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

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Running title: Mirikizumab in Crohn's disease treatment

Word Count: 4767

Abstract: 260

Tables: 4

Figures: 3

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This is the author's manuscript of the article published in final edited form as:

Sands, B. E., Peyrin-Biroulet, L., Kierkus, J., Higgins, P. D. R., Fischer, M., Jairath, V., Hirai, F., D'Haens, G., Belin, R. M., Miller, D., Gomez-Valderas, E., Naegeli, A. N., Tuttle, J. L., Pollack, P. F., & Sandborn, W. J. (2021). Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients with Crohn's Disease. Gastroenterology, 162(2), 495-508. https://doi.org/10.1053/j.gastro.2021.10.050

interpretation. **All authors** contributed to manuscript writing and/or critical review/analysis of the manuscript.

Acknowledgements: The authors would like to thank Linden Green for providing writing and editorial support, Catherine Milch for providing medical peer review, Lai Shan Chan for providing analytical support, and Zhantao Lin for providing statistical review.

Funding Support:

This study was funded by Eli Lilly and Company.

Conflicts of interest:

BES reports: research grants from Celgene, Janssen, Takeda, Pfizer, Theravance Biopharma R&D; consulting fees from 4D Pharma, Abbvie, Allergan, Amgen, Arena Pharmaceuticals, AstraZeneca, Bacainn Therapeutics, Boehringer-Ingelheim, Boston Pharmaceuticals, Capella Bioscience, Celgene, Celltrion Healthcare, F.Hoffmann-La Roche, Ferring, Gilead, Immunic, Index Pharmaceuticals, Ironwood Pharmaceuticals, Janssen, Lilly, Morphic Therapeutic, Oppilan Pharma, OSE Immunotherapeutics, Otsuka, Palatin Technologies, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Redhill Biopharma, Rheos Medicines, Salix Pharmaceuticals, Seres Therapeutics, Shire, Sienna Biopharmaceuticals, Surrozen, Takeda, Target PharmaSolutions, Theravance Biopharma R&D, USWM Enterprises, Viela Bio, Vivelix Pharmaceuticals.
WJS reports: research grants from Abbvie, Abivax, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Genentech, Gilead Sciences, Glaxo Smith Kline, Janssen, Lilly, Pfizer, Prometheus Biosciences, Seres Therapeutics, Shire, Takeda, Theravance Biopharma; consulting fees from Abbvie, Abivax, Admirx, Alfasigma, Alimentiv (Robarts Clinical Trials, owned by Health Academic Research Trust [HART]), Alivio Therapeutics, Allakos, Amgen, Applied Molecular Transport, Arena Pharmaceuticals, Bausch Health (Salix), Beigene, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Meyers Squibb, Celgene, Celltrion, Cellularity, Cosmo Pharmaceuticals, Escalier Biosciences, Equillium, Forbion, Genentech/Roche, Gilead Sciences, Glenmark Pharmaceuticals, Gossamer Bio, Immunic (Vital Therapies), Index Pharmaceuticals, Intact Therapeutics, Janssen, Kyverna Therapeutics, Landos Biopharma, Lilly, Oppilan Pharma, Otsuka, Pandion Therapeutics, Pfizer, Progenity, Prometheus Biosciences, Protagonists Therapeutics, Provention Bio, Reistone Biopharma, Seres Therapeutics, Shanghai Pharma Biotherapeutics, Shire, Shoreline Biosciences, Sublimity Therapeutics, Surrozen, Takeda, Theravance Biopharma, Thetis Pharmaceuticals, Tillotts Pharma, UCB, Vendata Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals, Vivreon Biosciences, Zealand Pharma; and stock or stock options from Allakos, BeiGene, Gossamer Bio, Oppilan Pharma, Prometheus Biosciences, Progenity, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences. Spouse: Iveric Bio - consultant, stock options; Progenity - stock; Oppilan Pharma - consultant, stock options; Prometheus Biosciences - employee, stock options; Ventyx Biosciences – stock options; Vimalan Biosciences – stock options.
VJ reports: consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena pharmaceuticals, Genetech, Pendopharm, Pfizer, Fresenius Kabi, Bristol Myers Squibb, Roche, Ferring, Sandoz, Merck, Takeda, Janssen, Alimentiv Inc (formerly Robarts Clinical Trials), Topivert, Celltrion, Mylan; speaker's fees from Takeda, Janssen, Shire, Ferring, Abbvie, Pfizer
MF reports: consulting fees from Eli Lilly, Abbvie, Janssen, Takeda, Bristol Myers Squibb
DM, EGV, JLT, RB, ANN, and PFP are current employees and shareholders of Eli Lilly and Company

JK reports: consulting fees from Eli Lilly, Abbvie, Nestle
FH reports: research grants from Eli Lilly, AbbVie, EA Pharma, JIMRO, Ayumi, Kissei, Mochida, Eisai, Asahi Kasei Medical; consulting fees from Kissei; speaker's fees from AbbVie, EA Pharma, Janssen, Mochida, Mitsubishi Tanabe, Takeda.
GD reports: advisor for AbbVie, Ablynx, Allergan, Alphabiomics, Amakem, Amgen, AM Pharma, Arena Pharmaceuticals, AstraZeneca, Avaxia, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene/Receptos, Celltrion, Cosmo, Dr Falk Pharma, Echo Pharmaceuticals, Eli Lilly and Company, Engene, Ferring, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Gossamerbio, Hospira/Pfizer, Immunic, Johnson and Johnson, Kintai Therapeutics, Lycera, Medimetrics, Medtronics, Merck Sharp Dome, Millenium/Takeda, Mitsubishi Pharma, Mundipharma, Nextbiotics, Novo Nordisk, Otsuka, Pfizer/Hospira, Photopill, Prodigest, Progenity, Prometheus Laboratories/Nestle, Protagonist, RedHill; Robarts Clinical Trials, Salix, Samsung Bioepis, Sandoz, Seres/Nestle, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant, and Vifor
PDRH reports: consultancy and/or advisory board fees from Abbvie, Eli Lilly and Company, and Takeda, and honoraria from Takeda
LPB reports: personal fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals , Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Inotrem, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine ; Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera, Theravance ; grants from Abbvie, MSD, Takeda ; stock options : CTMA.

Abstract

Background: Mirikizumab is a humanized monoclonal antibody targeting IL-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 1000mg mirikizumab, administered intravenously (IV) every 4 weeks (Q4W). Patients who received mirikizumab and achieved ≥1 point improvement in SES-CD at Week 12 (Re-randomized Maintenance Cohort) were re-randomized to continue their induction IV treatment (IV-C) or receive 300mg mirikizumab subcutaneously (SC) Q4W. Non-randomized Maintenance Cohort included endoscopic non-improvers (NI/1000mg) and PBO patients (PBO/1000mg) who received 1000mg 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 SES-CD) at Week 12.

Results: At Week 12, endoscopic response was significantly higher by the pre-defined 2-sided significance level of 0.1 for all mirikizumab groups compared to PBO (200mg: 25.8%, 8/31[95%CI: 10.4-41.2], p=0.079; 600mg: 37.5%, 12/32[95%CI: 20.7-54.3], p=0.003; 1000mg: 43.8%, 28/64[95%CI: 31.6-55.9], p<0.001; 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 mirikizumab groups were similar to PBO. Through Week 52, frequencies of TEAEs were similar across all groups. Frequencies of serious AE and discontinuations due to AE were higher in the Non-randomized 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.

Clinicaltrials.gov no: NCT02589665

KEY WORDS: IBD, cytokine, inhibitor

Introduction

Crohn's disease (CD) is a chronic, disabling, and progressive inflammatory disease of the gastrointestinal (GI) 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, TNFα inhibitors were the only biologics available. More recently, three biologics (vedolizumab, ustekinumab, 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 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 interleukin-12 (IL12) 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 in 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 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, UC, 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-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 14 Dec 2016 to 04 Sep 2018 and enrolled from 12 January 2017 to 24 Sep 2018. The final Week 52 patient visit was 27 September 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 Crohn's disease, with history of intolerance or inadequate response to aminosalicylates, 6-mercaptopurine (6-MP), azathioprine (AZA), or corticosteroids, or history of corticosteroid dependence; and/or have received treatment with ≥1 biologic agent (such as TNF antagonists, vedolizumab, experimental biologic Crohn's disease therapeutics except for those targeting IL23 p19) with or without documented history of intolerance or inadequate response. Concomitant treatment with oral 5-aminosalicylic (ASA) compounds, oral

corticosteroids, AZA, 6-MP, methotrexate (MTX), or Crohn's disease-specific antibiotics were allowed.

Patients were not eligible if they had complications of Crohn's disease such as strictures, stenoses, or any other manifestation for which surgery might be indicated or could confound the evaluation of efficacy; had any kind of bowel resection or diversion within 6 months or other intra-abdominal surgery within 3 months; had presence of a stoma; had 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 prior to the baseline); had received natalizumab or agents that deplete B or T cells within 12 months of screening; or had been treated with any investigational drug for Crohn's disease within 8 weeks prior to 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 (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.

Randomization and Blinding

Induction

Patients were randomized in a 2:1:1:2 ratio across treatment groups: PBO, mirikizumab 200mg, mirikizumab 600mg, or mirikizumab 1000mg, 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 Crohn's disease therapy (including experimental biologic Crohn's disease therapy) and at least 50% of the patients having experienced prior biologic Crohn's disease therapy (including experience with experimental biologic Crohn's disease therapy).

Maintenance

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

Re-randomized Maintenance Cohort

All patients who received mirikizumab treatment during induction (Weeks 0 to 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 (i) continue induction treatment assignment (IV mirikizumab 200mg, 600mg, or 1000mg Q4W; re-randomized IV were pooled for analysis [IV-C]) and placebo administered SC OR (ii) IV placebo Q4W and SC mirikizumab 300mg Q4W administered through Week 52 (IV/SC). Randomization was stratified based on endoscopic response (50% reduction in SES-CD score from baseline).

Non-randomized 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 non-improvers) as well as all

patients who received placebo during induction received IV mirikizumab 1000mg and SC placebo Q4W through Week 52 (NI/1000mg and PBO/1000mg, 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 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.

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 to 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 placebo 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 utilized to evaluate the endoscopy video that was collected during each patient endoscopic (colonoscopy) examination[18, 19]. The SES-CD score was determined by 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 placebo at Week 12, defined as a 50% reduction from baseline in SES-CD score[19]. Secondary objectives included 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), 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 (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 approximately 180 patients. Based on 60 patients per comparison treatment arm and the assumed mirikizumab and placebo endoscopic response rates of 35% and 15%, respectively, the test of the superiority versus placebo 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 were screen failures and 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 Crohn's disease therapy use (yes/no) in the model. Non-responder imputation (NRI) was used at Week 12 and at Week 52 for any subject who discontinued the study treatment at any time prior to 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 (MMRM) technique with treatment, geographic region, prior biologic Crohn's disease 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 14 Dec 2016 and 04 Sep 2018, 526 patients were screened for eligibility in study AMAG. Among the 191 patients who met inclusion criteria and were randomized, 92.1% of patients completed the first 12 weeks of the study (Supplemental 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 200mg group compared to the other groups, as were the percentage of patients receiving oral corticosteroids or immunosuppressants at baseline in the 200mg group. Prior biologic use was approximately 60% in all mirikizumab groups and 67.2% in the placebo group, with prior biologic failure rates of approximately 50% and 56.3% in the mirikizumab groups and placebo 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 to placebo (mean [95%CI]; mirikizumab 200mg: 8/31, 25.8% [10.4-41.2], p=0.079; mirikizumab 600mg: 12/32, 37.5% [20.7-54.3], p=0.003; mirikizumab 1000mg: 28/64, 43.8% [31.6-55.9], p<0.001; PBO: 7/64, 10.9% [3.3-18.6]) (Table 2, Figure 2A).

Secondary and Exploratory Endpoints

A total of 2/31 (6.5% [0-15.1]) in the mirikizumab 200mg group, 5/32 (15.6% [3.0-28.2], p=0.01) in the mirikizumab 600mg group, and 13/64 (20.3% [10.5-30.2], p<0.001) in the mirikizumab 1000mg group achieved endoscopic remission compared to 1 (1.6% [0-4.6]) patients in the placebo group (Table 2, Figure 2B).

PRO remission was achieved by 4/31 (12.9% [1.1-24.7]) patients in the mirikizumab 200mg group, 9/32 (28.1% [12.5-43.7], p=0.004) patients in the mirikizumab 600mg group, and 14/64 (21.9% [11.7-32.0], p=0.013) patients in the mirikizumab 1000mg group compared to 4/64 (6.3% [0.3-12.2]) patients in the placebo group. Similarly, PRO response during the 12-week induction period was significantly higher in the 3 mirikizumab groups compared to placebo (mirikizumab 200mg p=0.023, mirikizumab 600mg p=0.003, mirikizumab 1000mg p=0.006) (Table 2, Figure 2C-D), as was CDAI response (mirikizumab 200mg p=0.015, mirikizumab 600mg p=0.001, mirikizumab 1000mg p=0.026) (Table 2, Figure 2E). CDAI remission was significantly higher than placebo in the 600mg and 1000mg mirikizumab groups (mirikizumab 600mg p<0.001, mirikizumab 1000mg p=0.013) (Table 2, Figure 2F).

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 200mg group compared to those naïve to biologic treatment. For both remission and response, this difference decreased with the higher doses until rates were similar in the 1000mg group (Supplemental Figure 2A-B). In contrast, PRO response rates were similar between biologic experienced and biologic naïve patients in all dose groups (Supplemental Figure 2C), while PRO remission rates were similar with the exception of the 200mg dose group (Supplemental Figure 2D). CDAI response rates were higher in biologic experienced patients in both the 200mg and 600mg dose groups compared to biologic naïve patients (Supplemental Figure 2E). CDAI remission rates varied, with biologic naïve patients having higher rates in the 200mg and 1000mg dose groups, and biologic experienced patients having higher rates in the 600mg dose group (Supplemental Figure 2F).

Patients who received mirikizumab 600 or 1000mg had greater change from baseline in IBDQ scores at 4 weeks compared to placebo (p=0.03 for both groups). At 12 weeks, all mirikizumab groups had greater change from baseline in IBDQ scores compared to placebo (mirikizumab 200mg p<0.001, mirikizumab 600mg p<0.001, mirikizumab 1000mg p<0.001). Likewise, CDAI and PRO components SF and AP were demonstrated significantly greater decrease from baseline by 8 weeks in all dose groups compared to placebo; in the 600mg group all three outcomes were significantly improved versus placebo at 4 weeks (Supplemental Figure 3).

At Week 12, the percent change from baseline in hsCRP was significantly greater in all mirikizumab groups compared to placebo ([median Q1, Q3] PBO: 43.8 [-8.3, 145.5]; mirikizumab 200mg: -29.9 [-64.8, 25.9] p<0.001; mirikizumab 600mg: -39.8 [-70.6, 0.2] p<0.001; mirikizumab 1000mg: -48.6 [-76.1, 35.1] p<0.001), with the greatest change in the 1000mg group. The percent change from baseline in FCP was significantly greater in the mirikizumab 600 and 1000mg groups compared to placebo (PBO: 0.0 [-60.9, 54.1]; mirikizumab 200mg: -60.7 [-84.8, 68.0]; mirikizumab 600mg: -62.1 [-84.4, -13.2] p<0.05; mirikizumab 1000mg: -76.2 [-90.7, -54.9] p<0.001) (Table 2, Supplemental Figure 4), again with the greatest change in the 1000mg 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 to placebo, with the highest proportion of patients in the 1000mg mirikizumab group (CRP: PBO 9.1%; mirikizumab 200mg: 4.3%; mirikizumab 600mg: 26.1%, p<0.01; mirikizumab 1000mg: 33.3%, p<0.05) (FCP, 250mg/kg cutoff: PBO 13.0%; mirikizumab

200mg: 28.6%; mirikizumab 600mg: 33.3%, p<0.01; mirikizumab 1000mg: 40.8%, p<0.05) (Supplemental Figure 4).

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

Maintenance Period

Endoscopic Outcomes

Re-randomized Cohorts

There was no consistent relation between outcomes and dose observed at Week 52 (Supplemental Figure 5). Due to small sample sizes in maintenance, all patients achieving endoscopic improvement at Week 12 and who were re-randomized to IV in maintenance were pooled (IC-C cohort) and all patients who were re-randomized 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, 15/46 (32.6% [19.1-46.2]) in the IV/SC cohort (Table 3, Figure 3A-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, Supplemental Figure 6A-B).

Non-randomized 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 1000mg during maintenance (NI/1000mg IV cohort), and 25/59 (42.4% [29.8-55.0]) in patients who received placebo during induction and switched to mirikizumab 1000mg in maintenance (PBO/1000mg IV cohort). Endoscopic remission at Week 52 was achieved by 4/30 (13.3% [1.2-25.5]) in the NI/1000mg IV cohort, and 11/59 (18.6% [8.7, 28.6]) in the PBO/1000mg IV cohort. (Table 3, Figure 3A-B).

Patient Reported Outcome (PRO) Results

Re-randomized 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 3C-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, Supplemental Figure 6C).

Non-randomized Cohorts

PRO response at Week 52 was 18/30 (60.0% [42.5, 77.5]) in the NI/1000mg IV cohort, and 36/59 (61.0% [48.6-73.5]) in the PBO/1000mg IV cohort. PRO remission was 11/30 (36.7% [19.4-53.9]) in the NI/1000mg IV cohort, and 24/59 (40.7% [28.1-53.2]) in the PBO/1000mg IV cohort (Table 3, Figure 3C-D).

CDAI Results

Re-randomized 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 3E-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, Supplemental Figure 6D).

Non-randomized Cohorts

In the NI/1000mg IV cohort, 14/30 (46.7% [28.8-64.5]) achieved CDAI response and in the PBO/1000mg 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/1000mg IV cohort and 24/59 (40.7% [28.1-53.2]) in the PBO/1000mg IV cohort (Table 3, Figure 3E-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/1000mg IV cohort and 53.6 in the PBO/1000mg IV cohort (Supplemental Figure 7).

Circulating Biomarkers

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

Safety - Induction period

Treatment-emergent adverse events (TEAEs) occurred in 70.3% of the placebo group, 58.1% of the 200mg mirikizumab group, and 65.6% in each of the 600mg and 1000mg mirikizumab groups during the induction period (Table 4). The most frequent TEAEs among mirikizumab groups during the induction period included headache, worsening of Crohn's disease, 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 placebo group.

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

Safety - Maintenance period

Randomized Maintenance Group

During the maintenance period, there were no SAEs reported in the mirikizumab IV-C group and 2 in the mirikizumab 300mg SC group (worsening of Crohn's disease, pyelonephritis, and dehydration in one patient and ileal perforation [secondary to ileitis] and peritonitis in the other patient). Two of these patients (worsening of Crohn's disease, ileal perforation) discontinued due to their SAE.

Nonrandomized Maintenance Group

Eleven patients had ≥1 SAE: 8 in the induction placebo/1000mg group (anaphylactic reaction [2 patients], *Clostridioides difficile* infection, hypersensitivity, intestinal obstruction, non-cardiac chest pain, osteoarthritis, and worsening of Crohn's disease), and 3 in the Week 12 NI/1000mg group (spontaneous abortion, worsening of Crohn's disease, and pneumonia). Four patients discontinued due to their SAE (anaphylactic reaction [2 patients], hypersensitivity, worsening of Crohn's disease) while 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 one patient in the induction period (herpes zoster, PBO group) and three patients in the maintenance period (1 oral candidiasis, NI/1000mg group; 2 herpes zoster, PBO/1000mg 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 pre-treated, with approximately two-thirds of participants having received biologic therapy and approximately half of all patients in this trial having experienced at least one biologic failure (Table 1). These characteristics suggest a relatively difficult to treat population and have been associated with lower response rates in prior Crohn's disease studies. Nonetheless, mirikizumab-treated patients had significantly higher rates of endoscopic, PRO, and CDAI response and remission compared to patients given placebo, including patients with prior exposure to biologics. Additionally, response to mirikizumab was rapid, with CDAI, PRO and IBDQ showing significant improvements compared to placebo within 4 weeks of treatment.

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

doses were statistically significantly greater than placebo. The results of more objective assessments (hsCRP, fecal calprotectin, 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 continued to achieve these endpoints at Week 52. Furthermore, the rates of endoscopic response and remission as well as response and remission for the two clinical assessments (PRO and CDAI) were both similar or numerically higher at Week 52 compared to 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 to 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 utilized clinical outcomes as the basis for determining maintenance dosing. Only one other trial has employed 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 one year compared to those who had endoscopic improvement at Week 12, one out of five of these patients achieved endoscopic response and over 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 following 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, while 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 CD patients.

During the induction period, TEAEs and SAEs showed no difference between the different mirikizumab dose groups and were overall slightly lower than in the placebo group. In the maintenance period there were no apparent differences in TEAEs between the combined IV and the

IV/SC cohorts and the two cohorts in the Nonrandomized Maintenance Group. There were 2 SAEs in the Randomized Maintenance Group. The percentages of SAEs in the two 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 Placebo to 1000mg IV. These events occurred after initiation of infusion at a rate calculated to deliver the total dose over 30 minutes (2 gm/hr for the 1000mg 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 placebo group through the full year of evaluation. The latter was addressed to some extent by the combination of the blind throughout the trial utilizing 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 Crohn's disease in the ongoing VIVID Phase 3 program (NCT03926130).

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**.

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Figure 1: AMAG study design. IV=intravenous; Q4W=every 4 weeks; SC=subcutaneous; [a]miri non-improver is defined as failing to achieve any improvement from baseline SES-CD score at Week 12

Figure 2: Clinical and endoscopic outcomes at Week 12

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 200mg N=9, 600mg N=9, 1000mg N=23; All miri IV→SC 200mg N=10, 600mg N=11, 1000mg N=25.

Tables

Table 1: Baseline Demographics and Clinical Characteristics

	Treatment Groups			
		Miri		
Mean (SD) unless otherwise specified	**Placebo (N=64)**	**200mg (N=31)**	**600mg (N=32)**	**1000mg (N=64)**
Age, years	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, years	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)
Simple endoscopic score for Crohn's disease (SES-CD)	11.9 (5.6)	14.4 (7.9)	15.2 (7.4)	13.1 (6.8)
PRO scores				
Stool frequency	6.4 (3.1)	7.4 (3.0)	6.4 (3.8)	6.6 (5.5)
Abdominal pain	1.9 (0.6)	2.0 (0.6)	1.7 (0.7)	1.9 (0.6)
Crohn's Disease Activity Index (CDAI)	304.7 (93.1)	348.3 (92.1)	298.2 (103.7)	304.5 (94.4)
Previous biologic use*, n (%)	43 (67.2)	19 (61.3)	19 (59.4)	39 (60.9)
Previous biologic failure, 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)

Intent-to-treat population
* Although prior induction dosing of ustekinumab (UST) use was allowed, no patients had prior UST treatment
** Inadequate response, loss of response, or intolerance to medication
Patients with prior biologic exposure that were not biologic failures discontinued treatment for the following reasons: cannot afford, treatment availability, subject decision, completed treatment, and other

Table 2: Week 12 Efficacy results

	Treatment Groups			
		Miri		
	Placebo (N=64)	**200mg (N=31)**	**600mg (N=32)**	**1000mg (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 † (-64.8, 25.9)	-39.8† (-70.6, 0.2)	-48.6 † (-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** (-84.4, -13.2)	-76.2 † (-90.7, -54.9)

Intent-to-treat 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; * p<0.1, ** p<0.05, *** p<0.01, † p<0.001

Table 3: Week-52 efficacy results

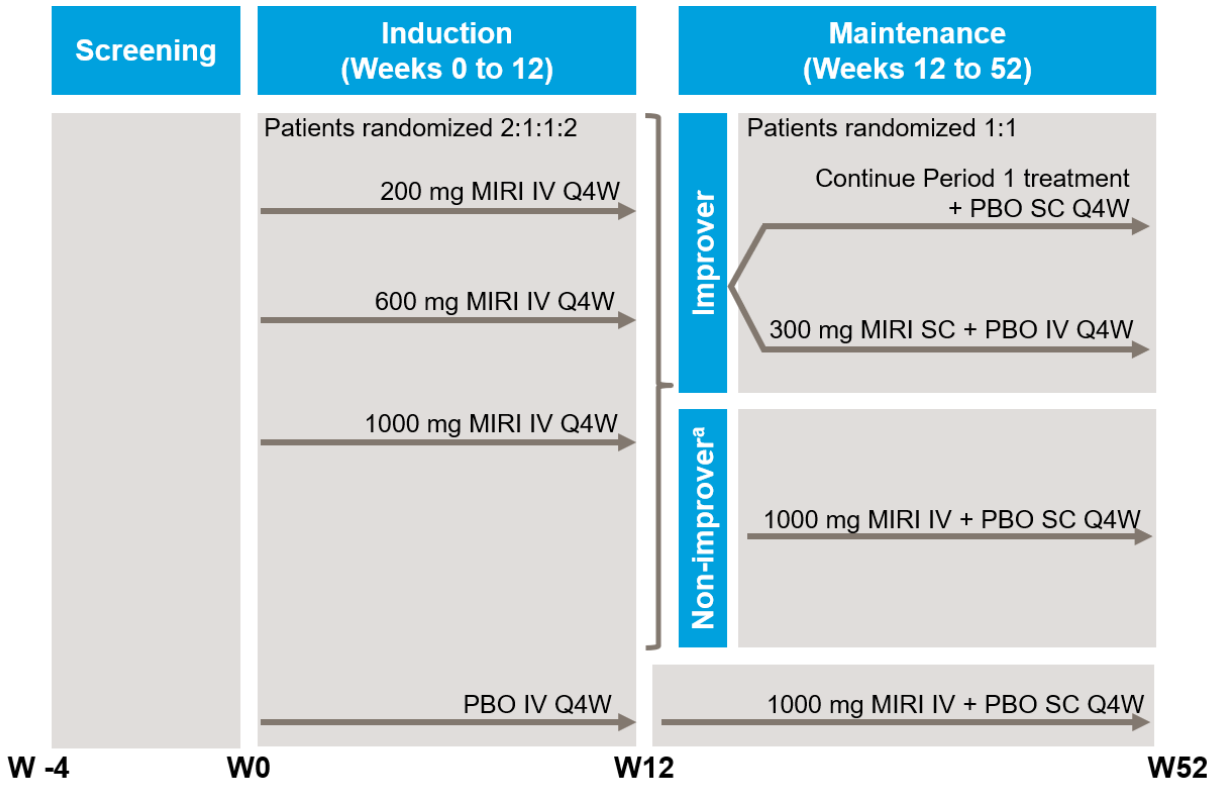
	Randomized Maintenance[a]		Non-randomized Maintenance	
	IV-C Q4W N=41	**300mg SC Q4W N=46**	**Placebo/1000mg IV Q4W (N=59)**	**Endoscopic Non-improvers/1000mg IV Q4W (N=30)**
	Week 12			
Endoscopic response[b], n (%)	23 (56.1)	24 (52.2)	7 (11.9)	0
Endoscopic remission[c], n (%)	6 (14.6)	14 (30.4)	1 (1.7)	0
PRO remission[d], n (%)	14 (34.1)	9 (19.6)	4 (6.8)	4 (13.3)
CDAI remission[e], n (%)	13 (31.7)	15 (32.6)	6 (10.2)	6 (20.0)
	Week 52*			
Endoscopic response[b], 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[b], 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[f], n (%)	28 (68.3)	33 (71.7)	36 (61.0)	18 (60.0)
PRO remission[d], 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[g], n (%)	22 (53.7)	32 (69.6)	31 (52.5)	14 (46.7)
CDAI remission[e], 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)

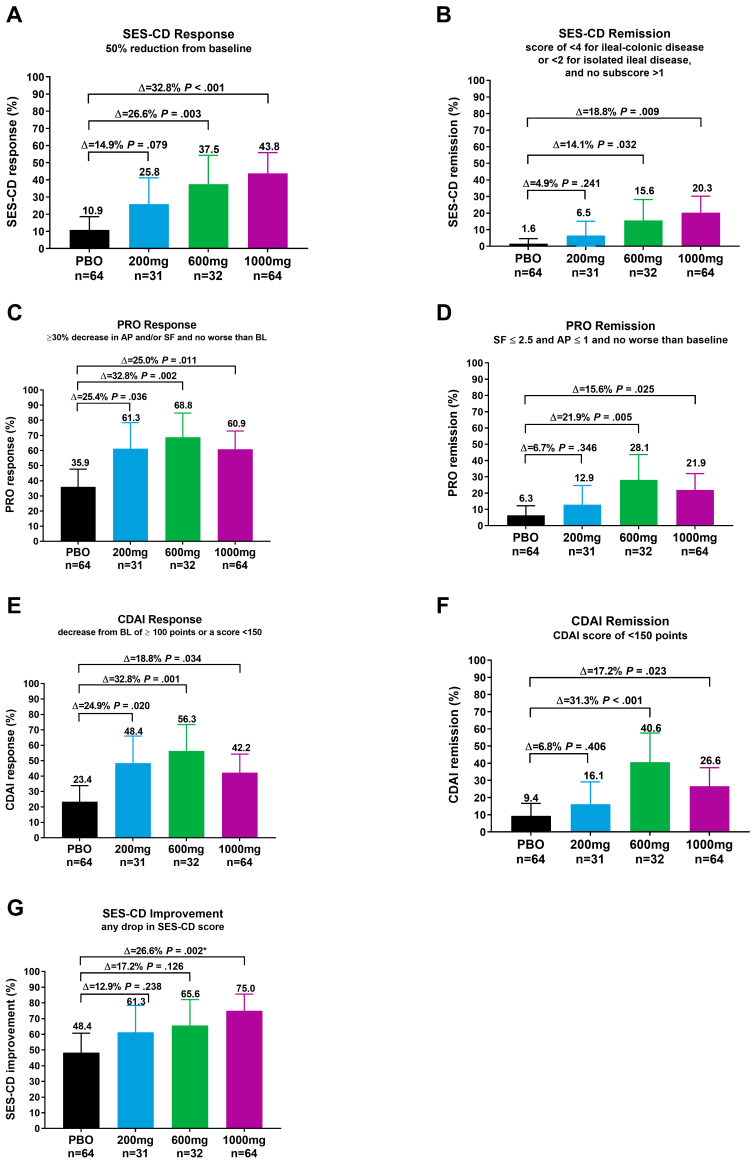
***** for all efficacy endpoints, IV-C and SC confidence intervals overlap; [a]**Patients with endoscopic improvement at Week 12:** ≥1 point improvement in SES-CD at Week 12; [b]**endoscopic response:** 50% reduction from baseline in SES-CD; [c]**endoscopic remission:** SES-CD score of <4 for ileal-colonic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

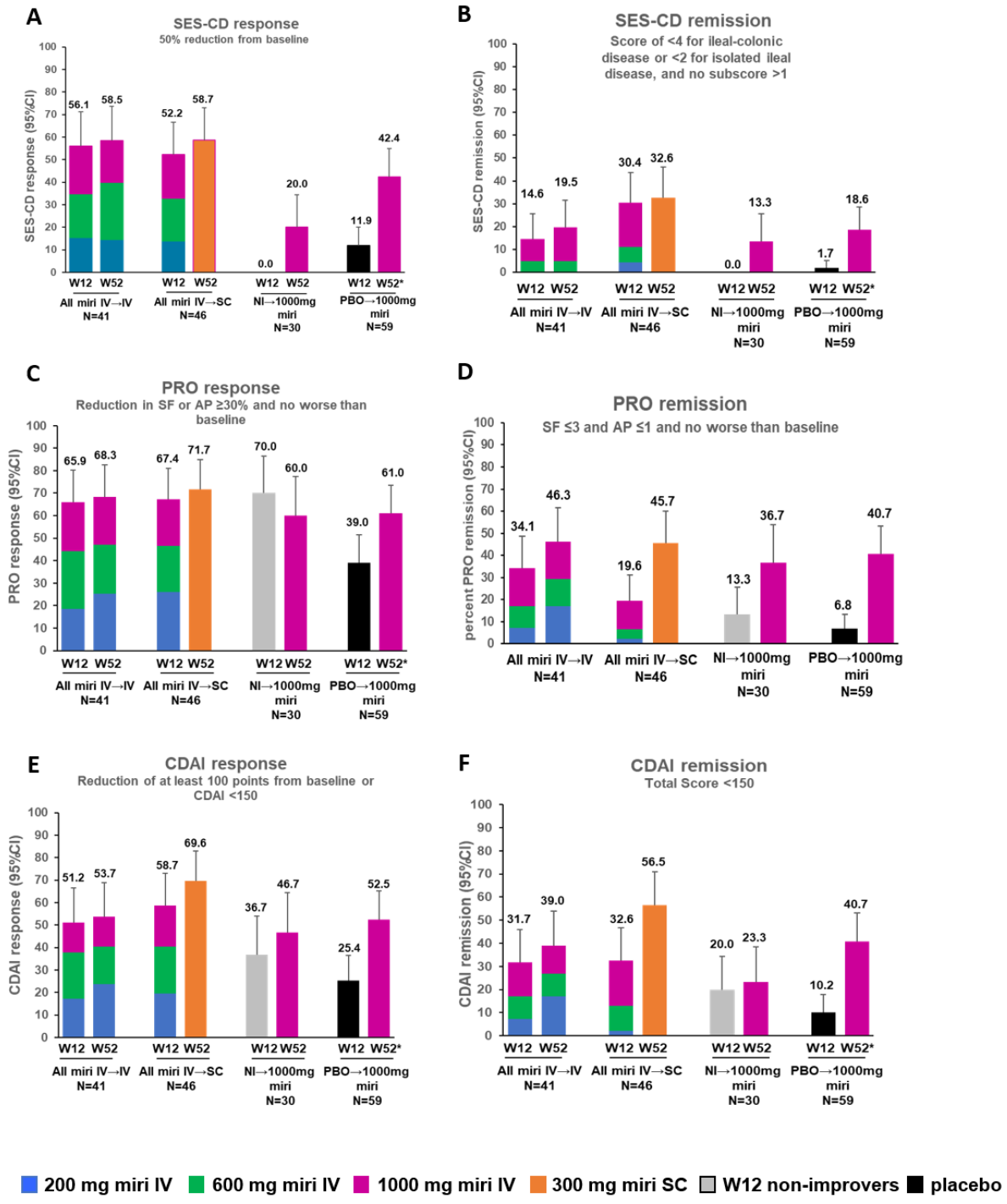
Table 4: Safety results

	Treatment Groups, Induction period			
		Miri		
	Placebo (N=64)	**200mg (N=31)**	**600mg (N=32)**	**1000mg (N=64)**
TEAE[a], n (%)	45 (70.3)	18 (58.1)	21 (65.6)	42 (65.6)
SAE[b], 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[c])				
Headache	2 (3.1)	2 (6.5)	2 (6.3)	7 (10.9)
Crohn's disease (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)
Anaemia	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		**Non-randomized Maintenance**	
	IV-C Q4W N=41	**300mg SC Q4W N=46**	**Placebo/1000mg IV Q4W (N=59)**	**Endoscopic Non-improvers/1000mg 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)
Anaemia	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]**TEAE:** treatment emergent adverse event; [b]**SAE:** serious adverse event; [c]**Most common TEAEs:** as percentage of total population. Only headache and Crohn's disease were above 5% frequency during induction.


Screening
Induction
(Weeks 0 to 12)
Maintenance
(Weeks 12 to 52)
Patients randomized 2:1:1:2
200 mg MIRI IV Q4W
600 mg MIRI IV Q4W
1000 mg MIRI IV Q4W
PBO IV Q4W
Improver
Patients randomized 1:1
Continue Period 1 treatment
+ PBO SC Q4W
300 mg MIRI SC + PBO IV Q4W
Non-improver[a]
1000 mg MIRI IV + PBO SC Q4W
1000 mg MIRI IV + PBO SC Q4W
W -4
W0
W12
W52


A
SES-CD Response
50% reduction from baseline
SES-CD response (%)
Δ=32.8% P < .001
Δ=26.6% P = .003
Δ=14.9% P = .079
10.9
25.8
37.5
43.8
PBO n=64
200mg n=31
600mg n=32
1000mg n=64
B
SES-CD Remission
score of <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1
SES-CD remission (%)
Δ=18.8% P = .009
Δ=14.1% P = .032
Δ=4.9% P = .241
1.6
6.5
15.6
20.3
PBO n=64
200mg n=31
600mg n=32
1000mg n=64
C
PRO Response
≥30% decrease in AP and/or SF and no worse than BL
PRO response (%)
Δ=25.0% P = .011
Δ=32.8% P = .002
Δ=25.4% P = .036
35.9
61.3
68.8
60.9
PBO n=64
200mg n=31
600mg n=32
1000mg n=64
D
PRO Remission
SF ≤ 2.5 and AP ≤ 1 and no worse than baseline
PRO remission (%)
Δ=15.6% P = .025
Δ=21.9% P = .005
Δ=6.7% P = .346
6.3
12.9
28.1
21.9
PBO n=64
200mg n=31
600mg n=32
1000mg n=64
E
CDAI Response
decrease from BL of ≥ 100 points or a score <150
CDAI response (%)
Δ=18.8% P = .034
Δ=32.8% P = .001
Δ=24.9% P = .020
23.4
48.4
56.3
42.2
PBO n=64
200mg n=31
600mg n=32
1000mg n=64
F
CDAI Remission
CDAI score of <150 points
CDAI remission (%)
Δ=17.2% P = .023
Δ=31.3% P < .001
Δ=6.8% P = .406
9.4
16.1
40.6
26.6
PBO n=64
200mg n=31
600mg n=32
1000mg n=64
G
SES-CD Improvement
any drop in SES-CD score
SES-CD improvement (%)
Δ=26.6% P = .002*
Δ=17.2% P = .126
Δ=12.9% P = .238
48.4
61.3
65.6
75.0
PBO n=64
200mg n=31
600mg n=32
1000mg n=64


A
SES-CD response
50% reduction from baseline
SES-CD response (95%CI)
56.1
58.5
52.2
58.7
0.0
20.0
11.9
42.4
W12 W52
All miri IV→IV N=41
All miri IV→SC N=46
NI→1000mg miri N=30
PBO→1000mg miri N=59
W12 W52*
B
SES-CD remission
Score of <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1
SES-CD remission (95%CI)
14.6
19.5
30.4
32.6
0.0
13.3
1.7
18.6
C
PRO response
Reduction in SF or AP ≥30% and no worse than baseline
PRO response (95%CI)
65.9
68.3
67.4
71.7
70.0
60.0
39.0
61.0
D
PRO remission
SF ≤3 and AP ≤1 and no worse than baseline
percent PRO remission (95%CI)
34.1
46.3
19.6
45.7
13.3
36.7
6.8
40.7
E
CDAI response
Reduction of at least 100 points from baseline or CDAI <150
CDAI response (95%CI)
51.2
53.7
58.7
69.6
36.7
46.7
25.4
52.5
F
CDAI remission
Total Score <150
CDAI remission (95%CI)
31.7
39.0
32.6
56.5
20.0
23.3
10.2
40.7
200 mg miri IV
600 mg miri IV
1000 mg miri IV
300 mg miri SC
W12 non-improvers
placebo

Lay summary

In this phase-2 study in patients with moderate-to-severely active Crohn's disease, mirikizumab demonstrated endoscopic and clinical efficacy compared to placebo after 12 weeks and maintained efficacy through 52 weeks of treatment.

What you need to know

Background and context: Interleukin 23 (IL23) contributes to pathogenesis of Crohn's disease (CD). Mirikizumab is a monoclonal antibody directed against the p19 subunit of IL-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 pre-treated patient population.

Supplemental Methods

Inclusion criteria

Subjects will be eligible for the study only if they meet all of the following criteria within the screening period, which is ≤28 days prior to the start of study treatment, unless specifically defined:

Type of Subject and Disease Characteristics

[1] have had a diagnosis of Crohn's disease for ≥3 months before baseline

[2] have active Crohn's disease as defined absolute SF ≥4 (loose and watery stools defined as Bristol Stool Scale Category 6 or 7) AND/OR AP ≥2 at baseline (refer Section 9.1.2 for details)

[3] have a SES-CD score ≥7 (centrally read) for subjects with ileal-colonic or ≥4 for subjects with isolated ileal disease within 14 days before the first dose of study treatment

Prior IBD Treatment

[4] must have received prior treatment for Crohn's disease (according to either "a)" or "b)" below or combination of both):

a) history of inadequate response to, or failure to tolerate treatment with aminosalicylates, 6-mercaptopurine (6-MP) or azathioprine (AZA), oral or IV corticosteroids or history of corticosteroid dependence (an inability to successfully taper corticosteroids without return of Crohn's disease)

OR

b) have received treatment with ≥1 biologic agents (such as TNF antagonists, vedolizumab, experimental biologic Crohn's disease therapeutics) with or without documented history of failure to respond to or tolerate such treatment. The treatment must have been discontinued according to the following timeline:

- anti-TNF therapy at least 8 weeks before baseline
- vedolizumab treatment at least 12 weeks before baseline
- experimental biologic Crohn's disease therapy at least 8 weeks before baseline.

[5] may be receiving a therapeutic dosage of the following drugs:

- Oral 5-aminosalicylic (ASA) compounds: if the prescribed dose has been stable for at least 3 weeks before screening colonoscopy or stopped treatment at least 3 weeks prior to screening colonoscopy.
- Oral corticosteroids must be at a prednisone-equivalent dose of ≤20 mg/day, or ≤9 mg/day of budesonide, and have been at a stable dose for at least 3 weeks prior to the screening colonoscopy. If stopping oral corticosteroid treatment prior to baseline, they must be stopped at least 3 weeks prior to screening colonoscopy.
- AZA, 6-MP, or methotrexate (MTX): if the prescribed dose has been stable for at least 4 weeks before screening endoscopy. Subjects who have discontinued therapy with AZA, 6-MP, or MTX must have stopped the medication at least 4 weeks prior to screening endoscopy to be considered eligible for enrollment.

- Crohn's disease-specific antibiotics: if the prescribed dose has been stable 4 weeks prior to baseline or stopped treatment at least 3 weeks prior to screening endoscopy.

Subject Characteristics

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

[7] Women of child-bearing potential must agree to either remain abstinent or use effective methods of contraception for the entirety of the study. Abstinence or contraception must continue 3 months following completion of study drug administration which is greater than 5 half-lives:

- Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.
- Two effective methods of contraception will be used. The subject may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

[8] Women not of child-bearing potential may participate and include those who are:

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Müllerian agenesis; or
- post-menopausal – defined as either
    - a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
        - cessation of menses for at least 1 year, or
        - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone (FSH) >40 mIU/mL; or
    - a woman ≥55 years of age not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
    - a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[9] venous access sufficient to allow blood sampling and IV administration as per the protocol

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

[11] have an adequate organ function, including:

- hematologic: absolute neutrophil count ≥1.5 x 109/L (≥1.5 x 103/μL or ≥1.5 GI/L), platelet count ≥100 x 109/L (≥100 x 103/μL or ≥100 GI/L), hemoglobin level ≥10.0 g/dL (≥100 g/L), absolute lymphocyte count >500 cells/μL (>0.50 x 103/μL or >0.50 GI/L, and total white blood cell count ≥3.0 x 109/L (≥3.0 x 103/μL or ≥3.0 GI/L)
- chemistry: serum creatinine, total bilirubin level (TBL; subjects with Gilbert's syndrome must have serum direct bilirubin <1.5 mg/dL), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels less than or equal to 2 times the upper limit of normal (≤2X ULN).

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

[13] are male or female subjects ≥18 and ≤75 years of age at the time of initial screening.

Exclusion criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria within the screening period, which is ≤28 days prior to the start of study treatment, unless specifically defined:

Study Disease Conditions or Treatments

[14] have complications of Crohn's disease such as strictures, stenoses, or any other manifestation for which surgery might be indicated or could confound the evaluation of efficacy

[15] diagnosis of conditions affecting the digestive tract, such as UC, indeterminate colitis, fistulizing disease, abdominal or perianal abscess, adenomatous colonic polyps not excised, colonic mucosal dysplasia, and short bowel syndrome

[16] have had any kind of bowel resection, diversion, or placement of a stoma within 6 months or any other intra-abdominal surgery within 3 months prior to screening

[17] have received any of the following for treatment of Crohn's disease:

- 6-thioguanine (6-TG), cyclosporine, tacrolimus, sirolimus, pentoxifylline, or mycophenolate mofetil within 8 weeks prior to baseline
- corticosteroid enemas, IV corticosteroids, corticosteroid suppositories, or topical treatment within 3 weeks prior to screening colonoscopy
- rectal 5-ASA within 3 weeks prior to screening colonoscopy
- have used apheresis (for example, Adacolumn apheresis) ≤2 weeks prior to screening.

[18] have previous exposure to any biologic therapy targeting IL-23 p19 either licensed or investigational. Patients who have been exposed to ustekinumab are excluded from the study, except for patients who have received a single IV "induction" dose of ustekinumab, at a marketed dose at least 12 weeks prior to the baseline, and discontinued treatment prior to receiving a subcutaneous (SC) "maintenance" dose, for reasons other than inadequate response, loss of response, or intolerance to medication.

[19] have received natalizumab or agents that deplete B or T cells (for example, rituximab, alemtuzumab, or visilizumab) within 12 months of screening, or, if after receiving these agents, evidence is available at screening of persistent depletion of the targeted lymphocyte population

[20] have been treated with any investigational drug for Crohn's disease within 8 weeks prior to baseline or 5 half-lives of the drug (whichever is longer), OR with interferon therapy within 8 weeks before baseline

General Eligibility Criteria

[21] have evidence of active or latent tuberculosis (TB) (see full TB testing details below)

[22] 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

[23] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[24] increases the risks associated with participating in the study if the presence or history within 12 months prior to screening of significant uncontrolled cerebrocardiovascular (for example, myocardial infarction, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association class III/IV], or cerebrovascular accident); presence of respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of data

[25] presence of significant uncontrolled neuropsychiatric disorder, have history of a suicide attempt or have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology–Self Report (16 Items) (QIDS-SR16) at screening (Visit 1) or baseline (Week 0; Visit 2)

[26] are 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.

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

[28] are currently 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

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

[30] have received live, attenuated vaccine(s) within 2 months of screening or intend 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 are allowed for all subjects.

[31] have human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or test positive for antibodies at screening

[32] 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

[33] 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

[34] had Clostridium difficile (C diff) infection within 60 days of screening 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.

[35] 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.

[36] have received a systemic (including oral) anti-infective agent for an infection within 28 days of baseline

[37] are pregnant, lactating, or planning pregnancy (both men and women) while enrolled in the study, or within 3 months after receiving the last dose of study agent

[38] have significant allergies to humanized monoclonal antibodies or any components of the LY3074828 product formulation

[39] history of alcohol or other drug abuse within the last year

[40] are 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.

Tapering of oral corticosteroids

Decrease of the steroid dosage due to tapering regimen was allowed during the study per investigator judgment, except during Period 1. If the steroid tapering was initiated, the daily dose of prednisone or equivalent was recommended to be decreased by 2.5 mg every week until dose 0.

If tapering of budesonide was commenced, it was recommended to be decreased by 3 mg every week until dose 0.

For immunosuppressive (azathioprine, 6-MP, methotrexate) dosages were to remain stable throughout the study unless the medication was discontinued because of toxicity. If stopped, the medication was not be restarted during the study.

TB testing details

Posterior-anterior view chest radiography (CXR) will be obtained at screening (unless local standards dictate posterior–anterior and lateral views), unless the radiographs or medical report from chest radiography performed within 3 months before initial screening (per local standard of care for TB evaluation) are available to the investigator for review. In addition, subjects will be tested for evidence of active or latent TB. A positive TB test result is indicated by a purified protein derivative (PPD) skin test response ≥5 mm induration documented 48 to 72 hours after test application (regardless of Bacillus Calmette-Guerin vaccination history). In countries where the QuantiFERON-TB Gold test (or equivalent, for example, T-SPOT) is available and is preferred (in the judgment of the investigator) as an alternative to the PPD skin test for the evaluation of TB infection in a subject, that test may be used instead of the PPD test. Retesting following a positive test is allowed in patients, who in the opinion of the investigator, are unlikely to be infected with *Mycobacterium tuberculosis*. In this circumstance, 2 positive tests is considered evidence of active or latent TB infection. Patients in whom retesting has been performed must be discussed with the medical monitor prior to inclusion in the study. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the subject is excluded from the study.

Subjects with documentation of negative TB test results within 3 months before initial screening may not need to repeat TB testing at screening based on judgment of the investigator. Documentation of this previous test result must include a record of the size (in millimeters) of the induration response. A PPD test recorded as "negative" without documenting the size of induration (in millimeters) will not be acceptable and will require a retest. However, subjects with a PPD skin test response ≥5 mm induration or a positive QuantiFERON-TB Gold test result at screening and no other evidence of active TB may be rescreened once and enrolled according to the following requirements:

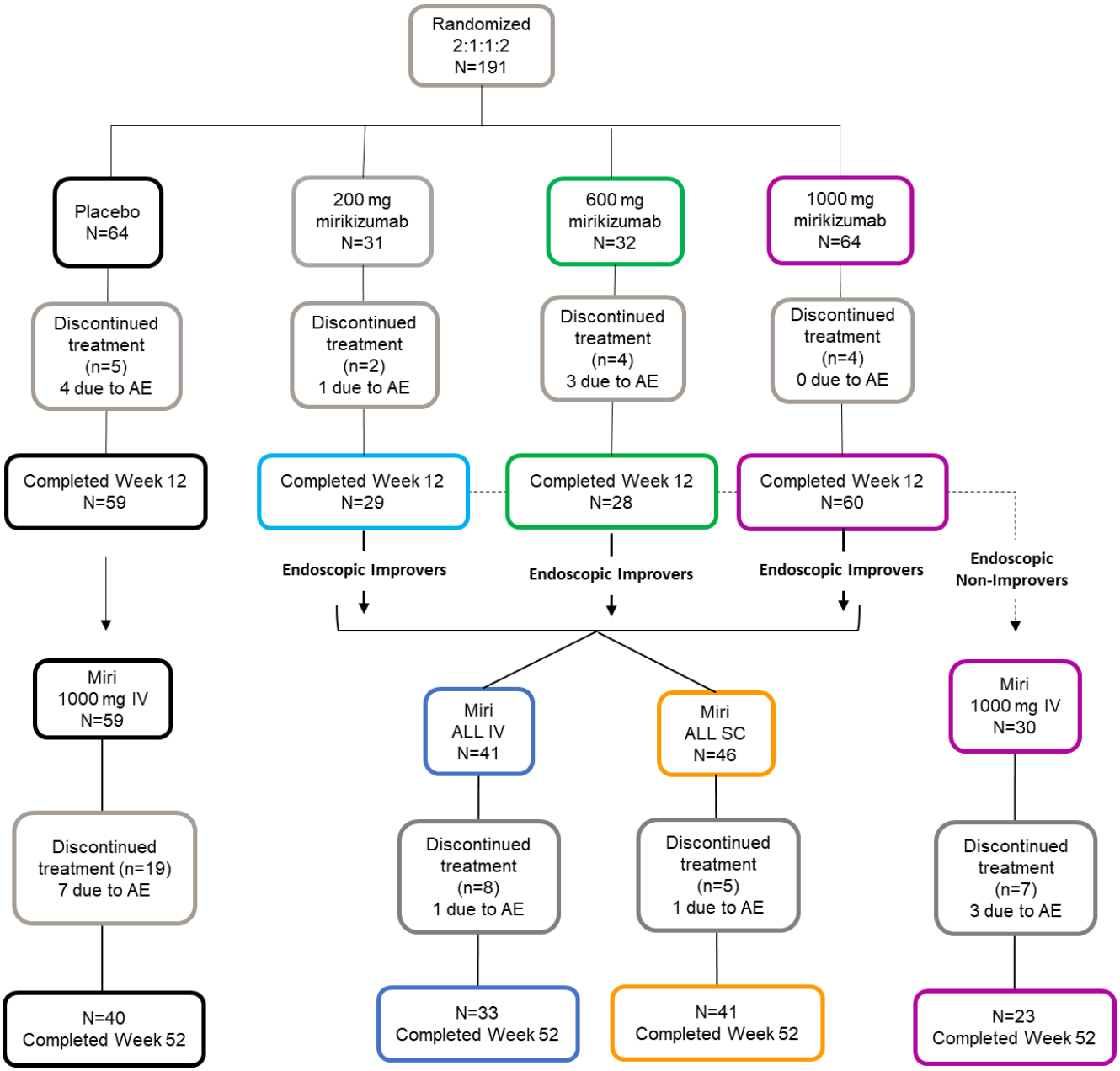
- after receiving at least 4 weeks of appropriate ongoing prophylactic therapy for latent TB as per local standard of care

- no evidence of treatment hepatotoxicity (ALT and AST levels must remain ≤2xULN) upon retesting of serum ALT and AST levels before randomization)

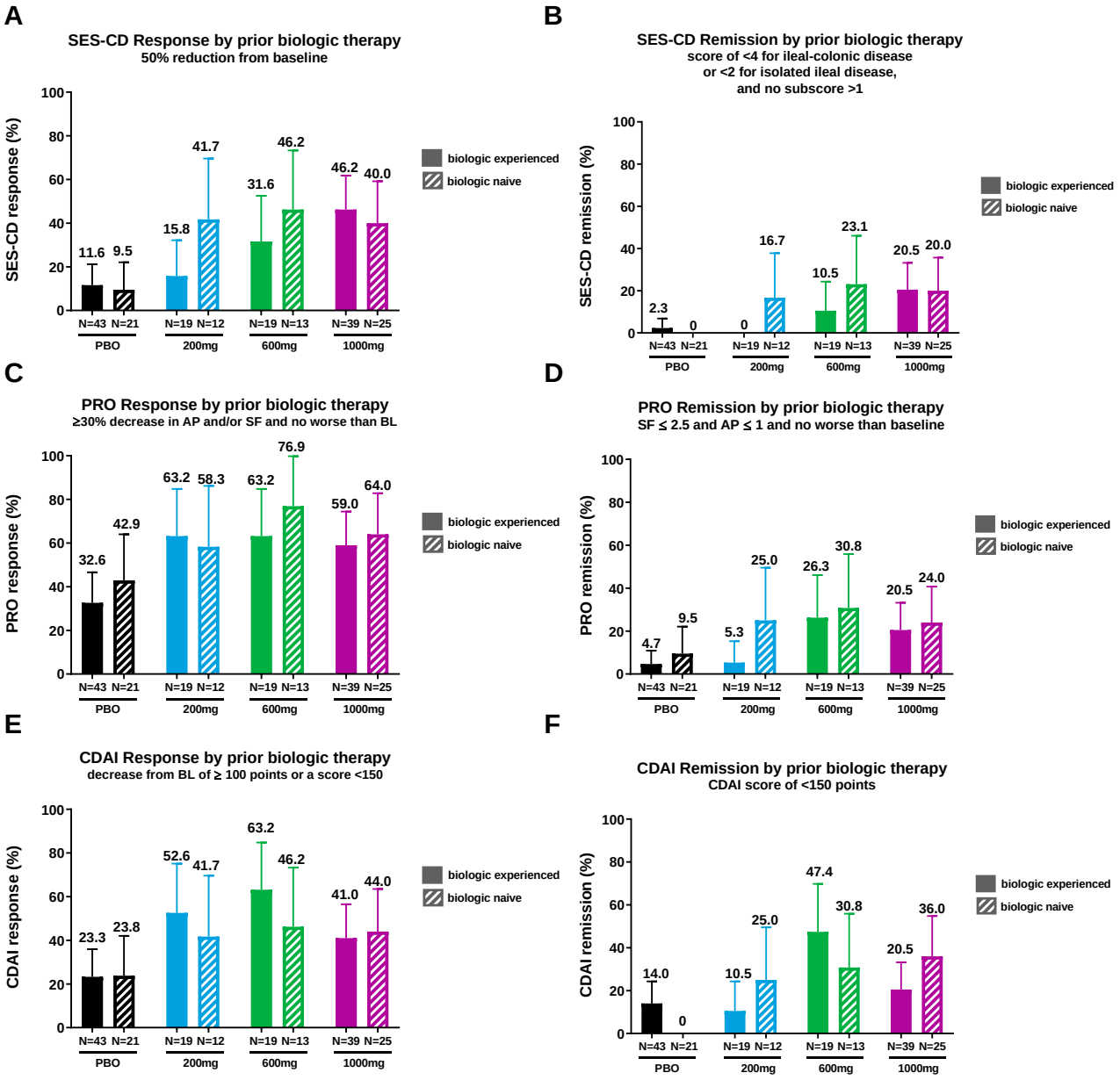
Such subjects must continue and complete appropriate latent TB therapy during the course of the study to remain eligible and must continue to meet all other inclusion and exclusion criteria for participation. Subjects who have a documented history of completing an appropriate TB prophylaxis regimen with no history of re-exposure since their treatments were completed and no evidence of active TB are eligible to participate in the study; these subjects should not undergo PPD testing. Subjects who have had household contact with a person with active TB must be excluded unless appropriate and documented prophylaxis for TB has been given, as described above. Subjects with any history of active TB are excluded from the study, regardless of previous or current TB treatments.

Supplemental Figures

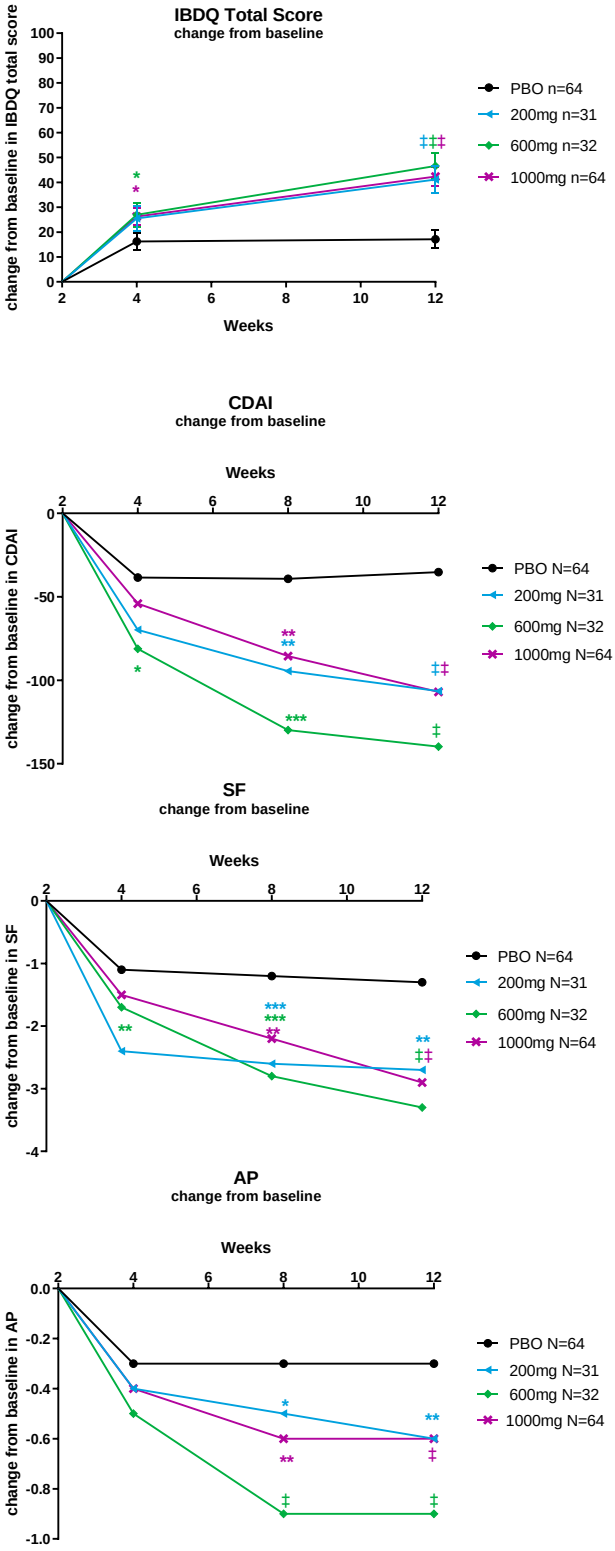
Supplemental Figure 1: CONSORT diagram



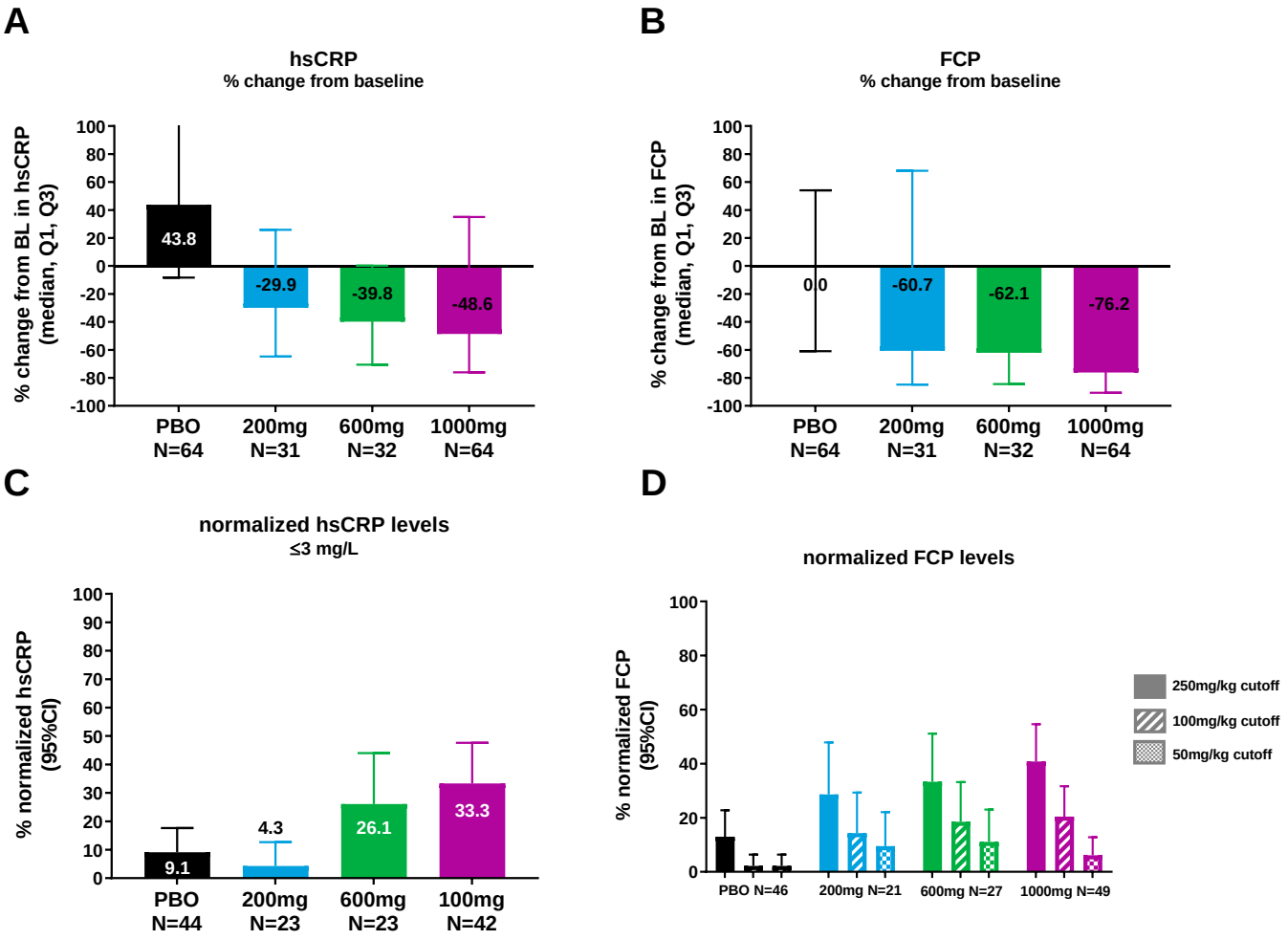
Supplemental Figure 2: Induction outcomes by biologic experience



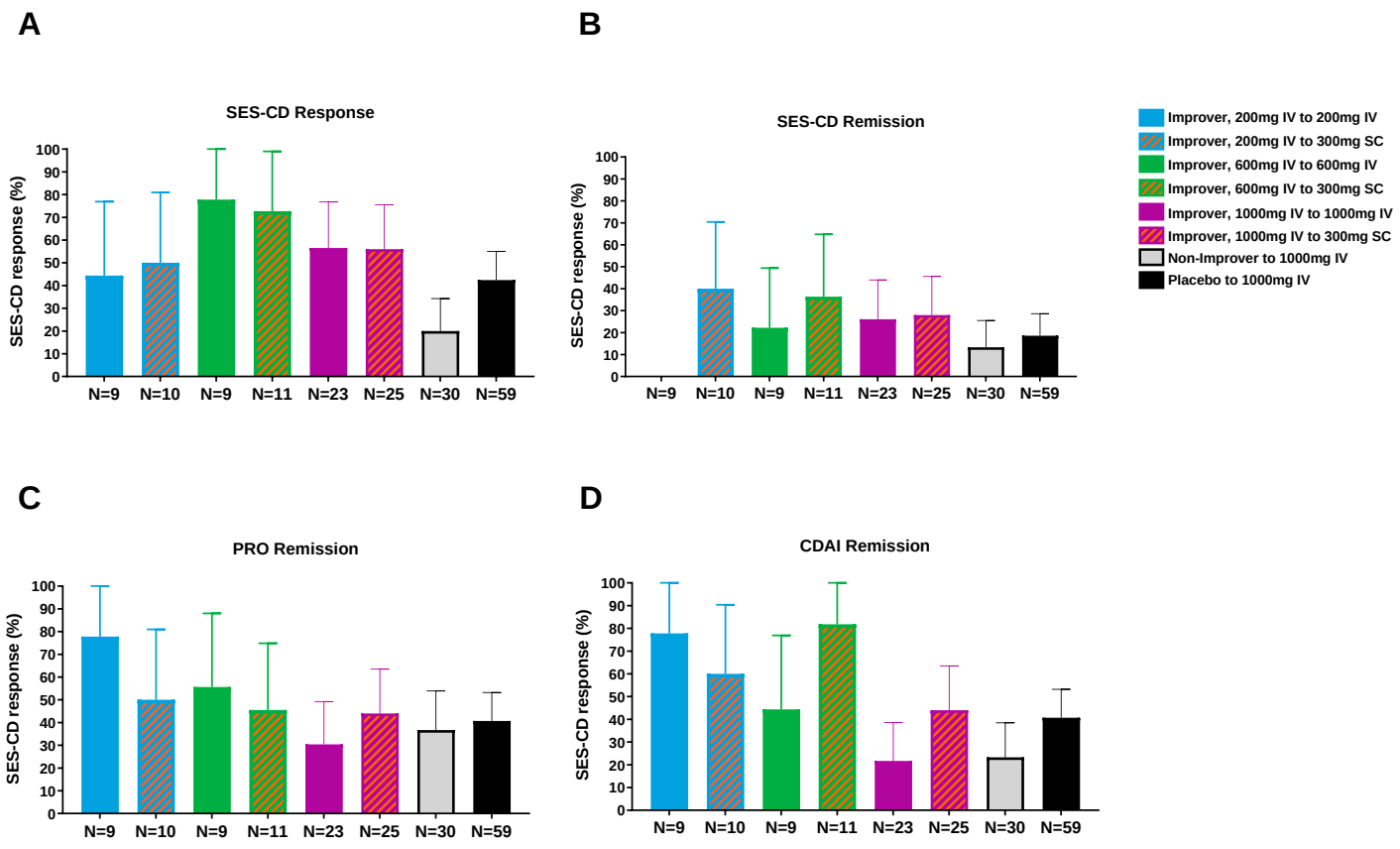
Supplemental Figure 3: Induction period IBDQ, CDAI, and PRO change from baseline. * p<0.1, ** p<0.05, *** p<0.01, ‡ p<0.001 vs placebo



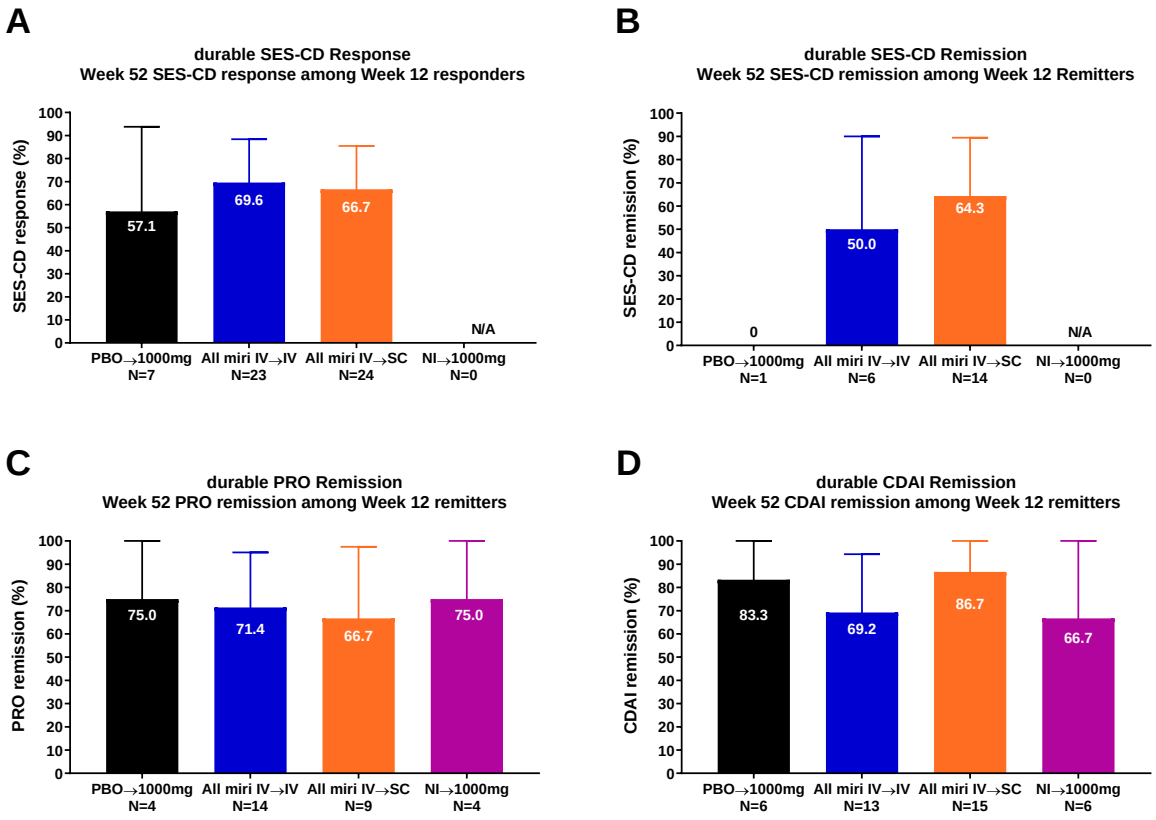
Supplemental Figure 4: Induction period biomarkers



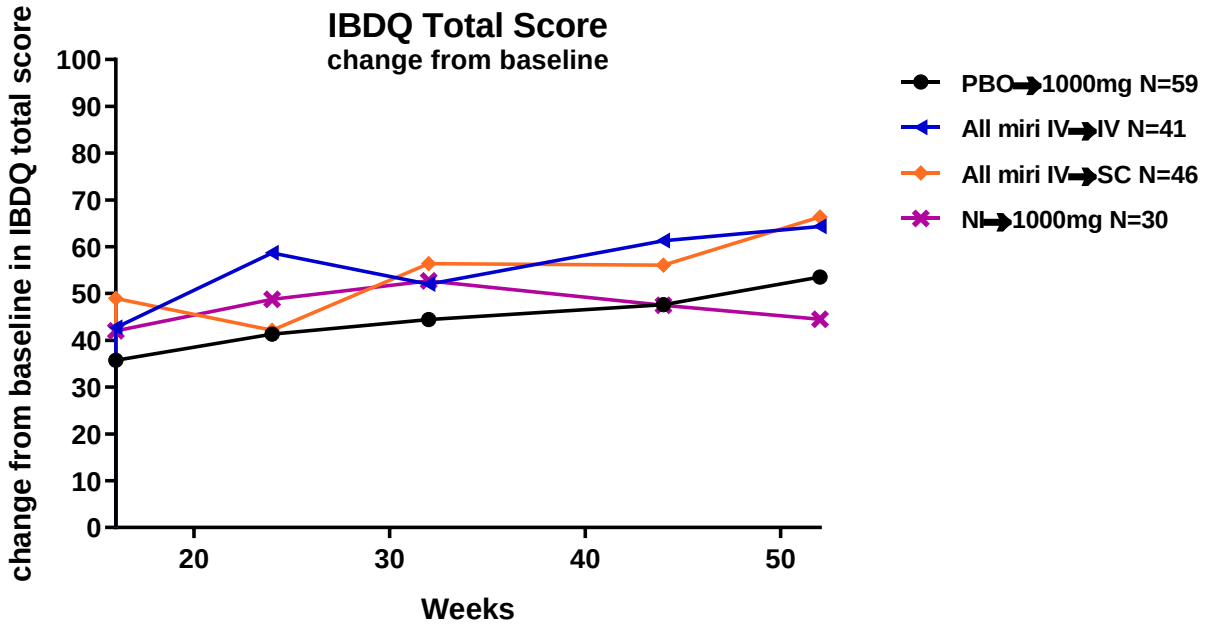
Supplemental Figure 5: Maintenance outcomes by dose



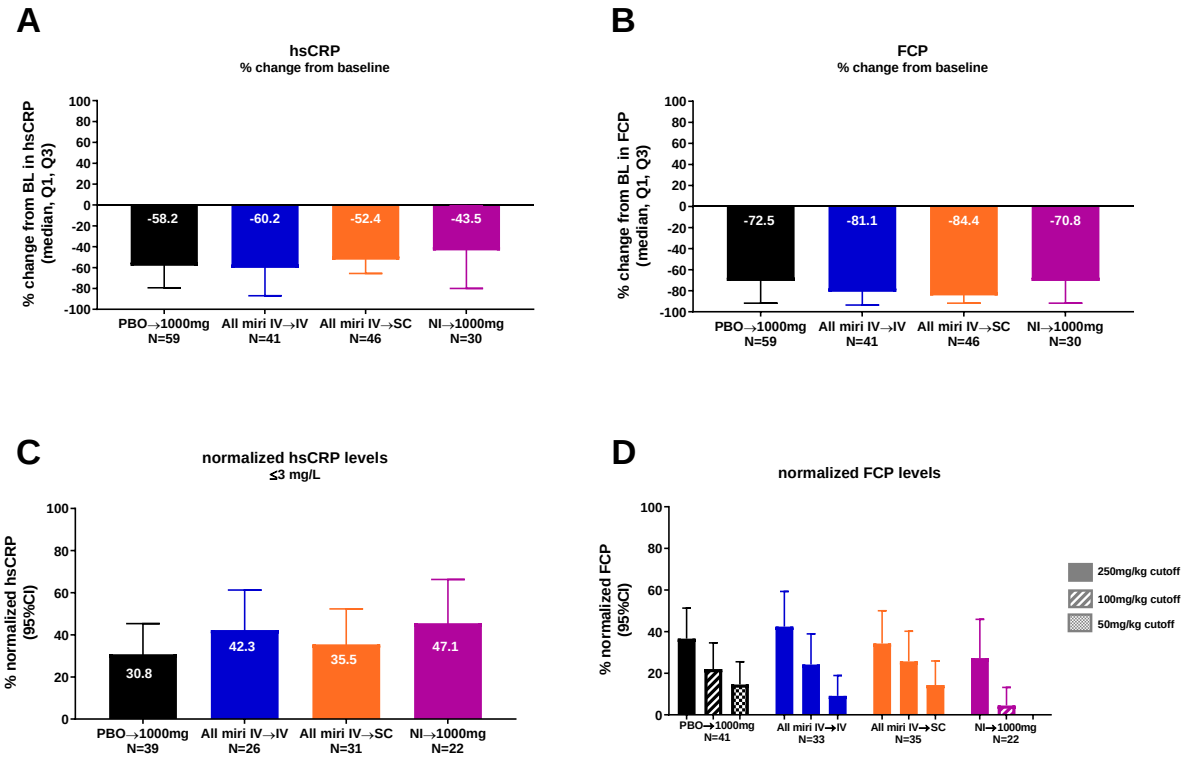
Supplemental Figure 6: Durability of response



Supplemental Figure 7: Maintenance period IBDQ change from baseline



Supplemental Figure 8: Maintenance period biomarkers



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