Efficacy of Mirikizumab in Comparison to Ustekinumab in Patients With Moderate-to-Severe Crohn's Disease: Results From the Phase 3 VIVID-1 Study

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Disclosures (1 of 2)

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Background and Objective

Background

- Mirikizumab is a p19-directed anti–interleukin(IL)-23 antibody approved for the treatment of moderately-to-severely active ulcerative colitis (UC) and is under development for Crohn's disease (CD)[1,2]
- In the Phase 3 treat-through VIVID-1 study of patients with moderately-to-severely active CD, mirikizumab demonstrated statistically significant and clinically meaningful improvements in the co-primary and all key secondary endpoints vs. placebo[3]

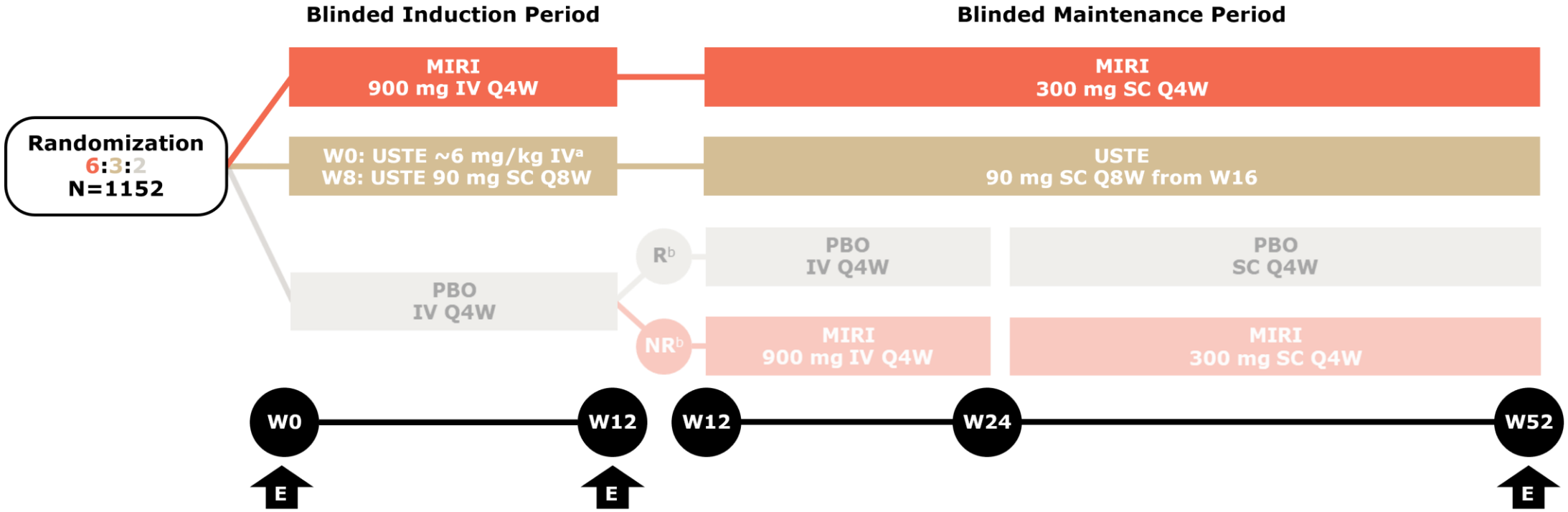
Objective

- To report the results of secondary endpoints from the Phase 3 VIVID-1 study (NCT03926130) for mirikizumab vs. ustekinumab, a p40-directed anti–IL-12/IL-23 inhibitor

1. OMVOH [Summary of Product Characteristics]. The Netherlands: Eli Lilly Nederland B.V., 2023. 2. Sands BE, et al. *Gastroenterology*. 2022;162:495-508.
3. Ferrante M, et al. Presentation at: *ECCO 2024.* Presentation OP05.

VIVID-1 Study Design

A Phase 3, Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled, Treat-Through Study



[a] Single dose; [b] Responders by PRO at Week 12 of VIVID-1, defined as having achieved ≥30% decrease in loose stool frequency and/or abdominal pain, with neither score higher than baseline. Notes: PBO was administered IV and SC from Weeks 8 to 20; otherwise administered IV at Weeks 0 and 4; from Week 24, PBO was administered SC only. Visits occurred every 2 weeks during induction except at W10 and every 4 weeks during maintenance

CDAI=Crohn's Disease Activity Index; E=endoscopy; IV=intravenous; MIRI=mirikizumab; NR=non-responder; PBO=placebo; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [stool frequency and abdominal pain]); Q4W=every 4 weeks; Q8W=every 8 weeks; R=responder; SC=subcutaneous; USTE=ustekinumab; W=Week

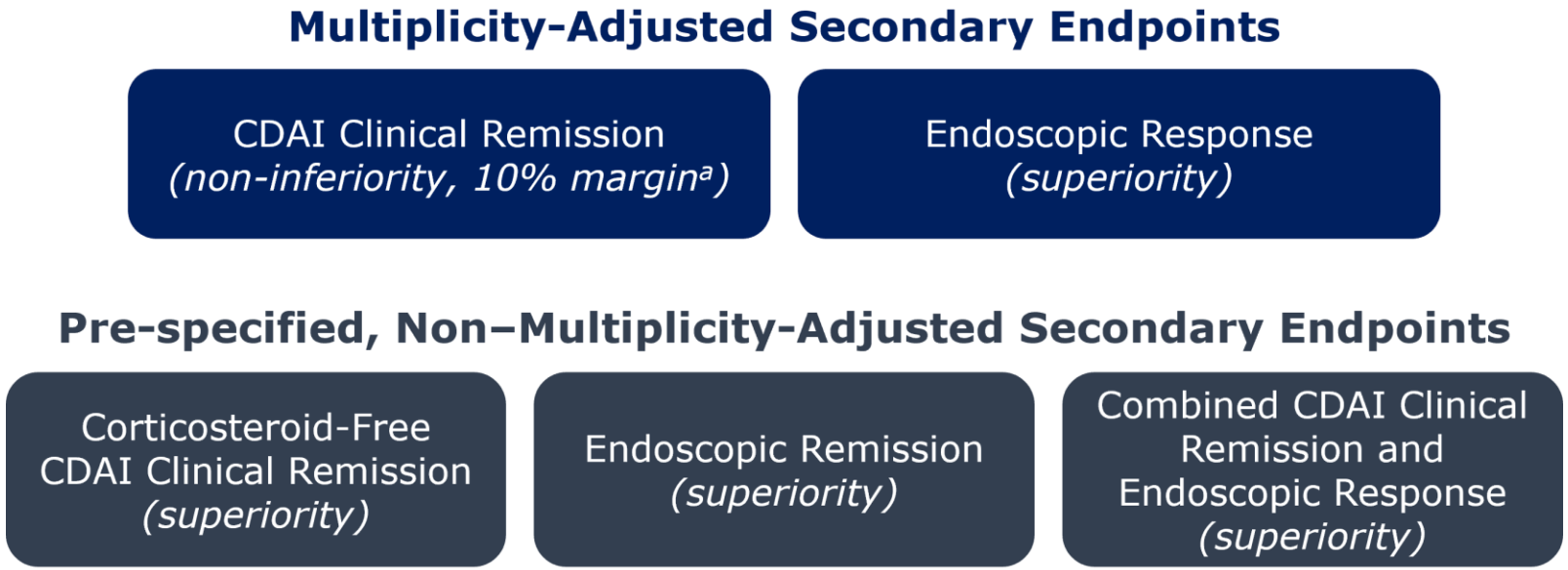
Key Eligibility Criteria

- Age ≥18 to ≤80 years
- Moderately-to-severely active CD:
  - Daily average loose stool frequency ≥4 and/or daily average abdominal pain score ≥2
  - Simple Endoscopic Score for CD (SES-CD) ≥7 for patients with ileal-colonic disease or ≥4 for patients with isolated ileal disease at screening [a]
- Had not previously received anti–IL-23 antibodies, except for a short course of ustekinumab (<3 doses and no failure or intolerance)
- Inadequate response, loss of response, or intolerance to ≥1 corticosteroid, immunomodulator, or approved biologic therapy for CD

[a] Enrollment of patients meeting the following criterion was limited to approximately 10% of total enrollment: SES-CD ≥3 and <7 (SES-CD <4 for isolated ileal disease) and presence of ≥1 large ulcer in the ileum, colon or both that results in a minimum score of 1 for the component of "ulcerated surface"

CD=Crohn's disease; IL=interleukin

Efficacy and Biomarker Endpoints



- Efficacy endpoints were evaluated at Week 52 for the Primary Analysis Set[b] and pre-specified subgroups, including patients with and without prior biologic failure
- Biomarker endpoints included fecal calprotectin and C-reactive protein change from baseline through Week 52

CDAI clinical remission: CDAI total score <150[1]
Endoscopic response: ≥50% reduction from baseline in SES-CD[2]
Corticosteroid-free CDAI clinical remission: Patients with CDAI clinical remission who were corticosteroid-free between Weeks 40-52
Endoscopic remission: SES-CD total score ≤4, a ≥2-point reduction from baseline, and no subscore >1 for any individual variable[3]
Combined CDAI clinical remission and endoscopic response: CDAI total score <150 and ≥50% reduction from baseline in SES-CD

[a] An event rate of 39% was assumed for mirikizumab and ustekinumab groups. A 10% margin was expected to preserve 50% of the ustekinumab effect in CDAI clinical remission at Week 52. The corresponding superiority test was not pre-specified in the graphical testing scheme; [b] Includes all randomized patients who received ≥1 dose of allocated treatment with baseline SES-CD ≥7 (or ≥4 for isolated ileal disease)

1. Best WR et al., *Gastroenterology*. 1976;70:439-444. 2. Vuitton L et al., *Gut*. 2016;65:1447-1455. 3. Feagan B et al., *Inflamm Bowel Dis.* 2018; 24:932-942

CDAI=Crohn's Disease Activity Index; SES-CD=Simple Endoscopic Score for Crohn's disease

Demographics and Baseline Characteristics

Characteristic	PBO (N=199)	MIRI (N=579)	USTE (N=287)
Age, years, mean (SD)	36.3 (12.7)	36.0 (13.2)	36.6 (12.7)
Male, n (%)	118 (59.3)	332 (57.3)	137 (47.7)
Weight, kg, mean (SD)	69.6 (19.0)	68.0 (18.3)	66.9 (17.6)
Duration of CD, years, median (IQR)	5.6 (2.0-10.4)	4.6 (1.7-9.3)	5.1 (2.2-9.0)
Baseline CDAI, median (IQR)	320.3 (259.6-374.7)	318.0 (268.0-374.9)	309.6 (247.0-379.0)
SF daily average	5.6 (4.1-7.1)	5.6 (4.1-6.7)	5.4 (4.1-7.0)
AP score daily average	2.0 (2.0-2.4)	2.0 (2.0-2.6)	2.0 (1.7-2.6)
SES-CD total score, median (IQR)	11.5 (8.7-17.0)	11.7 (8.5-17.5)	12.0 (8.5-18.0)
Disease location, n (%)			
Ileum only	19 (9.5)	65 (11.2)	29 (10.1)
Colon only	77 (38.7)	225 (38.9)	120 (41.8)
Ileum and colon	103 (51.8)	289 (49.9)	138 (48.1)
FCP, µg/g, median (IQR)	1161 (324-2170)	1315 (444-2676)	1489 (519-2814)
CRP, mg/L, median (IQR)	7.6 (2.9-18.8)	8.5 (2.9-25.0)	8.9 (3.4-24.8)

Note: Includes all randomized patients who received ≥1 dose of allocated treatment with baseline SES-CD ≥7 (or ≥4 for isolated ileal disease)

AP=abdominal pain; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; FCP=fecal calprotectin; IQR=interquartile range; MIRI=mirikizumab; PBO=placebo; SD=standard deviation; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab

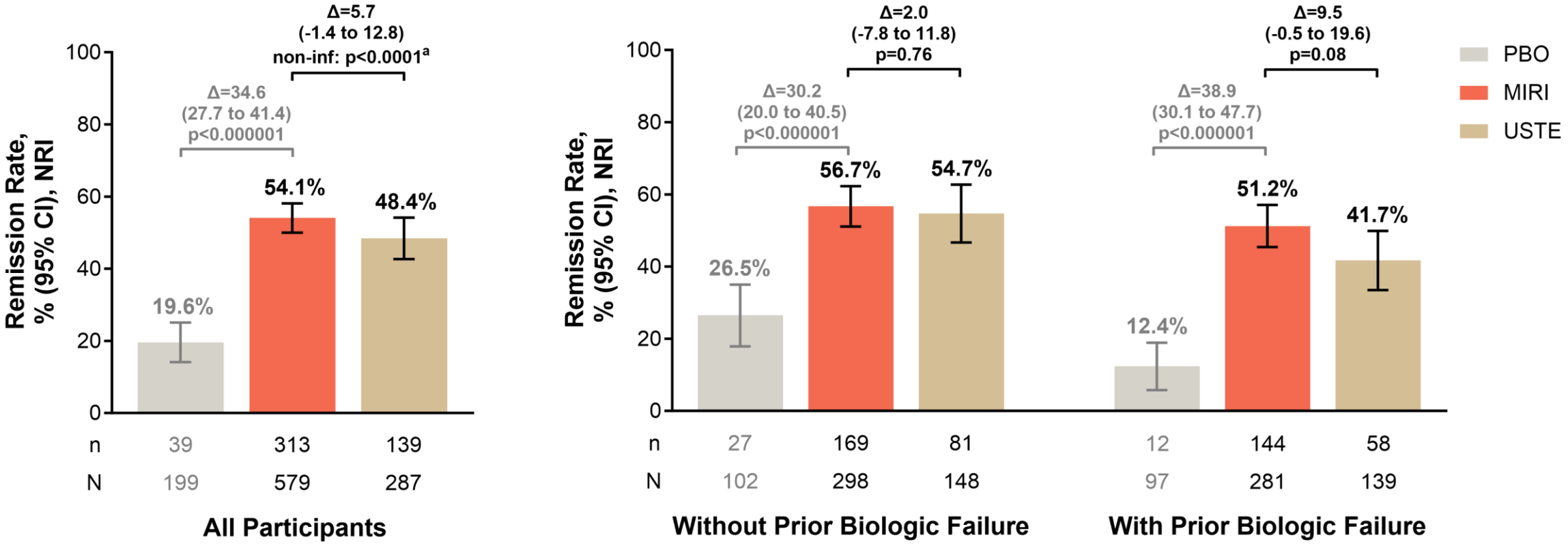
Concomitant and Previous Treatment

Characteristic	PBO (N=199)	MIRI (N=579)	USTE (N=287)
Corticosteroid use, n (%)	58 (29.1)	177 (30.6)	90 (31.4)
Prednisone equivalent dose, mg, median (range)	15 (5-30)	20 (3-30)	16 (5-100)
Budesonide use, n (%)	23 (11.6)	63 (10.9)	27 (9.4)
Immunomodulator use, n (%)	58 (29.1)	146 (25.2)	87 (30.3)
Prior USTE use, n (%)	2 (1.0)	4 (0.7)	1 (0.3)
Prior biologic failure, n (%)	97 (48.7)	281 (48.5)	139 (48.4)
Number of failed biologics, n (%)			
None	102 (51.3)	298 (51.5)	148 (51.6)
1	66 (33.2)	175 (30.2)	91 (31.7)
2	25 (12.6)	82 (14.2)	42 (14.6)
>2	6 (3.0)	24 (4.1)	6 (2.1)

Note: Includes all randomized patients who received ≥1 dose of allocated treatment with baseline SES-CD ≥7 (or ≥4 for isolated ileal disease)
MIRI=mirikizumab; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; USTE=ustekinumab

CDAI Clinical Remission at Week 52

Key Secondary Endpoint

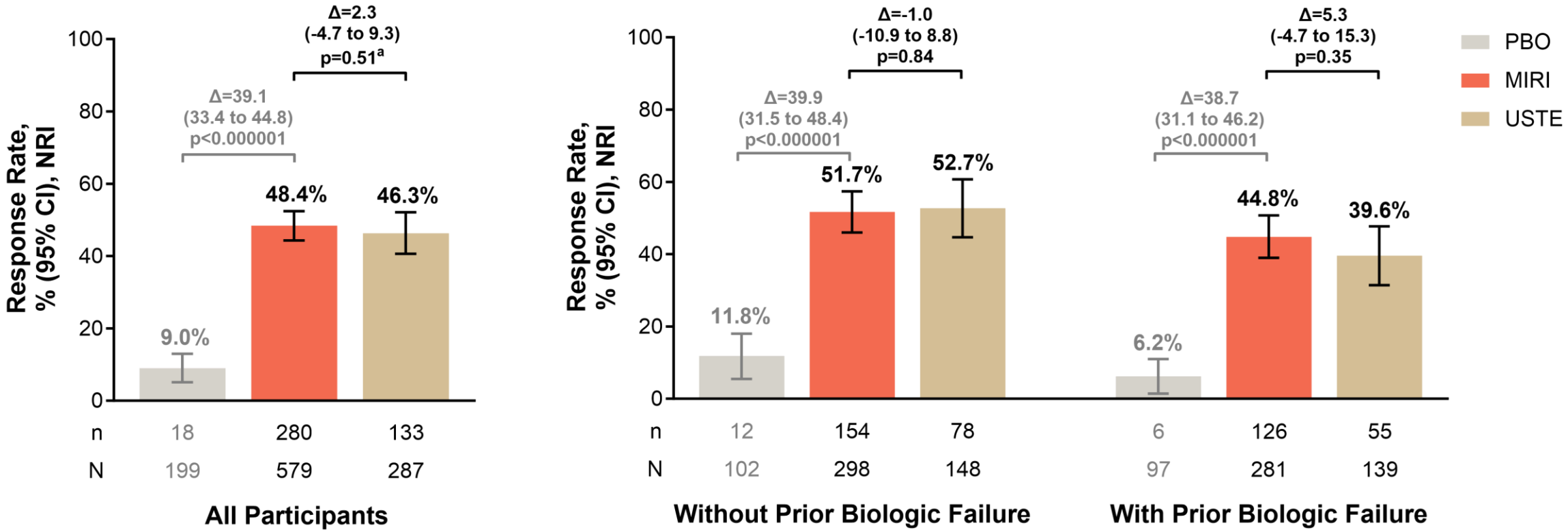


[a] Multiplicity-adjusted comparison using a **non-inferiority test with 10% margin.** The p-value for the corresponding superiority test is p=0.11

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. CDAI clinical remission was defined as CDAI total score <150. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients and unadjusted for the subgroup analysis. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; MIRI=mirikizumab; non-inf=non-inferior; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

Endoscopic Response at Week 52

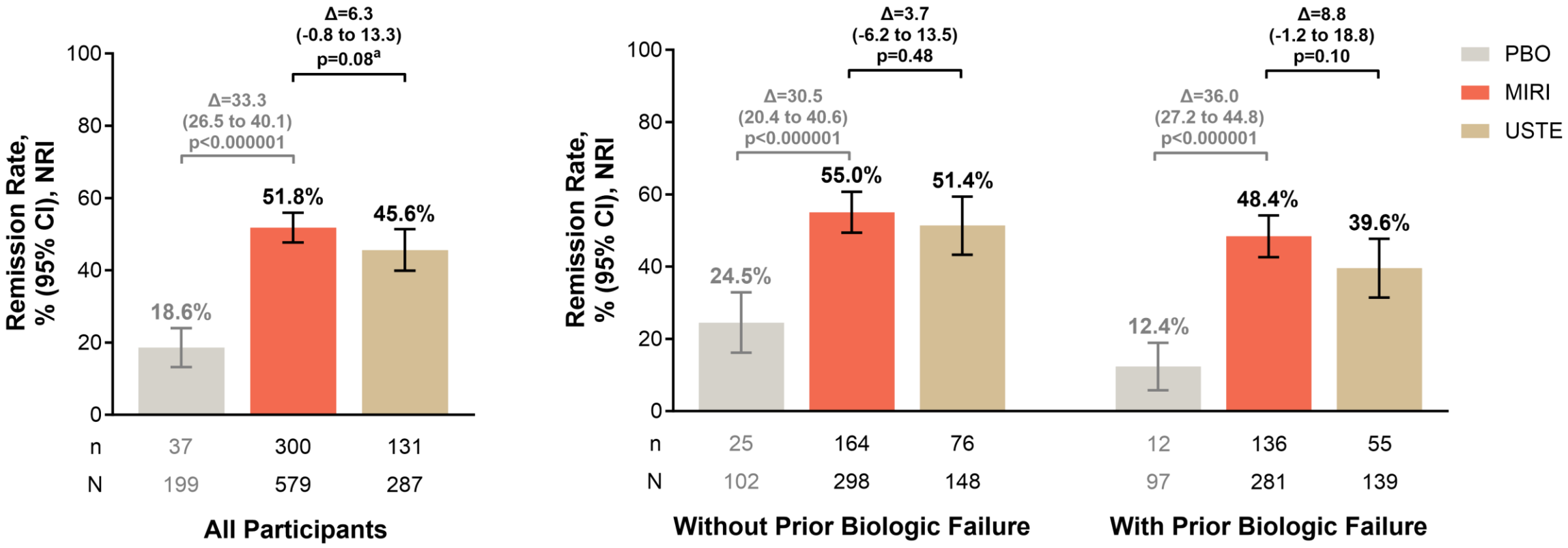
Key Secondary Endpoint



[a] Multiplicity-adjusted comparison using a **superiority test**

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. Endoscopic response was defined as ≥50% reduction from baseline in SES-CD. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients and unadjusted for the subgroup analysis. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

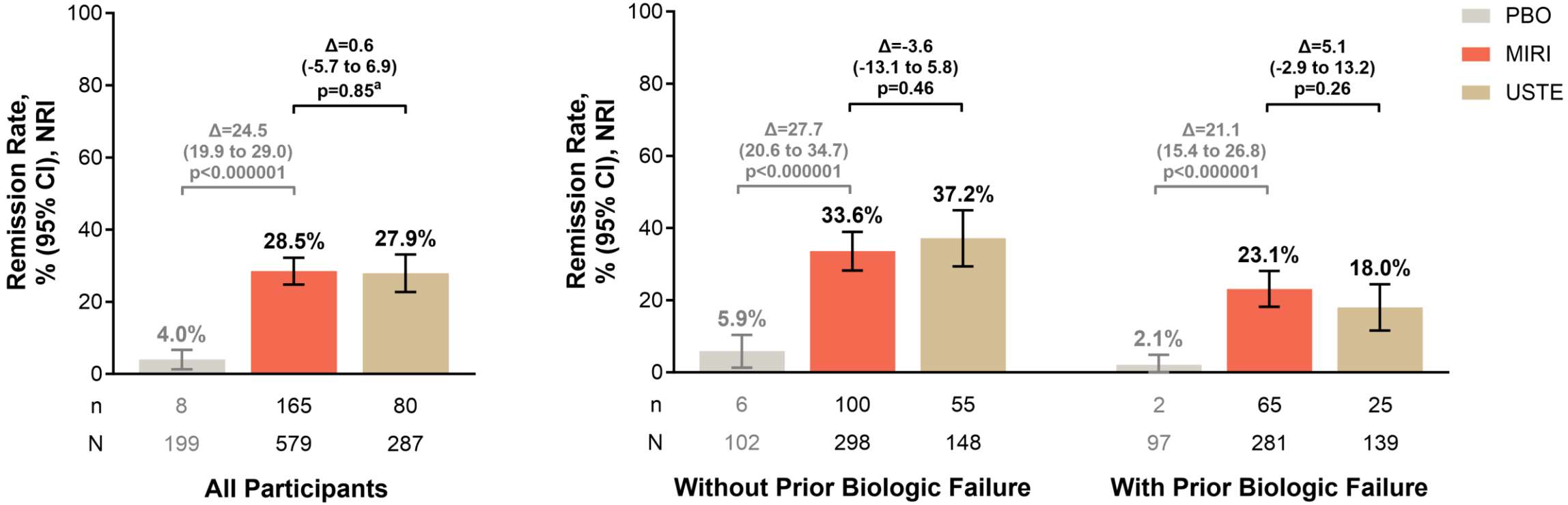
Corticosteroid-Free CDAI Remission at Week 52



[a] **Superiority test** not adjusted for multiplicity

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. CDAI clinical remission was defined as CDAI total score <150. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients and unadjusted for the subgroup analysis. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

Endoscopic Remission at Week 52



[a] **Superiority test** not adjusted for multiplicity

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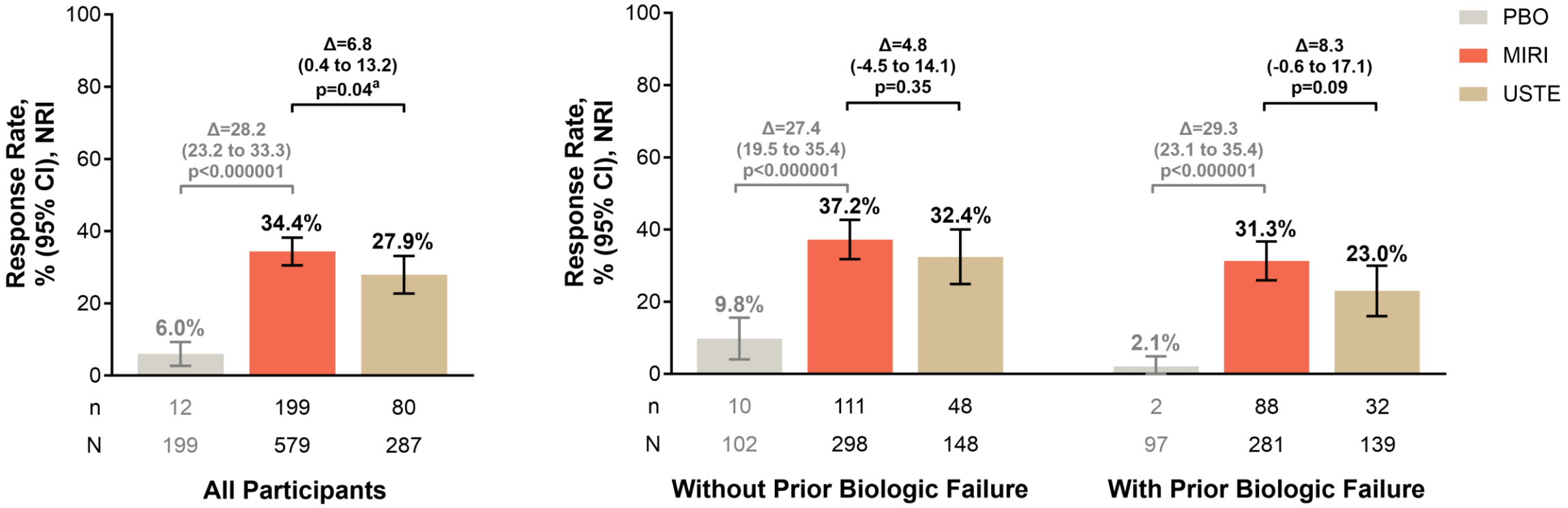
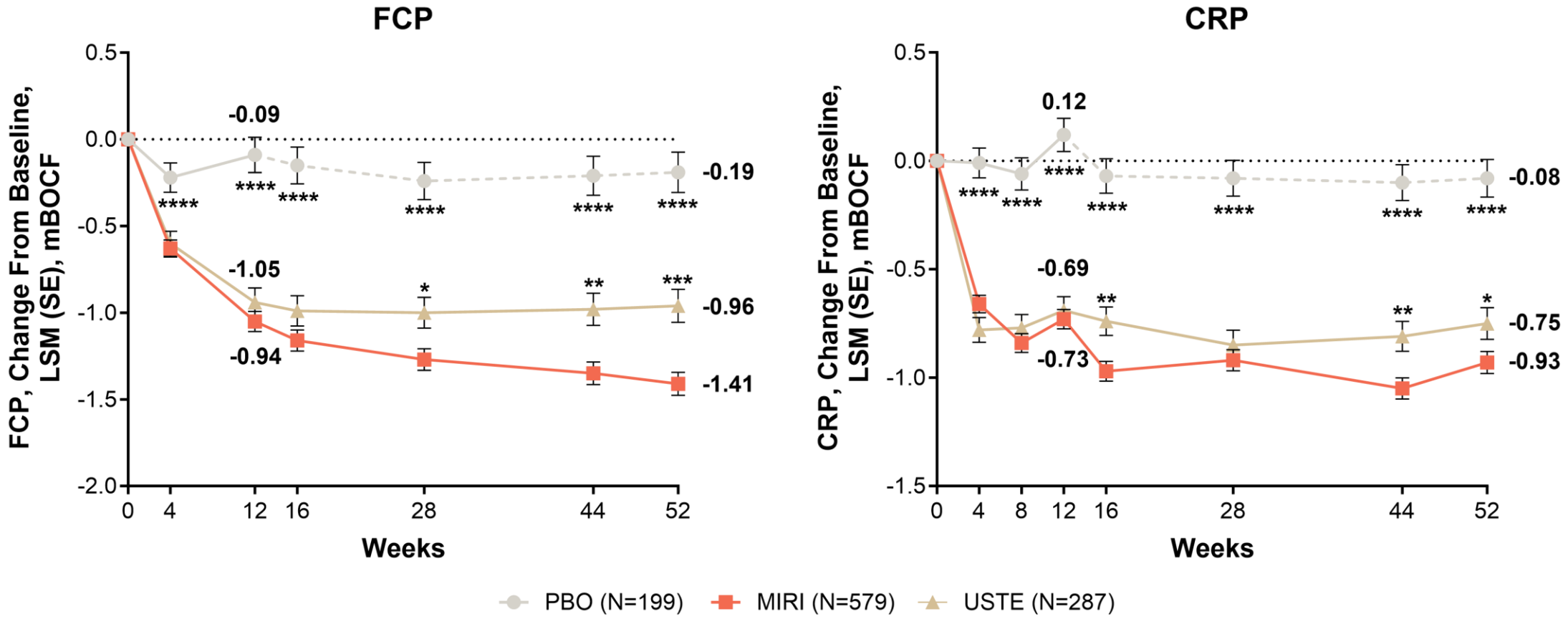
Combined CDAI Clinical Remission and Endoscopic Response at Week 52



[a] **Superiority test** not adjusted for multiplicity

Notes: Unless otherwise specified, comparisons are superiority test and not multiplicity-adjusted. CDAI clinical remission was as defined CDAI total score <150. Endoscopic response was defined as ≥50% reduction from baseline in SES-CD. Δ is the risk difference between the groups indicated and is adjusted for covariates (biologic-failed status [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline SF ≥7 and/or baseline AP ≥2.5 [yes or unknown/no]) for the analysis of all patients. For PBO, NRI is used for binary outcomes at Week 52 for patients who switched to MIRI at Week 12. *AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency; USTE=ustekinumab*

FCP and CRP Change From Baseline



* p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001 vs. MIRI

Notes: Data are LSM (SE) of log-transformed values. For participants in the PBO group who switched to MIRI at Week 12, baseline values were carried forward to derive the change from baseline at Week 52.

CRP=C-reactive protein; FCP=fecal calprotectin; LSM=least squares mean; mBOCF=modified baseline observation carried forward; MIRI=mirikizumab; PBO=placebo; SE=standard error; USTE=ustekinumab

Safety Overview

Induction and Maintenance Periods (Weeks 0-52), Safety Population[a]

Event	PBO (N=211)	MIRI (N=630)	USTE (N=309)
TEAE	154 (73.0)	495 (78.6)	239 (77.3)
Common TEAEs (>5% of patients)			
COVID-19	29 (13.7)	104 (16.5)	47 (15.2)
Anemia	14 (6.6)	42 (6.7)	15 (4.9)
Arthralgia	11 (5.2)	41 (6.5)	8 (2.6)
Headache	9 (4.3)	41 (6.5)	15 (4.9)
Upper respiratory tract infection	9 (4.3)	38 (6.0)	22 (7.1)
Nasopharyngitis	9 (4.3)	36 (5.7)	19 (6.1)
Diarrhea	10 (4.7)	35 (5.6)	12 (3.9)
Serious adverse events	36 (17.1)	65 (10.3)	33 (10.7)
Serious infection	6 (2.8)	14 (2.2)	9 (2.9)
Death	1 (0.5)[b]	0[c]	1 (0.3)[d]

Event	PBO (N=211)	MIRI (N=630)	USTE (N=309)
Opportunistic infection[e]	0	7 (1.1)	1 (0.3)
Malignancy	1 (0.5)	2 (0.3)	0
Basal cell carcinoma	1 (0.5)	1 (0.2)	0
Breast cancer	0	1 (0.2)	0
MACE (adjudicated and confirmed)	2 (0.9)	0	2 (0.6)
VTE[f]	1 (0.5)	0	0
Hepatic Laboratory			
ALT ≥3× ULN	0	12 (1.9)	6 (2.0)
≥5× ULN	0	3 (0.5)	1 (0.3)
AST ≥3× ULN	2 (1.0)	9 (1.4)	7 (2.3)
≥5× ULN	0	2 (0.3)	4 (1.3)
ALT/AST ≥3× ULN and TB ≥2× ULN	0	1 (0.2)	0
ALP ≥2× ULN and bilirubin ≥2× ULN	0	0	0
ALP ≥2× ULN	2 (1.0)	7 (1.1)	0

[a] All randomized participants who received ≥1 dose of study intervention; [b] 35-year-old male patient who died from pulmonary embolism; [c] One additional 23-year-old male PBO non-responder patient who switched to MIRI after Week 12 died from worsening of CD; [d] 63-year-old female patient who died from sepsis; [e] Most opportunistic infections were herpes zoster and 1 *Candida*; [f] One pulmonary embolism and no cases of deep venous thrombosis. Notes: For patients randomized to PBO, only the exposure period for PBO is included. Patients who were randomly assigned to PBO and were non-responders at Week 12 subsequently switched to MIRI treatment. Data from these participants after Week 12 are not included in the Week 0-52 analysis. *ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CD=Crohn's disease; MACE=major adverse cardiovascular event; MIRI=mirikizumab; PBO=placebo; TB=total bilirubin; TEAE=treatment-emergent adverse event; ULN=upper limit of normal; USTE=ustekinumab; VTE=venous thrombotic event*

Conclusions

- In this Phase 3 double blind, double dummy, PBO and active control, treat-through study, mirikizumab achieved non-inferiority to ustekinumab for Week 52 clinical remission as evaluated with CDAI
- Rates of endoscopic response, endoscopic remission, and corticosteroid-free CDAI clinical remission were not statistically different for mirikizumab and ustekinumab. However, mirikizumab showed numerically superior results for all these endpoints
- Mirikizumab was nominally statistically superior to ustekinumab in achieving combined CDAI clinical remission and endoscopic response at Week 52
- Mirikizumab reached nominal statistical superiority to ustekinumab in decreasing FCP and CRP
- Differences favouring mirikizumab were strongest among patients who had previously failed biologic therapy for CD
- The safety profiles of mirikizumab and ustekinumab were consistent with previous findings[1-3]

1. D'Haens G, et al. *N Engl J Med*. 2023;388:2444-2455. 2. Sands BE, et al. *Gastroenterology*. 2022;162:495-508. 3. STELARA [Summary of Product Characteristics]. The Netherlands: Janssen Biologics B.V., 2009.

CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; FCP=fecal calprotectin; PBO=placebo

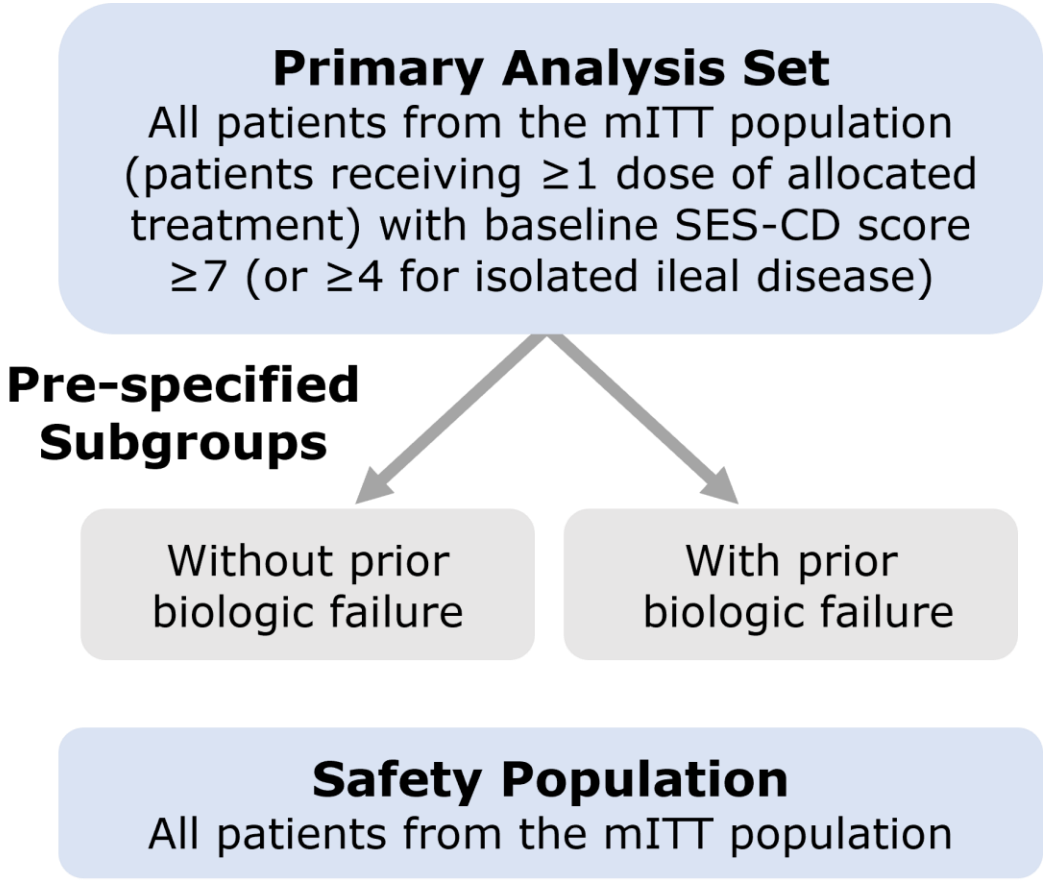
Backup Slides

Evaluation of Endpoints

- The sample size provided >90% power to demonstrate that mirikizumab is superior to ustekinumab for endoscopic response at Week 52; the power of the non-inferiority comparison was not determined
- Evaluation of endoscopic endpoints involved review of video recordings by central readers blinded to treatment assignment
- SES-CD score was calculated as a mean of scores read by 2 or 3 central readers. A third central reader was used only when there was discordance between the first 2 central readers

SES-CD=Simple Endoscopic Score for Crohn's disease

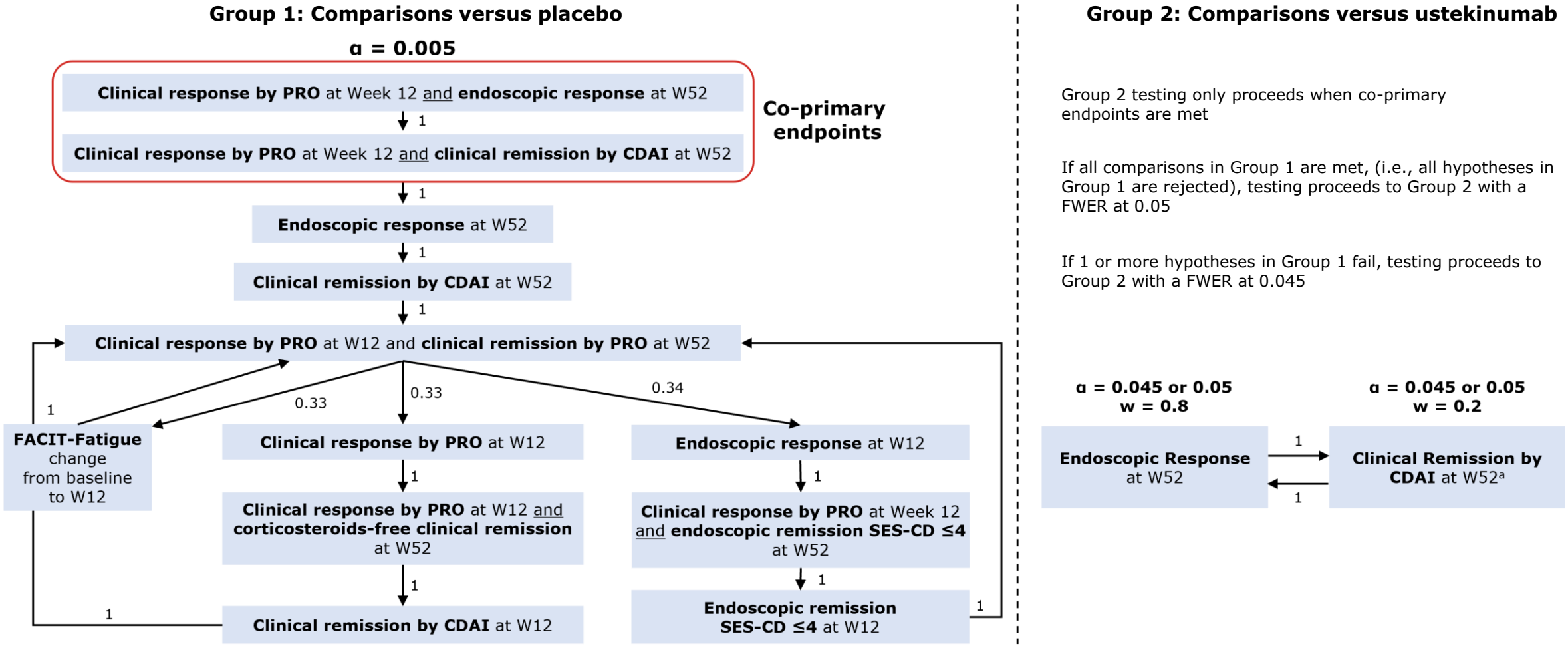
Statistical Analysis



- Response rates were compared between treatment arms using the Cochran-Mantel-Haenszel test in the primary analysis set and Fisher's exact test in subgroups, with missing data imputed as non-response
- Patients who switched from placebo to mirikizumab were subsequently treated as non-responders
- Biomarkers were analyzed with analysis of covariance
  - Baseline was defined as the last non-missing assessment recorded on or prior to the first dose of study drug

mITT=modified Intent-to-Treat; SES-CD=Simple Endoscopic Score for Crohn's disease

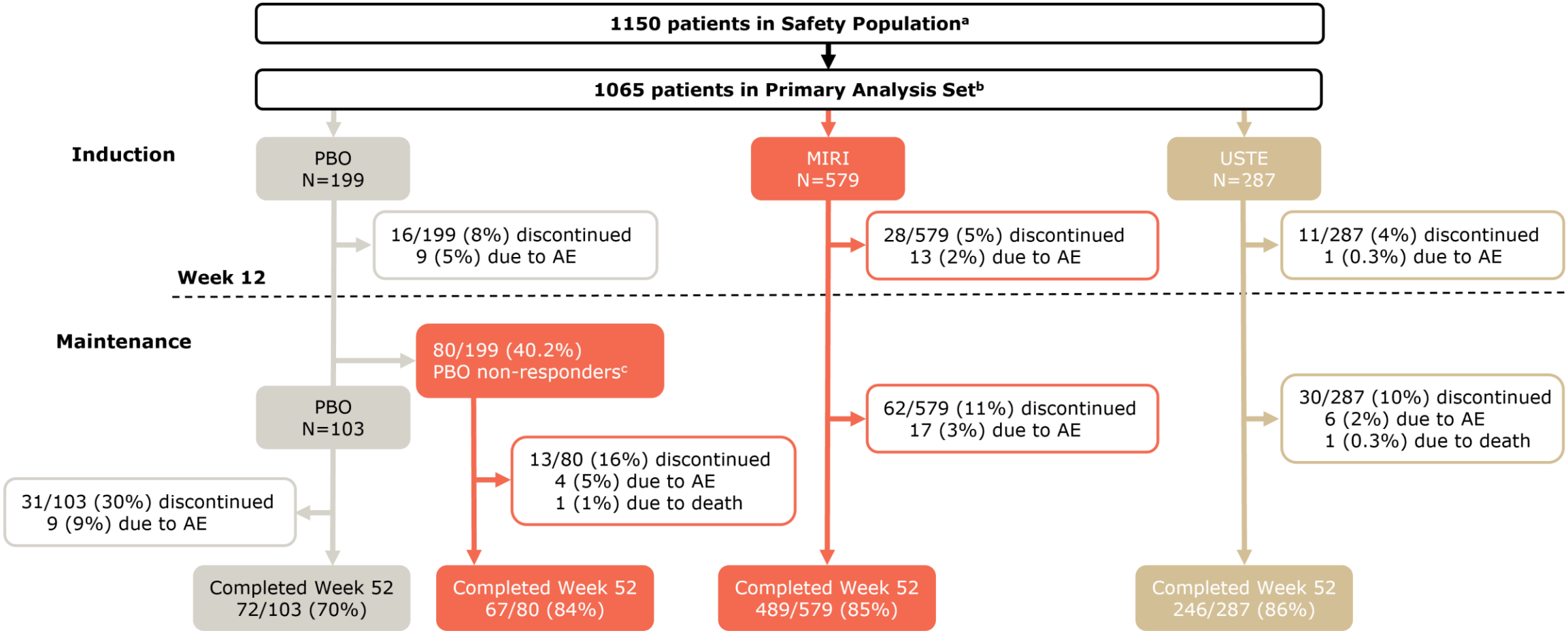
Graphical Testing Procedure



[a] Clinical remission by CDAI at W52 vs. ustekinumab is a non-inferiority hypothesis test. Note: Red border indicates all nodes must be rejected before alpha propagates

CDAI=Crohn's Disease Activity Index; FACIT=Functional Assessment of Chronic Illness Therapy; FWES=family-wise error rate; PBO=placebo; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [stool frequency and abdominal pain]); SES-CD=Simple Endoscopic Score for Crohn's Disease; W=Week

Patient Disposition



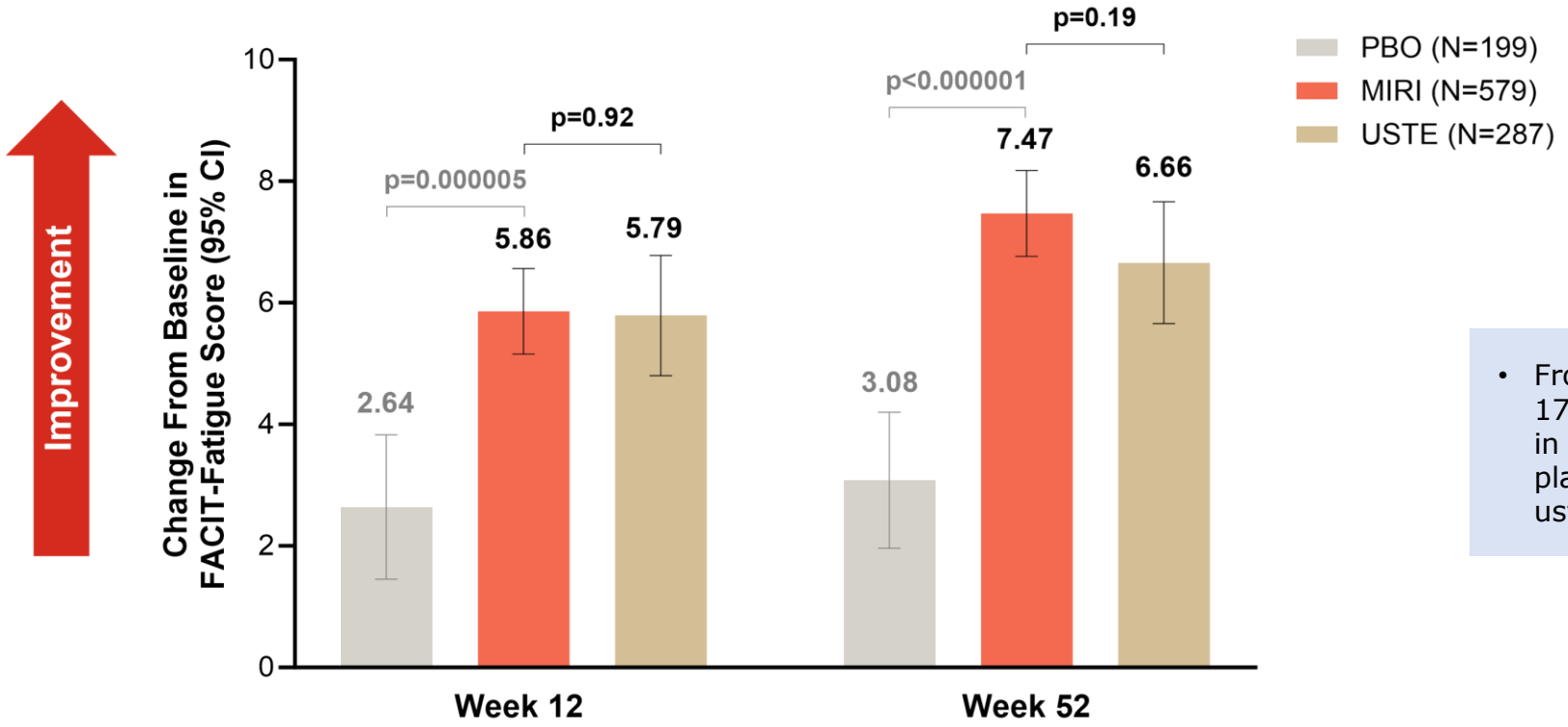
[a] All randomized patients who received ≥1 dose of allocated treatment (mITT); [b] All patients from the mITT population with baseline SES-CD ≥7 (or ≥4 for isolated ileal disease); [c] PBO non-responders at Week 12 re-assigned to MIRI 900 mg Q4W until Week 24, then MIRI 300 mg SC Q4W. *AE=adverse event; mITT= modified Intent-to-Treat; MIRI=mirikizumab; PBO=placebo; Q4W=every 4 weeks; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; USTE=ustekinumab*

Prior Biologic Failure by Drug Class

Characteristic	PBO (N=199)	MIRI (N=579)	USTE (N=287)
Prior biologic failure	97 (48.7)	281 (48.5)	139 (48.4)
Prior anti-TNF failure	89 (44.7)	265 (45.8)	133 (46.3)
Prior anti-integrin failure	24 (12.1)	68 (11.7)	31 (10.8)

Notes: Data are n (%). Includes all randomized patients who received ≥1 dose of allocated treatment with baseline SES-CD ≥7 (or ≥4 for isolated ileal disease)
MIRI=mirikizumab; PBO=placebo; TNF=tumor necrosis factor; USTE=ustekinumab

Fatigue at Week 12 and Week 52

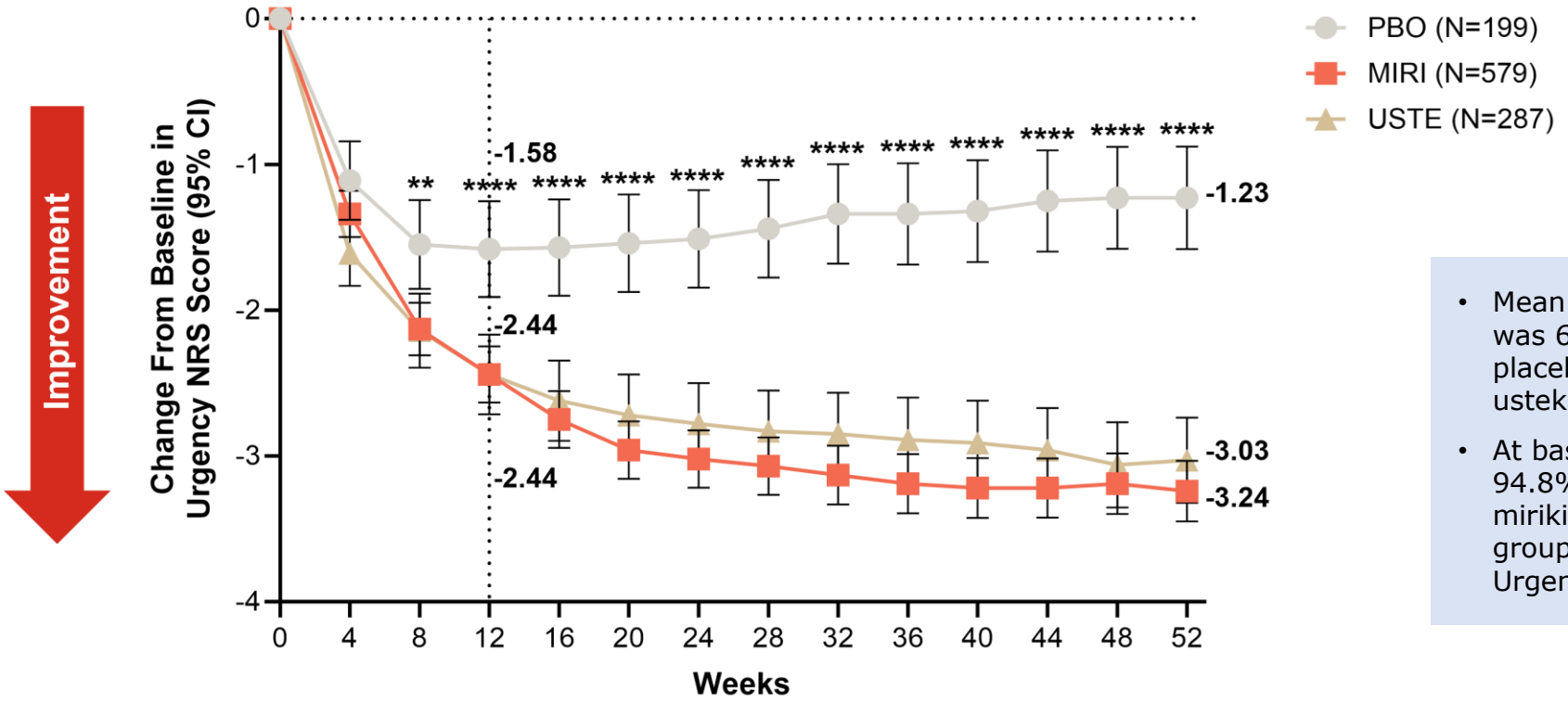


- From Week 12 to 52, there was a 17%, 27%, and 15% improvement in FACIT-Fatigue score in the placebo, mirikizumab, and ustekinumab groups, respectively

Notes: Data are LSM (95% CI), and comparisons were performed using ANCOVA with mBOCF. For participants in the placebo group who switched to mirikizumab at Week 12, baseline values were carried forward to derive the change from baseline at Week 52. Increase in FACIT-Fatigue score indicates improvement

ANCOVA=analysis of covariance; CI=confidence interval; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy-Fatigue; LSM=least squares mean; mBOCF=modified baseline observation carried forward; MIRI=mirikizumab; PBO=placebo; USTE=ustekinumab

Bowel Urgency Through Week 52



- Mean baseline Urgency NRS score was 6.6, 6.6, and 6.5 in the placebo, mirikizumab, ustekinumab groups, respectively
- At baseline, 93.5%, 94.5%, and 94.8% of patients in the placebo, mirikizumab, and ustekinumab groups, respectively, had an Urgency NRS score ≥3

** p<0.01; **** p<0.0001 vs. MIRI

Notes: Data are LSM (95% CI), and comparisons were performed using ANCOVA with mBOCF. For participants in the placebo group who switched to mirikizumab at Week 12, baseline values were carried forward to derive the change from baseline at Week 52.

ANCOVA=analysis of covariance; CI=confidence interval; LSM=least squares mean; mBOCF=modified baseline observation carried forward; MIRI=mirikizumab; NRS=Numeric Rating Scale; PBO=placebo; USTE=ustekinumab