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Title: Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Ulcerative Colitis

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WJS, JLT, JL, MD, SF, PK, and MMC contributed to study design. **WJS, BRB, JLT, JL, MD, JS, SF, PK, and MMC** contributed to data analysis **MF, BRB, EB, BGF, JL, JS, and GRDH** contributed to data collection. **WJS, MF, BRB, TH, JLT, MD**, **JS, SF, and PK** contributed to data interpretation. **WJS, MF, BRB, EB, BGF, TH, JLT, JL, MD, JS, SF, PK, MMC, and GRDH** contributed to manuscript writing and/or critical review/analysis of the manuscript.

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Abstract

Background & Aims: Interleukin 23 (IL23) contributes to pathogenesis of ulcerative colitis (UC). We investigated the effects of mirikizumab, a monoclonal antibody against the p19 subunit of IL23, in a phase 2 study of patients with UC.

Methods: We performed a trial of the efficacy and safety of mirikizumab in patients with moderate to severely active UC, enrolling patients from 14 countries from January 2016 through September 2017. Patients were randomly assigned to groups given intravenous placebo (n=63), mirikizumab 50 mg (n=63) or 200 mg (n=62) with exposure-based dosing, or mirikizumab 60 mg with fixed dosing (n=61), at weeks 0, 4, and 8. Of assigned patients, 63% had prior exposure to a biologic agent. Clinical responders (decrease in 9-point Mayo score, including ≥2 points and ≥35% from baseline with either a decrease of rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1) at week 12 who had received mirikizumab were randomly assigned to groups that received maintenance treatment with mirikizumab 200 mg subcutaneously every 4 weeks (n=47) or every 12 weeks (n=46). The primary endpoint was clinical remission (Mayo subscores of 0 for rectal bleeding, with 1-point decrease from baseline for stool frequency, and 0 or 1 for endoscopy) at week 12. A multiple testing procedure was used that began with the 600-mg dose group, and any non-significant comparison result ended the formal statistical testing procedure.

Results: At week 12, 15.9% (*P*=.066), 22.6% (*P*=.004), and 11.5% (*P*=.142) of patients in the 50-mg, 200-mg, and 600-mg groups achieved clinical remission, respectively, compared with 4.8% of patients given placebo. The primary endpoint was not significant (comparison to 600 mg, *P*>.05). Clinical responses occurred in 41.3% (*P*=.014), 59.7% (*P*<.001), and 49.2% (*P*=.001) of patients in the 50-mg, 200-mg, and 600-mg groups, respectively, compared to 20.6% of patients given placebo. At week 52, 46.8% of patients given subcutaneous mirikizumab 200 mg every 4 weeks and 37.0% given subcutaneous mirikizumab 200 mg every 12 weeks were in clinical remission.

Conclusions: In a randomized trial of patients with UC, mirikizumab was effective in inducing a clinical response after 12 weeks. Additional studies are required to determine the optimal dose for induction of remission. Mirikizumab demonstrated durable efficacy throughout the maintenance period. Clinicaltrials.gov no: NCT02589665

KEY WORDS: EB dosing, drug, cytokine, inhibitor

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease characterized by mucosal inflammation of the colon and rectum, with typical symptoms of rectal bleeding, diarrhoea, and urgency.[1] The goals of medical management are to reduce symptoms by controlling mucosal inflammation, and ultimately to prevent disability, colectomy and colorectal cancer.[1] Mono or combination treatment with aminosalicylates, corticosteroids, and thiopurines are often used as initial therapy.[1] Biologic agents targeting tumor necrosis factor (TNF) including infliximab, adalimumab and golimumab, or integrins (e.g. vedolizumab), and more recently a small molecule inhibitor targeting janus kinases (e.g. tofacitinib) are used in patients refractory or intolerant to conventional therapy, or who have more severe disease activity or worse prognosis.[2-7] Many patients have an inadequate response or lose response over time, thus, new treatment approaches are needed.

Interleukin-23 (IL23), a member of the interleukin-12 (IL-2) family of cytokines, has two components: the p40 subunit, which is shared by IL12, and the p19 subunit, which is found in IL23, but not IL12. IL23 plays a key role in the maintenance and amplification of T helper 17 (Th17) cells and stimulation of many innate immune cells, which are important in the pathogenesis of chronic inflammatory diseases including UC.[8-11] Ustekinumab, a monoclonal antibody directed to the shared p40 subunit of IL12 and IL23, is effective for treatment of Crohn's disease and psoriasis.[12-14] However, multiple studies in patients with psoriasis have suggested that more selective targeting of the IL23 pathway by blocking the p19 subunit of IL23 is more effective than ustekinumab.[15, 16] For example, in two recent Phase 3 trials, 75% of patients with psoriasis treated with risankizumab, an IL23-specific agent, achieved PASI 90 compared to less than 50% of ustekinumab-treated patients.[15] Whether a similar differentiation will be observed in the patients with UC is unknown, however promising Phase 2 results have been seen in patients with Crohn's disease (CD) following treatment specifically targeting the p19 subunit of IL23 compared to placebo.[17, 18]

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds to the p19 subunit of IL23 and does not bind to IL12. We evaluated the efficacy and safety of mirikizumab for the treatment of patients with moderately-to-severely active UC.

Methods

Study design and participants

Study I6T-MC-AMAC was a multicentre, randomised, double-blind, parallel-arm, placebo-controlled trial (See Figure 1 for complete study design figure) conducted at 75 sites in 14 countries (Australia, Belgium, Canada, Czech Republic, Denmark, Georgia, Hungary, Japan, Lithuania, Moldova, Netherlands, Poland, UK, and USA; see Supplementary Appendix for complete list of study sites). Patients were enrolled from January 2016 to September 2017.

Eligible patients were 18-75 years of age; with a diagnosis of UC for ≥3 months based upon endoscopy and histopathology findings, and had evidence of UC extending proximal to the rectum (≥15 cm of involved colon). Total Mayo score of 6 to 12 (including an endoscopic subscore ≥2, as determined by a central reader) was used to define a population that had moderately-to-severely active disease. Total Mayo score was used for inclusion into the study rather than a modified Mayo score (used to evaluate efficacy) given the limited information available at the study inception regarding modified Mayo score cut points that define a moderate-to-severe patient population. Stable doses of the following drugs were allowed: oral 5-ASA compounds, oral corticosteroids (prednisone ≤20 mg/d or equivalent), and AZA or 6-MP.

Patients were not eligible if they had surgery for treatment of UC or were likely to require surgery for UC during the study, had previous exposure to any other biologic therapy targeting IL23 (including ustekinumab), ileostomy, colostomy, or fixed symptomatic stenosis of the intestine. See Supplementary Appendix for complete list of inclusion and exclusion criteria.

This study was compliant with the International Conference on Harmonisation (ICH) guideline on good clinical practice. All informed consent forms and protocols were approved by appropriate ethical

review boards prior to initiation of the study. All patients gave written informed consent prior to receiving study drug.

Randomisation and masking

Patients were randomized to 1 of 4 double-blind treatment groups: placebo, 50-mg mirikizumab exposure-based (EB) dosing, 200-mg mirikizumab EB dosing, or the 600-mg mirikizumab fixed-dose treatment group in a 1:1:1:1 ratio. The randomisation was stratified by previous exposure to biologic therapy for treatment of UC, with planned distribution of around one-third biologic naïve and two-thirds previous biologic therapy. Patients who responded to mirikizumab at Week 12 were stratified according to their clinical remission status and re-randomized at a 1:1 ratio to receive 200-mg mirikizumab by subcutaneous (SC) injection every 4 (Q4W) or 12 (Q12W) weeks through Week 52. Patients who responded to placebo at Week 12 received SC placebo injections Q4W through Week 52.

A study site pharmacist or other trained person was unblinded at the site for investigational product preparation. In addition, there were 2 unblinded pharmacokinetic scientists employed by the sponsor involved in evaluating drug concentrations for managing possible dose adjustments in the EB dose groups. These two individuals were segregated from the investigators involved in the oversight and conduct of the study. Patients who met all criteria for enrollment were randomized to study drug at the baseline visit. Assignment to a double-blind investigational product was determined by a computer-generated random sequence using an interactive web-response system (IWRS), and the site was responsible for administering study drug to the patients.

Procedures

The 12-week induction period was designed to establish the efficacy and safety of mirikizumab administered IV at Weeks 0, 4, and 8. On the basis of serum concentrations of mirikizumab during the first 12 weeks of this study, the drug dose in individual patients within the 50-mg and 200-mg arms could be increased. Serum concentrations of mirikizumab were assessed at Weeks 2 and 6, and the dose was increased at Weeks 4 and 8 according to a pre-specified algorithm (Supplementary

Appendix, Tables 1 and 2). The dose increase ranged from 2 to 12 fold for patients in the 50-mg arm and ranged from 1.5 to 3 fold for patients in the 200-mg arm. The 600-mg dose arm remained at a fixed dose during the first 12 weeks. No patient was dosed above 600 mg in the induction period. The 52-week maintenance period was designed to explore the efficacy and safety of mirikizumab administered subcutaneously every 4 or 12 weeks. Endoscopic findings at each efficacy assessment were scored by a single central reader pool comprised of 3 central readers, which provided an objective evaluation of inflammation in the colonic mucosa. Histologic disease activity at each efficacy assessment was scored by a central reader pool comprised of 2 central readers using samples from two biopsies obtained during endoscopy from the most affected area lying at least 30 cm from the anal verge at baseline and Weeks 12 and 52. See Supplementary Appendix for details of histology analyses, as well as biomarker analyses in plasma and faeces.

Outcomes

The primary endpoint of this study was clinical remission at Week 12, defined as the proportion of patients with 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. Secondary objectives included evaluation of safety and tolerability, Week 52 clinical remission, Week 12 and 52 clinical response (a decrease in 9-point Mayo subscore [rectal bleeding, stool frequency, and endoscopy] inclusive of ≥2 points and ≥35% from baseline with either a decrease of rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1), durable clinical remission (proportion of patients who achieved clinical remission at both week 12 and 52), endoscopic remission (defined as having achieved a Mayo endoscopic subscore of 0), endoscopic improvement (defined as achieving an endoscopic findings subscore of 0 or 1), change from baseline in the Inflammatory Bowel Disease Questionnaire [IBDQ; see Supplementary appendix for further details] score and characterization of the pharmacokinetics of mirikizumab. Other exploratory objectives included change from baseline in the biomarkers C-reactive protein, faecal calprotectin, IL17A, and IL22, histologic remission (defined as Geboes histologic subscores of 0 for the neutrophils in lamina propria, neutrophils in epithelium, and erosion or ulceration parameters), change from baseline in symptomatic score (stool frequency plus rectal

bleeding Mayo subscores), symptomatic remission (defined as a stool frequency score of 0 or 1, and a rectal bleeding score of 0). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Versions 19-21 and summarised by system organ class, preferred term, severity and relationship to investigational product. A treatment-emergent AE (TEAE) was defined as an event that first occurred or worsened in severity after baseline.

Statistical analysis

Enrollment was planned for 240 patients (60 patients per dose group). Assuming a placebo remission rate of 7.5% and mirikizumab clinical remission rate of 30% at week 12, the trial had 89% power for testing superiority of the pairwise comparison of the primary endpoint using a chi-square test with a two-sided 0.05 significance. A multiple testing procedure was applied to the primary endpoint to control the overall family-wise type 1 error rate at a 2-sided α level of 0.05. This procedure was planned to evaluate mirikizumab dose group comparisons versus placebo in a step-wise manner, starting with the 600-mg group and concluding with the 50-mg group. A non-significant result from any comparison ended the formal statistical testing procedure and all subsequent p-values are considered as nominal.

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. The safety population included all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment to which they were assigned regardless of any errors or changes in dosing. The primary and secondary categorical outcome measures were analyzed using a logistic regression analysis with treatment group, geographic region, and prior biologic experience (prior biologic experience vs prior biologic naïve), and visit (when appropriate) in the model. Non-responder imputation (NRI) was utilized for patients who discontinued the study before receiving a week 12 or 52 endoscopic assessment. Secondary continuous endpoints were analyzed using a Mixed effect Model Repeat Measurement (MMRM) technique with treatment, visit, geographic region, prior biologic experience, treatment-by-visit interaction, as well as the continuous,

fixed covariates of baseline value and baseline value-by-visit interaction terms in the model. Sites within countries were grouped according to geographical region: North America, Asia (Japan) and rest of the world (including EU and Australia). Descriptive statistics were used to summarize differences in demographic and baseline disease characteristics.

For the maintenance phase of the study, the analysis population consisted of a subset of the intent-to-treat (ITT) population and includes those patients who were re-randomized to one of the two maintenance mirikizumab arms or continued on to subcutaneous placebo after demonstrating clinical response. Patients who were randomized into the maintenance mirikizumab arms were stratified according to their remission status at week 12.

All induction p-values reported, with the exception of the 600-mg vs placebo for the primary endpoint, were not adjusted for multiple comparisons and should be interpreted with caution. Maintenance efficacy and health outcomes analyses are considered exploratory and were summarized using descriptive statistics.

Mirikizumab pharmacokinetics were evaluated using graphical and population pharmacokinetic model-based approaches. See Supplementary Appendix for further details of biomarker analyses.

Safety was summarized using descriptive statistics in all randomly assigned patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT02589665.

All authors had access to the study data and reviewed and approved the final manuscript.

Data sharing statement

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

Between 09 December, 2015 and 29 September, 2017, 358 patients were screened for eligibility in study AMAC. Among the 249 patients who met inclusion criteria and were randomized, 95.6% of patients completed the first 12 weeks of the study (Supplemental Figure 1). Baseline characteristics were generally similar across treatment groups, except for numerically higher CS use, higher CRP levels, higher proportion of patients exposed to three or more biologics, and shorter disease duration in the 600 mg group (Table 1). Notably, more than 63% of patients had previously received treatment with a biologic. Average duration of UC was 7.8 and 9.5 years, respectively, in patients treated with mirikizumab and given placebo. Approximately 73% and 44% of patients in the 50 mg and 200 mg treatment groups underwent dose adjustment, resulting in overall average dose levels during the first 12 weeks of the study of 100 mg and 250 mg, respectively (Supplemental Figure 2). Per protocol, no exposure-based dose adjustments were allowed for patients in the 600-mg treatment group.

The result for the primary endpoint of clinical remission at week 12 for the mirikizumab 600-mg group compared to placebo yielded a non-significant p-value (p=0.142). Thus, all subsequent p-values comparing clinical remission at week 12 are not controlled for multiplicity and are considered nominal. At week 12, 10 (15.9% [6.8-24.9], p=0.066) of 63 patients in the mirikizumab 50-mg group, 14 (22.6% [12.2-33.0], p=0.004) of 62 patients in the mirikizumab 200-mg group, and seven (11.5% [3.5-19.5], p=0.142) of 61 patients in the mirikizumab 600-mg group were in clinical remission compared to three (4.8% [95% CI 0-10]) of 63 patients in the placebo group (Table 2, Figure 2A). A similar pattern was seen for clinical remission across dose groups amongst the biologic naïve and biologic experienced groups, with clinical remission rates numerically higher in all treatment groups amongst biologic-naïve patients (Figure 2B-C).

A total of 26 (41.3% [29.1-53.4], p=0.014) in the mirikizumab 50-mg group, 37 (59.7% [47.5-71.9], p<0.001) in the mirikizumab 200-mg group, and 30 (49.2% [36.6-61.7], p=0.001) in the mirikizumab 600-mg group had a clinical response compared to 13 (20.6% [10.6-30.6]) patients in the placebo group (Table 2, Figure 2D). Differences from placebo were similar regardless of prior biologic exposure (Figure 2E-F).

Endoscopic improvement during the 12-week induction period was achieved by 15 (23.8% [13.3-34.3], p=0.012) patients in the mirikizumab 50-mg group, 19 (30.6% [23.3-34.3], p=0.0007) patients in the mirikizumab 200-mg group, and eight (13.1% [4.6-21.6], p=0.215) patients in the mirikizumab 600-mg group compared to four (6.3% [0.3-12.4]) patients in the placebo group (Figure 2G). A similar pattern was seen for endoscopic improvement in each dose group amongst the biologic naïve and biologic experienced groups, with numerically higher proportions of patients in all treatment groups amongst biologic-naïve patients (Figure 2H-I). There were no differences in proportions of patients with endoscopic remission amongst treatment groups (Table 2). Numerically greater proportions of patients in the 200-mg and 600-mg dose groups achieved histologic remission relative to placebo (Table 2).

The proportion of patients in symptomatic remission was greater in all three mirikizumab groups compared to placebo (Table 2). Likewise, Mayo symptoms scores were lower in mirikizumab-treated patients compared to placebo with separation from placebo seen as early as week 2 for the 200-mg and 600-mg dose groups compared to placebo (Supplemental Figure 4A). On average, IBDQ scores were higher at 12 weeks amongst patients treated with mirikizumab versus given placebo (Table 2). C-reactive protein (CRP) and faecal calprotectin concentrations were lower in all mirikizumab-treated groups compared to placebo by week 12 (Supplemental Figure B-C). IL17 and IL22 serum concentrations were also lower in all mirikizumab-treated group compared to placebo by week 12 (Supplemental Figure 4D-E). Mirikizumab exposures increased in a dose-proportional manner across the dose groups (Supplemental Figure 2). The percentage of patients achieving clinical response, clinical remission, or endoscopic improvement first increased with median mirikizumab concentration up to approximately 16 µg/ml mirikizumab, then decreased (Supplemental Figure 6).

At the end of the 12 weeks induction period, 93 mirikizumab-treated patients achieved a clinical response and were re-randomized to 200 mg SC mirikizumab either every 4 (Q4W) or 12 (Q12W) weeks (Supplemental Figure 1). The mirikizumab 200-mg SC Q4W regimen produced a median trough concentration similar to that observed at week 12 in the 200-mg treatment group; the SC Q12W regimen produced trough concentrations in most patients that fell below the lower limit of detection of the mirikizumab assay. Thirteen patients given PBO achieved a clinical response and continued maintenance therapy with PBO. At week 52, 53.7% (22/47) and 39.7% (17/46) of patients treated with 200-mg mirikizumab Q4W and Q12W, respectively, achieved clinical remission. There were similar rates of clinical remission between biologic naïve and biologic experienced patients (Table 3, Figure 3A-C). Patients achieved similar rates of clinical response for the 200 mg mirikizumab Q4W and Q12W groups, at 80.9% and 76.1%, respectively (Table 3, Figure 3D-F). The rates of endoscopic remission (Mayo endoscopy subscore of 0) at week 52 were 14.9% (Q4W) and 28.3% (Q12W), and at 52 weeks 66.0% (Q4W) and 37.0% (Q12W) of patients achieved histologic remission. IBDQ scores improved 61.7 and 49.4 points on average in the Q4W and Q12W groups, respectively (Table 3). The proportion of patients who achieved clinical remission at both week 12 and 52 (durable clinical remission) was 61.1% (11/18) in the Q4W group and 38.5% (5/13) in the Q12W group (Table 3, Figure 3J). In addition, 80.9% (38/47) and 75.0% (33/44) patients on Q4W and Q12W doses, respectively, maintained a clinical response, and more than 35% of patients who had achieved clinical response but not clinical remission at week 12 continued to improve and achieved clinical remission at week 52 (Table 3, Figure 3K-L). Another measure of durable response was the proportion of patients in symptomatic remission from weeks 16-52. In both Q4W and Q12W, there was stability of symptomatic remission throughout the study, with an average of 77.5% and 75.2% throughout weeks 16-52 for Q4W and Q12W, respectively (Supplemental Figure 5).

The most frequent treatment-emergent adverse events (≥5% in any treatment group) included nasopharyngitis, worsening of UC, anaemia, headache, nausea, cough, and worsening of gastroenteritis during induction, and worsening of UC, nasopharyngitis, headache, upper respiratory tract infection, arthralgia, hypertension, and influenza during maintenance (Table 3). There were no

dose-related increases in the reporting of adverse events (AEs) associated with mirikizumab treatment (Table 3). Serious AEs (SAE) occurred in seven patients during the induction period (two each in the placebo and 200-mg groups, and three in the 600-mg group) and five patients during the maintenance period (two each in the Q4W and PBO groups, and one in the Q12W group). Specific SAEs are not identified by treatment group to preserve blinding in this ongoing trial. Of the induction period serious adverse events, two patients reported worsening of ulcerative colitis, and two reported gastroenteritis without clear aetiology. One patient was reported to have a large intestine perforation at week 12, with symptoms presenting immediately following the week-12 sigmoidoscopy. This patient had severe disease at baseline (total Mayo score=9; endoscopic score=3) and at week 12 (endoscopic score=3). One patient had a viral respiratory tract infection of moderate severity that required hospitalization; the patient recovered and remained in the study. Squamous cell carcinoma of the skin was reported in one patient approximately two weeks following the baseline study visit. Of the maintenance SAEs, two patients reported worsening of ulcerative colitis, one developed appendicitis and subsequent Streptococcal bacteraemia, one acquired a Clostridium difficile infection, and one patient received a head trauma. One patient discontinued due to non-treatment related AE; all other patients recovered and remained in the study. No deaths and no hypersensitivity reactions were reported for patients in the induction or maintenance period of the study. No clear relationship between any serious adverse events and study drug was determined. Numbers of discontinuations due to AEs were similar across treatment groups (Table 4).

Discussion

In this Phase 2, dose-ranging study, mirikizumab demonstrated evidence of inducing clinical remission and response, and endoscopic improvement after 12 weeks in patients with moderately-to-severely active UC, although the primary endpoint was not achieved. Previous studies have demonstrated the potential therapeutic benefit of monoclonal antibodies targeted to the IL23p19 subunit in patients with psoriasis, psoriatic arthritis and CD.[14, 16-21] However, this is the first randomized trial to demonstrate this approach may be beneficial for patients with moderately-to-severely active UC. Although the trial evaluated patients both naïve to biologic therapy and those who

had been previously exposed to these agents, 63.1% of participants were in the latter category and approximately 32% of all patients in this trial had been treated with two or more biologic drugs (Table 1). These characteristics suggest a relatively difficult to treat population. Nonetheless, among patients who were previously exposed to biologic therapy, numerically higher proportions of mirikizumab-treated patients had clinical response compared to patients given placebo.

The endpoints used to assess disease activity in UC and CD have been undergoing rigorous review beginning with the initial 2012 Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT) Workshop.[22] At the start of this study, updated regulatory guidance had yet to be published. Still, it was clear that greater focus on patient-reported outcomes and objective endoscopic endpoints for assessment of disease activity in both UC and CD studies were desired.[22] Therefore, a 9-point modified Mayo scoring system was utilized in this study including stool frequency, rectal bleeding and endoscopic findings scored centrally (excluding PGA) with more conservative remission and response definitions (see methods). Even with this conservative definition, the primary endpoint of clinical remission at week 12 was numerically higher in all mirikizumab dose groups, with the 200-mg dose group (with EB increase) showing the largest benefit. Moreover, nominally higher proportions of patients treated with any dose of mirikizumab had a clinical response compared to those treated with placebo at the end of induction period.

Endoscopic improvement (Mayo 0 or 1) was greater relative to placebo at the end of the induction period, however, only one or two reports of endoscopic remission (Mayo 0) was observed in each treatment group, likely reflecting the difficulty of achieving endoscopic remission in the induction period of this study Supporting the data observed for endoscopic improvement, patient symptoms also improved during the first 12 weeks of treatment. IBDQ scores were higher and Mayo symptoms scores lower at week 12 in mirikizumab-treated groups compared to placebo, with numerical differences observed as early as week 2 in the symptomatic score (rectal bleeding + stool frequency) for the 200-mg and 600-mg dose groups compared to placebo.

Evaluation of histologic disease activity in UC patients has received renewed focus coinciding with increasing evidence that histologic remission is predictive of improved long-term clinical outcomes, and new guidance from regulatory agencies regarding the utility of histologic evaluation during development of new medications for patients with UC.[23, 24] Additionally, in this study greater proportions of patients in the two highest mirikizumab dose groups achieved histologic remission compared to than those in the placebo group. Taken together with the observed endoscopic improvement, these data suggest that mirikizumab may be an effective therapy for healing the mucosa in UC patients.

A unique aspect of this study was that dose levels in the 50-mg and 200-mg dose groups were adjusted based upon drug exposures during the induction period (see Supplementary Appendix, Supplementary Tables 1 and 2). Given the hypothesis that inadequate drug exposure in some patients may be a contributing factor to lack of efficacy,[25] prospective dose-level adjustments were made to explore drug-level monitoring and increase the likelihood that patients in the lower dose groups received sufficient drug exposure during the induction period. Approximately 73% and 44% of patients in the 50-mg and 200-mg groups were dose adjusted, resulting in overall average dose levels during the induction period of 100 mg and 250 mg, respectively. The overall exposure during the induction period was similar in patients that were dose adjusted as compared to patients that were not dose adjusted in both the 50 and 200 mg groups (Supplementary Appendix, Supplementary Figure 3), indicating that the dose adjustments achieved the objective of increasing exposure in patients that had low exposure after the first or second dose of mirikizumab. Additionally, the clinical response and remission rates were not different in patients who were dose-adjusted (Data not shown). However, it is unknown what proportion of patients would have achieved clinical response or remission if the patients who were dose-adjusted did not have their doses increased. It is possible that the patients with the lowest exposures could have experienced lower clinical response and remission rates if their doses were not increased, especially among patients in the 50-mg group that had a higher likelihood of being lower on the exposure–response curve. In addition, there were no obvious exposure-dependent responses, as there were many patients who benefited within the lower end of the exposure range

tested. Future studies are needed to confirm the dose and exposure that optimizes efficacy across the patient population.

Despite the dose adjustments in the 50 and 200-mg groups, there were distinct exposure levels observed between the three mirikizumab-dose groups, with exposure increasing with dose (Supplementary Appendix, Supplementary Figure 2). Therefore, the numerically lower proportions of patients achieving response and remission observed in the 600-mg group were not the result of lower than expected mirikizumab exposure. In addition, the observation of a maximum effect at a dose lower than the highest evaluated dose is not unprecedented in UC studies[6, 26-28] and may be due to multiple factors, including biologic mechanisms, the endpoints used to evaluate efficacy, imbalance in patient baseline factors across the dose groups, and relatively small sample size.

In this study is there were no direct measures of target engagement in the intestinal mucosa. However, reductions in CRP and faecal calprotectin were observed following 12 weeks of treatment with mirikizumab, likely reflect a reduction in gut inflammation. Activated Th17 cells and group 3 innate lymphoid cells (ILC3) from patients with inflammatory bowel disease characteristically produce IL17 and IL22. Thus, the observed decrease in IL22 and IL17 in the circulation of mirikizumab-treated patients is consistent with the expected effects of blockade of the IL23 pathway. The role of IL22 in the aetiology of UC and CD is not well understood as reports have suggested both deleterious and protective effects.[29] Similar to observations in two positive studies where patients with CD were treated with IL23p19 monoclonal antibodies, in this study, IL22 levels were reduced from baseline following treatment with mirikizumab.[17, 18] The TH17 pathway clearly has a role in the pathology of UC and CD, however, the role of the IL17 cytokine may have more protective role supporting intestinal barrier function.[30] This could be, in part, why monoclonal antibodies directed against IL17 were not effective in treatment of patient with CD.[31, 32] While it is possible that reductions in IL17 due to IL23 blockade could deleteriously affect barrier function, in this study, blockade of IL23 with mirikizumab reduced plasma IL17 with levels approaching those observed in healthy subjects and no apparent difference based upon dose group (data not shown). In addition, IL23-independent IL17-

producing γδ T cells have been observed to be important for the maintenance barrier function in the intestinal mucosa.[33]

Given the small sample size, the maintenance period of the study was only intended to explore clinical activity of the mirikizumab 200 mg SC Q4W and Q12W dose regimens. Most patients in both regimens remained on study through week 52 and experienced robust clinical benefit as observed by relevant rates of clinical remission and response, as well as important endoscopic and histologic benefit at week 52. Patients in both groups demonstrated durable clinical benefit with many patients in clinical remission at week 12 and week 52. Interestingly, many patients experienced additional clinical benefit during maintenance by converting from a clinical response at week 12 to clinical remission at week 52.

Throughout this study, few patients treated with mirikizumab discontinued due to AEs, suggesting it was well-tolerated. Also, there were comparable frequencies of treatment-emergent AEs across treatment groups, with the exception of worsening of UC which was numerically higher in the placebo group compared to the mirikizumab treatment groups. In this study, the safety results appear consistent with published results from other IL23-targeting biologics.[16-18, 20, 21] Overall treatment with mirikizumab demonstrated a favourable benefit vs risk profile.

These are the first reported observations of clinical benefit in ulcerative colitis with a monoclonal p19-directed IL23 antibody, with results suggesting that selective inhibition of interleukin-23 with mirikizumab could be an effective therapy for in patients with moderately-to-severely active UC.

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Figure 1: AMAC study design

Figure 2: Clinical remission, clinical response, and endoscopic improvement in all patients, biologic naïve, and biologic experienced. (12W)

Figure 3: Clinical remission, clinical response, and endoscopic improvement in all patients, biologic naïve, and biologic experienced; durable clinical remission and response, conversion from response to remission. (52W)

Tables

Table 1: Baseline Demographics and Clinical Characteristics*

	Placebo IV Q4W (n=63)	Miri IV Q4W EB 50 mg (n=63)	Miri IV Q4W EB 200 mg (n=62)	Miri IV Q4W 600 mg (n=61)
Female sex, n (%)	27 (42.9)	25 (39.7)	25 (40.3)	23 (37.7)
Age – years, mean±SD	42.6±13.5	41.8±14.1	43.4±14.7	42.4±13.4
Weight – kg, mean ±SD	74.1 (16.9)	77.0 (17.2)	75.6 (17.3)	73.0 (15.1)
Current smoker, n (%)	18 (28.6)	18 (28.6)	25 (40.3)	23 (37.7)
White race, n (%)	52 (82.5)	57 (90.5)	44 (71.0)	56 (91.8)
Disease duration – years (mean±SD)	9.5 ±9.6	8.2 ±7.2	9.0 ±9.0	6.0 ±5.7
Mayo score, n (%),				
6-8	27 (42.9)	24 (38.7)	27 (44.3)	26 (42.6)
9-12	36 (57.1)	38 (61.3)	34 (55.7)	35 (57.4)
9-point modified Mayo score (mean±SD)	6.7 (1.2)	6.6 (1.3)	6.4 (1.4)	6.5 (1.3)
Mayo Symptoms score (mean±SD)	3.9 (1.1)	3.7 (1.3)	3.7 (1.3)	3.8 (1.1)
Mayo Endoscopy score 3, n (%)	47 (74.6)	50 (79.4)	41 (66.1)	45 (73.8)
CRP – mg/L, median (IQR)	3.9 (1.1-11.2)	4.5 (1.4-12.6)	3.6 (1.4-13.7)	6.2 (2.0-15.5)
Faecal Calprotectin- mg/kg, median (IQR)	1353 (618-2481)	1945 (510-2992)	1560 (399-2443)	1523 (619-2587)
IBDQ (mean±SD)	124.1 (29.8)	122.5 (29.2)	133.0 (34.7)	125.5 (33.9)
Concomitant therapies at baseline– n (%)				
5-ASA use	47 (74.6)	41 (65.1)	56 (90.3)	39 (63.9)
Corticosteroids	33 (52.4)	29 (46.0)	25 (40.3)	34 (55.7)
Thiopurines	25 (39.7)	14 (22.2)	18 (29.0)	11 (18.0)
Number of unique prior biologic therapies, n (%)				
0	25 (39.7)	27 (42.9)	22 (35.5)	23 (37.7)
1	17 (27.0)	14 (22.2)	27 (43.5)	15 (24.6)
2	15 (23.8)	16 (25.4)	7 (11.3)	14 (23.0)
≥3	6 (9.5)	6 (9.5)	6 (9.7)	9 (14.8)

* Intent-to-treat population

Nominal p-values were not significant for any group, except thiopurines where a difference was seen across the 4 dose groups; ASA= aminosalicylic acid; CRP=C Reactive Protein; EB=Exposure-Based; IBDQ=Inflammatory Bowel Disease Questionnaire; IQR=Interquartile Range

Table 2: Week-12 Efficacy results*

	Placebo IV Q4W (n=63)	Miri IV Q4W EB 50 mg (n=63)	Miri IV Q4W EB 200 mg (n=62)	Miri IV Q4W 600 mg (n=61)	Combined Miri
Clinical Remission, n (%)	3 (4.8%)	10 (15.9%)	14 (22.6%)	7 (11.5%)	31 (17.4%)
Difference vs placebo (95% CI, p value)	-	11.1% (0.7 to 21.6, p=0.066)	17.8% (6.2 to 29.5, p=0.004)	6.7% (-2.9 to 16.3, p=0.142)	11.9% (4.4 to 19.4, p=0.020)
Clinical Response, n (%)	13 (20.6%)	26 (41.3%)	37 (59.7%)	30 (49.2%)	93 (50.0%)
Difference vs placebo (95% CI, p value)	-	20.6% (4.9 to 36.4, p=0.014)	39.0% (23.3 to 54.8, p<0.0001)	28.5% (12.5 to 44.6, p=0.001)	29.4% (17.1 to 41.7, p<0.001)
Endoscopic Remission, n (%)	1 (1.6%)	2 (3.2%)	2 (3.2%)	1 (1.6%)	5 (2.7%)
Difference vs placebo (95% CI, p value)	-	1.6% (-3.7 to 6.9, p=0.56)	1.6% (-3.7 to 7.0, p=0.55)	0.1% (-4.4 to 4.5, p=0.99)	1.1% (-2.8 to 5.0, p=0.63)
Endoscopic Improvement, n (%)	4 (6.3%)	15 (23.8%)	19 (30.6%)	8 (13.1%)	42 (22.6%)
Difference vs placebo (95% CI, p value)	-	17.5% (5.3 to 29.6, p=0.012)	24.3% (11.3 to 37.3, p=0.0007)	6.8% (-3.6 to 17.2, p=0.21)	16.2% (7.7 to 24.7, p=0.006)
Symptomatic Remission, n (%)	13 (20.6%)	23 (36.5%)	36 (58.1%)	28 (45.9%)	87 (46.8%)
Difference vs placebo (95% CI, p value)	-	15.9% (0.3 to 31.4, p=0.054)	37.4% (21.6 to 53.3, p<0.0001)	25.3% (9.3 to 41.3, p=0.003)	26.1% (13.8 to 38.4, p<0.001)
Change from BL IBDQ Total Score, mean (SD)	19.9 (37.7)	31.3 (42.0)	38.1 (28.4)	43.8 (38.7)	-
LSMean Difference vs placebo (95% CI, p value)	-	11.1 (-.5 to 22.8, p=0.062)	20.9 (9.2 to 32.7, p=0.0005)	22.9 (11.1 to 34.8, p=0.0002)	-
Histologic remission, n (%)	11 (17.5)	9 (14.3)	28 (45.2)	21 (34.4)	58 (31.2%)
Difference vs placebo (95% CI, p value)	-	-3.2 (-15.9 to 9.6; p=0.632)	27.7 (12.2 to 43.2; p=0.001)	17.0 (1.8 to 32.1; p=0.028)	14.6 (2.6 to 26.6 p=0.032)

*Intent-to-treat population

All p-values presented are nominal with no adjustment for multiple comparisons; BL=Baseline; CI=Confidence Interval; EB=Exposure-Based; IBDQ=Inflammatory Bowel Disease Questionnaire; RHI= Robarts Histopathology Index

	Mirikizumab SC Q4W 200 mg (n=47)	Mirikizumab SC Q12W 200 mg (n=46)	Placebo SC Q4W (N=13)
Clinical Remission, n (%)	22 (46.8)	17 (37.0)	1 (7.7)
Clinical Response, n (%)	38 (80.9)	35 (76.1)	7 (53.8)
Endoscopic Remission, n (%)	7 (14.9)	13 (28.3)	1 (7.7)
Endoscopic Improvement, n (%)	27 (57.4)	22 (47.8)	2 (15.4)
Symptomatic Remission, n (%)	36 (76.6)	30 (65.2)	7 (53.8)
Histologic Remission, n (%)	31 (66.0)	17 (37.0)	5 (38.5)
Change from BL IBDQ Total Score, mean (SD)	61.7 (30.8)	49.4 (32.3)	70.8 (23.80)
Clinical Remission Durability, n/N (%)	11/18 (61.1)	5/13 (38.5)	0/3 (0.0)
Clinical Response Durability, n/N (%)	38/47 (80.9)	33/44 (75.0)	7/13 (53.8)
Clinical Response wk 12 to Remission wk 52, n/N (%)	11/29 (37.9)	12/33 (36.4)	
CRP, mg/L median (range)	2.55 (0.23, 20.10) N=41	1.55 (0.10, 22.70) N=43	1.48 (0.10, 14.0) N=9
Fecal calprotectin, mg/kg Median (Range)	103 (15, 1753) N=41	232 (15, 2502) N=36	342 (50, 2100) N=8
*Intent-to-treat population that advanced to maintenance			

Table 3: Week-52 efficacy results*

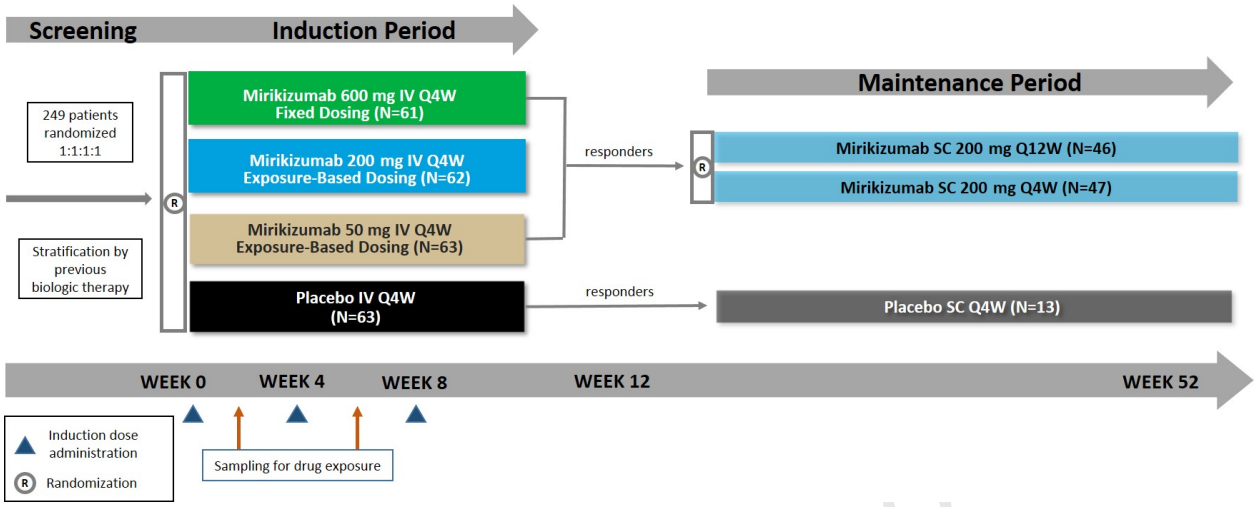
include (nominal) p-values

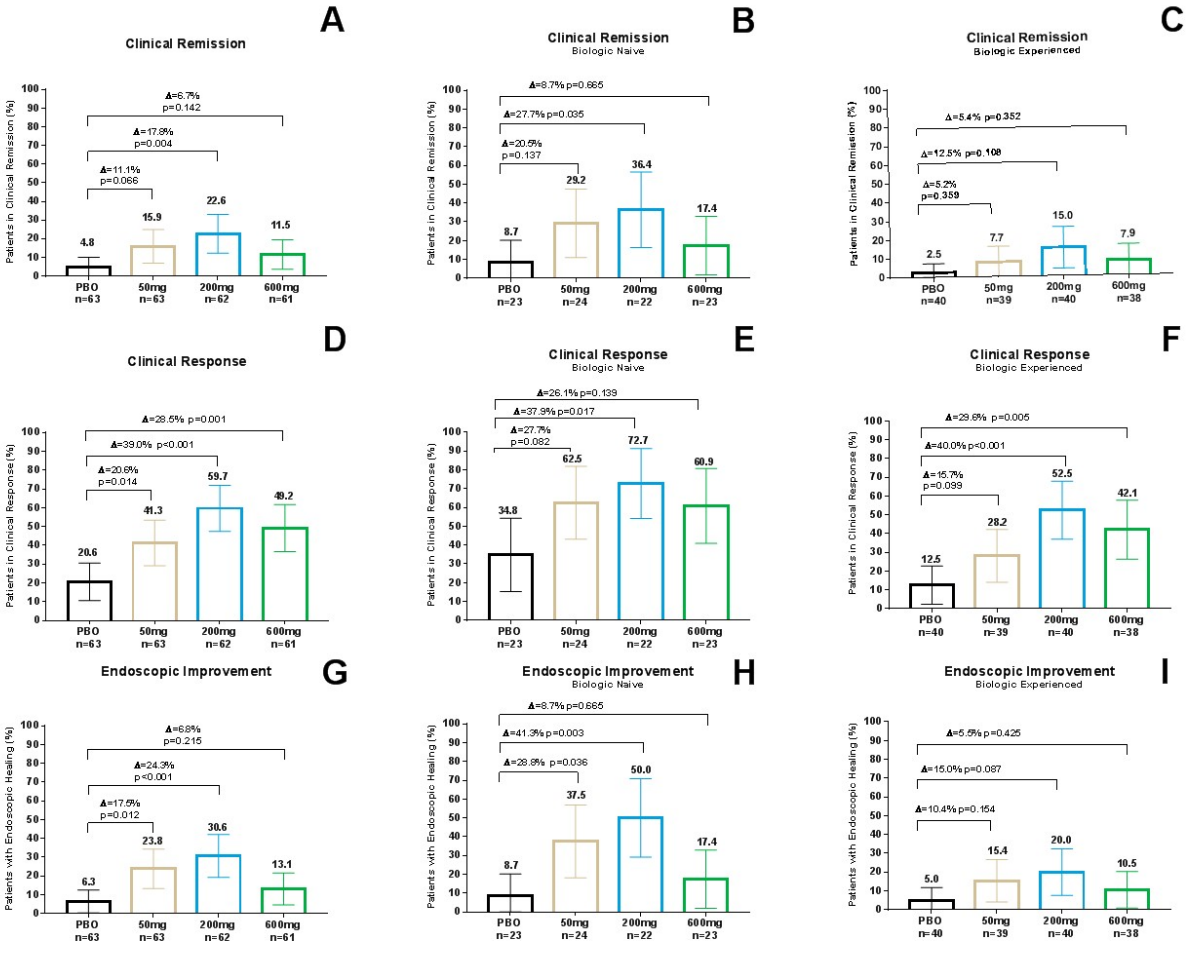
Table 4: Safety*	Week 12			
	Placebo IV Q4W (n=63)	**Miri IV Q4W EB 50 mg (n=63)**	**Miri IV Q4W EB 200 mg (n=62)**	**Miri IV Q4W 600 mg (n=60)**
TEAEs, n (%)	32 (50.8)	36 (57.1)	32 (51.6)	32 (53.3)
Serious adverse event, n (%)	2 (3.2)	0 (0)	2 (3.2)	3 (5.0)
Discontinuations due to adverse event, n (%)	3 (4.8)	0 (0)	1 (1.6)	2 (3.3)
Most common TEAEs (≥5% in any dose group)*				
Nasopharyngitis	6 (9.5)	5 (7.9)	3 (4.8)	5 (8.3)
Worsening of ulcerative colitis	6 (9.5)	2 (3.2)	2 (3.2)	2 (3.3)
Anemia	3 (4.8)	4 (6.3)	2 (3.2)	2 (3.3)
Headache	3 (4.8)	3 (4.8)	1 (1.6)	4 (6.7)
Nausea	4 (6.3)	2 (3.2)	2 (3.2)	3 (5.0)
Cough	4 (6.3)	0	0	2 (3.3)
Gastroenteritis	1 (1.6)	0	2 (3.2)	3 (5.0)
	Week 52			
	Miri SC Q4W 200 mg (n=47)	**Miri SC Q12W 200 mg (n=46)**	**Placebo (n=13)**	
TEAEs, n (%)	36 (76.6)	31 (67.4)	10 (76.9)	
Serious adverse event, n (%)	2 (4.3)	1 (2.2)	2 (15.4)	
Discontinuations due to adverse event, n (%)	0 (0)	1 (2.2)	0 (0)	
Most common TEAEs (≥5% in any dose group)*				

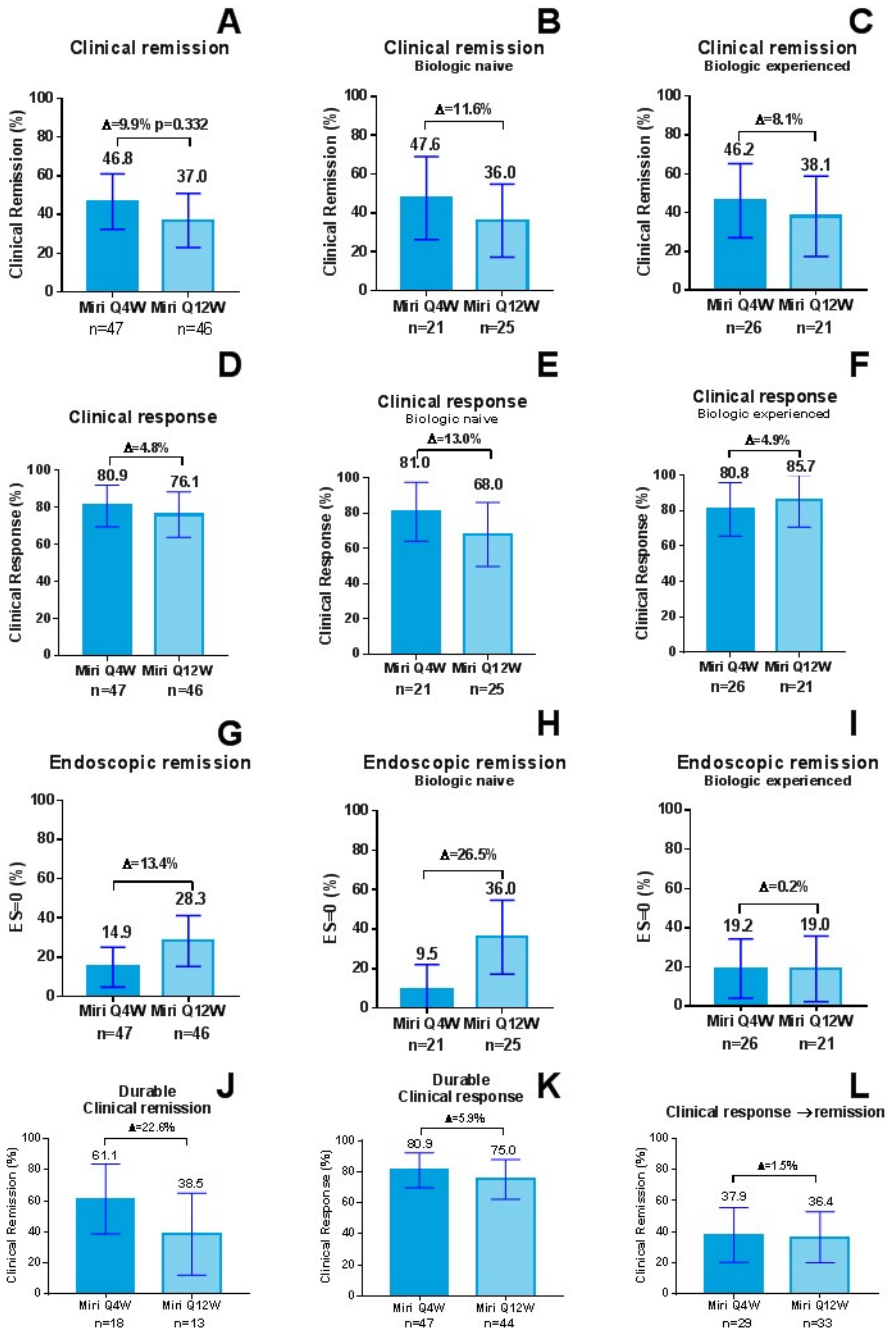
Worsening of UC	1 (2.1)	7 (15.2)	6 (46.2)
Nasopharyngitis	5 (10.6)	7 (15.2)	0 (0)
Headache	5 (10.6)	3 (6.5)	1 (7.7)
Upper Respiratory Tract Infection	5 (10.6)	2 (4.3)	2 (15.4)
Arthralgia	6 (12.8)	1 (2.2)	0 (0)
Hypertension	4 (8.5)	2 (4.3)	1 (7.7)
Influenza	3 (6.4)	4 (8.7)	0 (0)

*Safety population

TEAE=Treatment-Emergent Adverse Event; EB=Exposure Based Dosing




A
Clinical Remission
Patients in Clinical Remission (%)
Δ=6.7% p=0.142
Δ=17.8% p=0.004
Δ=11.1% p=0.066
4.8
15.9
22.6
11.5
PBO n=63
50mg n=63
200mg n=62
600mg n=61
B
Clinical Remission
Biologic Naive
Patients in Clinical Remission (%)
Δ=8.7% p=0.665
Δ=27.7% p=0.035
Δ=20.5% p=0.137
8.7
29.2
36.4
17.4
PBO n=23
50mg n=24
200mg n=22
600mg n=23
C
Clinical Remission
Biologic Experienced
Patients in Clinical Remission (%)
Δ=5.4% p=0.352
Δ=12.5% p=0.108
Δ=5.2% p=0.359
2.5
7.7
15.0
7.9
PBO n=40
50mg n=39
200mg n=40
600mg n=38
D
Clinical Response
Patients in Clinical Response (%)
Δ=28.5% p=0.001
Δ=39.0% p<0.001
Δ=20.6% p=0.014
20.6
41.3
59.7
49.2
PBO n=63
50mg n=63
200mg n=62
600mg n=61
E
Clinical Response
Biologic Naive
Patients in Clinical Response (%)
Δ=26.1% p=0.139
Δ=37.9% p=0.017
Δ=27.7% p=0.082
34.8
62.5
72.7
60.9
PBO n=23
50mg n=24
200mg n=22
600mg n=23
F
Clinical Response
Biologic Experienced
Patients in Clinical Response (%)
Δ=29.6% p=0.005
Δ=40.0% p<0.001
Δ=15.7% p=0.093
12.5
28.2
52.5
42.1
PBO n=40
50mg n=39
200mg n=40
600mg n=38
G
Endoscopic Improvement
Patients with Endoscopic Healing (%)
Δ=6.8% p=0.215
Δ=24.3% p<0.001
Δ=17.5% p=0.012
6.3
23.8
30.6
13.1
PBO n=63
50mg n=63
200mg n=62
600mg n=61
H
Endoscopic Improvement
Biologic Naive
Patients with Endoscopic Healing (%)
Δ=8.7% p=0.665
Δ=41.3% p=0.003
Δ=28.8% p=0.036
8.7
37.5
50.0
17.4
PBO n=23
50mg n=24
200mg n=22
600mg n=23
I
Endoscopic Improvement
Biologic Experienced
Patients with Endoscopic Healing (%)
Δ=5.5% p=0.425
Δ=15.0% p=0.087
Δ=10.4% p=0.154
5.0
15.4
20.0
10.5
PBO n=40
50mg n=39
200mg n=40
600mg n=38


A
Clinical remission
Clinical Remission (%)
Δ=9.9% p=0.332
46.8
37.0
Miri Q4W Miri Q12W
n=47 n=46
B
Clinical remission
Biologic naive
Clinical Remission (%)
Δ=11.6%
47.6
36.0
Miri Q4W Miri Q12W
n=21 n=25
C
Clinical remission
Biologic experienced
Clinical Remission (%)
Δ=8.1%
46.2
38.1
Miri Q4W Miri Q12W
n=26 n=21
D
Clinical response
Clinical Response (%)
Δ=4.8%
80.9
76.1
Miri Q4W Miri Q12W
n=47 n=46
E
Clinical response
Biologic naive
Clinical Response (%)
Δ=13.0%
81.0
68.0
Miri Q4W Miri Q12W
n=21 n=25
F
Clinical response
Biologic experienced
Clinical Response (%)
Δ=4.9%
80.8
85.7
Miri Q4W Miri Q12W
n=26 n=21
G
Endoscopic remission
ES=0 (%)
Δ=13.4%
14.9
28.3
Miri Q4W Miri Q12W
n=47 n=46
H
Endoscopic remission
Biologic naive
ES=0 (%)
Δ=26.5%
9.5
36.0
Miri Q4W Miri Q12W
n=21 n=25
I
Endoscopic remission
Biologic experienced
ES=0 (%)
Δ=0.2%
19.2
19.0
Miri Q4W Miri Q12W
n=26 n=21
J
Durable
Clinical remission
Clinical Remission (%)
Δ=22.6%
61.1
38.5
Miri Q4W Miri Q12W
n=18 n=13
K
Durable
Clinical response
Clinical Response (%)
Δ=5.9%
80.9
75.0
Miri Q4W Miri Q12W
n=47 n=44
L
Clinical response →remission
Clinical Remission (%)
Δ=1.5%
37.9
36.4
Miri Q4W Miri Q12W
n=29 n=33

What you need to know:
BACKGROUND AND CONTEXT: Many patients with ulcerative colitis (UC) treated with biologic therapies do not respond to or achieve remission, and some responding patients lose response. Interleukin 23 (IL23) contributes to pathogenesis of UC. We investigated the effects of mirikizumab, a monoclonal antibody against IL23 that is effective in treatment of psoriasis and Crohn's disease, in a randomized trial of patients with UC.

NEW FINDINGS: In patients with UC, mirikizumab was effective in inducing clinical response after 12 weeks. Mirikizumab demonstrated durable efficacy throughout the maintenance period

LIMITATIONS: The optimal dose for induction of remission requires additional investigation. Given the small sample size, the maintenance period of the study was only intended to explore clinical activity of the mirikizumab (200 mg, given subcutaneously every 4 or 12 weeks).

IMPACT: Mirikizumab appears to be safe and effective in treatment of UC in patients who did not respond to previous biologic therapies.

Lay summary: In study of patients with moderate to severely active ulcerative colitis, mirikizumab demonstrated clinical efficacy compared to placebo after 12 weeks and maintained efficacy through 40 weeks of treatment.

Supplementary Appendix

Complete List of Inclusion and Exclusion Criteria

Inclusion Criteria

Subjects with UC were eligible for enrolment 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 TNF 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-MP or AZA) 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 TNF 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-TNF 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 5-ASA compounds: if the prescribed dose has been stable for at least 2 weeks before screening endoscopy

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

[9c] AZA or 6-MP: 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 ≥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 ≤2× 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 CD

[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 5-ASA within 30 days of screening endoscopy

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

[15] have previous exposure to any biologic therapy targeting IL-23 (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 TB

[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 nonapproved 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 HIV/AIDS 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 extra-intestinal 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 (IBDQ)

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.

Histopathology

The histopathologic images were read centrally in a blinded manner by a qualified pathologist and scoring was performed using the Geboes Score.[2]

The Geboes score is an instrument that is used to standardize histologic assessment in UC. It is comprised of seven 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).[2] 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 Faeces

IL-17A levels were measured using the Quanterix Simoa IL-17 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

IL-22 cytokine level were assayed in a Meso Scale Discovery sandwich assay. In short, IL-22 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 2X MSD read buffer was added. Plates were read with MSD reader Quick Plex S120 and data 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 and tested by Covance Central laboratories.

CRP was measured in collected serum samples using a C - reactive protein HS immunonephelometry assay (Siemens BNII) and is 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, BMI, Previous Biologic Therapy, and modified Mayo score. Models were fit using the *lme* function from the R package *nlme*[3] and version 3.5.0 of the R statistical computing environment.[4] The pharmacodynamic contrast was defined as the change from baseline for a drug treated group minus the change from baseline for the placebo group.

(1) Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology*. 1989;96:804-810.
(2) Mosli M et al., Development and validation of a histological index for UC, Gut 2015, 0:1-9.
(3) Pinheiro J, Bates D, DebRoy S, Sarkar D and R Core Team (2018). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-137, https://CRAN.R-project.org/package=nlme.
(4) R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, http://www.R-project.org.

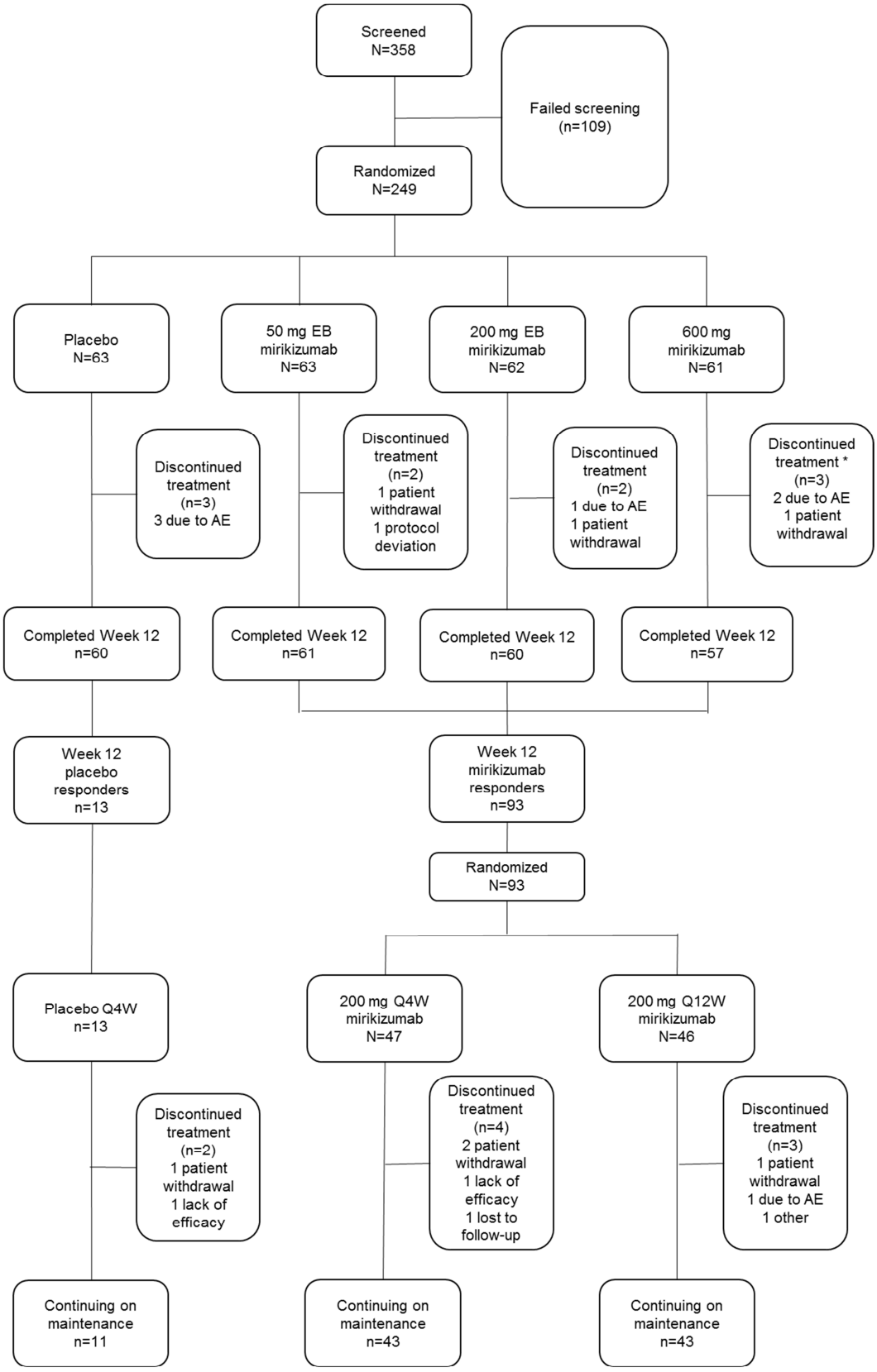
Supplementary Table 1. Dose Increase in Cohort that Receives Starting Dose of 50 mg at Week 0

Observed Concentration of mirikizumab at Week 2 or Week 6 (µg/ml)	Dose Increase at Week 4 or Week 8 (MAXIMUM DOSE = 600 mg)
≥ 1.6	No dose increase
≥ 0.8 and < 1.6	Increase dose 2X
≥ 0.4 and < 0.8	Increase dose 4X
≥ 0.27 and < 0.4	Increase dose 6X
< 0.27	Increase dose 12X

Supplementary Table 2. Dose Increase in Cohort that Receives Starting Dose of 200 mg at Week 0

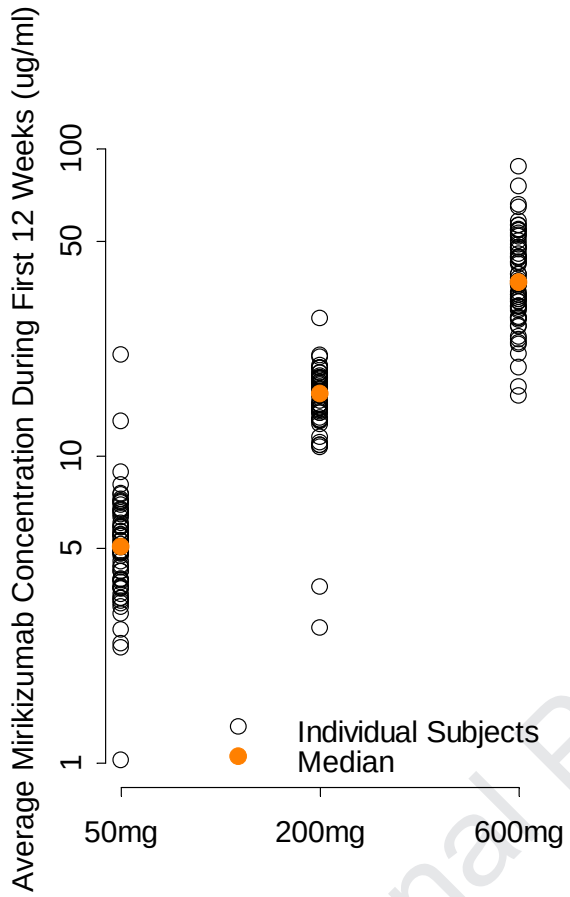
Observed Concentration of mirikizuamb at Week 2 or Week 6 (µg/ml)	Dose Increase at Week 4 or Week 8 (MAXIMUM DOSE = 600 mg)
≥ 6.0	No dose increase
≥ 4.0 and < 6.0	Increase dose 1.5X
≥ 3.0 and < 4.0	Increase dose 2X
≥ 2.4 and < 3.0	Increase dose 2.5X
< 2.4	Increase dose 3X

Supplementary Figure 1: CONSORT diagram



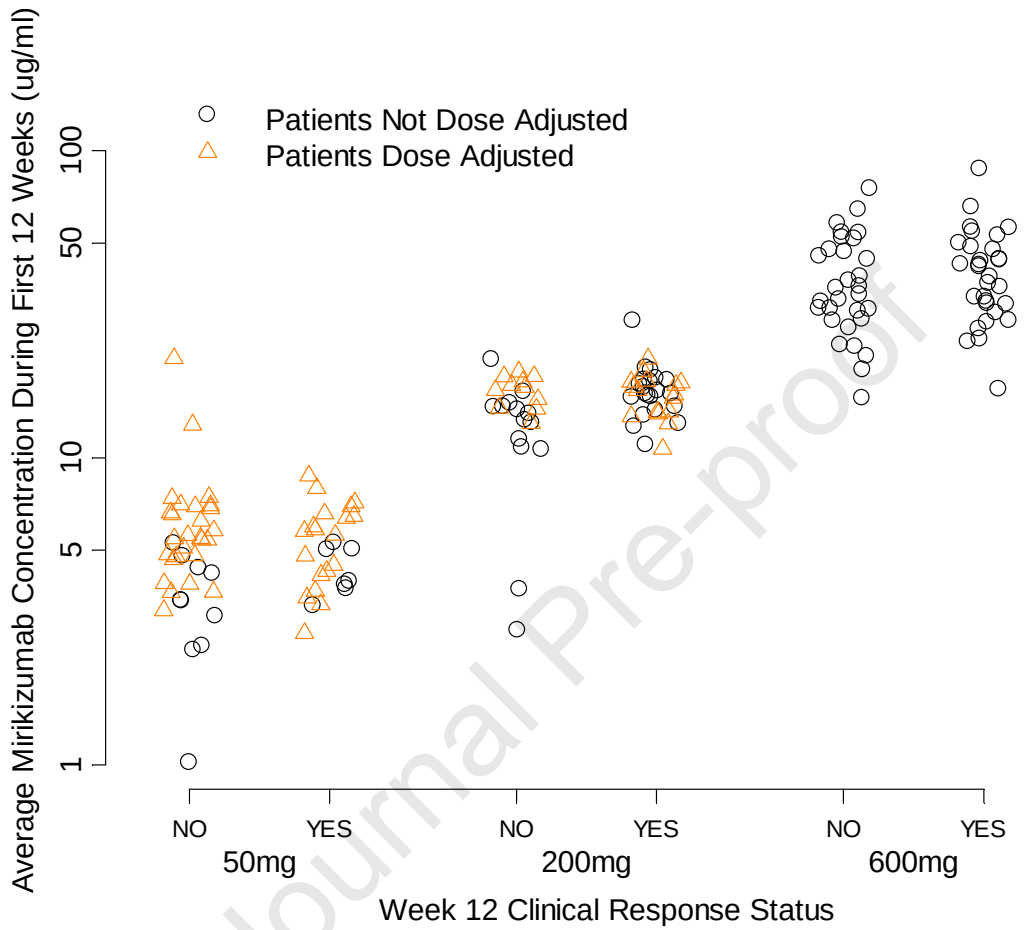
*1 additional patient randomized but did not receive treatment

Supplementary Figure 2. Average mirikizumab concentration during the first 12 Weeks of Study AMAC.



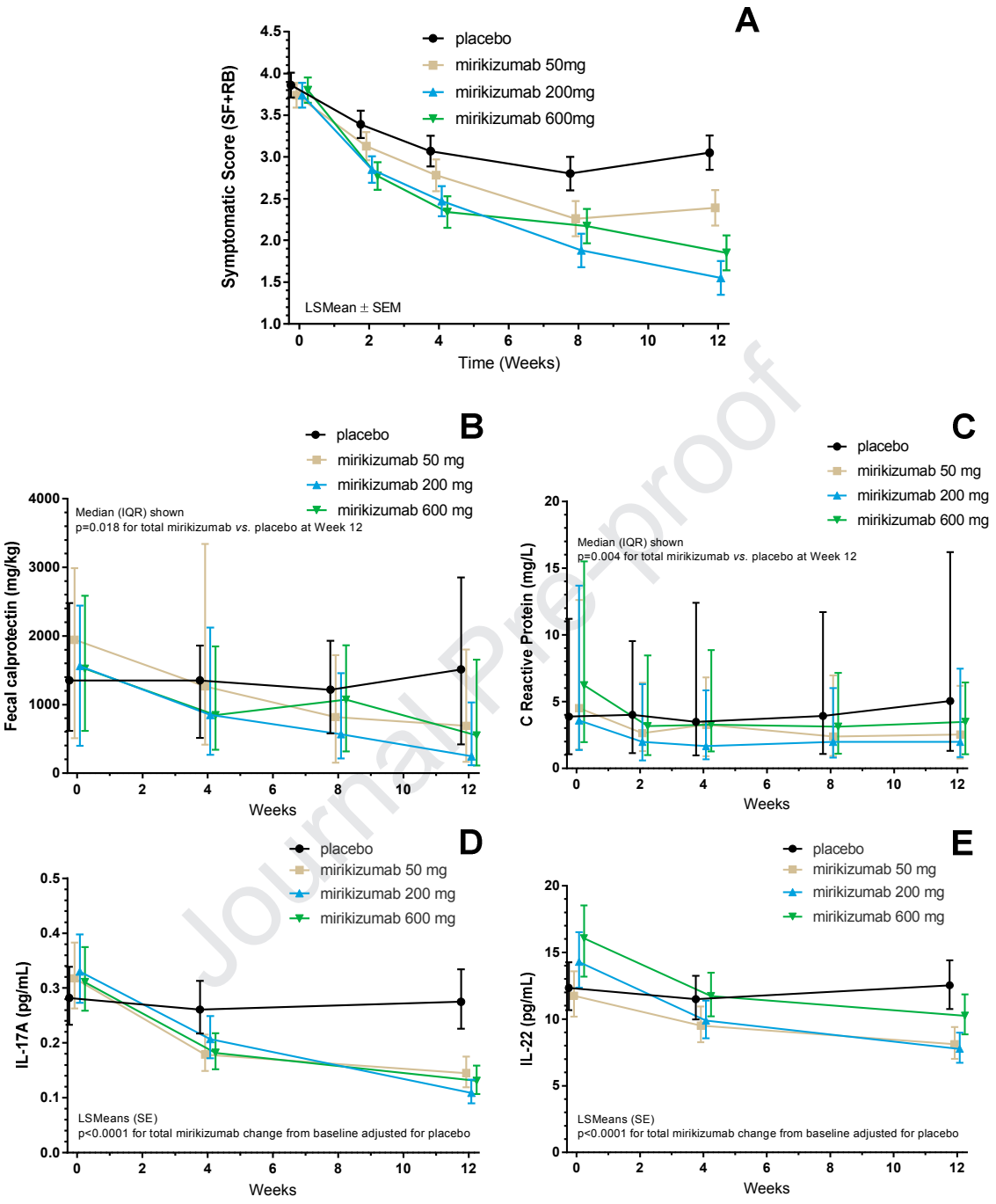
Footnotes: Average mirikizumab concentration for individual subjects during the first 12 weeks was calculated based on total mirikizumab dose administered at Weeks 0, 4 and 8 for each subject and the clearance for each subject estimated based on population PK analyses, and is equivalent to the AUC over the first 12 weeks divided by 12 weeks. The overall average doses in the 50-mg and 200-mg cohorts during induction were 100 mg and 250 mg, respectively.

Supplementary Figure 3. Average mirikizumab concentration during the first 12 Weeks of Study AMAC grouped based on Week 12 Clinical Response Status.

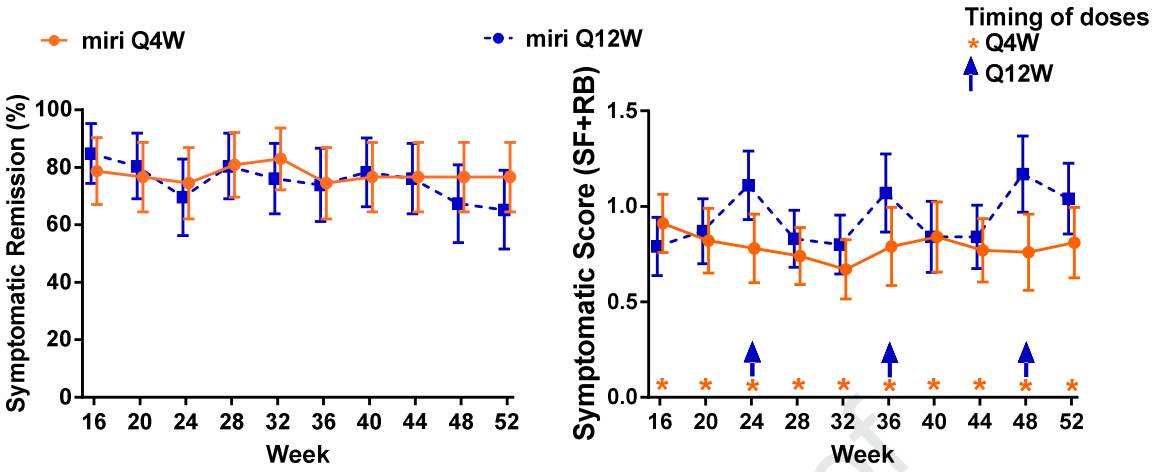


Footnotes: Average mirikizumab concentration was calculated as described in Supplemental Figure 2 footnotes.

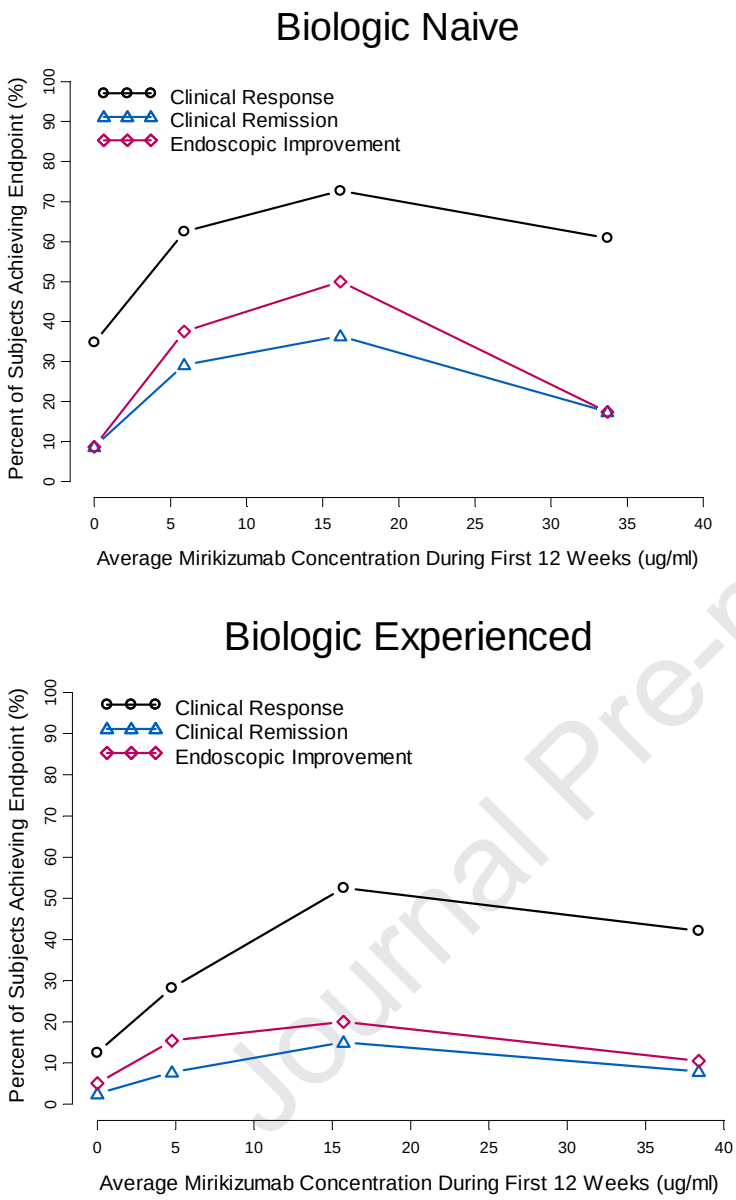
Supplementary Figure 4. 12-Wk continuous outcomes over time



Supplementary Figure 5. 52-Wk symptomatic data



Supplementary Figure 6. Patients achieving study endpoints by median mirikizumab concentration



Footnotes: Average mirikizumab concentration for individual subjects during the first 12 weeks was calculated based on total mirikizumab dose administered at Weeks 0, 4 and 8 for each subject and the clearance for each subject estimated based on population PK analyses, and is equivalent to the AUC over the first 12 weeks divided by 12 weeks. Points on graph represent the median of the mirikizumab concentration over 12 weeks for each treatment cohort. The overall average doses in the 50-mg and 200-mg cohorts during induction were 100 mg and 250 mg, respectively.

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