
2023 SCSG
GI SYMPOSIUM

Best of IBD at DDW 2023: Part II

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Conflict of Interest Disclosure
(over the past 24 months)

Commercial	Relationship
Pfizer	Research support, ad-hoc grant review panel

Three Take-Home Points

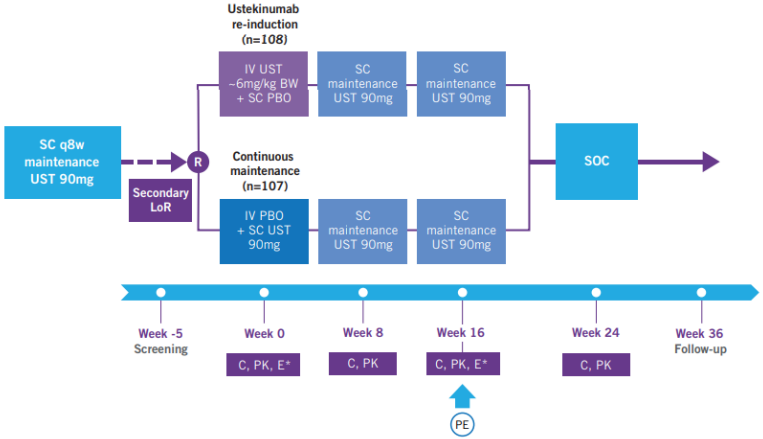
1. Re-induction with IV ustekinumab may be beneficial in partial responders
2. High meat intake may increase risk of relapse in patients with ulcerative colitis, but not Crohn’s disease
3. Thiopurine withdrawal in vedolizumab-treated patients with ulcerative colitis may worsen outcomes

POWER Trial – IV Re-induction with Ustekinumab in CD

Objectives

- **Objective:** Evaluate the efficacy and safety of a single IV re-induction UST dose vs. continued UST SC treatment in individuals with CD with loss of response to standard-dose SC UST Q8W
- **Design:** Phase 3B, multi-center RCT

Methods

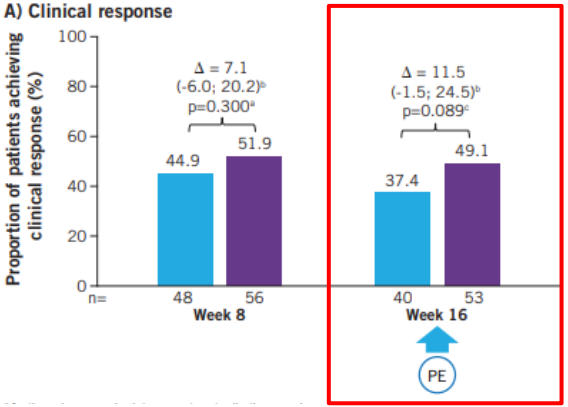


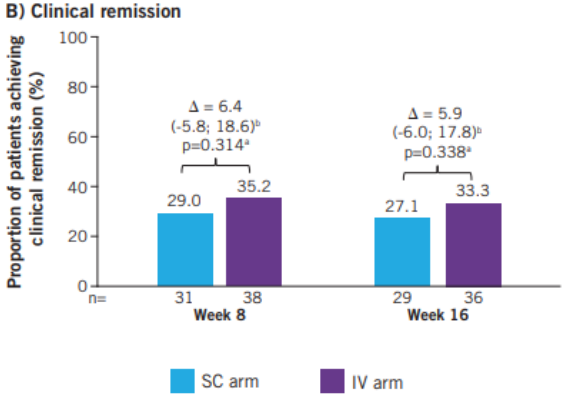
Primary endpoint: Clinical response (decrease of ≥100 points from W0/CDAI <150) at Week 16

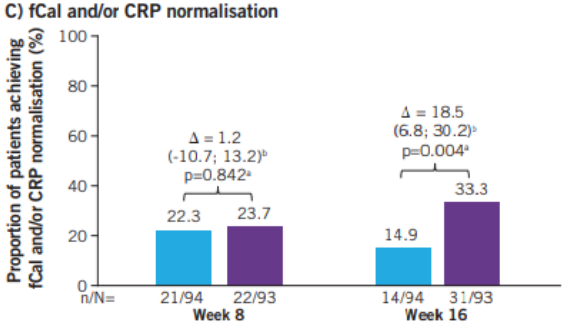
Secondary endpoints: Clinical, biomarker, endoscopic, and quality of life endpoints assessed at Weeks 8/16

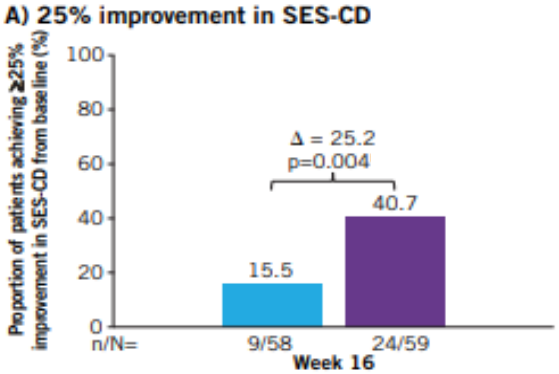
*Endoscopy was optional at Weeks 0 and 16 and only performed for patients that agreed to undergo the procedure. anti-TNF, anti-tumour necrosis factor; BW, bodyweight; C, clinical assessment; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; E, endoscopy; IV, intravenous; LoR, loss of response; PBO, placebo; PE, primary endpoint; PK, pharmacokinetic sampling; Q8W, every 8 weeks; R, randomization; SC, subcutaneous; SOC, standard of care; UST, ustekinumab.

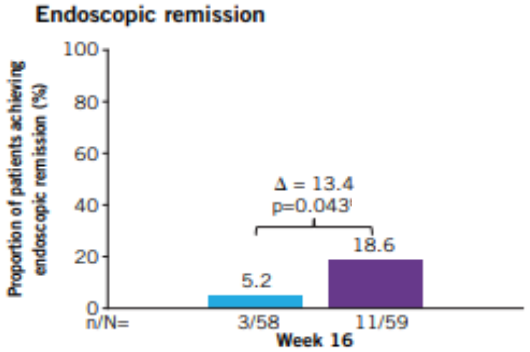
POWER Trial – Results











Lee S et al. Abstract 1027.

POWER Trial – Conclusions and Take Home

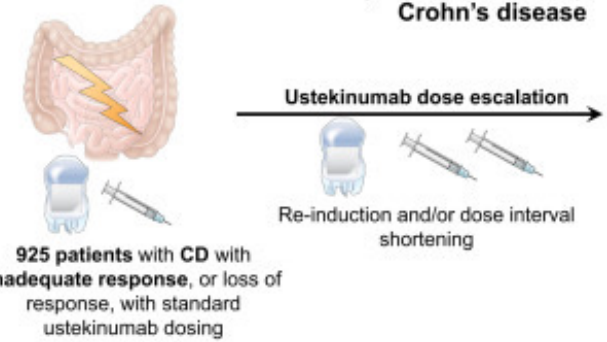
Conclusions

- IV ustekinumab re-induction vs. continued q8w SC UST in CD, with loss of response – did NOT meet primary endpoint of clinical response at Week 16
- However, objective endpoints of disease activity (secondary outcomes) suggest there may be a benefit in using IV reinduction in this refractory biologic-exposed cohort with long disease duration

My take home

IV UST reinduction is a viable option for those with refractory disease who have loss of response to SC UST

Ustekinumab dose escalation in those with active disease despite standard dose induction and maintenance **captures clinical response in majority** of patients with **Crohn's disease**



Capturing Response	
Clinical Response	55%
Steroid-free Clinical Remission	40%
Endoscopic Response	61%
Normalized CRP	21%

Clinical Gastroenterology and Hepatology

Lee S et al. Abstract 1027.

Meat Intake and Risk of IBD Flare – PREdiCCT Cohort

Objectives

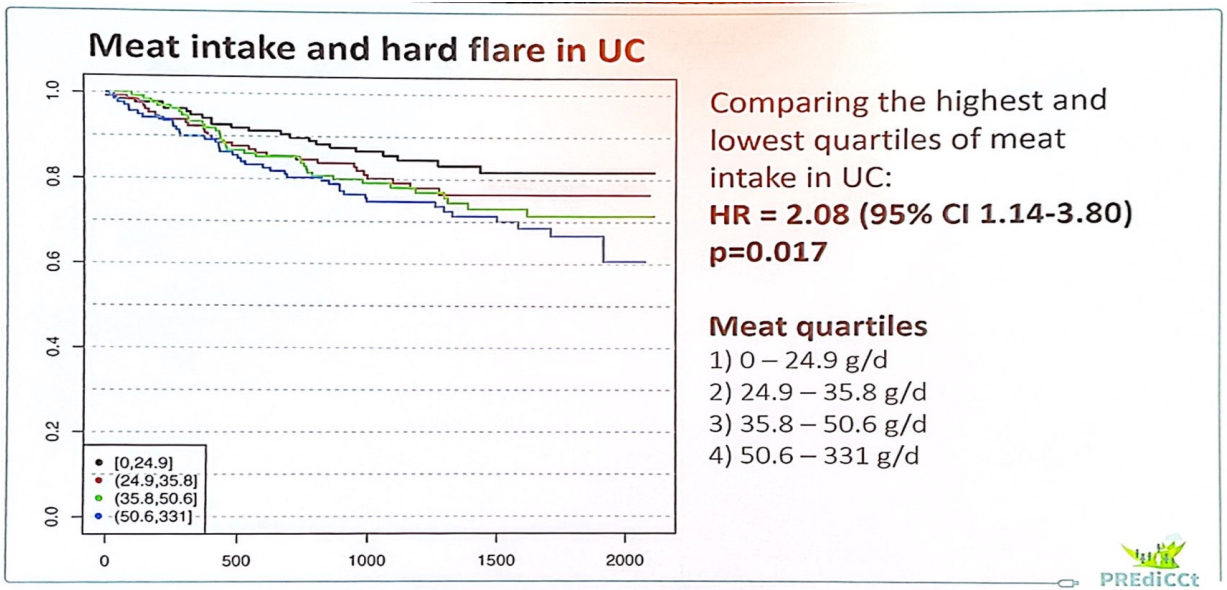
- **Objective:** To explore the association between IBD flare and total animal protein intake, dietary fibre, N-6 polyunsaturated fatty acids, and ultraprocessed foods
- **Design:** Prospective cohort study in UK, PREdiCCT, to examine dietary, environmental, genetic and gut microbiome factors predictive of relapse in patients with IBD in REMISSION

Methods

- 2629 patients with IBD in remission --> 1378 with complete dietary information at baseline included; 44% with males; 49% with Crohn's disease; 53% with fCal <50µg/g
- **Primary endpoint:** Time to first IBD flare
  - **Soft flare:** Patient-reported symptoms: "Do you think your disease has been well controlled in the past 1 month?" — No
  - **Hard flare:** Increase in symptoms + elevation of CRP (>5 mg/L) and/or calprotectin (>250 µg/g) + a change in IBD therapy
  - Analysis adjusted for smoking, total energy intake, gender, and social deprivation score

Lees C et al. Abstract 477c.

PREdiCCT Cohort – Results



Baseline intake of:
- Fiber
- N-6 polyunsaturated fatty acids
- Ultra-processed foods

was not associated with hard flares

No association between meat intake and risk of flare in patients with Crohn's disease

Lees C et al. Abstract 477c.

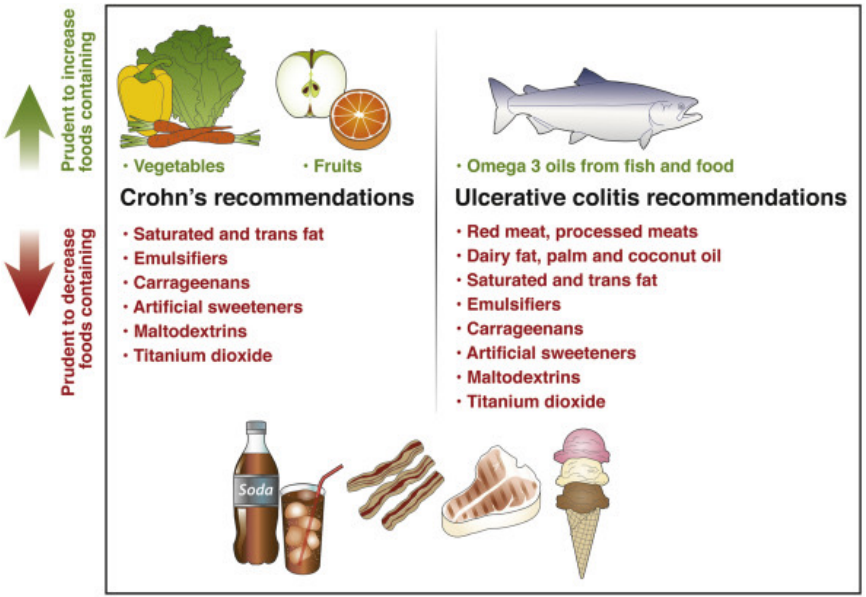
PREdiCCT – Conclusions and Take Home

Conclusions

- In this prospective diet study, baseline habitual meat intake was associated with an increased risk of disease flare in UC, but not CD, over 4.1 years of follow-up
- Calprotectin levels > 50 µg/g were associated with long-term hard IBD flares

My take home

Increasing body of evidence, albeit inconsistent, on impact of diet on disease course in IBD



Levine et al. *Clin Gastroenterol Hepatol*. 2020.

Guselkumab for Ulcerative Colitis – Phase III, QUASAR

Objectives

- **Objective:** To evaluate the efficacy and safety of guselkumab (Tremfya; IL23 p19 subunit antagonist) as induction therapy in patients with moderate to severe UC with an inadequate response or intolerance to conventional and/or advanced therapies
- Design: Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicentre study

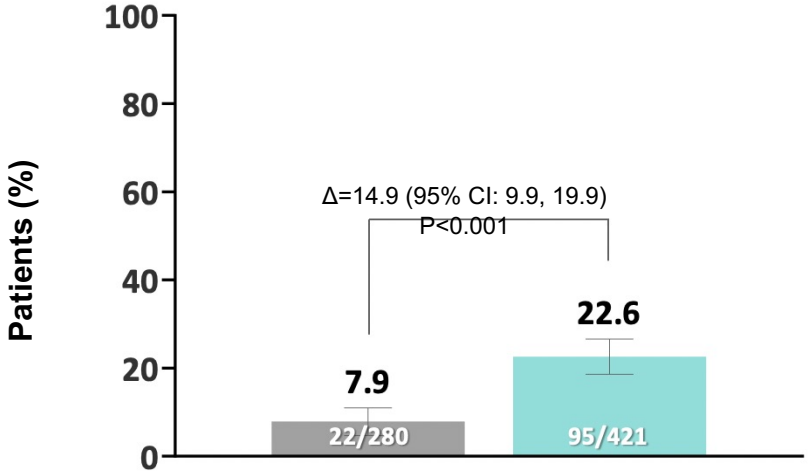
Methods

- Patients were randomized 3:2 to IV GUS 200 mg or placebo at Weeks 0, 4, and 8
- **Inclusion criteria**: Baseline modified Mayo score 5-9, rectal bleeding subscore ≥ 1, and endoscopy subscore ≥ 2 evaluated by central review
- **Primary endpoint**: Clinical remission at Week 12
- **Additional outcomes**: Symptomatic remission, clinical response, endoscopic improvement, histo-endoscopic mucosal improvement, endoscopic normalization, and safety

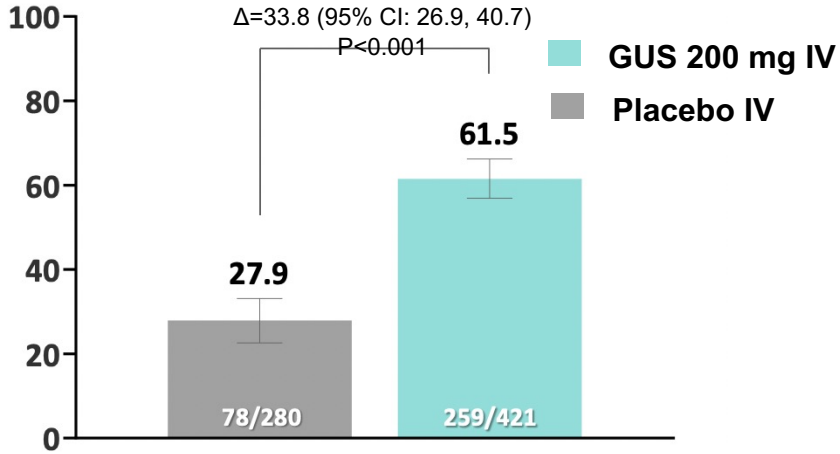
Allegretti J et al. Abstract 913b.

QUASAR – Results

Clinical Remission (primary endpoint)



Clinical response



Baseline corticosteroid use, 43.1%; ~50% of patients had failed an advanced therapy for UC

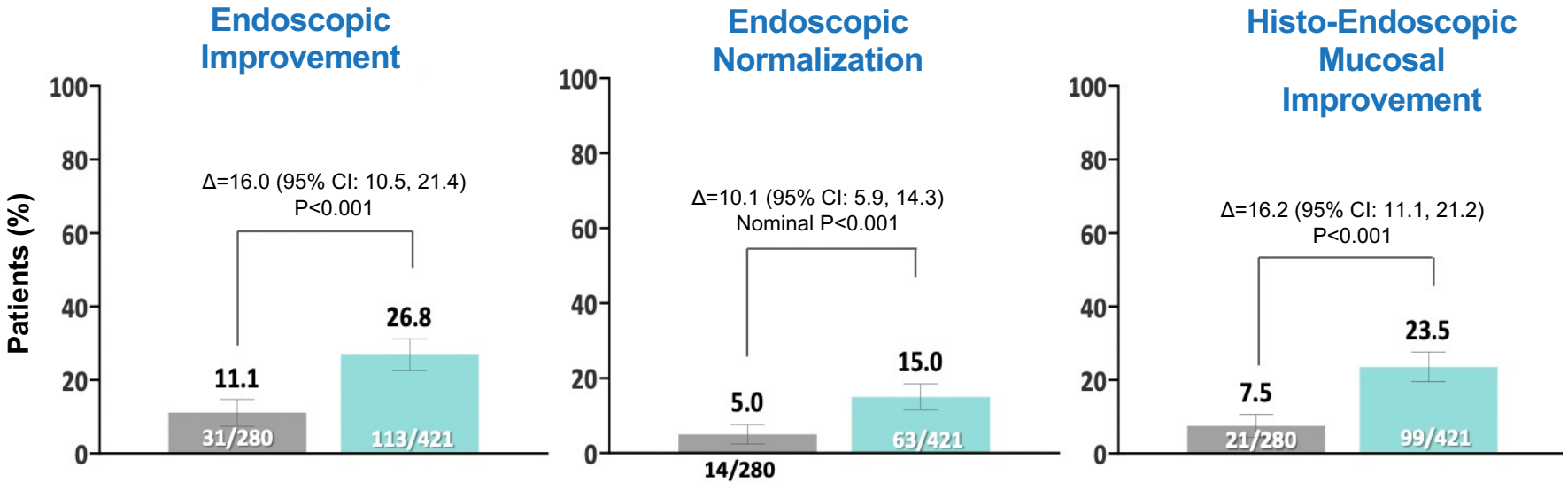
Clinical remission: A Mayo stool frequency subscore of 0 or 1 and not increased from baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on endoscopy. Clinical response: A decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.

Primary analysis population: Treated patients with modified Mayo score 5-9 at induction baseline. Error bars are 95% confidence intervals.

GUS, guselkumab; IV, intravenous; UC, ulcerative colitis

Allegretti J et al. Abstract 913b.

QUASAR – Results



Endoscopic improvement: An endoscopy subscore of 0 or 1 with no friability present on the endoscopy. Endoscopic normalization: An endoscopy subscore of 0. Histo-endoscopic mucosal improvement: Achieving a combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system, i.e., Geboes score ≤ 3.1) and endoscopic improvement.

Primary analysis population: Treated patients with modified Mayo score 5-9 at induction baseline. Error bars are 95% confidence intervals.

GUS, guselkumab; IV, intravenous; UC, ulcerative colitis

Allegretti J et al. *Abstract 913b.*

QUASAR – Conclusions and Take Home

Conclusions

- In this Phase 3 study, induction with GUS 200 mg IV was safe and effective in moderate to severe UC, leading to improvements in symptoms and histo-endoscopic outcomes
- Although these data are promising, data for maintenance therapy, persistence, and longer-term safety for GUS remain to be determined

My take home

- IL-23 is an emerging class of therapy in UC
- How we position this class of medications in patients with moderate-severe ulcerative colitis is TBD …. in the NEXT TALK :)

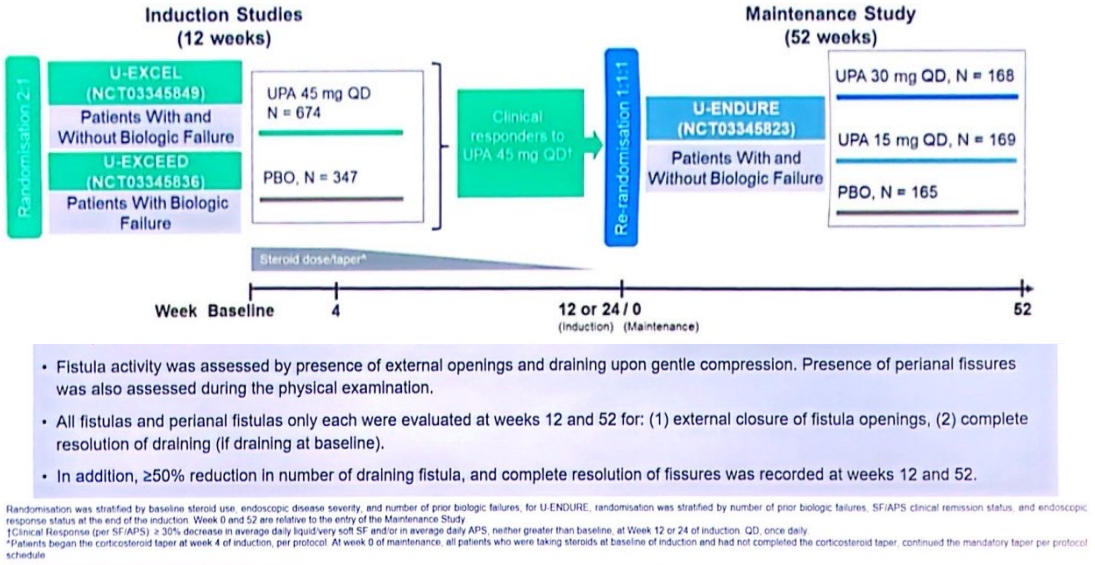
Levine et al. *Clin Gastroenterol Hepatol*. 2020.

Upadacitinib for CD-Related Fistulae – Post-Hoc Analyses

Objectives

- **Objective:** To evaluate improvements in fistulas and fissures in patients with CD who received UPA in Phase 3 studies (U-EXCEL, U-EXCEED, U-ENDURE)
- **Design:** Post-hoc analyses of Phase III trials

Methods



- Fistula activity was assessed by presence of external openings and draining upon gentle compression. Presence of perianal fissures was also assessed during the physical examination.
- All fistulas and perianal fistulas only each were evaluated at weeks 12 and 52 for: (1) external closure of fistula openings, (2) complete resolution of draining (if draining at baseline).
- In addition, ≥50% reduction in number of draining fistula, and complete resolution of fissures was recorded at weeks 12 and 52.

Randomisation was stratified by baseline steroid use, endoscopic disease severity, and number of prior biologic failures; for U-ENDURE, randomisation was stratified by number of prior biologic failures, SF/APS clinical remission status, and endoscopic response status at the end of the induction. Week 0 and 52 are relative to the entry of the Maintenance Study.
†Clinical Response (per SF/APS): ≥ 30% decrease in average daily liquid/very soft SF and/or in average daily APS, neither greater than baseline, at Week 12 or 24 of induction. QD, once daily.
*Patients began the corticosteroid taper at week 4 of induction, per protocol. At week 0 of maintenance, all patients who were taking steroids at baseline of induction and had not completed the corticosteroid taper, continued the mandatory taper per protocol schedule.

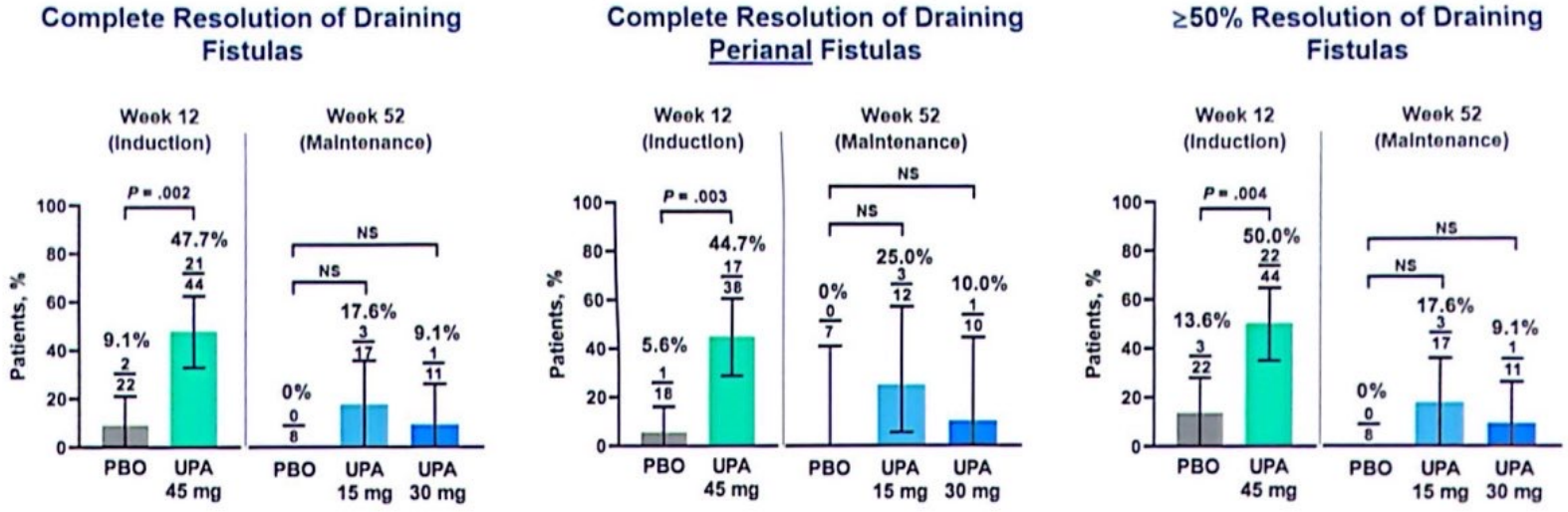
Colombel J-F et al. Abstract 947.

Upadacitinib for CD-Related Fistulae – Results

Characteristic	PBO N=59	UPA 45 mg QD N=113	TOTAL N=172
Age, years, mean (SD)	36.6 (10.7)	34.5 (11.9)	35.2 (11.5)
Female, n (%)	25 (42.4)	46 (40.7)	71 (41.3)
Crohn's disease duration, years, mean (SD)	10.0 (7.2)	10.1 (7.9)	10.1 (7.6)
Prior biologic failure, n (%)	49 (83.1)	95 (84.1)	144 (83.7)
Patients with fistulas, n	47	96	143
Draining fistulas, n (%)	18 (38.3%)	38 (39.6%)	56 (39.2%)
Number of fistulas, n (%)			
1	32 (54.2)	74 (65.5)	106 (61.6)
≥2	15 (25.4)	22 (19.5)	37 (21.5)
Location of fistulas, n (%)			
Perianal	41 (87.2)	83 (86.5)	124 (86.7)
Abdominal	2 (4.3)	2 (2.1)	4 (2.8)
Vaginal	3 (6.4)	8 (8.3)	11 (7.7)
Multiple	1 (2.1)	3 (3.1)	4 (2.8)
Patients with fissures, n (%)	19 (32.2)	35 (31.0)	54 (31.4)
CDAI, mean (SD)	334.2 (77.4)	322.8 (89.5)	326.7 (85.5)
SES-CD, mean (SD)	16.1 (7.6)	17.1 (7.7)	16.7 (7.7)

CDAI, Crohn's disease activity index; PBO, placebo; QD, once daily; SD, standard deviation; SES-CD, simple endoscopic score for CD; UPA, upadacitinib.
Colombel J-F et al. Abstract 947.

Upadacitinib for CD-Related Fistulae – Results



The proportion of patients who achieved complete resolution of draining, complete resolution of draining perianal fistulas, and ≥50% reduction in draining was higher with UPA compared with PBO at week 12.

CI, confidence interval; NS, not significant; PBO, placebo; UPA, upadacitinib. Data are percentage of patients (95% CI). Values above bars are percent of patients and n/n. Denominators are the number of patients with draining fistulas or draining perianal fistulas at baseline. Complete resolution of draining: Patients without draining fistulas or draining perianal fistulas upon gentle compression, in patients with draining fistulas or draining perianal fistulas at baseline. ≥50% resolution of draining: Patients with ≥50% reduction in number of draining fistulas upon gentle compression in patients with draining fistulas at baseline.

Colombel J et al. DDW 2023. Abstract 947.

Upadacitinib for CD-Related Fistulae – Results

Conclusions

- Among patients with CD complicated with fistulas and/or fissures at baseline, UPA led to higher rates of external closure of fistula openings, resolution of draining, and healing of fissures
- Although these data are promising, data for maintenance therapy, persistence, and longer-term safety for GUS remain to be determined

My take home

- UPA may represent a new, oral treatment option for patients with fistulizing CD
- RCT of upadacitinib in patients with fistulizing CD is warranted

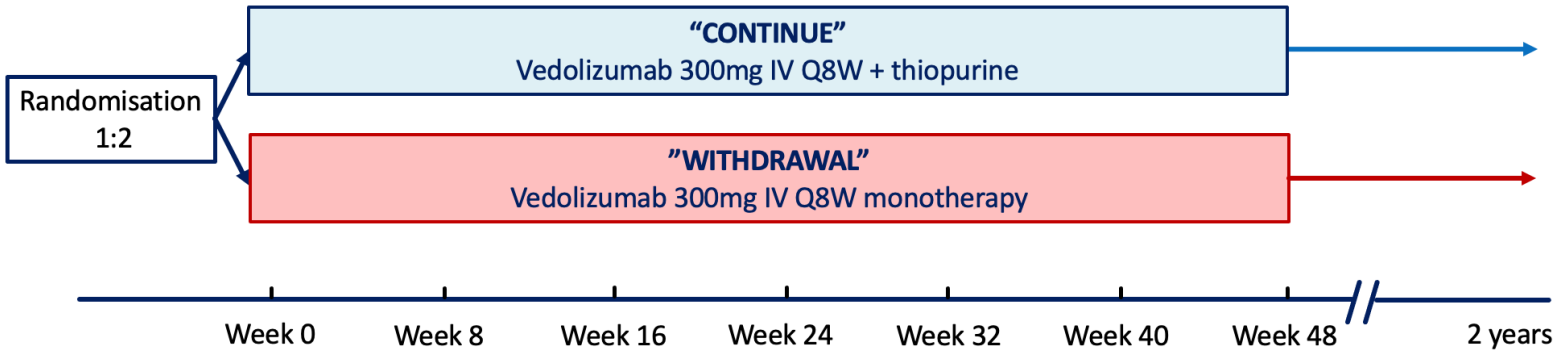
Levine et al. *Clin Gastroenterol Hepatol*. 2020.

VIEWS Trial – Thiopurine Withdrawal in Vedolizumab-Treated Patients With Ulcerative Colitis

Objectives

- **Objective:** To determine the impact of thiopurine withdrawal in patients with UC in remission on VDZ + thiopurine combination therapy
- **Design:** Prospective, multicentre, single-blind, randomized controlled trial

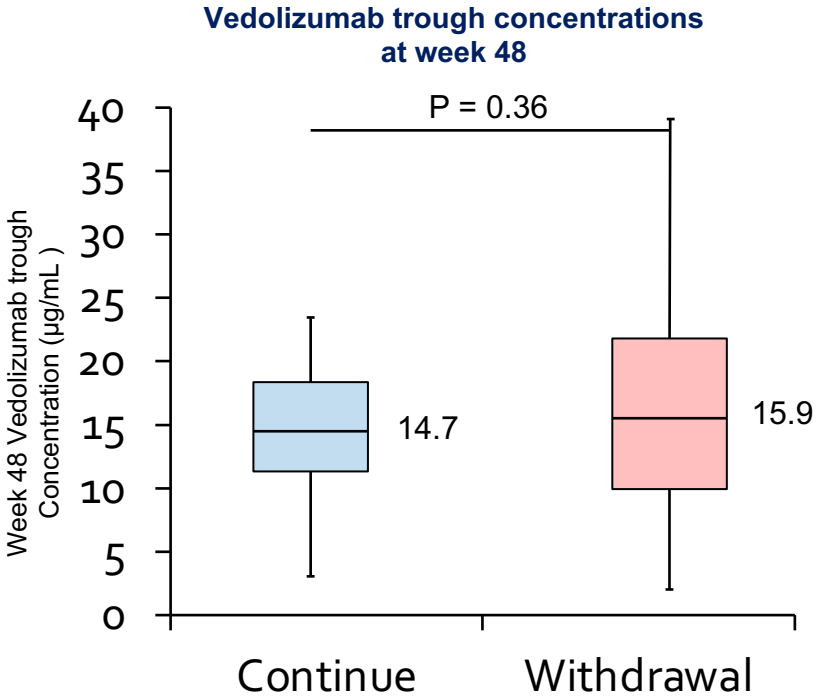
Methods



Pudipeddi A et al. Abstract 1029.

VIEWS Trial – Results

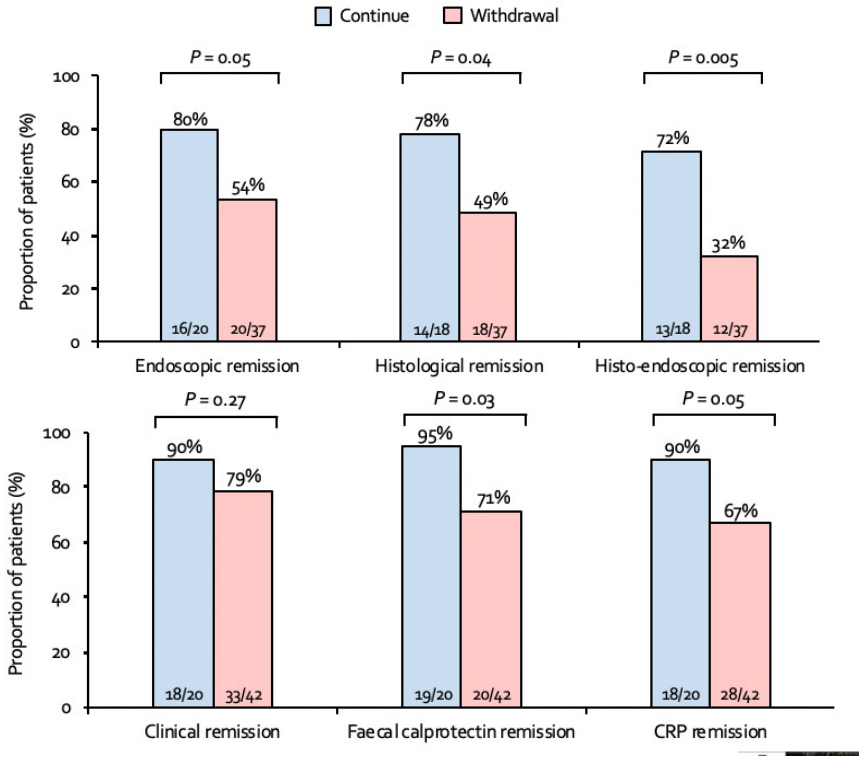
Characteristic		VED + thiopurine 'Continue' (n = 20)	VED monotherapy 'Withdrawal' (n = 42)
Age (years), median (IQR)		46.0 (27.3-53.0)	41.5 (26.8-60.3)
Male, n (%)		15 (75.0)	21 (50.0)
Disease duration (years), median (IQR)		6.5 (4.0-11.8)	8.0 (3.0-13.0)
Time combination therapy (weeks), median (IQR)		47.0 (28.0-118.8)	50.0 (31.0-109.3)
Disease extent, n (%)	Proctitis Left-sided colitis Pancolitis	0 (0) 14 (70.0) 6 (30.0)	3 (7.1) 24 (57.1) 15 (35.7)
Prior anti-TNF exposure, n (%)		4 (20.0)	12 (28.6)
TGN level, pmol/10^8, median (IQR)		311.5 (234.3-460.0)	299.0 (201.3-403.0)
Faecal calprotectin, µg/g, median (IQR)		36.3 (7.8-97.2)	18.6 (7.3-54.7)
C-reactive protein, mg/L, median (IQR)		0.8 (0.4-3.5)	1.2 (0.0-2.8)
Endoscopic activity, n (%)	MES = 0 MES = 1	15/18 (83.3) 3/18 (16.7)	28/36 (77.8) 8/36 (22.2)
Histologic activity, n (%)	NI = 0 NI ≥ 1	16/18 (88.9) 2/18 (11.1)	25/36 (69.4) 11/36 (30.6)

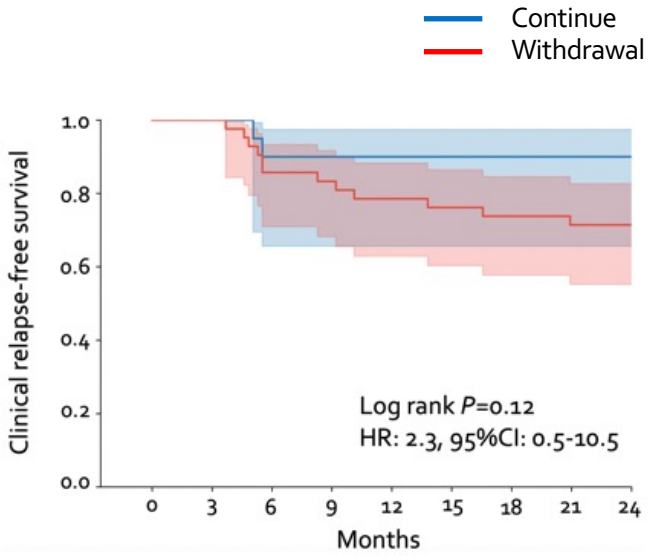


0 patients developed anti-VDZ antibodies in each group

IQR, interquartile range; TGN, 6-thioguanine nucleotide; VDZ, vedolizumab .
Pudipeddi A et al. Abstract 1029.

VIEWS Trial – Results





Multivariate analysis:
- Prior anti-TNF exposure: HR, 4.65 (1.13-19.18)
- Histologic activity at baseline: 7.54 (1.70-33.41)

anti-TNF, anti-tumour necrosis factor; HR, hazard ratio

Pudipeddi A et al. Abstract 1029.

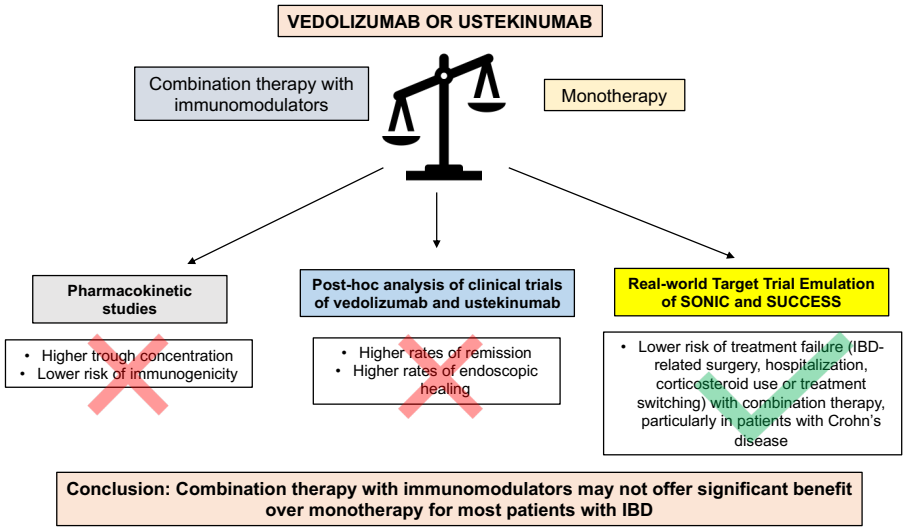
VIEWS Trial – Conclusion and Take Home

Conclusions

- Thiopurine withdrawal did not have a significant effect on VDZ trough levels
- Thiopurine withdrawal was associated with lower FC remission and lower rates of histologic and histo-endoscopic remission

My take home

- For patients taking combination therapy with VDZ and thiopurines, careful monitoring is required if stopping thiopurines, as these patients are more likely to have disease relapse
- Whether patients treated with vedolizumab benefit from upfront combination therapy is unknown



Pudipeddi A et al. Abstract 1029; Singh and Hou. *Clin Gastroenterol Hepatol*. 2023

Three Take-Home Points

1. Re-induction with IV ustekinumab may be beneficial in partial responders
2. High meat intake may increase risk of relapse in patients with ulcerative colitis, but not Crohn's disease
3. Thiopurine withdrawal in vedolizumab-treated patients with ulcerative colitis may worsen outcomes

Credits: Jeffrey McCurdy, MD, PhD, University of Ottawa and IBDUpdate.ca