Efficacy and Safety of Continued Treatment With Mirikizumab in a Phase 2 Trial of Patients With Ulcerative Colitis

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BACKGROUND & AIMS: **Mirikizumab is an antibody against the p19 subunit of interleukin 23 that has demonstrated clinical efficacy and was well tolerated following 12 weeks of induction treatment in a phase 2 trial of patients with moderate to severe ulcerative colitis. We present results of the open-label extended induction period in patients who did not initially respond to treatment with mirikizumab.**

METHODS: **This study was a continuation of I6T-MC-AMAC, a double-blind trial, performed at 75 sites in 14 countries, in which patients with moderate to severe ulcerative colitis were randomly assigned to 12 weeks induction therapy with 50 mg, 200 mg, or 600 mg mirikizumab or placebo. Patients without a clinical response (a 9-point decrease in Mayo subscore of ≥2 points and ≥35% from baseline and either a decrease of rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1) at week 12 were offered the opportunity to participate in an open-label, extended induction study for another 12 weeks, in which they received either 600 mg intravenous mirikizumab (n = 20) or, following a protocol amendment, 1000 mg intravenous mirikizumab (n = 64) every 4 weeks. At week 24, patients with a clinical response continued the extension maintenance period and received 200 mg subcutaneous mirikizumab. Endpoints included clinical remission (Mayo subscores of 0 for rectal bleeding, 0 or 1 with a 1-point decrease from baseline), clinical response, endoscopic remission (Mayo endoscopic subscore of 0), or endoscopic improvement (endoscopic subscore of 0 or 1), at study weeks 24 and 52. Data were analysed for patients who received mirikizumab or placebo during the induction phase of the study.**

RESULTS: **Among participants who did not respond to induction mirikizumab, 50.0% of those who received the 12-week extension of 600 mg mirikizumab and 43.8% who received the extension of 1000 mg mirikizumab achieved a clinical response; 15.0% and 9.4% achieved clinical remission, respectively. Endoscopic improvement was achieved by 20.0% of subjects in the 600 mg mirikizumab group and 15.6% subjects in the 1000 mg mirikizumab group. Among initial nonresponders to mirikizumab who had clinical response at study week 24 and continued into maintenance therapy, 65.8% maintained the clinical response, 26.3% achieved clinical remission, and 34.2% had endoscopic improvement at week 52. No new safety concerns were identified.**

CONCLUSIONS: **Extended doses of mirikizumab (600 mg and 1000 mg) for an additional 12 weeks produce a clinical response in up to 50% of patients who did not have a clinical response to 12 weeks of induction doses (50 mg, 200 mg, or 600 mg). Most of the responders to the extended doses maintained clinical response for up to 52 weeks. Clinicaltrials.gov no: NCT02589665**

Keywords: IBD; Drug; UC; Outcome.

Abbreviations used in this paper: CRP, C-reactive protein; EI, extended intravenous induction; EM, maintenance treatment; fCLP, fecal calprotectin; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; IND, induction; IV, intravenous; NR, nonresponder; pbo, placebo; SAE, serious adverse event; SF-36, Short Form 36; TNF, tumor necrosis factor; UC, ulcerative colitis.

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Ulcerative colitis (UC) is a chronic inflammatory disease characterized by mucosal inflammation of the colon and rectum, with typical symptoms of rectal bleeding, diarrhea, and urgency.[1] Current guidance from the American College of Gastroenterology states that a goal of medical management is to reduce symptoms by controlling mucosal inflammation, with an ultimate intent of preventing disability, colectomy, and colorectal cancer.[2] Aminosalicylates, corticosteroids, and thiopurines, alone or in combination, are frequently used as initial therapy.[1] Agents targeting tumor necrosis factor (TNF) (infliximab, adalimumab, golimumab), integrins (vedolizumab), interleukin (IL) 12/23 (p40), and Janus kinases (tofacitinib) are effective in patients who are refractory or intolerant to conventional or biologic therapy, or who have more severe disease activity or worse prognosis.[3–8] However, many patients have an inadequate response or lose response over time to these advanced treatments, leading to a need for new therapies.

Interleukin 23 (IL23), a member of the IL12 family of cytokines, has 2 components: the p40 subunit, which is shared by IL12, and the p19 subunit, which is part of IL23 but not IL12. IL23 plays a key role in the maintenance and amplification of T-helper 17 cells and stimulation of many innate immune cells, which are important in the pathogenesis of UC.[9–12] Ustekinumab, a monoclonal antibody directed to the p40 subunit of IL12 and IL23, has shown efficacy in treatment of UC.[13] Mirikizumab (LY3074828) is a humanized immunoglobulin G4 variant monoclonal antibody that specifically binds to the p19 subunit of IL23. Mirikizumab has demonstrated clinical efficacy in phase 2 studies of psoriasis,[14] Crohn's disease,[15] and UC.[16]

Induction regimens evaluated in most clinical trials are ≤12 weeks, and some patients, especially those less responsive to initial induction treatment, could potentially improve with additional intravenous (IV) induction doses of mirikizumab. We evaluated the safety and efficacy of 12 weeks of extended intravenous induction (EI) with mirikizumab, followed by an additional 28 weeks of maintenance treatment (EM) with subcutaneous administration of mirikizumab for those who responded to the extended induction.

What You Need to Know

Background

Mirikizumab is an antibody against the p19 subunit of interleukin 23 that has clinical efficacy and was well-tolerated after 12 weeks of induction treatment in a phase 2 trial of patients with moderate to severe ulcerative colitis.

Findings

Extended doses of mirikizumab (600 mg and 1000 mg) for 12 weeks produce a clinical response in up to 50% of patients who did not have a clinical response to 12 weeks of induction doses (50 mg, 200 mg, or 600 mg). Most of the responders to the extended doses maintained clinical response for up to 52 weeks.

Implications for patient care

Extended induction treatment with mirikizumab in patients who did not respond during the first 12 weeks resulted in clinical benefit and is a strategy that could be incorporated into clinical practice when mirikizumab becomes available.

Methods

Study Design and Participants

I6T-MC-AMAC was a multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial (study design, Supplementary Figure 1) that took place at 75 sites in 14 countries (see Supplementary Material for complete list of study sites). Patients were enrolled from January 2016 to September 2017 (see Supplementary Material for a full list of inclusion and exclusion criteria).

This study was compliant with the International Committee for Harmonisation guideline on good clinical practice. All informed consent forms and protocols were approved by appropriate ethical review boards before initiation of the study. All patients gave written informed consent before receiving the study drug.

Procedures

The 12-week placebo-controlled induction period was designed to establish the efficacy and safety of 50 mg or 200 mg of mirikizumab with the option of exposure-based dose adjustments or 600 mg of mirikizumab administered IV at weeks 0, 4, and 8. After 12 weeks of induction with mirikizumab or placebo, those patients who had not achieved clinical response (a decrease in 9-point Mayo subscore [composed of rectal bleeding, stool frequency, and endoscopy] of ≥2 points and ≥35% from baseline and either a decrease of rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1) had the option of participating in an open-label extended induction period. Initially, all patients continuing into the open-label extended induction period received 600 mg of mirikizumab, administered IV at study weeks 12, 16, and 20. After a protocol amendment, all subsequent patients received 1000 mg of mirikizumab instead. The protocol amendment (b) was primarily done to extend the maintenance part of the study another 52 weeks, but the sponsor also decided to increase the dose given to extension subjects to 1000 mg after review of 1200 mg safety data from a single-dose study in healthy subjects. Patients who responded to

treatment during the extended induction period had the option to continue into an extended maintenance period with 200 mg mirikizumab administered subcutaneously every 4 weeks.

Endoscopies were performed at study weeks 24 (after extended induction dosing) and 52 (28 weeks after extended induction dosing), and findings were scored by a blinded central reader to provide an objective evaluation of the appearance of the colonic mucosa. Histologic disease activity was assessed by a blinded central pathologist reader using samples from 2 biopsies obtained during endoscopy from the most affected area lying at least 30 cm from the anal verge (see Supplementary Material for additional details.)

Outcomes

Endpoints included clinical remission (Mayo subscores of 0 for rectal bleeding, 0 or 1 [with 1-point decrease from baseline] for stool frequency, and 0 or 1 for centrally read endoscopy); clinical response (defined above); endoscopic remission (Mayo endoscopic subscore of 0); and endoscopic improvement (endoscopic subscore of 0 or 1), at study week 24 and study week 52. Additional endpoints were histologic remission (Geboes histologic subscores of 0 for the neutrophils in lamina propria, neutrophils in epithelium, and erosion or ulceration parameters), change from baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ), Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Standard (SF-36), change in symptomatic score (rectal bleeding + stool frequency subscores) and symptomatic remission (stool frequency subscore of 0 or 1 plus a rectal bleeding subscore of 0), and change in the biomarkers C-reactive protein (CRP), fecal calprotectin (fCLP), IL17A, and IL22 (see Supplementary Material for biomarker analysis methods.)

Adverse events were coded according to the Medical Dictionary for Regulatory Activities Versions 19–21 and summarized by system organ class, preferred term, severity, and relationship to investigational product. A treatment-emergent adverse event was defined as an event that first occurred or worsened in severity after receipt of the study drug.

Statistical Analysis

The extended induction period population included patients who participated in the induction period, including those who received mirikizumab and those in the placebo group, who completed the induction period and did not achieve clinical response and who elected to continue into the extended induction period. After the extended induction period, responders had the option to continue into the extended maintenance period. All patients in the extended induction and maintenance periods received mirikizumab; therefore, the intent to treat population and the safety population were the same. Descriptive statistics were used to evaluate the baseline characteristics of participants.

Categorical outcome measures were analyzed by using a logistic regression model with treatment group, geographic region, prior biologic experience baseline status, and visit (when appropriate) in the model. Continuous endpoints were analyzed by using a mixed effect model repeat measurement technique with treatment, visit, geographic region, prior biologic experience status at baseline, treatment-by-visit interaction, the continuous variable value, fixed covariates of baseline value, and baseline value-by-visit interaction terms included in the model. Nonresponder (NR) imputation was used to impute missing data of categorical variables for patients who discontinued the study before receiving a study week 24 endoscopic assessment.

All authors had access to the study data and reviewed and approved the final manuscript. This study is registered with ClinicalTrials.gov, number NCT02589665.

Role of Funding Source

The funder of the study was involved in the study design, data collection, data analysis, and data interpretation. The study funder provided funding for writing support and editorial assistance with manuscript preparation.

Data Sharing Statement

Eli Lilly and Company (Lilly) provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request in a timely fashion after the indication studied has been approved in the US and EU and after primary publication acceptance. No expiration date of data requests is currently set once they are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

Results

Extended Induction

Between December 2015 and September 2017, 358 patients were screened for eligibility for the originator induction study; 249 were randomized for the 12-week

Table 1. Extended Induction Period Efficacy Results

	Blinded induction groups (nonresponders)			
	Induction miri NR		Induction pbo NR	
	OL EI miri IV 600 mg Q4W N = 20	OL EI miri IV 1000 mg Q4W N = 64	OL EI miri IV 600 mg Q4W N = 12	OL EI miri IV 1000 mg Q4W N = 32
Extension week 0 (study week 12)				
Symptomatic remission, n (%) [95% CI]	3 (15.0) [0.0–30.6]	11 (17.2) [7.9–26.4]	0 (0.0) [0.0–0.0]	4 (12.5) [1.0–24.0]
Symptomatic score	3.0 (1.4)	2.9 (1.5)	3.4 (1.1)	3.4 (1.3)
Change from BL	–0.6 (1.2)	–0.8 (1.2)	–0.1 (0.7)	–0.47 (0.9)
IBDQ	163.9 (29.2)	151.7 (39.9)	141.8 (37.8)	134.3 (40.1)
Change from BL	33.2 (42.2)	20.6 (32.8)	–1.1 (9.9)	–0.5 (14.8)
Extension week 12 (study week 24)				
Clinical remission, n (%) [95% CI]	3 (15) [0.0–30.6]	6 (9.4) [2.2–16.5]	3 (25.0) [0.5–49.5]	8 (25.0) [10.0–40.0]
Clinical response, n (%) [95% CI]	10 (50.0) [28.1–71.9]	28 (43.8) [31.6–55.9]	7 (58.3) [30.4–86.2]	23 (71.9) [56.3–87.5]
Endoscopic remission, n (%) [95% CI]	0 (0.0) [0.0–0.0]	2 (3.1) [0.0–7.4]	0 (0.0) [0.0–0.0]	3 (9.4) [0.0–19.5]
Endoscopic improvement, n (%) [95% CI]	4 (20.0) [2.5–37.5]	10 (15.6) [6.7–24.5]	3 (25.0) [0.5–49.5]	12 (37.5) [20.7–54.3]
Histologic remission, n (%) [95% CI]	5 (25.0) [6.0–44.0]	15 (23.4) [14.9–37.7]	3 (25.0) [1.0–53.6]	10 (31.5) [17.2–51.8]
RHI remission, n (%)	5 (25.0)	18 (28.1)	3 (25.0)	11 (34.4)
Symptomatic remission, n (%) [95% CI]	10 (50.0) [28.1–71.9]	25 (39.1)[27.1–51.0]	7 (58.3) [30.4–86.2]	18 (56.3) [39.1–73.4]
Symptomatic score	2.0 (1.7)	1.8 (1.3)	1.3 (1.2)	1.4 (1.2)
Change from BL	–1.7 (1.9)	–1.9 (1.6)	–2.1 (1.6)	–2.3 (1.3)
IBDQ	172.4 (27.9)	162.3 (40.8)	180.4 (41.8)	178.9 (27.4)
Change from BL	41.1 (33.4)	31.7 (38.8)	35.5 (35.9)	39.3 (38.6)
SF-36				
Physical Component Score	48.8 (7.6)	49.2 (7.4)	50.1 (8.3)	51.1 (6.2)
Mental Component Score	49.1 (8.4)	44.3 (11.9)	50.1 (11.9)	47.3 (9.4)
Change from BL				
Physical Component Score	6.3 (6.5)	6.5 (5.9)	5.5 (6.4)	5.3 (6.0)
Mental Component Score	8.9 (10.1)	5.5 (11.4)	8.1 (8.9)	6.5 (9.8)
CRP, *mg/L*, median (range)	2.3 (0.1–31.8)	3.5 (0.3–45.2)	4.9 (0.1–28.9)	2.0 (0.2–25.4)
Change from BL	–5.7 (11.7)	–2.9 (8.8)	–7.1 (7.2)	–2.1 (7.4)
Calprotectin, *mg/kg*,median (range)	1178.0 (15.0–2733.0)	665.0 (15.0–3473.0)	364.0 (15.0–2733.0)	198.0 (15.0–7105.0)
Change from BL	–667.8 (3332.3)	–2330.5 (5535.6)	–955.5 (521.8)	–959.5 (2532.8)

NOTE. Mean (standard deviation) unless otherwise specified.
BL, baseline; CI, confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; NR, nonresponder; OL EI, open-label extended induction; Q4W, every 4 weeks; RHI remission, calculated from the Geboes score, where RHI <3 with no neutrophils in the lamina propria or epithelium; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Standard.

induction period. Of the 238 who completed the induction period, 78.3% of placebo patients (47/60) and 47.8% of patients treated with mirikizumab (85/178) did not achieve clinical response.[16] Among the induction NRs, 44 of 47 placebo patients and 84 of 85 mirikizumab patients continued into the open-label extended induction period. Thirty-two of these received 600 mg mirikizumab IV every 4 weeks. After the protocol amendment, the subsequent 96 patients received 1000 mg (Supplementary Figure 2).

Mirikizumab Induction Nonresponders

Of the NR patients who had previously received mirikizumab during the initial induction period (IND-miri), 3 in the EI 600-mg group (15.0%, 0.0%–30.6%) and 6 in the EI 1000-mg group (9.4%, 2.2%–16.5%) were in clinical remission, whereas 10 in the 600-mg group (50.0%, 28.1%–71.9%) and 28 in the EI 1000-mg group (43.8%, 31.6%–55.9%) achieved clinical response at study week 24 (Table 1, Figure 1*A* and *B*).

Endoscopic improvement was achieved by 4 patients in the IND-miri/EI 600-mg group (20.0%, 2.5%–37.5%) and 10 in the IND-miri/EI 1000-mg group (15.6%, 6.7%–24.5%), whereas 0 patients in the IND-miri/EI 600-mg group and 2 in the EI 1000-mg group (3.1%, 0.0%–7.4%) had endoscopic remission. Histologic remission was achieved by 5 (25.0%, 6.5%–46.1%) and 15 (23.4%, 19.5%–43.6%) patients in the IND-miri/EI 600-mg and 1000-mg groups, respectively (Table 1, Figure 1*C*–*E*).

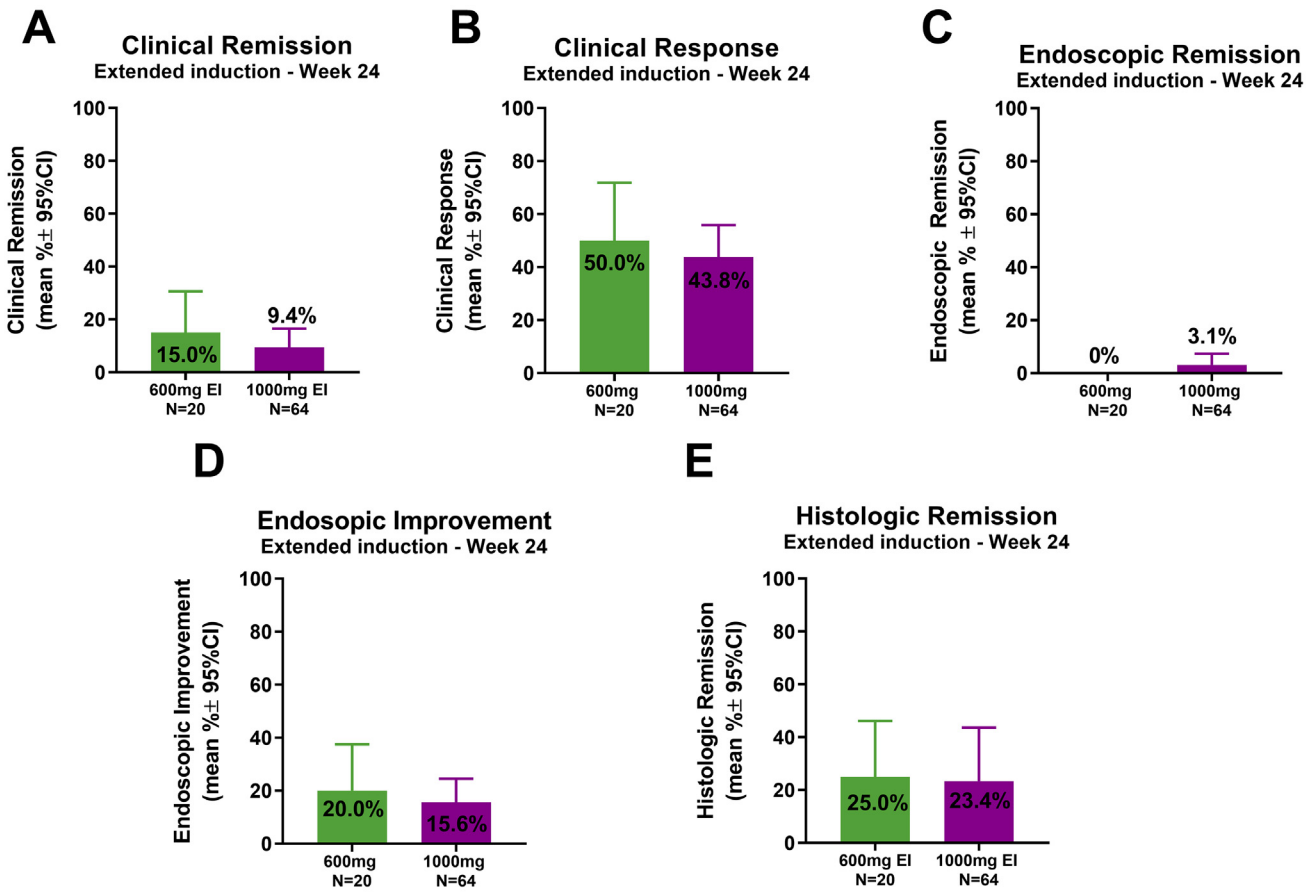

Figure 1. Mirikizumab induction nonresponders, extended induction results. Clinical remission (*A*), clinical response (*B*), endoscopic remission (*C*), endoscopic response (*D*), and histologic remission (*E*) after 12 weeks of extended induction in patients who received 50, 200, or 600 mg mirikizumab during the induction period but did not achieve clinical response at week 12. CI, confidence interval; EI, extended intravenous induction.

Ten patients in the IND-miri/EI 600-mg group (50%, 28.1%–71.9%) and 25 in the IND-miri/EI 1000-mg group (39.1%, 27.1%–51.0%) achieved symptomatic remission (Table 1, Supplementary Figure 3*A*). Symptomatic score (RB+SF) decreased by an average of 1.7 ± 1.9 and 1.9 ± 1.6 points in the IND-miri/EI 600-mg and 1000-mg groups, respectively (Table 1, Supplementary Figure 3*B*). IBDQ scores increased during the EI period by an average of 41.1 and 31.7 points in the IND-miri/EI 600-mg and 1000-mg groups, respectively (Table 1, Supplementary Figure 3*C*). Physical and Mental Components and 8 health domain scores of the SF-36 improved during the EI period for all groups (Supplementary Figure 4*B*).

CRP and fCLP decreased slightly during the EI period, as did serum levels of IL17 and IL22 cytokines (Table 1, Supplementary Figure 5*A*–*D*). Extended induction efficacy results by prior biologic exposure are shown (Supplementary Figure 6), demonstrating that many induction NRs benefit from an additional 12 weeks of induction therapy regardless of prior biologic exposure.

Placebo Induction Nonresponders

Of those NR patients who had received placebo during the induction period (IND-pbo) and received mirikizumab for the first time during extended induction, 3 in the EI 600-mg group (25.0%, 0.5%–49.5%) and 8 in the EI 1000-mg group (25.0%, 10.0%–40.0) were in clinical remission, whereas 7 in the EI 600-mg group (58.3%, 30.4%–86.2%) and 23 in the EI 1000-mg group (71.9%, 56.3%–87.5%) achieved clinical response (Table 1, Figure 2*A* and *B*).

Endoscopic improvement was achieved by 3 patients in the IND-pbo/EI 600-mg group (25.0%, 0.5%–49.5%) and 12 in the IND-pbo/EI 1000-mg group (37.5%, 20.7%–54.3%). No patients in the IND-pbo/EI 600-mg group achieved endoscopic remission at study week 24, whereas 3 (9.4%, 0.0%–19.5%) did in the IND-pbo/EI 1000-mg group. Histologic remission was achieved by 3 (25.0%, 7.9%–64.8%) and 12 (37.5%, 21.2%–57.4%) patients in the IND-pbo/EI 600-mg and 1000-mg groups, respectively (Table 1, Figure 2*C*–*E*).

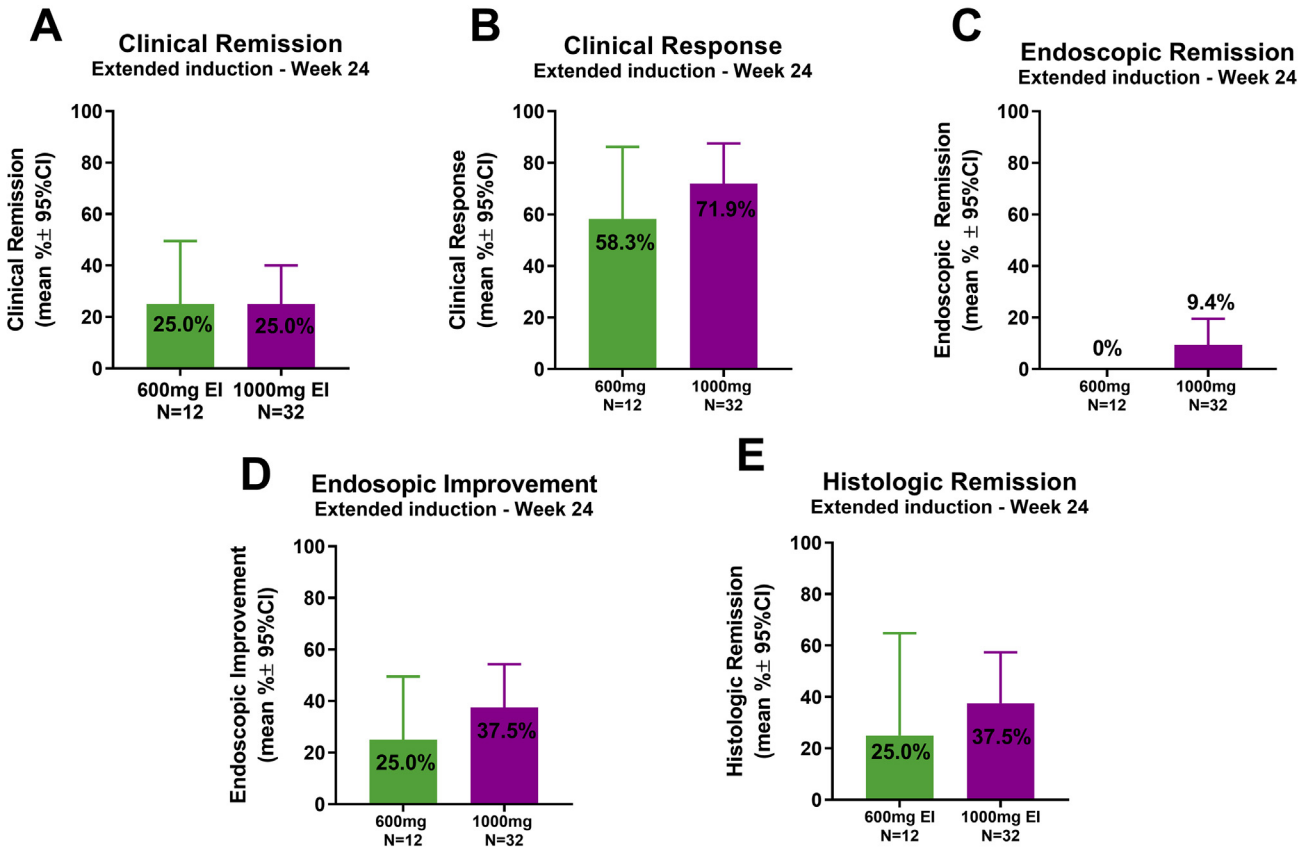

Figure 2. Placebo induction nonresponders, extended induction results. Clinical remission (*A*), clinical response (*B*), endoscopic remission (*C*), endoscopic response (*D*), and histologic remission (*E*) after 12 weeks of extended induction in patients who received placebo during the induction period and did not achieve clinical response at week 12. CI, confidence interval; EI, extended intravenous induction.

Of the IND-pbo patients, 7 (58.3%, 30.4%–86.2%) in the 600-mg group and 18 (56.3%, 39.1%–73.4%) in the 1000-mg group achieved symptomatic remission. Symptomatic score decreased by an average of 2.1 ± 1.6 and 2.3 ± 1.3 points in the IND-pbo/EI 600-mg and 1000-mg groups, respectively, and IBDQ scores increased by an average of 35.5 and 39.3 points in the IND-pbo/EI 600-mg and 1000-mg groups, respectively (Table 1, Supplementary Figure 3*D*–*F*). Physical and Mental Component Summaries and 8 health domain scores of the SF-36 improved during the EI period for both IND-pbo groups (Supplementary Figure 4*B*), as did levels of CRP, fCLP, and serum IL17 and IL22 (Table 1, Supplementary Figure 5*E*–*H*).

EI efficacy results by prior biologic exposure are shown (Supplementary Figure 6), demonstrating that many IND-pbo NRs also benefit from an additional 12 weeks of induction therapy regardless of prior biologic exposure.

Maintenance Treatment for Mirikizumab Extended Intravenous Induction Responders

All 68 patients who achieved clinical response in the EI phase (30 IND-pbo, 38 IND-miri) continued to the extended maintenance period and received 200-mg mirikizumab subcutaneously every 4 weeks (Supplementary Figure 2).

At study week 52, 7 of 10 patients (70.0%, 41.6%–98.4%) previously in the IND-miri/EI 600-mg group maintained a clinical response, as did 18 of 28 patients (64.3%, 46.5%–82.0%) in the IND-miri/EI 1000-mg group. Two (20.0%, 0.0%–44.8%) and 8 (28.6%, 11.8%–45.3%) patients in the IND-miri/EI 600-mg and 1000-mg groups, respectively, were in clinical remission. Endoscopic improvement rates were 30.0% and 35.7% in the IND-miri/EI 600-mg and 1000-mg groups, respectively, and endoscopic remission rates were 20.0% and 10.7% in the IND-miri/EI 600-mg and 1000-mg groups, respectively. Histologic remission rates were 40.0% and 50.0% in the IND-miri/EI 600-mg and 1000-mg groups, respectively (Table 2, Supplementary Figure 7*A*–*E*).

Extended Maintenance for Placebo Extended Intravenous Induction Responders

Of patients previously in the IND-pbo groups, 5 of 8 (62.5%, 29.0%–96.0%) and 21 of 22 (95.5%, 86.8%–100%) from the IND-pbo/EI 600-mg and 1000-mg

Table 2. Extended Maintenance Period Efficacy Results

	Induction miri NR		Induction pbo NR	
	OL EI miri IV 600 mg Q4W	OL EI miri IV 1000 mg Q4W	OL EI miri IV 600 mg Q4W	OL EI miri IV 1000 mg Q4W
	Extension week 40 (study week 52) OL EM miri 200 mg SC Q4W			
	N = 10	N = 28	N = 8	N = 22
Clinical remission, n (%) [95% CI]	2 (20.0) [0.0–44.8]	8 (28.6) [11.8–45.3]	3 (37.5) [4.0–71.0]	12 (54.5) [33.7–75.4]
Clinical response, n (%) [95% CI]	7 (70.0) [41.6–98.4]	18 (64.3) [46.5–82.0]	5 (62.5) [29.0–96.0]	21 (95.5) [86.8–100]
Endoscopic remission, n (%) [95% CI]	2 (20.0) [0.0–44.8]	3 (10.7) [0.0–22.2]	0	6 (27.3) [8.7–45.9]
Endoscopic improvement, n (%) [95% CI]	3 (30.0) [1.6–58.4]	10 (35.7) [18.0–53.5]	3 (37.5) [4.0–71.0]	15 (68.2) [48.7–87.6]
Histologic remission, n (%) [95% CI]	4 (40.0) [9.6–70.4]	14 (50.0) [29.3–67.0]	2 (25.0) [–4.9 to 62.0]	16 (72.7) [49.9–90.1]
RHI remission, n (%)	4 (40.0)	14 (50.0)	2 (25.0)	16 (72.7)
Symptomatic score Change from BL	1.0 (1.2) –3.0 (1.6)	1.2 (1.1) –2.7 (1.4)	0.7 (0.8) –2.5 (1.1)	0.8 (1.0) –2.9 (1.3)
IBDQ Change from BL	188.1 (26.8) 62.1 (40.9)	184.6 (21.8) 56.4 (41.5)	201.7 (30.5) 42.0 (39.3)	187.3 (26.8) 47.9 (33.8)
SF-36 Physical Component Score Mental Component Score	 51.4 (6.6) 51.2 (7.3)	 52.0 (5.1) 48.9 (9.0)	 54.3 (8.5) 57.3 (9.4)	 51.6 (6.7) 48.6 (9.7)
Change from BL				
Physical Component Score	7.7 (7.9)	8.5 (5.7)	9.6 (6.7)	5.0 (7.5)
Mental Component Score	11.7 (9.3)	11.4 (14.2)	9.5 (15.7)	8.6 (9.4)
CRP, *mg/L*, median (range) Change from BL	1.8 (0.1–22.0) –7.3 (13.2)	1.5 (0.1–26.5) –3.5 (7.4)	8.4 (0.2–47.6) 5.0 (13.4)	3.8 (3.8) –3.3 (7.3)
Calprotectin, *mg/kg*, median (range) Change from BL	127.5 (15.0–8251.0) –1300.7 (5558.5)	292.0 (15.0–4309.0) –3495.0 (6161.2)	417.5 (15.0–559.0) –1084.3 (787.6)	103.0 (15.0–10461.0) –534.5 (2172.7)

NOTE. Mean (standard deviation) unless otherwise specified.
BL, baseline; CI, confidence interval; C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; NR, nonresponder; OL EI, open-label extended induction; Q4W, every 4 weeks; RHI remission, calculated from the Geboes score, where RHI <3 with no neutrophils in the lamina propria or epithelium; SC, subcutaneous; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Standard.

groups, respectively, maintained a clinical response, whereas 3 (37.5%, 4.0%–71.0%) and 12 (54.5%, 33.7%–75.4%) patients in the IND-pbo/EI 600-mg and 1000-mg groups, respectively, were in clinical remission at week 52 (Table 2, Figure 1*E*). Endoscopic improvement rates were 37.5% and 68.2% in the IND-pbo/EI 600-mg and 1000-mg groups, respectively, whereas 0% and 27.3% in the IND-pbo/EI 600-mg and 1000-mg groups, respectively, had endoscopic remission. Histologic remission rates were 25.0% and 72.7% in the IND-pbo/EI 600-mg and 1000-mg groups, respectively (Table 2, Supplementary Figure 7*A*–*E*).

Symptomatic remission rates, symptomatic scores, IBDQ, and SF-36 scores remained stable throughout the maintenance period in both groups, as did CRP, fCLP, and IL17 and IL22 (Table 2, Supplementary Figure 7).

Safety

The most frequent treatment-emergent adverse events (≥5% in any treatment group) included nasopharyngitis, worsening of UC, headache, upper respiratory tract infection, arthralgia, and influenza (Table 3). Q10 Serious AEs (SAEs) occurred in 6 patients during the EI period (2 in the IND-miri/EI 1000-mg group, 1 in the IND-pbo/EI 600-mg group, and 3 in the IND-pbo/EI 1000-mg group) and in 3 patients during the maintenance period (2 in the IND-miri/EI 600-mg group and 1 in the IND-miri/EI 1000-mg group). SAEs reported during EI included 1 breast neoplasm (no pathology report or additional information was provided), 1 bilateral arthritis of the ankles, and 2 worsening UC. There were 2 reports of rectal cancer that were determined to be not

Table 3. Extension Period Safety Results

	Blinded induction groups (nonresponders)			
	Induction miri NR		Induction pbo NR	
	EI miri 600 mg Q4W N = 20	EI miri 1000 mg Q4W N = 64	EI miri 600 mg Q4W N = 12	EI miri 1000 mg Q4W N = 32
TEAEs, n (%)	12 (60.0)	31 (48.4)	5 (41.7)	14 (43.8)
Serious adverse event, n (%)	0 (0.0)	2 (3.1)	1 (8.3)	3 (9.4)
Treatment discontinuations due to adverse event, n (%)	0 (0.0)	3 (4.7)	0 (0.0)	1 (3.1)
Most common TEAEs[a]				
Nasopharyngitis	3 (15.0)	6 (9.4)	2 (16.7)	1 (3.1)
Ulcerative colitis	0	4 (6.3)	1 (8.3)	1 (3.1)
Headache	0	4 (6.3)	0	0
Upper respiratory tract infection	0	3 (4.7)	1 (8.3)	0
Arthralgia	0	4 (6.3)	0	0
Influenza	3 (15.0)	0	0	0
	Extension week 40 (study week 52) EM miri 200 mg SC			
	N = 10	N = 28	N = 8	N = 22
TEAEs, n (%)	8 (80.0)	18 (64.3)	6 (75.0)	15 (68.2)
Serious adverse event, n (%)	2 (20.0)	1 (3.6)	0	0
Treatment discontinuations due to adverse event, n (%)	0	2 (7.1)	0	0

NOTE. Mean (standard deviation) unless otherwise specified.
EI, extended induction; NR, nonresponder; SC, subcutaneous; TEAE, treatment-emergent adverse event.
[a]Presented as most to least frequent among all treatment groups combined.

related to study drug. Both subjects (male, ages 51 and 53) were enrolled at investigative sites in Japan with UC medical history of 6 and 12 years, respectively. Both had severe disease activity as indicated by a Mayo endoscopic score of 3 at baseline. One subject had received placebo induction followed by 1000 mg in EI, and the other had received 200 mg induction followed by 1000 mg in EI. On follow-up evaluation of endoscopic video, it was determined 1 subject may have had a rectal/sigmoid mass at baseline. SAEs reported during EM included 1 transient ischemic attack and 1 hip fracture. Another EM patient presented with a partial bowel obstruction and later developed an opiate dependency. No extension SAEs were determined to be treatment-related.

Discussion

In the extension period of the phase 2 study AMAC, induction phase NRs were treated with an additional 3 IV doses of mirikizumab over 12 weeks. There were 2 distinct populations: those who were assigned to placebo during the induction period and thus received mirikizumab for the first time during EI (IND-pbo) and those who had previously received mirikizumab but had not achieved clinical response at week 12 (IND-miri). Compared with the induction period responders, extension period patients in general had a higher percentage of prior biologic use, particularly in the IND-miri groups, and a higher percentage of patients who had been exposed to 3 or more biologics (Table 4), indicating a more refractory population in the extension phase than the general patient population, as would be expected with a NR population. Other disease characteristics, such as disease duration, baseline Mayo score, and usage of concomitant medications, were similar between induction responders and NRs. It is possible that the number of previously failed biologic therapies could inform as to which patients would benefit from a longer initial dosing regimen, although additional studies are needed to confirm. A more intensive induction dosing regimen might be able to help more patients in the initial induction period; however, the lack of a clear dose response in the induction period of this study does not provide a clear answer.

Throughout this study, few patients treated with mirikizumab, including those receiving the 1000-mg dose level, discontinued because of adverse events, suggesting that it was well-tolerated. The safety results appear consistent with published results from other IL23-targeting biologics,[16–21] demonstrating a positive safety profile after 52 weeks of mirikizumab treatment,

Table 4. Baseline Demographics and Disease Characteristics (Extension Patients Only)

	Blinded induction groups (nonresponders)				
	Induction miri NR		Induction PBO NR		
	OL EI miri IV 600 mg Q4W N = 20	OL EI miri IV 1000 mg Q4W N = 64	OL EI miri IV 600 mg Q4W N = 12	OL EI miri IV 1000 mg Q4W N = 32	Induction responders (N = 106)
Age, *y*	45.6 (14.3)	43.0 (14.3)	40.9 (13.6)	42.0 (12.7)	40.5 (13.7)
Sex, male, n (%)	15 (75.0)	45 (70.3)	5 (41.7)	18 (56.3)	56 (52.8)
Disease duration, *y*	9.2 (11.1)	7.2 (6.9)	9.8 (9.6)	10.1 (9.7)	7.5 (5.9)
Previous biologic use, n (%)	15 (75.0)	51 (79.7)	8 (66.7)	24 (75.0)	53 (50.0)
No. of unique prior biologic therapies, n (%)					
0	6 (30.0)	17 (26.6)	5 (41.7)	9 (28.1)	51 (48.1)
1	3 (15.0)	23 (35.9)	4 (33.3)	11 (34.4)	30 (28.3)
2	5 (25.0)	15 (23.4)	2 (16.7)	9 (28.1)	18 (17.0)
3	5 (25.0)	8 (12.5)	1 (8.3)	2 (6.3)	6 (5.7)
4+	1 (5.0)	1 (1.6)	0	1 (3.1)	1 (0.9)
Concomitant medications, n (%)					
Mesalamine	14 (70.0)	41 (64.1)	10 (83.3)	24 (75.0)	85 (80.2)
Corticosteroids	9 (45.0)	36 (56.3)	7 (58.3)	17 (53.1)	48 (45.3)
Thiopurines	2 (10.0)	16 (25.0)	4 (33.3)	13 (40.6)	29 (27.4)
Mayo score, n (%)					
6–8	11 (55.0)	25 (40.3)	6 (50.0)	11 (34.4)	46 (43.4)
9–12	9 (45.0)	37 (59.7)	6 (50.0)	21 (65.6)	60 (56.6)
Mayo symptomatic score	3.6 (0.9)	3.7 (1.2)	3.5 (1.1)	4.2 (1.0)	3.8 (1.3)
IBDQ	130.7 (30.2)	130.5 (36.3)	142.9 (39.1)	135.4 (37.5)	123.4 (30.0)
SF-36					
Physical Component Score	42.2 (6.8)	42.6 (7.2)	43.5 (7.6)	44.9 (7.0)	41.7 (7.8)
Mental Component Score	39.9 (9.9)	39.4 (12.0)	42.2 (10.3)	40.3 (11.3)	38.5 (9.8)
CRP, *mg/L*, median (range)	3.9 (0.1–41.0)	4.6 (0.1–67.4)	16.8 (0.1–42.5)	3.9 (0.3–138.0)	4.3 (0.10–164.0)
Calprotectin, *mg/kg*, median (range)	1497.5 (61.0–13,737.0)	1592.5 (15.0–31,680.0)	1496.0 (275.0–3730.0)	1558.0 (15.0–12,379.0)	1701 (15.0–31,680.0)

NOTE. Data expressed as mean (standard deviation) unless otherwise specified. Nominal *P* values were not significant for any group except thiopurines, where a difference was seen across the 4 dose groups.
CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; NR, nonresponder; OL EI, open-label extended induction; Q4W, every 4 weeks; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Standard.

even with exposure to the highest doses. Overall, mirikizumab continues to exhibit a favorable risk vs benefit profile.

The IND-pbo patients who received mirikizumab for the first time during the EI period were demographically similar to the initial mirikizumab-treated induction population and had rates of all outcome measures similar to those of the most effective induction mirikizumab dose of 200 mg.[16]

In contrast, the rates of clinical response and remission in IND-miri groups were similar to those of the pooled induction period mirikizumab groups (Supplementary Figure 8). Endoscopic remission rates were also similar between the induction and extended induction periods.[16] Histologic remission rates were slightly lower in the IND-miri EI treatment groups than in the induction treatment groups, but still comparable. These data demonstrate that an additional 3 doses of IV mirikizumab results in a similar clinical efficacy among induction NRs as 12 weeks of induction treatment did among the initial intent to treat population. Almost all IND-miri patients who achieved clinical response during the EI period continued to extended maintenance through week 52 and experienced clinical benefit as demonstrated by rates of clinical response and remission (roughly 65%–70% and 20%–30%, respectively), as well as endoscopic and histologic benefit. The majority of these outcome measures were only slightly lower than those of the induction responders who continued to maintenance treatment. Importantly, rates

of histologic remission, which is becoming increasingly recognized as a major therapeutic goal and endpoint for UC, were comparable between the 2 maintenance periods.[16]

In general, levels of inflammatory biomarkers in the IND-miri group continued the decrease observed during the induction period, whereas levels in the IND-pbo group started decreasing on the first administration of mirikizumab at the start of the extended induction period (Supplementary Figure 5). Together, these biomarker results indicate the effect of mirikizumab on the IL23 pathway.

Mirikizumab exposure in this and other studies has been found to be dose-proportional, and the average concentrations observed during the extension period for the 600- and 1000-mg treatment cohorts were 35.6 μg/mL and 61.8 μg/mL, respectively. The mirikizumab exposure for the 600-mg group was consistent with the exposure observed for the patients who received 600 mg during the initial induction period.[16]

These data suggest that extension treatment with mirikizumab may be of benefit to patients who do not initially achieve protocol defined response criteria; however, because of the relatively small sample size and the lack of a control arm, the extension part of this study was only intended to explore the clinical activity of a longer induction period, and no formal statistical comparisons were made between groups.

The design of this extension trial allowed for an additional 2 endoscopies at study weeks 24 and 52; thus, patients who completed the extended maintenance period had a total of 4 endoscopies, resulting in objective data that support efficacy of mirikizumab among induction NRs. Unlike most extension studies this trial used blinded centrally read endoscopy as opposed to local investigator score, which results in lower endoscopic remission and response rates but is considered to be more accurate.[22] Relatively low rates of endoscopic response and remission were expected in these patients on the basis of other extension studies. However, even with the more stringent readings, 15%–20% of mirikizumab induction NRs experienced endoscopic improvement during the EI period, and patients who continued into extended maintenance continued to show endoscopic improvement (Figure 1*C* and *D*, Supplementary Figure 7*C* and *D*).

These results indicate that a longer dosing period with mirikizumab may result in additional clinical benefit for those patients who do not respond to mirikizumab induction treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.09.028.

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Supplementary Material

Complete List of Inclusion and Exclusion Criteria

Inclusion criteria. Subjects with UC were eligible for enrollment only if they met all of the following criteria during screening:

[1] have given written informed consent approved by the ERB (ethical review board) governing the site

[2] were male or female subjects ≥18 and ≤75 years of age at the time of initial screening

[2a] male subjects agreed to use a reliable method of birth control during the study and for 3 months, which is greater than 5 half-lives, after the last dose of investigational product

[2b] female subjects:

- were women of childbearing potential whose serum pregnancy test results were negative and who agree to use a reliable method of birth control (eg, condom, sponge, or diaphragm combined with spermicidal foam, gel, or cream; ongoing hormonal contraception [oral, intramuscular, depot, or transdermal], such as Depo-Provera, Evra, or NuvaRing; an intrauterine device; or complete abstinence from sexual intercourse with men) during the study and for 3 months after the last dose of the investigational product

-or-

- were not women of childbearing potential, defined as having:
  - bilateral oophorectomy, tubal ligation, or hysterectomy at least 6 weeks before screening;
  - spontaneous amenorrhea for ≥12 months, not induced by a medical condition or medications; or
  - spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level greater than 40 mIU/mL at screening

[3] venous access sufficient to allow blood sampling and IV administration (if applicable), as per the protocol

[4] have had a diagnosis of UC for ≥3 months before baseline (endoscopic evidence corroborated by a histopathology report); a biopsy for a local histopathology evaluation (to obtain a report) can be obtained during the baseline endoscopy procedure if a histopathology report is not available

[5] have moderate to severe active UC as defined by a Mayo score of 6 to 12 with an endoscopic subscore ≥2 within 14 days before the first dose of study treatment (note: a partial Mayo score of at least 4 and other eligibility criteria must have been met before endoscopy is performed as a study procedure)

[6] have evidence of UC extending proximal to the rectum (≥15 cm of involved colon)

[7] have documentation of a surveillance colonoscopy (performed according to local standard) within 12 months before baseline (may be performed during screening) for subjects with pancolitis of >8-years duration or left-sided colitis of >12-years duration

[7a] up-to-date colorectal cancer surveillance (performed according to local standard), for subjects with family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor

[8] subjects must either:

[8a] be naive to biologic therapy (such as tumor necrosis factor antagonists, vedolizumab, or experimental UC biologics) and have at least 1 of the following:

- inadequate response or failure to tolerate current treatment with oral or IV corticosteroids or immunomodulators (6-mercaptopurine or azathioprine) or
- history of corticosteroid dependence (an inability to successfully taper corticosteroids without return of UC)

OR

[8b] have also received treatment with 1 or more biologic agents (such as tumor necrosis factor antagonists, vedolizumab, or experimental UC biologics) with or without documented history of failure to respond or tolerate such treatment

- the biologic treatment must have been discontinued according to the following timelines:
  - anti-tumor necrosis factor therapy at least 8 weeks before baseline
  - vedolizumab treatment at least 12 weeks before baseline
  - experimental biologic UC therapy at least 8 weeks before baseline

[9] may have been receiving a therapeutic dosage of the following drugs:

[9a] oral mesalamine compounds: if the prescribed dose has been stable for at least 2 weeks before screening endoscopy

[9b] oral corticosteroid therapy (prednisone $\leq$20 mg/d or equivalent): if the prescribed dose has been stable for at least the 2 weeks before screening endoscopy

[9c] azathioprine or 6-mercaptopurine: if the prescribed dose has been stable for at least 8 weeks before baseline

[10] was willing and able to complete the scheduled study assessments, including endoscopy

[11] have clinically acceptable laboratory results at screening, as assessed by the investigator, including:

[11a] hematologic: absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin level $\geq$10.0 g/dL, lymphocyte count $>$500 cells/μL, and total white blood cell count $\geq 3.0 \times 10^9$/L

[11b] chemistry: serum creatinine, total bilirubin level, alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels $\leq 2\times$ upper limit of normal (ULN)

Exclusion criteria. Subjects were excluded from study enrollment if they met any of the following criteria:

[12] have been diagnosed with indeterminate colitis, proctitis (distal disease involving the rectum only; less than 15 cm from the anal verge), or Crohn's disease

[13] have had surgery for treatment of UC or are likely to require surgery for UC during the study

[14] have received any of the following for treatment of UC:

[14a] cyclosporine or thalidomide within 30 days of screening endoscopy

[14b] corticosteroid enemas, corticosteroid suppositories, or topical treatment with mesalamine within 30 days of screening endoscopy

[14c] have used apheresis (eg, Adacolumn apheresis) $\leq$2 weeks before screening endoscopy

[15] have previous exposure to any biologic therapy targeting IL23 (including ustekinumab), either licensed or investigational

[16] have been treated with any investigational drug for UC within 30 days or 5 half-lives of the drug (whichever is longer) before the initial screening visit,

OR with interferon therapy within 8 weeks before baseline

[17] have evidence of abdominal abscess or toxic megacolon during screening

[18] have extensive colonic resection, subtotal or total colectomy, ileostomy, colostomy, or fixed symptomatic stenosis of the intestine

[19] have evidence of active or latent tuberculosis

[20] have had any malignancy within 5 years of screening, except for basal cell or squamous epithelial carcinoma of the skin that has been resected with no evidence of metastatic disease for at least 3 years OR cervical carcinoma in situ with no evidence of recurrence within 5 years of screening

[21] were investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[22] were Lilly employees or employees of third-party organizations (TPOs) involved with the study

[23] were at the time of screening enrolled in a clinical trial involving an investigational product or non-approved use of a drug or device, OR are concurrently enrolled in any other type of medical research not scientifically or medically compatible with this study, per investigator judgment

[24] have previously completed or withdrawn from this study or any other study investigating LY3074828. This criterion did not apply to subjects undergoing rescreening procedures

[25] have received live, attenuated vaccine(s) within 2 months of screening or intended to receive such during the study; vaccines should be avoided for 2 months after the last dose of study drug. Uses of nonlive (inactivated) vaccinations were allowed for all subjects

[26] have human immunodeficiency virus/acquired immunodeficiency syndrome or test positive for human immunodeficiency virus antibodies at screening

[27] have hepatitis B or test positive for hepatitis B virus (HBV) at screening, defined as: (1) positive for hepatitis B surface antigen or (2) positive for anti–hepatitis B core antibody (HBcAb+) and positive confirmatory polymerase chain reaction (PCR) for HBV, regardless of anti–hepatitis B surface antibody status

[28] have hepatitis C or test positive hepatitis C virus at screening, defined as: positive result for hepatitis C antibody and positive confirmatory PCR test for hepatitis C virus

[29] had *Clostridium difficile* infection within 30 days of screening endoscopy or test positive at screening, or other intestinal pathogen with 30 days before screening endoscopy. Subject must not have signs of an ongoing infection related to an intestinal pathogen.

[30] have any clinically significant extraintestinal infection or opportunistic, chronic, or recurring infection within 6 months before screening. Examples include but are not limited to infections requiring IV antibiotics, hospitalization, or prolonged treatment

[31] were unsuitable for inclusion in the study in the opinion of the investigator or sponsor for any reason that may compromise the subject's safety or confound data interpretation

[32] Exclusion criterion [32] applies to study sites in Japan only. For study sites in Japan: have known allergies to LY3074828, related compounds including humanized monoclonal antibodies, or any components of the formulation or history of significant atopy

[33] were pregnant, lactating, or planning pregnancy (either men or women) while enrolled in the study or within 4 months after receiving the last dose of study agent

Details of Inflammatory Bowel Disease Questionnaire

The IBDQ is a 32-item subject-completed questionnaire that measures 4 aspects of subjects' lives: symptoms directly related to the primary bowel disturbance, systemic symptoms, emotional function, and social function.[1] Responses are graded on a 7-point Likert scale in which 7 denotes "not a problem at all" and 1 denotes "a very severe problem." Scores range from 32 to 224; a higher score indicates a better quality of life.

Details of the 36-Item Short Form Health Survey v2 Standard (SF-36). The SF-36 is a 36-item subject-completed measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role-physical, role-emotional, bodily pain, vitality, social functioning, mental health, and general health.[2–4] The 2 overarching domains of mental well-being and physical well-being are captured by the mental and physical component summary scores. Responses are graded on Likert scales of varying lengths/points. The summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health.

Histopathology. All biopsy specimens were collected at least 30 cm from the anal verge according to the following instructions: Where discrete lesions are present, biopsies will be obtained at the edge of the lesion(s). Biopsies will be preferentially obtained from the edge of ulcers, but if ulcers are not present, they will be obtained from the edge of the aphthous erosions.

Where visible macroscopic disease is present but without discrete lesions (ie, ulcers or aphthous erosions), biopsies will be spaced throughout the affected mucosa. In the absence of macroscopic disease, biopsies will be obtained from throughout the segment.

The histopathologic images were read centrally in a blinded manner by a qualified pathologist, and scoring was performed by using the Geboes score.[5]

The Geboes score is an instrument that is used to standardize histologic assessment in UC. It is composed of 7 categories (or grades), each of which describes a histologic feature. These categories are structural (architectural change) (grade 0), chronic inflammatory infiltrate (grade 1), lamina propria eosinophils (grade 2A), lamina propria neutrophils (grade 2B), neutrophils in epithelium (grade 3), crypt destruction (grade 4), and erosion or ulceration (grade 5).[5] Each grade includes subscores that indicate the degree of abnormality seen for that histologic feature, with subscores of 0 indicating normal appearance and higher subscores indicating increasingly abnormal appearance.

Biomarker analysis in plasma and feces. IL17A levels were measured using the Quanterix Simoa (Billerica, MA) IL17 2.0 assay. The assay was performed per manufacturing instruction at a 1:5 dilution of plasma EDTA in assay buffer. The assay was read on the Quanterix Sioma HD-1 platform.

IL22 cytokine levels were assayed in a Meso Scale Discovery (Rockville, MD) sandwich assay. In short, IL22 specific antibodies were either biotinylated or Sulfo-Tagged. MSD Streptavidin Gold plates were washed, blocked, coated with biotinylated capture antibody, and washed. EDTA-plasma samples were diluted 1:4 in assay buffer and incubated for 2 hours at room temperature. Plates were washed, and Detection antibody was added for 1 hour. Plates were washed, and 2× MSD read buffer was added. Plates were read with MSD reader Quick Plex S120, and data were analyzed on MSD reader and back calculated to pg/mL.

Fecal calprotectin was measured in patient collected fecal samples using an enzyme immunoassay by Buhlman Laboratories (Schönenbuch, Switzerland) and tested by Covance Central laboratories (Indianapolis, IN).

CRP was measured in collected serum samples using a CRP HS immunonephelometry assay (Siemens BNII, Malvern, PA) and was performed at Covance Central.

Pharmacodynamic effects were assessed with a mixed effects model using log10 transformed cytokine concentration as the response, fixed effects for treatment, time, and the treatment by time interaction, a random patient effect with an unstructured covariance matrix,

and covariates that included baseline values for assay batch, age, sex, body mass index, previous biologic therapy, and modified Mayo score. Models were fit using the *lme* function from the R package *nlme*[6] and version 3.5.0 of the R statistical computing environment.[7] The pharmacodynamic contrast was defined as the change from baseline for a drug-treated group minus the change from baseline for the placebo group.

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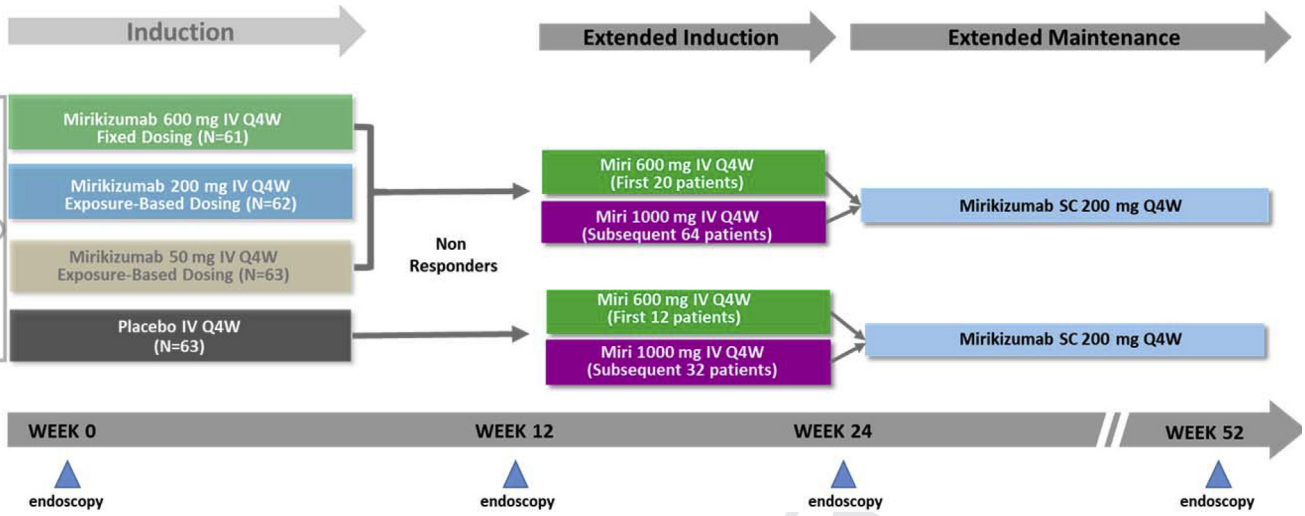

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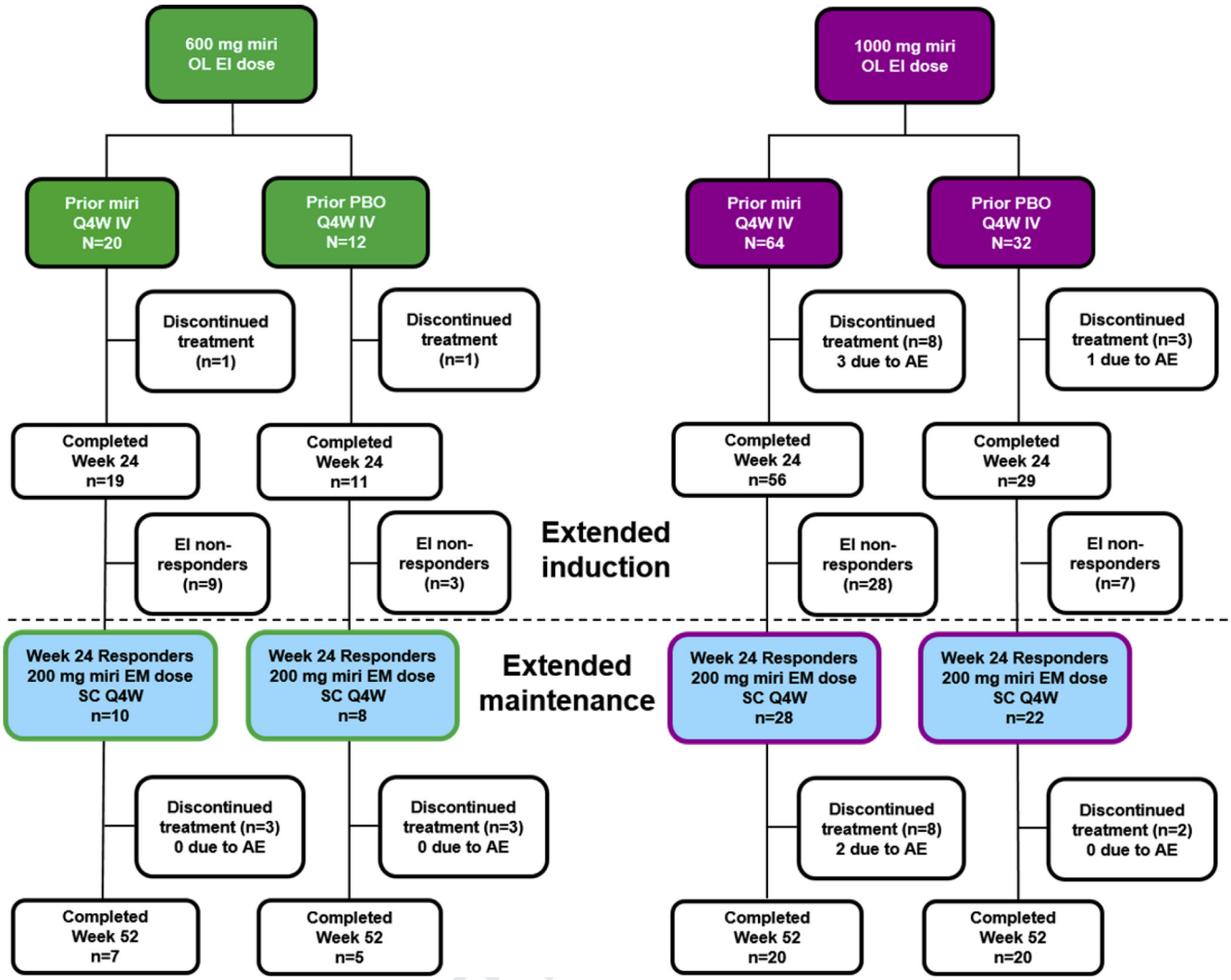
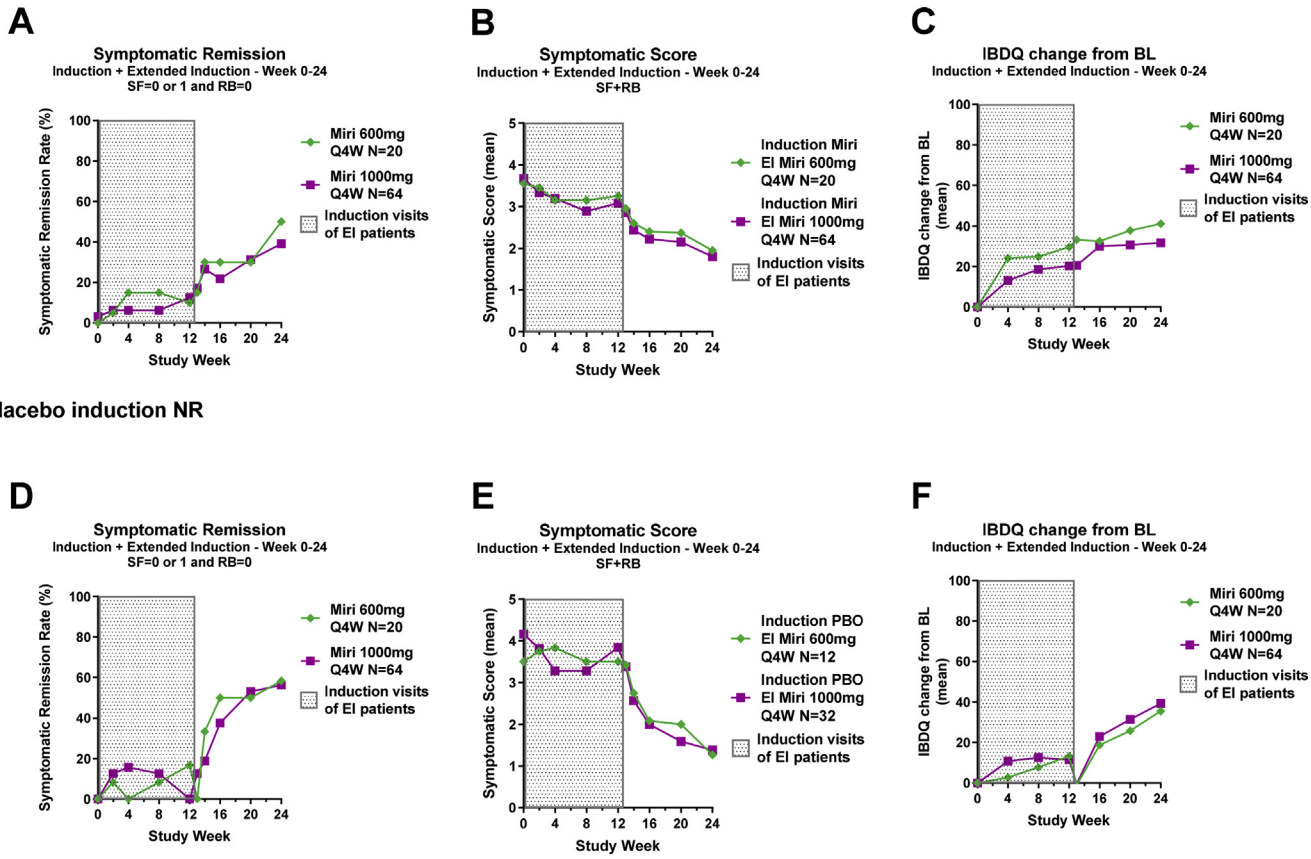
Supplementary Figure 1. AMAC study design. IV, intravenous; Q4W, every 4 weeks; SC, subcutaneous.



Supplementary Figure 2. Extension period CONSORT diagram. Thirty-two patients received 600 mg mirikizumab IV every 4 weeks. After the protocol amendment, the subsequent 96 patients received 1000 mg. AE, adverse effect; EM, maintenance treatment; OL EI, open-label extended induction; PBO, placebo; Q4W, every 4 weeks; SC, subcutaneous.

Mirikizumab induction NR



Placebo induction NR

* Induction period = Baseline to Weeks 11-12; Extended induction period = Weeks 12-13 to 24.

Supplementary Figure 3. Extended induction symptomatic results. BL, baseline; EI, extended induction; IBDQ, Inflammatory Bowel Disease Questionnaire; NR, nonresponder; PBO, placebo; Q4W, every 4 weeks.

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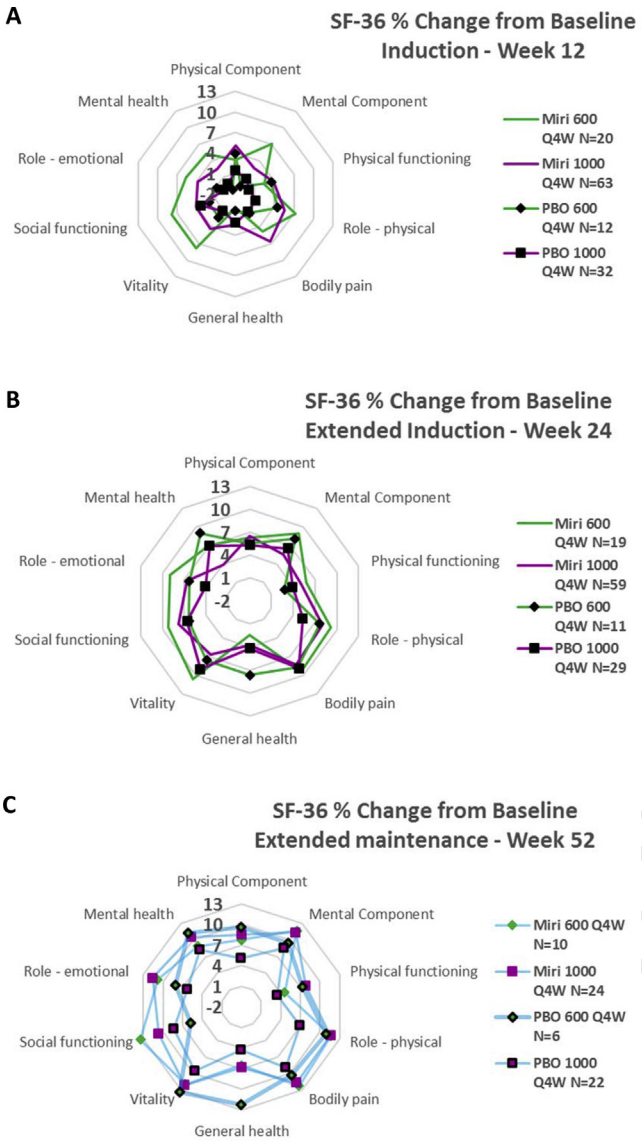
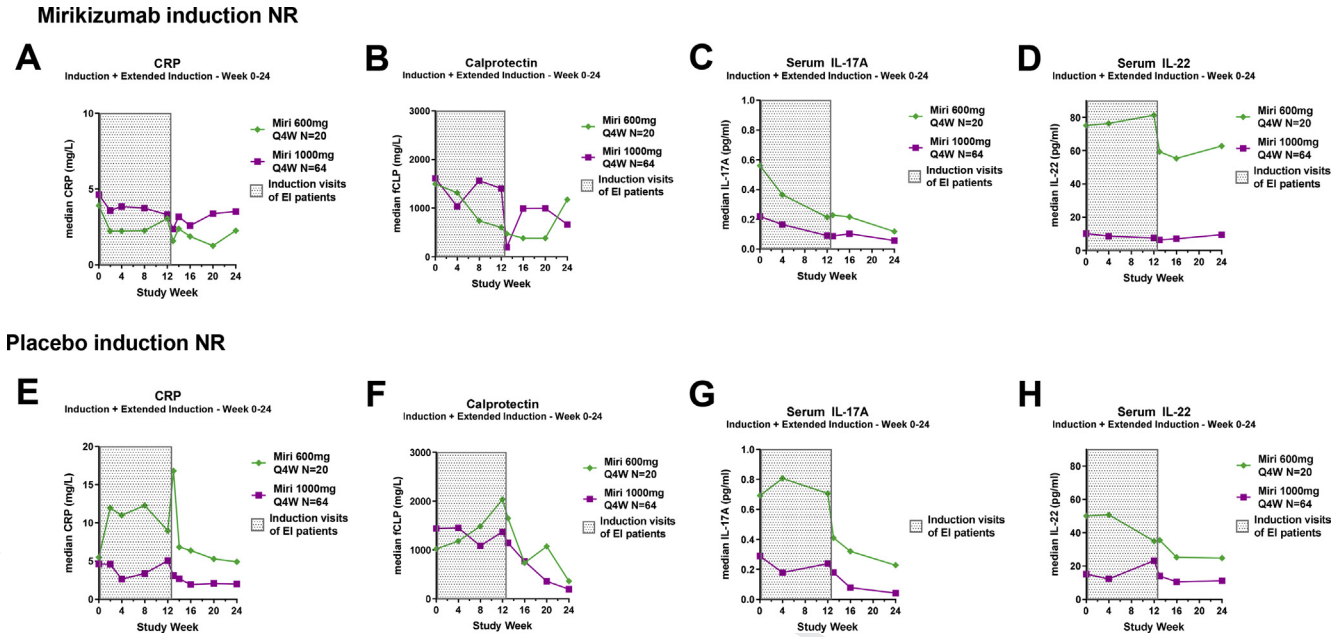
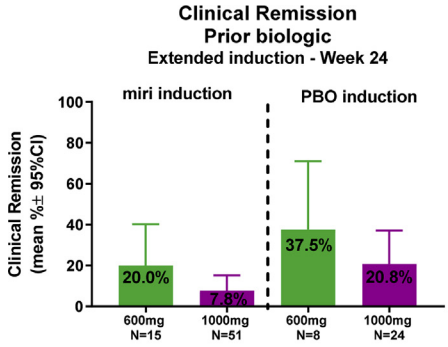
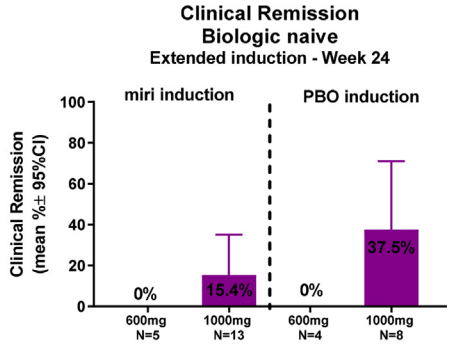


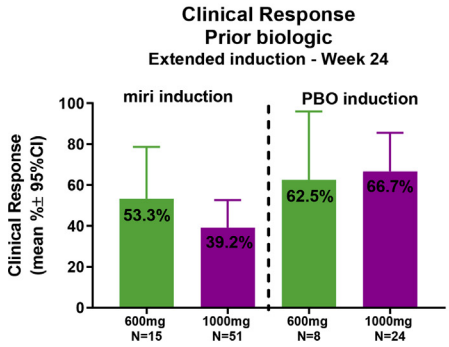
Supplementary Figure 4. SF-36 change from baseline. PBO, placebo; Q4W, every 4 weeks; SF-36, Short Form 36.

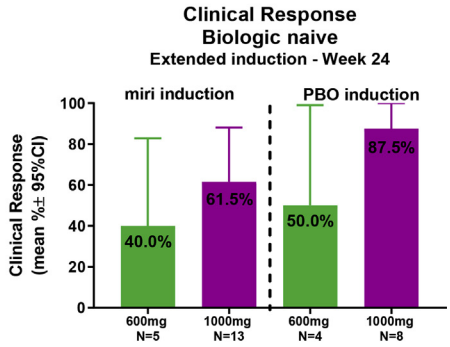


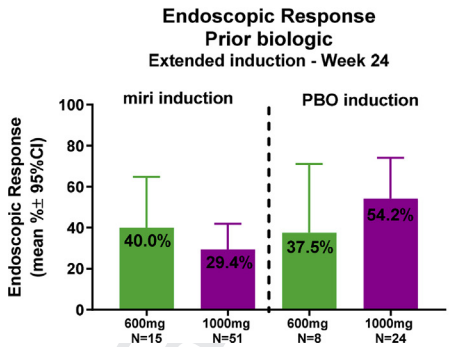
Supplementary Figure 5. Biomarkers over time. CRP, C-reactive protein; EI, extended induction; IL, interleukin; NR, nonresponder; Q4W, every 4 weeks.

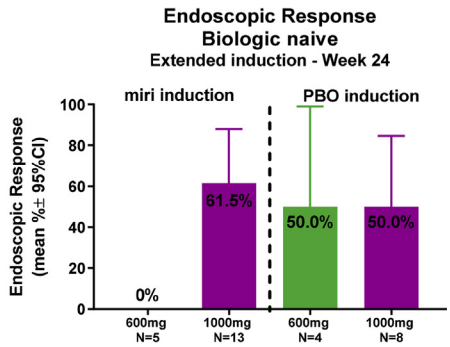












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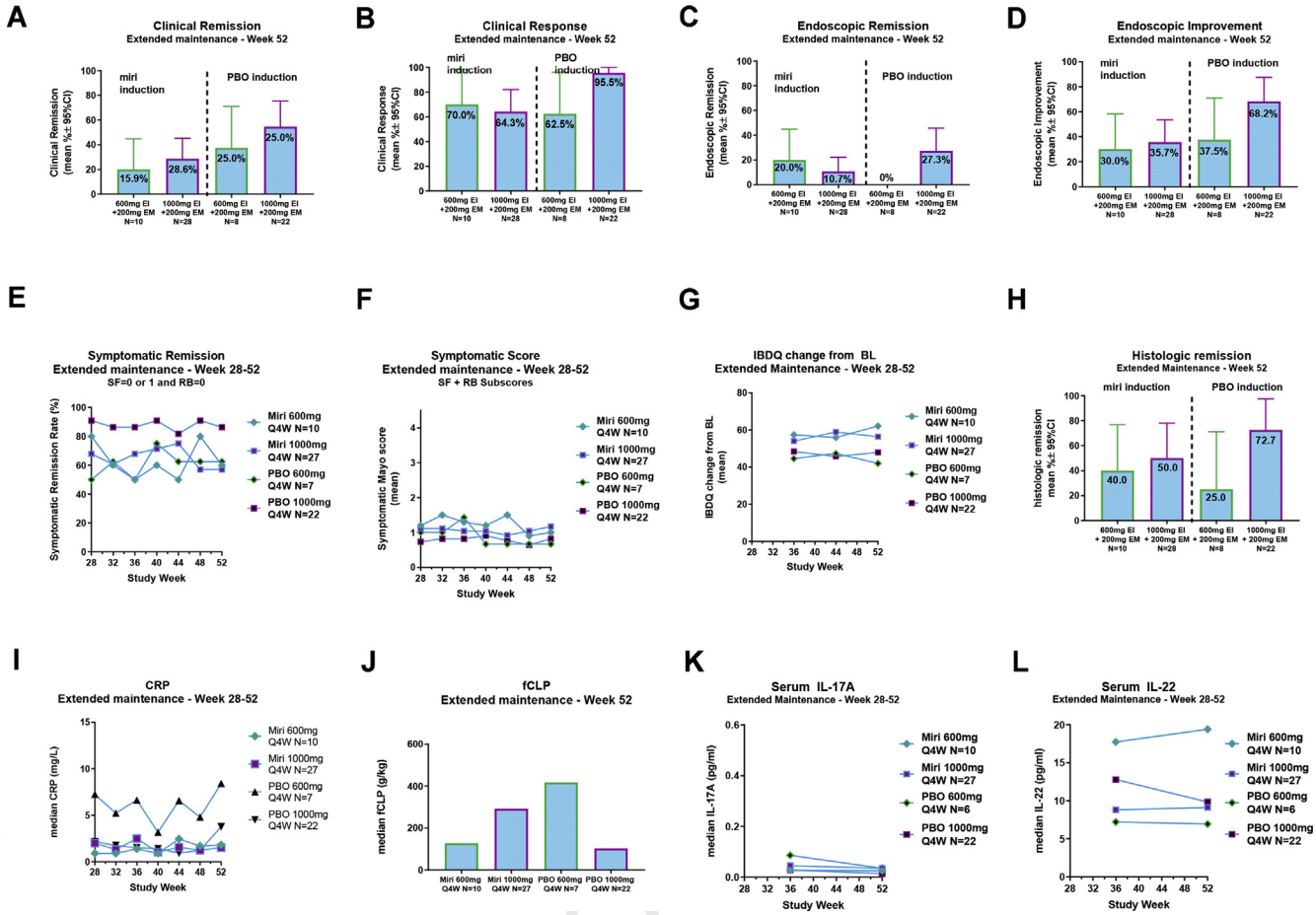
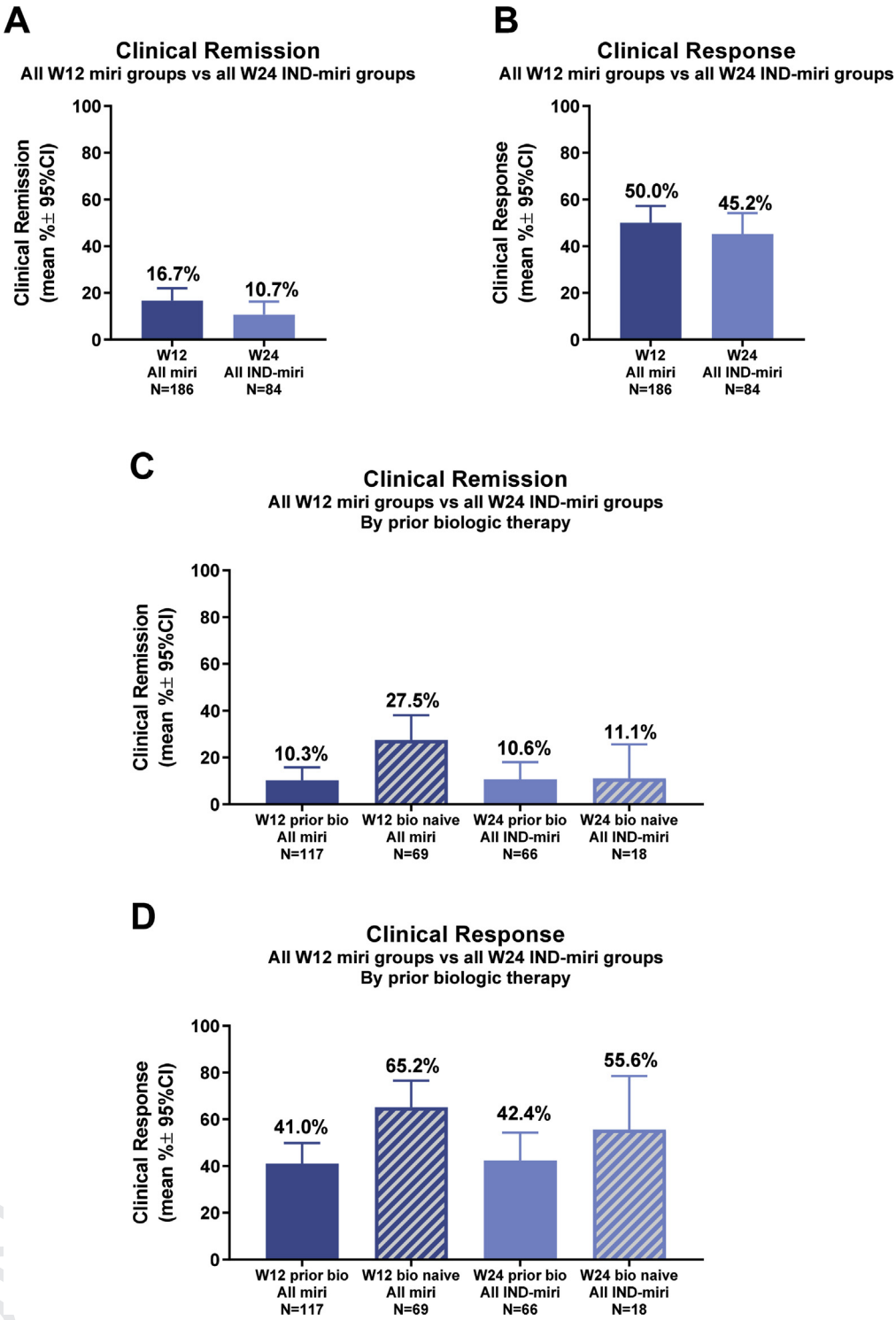
Supplementary Figure 6. Extended induction key efficacy results by prior biologic exposure. CI, confidence interval; PBO, placebo.



Supplementary Figure 7. Extension maintenance results. BL, baseline; CI, confidence interval; CRP, C-reactive protein; EI, extended induction; EM, maintenance treatment; fCLP, fecal calprotectin; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; PBO, placebo; Q4W, every 4 weeks.



Supplementary Figure 8. Clinical outcomes in patients treated with 12 (induction) or 24 (extended induction) weeks of mirikizumab. CI, confidence interval; W12, week, 12; W24, week 24.

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