Efficacy and safety of mirikizumab as maintenance therapy in patients with moderately to severely active ulcerative colitis: Results from the Phase 3 LUCENT-2 study

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Disclosures

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- Consultant for Abbvie, Arena, BMS, Celgene, Eli Lilly, Gilead, Janssen, Prometheus Labs, Prometheus Biosciences, Takeda, Target RWE
- Mirikizumab Steering Committee Member
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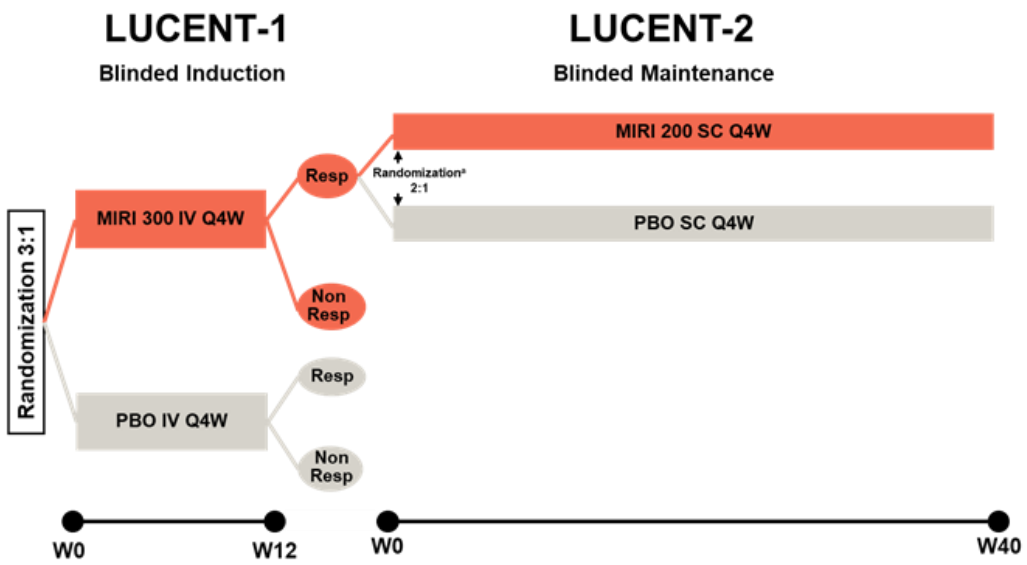
Mirikizumab and Ulcerative Colitis

- Interleukin-23 (IL-23) has been identified as a pro-inflammatory cytokine leading to mucosal inflammation in ulcerative colitis (UC).
- Mirikizumab is a humanized, IgG4 monoclonal antibody directed against the p19 subunit of IL-23.
- Mirikizumab demonstrated superiority to placebo in inducing clinical remission, as well as other symptomatic, clinical, endoscopic and histologic endpoints, and had an acceptable safety profile in the Phase 3 LUCENT-1 induction study (NCT03518086) in patients with moderately to severely active UC.
- LUCENT-2 was a Phase 3, double-blind, randomized withdrawal maintenance study in patients who responded to mirikizumab induction therapy in LUCENT-1.

LUCENT-2 Overview



LUCENT-2 Primary Efficacy Population

- Clinical responders to induction mirikizumab therapy at Week 12 of LUCENT-1 were randomized to receive maintenance mirikizumab therapy or placebo for 40 weeks.
- Patients were randomized in a 2:1 ratio to 200 mg mirikizumab SC or placebo SC every 4 weeks through Week 40 of LUCENT-2 (52 weeks mirikizumab treatment).

Resp = responders; Non Resp = non-responders; SC = subcutaneous
Clinical response: ≥2-point and ≥30% decrease in the modified Mayo score (MMS) from baseline with RB = 0 or 1, or ≥1-point decrease from baseline
a: Randomization was stratified by induction remission status, biologic failure status, baseline corticosteroid use, and world region.

Only data from induction mirikizumab responders randomized to maintenance treatment are presented here. Other LUCENT-2 arms will be presented in future disclosures.

LUCENT-2 Outcomes and Statistical Methods

Primary outcome

Clinical remission at Week 40 (52 weeks of mirikizumab treatment)

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

Key secondary outcomes (all multiplicity controlled):

- Corticosteroid-free clinical remission
- Maintenance of clinical remission
- Endoscopic remission
- Histologic-endoscopic mucosal remission (HEMR)
- Improvement in bowel urgency
- Bowel urgency remission

Statistical Methodology

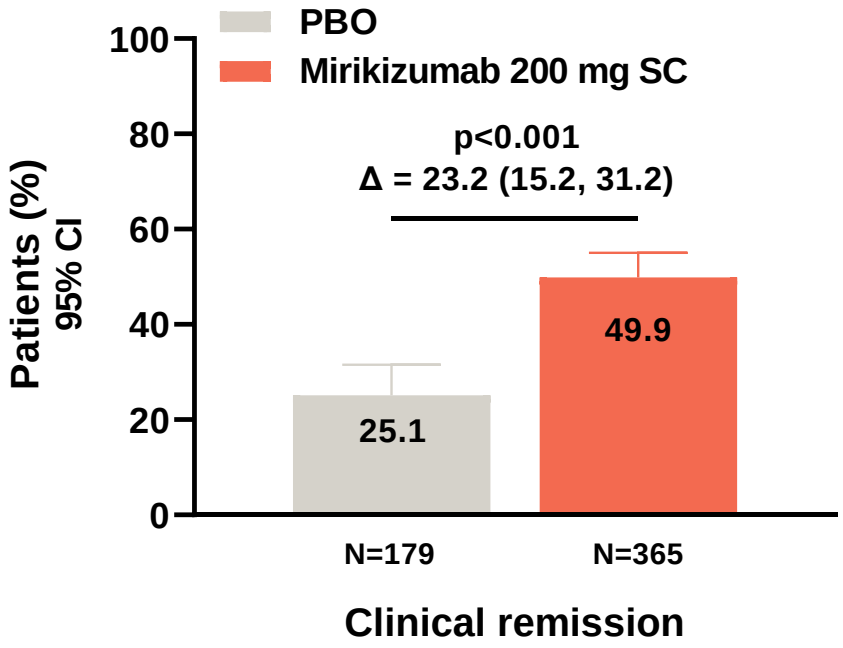
- Mixed Model for Repeated Measures was used to assess improvement in bowel urgency
- The Cochran-Mantel-Haenszel test (CMH), with missing data considered as non-response (NRI), was used across all other outcomes

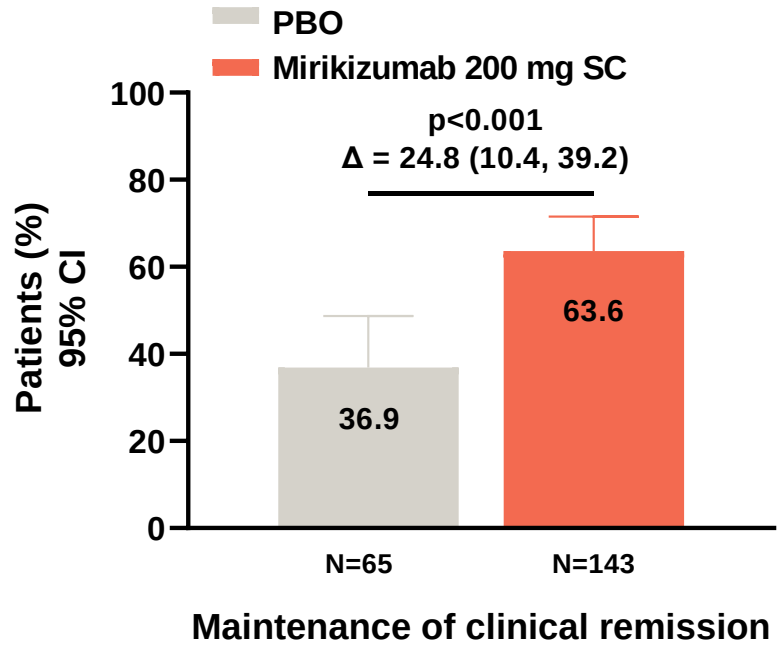
LUCENT-2 Baseline Characteristics

	PBO N=179	Miri 200 mg SC N=365
Age (years), mean (SD)	41.2 (12.8)	43.4 (14.2)
Male, n (%)	104 (58.1)	214 (58.6)
Disease duration (years), mean (SD)	6.7 (5.6)	6.9 (7.1)
Bowel Urgency severity[a], median (Q1, Q3)	6.0 (5.0, 8.0)	6.0 (5.0, 8.0)
Baseline corticosteroid use, n (%)	68 (38.0)	135 (37.0)
Baseline immunomodulator use, n (%)	39 (21.8)	78 (21.4)
Prior biologic (or tofacitinib) failure, n (%)	64 (35.8)	128 (35.1)
Prior anti-TNF failure, n (%)	58 (32.4)	112 (30.7)
Prior vedolizumab failure, n (%)	23 (12.8)	47 (12.9)
Prior tofacitinib failure, n (%)	8 (4.5)	8 (2.2)

"Baseline" refers to induction baseline (Week 0 of LUCENT-1). [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).
miri=mirikizumab; PBO=placebo; Q=quartile; SD=standard deviation

Clinical Remission after 52 Weeks Treatment (Week 40 of Maintenance)





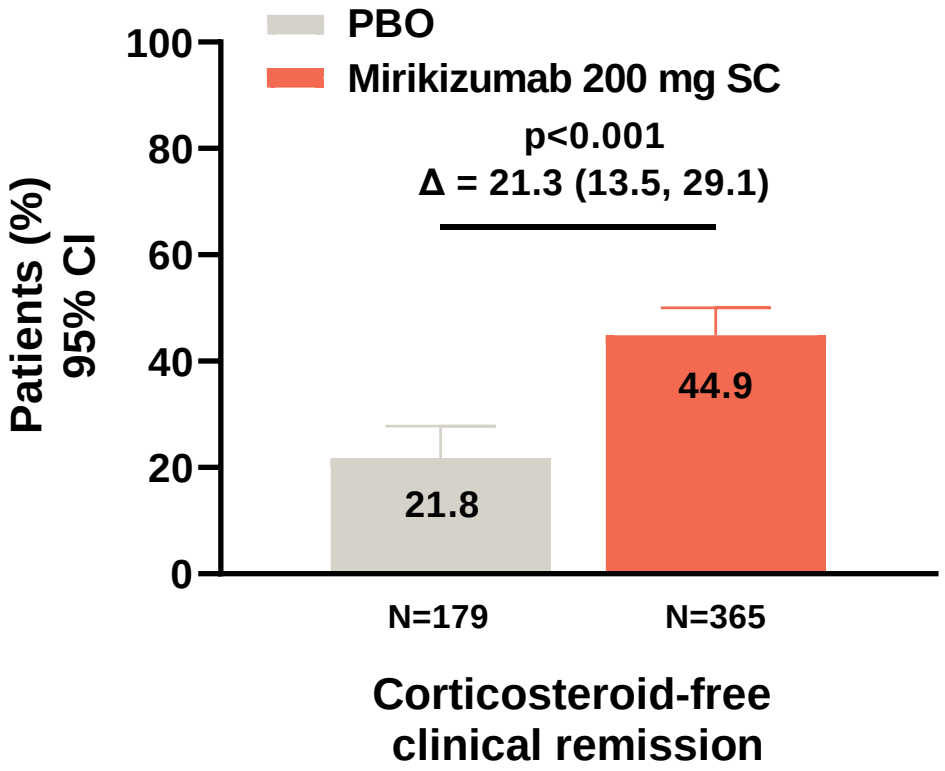
97.8% of mirikizumab treated patients in Clinical Remission at Week 40 were off corticosteroids

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

Maintenance of Clinical Remission: Clinical remission at Week 40 of maintenance in patients induced into clinical remission with mirikizumab at Week 12 of LUCENT-1

The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups. Δ indicates common risk difference vs placebo.

Corticosteroid-free Clinical Remission after 52 Weeks Treatment



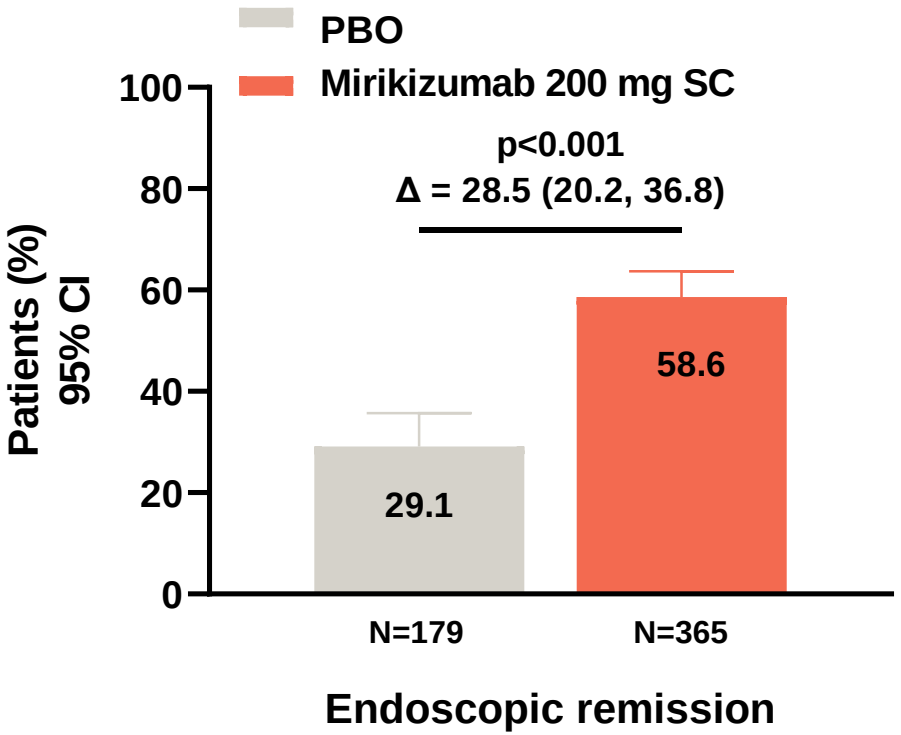
Corticosteroid Tapering: Corticosteroids were tapered starting at Week 0 of LUCENT-2 in patients who achieved clinical response in the LUCENT-1 induction study.

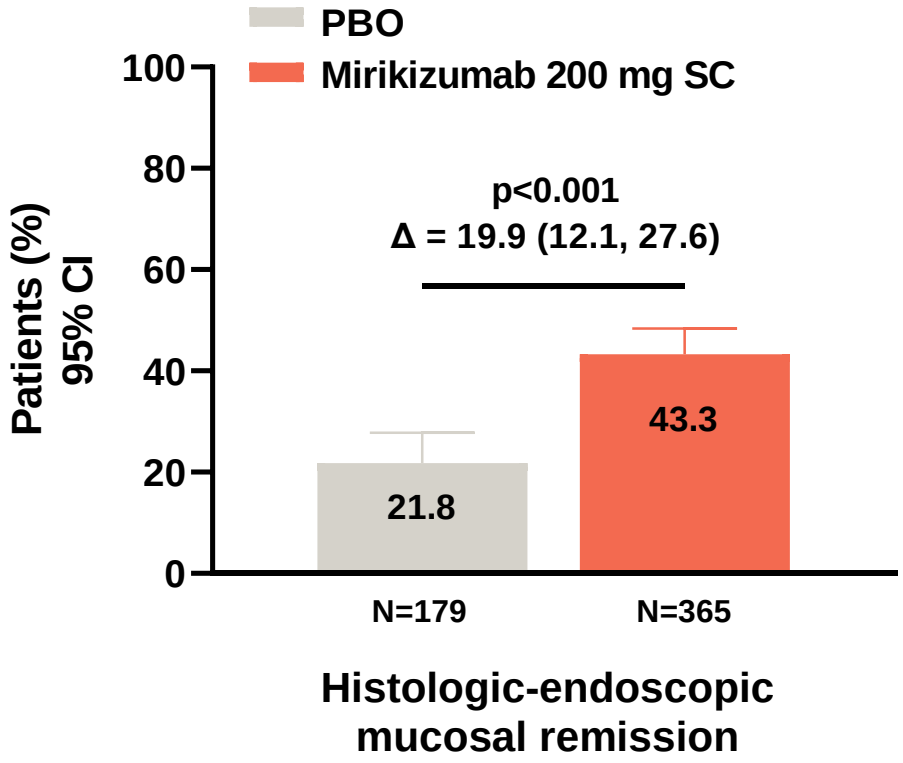
If patients could not tolerate the corticosteroid taper without recurrence of clinical symptoms, tapering was paused and/or corticosteroid dose increased up to baseline dose.

Corticosteroid-free clinical remission: Clinical remission at Week 40, and symptomatic remission (SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline; and RB=0) at Week 28, **and no corticosteroid use for ≥12 weeks prior to Week 40**

The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups. Δ indicates common risk difference vs placebo.

Endoscopic and Histologic Endpoints after 52 Weeks Treatment



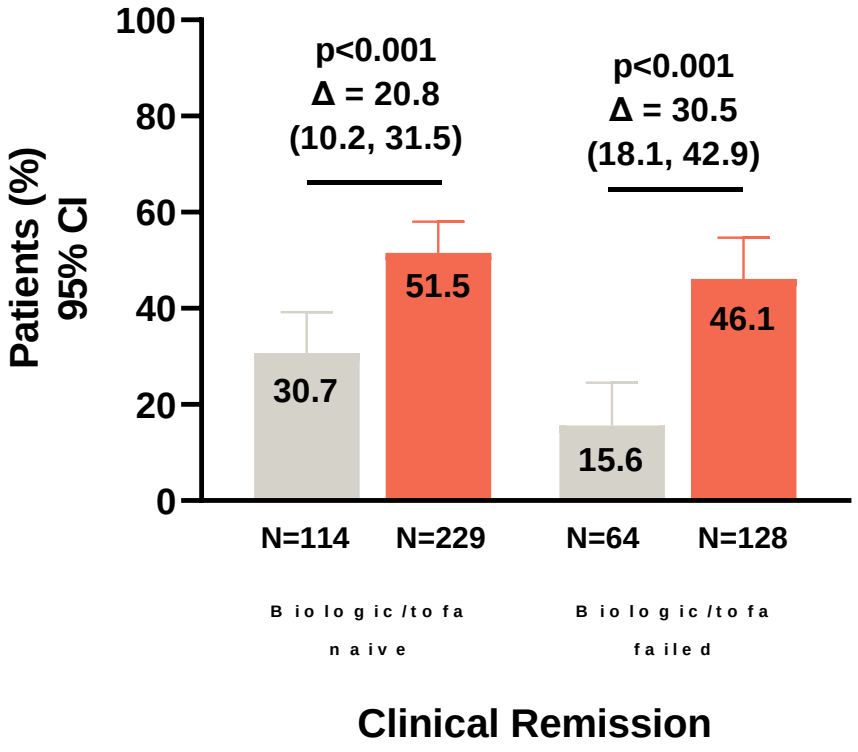


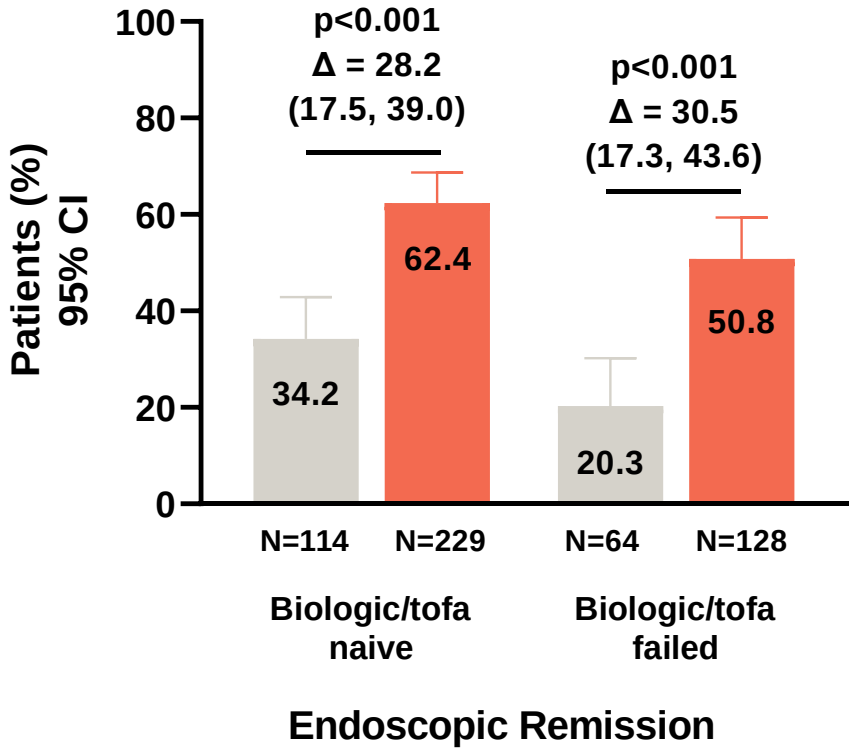
Endoscopic Remission: Endoscopic subscore = 0 or 1 (excluding friability)

HEMR: Histologic remission with resolution of mucosal neutrophils, determined by Geboes ≤2B.0 score

The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups. Δ indicates common risk difference vs placebo.

LUCENT-2 Endpoints by Biologic/Tofacitinib Failure Status



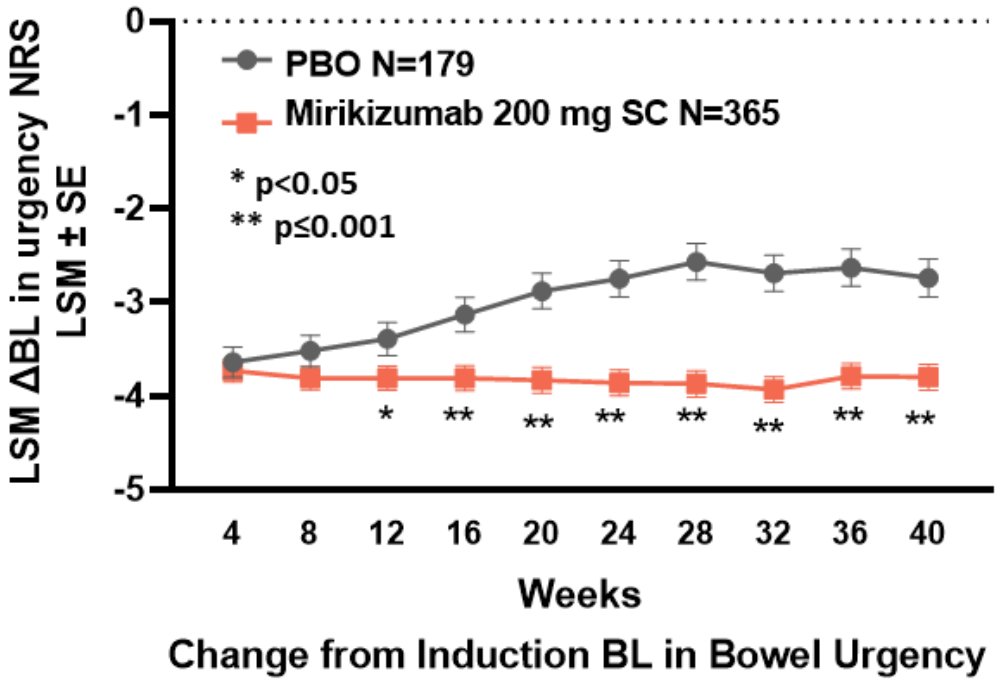


Clinical Remission: Stool frequency (SF) = 0, or SF = 1 with a ≥1-point decrease from baseline; rectal bleeding (RB) = 0; endoscopic subscore (ES) = 0 or 1 (excluding friability)

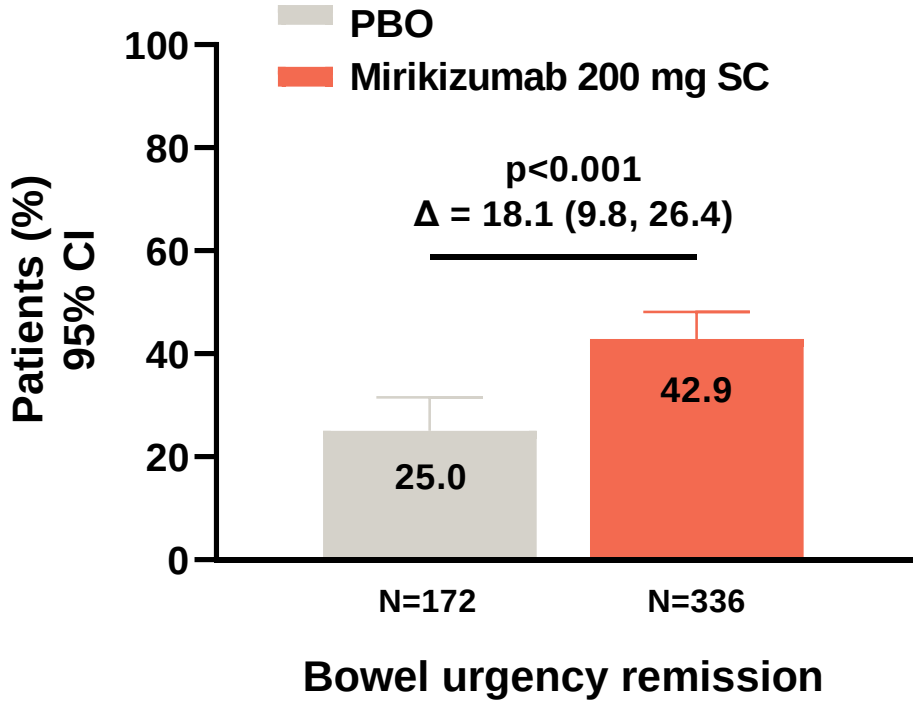
Endoscopic Remission: ES = 0 or 1 (excluding friability)

The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups. Δ indicates common risk difference vs placebo.

LUCENT-2 Bowel Urgency Endpoints



Change from Induction BL in Bowel Urgency



Bowel urgency remission

Bowel Urgency Improvement: Least square mean change in Urgency Numeric Rating Scale (NRS) from baseline

Bowel Urgency Remission: Urgency NRS = 0 or 1 in patients with Urgency NRS ≥3 at LUCENT-1 baseline

The Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment groups for urgency remission. Mixed Model for Repeated Measures (MMRM) was used to compare the treatment groups for bowel movement urgency improvement. Δ indicates common risk difference vs placebo.

LUCENT-2 Safety: Overview

	PBO N=192	Miri 200 mg SC N=389
TEAE, n (%)	132 (68.8)	251 (64.5)
Common TEAEs (≥3% in any treatment group[a]), n (%)		
Nasopharyngitis	11 (5.7)	28 (7.2)
Arthralgia	8 (4.2)	26 (6.7)
Ulcerative colitis	40 (20.8)	26 (6.7)
Injection site pain	6 (3.1)	17 (4.4)
Headache	2 (1.0)	16 (4.1)
Rash	0	14 (3.6)
Pyrexia	5 (2.6)	13 (3.3)
Anaemia	9 (4.7)	8 (2.1)
SAE, n (%)	15 (7.8)	13 (3.3)
Discontinuation due to AE, n (%)	16 (8.3)	6 (1.5)
Deaths[b], n (%)	1 (0.5)	0

TEAE=treatment-emergent adverse events; SAE=serious adverse events; AE=adverse events. a: by decreasing frequency in mirikizumab arm; b: placebo patient death was due to COVID-19 infection.

LUCENT-2 Safety: AEs of interest

	PBO N=192	Miri 200 mg SC N=389
Infections: All	44 (22.9)	93 (23.9)
Infections: Serious	3 (1.6)	3 (0.8)
Infections: Opportunistic[a]	0	5 (1.3)
Adjudicated cerebrocardiovascular events[b]	1 (0.5)	0
Malignancies[c]	1 (0.5)	1 (0.3)
Depression[d]	0	4 (1.0)
Suicide/self-injury[e]	0	1 (0.3)
Hepatic-related AEs	4 (2.1)	12 (3.1)
Immediate hypersensitivity events[f]	2 (1.0)	7 (1.8)
Injection site reactions	8 (4.2)	34 (8.7)

AE=adverse events; miri=mirikizumab; PBO=placebo; **a:** Based on Winthrop et al. (2015). One oral candidiasis and 4 herpes zoster infections in miri group; **b:** One adjudicated ischemic stroke in PBO group; **c:** One basal cell carcinoma in PBO group, one gastric cancer in miri group; **d:** Excluding suicide or self-injury;
e: One attempted suicide not considered related to study drug by investigator; **f:** One anaphylaxis in PBO group; no anaphylaxis, serious hypersensitivity reactions or discontinuations in miri group

LUCENT-2 Summary

- The primary endpoint of Clinical Remission and all key secondary endpoints across clinical, symptomatic, endoscopic, and histologic measures were met with statistical significance and clinically meaningful effect sizes after 52 weeks of mirikizumab treatment.
- Bowel Movement Urgency was measured using a novel NRS scale. Mirikizumab significantly improved bowel urgency severity compared to placebo after 52 weeks of treatment.
- After 52 weeks of treatment a significantly greater proportion of patients treated with mirikizumab compared to placebo achieved Urgency Remission (no or minimal urgency).
- The overall safety profile was similar to that of previous mirikizumab studies in UC and consistent with the safety profile of other anti-IL-23p19 antibodies.

LUCENT-2 Overall Conclusions

- Mirikizumab 200mg SC Q4W was effective as maintenance treatment for UC in patients who achieved Clinical Response to induction treatment with miri 300mg IV Q4W.
- The majority of patients (97.8%) treated with mirikizumab who achieved Clinical Remission after 52 weeks of treatment were off corticosteroids for at least 12 weeks.
- Mirikizumab is the first IL-23 p19-targeted biologic demonstrating efficacy in a Phase 3 trial of patients with moderately to severely active ulcerative colitis regardless of biologic or tofacitinib failed status.