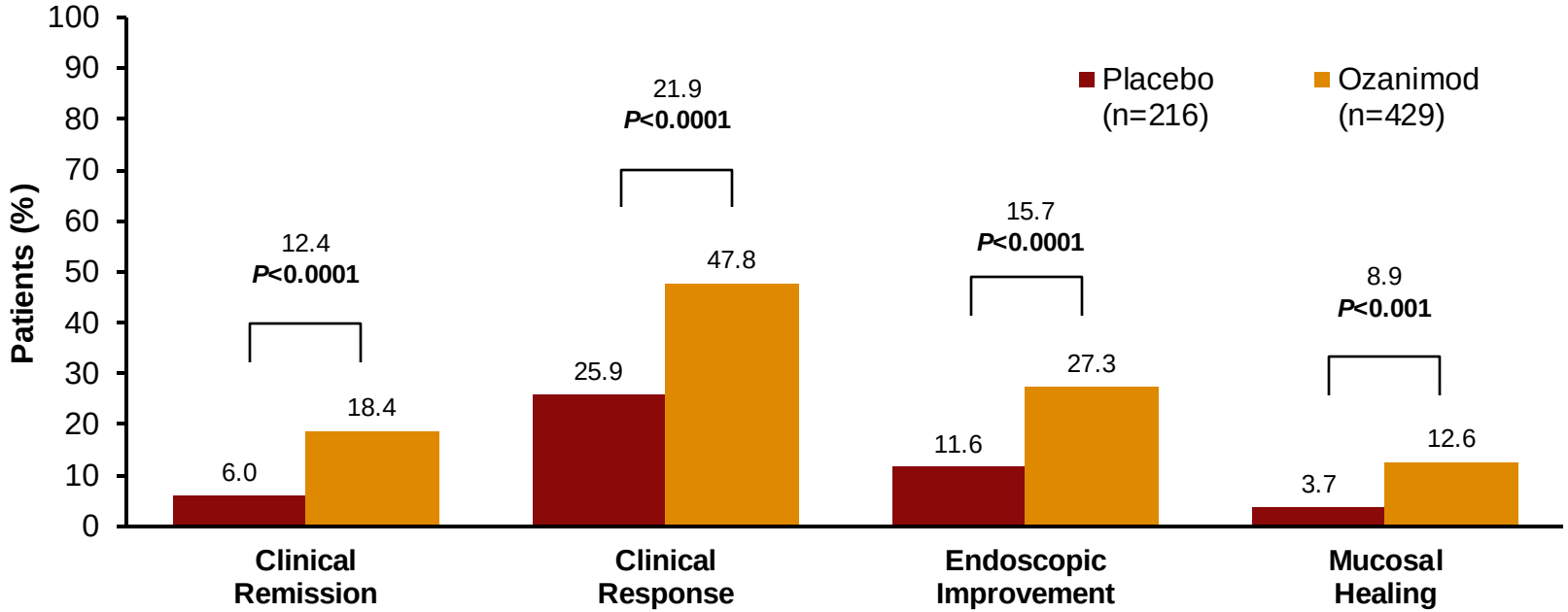
	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Treatment difference (95% CI)*	Upadacitinib 30 mg once daily (n=154)	Treatment difference (95% CI)*
Serious infection	6 (4%); 6·9	5 (3%); 4·2	−0·7 (−5·3 to 3·8)	4 (3%); 3·0	−1·4 (−5·8 to 3·0)
Opportunistic infection (excluding tuberculosis and herpes zoster)	0	1 (1%); 0·8	0·6 (−1·6 to 2·9)	0	0
Herpes zoster‡	0	6 (4%); 5·0	4·2 (0·5 to 7·8)	6 (4%); 4·4	3·8 (0·3 to 7·3)
Malignancy excluding NMSC§	1 (<1%); 1·1	1 (<1%); 0·8	0 (−2·7 to 2·6)	2 (1%); 1·5	0·6 (−2·3 to 3·5)
NMSC	0	0	0	2 (1%); 1·5	1·3 (−1·2 to 3·9)
Renal dysfunction	1 (<1%); 1·1	1 (<1%); 0·8	−0·1 (−2·7 to 2·5)	1 (<1%); 0·7	0 (−2·6 to 2·5)
Hepatic disorder	3 (2%); 5·7	10 (7%); 16·8	4·8 (−0·1 to 9·7)	8 (5%); 7·4	3·2 (−1·3 to 7·8)
Adjudicated gastrointestinal perforation§	1 (1%); 2·3	0	−0·7 (−3·0 to 1·6)	0	−0·7 (−3·0 to 1·6)
Adjudicated MACE§¶	1 (1%); 1·1	0	−0·7 (−2·9 to 1·6)	0	−0·7 (−2·9 to 1·6)
Adjudicated VTE‖	0	0	0	2 (1%); 1·5	1·3 (−1·2 to 3·9)
Anaemia‡	9 (6%); 12·6	7 (5%); 5·9	−1·2 (−6·5 to 4·1)	3 (2%); 2·2	−4·1 (−8·7 to 0·5)
Neutropenia‡	2 (1%); 2·3	4 (3%); 4·2	1·4 (−2·3 to 5·0)	9 (6%); 8·9	4·5 (0·1 to 8·9)
Lymphopenia‡	2 (1%); 3·4	3 (2%); 2·5	0·7 (−2·7 to 4·1)	3 (2%); 3·0	0·7 (−2·7 to 4·0)
CPK elevation	3 (2%); 3·4	9 (6%); 7·3	3·9 (−0·8 to 8·7)	13 (8%); 11·1	6·4 (1·2 to 11·5)

Danese S et al. *Lancet*. Published Online May 26, 2022 https://doi.org/10.1016/ S0140-6736(22)00581-5.

Upadacitinib in IBD: Practical Implications

- Black box warning necessitates second-line position after failure of TNFi
- Whether positioned after ustekinumab or vedolizumab, or after S1P receptor modulator in UC, depends upon risk-benefit considerations for individual patient (symptom severity, risk factors for MACE, cancer, thrombosis, risk aversion)
- Position in CD remains to be seen, but extraordinary efficacy may tip scale in favor of use (again, after failure of TNFi)

True North: Ph3 RCT of Ozanimod in Moderate-to-Severe UC at Week 10

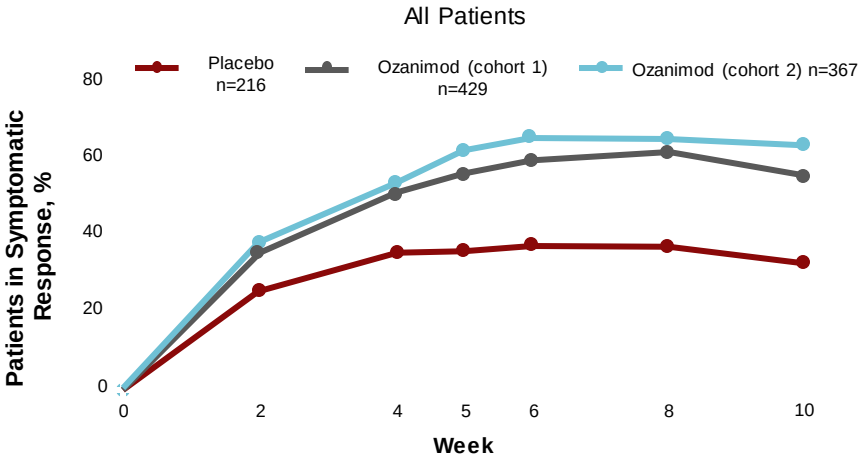


[a]3-component Mayo score results: rectal bleeding score (RBS) = 0, stool frequency score ≤1 and ≥1-point reduction from baseline, and mucosal endoscopy score (MES) ≤1 without friability; [b]Reduction in 3-component Mayo score of ≥2 points and ≥35%, and reduction in RBS of ≥1 point or absolute RBS of ≤1 point; [c]MES ≤1 without friability; [d]Endoscopic improvement plus histological remission (Geboes<2.0; no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue) in the same patient.

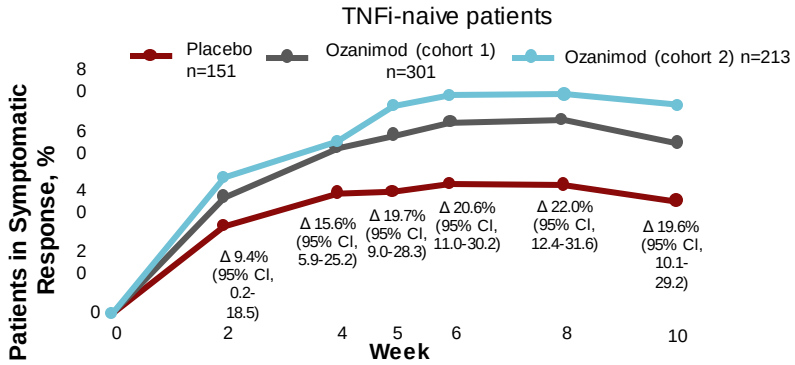
Data based on all randomized patients who received ≥1 dose of study treatment (intent-to-treat population). Missing data handled using non-responder imputation. *P*-values refer to odds ratios (not shown) based on 2-sided Cochran-Mantel-Haenszel test.

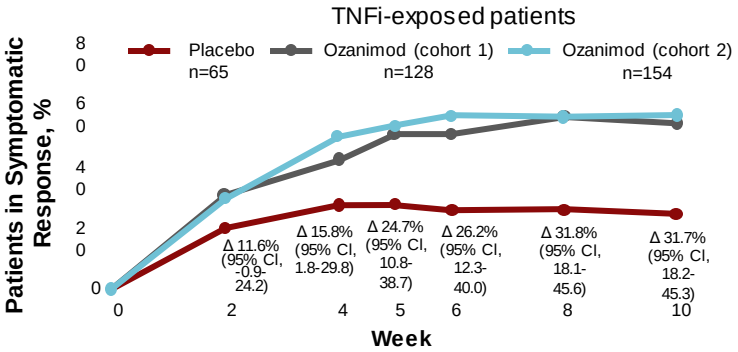
Sandborn WJ et al. *N Engl J Med. 2021*; 385:1280-1291.

True North: Symptomatic Response Through Week 10



Difference:	9.6%	14.0%	17.5%	20.2%	22.9%	22.1%
95% CI:	(2.1-17.0)	(5.8-22.1)	(9.2-25.8)	(12.0-28.5)	(14.6-31.3)	(13.5-30.6)



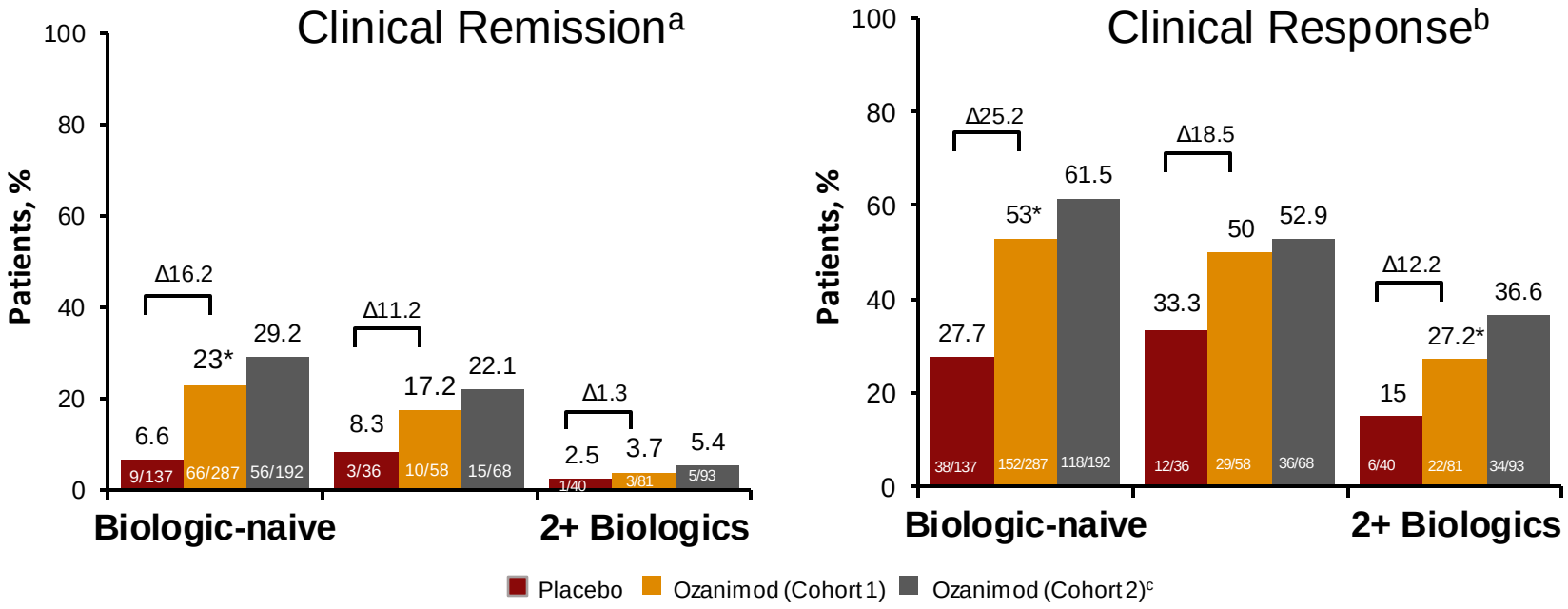


Symptomatic Response: ≥1 point and ≥30% decrease in adapted partial Mayo score vs BL and ≥1 point decrease in RBS vs BL or absolute RBS ≤1.

Afzali A et al. Digestive Disease Week 2022, San Diego, CA. Abstract Tu1472.

Ozanimod for Moderate to Severely Active UC

Induction Efficacy at Week 10: Outcomes by Prior Biologic Use



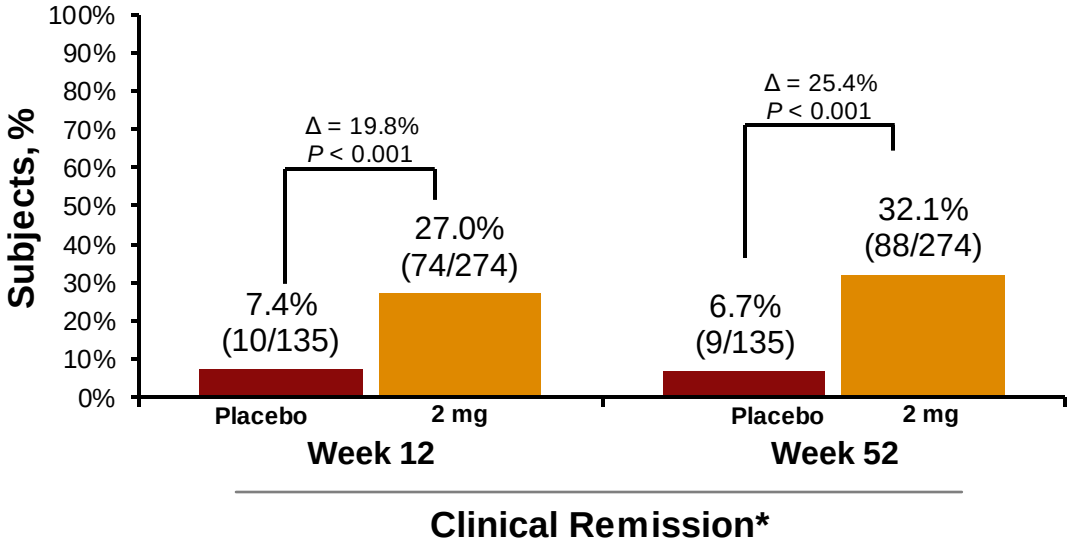
*Significant vs placebo.
[a]Defined as RBS = 0, SFS ≤ 1 (plus ≥ 1-point reduction from baseline), and MES ≤ 1 without friability. [b]Defined as reduction in 3-component Mayo score of ≥ 2 points and ≥ 35%, and reduction in RBS of ≥ 1 point or absolute RBS of ≤ 1 point. [c]Cohort 2 received open-label ozanimod, so a statistical analysis for comparison to placebo was not conducted.
MES, mucosal endoscopy subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore.
Sands BE et al. *ACG 2021*.

Ozanimod: Practical Implications

- Best positioned as first-line advance therapy
- If used as second-line advanced therapy, efficacy similar in those who failed 1 biologic
- Patients who failed ≥2 biologics may still respond but may take longer

ELEVATE UC 52 Primary Endpoint: Week 12 & Week 52 Clinical Remission

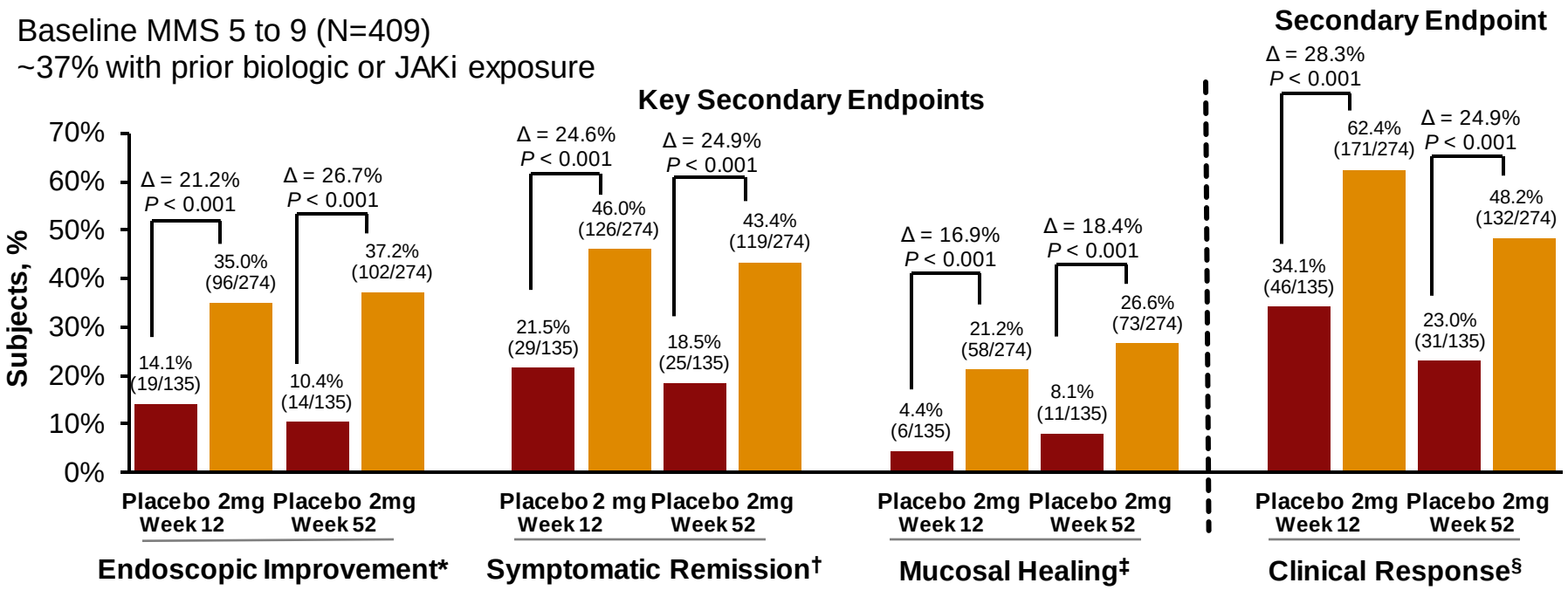
Baseline MMS 5 to 9 (N=409)
~37% with prior biologic or JAKi exposure



ES, endoscopic subscore; MMS, Modified Mayo Score; RB, rectal bleeding; SF, stool frequency.
Data were from reported randomized strata. Percent of patients with clinical remission at Week 12 was derived from Cochran-Mantel-Haenszel analysis.
* Clinical remission defined as SF subscore =0 (or 1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1 (excluding friability).
Sandborn WJ et al. Digestive Disease Week 2022, San Diego, CA. Abstract 968a.

ELEVATE UC 52: Key Secondary and Secondary Efficacy Endpoints at Weeks 12 and 52

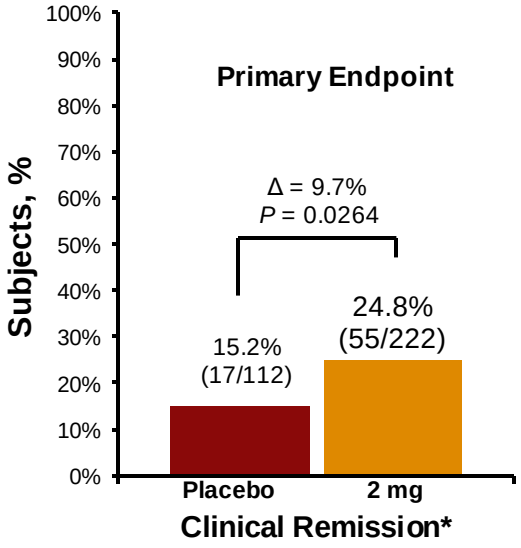
Baseline MMS 5 to 9 (N=409)
~37% with prior biologic or JAKi exposure

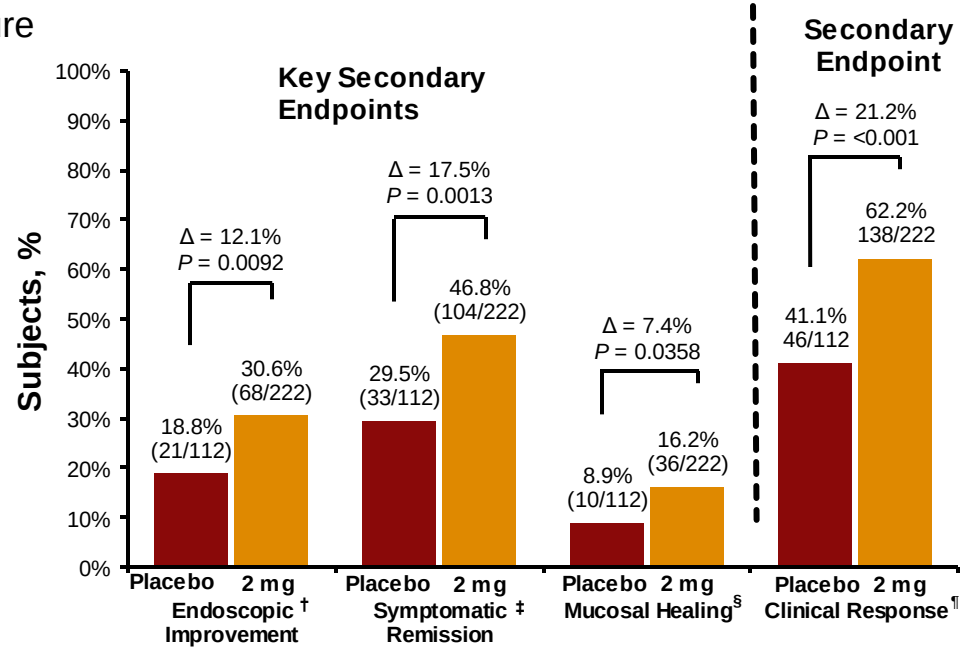


ES, endoscopic subscore; MMS, Modified Mayo Score; RB, rectal bleeding; SF, stool frequency.
* Endoscopic improvement defined as ES ≤1 (excluding friability); † Symptomatic remission defined as SF subscore = 0 (or 1, with a ≥1-pointdecrease from baseline) and RB subscore =0; ‡ Mucosal healing defined as ES of ≤1 (excluding friability) with histologic remission measured by a Geobes Index score <2; § Clinical response defined as ≥2 point & ≥30% decrease from baseline in MMS and ≥1-point decrease from baseline in RB subscore or an absolute RB subscore ≤1 and was not a key secondary endpoint.
Sandborn WJ et al. *Digestive Disease Week 2022*, San Diego, CA. Abstract 968a.

ELEVATE UC12: Primary and Key Secondary Efficacy Endpoints at Week 12

Baseline MMS 5 to 9 (N=334)
~ 37% with prior biologic or JAKi exposure



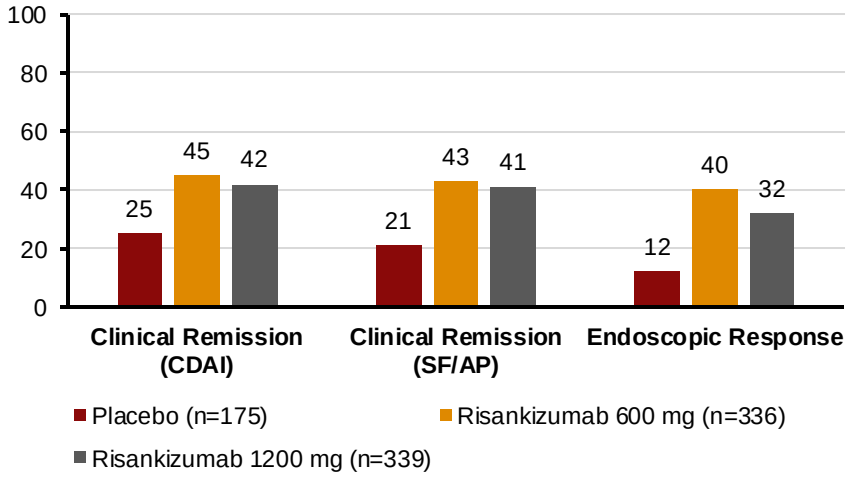


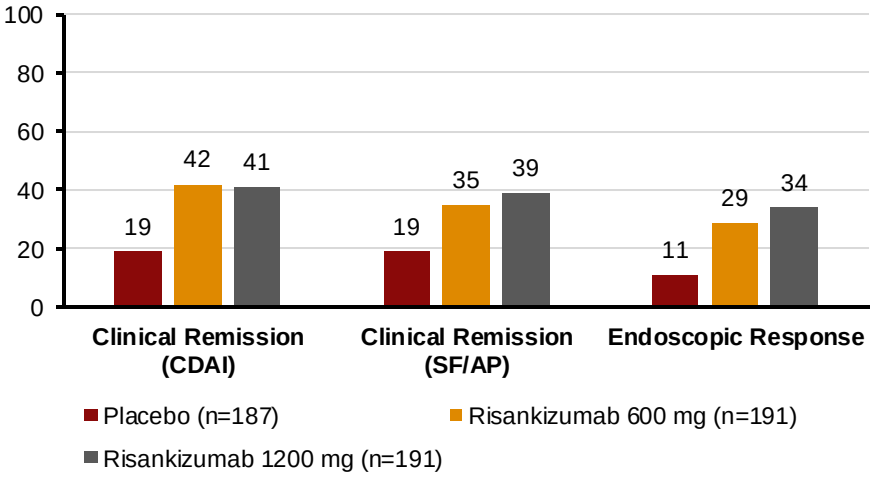
ES, endoscopic subscore; MMS, Modified Mayo Score; RB, rectal bleeding; SF, stool frequency.
* Clinical remission defined as SF subscore =0 (or 1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1 (excluding friability); † Endoscopic improvement defined as ES ≤1 (excluding friability); ‡ Symptomatic remission defined as SF subscore = 0 (or 1, with a ≥1-point decrease from baseline) and RB subscore =0; § Mucosal healing defined as ES of ≤1 (excluding friability) with histologic remission measured by aGeobes Index score <2; ¶ Clinical response defined as ≥2 point & ≥30% decrease from baseline in MMS and ≥1-point decrease from baseline in RB subscore or an absolute RB subscore ≤1 and was not a key secondary endpoint.
Sandborn WJ et al. Digestive Disease Week 2022, San Diego, CA. Abstract 968a.

Etrasimod: Practical Implications

- Efficacy similar to ozanimod, overall
- Safety profile likely similar to ozanimod
- Shorter t½ → faster washout and lymphocyte recovery
- Possible advantages in fewer drug-drug interactions?

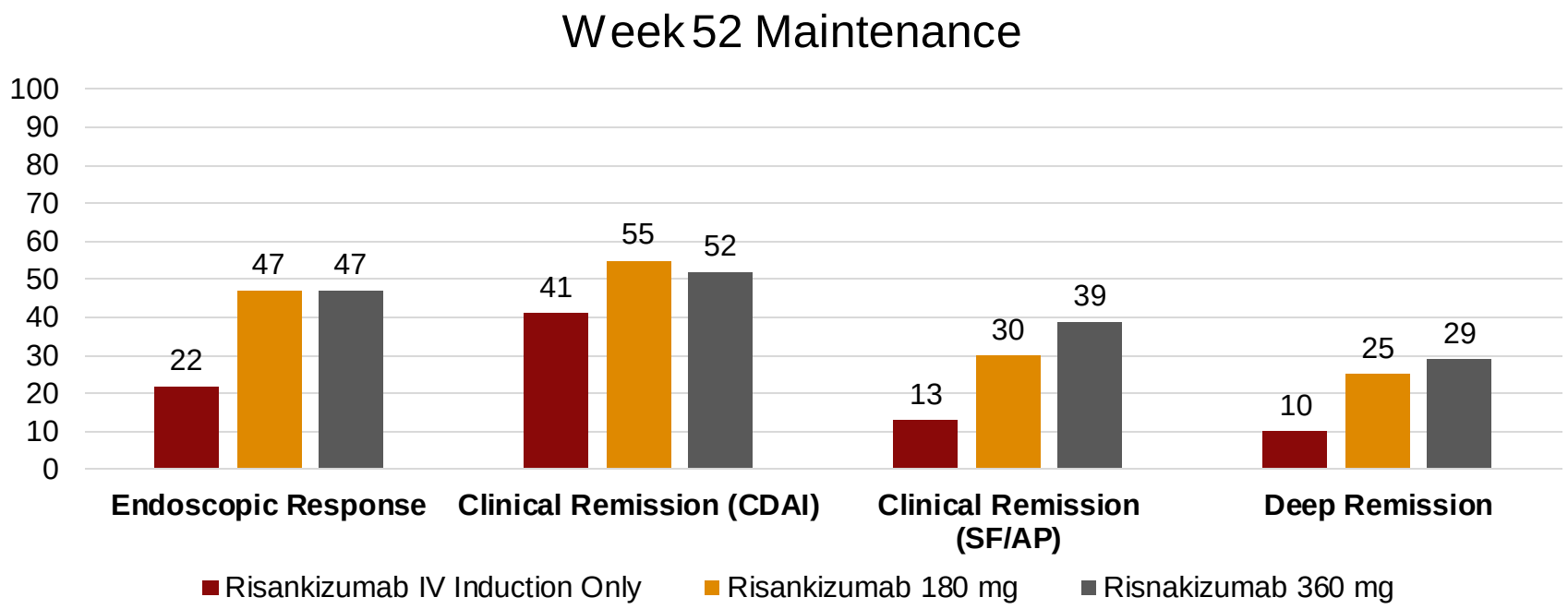
ADVANCE and MOTIVATE: Risankizumab (Anti-IL-23) in Crohn's Disease Phase 3: Week 12 Induction





D'Haens G et al. *Lancet*. 2022;399:2015-30.

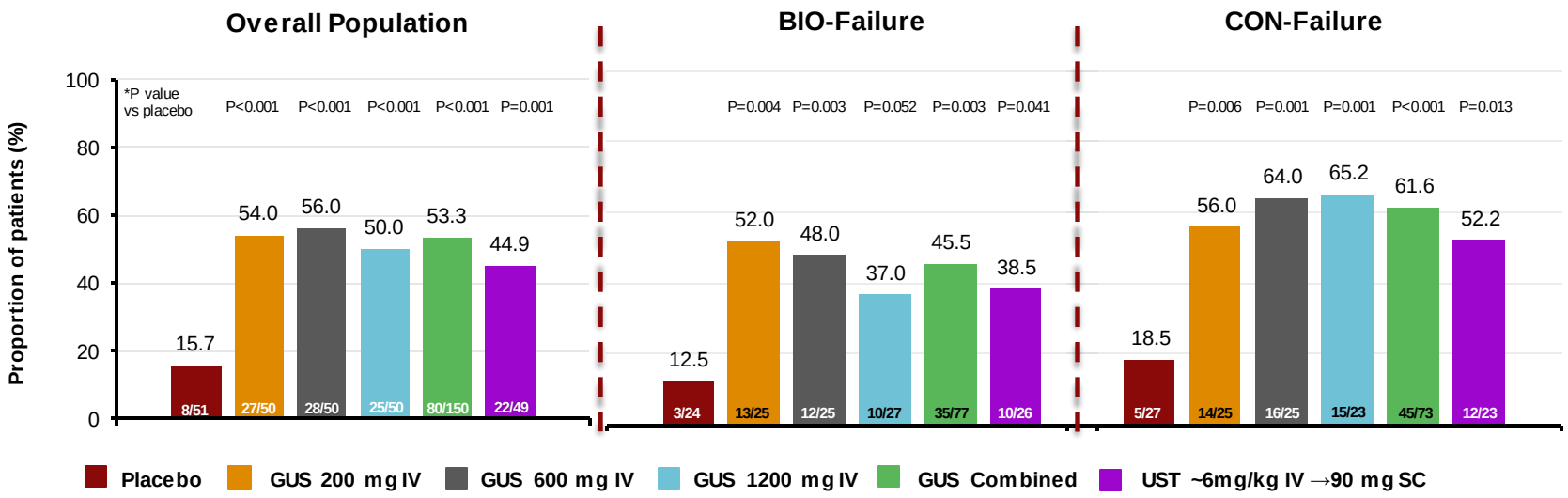
FORTIFY: Risankizumab (Anti-IL-23) in Crohn's Disease Phase 3



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

GALAXI 1: Guselkumab Induction Therapy in Patients With Moderate-to-Severe Crohn's Disease

Clinical Remission at Week 12



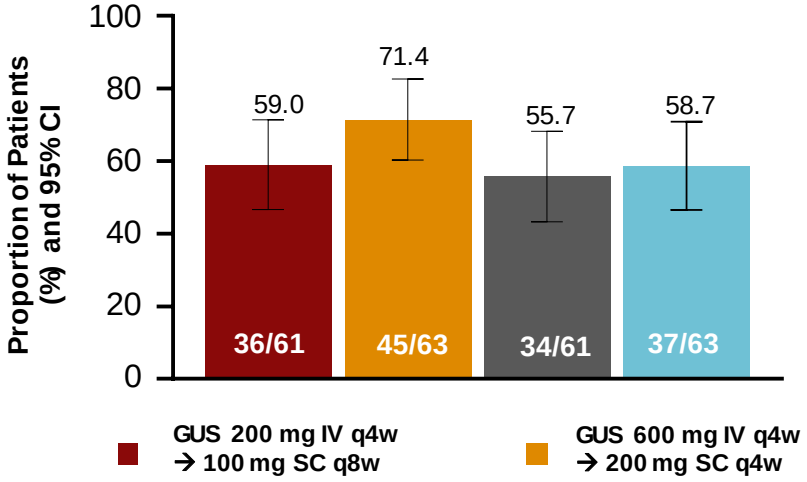
Clinical remission defined as CDAI score <150

~54% biologic-exposed

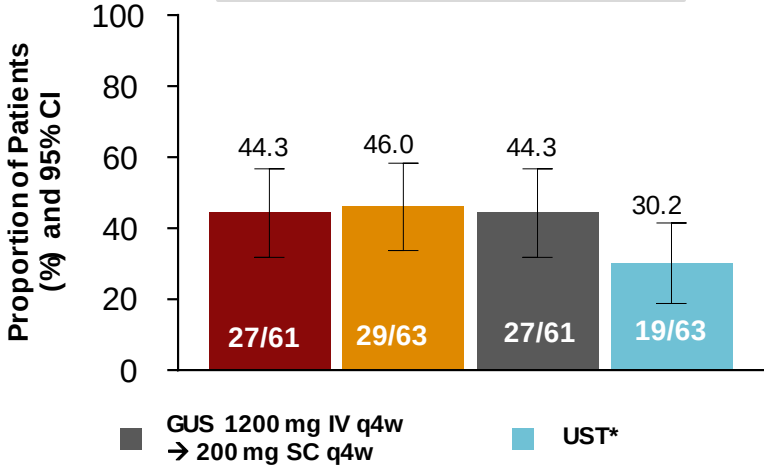
Sandborn W et al. *Gastroenterology*. In press February 05, 2022.

GALAXI 1: Guselkumab Induction Therapy in Patients With Moderate-to-Severe Crohn's Disease

Corticosteroid-Free Clinical Remission
CDAI score <150 and not receiving corticosteroids



Endoscopic response
≥50% improvement from baseline in SES-CD score or score ≤2



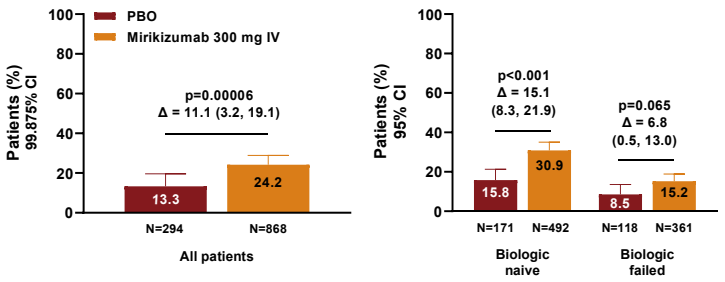
Data are presented as proportion of patients and 95% confidence interval (CI). CIs were based on the Wald statistic.
Pts who had a prohibited change in concomitant Crohn's disease medication, a Crohn's disease-related surgery, discontinued study agent due to lack of efficacy, an adverse event of worsening Crohn's disease, or insufficient data to calculate CDAI score at Week 48 were considered not to be in corticosteroid-free clinical remission at week 48. Pts who had discontinued study agent due to any other reasons prior to week 48 had their observed data used, if available, to determine responder and nonresponder status at Week 48.
*UST approximately 6 mg/kg IV → 90 mg SC
Panaccione R et al. Digestive Disease Week 2022, San Diego, CA. Abstract 888.

LUCENT-1: Mirikizumab (Anti-p19/IL-23 Antibody) in Ulcerative Colitis, Phase 3

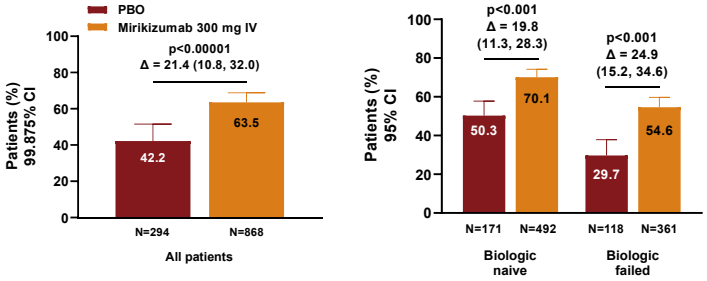
- 1,162 pts with moderate-to-severe UC (modified Mayo Score of 4 to 9 with endoscopic subscore ≥2) randomized 3:1 to Miri 300 mg IV Q4W x3 or PBO
- All had inadequate response, loss of response, or intolerance to ≥1:
  - Corticosteroid or immunomodulator
  - Biologic (TNF inhibitor or anti-integrin antibody)
  - JAK inhibitor (tofacitinib)

  } ~40%
- Excluded patients with prior exposure to anti-IL-12/23p40 or anti-IL-23p19 antibodies or failed ≥3 prior biologic therapies for UC

Primary Endpoint: Clinical Remission at Wk 12

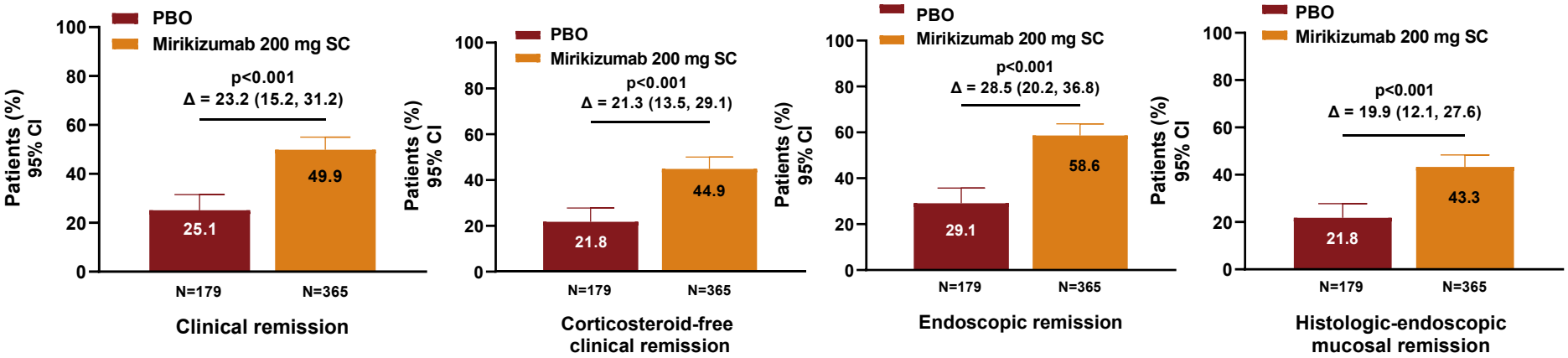


Clinical Response at Wk 12



D'Haens G et al. DDW 2022. Abstract 884.

LUCENT-2: Outcomes After 52 Weeks Treatment (Week 40 of Maintenance)



Clinical Remission: Stool frequency (SF) = 0, or SF = 1 with a ≥1-point decrease from baseline; rectal bleeding (RB) = 0; endoscopic subscore (ES) = 0 or 1 (excluding friability)

Corticosteroid-free clinical remission: Clinical remission at Week 40, and symptomatic remission (SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline; and RB=0) at Week 28, **<u>and no corticosteroid use for ≥12 weeks prior to Week 40</u>**

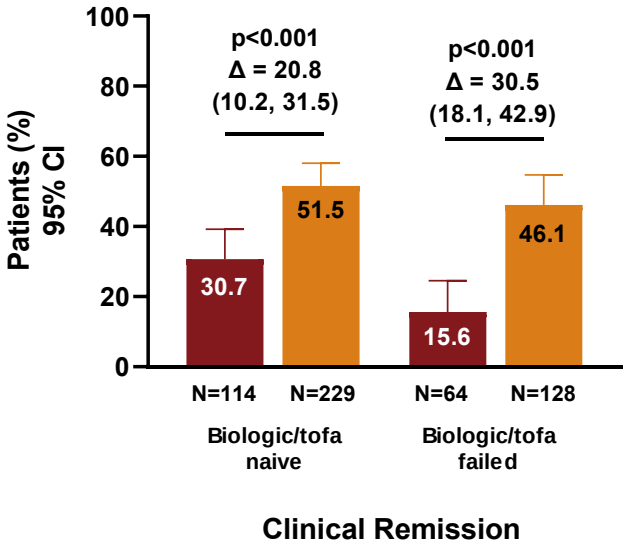
Endoscopic Remission: Endoscopic subscore = 0 or 1 (excluding friability)

HEMR: Histologic remission with resolution of mucosal neutrophils, determined by Geboes ≤2B.0 score

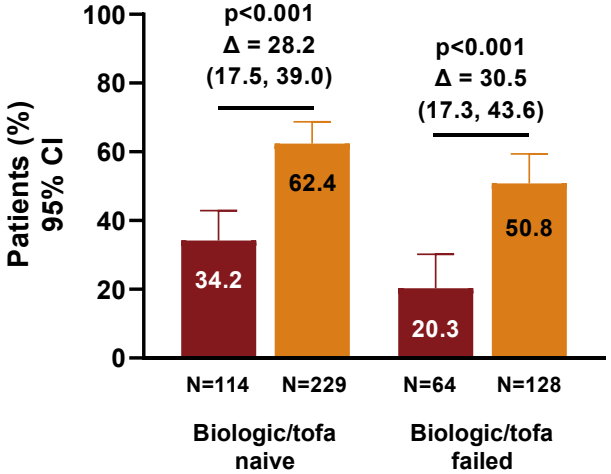
The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups. Δ indicates common risk difference vs placebo.

Dubinsky MC et al. *DDW 2022*, Abstract 867e.

LUCENT-2 Endpoints by Biologic/Tofacitinib Failure Status



Clinical Remission

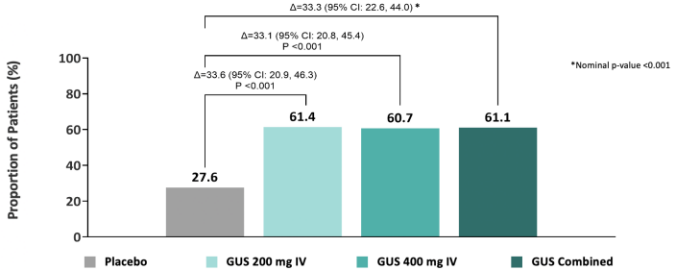


Endoscopic Remission

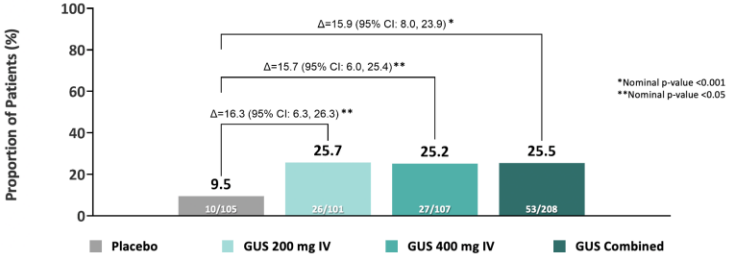
Clinical Remission: Stool frequency (SF) = 0, or SF = 1 with a ≥1-point decrease from baseline; rectal bleeding (RB) = 0; endoscopic subscore (ES) = 0 or 1 (excluding friability)
Endoscopic Remission: ES = 0 or 1 (excluding friability)
The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups. Δ indicates common risk difference vs placebo.
Dubinsky MC et al. *Digestive Disease Week 2022*, San Diego, CA. Abstract 867e.

QUASAR: Guselkumab (Anti-IL-23) in Ulcerative Colitis, Phase 2b

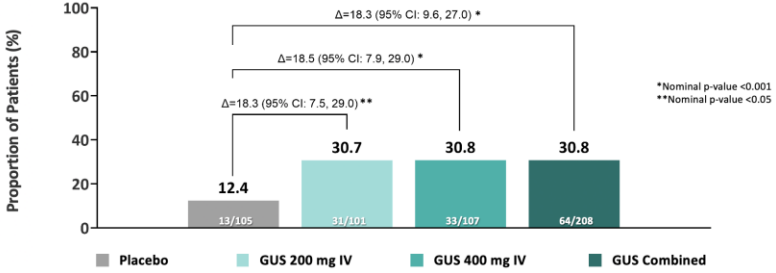
Primary Endpoint: Clinical Response at Wk 12



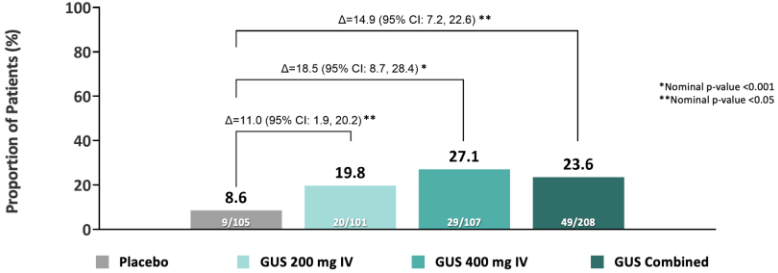
Key Secondary Endpoint: Clinical Remission at Wk 12



Major Secondary Endpoint: Endoscopic Improvement at Wk 12



Major Secondary Endpoint: Histo-Endoscopic Mucosal Improvement at Wk 12



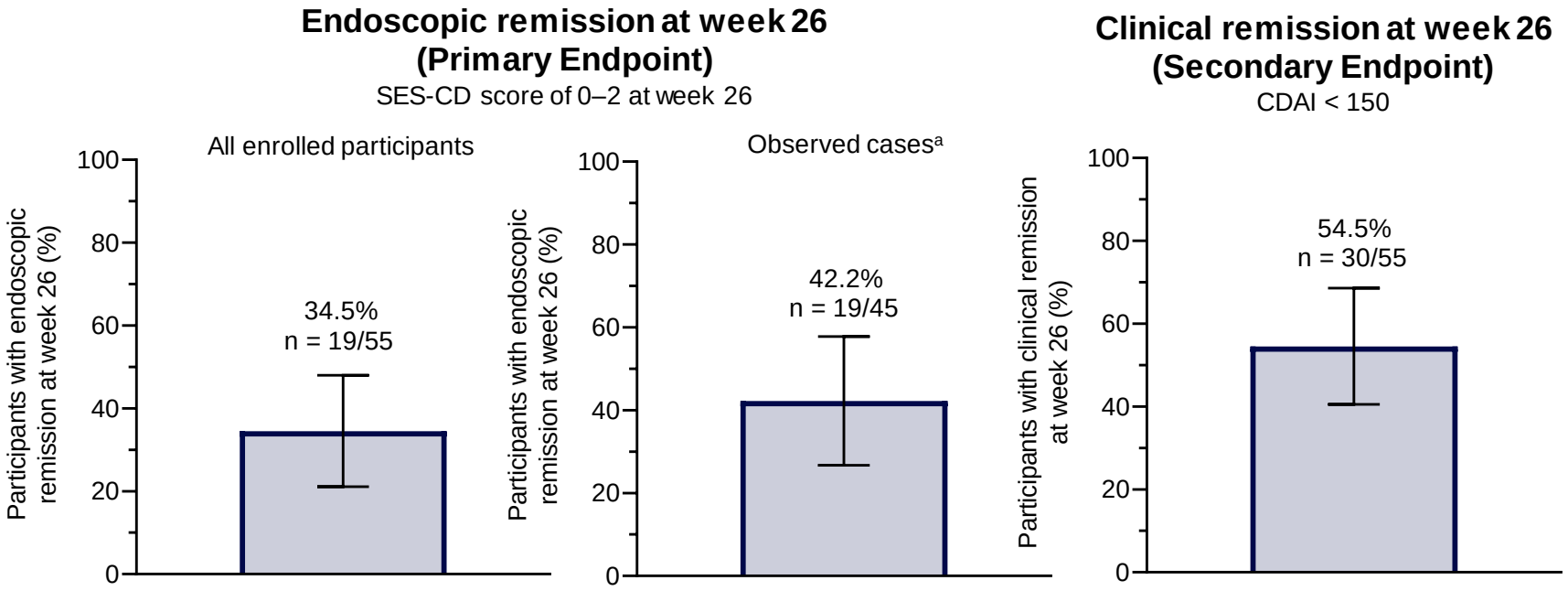
*History of inadequate response or intolerance to 1 or more advanced therapies in 47%.

Allegretti JR et al. Digestive Disease Week 2022, San Diego, CA, Abstract Tu1446.

Anti-IL-23 Antibodies in IBD

- Effective options as first- or second-line advanced therapies in IBD, and safer than TNFi
- As with all agents, slightly lower absolute efficacy in bio-experienced patients, though similar efficacy when placebo-adjusted
- Efficacy advantage over anti-IL-12/23 (ustekinumab) in CD may be ~10% margin
  - This has been enough of a margin to get some drugs to market!
  - Access will be determined by the market

EXPLORER: Open-label Study of Triple Combination Therapy (Vedolizumab, Adalimumab and Methotrexate) in Early CD



Mean SES-CD score at week 26 (observed cases) = 3.9
Mean reduction from baseline = 8.9 points

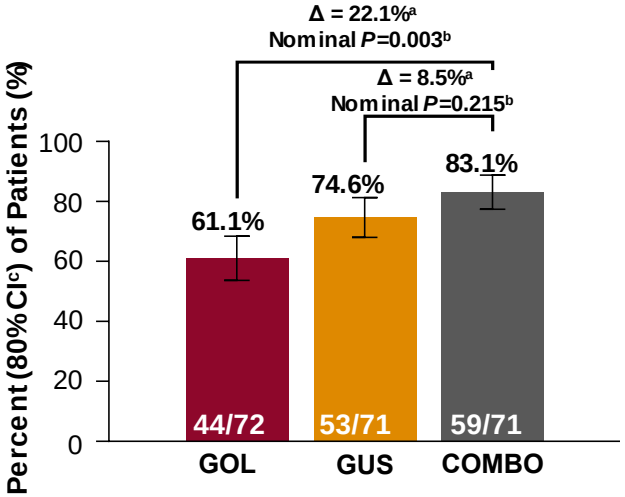
Intention-to-treat population

Colombel J-F et al. *Digestive Disease Week 2022*, San Diego, CA, Abstract 885.

VEGA: Ph2b Golimumb vs Guselkumab vs GOL+GUS in UC

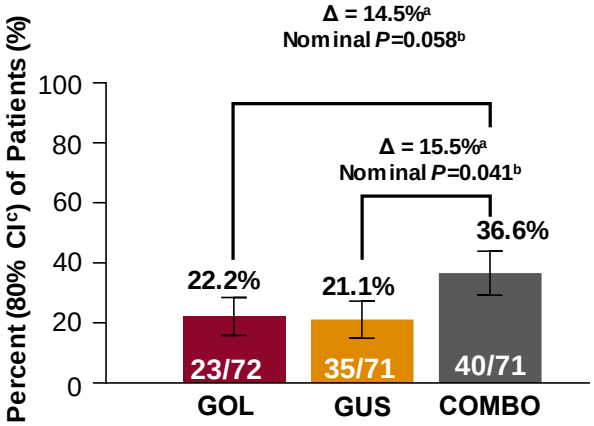
Primary Endpoint
Clinical Response at Wk 12

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



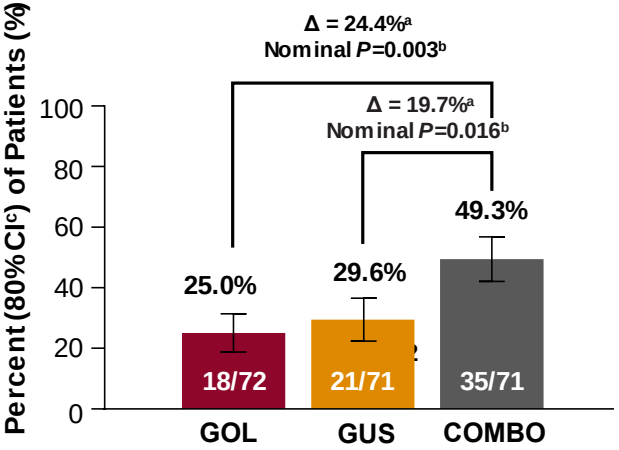
Major Secondary Endpoint
Clinical Remission at Wk 12

Mayo Score ≤2 with No Individual Subscore >1



Secondary Endpoint
Endoscopic Improvement at Wk 12

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.

Combining Advanced Therapies: Practical Implications

- Vedolizumab + adalimumab + MTX in CD very effective but not transformational
- Golimumab + guselkumab in UC at least additive in efficacy
- Not feasible at present due to cost; a future concept
- While current combinations consist of what we have now, future combinations may include non-immune targets (barrier, microbiome, other)

IBD Clinical Trials: Takeaways From DDW 2022

- Stop immunomodulators in stable patients on combination IFX + IM
- Don’t dose escalate vedolizumab for lack of clinical response (but perhaps give it more time than 6 weeks)
- Upadacitinib great choice for second line advanced therapy for UC (and eventually CD), but consider risk-benefit balance for the individual patient
- Anti-IL 23 antibodies safer than anti-TNF (and do not require combo therapy) and effective for CD and UC, likely with incremental efficacy over ustekinumab (CD)
- Combination therapy promising but not yet feasible in clinical practice today for most patients