What’s new in Crohn’s disease for 2024?

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Learning Objectives

After this session, health care professionals treating inflammatory bowel disease (IBD) will be able to:

- Discuss and interpret the results of the SEQUENCE study
- Be familiar with the new data on managing early non-responders to upadacitinib and other biologic therapies in moderate to severe CD

Available therapies for CD have grown in recent years

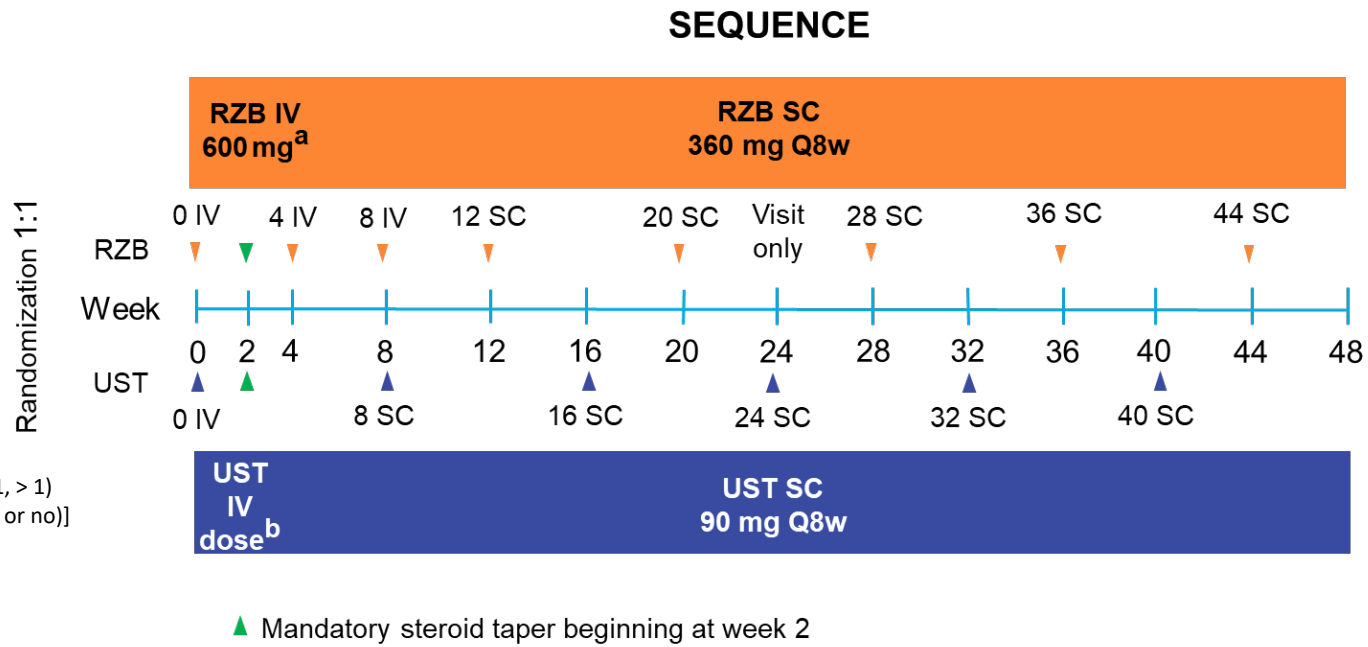
Aminosalicylates	Steroids and immunomodulators	Advanced therapies
• Mesalamine • Sulfasalazine	• Prednisone • Budesonide • Azathioprine • 6-mercaptopurine • Methotrexate	• Anti-TNF • Anti-IL-12/23 • Anti-integrin • Anti-IL-23 • JAKi

Old paradigm: step up through therapies according to clinical symptoms

CD, Crohn's disease; IL, interleukin; TNF, tumour necrosis factor.

Berg DR, et al. *Inflamm Bowel Dis.* 2019;25(12):1896–1905. Colombel JF, et al. *Gastroenterology*. 2017;152(2):351–61.e5.

SEQUENCE Study Design and Key Eligibility Criteria



Stratification Factors:

- Number of prior anti-TNF failure (1, > 1)
- Corticosteroid use at baseline (yes or no)]

Key Eligibility Criteria

Moderate to severe CD

- CDAI 220-450
- Average daily SF ≥4 and/or average daily APS ≥2
- SES-CD, excluding the narrowing component, ≥6 (≥4 for isolated ileal disease), as scored by the site Investigator and confirmed by a central reader

Prior failure of ≥1 anti-TNF therapies

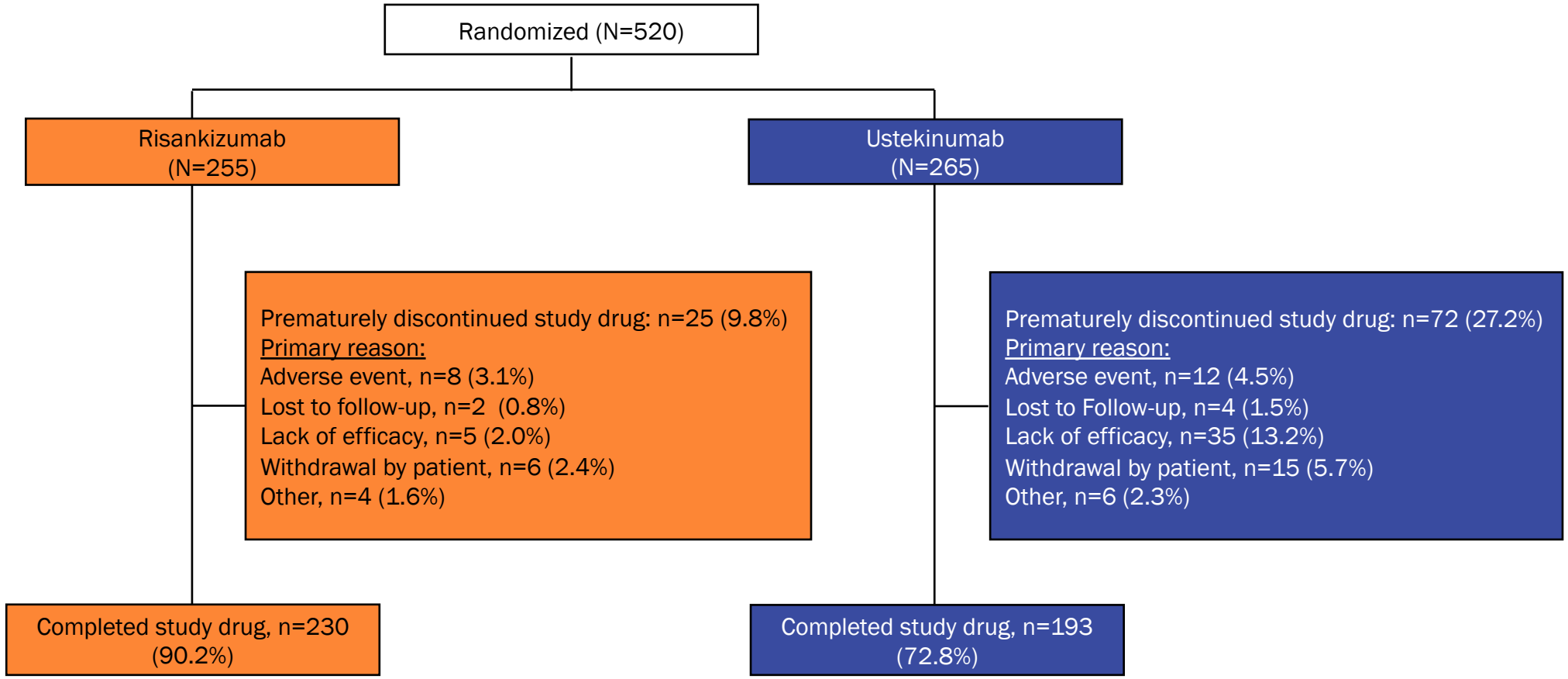
- Prior biologic therapy that could potentially influence the therapeutic impact on CD was exclusionary, including vedolizumab

APS, abdominal pain score; CD, Crohn's disease; CDAI, CD activity index; IV, intravenous; RZB, risankizumab; Q4w, every 4 weeks; Q8w, every 8 weeks; SC, subcutaneous; SES-CD, simple endoscopic score for CD; SF, stool frequency; TNF, tumour necrosis factor; UST, ustekinumab; wk, week

[a]Induction Q4w, weeks 0, 4, and 8

[b]UST baseline IV dose is weight-based: ≤55 kg, 260 mg; >55 kg to 85 kg, 390 kg; >85 kg, 520 mg

Patient Disposition (ITT1[a] Population)



The mean time to discontinuation of study drug (days) for risankizumab was 182.6 and ustekinumab was 156.3

[a]ITT1 population: includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug

Study Endpoints

Primary endpoints

1. CDAI clinical remission at wk 24 (non-inferiority [10% margin] RZB to UST assessed in 50% of patients)
2. Endoscopic remission at wk 48 (superiority RZB to UST)

Ranked secondary endpoints (all superiority RZB to UST)

1. Clinical remission at wk 48
2. Endoscopic response at wk 48
3. Endoscopic response at wk 24
4. Steroid-free endoscopic remission at wk 48
5. Steroid-free clinical remission at wk 48

Overall Type I error rate was strongly controlled at 2-sided alpha level of 0.05 by the fixed-sequence multiplicity control method for this study.

The site's investigator and personnel were blinded to CDAI and centrally read endoscopy scores during the study. Central reader for SES-CD was blinded to study treatment.

CD, Crohn's disease; CDAI, CD activity index; RZB, risankizumab; UST, ustekinumab; wk, week

Baseline Demographics and Disease Characteristics

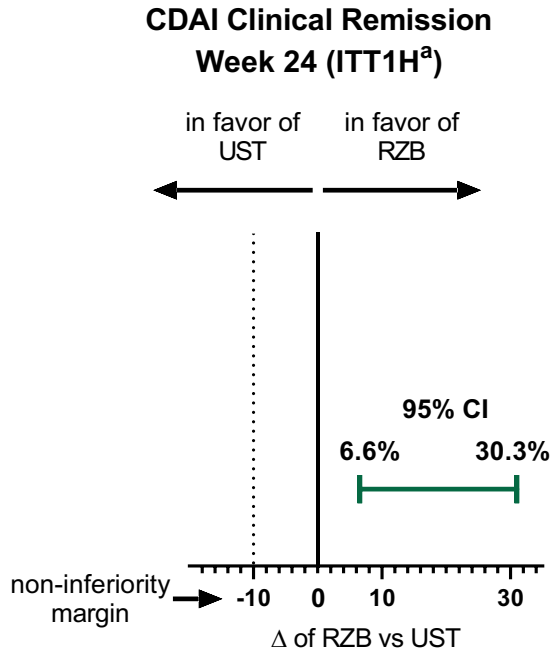
Variable (ITT1)[a]	Risankizumab N=255	Ustekinumab N=265
Age, years, mean (SD)	38.0 (13.1)	38.3 (13.8)
Female, n (%)	119 (46.7)	134 (50.6)
BMI, mean (SD)	23.8 (5.5)	24.8 (6.0)
Disease duration, years, mean (SD)	9.4 (7.8)	9.4 (8.7)
SES-CD, mean (SD)	13.5 (7.1)	14.1 (7.4)
Daily abdominal pain, n, mean (SD)	251,1.9 (0.5)	263,1.9 (0.6)
Daily stool frequency, n, mean (SD)	251, 5.5 (2.7)	263, 5.6 (2.5)
Immunomodulator use, n (%)	34 (13.3)	47 (17.7)
Corticosteroid use[b], n (%)	58 (22.7)	71 (26.8)
Baseline fecal calprotectin (mg/kg), n, median (min, max)	207, 1030 (30, 26823)	215, 1515 (30, 26361)
Baseline hs-CRP (mg/L), n, median (min, max)	246, 8.20 (0.2, 287.1)	257, 9.40 (0.2, 196.6)
CDAI, n, mean (SD)	251, 309.4 (61.7)	263, 310.1 (62.6)
Failed > 1 anti-TNFs[b], n (%)	59 (23.1)	61 (23.0)
Disease location, n (%)		
Ileal only	42 (16.5)	45 (17.0)
Colonic only	102 (40.0)	106 (40.0)
Ileal-colonic	111 (43.5)	114 (43.0)

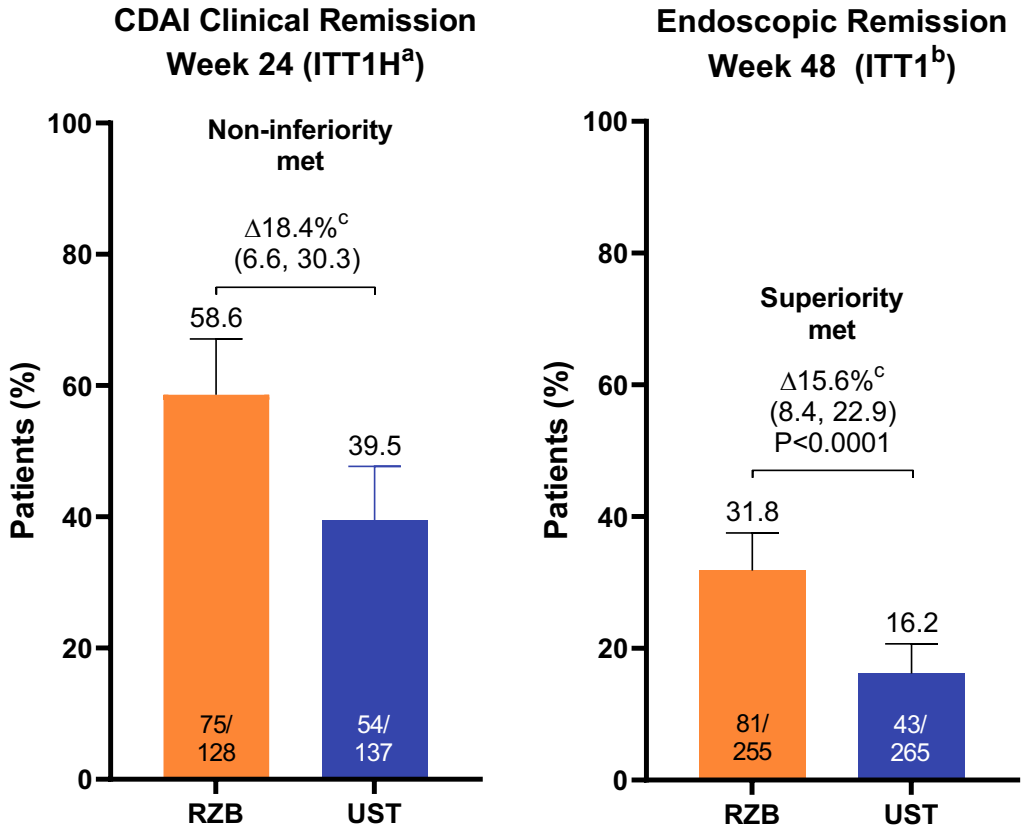
BMI, body mass index; CD, Crohn's disease; CDAI, CD activity index; hs-CRP, high-sensitivity C-reactive protein; SES-CD, simple endoscopic score for CD; SF, stool frequency; TNF, tumour necrosis factor; UST, ustekinumab

[a]ITT1 population: includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug

[b]Stratification factors

Primary Endpoints: RZB demonstrated non-inferiority to UST for achieving clinical remission at week 24 and superiority to UST for achieving endoscopic remission at week 48





CDAI clinical remission: CDAI < 150

Endoscopic remission: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer

Nominal *P* <0.01 from a post hoc analysis testing for superiority

[a]ITT1H population: a subset of ITT1 population which includes the first ~50% of ITT1 patients

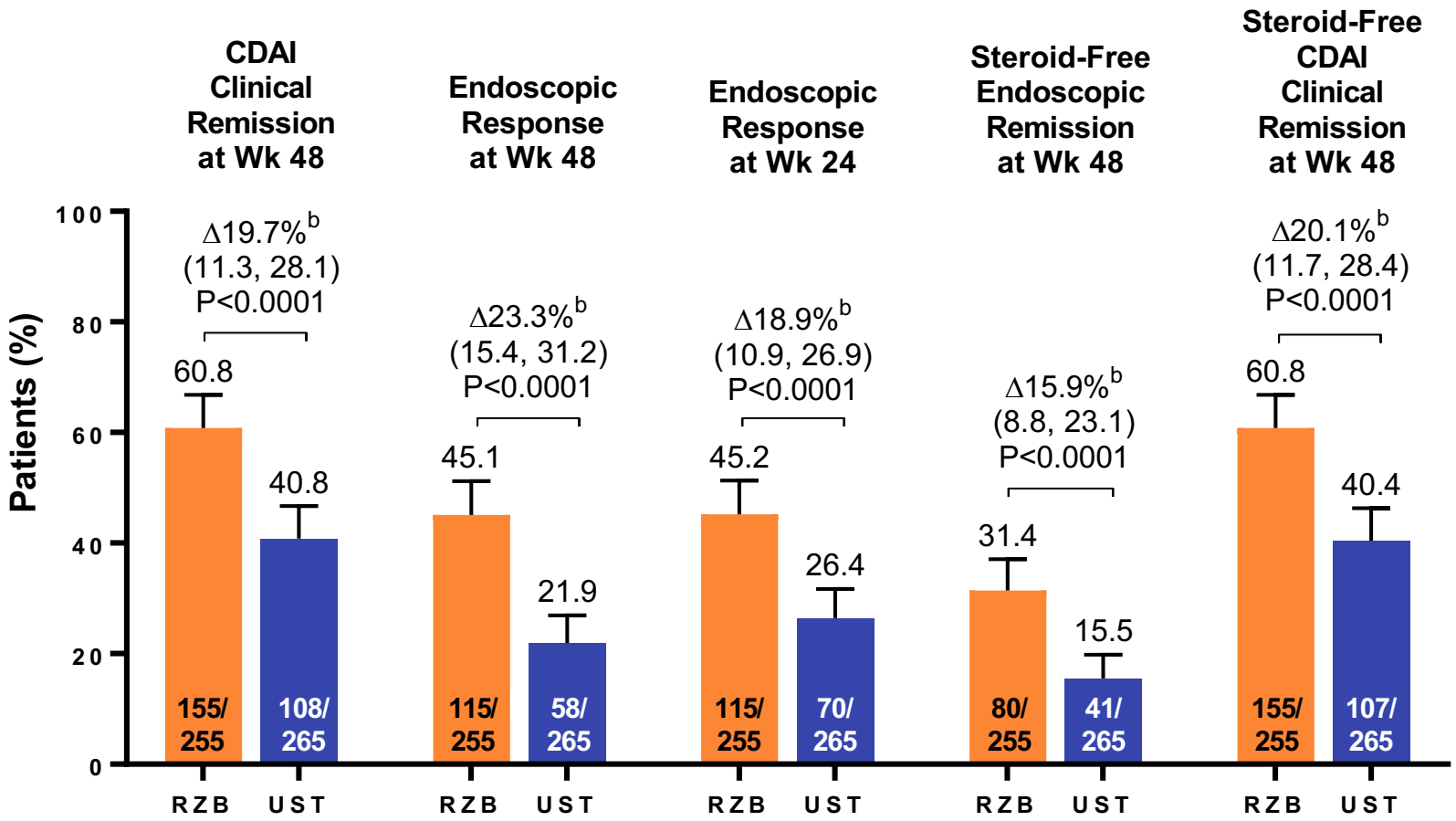
[b]ITT1 population includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug

[c]Differences adjusted by the stratification factors (number of times the subject failed prior anti-TNF therapy [≤ 1, > 1] and steroid use at baseline [yes, no])

% (n) represents the synthesized results from non-responder imputation incorporating multiple imputation to handle missing data

Non-inferiority for CDAI clinical remission at wk 24 was met if the lower bound of the 95% CI of adjusted risk difference was above -10%; if met, superiority for endoscopic remission at wk 48 was assessed

Ranked Secondary Endpoints (ITT1[a]): RZB demonstrated superiority to UST for all secondary endpoints



Superiority met for all endpoints

CDAI clinical remission: CDAI < 150
Endoscopic response: Decrease in SES-CD > 50% from BL (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central reviewer.
Endoscopic remission: SES-CD ≤ 4 and at least a 2-pt reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer
Steroid-free: Patient not receiving steroids at the corresponding visit

[a]ITT1 population - includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug
[b]Differences adjusted by the stratification factors (number of times the subject failed prior anti-TNF therapy [≤ 1, > 1] and steroid use at baseline [yes, no])
% (n) represents the synthesized results from non-responder imputation incorporating multiple imputation to handle missing data
Secondary endpoints tested sequentially in the order specified

Treatment Emergent Adverse Events (TEAEs) (SA1[a])

Treatment Emergent Adverse Events (TEAEs)	Risankizumab		Ustekinumab	
	N=262 n (%)	PYs=257.6 Events (E/100PYs)	N=265 n (%)	PYs=269.9 Events (E/100PYs)
Any TEAE	223 (85.1)	879 (341.2)	219 (82.6)	763 (282.7)
TEAEs related to study drug according to the investigator[b,c]	73 (27.9)	167 (64.8)	58 (21.9)	111 (41.1)
Severe TEAEs	42 (16.0)	60 (23.3)	51 (19.2)	82 (30.4)
Serious TEAEs	27 (10.3)	36 (14.0)	46 (17.4)	64 (23.7)
TEAEs leading to discontinuation of study drug	10 (3.8)	10 (3.9)	13 (4.9)	14 (5.2)
Deaths	0	0	0	0

E, events; PY, patient years
[a]SA1: all patients who were randomized and received at least one dose of study drug
[b]As assessed by investigator
[c]RZB related: 3 patients with SAEs related to RZB (anal fistula, anal abscess, campylobacter, cystitis, localized infection, genital fistula); 8 patients with SAEs related to UST (abdominal pain, anal fistula, Crohn's disease, ileal stenosis, vomiting)

SEQUENCE CONCLUSIONS

Both primary endpoints **were met** (non-inferiority of risankizumab to ustekinumab in achieving CDAI clinical remission at week 24 and superiority of risankizumab to ustekinumab in achieving endoscopic remission at week 48)

All ranked secondary endpoints (superiority of risankizumab to ustekinumab) were met

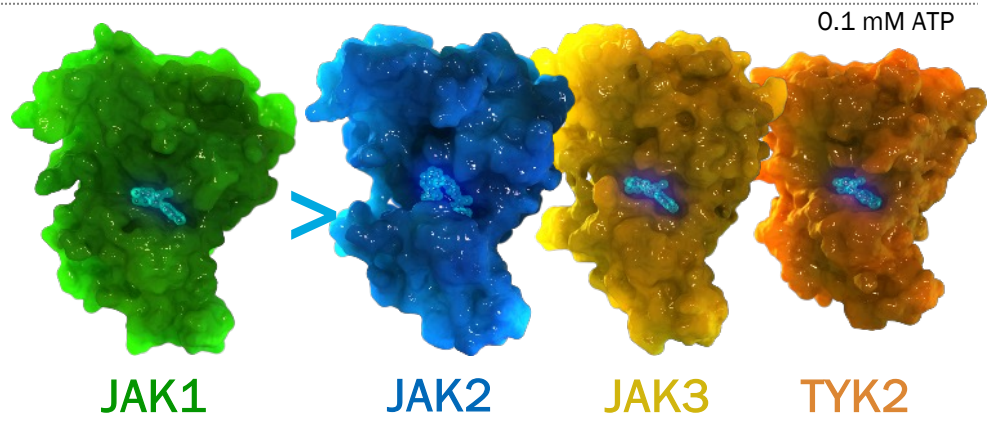
The overall incidence of TEAEs was similar with risankizumab vs ustekinumab, while the incidences of serious adverse events and adverse events leading to study drug discontinuation were numerically lower with risankizumab vs ustekinumab

No new safety risks were identified; safety profiles were consistent with the known safety profiles of risankizumab and ustekinumab

Upadacitinb was designed to target JAK1 over JAK2, with >40-fold selectivity over JAK3 and 100-fold selectivity over TYK2

UPA has greater potency and JAK1 selectivity on recombinant human catalytic enzymes than JAK2, JAK3, and TYK2

	JAK1	JAK2	JAK3	TYK2
UPA IC_{50} (nM)	**47**	**120**	**2,304**	**4,690**
Potency ratio vs JAK1	1	2.5	49	100



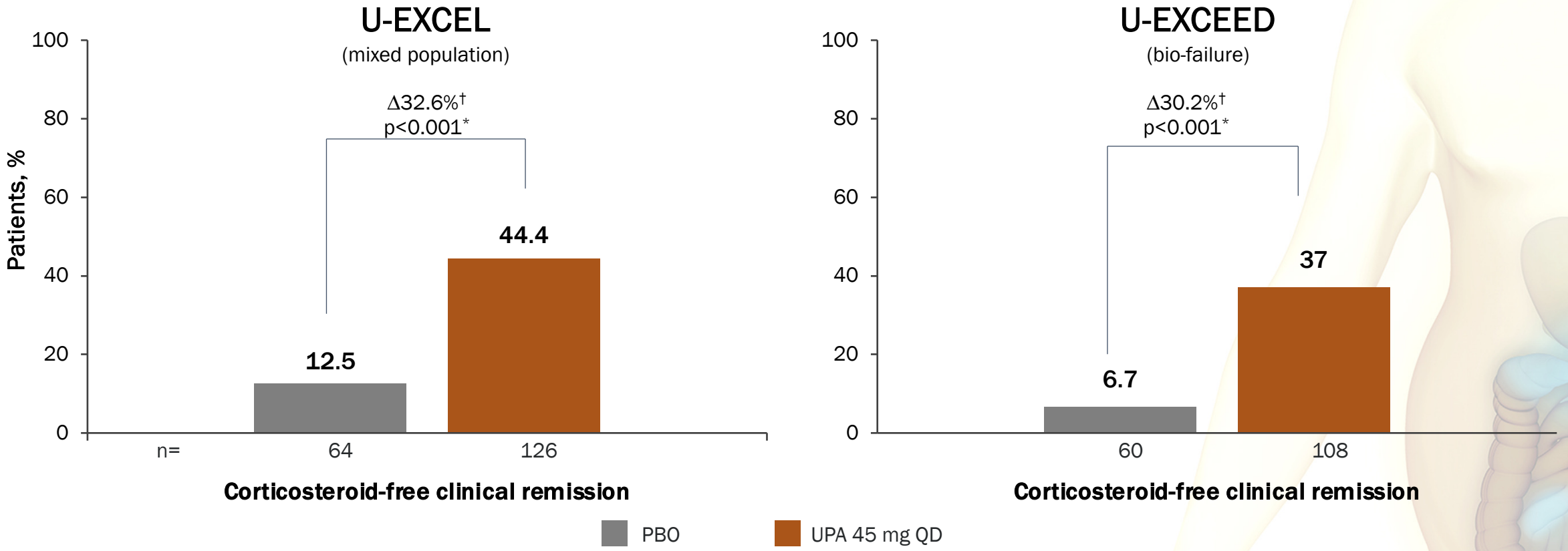
Hypothesis

Greater JAK1 selectivity over JAK2 will translate into a more favourable benefit–risk profile

ATP, adenosine triphosphate; IC_{50}, concentration of drug required for 50% inhibition; JAK, Janus kinase; JAKi, JAK inhibitor; TYK, tyrosine kinase; UPA, upadacitinib.
Parmentier JM, et al. *BMC Rheumatol*. 2018;2:23.

Corticosteroid-free clinical remission at Week 12 was achieved by significantly greater proportions of patients treated with UPA vs PBO

Secondary endpoints



*p-values controlled for multiplicity. †Adjusted treatment difference (see slide notes for details).

Corticosteroid-free clinical remission: Discontinuation of corticosteroid and achievement of clinical remission‡ among patients on corticosteroid at BL. **‡Clinical remission per SF/APS:** Average daily SF ≤2.8 and APS ≤1.0 and neither greater than BL.

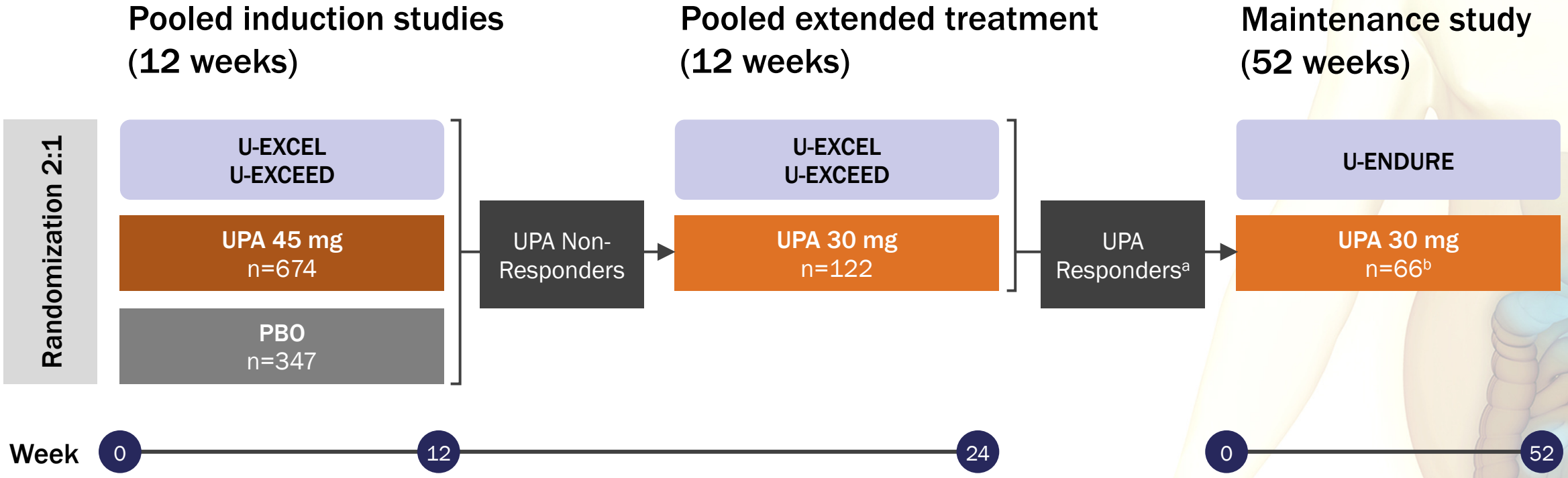
APS, abdominal pain score; BL, baseline; PBO, placebo; QD, once daily; SF, stool frequency; UPA, upadacitinib.

Loftus EV Jr, Panés J, et al. *N Engl J Med.* 2023;388(21):1966–80 and supplement.

If my patient has not responded to a JAKi by 12 weeks, what should I do?

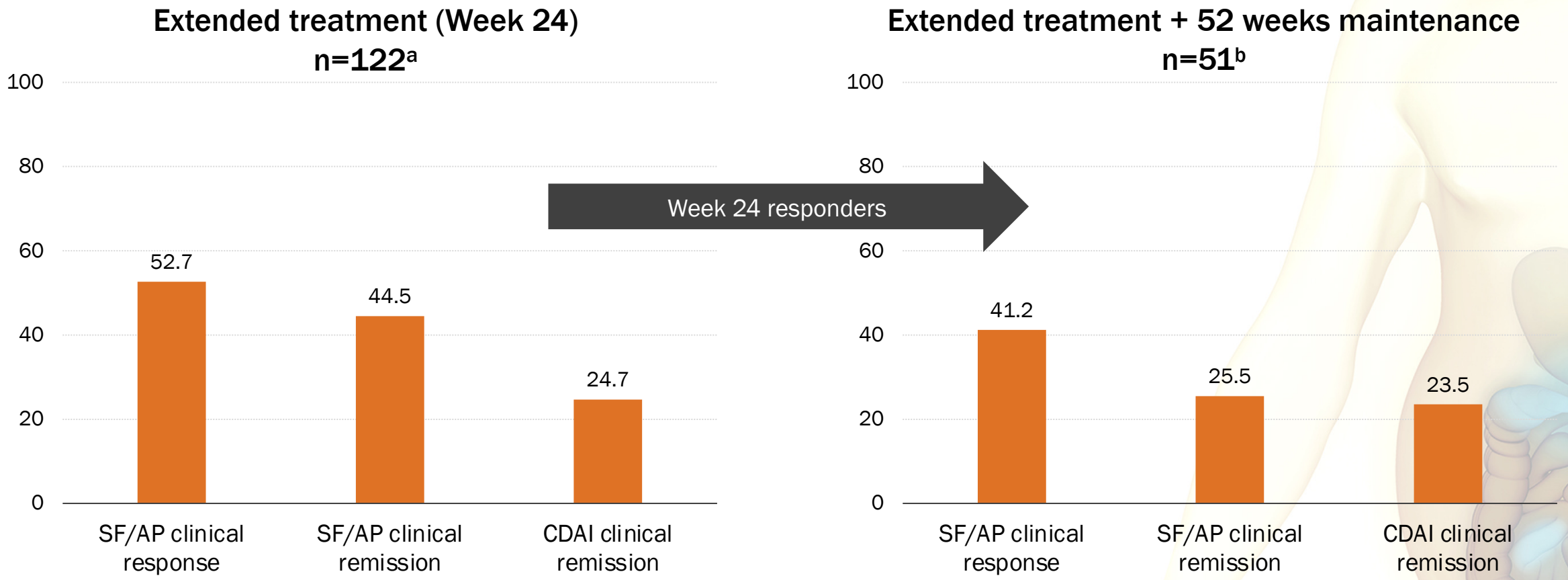
JAKi, Janus kinase inhibitor.

In U-EXCEL and U-EXCEED, Week 12 non-responders were transitioned to UPA 30 mg for an additional 12 weeks of treatment



[a]Clinical response defined as ≥30% decrease in average daily very soft or liquid stool frequency and/or ≥30% decrease in average daily abdominal pain score and both not worse than baseline.
[b]51 patients completed 52 weeks of study treatment or enrolled at least 52 weeks prior to the database lock but have prematurely withdrawn from the study.
PBO, placebo; UPA, upadacitinib.
D'Haens G, et al. Presented at Digestive Disease Week 2023. May 6–9, 2023. Chicago, USA: Poster Tu1705.

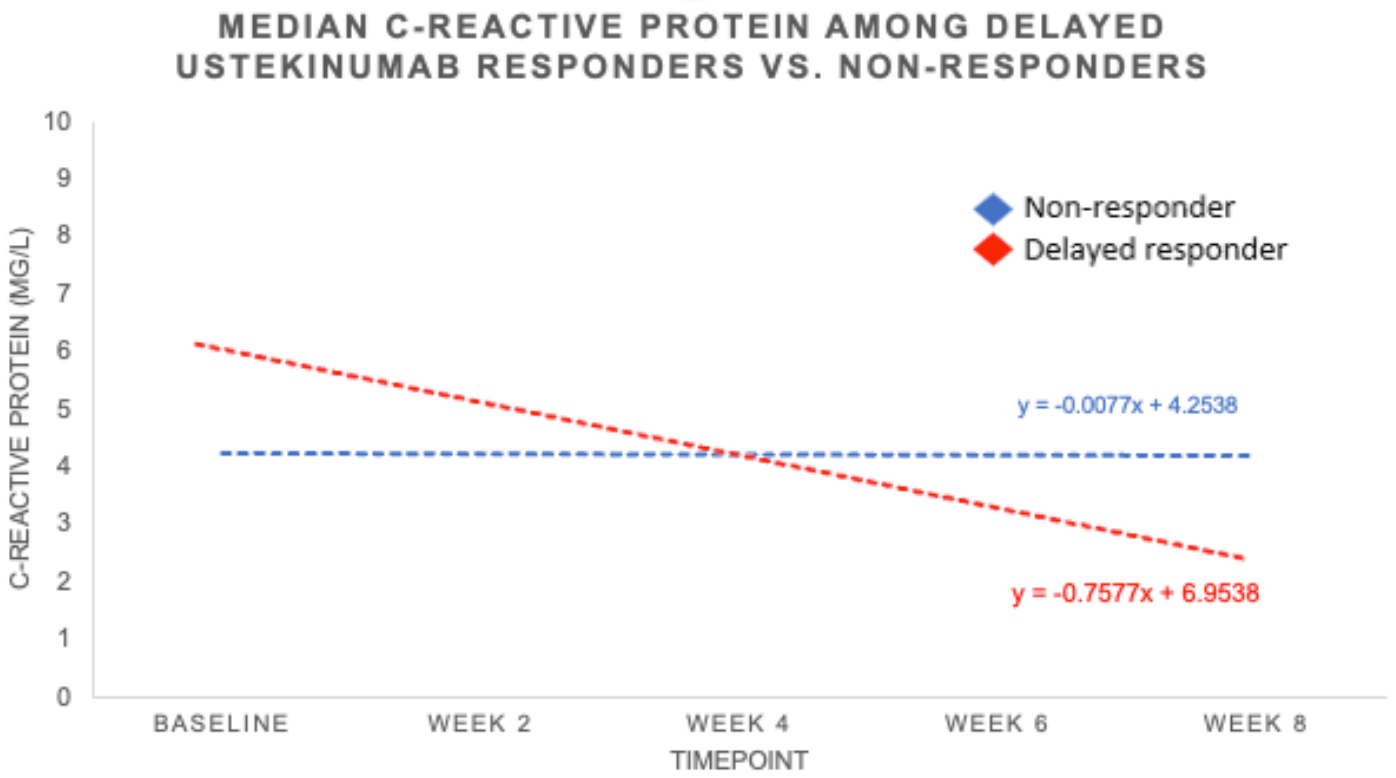
Delayed clinical response in patients with CD receiving upadacitinib therapy



[a]Includes patients who did not achieve a clinical response with 12 weeks of UPA 45 mg QD induction therapy and who received blinded extended treatment with UPA 30 mg QD for 12 weeks.
[b]Includes patients who received UPA 30 mg QD during the extended treatment period, achieved clinical response at Week 24, and completed Week 52 of maintenance treatment or enrolled at least 52 weeks prior to database lock but have prematurely withdrawn from the study.
AP, abdominal pain; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; QD, once daily; SF, stool frequency; UPA, upadacitinib.
D'Haens G, et al. Presented at Digestive Disease Week 2023. May 6–9, 2023. Chicago, USA: Poster Tu1705.

Are there biomarkers that can help differentiate delayed vs. no response to therapy? Post-hoc analysis from SEAVUE

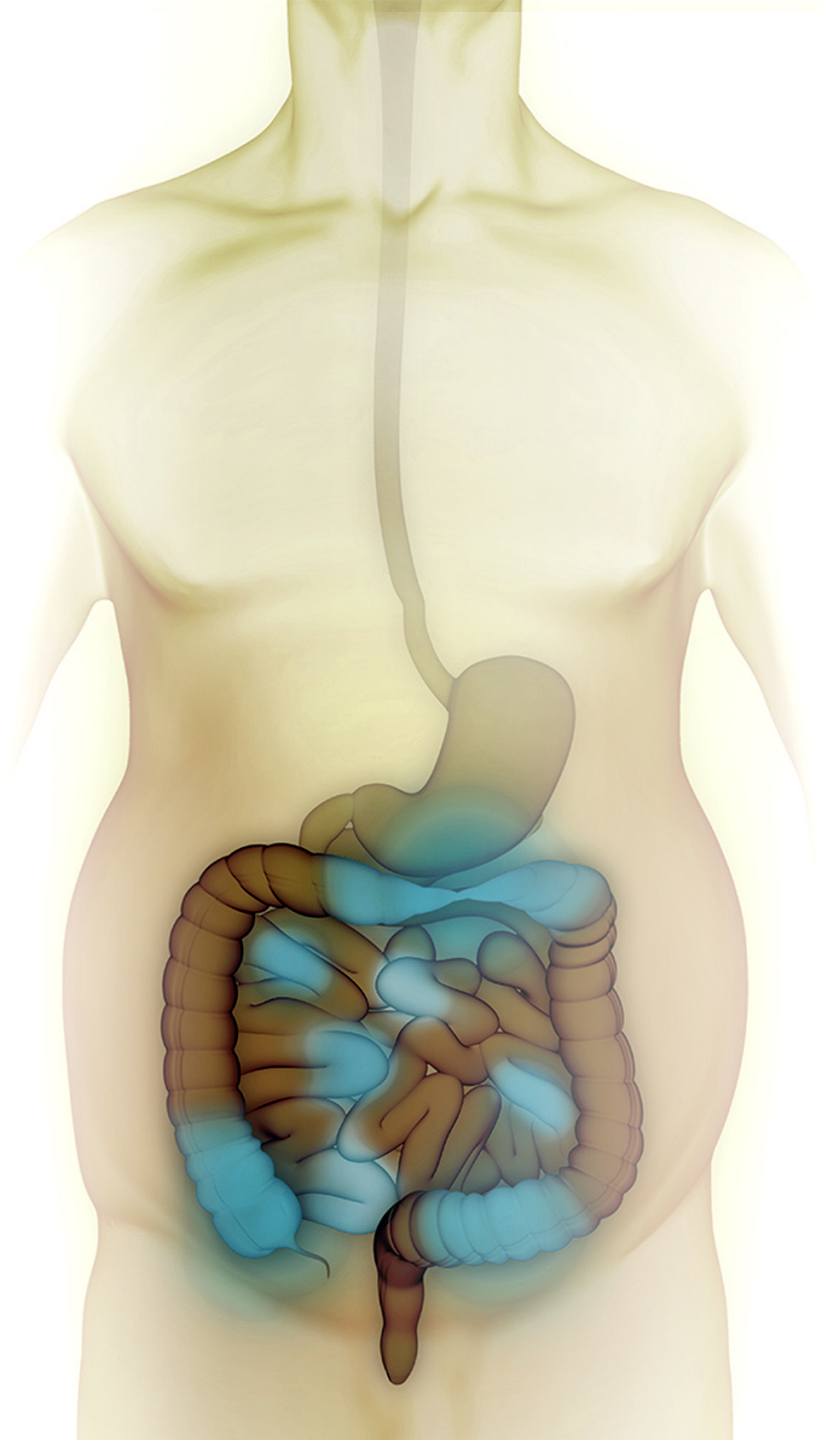
Median CRP levels (through week 8)



Compared to non-responders, delayed responders at week 16 had a significant decrease in CRP ($p = 0.001$) and FC ($p < 0.0001$) through week 8

Narula N, et al. Am J Gastroenterol – Accepted manuscript 2024.

WHAT ARE THE TAKE-HOME MESSAGES?



Conclusions

- SEQEUNCE trial supports use of risankizumab over ustekinumab in CD patients with anti-TNF failure
- Upadacitinib, a selective JAKi, is a new advanced oral therapy option for patients with IBD with strong efficacy and reasonable safety profile to date. But even for CD patients not responding to induction with advanced therapies, can monitor biomarkers during induction to determine if worthwhile to persist with extended trial of therapy

APS, abdominal pain score; CD, Crohn's disease; JAKi, Janus kinase inhibitor; SF, stool frequency.