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Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Crohn's Disease

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BACKGROUND: Mirikizumab is a humanized monoclonal antibody targeting interleukin 23p19 with demonstrated efficacy in psoriasis and ulcerative colitis. We investigated the safety and efficacy of mirikizumab in patients with moderate-to-severe Crohn's disease (CD). **METHODS:** Patients (N = 191) were randomized (2:1:1:2) to receive placebo (PBO), 200, 600, or 1000 mg mirikizumab, administered intravenously (IV) every 4 weeks. Patients who received mirikizumab and achieved ≥1 point improvement in Simple Endoscopic Score-CD at Week 12 (rerandomized maintenance cohort) were rerandomized to continue their induction IV treatment (IV-C) or receive 300 mg mirikizumab subcutaneously (SC) every 4 weeks. Nonrandomized maintenance cohort included endoscopic nonimprovers (1000 mg) and PBO patients (PBO/1000 mg) who received 1000 mg mirikizumab IV from Week 12. The primary objective was to evaluate superiority of mirikizumab to PBO in inducing endoscopic response (50% reduction from baseline in Simple Endoscopic Score-CD) at Week 12. **RESULTS:** At Week 12, endoscopic response was significantly higher by the predefined 2-sided significance level of 0.1 for all mirikizumab groups compared with PBO (200 mg: 25.8%, 8/31, 95% confidence interval [CI], 10.4–41.2, $P = .079$; 600 mg: 37.5%, 12/32, 95% CI, 20.7–54.3, $P = .003$; 1000 mg: 43.8%, 28/64, 95% CI, 31.6–55.9, $P < .001$; PBO: 10.9 %, 7/64, 95% CI, 3.3–18.6). Endoscopic response at Week 52 was 58.5% (24/41) and 58.7% (27/46) in the IV-C and SC groups, respectively. Frequencies of adverse events (AE) in the mirikizumab groups were similar to PBO. Through Week 52, frequencies of treatment-emergent AEs were similar across all groups. Frequencies of serious AE and discontinuations due to AE were higher in the nonrandomized maintenance cohort. **CONCLUSION:** Mirikizumab effectively induced endoscopic response after 12 weeks in patients with moderate-to-severe CD and demonstrated durable efficacy to Week 52. A detailed summary can be found in the Video Abstract.
ClinicalTrials.gov, Number: NCT02589665

Keywords: IBD; Cytokine; Inhibitor.

Crohn's disease (CD) is a chronic, disabling, and progressive inflammatory disease of the gastrointestinal tract, with typical symptoms of abdominal pain and diarrhea.[1] The goals of medical management are to achieve and maintain endoscopic and clinical remission, thus preventing progressive bowel damage and surgery.[2] Treatment of CD has been transformed with the advent of biologic therapies. For more than a decade, tumor necrosis factor–α inhibitors were the only biologics available. More recently, 3 biologics (vedolizumab, ustekinumab, and natalizumab) with different mechanisms of action have been approved[3–5] with others under development.[6–9] However, the efficacy of these agents is limited in that some patients may have an inadequate response or lose response over time, or may not tolerate a given drug, thus resulting in discontinuation of therapy or suboptimal treatment.[10] As such, a significant unmet need remains as suboptimal treatment is associated with higher rates of surgery, hospitalization, and/or prolonged corticosteroid use as well as impaired quality of life.[11,12] The interleukin (IL) 23p19 inhibitor class, which holds promise for enhanced efficacy and durability, is a prime candidate to address this need.

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 found in IL23, but not in 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 chronic inflammatory diseases including CD.[13–15]

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds specifically to the p19 subunit of IL23 and has demonstrated efficacy in psoriasis and ulcerative colitis,[16,17] and is currently in phase 3 testing for psoriasis, ulcerative colitis,

Abbreviations used in this paper: **AP, abdominal pain; CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; FCP, fecal calprotectin; hsCRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; Ig, immunoglobulin; IL, interleukin; ITT, intention-to-treat; IV, intravenous; IV-C, ■; NI, nonimprover; PBO, placebo; PRO, Patient-Reported Outcome; Q4W, every 4 weeks; SAE, ■■; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TEAE, treatment-emergent adverse event.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Interleukin 23 contributes to pathogenesis of Crohn's disease. Mirikizumab is a monoclonal antibody directed against the p19 subunit of interleukin 23 and has shown efficacy in treating psoriasis and ulcerative colitis.

NEW FINDINGS

Mirikizumab was effective in induction of endoscopic and clinical response after 12 weeks and demonstrated durable efficacy throughout the maintenance period.

LIMITATIONS

The limitations of the trial include the eventual small sample size of the individual dosing groups in maintenance and the lack of a placebo group through the full year of evaluation.

IMPACT

Mirikizumab can be delivered safely and provide therapeutic efficacy for patients with moderate-to-severe Crohn's disease, even in a heavily pretreated patient population.

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and CD. We evaluated the efficacy and safety of mirikizumab for the treatment of patients with moderately-to-severely active CD.

Methods

Study Design and Participants

Study I6T-MC-AMAG was a multicenter, randomized, parallel-arm, double-blind, placebo (PBO)-controlled trial (See Figure 1 for study design) conducted across 80 sites in 14 countries (see Supplementary Appendix for complete list of study sites). Patients were screened from December 14, 2016 to September 4, 2018 and enrolled from January 12, 2017 to September 24, 2018. The final Week 52 patient visit was September 27, 2019.

Eligible patients were 18–75 years of age with a diagnosis of CD for ≥3 months with moderate-to-severe disease defined as stool frequency (SF) ≥4 and/or abdominal pain (AP) ≥2 at baseline and a centrally read Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥7 for subjects with ileal-colonic, or ≥4 for subjects with isolated ileal disease within 14 days before the first dose of study treatment. Patients must have received prior treatment for CD, with history of intolerance or inadequate response to aminosalicylates, 6-mercaptopurine, azathioprine, or corticosteroids, or history of corticosteroid dependence; and/or have received treatment with ≥1 biologic agent (such as tumor necrosis factor antagonists, vedolizumab, experimental biologic CD therapeutics except for those targeting IL23 p19) with or without documented history of intolerance or inadequate response. Concomitant treatment with oral 5-aminosalicylic compounds, oral corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, or CD-specific antibiotics were allowed.

Patients were not eligible if they had the following: complications of CD such as strictures, stenoses, or any other manifestation for which surgery might be indicated or could confound the evaluation of efficacy; any kind of bowel resection or diversion within 6 months or other intra-abdominal surgery within 3 months; presence of a stoma; previous exposure to any other biologic therapy targeting IL23 p19 or ustekinumab (in a US-specific addendum, a single dose of ustekinumab was allowed if given at least 12 weeks before the baseline); received natalizumab or agents that deplete B or T cells within 12 months of screening; or been treated with any investigational drug for CD within 8 weeks before baseline or 5 half-lives of the drug (whichever is longer), or with interferon therapy within 8 weeks before baseline. See Supplementary Appendix for complete list of inclusion and exclusion criteria.

This study was compliant with the International Conference on 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 study drug.

Randomization and Blinding

Induction. Patients were randomized in a 2:1:1:2 ratio across treatment groups: PBO, mirikizumab 200 mg, mirikizumab 600 mg, or mirikizumab 1000 mg, to be administered intravenously (IV) every 4 weeks (Q4W) through Week 12. The randomization was stratified by previous exposure to biologic therapy for treatment of CD, with planned minimum distribution of approximately 30% of patients naive to biologic CD therapy (including experimental biologic CD therapy) and at least 50% of the patients having experienced prior biologic CD therapy (including experience with experimental biologic CD therapy).

Maintenance. All patients received both IV and subcutaneous (SC) dosing in a double-dummy design during the maintenance period (Weeks 12–52) to maintain the study blind.

Rerandomized Maintenance Cohort. All patients who received mirikizumab treatment during induction (Weeks 0–12) and who achieved an improvement (at least 1 point decrease) in their SES-CD score from baseline at Week 12 were randomized evenly to either (1) continue induction treatment assignment (IV mirikizumab 200 mg, 600 mg, or 1000 mg Q4W; rerandomized IV were pooled for analysis [IV-C]) and PBO administered SC or (2) IV PBO Q4W and SC mirikizumab 300 mg Q4W administered through Week 52 (IV/SC). Randomization was stratified based on endoscopic response (50% reduction in SES-CD score from baseline).

Nonrandomized Maintenance Cohort. All patients who received mirikizumab treatment during induction and who did not achieve an improvement from baseline SES-CD score at Week 12 (endoscopic nonimprovers [NI]) as well as all patients who received PBO during induction received IV mirikizumab 1000 mg and SC PBO Q4W through Week 52 (NI/1000 mg and PBO/1000 mg, respectively).

A study site pharmacist or other trained person was unblinded at the site for investigational product preparation. Patients who met all criteria for enrollment were randomized to the study drug at the baseline visit. Assignment to a double-blind investigational product was determined using a computer-generated random sequence using an interactive web-response system, and the site was responsible for administering the study drug to the patients.

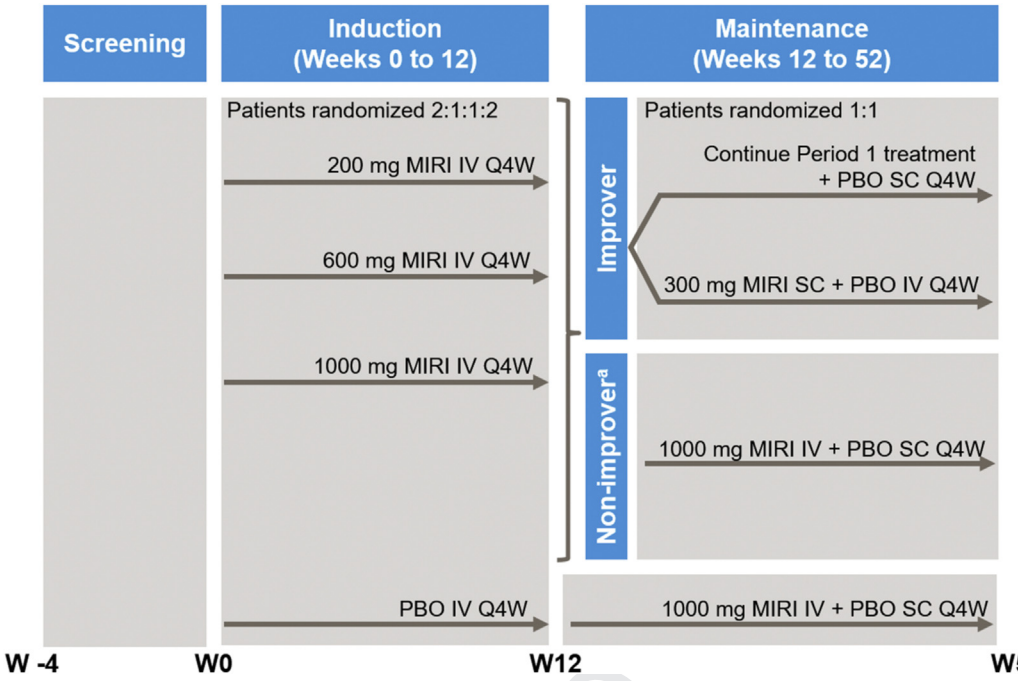

Figure 1. AMAG study design. MIRI, mirikizumab. [a]MIRI NI is defined as failing to achieve any improvement from baseline SES-CD score at Week 12.

Objectives and Procedures

The 12-week induction period was designed to establish the efficacy and safety of mirikizumab administered IV at Weeks 0, 4, and 8. The maintenance period was designed to assess the efficacy and safety of continuous IV treatment compared with subcutaneously administered mirikizumab in patients who have demonstrated a minimal degree of endoscopic improvement; patients who had not achieved this degree of improvement as well as all PBO patients were assessed for their response to the highest IV dose of mirikizumab for the remainder of the 52-week period.

The SES-CD was used to evaluate the endoscopy video that was collected during each patient endoscopic (colonoscopy) examination.[18,19] The SES-CD score was determined using one central reader and was used to determine study eligibility and endoscopic efficacy evaluation. The reader was masked to treatment group and visit throughout the induction and maintenance periods. See Supplementary Appendix for details of biomarker analyses in plasma and feces.

Outcomes

The primary endpoint of this study was endoscopic response of mirikizumab versus PBO at Week 12, defined as a 50% reduction from baseline in SES-CD score.[19] Secondary objectives included the following: evaluation of safety and tolerability; Week 52 endoscopic response; Week 12 and 52 endoscopic remission (SES-CD score of <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1); Week 12 and 52 Patient-Reported Outcome (PRO)[20] remission (average daily AP score ≤1 and average daily SF ≤2.5); and change from baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ) score. Other exploratory objectives included change from baseline in the biomarkers C-reactive protein (hsCRP) and fecal calprotectin (FCP); Crohn's disease activity index (CDAI) response (decrease from baseline in CDAI Score of 100 points or more or a CDAI score <150) at Weeks 12 and 52; CDAI remission (CDAI score of <150) at Weeks 12 and 52; PRO response (≥30% reduction in AP and/or SF and no worse than BL); and durability of outcomes at Week 52 (see Supplementary appendix for details). Adverse events were coded according to the Medical Dictionary for Regulatory Activities Versions 19-21 and summarized based on system organ class, preferred term, severity, and relationship to investigational product. A treatment-emergent adverse event (TEAE) was defined as an event that first occurred or worsened in severity after baseline.

Statistical Analysis

Enrollment was planned for approximately 180 patients. Based on 60 patients per comparison treatment arm and the assumed mirikizumab and PBO endoscopic response rates of 35% and 15%, respectively, the test of the superiority versus PBO has 81% power when performed via a chi-squared test at a 2-sided 0.1 significance level.

The intention-to-treat (ITT) population, which included all randomly assigned patients, was used to assess efficacy, demographics, baseline disease characteristics, and health outcome measures at Week 12. Subjects from the ITT population who entered the maintenance period were used to assess efficacy and health outcome measures at Week 52. Two subjects who failed the screening process and were inadvertently randomized did not receive study treatment and were excluded from the ITT population. The safety population included all randomized patients who received at least one dose of study drug and was summarized using descriptive statistics. The primary and secondary categorical outcome measures were analyzed using a logistic regression analysis with treatment, geographic region, and prior biologic CD therapy use (yes/no)

in the model. Nonresponder imputation was used at Week 12 and at Week 52 for any subject who discontinued the study treatment at any time before Week 12 (or Week 52) for any reason or failed to have an adequate Week 12 (or Week 52) efficacy assessment. Continuous efficacy and health outcome variables were analyzed using a Mixed Effect Model Repeat Measurement technique with treatment, geographic region, prior biologic CD therapy use, baseline value, visit, and the interactions of treatment-by-visit and baseline-by-visit as fixed factors. An unstructured covariance structure to model the within-patient errors was used. If the unstructured covariance matrix resulted in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, was used. The Kenward-Roger method was used to estimate the denominator degrees of freedom. Descriptive statistics were used to summarize differences in demographic and baseline disease characteristics.

This study is registered with ClinicalTrials.gov, number NCT02891226. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Induction Period

Between December 14, 2016 and September 4, 2018, 526 patients were screened for eligibility in study AMAG. Among the 191 patients who met inclusion criteria and

Table 1. Baseline Demographics and Clinical Characteristics

Mean (SD) unless otherwise specified	Treatment groups			
		MIRI		
	Placebo (N = 64)	200 mg (N = 31)	600 mg (N = 32)	1000 mg (N = 64)
Age (*y*)	39.0 (13.0)	38.1 (11.8)	40.4 (13.3)	37.7 (13.1)
Male, n (%)	28 (43.8)	17 (54.8)	14 (43.8)	34 (53.1)
Disease duration (*y*)	10.2 (9.8)	8.9 (7.4)	10.8 (9.7)	8.6 (6.7)
Disease location, n (%)				
Ileal	11 (17.2)	6 (19.4)	5 (15.6)	11 (17.2)
Colonic	25 (39.1)	14 (45.2)	10 (31.3)	26 (40.6)
Ileocolonic	28 (43.8)	11 (35.5)	17 (53.1)	27 (42.2)
SES-CD	11.9 (5.6)	14.4 (7.9)	15.2 (7.4)	13.1 (6.8)
PRO scores				
SF	6.4 (3.1)	7.4 (3.0)	6.4 (3.8)	6.6 (5.5)
AP	1.9 (0.6)	2.0 (0.6)	1.7 (0.7)	1.9 (0.6)
CDAI	304.7 (93.1)	348.3 (92.1)	298.2 (103.7)	304.5 (94.4)
Previous biologic use,[a] n (%)	43 (67.2)	19 (61.3)	19 (59.4)	39 (60.9)
Previous biologic failure,[b] n (%)	36 (56.3)	15 (48.4)	16 (50.0)	31 (48.4)
Prior vedolizumab use, n (%)	14 (21.9)	5 (16.1)	5 (15.6)	6 (9.4)
Prior anti-TNF use, n (%)				
0	25 (39.1)	14 (45.2)	14 (43.8)	26 (40.6)
1	16 (25.0)	10 (32.3)	9 (28.1)	22 (34.4)
2	22 (34.4)	7 (22.6)	5 (15.6)	14 (21.9)
3+	1 (1.6)	0	4 (12.5)	2 (3.1)
Concomitant oral corticosteroid use, n (%)	21 (32.8)	14 (45.2)	7 (21.9)	15 (23.4)
Concomitant immunosuppressant use, n (%)	19 (29.7)	12 (38.7)	10 (31.3)	21 (32.8)
IBDQ	113.88 (37.07)	104.77 (34.31)	127.03 (35.47)	120.31 (32.40)
hsCRP (median, Q1, Q3)	6.8 (1.8, 19.0)	7.4 (2.3, 31.4)	6.8 (2.7, 20.7)	4.5 (2.7, 15,5)
FCP (median, Q1, Q3)	799.5 (256.5, 1945.5)	877.0 (225.0, 4359.0)	822.5 (355.0, 2302.5)	773.0 (293.0, 1634.0)

NOTE. ITT population. Patients with prior biologic exposure who did not fail biologic treatment discontinued treatment for the following reasons: cannot afford, treatment availability, subject decision, completed treatment, and other.
MIRI, mirikizumab; UST, ustekinumab.
[a]Although prior induction dosing of UST use was allowed, no patients had prior UST treatment.
[b]Inadequate response, loss of response, or intolerance to medication.

were randomized, 92.1% of patients completed the first 12 weeks of the study (Supplementary Figure 1). Baseline characteristics were similar across treatment groups. Mean disease duration was similar in all groups, as well as baseline CDAI, AP, and SES-CD. Average SF was numerically higher in the 200 mg group compared with the other groups, as were the percentage of patients receiving oral corticosteroids or immunosuppressants at baseline in the 200 mg group. Prior biologic use was approximately 60% in all mirikizumab groups and 67.2% in the PBO group, with prior biologic failure rates of approximately 50% and 56.3% in the mirikizumab groups and PBO group, respectively (Table 1).

Primary Endpoint. The primary endpoint of endoscopic response at Week 12 was achieved, with significantly higher response in each of the 3 mirikizumab groups compared with PBO (mean [95% confidence interval {CI}]; mirikizumab 200 mg: 8/31, 25.8% [10.4–41.2], $P = .079$; mirikizumab 600 mg: 12/32, 37.5% [20.7–54.3], $P = .003$; mirikizumab 1000 mg: 28/64, 43.8% [31.6–55.9], $P < .001$; PBO: 7/64, 10.9% [3.3–18.6]) (Table 2, Figure 2*A*).

Secondary and Exploratory Endpoints. A total of 2/31 (6.5% [0–15.1]) in the mirikizumab 200 mg group, 5/32 (15.6% [3.0–28.2], $P = .01$) in the mirikizumab 600 mg group, and 13/64 (20.3% [10.5–30.2], $P < .001$) in the mirikizumab 1000 mg group achieved endoscopic remission compared with 1 (1.6% [0–4.6]) patient in the PBO group (Table 2, Figure 2*B*).

PRO remission was achieved by 4/31 (12.9% [1.1–24.7]) patients in the mirikizumab 200 mg group, 9/32 (28.1% [12.5–43.7], $P = .004$) patients in the mirikizumab 600 mg group, and 14/64 (21.9% [11.7–32.0], $P = .013$) patients in the mirikizumab 1000 mg group compared with 4/64 (6.3% [0.3-12.2]) patients in the PBO group. Similarly, PRO response during the 12-week induction period was significantly higher in the 3 mirikizumab groups compared with PBO (mirikizumab 200 mg $P = .023$, mirikizumab 600 mg $P = .003$, mirikizumab 1000 mg $P = .006$) (Table 2,

Table 2. Week 12 Efficacy results

	Treatment groups			
		MIRI		
	Placebo (N = 64)	200 mg (N = 31)	600 mg (N = 32)	1000 mg (N = 64)
Endoscopic response,[a] n (%)	7 (10.9)	8 (25.8)	12 (37.5)	28 (37.8)
Difference vs PBO (95% CI)		14.9 (-2.3, 32.1)	26.6 (8.1, 45.0)	32.8 (18.5, 47.2)
Endoscopic remission,[b] n (%)	1 (1.6)	2 (6.5)	5 (15.6)	13 (20.3)
Difference vs PBO (95% CI)		4.9 (-4.3, 14.1)	14.1 (1.1, 27)	18.8 (8.4, 29.1)
PRO response,[c] n (%)	23 (35.9)	19 (73.1)	22 (68.8)	39 (60.9)
Difference vs PBO (95% CI)		25.4 (4.6, 46.1)	32.8 (12.9, 52.7)	25.0 (8.2, 41.8)
PRO remission,[d] n (%)	4 (6.3)	4 (12.9)	9 (28.1)	14 (21.9)
Difference vs PBO (95% CI)		6.7 (-6.6, 19.9)	21.9 (5.2, 38.5)	15.6 (3.9, 27.4)
CDAI response,[e] n (%)	15 (23.4)	15 (48.4)	18 (56.3)	27 (42.2)
Difference vs PBO (95% CI)		24.9 (4.5, 45.4)	32.8 (12.7, 52.9)	18.8 (2.8, 34.7)
CDAI remission,[f] n (%)	6 (9.4)	5 (16.1)	13 (40.6)	17 (26.6)
Difference vs PBO (95% CI)		6.8 (-8, 21.5)	31.3 (12.8, 49.7)	17.2 (4.2, 30.2)
hsCRP % change from BL (median, Q1, Q3)	43.8 (-8.3, 145.5)	-29.9[j] (-64.8, 25.9)	-39.8[j] (-70.6, 0.2)	-48.6[j] (-76.1, 35.1)
FCP % change from BL (median, Q1, Q3)	0.0 (-60.9, 54.1)	-60.7 (-84.8, 68.0)	-62.1[h] (-84.4, -13.2)	-76.2[j] (-90.7, -54.9)

NOTE. ITT population.
[a]Endoscopic response: 50% reduction from baseline in SES-CD Score.
[b]Endoscopic remission: SES-CD score of <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1.
[c]PRO remission: SF ≤ 2.5 and AP ≤ 1 and no worse than baseline.
[d]PRO response: ≥30% decrease in AP and/or SF and no worse than BL.
[e]CDAI response: decrease from baseline in CDAI Score of 100 points or more or a CDAI score < 150.
[f]CDAI remission: A CDAI score of <150 points.
[g]$P < .1$.
[j]$P < .001$.
[h]$P < .05$.
[i]$P < .01$.

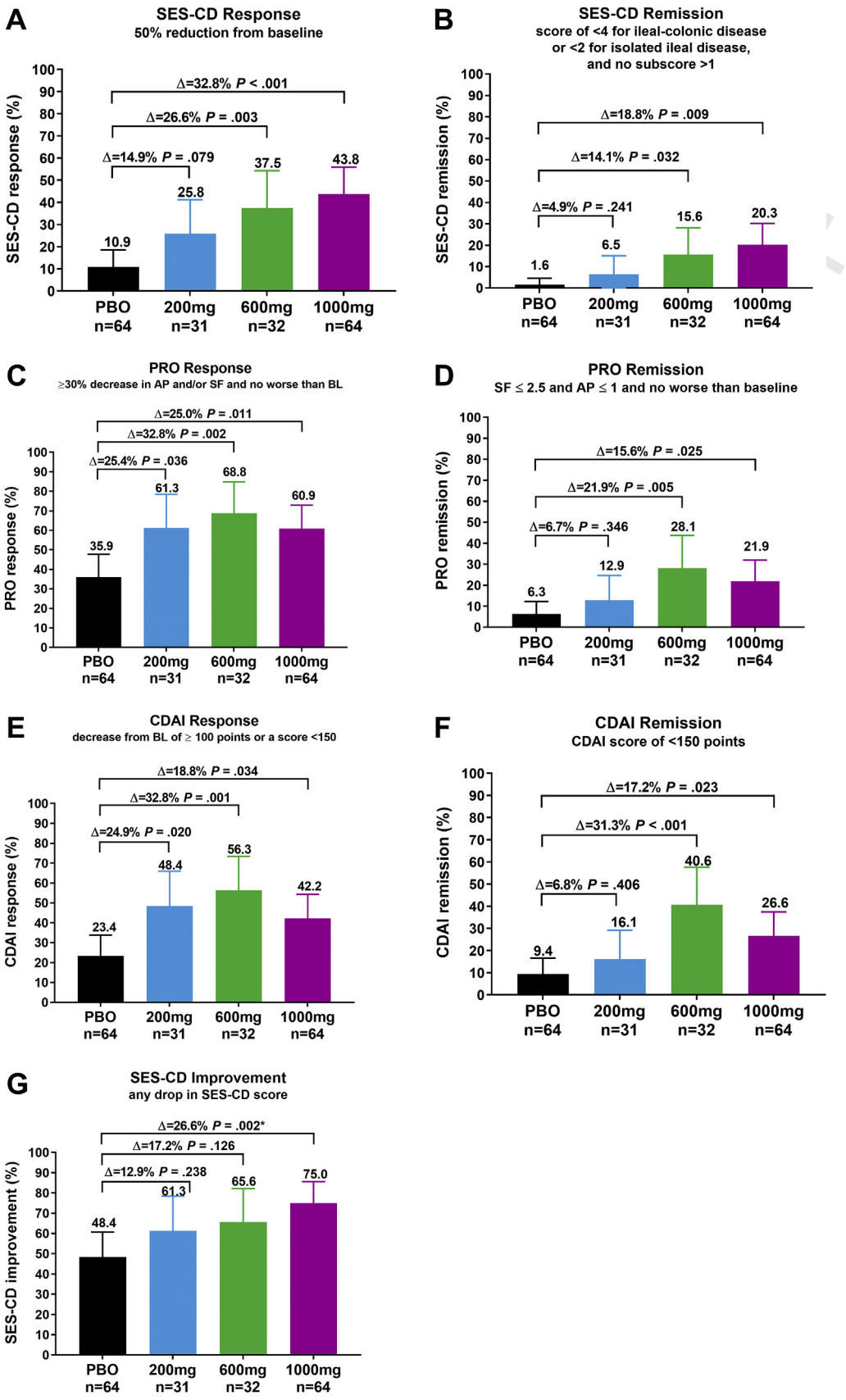

Figure 2. Clinical and endoscopic outcomes at Week 12.

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Figure 2*C* and *D*), as was CDAI response (mirikizumab 200 mg $P = .015$, mirikizumab 600 mg $P = .001$, mirikizumab 1000 mg $P = .026$) (Table 2, Figure 2*E*). CDAI remission was significantly higher than PBO in the 600 mg and 1000 mg mirikizumab groups (mirikizumab 600 mg $P < .001$, mirikizumab 1000 mg $P = .013$) (Table 2, Figure 2*F*).

Sample size was relatively low when outcomes were stratified by biologic experience. However, among biologic-experienced patients, both endoscopic response and remission rates were numerically lower in the 200 mg group compared with those naïve to biologic treatment. For both remission and response, this difference decreased with the higher doses until rates were similar in the 1000 mg group (Supplementary Figure 2*A* and *B*). In contrast, PRO response rates were similar between biologic-experienced and biologic-naïve patients in all dose groups (Supplementary Figure 2*C*), whereas PRO remission rates were similar with the exception of the 200 mg dose group (Supplementary Figure 2*D*). CDAI response rates were higher in biologic-experienced patients in both the 200 mg and 600 mg dose groups compared with biologic-naïve patients (Supplementary Figure 2*E*). CDAI remission rates varied, with biologic-naïve patients having higher rates in the 200 mg and 1000 mg dose groups, and biologic-experienced patients having higher rates in the 600 mg dose group (Supplementary Figure 2*F*).

Patients who received mirikizumab 600 or 1000 mg had greater change from baseline in IBDQ scores at 4 weeks compared with PBO ($P = .03$ for both groups). At 12 weeks, all mirikizumab groups had greater change from baseline in IBDQ scores compared with PBO (mirikizumab 200 mg $P < .001$, mirikizumab 600 mg $P < .001$, mirikizumab 1000 mg $P < .001$). Likewise, CDAI and PRO components SF and AP were demonstrated to have significantly greater decrease from baseline by 8 weeks in all dose groups compared with PBO; in the 600 mg group all 3 outcomes were significantly improved versus PBO at 4 weeks (Supplementary Figure 3).

At Week 12, the percentage change from baseline in hsCRP was significantly greater in all mirikizumab groups compared with PBO ([median Q1, Q3] PBO: 43.8 [-8.3, 145.5]; mirikizumab 200 mg: -29.9 [-64.8, 25.9] $P < .001$; mirikizumab 600 mg: -39.8 [-70.6, 0.2] $P < .001$; mirikizumab 1000 mg: -48.6 [-76.1, 35.1] $P < .001$), with the greatest change in the 1000 mg group. The percentage change from baseline in FCP was significantly greater in the mirikizumab 600 and 1000 mg groups compared with PBO (PBO: 0.0 [-60.9, 54.1]; mirikizumab 200 mg: -60.7 [-84.8, 68.0]; mirikizumab 600 mg: -62.1 [-84.4, -13.2] $P < .05$; mirikizumab 1000 mg: -76.2 [-90.7, -54.9] $P < .001$) (Table 2, Supplementary Figure 4), again with the greatest change in the 1000 mg group. The percentage of patients with normalized CRP (≤3 mg/L) or FCP (≤250, 100, and 50 mg/kg) levels was significantly higher after mirikizumab treatment compared with PBO, with the highest proportion of patients in the 1000 mg mirikizumab group (CRP: PBO 9.1%; mirikizumab 200 mg: 4.3%; mirikizumab 600 mg: 26.1%, $P < .01$; mirikizumab 1000 mg: 33.3%, $P < .05$) (FCP, 250 mg/kg cutoff: PBO 13.0%; mirikizumab 200 mg: 28.6%; mirikizumab 600 mg: 33.3%, $P < .01$; mirikizumab 1000 mg: 40.8%, $P < .05$) (Supplementary Figure 4).

At the end of the 12-week induction period, 88/127 (69.3%) mirikizumab-treated patients achieved endoscopic improvement (mirikizumab 200 mg: 19/31, 61.3% [44.1–78.4]; mirikizumab 600 mg: 21/32, 65.6% [49.2–82.1]; mirikizumab 1000 mg: 48/64, 75.0% [64.4–85.6]; Figure 2*G*) and were rerandomized to either continue induction IV mirikizumab dosing (200 mg, 600 mg, or 1000 mg mirikizumab) plus SC PBO, or receive SC mirikizumab 300 mg plus IV PBO every 4 weeks.

Maintenance Period

Endoscopic Outcomes. Regarding rerandomized cohorts, there was no consistent relationship between outcomes and dose observed at Week 52 (Supplementary Figure 5). Due to small sample sizes in maintenance, all patients achieving endoscopic improvement at Week 12 and who were rerandomized to IV in maintenance were pooled (IC-C cohort) and all patients who were rerandomized to the SC arm were pooled (IV/SC cohort). Endoscopic response rates at Week 52 were 24/41 (58.5% [43.5–73.6]) and 27/46 (58.7% [44.5–72.9]) in the IV-C and IV/SC cohorts, respectively. Endoscopic remission at Week 52 was achieved by 8/41 (19.5% [7.4–31.6]) in the IV-C cohort and 15/46 (32.6% [19.1–46.2]) in the IV/SC cohort (Table 3, Figure 3*A* and *B*).

Among those patients with endoscopic response at Week 12, 16/23 (69.6% [50.8–88.4]) and 16/24 (66.7% [47.8–85.5) in the IV-C and IV/SC cohorts, respectively, also had endoscopic response at Week 52, and among those patients with endoscopic remission at Week 12, 3/6 (50.0% [10.0–90.0]) and 9/14 (64.3% [39.2–89.4]) in the IV-C and IV/SC cohorts, respectively, also had endoscopic remission at Week 52 (Table 3, Supplementary Figure 6*A* and *B*).

Regarding nonrandomized cohorts, endoscopic response was 6/20 (20.0% [5.7–34.3]) in patients who had not shown endoscopic improvement at Week 12 who received mirikizumab 1000 mg during maintenance (NI/1000 mg IV cohort), and 25/59 (42.4% [29.8–55.0]) in patients who received PBO during induction and switched to mirikizumab 1000 mg in maintenance (PBO/1000 mg IV cohort). Endoscopic remission at Week 52 was achieved by 4/30 (13.3% [1.2–25.5]) in the NI/1000 mg IV cohort and 11/59 (18.6% [8.7, 28.6]) in the PBO/1000 mg IV cohort (Table 3, Figure 3*A* and *B*).

PRO Results. Regarding rerandomized cohorts, PRO response at Week 52 was 28/41 (68.3% [54.0–82.5]) and 33/46 (71.7% [58.7–84.8]) in the IV-C and IV/SC cohorts, respectively, and PRO remission was 19/41 (46.3% [31.1–61.6]) and 21/46 (45.7% [31.3, 60.0]) in the IV-C and IV/SC cohorts, respectively (Table 3, Figure 3*C* and *D*). Among those who achieved PRO remission at Week 12, 10/14 (71.4% [47.8–95.1]) in the IV-C and 6/9 (66.7% [35.9–97.5]) in the IV/SC cohorts were also in PRO remission at Week 52 (Table 3, Supplementary Figure 6*C*).

Regarding nonrandomized cohorts, PRO response at Week 52 was 18/30 (60.0% [42.5, 77.5]) in the NI/1000 mg

Table 3. Week-52 Efficacy Results

	Randomized maintenance[b]		Nonrandomized maintenance	
	IV-C Q4W N = 41	300 mg SC Q4W N = 46	Placebo/1000 mg IV Q4W (N = 59)	Endoscopic NI / 1000 mg IV Q4W (N = 30)
	Week 12			
Endoscopic response,[c] n (%)	23 (56.1)	24 (52.2)	7 (11.9)	0
Endoscopic remission,[d] n (%)	6 (14.6)	14 (30.4)	1 (1.7)	0
PRO remission,[e] n (%)	14 (34.1)	9 (19.6)	4 (6.8)	4 (13.3)
CDAI remission,[f] n (%)	13 (31.7)	15 (32.6)	6 (10.2)	6 (20.0)
	Week 52[a]			
Endoscopic response,[c] n (%)	24 (58.5)	27 (58.7)	25 (42.4)	6 (20.0)
Endoscopic response in W12 responders, n/N (%)	16/23 (69.6)	16/24 (66.7)	4/7 (57.1)	N/A
Endoscopic remission,[c] n (%)	8 (19.5)	15 (32.6)	11 (18.6)	4 (13.3)
Endoscopic remission in W12 remitters, n/N (%)	3/6 (50.0)	9/14 (64.3)	0/1 (0.0)	N/A
PRO response,[g] n (%)	28 (68.3)	33 (71.7)	36 (61.0)	18 (60.0)
PRO remission,[e] n (%)	19 (46.3)	21 (45.7)	24 (40.7)	11 (36.7)
PRO remission in W12 remitters, n/N (%)	10/14 (71.4)	6/9 (66.7)	3/4 (75.0)	3/4 (75.0)
CDAI response,[h] n (%)	22 (53.7)	32 (69.6)	31 (52.5)	14 (46.7)
CDAI remission,[f] n (%)	16 (39.0)	26 (56.5)	24 (40.7)	7 (23.3)
CDAI remission in W12 remitters, n/N (%)	9/13 (69.2)	13/15 (86.7)	5/6 (83.3)	4/6 (66.7)

[a]For all efficacy endpoints, IV-C and SC CIs overlap.
[b]Patients with endoscopic improvement at Week 12: ≥1-point improvement in SES-CD at Week 12.
[c]Endoscopic response: 50% reduction from baseline in SES-CD.
[d]Endoscopic remission: SES-CD score of <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1.
[e]PRO remission: SF ≤2.5 and AP ≤1 and no worse than baseline.
[f]CDAI remission: A CDAI score of <150 points.
[g]PRO response: ≥30% decrease in AP and/or SF and no worse than BL.
[h]CDAI response: decrease from baseline in CDAI Score of 100 points or more or a CDAI score <150.

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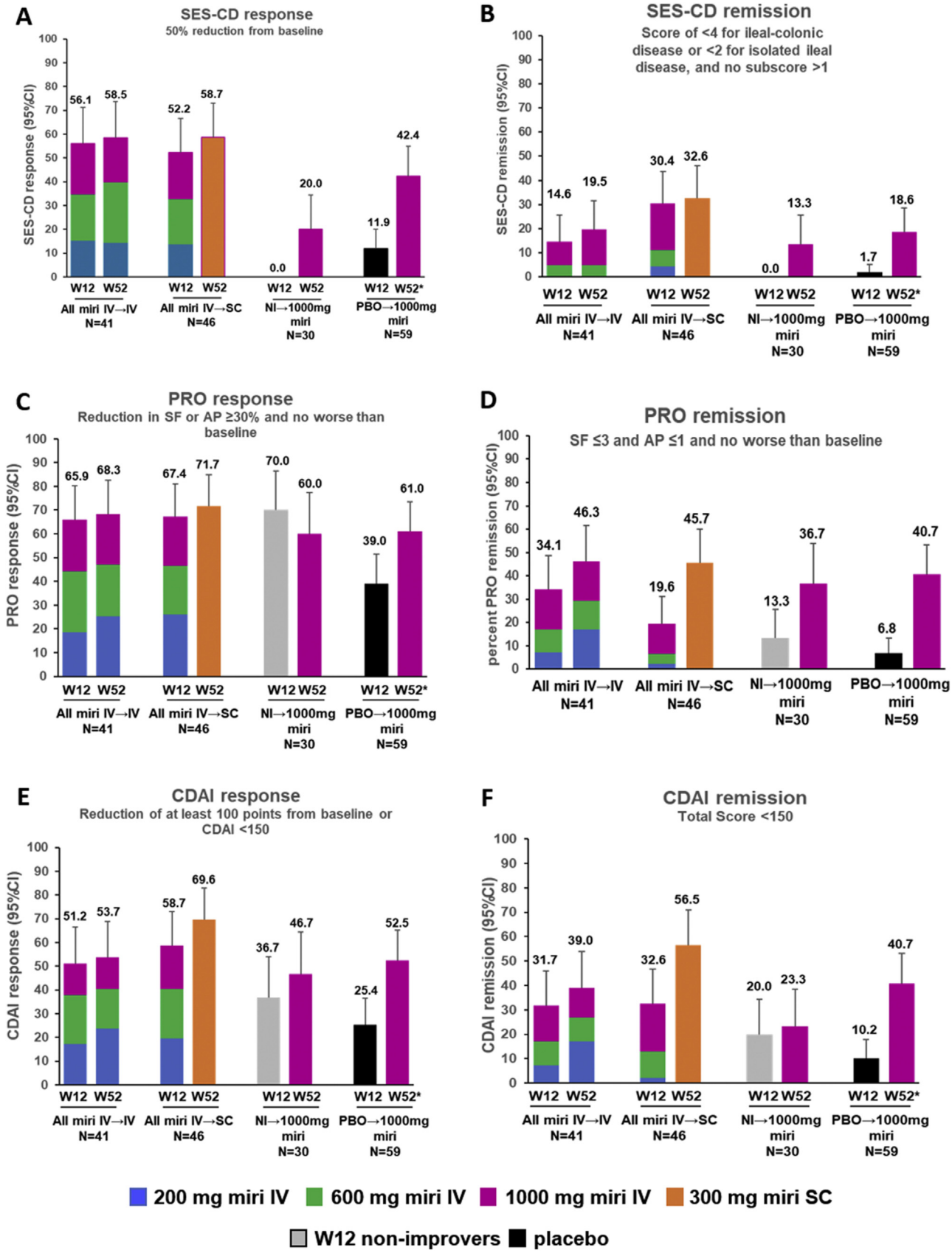

Figure 3. Clinical and endoscopic outcomes at Week 52. *40 weeks of active drug administration; total height of each bar represents the percentage of patients achieving each endpoint. Bar partitions symbolize relative contributions for each dose: all miri IV→IV 200 mg N = 9, 600 mg N = 9, 1000 mg N = 23; all miri IV→SC 200 mg N = 10, 600 mg N = 11, 1000 mg N = 25. Q36

Table 4. Safety Results

	Treatment groups, induction period			
		MIRI		
	Placebo (N = 64)	200 mg (N = 31)	600 mg (N = 32)	1000 mg (N = 64)
TEAE, n (%)	45 (70.3)	18 (58.1)	21 (65.6)	42 (65.6)
SAE, n (%)	7 (10.9)	0	3 (9.4)	2 (3.1)
Discontinuations due to AE, n (%)	3 (4.7)	1 (3.2)	3 (9.4)	0
Most common TEAEs, n (%) (decreasing frequency[a])				
Headache	2 (3.1)	2 (6.5)	2 (6.3)	7 (10.9)
CD (worsening of)	9 (14.1)	0	1 (3.1)	0
Arthralgia	3 (4.7)	1 (3.2)	1 (3.1)	3 (4.7)
Nasopharyngitis	1 (1.6)	0	2 (6.3)	4 (6.3)
Weight increased	0	1 (3.2)	2 (6.3)	3 (4.7)
Anemia	1 (1.6)	2 (6.5)	1 (3.1)	2 (3.1)
Nausea	2 (3.1)	0	2 (6.3)	2 (3.1)

	Treatment groups, maintenance period			
	Randomized maintenance		Nonrandomized maintenance	
	IV-C Q4W N = 41	300 mg SC Q4W N = 46	Placebo/1000 mg IV Q4W (N = 59)	Endoscopic NI/1000 mg IV Q4W (N = 30)
TEAE, n (%)	31 (75.6)	35 (76.1)	45 (76.3)	21 (70.0)
SAE, n (%)	0 (0)	2 (4.3)	8 (13.6)	3 (10.0)
Discontinuations due to AE, n (%)	1 (2.4)	1 (2.2)	7 (11.9)	3 (10.0)
Most common TEAEs, n (%) (≥5%, decreasing frequency)				
Nasopharyngitis	2 (4.9)	6 (13.0)	4 (6.8)	3 (10.0)
Headache	3 (7.3)	4 (8.7)	4 (6.8)	3 (10.0)
Arthralgia	3 (7.3)	6 (13.0)	3 (5.1)	1 (3.3)
Anemia	2 (4.9)	2 (4.3)	5 (8.5)	2 (6.7)
Injection site pain	2 (4.9)	4 (8.7)	3 (5.1)	1 (3.3)
Upper respiratory tract infection	2 (4.9)	3 (6.5)	3 (5.1)	2 (6.7)
Abdominal pain	3 (7.3)	3 (6.5)	3 (5.1)	0 (0)

[a]Most common TEAEs: as percentage of total population. Only headache and CD were >5% frequency during induction.

IV cohort and 36/59 (61.0% [48.6–73.5]) in the PBO/1000 mg IV cohort. PRO remission was 11/30 (36.7% [19.4–53.9]) in the NI/1000 mg IV cohort and 24/59 (40.7% [28.1–53.2]) in the PBO/1000 mg IV cohort (Table 3, Figure 3*C* and *D*).

CDAI Results. Regarding rerandomized cohorts, CDAI response was achieved by 22/41 (53.7% [38.4–68.9]) and 32/46 (69.6% [56.3–82.9]) in the IV-C and IV/SC cohorts, respectively. CDAI remission was 16/41 (39.0% [24.1–54.0]) and 26/46 (56.5% [42.2–70.8]) in the IV-C and IV/SC cohorts, respectively (Table 3, Figure 3*E* and *F*). Among those who achieved CDAI remission at Week 12, 9/13 (69.2% [44.1–94.3]) in the IV-C and 13/15 (86.7% [69.5–100]) in the IV/SC cohort were also in CDAI remission at Week 52 (Table 3, Supplementary Figure 6*D*).

Regarding nonrandomized cohorts, in the NI/1000 mg IV cohort, 14/30 (46.7% [28.8–64.5]) achieved CDAI response and in the PBO/1000 mg IV cohort, 31/59 (52.5% [39.8–65.3] achieved CDAI response. CDAI remission was achieved by 7/30 (23.3% [8.2–38.5]) in the NI/1000 mg IV cohort and 24/59 (40.7% [28.1–53.2]) in the PBO/1000 mg IV cohort (Table 3, Figure 3*E* and *F*).

IBDQ Outcomes. Among the Week 12 mirikizumab induction endoscopic improvers, the change from baseline in IBDQ was similar in both cohorts, with a total change of 64.3 and 66.4 points in the IV-C and IV/SC cohorts, respectively.

The IBDQ change from baseline was 44.5 in the NI/1000 mg IV cohort and 53.6 in the PBO/1000 mg IV cohort (Supplementary Figure 7).

Circulating Biomarkers. The median percentage change from baseline in both hsCRP and FCP were similar across all cohorts (hsCRP: IV-C -59.5%, IV-SC -52.4%, PBO/1000 mg IV -58.5%, and NI/1000 mg IV -45.9%; FCP: IV-C -78.2%, IV/SC -81.0%, PBO/1000 mg IV -72.5%, and NI/1000 mg IV -76.9%). The percentages of patients with normalized CRP (≤3 mg/L) or FCP (≤250, 100, and 50 mg/kg) levels were likewise similar across groups (Supplementary Figure 8).

Safety–Induction Period. TEAEs occurred in 70.3% of the PBO group, 58.1% of the 200 mg mirikizumab group, and 65.6% in each of the 600 mg and 1000 mg mirikizumab groups during the induction period (Table 4). The most frequent TEAEs among mirikizumab groups during the induction period included headache, worsening of CD, arthralgia, nasopharyngitis, increased weight, anemia, and nausea. There were no dose-related differences in the frequencies of patients reporting ≥1 TEAE among mirikizumab treatment groups, which were overall slightly lower than in the PBO group.

During the induction period, 12 patients had ≥1 SAE: 7 in the PBO group (worsening of CD [3 patients], hypokalemia, malaise, pneumatosis intestinalis, and pyrexia), 0 in the 200 mg mirikizumab group, 3 in the 600 mg mirikizumab group (chest pain, worsening of CD, colon perforation [found during endoscopy], and colonic stenosis), and 2 in the 1000 mg mirikizumab group (abdominal pain and back pain). Two patients discontinued their participation in the study due to their SAE (worsening of CD and large intestine perforation); all others recovered and remained in the study.

Safety–Maintenance Period. Regarding the randomized maintenance group, during the maintenance period, there were no SAEs reported in the mirikizumab IV-C group and 2 in the mirikizumab 300 mg SC group (worsening of CD, pyelonephritis, and dehydration in 1 patient and ileal perforation [secondary to ileitis] and peritonitis in the other patient). Two of these patients (worsening of CD, ileal perforation) discontinued their participation in the study due to their SAE.

Regarding the nonrandomized maintenance group, 11 patients had ≥1 SAE: 8 in the induction PBO/1000 mg group (anaphylactic reaction [2 patients], *Clostridioides difficile* infection, hypersensitivity, intestinal obstruction, noncardiac chest pain, osteoarthritis, and worsening of CD), and 3 in the Week 12 NI/1000 mg group (spontaneous abortion, worsening of CD, and pneumonia). Four patients discontinued their participation in the study due to their SAE (anaphylactic reaction [2 patients], hypersensitivity, worsening of CD) whereas the remaining patients recovered and remained in the study.

There were no deaths in any study period, and no malignancies or instances of veno-occlusive disease (including pulmonary embolism) reported in the induction or maintenance period of the study. Opportunistic infections were reported by 1 patient in the induction period (herpes zoster, PBO group) and 3 patients in the maintenance period (1 oral candidiasis, NI/1000 mg group; 2 herpes zoster, PBO/1000 mg group).

Discussion

In this phase 2, dose-ranging study, mirikizumab induced endoscopic and clinical remission and response after 12 weeks in patients with moderately-to-severely active CD, with robust proportions of patients continuing to demonstrate efficacy at Week 52. The trial evaluated patients both naïve and with prior exposure to biologic therapy; the patient population was predominantly pretreated, with approximately two thirds of participants having received biologic therapy and approximately half of all patients in this trial having experienced at least 1 biologic failure (Table 1). These characteristics suggest a relatively difficult to treat population and have been associated with lower response rates in prior CD studies. Nonetheless, mirikizumab-treated patients had significantly higher rates of endoscopic, PRO, and CDAI response and remission compared with patients given PBO, including patients with prior exposure to biologics. Additionally, response to mirikizumab was rapid, with CDAI, PRO, and IBDQ showing significant improvements compared with PBO within 4 weeks of treatment.

The 12-week endoscopic outcomes were consistently dose related with the greatest improvements in the 1000 mg mirikizumab group. PRO and CDAI outcomes showed similar increases with increasing dose, although the 1000 mg dose was numerically lower than the 600 mg dose. Nevertheless, both doses were statistically significantly

greater than PBO. The results of more objective assessments (hsCRP, FCP, as well as endoscopy) would support that near maximal efficacy has been achieved with the 2 highest doses. The totality of the evidence suggests that a slight increase in endoscopic efficacy may be achieved with the highest dose.

Results from the maintenance period supported the durability of the efficacy of mirikizumab as evidenced by the proportion of patients achieving key clinical and endoscopic endpoints at Week 12 that continued to achieve these endpoints at Week 52. Furthermore, the rates of endoscopic response and remission as well as response and remission for the 2 clinical assessments (PRO and CDAI) were both similar or numerically higher at Week 52 compared with Week 12, and the total CDAI score showed a progressive improvement with mirikizumab treatment over the year. Patients in both IV and SC regimens had 87.8% and 89.1% continuation through Week 52, respectively, and rates of endoscopic remission and response as well as PRO and CDAI improvement at Week 52 were similar. Patients in both groups demonstrated durable clinical benefit with close to 70% of patients in the IV-C and IV-SC groups in endoscopic response at both Week 12 and 52 with similar proportions for PRO and CDAI remission. These data would indicate that continuous intravenous therapy for an entire year at a range of doses may offer no advantage in supporting the durability of clinical and endoscopic efficacy compared with subcutaneously administered mirikizumab.

An important unique and novel aspect of this trial was the assignment of maintenance treatment based solely on the observation of any improvement in the SES-CD, rather than use of clinical outcomes. Previous studies in CD have almost uniformly used clinical outcomes as the basis for determining maintenance dosing. Only one other trial has used an endoscopic determination (25% improvement in SES-CD) to assign maintenance dosing, but the results describing the effect of this determination on endoscopic and clinical outcomes after maintenance therapy are not yet available.[21] In this trial, patients who had failed to demonstrate even a 1-point improvement in SES-CD by Week 12 were continued on mirikizumab at the highest dose through Week 52, and although this group had lower rates of endoscopic response and remission at 1 year compared with those who had endoscopic improvement at Week 12, 1 of 5 of these patients achieved endoscopic response and more than a third achieved PRO remission by Week 52. The significance of these observations is similar to other reports of early outcomes predicting later responses and should be further evaluated. Notably, and consistent with previous literature, the clinical outcomes (PRO, CDAI) were not as impacted in contrast to the endoscopic endpoints. This discordance between clinical and endoscopic outcomes has been previously noted.[22]

In this study there were no direct measures of target engagement in the intestinal mucosa. However, the dose-dependent reductions in hsCRP and FCP that were observed after 12 weeks of treatment with mirikizumab likely reflect a reduction in gut inflammation. Indeed, hsCRP is a known marker of acute systemic inflammation, which correlates with disease activity in the majority of patients, whereas FCP is a reliable biomarker of mucosal inflammation, specifically neutrophils in the gut mucosa.[23] In this study we found that, of those patients with elevated hsCRP or FCP at baseline, up to 40% had normalized values in a dose-dependent manner at Week 12. Taken together with the observed improvements in endoscopic measures, these data suggest that mirikizumab has the potential to be an effective therapy for healing the mucosa in patients with CD.

During the induction period, TEAEs and SAEs showed no difference between the different mirikizumab dose groups and were overall slightly lower than in the PBO group. In the maintenance period there were no apparent differences in TEAEs between the combined IV and the IV/SC cohorts and the 2 cohorts in the Nonrandomized Maintenance Group. There were 2 SAEs in the Randomized Maintenance Group. The percentages of SAEs in the 2 Nonrandomized Group cohorts were higher than in the Randomized Group. The majority of SAEs were those that may be typically associated with ongoing disease activity. Two cases of infusion reactions consistent with anaphylaxis were observed in patients moving from PBO to 1000 mg IV. These events occurred after initiation of infusion at a rate calculated to deliver the total dose over 30 minutes (2 g/h for the 1000 mg IV group) and in patients with a previous history of anaphylaxis or a severe hypersensitivity reaction to infliximab. Subsequent to these 2 events, the infusion rate was changed to no more than 600 mg/hr and no further cases of anaphylaxis were observed. Overall, treatment with mirikizumab demonstrated a safety profile consistent with what has been reported with other anti-IL23p19 antibodies, with no dose-related AE, even with long-term dosing at the highest dose level.

The strengths of this study include a robust evaluation of dosing in both induction and maintenance. The limitations of the trial include the eventual small sample size of the individual dosing groups in maintenance and the lack of a PBO group through the full year of evaluation. The latter was addressed to some extent by the combination of the blind throughout the trial using a double dummy design. Overall, these results demonstrate that IL23p19 blockade with mirikizumab results in early improvement in endoscopic and clinical outcomes with demonstration of durable long-term efficacy. These phase 2 data support continued characterization of mirikizumab efficacy and safety in CD in the ongoing VIVID Phase 3 program (NCT03926130). Q30

Data-Sharing Statement

Lilly provides access to all individual participant data Q31 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 United States and Euro- Q32 pean Union 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, and 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.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.10.050.

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Conflicts of interest

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