IL-23 Inhibitors & IBD

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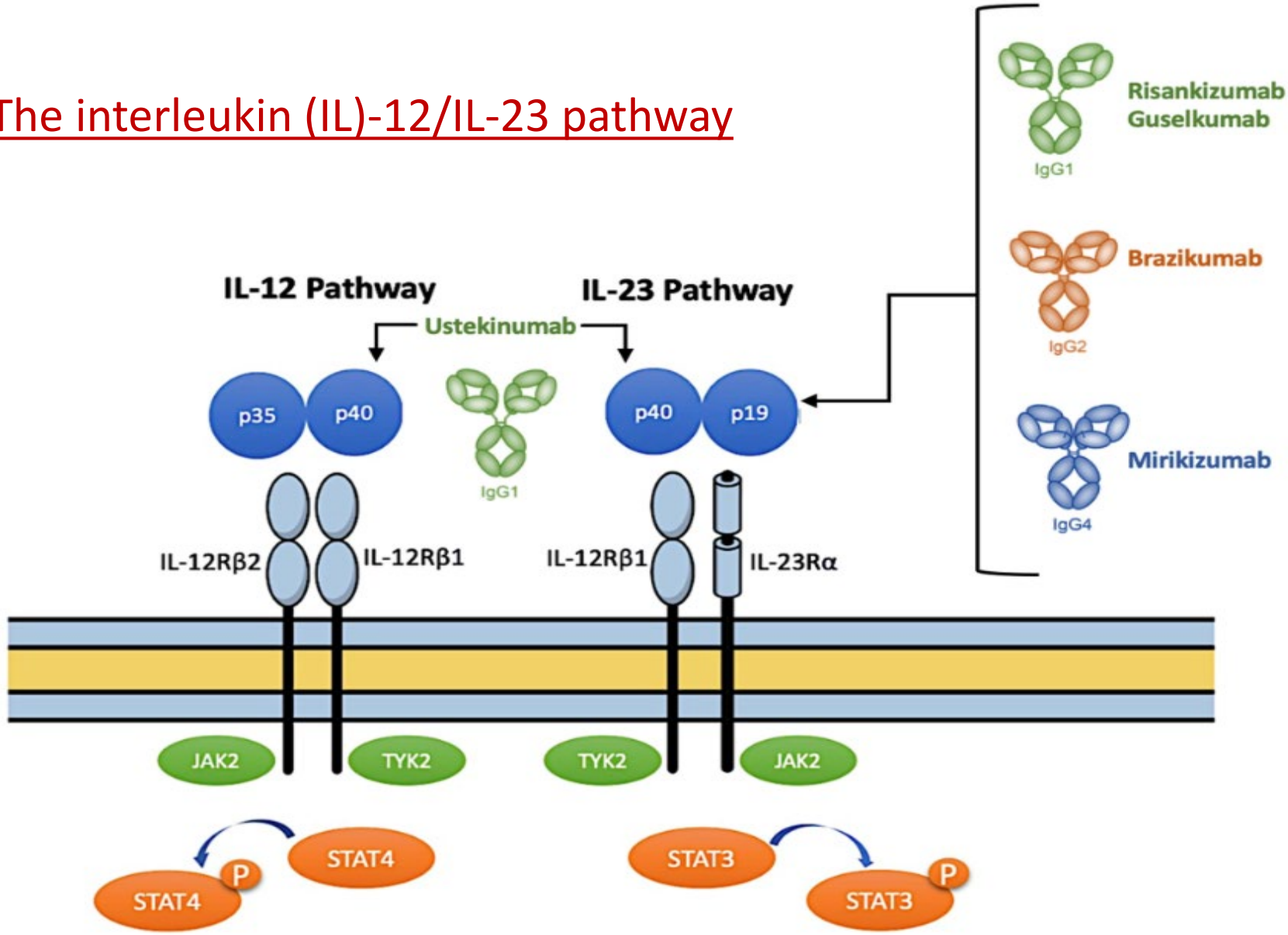
Apr.2025-Tabriz



Interleukin (IL) 23

- IL-23 is a member of the IL12 family of cytokines,
- Involved in maintains intestinal homeostasis and implicated in the **pathogenesis** of IBDs.
- IL23 is a heterodimer composed of disulfide-linked p19 and p40 subunits.
- Humanized monoclonal antibodies selectively targeting the p19 subunit of IL23 are poised to become prominent drugs in IBDs.

The interleukin (IL)-12/IL-23 pathway



J. Clin. Med. 2024, 13(1), 224;

Treatment of moderate to severe CD and UC with IL12– IL23 inhibitors has proven effective and safe, and led to the approval of the first IL12–IL23 inhibitor, **ustekinumab**

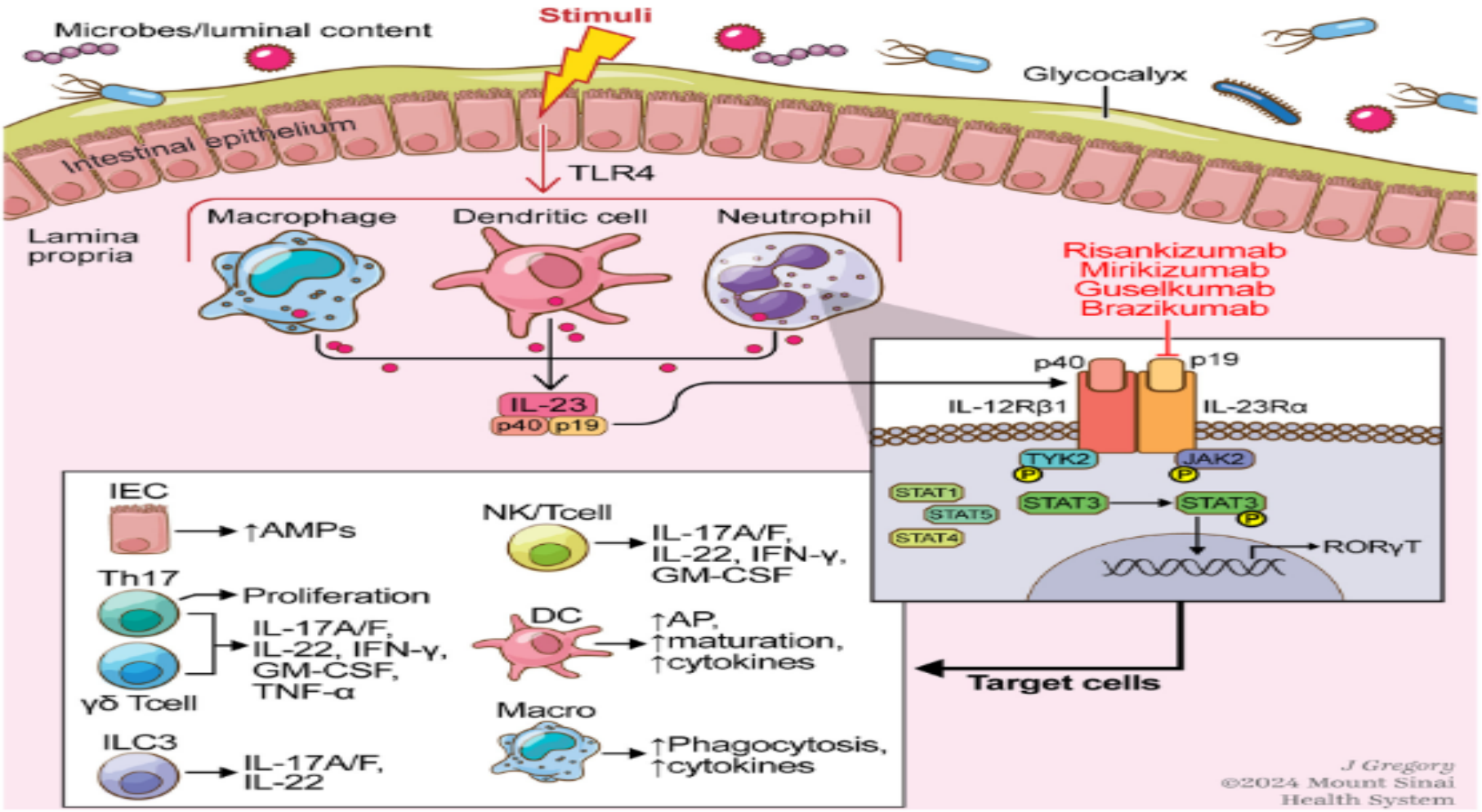
Agents selectively the **p19** subunit **unique** to IL23 proved to be **more effective** compared with those targeting both IL12 and IL23

Already , the selective IL23p19 inhibitors **risankizumab** and **mirikizumab** received **approval** for treatment of moderate to severely active CD and UC, respectively

Gastroenterology 2025;168:29–52, *J. Clin. Med.* **2024**, *13*(1), 224;ECCO2024

- ✓ The first generation to the inhibition of IL-23 is USTEKINUMAB (a p40 subunit **IgG1k** inhibitor of IL12/23)
- ✓ Initially approved in 2009 for **psoriasis**
- ✓ Demonstrating an excellent efficacy and safety profile for both IBD, since 2016 for CD and since 2019 for UC

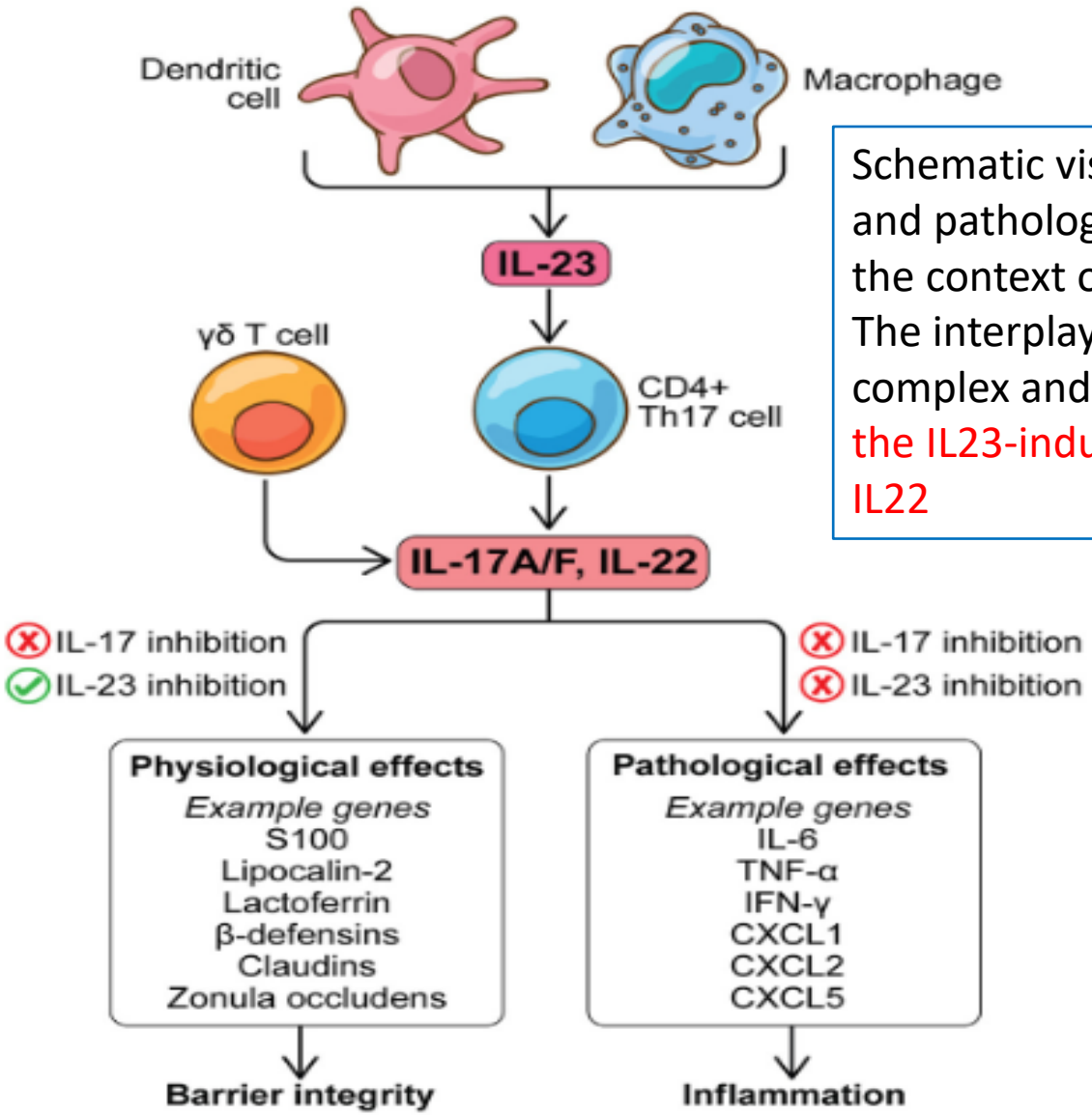
- ✓ The **second generation** of selective anti-IL-23 therapies targets IL-23p19, and they have demonstrated greater effectiveness compared to ustekinumab in treating other immune-mediated conditions



IL23 signaling in the intestinal mucosa;

The **principal cells** producing IL23 include macrophages, neutrophils, and dendritic cells (DCs), on microbial stimulation in a Toll-like receptor 4 (TLR4)-dependent fashion.
production by intestinal epithelial cells (IECs) has also been demonstrated

The role of IL23 in triggering intestinal inflammation:

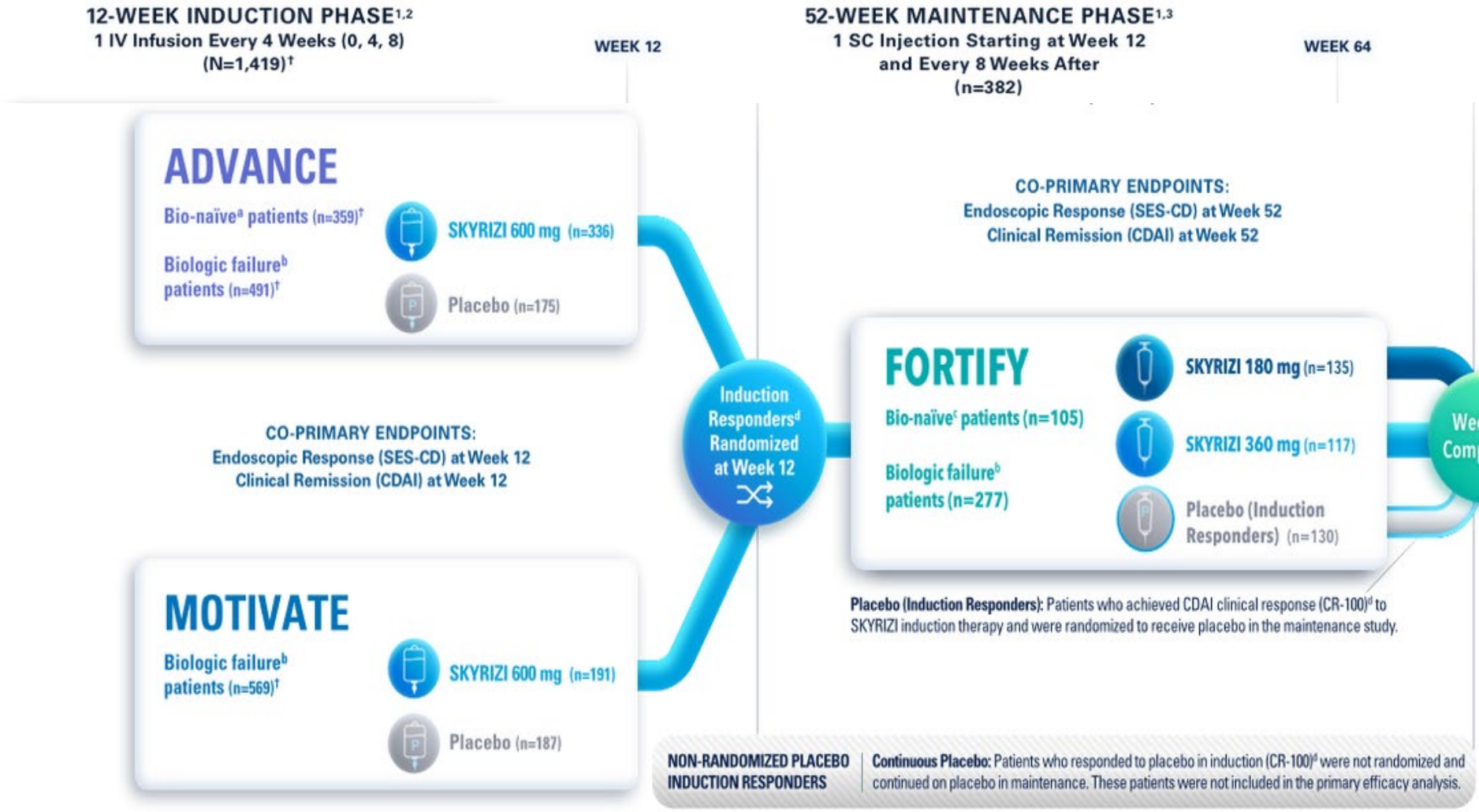


Schematic visualization of the homeostatic and pathologic effects of IL17 and IL22 in the context of IBD.
The interplay among IL23, IL17, and IL22 is complex and context dependent because the IL23-induced production of IL17 and IL22

Risankizumab (SKYRIZI)

- IgG2-variant monoclonal antibody binds to the **p19** subunit of IL-23 and inhibit IL23
- Approved treatments for moderately to severely active Crohn's disease
- RZB is available in a 150 mg/mL prefilled syringe and pen, a 600 mg/10 mL vial for IV infusion and a 180 mg/1.2 mL or 360 mg/2.4 mL single-dose prefilled cartridge with on-body injector.

1,419 PATIENTS ENROLLED ACROSS SKYRIZI TRIALS



Risankizumab,Phase3:three trials
Endpoints in *ADVANCE; MOTIVATE; FORTIFY*

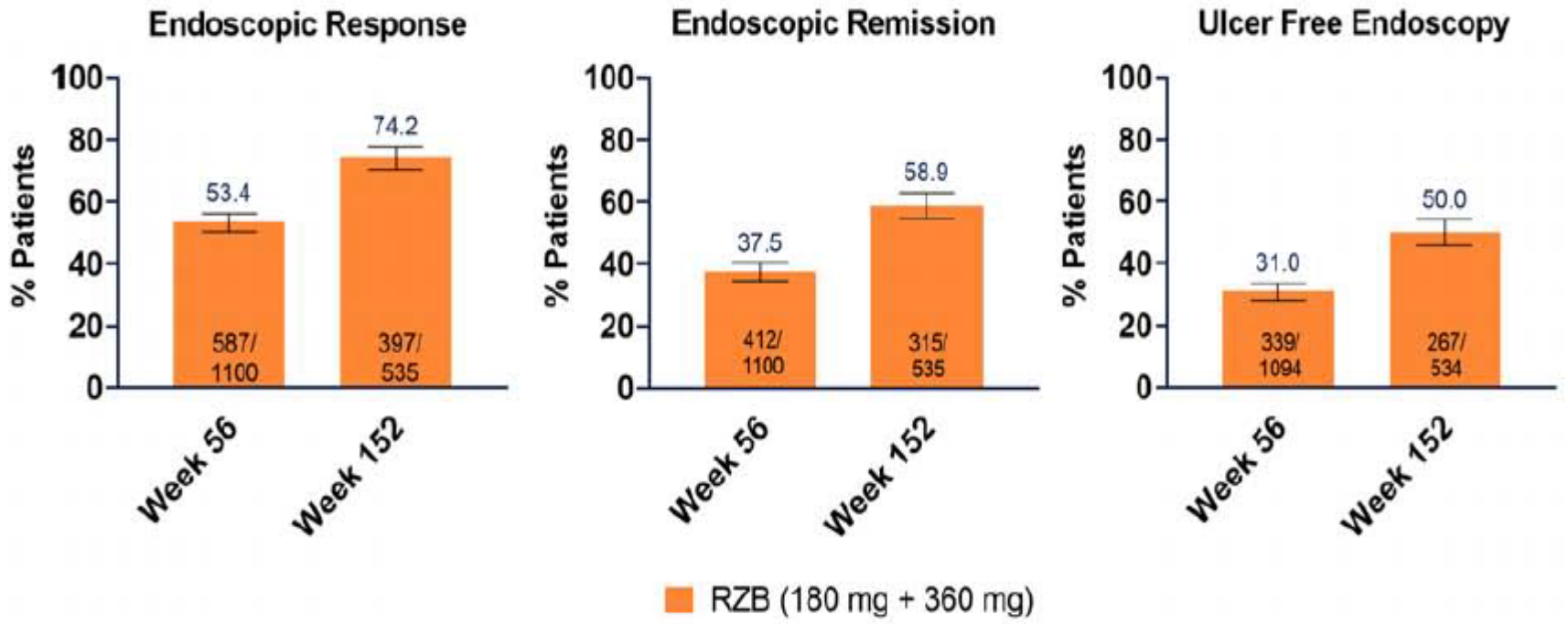
	ADVANCE Mixed Population*	MOTIVATE Biologic Failure Population†	FORTIFY Mixed Population*
	INDUCTION STUDIES (Week 12)		MAINTENANCE STUDY (Week 52)
CO-PRIMARY ENDPOINTS	$p<0.001$	$p<0.001$	$p<0.05$
Endoscopic Response (SES-CD)	SKYRIZI 600 mg IV 40% (135/336), Placebo 12% (21/175)	SKYRIZI 600 mg IV 29% (55/191), Placebo 11% (21/187)	SKYRIZI 360 mg SC 48% (56/117), SKYRIZI 180 mg SC 50% (67/135), Placebo (Induction Responders) 22% (28/130)
Clinical Remission (CDAI)	SKYRIZI 600 mg IV 45% (152/336), Placebo 25% (43/175)	SKYRIZI 600 mg IV 42% (80/191), Placebo 20% (37/187)	SKYRIZI 360 mg SC 57% (66/117), SKYRIZI 180 mg SC 61% (82/135), Placebo (Induction Responders) 46% (59/130)
SECONDARY ENDPOINT	$p<0.001$	$p<0.001$	
Endoscopic Remission	SKYRIZI 600 mg IV 24% (81/336), Placebo 9% (15/175)	SKYRIZI 600 mg IV 19% (37/191), Placebo 4% (8/187)	SKYRIZI 360 mg SC 41% (48/117), SKYRIZI 180 mg SC 33% (44/135), Placebo (Induction Responders) 13% (17/130) This endpoint was not statistically significant under the prespecified multiple testing procedure.

Abstract citation ID: jjad212.0093

Long-term Efficacy and **Safety** of **Risankizumab** in Patients with Moderate to Severe Crohn's Disease up to 3 Years of Treatment: Results From the FORTIFY Open-Label Long-term Extension

- Maintenance open-label extension (OLE)
- All pts received 180 mg SC RZB every Q8W starting at wk56 and who continued 360mg SC Q8w in the OLE till 3 years

Clinical response, 85.8% to 86.5%, respectively;
Enhanced clinical response, 88.6% to 89.2%;
CDAI clinical remission, 68.5% to 77.6%;
Stool frequency(SF)/abdominal pain(AP) score clinical remission 71.0%
Endoscopic response were 53.4% and 74.2%,
Endoscopic remission were 37.5%, and 58.9%,
Ulcer-free endoscopy were 31.0% and 50.0%.



APS, abdominal pain score; BL, baseline; CDAI, Crohn's disease activity index; CTE, continuous treatment extension; SES-CD, simple endoscopic score for Crohn's disease; SF, stool frequency

CDAI clinical response: Reduction of CDAI ≥ 100 points from baseline of the induction study; Enhanced clinical response: ≥ 60% decrease in average daily SF and/or ≥ 35% decrease in average daily APS and both not worse than BL of the induction study, and/or clinical remission; SF/APS Clinical remission: Average daily SF ≤ 2.8 and not worse than BL AND average daily APS ≤ 1 and not worse than BL of the induction study; CDAI clinical remission: CDAI < 150; Endoscopic response: Decrease in SES-CD > 50% from BL (or for patients with isolated ileal disease and a SES-CD of 4 at BL of the induction study, at least a 2 point reduction from BL of the induction study), as scored by central reader; Endoscopic remission: SES-CD ≤ 4 and at least a 2 point reduction versus BL of the induction study and no subscore greater than 1 in any individual variable, as scored by a central reader; Ulcer-free endoscopy: SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥ 1 at BL of the induction study, as scored by a central reader

Week 56 is the entry of M16-000 OLE and is based on the last non-missing value prior to the first dose of study drug in the OLE.

Abstract citation ID: jjad212.0093

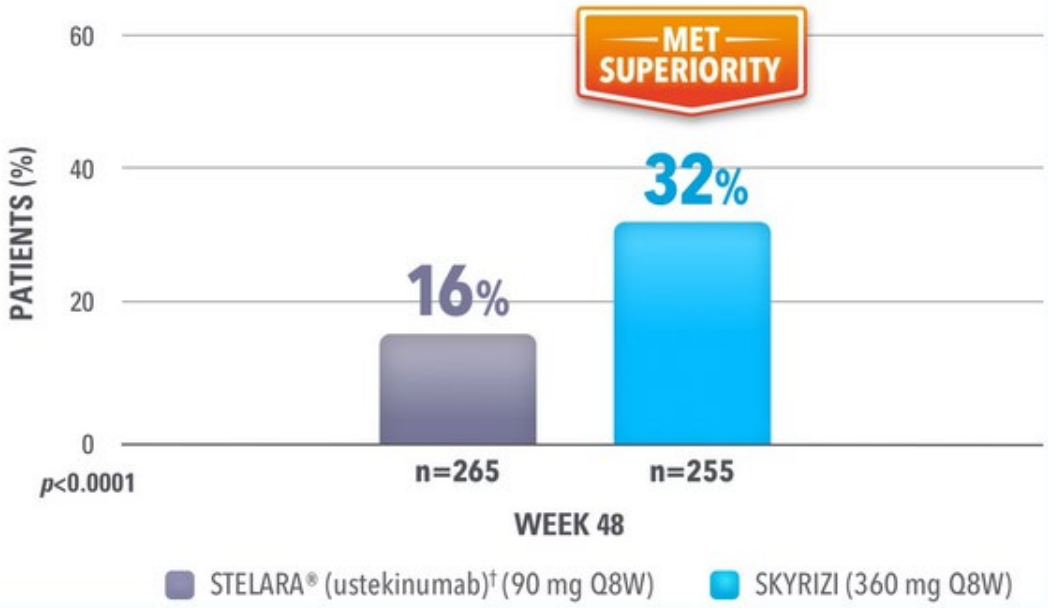


Study Design :

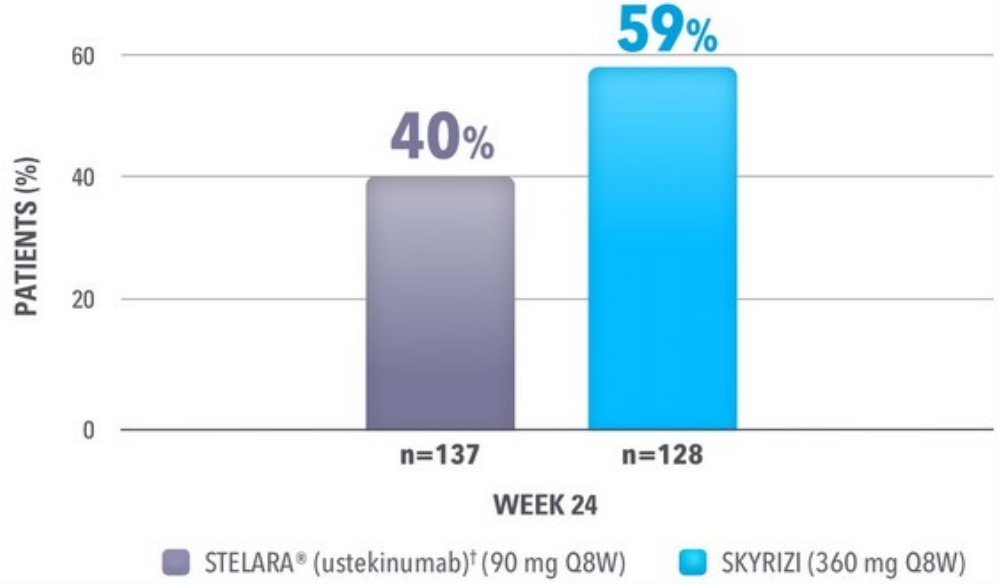
SEQUENCE was a **Phase 3**, multicenter, randomized, open-label, efficacy assessment-blinded study of **SKYRIZI (n=255)** compared to STELARA (ustekinumab) (n=265) for the treatment of adult patients with moderate to severe Crohn's disease who have ≥1 failed anti-TNF therapy.

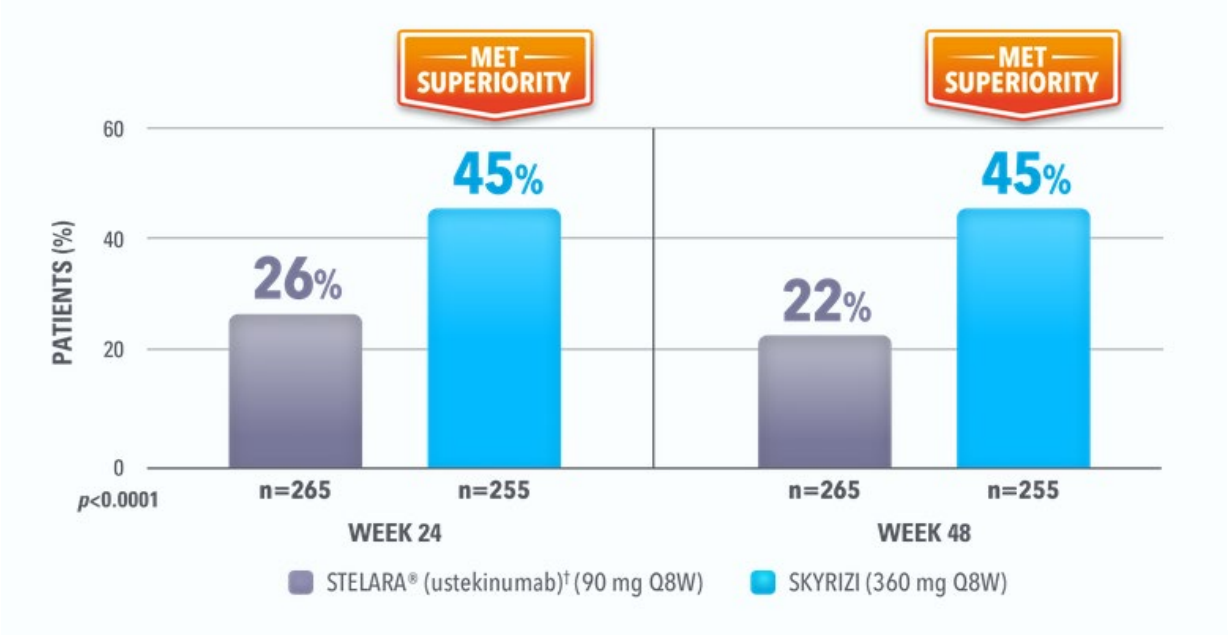
Patients were randomized (1:1) to receive either SKYRIZI (600 mg IV to 360 mg SC) or STELARA (weight-based IV to 90 mg SC). After induction dosing was completed, patients remained on their respective therapy throughout the duration of the maintenance period (treat-through study design).

Endoscopic Remission (SES-CD ≤4) (Superiority Endpoint)



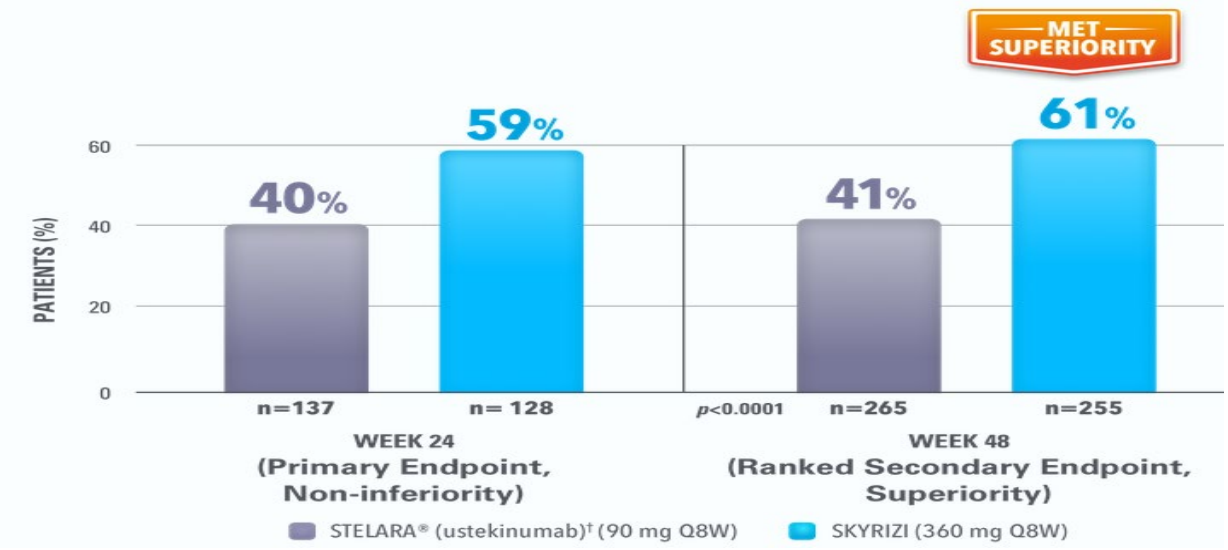
Clinical Remission (CDAI <150) (Non-inferiority Endpoint)





Endoscopic Response at Week 24 and Week 48

Clinical Remission at Week 24 and Week 48

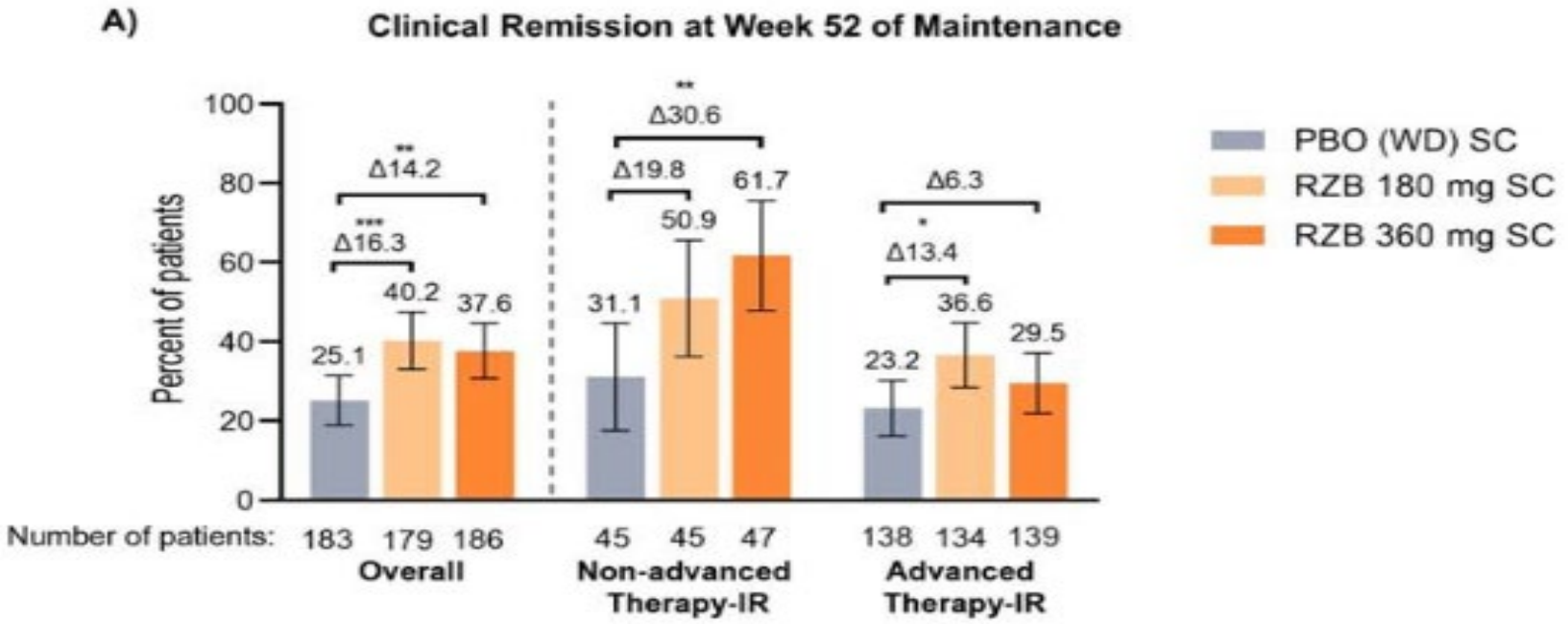


Lancet. 2022;399(10340):2015-2030.
Lancet. 2022;399(10340):2031-2046
Adv Ther . 2023 Sep;40(9):3896-3911

ECCO Abstract citation ID: jjad212.0006

Risankizumab Maintenance_therapy_in Patients with Moderately to Severely **Active UC**: Efficacy and Safety in the Randomized Phase 3 COMMAND Study

- ✓ Patients with moderately to severely active UC who achieved a clinical response per Adapted Mayo score after 12 or 24 weeks of RZB IV treatment in the phase 2b and phase 3 INSPIRE study
- ✓ Randomized 1:1:1 in COMMAND to RZB 180 mg, 360 mg , or PBO (RZB withdrawal) SC treatment every 8 wks for 52 wks.
- ✓ The primary endpoint was clinical remission per Adapted Mayo score at wk 52.
- ✓ Key secondary endpoints included endoscopic improvement, HEMI, endoscopic remission, steroid-free clinical remission, maintenance of clinical remission, no bowel urgency, and no abdominal pain at wk 52.



of 548 patients;; 75% had history of inadequate response or intolerance to ≥ 1 advanced therapy (AT).

Patients receiving RZB180 (40.2%) and RZB360 (37.6%) achieved significantly higher rates of clinical remission vs WD (25.1%).

Greater proportions of patients achieved SECONDARY ENDPOINT

Mirikizumab **(Omvoh™)**

Mirikizumab is a humanized IgG4-variant monoclonal antibody consisting of two heavy-chain and two light-chain subunits.

Mirikizumab binds with high affinity to the **p19** subunit (α subunit) of the heterodimeric IL-23

➢ Mirikizumab (Omvoh®)

- ✓ Mirikizumab was approved in March 2023 in Japan for use as induction and maintenance therapy in patients with moderate to severe ulcerative colitis who have an inadequate response to conventional therapy or therapies

- ✓ Mirikizumab accepted in the EU in March 2023

- ✓ For who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

Primary efficacy and safety of MIRIKIZUMAB in moderate to severe Crohn's Disease: Phase 3 VIVID 1 study

1-MIRIKIZUMAB 900 mg IV at weeks 0, 4, and 8, then 300 mg SC every 4 weeks from weeks 12 to 52

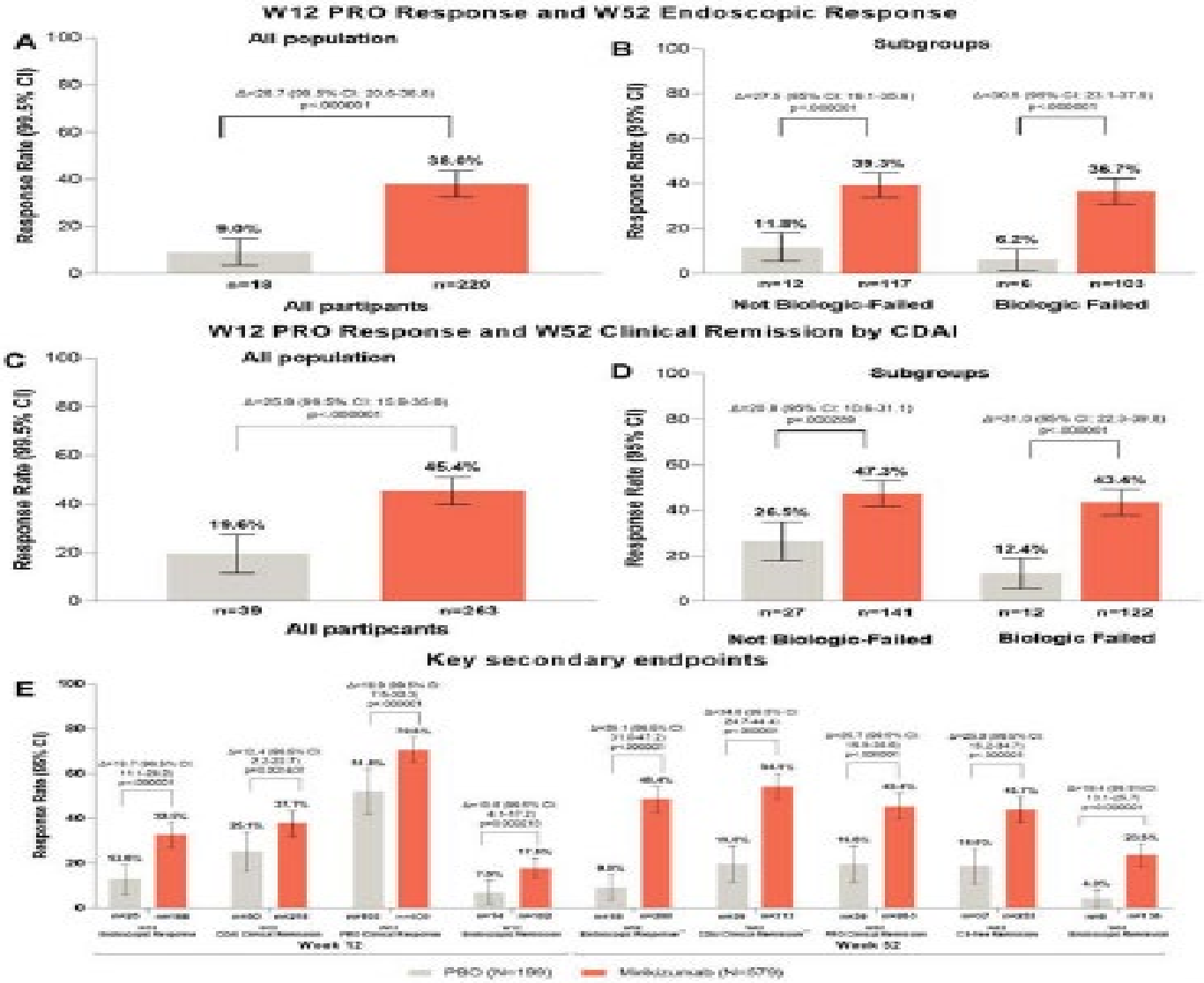
2-ustekinumab about 6 mg/kg IV at week 0, then 90 mg SC every 8 weeks from weeks 8 to 52

3- Placebo

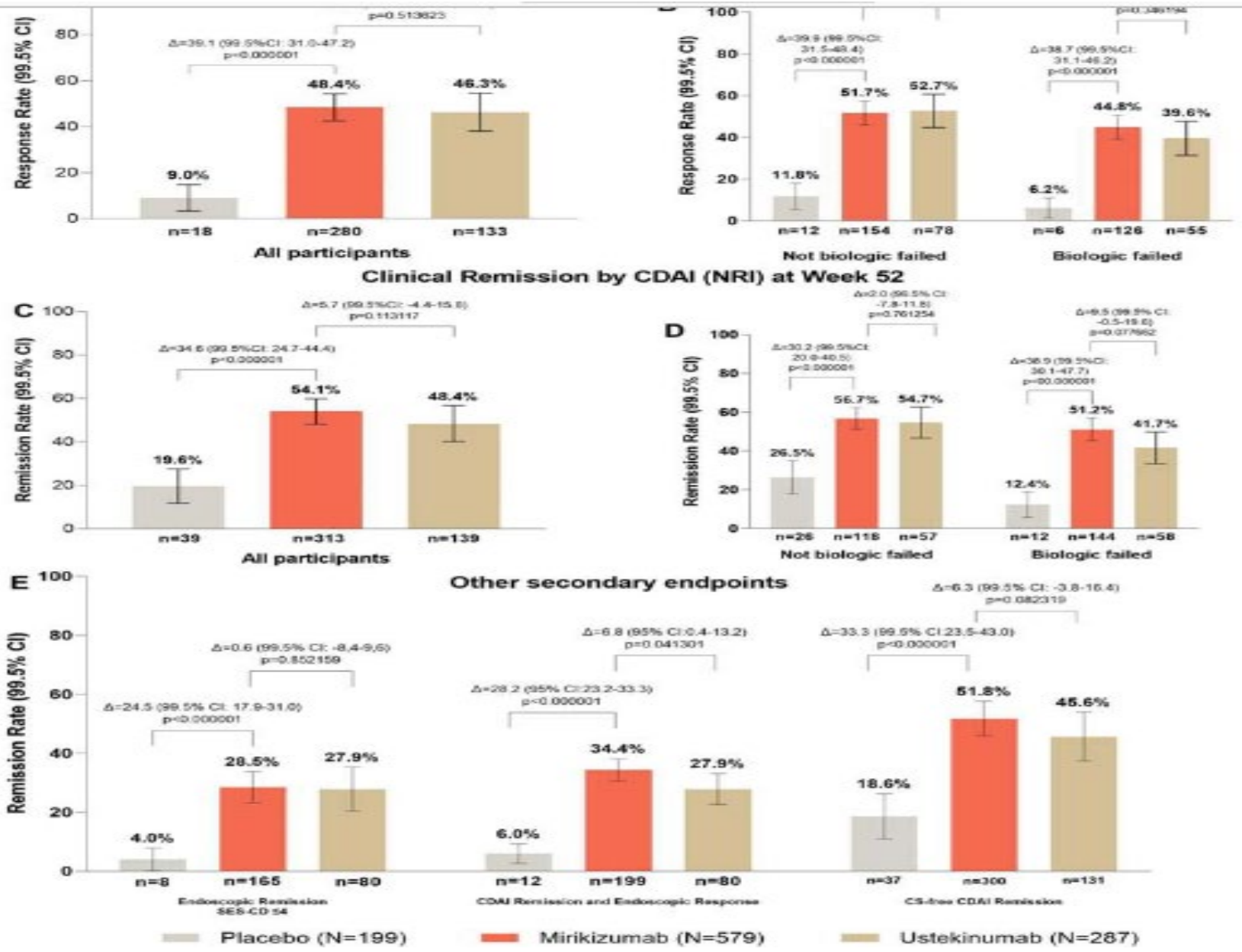
Miri (N=579) -**placebo** (PBO) (N=199)-**Ustekinumab** (N=287)

ENDPOINTS:

patient-reported outcome (PRO) clinical response at week 12 endoscopic response at week 52 and PRO clinical response at week 12 and Crohn's Disease Activity Index (CDAI) clinical remission at week 52



Unless otherwise specified, all W52 endpoints reflect composite endpoints of W12 PRO clinical response and the respective W52 endpoint. TF stands for Treat Through result and reflects the W52 endpoint result regardless of response status at W12. All participants refer to pts from mITT (all having received at least 1 dose of IP) who have baseline SES-CD≥3 or ≥4 for isolated ileal disease.



MIRIKIZUMAB in comparison to ustekinumab

Results phase 3 VIVID:

Conclusion: In this phase 3 CD study, **MIRIKI** demonstrated statistically significant and clinically meaningful improvements vs **PBO** and **Ustekinumab** in both co-primary composite endpoints and all key secondary endpoints, with an acceptable safety profile in moderate to severe CD

The overall safety profile were similar
Most common AEs were : anaemia, arthralgia, headache, upper respiratory tract infect. , nasopharyngitis, injection site reaction
Serious adverse events were comparable for miri (10.3%) and uste (10.7%).

Lucent study on Mirikizumab in UC

In LUCENT-1:

UC patients were randomized to receive 3 IV of 300 mg MIRI or PBO Q4W at W0,W4, and W8 (induction population).

In LUCENT 2 :

Responders to miri induction at W12 were **re-randomized** to subcutaneous (SC) 200mg miri or PBO Q4W through W52 of continuous therapy (maintenance population)

N Engl J Med 2023;388:2444-55

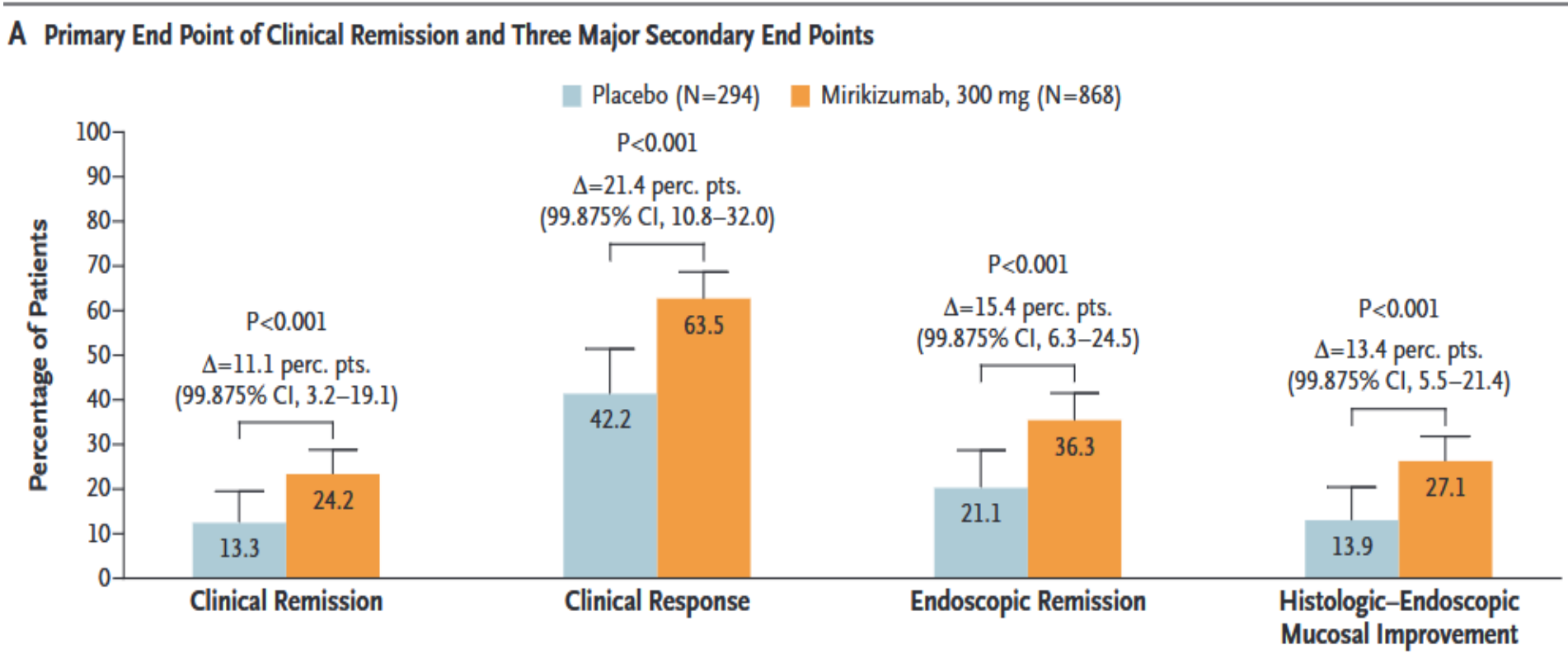
Lucent study

- **Endpoints evaluated were:**
- clinical response
- clinical remission
- symptomatic remission
- endoscopic remission
- corticosteroid (CS)-free remission,
- histologic-endoscopic mucosal remission

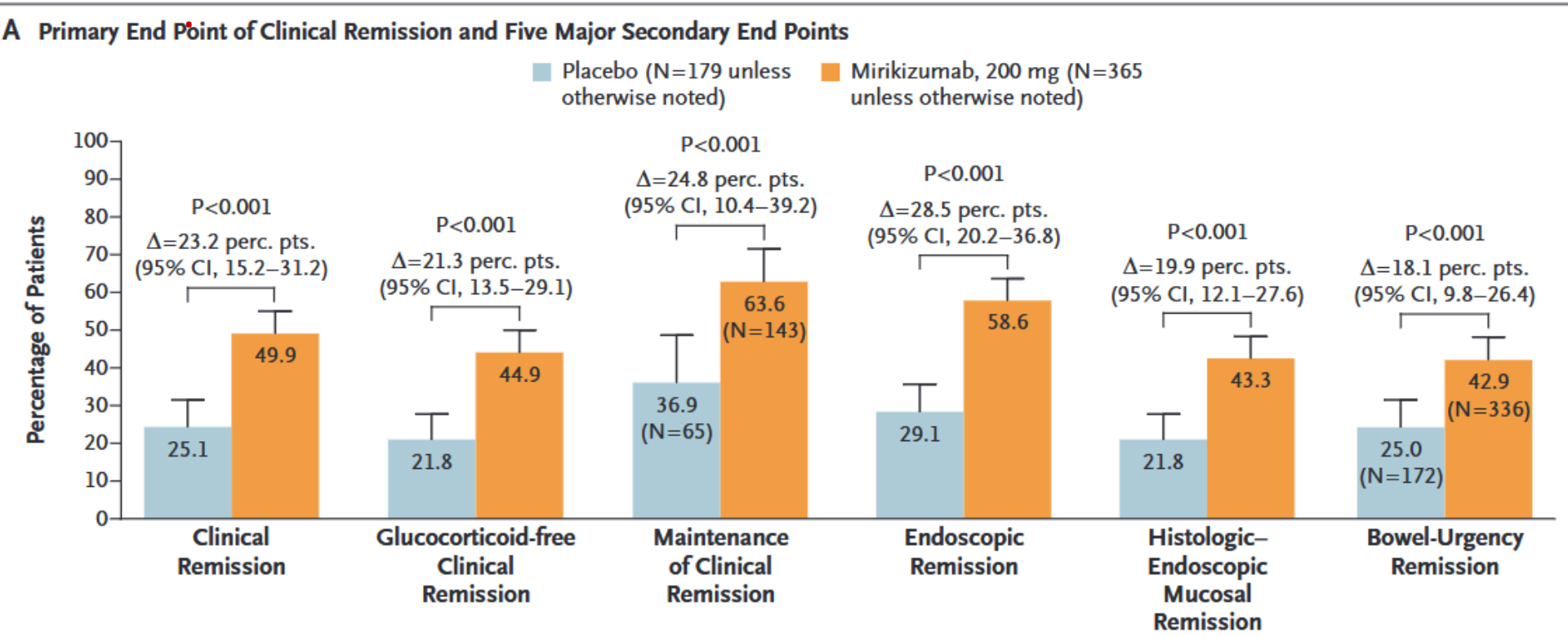
Results

- ✓ A total of 1281 patients underwent randomization in the induction trial
- ✓ 544 patients with a response to mirikizumab underwent randomization again in the maintenance trial.
- ✓ 45% of patients had one prior anti-TNF failure

Primary and Major Secondary End Points in the Miri Induction Trial



Primary and Major Secondary End Points in the Maintenance Trial (52W)



Mirikizumab is efficacious for induction and maintenance therapy

Table 2: Efficacy of miri vs PBO for Subjects with Only One Prior anti-TNF Failure [a]

	LUCENT-1 W12 (Induction Population)				LUCENT-2 W52 (Maintenance Population)			
	PBO IV n (%)	300mg Miri IV n (%)	p-value [b]	Risk Difference (95% CI) [c]	PBO SC n (%)	200mg miri SC n (%)	p-value [b]	Risk Difference (95% CI) [d]
Clinical Response	15 (34.1)	94 (64.4)	**0.00148**	27.4 (11.2, 43.5)	13 (44.8)	41 (67.2)	**0.03**	24.4 (3.1, 45.7)
Clinical Remission	6 (13.6)	27 (18.5)	0.66	2.9 (-9.4, 15.2)	5 (17.2)	27 (44.3)	**0.017**	27.3 (8.3, 46.2)
Symptomatic Remission	12 (27.3)	64 (43.8)	0.109	13.5 (-2.3, 29.4)	10 (34.5)	39 (63.9)	**0.005**	32.6 (11.6, 53.6)
Endoscopic Remission	7 (15.9)	44 (30.1)	0.105	12.8 (-0.8, 26.5)	8 (27.6)	29 (47.5)	0.073	20.4 (-0.1, 40.9)
CS-Free Remission					5 (17.2)	23 (37.7)	0.074	19.5 (0.7, 38.2)
HEMR					5 (17.2)	20 (32.8)	0.067	19.1 (1.3, 37.0)

	LUCENT-2 W24 (Extended Induction Population)	LUCENT-2 W52 (Extended Induction Responders)
	300mg miri IV, n (%)	200mg miri SC, n (%)
Clinical Response	21 (45.7)	15 (75)
Clinical Remission	2 (4.3)	6 (30)
Symptomatic Remission	13 (28.3)	11 (55)
Endoscopic Remission	5 (10.9)	8 (40)
CS-Free Remission		6 (30)
HEMR		6 (30)

Inflammatory Bowel Diseases, 2024, **XX**, 1–15
https://doi.org/10.1093/ibd/izae253
Advance access publication 25 October 2024
Original Research Article - Clinical

CROHN'S & COLITIS FOUNDATION

Three-Year Efficacy and Safety of Mirikizumab Following 152 Weeks of Continuous Treatment for Ulcerative Colitis: Results From the LUCENT-3 Open-Label Extension Study

LUCENT-3

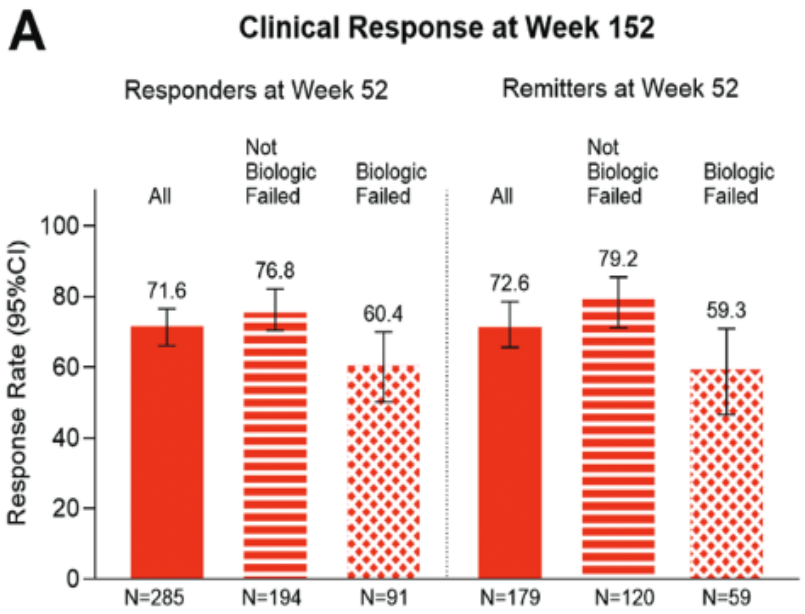
An ongoing single-arm, open-label, phase 3, multicenter, long-term extension study evaluating the efficacy and safety of mirikizumab in patients with moderately-to-severely active UC who participated in the LUCENT-1 and 2.

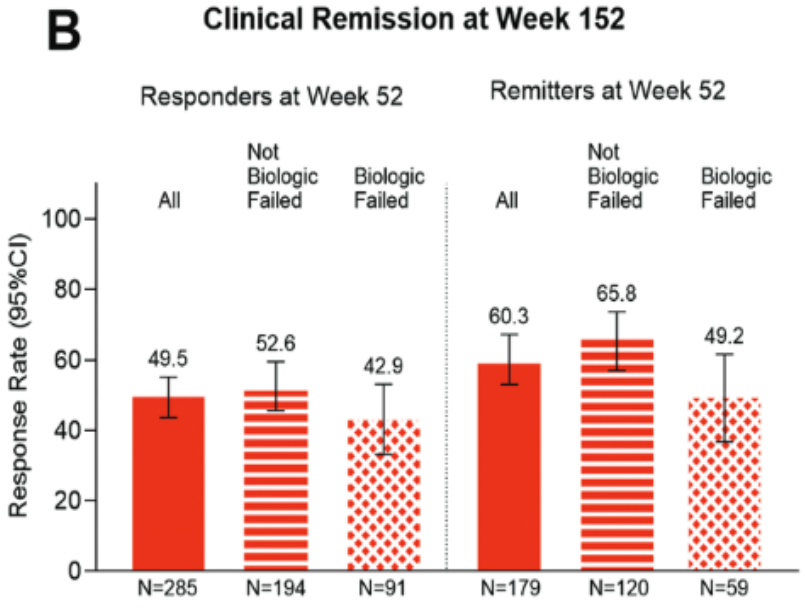
All patients received 200 mg mirikizumab every 4W, SC

544 were responders of whom 365 were rerandomized to mirikizumab maintenance.

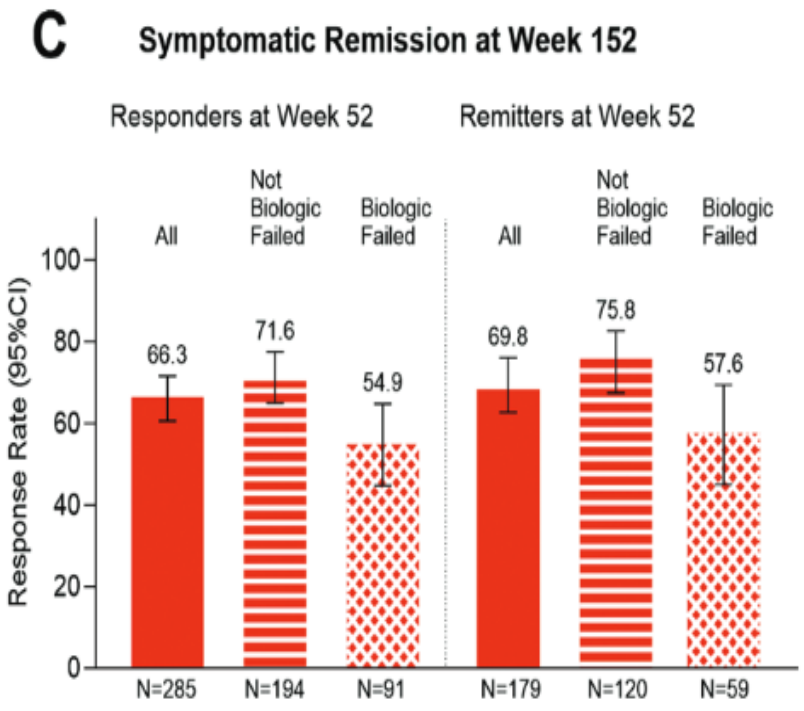
Of these, 316 entered extension treatment (186 week 52 responders; 179 week52 remitters).

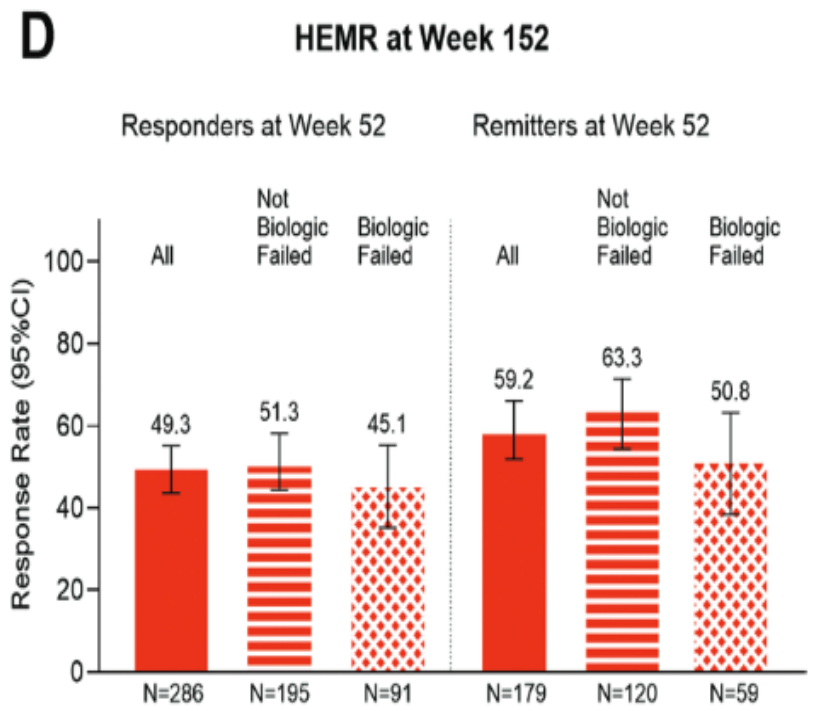
Results lucent 3 , Extension study ,3 years of MIRIKI for Severe UC





Results lucent 3 , Extension study ,3 years of MIRIKI for Severe UC



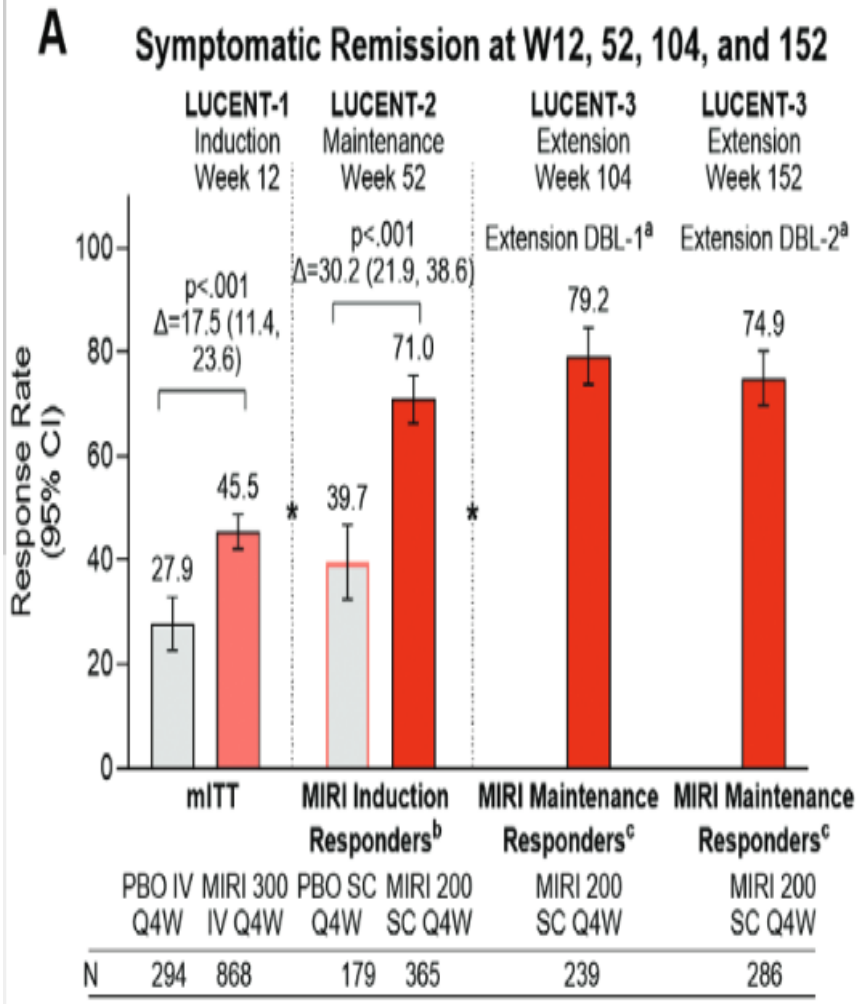


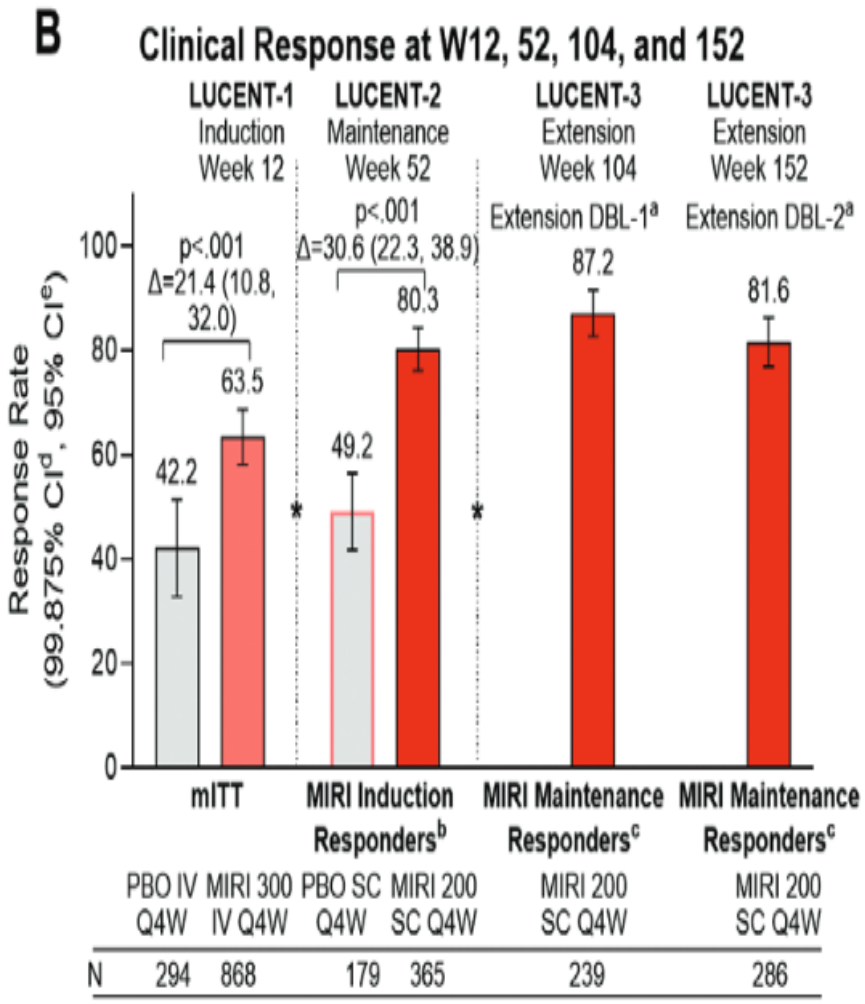
LUCENT-3 AEs.

Overall, in the safety population, 7.4% of patients reported severe adverse events (**AEs**);
5.3% discontinued treatment due to AEs.
AEs of special interest included opportunistic infection (1.8%), hepatic disorders (3.2%), CVA (1.5%), and malignancy (0.3%).
Patients with **antidrug antibodies** reduced over time from 23.6% in year 1 to 3.2% in year 3

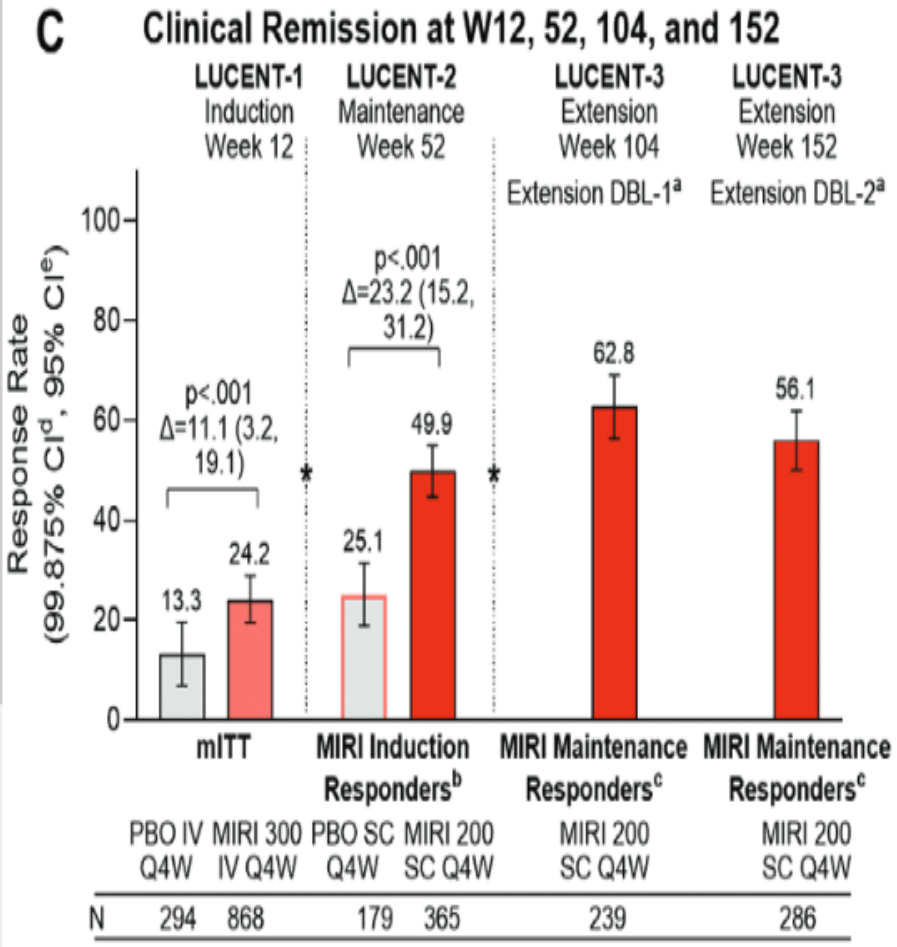
Outcome	Overall induction responder safety population
	Mirikizumab 200 mg Q4W SC ($N = 339$)[a]
TEAEs[b], *n* (%)	250 (73.7)
Mild	111 (32.7)
Moderate	114 (33.6)
Severe	25 (7.4)
SAEs, *n* (%)	30 (8.8)
Most Common TEAEs[c], *n* (%)	
COVID-19	76 (22.4)
Colitis ulcerative	54 (15.9)
Arthralgia	21 (6.2)
Nasopharyngitis	28 (8.3)
Headache	26 (7.7)
Pyrexia	20 (5.9)
Diarrhea	15 (4.4)
Gastroenteritis	15 (4.4)
Upper respiratory tract infection	15 (4.4)
Abdominal pain	14 (4.1)
Fatigue	10 (3.2)
AEs of Special Interest, *n* (%)	
Infections: all	144 (42.5)
Serious	8 (2.4)
Opportunistic[d]	6 (1.8)
Cerebrocardiovascular events[e]	5 (1.5)
Major adverse cardiac events (MACE)	1 (0.3)
Malignancies[f]	1 (0.3)
Depression	3 (0.9)
Suicide/self-injury[g]	1 (0.3)
Hepatic	11 (3.2)
Immediate hypersensitivity reactions[h]	4 (1.2)
Injection site reactions	19 (5.6)
Death, *n* (%)	1 (0.3)
Discontinuation due to AE, *n* (%)[i]	18 (5.3)

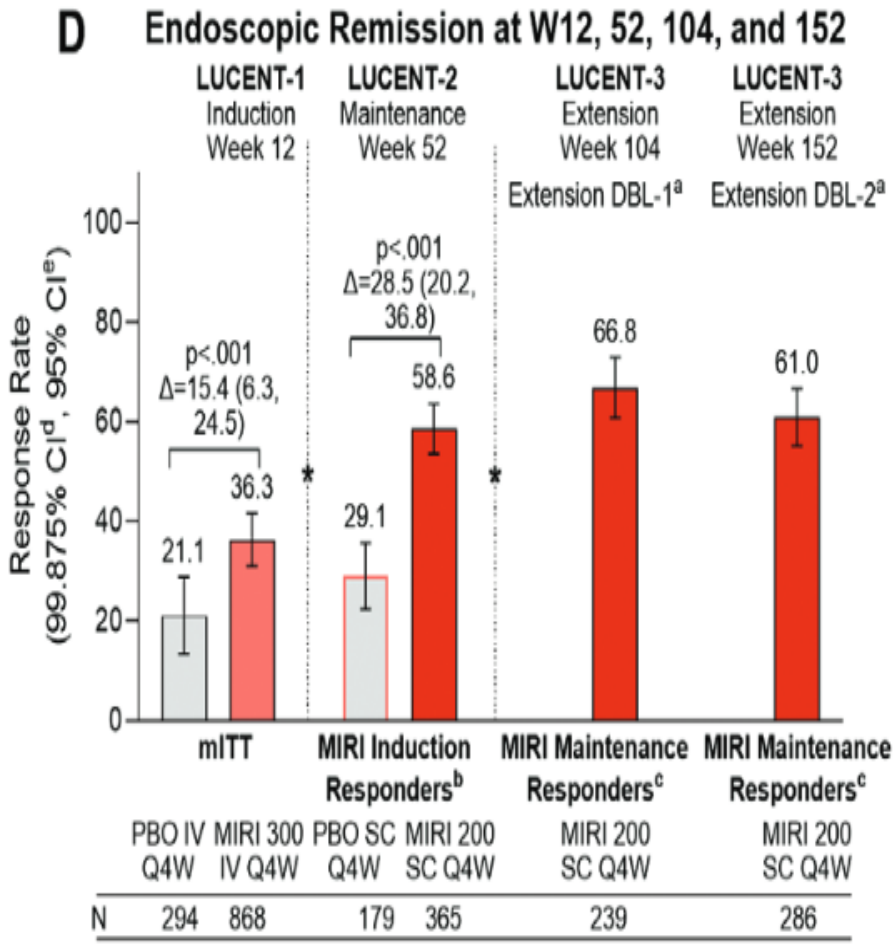
Remission rates at weeks 12, 52, 104, and 152



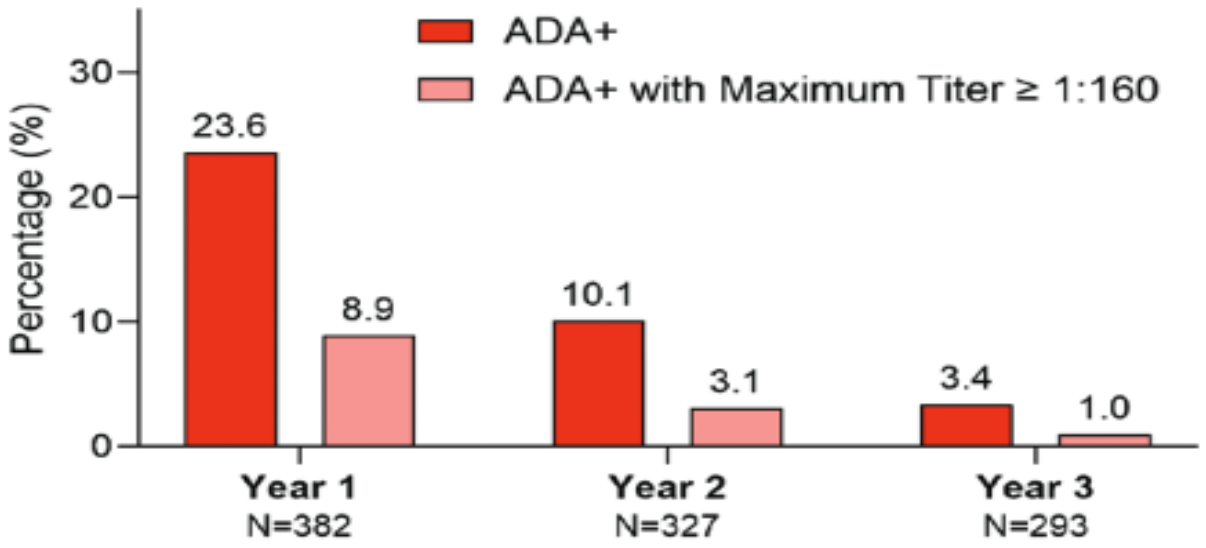


Remission rates at weeks 12, 52, 104, and 152





Incidence of Drug Antibodies events in evaluable patients over time.



Understanding ADAs is important because ADA+ can lead to diminished efficacy for patients over time.

<2% of patients developed an ADA+ titer ≥1:160 that was accompanied by a lower blood concentration of the drug and reduced efficacy during the first 52 weeks of treatment.

Guselkumab

Guselkumab is an all-human monoclonal antibody (**IgG1-lambda**) bind IL23 with high affinity and potency.
Launched under the **brand name** Tremfya is approved for the treatment of plaque psoriasis and psoriatic arthritis.
It work in the two ways: inhibit IL-23 & *CD64* on the cell

*CD64 +*cells ,on the surface of human inflammatory monocytes , are the main producers of IL-23 in UC

GALAXI Studies For CD :

The GALAXI program consists of **three studies** for Guselkumab efficacy and safety studies in patients with **moderately to severely** active **CD**:

GALAXI-1:a 48-week, phase 2,induction dose-finding study
GALAXI-2 and GALAXI-3: two identical 48-week phase 3 confirmatory studies

Results From the Phase 2 **GALAXI-1** Study: **Induction Therapy**

Double-blind, placebo controlled study, randomized patients ***5*** groups 1:1:1:1:1

Intravenous guselkumab **200** mg**, 600** mg, or **1200** mg at weeks 0, 4, and 8

Control:

intravenous **ustekinumab** **6 mg/kg** at week 0 and 90 mg ubcutaneously at week 8; or **placebo**.

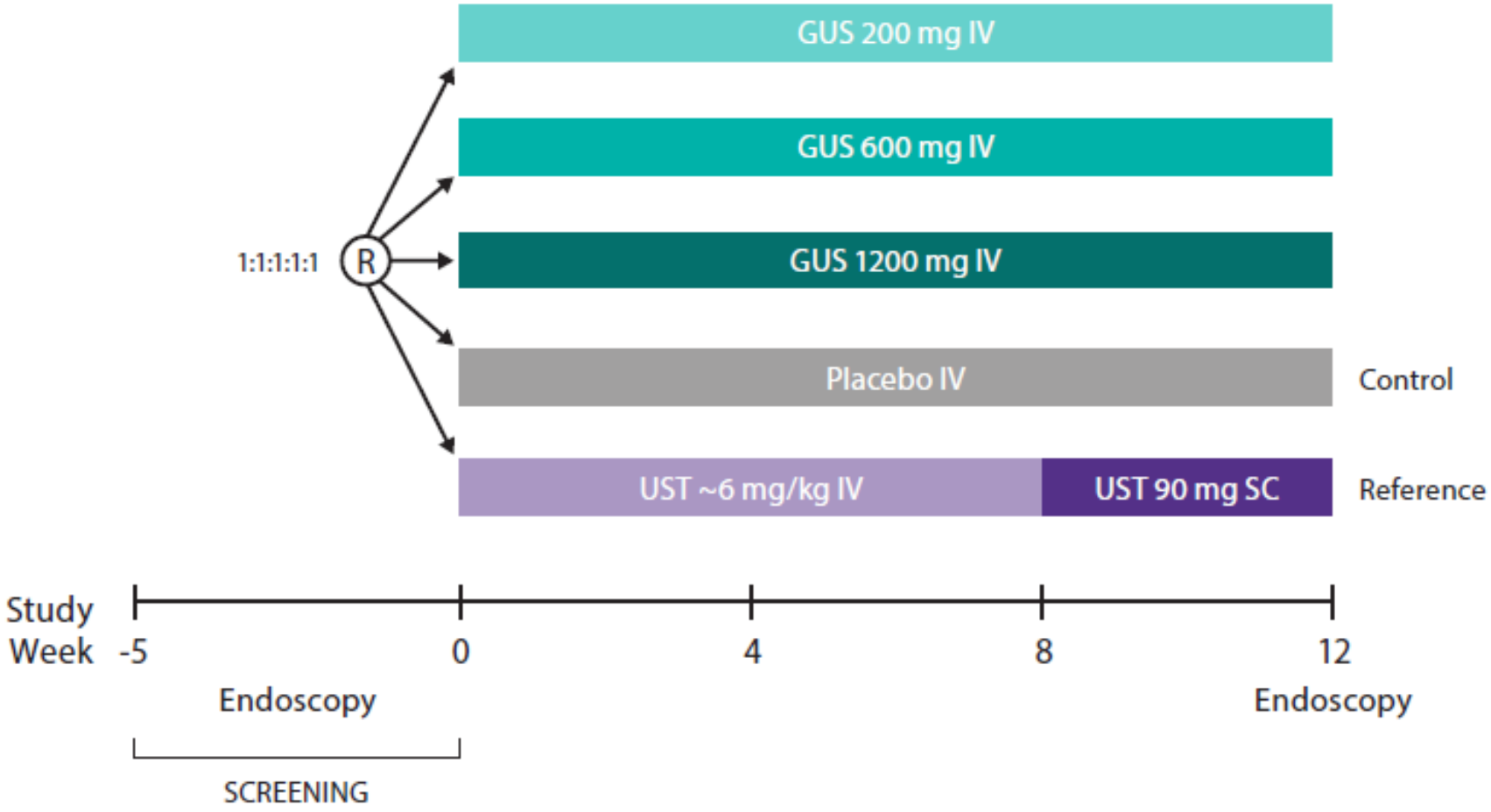
Primary end point: Change from baseline in Crohn's Disease Activity Index score

Secondary end points : clinical remission, clinical response, Patient Reported Outcomes-2 remission, clinical-biomarker response, endoscopic response

Safety

through week 12

GALAXI-1: induction therapy Study design.



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GALAXI-1: Study Population

- ✓ 18 years or older
- ✓ with moderately to severely active Crohn's disease of 3 months' duration.
- ✓ Patients with an inadequate response or intolerance to prior conventional treatment or biologic therapy
- ✓ Active Crohn's disease was defined: Crohn's Disease Activity Index [CDAI] score 220 but 450

Efficacy and Safety Assessments

- **Efficacy assessments included :**
- ✓ CDAI
- ✓ Patient Reported Outcome-2
- ✓ Endoscopic assessments
- ✓ Endoscopic healing and SES-CD
- ✓ Inflammatory markers, including CRP and fecal Calprotectin
- ✓ Fistula assessment
- ✓ Quality of life outcomes measures

Serum Guselkumab concentrations were measured at weeks 0,4, 8, and 12
The presence of antibodies to guselkumab in serum was determined

Safety evaluations including adverse events (AEs), serious AEs (SAEs), infections, and serious infections, were conducted at each study visit

Study End Points

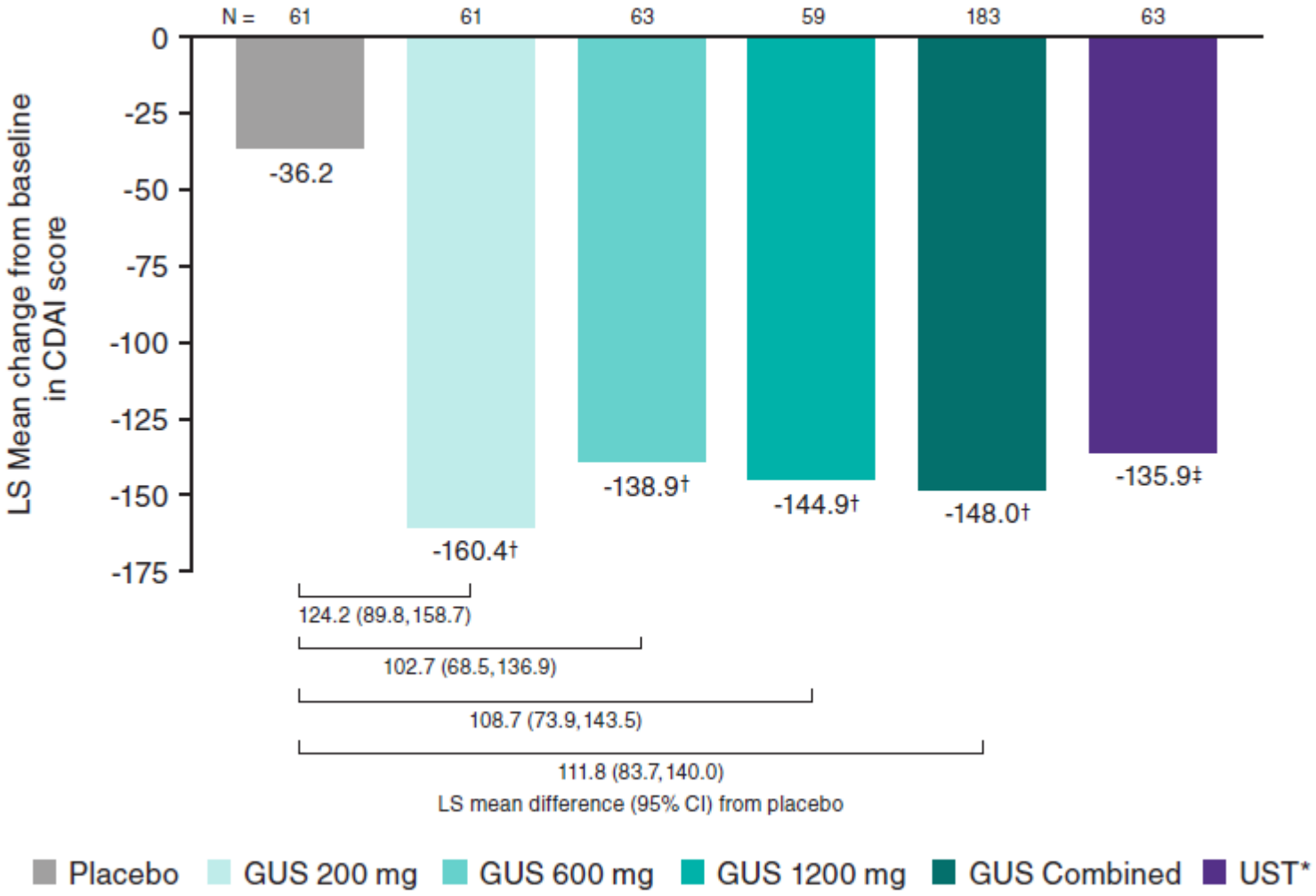
- ✓ The primary end point was the change from baseline in CDAI score at week 12.
- ➢ The major secondary end points were:
  - ✓ clinical remission at week 12 (CDAI score <150)
  - ✓ clinical response at week 12 (more than 100 point reduction of CDI or CDAI score <150)
  - ✓ endoscopic response at week 12 (50% improvement of SESCD score or SES-CD score 2);
  - ✓ clinical-biomarker response at week 12 (50% reduction of CRP or calprotectin).

RESULTS:

Of 309 patients evaluated, 50% had disease refractory to prior biologic therapy.

At week 12:

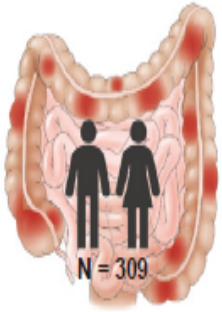
- ✓ significantly reductions in CDAI from baseline (least squares means: **200 mg: –160.4**, 600 mg: –138.9, and 1200 mg: –144.9 vs placebo: –36.2; all**, P < .05**)
- ✓ significantly proportions of patients achieved **clinical remission** in each **guselkumab** group vs *placebo* (CDAI <150; **57.4%**, 55.6%, and 45.9% vs 16.4%;all, P < .05).
- ✓ Greater proportions of patients receiving guselkumab achieved **clinical response**
- ✓ Patient Reported **Outcomes2 remission**, **biomarker response**, and **endoscopic response** at week 12 vs placebo.



GALAXI-1: Primary efficacy end point.

least squares; reductions from base line

ABSTRACT of Induction Results From the Phase 2 GALAXI-1 Study



Patients with moderately to severely active Crohn's disease with inadequate response or intolerance to prior biologic or conventional therapy

Phase 2, Double-blind, Randomized 1:1:1:1:1

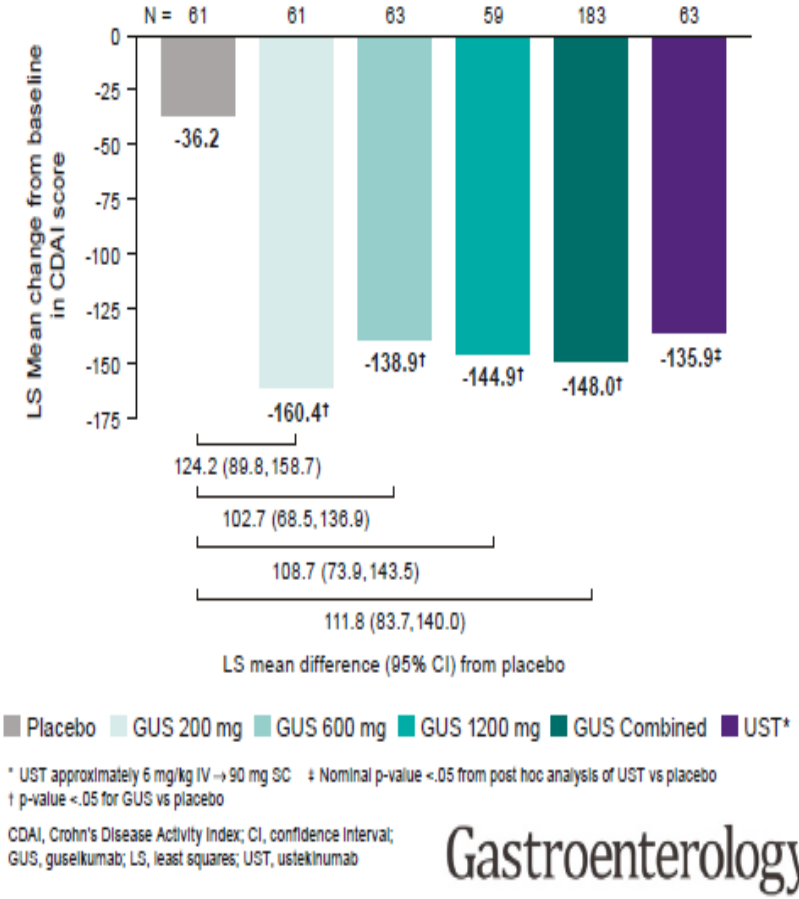
Guselkumab
IV at weeks 0, 4, 8

- 200 mg
- 600 mg
- 1200 mg
- Combined

Placebo
at weeks 0, 4, 8

Ustekinumab (reference arm)
IV ~6 mg/kg at week 0 and
90 mg SC at week 8

Primary endpoint: Change from baseline to week 12 in CDAI score



* UST approximately 6 mg/kg IV → 90 mg SC ‡ Nominal p-value <.05 from post hoc analysis of UST vs placebo
† p-value <.05 for GUS vs placebo

CDAI, Crohn's Disease Activity Index; CI, confidence interval; GUS, guselkumab; LS, least squares; UST, ustekinumab

Gastroenterology

Results from the phase 2; GALAXI-1 trial
Maintenance Therapy for 48w

Randomized, multicenter, double-blind trial.
Adult patients with moderately to severely active CD were randomly allocated

Five treatment groups, with regimens consisting of an intravenous induction phase transitioning to a subcutaneous maintenance phase

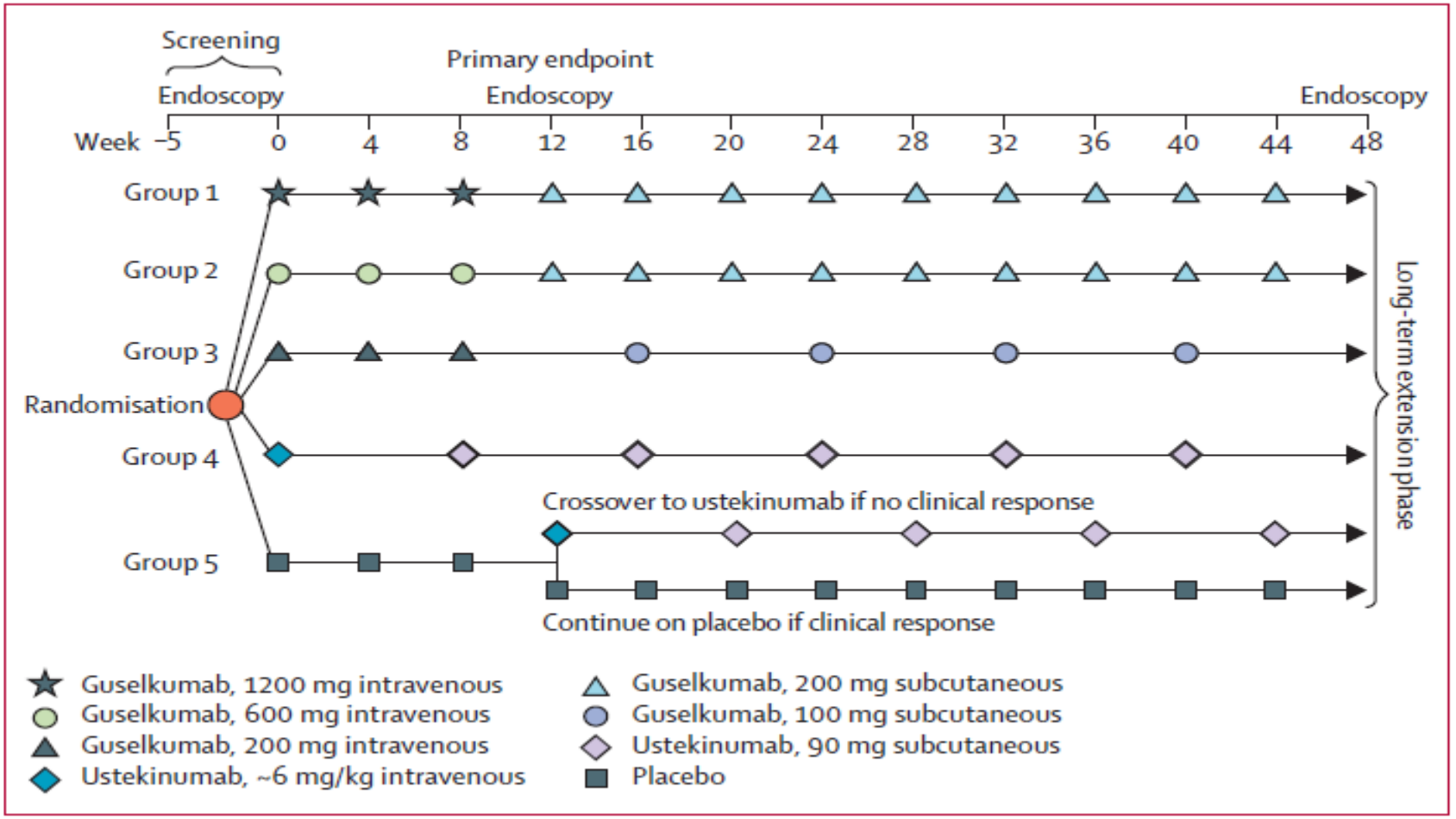
(1) guselkumab 200→100 mg group (200 mg intravenous at weeks 0, 4, and 8, then 100 mg subcutaneous every 8 weeks)
(2) guselkumab 600→200 mg group (600 mg intravenous at weeks 0, 4, and 8, then 200 mg subcutaneous every 4 weeks)
(3) guselkumab 1200→200 mg group (1200 mg intravenous at weeks 0, 4, and 8, then 200 mg subcutaneous every 4 weeks)
(4) ustekinumab group (approximately 6 mg/kg intravenous at week 0, then 90 mg subcutaneous every 8 weeks)
(5) placebo group

Endpoints assessed at week 48:

CDAI remission (CDAI score <150),

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

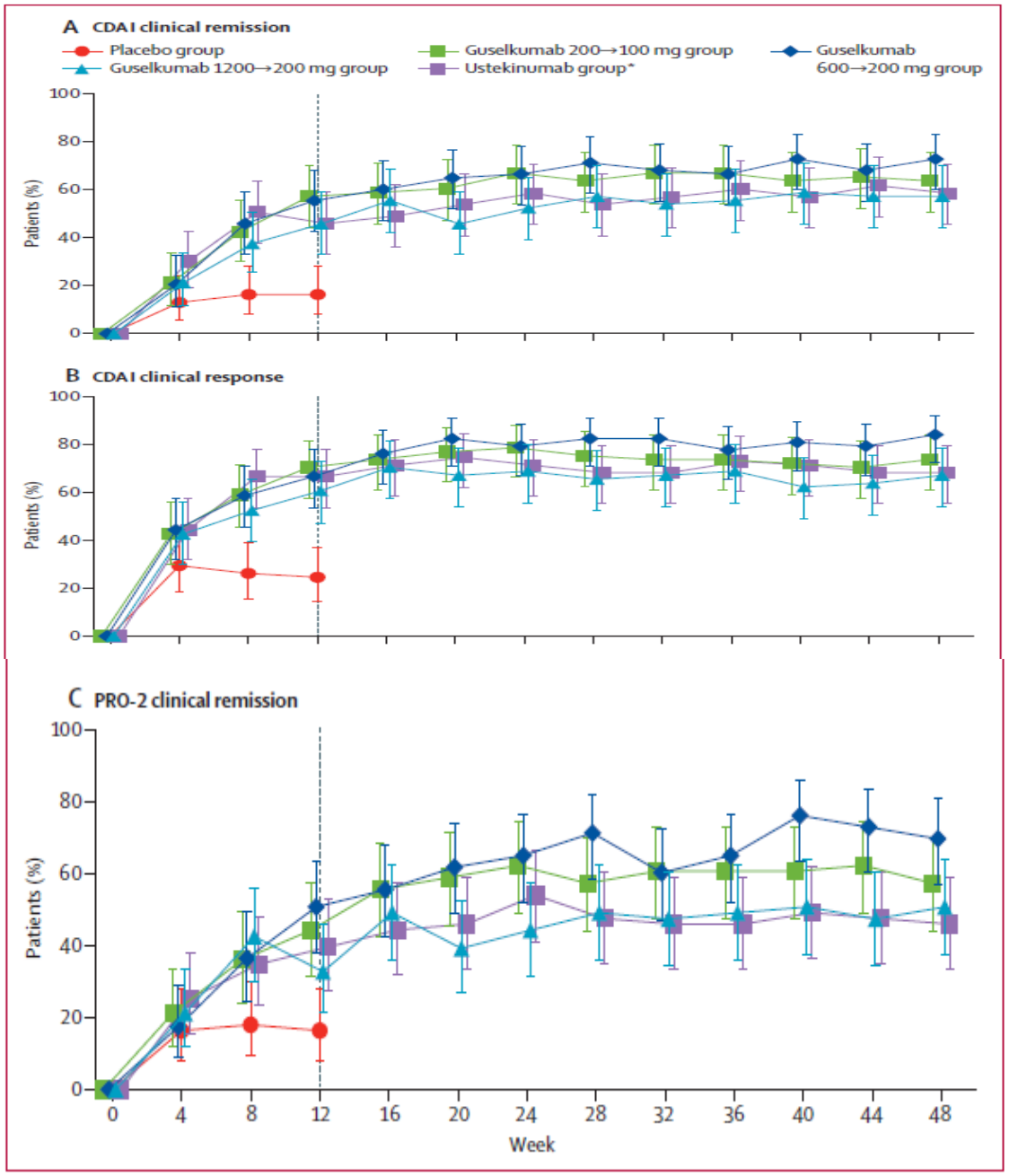
Endoscopic remission (SES-CD score ≤2) in the primary efficacy analysis



Key exclusion criteria :

presence of complications of Crohn's disease that could require surgery, presence or suspicion of : an abscess, draining stoma or ostomy, recent surgery, and evidence of enteric infection (in the past 4 months).
Patients who previously received IL-12 and IL-23, or IL-23 alone

stable doses of **5-aminosalicylates** and **immunomodulators** were **maintained** from induction baseline to maintenance week 48, unless otherwise stated in protocol.
Corticosteroid therapy at a prednisone-equivalent dose at or below 40 mg/day, or 9 mg/day of budesonide, or 5 mg/day beclomethasone dipropionate was **permitted at entry**, with mandatory tapering from week 12 according to a protocol recommended tapering schedule



(A) CDAI clinical remission, CDAI score less than 150.
(B)CDAI clinical response, defined as a reduction of at least 100 points from baseline CDAI score, or a CDAI score less than 150.
(C) PRO-2 clinical remission, defined as a daily average abdominal pain score no higher than 1 and a daily stool frequency of no more than 3, and no worsening of abdominal pain or stool frequency from baseline.

	Guselkumab			
	200 mg IV→ 100 mg SC	600 mg IV→ 200 mg SC	1200 mg IV→200 mg SC	Ustekinumab
Primary efficacy analysis set	61	63	61	63
Discontinued agent prior to week 48, n (%)	4 (6.6)	5 (7.9)	8 (13.1)	2 (2.3)
Clinical remission (CDAI score <150),[a,b] (95% CI)[c]	63.9% (51.9, 76.0)	73.0% (62.1, 84.0)	57.4% (45.0, 69.8)	58.7% (46.6, 70.9)
Corticosteroid-free clinical remission (CDAI score <150 at Wk 48 and not receiving corticosteroids at Wk 48),[a,b] (95% CI)[c]	59.0% (46.7, 71.4)	71.4% (60.3, 82.6)	55.7% (43.3, 68.2)	58.7% (46.6, 70.9)
PRO-2 remission (unweighted CDAI component of daily average AP score ≤1 AND the unweighted CDAI component of daily average SF ≤3, and no worsening of AP or SF from baseline),[a,d] (95% CI)[c]	57.4% (45.0, 69.8)	69.8% (58.5, 81.2)	50.8% (38.3, 63.4)	46.0% (33.7, 58.3)
Clinical response (≥100-point reduction from baseline in CDAI score or CDAI score <150),[a,b] (95% CI)[c]	73.8% (62.7, 84.8)	84.1% (75.1, 93.2)	67.2% (55.4, 79.0)	68.3% (56.8, 79.7)
Number of patients with a daily average AP >1 at baseline	57	58	59	60
Patients with abdominal pain score ≤1,[a,e] (95% CI)[c]	73.7% (62.3, 85.1)	74.1% (62.9, 85.4)	59.3% (46.8, 71.9)	61.7% (49.4, 74.0)
Number of patients with daily average number of liquid or very soft stools >3 at baseline	47	52	48	56
Patients with daily average number of liquid or very soft stools ≤3,[a,f] (95% CI)[c]	55.3% (41.1, 69.5)	75.0% (63.2, 86.8)	62.5% (48.8, 76.2)	53.6% (40.5, 66.6)

CDAI, Crohn's disease activity index; CI, confidence interval; PRO-2, Patient-reported outcome; AP, abdominal pain;

	Guselkumab			
	200 mg IV→ 100 mg SC	600 mg IV→ 200 mg SC	1200 mg IV→200 mg SC	Ustekinumab
Safety analysis set	73	73	73	71
Patients with ≥1 adverse events, n (%)	52 (71.2%)	59 (80.8%)	51 (69.9%)	60 (84.5%)
Patients with ≥1 serious adverse events, n (%)	6 (8.2%)	5 (6.8%)	5 (6.8%)	9 (12.7%)
Patients with ≥1 adverse events leading to discontinuation of study agent, n (%)	5 (6.8%)	2 (2.7%)	6 (8.2%)	6 (8.5%)
Patients with ≥1 infections[a], n (%)	25 (34.2%)	30 (41.1%)	25 (34.2%)	26 (36.6%)
Patients with ≥1 serious infections[a], n (%)	2 (2.7%)	2 (2.7%)	1 (1.4%)	1 (1.4%)

[a] Infection as assessed by the investigator

Only one patient who responded to placebo induction and two guselkumab-treated patients had serious infections.

Efficacy and safety of **guselkumab** therapy in patients with moderately to severely active Crohn's disease: **Results of the GALAXI 2 & 3 phase 3 studies**

GALAXI 2 & 3 are identical 48-week, randomized, double-blind, double-dummy, placebo (PBO)- and active-comparator

Eligible Pts :

moderately to severely active CD (CDAI 220–450 + mean daily SF>3 or AP>1),

SES-CD≥6 (≥4 for isolated ileal disease)

inadequate response or intolerance to conventional or biologic (BIO-ir) therapy

GALAXI 2 & 3 phase 3 studies

Randomization was stratified by CDAI (≤300 or >300), SES-CD (≤12 or >12), BIO-ir status,

Patients assigned **2:2:2:1** to
1-GUS 200mg IV q4w (x3)→200mg SC q4w,
2-GUS 200mg IV q4w (x3)→100mg SC q8w,
3-UST ~6mg/kg IV (x1)→90mg SC q8w,
4-PBO

PBO pts not in clinical response at week 12 (W12) switched to UST IV→90mg SC q8w.

primary endpoints were clinical response at W12 + clinical remission at W48 and clinical response at W12 + endoscopic response at W48,

GALAXI 2 & 3 (G2 & G3) included 508 and 513 pts, respectively
Baseline characteristics were similar across trials:
CDAI (G2: 295.0, G3: 294.7), SES-CD (13.1,12.8), BIO- history (52.8%, 51.9%), oral CS use (37.4%, 36.1%)

- **At W12:**

Pts receiving GUS 200mg IV had significantly greater (P<.001) rates of:
clinical remission (G2: 47.1% vs 22.4% , G3: 47.1% vs 15.3%,)
endoscopic response (G2: 37.7% vs 10.5%, ; G3: 36.2% vs 13.9%) to PBO .

Fig 1a: Composite endpoint of Clinical Response W12 + Clinical Remission W48

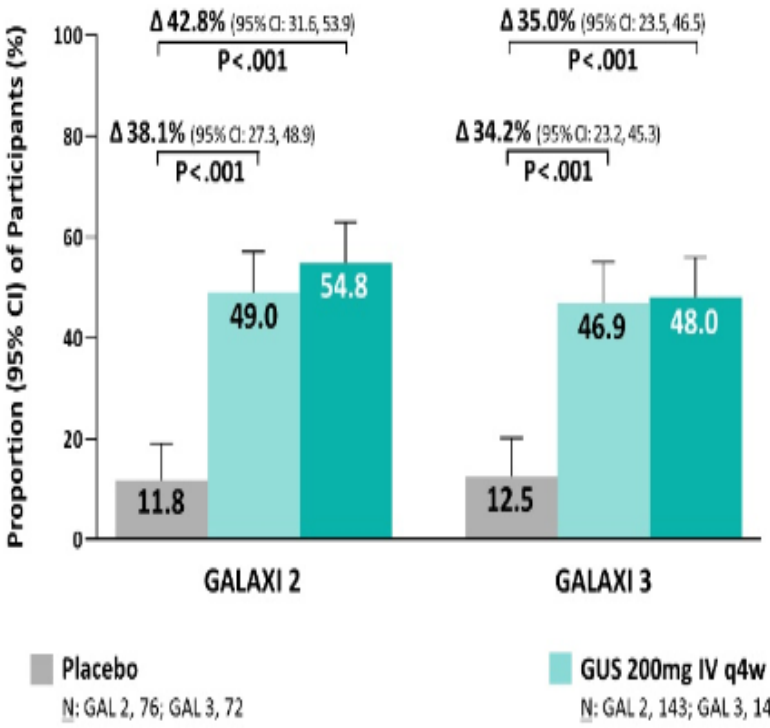
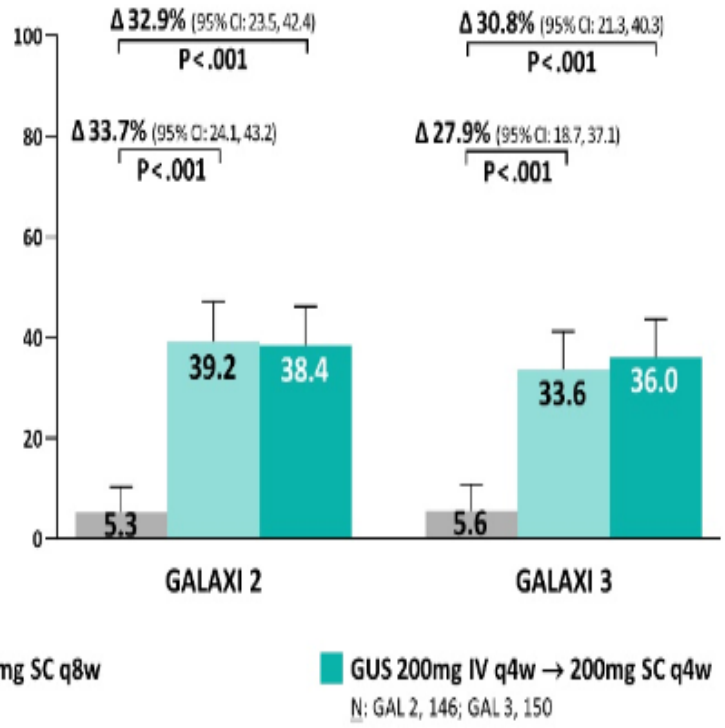


Fig 1b: Composite endpoint of Clinical Response W12 + Endoscopic Response W48

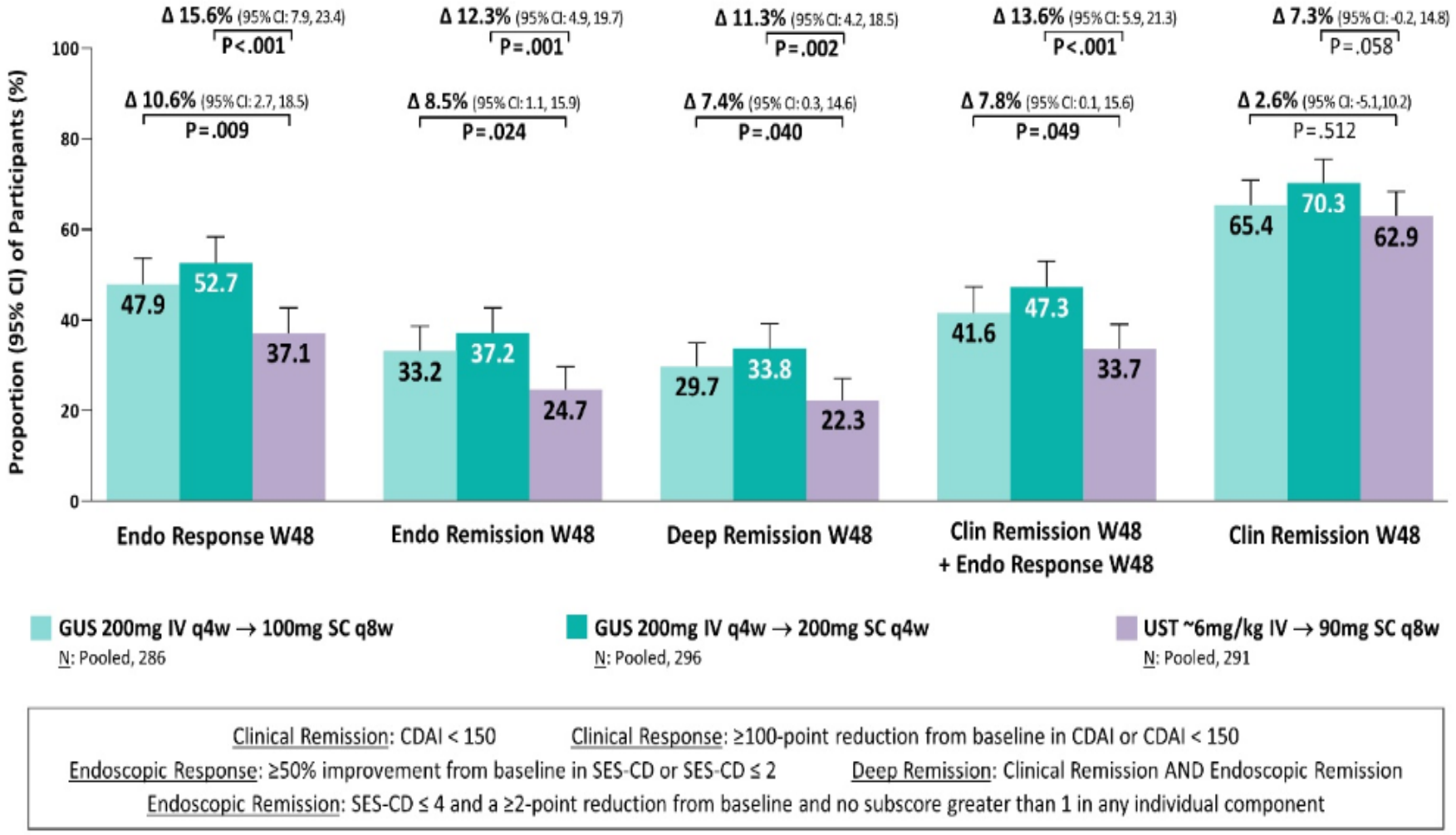


significantly greater (P<.001) proportions of pts receiving GUS 100mg SC q8w or 200mg SC q4w achieved the co-primary endpoints relative to PBO

In the W48 (G2 & G3) pooled analyses :

Both GUS doses demonstrated superiority to **UST** for
Endoscopic response (GUS 100mg SC q8w vs UST: Δ10.6%, GUS 200mg SC q4w vs UST: Δ15.6%)
Endoscopic remission (Δ8.5%, Δ12.3%),
Deep remission (Δ7.4%, Δ11.3%)
Clinical remission + endoscopic response (Δ7.8%, Δ13.6%).

Through W48, the proportions of GUS pts with ≥1 AEs, ≥1 SAEs, AEs leading to discontinuation, and infections were similar to PBO and UST



Clinical Remission: CDAI < 150 Clinical Response: ≥100-point reduction from baseline in CDAI or CDAI < 150

Endoscopic Response: ≥50% improvement from baseline in SES-CD or SES-CD ≤ 2 Deep Remission: Clinical Remission AND Endoscopic Remission

Endoscopic Remission: SES-CD ≤ 4 and a ≥2-point reduction from baseline and no subscore greater than 1 in any individual component

GUS was statistically superior to PBO for short- and long-term clinical and endoscopic endpoints.

Both GUS doses were statistically superior to **UST at W48** across multiple major secondary endpoints in the pooled analyses.

Guselkumab in Patients with Moderately to Severe Active UC
QUASAR Phase 2b Induction Study

Patients:

Modified Mayo score of 5 to 9, inclusive; with a Mayo rectal bleeding subscore ≥ 1 , a Mayo endoscopy subscore ≥ 2

Patients were **randomized 1:1:1** to receive

IV GUS **200** mg, **400** mg, or **placebo** at Weeks 0, 4, and 8.

The primary endpoint was:

clinical response at week 12

Secondary endpoints included:

clinical remission, symptomatic remission, endoscopic improvement, histo-endoscopic mucosal improvement, and endoscopic normalization at week 12

Results:

330 patients were randomized in the primary analysis:

(mean age, 41.6 yrs; male 59%, mean UC duration, 7.55 yrs; severe disease, 70%; baseline oral corticosteroid use, 40%).

about 50% had a prior inadequate response or intolerance to advanced therapy for UC.

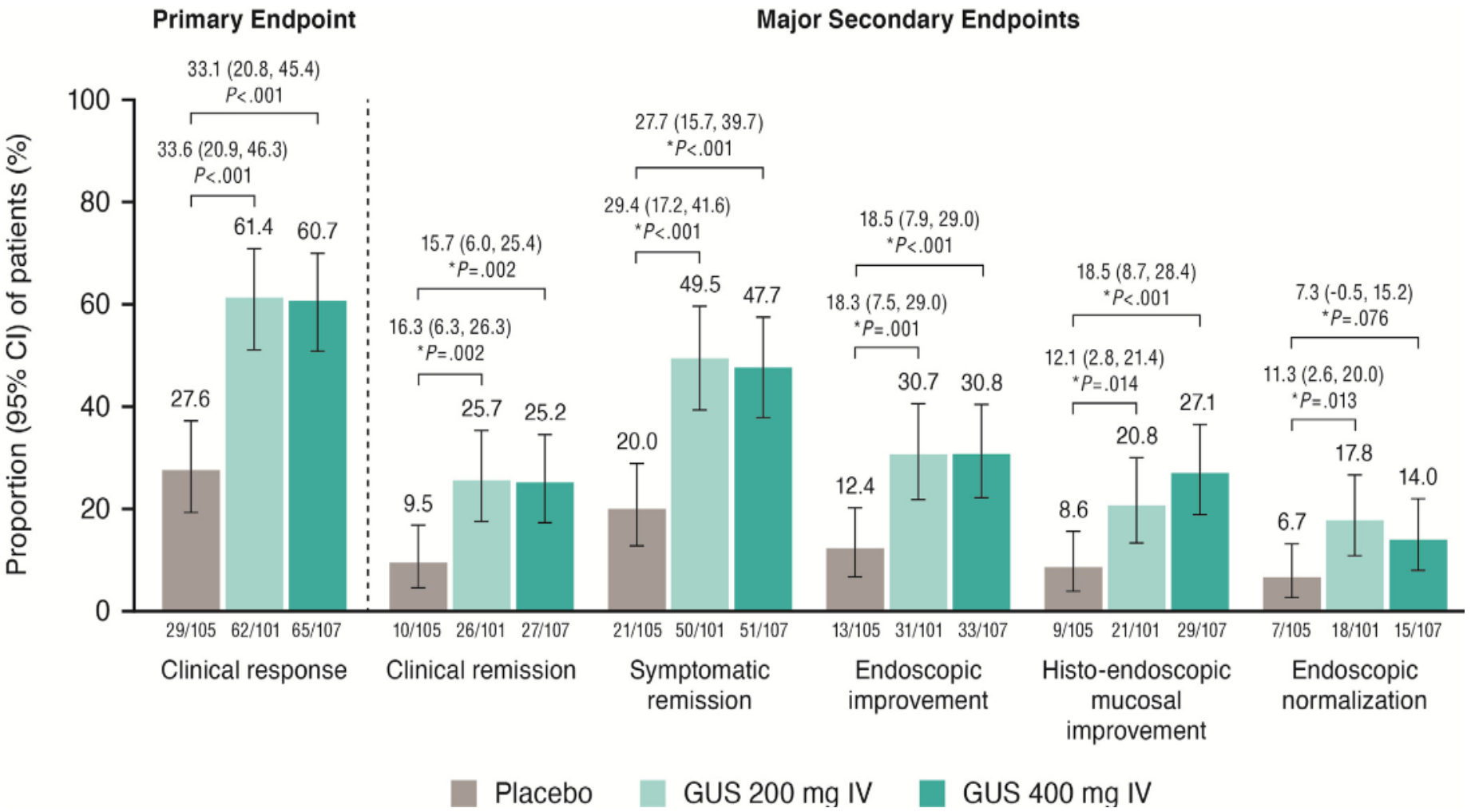
baseline modified Mayo scores ≥5 and≤9

Intravenous guselkumab

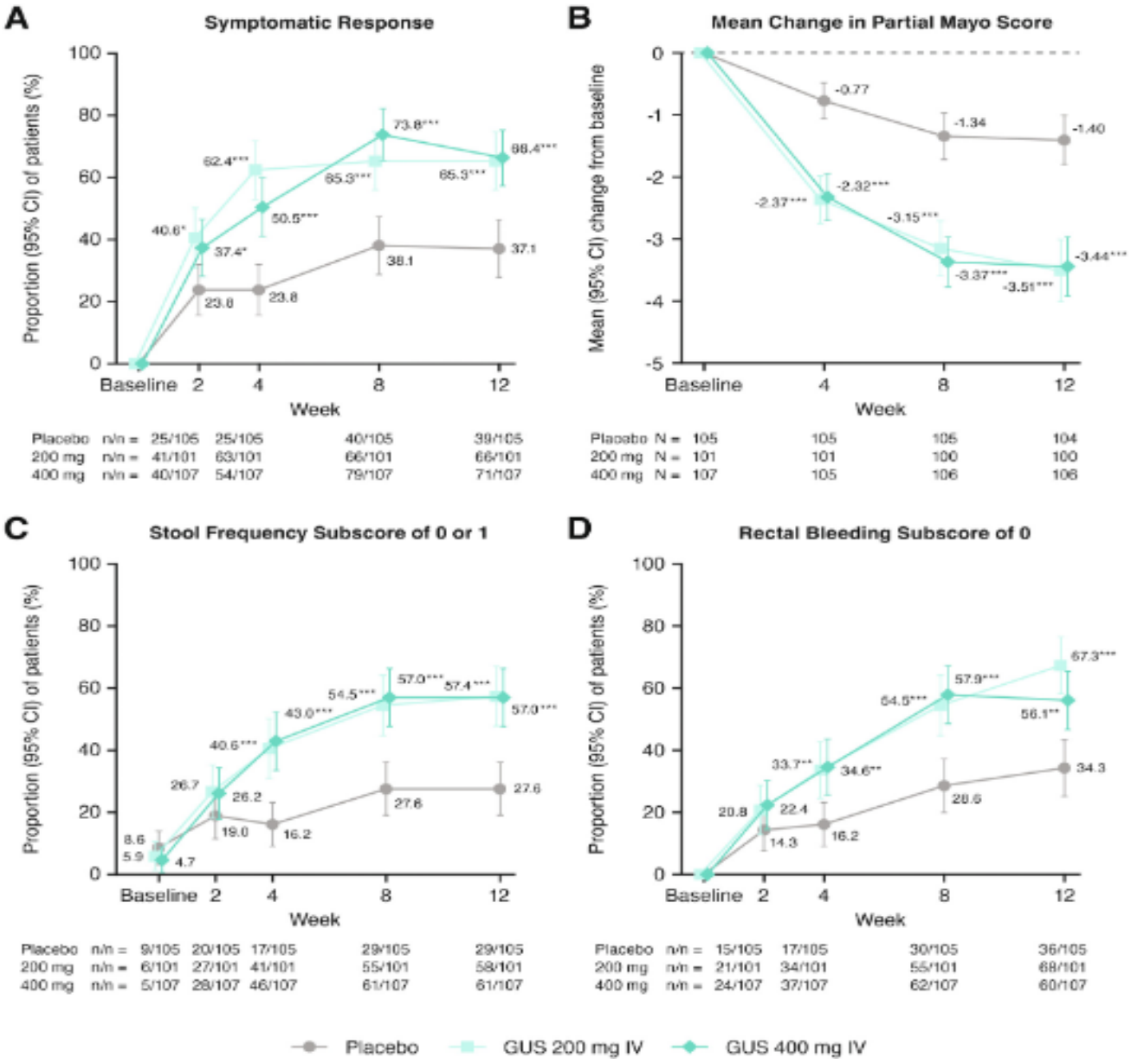
200 mg, n = 101

400 mg, n =107

placebo, n = 105



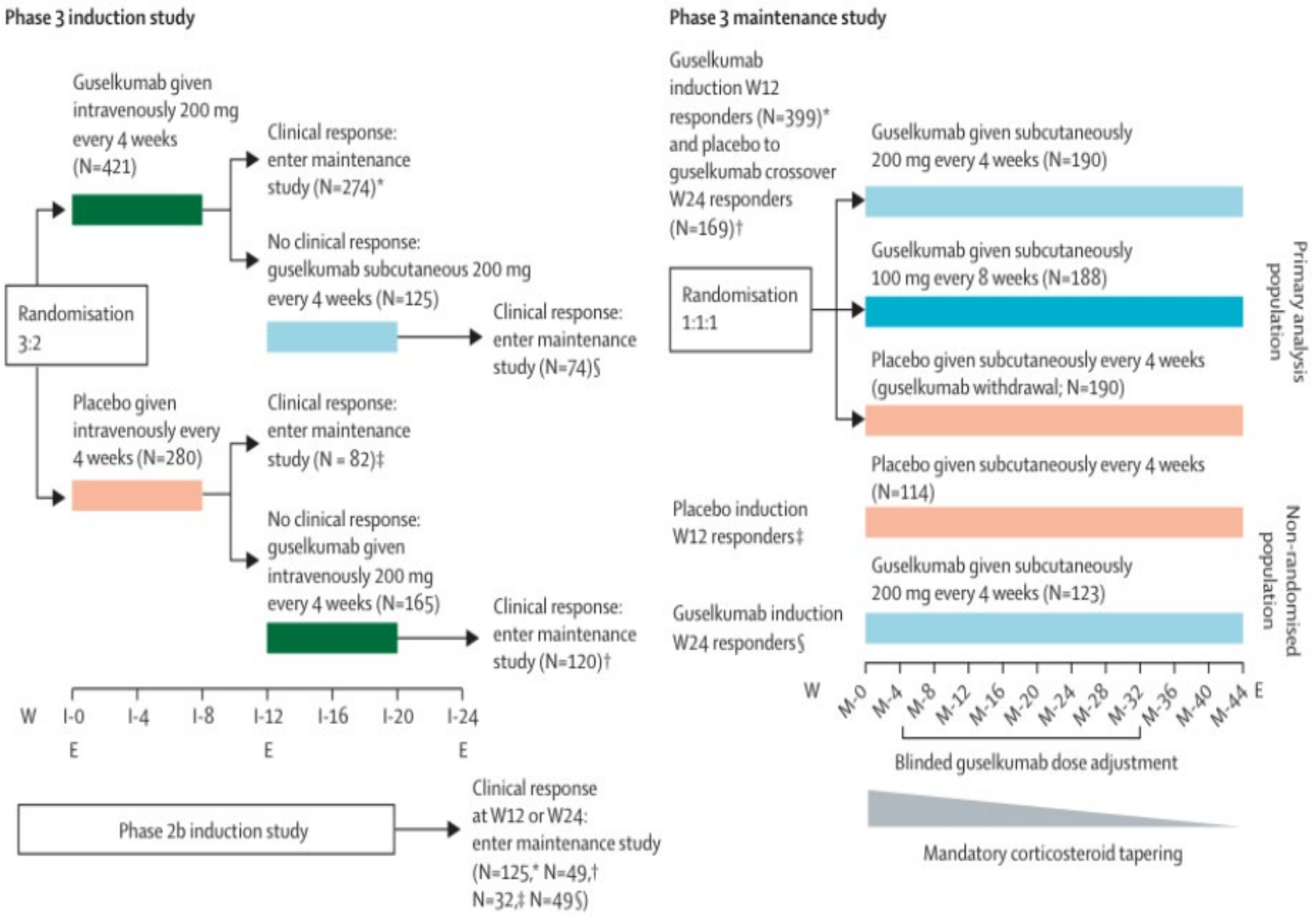
The primary endpoint of clinical response at week 12 and the major secondary endpoints of clinical remission, Consider the dose of GUS (efficacy of 200>400 mg group)


A
Symptomatic Response
Proportion (95% CI) of patients (%)
Week
Baseline
2
4
8
12
40.6*
62.4***
37.4*
50.5***
23.8
23.8
38.1
65.3***
73.8***
65.3***
66.4***
37.1
Placebo n/n = 25/105 25/105 40/105 39/105
200 mg n/n = 41/101 63/101 66/101 66/101
400 mg n/n = 40/107 54/107 79/107 71/107
B
Mean Change in Partial Mayo Score
Mean (95% CI) change from baseline
-0.77
-1.34
-1.40
-2.37***
-2.32***
-3.15***
-3.37***
-3.51***
-3.44***
Placebo N = 105 105 105 104
200 mg N = 101 101 100 100
400 mg N = 107 105 106 106
C
Stool Frequency Subscore of 0 or 1
Proportion (95% CI) of patients (%)
8.6
5.9
4.7
26.7
40.6***
26.2
19.0
43.0***
54.5***
16.2
57.0***
57.4***
57.0***
27.6
27.6
Placebo n/n = 9/105 20/105 17/105 29/105 29/105
200 mg n/n = 6/101 27/101 41/101 55/101 58/101
400 mg n/n = 5/107 28/107 46/107 61/107 61/107
D
Rectal Bleeding Subscore of 0
Proportion (95% CI) of patients (%)
20.8
33.7**
22.4
14.3
34.6**
16.2
54.5***
57.9***
56.1**
67.3***
28.6
34.3
Placebo n/n = 15/105 17/105 30/105 36/105
200 mg n/n = 21/101 34/101 55/101 68/101
400 mg n/n = 24/107 37/107 62/107 60/107
Placebo
GUS 200 mg IV
GUS 400 mg IV

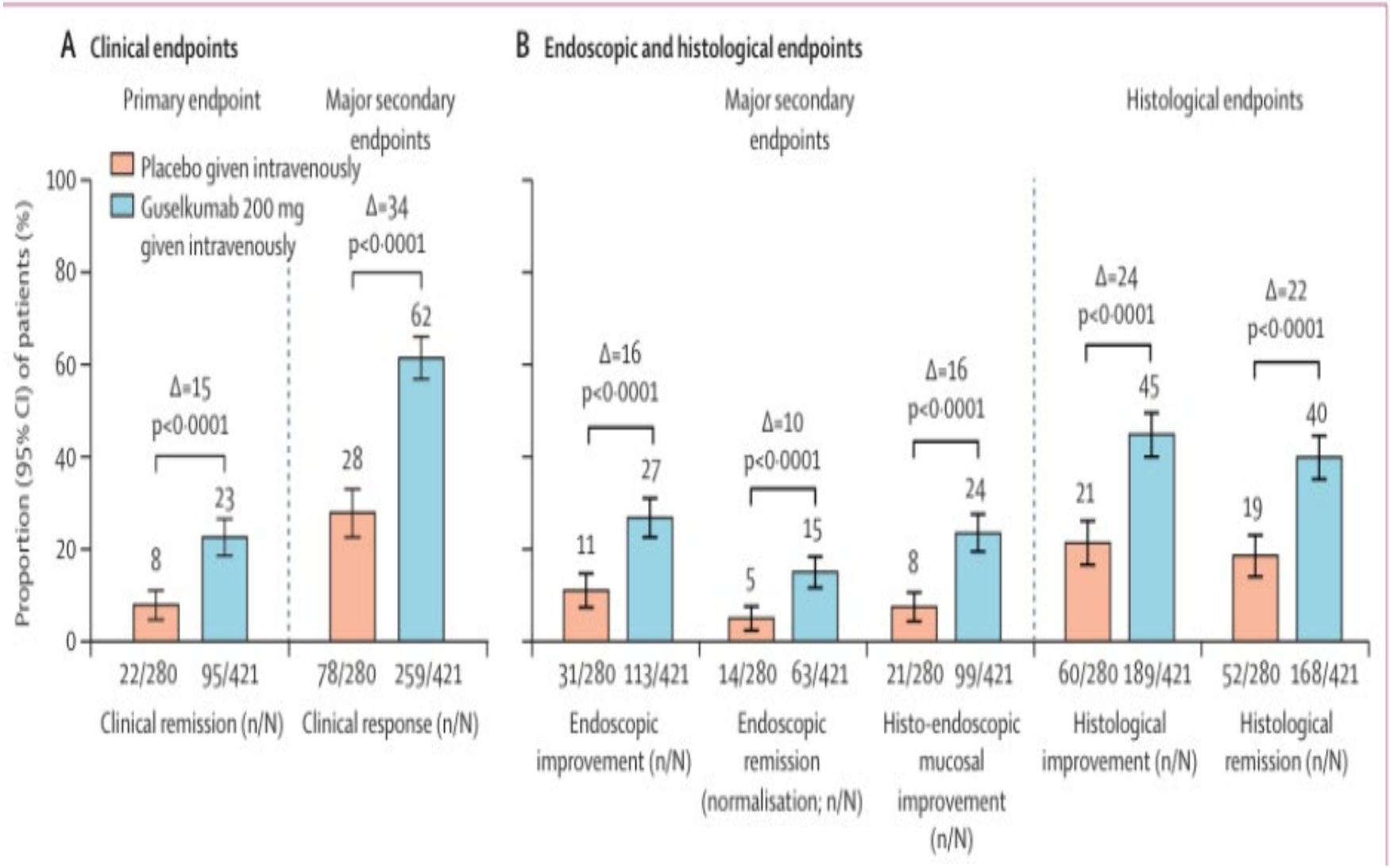
QUASAR: phase 3

Patients were randomly assigned (3:2) to receive guselkumab 200 mg given intravenously or placebo at weeks 0, 4, and 8 (phase 3 induction study).
Patients in clinical response 12 W after guselkumab induction given intravenously (from QUASAR phase 2b and phase 3 induction studies) were randomly assigned (**1:1:1**) at maintenance week 0 to guselkumab 200 mg given subcutaneously every 4 weeks or 100 mg every 8 weeks or placebo for 44 weeks (maintenance).

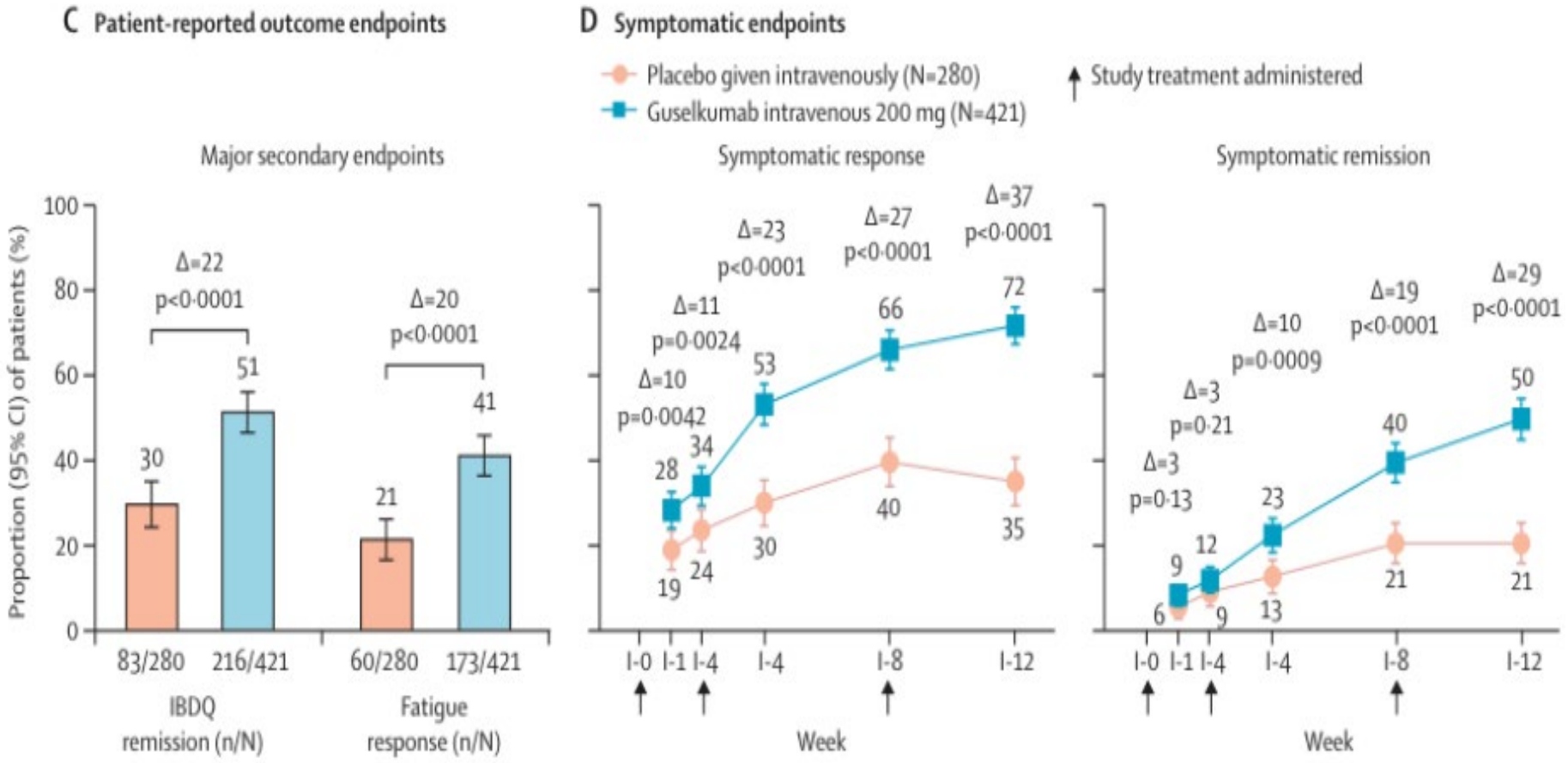
Primary endpoints were clinical remission at induction week 12 and maintenance week 44

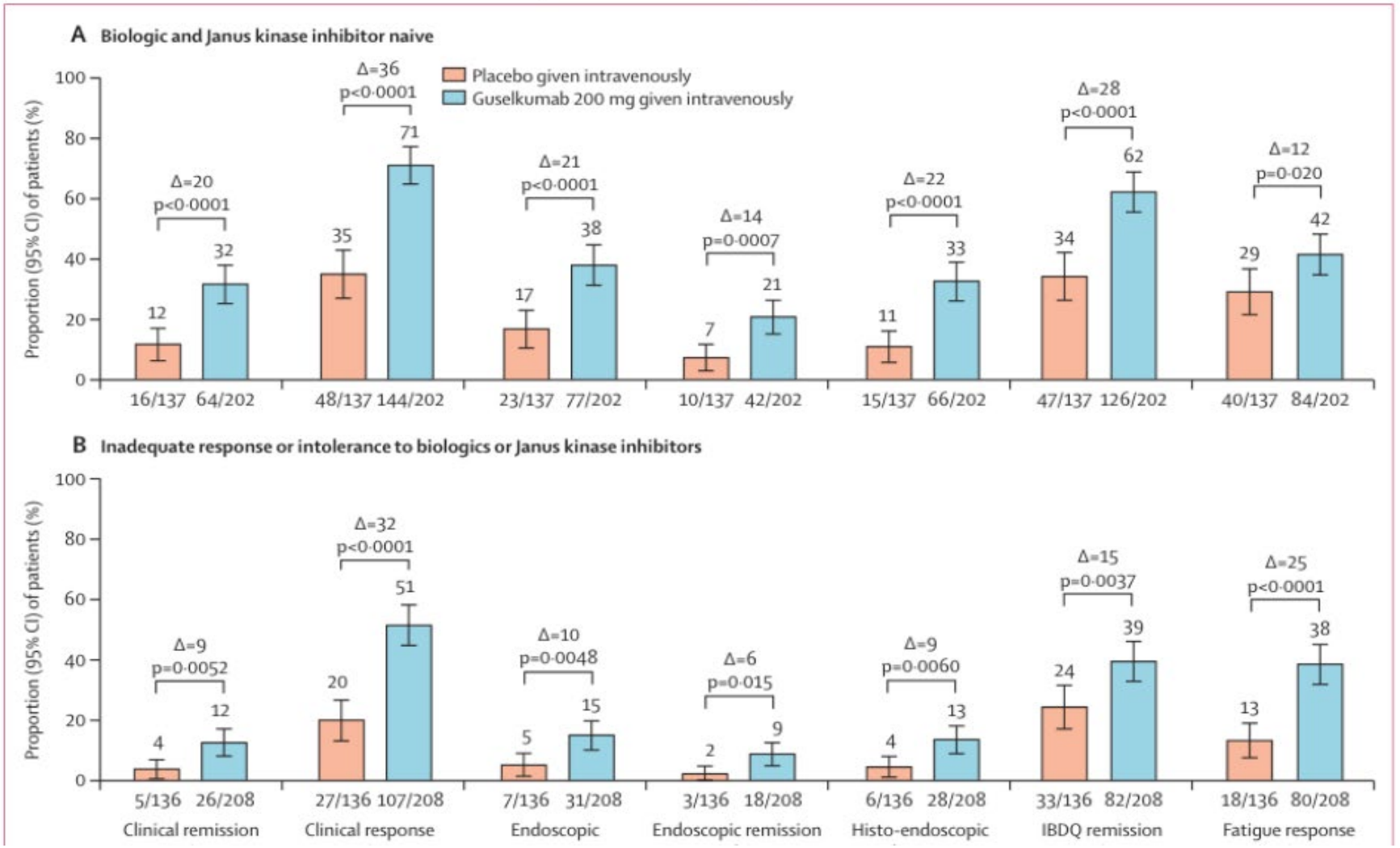

Phase 3 induction study
Guselkumab given intravenously 200 mg every 4 weeks (N=421)
Clinical response: enter maintenance study (N=274)*
No clinical response: guselkumab subcutaneous 200 mg every 4 weeks (N=125)
Clinical response: enter maintenance study (N=74)§
Randomisation 3:2
Placebo given intravenously every 4 weeks (N=280)
Clinical response: enter maintenance study (N = 82)‡
No clinical response: guselkumab given intravenously 200 mg every 4 weeks (N=165)
Clinical response: enter maintenance study (N=120)†
W I-0 I-4 I-8 I-12 I-16 I-20 I-24
E E E
Phase 2b induction study
Clinical response at W12 or W24: enter maintenance study (N=125,* N=49,† N=32,‡ N=49§)
Phase 3 maintenance study
Guselkumab induction W12 responders (N=399)* and placebo to guselkumab crossover W24 responders (N=169)†
Randomisation 1:1:1
Guselkumab given subcutaneously 200 mg every 4 weeks (N=190)
Guselkumab given subcutaneously 100 mg every 8 weeks (N=188)
Placebo given subcutaneously every 4 weeks (guselkumab withdrawal; N=190)
Primary analysis population
Placebo induction W12 responders‡
Placebo given subcutaneously every 4 weeks (N=114)
Guselkumab induction W24 responders§
Guselkumab given subcutaneously 200 mg every 4 weeks (N=123)
Non-randomised population
W M-0 M-4 M-8 M-12 M-16 M-20 M-24 M-28 M-32 M-36 M-40 M-44 E
Blinded guselkumab dose adjustment
Mandatory corticosteroid tapering

week 12 in the phase 3 induction study



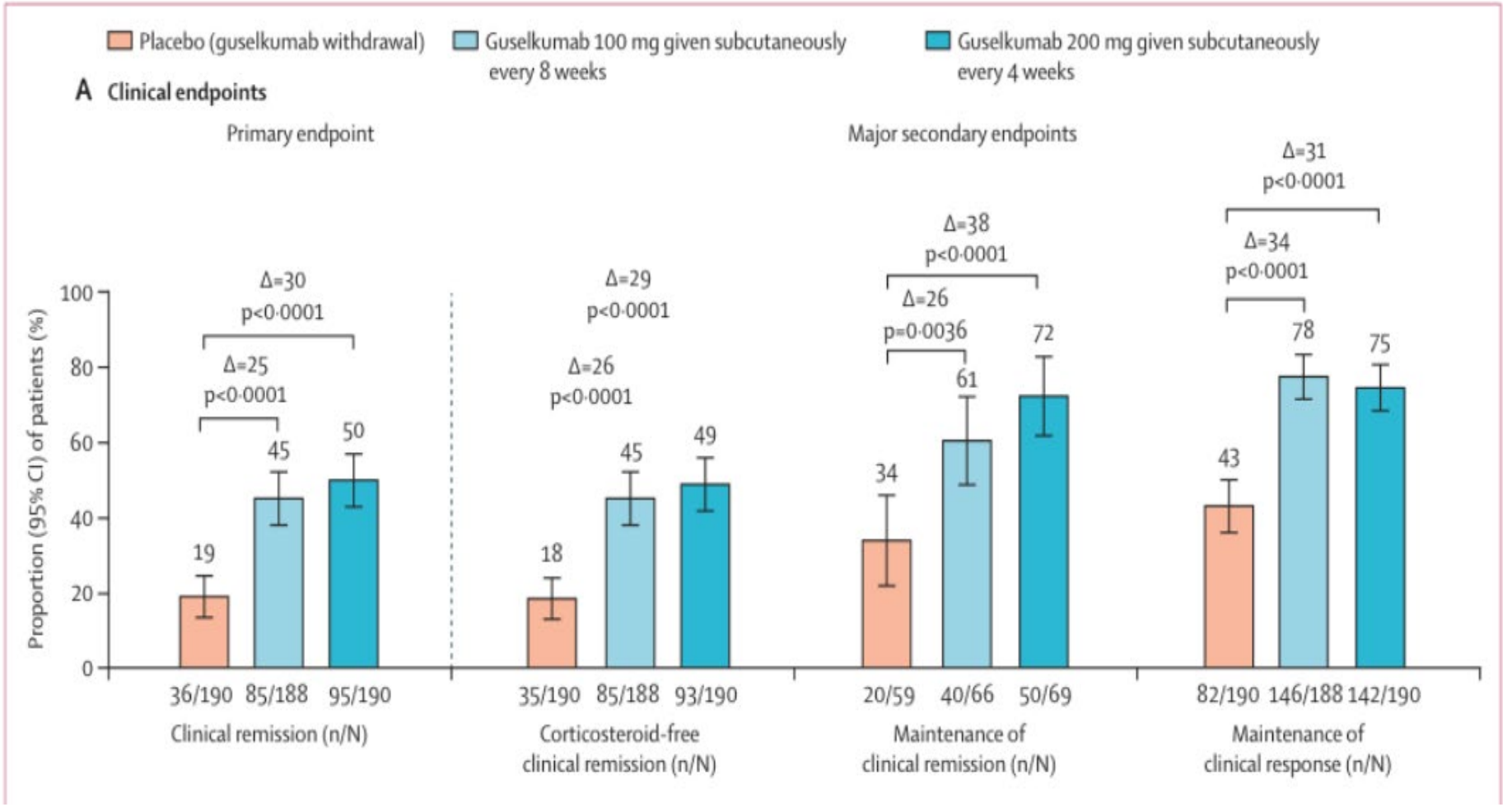
week 12 in the phase 3 induction study





Guselkumab efficacy was observed in Biologic and JAK-inh naïve patients as well as with a history of **inadequate** response or **intolerance**

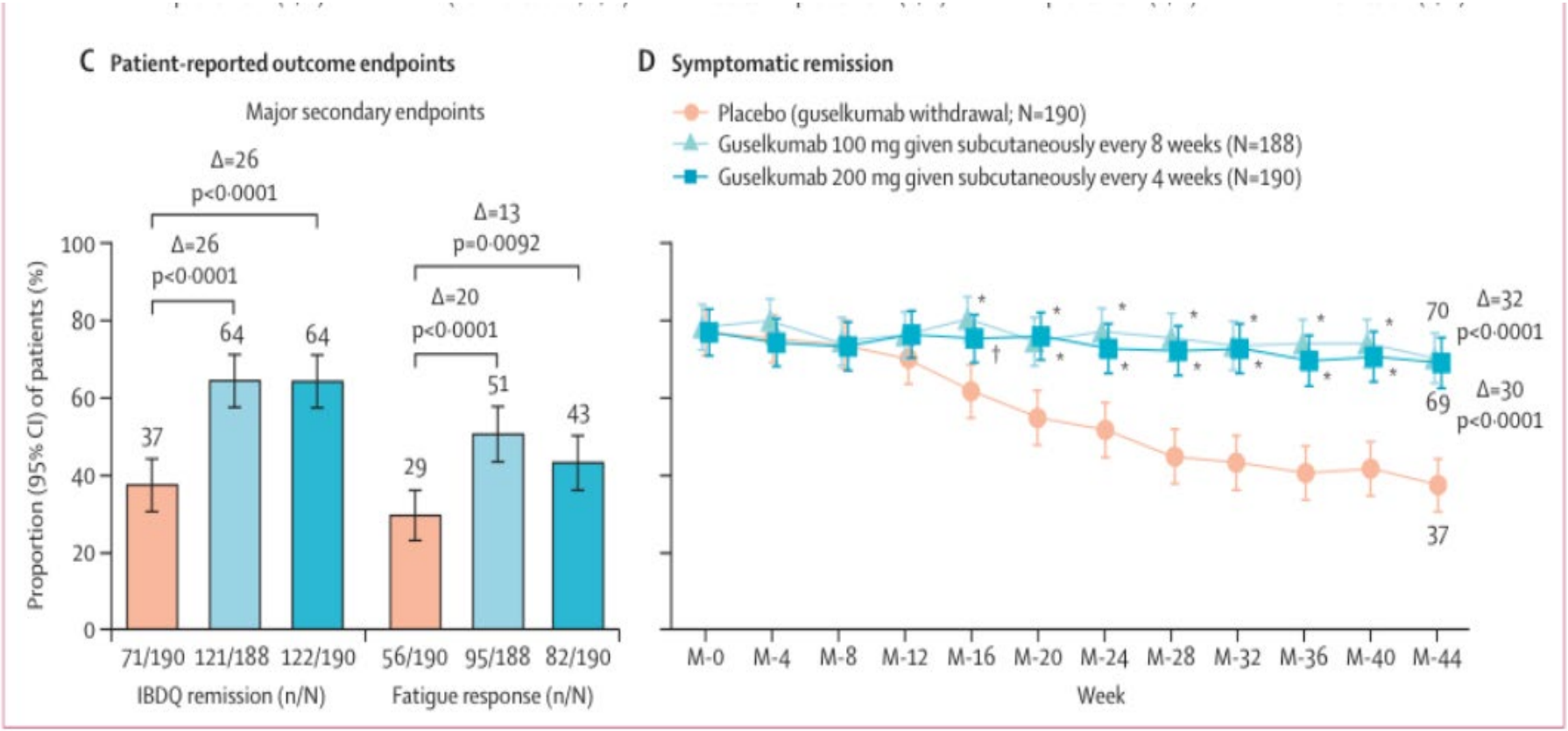
week 44 in the maintenance Treatment



Clinical remission at w 44 was achieved TO placebo :

GUS 200 mg given subcutaneously every 4 weeks (50% [95 of 190 patients];

GUS 100 mg every 8 weeks (45% [85 of 188 patients]; p<0·0001)



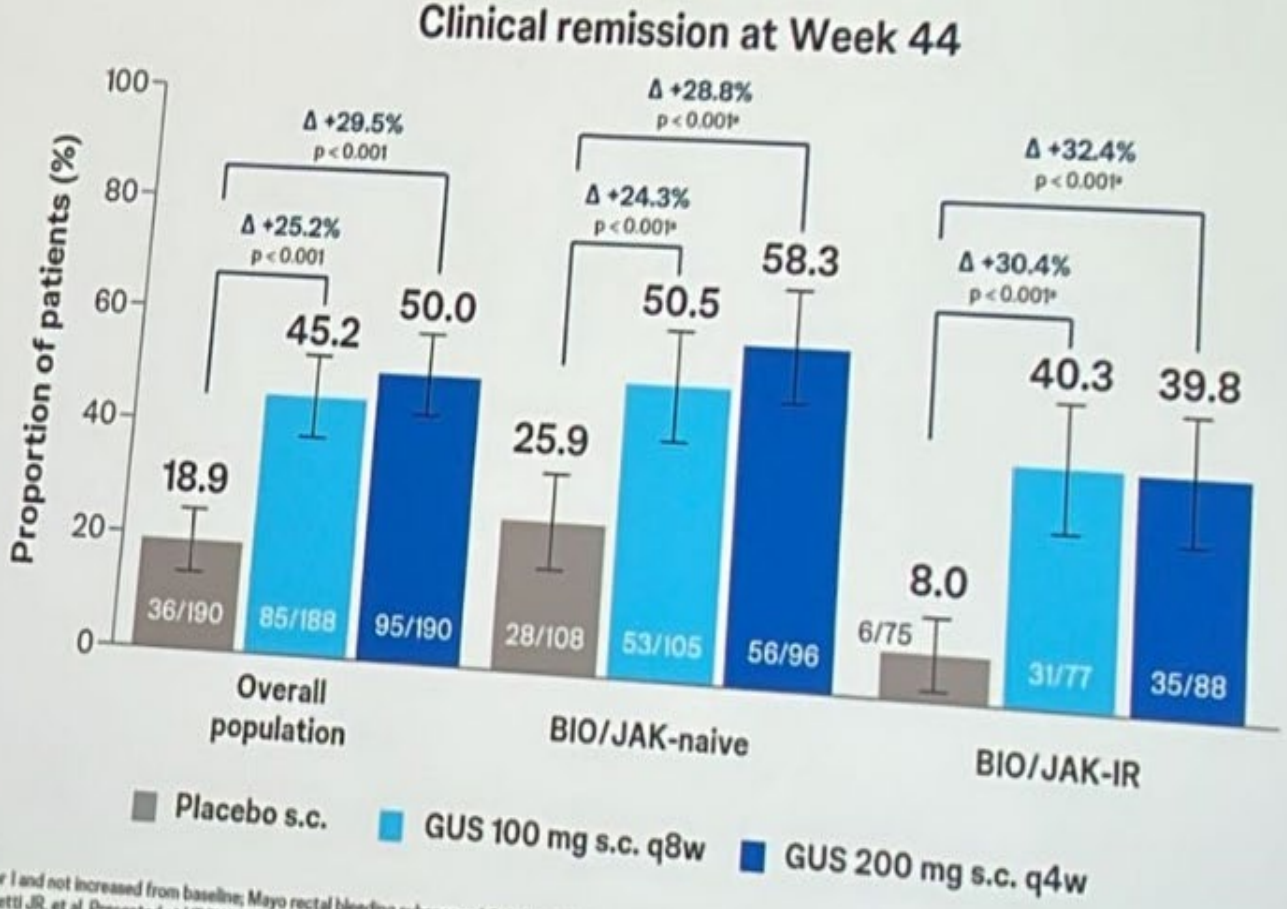
improvement in abdominal pain and bowel urgency was sustained observed in many patients maintenance week 44

High rates of clinical remission with guselkumab, irrespective of previous treatment history

QUASAR
Phase 3 maintenanc



Clinical remission includes endoscopy scoring:
Mayo stool frequency subscore of 0 or 1 and not increased from baseline; Mayo rectal bleeding subscore of 0; Mayo endoscopy subscore of 0 or 1 with no friability.



Johnson&Johnson

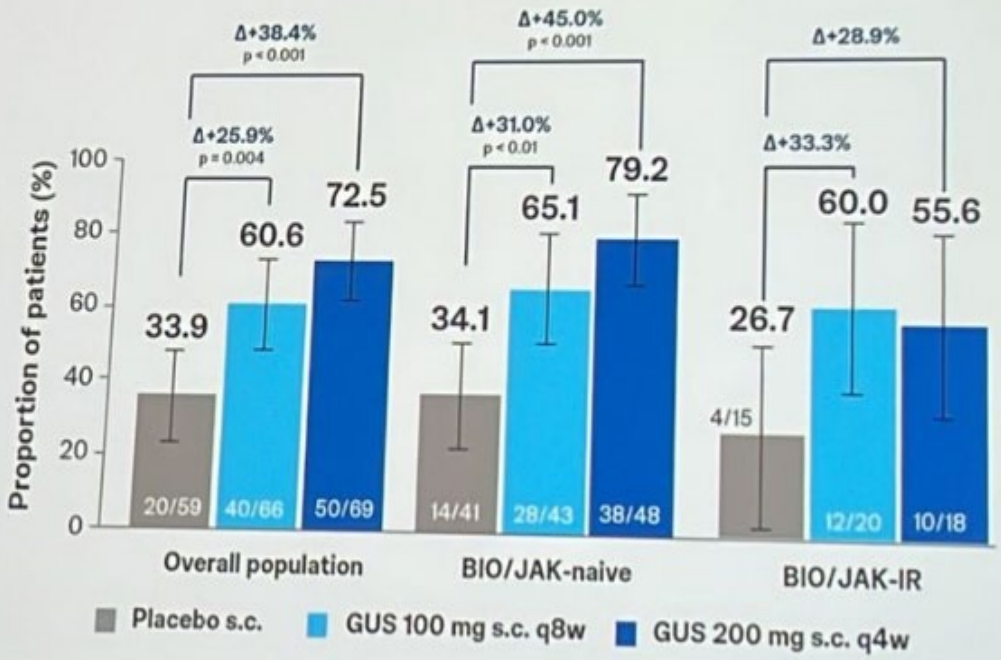
Clinical remission: Mayo stool frequency subscore of 0 or 1 and not increased from baseline; Mayo rectal bleeding subscore of 0; Mayo endoscopy

Rubin DT, et al. Presented at DDW 2024; DOP759. Allegretti JR, et al. Presented at UEGW 2024; OP082.

More than two-thirds of patients maintained clinical remission with guselkumab through 1 year

QUASAR
Phase 3 maintenance





Johnson&Johnson

Maintenance of clinical remission: clinical remission at Week 44 among patients in clinical remission at maintenance baseline.
Rubin DT, et al. Presented at DDW 2024; DOP759. Allegretti JR, et al. Presented at UEGW 2024; OP082. Rubin DT, et al. Lancet 2025;405:33-49.

Medical Education

Clinically meaningful improvements in HRQoL at Week 44 with guselkumab

QUASAR
Phase 3 maintenance



Guselkumab 200 mg s.c. q4w (n = 190)

Guselkumab 100 mg s.c. q8w (n = 188)

Placebo s.c. (Guselkumab withdrawal, n = 190)

Clinically meaningful improvements in

	Fatigue	Depression	Physical function
Guselkumab 200 mg s.c. q4w (n = 190)	36.3%***	35.8%***	36.8%**
Guselkumab 100 mg s.c. q8w (n = 188)	46.3%***	43.1%***	43.1%***
Placebo s.c. (Guselkumab withdrawal, n = 190)	26.3%	17.9%	23.2%

	Pain intensity	Sleep disturbance	Social participation
Guselkumab 200 mg s.c. q4w (n = 190)	54.5%***	34.7%**	47.4%***
Guselkumab 100 mg s.c. q8w (n = 188)	55.9%***	41.5%***	53.2%***
Placebo s.c. (Guselkumab withdrawal, n = 190)	28.9%	21.1%	28.9%

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** Nominal p value: p < 0.05 vs placebo s.c. *** Nominal p value: p < 0.001 vs placebo s.c.
Scores have been measured by the PROMIS-29 (7 domains; anxiety, depression, fatigue, pain interference, sleep disturbance,
intensity numeric rating scale). Depending on the domain/score, improvement of
PROMIS, Patient Reported Outcomes

ADVERSE EVENTS: Reported by 49% of patients in both groups:

SERIOUS adverse events were reported by 3% (12 of 421) of guselkumab group and 7% (20 of 280) of placebo group.

DISCONTINUATION were reported by 2% (seven of 421) of GUS and 4% (11 of 280) of placebo group

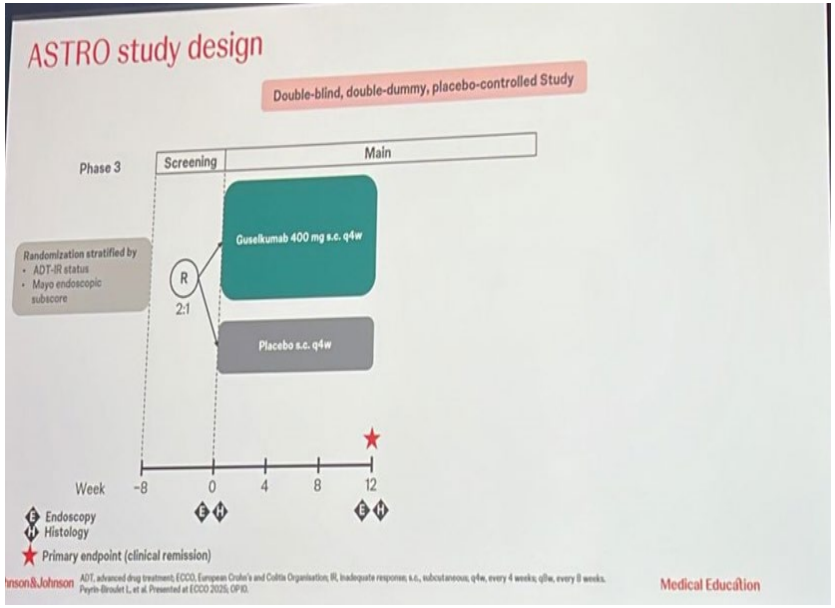
The most frequently reported adverse events in all groups were ulcerative colitis, COVID-19 and arthralgia.

No active tuberculosis, anaphylaxis, serum sickness, or clinically important hepatic disorders were reported in either study.

	Induction study		Maintenance study		
	Placebo given intravenously every 4 weeks (N=280)	Guselkumab 200 mg given intravenously every 4 weeks (N=421)	Placebo given subcutaneously (guselkumab withdrawal; N=192)	Guselkumab 100 mg given subcutaneously every 8 weeks (N=186)	Guselkumab 200 mg given subcutaneously every 4 weeks (N=190)
Mean duration of follow-up, weeks	11·9	12·2	34·0	40·5	39·2
Mean exposure (number of administrations)	2·9	2·9	8·2	9·9	9·6
Adverse events	138 (49%)	208 (49%)	131 (68%)	120 (65%)	133 (70%)
Serious adverse events	20 (7%)	12 (3%)	1 (1%)	5 (3%)	12 (6%)
Deaths	2 (1%)*	1 (0·2%)†	0	0	0
Adverse events leading to discontinuation of study agent	11 (4%)	7 (2%)	13 (7%)	7 (4%)	5 (3%)
Most frequent adverse events (≥5% of patients in any treatment group)					
Ulcerative colitis	23 (8%)	10 (2%)	57 (30%)	17 (9%)	25 (13%)
Anaemia	19 (7%)	21 (5%)	5 (3%)	4 (2%)	6 (3%)
COVID-19	12 (4%)	21 (5%)	27 (14%)	24 (13%)	18 (9%)
Headache	8 (3%)	13 (3%)	12 (6%)	7 (4%)	8 (4%)
Arthralgia	6 (2%)	6 (1%)	13 (7%)	8 (4%)	15 (8%)
Upper respiratory tract infection	1 (0·4%)	3 (1%)	8 (4%)	6 (3%)	13 (7%)
Targeted adverse events					
Serious infections‡	1 (0·4%)	3 (1%)	0	1 (1%)	2 (1%)
Opportunistic infections‡	1 (0·4%)§	0	0	0	0
Active tuberculosis	0	0	0	0	0
Major adverse cardiovascular event	2 (1%)¶	2 (0·5%)‖	0	0	1 (1%)**
Clinically important hepatic disorders††	0	0	0	0	0
Malignancies‡‡	0	0	2 (1%)§§	0	1 (1%)¶¶
Non-melanoma skin cancer	0	2 (0·5%)	2 (1%)	0	0
Anaphylactic reactions	0	0	0	0	0
Serum sickness reactions	0	0	0	0	0

Efficacy and safety of subcutaneous guselkumab induction therapy in patients with Ulcerative Colitis:

Results through week 12 from the phase 3 ASTRO study



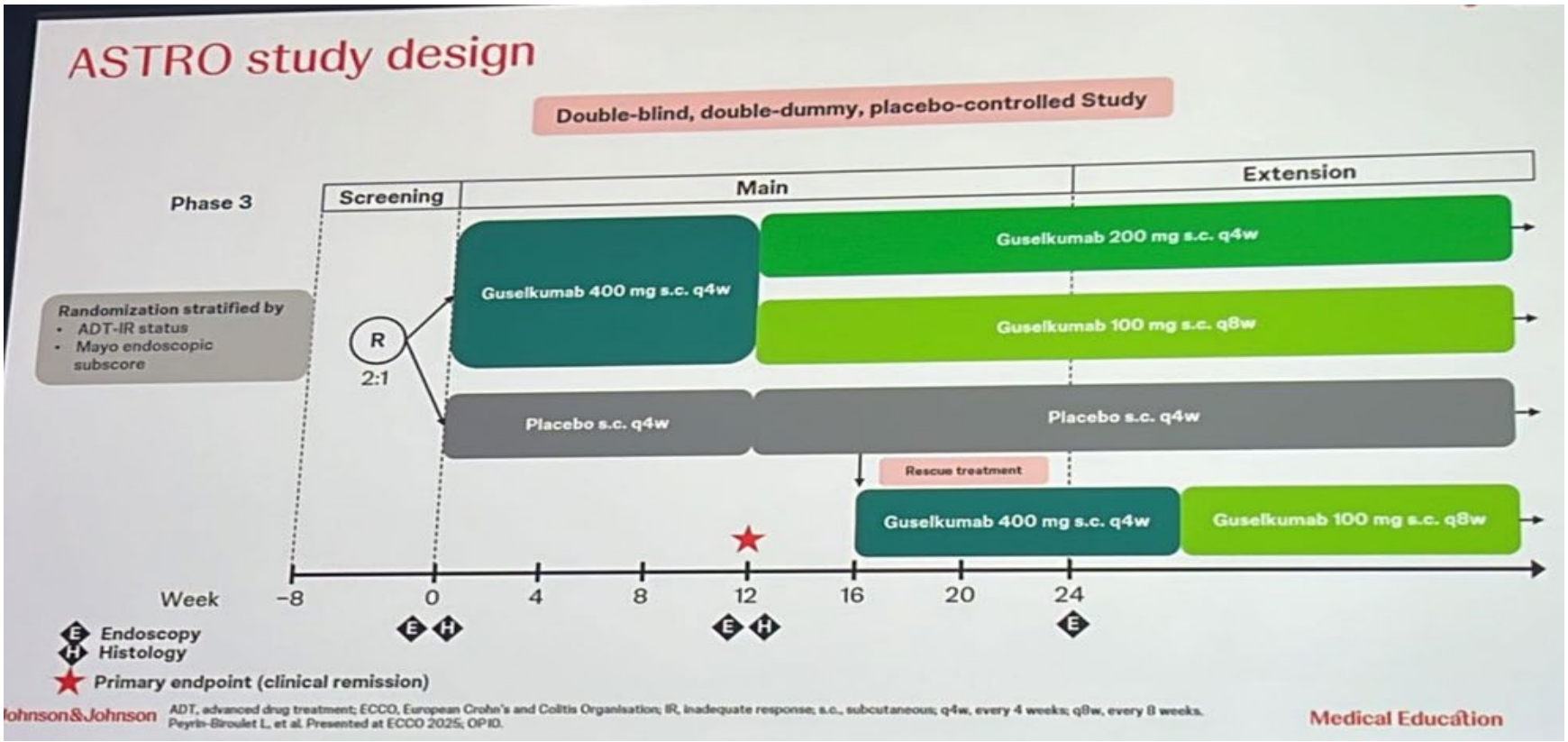
ASTRO:
assess the safety and efficacy of a guselkumab SC induction regimen in patients with moderately to severely active UC
who had an inadequate response or intolerance to conventional therapy ;prior biologics ;and/or ozanimod or Janus kinase (JAK) inhibitors

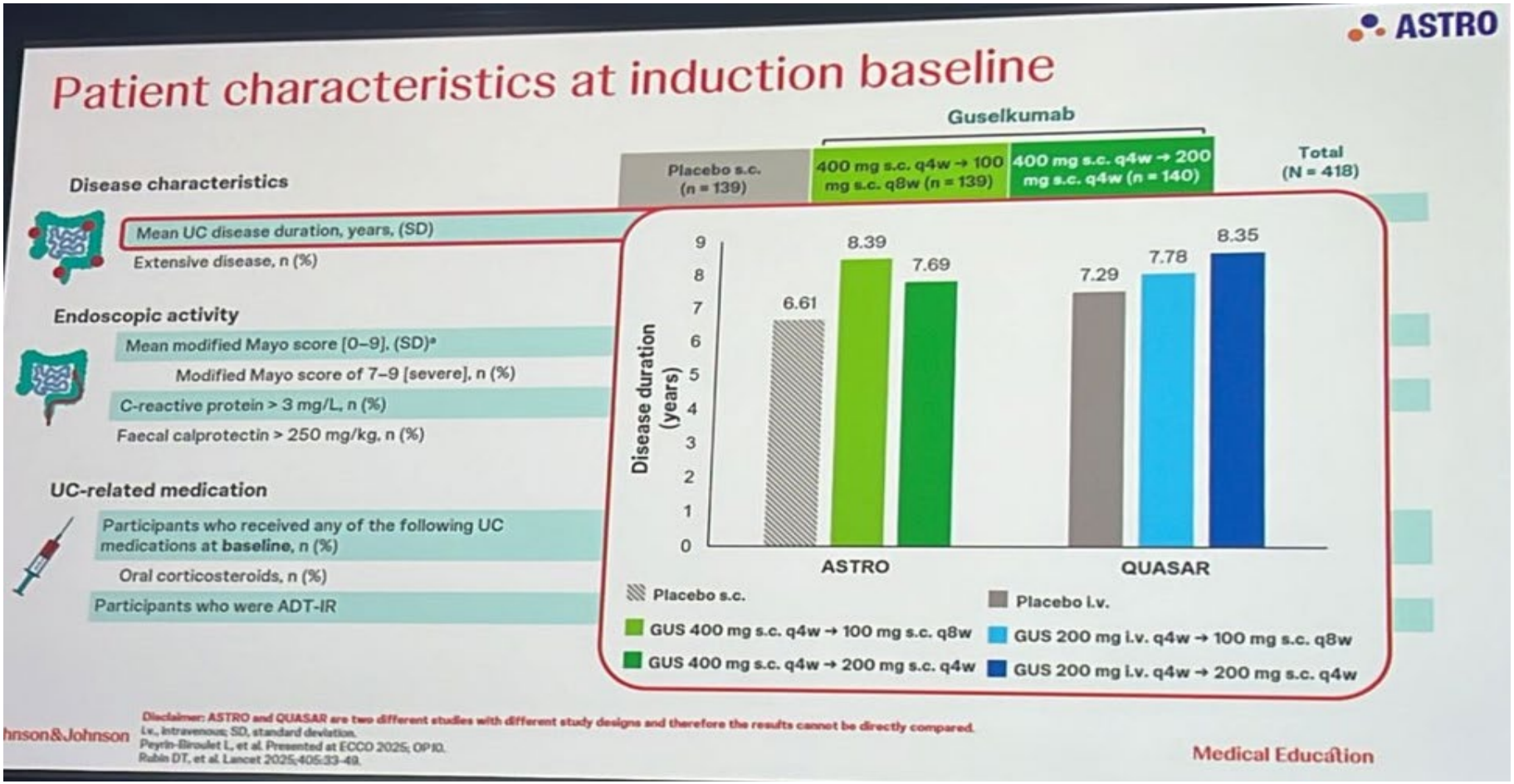
Study participants were randomly assigned 1:1:1 to receive
1-guselkumab **400mg SC** induction at weeks 0, 4, and 8 followed by guselkumab **200mg** SC every 4 weeks;
2-guselkumab **400mg SC induction** at weeks 0, 4, and 8 followed by guselkumab **100mg SC every 8 weeks**;
3- placebo.

The primary endpoint was:

clinical remission (Mayo stool frequency subscore 0/1 not increased from BL, rectal bleeding subscore 0, MES 0/1 with no friability) at W12.

secondary endpoints are clinical response, symptomatic remission, endoscopic improvement, and histo-endoscopic mucosal improvement (HEMI)





Basic Characteristics were similar across treatment groups (overall mean age, 41.7 years; mean UC duration, 7.6 years; mean modified Mayo score, 6.7; MES=3, 56.0%; BIO/JAKi/S1Pi-IR, 40.2%).

At W12,

significantly greater proportions of pts treated with GUS 400 mg SC induction than PBO achieved

clinical remission (27.6% vs 6.5%, respectively; adj Δ: 21.1%; P<0.001),

clinical response (65.6% vs 34.5%; adj Δ: 31.0%; P<0.001),

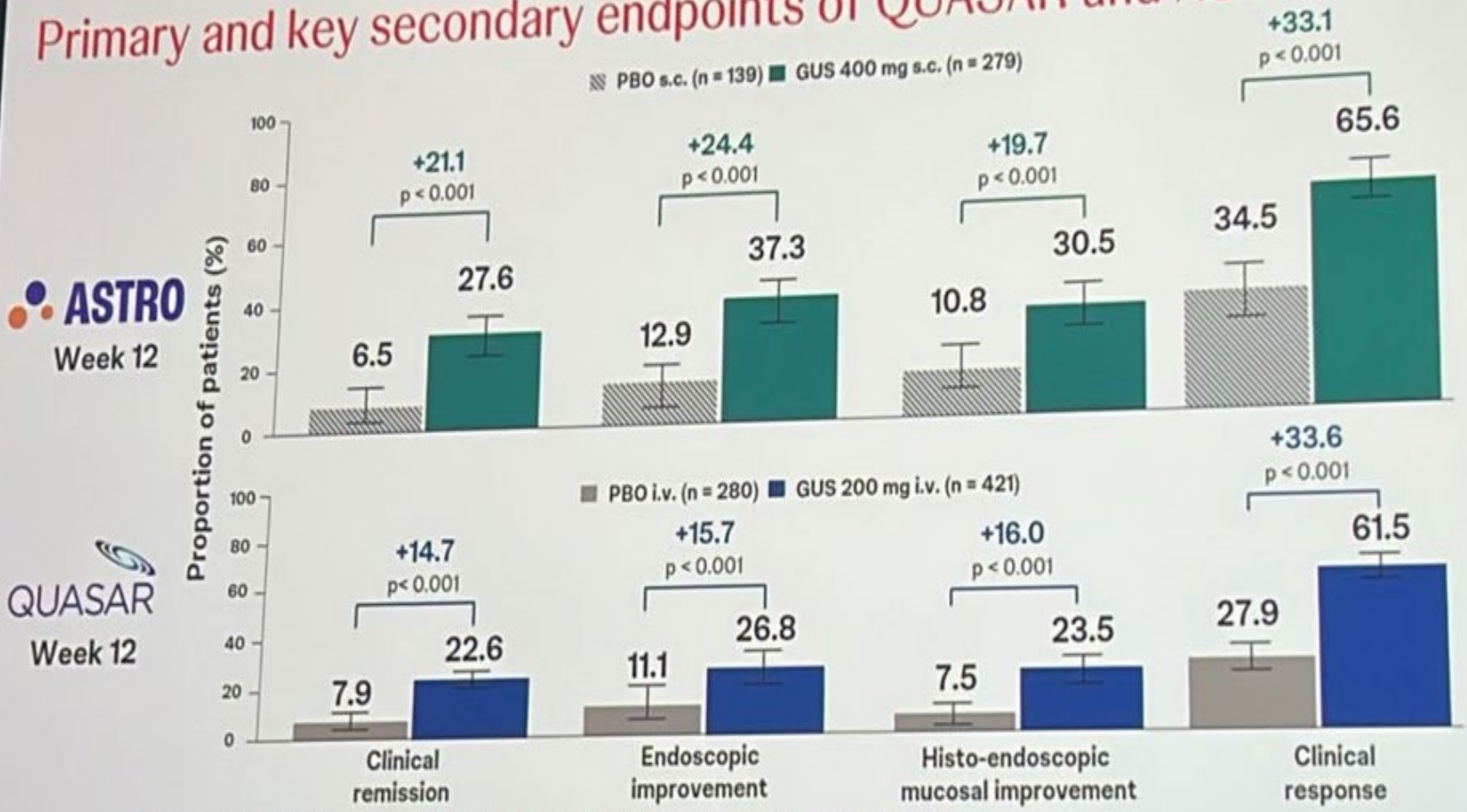
symptomatic remission (51.3% vs 20.9%; adj Δ: 30.4%; P<0.001),

endoscopic improvement (37.3% vs 12.9%; adj Δ: 24.3%; P<0.001),

HEMI (30.5% vs 10.8%; adj Δ: 19.6%; P<0.001).

a significantly greater proportion of patients treated with the SC induction regimen achieved clinical remission

Primary and key secondary endpoints of QUASAR and ASTRO



Disclaimer: ASTRO and QUASAR are two different studies with different study designs and therefore the results cannot be directly compared.

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 endoscopic subscore of 0, or 1 with no friability present on the endoscopy. **Endoscopic improvement:** an endoscopic subscore of 0, or 1 with no friability present on the 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. **Histo-endoscopic mucosal improvement:** achieving a combination of histological improvement (neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue per Geboes grading system [i.e., Geboes score ≤ 3.1]) and endoscopic improvement.

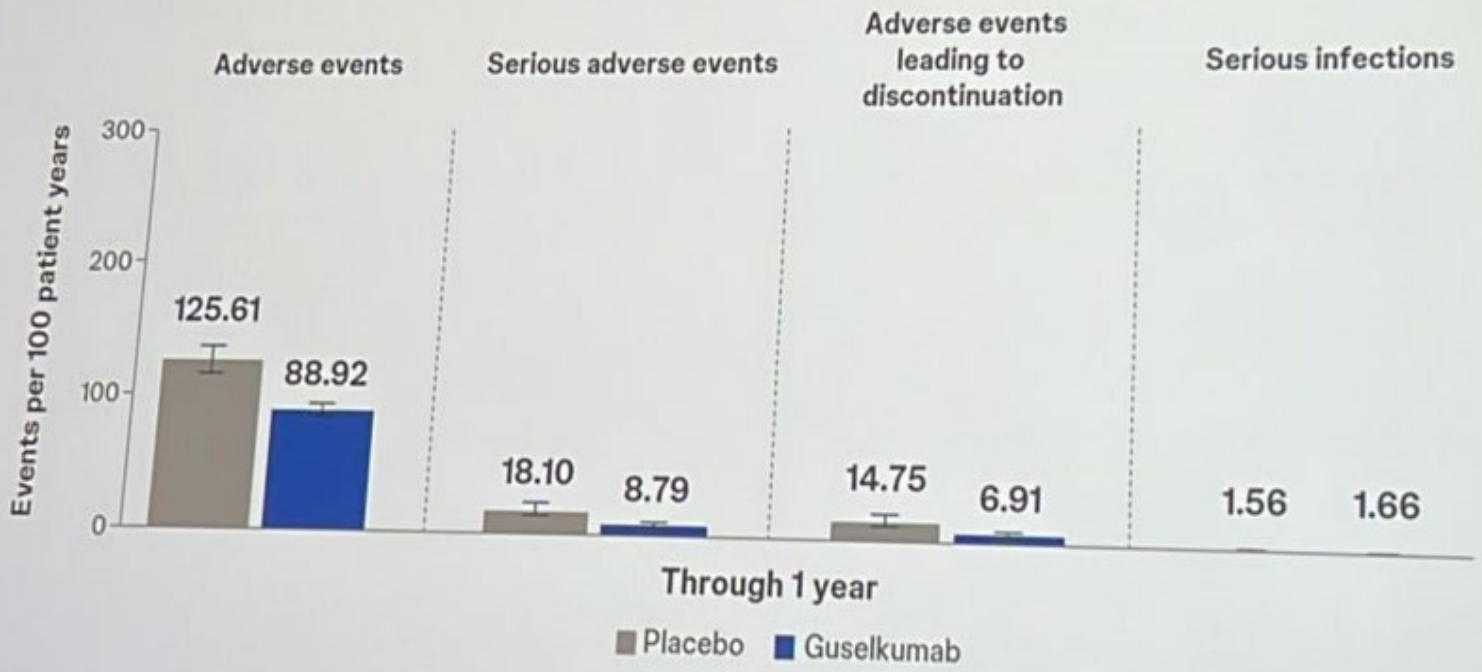
Allegretti JR, et al. Presented at DDW 2023; Abstract 91Eb. Rubin DT, et al. Lancet 2025;405:33-49. Peyrin-Biroulet L, et al. Presented at ECCO 2025; OP10.

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Medical Education

Safety of guselkumab among 3,006 patients across four IBD trials

Key safety events in phase 2/3 IBD clinical studies through 1 year (GALAXI 1, 2, & 3, GRAVITI, QUASAR Induction Study 1, Induction Study 2, and Maintenance Study, and VEGA-guselkumab monotherapy arm only)



Johnson&Johnson Sands BE, et al. Presented at ECCO 2025; P0608.

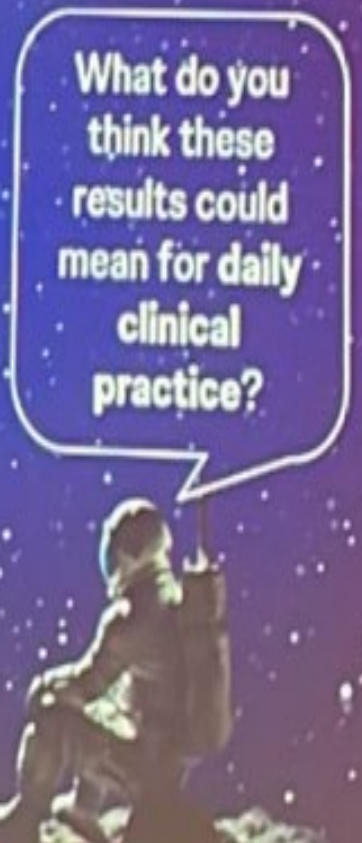
Medical Education

What to look out for?
Key learnings for evolving treatment strategies in UC

Impact on clinical endpoints and patient-reported outcomes

Guselkumab showed efficacy in clinical trials for short- and long-term endpoints, with 72% of patients maintaining clinical remission through Week 44, irrespective of previous advanced therapy use





Rubin DT, et al. Lancet 2025;405:33-49.

Expanding the universe in IBD: going beyond in ulcerative colitis

Guselkumab brings a new opportunity for biologic-naive and biologic-experienced populations in UC, while maintaining its known safety profile[2]

- 72% maintenance of clinical remission
- 35% endoscopic remission
- 61% histological remission
- 98% corticosteroid-free clinical remission

Clinical data

Guselkumab is the only IL-23 inhibitor that has been shown to bind to CD64 and neutralize IL-23 at its cellular source in vitro[1,a]

MoA

Flexibility

Guselkumab has demonstrated efficacy in clinical trials with both i.v. and s.c. induction in UC, offering flexibility[2,3]

[a] Based on in vitro studies in an inflammatory monocyte model. The clinical significance of these findings is not known.
CD, cluster of differentiation; IL, interleukin; MoA, mechanism of action; UC, ulcerative colitis.

1. Atreya R, et al. Presented at UEGW 2024; OP#03.
2. Rubin DT, et al. Lancet 2025;405:33-49.
3. Peyrin-Biroulet L, et al. Presented at ECCO 2025; OP#0.

