New therapies on deck: What to know about recent approvals in IBD.

What's New in GI
Feb 22nd 2025
Song Mingjun

Overview

Old drugs, new ways:

- SC infliximab-dyyb (*10/2023 for UC & CD)
- SC vedolizumab (*9/2023 for UC, ***4/2024** for CD)

New but similar:

- Guselkumab (***9/2024** for UC; *submitted for CD approval 6/2024*)
- Risankizumab (*6/2022 for CD, ***6/2024** for UC)
- Mirikizumab (*10/2023 for UC, ***1/2025** for CD)

Future drugs: can we break the therapeutic ceiling?

- Anti TL1A
- Neutrophil Modulator

*FDA approved

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SC Infliximab-dyyb

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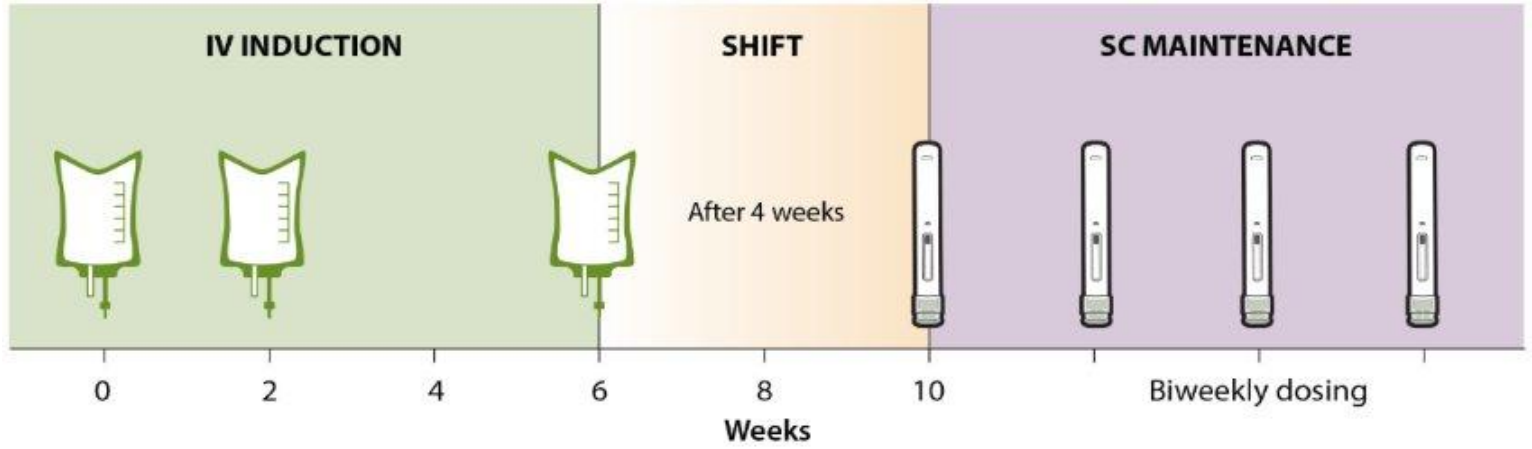
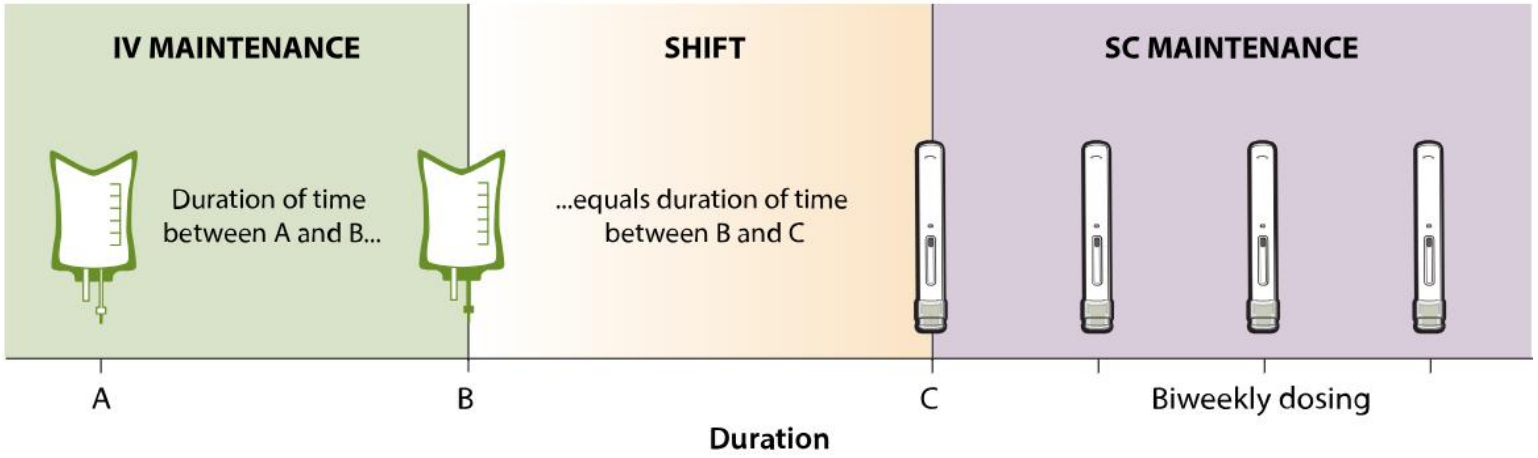
SC Infliximab-dyyb





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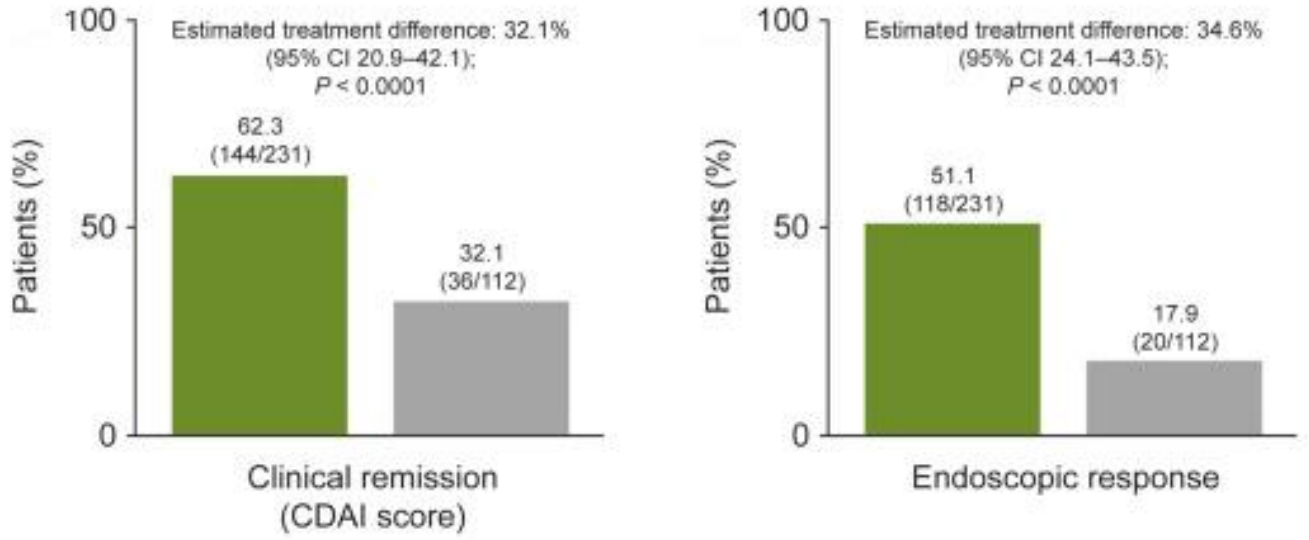
SC Infliximab-dyyb

Proof of concept

- LIBERTY (Hanauer et al. Gastro Oct 2024)

In CD:



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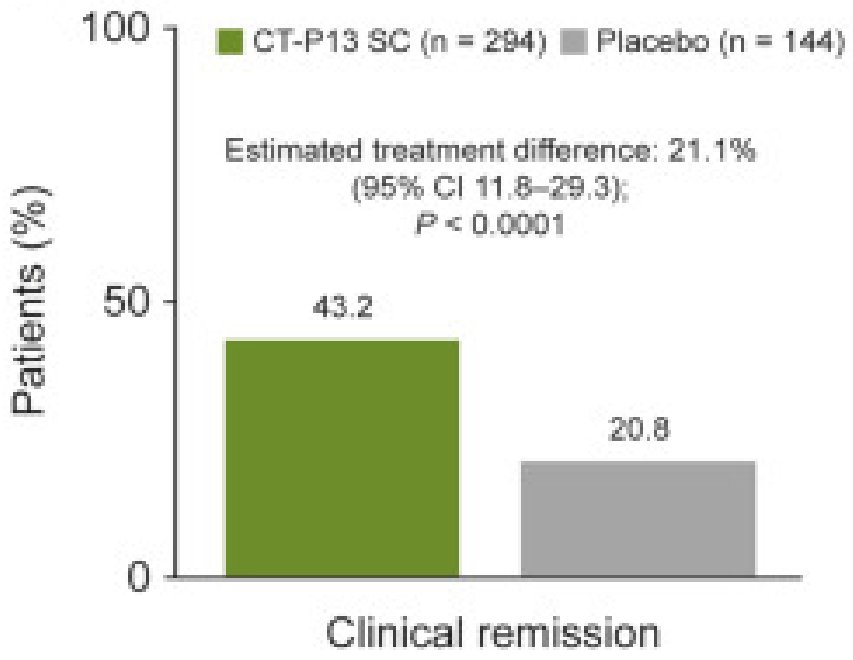
SC Infliximab-dyyb

Proof of concept

- LIBERTY (Hanauer et al. Gastro Oct 2024)

In UC:



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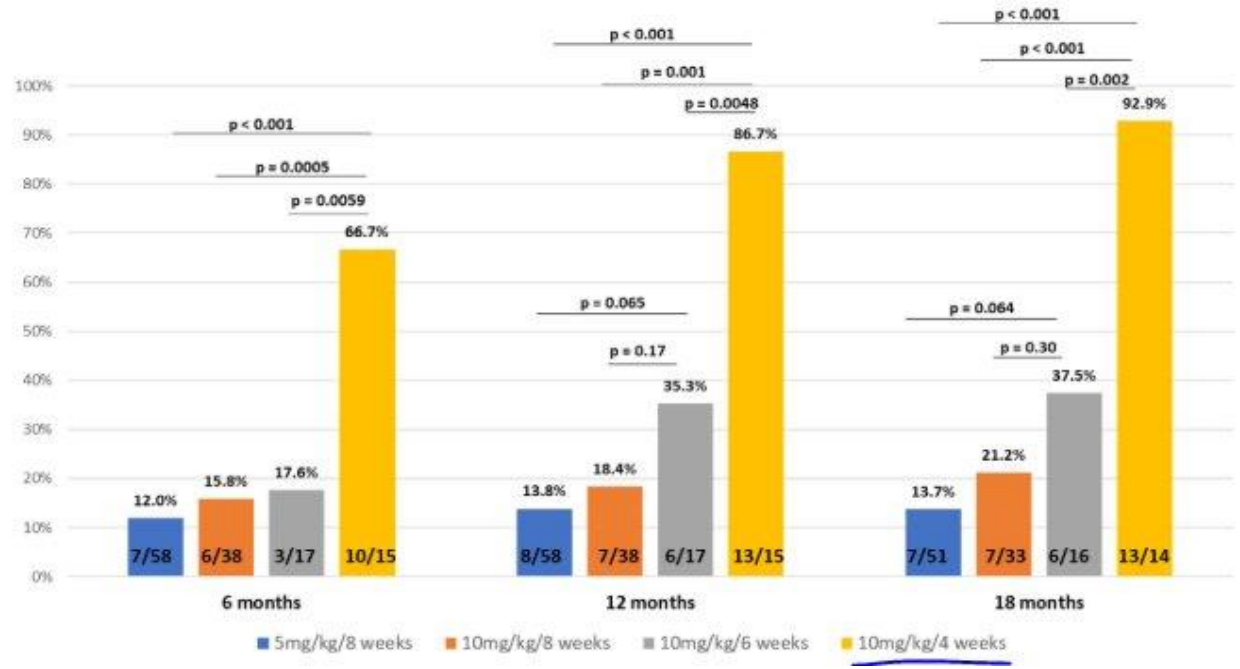
SC Infliximab-dyyb

REMSWITCH (Buisson et al. Clin Gastroenterol Hepatol. 2023); **REMSWITCH-LT** (Buisson et al, Aliment Pharmacol Ther 2023)

- 84-89% maintained remission over 6–12 months after switch from IV to SC in cohort studies
- However, those on **10mg/kg q4W** at baseline had a high rate of relapse when switched to SC 120mg q2W



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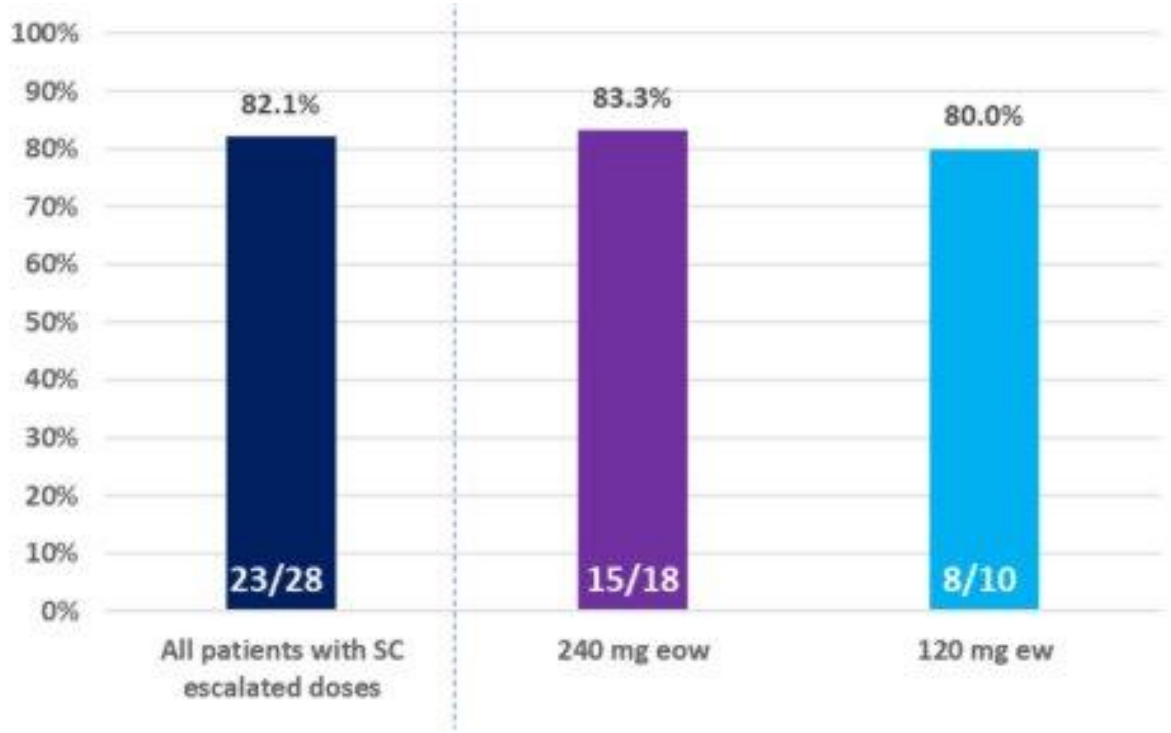
SC Infliximab-dyyb

- majority of patients with relapse on SC could re-capture response by escalation of SC dosing



A separate review found 240mg Q2W may achieve greater drug level increments than 120mg QW

- Little RD et al. J Clin Med. 2022;11:6173.

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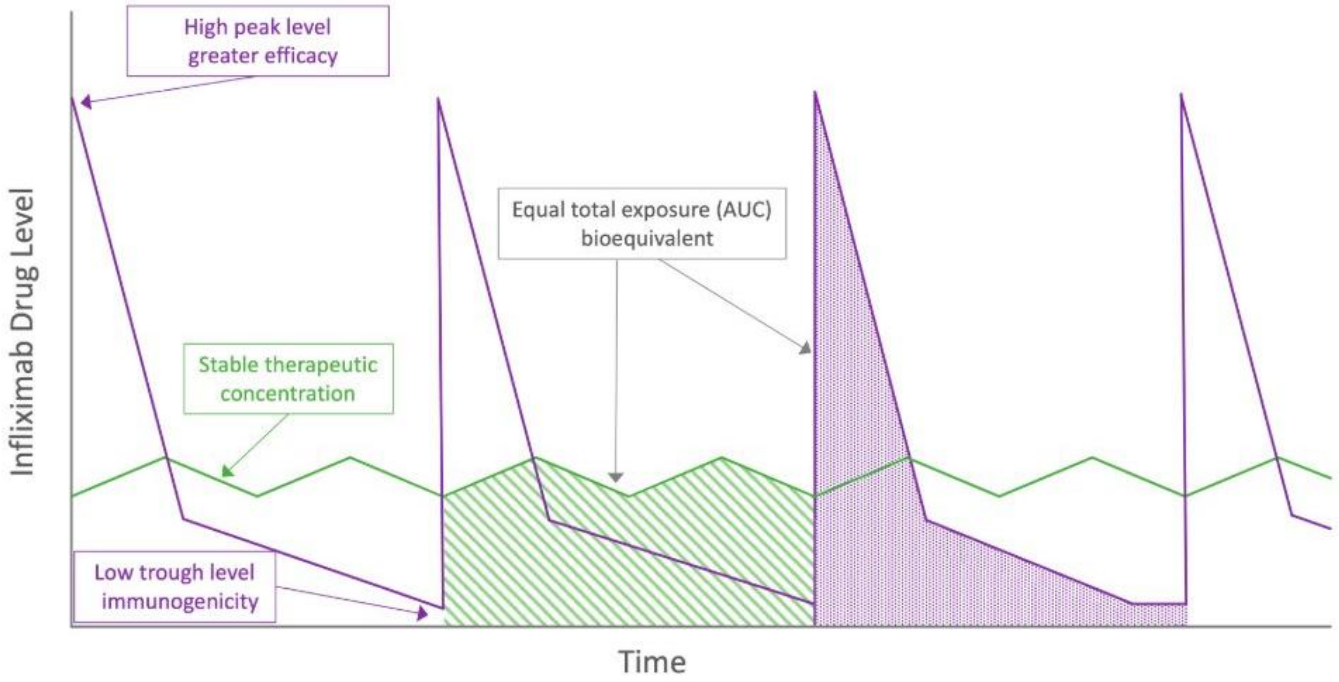
SC Infliximab-dyyb

Pharmacokinetic advantage of low immunogenicity?

- **REMSWITCH-LT** (Buisson et al, Aliment Pharmacol Ther 2023)
  - In long term follow up (median 18 months) only 4 patients developed drug antibodies; 2 with high titer (**< 5%**)



Little RD et al. J Clin Med. 2022;11:6173.

***PASSPORT:** Evaluate pharmacokinetics, efficacy and safety of SC infliximab (CT-P13) as induction for CD or UC
Recruiting

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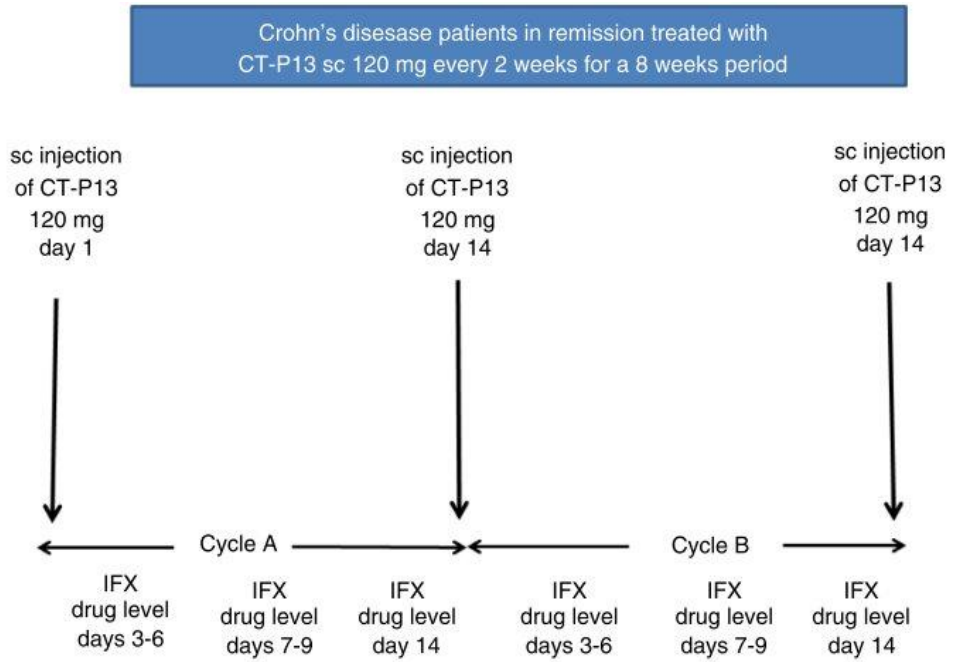
SC Infliximab-dyyb

No need to time blood draw for a 'trough'



Median IFX drug levels

Visits	Cycle A	Cycle B	*p*
1	11.1 (7.8–14.5)	11.6 (7.9–14.9)	0.65
2	12.0 (7.2–16.1)	11.4 (8.1–15.2)	0.25
3	11.0 (7.5–15.1)	10.9 (7.9–15.6)	0.21
p	0.62 between V1 and V2 0.88 between V1 and V3 0.52 between V2 and V3	0.87 between V1 and V2 0.65 between V1 and V3 0.49 between V2 and V3	

Veyrard P, et al. Aliment Pharmacol Ther. July 2022

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SC Infliximab-dyyb

An option for patients with high titer drug Ab on IV infliximab?

- retrospective study; 20 CD patients -- 90% had previous treatment with ≥ 3 biologics including IFX IV; all had high titers of anti-infliximab antibodies

- Treatment persistence:
    - Baseline ~ 100% ADA – *85% detectable ADA at start of study*
  - At 6 months: **15/20** - **2** had delayed allergy on week 2 and week 4 (urticaria, angioedema); **3** (ineffective)
    - ADA detected in 33.3%
  - At 12 months: **10**/20 - **4** (ineffective), **1** (loss to follow up)
    - ADA detected in 10%

Husman J, et al. Int J Colorectal Dis. 2024 Sep 25;39(1):151.

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SC Vedolizumab

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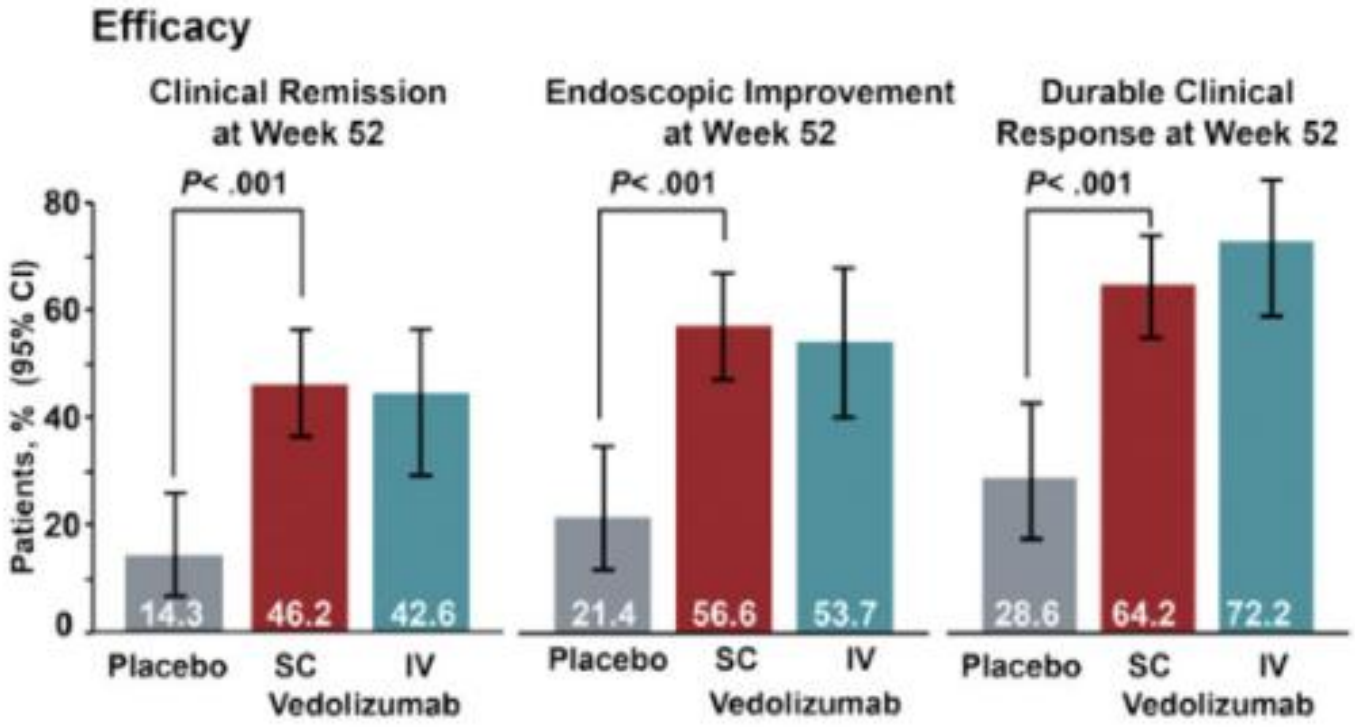
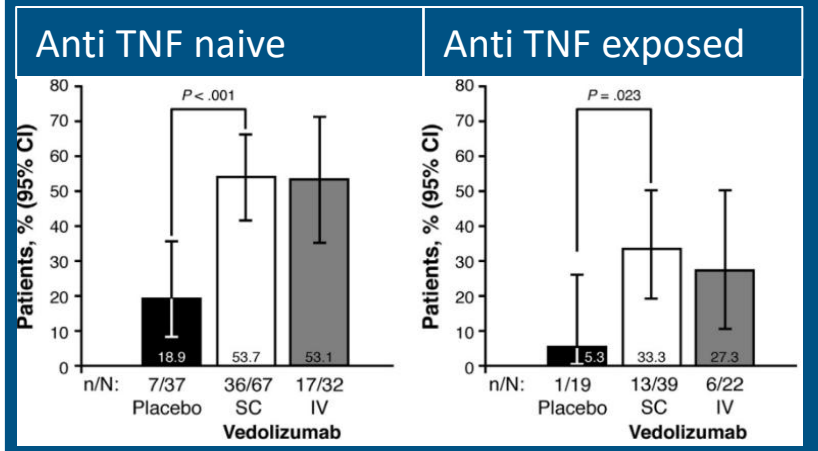
SC Vedolizumab

Proof of concept

- **VISIBLE 1** (Sandborn et al. Gastro Feb 2020) **for UC**
  - Median serum vedolizumab trough was higher for SC (34.6 ug/mL) vs IV (11.1 ug/ml); ADA 6% in SC and IV group
  - Injection site reaction ~ 10%



Clinical remission at week 52



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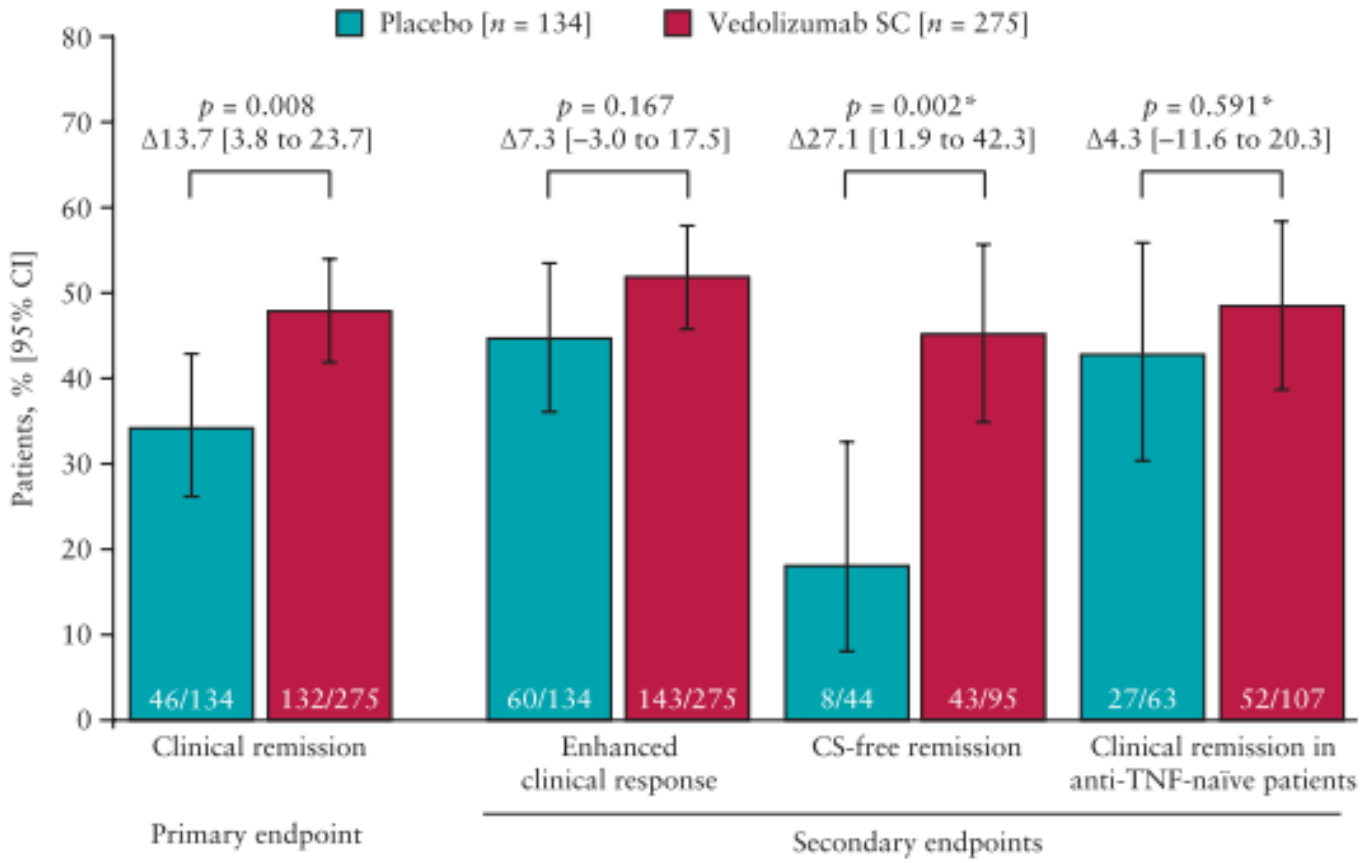
SC Vedolizumab

Proof of concept

- **VISIBLE 2** (Vermeire et al. JCC Aug 2021) **for CD**



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SC Vedolizumab

VISIBLE Open-Label Extension (Sandborn et al, C&C 360, Aug 2023)

- Non-responders at week 6 received a 3rd IV vedo infusion – response by week 14 – given SC Vedo q2w
- Patients who completed VISIBLE 1 and VISIBLE 2 (**placebo** or real drug) went on to open label SC Vedo q2w
- Patients who terminated VISIBLE 1 or 2 early due to worsening disease/rescue steroids could enroll in VISIBLE OLE for **WEEKLY** SC Vedo
  - In patients with loss of response on SC Vedo Q2W, **escalation to weekly** dosing resulted in **>/= 45%** of patients regaining response
  - Restarting therapy with **SC Vedo** after interruptions up to 46 weeks can still be effective (w/o IV induction)

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The IL-23 selective antagonists

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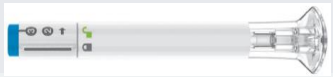
	Guselkumab	Risankizumab	Mirikizumab
MOA	**Human IgG1**, binds to the p19 subunit of IL-23. **Binds to CD64, a receptor on myeloid cells that produce IL-23 (in-vitro)**	**Humanized IgG1,** binds to the p19 subunit of IL-23.	**Humanized IgG4,** binds to the p19 subunit of IL-23. .
Dosing	**UC** Induction: IV 200mg [20ml over 1 hr] on week 0, 4, 8 ***Possible SC induction [GRAVITI].*** **Lower maintenance:** • SC 100mg on week 12 then q8w **Higher maintenance:** • SC 200mg on week 12 then q4w	**UC** IV induction 1200mg week 0, 4, 8 **Maintenance:** • OBI 180mg or 360mg on week 12 then q8w **CD** IV induction 600mg week 0, 4, 8 ***Possible SC induction [AFFIRM]*** **Maintenance:** • OBI 180mg or 360mg on week 12 then q8w	**UC** IV induction 300mg (over >/= 30 mins) week 0, 4, 8 **Maintenance:** • SC 200mg at week 12 then q4W *[* ***2 injections 100mg + 100mg****]* **CD** IV induction 900mg (over >/= 90mins) week 0, 4, 8 **Maintenance** • SC 300mg at week 12 then q4w *[* ***2 injections 100mg + 200mg****]*



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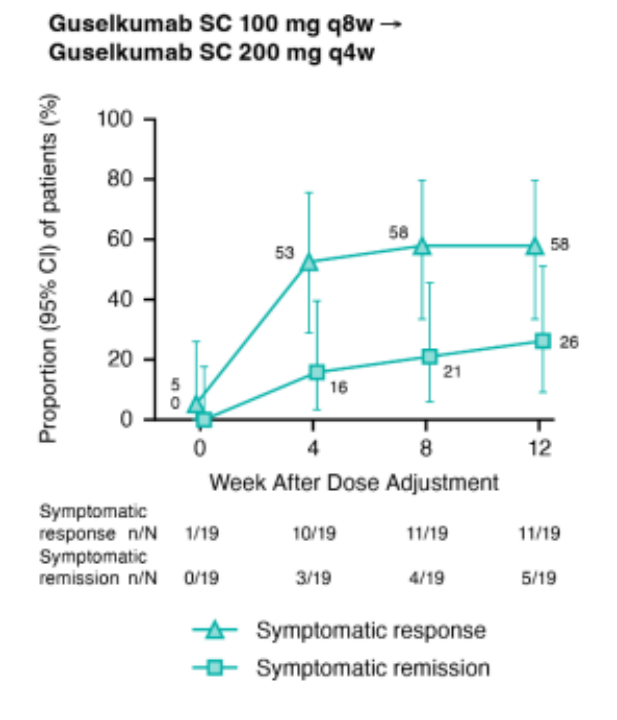
QUASAR : Guselkumab for mod-severe UC

- 49% with prior inadequate response or intolerance to other advanced therapies (***excluding*** ustekinumab)
    - In those who received IV Gus 200mg q4w x 3 doses:
        - 12 week responders --> 1:1:1 randomization (*placebo* vs *SC Gus 200mg q4w* vs *SC Gus 100mg q8w*)
        - 12 week NON-responders --> SC Gus 200mg q4w X 3 doses --> 24 week responder ***in 55%*** *(66/120 patients)* --> joined 200mg q4W group
    - In those who received placebo induction
        - 12 week responders --> joined placebo group in maintenance study
        - 12 week NON-responders --> IV Gus 200mg q4w x 3 --> 24 week responder --> 1:1:1 randomization

- Phase 3 maintenance study
    - Patients who lost clinical response underwent blinded Gus dose adjustment



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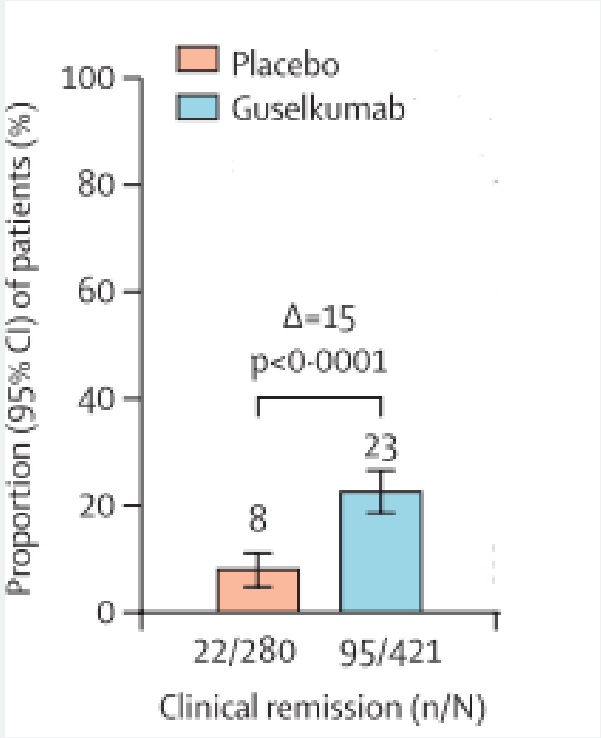
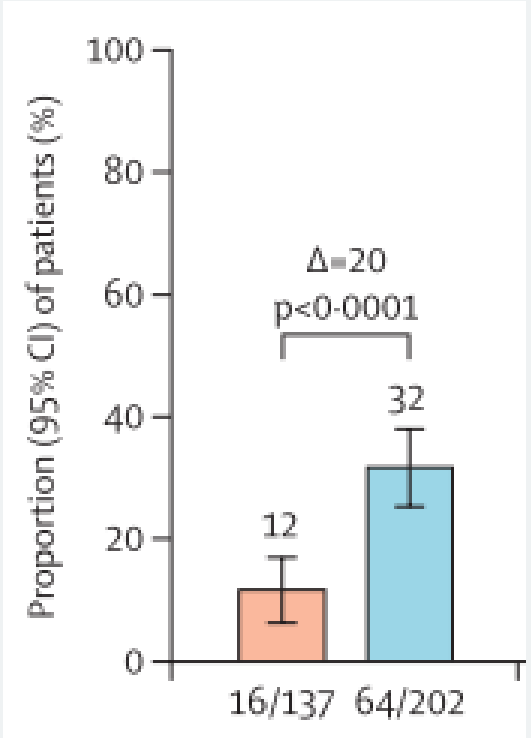
Rubin DT, et al. Lancet. 2025 Jan 4;405(10472):33-49.

QUASAR : Guselkumab for mod-severe UC

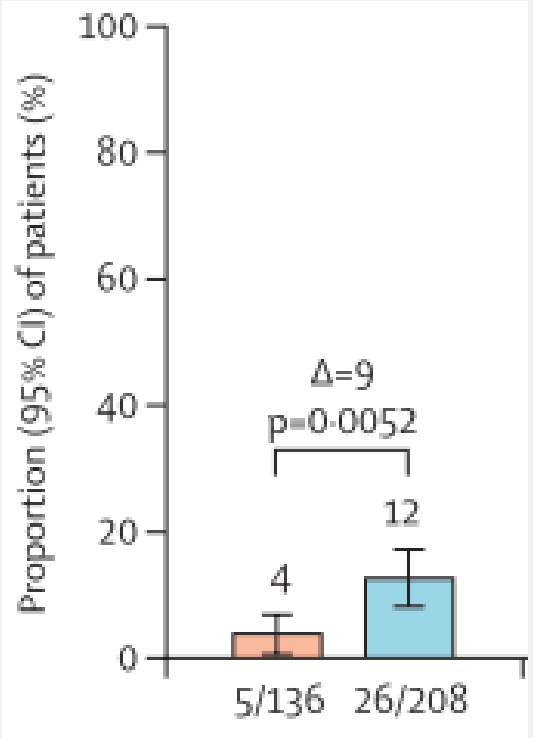
Week 12 clinical remission



All patients



Biologic and JAK inhibitor naive



Prior intolerance/inadequate response to biologic and JAK inhibitor

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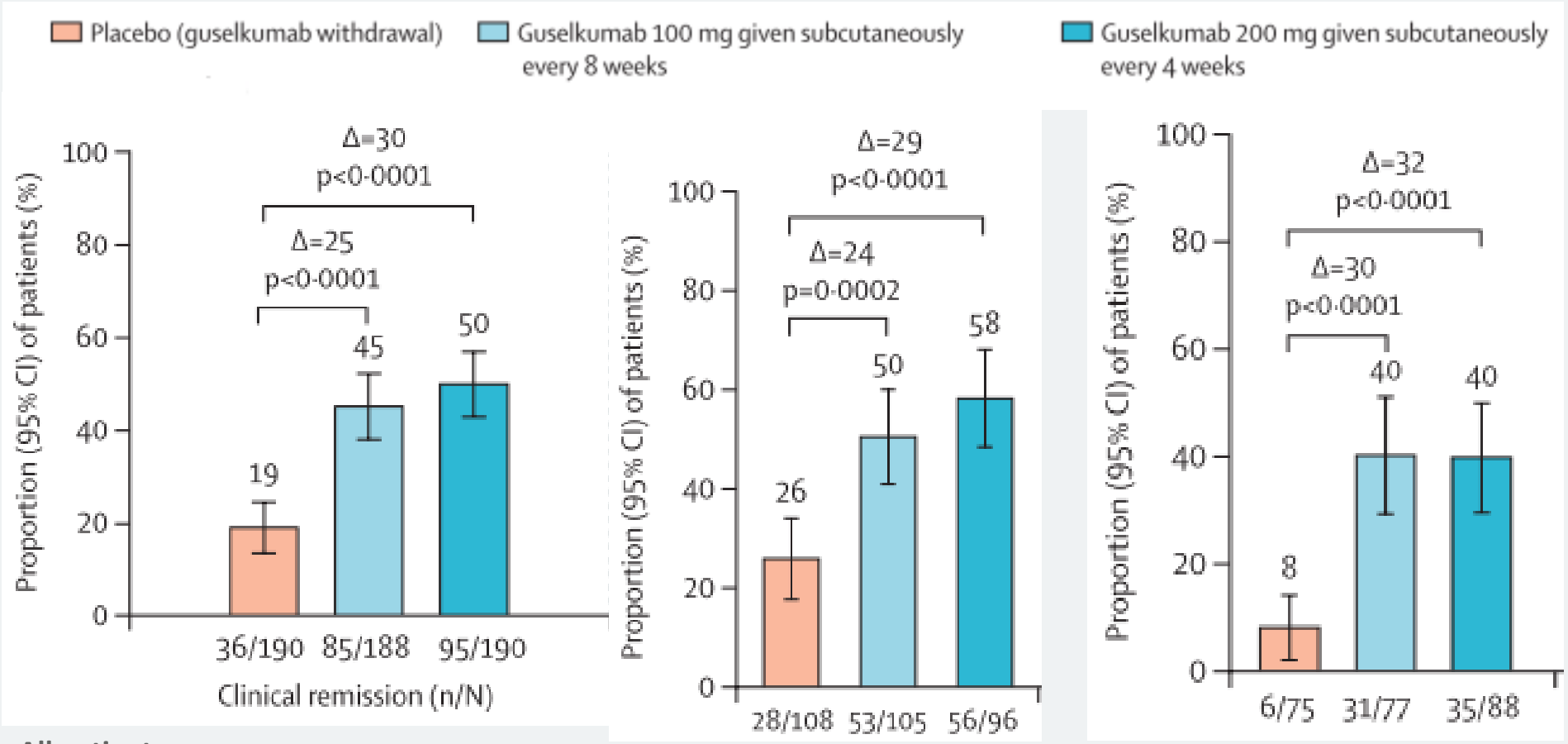
Rubin DT, et al. Lancet. 2025 Jan 4;405(10472):33-49.

QUASAR : Guselkumab for mod-severe UC

Week 44 clinical remission



All patients

Biologic and JAK inhibitor naive

Prior intolerance/inadequate response to biologic and JAK inhibitor

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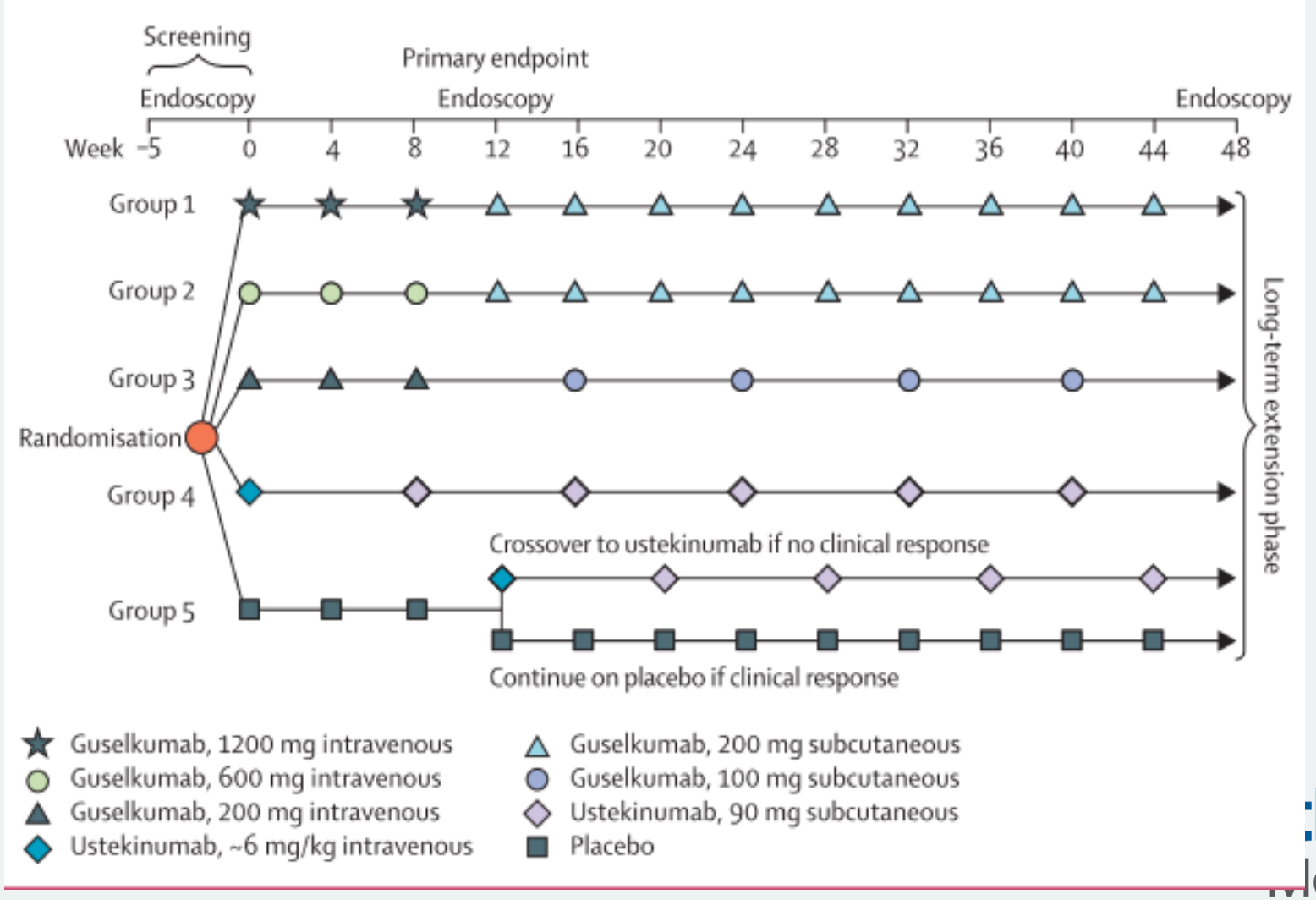
Rubin DT, et al. Lancet. 2025 Jan 4;405(10472):33-49.

GALAXI-1: Guselkumab for mod-severe Crohn's disease

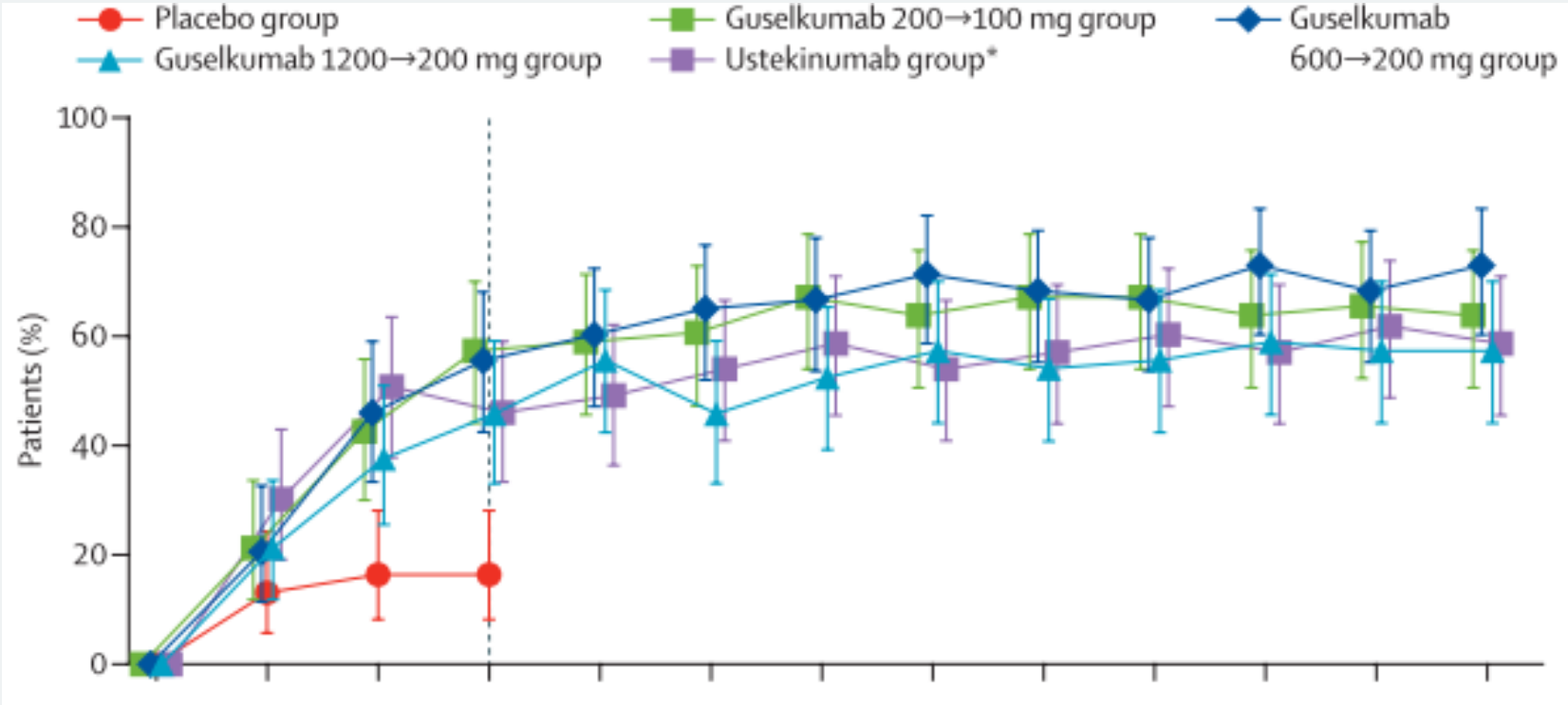
- Treat-through design
- > 50% prior inadequate response or intolerance to biologics
- ***Limited ustekinumab exposure*** >/= 16 weeks prior study entry was allowed *(but not if there was evidence of ustekinumab failure or intolerance)*



Danese S, et al. Lancet Gastroenterol Hepatol. 2024 Feb;9(2):133-146.

GALAXI: Guselkumab for mod-severe Crohn's disease

- **Week 48 CDAI clinical remission rates:**
  - Gus 200--> 100 mg: 64%
  - **Gus 600-->200 mg: 73%**
  - Gus 1200-->200mg: 57%
  - Ust group: 59%



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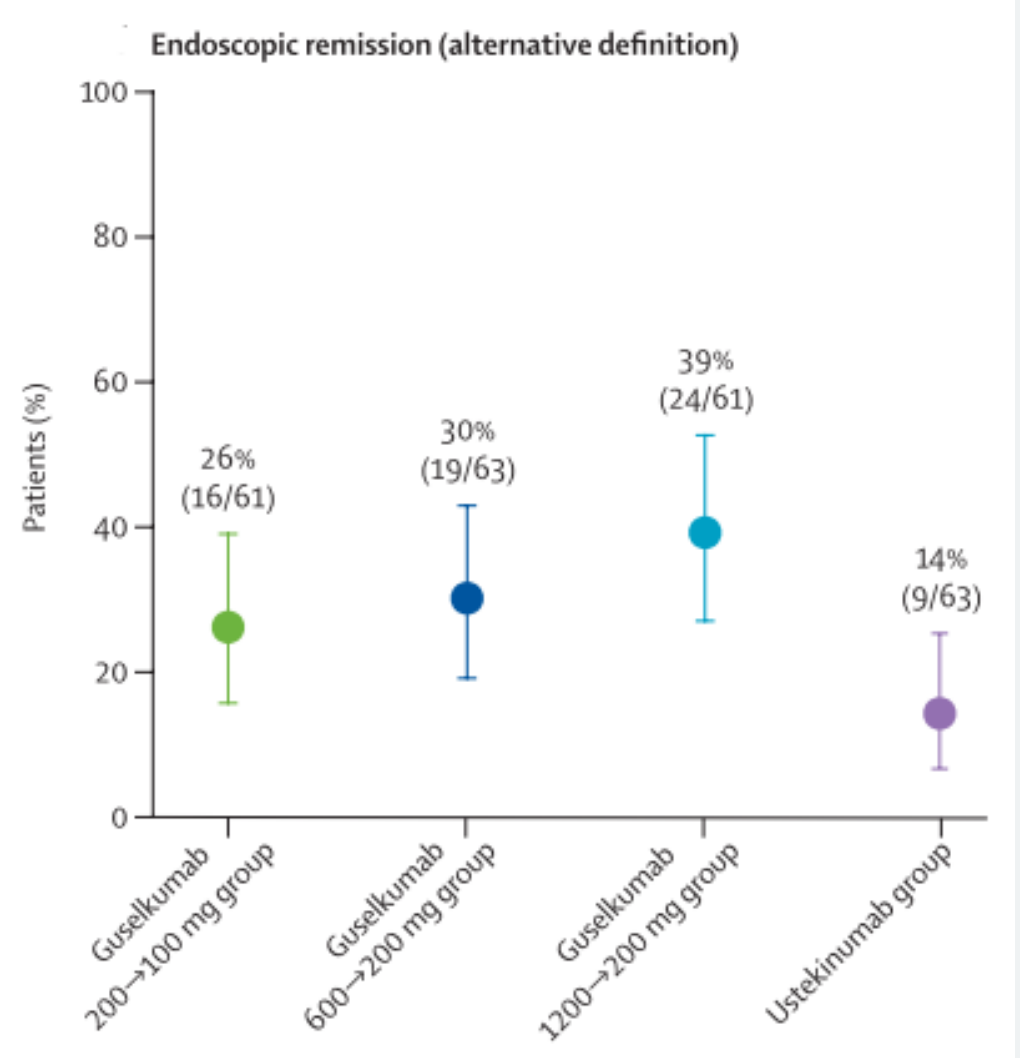
Danese S, et al. Lancet Gastroenterol Hepatol. 2024 Feb;9(2):133-146.

GALAXI: Guselkumab for mod-severe Crohn's disease

- **Week 48 endoscopic response:**
  - Gus 200--> 100 mg: 44%
  - **Gus 600-->200 mg: 46%**
  - Gus 1200-->200mg: 44%
  - Ust group: 30%

- **Week 48 alternative definition for endoscopic response:**
  - SES-CD score 4 or less AND at least 2 point reduction from baseline, AND no subscore > 1 on any variable
  - excluded non-traversable strictures



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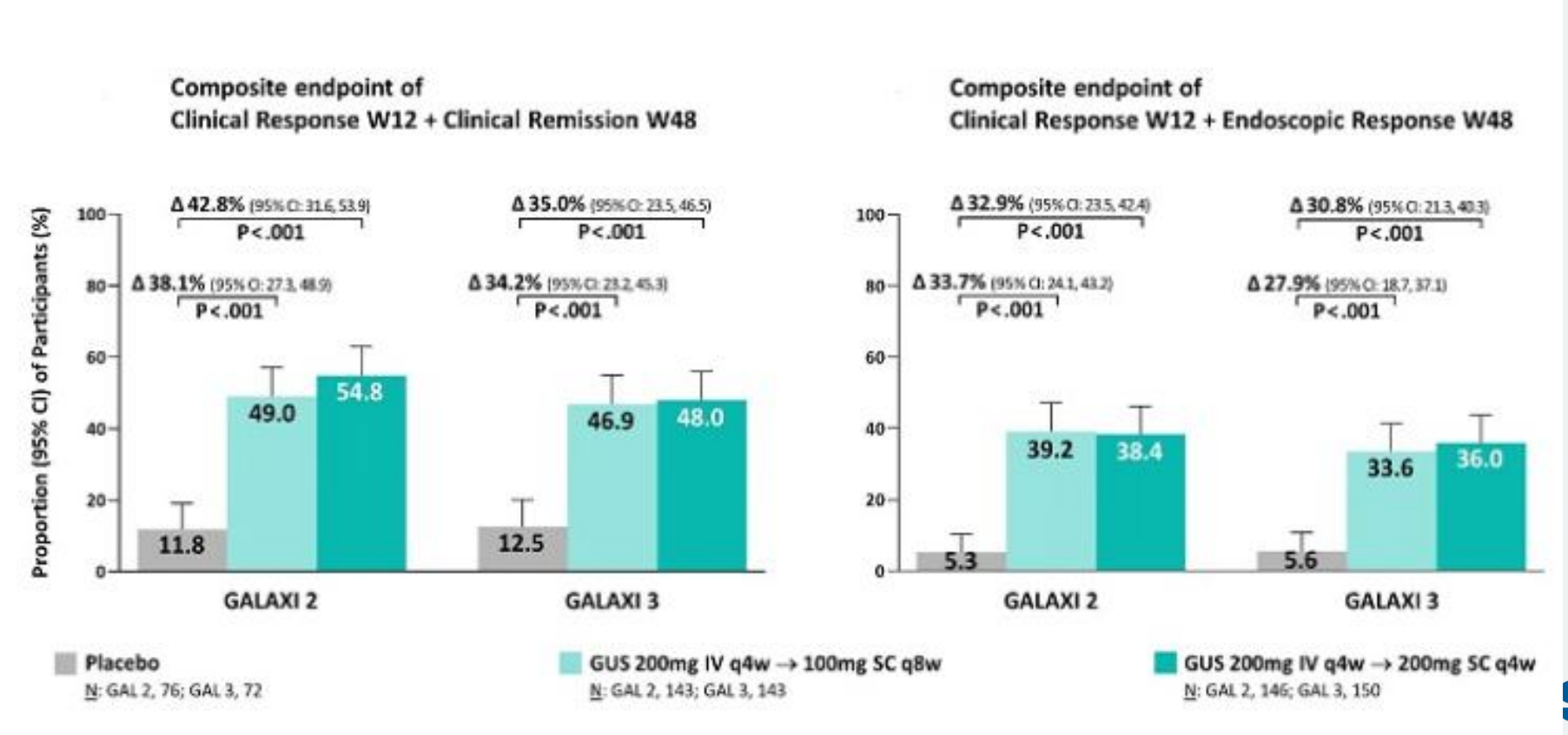
Danese S, et al. Lancet Gastroenterol Hepatol. 2024 Feb;9(2):133-146.

GALAXI 2 & 3: Guselkumab for mod-severe Crohn's disease

- Treat-through design
- 2:2:2:1 randomization:
  - **GUS IV 200mg** q4w X 3 --> SC 200mg q4w
  - **GUS IV 200mg** q4w x 3 --> SC 100mg q8w
  - UST 6mg/kg IV induction --> SC 90mg q8w
  - Placebo --> 12 week non-responder --> UST IV induction then 90mg q8w



Panaccione, R et al. Oral presentation (Abstract #1057b) at Digestive Disease Week (DDW) 2024. May 2024.

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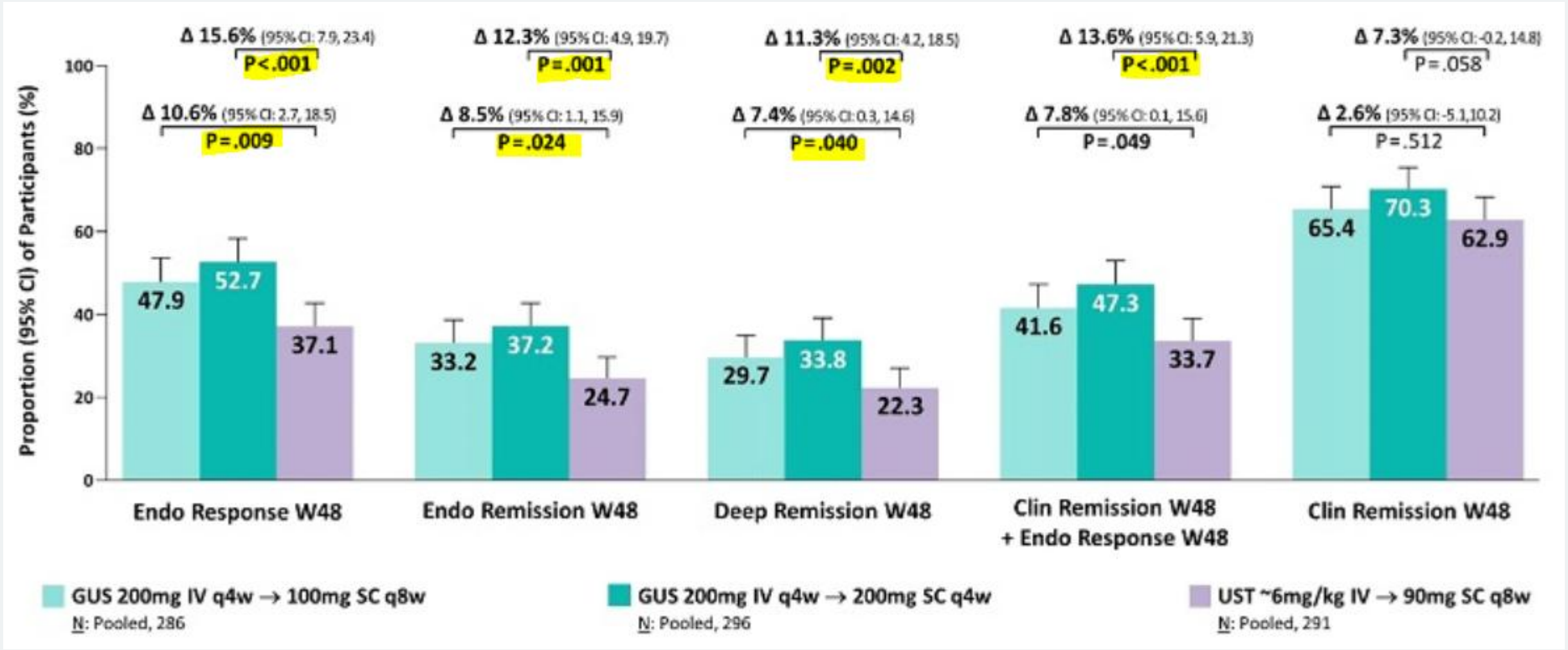
GALAXI 2 & 3: Guselkumab for mod-severe Crohn's disease



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Panaccione, R et al. Oral presentation (Abstract #1057b) at Digestive Disease Week (DDW) 2024. May 2024.

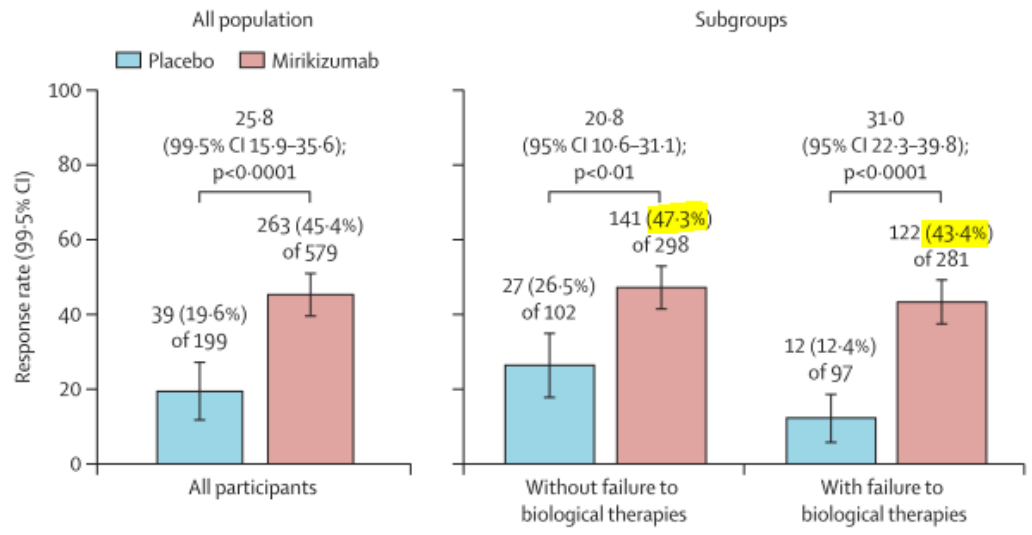
VIVID-1 : Mirikizumab for mod-severe Crohn's disease

- Prior biologic failure 48.5%
- Randomization 6:3:2
  - Mirikizumab
  - Ustekinumab 6mg/kg IV induction x 1, then 90mg SC every 8 weeks
  - Placebo
    - At week 12, placebo "non-responders" [n=80; 40%] switched directly to Mirikizumab SC 300mg q4w

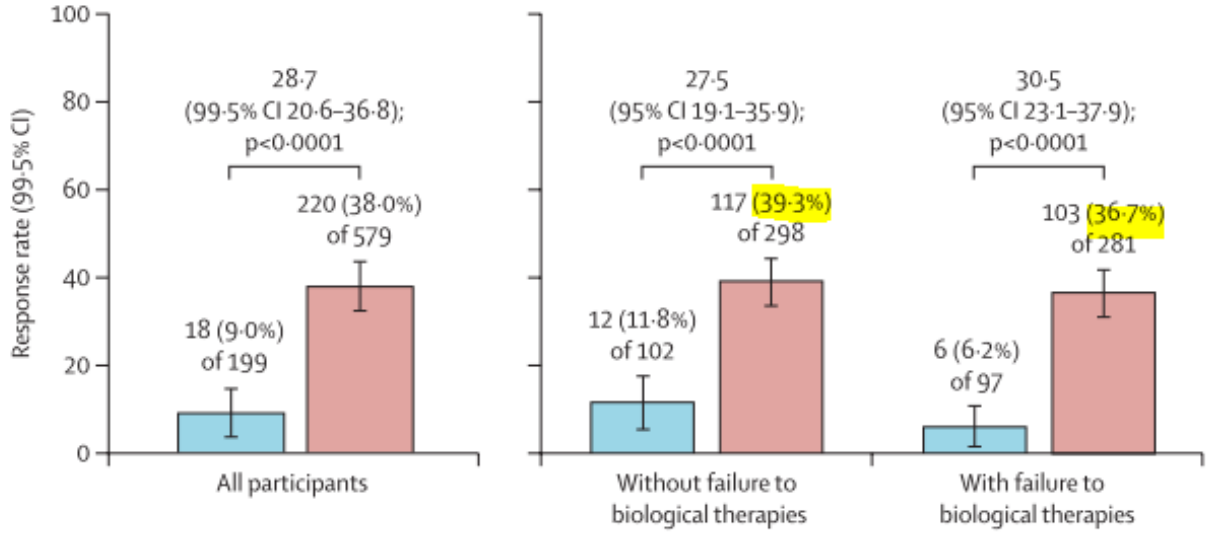
- Treat-through design; no rescue medication allowed other than placebo non-responders

Primary endpoints:

Week 52 CDAI clinical remission-composite (week 12 clinical response + week 52 clinical remission)



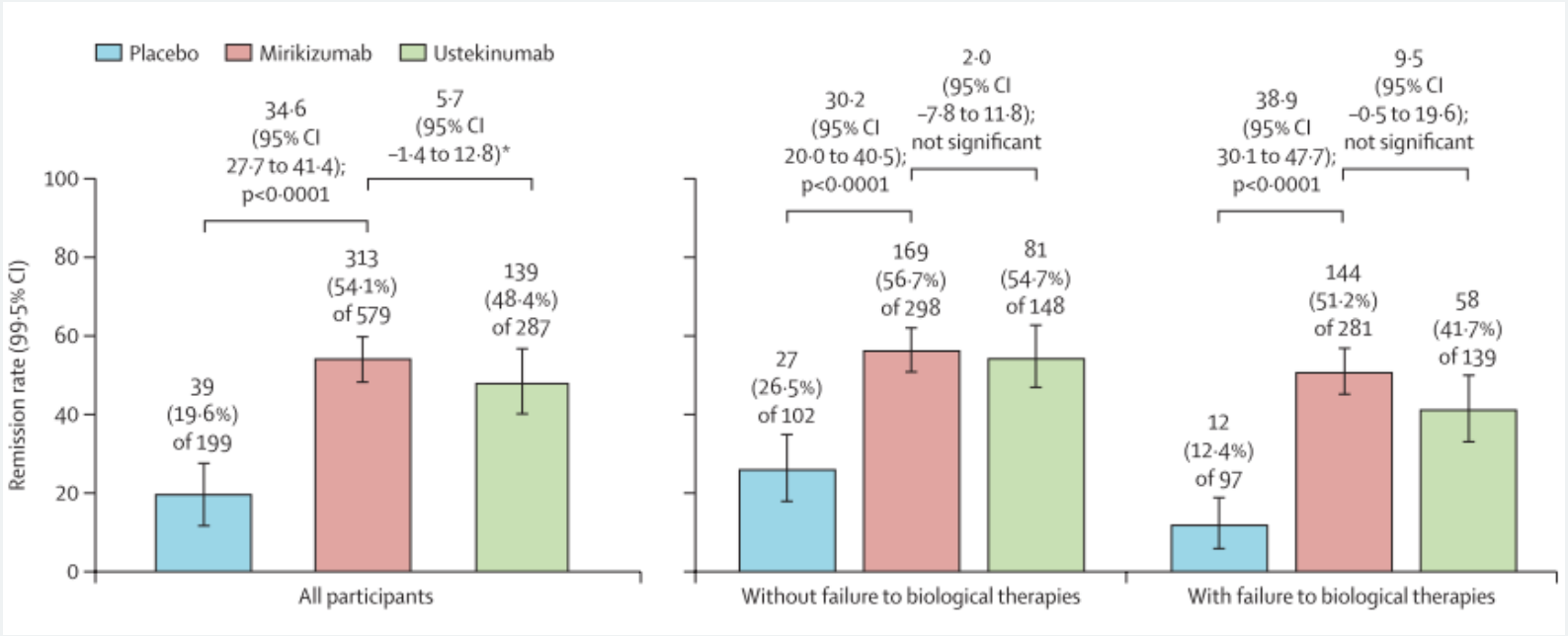
Week 52 endoscopic response-composite (week 12 clinical response + week 52 endoscopic response)



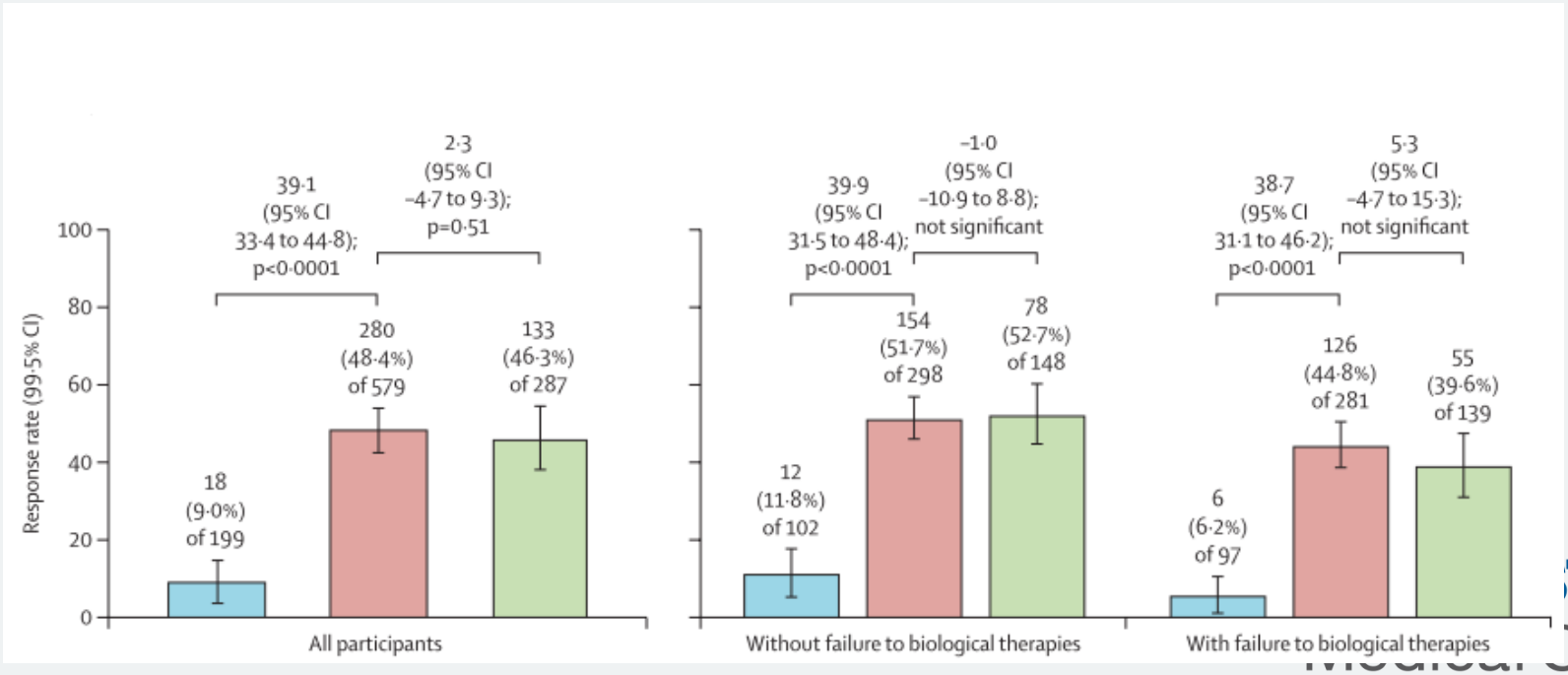
Ferrante M, et al. Lancet. 2024 Dec 14;404(10470):2423-2436

VIVID-1 Secondary endpoints:

Week 52 CDAI clinical remission; Mirikizumab non-inferior to ustekinumab



Week 52 endoscopic response; Mirikizumab not superior to ustekinumab



Ferrante M, et al. Lancet. 2024 Dec 14;404(10470):2423-2436

Future drugs: can we break the therapeutic ceiling?

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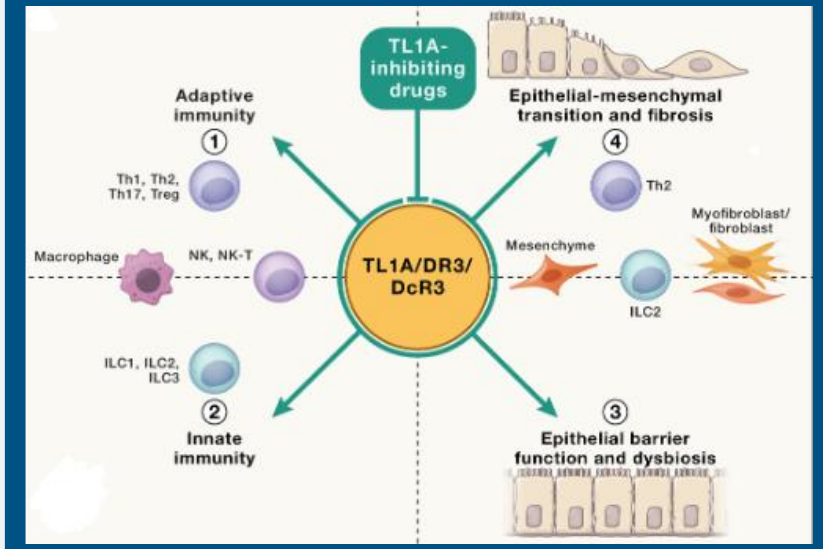
Anti-TL1A

- MOA: selectively binds to membrane bound and soluble TL1A – blocks interaction of TL1A and DR3 --> suppresses downstream inflammatory responses by helper T cells
  - ?anti fibrotic downstream effect – mice studies – reversed colonic fibrosis, reduced numbers of fibroblasts and myelofibroblasts
  - ?Good choice for EIM – broad involvement of TL1A in skin, eye & joints

- TL1A and its receptor DR3 are upregulated in intestinal inflammation
  - Gene encoding TL1A (TNFSF15) and DR3 (TNFRSF25) are a/w increased susceptibility for IBD

- **Phase 2 studies**
  - TUSCANY (PF-06480605; IV; open label single arm) published 2021
  - **ARTEMIS-UC trial** for UC (**Tulisokibart** in IV form) - NEJM 2024
  - RELIEVE UCCD for UC & CD (TEV-48574 in SC form) - abstract form

- **Phase 3 studies**
  - ATLAS-UC in process (Tulisokibart in IV or SC)
  - Tulisokibart for mod-severe CD (in process; clinical trails.gov ID NCT06430801)
  - AMETRINE study for UC (RO7790121)



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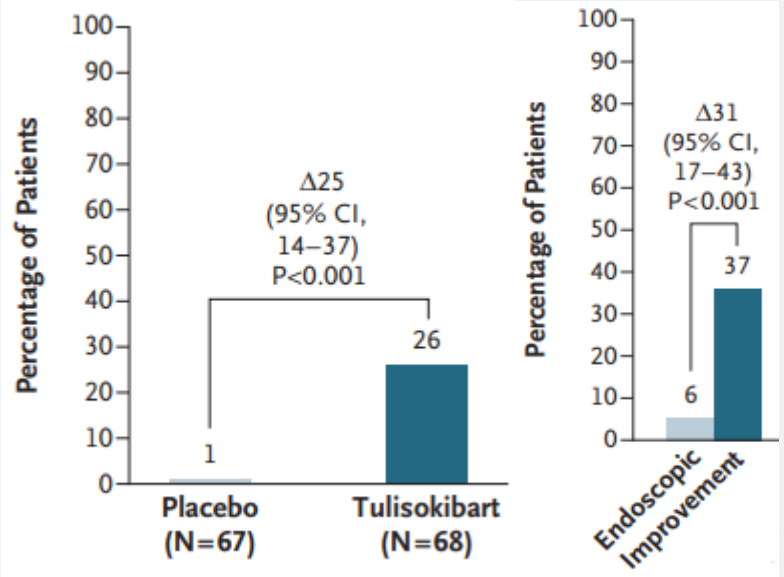
Virginia Solitano, et al, Med, Volume 5, Issue 5, 2024, Pages 386-400

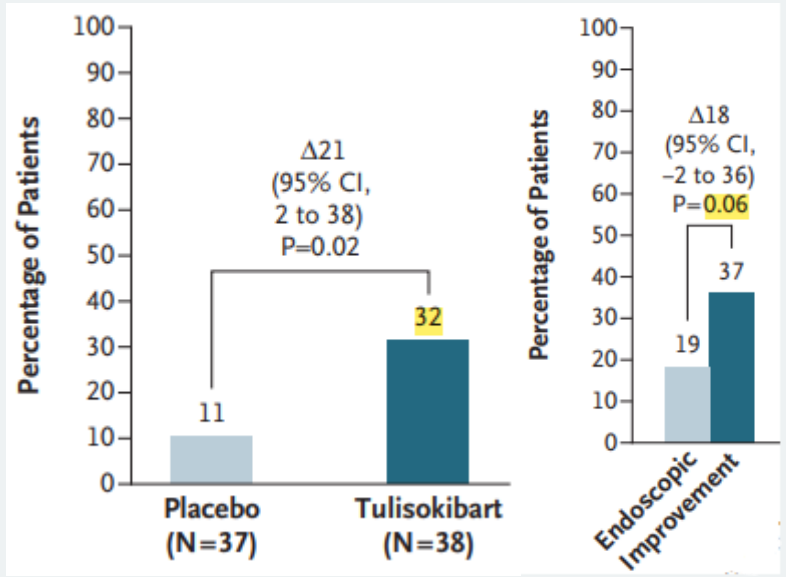
ARTEMIS-UC trial (phase 2)

- mod to severe UC patients who are steroid dep or failed conventional or advanced therapy
- 1:1 randomisation
- **Tulisokibart**
  - IV 1000mg on week 0, then 500mg on week 2, week 6, week 10

12 week clinical remission in all patients



12 week clinical remission in patients deemed 'higher likelihood of response' i.e positive for TNFSF15/TNFRSF25 genes



N Engl J Med. 2024 Sep 26;391(12):1119-1129

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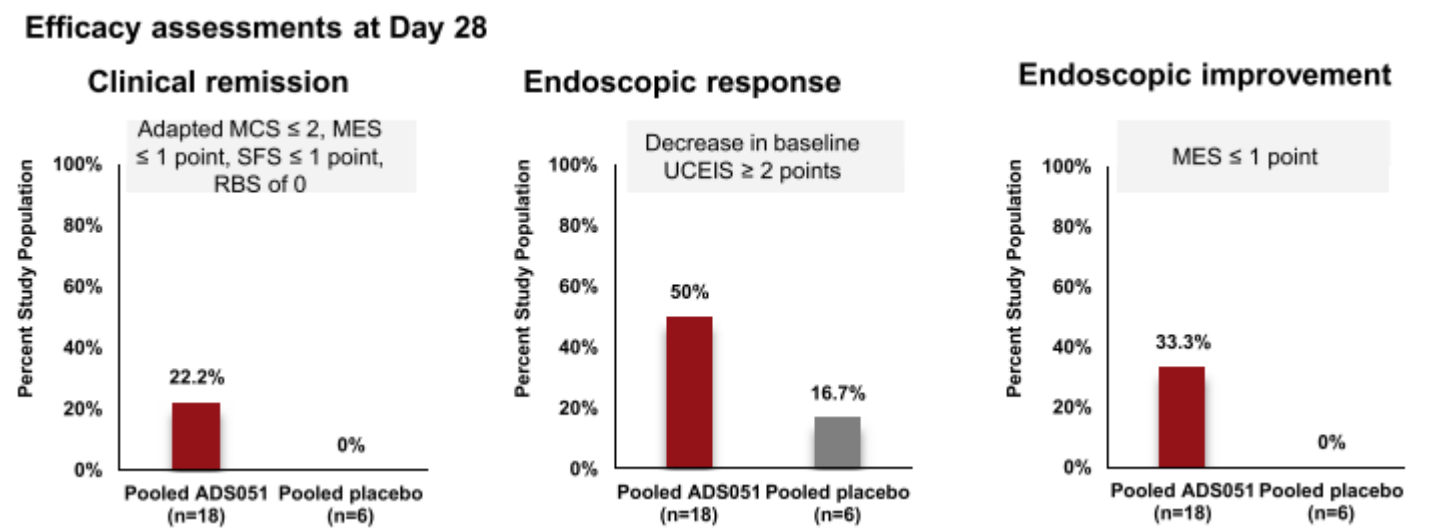
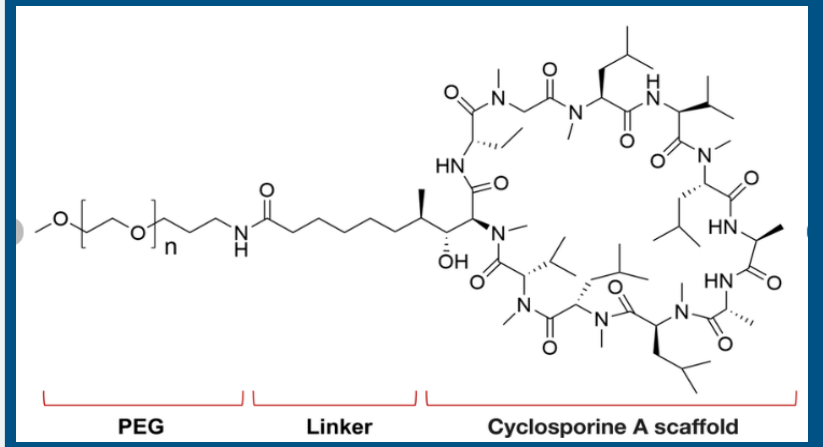
Neutrophil Modulator

- ADS051 – an oral small molecule that targets neutrophil migration and activation in the colon
- Phase 1b multidose trial in UC (Allegretti, Jessica R. et al. The American J of Gastro; Dec 31, 2024)





- ADS051 found to be safe & well tolerated up to 3200mg once a day
- Gut concentrated – with high stool concentrations and minimal systemic exposure

Phase 2 study in progress

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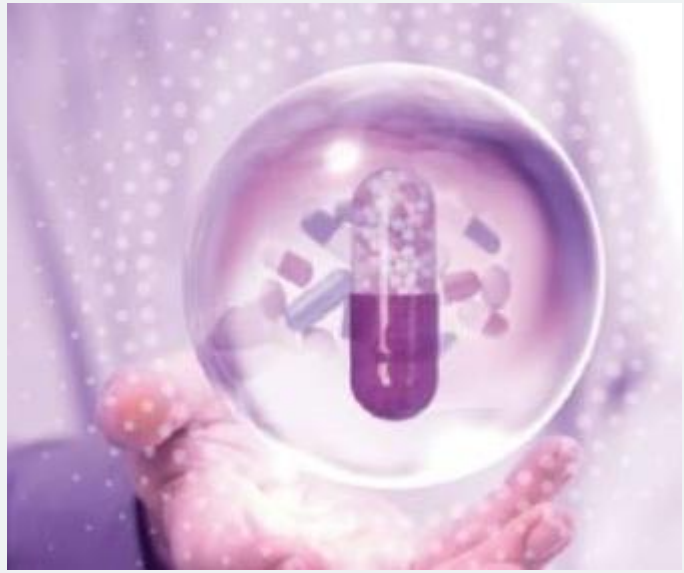
Thank you



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