Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease: a phase 3, multicentre, randomised, double-blind, placebo-controlled and active-controlled, treat-through study

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Summary

Background Mirikizumab, a humanised monoclonal antibody that inhibits IL-23p19, is effective in moderate-to-severe ulcerative colitis. We aimed to evaluate the efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease.

Methods VIVID-1 was a global phase 3, randomised, double-blind, double-dummy, placebo-controlled and active-controlled, treat-through study. The study enrolled adult patients at 324 sites (hospitals or medical centres, clinical practices, and clinical research sites) in 33 countries across Europe, Asia, North America, Central America, South America, and Australia. Adult patients with moderately-to-severely active Crohn's disease and previous inadequate response, loss of response, or intolerance to one or more approved biological therapies or conventional therapies were randomly assigned 6:3:2 to receive mirikizumab 900 mg intravenously at weeks 0, 4, and 8, then 300 mg subcutaneously every 4 weeks from weeks 12 to 52; ustekinumab about 6 mg/kg intravenously at week 0, then 90 mg subcutaneously every 8 weeks from weeks 8 to 52; or placebo. The coprimary endpoints assessing superiority of mirikizumab over placebo were composite endpoints: patient-reported outcome (PRO) clinical response at week 12 and endoscopic response at week 52 (endoscopic response-composite), and PRO clinical response at week 12 and Crohn's Disease Activity Index (CDAI) clinical remission at week 52 (CDAI clinical remission-composite). The adjusted risk differences were calculated, and the comparison was performed by the Cochran–Mantel–Haenszel test. Non-responder imputation was used. VIVID-1 was registered on ClinicalTrials.gov, NCT03926130, and is now complete.

Findings Between July 23, 2019, and Aug 23, 2023, 1150 patients were randomly assigned and received study treatment (safety population); 1065 patients were included in the efficacy population and received mirikizumab (n=579), ustekinumab (n=287), or placebo (n=199). Both coprimary endpoints were met: endoscopic response-composite was reached in 220 (38·0%) of 579 patients on mirikizumab versus 18 (9·0%) of 199 on placebo (99·5% CI 20·6–36·8; p<0·0001); CDAI clinical remission-composite was reached in 263 (45·4%) of 579 patients on mirikizumab versus 39 (19·6%) of 199 patients on placebo (99·5% CI 15·9–35·6; p<0·0001). The incidence rates of overall adverse events and discontinuations in patients treated with mirikizumab were lower compared with placebo. The most common adverse event across the three groups was COVID-19. Serious adverse events were reported in 65 (10·3%) of 630 patients on mirikizumab, 33 (10·7%) of 309 patients on ustekinumab, and 36 (17·1%) of 211 patients on placebo. There were three deaths during VIVID-1, one in the ustekinumab group, and two in the placebo group, including one in a placebo non-responder who switched to mirikizumab after week 12. None of the deaths were considered related to the study drug. The safety of mirikizumab in Crohn's disease was consistent with its known favourable profile.

Interpretation Mirikizumab was safe and effective as induction and maintenance treatment for patients with moderately-to-severely active Crohn's disease who had intolerance, inadequate response, or loss of response to standard therapy.

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Introduction

Crohn's disease is a chronic, progressive, immune-mediated inflammatory bowel disease characterised by transmural inflammation[1–3] that, if not adequately treated, might result in irreversible bowel damage and disability.[4] Current treatment targets include early symptom control and resolution of objective markers of inflammation such as biomarkers and endoscopic activity.[5] Even more, the

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed using the terms "Crohn's disease," "biologic therapy," and "selective Janus kinase inhibitors" for research articles from database inception to Oct 31, 2023, in English. Most clinical development programmes in Crohn's disease to date were designed with placebo-controlled induction studies followed by a placebo-controlled, randomised withdrawal maintenance study in induction responders. Biological therapies, such as tumour necrosis factor inhibitors and anti-integrins, are a major advance in the treatment of inflammatory bowel diseases, and more recently, Janus kinase inhibitors have also become available. However, many patients with moderately-to-severely active Crohn's disease do not respond, lose response over time, or have side-effects leading to discontinuation. Mirikizumab, a monoclonal antibody specifically binding to the p19 subunit of IL-23, has shown to be effective in the treatment of ulcerative colitis. The phase 2 study of mirikizumab in moderately-to-severely active Crohn's disease supported the efficacy and safety of mirikizumab in inducing and maintaining clinical remission and endoscopic response, both in patients with and without previous failure to biological therapies.

Added value of this study

VIVID-1 was a placebo-controlled and active-controlled study that evaluated mirikizumab in patients with moderately-to-severely active Crohn's disease. This is the first completed phase 3 study in Crohn's disease with a treat-through design including comparisons to active treatment and placebo over 1 year of treatment. The treat-through design aligns well with clinical practice and aims to better understand long-term treatment effects in the enrolled population, including in initial non-responders. Mirikizumab showed clinically meaningful and statistically significant efficacy, across clinical and endoscopic endpoints up to week 52, including in patients with previous failure to biological therapies. Additionally, mirikizumab showed non-inferiority to ustekinumab on clinical remission by Crohn's Disease Activity Index at week 52. Continued mirikizumab treatment led to improved response rates for treat-through endpoints up to week 52, suggesting that a subset of initial non-responders might benefit from treatment beyond the 12-week induction period. The safety evaluation in patients with Crohn's disease was consistent with the known safety profile of mirikizumab.

Implications of all the available evidence

These findings reinforce the importance of IL-23 in driving the pathogenesis of Crohn's disease and suggest that mirikizumab is a treatment with a favourable benefit–risk profile in patients with moderately-to-severely active Crohn's disease, regardless of previous failure to biological therapies. Although profound differences in study design limit conclusions on relative efficacy between risankizumab and mirikizumab, VIVID-1 and SEQUENCE both suggest a potential benefit for an IL-23 inhibitor over ustekinumab in patients with Crohn's disease and previous failure to biological therapies.

current clinical focus has extended to important patient-centred endpoints (eg, quality of life, prevention of disabilities, and work productivity).[5,6] Collectively, these treatment goals are not easily achieved by current treatments. Furthermore, patients might lose response over time or discontinue therapy due to intolerance.[7–9] Given the chronic and often progressive nature of Crohn's disease, additional new therapeutic options that can deliver robust improvements in symptoms, mucosal healing, and health-related quality-of-life outcomes, and have an improved safety profile, are needed.[10,11]

Studies have shown that a multitude of cytokines are important in the development and perpetuation of Crohn's disease;[12] IL-23 in particular has been proven to be involved in the pathogenesis of Crohn's disease.[13] A polymorphism in the gene encoding IL-23 receptor was found to be associated with inflammatory bowel disease through a genome-wide association study; this study showed that IL-23 is important in mucosal inflammation.[12] IL-23 is mainly expressed by CD14 intestinal macrophages, key players in mediating the perpetuation of inflammation by infiltrating the inflamed intestine of patients with Crohn's disease.[14] IL-23 has two components: the p40 subunit that is shared with IL-12 and the p19 subunit that is unique to IL-23. IL-23 plays a key role in the maintenance and amplification of T-helper-17 cells and stimulation of innate immune cells, which are important in the pathogenesis of Crohn's disease.[15–17] Anti-IL-23 and anti-IL12/23 therapies have been shown to be efficacious in the treatment of Crohn's disease.[18]

Mirikizumab (LY3074828) is a humanised IgG4 selective monoclonal antibody specifically binding to the p19 subunit of IL-23 and is currently approved for the treatment of ulcerative colitis. In a phase 2 study in Crohn's disease, mirikizumab effectively induced endoscopic response, endoscopic remission, clinical response and clinical remission (both patient-reported outcome [PRO] and Crohn's Disease Activity Index [CDAI]) in patients with moderately-to-severely active Crohn's disease with demonstrated durable efficacy to week 52 in patients with and without previous failure to biological therapies.[19,20] We aimed to further evaluate the efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease.

Methods

Study design and trial oversight

VIVID-1 is a phase 3, multicentre, randomised, double-blind, double-dummy, parallel-group, and

placebo-controlled and active-controlled study with a treat-through design, evaluating the safety and efficacy of mirikizumab in patients with moderately-to-severely active Crohn's disease (appendix p 18). The study enrolled adult patients at 324 sites in 33 countries across Europe, Asia, North America, Central America, South America, and Australia. Investigators and sites are listed in the appendix (p 38). At week 0, patients were randomly assigned to receive mirikizumab 900 mg intravenously every 4 weeks for three doses (weeks 0, 4, and 8) and then 300 mg subcutaneously every 4 weeks from week 12 onwards; ustekinumab about 6 mg/kg intravenously for one dose and then 90 mg subcutaneously every 8 weeks from week 8 onwards; or placebo. At week 12, placebo responders continued placebo to week 52; placebo non-responders switched to the masked mirikizumab regimen described above. The study did not include rescue therapy for patients who were assigned to active study drug. This study included a screening period of up to 5 weeks, a 12-week induction period, and a 40-week maintenance period for total treatment duration of 52 weeks. VIVID-1 was registered on ClinicalTrials.gov, NCT03926130, and is now complete.

The VIVID-1 protocol was approved by local ethical review boards and the study was done according to the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The principal investigator was responsible for submitting the protocol, informed consent forms, and other relevant documents to the Institutional Review Board (IRB) to be reviewed and approved by the IRB before the site was initiated. The principal investigator provided oversight of study conduct at the site, ensuring adherence to the requirements of the 21 Code of Federal Regulations, International Conference on Harmonisation guidelines, the IRB, and all other applicable regulations. The principal investigator responsibilities included providing written summaries of the status of the study to the IRB, submitting protocol amendments to the IRB, and notifying the IRB of protocol deviations and safety findings over the course of the study. An external data monitoring committee (appendix p 12) kept oversight of the study. The role of the data monitoring committee was to review unmasked safety data to assess the safety and wellbeing of study participants.

Participants

The VIVID-1 study enrolled patients with demonstrated intolerance, inadequate response, or loss of response to conventional therapies (ie, without previous failure to biological therapies) or to biological therapies (appendix pp 5–6). Eligible patients were aged 18–80 years with a confirmed diagnosis of Crohn's disease by clinical, endoscopic, and histological criteria, for at least 3 months before baseline and with moderately-to-severely active disease defined by an average daily stool frequency of 4 or more, or an average daily abdominal pain score of 2 or more, or both, at baseline, and endoscopic evidence of mucosal inflammation by a Simple Endoscopic Score for Crohn's disease (SES-CD) score of 7 or more (or ≥4 for patients with isolated ileal disease). All endoscopic videos were scored by two masked central readers independently with a third central reader if discrepant scoring occurred between the first two readers. Final SES-CD score reflects the mean of all reader scores (details of the central reading paradigm are in the appendix p 20). Early during enrolment, the protocol was amended to allow enrolment of a subset of patients with an SES-CD of 3 or more to less than 7 for colonic or ileal-colonic disease (SES-CD <4 for participants with isolated ileal disease); these patients were included in the safety analyses but not in the primary population for efficacy analyses. All patients gave written informed consent for participation in the study. For a list of inclusion and exclusion criteria see the appendix (pp 3–11).

Randomisation and masking

Enrolled participants were randomly assigned with an interactive web response system (6:3:2) to receive mirikizumab, ustekinumab, or placebo. Randomisation was stratified by (1) failure to biological therapies (yes or no), (2) baseline corticosteroid use (yes or no), (3) baseline SES-CD total score (<12 or ≥12), (4) region (North America, Europe, or other), and (5) combined stratification factor using either baseline stool frequency of 7 or more or baseline abdominal pain score of 2·5 or more (yes or no), or both. All treatments were masked. To maintain masking, placebo was administered as appropriate, either intravenously, subcutaneously, or both, using a double-dummy design. An unmasked pharmacist (or qualified designee) prepared the intravenous solutions. Study investigators, study site personnel, and participants were masked to treatment allocation. Additional details on randomisation and masking are given in the appendix (p 14).

Procedures

Participants assigned to mirikizumab or placebo received a single dose intravenously at weeks 0, 4, and 8. Participants assigned to ustekinumab received a single intravenous dose at week 0 followed by placebo intravenous administrations at weeks 4 and 8. Subcutaneous injections were administered every 4 weeks for mirikizumab and every 8 weeks for ustekinumab with prefilled manual syringes (for the complete dosing schedule see appendix p 22). Participants taking permitted Crohn's disease concomitant medications were to keep doses stable unless modifications were needed due to adverse events or for appropriate medical management. Corticosteroid doses were to remain stable until week 12. Corticosteroid tapering was required once patients had a clinical response by PRO, at week 12 or after week 12. Unless specified, visits occurred in person. Efficacy and safety assessments occurred during study

visits at weeks 0, 2 (telephone visit), 4, 6 (telephone visit), and 8, and every 4 weeks thereafter up to week 52. Participants recorded symptoms related to Crohn's disease in an electronic daily diary. Blood samples were collected to measure concentrations of high-sensitivity C-reactive protein (CRP) and stool samples were collected to measure faecal calprotectin at weeks 0, 4, 8 (not faecal calprotectin), 12, 16, 28, 44, and 52. Immunogenicity (anti-drug antibodies) samples were collected at weeks 0, 4, 12, 16, 24, 36, and 52. Endoscopy was video-recorded and blindly assessed at screening and at weeks 12 and 52. Safety was monitored throughout the study.

Outcomes

The coprimary composite endpoints (mirikizumab *vs* placebo) of this study were as follows: (1) the proportion of patients who had a clinical response by PRO (≥30% decrease in stool frequency or abdominal pain score, or both, and neither score worse than baseline) at week 12 and clinical remission by CDAI (CDAI score <150) at week 52 (hereafter referred to as week 52 CDAI clinical remission-composite) and (2) the proportion of patients who had a clinical response by PRO at week 12 and endoscopic response (≥50% reduction from baseline in SES-CD total score) at week 52 (hereafter referred to as week 52 endoscopic response-composite). Unless specified, all binary endpoints compared with placebo measured after week 12 are defined as composite endpoints with week 12 clinical response by PRO in consideration of the fact that placebo non-responders are switched to mirikizumab after week 12. Endoscopic response alone and CDAI clinical remission alone were also evaluated as major secondary endpoints (multiplicity controlled) at week 52 regardless of week 12 PRO clinical response (hereafter referred to as week 52 endoscopic response-treat-through and week 52 CDAI clinical remission-treat-through). The other major secondary endpoints (multiplicity controlled) that evaluated superiority of mirikizumab over placebo at week 12 or at week 52 were CDAI clinical remission, PRO (stool frequency and abdominal pain score) clinical remission, PRO clinical response, corticosteroid-free CDAI clinical remission (clinical remission by CDAI at week 52 and corticosteroid-free from weeks 40 to 52), endoscopic response, endoscopic remission, and fatigue improvement as described in the statistical analysis section. Endoscopic remission was defined as an SES-CD total score of 4 or less and at least a 2-point reduction from baseline with no subscore of more than 1. The criteria of no subscore more than 1 was determined using both a prespecified stringent calculation and a post-hoc conventional calculation (appendix p 24). The conventional analysis is consistent with previous trials,[21,22] and prevents patients with minimal findings being classified as not having an endoscopic remission. Two major secondary endpoints assessed mirikizumab versus ustekinumab for non-inferiority in CDAI clinical remission at week 52 (week 52 CDAI clinical remission-treat-through) and for superiority in endoscopic response at week 52 (week 52 endoscopic response-treat-through). Definitions of the above-mentioned endpoints are provided in the appendix (p 24), and additional secondary endpoints, including improvements in bowel urgency, fatigue, and health-related quality of life, will be reported in future publications.

Safety assessments included incidence of adverse events, such as serious adverse events and adverse events of special interest defined in the protocol (infusion and injection site reactions, hypersensitivity, infections, cerebro-cardiovascular event, malignancies, depression, suicide and self-injury, and hepatic safety), changes in vital signs or laboratory analyses, and results of physical examination in all patients who received at least one dose of study drug (safety population). A treatment-emergent adverse event was defined as an event that first occurred or worsened in severity after baseline. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 26.0).

Safety analyses were done to compare exposure adjusted incidence rates at week 52 for the three randomised groups: mirikizumab, ustekinumab, and placebo. For patients on placebo, only data from when they were on placebo were included in the safety analysis.

Statistical analysis

The sample size was calculated to provide more than 90% power to detect treatment differences between mirikizumab and placebo for each coprimary endpoint using a χ^2 test at a two-sided α level of 0·005, assuming that treatment response rates of both coprimary endpoints are 33% for mirikizumab and 10% for placebo (appendix pp 14–16). The primary analysis set (efficacy population) included participants who had a baseline SES-CD of at least 7 (≥4 for isolated ileal disease) and received at least one dose of study drug. The coprimary and major secondary endpoints were also analysed between the subgroups: baseline demographics (appendix pp 28–29), baseline disease characteristics (appendix pp 30–31), and with and without previous failure to biological therapies (appendix pp 26–27). The safety population represented all randomly assigned patients who received at least one dose of study drug. The coprimary endpoints were analysed separately with each coprimary endpoint having to meet statistical significance to claim study success. To control the family wise type I error rate of the primary and major secondary endpoints, a graphical multiple testing procedure was used (appendix p 18). The primary and major secondary endpoints comparisons between mirikizumab and placebo were controlled at a family wise error rate of 0·005, whereas the overall family wise error rate of all primary and major secondary endpoints including comparison of mirikizumab versus ustekinumab were controlled at 0·05 (appendix p 16).

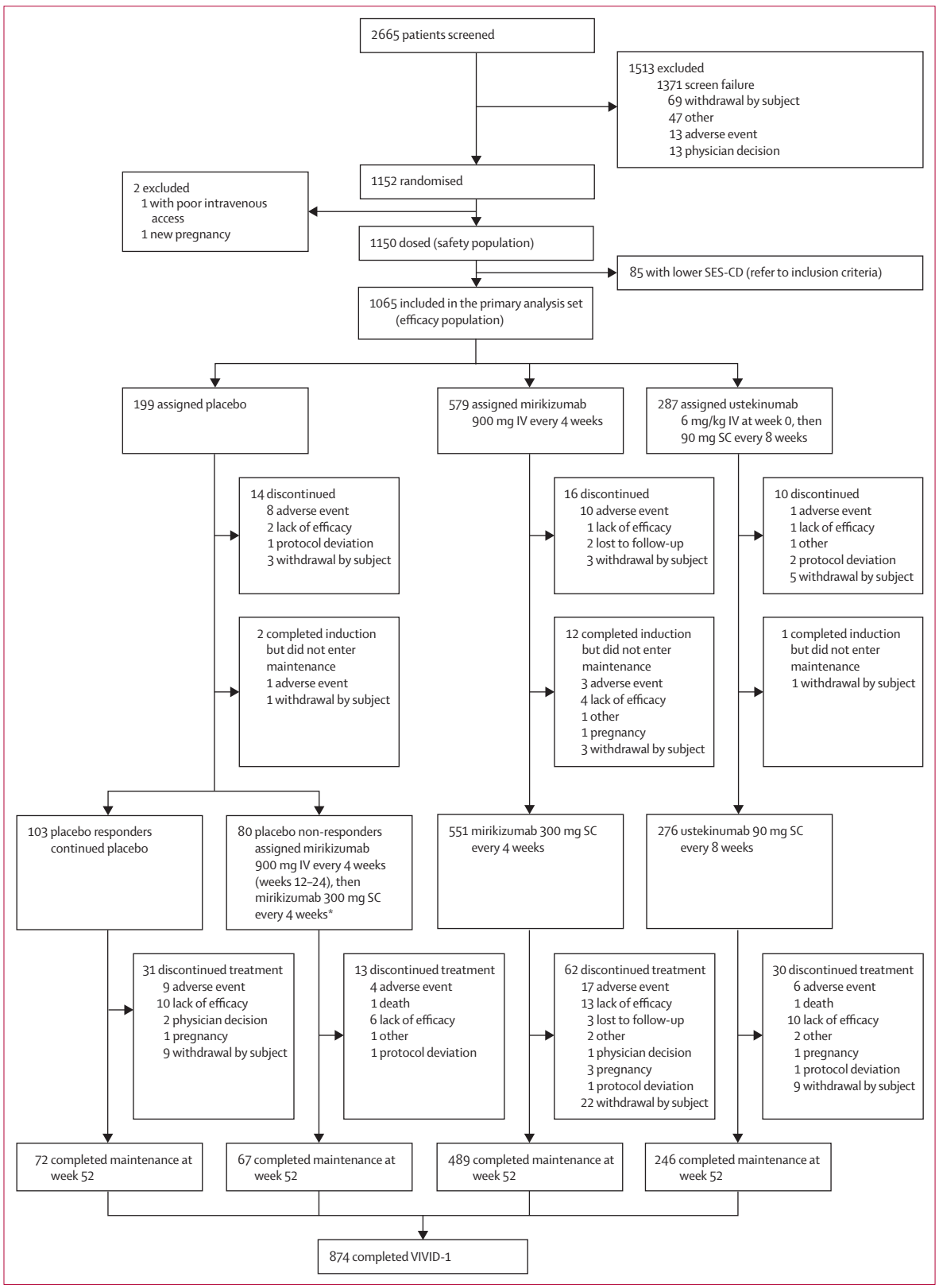

Figure 1: **Trial profile**
All participants who signed informed consent were screened (n=2665). All randomly assigned participants, even if they did not take the assigned study intervention, did not receive the correct study intervention, or otherwise did not follow the protocol, were included in the ITT population (n=1152). All participants in the ITT population who took at least one dose of study intervention, were included in the safety population (n=1150). All participants in the safety population with a baseline SES-CD of at least 7 (≥4 for isolated ileal disease) were included in the primary analysis set (n=1065). IV=intravenously. ITT=intention-to-treat. SC=subcutaneously. SES-CD=Simple Endoscopic Score for Crohn's disease. *Placebo non-responders at week 12 were reassigned to mirikizumab 900 mg IV every 4 weeks until week 24, then mirikizumab 300 mg SC every 4 weeks.

All categorical endpoints of superiority comparison were analysed with the Cochran–Mantel–Haenszel test adjusted by stratification factors. Subgroups were analysed using Fisher's exact test. Categorical endpoints of non-inferiority comparison were analysed using a Z test on the adjusted risk difference with a 10% non-inferiority margin. A prespecified non-inferiority margin of 10% was used as this margin was expected to preserve 50% of the ustekinumab effect in CDAI remission at week 52. Non-responder imputation was used for categorical endpoints; that is, patients with missing data at the timepoint of interest were counted as non-responders. Categorical endpoints measured after specified changes in the concomitant Crohn's disease medication were also counted as non-responders. Adjusted percentage difference with 99·5% and 95% CIs and p values was calculated based on the Cochran–Mantel–Haenszel test adjusted for strata (failure to biological therapies [yes or no], baseline SES-CD total score [<12 or ≥12], and either baseline stool frequency ≥7 or baseline abdominal pain score ≥2·5 [yes, no, or unknown]) for the comparison of treatment groups. Continuous endpoints were analysed by analysis of covariance with modified baseline observation carried forward at each timepoint separately.

	Mirikizumab (n=579)	Ustekinumab (n=287)	Placebo (n=199)	Total (n=1065)
Age, years	36·0 (13·2)	36·6 (12·7)	36·3 (12·7)	36·2 (13·0)
Sex				
Male	332 (57·3%)	137 (47·7%)	118 (59·3%)	587 (55·1%)
Female	247 (42·7%)	150 (52·3%)	81 (40·7%)	478 (44·9%)
Weight, kg	68·02 (18·3)	66·86 (17·6)	69·55 (19·0)	67·99 (18·3)
BMI	23·2 (5·4)	23·3 (5·5)	23·8 (5·8)	23·4 (5·5)
Race				
White	408 (71·5%)	201 (70·3%)	144 (74·6%)	753 (71·7%)
Black or African American	10 (1·8%)	8 (2·8%)	5 (2·6%)	23 (2·2%)
Asian	148 (25·9%)	74 (25·9%)	42 (21·8%)	264 (25·1%)
American Indian or Alaska Native	2 (0·4%)	2 (0·7%)	2 (1·0%)	6 (0·6%)
Multiple	3 (0·5%)	1 (0·3%)	0	4 (0·4%)
Geographical region				
Europe and rest of world	319 (55·1%)	155 (54·0%)	117 (58·8%)	591 (55·5%)
North America	77 (13·3%)	37 (12·9%)	27 (13·6%)	141 (13·2%)
Central America or South America	30 (5·2%)	20 (7·0%)	9 (4·5%)	59 (5·5%)
Asia	153 (26·4%)	75 (26·1%)	46 (23·1%)	274 (25·7%)
Duration of Crohn's disease, years	7·4 (8·2)	7·2 (7·7)	7·8 (7·4)	7·4 (7·9)
History of surgical bowel resection, yes	89 (15·4%)	29 (10·1%)	33 (16·6%)	151 (14·2%)
Disease location				
Ileum only	65 (11·2%)	29 (10·1%)	19 (9·5%)	113 (10·6%)
Colon only	225 (38·9%)	120 (41·8%)	77 (38·7%)	422 (39·6%)
Ileum and colon	289 (49·9%)	138 (48·1%)	103 (51·8%)	530 (49·8%)
Baseline Crohn's Disease Activity Index	323·1 (85·8)	318·5 (93·2)	318·9 (86·2)	321·1 (87·9)
Stool frequency daily average	5·7 (3·0)	5·7 (2·9)	5·8 (3·2)	5·7 (3·0)
Abdominal pain score daily average	2·1 (0·6)	2·1 (0·6)	2·1 (0·6)	2·1 (0·6)
SES-CD total score	13·5 (6·6)	13·9 (6·6)	13·1 (6·0)	13·5 (6·5)
Mean C-reactive protein, mg/L	8·5 (2·9–25·0)	8·9 (3·4–24·8)	7·6 (2·9–18·8)	8·3 (3·0–23·7)
Mean faecal calprotectin, mg/kg	1315·0 (444·0–2676·0)	1489·0 (519·0–2814·0)	1161·0 (324·0–2170·0)	1315·0 (452·0–2610·0)
Corticosteroid use	177 (30·6%)	90 (31·4%)	58 (29·1%)	325 (30·5%)
Immunomodulator use	146 (25·2%)	87 (30·3%)	58 (29·1%)	291 (27·3%)
Previous biologic failure	281 (48·5%)	139 (48·4%)	97 (48·7%)	517 (48·5%)
Previous anti-tumour necrosis factor failure	265 (45·8%)	133 (46·3%)	89 (44·7%)	487 (45·7%)
Previous anti-integrin failure	68 (11·7%)	31 (10·8%)	24 (12·1%)	123 (11·5%)
Number of failed biologics				
None	298 (51·5%)	148 (51·6%)	102 (51·3%)	548 (51·5%)
1	175 (30·2%)	91 (31·7%)	66 (33·2%)	332 (31·2%)
≥2	106 (18·3%)	48 (16·7%)	31 (15·6%)	185 (17·4%)

Data are mean (SD), n (%), or median (IQR). SES-CD=Simple Endoscopic Score for Crohn's disease.

Table 1: **Patient demographics and baseline characteristics for the primary analysis set**

For measurements after study intervention discontinuation, specified changes in the concomitant Crohn's disease medication or participants in the placebo group switching to mirikizumab, the baseline observation carry forward method was used for imputation. For sporadically missing measurements, the last non-missing observation before the sporadically missing data was used for imputation. Safety and immunogenicity data were summarised descriptively.

Role of the funding source

Eli Lilly and Company contributed to study design, data collection, data analysis, data interpretation, manuscript preparation, and the decision to submit the manuscript for publication. An academic advisory committee was also involved in the study design and data interpretation, together with authors from Eli Lilly and Company.

Results

The VIVID-1 study was done from July 23, 2019, to Aug 23, 2023. 2665 patients were assessed for eligibility. 1150 patients were randomly assigned and took at least one dose of study treatment (safety population) and of those, 1065 had a baseline SES-CD of 7 or greater (≥4 for isolated ileal disease) and were included in the efficacy population (figure 1). Of the 1065 patients, 199 were assigned placebo, 579 were assigned mirikizumab, and 287 were assigned ustekinumab. 80 (40·2%) of 199 patients in the placebo group did not have a PRO clinical response at week 12 and were switched to the mirikizumab treatment and masked to this switch. A greater proportion of patients completed the study on their originally assigned treatment in the mirikizumab and ustekinumab groups compared with placebo up to week 52. The most frequent primary reasons for study discontinuation were adverse events, lack of efficacy, or withdrawal by patient, which were generally reported more often in the placebo group (figure 1).

Patient demographics and baseline characteristics were similar across treatment groups (table 1) and reflective of a population with moderately-to-severely active Crohn's disease. The mean duration of Crohn's disease was 7·4 years (SD 7·9). In addition, 281 (48·5%) of 579 in the mirikizumab group, 139 (48·4%) of 287 in the ustekinumab group, and 97 (48·7%) of 199 patients in the placebo group had experienced therapy failure to at least one biological therapies. Furthermore, 106 (18·3%) of 579 in the mirikizumab group, 31 (15·6%) of 199 in the placebo group, and 48 (16·7%) of 287 in the ustekinumab group had experienced therapy failure to two or more biological therapies.

Both coprimary endpoints were met: 263 (45·4%) of 579 patients in the mirikizumab group and 39 (19·6%) of 199 patients in the placebo group had a week 52 CDAI clinical remission-composite (adjusted difference 25·8% [99·5% CI 15·9–35·6]; p<0·0001; figure 2A), and 220 (38·0%) of 579 patients in the mirikizumab group and 18 (9·0%) of 199 patients in the placebo group had a week 52 endoscopic response-composite (adjusted difference 28·7% [99·5% CI 20·6–36·8]; p<0·0001; figure 2B). In the subgroup of patients with previous treatment failure to biological therapies, the percentages of patients who met the coprimary endpoints were statistically significantly greater in the mirikizumab group (clinical remission by CDAI-composite: mirikizumab: 122 [43·4%] of 281; placebo: 12 [12·4%] of 97; endoscopic response-composite: mirikizumab: 103 [36·7%] of 281; placebo: 6 [6·2%] of 97); figure 2). Statistically significant differences between mirikizumab and placebo were also seen in patients with no previous failure to biological therapies (figure 2).

Mirikizumab showed superiority over placebo for all the week 12 and week 52 secondary endpoints included in the multiplicity adjusted testing scheme. Statistically significantly greater treatment effects of mirikizumab compared with placebo were observed at week 12 for clinical response by PRO (mirikizumab: 409 [70·6%] of 579; placebo: 103 [51·8%] of 199; 18·9% [99·5% CI

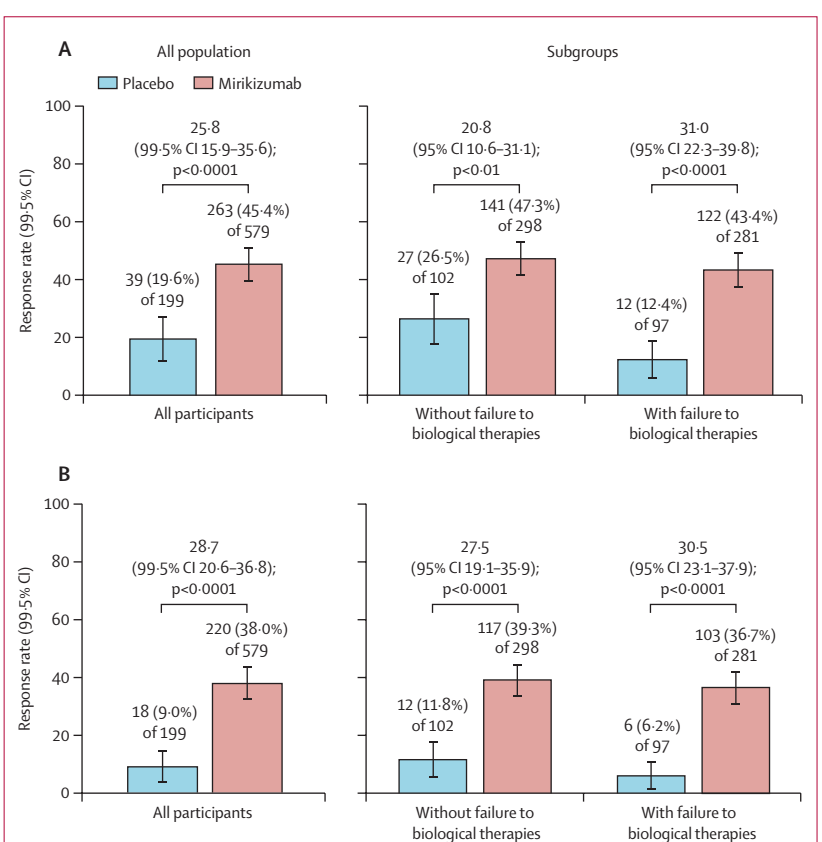

Figure 2: **Coprimary endpoints: mirikizumab versus placebo for all participants, and patients with or without previous failure to biological therapies**

(A) Clinical response by PRO at week 12 and clinical remission by CDAI at week 52 (NRI). (B) Clinical response by PRO at week 12 and endoscopic response at week 52 (NRI). All participants are from the primary analysis set. Difference is adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; p value is mirikizumab versus placebo. CDAI=Crohn's Disease Activity Index. NRI=non-responder imputation. PRO=patient-reported outcome; two of the patient-reported items of the CDAI (stool frequency and abdominal pain).

7·5–30·3]; p<0·0001), clinical remission by CDAI (mirikizumab: 218 [37·7%] of 579; placebo: 50 [25·1%] of 199; 12·4% [99·5% CI 2·2–22·7]; p=0·0014), endoscopic response (mirikizumab: 188 [32·5%] of 579; placebo: 25 [12·6%] of 199; 19·7% [99·5% CI 11·1–28·2]; p<0·0001), and Functional Assessment of Chronic Illness Therapy-Fatigue change from baseline (mirikizumab: least squares mean [LSM] 5·86; placebo: 2·64; LSM difference 3·22 [99·5% CI 1·24–5·19]; p<0·0001; table 2). Across stringent endpoints at week 52, statistically significantly greater treatment effects of mirikizumab compared with placebo were observed including endoscopic response-treat-through (mirikizumab: 280 [48·4%] of 579; placebo: 18 [9·0%] of 199; 39·1% [99·5% CI 31·0–47·2]; p<0·0001), clinical remission by CDAI-treat-through (mirikizumab: 313 [54·1%] of 579; placebo: 39 [19·6%] of 199; 34·6% [99·5% CI 24·7–44·4]; p<0·0001), clinical remission by PRO-composite (mirikizumab: 263 [45·4%] of 579; placebo: 39 [19·6%] of 199; 25·7% [99·5% CI 15·9–35·6]; p<0·0001) and corticosteroid-free clinical remission-composite (mirikizumab: 253 [43·7%] of 579; placebo: 37 [18·6%] of 199; 25·0% [99·5% CI 15·2–34·7]; p<0·0001; table 2).

	Mirikizumab (n=579)	Placebo (n=199)	Ustekinumab (n=287)	p value	Difference *vs* placebo (99·5% CI)
Mirikizumab to placebo comparisons					
Clinical response by PRO at week 12	409 (70·6%)	103 (51·8%)	..	p<0·0001	18·9 (7·5 to 30·3)
Endoscopic response at week 12	188 (32·5%)	25 (12·6%)	..	p<0·0001	19·7 (11·1 to 28·2)
Endoscopic remission at week 12*	63 (10·9%)	8 (4·0%)	..	p=0·0034	6·8 (1·6 to 12·1)
Clinical remission by CDAI at week 12	218 (37·7%)	50 (25·1%)	..	p=0·0014	12·4 (2·2 to 22·7)
Endoscopic response at week 52	280 (48·4%)	18 (9·0%)	..	p<0·0001	39·1 (31·0 to 47·2)
Clinical remission by CDAI at week 52	313 (54·1%)	39 (19·6%)	..	p<0·0001	34·6 (24·7 to 44·4)
Clinical response by PRO at week 12 and endoscopic remission at week 52*	92 (15·9%)	4 (2·0%)	..	p<0·0001	13·8 (8·7 to 18·9)
Clinical response by PRO at week 12 and clinical remission by PRO at week 52	263 (45·4%)	39 (19·6%)	..	p<0·0001	25·7 (15·9 to 35·6)
Clinical response by PRO at week 12 and corticosteroid-free clinical remission by CDAI at week 52	253 (43·7%)	37 (18·6%)	..	p<0·0001	25·0 (15·2 to 34·7)
FACIT-F change from baseline at week 12	5·9 (0·4)	2·6 (0·6)	..	p<0·0001	3·2 (1·2 to 5·2)†
Mirikizumab to ustekinumab comparisons					
Clinical remission by CDAI at week 52 (non-inferiority)‡	313 (54·1%)	..	139 (48·4%)	..	5·7 (–1·4 to 12·8)§
Endoscopic response at week 52 (superiority)	280 (48·4%)	..	133 (46·3%)	p=0·51	2·3 (–4·7 to 9·3)§

Data are n (%) or least squares mean (SE), unless stated otherwise. All participants are from the primary analysis set. CDAI=Crohn's Disease Activity Index. FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue. PRO=patient-reported outcome; two of the patient-reported items of the CDAI (stool frequency and abdominal pain). *As a post-hoc exercise, we also assessed the conventional version of endoscopic remission typically defined in other trials; the conventional definition prevents patients with minimal findings being classified as not achieving endoscopic remission; statistical significance for conventional endoscopic remission endpoints was consistent with the multiplicity controlled endoscopic remission endpoints (appendix pp 24, 37). †Least squares mean difference versus placebo (99·5% CI). ‡Non-inferiority met after accounting for multiplicity. §Difference versus ustekinumab (95% CI).

Table 2: **Major secondary endpoints for the primary analysis set**

In addition to the prespecified stringent version of endoscopic remission (table 2), we also did a post-hoc assessment, the conventional version of endoscopic remission that is consistent with previous trials (appendix p 24). Statistically significantly greater treatment effects of mirikizumab compared with placebo were observed at week 12 for conventional endoscopic remission (mirikizumab: 102 of [17·6%] 579; placebo: 14 of [7·0%] 199; 10·6% [99·5% CI 4·1–17·2]; p=0·0002), and at week 52 for conventional endoscopic remission-composite (mirikizumab: 136 [23·5%] of 579; placebo: 8 [4·0%] of 199; 19·4% [99·5% CI 13·1–25·7]; appendix p 37).

Additionally, a robust treatment effect was observed in patients with and without previous failure to biological therapies in which statistically significant and consistent response rates and similar treatment effects were reached at week 52 across multiple secondary endpoints (appendix pp 26–27). Treatment benefit, as measured by the coprimary endpoints, was observed versus placebo across demographic and baseline disease characteristics subgroups (appendix pp 28–31).

Statistically significant results were observed as early as week 4 in change from baseline in abdominal pain (mirikizumab: LSM –0·55; placebo: –0·43; LSM difference –0·12 [95% CI –0·21 to –0·02]), and as early as week 6 in change from baseline in stool frequency (mirikizumab: LSM –2·20; placebo: –1·81; LSM difference –0·40 [95% CI –0·75 to –0·05]). Statistically significant reductions from baseline in high-sensitivity CRP and faecal calprotectin were observed in the mirikizumab treatment group compared with placebo at week 4 with continued reduction and separation from placebo up to week 12 and week 52 (appendix p 19).

Patients in the mirikizumab group had non-inferiority to ustekinumab for clinical remission by CDAI-treat-through (mirikizumab: 313 [54·1%] of 579; ustekinumab: 139 [48·4%] of 287; 5·7% [95% CI –1·4 to 12·8]) at week 52 (figure 3A; appendix pp 18, 21). A post-hoc sensitivity analysis in a per-protocol population yielded consistent results (appendix p 36). Superiority to ustekinumab for endoscopic response-treat-through was not reached (mirikizumab: 280 [48·4%] of 579; ustekinumab: 133 [46·3%] of 287; 2·3% [95% CI –4·7 to 9·3]; p=0·51; figure 3B). In patients with previous failure to biological therapies, numerically greater response rates were observed at week 52 with mirikizumab compared with ustekinumab for endoscopic response-treat-through

(mirikizumab: 126 [44·8%] of 281; ustekinumab: 55 [39·6%] of 139) and clinical remission by CDAI-treat-through (mirikizumab: 144 [51·2%] of 281; ustekinumab: 58 [41·7%] of 139; figure 3). Reductions were seen for faecal calprotectin in the mirikizumab group compared with the ustekinumab group at weeks 28, 44, and 52, and reductions in high-sensitivity CRP were also observed in the mirikizumab group compared with the ustekinumab group at weeks 16, 44, and 52 (appendix p 19). At week 52, a higher percentage of patients had combined endoscopic response-treat-through and clinical remission by CDAI-treat-through in the mirikizumab group compared with the ustekinumab group (mirikizumab: 199 [34·4%] of 579; ustekinumab: 80 [27·9%] of 287; 95% CI 0·4 to 13·2). Additional secondary endpoints for comparisons between mirikizumab and ustekinumab at week 52 are provided in the appendix (p 32).

In the safety population (n=1150), the adjusted incidence rates of patients reporting treatment-emergent adverse events, serious adverse events, and adverse events or events leading to discontinuation were higher in the placebo group than in the mirikizumab group. The most common adverse events (occurring in ≥5% of patients) in the mirikizumab group were COVID-19, anaemia, arthralgia, headache, upper respiratory tract infection, nasopharyngitis, and diarrhoea, all of which were reported with a higher adjusted incidence rate in placebo patients than in mirikizumab patients. The majority of treatment-emergent adverse events were mild or moderate (table 3).

Among the adverse events of special interest, adjusted incidence rates for hepatic events, overall infections, and serious infections were higher in the placebo group than in the mirikizumab group. Adjusted incidence rates for

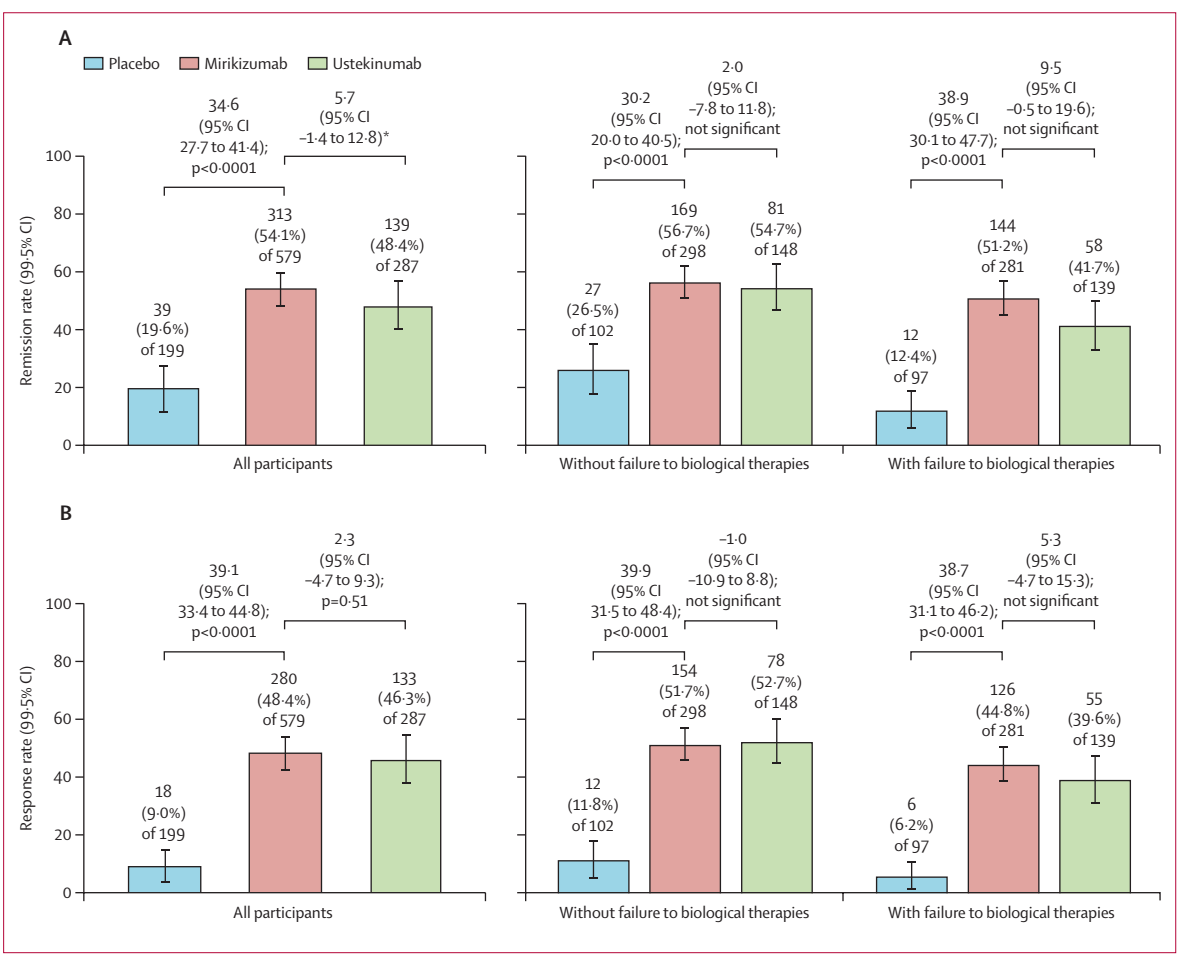

Figure 3: **Treat-through results in all participants, and subgroups with or without previous failure to biological therapies, for mirikizumab versus ustekinumab**

(A) Clinical remission by CDAI (NRI) at week 52. (B) Endoscopic response (NRI) at week 52. All participants are from the primary analysis set; total number of patients in the subgroups with failure to biological therapies (placebo, n=97; mirikizumab, n=281; and ustekinumab, n=139) and without failure to biological therapies (placebo, n=102; mirikizumab, n=298; ustekinumab, n=148). Difference is the adjusted risk difference in all participants and is the unadjusted risk difference in the subgroups. Endpoint definitions: clinical remission by CDAI: CDAI total score less than 150. Endoscopic response: 50% or more reduction from baseline in SES-CD total score. CDAI=Crohn's Disease Activity Index. NRI=non-responder imputation. SES-CD=Simple Endoscopic Score for Crohn's disease. *Non-inferiority met after accounting for multiplicity.

injection site reactions and hypersensitivity reactions were higher in the mirikizumab group than in the placebo group. Opportunistic infections were uncommonly (as per the Summary of Product Characteristics guidelines)[24] reported in patients treated with mirikizumab. Seven (1·1%) of 630 patients in the mirikizumab group reported opportunistic infections, including five events of herpes zoster (all affected one

	Mirikizumab (n=630)	Ustekinumab (n=309)	Placebo (n=211)	Mirikizumab *vs* ustekinumab, estimated rate difference (95% CI)	Mirikizumab *vs* placebo, estimated rate difference (95% CI)
Patient years of exposure	593·6	293·3	119·5	..	..
Treatment-emergent adverse events	495 (78·6); 201·9	239 (77·3); 180·4	154 (73·0); 291·8	21·5 (–7·5 to 50·5)	–89·8 (–139·2 to –40·4)
Mild	233 (37·0)	121 (39·2)	60 (28·4)	..	..
Moderate	204 (32·4)	94 (30·4)	62 (29·4)	..	..
Severe	58 (9·2)	24 (7·8)	32 (15·2)	..	..
Serious adverse events	65 (10·3); 11·5	33 (10·7); 11·8	36 (17·1); 32·5	–0·3 (–5·2 to 4·6)	–21 (–32 to –10)
Treatment discontinuation due to adverse event	32 (5·1); 5·4	8 (2·6); 2·7	20 (9·5); 17·1	2·7 (0 to 5·3)	–11·6 (–19·4 to –3·9)
Death*	0	1 (0·3); 0·3	1 (0·5); 0·8	–0·3 (–1 to 0·3)	–0·8 (–2·5 to 0·8)
Common treatment-emergent adverse events†					
COVID-19	104 (16·5); 19·3	47 (15·2); 17·3	29 (13·7); 26·4	..	..
Anaemia	42 (6·7); 7·4	15 (4·9); 5·3	14 (6·6); 12·2	..	..
Arthralgia	41 (6·5); 7·2	8 (2·6); 2·8	11 (5·2); 9·6	..	..
Headache	41 (6·5); 7·2	15 (4·9); 5·3	9 (4·3); 7·8	..	..
Upper respiratory tract infection	38 (6·0); 6·7	22 (7·1); 7·8	9 (4·3); 7·8	..	..
Nasopharyngitis	36 (5·7); 6·3	19 (6·1); 6·7	9 (4·3); 7·7	..	..
Adverse events of special interest					
Infusion site reaction, high-level terms	1 (0·2); 0·7	4 (1·3); 8·2	0	–7·6 (–15·7 to 0·6)	0·7 (–0·6 to 2)
Injection site reaction, high-level terms	65 (10·8); 15·3	17 (5·8); 7·1	7 (6·5); 10·4	8·2 (3·1 to 13·2)	4·9 (–3·6 to 13·4)
Hypersensitivity reaction on the day of study treatment administration (narrow)	24 (3·8); 4·1	7 (2·3); 2·4	5 (2·4); 4·2	1·7 (–0·7 to 4·1)	–0·1 (–4·2 to 4)
Hypersensitivity reaction after the day of study treatment administration (narrow)	50 (7·9); 8·9	18 (5·8); 6·4	11 (5·2); 9·6	2·5 (–1·4 to 6·3)	–0·7 (–6·9 to 5·5)
Infection	261 (41·4); 59·7	130 (42·1); 58·1	73 (34·6); 81·3	1·6 (–10·7 to 14)	–21·6 (–41·6 to –1·6)
Serious infection	14 (2·2); 2·4	9 (2·9); 3·1	6 (2·8); 5·1	..	..
Opportunistic infection	7 (1·1); 1·2	1 (0·3); 0·3	0	..	..
Oral candidiasis	1 (0·2); 0·2	0	0	..	..
Herpes zoster	5 (0·8); 0·8	1 (0·3); 0·3	0	..	..
Typhoid fever	1 (0·2); 0·2	0	0	..	..
Adjudicated cerebro-cardiovascular events	3 (0·5); 0·5	2 (0·6); 0·7	2 (0·9); 1·7	–0·2 (–1·3 to 0·9)	–1·2 (–3·6 to 1·2)
Major adverse cardiovascular events	0	2 (0.6); 0.7	2 (0·9); 1·7	..	..
Malignancies	2 (0·3); 0·3	0	1 (0·5); 0·8	0·3 (–0·1 to 0·8)	–0·5 (–2·2 to 1·2)
Non-melanoma skin cancer	1 (0·2); 0·2	0	1 (0·5); 0·8	..	..
Malignancies excluding non-melanoma skin cancer	1 (0·2); 0·2	0	0	..	..
Depression	5 (0·8); 0·8	2 (0·6); 0·7	0	0·2 (–1 to 1·4)	0·8 (0·1 to 1·6)
Suicide or self-injury (narrow)‡	2 (0·3); 0·3	0	0	0·3 (–0·1 to 0·8)	0·3 (–0·1 to 0·8)
Hepatic events§	39 (6·2); 6·8	8 (2·6); 2·8	9 (4·3); 7·8	4 (1·1 to 6·9)	–1 (–6·5 to 4·5)

(Table 3 continues on next page)

	Mirikizumab (n=630)	Ustekinumab (n=309)	Placebo (n=211)	Mirikizumab *vs* ustekinumab, estimated rate difference (95% CI)	Mirikizumab *vs* placebo, estimated rate difference (95% CI)
(Continued from previous page)					
Hepatic laboratory¶					
ALT of ≥3 times of ULN	12 (1·9)	6 (2·0)	0	..	..
ALT of ≥5 times of ULN	3 (0·5)	1 (0·3)	0	..	..
AST of ≥3 times of ULN	9 (1·4)	7 (2·3)	2 (1·0)	..	..
AST of ≥5 times of ULN	2 (0·3)	4 (1·3)	0	..	..
ALT or AST of ≥3 times of ULN and total bilirubin of ≥2 times of ULN	1 (0.2)	0	0	..	..
ALP of ≥2 times of ULN and bilirubin of ≥2 times of ULN	0	0	0	..	..
ALP of ≥2 times of ULN	7 (1·1)	0	2 (1·0)	..	..

Data are n (%); EAIR, unless stated otherwise. The safety population is all patients who received at least one dose of the study drug. Confidence intervals for EAIR difference were calculated using the Wald-like method.[23] ALT=alanine aminotransferase. AST=aspartate transferase. ALP=alkaline phosphatase. EAIR=exposure adjusted incidence rate. ULN=upper limit of normal. *One male patient aged 35 years who died due to pulmonary embolism, one male patient aged 23 years who was a placebo non-responder who switched to mirikizumab after week 12 died due to worsening of Crohn's disease, and one female patient aged 63 years who died due to sepsis. †Events that occurred in at least 5% of the patients in any trial group; events are listed according to decreasing frequency in the mirikizumab group. ‡Both events were suicidal ideation; one participant had previous history of suicide attempt, the other had a history of anxiety. §One participant presented with increases in ALT, AST, and total bilirubin; these increases were not concomitant; the participant had a diagnosis of Gilbert's syndrome with fluctuating indirect hyperbilirubinaemia throughout the study and a one-time ALT increase (3·6-fold ULN) at week 48 when total bilirubin was normal. ¶No ALT or AST shifts of ≥10 times of ULN were reported in the mirikizumab treatment or placebo groups; one participant (EAIR=0·3 per 100 patient years of exposure) in the ustekinumab group reported ALT shifts of ≥10 times of ULN. Two participants (EAIR=0·7 per 100 patient years of exposure) in the ustekinumab group reported AST shifts of ≥10 times of ULN.

Table 3: **Safety data from weeks 0 to 52**

dermatome and recovered without sequelae). Malignancies were uncommonly reported in mirikizumab patients (one basal cell carcinoma and one breast cancer). There were no adjudicated major adverse cardiovascular events reported in patients treated with mirikizumab.

There were three participant deaths during VIVID-1, one in the placebo group (due to a pulmonary embolism), one in the ustekinumab group (due to *Escherichia coli* sepsis), and one in the placebo non-responder group that switched to mirikizumab after week 12 (due to Crohn's disease worsening). None of the deaths were considered related to the study drug or study procedure by the study investigator. There were no clinically meaningful shifts in vital signs that were considered adverse. Mild liver enzyme increases (alanine and aspartate aminotransferase) were uncommonly observed (table 3).

Across 52 weeks, 12·6% of mirikizumab-treated patients in the primary analysis set developed anti-drug antibodies, most of which were of low titre, transient, and tested positive for neutralising activity. There was no identified clinically statistically significant effect of anti-drug antibodies on effectiveness of mirikizumab (appendix p 33).

Discussion

In VIVID-1, mirikizumab showed statistically significant and clinically meaningful efficacy across multiple endpoints compared with placebo in patients with moderately-to-severely active Crohn's disease, meeting the coprimary composite endpoints and all major secondary endpoints. Statistical significance was also observed in subgroups with and without failure to biological therapies for coprimary endpoints and most major secondary endpoints. Observed efficacy in the subgroup with failure to biological therapies suggests a highly effective therapy in an area of unmet medical need. VIVID-1 is the first completed phase 3 study in Crohn's disease with a treat-through design, including a placebo and an active control group and defining coprimary endpoints as a composite of week 12 clinical response and the respective week 52 endpoints, allowing for a comparison to placebo over 1 year. The treat-through design rather than a mandated switch at a fixed timepoint aligns with clinical practice and aims to better understand long-term treatment effects in the enrolled population, including in initial non-responders.

Symptomatic improvement was evident as early as week 4 accompanied by a statistically significant reduction in high-sensitivity CRP and faecal calprotectin, and endoscopic response was seen at week 12. Together, this shows early treatment effect, which is important for patients with ongoing symptoms of Crohn's disease. Continued mirikizumab treatment led to improved response rates at week 52 across endpoints, underscoring durable efficacy. Of note, greater response rates were observed with mirikizumab in the treat-through endpoints, compared with the corresponding composite endpoints with week 12 clinical response. This observation reflects that although the denominator is identical for both endpoints, response is measured in all participants on mirikizumab with the treat-through

endpoint and only in week 12 clinical responders with the composite endpoint. This suggests that a subset of patients might require, and respond to, treatment beyond the induction period. This is consistent with the findings of the mirikizumab ulcerative colitis programme (LUCENT), in which many patients were noted to respond to a formal extended induction period, among week 12 non-responders.[25] Given high rates of initial non-response, secondary non-response, and 1-year discontinuation of other biological therapies,[7,26] highly effective therapies with durable efficacy, such as mirikizumab, have a potentially important role in the treatment of this chronic disease.

Mirikizumab reached non-inferiority versus ustekinumab for clinical remission by CDAI at week 52. Superiority over ustekinumab in endoscopic response at week 52 was not reached, with the endoscopic response rate for ustekinumab in VIVID-1 greater than anticipated based on previous trials.[27,28] However, for both of the above endpoints in patients with previous failure to biological therapies, mirikizumab data show a numerical trend towards greater response rates compared with ustekinumab. Further, mirikizumab showed statistically significantly greater improvements from baseline in faecal calprotectin and CRP compared to ustekinumab. In addition, a greater percentage of patients reached the combination endpoint of endoscopic response and clinical remission by CDAI at week 52 in the mirikizumab group compared with those receiving ustekinumab. As both clinical remission and endoscopic response are important endpoints for patients and clinicians, the ability to reach both simultaneously is crucial.

The mirikizumab safety profile in VIVID-1 was consistent with the known safety profile in ulcerative colitis[25] with no new safety risks identified. Overall, exposure adjusted incidence rates of adverse events and serious adverse events were higher in the placebo group compared with the mirikizumab group, supporting a strong and positive benefit–risk profile.

Traditionally, phase 3 clinical trials in Crohn's disease have used a randomised withdrawal study design with an analysis among responders to active induction therapy, rather than a treat-through design with composite endpoints as in VIVID-1. To examine the effect of study design and analysis on reported outcomes, we evaluated clinical remission by CDAI at week 52 in VIVID-1 using each of the following: (1) the prespecified treat-through analysis with composite endpoint; (2) a prespecified, traditional treat-though analysis (ie, without the week 12 response requirement); and (3) a post-hoc exploratory analysis reflecting the more traditional Crohn's disease study designs by evaluating week 52 results among induction responders only. At week 52, 45·4% of patients treated with mirikizumab met the endpoint of clinical remission by CDAI in the treat-through analysis with composite endpoint, 54·1% met the endpoint in the treat-through analysis, and 64·3% met the endpoint in the responder analysis. This example, with a range of nearly 20% percentage points depending on analysis type, shows the profound limitations in comparing unadjusted outcomes across phase 3 trials with different study designs, even before accounting for other potential differences between studies, such as in endpoint definitions, timepoints, and inclusion criteria.

Cross-trial comparisons between rigorous phase 3 trials such as VIVID-1 and later phase 3b/4 trials might carry additional challenges. For example, both VIVID-1 (mirikizumab) and SEQUENCE (risankizumab) examined the efficacy of an IL-23 inhibitor versus ustekinumab in patients with Crohn's disease.[29] However, due to profound differences between these trials, including study design (VIVID-1: double-blind, placebo-controlled, double-dummy; SEQUENCE: open-label study drug with masked assessment), patient populations (VIVID-1: mixed patient population with Crohn's disease; SEQUENCE: subpopulation of previous anti-tumour necrosis factor failure), endoscopic reading paradigm (VIVID-1: masked central readers; SEQUENCE: site reader with central reader confirmation), mandatory steroid taper (VIVID-1: beginning at week 12; SEQUENCE: beginning at week 2) and differing discontinuation rates between VIVID-1 and SEQUENCE, no conclusions on relative efficacy can be drawn.

A key strength of VIVID-1 is the comprehensive assessment across a broad spectrum of disease outcomes including mucosal inflammation, inflammatory biomarkers, patient-reported symptoms such as abdominal pain, stool frequency, and fatigue. VIVID-1 also is the first treat-through study for Crohn's disease with a placebo control group over a 1-year period.

A key limitation is the use of composite endpoints for comparisons with placebo after week 12, as placebo non-responders switched to mirikizumab at the end of induction. The benefits of mirikizumab over placebo were robust; however, the interpretation of results using composite endpoints might be difficult. Comparisons between mirikizumab and ustekinumab after week 12 did not require composite endpoints. Another limitation is that the study did not assess the safety and efficacy of extended intravenous induction or intravenous rescue therapy in patients who had inadequate response or initially responded and subsequently lost response. Our results indicate that some patients might respond to treatment beyond the induction period. This should be considered when assessing therapeutic benefit. The ongoing long-term extension VIVID-2 (NCT04232553) will evaluate repeated intravenous induction with mirikizumab. Finally, this study was not powered to detect a statistically significant difference between mirikizumab and ustekinumab in patients with previous failure to biological therapies. However, numerically higher results were observed with mirikizumab compared with ustekinumab at week 52 in patients with previous failure to biological therapies for

clinical remission by CDAI and endoscopic response, which could indicate potential benefits of an IL-23 inhibitor mechanism over ustekinumab in this patient population, consistent with conclusions from the SEQUENCE[29] trial.

Mirikizumab was effective in achieving and maintaining symptomatic improvement, clinical remission, and endoscopic response. Specifically, mirikizumab showed both early and long-term efficacy, similar in magnitude for both patients with and without failure to biological therapies. The safety profile was consistent with the known safety profile in patients with ulcerative colitis. The collective VIVID-1 data reported here support a favourable benefit–risk for the use of mirikizumab in clinical practice in patients with moderately-to-severely active Crohn's disease with or without previous failure to biological therapies.

Contributors

MF, SD, GD'H, SG, TH, VJ, JK, and BS contributed to the conception and design. NM and ZL contributed to the acquisition, analysis, and interpretation of data. HC, WC, MP, SMB, FD, EH, MUL, NM, and ZL contributed to the analysis and interpretation of the data and drafting of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content and participated sufficiently in the work to agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study, gave final approval of the version to be published, and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of 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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