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ORIGINAL RESEARCH

Dupilumab Versus Mepolizumab for COPD: Evaluating Efficacy Outcomes Using Placebo-Adjusted Indirect Treatment Comparison

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ABSTRACT

Introduction: Up to 40% of patients with chronic obstructive pulmonary disease (COPD) exhibit elevated blood eosinophils, reflective of type 2 inflammation. Dupilumab and mepolizumab versus standard of care have demonstrated moderate-to-severe exacerbation reductions of 30–34% and 15–18%, respectively, over 52 weeks. This study compared their relative efficacy using indirect treatment comparison (ITC).

Methods: A Bucher ITC was performed on 52-week phase 3 trials of dupilumab (BOREAS/NOTUS) and mepolizumab (MATINEE/METREX/METREO). The primary ITC endpoint was annualized moderate-to-severe exacerbation rates in patients from BOREAS + NOTUS versus MATINEE + METREX (modified intention-to-treat high stratum cohort, representing an eosinophilic phenotype); sensitivity analyses were performed using different combinations of mepolizumab data including MATINEE + METREX + METREO (100-mg arm). Other 52-week endpoints included mean difference in pre-bronchodilator forced expiratory volume in 1 s (FEV_1), proportion of St. George's Respiratory Questionnaire (SGRQ) improvement ≥ 4 points, proportion of Evaluating Respiratory Symptoms in COPD (E-RS:COPD) improvement ≥ 2 points, and annualized severe exacerbation rate. Rate ratios (RRs)/odds ratios (ORs) with 95% confidence intervals (CIs) are reported.

Results: The primary ITC resulted in an RR of 0.82 (95% CI 0.66, 1.01), showing a numerical advantage for dupilumab versus mepolizumab in reducing moderate-to-severe exacerbation. Sensitivity analyses confirmed findings from the primary ITC (BOREAS + NOTUS vs. MATINEE + METREX + METREO: RR 0.83 [95% CI 0.68, 1.01]). Dupilumab demonstrated significantly greater FEV_1 improvement (mean difference

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83.4 mL [95% CI 36.1, 130.7]) and proportion of E-RS:COPD improvement ≥ 2 points (OR 1.71; [95% CI 1.18, 2.48]), with a numerical difference favoring dupilumab for the proportion of SGRQ improvement ≥ 4 points (OR 1.16; [95% CI 0.86, 1.56]) and for annualized severe exacerbation rate (RR 0.61 [95% CI 0.33, 1.13]) versus mepolizumab.

Conclusion: This ITC suggests potential clinical benefits of dupilumab over mepolizumab in reducing exacerbations and improving lung function, respiratory symptoms, and quality of life in patients with COPD and type 2 inflammation. Direct head-to-head trials are necessary to confirm these results and better guide treatment choices.

PLAIN LANGUAGE SUMMARY

Chronic obstructive pulmonary disease (COPD) is a long-term lung condition that causes breathing difficulties and frequent flare-ups, also known as exacerbations. In some people with COPD, a type of inflammation known as type 2 inflammation is present. This inflammation is often linked to higher levels of white blood cells called eosinophils. These patients may be more likely to experience exacerbations and worsening symptoms. Two injectable treatments, dupilumab and mepolizumab, have recently been studied in people with COPD who have this type of inflammation (so-called eosinophilic phenotype). Both drugs have shown benefits when added to triple inhaler therapy regimen, but they have not been directly compared in the same clinical trial. This study used a method called an indirect treatment comparison, which uses results from dupilumab and mepolizumab trials to estimate how well these two treatments compare. The results indicate a trend suggesting that dupilumab may offer greater benefit than mepolizumab in reducing the number of moderate or severe COPD exacerbations. People treated with dupilumab also experienced better lung function and were more likely to report fewer breathing symptoms, as well as improved quality of life. Although safety comparisons were not part of the indirect treatment comparison, safety results from dupilumab and mepolizumab trials appeared to be similar. These findings suggest that dupilumab may offer greater overall benefits for people with COPD and type 2 inflammation. However, direct head-to-head trials are necessary to confirm these results and better guide treatment choices.

Keywords: COPD; Dupilumab; Exacerbations; FEV_1; Indirect treatment comparison; Mepolizumab; Quality of life

Key Summary Points

Why carry out this study?

Type 2 inflammation occurs in up to 40% of patients with chronic obstructive pulmonary disease (COPD) and contributes to exacerbation risk.

Results from the phase 3 trials of dupilumab and mepolizumab in patients with COPD and type 2 inflammation showed that dupilumab demonstrated a 30–34% reduction in the rate of moderate-to-severe exacerbations versus triple therapy at 52 weeks, and mepolizumab demonstrated a reduction of between 15% and 18% at 52 weeks and 25% at 104 weeks for moderate-to-severe exacerbations (mepolizumab MATINEE study was extended from 52 to 104 weeks) versus triple therapy. Dupilumab and mepolizumab have not been directly compared in a head-to-head trial.

This analysis was designed to evaluate the efficacy of dupilumab versus mepolizumab for patients with COPD using an anchored Bucher indirect treatment comparison (ITC).

What was learned from the study?

According to the ITC methodology, dupilumab provided a numerically favorable reduction (rate ratio 0.82 [95% CI 0.66, 1.01]) in the rate of moderate-to-severe exacerbations compared with mepolizumab, as well as an 83-mL improvement in lung function (pre-bronchodilator forced expiratory volume in 1 s), compared with mepolizumab; patients taking dupilumab had 71% higher odds of symptom improvement (Evaluating Respiratory Symptoms in COPD) and 16% higher odds of quality-of-life improvement (St. George's Respiratory Questionnaire) compared with those who received mepolizumab.

INTRODUCTION

It is estimated that up to 20–40% of patients with chronic obstructive pulmonary disease (COPD) exhibit elevated circulating eosinophil levels, consistent with type 2 inflammation [1–6]. Patients with COPD and elevated blood eosinophil levels are at higher risk of exacerbation [6, 7]. Two biologic agents, dupilumab and mepolizumab, have demonstrated efficacy and safety in phase 3 trials of COPD, and have been approved for the treatment of patients with COPD with an eosinophilic phenotype [8–11].

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, inhibiting signaling of both IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases [12]. Dupilumab is approved by the Food and Drug Administration (FDA), European Medicines Agency, and agencies in other countries for use as an add-on maintenance treatment for adults with inadequately controlled COPD and an eosinophilic phenotype [13, 14].

Mepolizumab is a humanized monoclonal antibody directed against IL-5, a type 2 inflammatory cytokine known to orchestrate eosinophil responses [10]. By blocking IL-5, mepolizumab reduces eosinophil counts in tissue and in the circulation. Mepolizumab was recently approved by the FDA for adults with COPD with an eosinophilic phenotype [15].

While both dupilumab and mepolizumab have demonstrated efficacy in patients with COPD, no head-to-head trials exist; therefore, we performed an indirect treatment comparison (ITC). Bucher ITC estimates relative efficacy by linking treatments through a shared comparator, such as a placebo [16]. This anchored method is widely regarded as the preferred approach when direct head-to-head trials are lacking and placebo-controlled data are available [17, 18]. This is especially true when background therapy is standardized and consistent between trials. Because randomized trials serve as the foundation, both known and unknown confounders are balanced by randomization, offering more reliable estimates than unanchored methods.

The objective of this analysis was to compare the efficacy of dupilumab versus mepolizumab in patients with COPD and type 2 inflammation using placebo-controlled Bucher ITC.

METHODS

Review of Phase 3 Trials

Five phase 3 trials have evaluated dupilumab and mepolizumab in COPD: dupilumab in BOREAS (NCT03930732) and NOTUS (NCT04456673) and mepolizumab in METREX (NCT02105948), METREO (NCT02105961), and MATINEE (NCT04133909) (Fig. 1a, Timelines and b, Designs).

The dupilumab trials enrolled patients with moderate-to-severe COPD and type 2 inflammation, indicated by a blood eosinophil count ≥ 300 cells/μL at screening [8, 9]. Patients received an approved 300-mg dose of dupilumab every 2 weeks (q2w) subcutaneously for 52 weeks. Dupilumab significantly reduced exacerbation rates (BOREAS: rate ratio [RR] 0.70; NOTUS: RR 0.66; both $p < 0.001$) and improved lung function. Quality-of-life improvements (St. George's

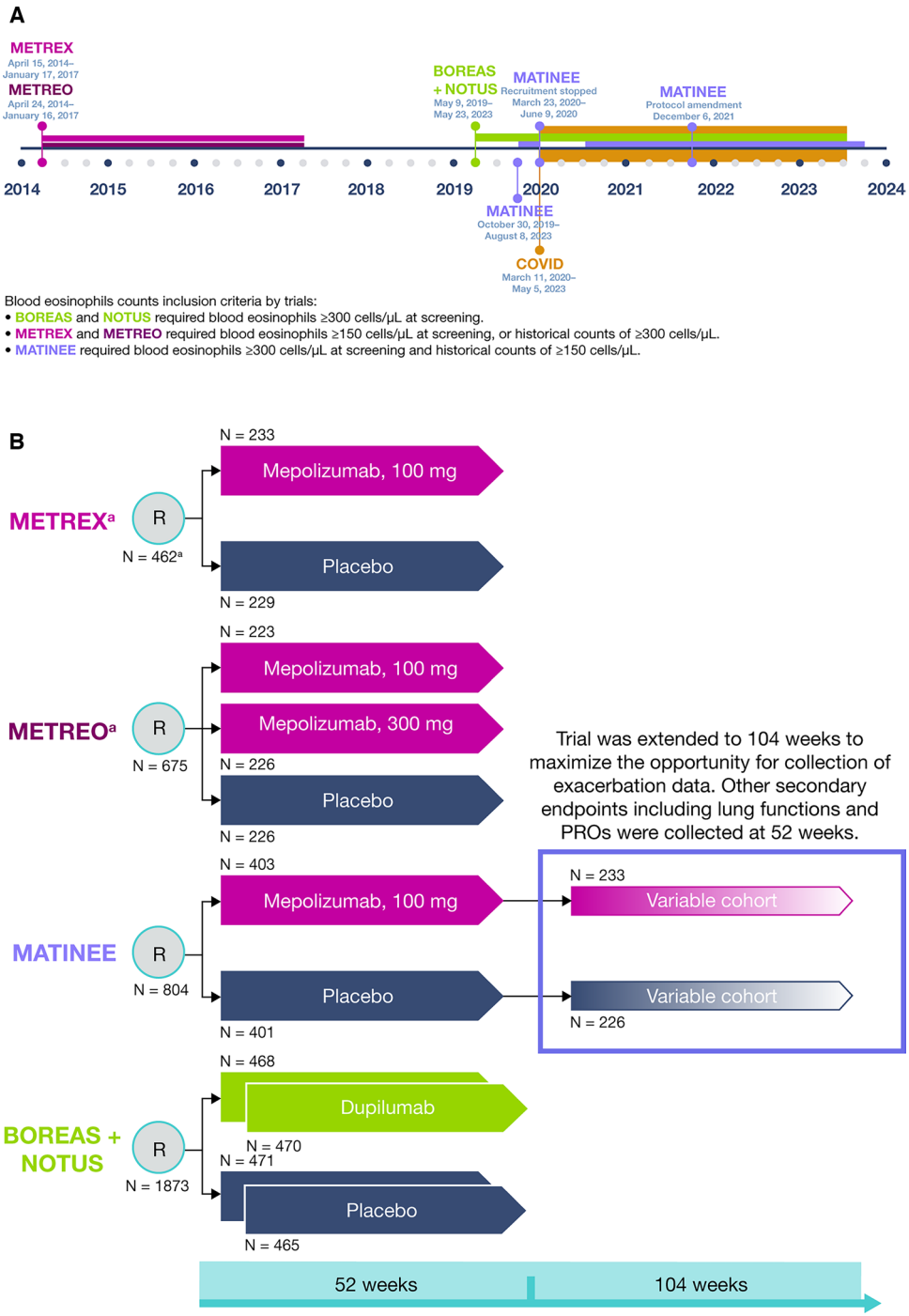

Fig. 1 Timelines (**a**) and designs (**b**) of BOREAS, NOTUS, METREX, METREO, and MATINEE. *mITT* modified intention-to-treat, *PROs* patient-reported outcomes, *R* randomization. [a]In total, 837 patients were randomized to METREX, stratified by eosinophilic phenotype. Characteristics and outcomes were extracted specifically for the mITT population with an eosinophilic phenotype (mITT high stratum). In METREO and MATINEE, only patients who had an eosinophilic phenotype were eligible for inclusion

Respiratory Questionnaire [SGRQ] scores) were statistically significant in BOREAS (least squares [LS] mean difference vs. placebo: −3.4 [95% confidence interval (CI) −5.5, −1.3]; $p=0.002$) but not in NOTUS (LS mean difference vs. placebo: −3.4 [95% CI −5.8, −0.9]), which was stopped early due to a positive interim analysis, resulting in 214 patients not having a chance to reach week 52 time-point assessment [9]. In a pooled analysis of the intention-to-treat (ITT) populations of BOREAS and NOTUS, dupilumab significantly reduced moderate-to-severe exacerbations versus placebo (RR 0.69; $p<0.0001$) and significantly improved SGRQ scores [19].

The mepolizumab trials METREX, METREO, and MATINEE enrolled patients with COPD and an eosinophilic phenotype; METREX also enrolled patients without an eosinophilic phenotype [10, 11]. METREO did not reach statistical significance for the primary endpoint, and no improvements in patient-reported outcome measures (SGRQ) or COPD assessment test (CAT) scores were observed. METREO results were not included in the clinical efficacy analysis in the US prescription drug label [15]. The approved 100-mg dose of mepolizumab every 4 weeks (q4w) was used in METREX and MATINEE, whereas METREO included both 100-mg and 300-mg doses, all over 52 weeks.

Mepolizumab significantly reduced exacerbation rates in the subgroup with an eosinophilic phenotype (modified intention-to-treat [mITT] high stratum subgroup: blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in the year prior to the study) in METREX (RR 0.82; $p=0.04$), although no improvements in lung function, SGRQ, or CAT scores were observed. In the mITT high stratum populations of METREX and METREO that received 100-mg mepolizumab, patients with eosinophils between 150 and 300 cells/μL at screening had an 8% rate reduction in moderate-to-severe exacerbations [10, 15].

The MATINEE trial enrolled patients with COPD and blood eosinophils ≥ 300 cells/μL at screening and ≥ 150 cells/μL in the year prior to the study. MATINEE was originally designed as a 52-week study, but was later modified to increase the sample size and extend treatment to 104 weeks because of unexpectedly low exacerbation rates during the COVID-19 pandemic [11]. Mepolizumab versus placebo reduced exacerbation rates by 15% over 52 weeks and by 25% over 104 weeks of treatment (total reduction 18%; RR 0.79; $p=0.01$); however, secondary endpoints, including quality of life (SGRQ and CAT scores) and symptoms (Evaluating Respiratory Symptoms in COPD [E-RS:COPD] score) did not reach statistical significance.

Across all dupilumab and mepolizumab trials, the safety profiles were comparable with placebo.

Comparability of Trials

All five trials enrolled adults ≥ 40 years of age with moderate-to-severe COPD and a history of exacerbations while on triple inhaled therapy. MATINEE also enrolled patients with very severe (GOLD stage 4) COPD. In BOREAS, NOTUS, and MATINEE, patients with asthma were excluded; however, in METREX and METREO, patients with a history of asthma were included.

The trials differed in their eosinophil count inclusion criterion (Supplementary Material Table S1). BOREAS and NOTUS required counts of ≥ 300 cells/μL at screening, while METREX and METREO allowed counts of ≥ 300 cells/μL in the year prior to the study or screening counts of ≥ 150 cells/μL, and MATINEE required ≥ 300 cells/μL at screening and historical counts of ≥ 150 cells/μL. In addition, METREX enrolled patients with and without elevated blood eosinophil levels, unlike the other studies, which included only the population with elevated blood eosinophil levels. These differences highlight variations in patient populations, which may have influenced trial outcomes. This ITC compared only those patients with elevated blood eosinophil levels, excluding patients without an eosinophilic phenotype in METREX. Including patients with elevated blood eosinophil levels without a specific cutoff was an approach selected due to its likelihood to provide a fair comparison, given variations in eosinophil levels over time, and the sensitivity of eosinophil levels to treatment with inhaled corticosteroids (ICS), which nearly all patients

in these trials were on as part of standard-of-care background medication [7, 20].

In this study, only data from patients who received the approved dosage (300 mg q2w dupilumab or 100 mg q4w mepolizumab) were included. In addition, the results from METREO were excluded from the base-case ITC analysis but were included as part of the sensitivity analysis. This decision was made because METREO was not included in the FDA label for the COPD indication due to its failure to meet the primary endpoint.

Importantly, all endpoints included in the ITC analysis were reported at 52 weeks, except for certain scenarios in the sensitivity analysis. In the MATINEE trial, secondary endpoints, including improvements in pre-bronchodilator forced expiratory volume in 1 s (FEV_1), SGRQ, and E-RS:COPD, were collected at 52 weeks and reported for the entire cohort, including those who completed 52 to 104 weeks of treatment.

Bucher ITC

To compare the relative efficacy of dupilumab versus mepolizumab, a placebo-adjusted Bucher ITC for each outcome of interest was run using aggregate clinical trial data from BOREAS, NOTUS, METREX, and MATINEE [8–11]. Unless the data were not disclosed or not collected in a trial, all ITC analyses used data from the ITT population from BOREAS and NOTUS for dupilumab 300 mg and the 52-week results from the MATINEE and METREX mITT high stratum cohort (defined as patients with blood eosinophil count ≥ 150 cells/μL at screening or ≥ 300 cells/μL in the previous 12 months only) for mepolizumab 100 mg. This arrangement ensured the maximum comparability across the trials and consistency with the FDA label for the respective biologics.

For the ITC for moderate-to-severe exacerbation rate, a number of sensitivity analyses were performed comparing BOREAS and NOTUS with (1) MATINEE alone mITT, (2) MATINEE alone 52-week fixed cohort, (3) MATINEE mITT and METREX eosinophilic subgroup (mITT high stratum), and (4) totality of mepolizumab data in eosinophilic COPD from MATINEE 52-week fixed cohort, and METREX eosinophilic subgroup (mITT high stratum), and METREO (mepolizumab 100-mg dose, eosinophils ≥ 150 cells/μL subgroup). METREX mITT high stratum and METREO ≥ 150 cells/μL are presented as pooled analyses in Pavord et al. [10]. Secondary endpoints were also evaluated in BOREAS and NOTUS compared with the totality of mepolizumab data, as described above. In addition, the subgroup of patients with baseline eosinophil counts between 150 and 300 cells/μL in BOREAS and NOTUS was compared with the corresponding subgroup in METREX; MATINEE did not report moderate-to-severe exacerbation rates for this subgroup.

Endpoints

The primary endpoint for the ITC was the rate of moderate or severe COPD exacerbations over the first 52 weeks of treatment. Other efficacy endpoints evaluated at 52 weeks included the change from baseline in pre-bronchodilator FEV_1 (mL), the proportion of patients with SGRQ improvement of ≥ 4 points from baseline (minimal clinically important difference = 4 points), the proportion of patients with E-RS:COPD total score improvement ≥ 2 points from baseline, and the annualized rate of severe exacerbations.

The proportion of patients with adverse events (AEs), treatment-emergent adverse events (TEAEs), or serious adverse events (SAEs) was also evaluated; however, safety was not included in the Bucher ITC. The safety data are presented in Tables S2 and S3, which show that there was no meaningful difference in AE/TEAE or SAE for the treatment arm versus placebo in the trials for both dupilumab and mepolizumab.

Statistical Analysis

Meta-analyses were conducted using the "metafor" package (version 4.8–0) in R (version 4.3.2). RRs with 95% CI are reported to compare the rate of moderate or severe exacerbations and the rate of severe exacerbations; odds ratios (ORs) with 95% CI are reported for the proportion of

patients achieving SGRQ improvement of ≥ 4 points from baseline and E-RS:COPD total score improvement ≥ 2 points from baseline; LS mean difference with 95% CI is reported for change from baseline in pre-bronchodilator FEV_1.

Compliance with Ethical Guidelines

This article is based on data from previously conducted trials and does not contain any new studies with human participants or animals performed by any of the authors. Please see the original publications for each trial for full details of ethical approvals [8–11].

RESULTS

Baseline characteristics of patients included in all trials are shown in Table S4. While baseline characteristics were generally similar across studies in terms of age, sex, exacerbation history, lung function, and the proportion of current and former smokers enrolled in each study, not all studies reported the same characteristics, and therefore some comparisons could not be made. Notably, the mean baseline blood eosinophil levels were lower in the METREX mITT (mepolizumab: 260 cells/μL; placebo: 290 cells/μL) and METREO (mepolizumab: 300 cells/μL; placebo: 310 cells/μL) studies than in BOREAS (dupilumab: 330 cells/μL; placebo: 320 cells/μL), NOTUS (dupilumab: 326 cells/μL; placebo: 319 cells/μL), or MATINEE (mepolizumab: 480 cells/μL; placebo: 480 cells/μL) (Table S4). Endpoints shared across trials were identified (Table 1).

Primary Analysis: Moderate-to-Severe Exacerbation Rate

In the combined data from BOREAS and NOTUS, dupilumab versus placebo reduced the risk of moderate-to-severe exacerbation by 32% (RR 0.68 [95% CI 0.59, 0.79]); in the combined MATINEE (52-week fixed) and METREX (mITT high stratum, representing an eosinophilic phenotype), mepolizumab versus placebo reduced the risk of moderate-to-severe exacerbations by 17% (RR 0.83 [95% CI 0.71, 0.97]) (Table 2). In these populations, the placebo-adjusted Bucher ITC comparing risk reduction in the annualized rate of moderate-to-severe exacerbations numerically favored dupilumab (RR 0.82 [95% CI 0.66, 1.01]); however, statistical significance was not achieved (Table 2).

Sensitivity analyses were conducted to understand the impact of different data cutoff points for mepolizumab trial data when compared with dupilumab trial data (Tables S5–S7). These confirmed the findings of the primary endpoint analysis, with the Bucher ITC revealing numerically favorable RRs for NOTUS and BOREAS versus combinations of mepolizumab trial data. In particular, the scenario comparing all mepolizumab 52-week data (MATINEE + METREX mITT high stratum cohort + METREO) yielded an RR of 0.83 (95% CI 0.68, 1.01) (Table S8). In addition, the sensitivity analysis of the subgroup with baseline eosinophil levels between 150 and 300 cells/μL (pooled BOREAS and NOTUS: RR 0.67 [95% CI 0.52, 0.87]; METREX mITT high stratum: RR 0.92 [95% CI 0.73, 1.16]) also indicated a numerically favorable ITC result for dupilumab versus mepolizumab in this subgroup (Table S9).

Due to the absence of the 52-week results of the annualized exacerbation rate for the entire MATINEE cohort ($N = 804$) for the Bucher ITC, a comparison of the relative reduction in cumulative events of moderate-to-severe exacerbation up to 52 weeks was carried out across the entire cohort in the BOREAS, NOTUS, and MATINEE (cumulative event data for the entire cohort are available in the figure of the cumulative event curve [11]), and the METREX mITT high stratum cohort, as shown in Fig. 2. In the first 12 weeks, compared with their respective placebo arm, dupilumab and mepolizumab achieved a similar level of reduction in total moderate-to-severe exacerbations. Over a 52-week period, the cumulative moderate-to-severe exacerbation events curve revealed a widening difference between dupilumab versus placebo compared with

Table 1 Primary and secondary endpoints from BOREAS, NOTUS, MATINEE (52-week fixed), METREX (mITT HS), and METREO (100 mg) after 52 weeks of treatment

	BOREAS ***N*** **= 939**	**NOTUS** ***N*** **= 721**	**MATINEE (52 weeks)[a]** ***N*** **varied by endpoints**	**METREX (mITT HS)[b]** ***N*** **= 462**	**METREO (100 mg)[c]** ***N*** **= 449**
Primary endpoint					
Annualized rate of moderate or severe exacerbations, RR (95% CI)	0.70 (0.58, 0.86)	0.66 (0.54, 0.82)	0.85 (0.62, 1.16)	0.82 (0.68, 0.98)	0.80 (0.65, 0.98)[d]
Secondary and other endpoints					
Pre-bronchodilator FEV_1 (L), mean difference (95% CI)	83.0 (38.0, 128.0)	62.0 (11.0, 113.0)	−9.0 (−60.1, 42.1)	−10 (−54, 33)	19 (−29, 67)
SGRQ total score, mean difference (95% CI)	−3.4 (−5.5, −1.3)	−3.4 (−5.8, −0.9)[e]	−2.3 (−4.6, 0.1)	0.2 (−2.8, 3.2)	−1.8 (−4.5, 0.8)
E-RS:COPD score, mean difference (95% CI)	−1.1 (−1.8, −0.4)	−0.6 (−1.4, 0.2)	−0.2 (−1.0, 0.6)	Not included in trial	Not included in trial
Annualized rate of severe exacerbations, RR (95% CI)	0.85 (0.45, 1.60)	0.56 (0.31, 1.02)	52-week NR	1.12 (0.72, 1.74)	0.63 (0.36, 1.09)[d]
Time to first moderate-to-severe exacerbation, HR (95% CI)	0.80 (0.66, 0.98)	0.71 (0.57, 0.89)	52-week NR	0.75 (0.64, 0.94)	0.82 (0.64, 1.04)
CAT score, mean difference (95% CI)	Not included in trial	Not included in trial	0.4 (−0.5, 1.4)	−0.8 (−2.0, 0.5)	−1.1 (−2.3, 0.0)

Green shaded cells indicate statistically significant results per the predefined statistical method for each trial; orange shaded cells indicate non-statistically significant results; gray shaded cells indicate endpoints not included or NR in the trial

CAT COPD Assessment Test, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *E-RS:COPD* Evaluating Respiratory Symptoms in COPD, FEV_1 forced expiratory volume in 1 s, *HR* hazard ratio, *HS* high stratum, *mITT* modified intention-to-treat, *NR* not reported, *RR* rate ratio, *SGRQ* St. George's Respiratory Questionnaire

[a]Main results provided within Sciurba et al. [11], based on patients assessed on either a 52-week or 104-week basis; these results are from the 52-week fixed cohort. $N = 345$ for the 52-week primary endpoint (moderate-to-severe exacerbations); $N = 804$ for the reported 52-week secondary endpoints, which varied slightly across endpoints

[b]Includes patients with blood eosinophil counts ≥ 150 cells/μL at screening or ≥ 300 cells/μL in the year prior to the study

[c]Includes patients who received 100-mg mepolizumab or placebo

[d]Although the 95% CI excluded the null value, the METREO endpoints did not reach statistical significance because they failed to meet the multiplicity-adjusted α-level specified in the preplanned analysis. Details of the multiplicity-control strategy are provided in the Supplementary Material of Pavord et al. [10]

[e]Not statistically significant per the NOTUS prespecified statistical method adjusting for multiplicity

Table 2 Bucher ITC of the annualized rate of moderate or severe COPD exacerbations in BOREAS and NOTUS versus MATINEE (52-week fixed cohort) and METREX (mITT HS cohort)[a]

Study	Treatment	*N*	Annualized rate of moderate or severe COPD exacerbation (95% CI)	Rate ratio (95% CI)	Rate ratio meta-analysis estimate (95% CI)	Bucher ITC: dupilumab 300 mg vs. mepolizumab 100 mg
BOREAS	Dupilumab 300 mg	468	0.78 (0.64, 0.93)	0.70 (0.58, 0.86)	0.68 (0.59, 0.79)	0.82 (0.66, 1.01)
	Placebo	471	1.10 (0.93, 1.30)			
NOTUS	Dupilumab 300 mg	470	0.86 (0.70, 1.06)	0.66 (0.54, 0.82)		
	Placebo	465	1.30 (1.05, 1.60)			
MATINEE (52-week fixed)[b]	Mepolizumab 100 mg	170	0.75 (0.60, 0.94)	0.85 (0.62, 1.16)	0.83 (0.71, 0.97)	
	Placebo	175	0.89 (0.71, 1.10)			
METREX (mITT HS)[c]	Mepolizumab 100 mg	223	1.40 (NR, NR)	0.82 (0.68, 0.98)		
	Placebo	229	1.71 (NR, NR)			

CI confidence interval, *COPD* chronic obstructive pulmonary disease, *HS* high stratum, *ITC* indirect treatment comparison, *mITT* modified intention-to-treat, *NR* not reported

[a]Upper bound to estimate the relative effect between dupilumab and mepolizumab

[b]Main results provided within Sciurba et al. [11], based on patients assessed on either a 52-week or 104-week basis; this analysis was restricted to the 52-week fixed cohort. All other trials were assessed at 52 weeks

[c]Patients with blood eosinophil count ≥ 150 cells/μL at screening or ≥ 300 cells/μL in the previous 12 months only

mepolizumab versus placebo, with dupilumab achieving a 28% reduction at 52 weeks in the pooled BOREAS and NOTUS data versus mepolizumab achieving 17% and 16% reduction in MATINEE (104-week cohort) and METREX (mITT high stratum cohort), respectively.

Secondary and Other Endpoints

The placebo-adjusted Bucher ITC evaluating the change in pre-bronchodilator FEV_1 at week 52 significantly favored dupilumab versus mepolizumab (MATINEE 52-week fixed and METREX mITT high stratum cohorts) (mean difference: 83.4 [95% CI 36.1, 130.7]) (Fig. 3a). The Bucher ITC evaluating the proportion of patients with SGRQ total score improvement ≥ 4 points revealed a numerically favorable OR for dupilumab versus mepolizumab (MATINEE 52-week fixed and METREX mITT high stratum cohorts) (OR 1.16 [95% CI 0.86, 1.56]) (Fig. 3b). Similarly, the Bucher ITC evaluating the proportion of patients with E-RS:COPD total score improvement ≥ 2 points significantly favored dupilumab (pooled BOREAS and NOTUS) versus mepolizumab (MATINEE 52-week fixed cohort only; E-RS:COPD was not evaluated in METREX) (OR 1.71 [95% CI 1.18, 2.48]) (Fig. 3c). The RR for dupilumab versus mepolizumab (METREX mITT high stratum cohort) for the annualized

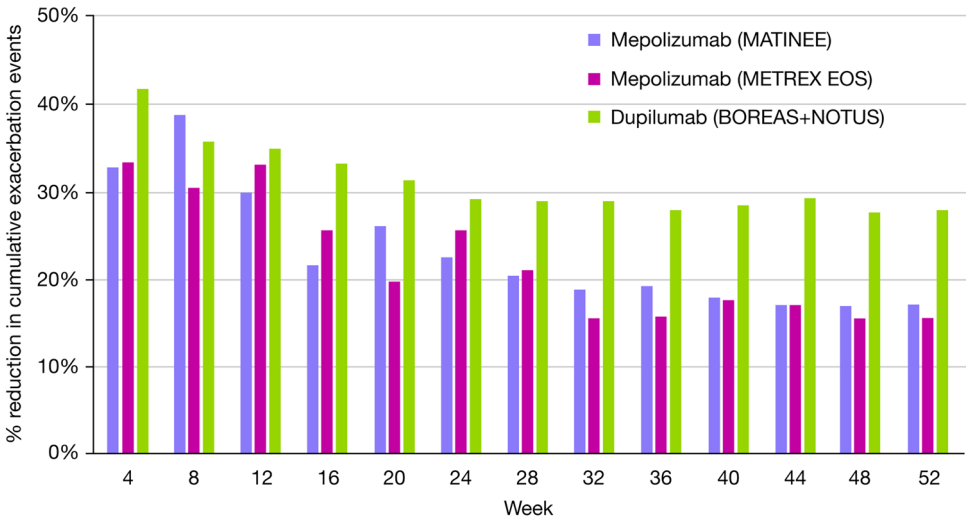

Fig. 2 Relative reduction[a,b] in cumulative moderate-to-severe exacerbations in BOREAS, NOTUS, MATINEE, and METREX (mITT high stratum cohort) up to 52 weeks. *mITT* modified intention-to-treat. [a]Reduction versus placebo arm per each trial reported data. [b]Calculation of relative reduction at various time points used the following formula: (cumulative events per enrollee at time *t* in placebo arm – cumulative events per enrollee at time *t* in treatment arm)/cumulative events per enrollee at time *t* in placebo arm. The values of cumulative events at time *t* were extracted through digitization of Fig. 1a of the BOREAS and NOTUS pooled study [19], Fig. 1a of the MATINEE study [11], and Fig. 3a of the METREX and METREO study [10]

rate of severe exacerbations (as defined by the protocol) was 0.61 (95% CI 0.33, 1.13) (Fig. 3d). Similar results were observed across these secondary and other endpoints when comparing BOREAS and NOTUS to MATINEE 52-week fixed and METREX mITT high stratum cohort and METREO 100-mg cohort (Table S8).

DISCUSSION

Key health technology assessment and research organizations, such as the National Institute for Health and Care Excellence (NICE) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), consider anchored ITCs a robust approach because they preserve the benefits of randomization by linking treatments through a common comparator, reducing susceptibility to bias [17, 18, 21]. In the absence of head-to-head trials, this anchored Bucher ITC provides comparative data on the efficacy of dupilumab and mepolizumab for patients with COPD and type 2 inflammation. Although the results of this ITC for the primary endpoint did not reach statistical significance, dupilumab consistently showed numerical benefits compared with mepolizumab across analyses, with a greater percentage reduction in 52-week cumulative exacerbation events. Dupilumab also demonstrated a benefit over mepolizumab in lung function improvement and patient-reported outcomes such as E-RS-COPD and SGRQ. Reducing respiratory symptoms is one of the main treatment goals in COPD because of the impact of symptoms on the daily quality of life of patients with COPD [22].

To date, dupilumab is the first and only add-on biologic therapy to demonstrate moderate and/or severe exacerbation reduction while improving lung function and quality of life and reducing symptoms beyond triple inhaled therapy. The clinical effects of dupilumab may be due to differences in the mechanism of action of dupilumab, which targets IL-4 and IL-13 signaling, as compared with mepolizumab, which targets the IL-5 pathway. IL-4 and IL-13 promote type 2 inflammatory cell infiltration

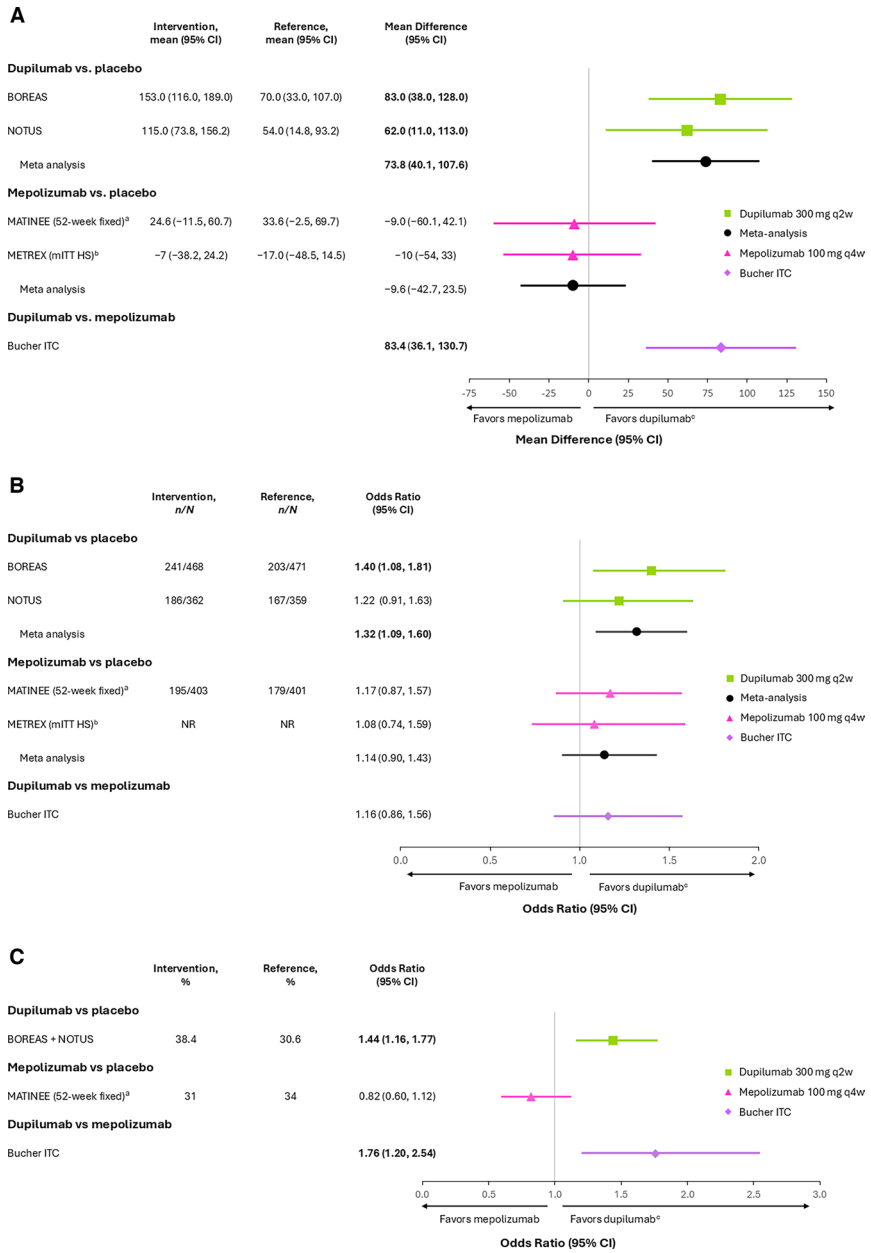

Fig. 3 Bucher ITC of secondary endpoints **a** change in pre-bronchodilator FEV_1 (mL) at 52 weeks, **b** SGRQ total score improvement (≥ 4) at 52 weeks, **c** E-RS:COPD improvement (≥ 2) at 52 weeks, and **d** severe exacerbations up to treatment week 52. *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *E-RS:COPD* Evaluating Respiratory Symptoms in COPD, *FEV_1* forced expiratory volume in 1 s, *HS* high stratum, *ITC* indirect treatment comparison, *mITT* modified intention-to-treat, *q2w* every 2 weeks, *q4w* every 4 weeks, *SGRQ* St. George's Respiratory Questionnaire. For BOREAS and NOTUS, separate data for individual trials were used whenever available. If the individual trial data were not available, the pooled data from the combined trial analysis [19] were used. [a]Main results provided within Sciurba et al. [11], based on patients assessed on either a 52-week or 104-week basis; this analysis was restricted to the 52-week fixed cohort. All other trials were assessed at 52 weeks. [b]Patients with blood eosinophil count ≥ 150 cells/μL at screening or ≥ 300 cells/μL in the previous 12 months only. [c]Intervention refers to the treatment being tested; reference refers to the comparator; for Bucher ITC, dupilumab is the intervention versus mepolizumab as the comparator

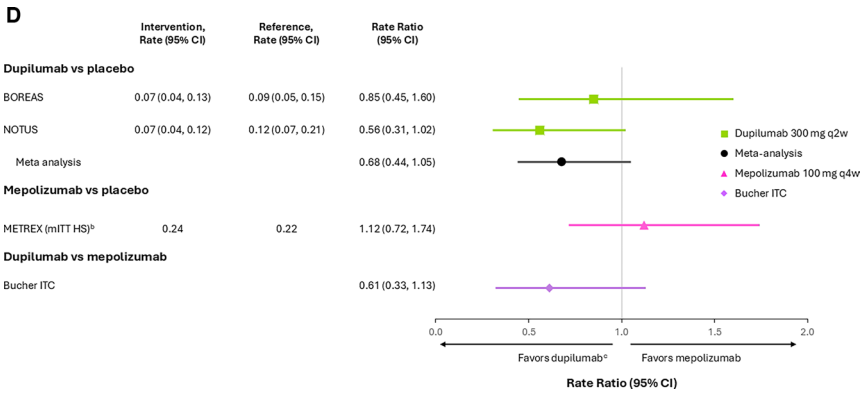

Fig. 3 continued

in the lungs that may increase airway hyperreactivity and impair barrier dysfunction that leads to airway remodeling [23–26]. Additionally, IL-4 and IL-13 are associated with goblet cell hyperplasia, mucociliary dysfunction, and mucus hypersecretion, which together with the effects on airway smooth muscle and inflammation are associated with lung function decline [23–27]. Dupilumab blocks the shared component between the IL-4 and IL-13 receptors and has demonstrated clinical features associated with disrupting this inflammatory pathway, including exacerbation reduction, lung function improvement, and symptom reduction [8, 9, 19, 28]. IL-5 is a key component of type 2 inflammation, and is primarily associated with eosinophil maturation in the bone marrow and survival in tissues [29]. Mepolizumab leads to a reduction in blood and tissue eosinophils as well as a reduction in exacerbations in clinical trials [10, 11, 30]. Mepolizumab's lack of impact on lung function may indicate that airway remodeling that occurs over time is largely independent of eosinophilic inflammation. It may also reflect the overlapping nature of multiple pathways that contribute to inflammation and structural airway changes over time in patients with COPD.

Although reducing exacerbations may be the highest priority for the healthcare system and physicians due to the associated costs and detrimental clinical outcomes, patients prioritize reducing the daily symptoms that drastically affect their quality of life. Taking all aspects of the patient's experience into consideration is necessary in practicing shared decision-making medicine to ensure medication adherence and in assessing benefit.

Of the five phase 3 trials identified, BOREAS, NOTUS, and MATINEE were conducted during the COVID-19 pandemic. All three studies noted exacerbation rates that were lower than anticipated and lower than those observed in the years prior to the COVID-19 pandemic [8, 9, 11]. To mitigate the low exacerbation rate, an amendment to the MATINEE protocol was added to extend the treatment period from 52 to 104 weeks, allowing patients to self-select to extend treatment [11]. This selection was offered only to patients enrolled before the amendment, while those enrolled afterwards were automatically assigned to the longer follow-up period. This situation created two analytically distinct cohorts: a fixed-duration cohort (52 weeks fixed) and a variable-duration cohort (up to 104 weeks). The absence of reporting for the full randomized population at 52 weeks limits comparability and undermines the interpretability of long-term efficacy claims. The trial's primary endpoint, the annualized rate of moderate-to-severe exacerbations, was reported for the entire cohort over variable durations, potentially conflating treatment effects with time-dependent confounders. In addition, the statistical analysis plan of MATINEE does not appear to include

sensitivity analyses stratified by follow-up duration, nor does it report whether the treatment effect differed between the 52-week and 104-week cohorts. This omission is critical, as the treatment effect observed in the 52-week subset (RR 0.85 [95% CI 0.62, 1.16]) was more modest than that reported for the full cohort (RR 0.79; $P=0.01$), suggesting potential effect modification by follow-up duration.

Clinical data suggest that 2 years after the initiation of biologic treatment, exacerbation risk may be reduced even further than when measured at week 52 [31]. Additionally, background triple therapy may amplify the reduction of exacerbation risk over time. It is widely accepted that the best predictor of future exacerbations and mortality is prior exacerbations, and that the risk of a future exacerbation is increased with each subsequent exacerbation, particularly a severe exacerbation [32].

The results presented in this ITC align with those reported in several recent systematic reviews and meta-analyses, which concluded that dupilumab, but not mepolizumab, exhibited significant therapeutic efficacy in patients with COPD and elevated eosinophil levels, specifically with regard to exacerbation reduction, lung function improvement, and improvements in SGRQ [33, 34]. Similar results have been previously reported in asthma, where ITC demonstrated lower rates of severe exacerbation and greater improvements in lung function with dupilumab versus mepolizumab in patients with asthma on background therapy with ICS and long-acting β_2-agonists (LABA) [35].

Exacerbations have a significant impact on patients' health status and quality of life; therefore, reducing exacerbations is a key treatment goal in COPD [22]. However, the impact of lung function decline in patients with COPD is often underappreciated. Low lung function is a prognostic factor for future exacerbations [36], and this can become a self-perpetuating cycle, because even a single moderate-to-severe exacerbation can nearly double the rate of lung function decline (an annual loss of 77 mL/year vs. 39 mL/year before versus after an exacerbation event) [37–39]. In addition, lung function decline and exacerbations are both independently associated with declining health-related quality of life [40]. Therefore, improving lung function may reduce future exacerbations and improve quality of life. When practicing shared decision-making, patient input and priorities are important [41]. Patients typically prioritize improving their daily symptoms and quality of life, important considerations when choosing an add-on COPD therapy [42, 43].

Limitations

While this anchored Bucher ITC offers insights into the relative efficacy of dupilumab and mepolizumab in patients with COPD and type 2 inflammation, these results must be viewed within the limitations of the study design. ITCs cannot provide direct evidence and can only approximate the relative efficacy of these two treatments. The Bucher ITC design ensured that treatment effects were anchored to placebo comparators from randomized controlled trials, minimizing bias [16]. However, heterogeneity in patient populations or study conditions may also introduce bias [44]. To overcome the limitations posed by between-trial heterogeneity in ITCs, a head-to-head clinical trial is necessary to provide more definitive evidence.

One such limitation relates to differences in inclusion criteria and definitions of an eosinophilic phenotype across trials. Whereas BOREAS, NOTUS, and MATINEE excluded patients with asthma, patients with a history of asthma were permitted to enroll in METREX and METREO. To identify patients with eosinophilic inflammation, BOREAS and NOTUS used the criteria of eosinophils ≥ 300 cells/μL at screening, while METREX used a historical count of ≥ 300 cells/μL or screening counts of 150 cells/μL to define the "high stratum" eosinophilic phenotype, and MATINEE used eosinophils ≥ 300 cells/μL at screening and recent historical counts of ≥ 150 cells/μL. These differences impact the comparability of the results. Baseline eosinophil levels also varied, with the lowest baseline levels observed in METREX and METREO, which may have influenced treatment effects. Evidence suggests that lower circulating eosinophil levels likely reflect less eosinophilic inflammation in the lung [20, 45], a situation where a biologic

targeting type 2 inflammatory pathways may be less effective. Some, although not all, studies suggest an association between higher circulating eosinophil counts and future exacerbation risk, indicating that patients with lower eosinophil levels may have a different level of exacerbation risk than patients with higher eosinophil levels [6, 7].

Another limitation is that a comparison of safety between dupilumab and mepolizumab was not included in the Bucher ITC because no meaningful differences in AEs or SAEs were observed in the studies. While long-term safety data have been reported for mepolizumab (up to 10 years) and dupilumab (up to 5 years) in other indications [46–48], longer-term follow-up is needed to identify any potential new safety signals or long-term effects.

A third limitation is that the ITC for the primary endpoint only includes the subset of MATINEE patients whose 52-week results were reported, that is, the proportion of patients who did not continue to 104 weeks; therefore, this analysis is missing more than 50% of the patients. The comparison relying on the MATINEE 52-week fixed cohort subgroup lacks statistical power due to a smaller sample size. The ITC should be updated when and if the 52-week results of moderate-to-severe exacerbations for the entire MATINEE cohort are disclosed.

CONCLUSION

This ITC demonstrates a statistically significant advantage of dupilumab over mepolizumab for improvements in lung function, symptoms, and quality of life; a consistent numerical, but not statistically significant, benefit of dupilumab over mepolizumab in exacerbation reduction was observed across sensitivity analyses. Despite the limitations, the totality of the data suggests consistent numerical benefit across outcomes with dupilumab versus mepolizumab treatment. While this study was hypothesis-generating, overall these results support the clinical utility of dupilumab in patients with COPD and an eosinophilic phenotype.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author, Yingxin Xu, on reasonable request. Submit requests to https://www.vivli.org.

Declarations

Conflict of Interest. Surya P. Bhatt is supported by NIH grants R01HL151421 and UH3HL155806. The author serves on advisory boards and is a consultant for Apreo, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GSK, Merck, Polarean, Regeneron Pharmaceuticals Inc., Sanofi, and Verona Pharma; has received honoraria from Horizon CME,

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Ethical Approval. This article is based on data from previously conducted trials and does not contain any new studies with human participants or animals performed by any of the authors. Please see the original publications for each trial for full details of ethical approvals.

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