EFFICACY AND SAFETY OF THE FIRST CO-ANTIBODY THERAPY, JNJ-78934804, IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS REFRACTORY TO SYSTEMIC THERAPIES

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Disclosure Information

Maria T. Abreu

I disclose the following financial relationship(s) with a commercial interest

Consultant/advisory board member for AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly and Company, Genentech, Gilead Sciences, Johnson & Johnson, Pfizer, Takeda, and UCB

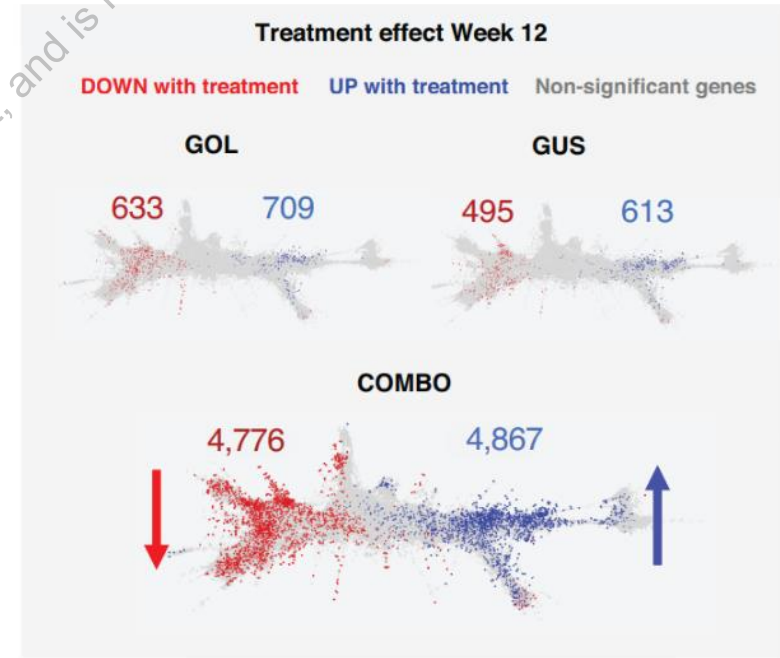
Background

In the Phase 2a VEGA study in ulcerative colitis,[1,2] guselkumab and golimumab combination therapy showed higher efficacy over either monotherapy

This combination was informed by preclinical evidence of complementary and distinct IL-23 and TNF-α activity, with molecular synergy demonstrated in VEGA

JNJ-4804 (JNJ-78934804; guselkumab and golimumab fixed-dose combination), the first co-antibody therapy in IBD, aims to address the high unmet need in patients with disease refractory to current systemic therapies

Molecular synergy observed in VEGA



Combination associated with reduced inflammation and restoration of epithelial repair[3]

[1]Feagan BG, et al. *Lancet Gastroenterol Hepatol.* 2023;8(4):307–320. [2]VEGA was an anti-TNF-naïve study population. [3]Desai P, et al. *Am J Gastroenterol.* 2022;117(10S):e527. "Systemic therapies" are also referred to as "advanced therapies" (biologics and small molecules).

***COMBO**=combination golimumab + guselkumab, **GOL**=golimumab, **GUS**=guselkumab, **IBD**=inflammatory bowel disease, **IL**=interleukin, **TNF**=tumor necrosis factor.*

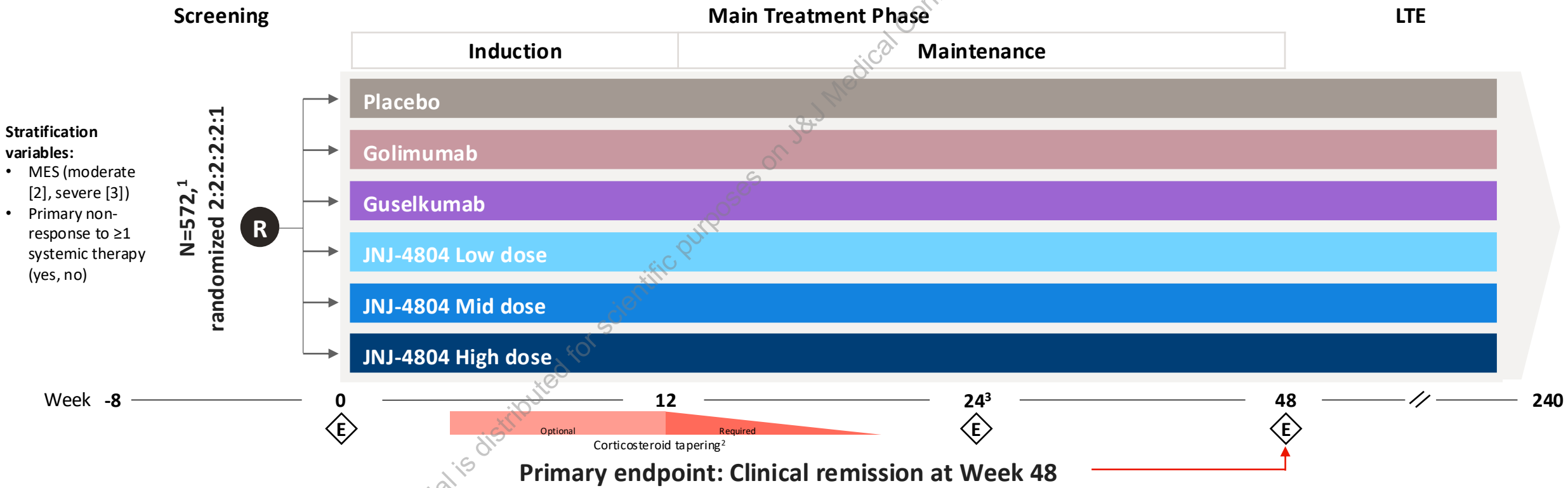
Objective

The Phase 2b DUET-UC trial (NCT05242484) evaluated the efficacy and safety of **JNJ-4804** compared with the component monotherapies in patients with moderately to severely active ulcerative colitis refractory to systemic therapies

***UC**=ulcerative colitis.*

DUET-UC: Phase 2b Randomized, Double-Blind, Active- and Placebo-Controlled Treat-Through Study in a Refractory Population

- Moderately to severely active UC
- Inadequate response or intolerance to ≥1 systemic therapy mechanism (anti-TNF, IL-12/23, IL-23p19, integrin, JAK inhibitor, or S1PR modulator)
- Caps for prior systemic therapy mechanisms: 1 (50%), 2 (35%), >2 (15%)
- All study medications were administered subcutaneously



[1]Full Analysis Set; 559 were included in the modified Full Analysis Set (13 did not meet mMayo inclusion criteria at baseline).
[2]Participants taking corticosteroids at Week 0 could begin tapering as early as Week 4 but no later than Week 12.
[3]Participants who met inadequate response criteria at Week 24 received a JNJ-4804 regimen (regardless of treatment assignment).
***E**=endoscopy, **IL**=interleukin, **JAK**=Janus kinase, **LTE**=long-term extension, **MES**=Mayo Endoscopic Score, **mMayo**=modified Mayo, **R**=randomization, **S1PR**=sphingosine-1-phosphate receptor, **TNF**=tumor necrosis factor, **UC**=ulcerative colitis.*

Endpoints and Statistical Considerations

Primary endpoint

- Clinical remission at Week 48

Other key endpoints

- Endoscopic improvement
- Histologic remission AND endoscopic improvement
- Corticosteroid-free clinical remission

Statistical considerations

- Participants who met prespecified treatment failure rules or had missing data were considered not to have met endpoints[1]
- Participants who met rescue criteria were considered treatment failures at Week 48[1]
- Analyses of subpopulations by systemic therapy history were prespecified[2] but not multiplicity controlled

[1]Participants were considered not to have met the Week 48 endpoint if any of the following occurred prior to Week 48: An ostomy or colectomy (partial or total); prohibited change in UC medication; treatment escalation due to inadequate response at Week 24; discontinuation of study treatment due to lack of efficacy or an AE of worsening UC; discontinuation of study treatment due to COVID-19 infection or any other reason. Participants who discontinued study treatment for COVID-19-related reasons (excluding COVID-19 infection) had their observed data used, if available. Missing data imputation: After accounting for these conditions, participants with missing Mayo subscores (any or all) at Week 48 (for clinical remission and corticosteroid-free clinical remission), missing endoscopy subscores at Week 48 (for endoscopic improvement and HREI), or missing histology data at Week 48 (for HREI) were considered not to have met the endpoint at Week 48.

[2]Analyses of subpopulations with 1, 2, and >2 prior systemic therapy mechanisms-IR were prespecified; the combined ≥2 systemic therapy mechanisms-IR subpopulation was evaluated based on these results.

***AE**=adverse event, **HREI**=histologic remission AND endoscopic improvement, **IR**=inadequate response or intolerance, **UC**=ulcerative colitis.*

Baseline Demographics, Disease Characteristics, and Concomitant Medications

		Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose	Total
Full analysis set		52	104	103	103	105	105	572
Age in years, mean (SD)		38.6 (11.51)	38.5 (12.86)	40.3 (12.32)	39.8 (13.44)	39.6 (13.27)	38.0 (12.05)	39.2 (12.66)
Sex, n (%)	**Male**	33 (63.5%)	59 (56.7%)	54 (52.4%)	57 (55.3%)	61 (58.1%)	62 (59.0%)	326 (57.0%)
UC disease duration, years	**Mean (SD)**	9.3 (6.95)	8.5 (7.40)	9.4 (6.81)	9.7 (8.21)	8.9 (7.23)	8.9 (8.24)	9.1 (7.52)
Extent of disease, n (%)	**Extensive**	22 (42.3%)	50 (48.1%)	56 (54.4%)	52 (50.5%)	48 (45.7%)	49 (46.7%)	277 (48.4%)
mMayo Score[1]	**Mean (SD)**	7.0 (1.24)	7.1 (1.02)	7.0 (1.28)	7.0 (1.09)	7.2 (1.30)	7.1 (1.13)	7.1 (1.17)
Severity of UC disease, n (%)[1]	**Severe (mMayo Score 7–9)**	37 (71.2%)	71 (68.9%)	69 (67.6%)	74 (72.5%)	72 (69.2%)	75 (72.1%)	398 (70.2%)
Mayo Endoscopy Subscore, n (%)	**Subscore of 3 (severe)**	37 (71.2%)	78 (75.0%)	73 (70.9%)	73 (70.9%)	76 (72.4%)	73 (69.5%)	410 (71.7%)
Abnormal fecal calprotectin (>250 mg/kg)[2]	**n (%)**	41 (85.4%)	92 (95.8%)	83 (89.2%)	86 (91.5%)	80 (89.9%)	81 (91.0%)	463 (91.0%)
Fecal calprotectin (mg/kg)[2]	**Median**	1551.7	1689.5	1789.8	2220.4	1798.3	1634.0	1744.0
Concomitant medications at baseline								
Immunomodulators		5 (9.6%)	16 (15.4%)	14 (13.6%)	20 (19.4%)	17 (16.2%)	11 (10.5%)	83 (14.5%)
Oral corticosteroids		20 (38.5%)	38 (36.5%)	45 (43.7%)	36 (35.0%)	52 (49.5%)	51 (48.6%)	242 (42.3%)

[1]Means or percentages are based on the following numbers of participants with non-missing data: 52 (placebo), 103 (golimumab), 102 (guselkumab), 102 (JNJ-4804 low dose), 104 (JNJ-4804 mid dose), 104 (JNJ-4804 high dose), 567 (total).
[2]Medians or percentages are based on the following numbers of participants with non-missing data: 48 (placebo), 96 (golimumab), 93 (guselkumab), 94 (JNJ-4804 low dose), 89 (JNJ-4804 mid dose), 89 (JNJ-4804 high dose), 509 (total).
***mMayo**=modified Mayo, **UC**=ulcerative colitis.*

Highly Treatment-Refractory Population With Inadequate Response or Intolerance to Systemic Therapies

		Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose	Total
Full analysis set		52	104	103	103	105	105	572
Participants with inadequate response to 1 or more systemic therapy mechanisms[1]								
Number of systemic therapy mechanisms - inadequate responders, n (%)[2]	**1**	30 (58.8%)	56 (53.8%)	51 (49.5%)	63 (61.2%)	58 (55.2%)	58 (55.8%)	316 (55.4%)
	≥2	21 (41.2%)	48 (46.2%)	52 (50.5%)	40 (38.8%)	47 (44.8%)	46 (44.2%)	254 (44.6%)

44.6% were refractory to 2 or more systemic therapy mechanisms

History of inadequate response or intolerance by system therapy mechanism in the overall population

- Anti-TNF: 74%
- Anti-integrin: 44%
- JAK inhibitor: 26%
- Ustekinumab: 19%
- S1PR modulator: 4%
- Anti-IL-23: 1%

60% of participants with disease refractory to 1 systemic therapy had inadequate response to an anti-TNF only

[1]Anti-TNF, anti-IL-12/23, anti-IL-23p19, anti-integrin, JAK inhibitor, and S1PR modulator
[2]Denominators are the numbers of participants with inadequate response to 1 or more systemic therapy mechanisms.
***JAK**=Janus kinase, **S1PR**=sphingosine-1-phosphate receptor, **TNF**=tumor necrosis factor, **UC**=ulcerative colitis.*

Treatment Disposition Through Week 48

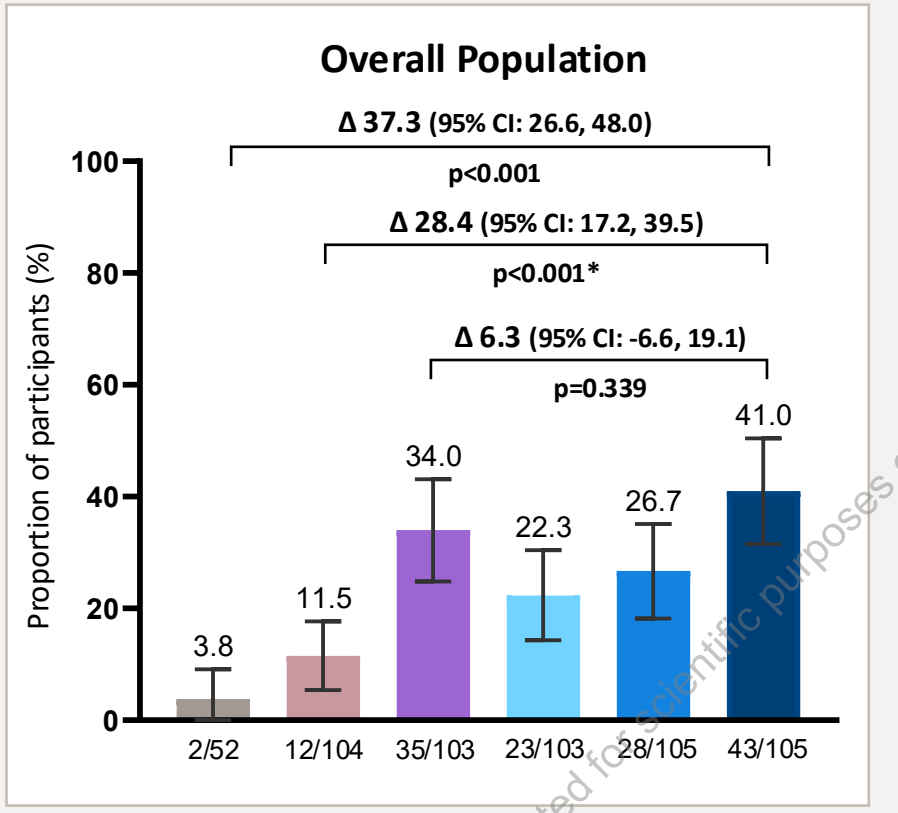
Lowest Discontinuation Rates Observed in JNJ-4804 High-Dose Group

	Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose	Total
Full analysis set	52	104	103	103	105	105	572
Number of participants who:							
Discontinued study treatment before Week 48	17 (32.7%)	32 (30.8%)	23 (22.3%)	24 (23.3%)	23 (21.9%)	14 (13.3%)	133 (23.3%)
Most common reasons for discontinuation							
Lack of efficacy	3 (5.8%)	6 (5.8%)	13 (12.6%)	5 (4.9%)	7 (6.7%)	5 (4.8%)	39 (6.8%)
Withdrawal by participant	5 (9.6%)	11 (10.6%)	4 (3.9%)	6 (5.8%)	6 (5.7%)	2 (1.9%)	34 (5.9%)
Adverse event - worsening of UC	7 (13.5%)	11 (10.6%)	3 (2.9%)	5 (4.9%)	3 (2.9%)	5 (4.8%)	34 (5.9%)
Adverse event - other	0	2 (1.9%)	1 (1.0%)	4 (3.9%)	3 (2.9%)	0	10 (1.7%)
Initiated prohibited medication	1 (1.9%)	0	2 (1.9%)	1 (1.0%)	0	0	4 (0.7%)

Note: Final dosing for the main treatment period was received 4 weeks prior to Week 48. Participants are presented in the treatment group assigned at Week 0.

***UC**=ulcerative colitis.*

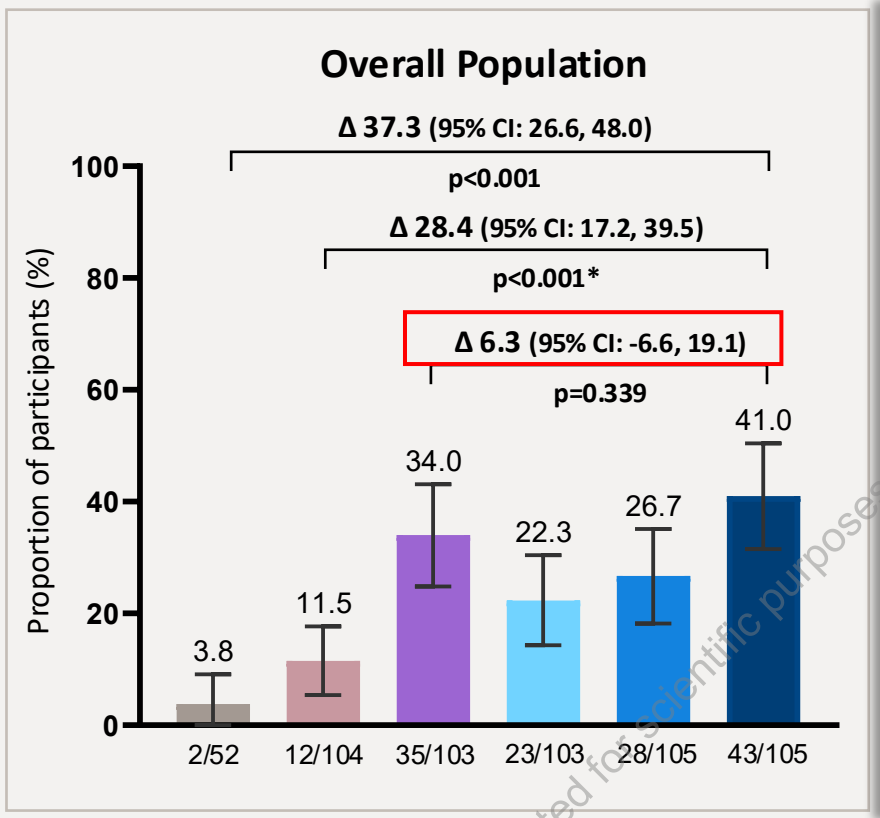
Primary Endpoint: Clinical Remission at Week 48

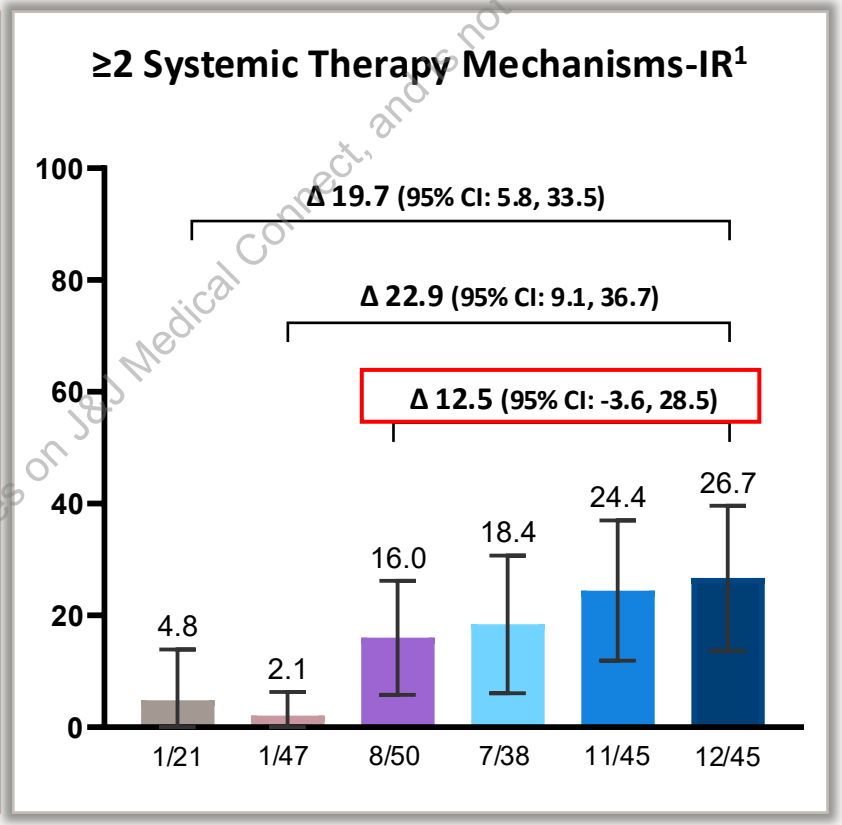


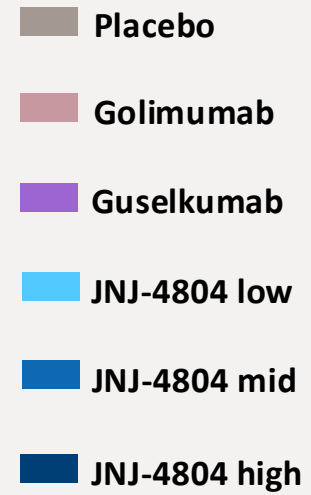
Clinical remission: stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopy subscore of 0 or 1 per central review of the video endoscopy

*Statistically significant. All other p-values are nominal.
***CI**=confidence interval.*

Primary Endpoint: Clinical Remission at Week 48







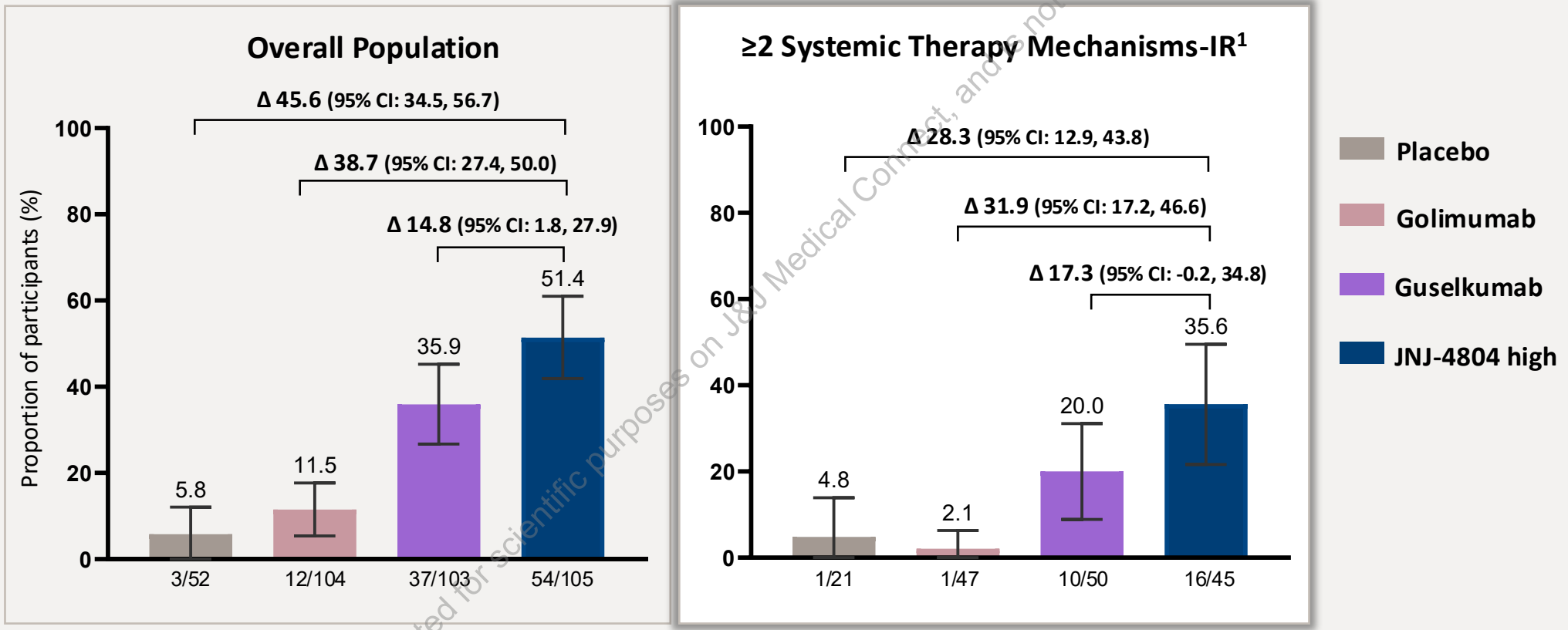
Clinical remission: stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopy subscore of 0 or 1 per central review of the video endoscopy

*Statistically significant. All other p-values are nominal.

[1]Patients who were inadequate responders to two or more mechanisms of systemic therapies. Modified Full analysis set (Full analysis set excluding participants with a modified Mayo <5 or missing at baseline).

***CI**=confidence interval, **IR**=inadequate response or intolerance.*

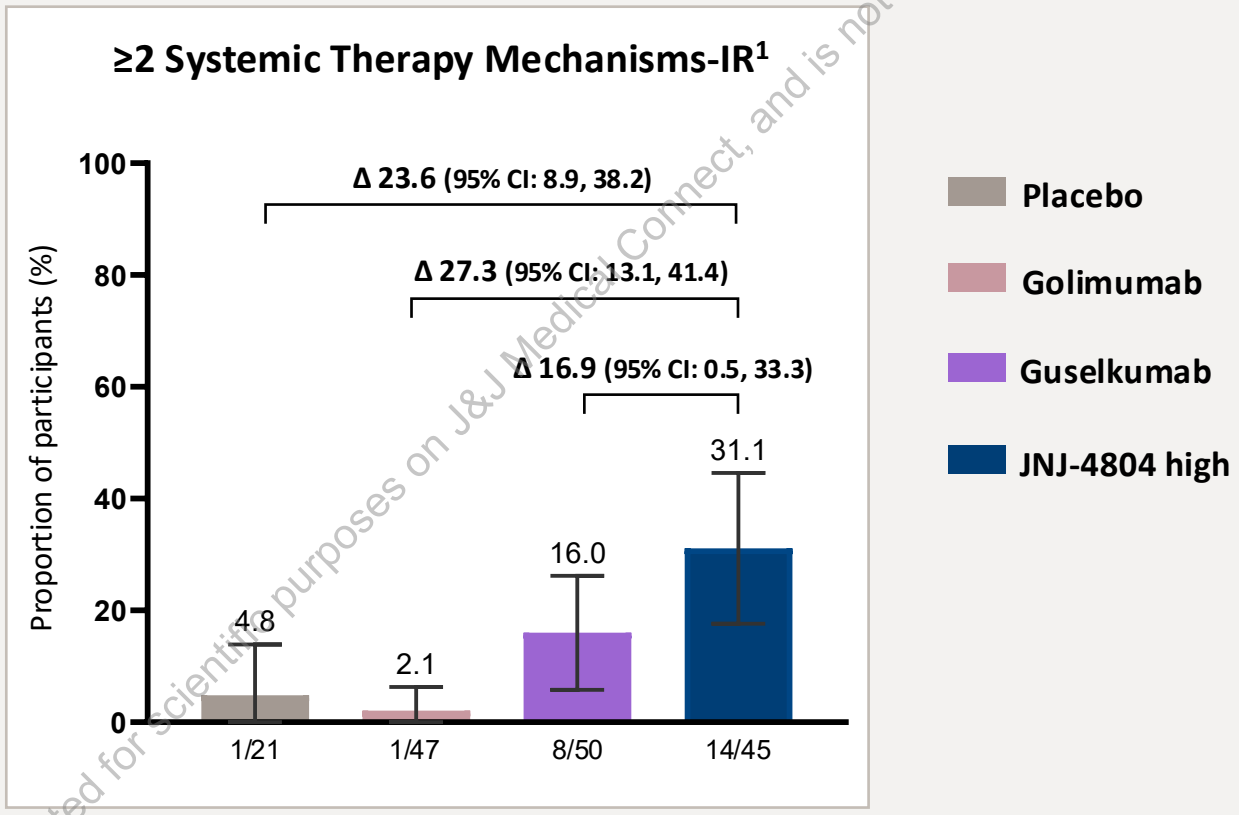
Key Secondary Endpoint: Endoscopic Improvement at Week 48



Endoscopic improvement: endoscopy subscore of 0 or 1 per central review of the video endoscopy

[1]Patients who were inadequate responders to two or more mechanisms of systemic therapies. Modified Full analysis set (Full analysis set excluding participants with a modified Mayo <5 or missing at baseline).
***CI**=confidence interval, **IR**=inadequate response or intolerance.*

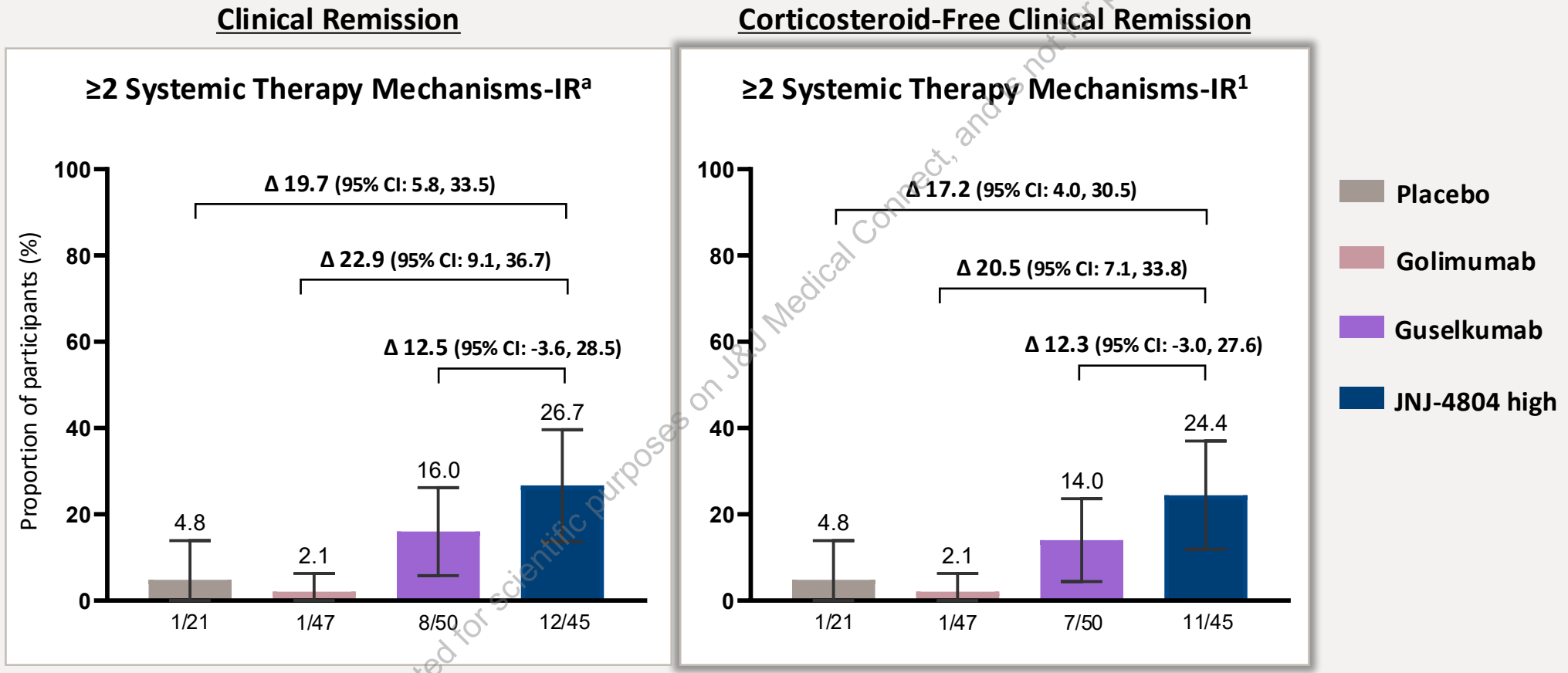
Key Secondary Endpoint: Histologic Remission AND Endoscopic Improvement at Week 48 (≥2 Systemic Therapy Mechanisms-IR Population)



Histologic remission AND endoscopic improvement: absence of neutrophils from the mucosa (both lamina propria and epithelium), no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system, and an endoscopy subscore of 0 or 1 per central review of the video endoscopy

[1]Patients who were inadequate responders to two or more mechanisms of systemic therapies. Modified Full analysis set (Full analysis set excluding participants with a modified Mayo <5 or missing at baseline).
***CI**=confidence interval, **IR**=inadequate response or intolerance.*

Key Secondary Endpoint: Corticosteroid-Free Clinical Remission at Week 48 (≥2 Systemic Therapy Mechanisms-IR Population)



Corticosteroid-free clinical remission: a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 per central review of the video endoscopy, with no corticosteroids received for at least 60 days

Of the participants in clinical remission at Week 48 in the JNJ-4804 high dose group, 11/12 (91.7%) were corticosteroid-free

[1]Patients who were inadequate responders to two or more mechanisms of systemic therapies. Modified Full analysis set (Full analysis set excluding participants with a modified Mayo <5 or missing at baseline).

***CI**=confidence interval, **IR**=inadequate response or intolerance.*

Summary of Exposure-Adjusted Adverse Events Through Week 48[1] (Overall Population)

	Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose	JNJ-4804 Combined
Safety analysis set	52	104	103	103	105	105	313
Total patient-years of follow-up	25.5	65.0	73.0	72.2	76.1	85.1	233.4
Events per hundred patient-years [number of events]							
AEs	490.2 [125]	449.2 [292]	419.0 [306]	405.7 [293]	385.1 [293]	490.1 [417]	429.7 [1003]
SAEs	27.5 [7]	21.5 [14]	9.6 [7]	19.4 [14]	11.8 [9]	10.6 [9]	13.7 [32]
AEs leading to discontinuation of study treatment	27.5 [7]	18.5 [12]	5.5 [4]	12.5 [9]	6.6 [5]	3.5 [3]	7.3 [17]
Infections	109.8 [28]	100.0 [65]	98.6 [72]	98.3 [71]	93.3 [71]	82.3 [70]	90.8 [212]
Serious infections	3.9 [1]	7.7 [5]	0.0 [0]	1.4 [1]	3.9 [3]	3.5 [3]	3.0 [7]
Deaths	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]

Most infections were mild or moderate and did not result in treatment discontinuation

The most frequently reported treatment-emergent AEs (reported in ≥5% of participants for all groups) were ulcerative colitis and nasopharyngitis

[1]Excludes inadequate responder events after treatment escalation at Week 24.

***AE**=adverse event, **SAE**=serious adverse event.*

Treatment-Emergent AEs of Interest Through Week 48[1]

	Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose
Safety analysis set	52	104	103	103	105	105
Major adverse cardiovascular events	0	1 (1.0%)	0	1 (1.0%)	0	0
Venous thromboembolism	0	3 (2.9%)	0	0	0	1 (1.0%)
Clinically important hepatic disorders	0	0	0	0	0	0
Opportunistic infection	0	0	1 (1.0%)	0	1 (1.0%)	0
Participants with ≥1 AE of special interest						
Invasive fungal infection	0	0	0	0	0	0
Hepatitis B reactivation	0	0	0	0	0	0
Tuberculosis	0	0	0	0	1 (1.0%)	0
Malignancy	0	0	1 (1.0%)	1 (1.0%)	1 (1.0%)	0
Hypersensitivity reaction	0	0	0	1 (1.0%)	0	0
Congestive heart failure	0	0	0	1 (1.0%)	0	0
Demyelinating disorders	0	0	0	0	0	0
Lupus-like syndrome	0	0	0	0	0	0

1 case of active tuberculosis (JNJ-4804 mid-dose), and 1 other opportunistic infection of esophageal candidiasis (GUS)

3 malignancies, all basal cell carcinomas, in participants with no prior history; all continued in study after excision

[1]Excludes inadequate responder events after treatment escalation at Week 24

***AE**=adverse event, **GUS**=guselkumab.*

Conclusions

- JNJ-4804, the first co-antibody therapy in development for IBD, delivered clinically meaningful efficacy exceeding that of the monotherapies in patients with treatment-refractory disease
- In the overall population, efficacy of high-dose JNJ-4804 was superior to golimumab and numerically greater than guselkumab
- In patients with disease refractory to two or more systemic therapy mechanisms, high-dose JNJ-4804 exceeded the additive effects of golimumab and guselkumab across all key clinical, endoscopic, and histologic-endoscopic endpoints
- The safety profile of JNJ-4804 through 48 weeks was consistent with the well-established safety profiles of the component monotherapies
- Building on the molecular synergy seen in VEGA, the DUET-UC results support advancement to Phase 3 in patients with disease refractory to systemic therapies, a population with high unmet need

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