Efficacy and safety of mirikizumab as induction therapy in patients with moderately to severely active ulcerative colitis: Results from the Phase 3 LUCENT-1 study

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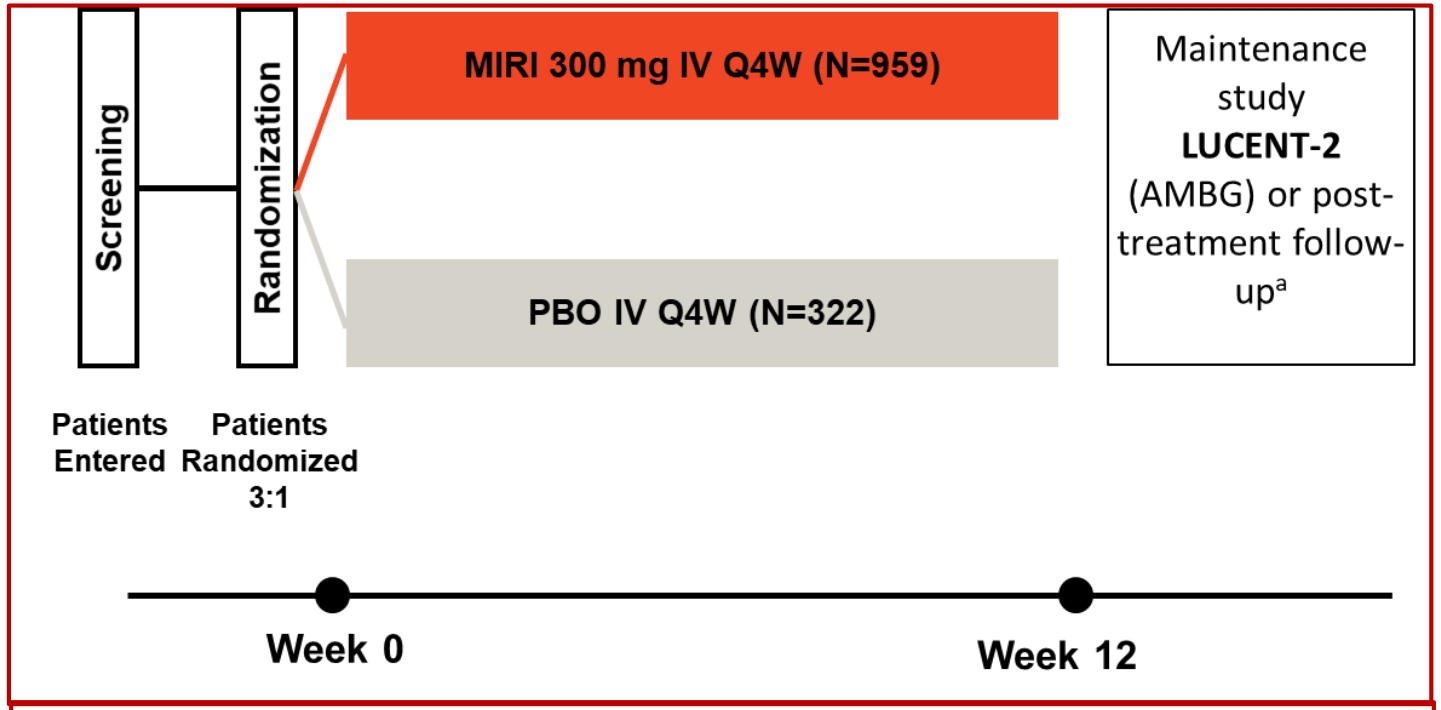
Mirikizumab and Ulcerative Colitis

- Ulcerative colitis (UC) is a chronic, relapsing-remitting disease of unknown etiology that is characterized by inflammation of the rectum and colon.
- Interleukin-23 (IL-23) has been identified as a pro-inflammatory factor in mucosal inflammation in UC.
- Mirikizumab is a humanized, IgG4 monoclonal antibody directed against the p19 subunit of IL-23 and has demonstrated efficacy versus placebo in a Phase 2 study in patients with moderately to severely active UC (NCT02589665).
- LUCENT-1 was a Phase 3, multi-center, randomized, parallel-arm, double-blind, placebo-controlled trial of mirikizumab in patients with moderately to severely active UC.

LUCENT-1 Overview



Randomization was stratified by biologic failure status, baseline corticosteroid use, baseline disease activity as measured by modified Mayo score, and world region.

Study Population

- Aged ≥18 and ≤80 years
- Moderately to severely active UC (Modified Mayo Score of 4 to 9 with endoscopic subscore ≥2)
- Inadequate response, loss of response, or intolerance to ≥1:
  - Corticosteroid or immunomodulator
  - Biologic (TNF inhibitor or anti-integrin antibody)
  - JAK inhibitor (tofacitinib)
- Excluded patients with prior exposure to anti-IL-12/23p40 or anti-IL-23p19 antibodies or failed ≥3 prior biologic therapies for UC

[a]Patients who discontinued treatment prior to the Week 12 assessment, or those unable or unwilling to participate in the maintenance study LUCENT-2 (AMBG), completed post-treatment follow-up 16 weeks after their last visit.

Objectives

Primary objective

Determine whether mirikizumab is superior to PBO in inducing clinical remission at Week 12

Key secondary objectives:

- Clinical response
- Endoscopic remission
- Symptomatic remission
- Clinical response in biologic-failed patients
- Histologic-endoscopic mucosal improvement (HEMI)
- Improvement in bowel urgency

- Mixed Model for Repeated Measures was used to assess urgency.
- The Cochran-Mantel-Haenszel test, with missing data imputed as nonresponse (NRI), was used to assess all other outcomes.
- A p value of 0.00125 was considered significant.

Baseline Demographics and Disease Characteristics

	PBO N=294	Miri 300 mg IV N=868
Age (years), mean (SD)	41.3 (13.8)	42.9 (13.9)
Male, n (%)	165 (56.1)	530 (61.1)
Weight (kg), mean (SD)	70.9 (16.7)	72.6 (17.3)
Disease duration (years), mean (SD)	6.9 (7.0)	7.2 (6.7)
Disease extent, n (%)		
Left-sided colitis	188 (64.2)	544 (62.7)
Pancolitis	103 (35.2)	318 (36.6)
Modified Mayo Score category, n (%)		
Moderate (4-6)	138 (47.1)	404 (46.5)
Severe (7-9)	155 (52.9)	463 (53.3)
Mayo endoscopic subscore: severe disease (3), n (%)	200 (68.3)	574 (66.1)
Bowel Urgency severity[a], median (Q1, Q3)	7.0 (5.0, 8.0)	6.0 (5.0, 8.0)
Fecal calprotectin (fCLP), µg/g, median (Q1, Q3)	1471.5 (626.5, 2944.5)	1559.0 (634.0, 3210.0)
C-reactive protein (CRP), mg/L, median (Q1, Q3)	4.2 (1.2, 9.5)	4.1 (1.5, 9.6)

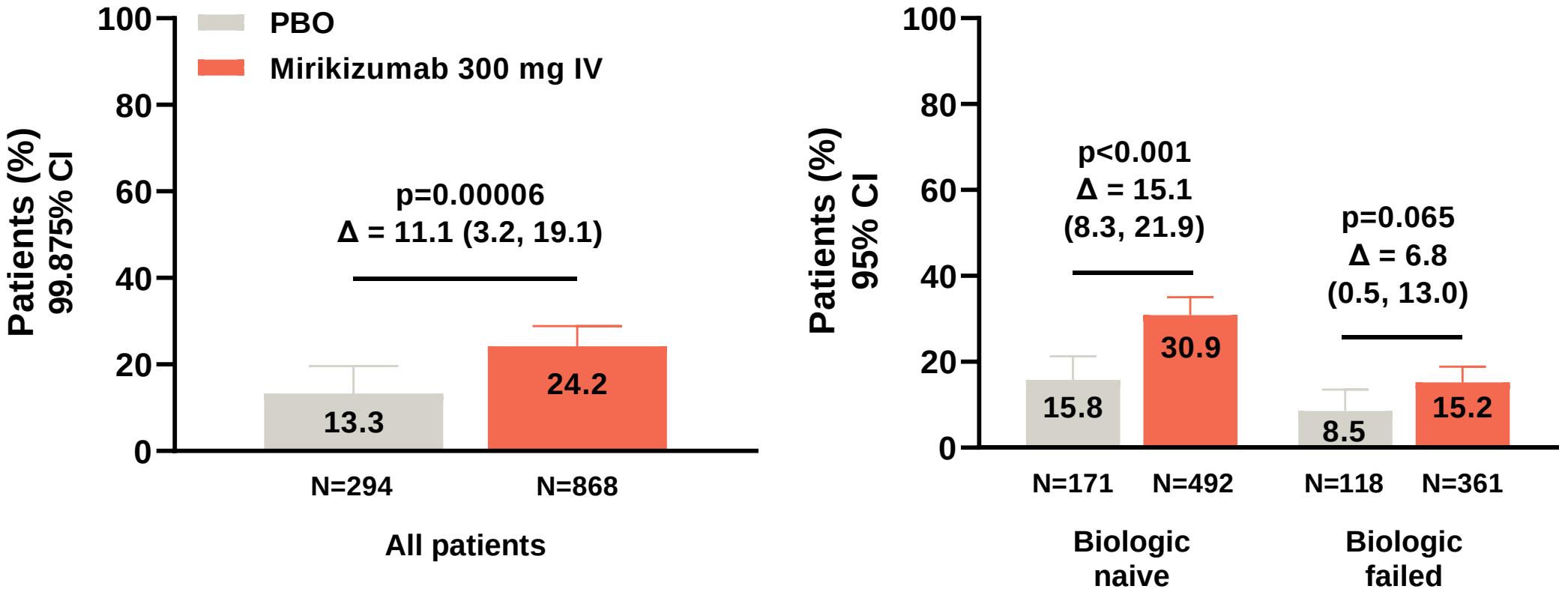
a The Urgency Numeric Rating Scale (NRS) is a patient-reported measure of the severity for the urgency (sudden or immediate need) to have a bowel movement in the past 24 hours using an 11-point NRS ranging from 0 (no urgency) to 10 (worst possible urgency). Q=quartile

Baseline and Prior UC Therapy

	PBO N=294	Miri 300 mg IV N=868
Baseline corticosteroid use, n (%)	113 (38.4)	351 (40.4)
Baseline immunomodulator use, n (%)	69 (23.5)	211 (24.3)
Prior biologic (or tofacitinib) failure, n (%)	118 (40.1)	361 (41.6)
Prior anti-TNF failure, n (%)	97 (33.0)	325 (37.4)
Prior vedolizumab failure, n (%)	59 (20.1)	159 (18.3)
Prior tofacitinib failure, n (%)	6 (2.0)	34 (3.9)
Number of failed biologics (or tofacitinib), n (%)*		
0	176 (59.9)	507 (58.4)
1	65 (22.1)	180 (20.7)
2	49 (16.7)	154 (17.7)
>2	4 (1.4)	27 (3.1)

*In the published abstract the ITT population values for number of failed biologics were reported. To ensure consistency with other endpoints, here we report those data in the modified ITT population which excludes patients impacted by the eCOA transcription error in Poland and Turkey.

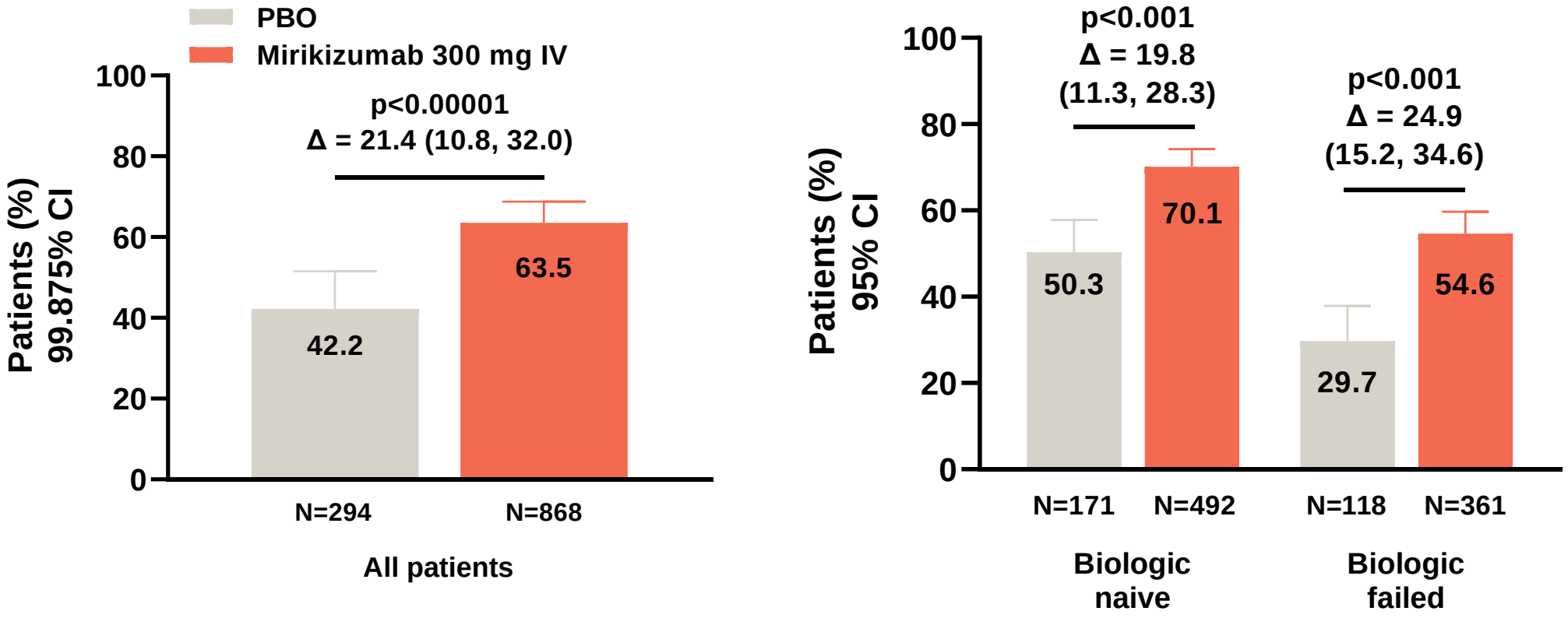
Clinical Remission, Week 12



Clinical Remission: Stool frequency (SF) = 0, or SF = 1 with a ≥1-point decrease from baseline; rectal bleeding = 0; Mayo endoscopic subscore = 0 or 1 (excluding friability)

Biologic naïve/failed includes tofacitinib naïve/failed patients; a small group of patients were exposed, but not failed, to biologics or tofacitinib (PBO N=5, miri N=15); the Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups while adjusting for the stratification factors. A p value of 0.00125 was considered significant. Subgroup analyses by biologic-failed status in the right panel were not multiplicity controlled. Δ indicates common risk difference vs placebo.

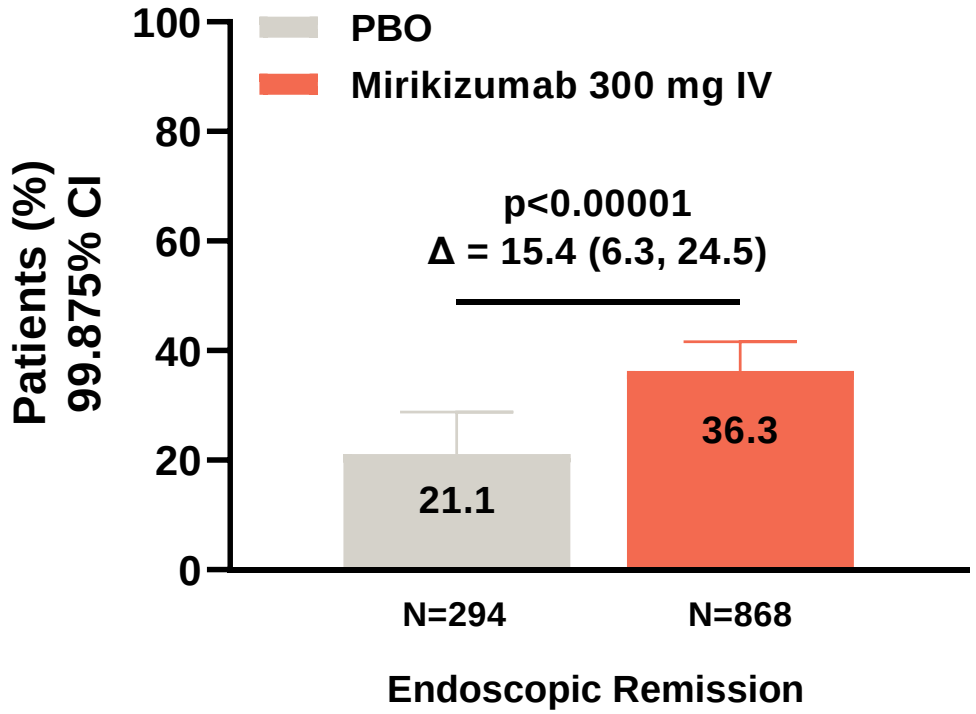
Clinical Response, Week 12

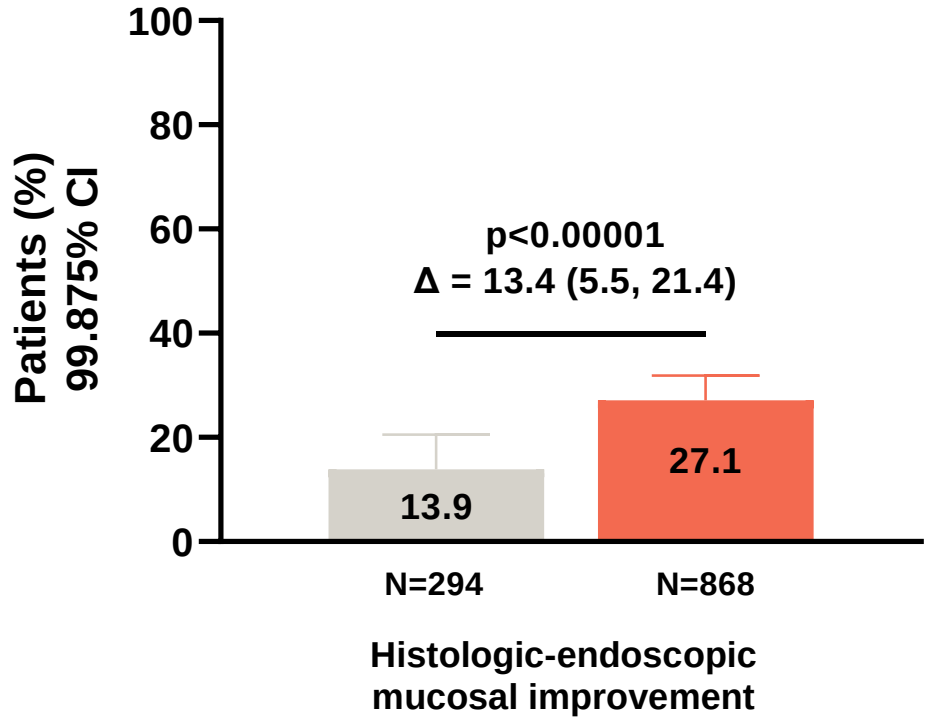


Clinical Response: decrease in the modified Mayo score of ≥2 points and ≥30% decrease from baseline (BL), and decrease of ≥1 point in the rectal bleeding (RB) subscore from BL or an RB score of 0 or 1

Biologic naïve/failed includes tofacitinib naïve/failed patients; a small group of patients were exposed, but not failed, to biologics or tofacitinib (PBO N=5, miri N=15); the Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups while adjusting for the stratification factors. A p value of 0.00125 was considered significant. Subgroup analyses by biologic-naive status in the right panel were not multiplicity controlled. Δ indicates common risk difference vs placebo.

Endoscopic and Histologic Endpoints, Week 12

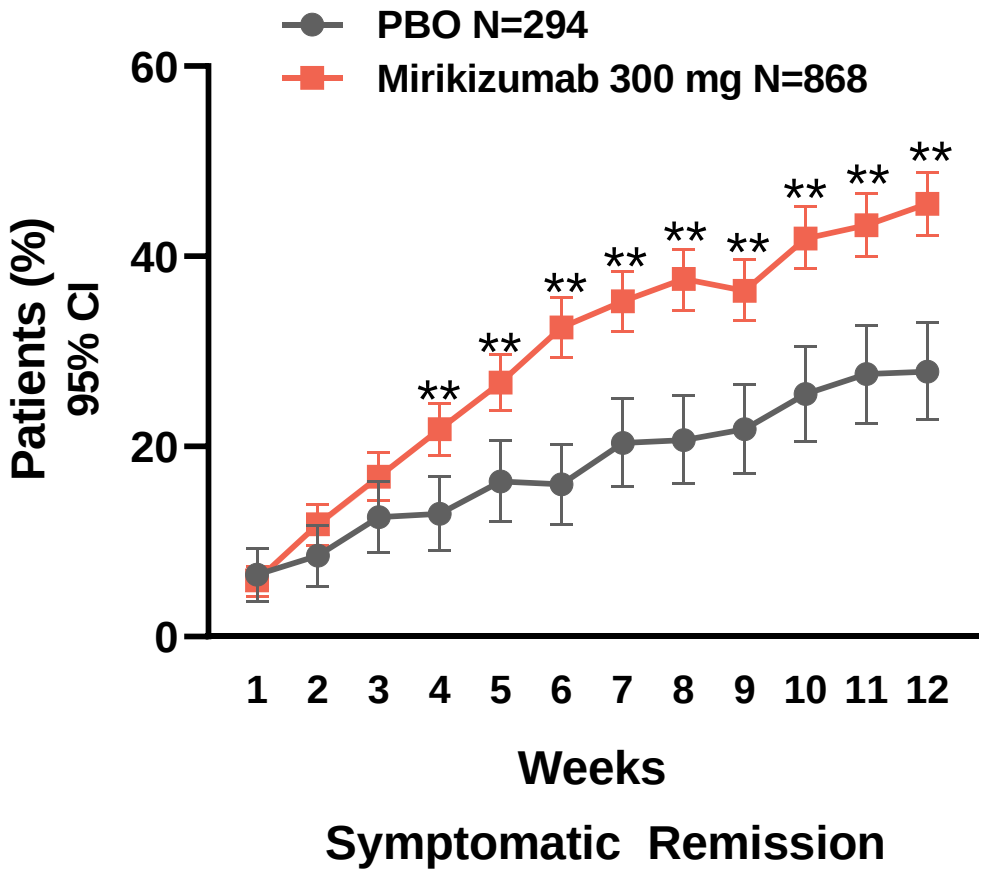




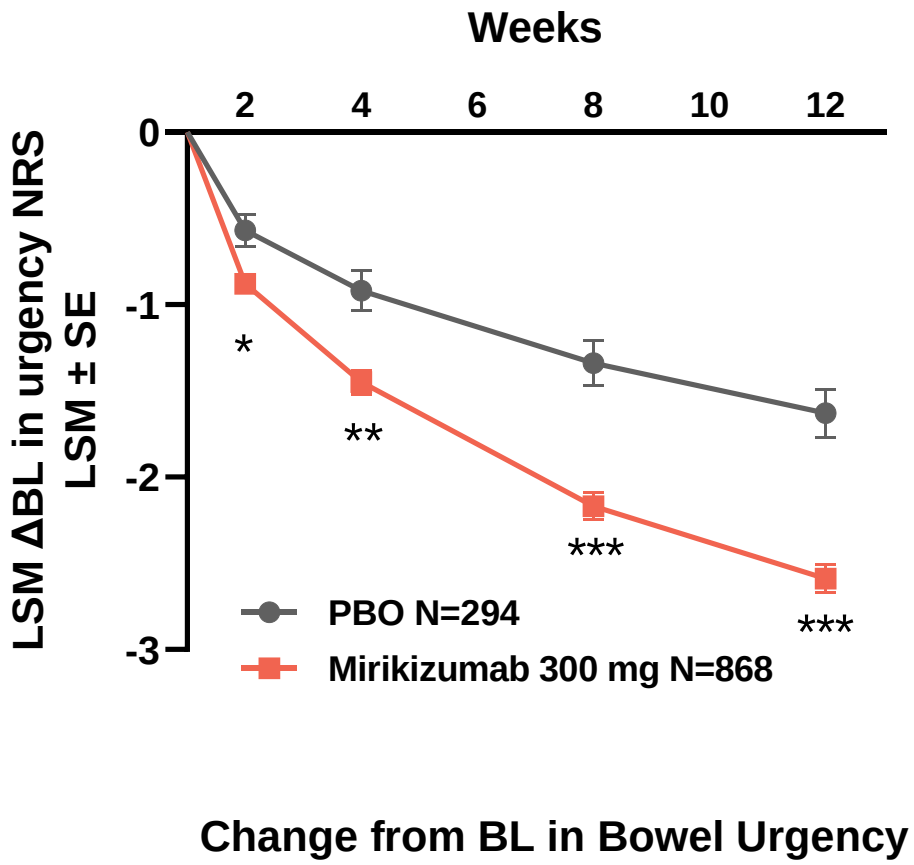
Endoscopic Remission: Mayo endoscopic subscore = 0 or 1 (excluding friability)
HEMI: Histologic improvement, defined using Geboes scoring system with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue; and endoscopic remission.

The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups while adjusting for the stratification factors. A p value of 0.00125 was considered significant. Δ indicates common risk difference vs placebo.

Symptomatic Endpoints During Induction



Symptomatic Remission



Change from BL in Bowel Urgency

Symptomatic Remission: stool frequency (SF) = 0, or SF = 1 with a ≥1-point decrease from baseline and rectal bleeding = 0
Urgency NRS (numeric rating scale) ΔBL: least square mean change in urgency NRS from baseline

The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups for symptomatic remission while adjusting for the stratification factors. Mixed Model for Repeated Measures (MMRM) was used to compare the treatment groups for bowel movement urgency improvement

Safety

	PBO N=321	Miri 300 mg IV N=958
TEAE, n (%)	148 (46.1)	426 (44.5)
Most common TEAEs (≥3% in any treatment group[a]), n (%)		
Nasopharyngitis	10 (3.1)	39 (4.1)
Anemia	19 (5.9)	32 (3.3)
Headache	9 (2.8)	32 (3.3)
Ulcerative colitis	24 (7.5)	17 (1.8)
AEs of interest		
Infections: All	45 (14.0)	145 (15.1)
Infections: Serious	2 (0.6)	7 (0.7)
Infections: Opportunistic	1 (0.3)	5 (0.5)
Cerebrocardiovascular events[b]	2 (0.6)	1 (0.1)
Malignancies[c]	0	2 (0.2)
Depression[d]	2 (0.6)	4 (0.4)
Hepatic	5 (1.6)	15 (1.6)
Immediate hypersensitivity events[e]	1 (0.3)	10 (1.0)
Infusion reactions	1 (0.3)	4 (0.4)
SAE, n (%)	17 (5.3)	27 (2.8)
Discontinuation due to AE, n (%)	23 (7.2)	15 (1.6)
Deaths, n (%)	0	0

TEAE=treatment-emergent adverse events; SAE=serious adverse events; AE=adverse events; a: by decreasing frequency in mirikizumab arm; b: no instances of major adverse cardiac event (MACE) in either arm; c: two instances of colon cancer; d: no incidences of suicide or self-injury; e: within 24 hours of drug administration, or on the day of drug administration when time is missing. No serious hypersensitivity or anaphylactic reactions.

Conclusions

- Mirikizumab demonstrated superiority over placebo in this induction study for the primary endpoint of clinical remission at 12 weeks, as well as all key secondary endpoints across clinical, endoscopic, histologic, and symptomatic measures.
  - All gated endpoints were achieved with high statistical significance and clinically meaningful effect sizes.
- Symptoms, including bowel urgency, were significantly reduced with mirikizumab compared to placebo.
  - Significant decrease in bowel urgency as early as 2 weeks after starting treatment.
  - Significantly improved symptomatic remission rates as early as 4 weeks after starting treatment.
- The frequency of SAEs and discontinuations due to AE among patients treated with mirikizumab were numerically lower compared to placebo.
- The overall safety profile was similar to that of previous mirikizumab studies in UC and consistent with that of other anti-IL-23p19 antibodies.
- These results confirm the efficacy and safety noted in the Phase 2 induction data and supports mirikizumab's potential as a treatment for UC.
- Maintenance data are forthcoming.