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Observations and Research

Efficacy and Safety of Mirikizumab in the Treatment of Moderately to Severely Active Ulcerative Colitis Regardless of Baseline Modified Mayo Score: Results From the Phase 3 LUCENT Trials

Bincy Abraham, MD,[*] Jianmin Wu, PhD,[†] Séverine Vermeire, MD, PhD,[‡] Gil Melmed, MD,[§] Ryan Ungaro, MD,[¶] Aline Charabaty, MD,[‖] Richard Moses, DO, JD,[†] Faye Chan-Diehl, RPh, MBA,[†] Jerome Paulissen, MS,[**] Baojin Zhu, PhD,[†] Edward L. Barnes, MD, MPH,[††] Adam C. Ehrlich, MD, MPH,[‡‡] and David T. Rubin, MD[§§]

[*]Department of Medicine, Houston Methodist, Houston, TX, USA
[†]Eli Lilly and Company, Indianapolis, IN, USA
[‡]Gastroenterology & Hepatology Department, University Hospitals Leuven, Leuven, Belgium
[§]IM Gastroenterology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[¶]Gastroenterology, Mount Sinai, New York, NY, USA
[‖]Gastroenterology, Johns Hopkins University School of Medicine, Washington, DC, USA
[**]Syneos Health, Morrisville, NC, USA
[††]Deptartment of Medicine, The University of North Carolina, Chapel Hill, NC, USA
[‡‡]Lewis Katz School of Medicine, Temple University, Philadelphia, PA, USA
[§§]Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, IL, USA

Address correspondence to: Jianmin Wu, PhD, Eli Lilly and Company, Indianapolis, IN 46285, USA. Tel.: 317-719-9787 (wu_jianmin@lilly.com).

Background: The modified Mayo score (mMS) is a measure for ulcerative colitis (UC) disease activity. Recent US Food and Drug Administration guidance for moderately to severely active UC trials suggests that patients should have baseline mMS of 5–9 including an endoscopy score of at least 2, as opposed to the previous range of 4–9. This disclosure reports results from patients with UC with baseline mMS of 5–9 who received mirikizumab, a monoclonal antibody directed against the interleukin-23 p19 subunit, or placebo in the phase 3 LUCENT trials.

Methods: Mirikizumab was evaluated in the randomized, double-blind, placebo-controlled LUCENT-1 (NCT03518086) and LUCENT-2 (NCT03524092) trials, and the ongoing long-term LUCENT-3 (NCT03519945) trial, which use mMS 4–9. Analyses for patients with baseline mMS of 5–9 (excluding patients with mMS of 4) were conducted according to LUCENT trial statistical analysis plans. Categorical efficacy endpoints were summarized using proportions and confidence intervals. Continuous efficacy endpoints are presented as least-squares mean (standard error) changes from baseline.

Results: Mirikizumab demonstrated efficacy for the primary endpoint of clinical remission and major secondary endpoints including clinical response, endoscopic improvement, histologic–endoscopic mucosal improvement/remission, bowel urgency remission, and corticosteroid-free remission. Importantly, mirikizumab exhibited greater improvements versus placebo in the Inflammatory Bowel Disease Questionnaire, fatigue, symptomatic remission, and work productivity. Finally, mirikizumab demonstrated long-term (104-week) sustained, durable efficacy across all studied endpoints. No new safety signals were identified during the 2-year follow-up.

Conclusions: Mirikizumab delivered significant clinical benefit for patients with baseline mMS of 5–9 and demonstrated a favorable safety profile.

Lay Summary

The impact of mirikizumab on adults with ulcerative colitis was assessed, using baseline modified Mayo score (mMS—disease activity measurement) of 5–9, including an endoscopy subscore of at least 2. Results consistently demonstrated clinical benefit regardless of baseline mMS.

Key Words: mirikizumab, ulcerative colitis, modified Mayo score, fatigue, urgency

Introduction

Ulcerative colitis (UC) is a chronic, relapsing, and remitting inflammatory disease of the rectum and colon.[1] Reaching treatment targets within distinct time frames could help patients achieve better clinical outcomes. Maintenance of endoscopic and histologic remission in addition to symptom control are treatment goals that may help modify the course of the disease and impact patients' quality of life.[2] The modified Mayo score (mMS) is a cross-sectional disease activity assessment tool recommended in US Food and Drug Administration (FDA) guidance[3,4] that uses endpoint

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definitions based on 3 subscores: stool frequency, rectal bleeding, and endoscopic findings. Each component is scored from 0 (normal) to 3 (most severe); therefore, the range of the total mMS is 0–9.[5]

Mirikizumab is a monoclonal antibody directed against the p19 subunit of interleukin-23, which is involved in the inflammatory process of UC through a cell-mediated immune response.[6,7] Mirikizumab was studied in 2 phase 3 trials (LUCENT-1 and LUCENT-2) that were designed based on guidance from the FDA[3] and the European Medicines Agency[8] (EMA), enrolling adult patients with moderately to severely active UC as defined by a baseline mMS of 4–9 with an endoscopic subscore ≥2. Both trials met the primary endpoint and all key secondary endpoints and demonstrated acceptable safety.[9–11] A long-term open-label extension study (LUCENT-3) is ongoing and has demonstrated clinical efficacy and safety after 104 weeks of continuous treatment with mirikizumab.[12] In these phase 3 LUCENT trials, mirikizumab-related data disclosures were planned and conducted based on the enrolled trial population (patients with a baseline mMS of 4–9). However, in the recent FDA clinical trial guidance for drugs intended to treat moderately to severely active UC, it was suggested that trial patients should now have a baseline mMS of 5–9 (moderate mMS = 5–6; severe mMS = 7–9), including an endoscopic subscore of at least 2.[4,13] Therefore, the approval of mirikizumab in the United States was based on efficacy data from patients with moderately to severely active UC with an mMS of 5–9 at induction baseline, along with safety data from the entire LUCENT-1 and LUCENT-2 trial population.[11] Although mirikizumab efficacy results are similar and comparable across the different patient populations, including baseline mMS of 5–9 (excluding mMS scores of 4), these data have not previously been disclosed or communicated externally beyond the information included in the US prescribing information (USPI).[11]

The purposes of this report are to describe the results of mirikizumab for patients with an induction baseline mMS of 5–9 from the LUCENT-1, -2, and -3 trials, provide an overview of the safety and immunogenicity data from the LUCENT trial population, and clarify the definition and terminology differences for some endpoints reported in the mirikizumab USPI (patients with baseline mMS of 5–9) versus the entire trial population (patients with baseline mMS of 4–9).[9,11,12]

Methods

Ethical Considerations

All patients involved in this study provided written 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 and 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.[14] An independent data monitoring committee monitored LUCENT-1, LUCENT-2, and LUCENT-3. The trials were registered at ClinicalTrials.gov: NCT03518086 (LUCENT-1), NCT03524092 (LUCENT-2), and NCT03519945 (LUCENT-3).

Trial Design

Mirikizumab was evaluated in 2 randomized, double-blind, placebo-controlled clinical trials (LUCENT-1 [NCT03518086] and LUCENT-2 [NCT03524092]) in adult patients with moderately to severely active UC who had an inadequate response or loss of response to or were unable to tolerate any of the following: corticosteroids, 6-mercaptopurine, azathioprine, biologic therapy (tumor necrosis factor inhibitors [TNFis] or vedolizumab), or tofacitinib.[9] In LUCENT-1, patients with a baseline mMS of 4–9 were randomized 3:1 to receive mirikizumab 300 mg or placebo administered intravenously every 4 weeks (ie, at weeks 0, 4, and 8). Patients from the 12-week intravenous induction trial (LUCENT-1) with a clinical response to mirikizumab therapy at week 12 (defined as a ≥2-point decrease and ≥30% decrease from baseline in the mMS in addition to either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1) were then randomized by 2:1 stratification to receive mirikizumab or placebo in LUCENT-2. Mirikizumab was administered as a 200-mg subcutaneous injection every 4 weeks in the maintenance study (LUCENT-2) for 40 weeks (a total of 52 weeks of treatment) or until loss of response (defined as inadequate response or intolerance to medication). A patient disposition flowchart can be found in Figure S1. The long-term safety and efficacy of mirikizumab are under continued evaluation in LUCENT-3, a single-arm, open-label, ongoing, long-term extension study in patients who participated in an originator mirikizumab UC studies including the phase 2 study and the phase 3 LUCENT-2 study.[12] The first interim analyses of LUCENT-3 focused on patients who received subcutaneous doses of blinded mirikizumab and completed LUCENT-2 and entered LUCENT-3 for up to 52 weeks of treatment.[12] Weeks are shown as cumulative; for example, week 52 in LUCENT-3 equates to 104 weeks of continuous treatment.

Efficacy and Safety Assessment

The primary endpoint for the LUCENT trials was clinical remission at week 12 in LUCENT-1, clinical remission at week 40 (total of 52 weeks of treatment) in LUCENT-2, and clinical remission at week 52 (104 weeks of treatment) in LUCENT-3. Depending on the trial, key secondary endpoints may have included clinical response, endoscopic remission/improvement, histologic–endoscopic mucosal improvement (HEMI), bowel urgency remission, corticosteroid-free clinical remission, and maintenance of clinical remission. At week 12, HEMI is defined as both endoscopic improvement (centrally read endoscopic subscore [ES] of 0 or 1, excluding friability) and histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system) while at week 52, HEMI is defined as both endoscopic improvement (centrally read ES of 0 or 1, excluding friability) and histologic improvement (no neutrophils in crypts or lamina propria, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system). Patient-reported outcomes (PROs) included the Inflammatory Bowel Disease Questionnaire (IBDQ), Work Productivity and Activity Impairment, Ulcerative Colitis questionnaire, fatigue numeric rating scale, and symptomatic remission. Subgroup analyses were conducted on data from patients with prior treatment failure of biologics/Janus kinase inhibitor (JAKi;

only tofacitinib available at this time, TNFi, and vedolizumab) and from patients who were treatment naïve or had no prior treatment failure with any of these therapies. The methods for evaluating safety outcomes and immunogenicity were published elsewhere.[9,15]

Statistical Analyses

The primary and major secondary endpoints based on patients with a baseline mMS of 5–9 (excluding patients with baseline mMS of 4) were controlled for multiplicity at an α level of 0.00125 in LUCENT-1 and 0.05 in LUCENT-2 with the use of a similar prespecified graphical scheme as the gate-keeping strategy to the one used for the trial cohort with baseline mMS of 4–9.[9,11] Categorical efficacy endpoints were summarized using proportions and confidence intervals; confidence intervals were calculated using the Wilson score method, unless otherwise specified.[16,17] Continuous efficacy endpoints are reported using least-squares mean change from the LUCENT-1 study baseline, along with the standard error. Efficacy analyses were performed on the modified intention-to-treat population. The LUCENT-3 analyses were based on mirikizumab responders at week 52 from LUCENT-2. Treatment comparisons for categorical efficacy endpoints were conducted using the Cochran-Mantel-Haenszel test and adjusted for the following stratification factors: prior treatment failure with a biologic agent or tofacitinib (yes or no), baseline corticosteroid use (yes or no), baseline disease activity (mMS of ≤6 or 7–9) for LUCENT-1, clinical remission at week 12 of LUCENT-1 trial for LUCENT-2, and geographic region (North America, Europe, or other). For subgroup analyses, the Fisher exact test was used for binary outcome treatment comparisons. Missing data were imputed using the nonresponder imputation method for the LUCENT-1 and LUCENT-2 trials. The modified nonresponder imputation method[18] was used to handle missing data for the long-term LUCENT-3 trial. Comparisons of continuous efficacy outcomes were made with an analysis of covariance model using the modified baseline observation carried forward method. This model included a trial group, baseline value, and the stratification factors listed above.[9] Efficacy analyses were performed in the modified intention-to-treat populations of both trials. Safety analyses encompassed all randomized patients who received any dosage of mirikizumab or placebo, including those affected by the transcription error in electronic clinical outcome assessments.

Results

Demographics

Patient demographics for the LUCENT trial population have previously been reported.[9] A partial review of those data, along with the data for patients with an mMS of 5–9 (USPI label population), is shown in Tables S1 and S2. The baseline demographics and disease characteristics of patients with a baseline mMS of 5–9 ($N = 1062$) were similar to those with a baseline mMS of 4–9 ($N = 1162$) in LUCENT-1. Patients with a baseline mMS of 5–9 had a median mMS of 7, and 58% had severely active disease (mMS of 7–9). About 57% of patients were biologic and JAKi treatment naïve, 41% had treatment failure with at least one biologic, 4% had treatment failure with a JAKi, and 2% had previously received a biologic or JAKi without treatment failure.

Efficacy

Primary endpoint and major secondary endpoint outcomes in LUCENT-1 and LUCENT-2

Figure 1 shows the primary endpoint of clinical remission and major secondary endpoints of clinical response, endoscopic improvement, HEMI, bowel urgency remission, and corticosteroid-free clinical remission at week 12 (LUCENT-1) and week 52 (LUCENT-2). In both trials, a significantly greater proportion of patients achieved clinical remission and all secondary outcomes in the mirikizumab group versus the placebo group in patients with a baseline mMS of 5–9, which is consistent with the findings reported in patients with a baseline mMS of 4–9 (Tables S3 and S4).[9,11] Endpoint definitions for clinical remission, corticosteroid-free clinical remission, HEMI, and bowel urgency remission for patients with baseline mMS of 4–9 and 5–9 are specified in Tables S3 and S4, respectively.

Clinical outcomes by prior therapies in LUCENT-1 and LUCENT-2

Across subgroups by type of prior experience with biologic/JAKi treatment (biologic and JAKi treatment naïve and treatment failure of biologics/JAKi, biologics, TNFi, and/or vedolizumab), larger proportions of patients receiving mirikizumab versus placebo achieved clinical remission, endoscopic improvement, and HEMI at week 12 of LUCENT-1 (Figure 2). The efficacy of mirikizumab was consistently demonstrated with even greater magnitude across the various bio-naïve and bio-experienced subgroups at week 52 of LUCENT-2 (Figure 3). The impact of mirikizumab on clinical, endoscopic, and histologic endpoints by types of prior biologic/JAKi experience for patients with a baseline mMS of 5–9 and 4–9 is summarized in Tables S3 and S4. The clinical, endoscopic, and histologic differences were consistently observed with mirikizumab induction and maintenance treatment regardless of the number of prior biologics/JAKi failed in both populations with an mMS of 5–9 and 4–9 (Table S5).

Patient-reported outcomes from LUCENT-1 and LUCENT-2

The impact of mirikizumab on PROs is presented in Figure 4. The IBDQ response was observed in 73% (mirikizumab) versus 54% (placebo) of patients at week 12 of LUCENT-1 and 80% (mirikizumab) versus 49% (placebo) of patients at week 52. The IBDQ remission was achieved by 56.6% (mirikizumab) versus 37.8% (placebo) of patients in LUCENT-1 and by 71.2% (mirikizumab) versus 42% (placebo) in LUCENT-2. Mirikizumab-treated patients had a greater improvement in work productivity than placebo-treated patients, as illustrated by reductions in activity impairment, presenteeism, and overall work impairment at weeks 12 and 52. A similar trend was observed in fatigue improvement. The proportion of patients achieving symptomatic remission was 45% versus 29% at week 12 and 72% versus 39% (mirikizumab vs. placebo) at week 52. Tables S6 and S7 display the patient-reported endpoints for the 5–9 mMS population as well as the 4–9 mMS patient population side by side at week 12 and week 52, respectively.

Long-term efficacy data in LUCENT-3

Figure 5 shows the clinical remission and other key outcomes from the LUCENT-3 long-term extension study following 2-year continuous treatment with mirikizumab for patients with induction baseline mMS of 5–9. About 63%

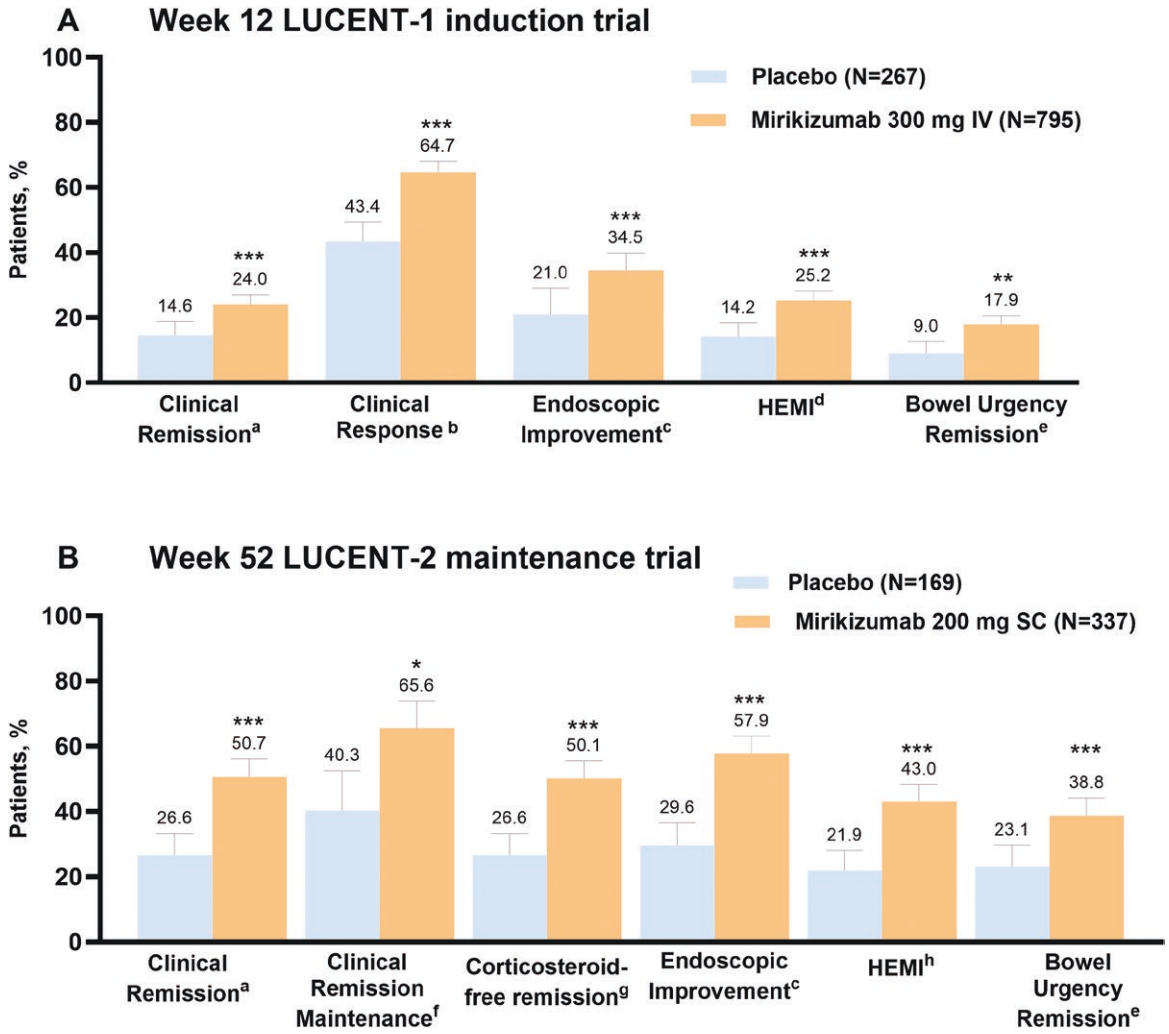

Figure 1. The primary endpoint (clinical remission) and major secondary endpoints at week 12 of the LUCENT-1 induction trial (A) and week 52 of the LUCENT-2 maintenance trial (B) among patients with induction baseline mMS of 5–9. Error bars indicate the upper limit of the 95% confidence intervals for each outcome unless otherwise specified. *P < .01, **P = .001, ***P < .001. [a]Clinical remission is defined as an SF of 0 or 1, with a ≥1-point decrease from baseline, RB of 0, and ES of 0 or 1 (excluding friability). [b]Clinical response is defined as a ≥2-point and ≥30% decrease in mMS from baseline, RB of 0 or 1, or RB ≥1-point decrease from baseline. [c]Endoscopic improvement is defined as an ES of 0 or 1 (excluding friability). [d]HEMI is defined as both endoscopic improvement (centrally read ES of 0 or 1, excluding friability) and histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system). [e]Bowel urgency remission is defined as an Urgency NRS weekly average score of 0 to 1 among subjects with a baseline Urgency NRS of ≥3. At week 12: placebo N = 245, mirikizumab N = 728; at week 52: placebo N = 160, mirikizumab N = 307. [f]Clinical remission maintenance is defined as achievement of clinical remission at Week 52 in patients who were in clinical remission at Week 12; Placebo N = 62, Mirikizumab N = 128. [g]CSF clinical remission is defined as clinical remission at week 40 and no corticosteroid use for ≥12 weeks prior to the week 40 assessment. [h]HEMI is defined as both endoscopic improvement (centrally read ES of 0 or 1, excluding friability) and histologic improvement (no neutrophils in crypts or lamina propria, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system). CSF, corticosteroid-free; ES, endoscopic subscore; HEMI, histologic–endoscopic mucosal improvement; IV, intravenous; mMS, modified Mayo score; NRS, numeric rating scale; RB, rectal bleeding; SC, subcutaneous; SF, stool frequency.

of patients achieved clinical remission at week 104 among the mirikizumab responders at week 52. The proportion of patients on mirikizumab also achieving corticosteroid-free clinical remission, endoscopic improvement, HEMI, and bowel urgency remission at 2 years were 61.0%, 66.4%, 51.6%, and 54.3%, respectively. The corresponding endpoints from patients with baseline mMS of 4–9 have been previously reported and are also included in Table S8.[12]

Safety and Immunogenicity

Safety

Analysis of the safety population for LUCENT-1 and LUCENT-2 shows that mirikizumab-treated patients had a numerically lower frequency of serious adverse events (AEs) and treatment discontinuations than placebo-treated patients. The most common AEs (≥2%) associated with mirikizumab treatment were upper respiratory tract infections and arthralgia during LUCENT-1 induction and upper respiratory tract infections, injection site reactions, arthralgia, rash, headache, and herpes viral infection during LUCENT-2 maintenance.[9,11] The 2-year safety data (LUCENT-3) of mirikizumab are consistent with the findings from LUCENT-1 and LUCENT-2, and no new safety signals were identified.[9,11]

Immunogenicity

Among patients who were treated with mirikizumab in both LUCENT-1 and LUCENT-2 and eligible for anti-drug antibody (ADA) evaluation, 23% (n = 88/378) developed ADAs.

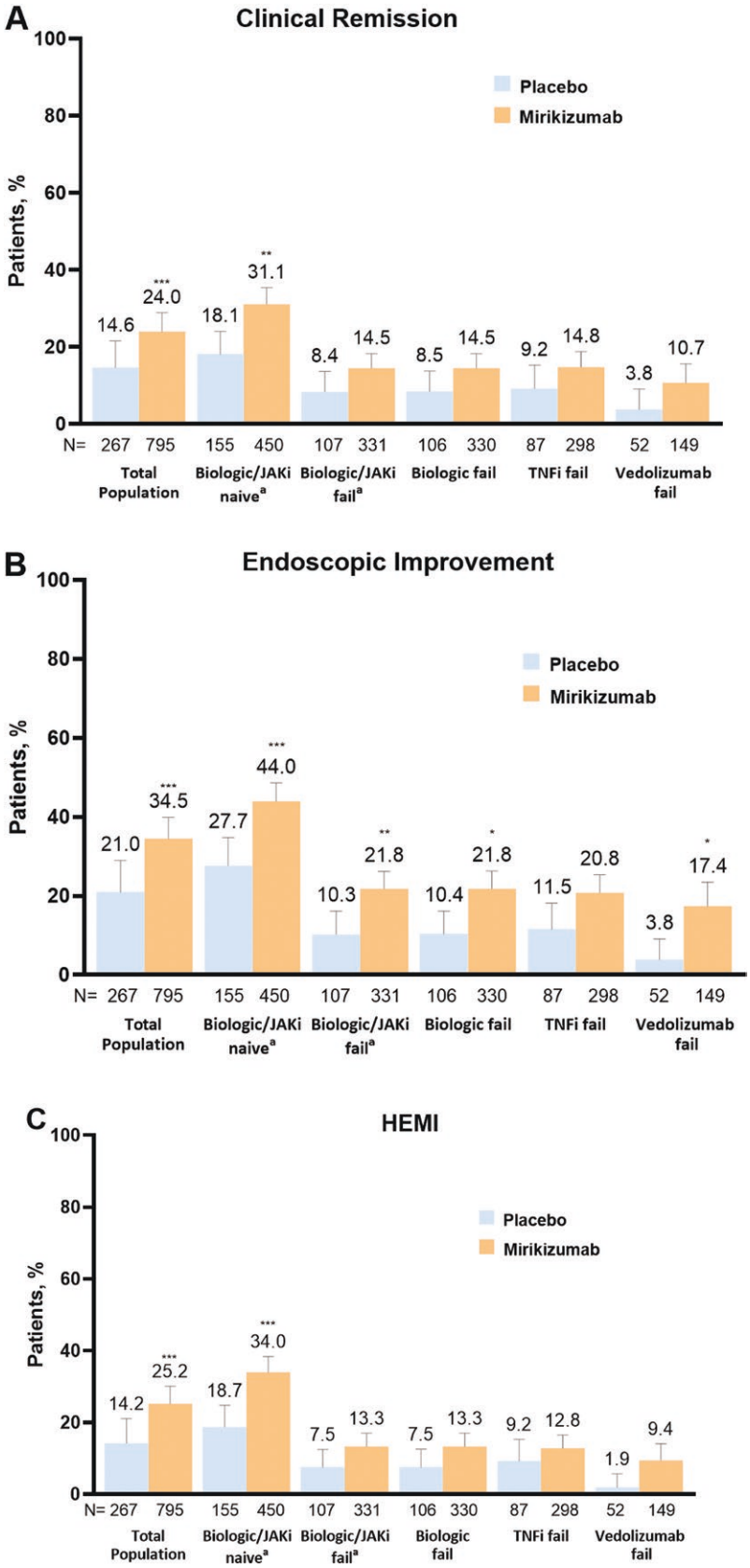

Figure 2. Efficacy by prior types of biologic/JAKi therapies at week 12 in LUCENT-1 in patients with baseline mMS of 5–9: clinical remission (A), endoscopic improvement (B), and HEMI (C). Error bars on the figures represent the upper 95% confidence intervals for each outcome. The definitions for each endpoint remained consistent with those outlined in Figure 1 or as otherwise annotated. **P* < .05, ***P* < .01, ****P* < .001. [a]Tofacitinib was the only JAKi available at the time of the study. HEMI, histologic–endoscopic mucosal improvement; JAKi, Janus kinase inhibitor; mMS, modified Mayo score; TNFi, tumor necrosis factor inhibitor.

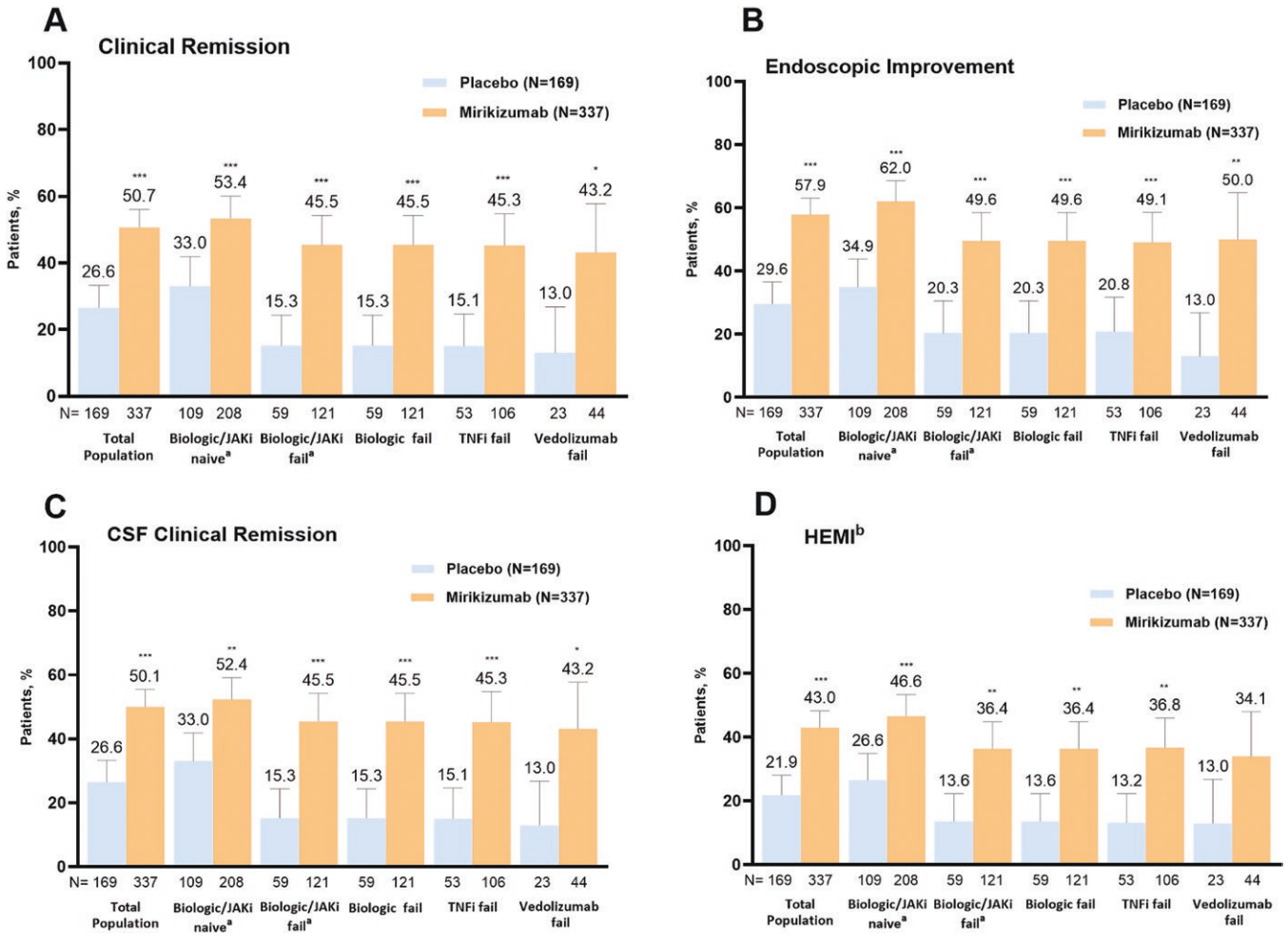

Figure 3. Efficacy by prior types of biologic/JAKi therapies at week 52 in LUCENT-2: clinical remission (A), endoscopic improvement (B), CSF clinical remission (C), and HEMI (D). Error bars on the figures represent the upper 95% confidence intervals for each outcome. The definitions for each endpoint remained consistent with those outlined in Figure 1 or as otherwise annotated. *$P < .05$, **$P < .01$, ***$P < .001$. [a]Tofacitinib was the only JAKi available at the time of the study. [b]HEMI is defined as both endoscopic improvement (centrally read ES of 0 or 1, excluding friability) and histologic improvement (no neutrophils in crypts or lamina propria, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system). CSF, corticosteroid-free; HEMI, histologic–endoscopic mucosal improvement; JAKi, Janus kinase inhibitor; mMS, modified Mayo score; TNFi, tumor necrosis factor inhibitor.

Of those who developed ADAs, 38% (n = 33/88) developed titers ≥1:160. Of these 33 mirikizumab-treated patients, 10 had reduced serum trough concentrations of mirikizumab compared to patients who did not develop mirikizumab ADAs, and 5 of these 10 patients did not achieve clinical response at week 52. Therefore, less than 2% of assessed patients did not achieve clinical response attributable to ADAs. There are insufficient data to assess whether the observed ADA-associated pharmacokinetic changes reduced effectiveness or if this was due to other factors. There is no identified clinically significant effect of ADAs on the safety of mirikizumab over the treatment duration of 52 weeks.[13]

Discussion

Treatment of moderately to severely active UC with mirikizumab involves a novel mechanism of selective binding of the p19 subunit of interleukin-23. In both phase 3 and long-term extension studies, mirikizumab demonstrated significant clinical benefits and proved effective in inducing and maintaining long-term clinical, endoscopic, and histologic remission, bowel urgency remission, and other outcomes significant to patients. Improvements in clinical, endoscopic, and histologic outcomes were observed with mirikizumab induction and maintenance treatment, regardless of the number, and type of prior treatment failures with biologics/JAKi. The clinical benefits were also consistently demonstrated in patients with baseline mMS of 4–9 and those with mMS of 5–9, maintaining a favorable safety profile.[12]

The mMS is a commonly used UC disease severity assessment tool recommended for use by the FDA to support registration trials. The FDA recently updated their Guidance Document to better define the trial population for moderately to severely active UC, stating that patients should have an mMS of 5–9, including an endoscopy subscore of at least 2.[4] The phase 3 LUCENT trials supporting the registration of mirikizumab for treatment of moderately to severely active UC were completed prior to the recommendations of the new mMS guidelines, so the previously published data were based on a baseline patient population with mMS of 4–9.[9] To support mirikizumab review and subsequent approval in the United States, in this report these data were therefore

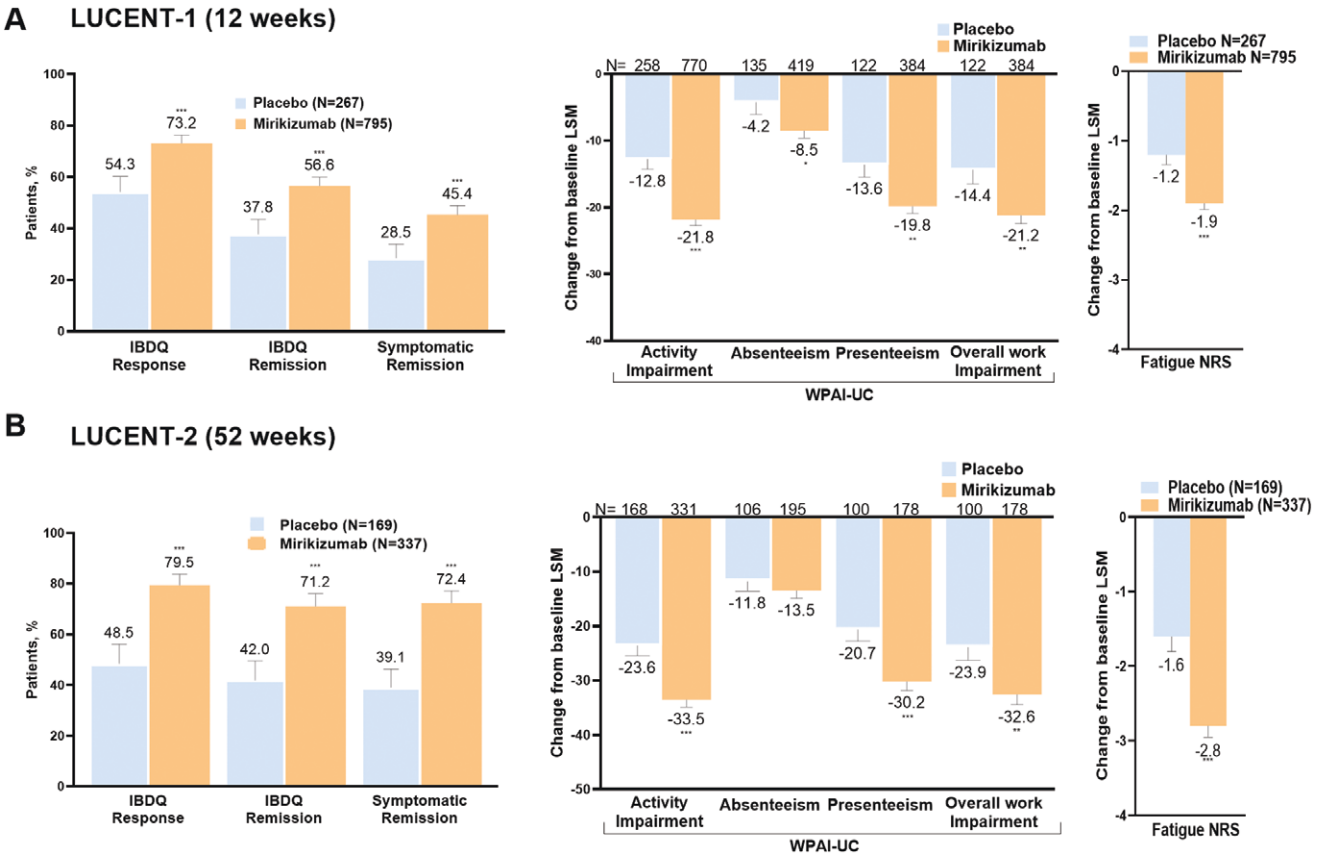

Figure 4. Patient-reported outcomes from LUCENT-1 (A) and LUCENT-2 (B) for patients with induction baseline mMS of 5–9. Error bars on the figure represent the upper limit of the 95% confidence intervals (left) and standard error (center and right). *$P < .05$, **$P < .01$, ***$P < .001$. IBDQ remission, IBDQ response, and systematic remission were analyzed with a Cochran-Mantel-Haenszel test with adjustment for stratification factors (corticosteroid use [yes/no] at LUCENT-1 baseline, prior biologic or tofacitinib failure [yes/no], baseline disease activity [mMS: 5–6, 7–9], and geographic region [North America, Europe, and Other]). For LUCENT-2, clinical remission at LUCENT-1 week 12 (yes/no) replaces baseline disease activity. WPAI and fatigue outcomes were analyzed with an analysis of covariance model that included trial group, baseline value, corticosteroid use (yes/no) at LUCENT-1 baseline, prior biologic or tofacitinib failure (yes/no), baseline disease activity (mMS: [5–6] or [7–9]), and geographic region (North America, Europe, and Other). For LUCENT-2, clinical remission at LUCENT-1 week 12 (yes/no) replaces baseline disease activity. Presenteeism, absenteeism, and work impairment are in patients with baseline employment. Overall work impairment score, aggregate of absenteeism and presenteeism. IBDQ, Inflammatory Bowel Disease Questionnaire; LSM, least square means; mMS, modified Mayo score; NRS, numeric rating scale; Presenteeism, reduced productivity while at work; WPAI-UC, Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis

analyzed using the patient population with mMS of 5–9 (excluding patients with scores of 4). As shown in Figure S1, this analysis does not include 100 patients from LUCENT-1 with an mMS of 4 ($n = 27$ from placebo, $n = 73$ from mirikizumab treatment), as well as 38 patients from LUCENT-2 ($n = 10$ from placebo, $n = 28$ from mirikizumab treatment). Although a small population difference overall, it does have the potential to elucidate specific trends and was deemed to be sufficient to analyze based on the updated FDA guidance.

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) II recommendations extend beyond symptomatic or endoscopic improvement and introduce more rigorous goals such as resolving acute inflammatory cell infiltration evident on histologic testing.[19] Growing evidence suggests that microscopic activity persists even in cases of endoscopically quiescent UC, and the absence of histological activity is linked to lower rates of relapse, hospitalization, surgery, and subsequent neoplasia.[20,21] Recent literature advocates the absence of intraepithelial neutrophils as a minimal requirement for remission based on histologic testing.[22,23] In line with the recommendations and emerging advocacies, achieving HEMI at the end of the LUCENT maintenance trial and 2 years of long-term study necessitate the absence of mucosal neutrophils, which accumulate with persistent acute inflammation in UC. Notably, after 1 year of treatment with mirikizumab, over 40% of patients had no mucosal neutrophils and over 50% of patients showed maintained improvement at 2 years among those who had an initial response to mirikizumab after the maintenance trial.[9,11]

Despite significant progress in understanding UC and the availability of diverse treatment options for its many clinical manifestations, there remains an unmet need for patients in whom advanced therapies, including biologics and JAKis, have failed. Notably, this analysis reports clinical remission of mirikizumab-treated patients who were biologic/JAKi naïve reached 53% at Week 52, while those who were biologic/JAKi treatment failures reached 46%. Moreover, the difference between mirikizumab treatment and placebo for all primary and major secondary endpoints, was always higher in biologic/JAKi failed patients at 52 weeks compared to biologic/JAKi naïve. Additionally, at 52 weeks, efficacy for all measured outcomes remained above 41% for

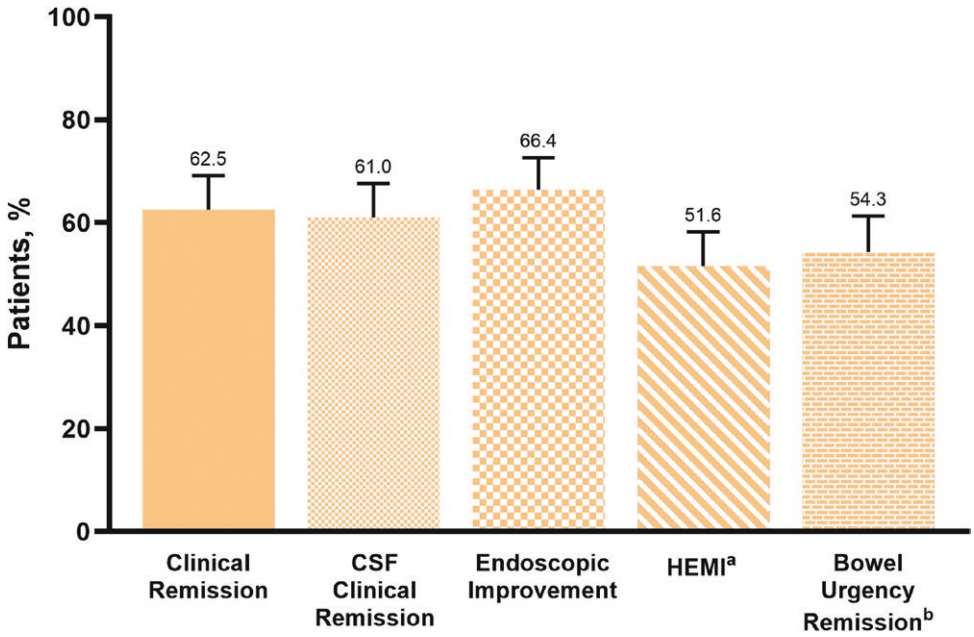

Figure 5. Efficacy at 104 weeks (2 years) of continuous treatment for clinical remission, CSF clinical remission, endoscopic improvement, HEMI, and bowel urgency remission (mMS of 5–9 at LUCENT-1 baseline, mNRI) for maintenance responders in LUCENT-3. Error bars on the figure represent the upper 95% confidence intervals for each outcome. The outcome definitions remained consistent with those outlined in Figure 1 or as otherwise specified below. [a]HEMI is defined as both endoscopic improvement (centrally read endoscopic subscore of 0 or 1, excluding friability) and histologic improvement (no neutrophils in crypts or lamina propria, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system). [b]Bowel urgency remission is defined as an Urgency NRS weekly average score of 0–1. CSF, corticosteroid-free; HEMI, histologic–endoscopic mucosal improvement; mMS, modified Mayo Score; mNRI, modified nonresponder imputation; NRS, numeric rating scale.

mirikizumab-treated patients who had previously failed ≥2 prior biologic treatments. Together, these results demonstrate that mirikizumab can serve as both a first-line treatment as well as a second-line and above option for those who failed their advanced therapies.

An essential unmet need for patients diagnosed with UC is understanding the impact of the condition on their ability to lead a normal life. In patients with baseline mMS of 4–9 and 5–9, mirikizumab demonstrated substantially greater improvements in IBDQ, and symptomatic remission compared to those who received placebo.[24] Compared to placebo, mirikizumab exhibited noteworthy improvement in activity impairment, presenteeism, and overall work impairment at both week 12 and week 52.

The American College of Gastroenterology guidelines for managing UC define disease remission, including the absence of bowel urgency.[25] In the LUCENT trial program, new endpoints related to bowel urgency were introduced by assessing bowel urgency severity using a validated patient-reported Urgency Numeric Rating Scale. Patients reported reductions in bowel urgency severity with mirikizumab, and these improvements were sustained during the maintenance trial in patients with baseline mMS of both 4–9 and 5–9.[9]

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, and endoscopic remission. The current data demonstrate long-term (104 weeks) sustained, durable efficacy of mirikizumab in most patients who initially responded to treatment, long-term efficacy benefits across all studied endpoints for patients with both mMS baseline scores of 4–9 and 5–9, and a positive benefit-risk safety profile. Although the sample size for the mMS 5–9 subgroup was smaller than for the mMS 4–9 subgroup, significant findings were still demonstrated for primary and key secondary outcomes in both groups. No new safety signals were identified across the LUCENT trial program, and the discontinuation rate due to AEs was very low.

Although some patients developed ADAs, less than 2% of assessed patients did not achieve clinical response due to ADAs or experience clinically meaningful impact on clinical efficacy and tolerability. This could be due to factors such as not reaching sufficient ADA levels, low persistence of ADA levels over time, patient- and drug-specific factors, or low ADA-neutralizing capacity that do not significantly affect drug bioavailability and activity.[5–8] When ADAs are present at a high enough titer, pharmacokinetics of therapeutic drugs may be altered and brought below the therapeutic threshold, thereby impacting efficacy.[1] Anti-drug antibodies are clinically relevant if they impact clinical endpoints including safety, efficacy, or drug levels.[2] Additionally, ADA assays are not comparable across molecules. Detection of antibody formation is highly dependent on the sensitivity and specificity of the particular assay. The positivity of an assay may be influenced by several factors (assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease).[13]

Several aspects necessitate further investigation, including the efficacy and safety of mirikizumab in older adults and other patient populations not well represented in the initial clinical development program as well as its impact on pregnant or breastfeeding women. The outcomes of the long-term extension study may be influenced by investigators selectively including patients believed to benefit from continued treatment with mirikizumab. The utility of patient subgroups that have used different primary treatments prior to mirikizumab will likely be of clinical interest but some treatments were

outside the scope of this study. As previously reported, LUCENT placebo groups generally had higher rates than those of other UC studies.[9,26–28] Finally, the patients enrolled in the clinical trials may not represent the broader real-world UC population. Consequently, assessing mirikizumab in real-world studies becomes essential.

Conclusions

Here, we report trial data using the recent FDA guidance, employing the definition of mMS of 5–9 for moderately to severely active UC. Mirikizumab demonstrated comparable treatment effect size for primary efficacy and key secondary endpoints for the patient population with a baseline mMS score of 5–9 compared to the patient population with a baseline mMS score of 4–9. Overall, mirikizumab consistently provided clinical benefits irrespective of patients' baseline mMS while maintaining a favorable safety profile.

Supplementary Data

Supplementary data are available at *Crohn's & Colitis 360* online.

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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. B.A., S.V., G.M., R.U., A.C., E.L.B., A.C.E., and D.T.R. contributed to the conception of the work and the study design. J.P. and B.Z. contributed to the data analysis. All authors contributed to 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.

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Conflicts of Interest

A.D. holds the position of Deputy Editor for *Crohn's & Colitis 360* and has been recused from reviewing or making decisions for the manuscript. Dr. Charabaty is also a consultant and advisory board member for AbbVie, Eli Lilly and Company, Janssen, Pfizer, and Takeda. E.L.B. is a consultant for AbbVie. A.C.E. is a consultant and speaker for AbbVie, Bristol Myers Squibb, and Eli Lilly and Company; consultant for Janssen; and speaker for Nestlé/Aimmune Therapeutics.

Data Availability

Data are available on reasonable request. Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization. Data are available to request after primary publication acceptance. No expiration date for data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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