Inflammatory Bowel Diseases, 2025, **31**, 1876–1890
https://doi.org/10.1093/ibd/izae253
Advance access publication 25 October 2024
Original Research Article - Clinical

Three-Year Efficacy and Safety of Mirikizumab Following 152 Weeks of Continuous Treatment for Ulcerative Colitis: Results From the LUCENT-3 Open-Label Extension Study

Bruce E. Sands, MD,[*] Geert D'Haens, MD, PhD,[†] David B. Clemow, PhD,[‡] Peter M. Irving, MA, MD, FRCP,[§] Jordan T. Johns, PhD,[‡] Theresa Hunter Gibble, PhD,[‡] Maria T. Abreu, MD,[¶] Scott D. Lee, MD,[‖] Tadakazu Hisamatsu, MD, PhD,[**] Taku Kobayashi, MD, PhD,[††] Marla C. Dubinsky, MD,[‡‡] Severine Vermeire, MD, PhD,[§§] Corey A. Siegel, MD, MS,[¶¶] Laurent Peyrin-Biroulet, MD, PhD,[‖‖,*,†††] Richard E. Moses, DO, JD,[‡] Joe Milata, BSN, RN,[‡] Remo Panaccione, MD, FRCPC,[‡‡‡] and Axel Dignass, MD, PhD[§§§]**

[*]Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[†]Amsterdam University Medical Centers, Amsterdam, The Netherlands
[‡]Eli Lilly and Company, Indianapolis, IN, USA
[§]Guy's and St. Thomas' NHS Foundation Trust, London, King's College, London, UK
[¶]UHealth Crohn's and Colitis Center, University of Miami Miller School of Medicine, Miami, FL, USA
[‖]Digestive Health Center, University of Washington Medical Center, Seattle, WA, USA
[**]Department of Gastroenterology and Hepatology, Kyorin University School of Medicine, Tokyo, Japan
[††]Center for Advanced IBD Research and Treatment, Kitasato University, Kitasato Institute Hospital, Tokyo, Japan
[‡‡]Icahn School of Medicine at Mount Sinai, New York, NY, USA
[§§]Department of Gastroenterology and Hepatology, UZ Leuven, Leuven, Belgium
[¶¶]Dartmouth Hitchcock Medical Center, Lebanon, NH, USA
[‖‖]Department of Gastroenterology, INFINY Institute, FHU-CURE, INSERM NGERE, Nancy University Hospital, Nancy, France
[***]Groupe Hospitalier Privé Ambroise Paré–Hartmann, Paris IBD Center, Neuilly-sur-Seine, France
[†††]Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, Quebec, Canada
[‡‡‡]Inflammatory Bowel Disease Group, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[§§§]Department of Medicine I, Agaplesion Markus Krankenhaus, Frankfurt, Germany

Address correspondence to: David B. Clemow, PhD, Eli Lilly and Company, Lilly Corporate Center, 893 Delaware Street, Indianapolis, IN 46285, USA; Tel: +1 317-435-5307 (davidclemow@lilly.com).

Background: Mirikizumab, a p19-directed interleukin-23 monoclonal antibody, has demonstrated induction of clinical remission at week 12 with maintenance through week 104 in patients with moderately-to-severely active ulcerative colitis (UC). Results are presented from the LUCENT-3 open-label extension study through week 152.

Methods: Of 868 LUCENT clinical trial program mirikizumab-treated induction patients, 544 were responders of whom 365 were rerandomized to mirikizumab maintenance. Of these, 324 completed week 52 and 316 entered extension treatment (286 week 52 responders; 179 week 52 remitters). Efficacy and safety outcomes are reported for mirikizumab-treated LUCENT-3 participants, including biologic-failed patients, with data for week 52 maintenance responders/remitters. Discontinuations or missing data were handled by nonresponder imputation, modified nonresponder imputation (mNRI), and observed cases.

Results: Using mNRI, 81.6% of week 52 responders demonstrated clinical response at week 152. Week 152 remission rates for week 52 responders included clinical (56.1%), corticosteroid-free (CSF; 54.5%), endoscopic (61.0%), histologic-endoscopic mucosal remission (HEMR; 52.6%), symptomatic (74.9%), and bowel urgency (BU; 58.6%). At week 152, 53.3% of week 52 responders achieved histologic-endoscopic mucosal improvement (HEMI) and 74.3% achieved BU clinically meaningful improvement (CMI). Among week 52 remitters, 85.4% showed a clinical response at week 152, with clinical (70.1%), CSF (68.9%), endoscopic (72.0%), HEMR (63.4%), symptomatic (81.4%), and BU (60.8%) remission. At week 152, among week 52 remitters, 64.0% of patients achieved HEMI and 75.6% achieved BU CMI. Stool frequency, rectal bleeding, BU, and abdominal pain score reductions from induction baseline to maintenance week 52 were sustained through week 152 for week 52 completers. Overall, in the safety population, 74% of patients reported severe adverse events (AEs); 5.3% discontinued treatment due to AEs. AEs of special interest included opportunistic infection (1.8%), hepatic disorders (3.2%), cerebrocardiovascular events (1.5%), and malignancy (0.3%). Patients with antidrug antibodies reduced over time from 23.6% in year 1 to 3.2% in year 3.

Conclusions: Symptomatic, clinical, endoscopic, histologic, and quality-of-life outcomes support long-term sustained benefit of mirikizumab treatment up to 152 weeks in patients with UC, including biologic-failed patients, with no new safety concerns.

Clinical Trial Registry: ClinicalTrials.gov: NCT03518086; NCT03524092; NCT03519945.

Received for publication: July 19, 2024. Editorial Decision: October 10, 2024

Lay Summary

Long-term symptomatic, clinical response/remission, endoscopic, and histologic data from an open-label study of patients with moderately-to-severely active ulcerative colitis demonstrate that 3-year continuous treatment with mirikizumab maintained clinical remission in most induction clinical responders, regardless of previous biologic failure status.

Key Words: mirikizumab, ulcerative colitis, interleukin-23 p19 antibody, long-term extension, week 152 results

Key Messages

What is already known?

Mirikizumab, a p19-directed interleukin-23 monoclonal antibody, is effective at 12 weeks of induction with maintenance through 52 and 104 weeks in patients with moderately-to-severely active ulcerative colitis (UC).

What is new here?

Long-term treatment with mirikizumab up to 152 weeks is associated with sustained and durable effects on symptomatic, clinical response/remission, endoscopic, histologic, and quality-of-life outcomes in patients with and without previous biological therapy failure.

How can this study help patient care?

This study provides long-term (3-year) data for mirikizumab, informing benefit-risk decisions when prescribing this new biologic to patients with moderately-to-severely active UC.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition affecting the colon and rectum, causing recurring symptoms that negatively impact patients' quality of life.[1] Treatment objectives include managing symptoms, inducing response, and maintaining remission, with the ultimate aim of endoscopic remission to minimize disease-related disability and enhance quality of life.[1,2] Despite the availability of various medication classes, including corticosteroids, immunosuppressants, 5-aminosalicylates, sphingosine-1 phosphate modulators, Janus kinase inhibitors, and biologics, patients with moderately-to-severely active UC often face limited treatment success.[3]

Up to one-third of patients do not exhibit an initial response to treatment, and about 40% of those who initially respond may later experience a loss of response.[4] Consequently, despite the availability of numerous treatment avenues for inflammatory bowel disease (IBD), there persists a significant gap in meeting the demand for novel therapeutic approaches that provide and maintain efficacy.[4]

Achieving optimal outcomes for all patients with UC remains challenging,[5–7] with many experiencing ongoing physical and psychological distress, sometimes necessitating surgical intervention like restorative proctocolectomy.[8] Key objectives to achieve the best possible long-term outcomes not only include control of clinical symptoms but also mucosal healing determined by histologic-endoscopic mucosal remission (HEMR).[9] Major unmet needs include corticosteroid-free remission, bowel urgency (BU) remission, and overall improvement in the quality of life.

Interleukin-23 (IL-23) plays a pivotal role in UC pathogenesis by promoting a specific Th17 cell-based immune response.[1] Mirikizumab, an IL-23 specific blocker targeting the p19 subunit, represents a novel therapeutic approach for patients with UC, including those with UC refractory to conventional treatments. Mirikizumab, a humanized monoclonal antibody, is the first approved antibody therapy in its class for UC. Previous studies have demonstrated the induction and maintenance efficacy of mirikizumab in patients with moderately-to-severely active UC.[10–12]

Here, we present data from LUCENT-3, an ongoing study assessing the long-term effectiveness and safety of mirikizumab over 152 weeks of continuous treatment in UC patients.

Methods

Study Oversight

All patients provided informed consent. The protocol, amendments, and consent documentation were approved by local ethical review boards. The study was registered at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, including Good Clinical Practices and Good Pharmacoepidemiology Practices.[9,13] An independent data monitoring committee monitored LUCENT-1, LUCENT-2, and LUCENT-3. The trials were registered at Clinical Trials.gov: NCT03518086, NCT03524092, and NCT03519945, respectively.

Study Design

The study design and treatment protocols of the 12-week LUCENT-1 induction study, 40-week LUCENT-2 maintenance study, and current LUCENT-3 long-term extension study have been previously described.[9,10] LUCENT-3 is an ongoing single-arm, open-label, phase 3, multicenter, long-term extension study evaluating the efficacy and safety of mirikizumab in patients with moderately-to-severely active UC who participated in the LUCENT-1 induction study and LUCENT-2 maintenance study (Supplementary Figure 1). Efficacy and safety data from the first 52 weeks of LUCENT-3 (104 weeks of continuous treatment) have been previously disclosed.[9] In LUCENT-1, patients received mirikizumab 300 mg intravenously (IV) at weeks 0, 4, and 8. In LUCENT-2, mirikizumab induction responders received 200 mg every 4 weeks subcutaneously from weeks 12 (week 0 of maintenance) to 52. From week 12, induction nonresponders received extended induction with mirikizumab 300 mg IV at weeks 12, 16, and 20; extended induction responders received an additional 200 mg mirikizumab every 4 weeks subcutaneously from week 24 (week 12 of maintenance). Mirikizumab induction responders who experienced a loss of treatment response received reinduction, with 3 doses of mirikizumab 300 mg IV every 4 weeks, after which patients who demonstrated benefit from therapy based on the investigator's opinion were

returned to 200 mg mirikizumab every 4 weeks subcutaneously by entering LUCENT-3 (reinduction responders). In LUCENT-3, all patients received 200 mg mirikizumab every 4 weeks subcutaneously. Other patient cohorts included in the LUCENT studies not currently discussed have been previously described.[10–12] Examination of the extended induction and loss of response cohorts for 3-year data will be examined in a separate publication; the 2-year results are already published.[9]

The key inclusion criterion for LUCENT-3 was patients from the phase 3 maintenance study LUCENT-2 who completed the week 52 (week 40 in LUCENT-2) visit on blinded subcutaneous therapy and, per investigator opinion, would benefit from continuing treatment with mirikizumab in LUCENT-3. Weeks are shown as cumulative; week 12 of LUCENT-2 is defined as week 24 overall, such that week 40 in LUCENT-2 is equivalent to 52 weeks of continuous treatment, and week 52 and week 100 in LUCENT-3 are equivalent to 104 weeks and 152 weeks, respectively, of continuous treatment.

Rescue treatment for loss of response could not be administered until the patient received at least 12 weeks of blinded maintenance therapy, and these patients rolled over into LUCENT-3 directly after reinduction treatment. These patients received 12 weeks of treatment in LUCENT-1 (induction), at least 12 weeks of treatment in LUCENT-2 (maintenance), and 12 weeks of reinduction treatment in LUCENT-2, constituting a minimum of 36 weeks of mirikizumab in LUCENT-1 and LUCENT-2 before entering LUCENT-3. Thus, loss of response rescue patients had at least 88 weeks or at least 136 weeks of continuous treatment when assessed at week 52 and week 100 of LUCENT-3, respectively.

Patient Groups

Of the modified intent-to-treat population (N = 1162), in the LUCENT clinical program, 868 patients were randomized to receive mirikizumab induction treatment in LUCENT-1. Of these patients, 816 entered the LUCENT-2 maintenance study: 544 entered as mirikizumab induction responders and 272 as mirikizumab induction nonresponders who at first received extended induction treatment. Among the mirikizumab induction responders, 365 were rerandomized to continue mirikizumab treatment maintenance therapy, and 324 completed 52 weeks of treatment. Among the mirikizumab induction nonresponders, 134 were delayed responders and completed 52 weeks of treatment.

Among the LUCENT-2 week 52 completers that entered into LUCENT-3 and were eligible for the LUCENT-3 database lock at week 52 (104 weeks of continuous treatment), 266 mirikizumab induction responders were included in the week 104 analyses.[9] For the week 104 analyses, 50 mirikizumab induction responders were not included because the protocol addendum allowing for interim database locks was not approved in time at the associated study sites. Therefore, data for these patients are included in the current analyses. Thus, 316 LUCENT-2 week 52 completers entered into LUCENT-3 and were eligible for the current LUCENT-3 database lock and associated interim analyses at week 100 (152 weeks of continuous treatment).

Several populations are relevant for the current analyses:

- *Induction responders*: LUCENT-1 induction week 12 mirikizumab induction responders at week 12 who continued blinded mirikizumab treatment during LUCENT-2 maintenance and continued to LUCENT-3; main analysis cohort (blinded maintenance completers);
- *Maintenance remitters*: Induction responders who were subsequently clinical remitters in LUCENT-2 at week 40 (week 52 of continuous mirikizumab treatment);
- *Maintenance responders*: Induction responders who were subsequently clinical responders in LUCENT-2 at week 40 (week 52 of continuous mirikizumab treatment);
- *Modified intent-to-treat population:* All patients who received any study treatment during this study; excluding patients impacted by an electronic clinical outcome assessment transcription error in Poland and Turkey,[10] regardless of whether the patient received the correct treatment, or did not otherwise follow the protocol;
- *Safety population*: All patients who received any amount of study treatment, regardless of whether the patient received the correct treatment or did not otherwise follow the protocol; and
- Induction baseline biologic-failed and not biologic-failed subgroups were also analyzed:
- *Biologic failed*: Patients with a prior inadequate response, loss of response, or intolerance to biologic therapy or Janus kinase inhibitors (tofacitinib) as of LUCENT-1 induction baseline; and
- *Not biologic failed:* Patients who did not meet the biologic failed definition for whom, however, a conventional therapy such as immunomodulators or corticosteroids had failed as of LUCENT-1 induction baseline.

Not all patients met the responder or remitter definition at their last visit assessment in LUCENT-2. Thus, the maintenance responder and maintenance remitter subgroups are considered subsets of the induction responder population when moved into LUCENT-3. For patients included in the LUCENT-3 analyses at week 100 (week 152 continuous treatment), only 30 of 316 induction responders did not meet the response criteria at LUCENT-2 week 40 (week 52 of continuous treatment).

No patients who received a placebo, whether directly from LUCENT-2 or in the induction responder population randomly assigned to receive a placebo in LUCENT-2, were included in the analysis.

Outcome Measures

The primary endpoints and major secondary endpoints for LUCENT-1 and LUCENT-2 have been previously reported.[10] Endpoints associated with the current analyses are as follows:

- *Abdominal pain ≥30% improvement*: ≥30% change from baseline in the Abdominal Pain Numeric Rating Scale (NRS) score in patients with Abdominal Pain NRS score ≥3 at baseline;
- *Abdominal pain severity*: Change in the Abdominal Pain NRS score from induction baseline;
- *Alternate clinical remission*: Stool frequency (SF) = 0 or SF = 1, rectal bleeding (RB) = 0, and endoscopic subscore (ES) = 0 or 1 (excluding friability);
- *BU clinically meaningful improvement (CMI):* Decrease from baseline in the Urgency NRS score ≥ 3 in patients with an Urgency NRS ≥ 3 at induction baseline[14];
- *BU remission*: Urgency NRS = 0 or 1;

- *BU severity*: Change in Urgency NRS score from induction baseline;
- *Clinical remission*: SF = 0 or 1 with ≥1-point decrease in modified Mayo score (MMS) from baseline, RB = 0, and ES = 0 or 1 (excluding friability);
- *Clinical response*: ≥2-point and ≥30% decrease in the MMS from baseline, RB = 0 or 1, or RB ≥ 1-point decrease from baseline;
- *Corticosteroid-free remission*: Clinical remission with no corticosteroid use for ≥12 weeks;
- *Endoscopic remission*: ES = 0 or 1 (excluding friability);
- *Histologic-endoscopic mucosal improvement (HEMI):* Geboes score ≤ 3.1 and ES = 0 or 1 (excluding friability); histologic improvement, defined using Geboes scoring system with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue;
- *HEMR:* Geboes score ≤ 2B.0 and ES = 0 or 1 (excluding friability); histologic remission with resolution of neutrophils, defined using Geboes scoring of ≤2B.0; Geboes subscores of 0 for grades: 2B (lamina propria neutrophils), 3 (neutrophils in epithelium), 4 (crypt destruction), and 5 (erosion or ulceration);
- *Inflammatory Bowel Disease Questionnaire (IBDQ) remission*: IBDQ total score ≥170[15];
- *IBDQ response*: ≥16-point improvement from baseline[15];
- *IBDQ severity*: Change in IBDQ total score and domain scores (bowel symptoms, emotional function, social function, and systematic symptoms) from induction baseline;
- *Rectal bleeding severity*: Change in RB MMS subscore from induction baseline;
- *Stool frequency severity*: Change in SF MMS subscore from induction baseline; and
- *Symptomatic remission*: SF = 0 or SF = 1 with ≥1-point decrease in MMS from baseline, RB = 0.

The baseline for the current analyses was defined as the induction baseline from LUCENT-1.

Stool frequency and RB were measured as subscores from the MMS. Based upon the MMS-based definitions of clinical response and clinical remission used for the LUCENT clinical development program, an SF of ≥1 on the 0-3 subscore and an RB score of ≥1 on the 0-3 subscore were chosen to define clinically meaningful changes from baseline.[10] For abdominal pain, in alignment with what has been designated for irritable bowel syndrome and previously for UC,[10,16] a ≥3-point change on the 0 to 10-point Abdominal Pain NRS or a ≥30% change from baseline was chosen to denote a CMI.

For maintenance outcome analyses, only the patients who met the endpoint at week 52 (week 40 LUCENT-2) were included in the analyses to ascertain durable maintenance of that endpoint from 52 to 152 weeks of treatment.

Antidrug Antibody Assessment

Venous blood samples were taken to assess antidrug antibodies (ADAs) against mirikizumab at baseline of LUCENT-1 and approximately monthly through the LUCENT-1 and LUCENT-2 studies and at weeks 12, 24, 52, 76, 100, 124, and 148 in LUCENT-3. ADA were detected using a validated, drug-tolerant up-front acid treatment affinity capture elution bridge electrochemiluminescence assay on a MesoScale Discovery platform. The assay had a sensitivity of 3.0 ng/mL and drug tolerance of 229 ug/mL mirikizumab at 100 ng/mL of ADA. All treated patients with a baseline ADA sample and at least one postbaseline ADA sample were evaluated for treatment-emergent ADA (ADA+). A participant was considered ADA+ if either the participant had no ADA detected at baseline and at least 1 postbaseline titer of 1:20 (twice the minimum required dilution of the assay) or greater or had ADA detected at baseline and at least 1 postbaseline titer of 4 times (2 dilutions) greater than the baseline titer.

Statistical Analyses

Endpoints are summarized using descriptive statistics. Categorical efficacy endpoints are summarized using proportions and confidence intervals. Where confidence intervals are calculated, the Wilson Score method was used,[17,18] unless otherwise specified. Continuous efficacy endpoints are summarized using mean change from the LUCENT-1 study induction baseline with standard deviation. The modified intent-to-treat population at the indicated time point was used to perform efficacy analyses. Safety summaries are provided for the safety population and include events or results during week 52 to week 152 (weeks 0 to 100 of LUCENT-3) of treatment.

Missing Data Handling

Approximately 25% of patients in the mITT population had missing data at week 152 of LUCENT-3 due to early discontinuation or being sporadically missing (missing at random). For full details, see the Supplemental Content on Missing Data Handling and the Importance of Data Interpretation Based Upon Analytical Method for the previously published LUCENT-3 week 52 (104 weeks of continuous treatment) data.[9]

For symptom efficacy analyses, missing data were primarily from patient diaries. Ten patients in the maintenance responders had missing endoscopies and 40 patients discontinued early. Sporadic missingness is defined as missing data needed to assess the endpoint due to reasons other than treatment discontinuation, such as insufficient days of diary data, or missing an endoscopy. For all patients with sporadically missing observations before discontinuation, the last non-missing observation before the sporadically missing observation was carried forward to the corresponding visit. The safety population for induction responders includes individuals impacted by the electronic clinical outcome assessment transcription error in Poland and Turkey (N = 23).[10]

Nonresponder imputation (NRI) was prespecified as the primary approach to handle missing data for all categorical or binary endpoints, and patients who discontinued treatment or were missing endpoint assessments were treated as nonresponders. NRI is a conservative analytical approach and can be biased to show low remission/response rates. For continuous efficacy variables over time, a mixed-effects model for repeated measures was used to estimate the mean change from baseline. The visit was the only additional variable added to the model. For continuous measures at a single time point, modified baseline observation carried forward was applied in the case of missing data. For patients who discontinued mirikizumab due to an adverse event (AE), the baseline observation for the endpoint was carried forward to the corresponding visit for all missing observations after the

patient discontinued study treatment. For patients who discontinued mirikizumab for any other reason, the last nonmissing postbaseline observation before discontinuation was carried forward to the corresponding visit for all missing observations. Patients without at least 1 postbaseline observation were not included in the evaluation.

Observed case (OC) analyses were performed as secondary analyses for categorical data, where patients with missing data were not included and missing data were not imputed. Observed case analyses can be biased to show high remission/response rates.

As such, modified NRI (mNRI) was applied; mNRI includes multiple imputation[19] and is a balance between NRI and OC analyses because it counts treatment discontinuation as nonresponse but addresses sporadic missing data. For mNRI, for patients who discontinued treatment for any reason other than commercial availability of mirikizumab or geopolitical restrictions, NRI was used to impute the missing data. For patients with sporadic missing data or discontinuing due to commercial availability of mirikizumab or geopolitical restrictions, multiple imputation was used. Multiple imputation uses logistic regression to make multiple predictions of the missing values and obtains multiple estimations for each of these predictions, providing an imputation value. The percentage of response and the confidence intervals are calculated using the Rubin rules[19] to combine multiple imputation datasets. As multiple imputation uses multiple estimates, there is no end result of the number of patients in the analyses, but rather the estimated proportion responding using the modeling.

Results

Baseline Demographics and Disease Characteristics

Baseline demographics for the induction responder population, maintenance completers, maintenance responders, and maintenance remitters were generally similar (Supplementary Table 1).

Efficacy

Clinical endpoint outcomes

Using NRI, 71.6% of week 52 mirikizumab responders ($N = 285$) demonstrated clinical response at week 152 (Figure 1). Supplementary Figure 2 provides additional data for week 52 mirikizumab responders and data for week 52 remitters ($N = 179$). For corticosteroid-free remission analyses, it is important to note that 33.6% of mirikizumab responders were on corticosteroids at baseline; 21.3% were on immunomodulators (Supplementary Table 1). Importantly, 97% (137/141) of LUCENT-2 week 52 responders who achieved clinical remission in LUCENT-3 after 3 years of treatment with mirikizumab were corticosteroid-free for at least the previous 12 weeks; for week 52 remitters it was 98% (106/108). Remission rates at week 152 for week 52 clinical responders were 49.5% clinical, 48.1% corticosteroid-free, 59.1% endoscopic, 49.3% HEMR, 66.3% symptomatic, and 51.6% BU (Figures 1 and 2). Week 52 responders achieving HEMI and BU CMI at week 152 were 50.3% and 65.4%, respectively (Figure 2). Biologic-failed and not biologic-failed subgroup data were generally similar, with differences of 10% to 16% depending upon the endpoint (Figure 3; Supplementary Figure 2).

Using mNRI, among week 52 mirikizumab responders, 81.6% demonstrated clinical response, and 56.1% demonstrated clinical remission at week 152 (Figure 1). For week 52 mirikizumab remitters, 85.4% demonstrated clinical response, and 70.1% demonstrated clinical remission at week 152 (Figure 1). Figures 2 and 3 show efficacy endpoint data for week 52 mirikizumab responders and remitters, providing endpoint outcomes for NRI, mNRI, and OC analyses.

Maintenance of outcomes

Figure 1 shows durable maintenance at week 152 (LUCENT-3) for clinical response (responders at week 52) and clinical remission (remitters at week 52) using NRI, mNRI, and OC methods. Using mNRI, 81.6% of patients maintained clinical response, and 70.1% maintained clinical remission. Supplementary Figure 3 shows that 69.6% of patients maintained symptomatic remission, 62.8% maintained HEMR, and 66.9% maintained BU remission. For mNRI at week 152 (LUCENT-3), 81.6% of patients maintained clinical response, and 70.1% maintained clinical remission. Biologic-failed and not biologic-failed patients had generally similar results to the overall population as shown in Supplementary Figure 4, which shows NRI data.

Symptom Scores Over Time

Patients treated with mirikizumab for 52 weeks (LUCENT-2, week 40) who continued mirikizumab treatment in LUCENT-3 for an additional 100 weeks demonstrated a sustained CMI in symptom score reduction for BU, SF, RB (Figure 4), and abdominal pain (Supplementary Figure 5) from induction baseline (LUCENT-1, week 0 on continuous treatment) through week 152 of LUCENT-3. Supplementary Figure 5 provides a change from baseline in abdominal pain for weeks 104 through 152 in LUCENT-3, as the data were not available for LUCENT-1 and LUCENT-2.

A change from a baseline of ≥3 on the Urgency NRS 0 to 10 scale is a CMI,[14] and mirikizumab responders had a ≥3 change that was maintained through week 152. Mirikizumab responders had a change of ≥1 for both SF and RB that was maintained through week 152, suggesting maintained clinically meaningful symptom control.

Clinical Endpoint Scores Over Time

Figure 5 provides remission rates at weeks 12, 52, 104, and 152 for symptomatic remission, clinical response, clinical remission, and endoscopic remission to demonstrate sustained efficacy over time. Supplementary Figure 6 shows the proportion of patients achieving ≥30% improvement in abdominal pain from LUCENT-1 week 0 through LUCENT-3 week 152. Supplementary Figure 7 shows BU remission rates over time. These data demonstrate the maintenance of effect over time.

Quality-of-Life Outcomes

Using NRI, least squares mean improvements from the induction baseline in IBDQ total and domain scores were sustained at week 152, with LUCENT-2 clinical responders or remitters achieving over a 59-point improvement in the IBDQ total score (Supplementary Figure 8). Improvements in IBDQ scores were seen across all IBDQ domains: bowel symptoms, emotional function, social function, and systemic symptoms. IBDQ response at week 152 was seen in over 78.0% of patients and was comparable across biologic failure

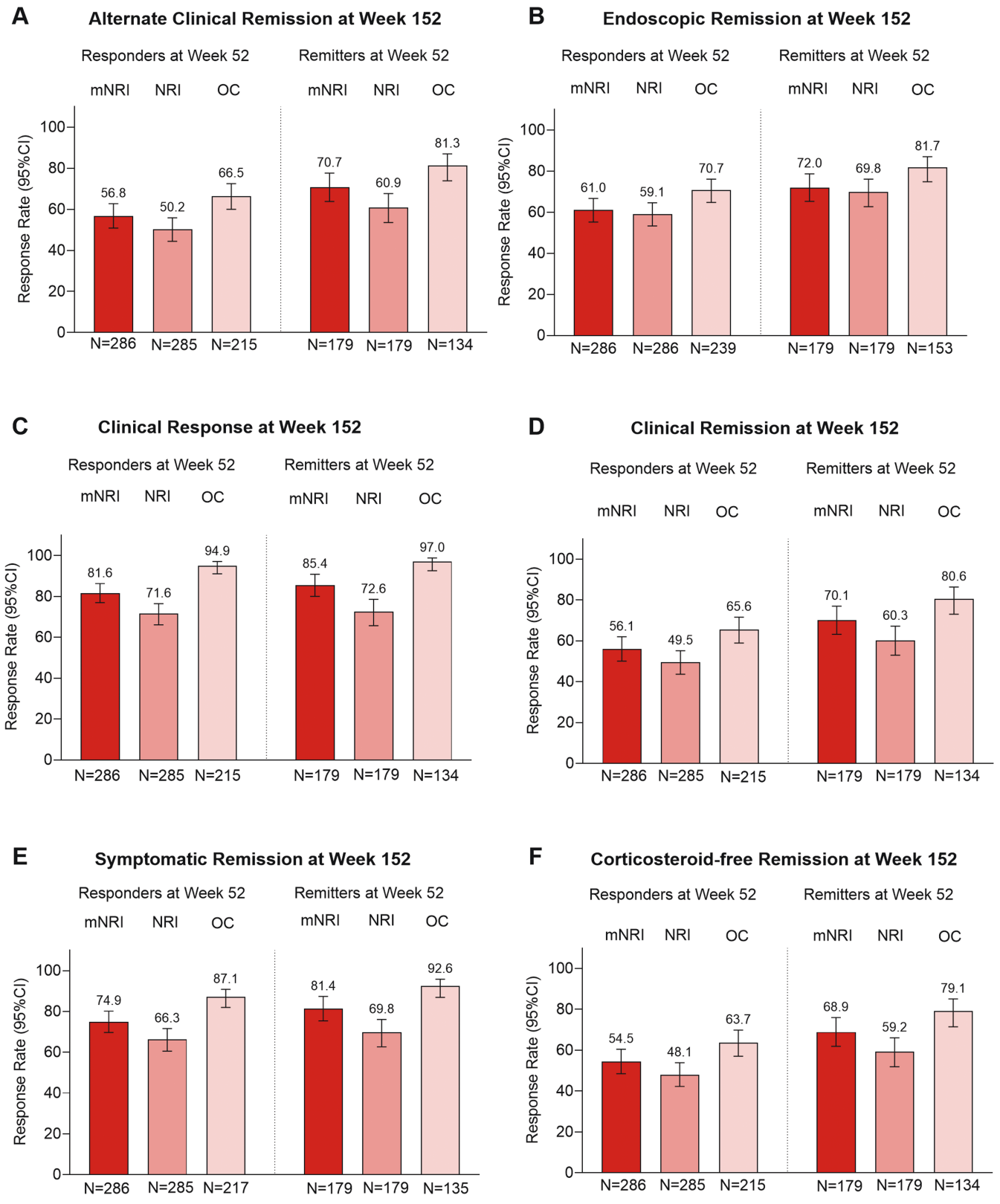

Figure 1. LUCENT-3 rates at 152 weeks of continuous treatment in LUCENT-2 week 52 responders and remitters for (A) alternate clinical remission, (B) endoscopic remission, (C) clinical response, (D) clinical remission, (E) symptomatic remission, and (F) corticosteroid-free remission (nonresponder imputation [NRI], modified NRI [mNRI], observed case [OC]). The modified intention-to-treat population was used with NRI, mNRI, and OC methods for missing data. Responders: ≥30% and 2-point decrease from baseline in the composite clinical endpoint of the sum of endoscopic subscore (ES), stool frequency (SF) subscore, and rectal bleeding (RB) subscore, and RB of 0 or 1, or a ≥1-point decrease from baseline. Remitters: modified Mayo score (MMS) SF of 0 or SF of 1 with a ≥1-point decrease from baseline; RB of 0; and ES of 0 or 1. Symptomatic remission: SF of 0 or SF of 1 with a ≥1-point decrease in MMS from baseline; and RB of 0. Corticosteroid-free remission: clinical remission with no corticosteroid use for ≥12 weeks. Alternate clinical remission: SF of 0 or 1; RB of 0; and ES of 0 or 1 (excluding friability). Endoscopic remission: ES of 0 or 1 (excluding friability). Abbreviations: CI, confidence interval.

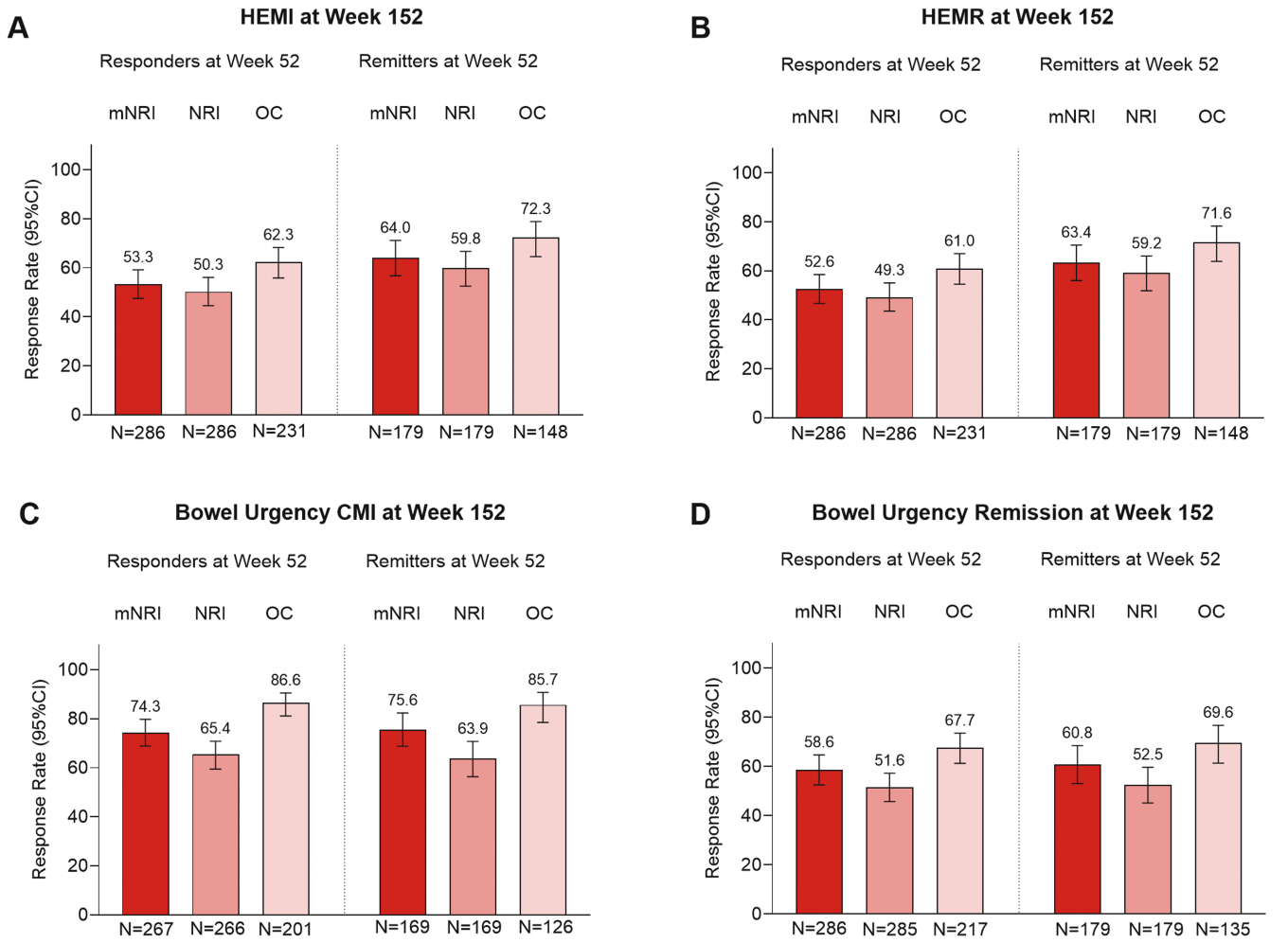

Figure 2. LUCENT-3 rates at 152 weeks of continuous treatment in LUCENT-2 week 52 responders and remitters for (A) histologic-endoscopic mucosal improvement (HEMI), (B) histologic-endoscopic mucosal remission (HEMR), (C) bowel urgency (BU) clinically meaningful improvement (CMI), and (D) BU remission (nonresponder imputation [NRI], modified NRI [mNRI], observed case [OC]). The modified intention-to-treat population was used with NRI, mNRI, and OC methods for missing data. Responders: ≥30% and 2-point decrease from baseline in the composite clinical endpoint of the sum of endoscopic subscore (ES), stool frequency (SF) subscore, and rectal bleeding (RB) subscore, and RB of 0 or 1, or a ≥1-point decrease from baseline. Remitters: modified Mayo score (MMS) SF of 0 or SF of 1 with a ≥1-point decrease from baseline; RB of 0; and ES of 0 or 1. Bowel urgency remission: Urgency Numeric Rating Scale (NRS) score of 0 or 1. CMI: change from baseline in Urgency NRS score ≥ 3 in patients with Urgency NRS score ≥ 3 at induction baseline. HEMI: Geboes score ≤ 3.1 and ES of 0 or 1 (excluding friability). HEMR: Geboes score ≤ 2B.0 and ES of 0 or 1 (excluding friability). Abbreviations: CI, confidence interval.

status subgroups. IBDQ remission rates in clinical responders (76.9%) and clinical remitters (79.3%) were sustained in patients regardless of whether they were in the biologic-failed or not biologic-failed subgroups.

Using NRI, among the 286 patients with clinical response at 52 weeks, 223 (78%) achieved IBDQ response, and 220 (76.9%) patients achieved IBDQ remission at week 152. Of the 179 patients with clinical remission at week 52, 142 (79.3%) achieved IBDQ response and IBDQ remission at week 152.

Antidrug Antibodies

The impact of ADA+ was evaluated over the entire course of the LUCENT clinical trial program: LUCENT-1 induction (weeks 0-12), LUCENT-2 maintenance (weeks 12-52), and LUCENT-3 extension (weeks 52-152).

For the first 52 weeks of treatment, 23.6% (90/382) of mirikizumab-treated patients had ADA+, and 8.9% (34/382) had ADA+ titers ≥1:160. Less than 2% (6/360) of patients treated with mirikizumab had antibody titer ≥1:160 associated with lower trough mirikizumab concentrations (<0.511 µg/mL, 5th percentile) and a reduced clinical response, which was defined as clinical response observed at Week 12 but not observed at week 52.

During LUCENT-3 extension treatment, 2/312 (0.6%) developed ADA after not having had ADA during the induction and maintenance treatment periods. Figure 6 demonstrates that patients with ADA+ generally had titers reach a maximum during their initial 52 weeks of treatment followed by a decrease through the remainder of the clinical program such that they had low titers or undetected ADA during their third year of treatment. During the third year, only 3.4% (10/293) of patients had ADA+ and only 1.0% (3/293) with an ADA+ ≥1:160 titer.

Supplementary Table 2 shows the proportion of patients achieving various efficacy endpoints at week 152 by ADA+

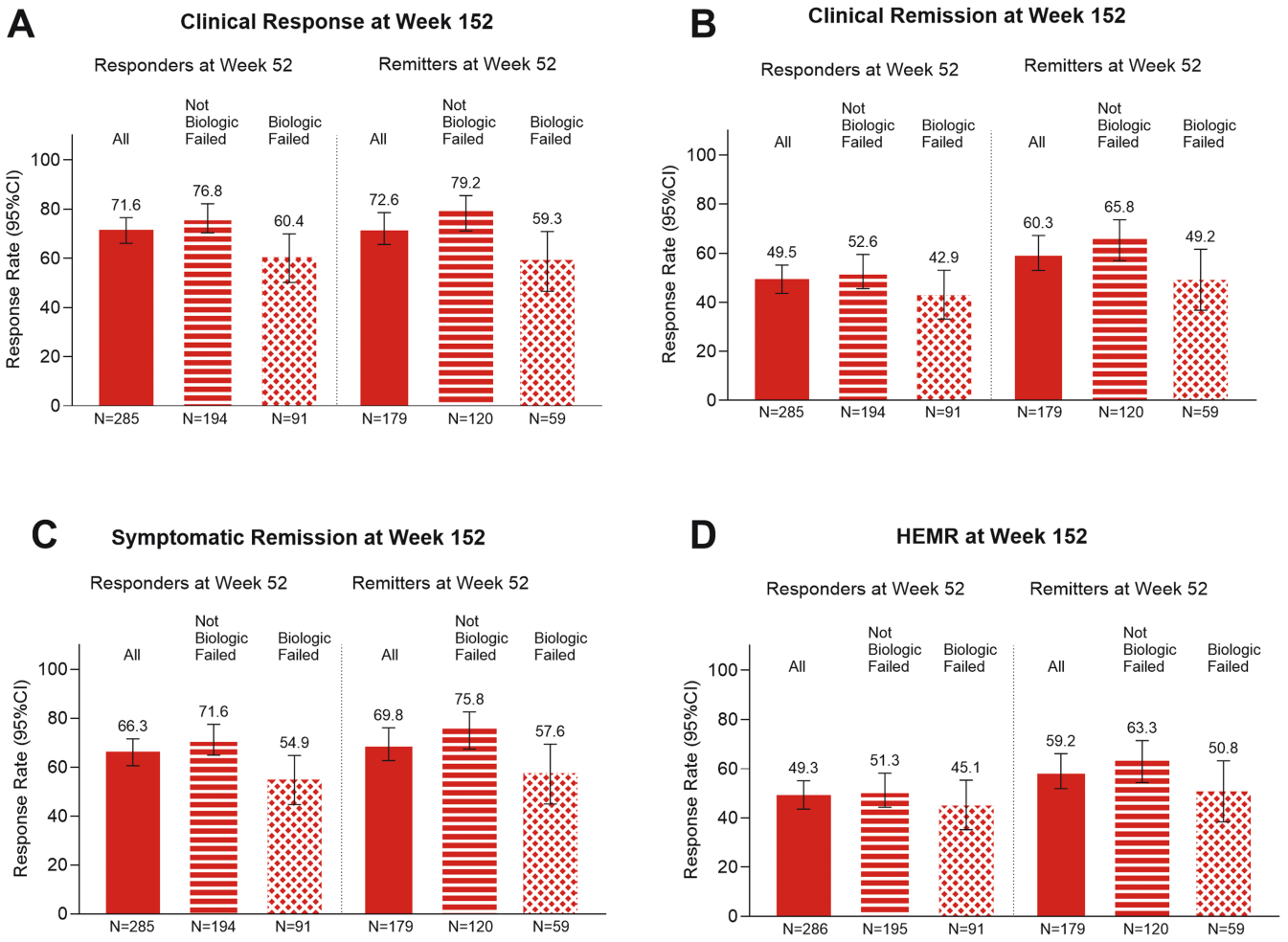

Figure 3. LUCENT-3 rates at 152 weeks of continuous treatment in LUCENT-2 week 52 responders and remitters by biologic-failed and not biologic-failed treatment status for (A) clinical response, (B) clinical remission, (C) symptomatic remission, and (D) histologic-endoscopic mucosal remission (HEMR; nonresponder imputation). The modified intention-to-treat population was used with nonresponder imputation methods for missing data. Responders: ≥30% and 2-point decrease from baseline in the composite clinical endpoint of the sum of endoscopic subscore (ES), stool frequency (SF) subscore, and rectal bleeding (RB) subscore, and RB of 0 or 1, or a ≥1-point decrease from baseline. Remitters: modified Mayo score (MMS) SF of 0 or SF of 1 with a ≥1-point decrease from baseline; RB of 0; and ES of 0 or 1. Biologic failed refers to patients with prior inadequate response, loss of response, or intolerance to biologic therapy or Janus kinase inhibitors (tofacitinib) at LUCENT-1 induction baseline. Not biologic failed refers to patients not meeting the biologic-failed definition at LUCENT-1 induction baseline. Symptomatic remission: SF of 0 or SF of 1 with a ≥1-point decrease in MMS from baseline; and RB of 0. HEMR: Geboes score ≤ 2B.0 and ES of 0 or 1 (excluding friability). Abbreviations: CI, confidence interval.

and ADA– subgroups compared to the overall population using both mNRI and OC methodology to assess efficacy for both the LUCENT-2 week 52 responders and LUCENT-2 week 52 blinded maintenance completers. The percentage of patients achieving symptomatic remission, clinical response, clinical remission, or endoscopic remission was similar for all patients, ADA+ evaluable patients, ADA– patients, ADA+ patients, and patients with ADA+ maximum titer ≥1:160, with the exception of clinical remission for patients with ADA+ maximum titer ≥1:160 who had ~10% lower percentage than other subgroups. The ADA+ maximum titer ≥1:160 subgroup is less than 10% of the population, and amongst them, only a small percentage of patients drives the subgroup's lower rate such that this affects <1% of the LUCENT-3 patients.

Safety

Adverse events

For the 0 to 100-week period of LUCENT-3 (week 52 to week 154 continuous mirikizumab treatment), Table 1 provides the incidence of treatment-emergent AEs for the safety population (see Patient Groups for population definitions). Severe treatment-emergent AEs were reported in 7.4% of patients with 8.8% experiencing serious AEs, and 5.3% discontinuing treatment due to an AE. The most common treatment-emergent AEs were COVID-19 and UC. There was 1 (0.3%) death due to thrombotic thrombocytopenic purpura on day 463 of the study.

AEs of special interest included opportunistic infection (1.8%), cerebrocardiovascular events (1.5%), and malignancy (0.3%; Table 1). For the 100-week period of LUCENT-3 in the induction responder safety population, 11 (3.2%) patients reported hepatic disorders, with 3 (0.9%) patients having elevated alanine aminotransferase ≥3× the upper limit of normal, 4 (1.2%) patients having elevated aspartate transaminase (≥3× the upper limit of normal), and 6 (1.8%) patients having elevated total bilirubin (≥2× the upper limit of normal). No patients had liver enzymes that were 5× or 10× the upper limit of normal except 1 patient who had elevated

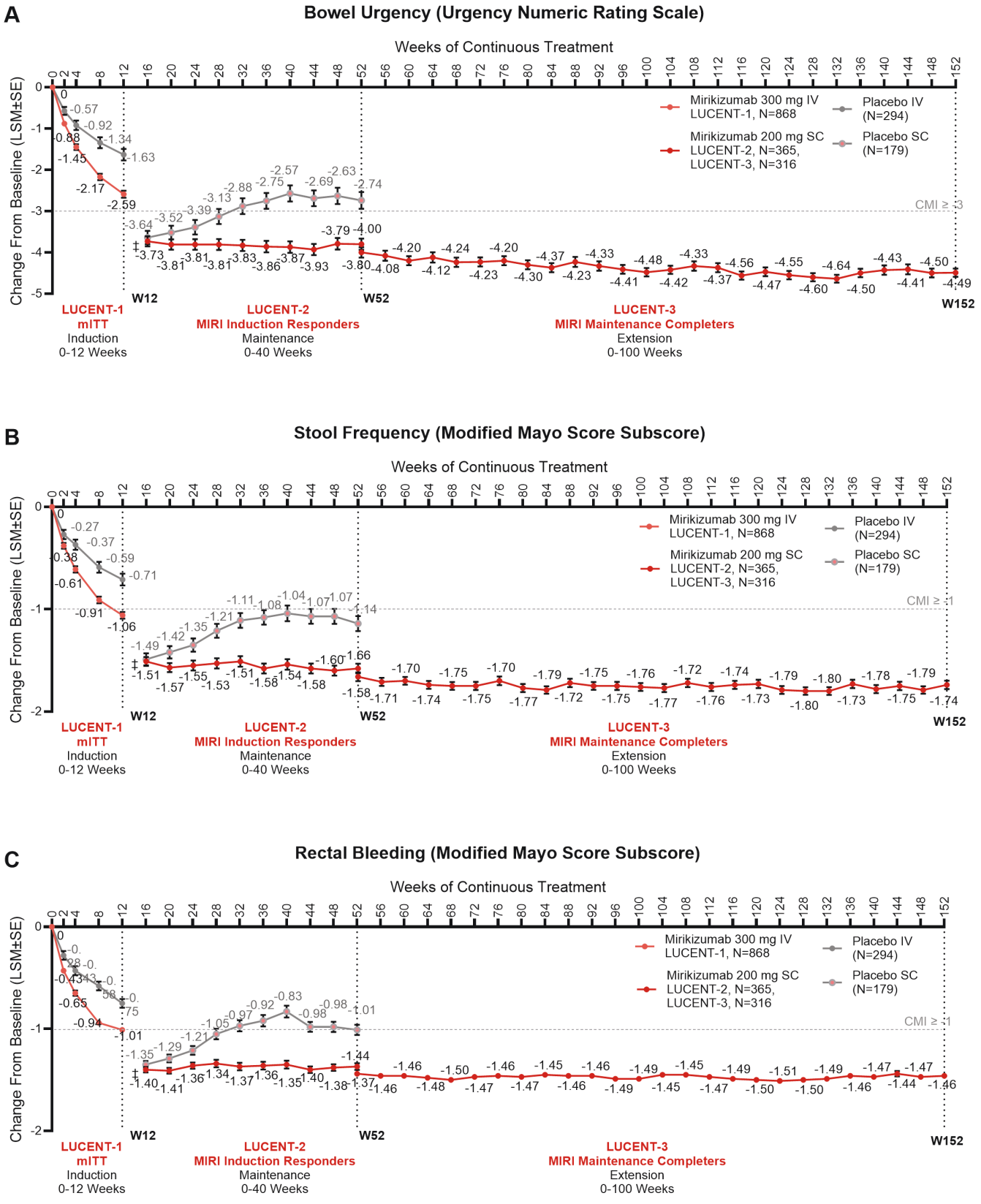

Figure 4. Change from induction baseline in UC symptoms by visit through week 152 of continuous mirikizumab treatment in the modified intention-to-treat (mITT) population (LUCENT-1), mirikizumab induction responders (LUCENT-2), and maintenance completers (LUCENT-3, open-label) for (A) bowel urgency, (B) stool frequency, and (C) rectal bleeding (RB; mixed-effects model for repeated measures [MMRM]). The mITT population was used with MMRM to estimate the least squares mean (LSM) change from baseline. The LUCENT program is 3 separate studies with different study designs, and patients flow from one study to the next; thus, the patient population is changing across studies: LUCENT-1 (mITT), LUCENT-2 (mirikizumab induction responders), LUCENT-3 (mirikizumab maintenance completers). See Figure 1 for patient flow and the current examined population that follows

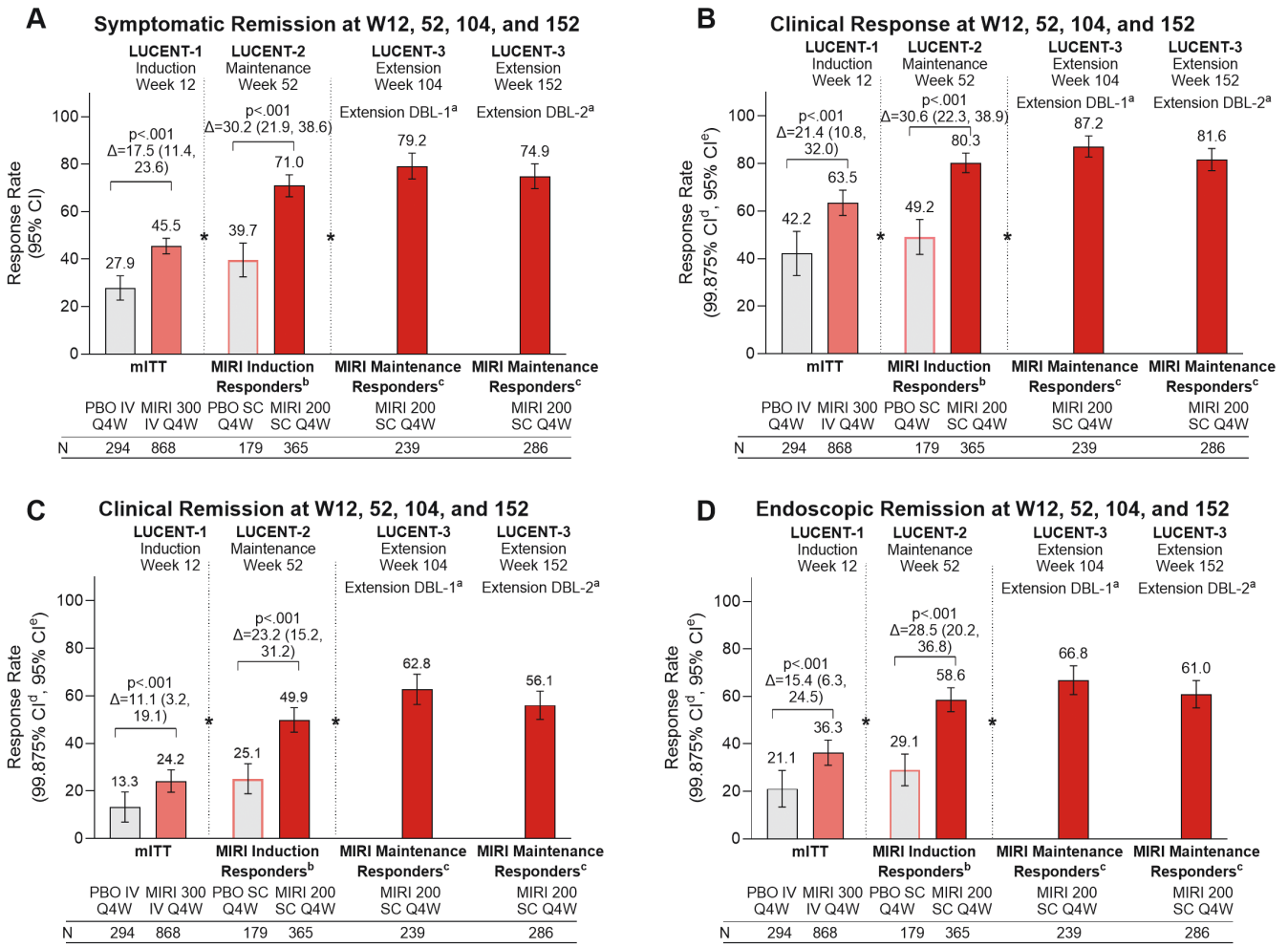

Figure 5. Remission rates at weeks 12, 52, 104, and 152 for (A) symptomatic remission, (B) clinical response, (C) clinical remission, and (D) endoscopic remission in the modified intention-to-treat (mITT) population (overall efficacy population; LUCENT-1), mirikizumab induction responders (LUCENT-2; nonresponder imputation [NRI]), and LUCENT-2 maintenance responders (LUCENT-3; modified NRI [mNRI]). *Based upon study designs, after induction, responders are being followed over time; thus, the population changes and the week (W) 152 percentages are based on the noted population not the original LUCENT-1 baseline population. Missing data are not a factor for LUCENT-1 and LUCENT-2, and mNRI data for these studies are not available; thus, NRI data are shown. For LUCENT-3, to address missingness and allow for better over-time comparison, mNRI data are shown. [a]Database lock (DBL)-1 and DBL-2 are interim DBLs with differences in the number of patients included due to some study sites not being included for DBL-1. [b]LUCENT-1 MIRI induction responders rerandomized to MIRI or PBO (MIRI withdrawal). [c]Responder population (n = 285) of LUCENT-2 MIRI blinded maintenance completers population (n = 316). [d]CI for LUCENT-1. [e]CI for LUCENT-2 and LUCENT-3. Symptomatic remission: stool frequency (SF) of 0 or SF of 1 with ≥1-point decrease in modified Mayo score (MMS) from baseline; and rectal bleeding (RB) of 0. Endoscopic remission: endoscopic subscore (ES) of 0 or 1 (excluding friability). Clinical response: ≥30% and 2-point decrease from baseline in the composite clinical endpoint of the sum of ES, SF, and RB subscores, and RB of 0 or 1, or a ≥1-point decrease from baseline. Clinical remission: MMS SF of 0 or SF of 1 with a ≥1-point decrease from baseline; RB of 0; and ES of 0 or 1. Endoscopic remission: ES of 0 or 1 (excluding friability). Treatment comparison was made with the Cochran-Mantel-Haenszel test adjusted for stratification factors. Abbreviations: CI, confidence interval; IV, intravenous; MIRI, mirikizumab; N, number of patients in the analysis population; PBO, placebo; Q4W, every 4 weeks; SC, subcutaneous.

aspartate transaminase ≥5× the upper limit of normal, nor did any patients meet Hy's law criteria.[21] For treatment-emergent AEs, 0.9% (3/339) of patients reported rash.

Immunogenicity

There was no identified clinically significant effect of ADA+ on the safety of mirikizumab over the treatment duration of 152 weeks, with no association found between ADA+ and hypersensitivity or injection site reaction.

Discussion

In the maturing UC clinical landscape, treatment targets now include goals beyond endoscopic improvement and control

mirikizumab induction responders through the LUCENT clinical program. The Urgency Numeric Rating Scale (0- to 10-point severity scale with 0 denoting no urgency and 10 denoting the worst possible urgency, with a ≥3-point decrease considered a CMI),[20] modified Mayo score (MMS) stool frequency subscore (0 to 3 score; 0 = normal; 1 = 1-2 stools more than normal; 2 = 3-4 stools more than normal; 3 = ≥5 stools more than normal), and MMS RB subscore (0-3 score; 0 = normal; 1 = streaks of blood with stool less than half the time; 2 = obvious blood with stool most of the time; 3 = blood alone passed) measure changes in the respective symptom from the induction baseline. LSM was reported for each treatment group except for week 0 of maintenance (‡; week 12). Abbreviations: CMI, clinically meaningful improvement; IV, intravenous; MIRI, mirikizumab; SC, subcutaneous; W, week.

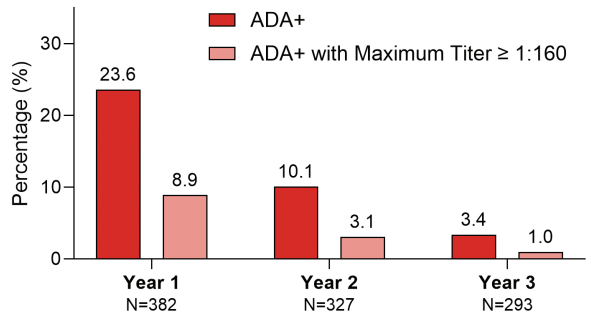

Figure 6. Incidence of ADA+ events in evaluable patients over time. Year 1 (weeks 0 to 52); year 2 (weeks 52 to 104); year 3 (weeks 104 to 152). Abbreviations: ADA, antidrug antibody; N, denominator, number of ADA+ evaluable patients for each time point.

of SF and RB. Targets now include BU[22] and histological improvement or remission.[20,23,24] Gaps in treatment care exist for many patients with UC whose treatment efficacy is not maintained over time; approximately 40% of patients who respond to treatment subsequently lose response.[4] LUCENT-3 is one of the first long-term extension studies in UC to provide data for endpoints such as clinical response, clinical remission, HEMI, HEMR, and endoscopic remission as long-term extension studies of other therapeutics generally only included symptom-driven clinical response or remission definitions and safety data.

Consistent with the 104-week data,[9] the current 152-week data suggest that mirikizumab provides sustained long-term efficacy for patients who initially respond to treatment. Findings were consistent across a broad panel of endpoints examined over 3 years of treatment. These data suggest that mirikizumab treatment is effective in improving patient symptoms as well as endoscopic and histologic mucosal healing that results in improved patient quality of life. Mirikizumab was effective long-term in both biologic-naïve and previously biologic-failed patients.

Compared with the overall population, a lower proportion of patients in the biologic-failed subgroup met the endpoint criteria. When examining the maintenance of effect over time, small decreases from weeks 104 to 152 also appear greater for the biologic-failed group. This is not unexpected, as the biologic-failed subgroup appears to be a more refractory population.[10] The small decreases are influenced by the smaller number of patients in the biologic-failed subgroup and the imputation method rather than the overall change in maintenance of efficacy. For the maintenance responders' clinical response using NRI as an example (Figure 3), 71.6% (204/285) of the overall blinded maintenance responders and 60.4% (55/91) of the biologic-failed subgroup had a response at week 152. For the week 104 analyses, the corresponding rates were 74.5% for the total population and 68.5% for the biologic-failed subgroup.[9] The difference in denominators between the total population and the biologic-failed subgroup is 194 patients, where a change in N of 2 equates to 0.7% for the overall population and 2.2% for the biologic-failed subgroup. Treatment discontinuations are a large driving factor in determining nonresponse and the associated decreases in endpoint maintenance. During the 2 years of the LUCENT-3 long-term extension, there were 47 total treatment discontinuations: efficacy 11 (23% of discontinuations); AE 15 (32%); lost to follow-up or withdrawal by subject for other reasons 21 (45%).

Table 1. LUCENT-3 AEs.

Outcome	Overall induction responder safety population
	Mirikizumab 200 mg Q4W SC (*N* = 339)[a]
TEAEs[b], *n* (%)	250 (73.7)
Mild	111 (32.7)
Moderate	114 (33.6)
Severe	25 (7.4)
SAEs, *n* (%)	30 (8.8)
Most Common TEAEs[c], *n* (%)	
COVID-19	76 (22.4)
Colitis ulcerative	54 (15.9)
Arthralgia	21 (6.2)
Nasopharyngitis	28 (8.3)
Headache	26 (7.7)
Pyrexia	20 (5.9)
Diarrhea	15 (4.4)
Gastroenteritis	15 (4.4)
Upper respiratory tract infection	15 (4.4)
Abdominal pain	14 (4.1)
Fatigue	10 (3.2)
AEs of Special Interest, *n* (%)	
Infections: all	144 (42.5)
Serious	8 (2.4)
Opportunistic[d]	6 (1.8)
Cerebrocardiovascular events[e]	5 (1.5)
Major adverse cardiac events (MACE)	1 (0.3)
Malignancies[f]	1 (0.3)
Depression	3 (0.9)
Suicide/self-injury[g]	1 (0.3)
Hepatic	11 (3.2)
Immediate hypersensitivity reactions[h]	4 (1.2)
Injection site reactions	19 (5.6)
Death, *n* (%)	1 (0.3)
Discontinuation due to AE, *n* (%)[i]	18 (5.3)

Abbreviations: AE, adverse events; N, number of patients with at least one sample collected for clinical lab evaluation; Q4W, every 4 weeks; SAE, serious adverse events; SC, subcutaneous; TEAE, treatment-emergent adverse events.
[a]The safety population was used for AE assessments and includes participants from Poland and Turkey affected by the electronic clinical outcome assessment error in LUCENT-1 and LUCENT-2, as well as patients on blinded mirikizumab at the end of LUCENT-2 who were not in remission or response and who are not included in the efficacy analysis.
[b]Patients with multiple occurrences of the same event are counted under the highest severity.
[c]TEAEs affecting ≥3% of patients.
[d]Opportunistic infections: narrow, *n* (%): 6 (1.8). Breakdown: herpes zoster, *n* (%): 4 (1.2); esophageal candidiasis, *n* (%): 2 (0.6); oral candidiasis, *n* (%): 1 (0.3).
[e]Major adverse cardiac event, *n* (%): 1 (0.3), determined by the investigator as not related to mirikizumab.
[f]Ongoing metastatic thyroid cancer.
[g]Suicide attempt, determined by the investigator as not related to mirikizumab.
[h]Hypersensitivity reactions (narrow) included: allergic sinusitis, *n* (%): 1 (0.3%); eczema, *n* (%): 1 (0.3); injection site hypersensitivity, *n* (%): 1 (0.3); injection site urticaria, *n* (%): 1 (0.3).
[i]Injection site reactions: injection site pain, *n* (%): 10 (2.9); injection site reaction, *n* (%): 8 (2.4); injection site erythema, *n* (%): 4 (1.2); injection site hypersensitivity, *n* (%): 1 (0.3); injection site pruritus, *n* (%): 1 (0.3); injection site urticaria, *n* (%): 1 (0.3).
[j]Reasons, *n* (%): 1 (0.3) dermatitis, 9 (2.7) colitis ulcerative, 1 (0.3) haematochezia, 1 (0.3) meningitis.

Long-term efficacy and safety data have been disclosed for vedolizumab, an α4β7-integrin inhibitor,[25] and for ustekinumab, an IL-12 and IL-23p40 inhibitor,[26] both approved for the treatment of UC. However, no full-study long-term extension endoscopy data have been collected for these compounds. In contrast, endoscopy and histology clinical data have been reported for mirikizumab, including endoscopy-based response and remission endpoints, as well as HEMI and HEMR. In mirikizumab responders, early histological and endoscopic efficacy is sustained long-term (3 years), which may be important because it is associated with better UC outcomes.[27]

Patients with UC frequently consider it more important to control BU than SF or RB.[28,29] BU was currently assessed with the Urgency NRS which is validated to assess BU severity improvement over time as opposed to a simple yes versus no identification.[14,30,31] Mirikizumab demonstrated sustained resolution of BU, which is associated with better UC outcomes.[27]

Anti-tumor necrosis factor (TNF)-α biologics such as adalimumab or infliximab are often the first-line treatment for moderate-to-severe UC[32]; however, some primary responders experience secondary loss of response with anti-TNF agents.[33] Mirikizumab maintained long-term efficacy for induction responders, which is likely tied to its ability to decrease the expression of transcripts associated with resistance to anti-TNF agents.[4,34,35]

Safety findings were consistent with findings from the LUCENT-1 and LUCENT-2 studies.[10] Consistent with mirikizumab 2-year continuous treatment evaluations,[9] the current data do not suggest an issue with clinically meaningful long-term hepatic AEs. Infection and malignancy rates do not indicate a profound systemic immune suppression. COVID-19 was the most commonly observed AE, which is consistent with the fact that this study was held during the COVID-19 pandemic.

Understanding ADAs is important because ADA+ can lead to diminished efficacy for patients over time. For example, a loss of response due to the development of ADA+ is seen annually in approximately 20% of patients with IBD receiving anti-TNF therapy[36] and up to 50% of patients stop therapy after an initial clinical response either due to secondary loss of response or a serious AE.[37] In general, ADA+ could potentially lead to safety issues not directly related to the therapeutic mechanism of action, such as anaphylaxis, cytokine release syndrome, infusion reaction, or cross-reactivity.[38] For mirikizumab, <2% of patients developed an ADA+ titer ≥1:160 that was accompanied by a lower blood concentration of the drug and reduced efficacy during the first 52 weeks of treatment. The incidence of ADA+ as well as ADA+ titer ≥1:160 diminished over time from weeks 52 to 152. Outcomes for patients with ADA+ were comparable to the overall population, even for patients with higher titer. No safety concerns were observed. These data suggest that ADA+ is not significant in affecting 3-year mirikizumab treatment outcomes. Of note, pharmacokinetic exposure-response data through week 52 show that mirikizumab exposure (μg/mL) plotted against change in the MMS demonstrates such a wide spread that the range of response was broad at both low and high drug blood concentrations.[39] The pharmacokinetic data along with the current ADA+ data show that ADAs do not drive treatment outcomes.

Future analyses from the ongoing open-label extension LUCENT-3 study will provide robust long-term 4-year data.

Limitations

Limitations of LUCENT-3 have been previously described, including the open-label study design and focus on only the induction responder population due to the LUCENT program having a responder randomization methodology, where only patients who responded during induction were rerandomized for maintenance.[9] Because of this study design, induction failures were not included in long-term maintenance analyses such that response proportions reported were lower than they would be if the entire baseline population had been included.

Participation of Black or African American patients was limited (4/316, 1.3% of maintenance completers); thus, the results cannot be fully generalizable.

Conclusion

These data support the long-term benefit of continuous mirikizumab treatment for 152 weeks on symptomatic, clinical, endoscopic, and histologic endpoints, for both biologic-naïve and biologic-failed patients. No new safety signals were identified, and the discontinuation rate due to AEs was 5.3%.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

Acknowledgments

The authors thank the participants, caregivers, and investigators of this study. The authors thank Greg Anglin, Paweł Piela, and Sihe Wang for their data management, analysis, and interpretation of the ADA+ data. The authors also thank Deborah Fisher and Baojin Zhu of Eli Lilly and Company for their comments and input during the drafting of the manuscript and review stages, as well as Nic Paquette and Farokh Dotiwala of Syneos Health for their medical writing and project management support.

Author Contributions

Eli Lilly and Company contributed to the study design, data collection, data analysis, data interpretation, preparation of the manuscript, and the decision to submit the paper for publication. J.T.J. contributed to data analysis. All authors contributed to the conception of the work and the interpretation of data. All authors had full access to all the data in the study, reviewed drafts, and approved the final version of the manuscript.

Funding

This study was funded by Eli Lilly and Company.

Conflicts of Interest

B.E.S. reports consulting fees from AbbVie, Alimentiv, Amgen, Arena Pharmaceuticals, Artugen Therapeutics, AstraZeneca, Biora Therapeutics, Inc., Boehringer Ingelheim, Boston Pharmaceuticals, Calibr, Celgene, Celltrion, ClostraBio, Enthera, Equillium, Evommune, Fresenius Kabi, Galapagos, Genentech (Roche), Gilead Sciences, GlaxoSmithKline,

Gossamer Bio, Index Pharmaceuticals, Innovation Pharmaceuticals Inc, Inotrem, Kaleido Biosciences, Kallyope, Merck & Co., Inc., Morphic Therapeutic, MRM Health, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics Inc, Q32 Bio, Sun Pharma, Surrozen, Target RWE, Teva Pharmaceuticals, TLL Pharmaceutical LLC, and Ventyx Biosciences; consulting and speaking fees from Abivax; consulting and speaking fees and other support from Eli Lilly and Company; research grants, consulting and speaking fees, and other support from Bristol Myers Squibb, Janssen, Pfizer, and Takeda Pharmaceuticals; research grants and consulting fees from Theravance Biopharma; and stock options from Ventyx Biosciences. G.D. reports advisor fees from AbbVie, Alimentiv, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly and Company, Galapagos, GlaxoSmithKline, Gossamer Bio, Immunic Therapeutics, Johnson & Johnson, Pfizer, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics Inc, Samsung Biologics, Seres Therapeutics, Takeda Pharmaceuticals, Tillotts Pharma AG, and Ventyx Biosciences. D.B.C., J.T.J., T.H.G., R.E.M., and J.M. are employees and stockholders of Eli Lilly and Company. P.M.I. reports research grants from Celltrion, Galapagos, Pfizer, and Takeda Pharmaceuticals; consulting fees from AbbVie, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Elasmogen, Eli Lilly and Company, Gilead Sciences, Janssen, Pfizer, Prometheus, and Sandoz; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, Bristol Myers Squibb, Celgene, Celltrion, Dr. Falk Pharma, Eli Lilly and Company, Galapagos, Gilead Sciences, Janssen, Pfizer, Takeda Pharmaceuticals, and Tillotts Pharma AG; and support for attending meetings and/or travel from AbbVie and Tillotts Pharma AG. M.T.A. reports consulting and/or serving on an advisory board for AbbVie, Amgen, Arena Pharmaceuticals, Bristol Myers Squibb, Celsius Therapeutics, Eli Lilly and Company, Gilead Sciences, Janssen, Pfizer, Prometheus Biosciences, and UCB; and teaching, lecturing, or speaking from Alimentiv. S.L. reports grants and research support from AbbVie, Arena Pharmaceuticals, Atlantic Pharmaceuticals, Celgene, Gilead Sciences, Janssen, Pfizer, Salix Pharmaceuticals, Shield Therapeutics, Takeda Pharmaceuticals, Tetherex Pharmaceuticals, and UCB; and consulting for Arena Pharmaceuticals, Celgene, Celltrion, Cornerstone Pharmaceuticals, Eli Lilly and Company, Janssen, Mesoblast, Pfizer, Salix Pharmaceuticals, Takeda Pharmaceuticals, and UCB. T.H. reports lecture fees from AbbVie, EA Pharma, Gilead Sciences, Janssen, JIMRO, Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co., Ltd., Pfizer, and Takeda Pharmaceuticals; advisory/consultancy fees from AbbVie, EA Pharma, Eli Lilly and Company, Gilead Sciences, Janssen, Mitsubishi Tanabe Pharma Corporation, Pfizer, and Takeda Pharmaceuticals; and pharmaceutical/research grants from AbbVie, Alfresa Pharma, Daiichi Sankyo, EA Pharma, JIMRO, Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co., Ltd., Nichi-Iko Pharmaceutical Co., Ltd., Nippon Kayaku, Pfizer, Takeda Pharmaceuticals, and Zeria Pharmaceutical Co., Ltd. T.K. reports serving as a speaker, consultant, or advisory board member for AbbVie, Alfresa Pharma, Bristol Myers Squibb, Celltrion, Covidien, EA Pharma, Eiken Chemical Co., Ltd., Eli Lilly and Company, Ferring Pharmaceuticals, Gilead Sciences, Janssen, JIMRO, Kissei Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co., Ltd., Nippon Kayaku, Pfizer, Sekisui Medical Co., Ltd., Takeda Pharmaceuticals, and Zeria Pharmaceutical Co., Ltd.; research funding from AbbVie, Alfresa Pharma, EA Pharma, Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Nippon Kayaku, Otsuka Holdings Co., Ltd., Pfizer, Sekisui Medical Co., Ltd., and Zeria Pharmaceutical Co., Ltd. M.C.D. reports consulting fees from AbbVie, Arena Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Genentech (Roche), Gilead Sciences, Janssen, Pfizer, Prometheus Biosciences, Roche, Takeda Pharmaceuticals, and UCB; contracted research from AbbVie and Janssen; stock interest in Trellus Health; and licensing fees from Takeda Pharmaceuticals. S.V. reports grants from AbbVie, Galapagos, Johnson & Johnson, Pfizer, and Takeda Pharmaceuticals; and consulting and/or speaking fees from AbbVie, Abivax, AbolerIS Pharma, Agomab Therapeutics, Alimentiv, Arena Pharmaceuticals, AstraZeneca, Avaxia Biologics, Biora Therapeutics, Inc., Bristol Myers Squibb, Boehringer Ingelheim, Celgene, CVasThera, Cytoki Pharma, Dr. Falk Pharma, Eli Lilly and Company, Ferring Pharmaceuticals, Galapagos, Genentech (Roche), Gilead Sciences, GlaxoSmithKline, Hospira, IMIDomics, Janssen, Johnson & Johnson, Materias Primas Farmacéuticas, Mestag Therapeutics, MiroBio, Morphic Therapeutic, MRM Health, Mundipharma, MSD, Pfizer, ProDigest, Prometheus, Second Genome, Shire Pharma, Surrozen, Takeda Pharmaceuticals, Theravance Biopharma, Tillotts Pharma AG, VectivBio, Ventyx Biosciences, and Zealand Pharma. C.A.S. reports consulting for AbbVie, Bristol Myers Squibb, Eli Lilly and Company, Fresenius Kabi, Janssen, Napo Pharmaceuticals, Pfizer, ProciseDx, Prometheus, Takeda Pharmaceuticals, and Trellus Health; speaker for continuing medical education activities for AbbVie, Janssen, Pfizer, and Takeda Pharmaceuticals; and grant support from AbbVie, Janssen, Pfizer, and Takeda Pharmaceuticals. L.P.-B. reports personal fees from AbbVie, Abivax, Adacyte Therapeutics, Alimentiv, Alma Bio Therapeutics, Amgen, Applied Molecular Transport, Arena Pharmaceuticals, Biogen, Bristol Myers Squibb, Celltrion, Connect Biopharma, Cytoki Pharma, Eli Lilly and Company, Enthera, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos, Genentech (Roche), Gilead Sciences, GlaxoSmithKline, Gossamer Bio, H.A.C. Pharma, IAG Image Analysis Group, Index Pharmaceuticals, Inotrem, Janssen, Medac Pharma, Mopac Biologics, Morphic Therapeutic, MSD, Nordic Pharma, Norgine, Novartis, OM Pharma, ONO Pharmaceutical Co., Ltd., OSE Immunotherapeutics, Pandion Therapeutics, Par'Immune, Pfizer, Prometheus Biosciences, Protagonist Therapeutics Inc, Roche, Roivant, Samsung Biologics, Sandoz, Sanofi, Takeda Pharmaceuticals, Theravance Biopharma, Thermo Fisher Scientific, TiGenix, Tillotts Pharma AG, VectivBio, Ventyx Bioscience, Viatris, Vifor Pharma, and YSOPIA Bioscience. R.P. reports acting as a consultant for Abbott, AbbVie, Abivax, Alimentiv, Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Biora Therapeutics, Inc., Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Cosmo Pharmaceuticals, Eisai, Elan Pharmaceuticals, Eli Lilly and Company, Ferring Pharmaceuticals, Fresenius

Kabi, Galapagos, Genentech (Roche), Gilead Sciences, GlaxoSmithKline, JAMP Pharma, Janssen, Merck & Co., Inc., Novartis, Oppilan Pharma, Organon, Pandion Therapeutics, Pendopharm G.I. Solutions, Pfizer, Prometheus Biosciences, Protagonist Therapeutics Inc, Roche, Sandoz, Satisfai Health, Shire Pharma, Sublimity Therapeutics, Takeda Pharmaceuticals, Theravance Biopharma, Trellus Health, Ventyx Biosciences, Viatris, and UCB; speaker's fees from AbbVie, Amgen, Arena Pharmaceuticals, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Ferring Pharmaceuticals, Fresenius Kabi, Gilead Sciences, Janssen, Merck & Co., Inc., Organon, Pfizer, Roche, Sandoz, Shire Pharma, and Takeda Pharmaceuticals; and advisory boards for AbbVie, Alimentiv, Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Biora Therapeutics, Inc., Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Ferring Pharmaceuticals, Fresenius Kabi, Genentech (Roche), Gilead Sciences, GlaxoSmithKline, JAMP Pharma, Janssen, Merck & Co., Inc., Novartis, Organon, Pandion Therapeutics, Pfizer, Protagonist Therapeutics Inc, Roche, Sandoz, Shire Pharma, Sublimity Therapeutics, Takeda Pharmaceuticals, Ventyx Biosciences, and Viatris. A.D. reports received fees for participation in clinical trials, review activities such as data monitoring boards, statistical analysis, and end point committees from AbbVie, Abivax, Arena Pharmaceuticals, Bristol Myers Squibb, Celgene, Falk Foundation, Galapagos, Gilead Sciences, Janssen, and Pfizer; consultancy fees from AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly and Company, Falk Foundation, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos, Genentech (Roche), Janssen, MSD, Pfizer, Pharmacosmos, Sandoz/Hexal, Takeda Pharmaceuticals, Tillotts Pharma AG, and Vifor Pharma; payment from lectures including service on speakers bureaus from AbbVie, Biogen, CED Service GmbH, Celltrion, Falk Foundation, Ferring Pharmaceuticals, Galapagos, Gilead Sciences, High5MD, Janssen, Materias Primas Farmacéuticas, MedToday, MSD, Pfizer, Takeda Pharmaceuticals, Tillotts Pharma AG, and Vifor Pharma; and payment for manuscript preparation from Falk Foundation, Takeda Pharmaceuticals, Thieme, and UNI-MED Verlag AG.

References

1. Gros B, Kaplan GG. Ulcerative colitis in adults: a review. *JAMA*. 2023;330(10):951-965. doi:10.1001/jama.2023.15389
2. Dubinsky MC, Watanabe K, Molander P, et al. Ulcerative colitis narrative global survey findings: the impact of living with ulcerative colitis-patients' and physicians' view. *Inflamm Bowel Dis*. 2021;27(11):1747-1755. doi:10.1093/ibd/izab016
3. Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. *Lancet*. 2023;402(10401):571-584. doi:10.1016/S0140-6736(23)00966-2
4. Steere B, Schmitz J, Powell N, et al. Mirikizumab regulates genes involved in ulcerative colitis disease activity and anti-TNF resistance: results from a phase 2 study. *Clin Transl Gastroenterol*. 2023;14(7):e00578. doi:10.14309/ctg.0000000000000578
5. Danese S, Allez M, van Bodegraven AA, et al. Unmet medical needs in ulcerative colitis: an expert group consensus. *Dig Dis*. 2019;37(4):266-283. doi:10.1159/000496739
6. Daperno M, Armuzzi A, Danese S, et al. Unmet medical needs in the management of ulcerative colitis: results of an italian delphi consensus. *Gastroenterol Res Pract*. 2019;2019(Sep 2):3108025. doi:10.1155/2019/3108025
7. Gordon JP, McEwan PC, Maguire A, Sugrue DM, Puelles J. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. *Eur J Gastroenterol Hepatol*. 2015;27(7):804-812. doi:10.1097/MEG.0000000000000378
8. Kobayashi T, Siegmund B, Le Berre C, et al. Ulcerative colitis. *Nat Rev Dis Primers*. 2020;6(1):74. doi:10.1038/s41572-020-0205-x
9. Sands BE, D'Haens G, Clemow DB, et al. Two-year efficacy and safety of mirikizumab following 104 weeks of continuous treatment for ulcerative colitis: results from the LUCENT-3 open-label extension study. *Inflamm Bowel Dis*. 2024;30(6):1044-1045. doi:10.1093/ibd/izae024
10. D'Haens G, Dubinsky M, Kobayashi T, et al.; LUCENT Study Group. Mirikizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2023;388(26):2444-2455. doi:10.1056/NEJMoa2207940
11. Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and safety of mirikizumab in a randomized phase 2 study of patients with ulcerative colitis. *Gastroenterology*. 2020;158(3):537-549.e10. doi:10.1053/j.gastro.2019.08.043
12. Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and safety of continued treatment with mirikizumab in a phase 2 trial of patients with ulcerative colitis. *Clin Gastroenterol Hepatol*. 2022;20(1):105-115.e14. doi:10.1016/j.cgh.2020.09.028
13. Public Policy Committee ISoP. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf*. 2016;25(1):2-10. doi:10.1002/pds.3891
14. Dubinsky MC, Shan M, Delbecque L, et al. Psychometric evaluation of the urgency NRS as a new patient-reported outcome measure for patients with ulcerative colitis. *J Patient Rep Outcomes*. 2022;6(1):114. doi:10.1186/s41687-022-00522-2
15. Irvine EJ. Quality of life of patients with ulcerative colitis: past, present, and future. *Inflamm Bowel Dis*. 2008;14(4):554-565. doi:10.1002/ibd.20301
16. Spiegel B, Bolus R, Harris LA, et al. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. *Aliment Pharmacol Ther*. 2009;30(11-12):1159-1170. doi:10.1111/j.1365-2036.2009.04144.x
17. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998;17(8):873-890. doi:10.1002/(sici)1097-0258(19980430)17:8<873::aid-sim779>3.0.co;2-i
18. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc*. 1927;22(158):209-212. doi:10.2307/2276774
19. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Wiley; 1987.
20. Dubinsky MC, Clemow DB, Hunter Gibble T, et al. Clinical effect of mirikizumab treatment on bowel urgency in patients with moderately to severely active ulcerative colitis and the clinical relevance of bowel urgency improvement for disease remission. *Crohns Colitis 360*. 2023;5(1):otac044. doi:10.1093/crocol/otac044
21. Robles-Diaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. *Gastroenterology*. 2014;147(1):109-118. doi:10.1053/j.gastro.2014.03.050
22. Danese S, Roda G, Peyrin-Biroulet L. Evolving therapeutic goals in ulcerative colitis: towards disease clearance. *Nat Rev Gastroenterol Hepatol*. 2020;17(1):1-2. doi:10.1038/s41575-019-0211-1
23. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413. doi:10.14309/ajg.0000000000000152
24. Turner D, Ricciuto A, Lewis A, et al.; International Organization for the Study of IBD. STRIDE-II: an update on the selecting

therapeutic targets in inflammatory bowel disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology*. 2021;160(5):1570-1583. doi:10.1053/j.gastro.2020.12.031
25. Loftus EV, Jr, Colombel JF, Feagan BG, et al. Long-term efficacy of vedolizumab for ulcerative colitis. *J Crohns Colitis*. 2017;11(4):400-411. doi:10.1093/ecco-jcc/jjw177
26. Panaccione R, Danese S, Sandborn WJ, et al. Ustekinumab is effective and safe for ulcerative colitis through 2 years of maintenance therapy. *Aliment Pharmacol Ther*. 2020;52(11-12):1658-1675. doi:10.1111/apt.16119
27. Magro F, Pai RK, Kobayashi T, et al. Resolving histological inflammation in ulcerative colitis with mirikizumab in the LUCENT induction and maintenance trial programmes. *J Crohns Colitis*. 2023;17(9):1457-1470. doi:10.1093/ecco-jcc/jjad050
28. Louis E, Ramos-Goni JM, Cuervo J, et al. A qualitative research for defining meaningful attributes for the treatment of inflammatory bowel disease from the patient perspective. *Patient*. 2020;13(3):317-325. doi:10.1007/s40271-019-00407-5
29. van Deen WK, Obremskey A, Moore G, van den Akker-van Marle ME, Doctor JN, Hwang C. An assessment of symptom burden in inflammatory bowel diseases to develop a patient preference-weighted symptom score. *Qual Life Res*. 2020;29(12):3387-3396. doi:10.1007/s11136-020-02606-2
30. Dubinsky MC, Irving PM, Panaccione R, et al. Incorporating patient experience into drug development for ulcerative colitis: development of the urgency numeric rating scale, a patient-reported outcome measure to assess bowel urgency in adults. *J Patient Rep Outcomes*. 2022;6(1):31. doi:10.1186/s41687-022-00439-w
31. Dubinsky MC, Newton L, Delbecque L, et al. Exploring disease remission and bowel urgency severity among adults with moderate to severe ulcerative colitis: a qualitative study. *Patient Relat Outcome Meas*. 2022;13(Dec 22):287-300. doi:10.2147/PROM.S378759
32. Feuerstein JD, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S; AGA Institute Clinical Guidelines Committee. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158(5):1450-1461. doi:10.1053/j.gastro.2020.01.006
33. Gisbert JP, Chaparro M. Primary failure to an anti-TNF agent in inflammatory bowel disease: switch (to a second anti-TNF agent) or swap (for another mechanism of action)? *J Clin Med*. 2021;10(22):5318. doi:10.3390/jcm10225318
34. Johnson T, Steere B, Zhang P, et al. DOP09 mirikizumab-induced transcriptome changes in patient biopsies at week 12 are maintained through week 52 in patients with ulcerative colitis. *J Crohns Colitis*. 2021;15(Supplement_1):S047-S048. doi:10.1093/ecco-jcc/jjab073.048
35. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a systematic review. *Am J Gastroenterol*. 2019;114(6):874-883. doi:10.14309/ajg.0000000000000183
36. Fousekis FS, Papamichael K, Kourtis G, et al. The efficacy of immunomodulators in the prevention and suppression of anti-drug antibodies to anti-tumor necrosis factor therapy in inflammatory bowel disease. *Ann Gastroenterol*. 2022;35(1):1-7. doi:10.20524/aog.2021.0682
37. Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2019;17(9):1655-1668.e3. doi:10.1016/j.cgh.2019.03.037
38. US-FDA. *Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products*. US Food and Drug Administration, 2014.
39. Friedrich S, Chua L, Zhang XC. P519 Mirikizumab pharmacokinetics and exposure-response relationships in patients with moderately to severely active ulcerative colitis: results from randomised phase 2 and phase 3 induction and maintenance trials. *J Crohns Colitis*. 2023;17(Supplement_1):i646-i646. doi:10.1093/ecco-jcc/jjac190.0649