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ORIGINAL RESEARCH

Efficacy and Safety of Advanced Therapies in Moderately-to-Severely Active Ulcerative Colitis: a Systematic Review and Network Meta-analysis

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ABSTRACT

***Introduction*:** This study aimed to compare the efficacy and safety of biologics and small molecules for treatment of adults with moderately-to-severely active ulcerative colitis (UC).

***Methods*:** A systematic literature review was conducted to identify randomised controlled trials evaluating approved and emerging targeted therapies for patients with UC. A Bayesian network meta-analysis (NMA) approach was applied. Outcomes assessed included clinical response and remission, endoscopic mucosal healing, and safety.

***Results*:** Thirty studies were included in the NMA following a feasibility assessment comparing approved induction dosing regimens and 22 studies comparing approved maintenance dosing regimens. In the biologic/Janus kinase inhibitor (JAKi)-naïve population, induction studies showed similar clinical response and remission rates across most interventions, with upadacitinib demonstrating significant improvements versus most other interventions. For maintenance studies, mirikizumab demonstrated significant improvements in clinical response and remission versus most other interventions. In the biologic/JAKi-experienced population, no significant differences were observed between most interventions in induction studies, except for significantly improved clinical response and remission for mirikizumab versus adalimumab, and upadacitinib demonstrated significant improvement versus all other interventions. Few differences between active treatments were observed in maintenance studies. In both populations, all active interventions had similar efficacy in terms of endoscopic mucosal healing

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in both induction and maintenance studies. Regardless of prior treatment exposure, similar rates of serious adverse events were seen across all active interventions in the induction period. ***Conclusion***: Among the available interventions, owing to its favourable efficacy and safety profile, mirikizumab has a relevant role in the long-term treatment of UC.

Keywords: Advanced therapies; Biologics; Comparative efficacy; Mirikizumab; IL-23 inhibitors; Small molecules; Ulcerative colitis

Key Summary Points

Current targeted therapeutic options for patients with moderately-to-severely active ulcerative colitis (UC) who have an inadequate response to conventional therapies or other biologics include adalimumab, filgotinib, golimumab, infliximab, ozanimod, tofacitinib, upadacitinib, ustekinumab, vedolizumab and the recently approved interleukin (IL)-23p19 inhibitor mirikizumab, but there has been no direct comparison of mirikizumab with other biological or small molecule therapy for UC.

This is the first network meta-analysis (NMA) based on a comprehensive systematic literature review of approved UC treatments to include the IL-23p19 inhibitor mirikizumab and shows superiority of mirikizumab to anti-tumour necrosis factor inhibitors, vedolizumab, tofacitinib, ozanimod and upadacitinib 15 mg for maintenance treatment of biologic/Janus kinase inhibitor-naïve patients.

All included active treatments demonstrated improvements in clinical response and remission versus placebo, provided effective treatment options with acceptable safety profiles and demonstrated similar efficacy in terms of endoscopic mucosal healing.

International healthcare decision makers require comparative data to support decisions on funding or resource allocation.

This NMA provides indirect comparative efficacy and safety evidence for mirikizumab versus approved doses of advanced therapies in the treatment of adults with moderately-to-severely active UC, in both induction and maintenance settings, suggesting that mirikizumab will broaden the treatment options in patients with UC.

INTRODUCTION

Ulcerative colitis (UC) is characterised by inflammation and ulceration of the colon following a relapsing–remitting course. Symptoms during an active phase include diarrhoea, rectal bleeding and urgency [1–3].

The primary aim of pharmacological treatment is to induce and maintain remission, and resolve intestinal inflammation [4]. Over recent years, the approval of biologics and small molecules targeting different mechanisms of action has expanded the treatment options for UC. Although biologic agents have not replaced conventional treatments such as the aminosalicylates, corticosteroids and immunomodulators (azathioprine, calcineurin inhibitors), 30–40% of patients fail to respond to initial treatment and subsequently progress to biologics as second-line therapy [4].

Since the 2000s, the tumour necrosis factor (TNF)-α inhibitors adalimumab, golimumab and infliximab have revolutionised the clinical care of moderately-to-severely active UC, leading to significantly improved outcomes [5–7]. However, there remains a significant subset of patients who would benefit from an alternative treatment strategy [8]. An increased understanding of the immunopathology of UC has facilitated the development and approval of novel biological therapies [9], such as vedolizumab and ustekinumab, and both these therapies were shown to be effective in inducing and maintaining remission in patients with moderately-to-severely active UC [10, 11].

In addition, small molecules including the Janus kinase inhibitors (JAKi) tofacitinib, filgotinib and upadacitinib and the sphingosine 1-phosphate modulator ozanimod have been shown to be effective in this setting [12–15].

Recently, mirikizumab (LY3074828), a humanised immunoglobulin G4 monoclonal antibody that binds to the p19 subunit of interleukin (IL)-23, has been approved for the treatment of moderately-to-severely active UC [16, 17]. In phase 3 randomised controlled trials (RCTs), mirikizumab induction (LUCENT 1, NCT03518086) and maintenance (LUCENT 2, NCT03524092) treatment demonstrated significantly improved clinical outcomes compared with placebo. In LUCENT 1, mirikizumab-treated patients achieved statistically and clinically meaningful improvements across all primary and key secondary endpoints compared with placebo, with an acceptable safety profile [18]. In LUCENT 2, mirikizumab-treated patients in clinical response at 12 weeks achieved and maintained statistically superior and clinically meaningful improvements at 1 year across the primary endpoint of clinical remission and all key secondary endpoints, with an overall safety profile consistent with previous mirikizumab studies in UC [18].

Where direct comparative evidence based on RCTs is lacking, international healthcare decision makers as well as treating physicians increasingly accept and use indirect comparisons or network meta-analyses (NMAs) to support decisions on treatment selection, funding or resource allocation. With the scarcity of active comparator RCTs, this NMA aimed to provide comparative efficacy and safety evidence for mirikizumab among all currently approved biologic and small-molecule-based advanced therapies in the treatment of adults with moderately-to-severely active UC, in both the induction and maintenance settings.

METHODS

Systematic Literature Review

A systematic literature review (SLR) was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [19] statement and guidance published by Cochrane and the Centre for Reviews and Dissemination [20–22].

Searches for the SLR were conducted at regular intervals between November 2018 and June 2022, according to predefined population, intervention, comparator, outcome and study design (PICOS) criteria, as detailed in Supplemental Table 1, in EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. In addition, conference proceedings during the period 2016–2022 were searched electronically or manually (details of the conferences searched are provided in the Supplemental Materials). RCTs were eligible for inclusion if they evaluated treatments of interest for adult patients with moderately-to-severely active UC as defined by the Mayo score or the UC disease activity index (UC-DAI).

Data Screening, Extraction and Quality Assessment

All articles were screened independently by two researchers, with study selection following published best practice guidelines for SLRs [20–22]. Data on study design, patient characteristics, efficacy of dosing regimen and safety were extracted in a predefined data extraction process.

NMA Feasibility Assessment

To provide robust results, an NMA requires sufficient levels of similarity, homogeneity and consistency of the included evidence. A comprehensive feasibility assessment (FA) investigated areas of heterogeneity across the studies considered for inclusion and potential treatment effect modifiers, which were identified from previously reported studies [23–27]. As a result, the FA included a qualitative comparison of patient characteristics, outcomes definitions and assessment time points, as well as study design aspects of the included trials across both induction and maintenance phases.

Network Meta-analysis

The NMA was conducted in line with the PRISMA extension statement for NMA [28] and the framework of Dias et al. [29].

Population

Since prior treatment with advanced therapy has been shown to be a significant treatment effect modifier [23–26], analyses for efficacy outcomes were conducted separately for patients who were biologic/JAKi naïve and those who were biologic/JAKi experienced.

NMAs of safety outcomes were performed for the overall population only as safety outcome data were typically reported for the overall study populations in the included trials, regardless of prior exposure to advanced therapy, in line with Consolidated Standards of Reporting Trials (CONSORT) recommendations [30, 31].

Treatment and Comparators of Interest

Only the European Medicines Agency- and the US Food and Drug Administration-approved doses and regimens (at the time the NMA was conducted) of advanced therapies for the treatment of moderately-to-severely active UC were included in the NMA (Supplemental Table 2); different dosing arms of the same drug were treated as individual comparators.

Outcomes

Three efficacy endpoints (clinical response and remission, and mucosal healing) and two safety endpoints (all-cause discontinuation and serious adverse events [SAEs]) were selected for the NMA. All efficacy analyses were conducted separately for induction and maintenance time points. For the purpose of this NMA, it was assumed that all definitions of clinical response and remission were comparable, and mucosal healing was defined as endoscopic subscore of 0 or 1.

End of induction time points (6–14 weeks) were used in the induction networks; for maintenance networks, the time points of assessment were limited to those between 52 and 60 weeks.

As a result of heterogeneity in the placebo safety population definitions across maintenance trials, safety outcomes were assessed at the end of induction.

Study Design

The identified clinical trials for maintenance were categorised as either treat-through (patients randomised at baseline and outcomes measured following induction and maintenance phases) or re-randomised responder trials (only end-of-induction responders continue to maintenance and are re-randomised to intervention or placebo/active comparator at maintenance doses), as patients entering the maintenance phase are systematically different between the two study designs. Therefore, statistical adjustments were required to better align the populations prior to performing the NMA. In line with previous approaches [32–35], treat-through trial results for response and remission were adjusted to match the re-randomised responder trials. In addition to the primary NMAs of maintenance of clinical response and remission, sensitivity analyses were performed restricting the evidence base to re-randomised studies (i.e. excluding treat-through studies; detailed results are not reported).

Statistical Analysis

NMAs of clinical response and remission were performed using a multinomial ordered model with probit link. A binomial model with logit link was used for NMAs of mucosal healing, all-cause discontinuations and SAEs. In addition, analyses for baseline risk adjustment using meta-regression models [36] were conducted to account for possible variability in placebo response across UC trials [23–26, 37]. Further details on the statistical analyses are available in the Supplemental Materials and Supplemental Table 3.

All NMAs were conducted using Bayesian methods in accordance with the National Institute for Health and Care Excellence (NICE) guidelines [29, 36, 38, 39] and were carried out in R 4.1.1 using Stan 2.21.0 software (Stan Development Team Stan Modeling Language Users Guide and Reference Manual, https://mc-stan.org) and the multinma R package version 0.5.1 [40].

Bayesian NMA results are presented as posterior median odds ratios (ORs) and 95% credible intervals (95% CrI). A 95% CrI can be interpreted as a 95% probability that the true treatment effect lies within the interval. If this interval excludes 1 (i.e. an OR indicating no difference), there is a 95% probability that the two treatments are different, and this is described as significant in the interpretation.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Literature Search and Feasibility Assessment

Detailed results of the literature search and FA are provided in the supplemental materials. Figure 1 depicts the inclusion/exclusion of articles at each stage of the review process.

Several areas of heterogeneity were identified in the NMA FA, including differences in patient populations regarding prior treatment and background medication, differences in endpoint definitions and time points, as well as differences in trial design. The majority of studies defined clinical response as a decrease in the total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding subscore (RBS) of ≥1 point or an absolute RBS of 0 or 1, and the majority defined clinical remission as a total Mayo score of ≤2 points, with no individual subscore>1.

Studies Included in the NMA

After exclusion procedures (see Supplemental Table 4 for more details), 37 studies were included in the NMA. Supplemental Table 5 presents an overview of the 37 studies included by study design, intervention and dosing, population and outcome availability. All but one trial were placebo controlled. The other trial (VARSITY) was a head-to-head trial of vedolizumab and adalimumab [10]. Supplemental Table 6 provides a summary of the key baseline characteristics of the studies (age, gender, disease duration, Mayo score defining moderately-to-severely active UC, concomitant glucocorticoids and/or immunosuppressants) by population and time point (induction or maintenance).

Results from the best fitting model (according to predefined model performance criteria) for each network are reported throughout this manuscript and model fit statistics are summarised in Supplemental Table 7. For the sensitivity analyses excluding the treat-through studies, findings are not reported in detail. The results for the biologic/JAKi-experienced population broadly align with the base case. For the biologic/JAKi-naïve population, however, the sensitivity analysis criteria reduced the evidence base by four studies (and two comparators) and impacted the previously observed variability in placebo response. As a result, the choice of the best fitting statistical model changed, leading to increased uncertainty, preventing results from being easily compared with the base case.

Efficacy in the Biologic/JAKi-Naïve Population

Induction

Network plots for the induction period in the biologic/JAKi-naïve population are shown in Fig. 2A, B. The analysis evaluated 10 interventions across 24 studies for clinical response and remission and 19 studies for endoscopic mucosal healing. For clinical response and remission, results from the unadjusted random effects model suggested that all interventions offered significant improvements compared with placebo (Fig. 2C, D; absolute clinical response and remission rates for each intervention are presented in Supplemental Table 8). Between active treatments, significantly higher rates of clinical response and remission were

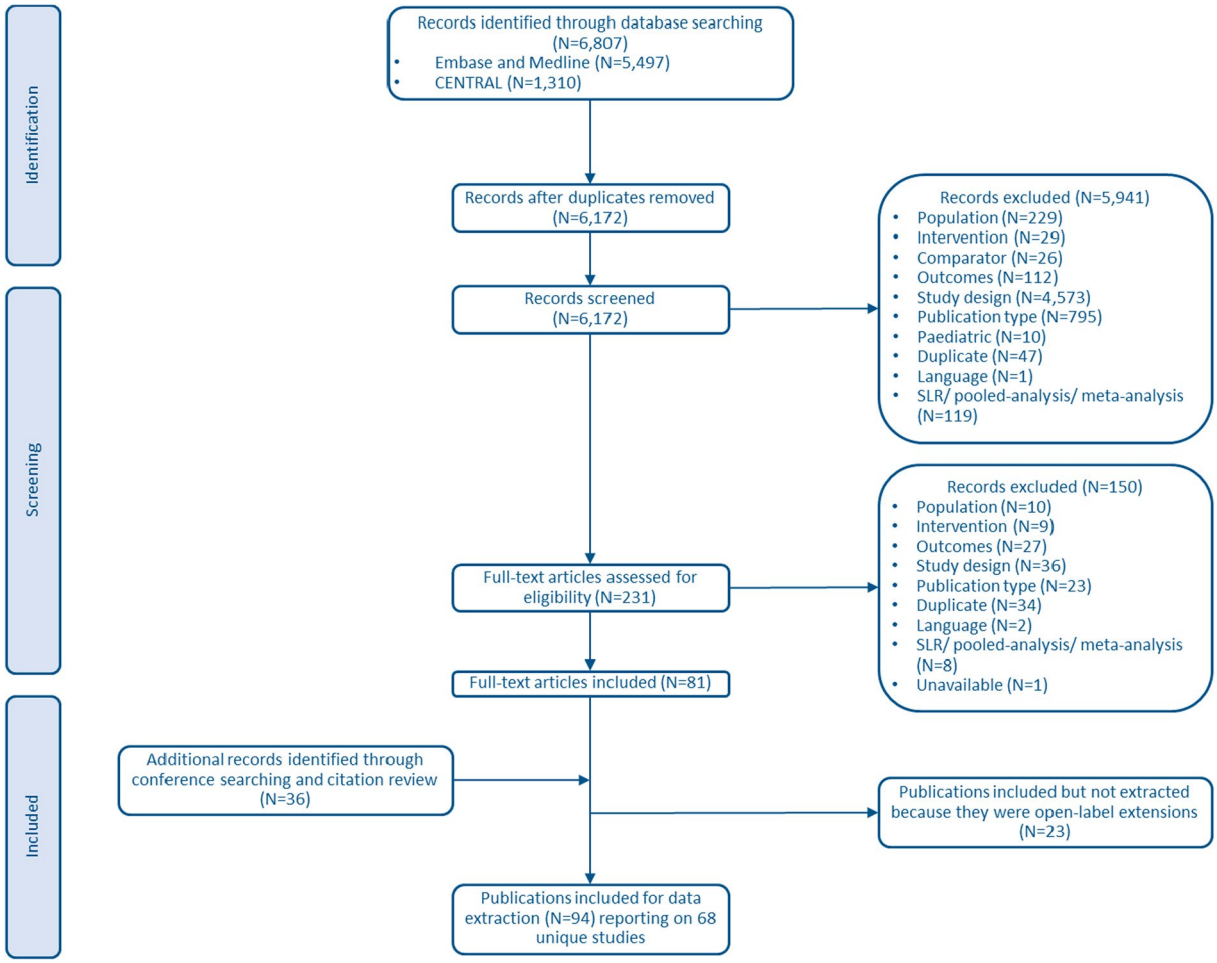

Fig. 1 PRISMA flow diagram: Identification and selection of relevant publications. *CENTRAL* Cochrane Central Register of Controlled Trials, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analysis, *SLR* systematic literature review

observed for upadacitinib 45 mg versus most comparators except for infliximab 5 mg (Supplemental Figs. 1A, B), and for vedolizumab 300 mg and infliximab 5 mg versus adalimumab 160 mg/80 mg.

For mucosal healing, results from the adjusted random effects model suggested that all interventions except for ustekinumab 6 mg/kg offered significant improvements compared with placebo (Fig. 2E). Significantly higher rates of mucosal healing were observed for infliximab 5 mg versus tofacitinb 10 mg, golimumab 200 mg/100 mg, filgotinib 200 mg, and ustekinumab, and for upadacitinib versus filgotinib 200 mg and ustekinumab 6 mg/kg (Supplemental Fig. 1C).

Maintenance

Network plots for the maintenance period in the biologic/JAKi-naïve population are shown in Fig. 3A, B. The analysis evaluated 10 interventions across 15 studies for clinical response and remission and 12 studies for endoscopic mucosal healing. For clinical response and remission, results from the adjusted fixed effect model suggested that all interventions offered significant improvements compared with

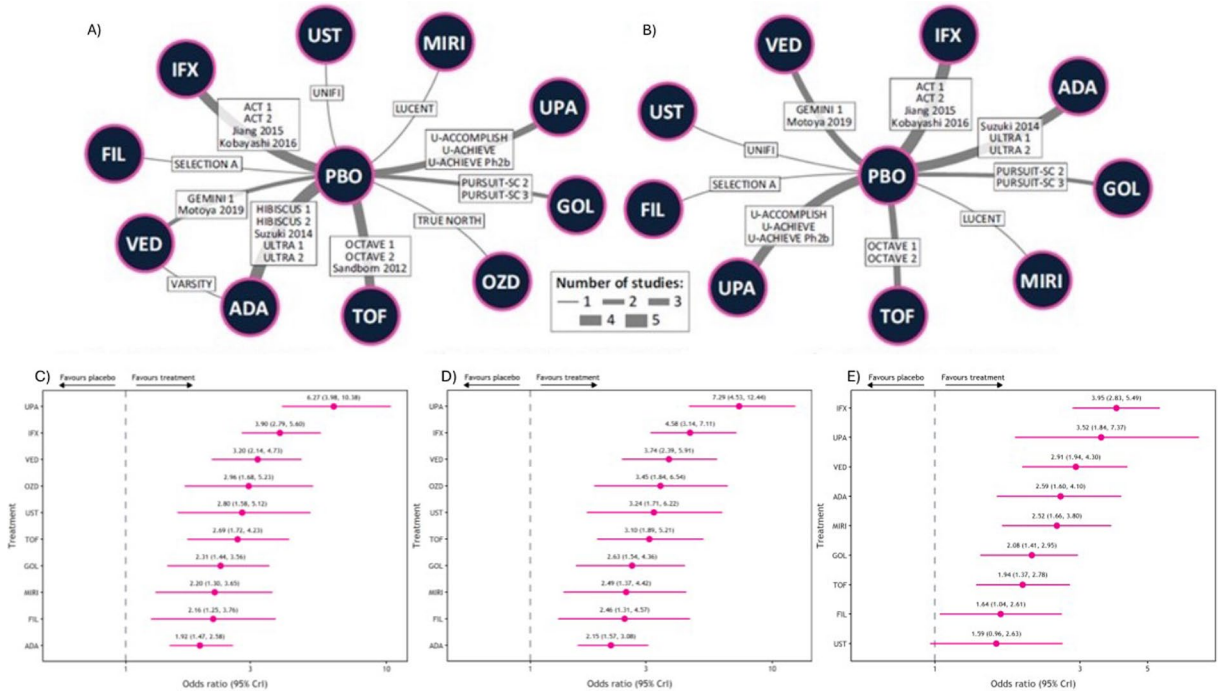

Fig. 2 Network plot for clinical response and remission (**A**) and mucosal healing (**B**) in the induction period for the biologic/JAKi-naïve population and median ORs (95% credible intervals) versus placebo for clinical response (**C**), clinical remission (**D**) and mucosal healing (**E**). *ADA* adalimumab, *CrI* credible interval, *FIL* filgotinib, *GOL* golimumab, *IFX* infliximab, *JAKi* Janus kinase inhibitor, *MIRI* mirikizumab, *OR* odds ratio, *OZD* ozanimod, *PBO* placebo, *TOF* tofacitinib, *UPA* upadacitinib, *UST* ustekinumab, *VED* vedolizumab

placebo (Fig. 3C, D; absolute clinical response and remission rates for each intervention are presented in Supplemental Table 9). Between active treatments, significantly higher rates of clinical response and remission were observed for mirikizumab 200 mg versus anti-TNFs, vedolizumab, tofacitinib, ozanimod and upadacitinib 15 mg (Fig. 4A, B). Significantly different rates of clinical response and remission were also observed for other pairwise comparisons of active treatments, including higher rates for filgotinib 200 mg, ustekinumab and upadacitinib 30 mg when compared with golimumab and adalimumab (Fig. 4A, B).

For mucosal healing, results from the unadjusted random effects model suggested that no significant differences were observed between the active treatments (Fig. 4C). All treatments except for ustekinumab showed significant improvements compared with placebo.

Efficacy in the Biologic/JAKi-Experienced Population

Induction

Network plots for the induction period in the biologic/JAKi-experienced population are shown in Fig. 5A, B. The analysis evaluated 8 interventions across 14 studies for clinical response and remission and 11 studies for endoscopic mucosal healing. For clinical response and remission, results from the unadjusted fixed-effect model suggested that almost all interventions (except for adalimumab) offered significant improvements compared with placebo (Fig. 5C, D; absolute clinical response and remission rates for each intervention are presented in Supplemental Table 10). Between active treatments, significantly higher rates of clinical response and remission were

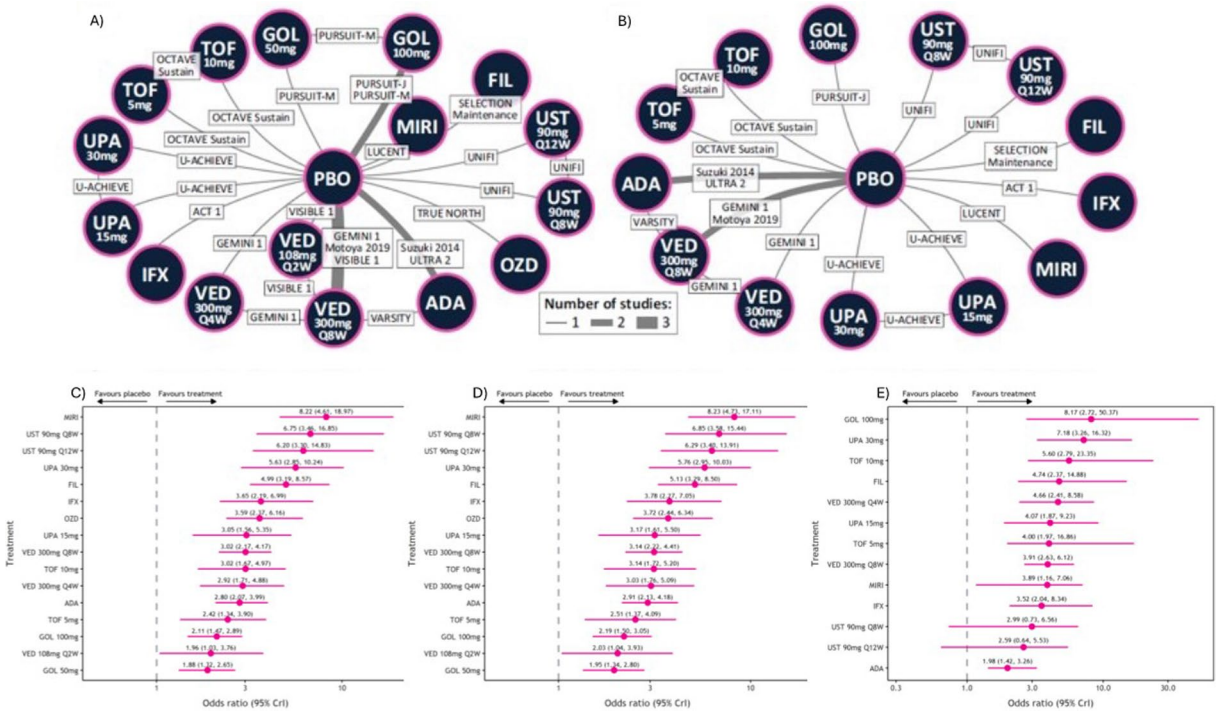

Fig. 3 Network plot for clinical response and remission (**A**) and mucosal healing (**B**) in the maintenance period for the biologic/JAKi-naïve population and median ORs (95% credible intervals) versus placebo for clinical response (**C**), clinical remission (**D**) and mucosal healing (**E**). *ADA* adalimumab, *CrI* credible interval, *FIL* filgotinib, *GOL* golimumab, *IFX* infliximab, *JAKi* Janus kinase inhibitor, *MIRI* mirikizumab, *OR* odds ratio, *OZD* ozanimod, *PBO* placebo, *TOF* tofacitinib, *UPA* upadacitinib, *UST* ustekinumab, *VED* vedolizumab

observed for all treatments versus adalimumab (Supplemental Figs. 2A, B). Upadacitinib 45 mg also demonstrated significantly higher rates compared with all other treatments, and filgotinib 200 mg showed a significantly higher rate of clinical response and remission when compared with vedolizumab 300 mg.

For mucosal healing, results from the adjusted fixed effect model suggested that all interventions offered significant improvements compared with placebo (Fig. 5E). Significantly higher rates of mucosal healing were observed for upadacitinib 45 mg versus most treatments except for vedolizumab 300 mg and adalimumab 160 mg/80 mg (Supplemental Fig. 2C).

Maintenance

Network plots for the maintenance period in the biologic/JAKi-experienced population are shown in Fig. 6A, B. The analysis evaluated 8 interventions across 11 studies for clinical response and remission and 9 studies for endoscopic mucosal healing. For clinical response and remission, results from the unadjusted fixed-effect model suggested that almost all interventions (except for ustekinumab 90 mg every 12 weeks [Q12W]) offered significant improvements compared with placebo (Fig. 6C, D; absolute clinical response and remission rates for each intervention are presented in Supplemental Table 11). Between active treatments, significantly higher rates of clinical response and remission were observed for upadacitinib 30 mg compared with vedolizumab 300 mg Q8W, tofacitinib, ozanimod, mirikizumab 200 mg, ustekinumab 90 mg Q8W and ustekinumab 90 mg Q12W (Supplemental Figs. 3A, B). Vedolizumab 108 mg Q2W, vedolizumab 300 mg Q8W, tofacitinib 10 mg, and upadacitinib 15 mg also demonstrated a significantly higher rate of clinical response and remission when compared with

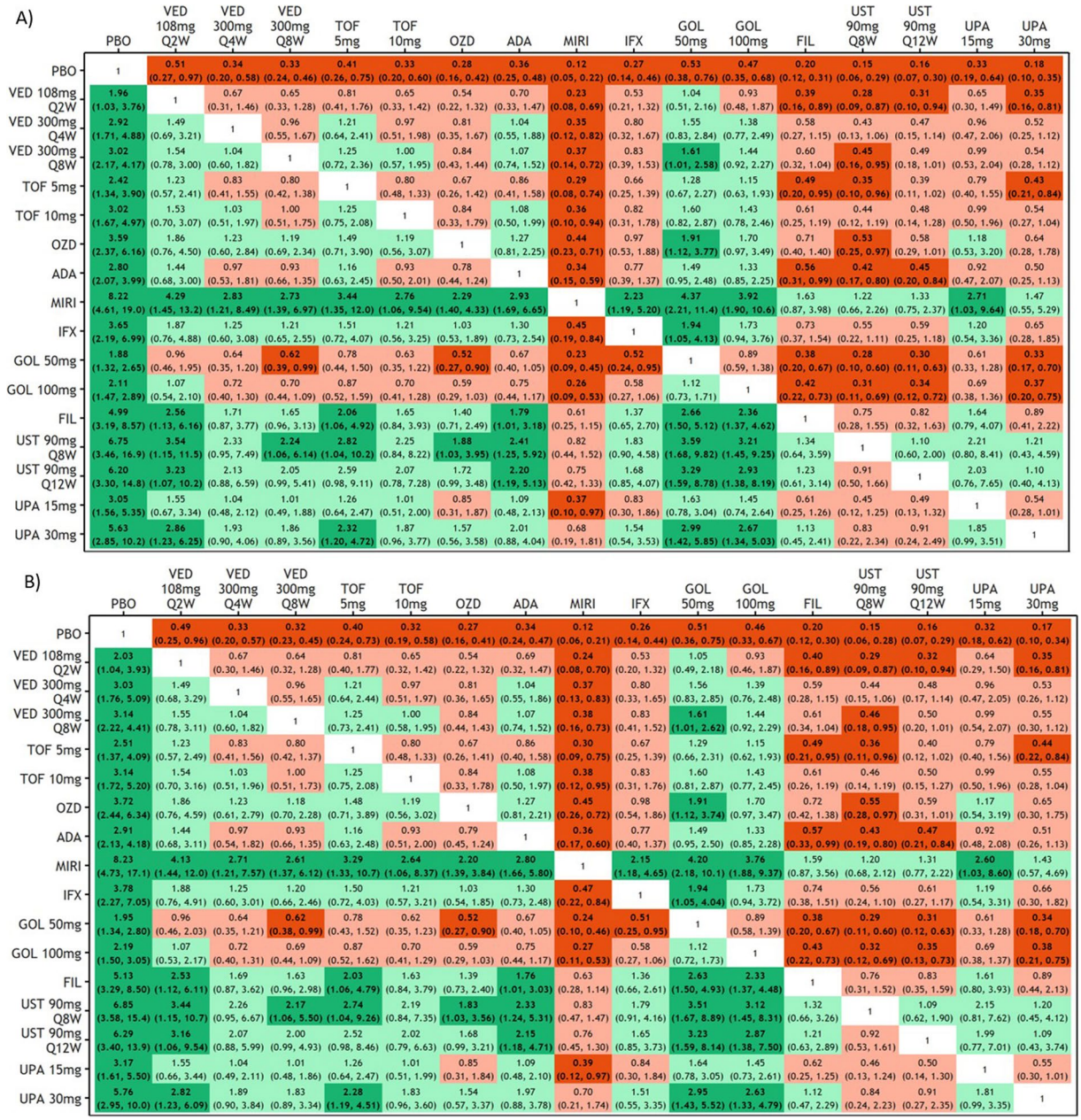

Fig. 4 All pairwise ORs in the maintenance period for the biologic/JAKi-naïve population for clinical response (**A**), clinical remission (**B**) and mucosal healing (**C**). Median ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment (i.e. an OR > 1 illustrates a result in favour of the row treatment). *ADA* adalimumab, *CrI* credible interval, *FIL* filgotinib, *GOL* golimumab, *IFX* infliximab, *JAKi* Janus kinase inhibitor, *MIRI* mirikizumab, *OR* odds ratio, *OZD* ozanimod, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *Q12W* every 12 weeks, *TOF* tofacitinib, *UPA* upadacitinib, *UST* ustekinumab, *VED* vedolizumab

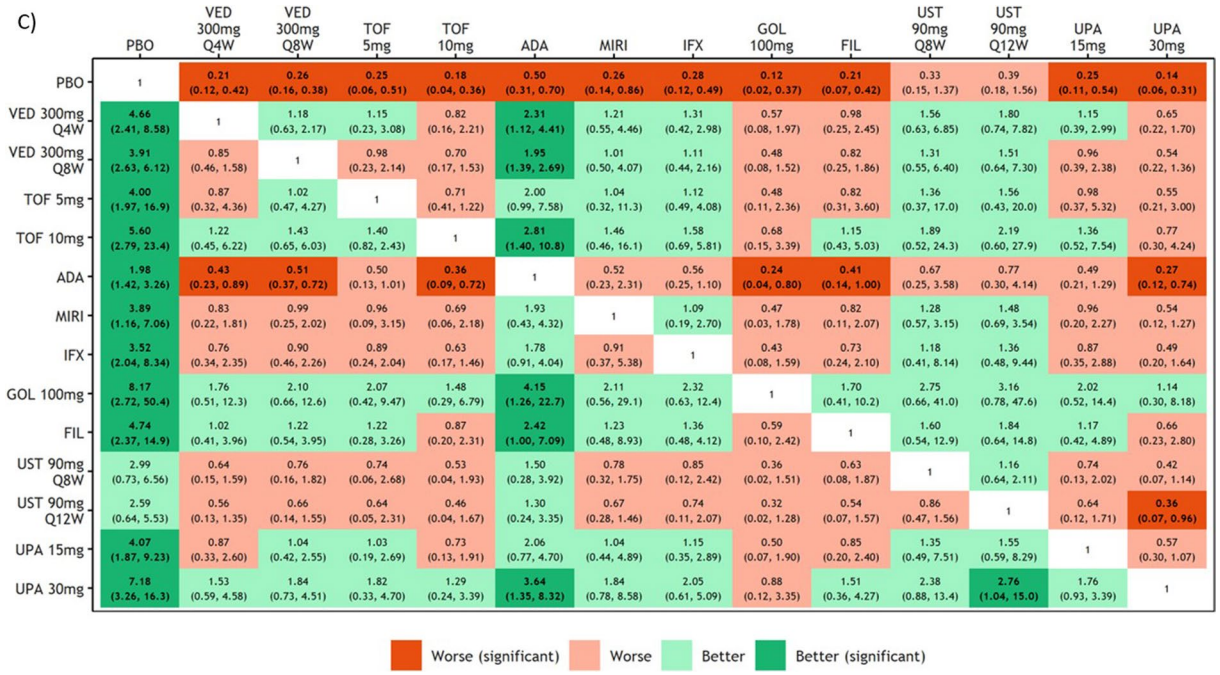

Fig. 4 continued

ustekinumab 90 mg Q12W. Significantly higher rates of clinical response and remission were also demonstrated for tofacitinib 10 mg versus tofacitinib 5 mg and ustekinumab 90 mg Q8W, and for upadacitinib 15 mg versus ustekinumab 90 mg Q8W.

For mucosal healing, results from the unadjusted fixed-effect model suggested that all interventions except for ustekinumab 90 mg Q12W offered significant improvements compared with placebo (Fig. 6E). Significantly higher rates of mucosal healing were observed for upadacitinib 30 mg versus most treatments except for vedolizumab 300 mg Q4W and upadacitinib 15 mg (Supplemental Fig. 3C). Further, significantly higher rates of mucosal healing were demonstrated for patients who received most active treatments (vedolizumab 300 mg Q4W, vedolizumab 300 mg Q8W, tofacitinib 10 mg, mirikizumab 200 mg, ustekinumab 90 mg Q8W, and upadacitinib 15 mg) when compared with ustekinumab 90 mg Q12W. Vedolizumab 300 mg Q4W and upadacitinib 15 mg demonstrated higher rates of mucosal healing versus adalimumab, as did patients treated with upadacitinib 15 mg versus ustekinumab 90 mg Q8W.

Safety in the Overall Population at Induction

Network plots for all-cause discontinuations and SAEs in the induction period in the overall population are shown in Supplemental Fig. 4A, B. A total of 19 and 20 studies were included in the NMAs of all-cause discontinuation and SAEs, respectively. Results from the NMA of all-cause discontinuation under a fixed-effect model were highly uncertain, as reflected by wide credible intervals for some comparisons (Supplemental Fig. 4C), which were presumed to be a result of the low discontinuation rates across studies during the induction period. Significantly lower rates of all-cause discontinuation were observed for ozanimod, mirikizumab, ustekinumab and upadacitinib versus placebo. All pairwise comparisons of all-cause discontinuations are presented in Supplemental Fig. 4E. In the NMA of SAEs, under a random-effects model, a significant difference in the rate of SAEs was only

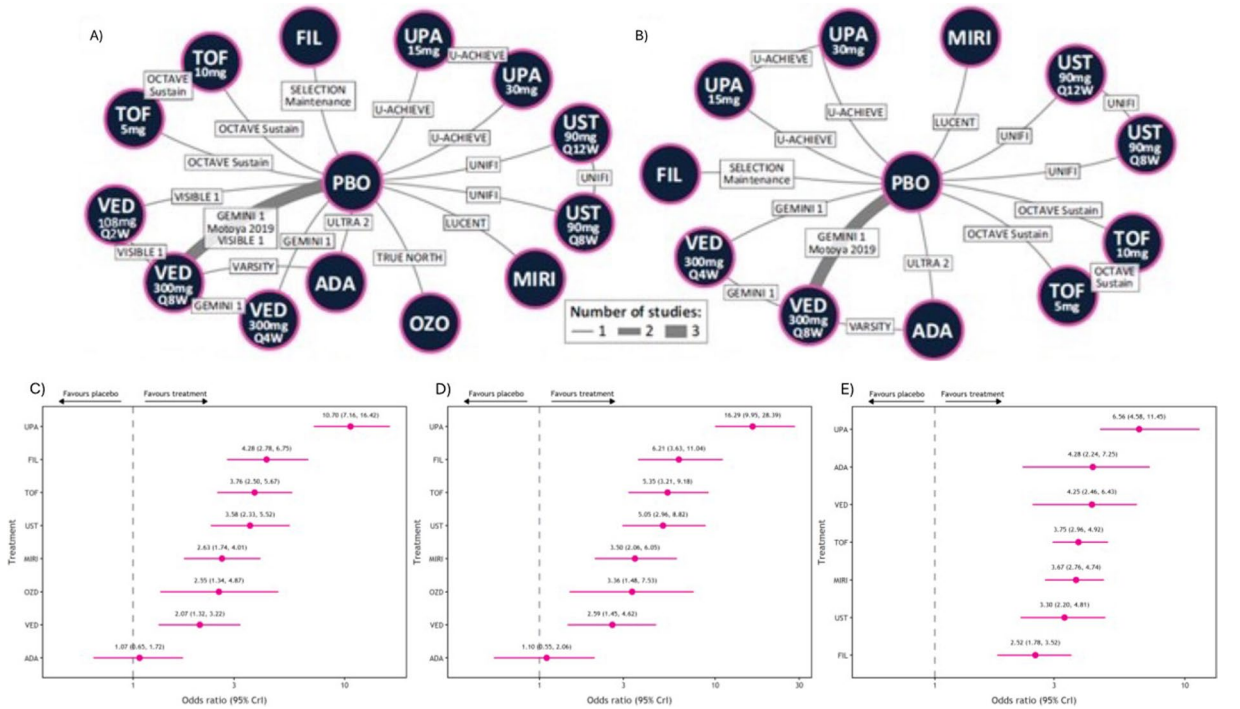

Fig. 5 Network plot for clinical response and remission (**A**) and mucosal healing (**B**) in the induction period for the biologic/JAKi-experienced population and median ORs (95% credible intervals) versus placebo for clinical response (**C**), clinical remission (**D**) and mucosal healing (**E**). *ADA* adalimumab, *CrI* credible interval, *FIL* filgotinib, *GOL* golimumab, *IFX* infliximab, *JAKi* Janus kinase inhibitor, *MIRI* mirikizumab, *OR* odds ratio, *OZD* ozanimod, *PBO* placebo, *TOF* tofacitinib, *UPA* upadacitinib, *UST* ustekinumab, *VED* vedolizumab

demonstrated for adalimumab when compared with placebo (Supplemental Fig. 4D, F).

DISCUSSION

In the absence of head-to-head trials, NMAs are an important means of providing comparative estimates of efficacy and safety. To our knowledge, this is the first NMA of all approved therapies for moderately-to-severely active UC including mirikizumab, stratified by study period (induction and maintenance) and prior therapy.

This analysis comprised a comprehensive series of NMAs, which demonstrated the overall clinical benefits in terms of clinical response and remission, as well as endoscopic mucosal healing and safety for most advanced therapies compared with placebo. Further, the analyses demonstrate that mirikizumab was similarly effective as most other biologics and small molecules in terms of clinical response and remission, and endoscopic mucosal healing, regardless of treatment period and prior biologic/small molecule therapy, with some significant improvements in efficacy observed. In the biologic/JAKi-naïve maintenance population, mirikizumab demonstrated superiority to anti-TNFs, vedolizumab, tofacitinib, ozanimod and upadacitinib 15 mg. In addition, mirikizumab also showed comparable results to ustekinumab, filgotinib and upadacitinib 30 mg. In the biologic/JAKi-experienced population, mirikizumab had significantly higher rates of clinical response and remission at induction compared with adalimumab, as well as for mucosal healing compared with ustekinumab 90 mg Q12W. Between the IL-23p19 and IL-12/23 classes, efficacy estimates were largely comparable, with mirikizumab showing some numerically higher rates of clinical response and remission and mucosal healing across the

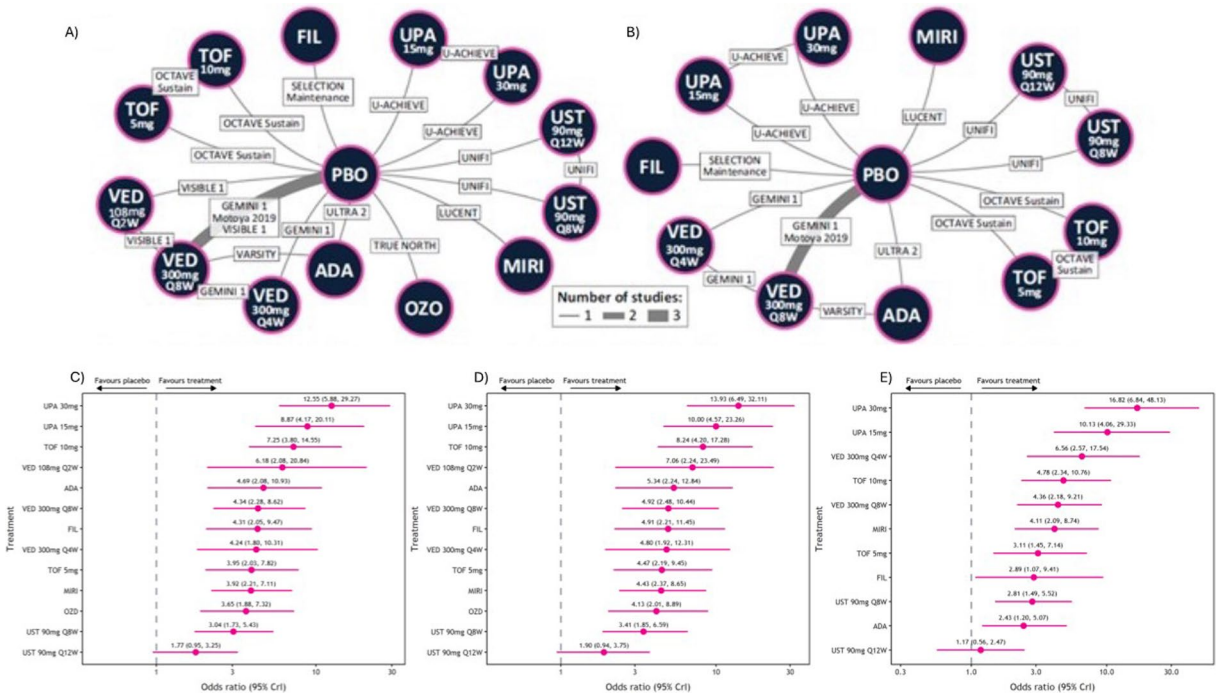

Fig. 6 Network plot for clinical response and remission (**A**) and mucosal healing (**B**) in the maintenance period for the biologic/JAKi-experienced population and median ORs (95% credible intervals) versus placebo for clinical response (**C**), clinical remission (**D**) and mucosal healing (**E**). *ADA* adalimumab, *CrI* credible interval, *FIL* filgotinib, *GOL* golimumab, *IFX* infliximab, *JAKi* Janus kinase inhibitor, *MIRI* mirikizumab, *OR* odds ratio, *OZD* ozanimod, *PBO* placebo, *TOF* tofacitinib, *UPA* upadacitinib, *UST* ustekinumab, *VED* vedolizumab

populations. These results highlight the potential of IL-23 inhibition as a potent treatment for moderately-to-severely active UC. At both induction and maintenance, different doses of upadacitinib (45 mg and 30 mg, respectively) showed significantly higher rates of clinical response and remission compared with almost all interventions across the biologic/JAKi-experienced population; at induction, these responses were also seen in the biologic/JAKi-naïve population, with the exception of mucosal healing where infliximab ranked first.

The findings from our analysis add to those of previously published NMAs of biologic therapies in patients with moderately-to-severely active UC, including several that were performed under a Bayesian framework [41–48]. The estimates from our NMA are generally aligned with previous research. Nevertheless, approaches and methodologies differed, including study inclusion criteria, evidence base and statistical methods—in particular regarding trial design adjustments, making a more in-depth comparison of results difficult. Discussions on the statistical rigour of the data are included in the Supplemental Materials.

This NMA draws from an extensive evidence base with a larger number of comparators. Further, to our knowledge, few NMAs in UC have provided comparative estimates for endoscopic mucosal healing, an endpoint of increasing clinical interest [41, 42].

The current NMA follows a robust methodology. A rigorous SLR in line with best practice guidelines provided the evidence base, and the studies considered for inclusion underwent an extensive FA to investigate comparability as well as to understand areas of heterogeneity and treatment effect modifiers. Measures to reduce heterogeneity included analysing the biologic/JAKi-naïve and -experienced populations independently, limiting the time point of assessment

at maintenance, and accounting for differences in placebo rates across studies, which may reflect areas of heterogeneity difficult to otherwise control for, by exploring baseline risk adjustment via a meta-regression model with baseline risk as the covariate.

There are several limitations to the current analysis. While mostly consistent across trials, differing definitions of clinical response and remission were observed for some studies, and in some cases a definition was not provided. However, the approach to assessing mucosal healing was strengthened through the use of a consistently applied definition in line with LUCENT studies, regardless of terminology used to describe the outcome.

The designs of the induction phase studies were consistent; however, their durations varied from 6 to 14 weeks—a wider variation compared with those included in other NMAs (6–10 weeks [41, 43, 46] and 6–8 weeks [44, 48], but narrower than that used by Lu and colleagues [42] (6–16 weeks)). The variation in induction studies is to be expected based on the differences in mechanism of action. In this NMA, maintenance time points were restricted to 52–60 weeks. Comparisons across maintenance trials in UC are challenging because of the differences in study designs, and require substantial data handling to align outcomes and allow for comparison, as has been done in previous NMAs [41–48].

In addition, heterogeneity was observed in the definitions and details of previous therapies received for biologic/JAKi-naïve and -experienced populations across studies.

The observed differences in placebo rates may potentially be driven by multiple factors such as differences in baseline concomitant medication use. In addition, length of induction period, lack of a 'pure' placebo group, proportion of biologic-naïve patients, route of administration or other drug and study characteristics have all been shown to impact effect sizes. It has been recognised that concurrent corticosteroid use may be associated with symptomatic improvement and attenuation of observed treatment effects, while the impact of concomitant use of immunomodulators is less straightforward [49]; however, their exclusion may contribute to the observed treatment effects within the upadacitinib trials [15].

Results across different efficacy endpoints cannot intuitively be compared. The statistical models used for each network were those with the best fit for the identified evidence base for that network. This evidence base could include different numbers of studies, greater or fewer numbers of events and sample sizes, as well as varying placebo rates (or baseline risk) for each network, with each component impacting the NMA for that network, including the results, level of uncertainty, and the best fitting model selection. Consequently, model selections did not align across outcomes (clinical response and remission, and mucosal healing) within the same population and time point (e.g. naïve maintenance). This prevented comparison of results when adjusted models were chosen for one outcome (e.g. clinical response and remission), but unadjusted models were selected for another outcome (e.g. mucosal healing).

NMAs of safety outcomes were performed for the overall population in a single analysis as safety outcome data are frequently reported for the overall study population (i.e. regardless of prior exposure to biologic therapy) in line with CONSORT recommendations [30, 31]. In addition, safety analyses were only considered for induction.

CONCLUSION

This NMA, based on robust methodology, expands the understanding of the comparative efficacy and safety of treatments for patients with moderately-to-severely active UC, including treatments not previously studied.

In this NMA, we found that clinical response and remission results favoured upadacitinib for induction treatment in both populations studied, and upadacitinib and mirikizumab for maintenance treatment in the biologic/JAKi-experienced and -naïve populations, respectively. With respect to mucosal healing, induction and maintenance results favoured upadacitinib in the biologic/JAKi-experienced population, while in the biologic/JAKi-naïve population, results

favoured infliximab for induction treatment and golimumab for maintenance.

In the absence of head-to-head studies, this NMA showed that mirikizumab offered consistent efficacy for clinical response, clinical remission and endoscopic mucosal healing compared with other advanced therapies. For maintenance therapy, irrespective of prior biologic/JAKi therapy exposure, results suggest mirikizumab offers clinical benefits in terms of clinical response and remission, and endoscopic mucosal healing. Although these results should be interpreted with caution given the underlying areas of heterogeneity and uncertainty, which cannot be fully addressed in this disease area, the robustness of the evidence base, methodology and statistical analysis together suggest that this is one of the strongest NMAs in UC yet. In the absence of head-to-head studies for most active treatments, this study provides supportive evidence to inform decision-making in the treatment of patients with moderately-to-severely active UC.

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Declarations

Conflict of interest. Axel Dignass reports no conflicts of interest for the work under consideration for publication. Claire Ainsworth, Niels Dunnewind, Sonja Kroep, Nicholas Halfpenny and Emanuele Arcà are employees of OPEN Health at the time of this study and its analysis. OPEN Health received funding from Eli Lilly and Company for the design and conduct of this study, statistical analysis and study report preparation. Susanne Hartz, Isabel Redondo and Christophe Sapin are employees and minor shareholders of Eli Lilly and Company. Sami Hoque has no competing interests to declare.

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