

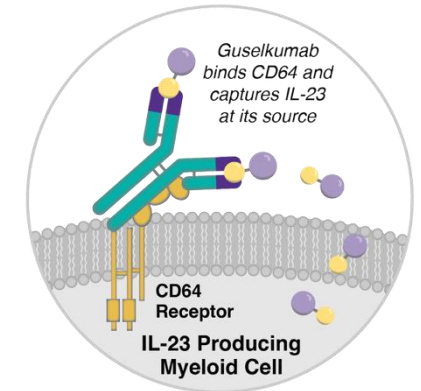
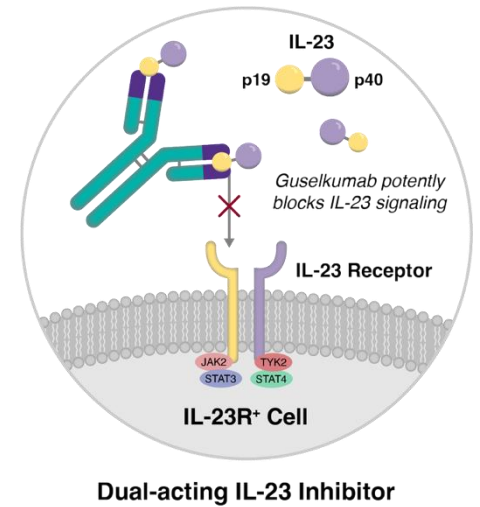
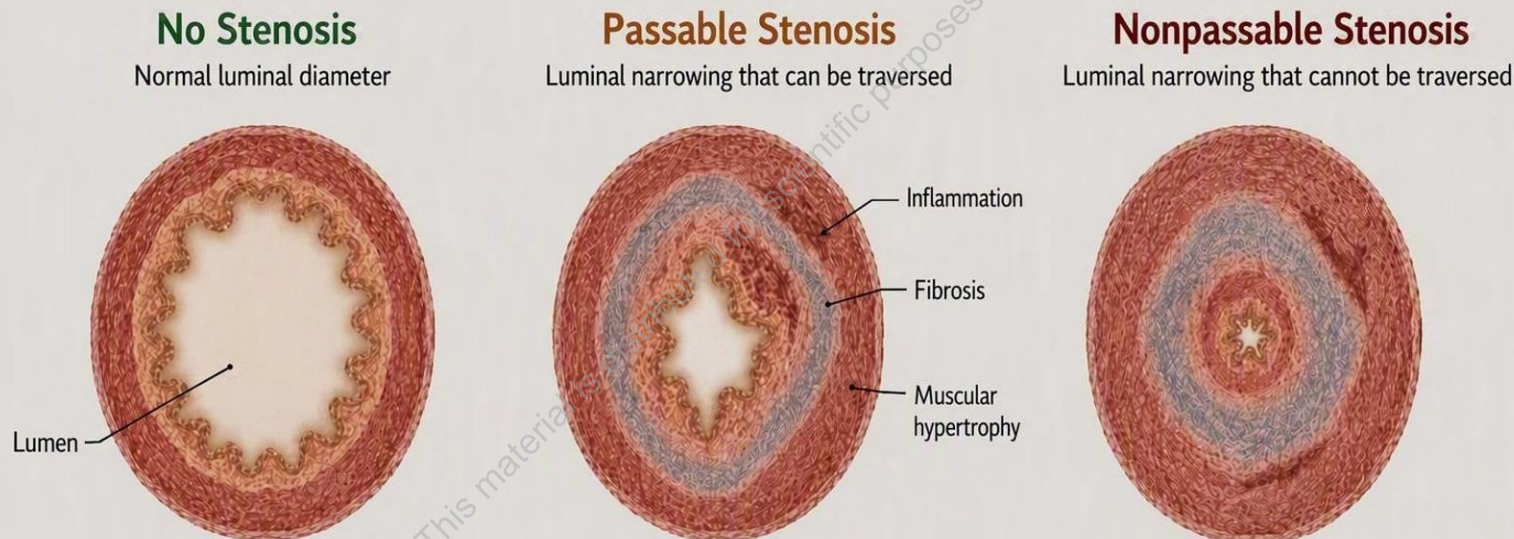
Changes in Intestinal Stenosis Among Patients With Moderately to Severely Active Crohn's Disease Treated With Guselkumab: Results From the Phase 3 GALAXI and GRAVITI Studies

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Background

- Guselkumab is a dual-acting IL-23p19 subunit inhibitor that potently blocks IL-23 and binds to CD64, a receptor on immune cells that produce IL-23¹
- The phase 3 GALAXI and GRAVITI studies (NCT03466411 and NCT05197049, respectively) evaluated guselkumab in participants with moderately to severely active Crohn's disease
- Intestinal stenosis in Crohn's disease can lead to obstructive symptoms and interventions; evidence regarding the impact of biologics on stenosis remains limited²



1. Sachin K, Hammaker D, Sarabia I, et al. *Front Immunol*. 2025; doi:10.3389/fimmu.2025.1532852.
2. Narula N, Wong ECL, Dulai PS, et al. *J Crohns Colitis*. 2021; 15(10):1649-57.

Objective

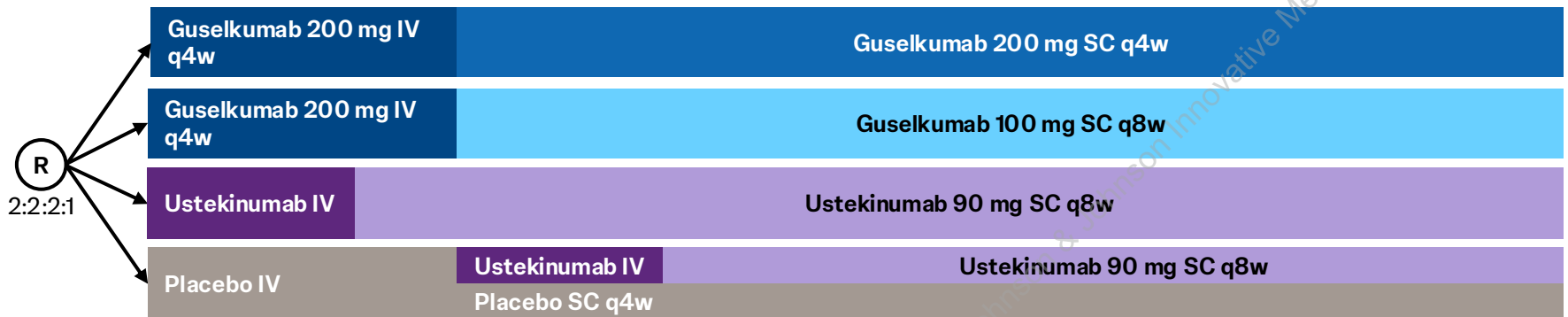
Here, we present descriptive post hoc results through Week 96 from participants with non-passable endoscopic intestinal stenosis at baseline enrolled in the phase 3 GALAXI and GRAVITI studies, together with complementary translational analyses evaluating stenosis-associated fibroblast biology

Phase 3 GALAXI and GRAVITI Study Designs

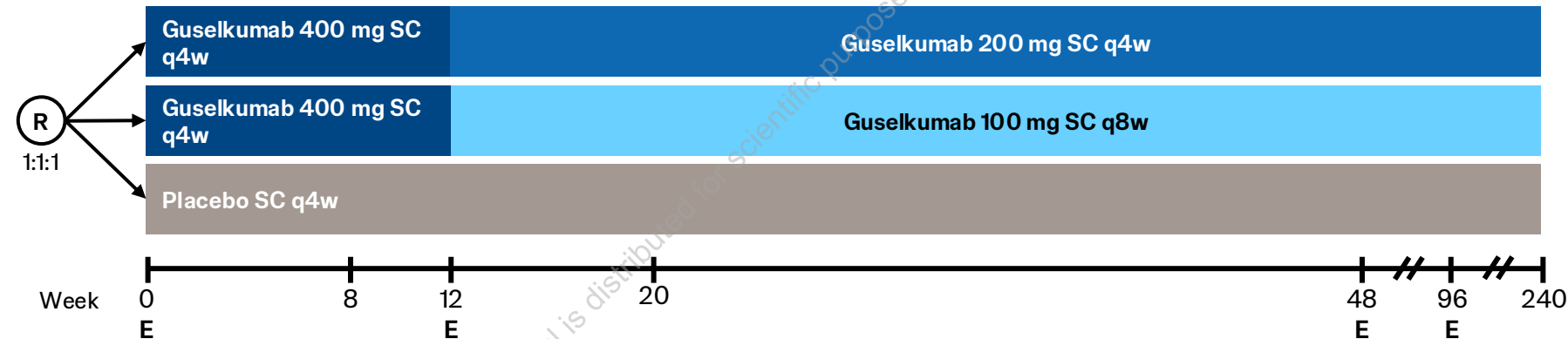
Key eligibility criteria: Moderately to severely active Crohn's disease (CDAI score 220–450 AND either mean daily SF OR AP above protocol thresholds^a), SES-CD score ≥6 (or ≥4 for isolated ileal disease), and inadequate response/intolerance to oral corticosteroids, 6-MP/AZA/MTX, or biologic therapies^b

Randomization stratified by: CDAI score (≤300 or >300), SES-CD (≤12 or >12), BIO-IR status, and corticosteroid use at baseline (GALAXI only)

GALAXI 2 & 3



GRAVITI



Participants with symptomatic stenoses, or stenoses requiring surgical intervention, were excluded from enrollment

AP= abdominal pain; BIO= biologic; CDAI=Crohn's disease activity index; E= endoscopy; IR= inadequate response or intolerance; IV=intravenous; LTE= long-term extension; R=randomization; SES-CD= simple endoscopic score for Crohn's disease; SF= stool frequency; SC=subcutaneous.

^a GALAXI: Mean daily SF count >3 OR AP score >1; GRAVITI: Mean daily SF count ≥4 OR AP score ≥2. ^b Biologic therapies: TNF antagonists or vedolizumab.

Note: Entry into the LTE was determined based on investigator discretion.

Analysis Considerations

- Analyses were post hoc, as observed, and descriptive; no formal statistical hypothesis testing was performed
- In GALAXI, participants meeting prespecified criteria could dose adjust from guselkumab 100 mg to 200 mg between Weeks 52–80; these participants were analyzed within their original randomized arm
- Stenosis status was determined using the SES-CD narrowing component at Weeks 12, 48, and 96
- Participants with non-passable stenosis at baseline were evaluated at each post-baseline endoscopic assessment
- Participants with missing SES-CD data at a given timepoint were excluded from the analysis at that timepoint because stenosis status could not be determined

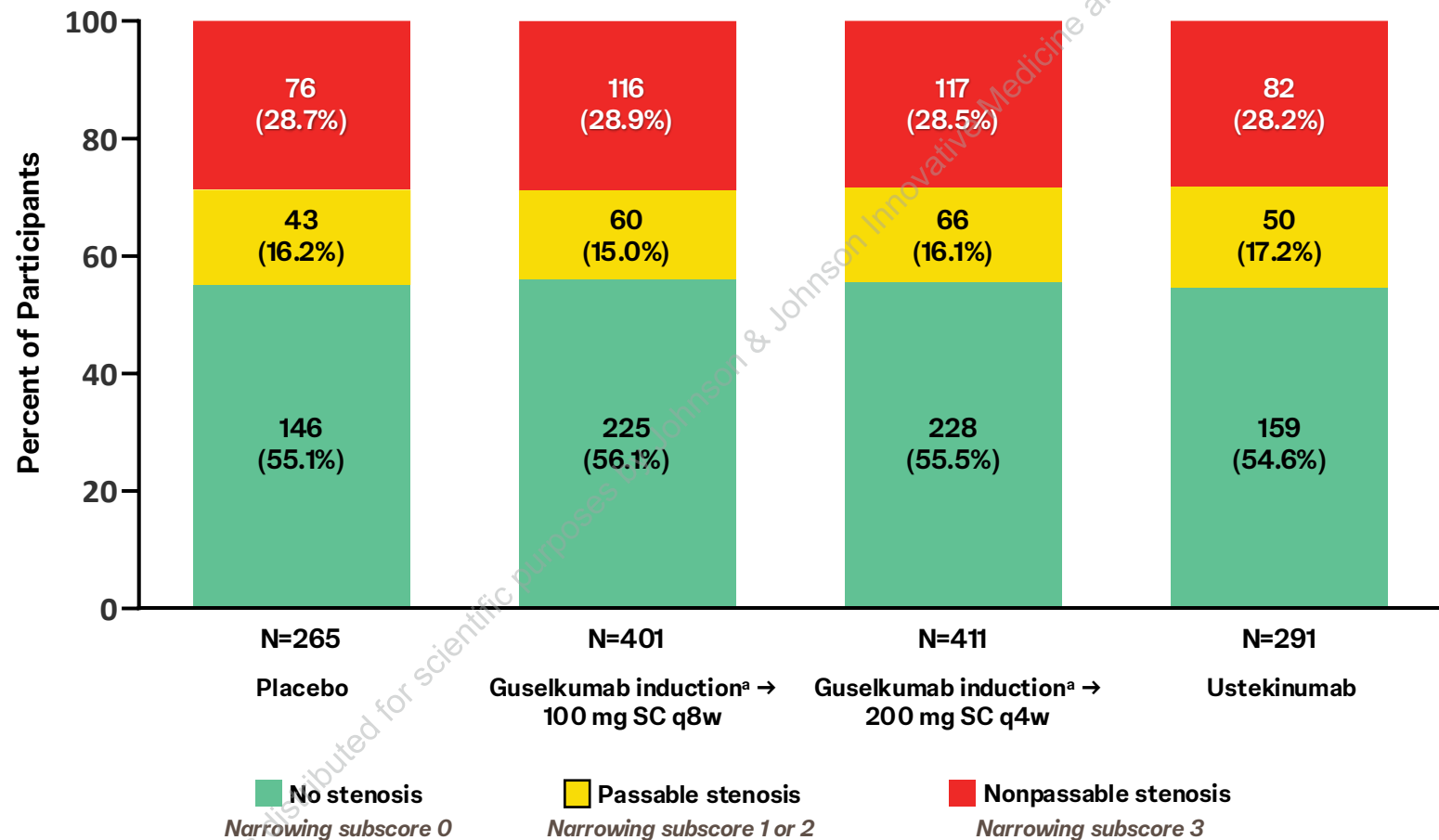
SES-CD narrowing (stenosis) component

- 0** No narrowing
- 1** Single narrowing, can be passed
- 2** Multiple narrowings, can be passed
- 3** **Narrowing that cannot be passed (non-passable)**

Scored per ileocolonic segment; narrowing is 1 of 4 SES-CD components.

Baseline Distribution of Stenoses Across Treatment Arms:

GALAXI 2 & 3 and GRAVITI



IV= intravenous; SC= subcutaneous.
^a Guselkumab 200 mg IV or 400 mg SC at Weeks 0, 4, and 8.

Baseline Disease Characteristics in Participants With Non-passable Stenoses at Study Entry

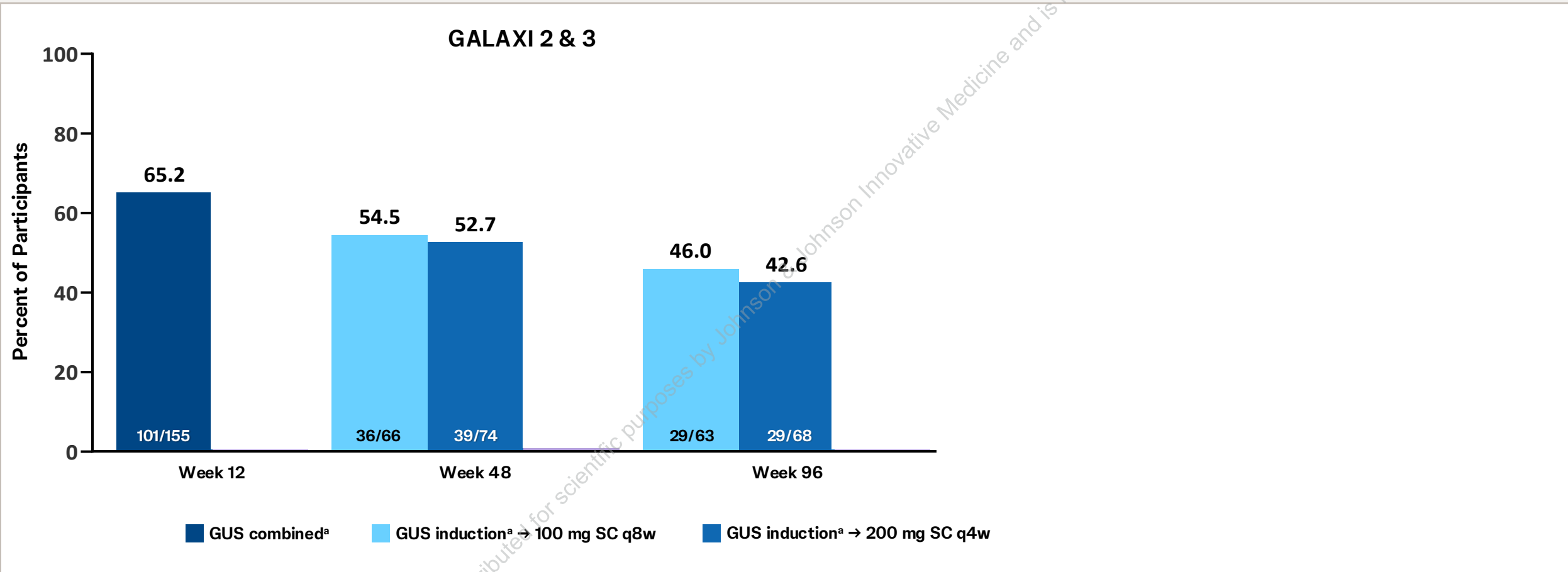
	GALAXI 2 & 3			GRAVITI	
	Non-passable stenosis at baseline			Non-passable stenosis at baseline	
	GUS 100 ^a N=76	GUS 200 ^b N=82	UST ^c N=82	GUS 100 ^d N=40	GUS 200 ^e N=35
CD duration in years, median (IQR)	4.88 (1.69; 9.43)	5.02 (1.85; 10.98)	6.05 (3.02; 10.81)	3.90 (1.15; 9.28)	5.80 (3.61; 12.84)
CDAI score, median (IQR)	298.0 (253.5; 342.0)	274.0 (251.0; 336.0)	290.0 (261.0; 331.0)	280.5 (250.0; 320.0)	291.0 (264.0; 351.0)
SES-CD score, median (IQR)	10.0 (7.0; 15.0)	9.5 (7.0; 15.0)	10.0 (7.0; 16.0)	9.0 (7.0; 12.5)	10.0 (6.0; 16.0)
Ulcer component ^f	5.0 (3.0; 8.0)	4.0 (3.0; 7.0)	5.0 (3.0; 8.0)	4.0 (2.5; 6.0)	5.0 (2.0; 9.0)
Stricture component ^g	3.0 (3.0; 3.0)	3.0 (3.0; 3.0)	3.0 (3.0; 3.0)	3.0 (3.0; 3.0)	3.0 (3.0; 3.0)
No history of intestinal resection surgery, ^h n (%)	63 (82.9%)	61 (74.4%)	58 (70.7%)	27 (67.5%)	29 (82.9%)
Non-passable stenosis location by central reader, ⁱ n (%)					
Ileum	31 (40.8%)	36 (43.9%)	36 (43.9%)	18 (45.0%)	16 (45.7%)
Right colon	35 (46.1%)	32 (39.0%)	38 (46.3%)	17 (42.5%)	16 (45.7%)
Transverse colon	3 (3.9%)	7 (8.5%)	5 (6.1%)	1 (2.5%)	3 (8.6%)
Left colon	6 (7.9%)	6 (7.3%)	2 (2.4%)	4 (10.0%)	0
Rectum	1 (1.3%)	1 (1.2%)	1 (1.2%)	0	0
Biologic medication history, n (%)					
Bionai ^{ve}	35 (46.1%)	37 (45.1%)	31 (37.8%)	23 (57.5%)	13 (37.1%)
History of inadequate response/intolerance ^j to biologic therapy	32 (42.1%)	39 (47.6%)	49 (59.8%)	14 (35.0%)	19 (54.3%)

CD= Crohn's disease; CDAI= Crohn's disease activity index; GUS= guselkumab; IQR= interquartile range; IV= intravenous; SC= subcutaneous; SES-CD= simple endoscopic score for Crohn's disease; UST= ustekinumab.

^a Participants randomized to guselkumab 200 mg IV q4w → 100 mg SC q8w. ^b Participants randomized to guselkumab 200 mg IV q4w → 200 mg SC q4w. ^c Participants randomized to ustekinumab ~6 mg/kg IV → 90 mg SC q8w. ^d Participants randomized to guselkumab 400 mg SC q4w → 100 mg SC q8w. ^e Participants randomized to guselkumab 400 mg SC q4w → 200 mg SC q4w. ^f Includes the presence and size of ulcers component and extent of ulcerated surface component. ^g Includes the presence and type of narrowings component across all evaluable segments. ^h Includes participants who did not have a "Total or Sub-total colectomy" or a "Partial bowel resection" or a "Other Crohn's Disease related surgery" prior to study entry. ⁱ The first non-passable stenosis encountered (distal to proximal) is the one whose location is being reported. ^j Primary nonresponse, secondary nonresponse, or intolerance.

Persistence of Non-passable Stenosis Through Week 96:

Participants with non-passable stenosis at baseline



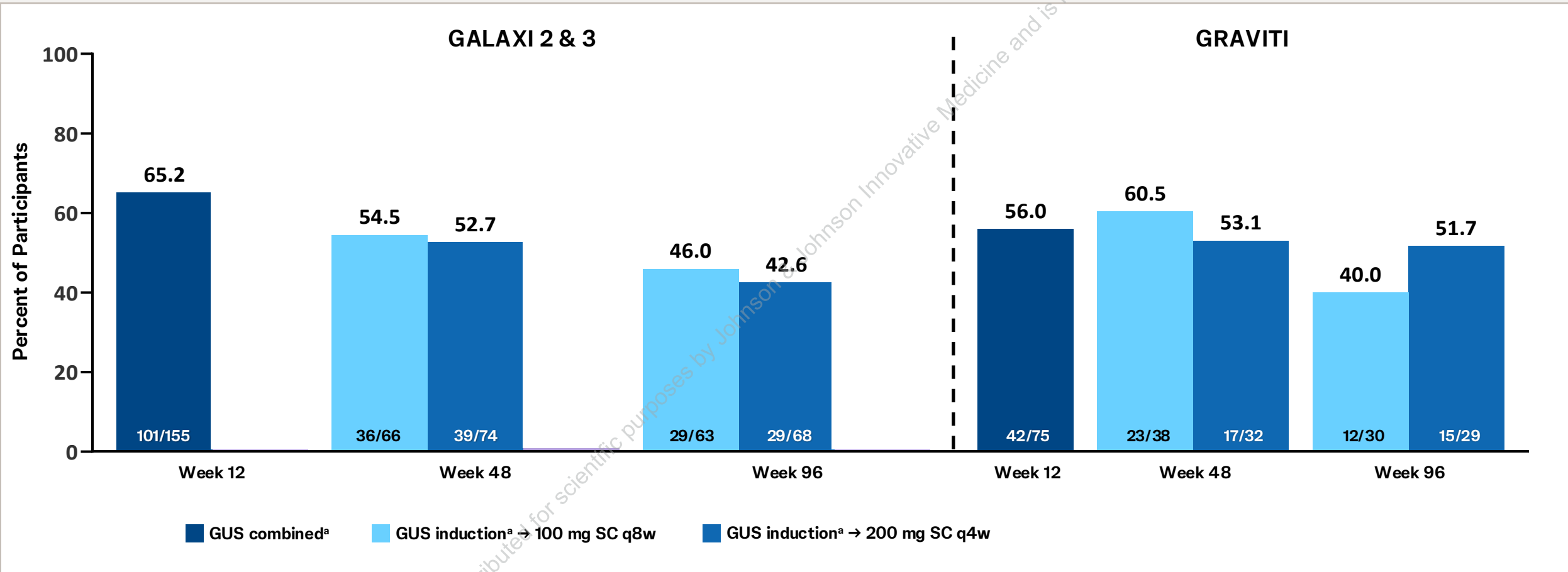
GUS= guselkumab; IV= intravenous; SC= subcutaneous; SES-CD=simple endoscopic score for Crohn's disease; UST= ustekinumab.

^a Guselkumab 200 mg IV or 400 mg SC at Weeks 0, 4, and 8.

Note: Denominators are defined as participants with non-passable stenosis at baseline minus the missing SES-CD data at the respective time point. Missing SES-CD data is defined as participants who had a non-passable stenosis at baseline and did not have a dilation procedure or an intestinal resection surgery prior to the respective timepoint, and did not have any SES-CD data at the respective timepoint, so it was unknown whether they improved.

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Participants with non-passable stenosis at baseline



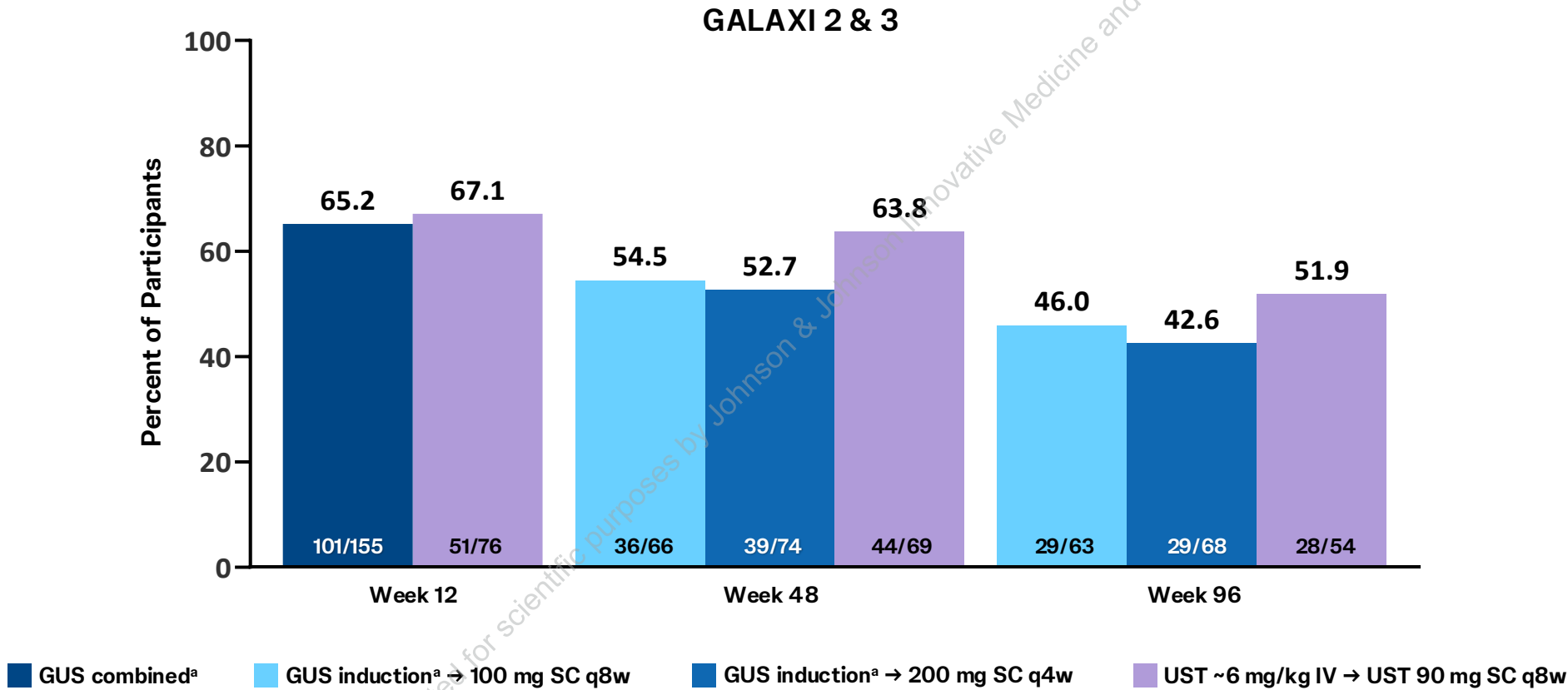
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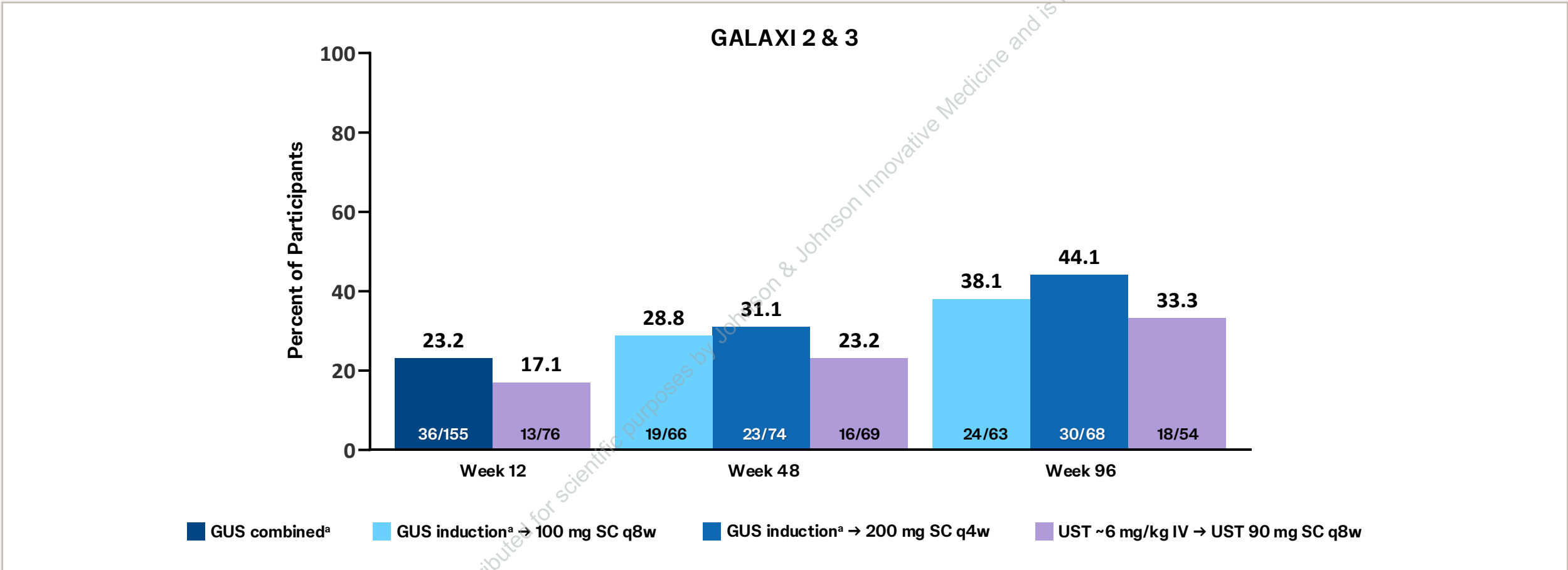
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Resolution to No Stenosis Through Week 96:

Participants with non-passable stenosis at baseline



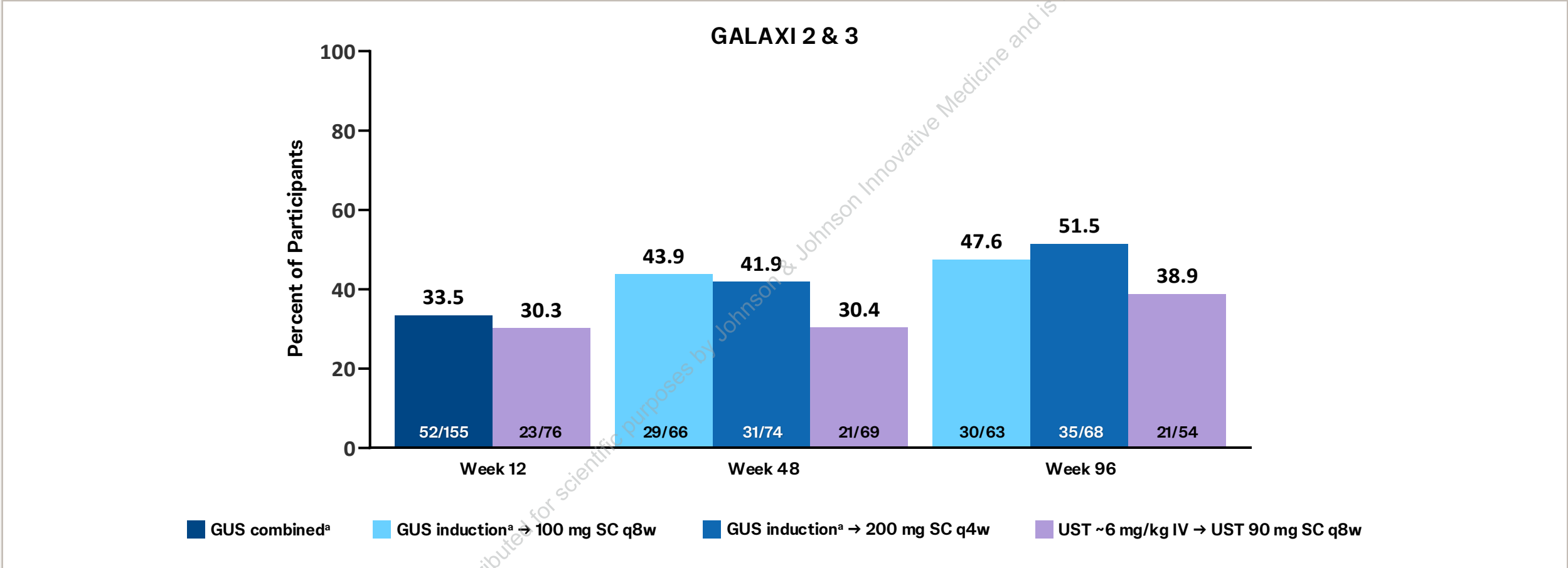
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Improvement to Passable or No Stenosis Through Week 96:

Participants with non-passable stenosis at baseline



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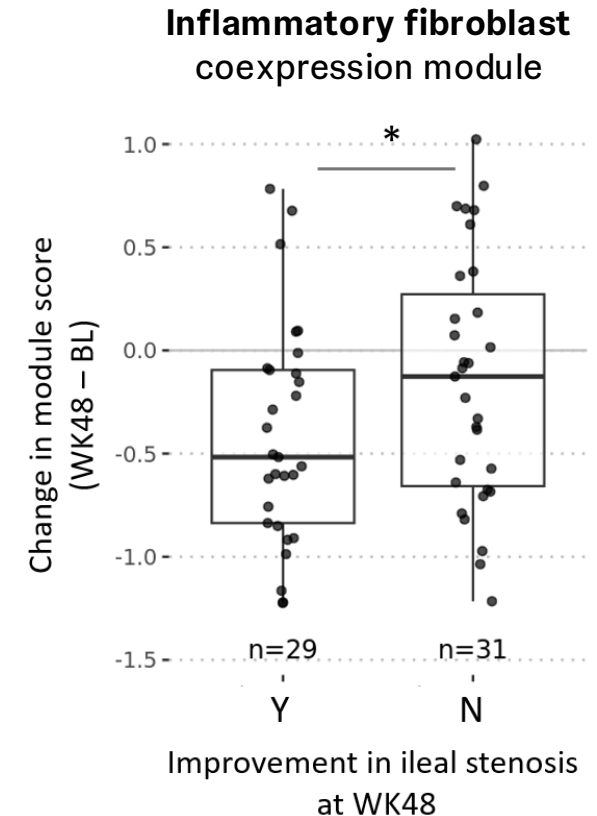
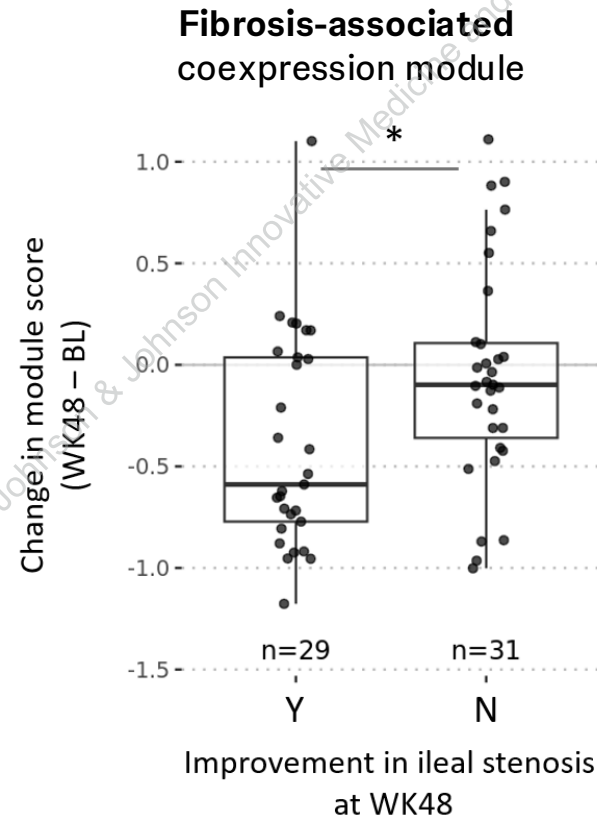
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Inflammatory and Fibrosis-related Biology is Reduced in Participants With Improved Ileal Stenosis

Analysis approach

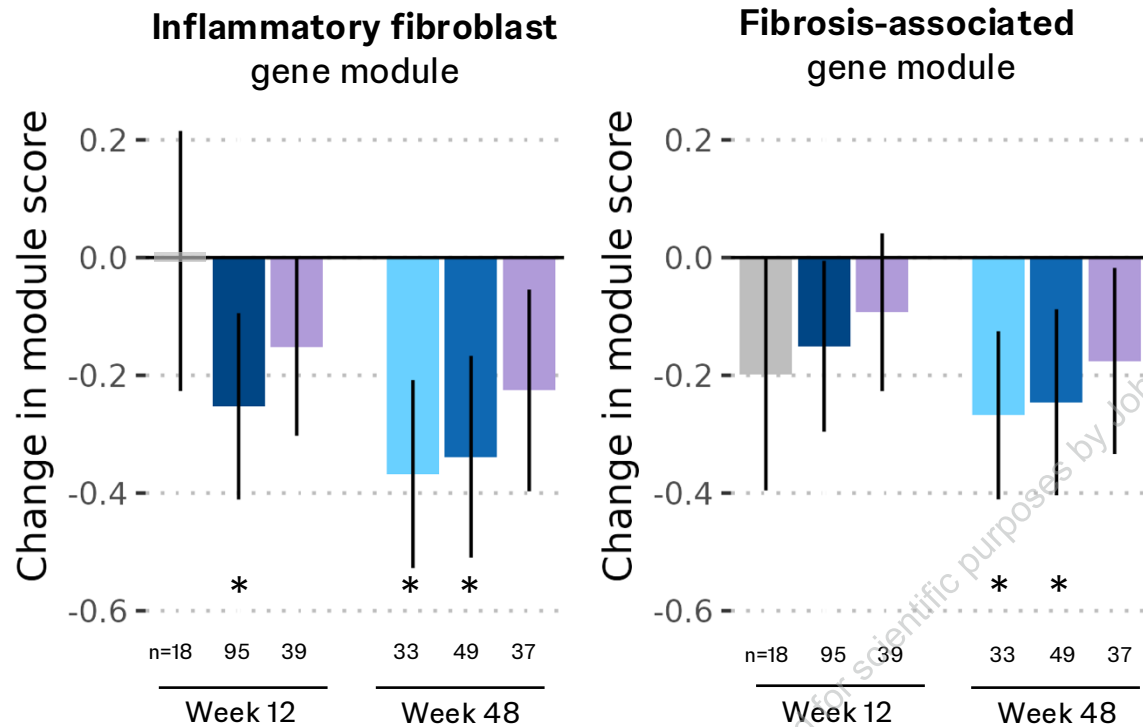
- Single cell-based gene correlation network analysis in IBD data defines fibroblast-derived gene coexpression modules for bulk disease interpretation¹
- RNA-sequencing of ileum biopsies in subset of participants in GALAXI (total set) were collected at Weeks 0, 12, 48 to evaluate changes in fibroblast-associated biology
 - ~33% of samples were from participants with any ileal stenosis at baseline (stenotic subset)



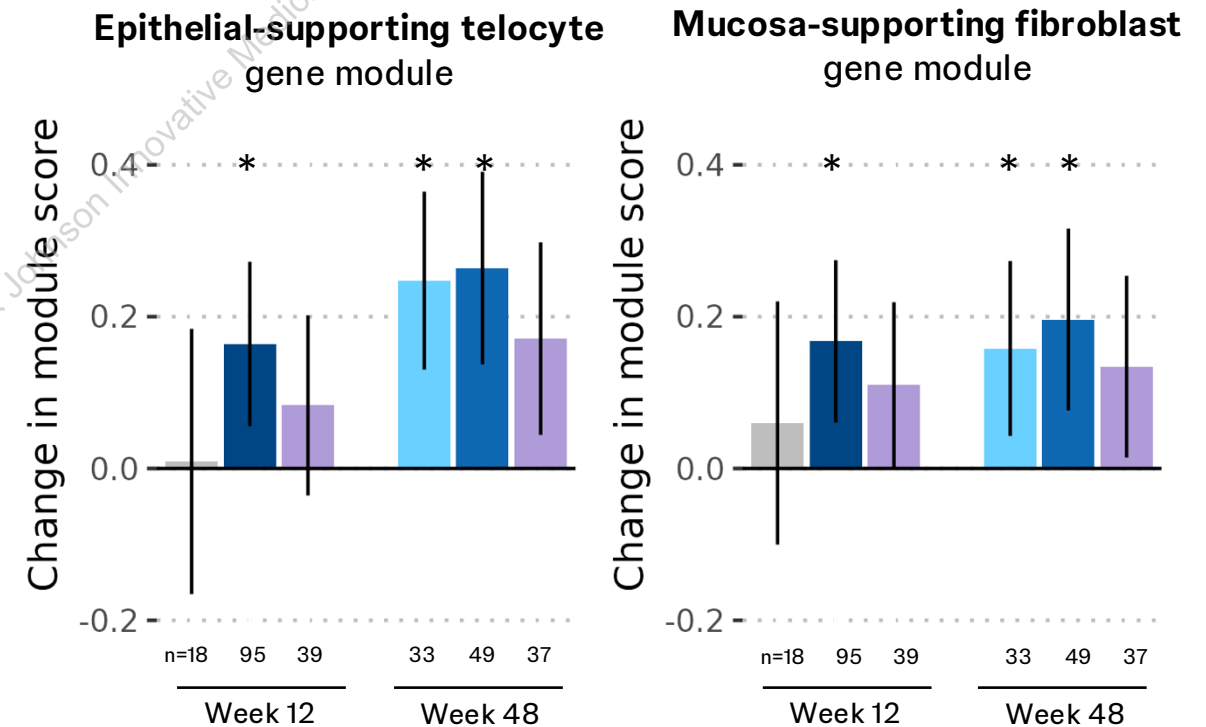
* P-value < 0.05 Independent t-test; Analysis in stenotic subset

Reduction of Inflammatory Fibroblast Biology at Week 12 With Guselkumab is Followed by Further Reduction in Fibrosis-related Biology by Week 48 in Ileum

Inflammation-associated biology



Homeostatic stromal biology



■ Placebo ■ GUS combined^a ■ GUS induction^a → 100 mg SC q8w ■ GUS induction^a → 200 mg SC q4w ■ UST ~6 mg/kg IV → UST 90 mg SC q8w

* Adjusted p-value < 0.05; Analysis in total set from pooled GALAXI 2 & 3

Linear mixed effect model: Fibroblast modules ~ treatment time contrasts with participant random effect

^a Guselkumab 200 mg IV at Weeks 0, 4, and 8.

Key Takeaways

- Among participants with moderately to severely active Crohn's disease and non-passable stenosis at baseline, improvement to passable or no stenosis was observed as early as Week 12 with guselkumab and was maintained through 2 years
- Guselkumab induced greater and earlier improvement in disease-associated fibroblast biology in the ileum, while ustekinumab showed limited changes
- These findings suggest that guselkumab may improve endoscopic intestinal stenosis while inducing early changes in stenosis-associated fibroblast biology

Acknowledgments

The authors thank the participants, investigators, and study personnel who made the GALAXI and GRAVITI studies possible

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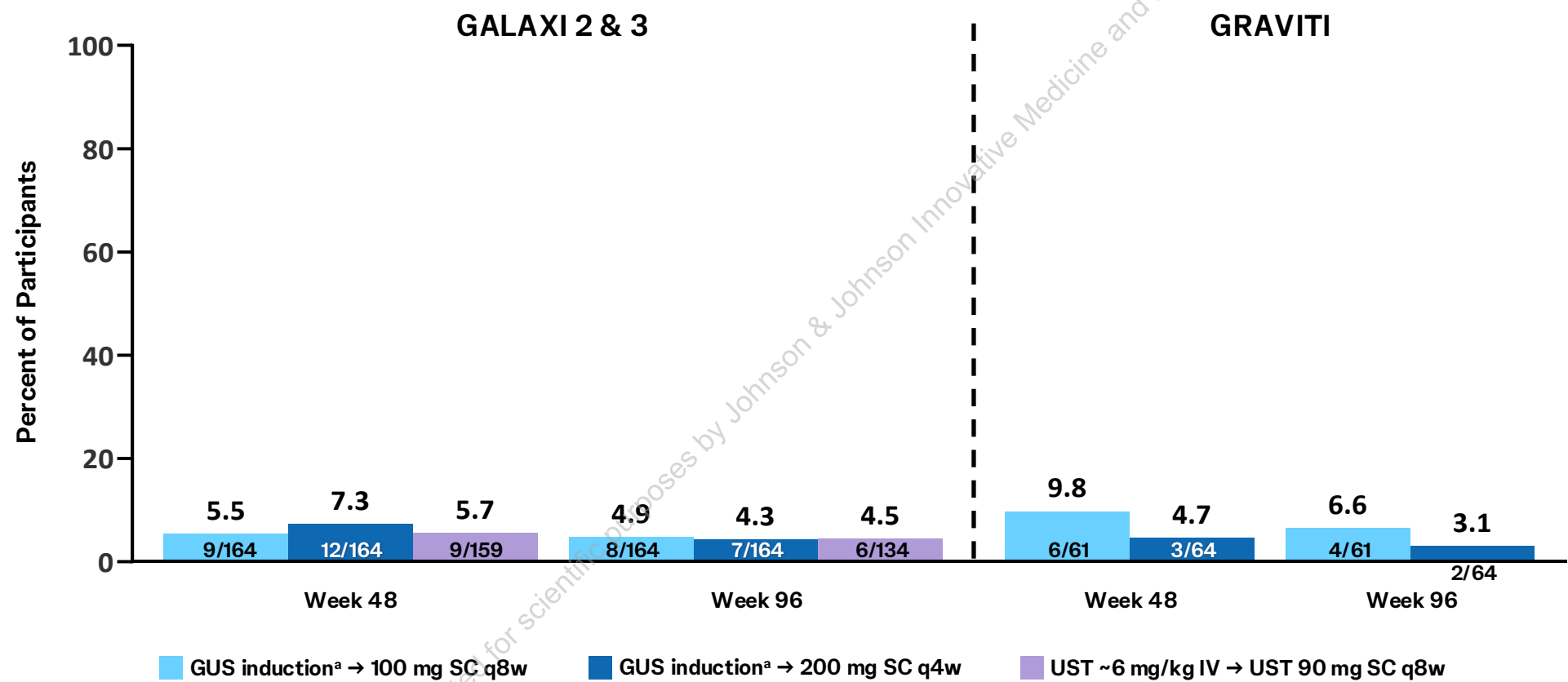
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Back-up

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De Novo Non-passable Stenosis Through Week 96:

Participants with no stenosis at baseline



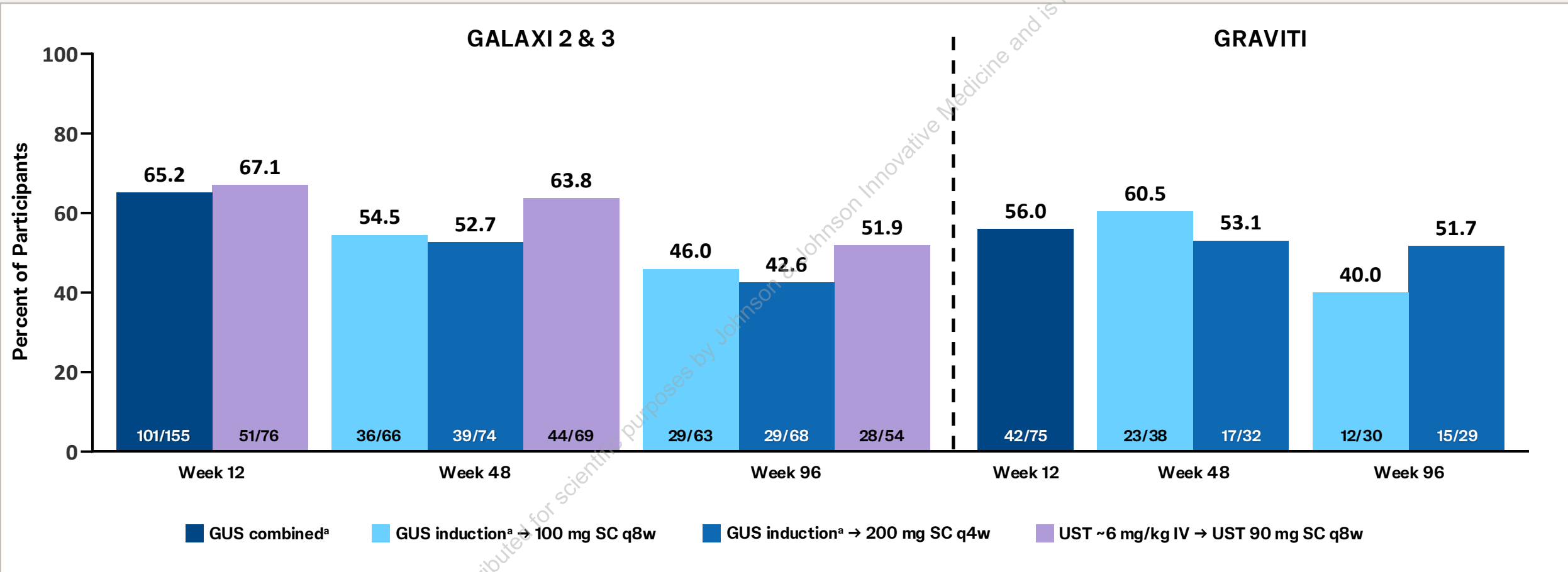
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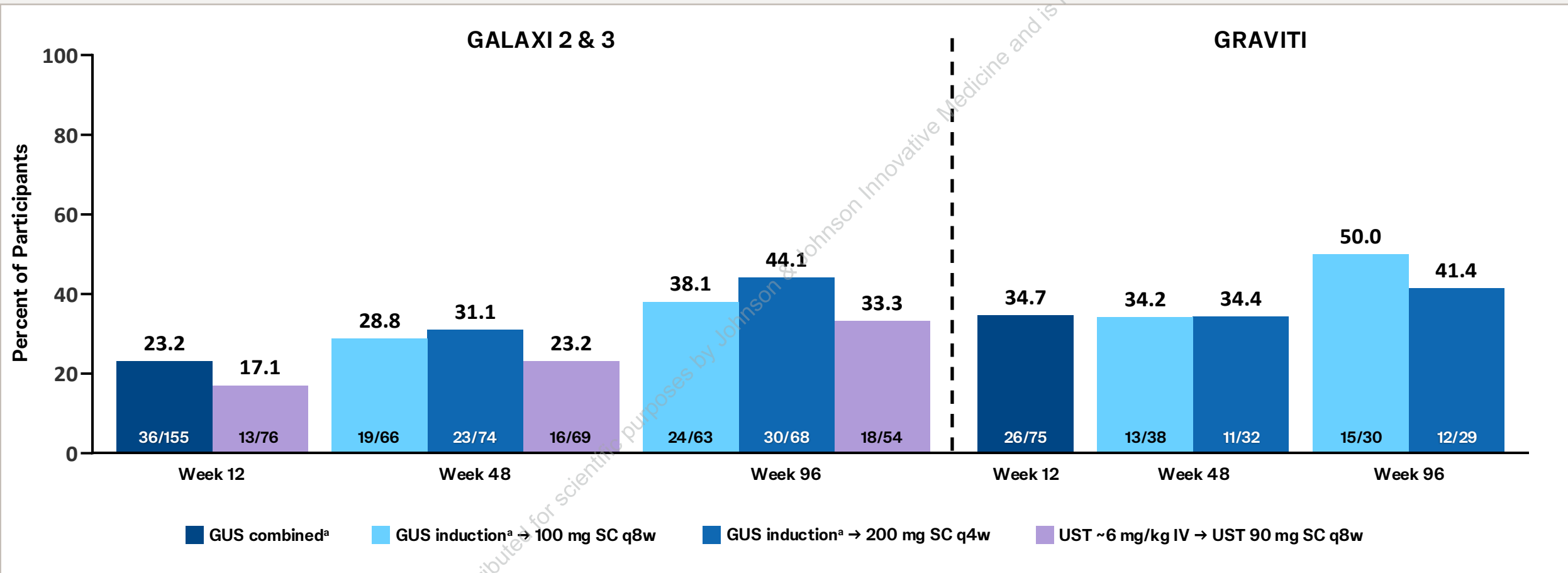
Participants with non-passable stenosis at baseline



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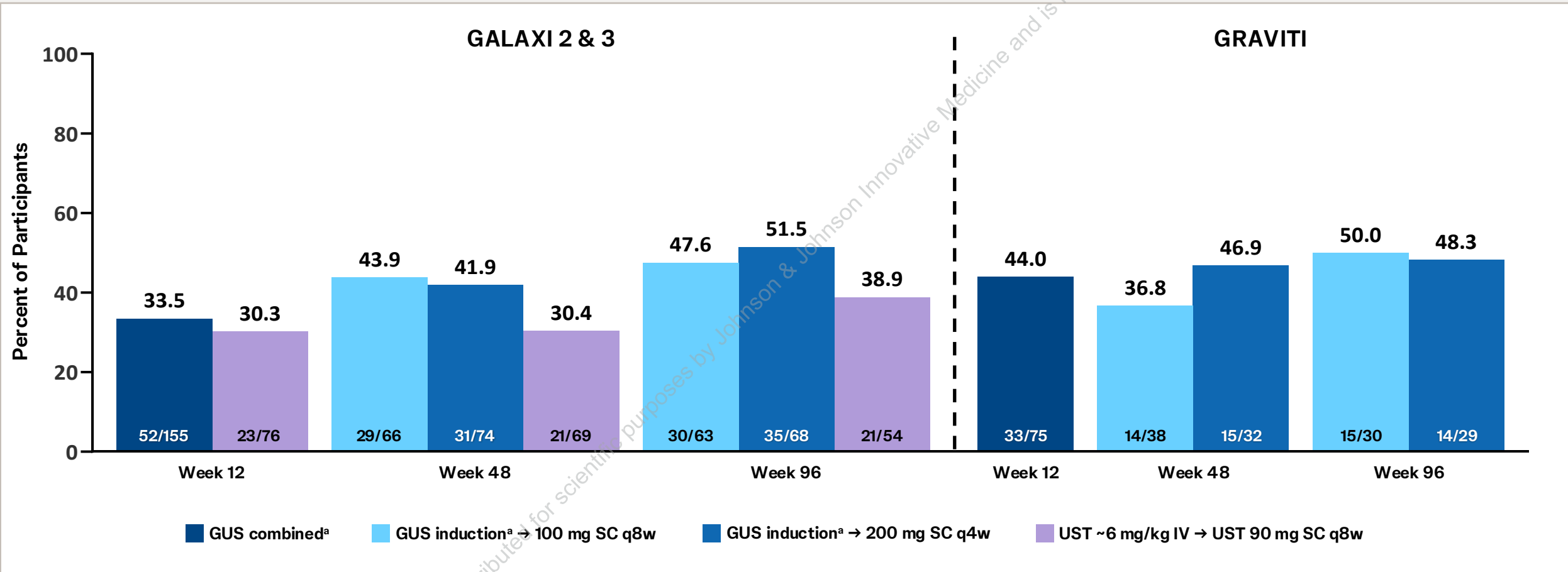
Participants with non-passable stenosis at baseline



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