Primary Efficacy and Safety of Mirikizumab in Moderate to Severe Crohn's Disease: Results of the Treat-Through VIVID 1 Study

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Background and Objective

Background

- Mirikizumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that inhibits anti–interleukin (IL)-23 by binding to an epitope on the p19 subunit
- Mirikizumab is approved for the treatment of moderate to severe ulcerative colitis (UC) and is under development for Crohn's disease (CD)[1,2]
- VIVID-1 is a Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled, treat-through study evaluating the efficacy and safety of mirikizumab in patients with moderate to severe active CD

Objective

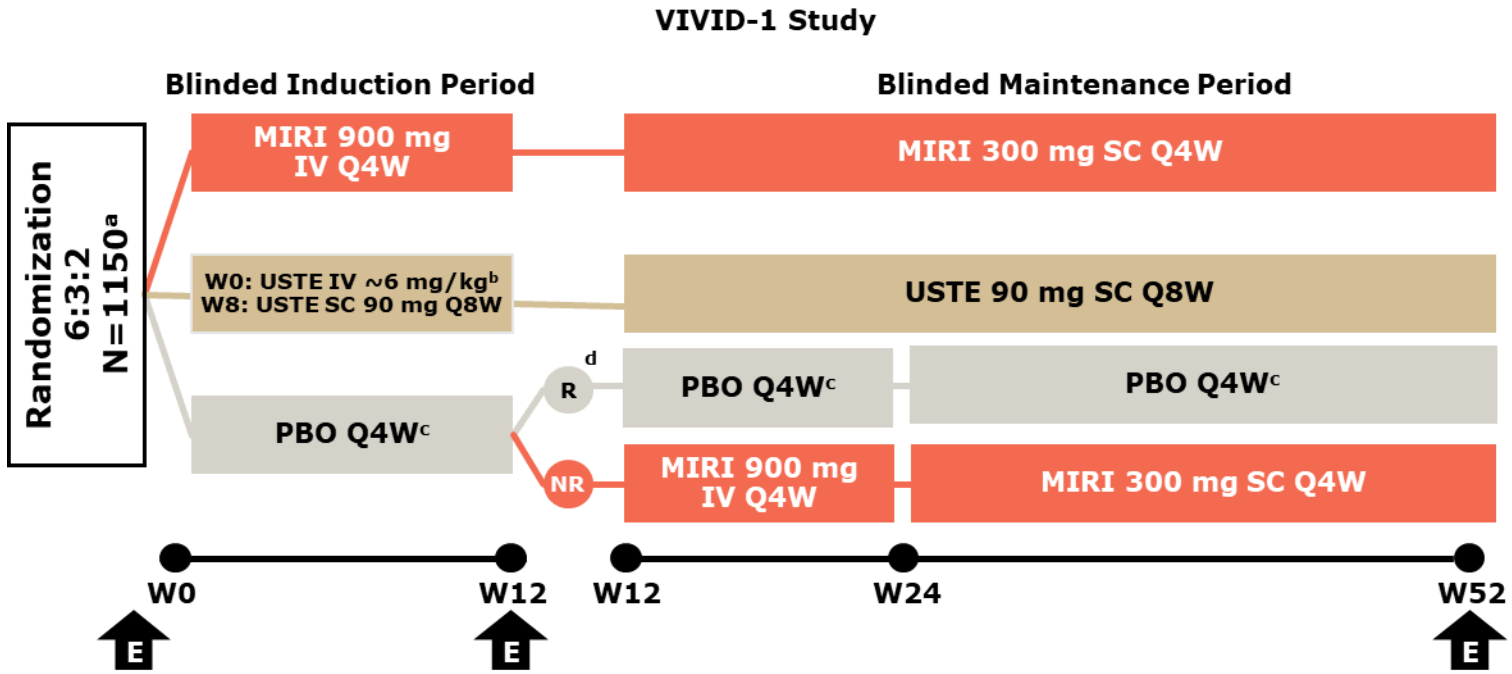
- To report the primary efficacy and safety of mirikizumab compared with placebo up to Week 52 from the Phase 3 VIVID-1 study in patients with moderate to severe CD

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

VIVID-1 Study Design and Key Entry Criteria

Key Entry Criteria

- Adults aged ≥18 and ≤80 years
- Diagnosis of CD or fistulizing CD for ≥3 months
- Average daily liquid/soft stool frequency (SF) ≥4 and/or average daily abdominal pain (AP) ≥2
- Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥7 (or ≥4 for patients with isolated ileal disease)
- Inadequate response, loss of response, or intolerant to conventional or biologic therapy



[a] Number of patients in the Safety Population; [b] Single dose; [c] Placebo 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; [d] Responders by PRO at W12 of VIVID-1, defined as having achieved ≥30% decrease in loose SF and/or AP, with neither score higher than baseline

AP=abdominal pain; CD=Crohn's disease; 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 [SF and AP]); Q4W=every 4 weeks; Q8W=every 8 weeks; R=responder; SC=subcutaneous; SF=stool frequency; USTE=ustekinumab; W=Week

Efficacy Endpoints

- Co-primary composite endpoints assessed superiority of mirikizumab over placebo[a]:
  - Clinical response by PRO[b] at Week 12 and endoscopic response by SES-CD at Week 52
  - Clinical response by PRO[b] at Week 12 and Crohn's Disease Activity Index (CDAI) clinical remission at Week 52
- Major secondary endpoints vs. placebo:
  - Endoscopic response by SES-CD at Week 12
  - Endoscopic response by SES-CD at Week 52
  - Endoscopic remission by SES-CD at Week 12
  - Clinical remission by CDAI at Week 12
  - Clinical remission by CDAI at Week 52
  - Clinical response by PRO at Week 12
  - Clinical response by PRO at Week 12 and clinical remission by PRO at Week 52
  - Clinical response by PRO at Week 12 and corticosteroid-free remission at Week 52
  - Clinical response by PRO at Week 12 and endoscopic remission by SES-CD at Week 52

[a] Both co-primary composite endpoints needed to be met to demonstrate superiority of mirikizumab over placebo; [b] *PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [SF and AP])*

Note: The efficacy of mirikizumab in comparison to ustekinumab is presented in: Jairath V, et al. Presented at: *ECCO 2024.* Presentation number OP35

AP=abdominal pain; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [SF and AP]); SES-CD=Simple Endoscopic Score for Crohn's Disease; SF=stool frequency

Statistical Analysis

- Efficacy analyses were performed using the primary analysis set (patients from the mITT population who had baseline SES-CD ≥7 [or ≥4 for isolated ileal disease])
- Safety analyses were performed using the mITT population (patients who took ≥1 dose of the study intervention)
- Unless otherwise specified, all Week 52 endpoints were defined as a composite of Week 12 clinical response by PRO and the respective Week 52 endpoint
  - Treat-through analysis shows Week 52 results for mirikizumab, regardless of Week 12 clinical response by PRO[a]
- Co-primary composite endpoints and major secondary endpoints were multiplicity-controlled
- Comparisons between mirikizumab and placebo were performed using the Cochran-Mantel-Haenszel test in all patients and by Fisher exact test in the subgroups (no prior biologic failure and prior biologic failure)[b]
  - Non-responder imputation was used for missing data

[a] Patients who received placebo who did not achieve a clinical response by PRO at Week 12 were considered non-responders at Week 52; [b] Prior biologic failure was defined as inadequate response, loss of response, or intolerance to ≥1 biologic medication approved for the treatment of CD

CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; mITT=modified Intent-to-Treat; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [SF and AP]); SES-CD=Simple Endoscopic Score for Crohn's disease

Patient Demographics and Baseline Characteristics

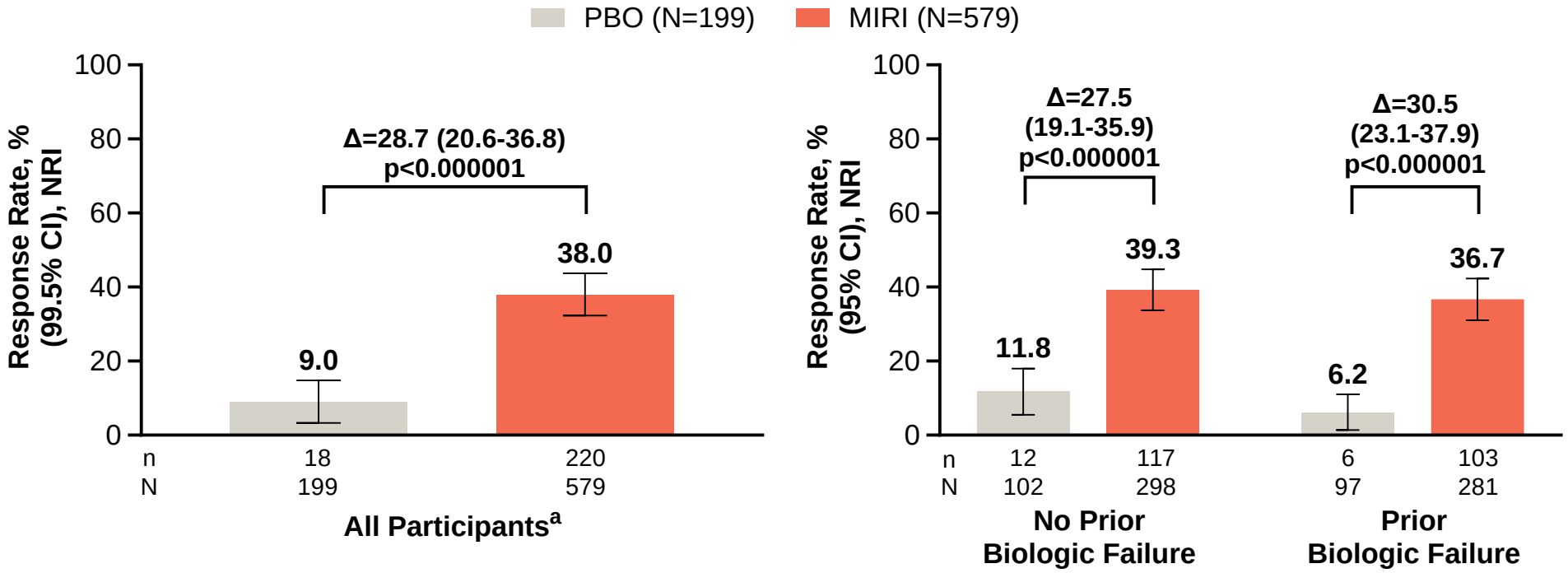
Characteristic	PBO (N=199)	MIRI (N=579)
Age, years	36.3 (12.7)	36.0 (13.2)
Male, n (%)	118 (59.3)	332 (57.3)
Weight, kg	69.6 (19.0)	68.0 (18.3)
BMI, kg/m^2	23.8 (5.8)	23.2 (5.4)
Duration of CD, years	7.8 (7.4)	7.4 (8.2)
Baseline CDAI	318.9 (86.2)	323.1 (85.8)
SF daily average	5.8 (3.2)	5.7 (3.0)
AP daily average	2.1 (0.6)	2.1 (0.6)
SES-CD total score	13.1 (6.0)	13.5 (6.6)
Disease location, n (%)		
Ileum only	19 (9.5)	65 (11.2)
Colon only	77 (38.7)	225 (38.9)
Ileum and colon	103 (51.8)	289 (49.9)
Corticosteroid use, n (%)	58 (29.1)	177 (30.6)
Immunomodulator use, n (%)	58 (29.1)	146 (25.2)
Prior biologic failure, n (%)	97 (48.7)	281 (48.5)
Number of failed biologics, n (%)		
None	102 (51.3)	298 (51.5)
1	66 (33.2)	175 (30.2)
≥2	31 (15.6)	106 (18.3)

Note: Data are mean (SD) unless stated otherwise; Primary Analysis Set population

AP=abdominal pain; BMI=body mass index; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; MIRI=mirikizumab; PBO=placebo; SD=standard deviation; SES-CD=Simple Endoscopic Score for Crohn's disease; SF=stool frequency

A Greater Proportion of Patients Achieved the Co-Primary Endpoints With Mirikizumab vs. Placebo (1/2)

Clinical Response by PRO at Week 12 and Endoscopic Response by SES-CD at Week 52



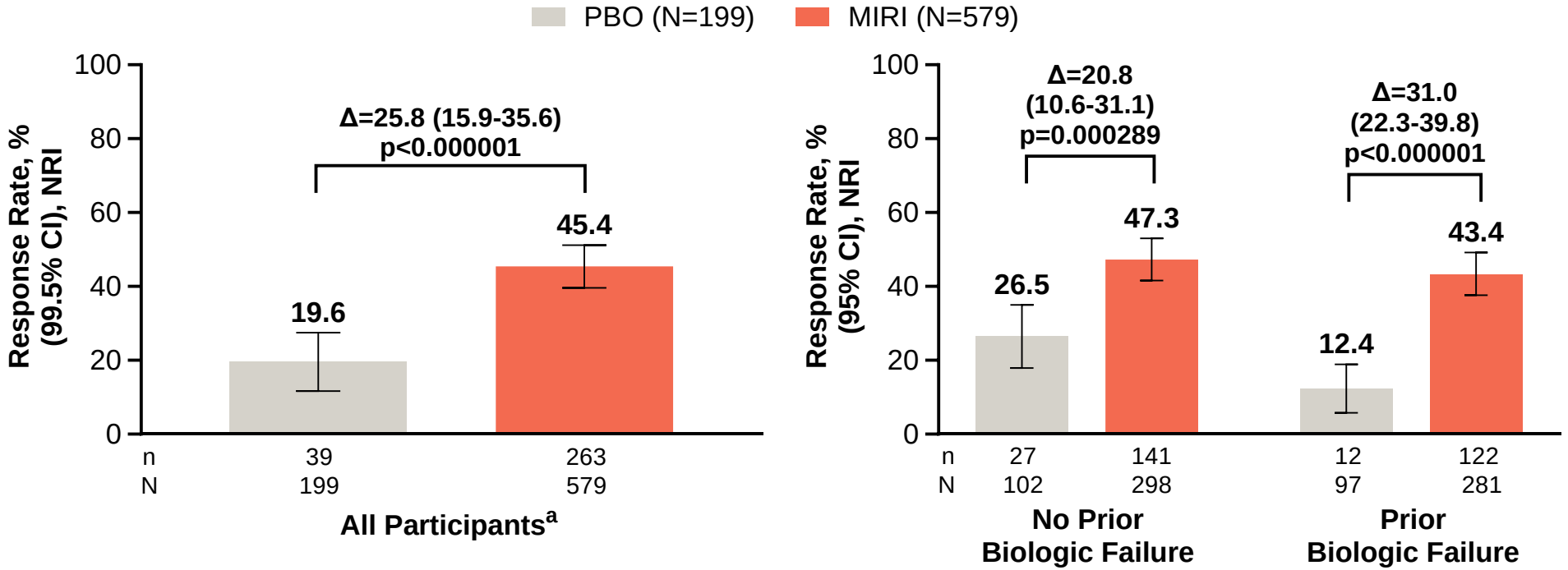
[a] Primary Analysis Set

Notes: PRO clinical response was defined as ≥30% decrease in SF and/or AP, with neither score worse than baseline; endoscopic response was defined as ≥50% reduction from baseline in SES-CD total score. 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

AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [SF and AP]); SES-CD=Simple Endoscopic Score for Crohn's Disease; SF=stool frequency

A Greater Proportion of Patients Achieved the Co-Primary Endpoints With Mirikizumab vs. Placebo (2/2)

Clinical Response by PRO at Week 12 and Clinical Remission by CDAI at Week 52

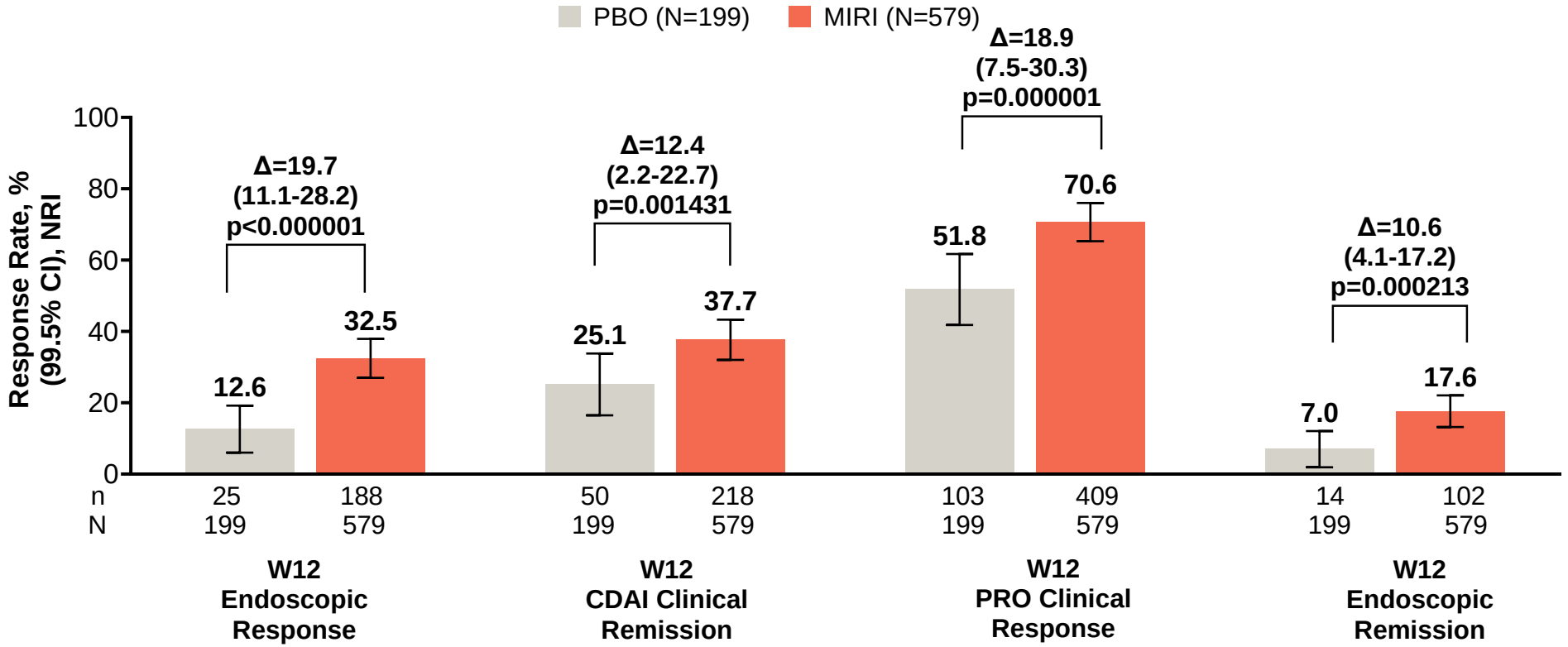


[a] Primary Analysis Set

Notes: PRO clinical response was defined as ≥30% decrease in SF and/or AP, with neither score worse than baseline; 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

AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [SF and AP]); SES-CD=Simple Endoscopic Score for Crohn's Disease; SF=stool frequency

A Greater Proportion of Patients Achieved All Week 12 Major Secondary Endpoints With Mirikizumab vs. Placebo



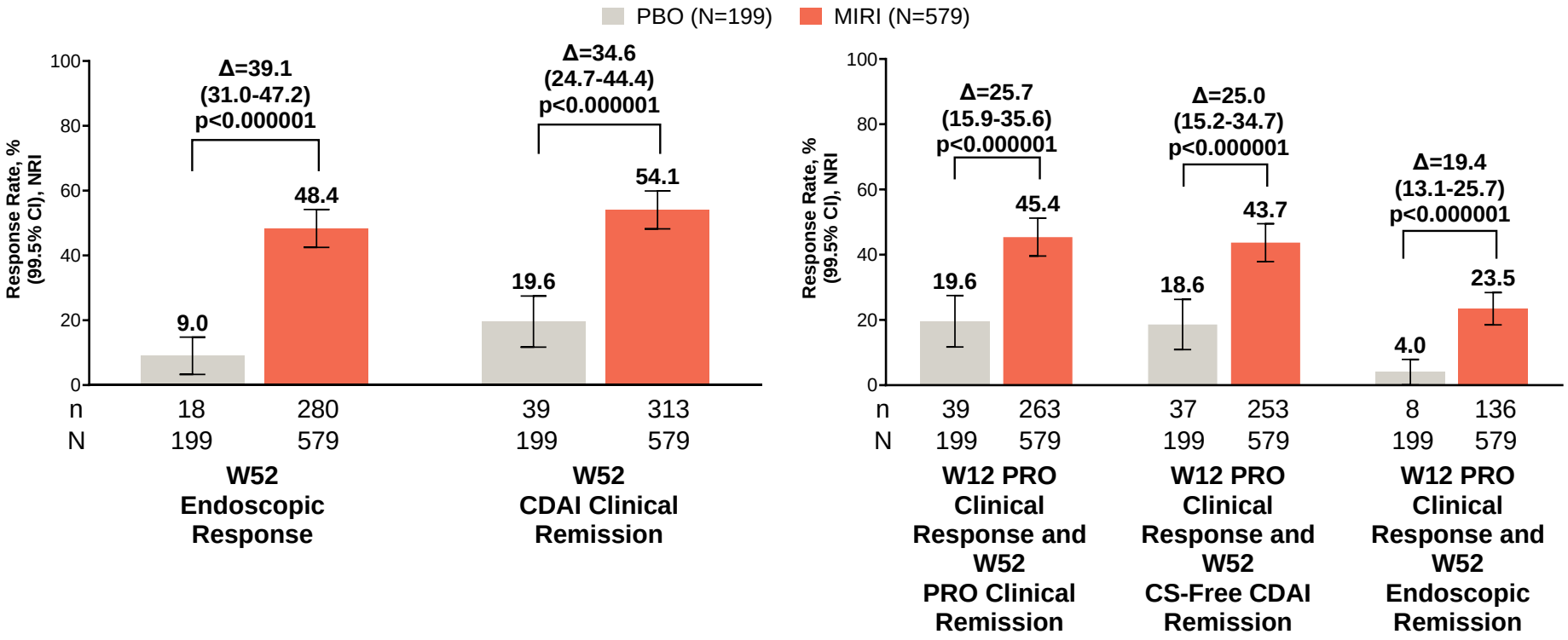
Notes: PRO clinical response was defined as ≥30% decrease in SF and/or AP, with neither score worse than baseline; endoscopic response was defined as ≥50% reduction from baseline in SES-CD total score; CDAI clinical remission was defined as CDAI total score <150; PRO clinical remission was defined as unweighted daily average SF ≤3 (per Bristol Stool Scale Category 6 or 7) and unweighted daily average AP ≤1, with neither score worse than baseline; endoscopic remission was defined as SES-CD total score ≤4, a ≥2-point reduction from baseline, and no subscore >1 in any individual variable. 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

AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; CS=corticosteroid; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [SF and AP]); SES-CD=Simple Endoscopic Score for Crohn's Disease; SF=stool frequency; TT=treat-through; W=Week

A Greater Proportion of Patients Achieved All Week 52 Major Secondary Endpoints With Mirikizumab vs. Placebo

Treat-Through Endpoints

Composite Endpoints



Notes: Treat-through reflects the Week 52 mirikizumab endpoint result, regardless of response status at Week 12. Composite endpoints were defined as a composite of Week 12 PRO clinical response and the respective Week 52 endpoint. PRO clinical response was defined as ≥30% decrease in SF and/or AP, with neither score worse than baseline; endoscopic response was defined as ≥50% reduction from baseline in SES-CD total score; CDAI clinical remission was defined as CDAI total score <150; PRO clinical remission was defined as unweighted daily average SF ≤3 (per Bristol Stool Scale Category 6 or 7) and unweighted daily average AP ≤1, with neither score worse than baseline; endoscopic remission was defined as SES-CD total score ≤4, a ≥2-point reduction from baseline, and no subscore >1 in any individual variable. 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

AP=abdominal pain; CDAI=Crohn's Disease Activity Index; CI=confidence interval; CS=corticosteroid; MIRI=mirikizumab; NRI=non-responder imputation; PBO=placebo; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [SF and AP]); SES-CD=Simple Endoscopic Score for Crohn's Disease; SF=stool frequency; W=Week

Overall Safety During The Week 52 Treatment Period Was Consistent With the Known Safety Profile of Mirikizumab

Event, n (%) [EAIR]	PBO[a] (N=211) PYE=119.5	MIRI (N=630) PYE=593.6	Event, n (%) [EAIR]	PBO[a] (N=211) PYE=119.5	MIRI (N=630) PYE=593.6
TEAE	154 (73.0) [291.8]	495 (78.6) [201.9]	**Opportunistic infection[d]**	0	7 (1.1) [1.2]
Common TEAEs (>5% of patients)			**Malignancy**	1 (0.5) [0.8]	2 (0.3) [0.3]
COVID-19	29 (13.7) [26.4]	104 (16.5) [19.3]	**Basal cell carcinoma**	1 (0.5) [0.8]	1 (0.2) [0.2]
Anaemia	14 (6.6) [12.2]	42 (6.7) [7.4]	**Breast cancer**	0	1 (0.2) [0.2]
Arthralgia	11 (5.2) [9.6]	41 (6.5) [7.2]	**MACE (adjudicated and confirmed)**	2 (0.9) [1.7]	0
Headache	9 (4.3) [7.8]	41 (6.5) [7.2]	**VTE[e]**	1 (0.5) [0.8]	0
Upper respiratory tract infection	9 (4.3) [7.8]	38 (6.0) [6.7]	**Hepatic Laboratory**		
Nasopharyngitis	9 (4.3) [7.7]	36 (5.7) [6.3]	**ALT ≥3x ULN**	0	12 (1.9) [2.0]
Diarrhoea	10 (4.7) [8.6]	35 (5.6) [6.1]	**≥5x ULN**	0	3 (0.5) [0.5]
Serious adverse events	36 (17.1) [32.5]	65 (10.3) [11.5]	**AST ≥3x ULN**	2 (1.0) [1.7]	9 (1.4) [1.5]
Serious infection	6 (2.8) [5.1]	14 (2.2) [2.4]	**≥5x ULN**	0	2 (0.3) [0.3]
Death	1 (0.5)[b] [0.8]	0[c]	**ALP ≥2x ULN**	2 (1.0) [1.7]	7 (1.1) [1.2]

[a] For patients randomized to PBO, only the exposure period to PBO is included; [b] 35-year-old male patient who died due to pulmonary embolism; [c] One additional 23-year-old male placebo non-responder patient who switched to mirikizumab after Week 12 died due to worsening of CD; [d] Most opportunistic infections were herpes zoster and 1 *Candida*; [e] One pulmonary embolism and no cases of deep venous thrombosis. Notes: 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; VTE=venous thrombotic event

Conclusions

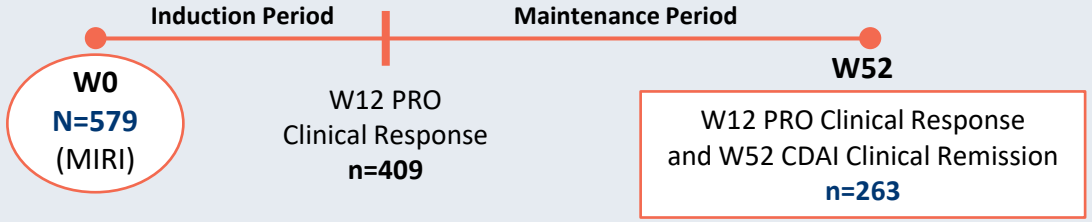
- In this Phase 3 CD study, mirikizumab demonstrated statistically significant and clinically meaningful improvements in both co-primary composite endpoints and all major secondary endpoints compared with placebo
- Response rates and effect sizes were robust and similar between the subgroups of patients with prior biologic failure and without prior biologic failure
- Mirikizumab demonstrated an acceptable safety profile in patients with moderate to severe CD that was consistent with the known safety profile in patients with moderate to severe UC[1]

1. D'Haens G, et al. *N Engl J Med*. 2023;388:2444-2455.

CD=Crohn's disease; UC=ulcerative colitis

Implications of Different Study Designs on Calculating the Proportion of Patients Achieving W52 Endpoints

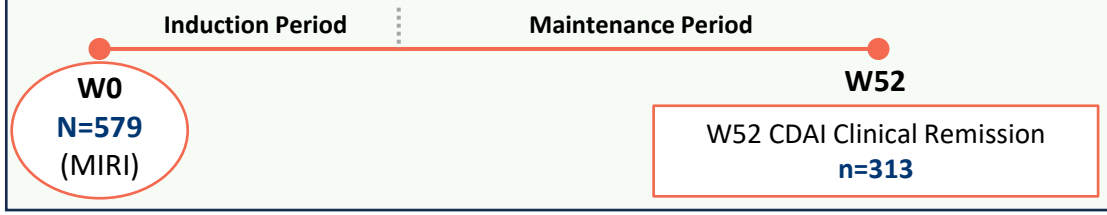
Treat-Through Study With Composite Endpoint



Pts with W12 PRO clinical response and W52 CDAI clinical remission (**n=263**) / All pts randomised to MIRI (**N=579**) **x 100**

45.4%

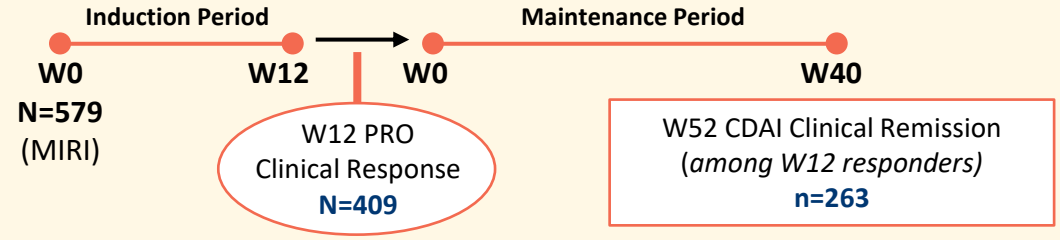
Treat-Through Study Without W12 Response Requirement



Pts with W52 CDAI clinical remission (**n=313**) / All pts randomised to MIRI (**N=579**) **x 100**

54.1%

Post hoc Exploratory Analysis Evaluating W52 Response Among Induction Responders Only



W12 responders with W52 CDAI clinical remission (**n=263**) / Pts with W12 PRO clinical response (**N=409**) **x 100**

64.3%

- This example shows a range of approximately 20% depending on analysis type
- There are profound limitations comparing outcomes across Phase 3 trials with different study designs

CDAI=Crohn's Disease Activity Index; MIRI=mirikizumab; PRO=Patient Reported Outcome (2 of the patient-reported items of the CDAI [SF and AP]); pts=patients; W=Week