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Systematic review and network meta-analysis of the efficacy and safety of glycopyrrolate/formoterol fumarate metered dose inhaler in comparison with other long-acting muscarinic antagonist/long-acting β_2-agonist fixed-dose combinations in COPD

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Abstract

Background: Dual bronchodilation with a long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) fixed-dose combination (FDC) is an established treatment strategy for chronic obstructive pulmonary disease (COPD). The relative efficacy and safety of glycopyrrolate/formoterol fumarate metered dose inhaler (GFF MDI 18/9.6 µg) in patients with moderate-to-very severe COPD, compared with other licensed LAMA/LABA FDCs, was investigated using an integrated Bayesian network meta-analysis (NMA).

Methods: A systematic literature review and subsequent screening process identified randomized controlled trials of ⩾10 weeks' duration that enrolled patients aged ⩾40 years with moderate-to-very severe COPD and included at least one LAMA/LABA FDC or open LAMA + LABA treatment arm. NMAs were conducted for outcomes including change from baseline in forced expiratory volume in 1 s (FEV_1), St George's Respiratory Questionnaire (SGRQ), and transition dyspnea index (TDI) parameters, annualized rate of exacerbations, use of rescue medication, adverse events, and all-cause withdrawals. Meta-regression and sensitivity analyses accounted for heterogeneity across studies.

Results: In total, 29 studies including 34,617 patients contributed to the NMA for efficacy or safety outcomes at week 24 or exacerbations. For all LAMA/LABA FDCs with data available, significantly greater improvements in FEV_1 [trough, peak, and area under the curve $(AUC)_{0–4}$], SGRQ total score and TDI focal score at week 24, and annualized rate of moderate-to-severe exacerbations, were observed *versus* placebo. Where indirect comparisons were possible, differences between GFF MDI and other LAMA/LABA FDCs were small relative to established margins of clinical relevance, and not statistically significant. The safety and tolerability profile of GFF MDI was consistent with other LAMA/LABA FDCs and placebo. The results of the meta-regression were generally similar to the base case.

Conclusions: GFF MDI demonstrated comparable efficacy and safety outcomes to other LAMA/LABA FDCs. Personalization of treatment choice within the class on the basis of other factors such as patient preference may be appropriate.

Keywords: chronic obstructive pulmonary disease, fixed-dose combination, glycopyrrolate/formoterol fumarate metered dose inhaler (GFF MDI), long-acting β_2-agonist (LABA), long-acting muscarinic antagonist (LAMA), network meta-analysis

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Introduction

Appropriate pharmacological treatment of chronic obstructive pulmonary disease (COPD), guided by patients' individual needs, is key to reducing symptom burden and frequency of exacerbations in order to improve patients' quality of life.[1,2] Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), feature prominently in pharmacological treatment algorithms for COPD.[2] Due to their distinct mechanisms of action, the potential synergistic effects of these two classes of drug have been studied extensively over recent years,[3–5] with clinical studies generally showing that LAMA/LABA combinations exert greater benefit to the patient, in terms of improvement in lung function, symptoms, and quality-of-life scores, than either class of medication delivered alone, and with similar safety profiles to the monocomponents.[6–16]

The glycopyrrolate/formoterol fumarate metered dose inhaler (GFF MDI) 18/9.6 μg, is a fixed-dose combination (FDC) of the LAMA glycopyrrolate and the LABA formoterol fumarate (equivalent to glycopyrronium/formoterol fumarate dihydrate 14.4/10 μg) delivered using innovative cosuspension delivery technology (Bevespi Aerosphere®).[17] The efficacy and safety of GFF MDI have been compared with those of its monocomponents in patients with moderate-to-very severe COPD in the pivotal phase III studies PINNACLE-1, PINNACLE-2, and PINNACLE-4 (24 weeks' duration; NCT01854645, NCT01854658, and NCT02343458), and PINNACLE-3 (28-week safety extension; NCT01970878), which were conducted variously across the USA, Asia, Europe, Australia, and New Zealand.[8,9,18] The benefits of GFF MDI 18/9.6 μg treatment in improving lung function and symptoms outcomes over placebo and monotherapy have been shown in patients with moderate-to-very severe COPD.[8,9,18]

Four other LAMA/LABA FDCs [aclidinium/formoterol (ACL/FOR); glycopyrrolate/indacaterol (GLY/IND); umeclidinium/vilanterol (UMEC/VIL); and olodaterol/tiotropium (OLO/TIO)] are currently approved for the maintenance treatment of patients with COPD.[2] To date, GFF MDI 18/9.6 μg is the only approved LAMA/LABA FDC that is available as a pressurized MDI, with the other options employing dry powder or soft mist inhaler modes of delivery.[2,17] Given the choice of available treatment options, comparative data are highly valued in the clinical decision-making process.

Only four published direct head-to-head trials have compared the efficacy and safety of LAMA/LABA FDCs in patients with COPD to date [UMEC/VIL *versus* OLO/TIO; UMEC/VIL *versus* GLY/IND (two studies); and GFF MDI *versus* UMEC/VIL], three of which were crossover studies of only 8- or 12-weeks' treatment duration.[19–21] More recently, the efficacy and safety of GFF MDI relative to UMEC/VIL dry powder inhaler was examined in a phase IIIb study in patients with moderate-to-very severe COPD over 24 weeks of treatment.[21] In the absence of head-to-head trials comparing all available LAMA/LABAs, several meta-analyses have indirectly assessed the relative treatment effects of LAMA/LABA FDCs and have generally found similarities in terms of their efficacy and safety profiles.[22–26] However, due to the relatively recent approval of GFF MDI, data for this novel dual therapy were not captured in these analyses. For the first time, we analyzed the relative treatment efficacy and safety of GFF MDI compared with other inhaled dual LAMA/LABA FDCs in patients with moderate-to-very severe COPD, using an integrated Bayesian network meta-analysis (NMA) based on the results of a systematic literature review (SLR).

Methods

SLR

An SLR was conducted to identify randomized clinical trials investigating the efficacy and safety of dual bronchodilator LAMA/LABA FDCs for moderate-to-very severe COPD (Table S1). The search strategy utilized the MEDLINE®, Embase®, MEDLINE® In-Process, and CENTRAL databases, with searches run from database inception to October 16, 2018, using the search terms presented in Table S2. Only articles published in English were included. Additionally, abstracts from selected conference proceedings [American Thoracic Society (ATS), European Respiratory Society (ERS), and American College of Chest Physicians (ACCP)] were hand-searched for the years 2016–2018 to retrieve studies that have not yet been published in full-text articles, or abstracts reporting supplementary results of previously published studies. Clinical trial registries [ClinicalTrials.gov of the US National

Institute of Health (NIH), International Clinical Trials Registry Platform, Australian New Zealand Clinical Trials Registry, and companies' websites (including the GlaxoSmithKline register)] were also searched to capture unpublished data. The inclusion criteria for the SLR were sufficiently broad to identify all potentially relevant studies.

The primary objectives of the NMA were to determine the relative treatment efficacy [based on lung function outcomes] and safety of GFF MDI compared with other inhaled LAMA/LABA FDCs for the treatment of patients with moderate-to-very severe COPD. The secondary NMA objectives were to determine the relative treatment efficacy of GFF MDI compared with other inhaled LAMA/LABA FDCs on St George's Respiratory Questionnaire (SGRQ), transition dyspnea index (TDI), rescue medication use, and exacerbations outcomes. To this end, following the SLR, pre-specified eligibility criteria specific to the NMA [participants, interventions, comparisons, outcomes, and study design (PICOS) criteria] were applied to the retrieved studies to determine which studies should populate the base case network and sensitivity analyses (Table 1). Suitable studies included those that assessed LAMA/LABA FDC or open LAMA + LABA combinations in at least one treatment arm. Only data for the licensed dose of the LAMA/LABA FDC were included in the NMA (Figure 1; Table 1). The GLY/IND FDC is licensed and marketed in the United States as UTIBRON® NEOHALER® (15.6/27.5 µg, twice daily) only, and elsewhere as ULTIBRO® BREEZHALER® (63/110 µg, once daily), with the results for the most widely marketed 63/110 µg dose combination presented in this analysis.

Both data collection (first screening of titles and abstracts and second screening of full-text articles) and data extraction activities were conducted by two reviewers working independently, with any discrepancy being reconciled by a third reviewer. Data were extracted using a predefined extraction grid, which included details on trial design, inclusion criteria, study population characteristics, interventions, outcome measures, and length of follow-up. Risk of bias within studies was assessed by critical appraisal of included studies using comprehensive assessment criteria based on the recommendations in the National Institute for Health and Care Excellence (NICE) manufacturer's template;[27] risk of bias was assessed with respect to the method of randomization and allocation concealment, baseline characteristics, blinding, reporting withdrawals, outcomes reporting, and statistical analysis.

NMA methodology

The NMA methodology followed the recommended best practice of the NICE Decision Support Unit for evidence synthesis.[28,29] Separate NMAs were performed for the change from baseline to week 24 in lung function [peak forced expiratory volume in 1 s (FEV_1), trough FEV_1, and area under the FEV_1 curve (AUC FEV_1)], SGRQ total score, TDI focal score, SGRQ responders [patients who reported improvements that met or exceeded the minimal clinically important difference (MCID) for SGRQ ($\geq$4 units)],[30] and TDI responders [patients who reported improvements that met or exceeded the MCID for TDI ($\geq$1 unit)].[30] NMAs were also performed for change from baseline in daily rescue medication use over 24 weeks, mean rate of exacerbations per patient per year and adverse events (AE), serious AEs (SAEs), and all-cause withdrawals. The week 24 analysis time-point was selected on the grounds that the majority of pivotal phase III studies of LAMA/LABA FDCs were of 24 weeks' duration.[6–8,10,13–15,18] Studies that reported data between 22 and 26 weeks were included in the 24-week analysis (studies >26 weeks' duration, but reporting data at, or over, 22–26 weeks, were also included). For exacerbation outcomes, all studies of $\geq$10 weeks' duration were included in the analysis.

The relevant study results were combined using a three-level hierarchical Bayesian NMA treatment class model[31,32] (refer to the Supplementary Materials for further details). The synthesis was conducted using WinBUGS (a Markov Chain Monte Carlo simulation-based software for Bayesian inference). Results were generated using both random- and fixed-effects models and compared for goodness-of-fit to the data, assessed by deviance information criteria (DIC) and residual deviance (a model with lower DIC and residual deviance values indicated a better fit). For most outcomes, the random-effects model was a better fit than the fixed-effect model, and in cases where the DIC and residual deviance values were similar, the random-effects model was preferred, given that it takes into account study heterogeneity. Inconsistencies between direct and indirect estimates were checked for all outcomes whose networks included 'closed loops'. For each

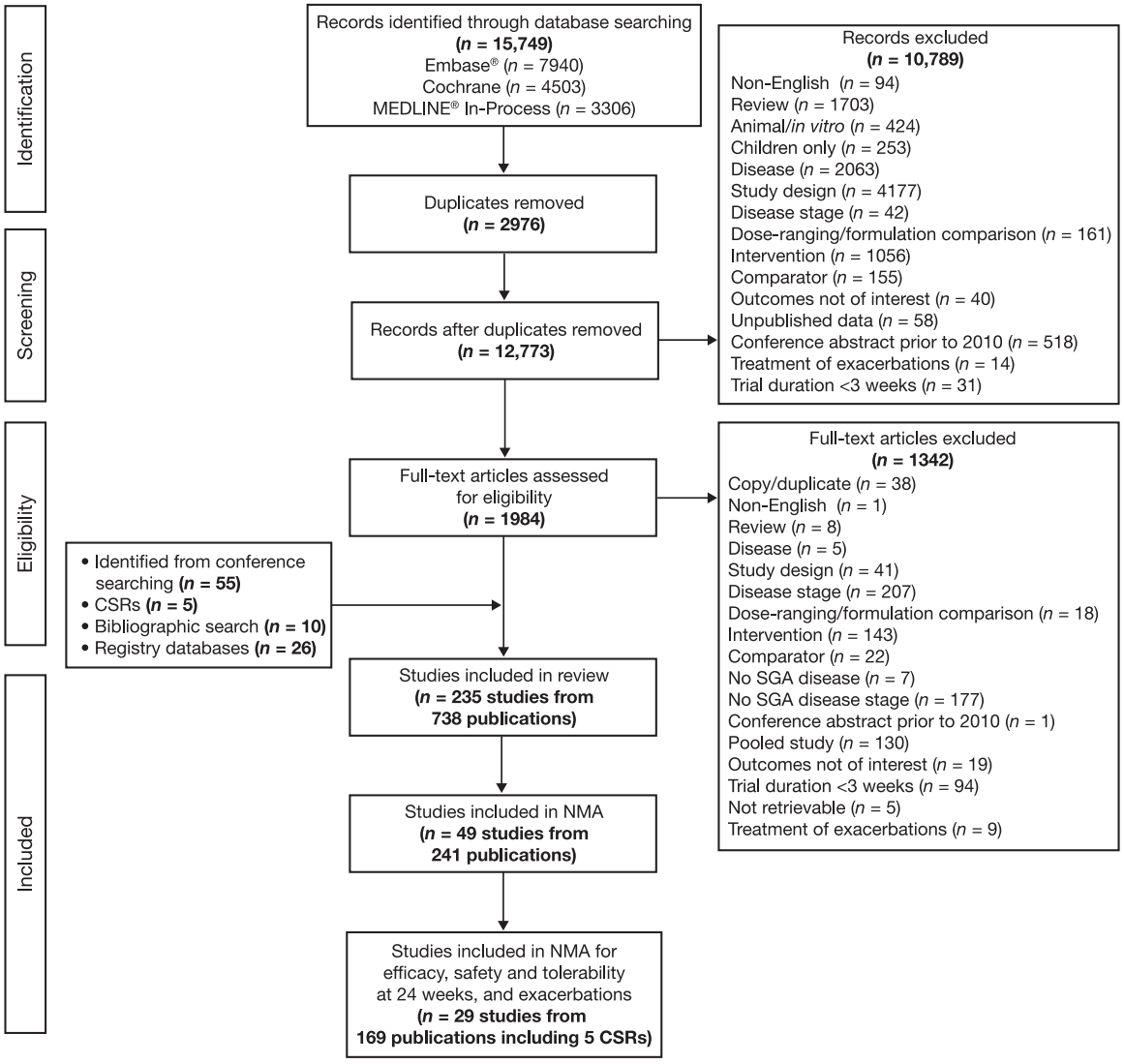

Figure 1. Study selection summary.
Studies of ⩾10 weeks' duration were included for the analyses of annualized exacerbation rates.
CSR, clinical study report; NMA, network meta-analysis; SGA, subgroup analysis.

outcome, one common heterogeneity parameter between-study variability was assumed across comparisons, with standard deviation (SD) corresponding to the variance of the underlying distribution. For this analysis, we considered an SD value ⩾0.7 to be indicative of intrastudy variability. The 95% credible intervals (CrIs) were calculated for each SD.

Results for continuous outcomes (e.g. trough FEV_1) were reported as the mean difference in the change from baseline. The results (effect size, 95% CrI) are presented up to two decimal points to maintain consistency. Odds ratios (ORs) were used to report dichotomous outcomes (e.g. SGRQ responders and safety), and rate ratios (RRs) were used for the rates of exacerbations. All outcomes were presented with the associated 95% CrI. To account for the exchangeability of treatment effects within the same class, underlying treatment effects within each class were assumed to follow a normal distribution with class-specific mean and common variance. Analyses were made without adjustment for multiple comparisons. Given the Bayesian framework, formal significance testing was not conducted, but, in common with other studies of this nature,[25] results are described as statistically significant wherever 95% CrIs did not

Table 1. PICOS criteria for inclusion in the NMA.

Population[a]	**Adult patients aged ⩾40 years with moderate-to-very severe COPD**
Interventions[b]	Glycopyrrolate/formoterol (GFF MDI; Bevespi Aerosphere™); Glycopyrrolate/indacaterol (GLY/IND; Ultibro Breezhaler®, Utibron® Neohaler®); Umeclidinium/vilanterol (UMEC/VIL; Anoro Ellipta); Aclidinium/formoterol (ACL/FOR; Duaklir Genuair); Tiotropium/olodaterol (TIO/OLO; Stiolto™ Respimat®, Spiolto™ Respimat®)
Comparators	Any intervention listed above, in combination or as monotherapy (i.e. LAMA monotherapy, LABA monotherapy, or LAMA and LABA open combination therapy); Placebo or best supportive care
Outcomes	Efficacy outcomes: Trough FEV_1; Peak FEV_1; AUC FEV_1; Rescue medication; SGRQ; TDI; Exacerbations Safety outcomes: Any AEs; Any SAEs; Specific AEs Tolerability outcomes: All withdrawals; Withdrawals due to AE; Withdrawals due to lack of efficacy
Study designs	Randomized controlled trials[c,d] At least 10 weeks: Studies were classified into outcomes at 12 and 24 weeks, and the analysis was based primarily on 24-week data, given that the pivotal phase III studies of GFF MDI were 24 weeks in duration

[a]Animal or *in vitro* studies were excluded.
[b]For the NMA, studies assessing ⩾1 approved dual LAMA/LABA FDC were included.
[c]Irrespective of blinding status and number of arms randomized.
[d]All other types of studies (nonrandomized studies, long-term extensions, editorials, case reports, reviews etc) were excluded.
ACL, aclidinium; AE, adverse event; AUC, area under the curve; COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 s; FOR, formoterol; GFF MDI, glycopyrrolate/formoterol fumarate metered dose inhaler; GLY, glycopyrrolate; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NMA, network meta-analysis; OLO, olodaterol; PICOS, Participants, interventions, comparisons, outcomes, and study design; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnea index; TIO, tiotropium; VIL, vilanterol; UMEC, umeclidinium.

cross the null value (zero for differences, one for ORs).

Subgroup, meta-regression, and sensitivity analyses

Given that some of the studies included in the NMA recruited only patients exhibiting a required level of symptoms at baseline, and considering that baseline symptomatic status could be an important key effect modifier, a subgroup analysis was also conducted for selected endpoints (change from baseline in SGRQ scores at 24 weeks; SGRQ responders at 24 weeks; TDI score at 24 weeks; TDI responders at 24 weeks; and annualized rate of moderate-to-severe exacerbations) within the symptomatic population. As the definition of symptomatic populations varied between studies, the analysis was conducted in studies/subgroups defined as symptomatic by either a modified Medical Research Council dyspnea scale (mMRC) grade ⩾2, a COPD assessment test (CAT) score ⩾15, or diary-based assessment criteria. Additionally, a meta-regression analysis was conducted for the efficacy outcomes to account for differences in selected baseline patient characteristics that could be acting as key effect modifiers [FEV_1 percent predicted, SGRQ total score, and inhaled corticosteroid (ICS) use at baseline].

Finally, to assess the impact of the inclusion of open-label studies/treatments in the NMA, a sensitivity analysis was conducted following the exclusion of such studies/treatments.

Results

Study selection and characteristics

The electronic database search retrieved a total of 15,749 separate references, of which 2976 were excluded as duplicates due to overlap of evidence across the databases examined (Figure 1). A further 10,789 citations were excluded after initial screening of 'title and abstract only' and 1342 were excluded after screening of the full-text articles, in alignment with predefined eligibility criteria (Table 1). Hand-searching of conference proceedings identified an additional 55 citations, 10 of which came from bibliography searches, 26 from registry databases, and five from clinical study reports (Figure 1). Of the 738 citations remaining after the full-text screening process, 49 studies met NMA inclusion criteria and were included in the final selection. Of these, 29 studies contributed to the NMA for efficacy or safety outcomes at week 24 or exacerbation outcomes reported here (Table 2). The network diagram for studies evaluating LABA + LAMA FDCs for trough FEV_1 at 24 weeks is shown in Figure 2.

Overall, 34,617 patients contributed to the NMA for efficacy or safety outcomes at week 24 or exacerbation outcomes. The characteristics of patients enrolled in the studies are summarized in Table S3. For studies reporting patient demographic data, mean ages ranged from 62 to 70 years, and the proportions of male patients and current smokers ranged from 52% to 95% and from 26% to 63%, respectively. The mean post bronchodilator FEV_1 predicted at baseline ranged from 44% to 60%, and the percentage of patients with severe COPD ranged from 20% to 58%. The proportion of patients experiencing at least one exacerbation in the prior year varied greatly between studies (range: <1–100%).

The majority of studies included in the NMA were considered to pose a low risk of bias with respect to the method of randomization, reporting of trial dropouts or withdrawals, and statistical methodology. A high risk of bias was identified for one study in terms of its baseline characteristics (imbalance in patient characteristics across treatment arm),[35] one study in terms of blinding (open-label trial),[34] and two studies in terms of outcomes selection and reporting (fewer outcomes reported in the publication than mentioned in the protocol).[6,36] In five studies, randomization and allocation concealment could not be judged, and these studies were therefore marked as having an unclear risk of bias.[6,34,35,44,46] For the majority of outcomes, no inconsistency was observed between direct and indirect evidence, suggesting that the consistency assumption was not violated (refer to Supplementary Material for details; Supplementary Figure S1).

Lung function

Data at 24 weeks for the change from baseline in trough FEV_1, peak change from baseline in FEV_1, and change from baseline in FEV_1 $AUC_{0–4}$ were reported in 21,[6–8,10,12–14,18,21,33–39,45,47] 13,[6–8,13,14,18,21,37–39,46] and eight studies,[8,10,18,21,38,45] respectively. Estimates for the change from baseline in trough FEV_1 from one study did not converge in the model, and this study was subsequently removed from the analysis.[36] At 24 weeks, all assessed LAMA/LABA FDCs significantly improved the change from baseline in trough FEV_1 compared with placebo, to a clinically relevant degree (i.e. an increase of 100 mL)[48] (Figure 3a). Changes from baseline in peak FEV_1 and FEV_1 $AUC_{0–4}$ at 24 weeks were significantly greater with all LAMA/LABA FDCs with available data *versus* placebo (Figure 3b and c).

In general, there were no statistically significant differences in the improvements in lung function associated with GFF MDI relative to the other analyzable LAMA/LABA FDCs, with the exception of the peak change from baseline FEV_1 following treatment with GFF MDI relative to UMEC/VIL, which reached statistical significance (mean difference 24 mL; 95% CrI 1, 50; Figure 3b). Comparisons of GFF MDI for at least one of the two postdose spirometry endpoints assessed (peak FEV_1 and FEV_1 $AUC_{0–4}$) were available for all FDCs. However, a comparison of GFF MDI *versus* TIO/OLO could not be made for peak FEV_1, or a comparison with ACL/FOR for FEV_1 $AUC_{0–4}$.

Table 2. Characteristics of studies contributing to the NMA.

Study	Treatment	Patients (*N*), FAS	No. patients randomized and treated	Data source	Method of randomization	Blinding	Setting	Phase	Contribution to NMA
ACLIFORM-COPD[7]	ACL 400 µg BID	385	1729	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks, safety
	ACL 400 µg BID + FOR 12 µg BID	385							
	ACL 400 µg BID + FOR 6 µg BID	381							
	FOR 12 µg BID	384							
	Placebo	194							
AERISTO[21]	GLY 14.4 µg BID + FOR 9.6 µg BID	552	1104	CSR	Adequate	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	UMEC 62.5 µg OD + VIL 25 µg OD	552							
AMPLIFY[33]	ACL 400 µg BID + FOR 12 µg BID	314	1583	Conference abstract	Unclear	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	ACL 400 µg BID	475							
	FOR 12 µg BID	319							
	TIO 18 µg OD	475							
ARISE[34]	GLY 50 µg OD + IND 110 µg OD	121	160	Conference abstract	Unclear	Open-label	Multicenter	III	24 weeks
	TIO 18 µg OD	30							
AUGMENT COPD[6]	ACL 400 µg BID	337	1668	Journal	Unclear	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	ACL 400 µg BID + FOR 12 µg BID	335							
	ACL 400 µg BID + FOR 6 µg BID	333							
	FOR 12 µg BID	332							
	Placebo	331							

(Continued)

Table 2. (Continued)

Study	Treatment	Patients (*N*), FAS	No. patients randomized and treated	Data source	Method of randomization	Blinding	Setting	Phase	Contribution to NMA
DB2113374[14]	TIO 18 µg OD	215	869	Journal	Adequate	Blinded	Multicenter International	III	24 weeks, exacerbation, safety
	UMEC 125 µg OD	222							
	UMEC 125 µg OD + VIL 25 µg OD	215							
	UMEC 62.5 µg OD + VIL 25 µg OD	217							
DB2113360[14]	TIO 18 µg OD	208	843	Journal	Adequate	Blinded	Multicenter International	III	24 weeks, exacerbation, safety
	UMEC 125 µg OD + VIL 25 µg OD	214							
	UMEC 62.5 µg OD + VIL 25 µg OD	212							
	VIL 25 µg OD	209							
Donohue 2013[13]	Placebo	280	1532	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	UMEC 62.5 µg OD	418							
	VIL 25 µg OD	421							
	UMEC 62.5 µg OD + VIL 25 µg OD	413							
ENLIGHTEN[35]	GLY 50 µg OD + IND 110 µg OD	225	338	Journal	Unclear	Double-blind	Multicenter International	III	24 weeks
	Placebo	113							
FLAME[36]	GLY 50 µg OD + IND 110 µg OD	1680	3362	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks, exacerbation
	FLU 500 µg BID + SAL 50 µg BID	1682							
ILLUMINATE[37]	FLU 500 µg BID + SAL 50 µg BID	264	522	Journal	Unclear	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	GLY 50 µg OD + IND 110 µg OD	258							

(Continued)

Table 2. (Continued)

Study	Treatment	Patients (*N*), FAS	No. patients randomized and treated	Data source	Method of randomization	Blinding	Setting	Phase	Contribution to NMA
LANTERN[38]	FLU 500 µg BID + SAL 50 µg BID	369	741	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	GLY 50 µg OD + IND 110 µg OD	372							
Maleki-Yazdi 2014[39]	TIO 18 µg OD	451	905	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks, safety
	UMEC 62.5 µg + VIL 25 µg OD	454							
PINNACLE-1[8]	FOR 9.6 µg BID	452	2103	CSR	Adequate	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	GLY 14.4 µg BID + FOR 9.6 µg BID	527							
	GLY 14.4 µg BID	451							
	Placebo	220							
	TIO 18 µg OD	453							
PINNACLE-2[8]	FOR 9.6 µg BID	439	1615	CSR	Adequate	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	GLY 14.4 µg BID + FOR 9.6 µg BID	512							
	GLY 14.4 µg BID	440							
	Placebo	224							
PINNACLE-4[18]	GLY 14.4 µg BID + FOR 9.6 µg BID	551	1756	CSR	Adequate	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	FOR 9.6 µg BID	480							
	GLY 14.4 µg BID	474							
	Placebo	235							

(Continued)

Table 2. (Continued)

Study	Treatment	Patients (*N*), FAS	No. patients randomized and treated	Data source	Method of randomization	Blinding	Setting	Phase	Contribution to NMA
QUANTIFY[12]	FOR 12 µg BID + TIO 18 µg OD	458	934	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks, safety
	GLY 50 µg OD + IND 110 µg OD	476							
Riley 2016[40]	UMEC 62.5 µg OD + VIL 25 µg OD	484	967	Journal	Adequate	Double-blind	Multicenter International	III	Exacerbation
	IND 150 µg OD + TIO 18 µg OD	483							
SHINE[10]	GLY 50 µg OD	473	2135	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks, exacerbation, safety
	GLY 50 µg OD + IND 110 µg OD	474							
	IND 150 µg OD	476							
	Placebo	232							
	TIO 18 µg OD	480							
Siler 2016[41]	UMEC 62.5 µg OD + VIL 25 µg OD	248	498	Journal	Adequate	Double-blind	Multicenter International	III	Exacerbation
	Placebo	248							
Study 114930[42]	FLU 250 µg BID + SAL 50 µg BID	353	707	Journal	Adequate	Double-blind	Multicenter International	III	Exacerbation
	UMEC 62.5 µg OD + VIL 25 µg OD	353							
Study 114951[42]	FLU 250 µg BID + SAL 50 µg BID	348	700	Journal	Adequate	Double-blind	Multicenter International	III	Exacerbation
	UMEC 62.5 µg OD + VIL 25 µg OD	349							

(Continued)

Table 2. (Continued)

Study	Treatment	Patients (*N*), FAS	No. patients randomized and treated	Data source	Method of randomization	Blinding	Setting	Phase	Contribution to NMA
Study 417[43]	Placebo	170	641	Journal	Adequate	Double-blind	Multicenter International	III	Exacerbation, safety
	UMEC 125 µg OD	50							
	UMEC 125 µg OD + VIL 25 µg OD	144							
	UMEC 62.5 µg OD	49							
	UMEC 62.5 µg OD + VIL 25 µg OD	152							
	VIL 25 µg OD	76							
Study 418[43]	Placebo	151	554	Journal	Adequate	Double-blind	Multicenter International	III	Exacerbation, safety
	UMEC 125 µg OD	41							
	UMEC 125 µg OD + VIL 25 µg OD	128							
	UMEC 62.5 µg OD	40							
	UMEC 62.5 µg OD + VIL 25 µg OD	130							
	VIL 25 µg OD	64							
Suzuki 2010[44]	Placebo	10	20 (9 patients included in analysis)	Journal	Unclear	Unclear	Single center	Unclear	24 weeks
	SAL 50 µg BID + TIO 18 µg OD	10							

(Continued)

Table 2. (Continued)

Study	Treatment	Patients (*N*), FAS	No. patients randomized and treated	Data source	Method of randomization	Blinding	Setting	Phase	Contribution to NMA
Tonado 1[45]	OLO 5 µg OD	528	2624	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks
	OLO 5 µg OD + TIO 2.5 µg OD	522							
	OLO 5 µg OD + TIO 5 µg OD	522							
	TIO 2.5 µg OD	525							
	TIO 5 µg OD	527							
Tonado 2[45]	OLO 5 µg OD	510	2538	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks
	OLO 5 µg OD + TIO 2.5 µg OD	508							
	OLO 5 µg OD + TIO 5 µg OD	507							
	TIO 2.5 µg OD	507							
	TIO 5 µg OD	506							
Vogelmeier 2016[46]	ACL 400 µg BID + FOR 12 µg BID	468	931	Journal	Unclear	Double-blind	Unclear	III	Safety
	FLU 500 µg BID + SAL 50 µg BID	463							
Zheng 2015[47]	Placebo	193	580	Journal	Adequate	Double-blind	Multicenter International	III	24 weeks, safety
	UMEC 62.5 µg OD + VIL 25 µg OD	194							
	UMEC 125 µg OD + VIL 25 µg OD	193							

ACL, aclidinium; BID, twice daily; COPD, chronic obstructive pulmonary disease; CSR, clinical study report; FAS, full analysis set; FLU, fluticasone; FOR, formoterol; GLY, glycopyrrolate; IND, indacaterol; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; NMA, network meta-analysis; OD, once-daily; OLO, olodaterol; SAL, salmeterol; TIO, tiotropium; VIL, vilanterol; UMEC, umeclidinium.

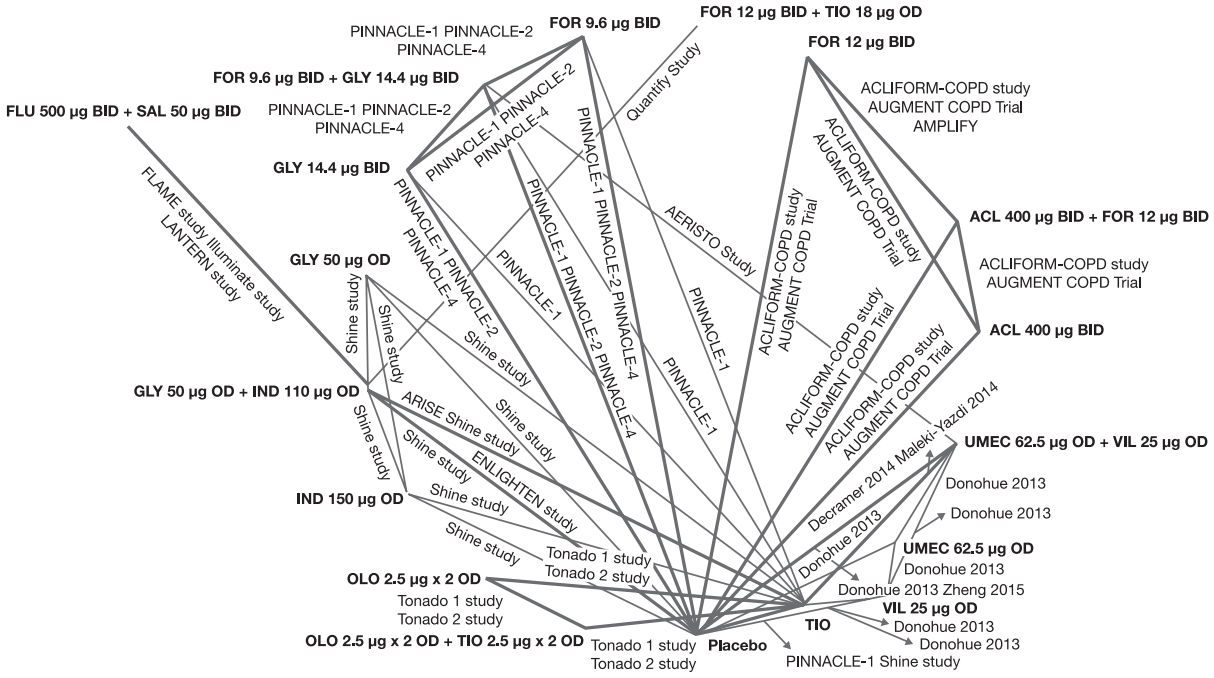

Figure 2. Network diagram for studies evaluating LABA + LAMA FDCs for trough FEV_1 at 24 weeks.
ACL, aclidinium; BID, twice daily; COPD, chronic obstructive pulmonary disease; FDS, fixed-dose combination; FLU, fluticasone; FOR, formoterol; GLY, glycopyrrolate; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OD, once daily; OLO, olodaterol; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VIL, vilanterol.

Quality of life and symptoms

In total, 16 studies evaluating the LAMA/LABA FDCs presented results for the change from baseline in SGRQ total score at week 24,[6–8,10,12–14,18,34,36,39,44,45,47] and 12 studies reported TDI focal score at this time point.[6,7,10,12–14,18,21,38,45,47] Compared with placebo, all LAMA/LABA FDCs significantly improved the change from baseline in SGRQ score and TDI score (Figures 4a and 5a). Improvements in quality of life and symptoms associated with GFF MDI were not significantly different from those associated with the other LAMA/LABA FDCs analyzed (Figures 4a and 5a). In terms of patients meeting SGRQ and TDI response criteria, all LAMA/LABA FDC treatment groups had significantly more responders than the respective placebo groups, and findings for GFF MDI did not differ significantly from the other analyzable LAMA/LABA FDCs (Supplementary Figure S2a and S2c). A comparison of GFF MDI *versus* TIO/OLO could not be made for TDI responders at 24 weeks.

Quality of life and symptoms in symptomatic patients. Given the possibility that baseline symptom burden could be an important effect modifier for changes observed in SGRQ and TDI scores, and considering that the studies in the NMA varied in their baseline symptom inclusion criteria, a supportive analysis was conducted in a symptomatic subgroup of patients. The SD for the change from baseline in SGRQ at week 24 was 0.7606, suggesting moderate-to-high heterogeneity in the network, thereby providing a rationale for further analyses of this endpoint in symptomatic patients. The TIO/OLO and ACL/FOR FDCs were not included in the subgroup analysis due to a lack of symptomatic patient data.

The change from baseline in SGRQ total score and TDI focal score data for symptomatic patients at week 24 were reported in 10[8,10,13,14,18,36,39,47] and eight[10,13,14,18,21,38,47] studies, respectively. In symptomatic patients, all analyzable LAMA/LABA FDCs significantly improved SGRQ and TDI scores compared with placebo, and there were no significant differences between GFF MDI and other LAMA/LABA FDCs (Figures 4b and 5b). GFF MDI and GLY/IND showed a clinically meaningful improvement in SGRQ score (i.e. a reduction of ⩾4 units)[30] *versus* placebo in symptomatic populations (Figure 4b). For symptomatic

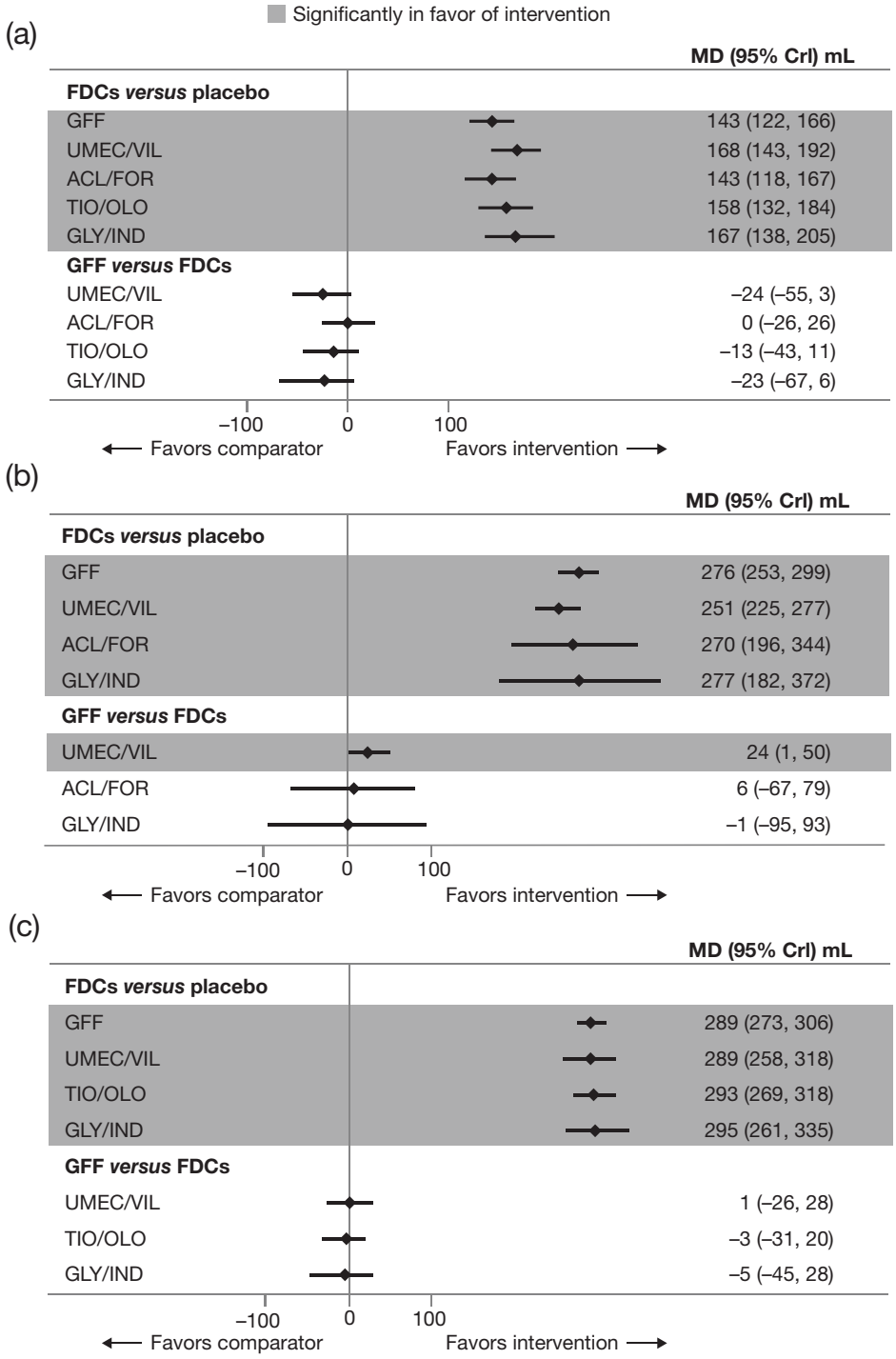

Figure 3. Lung function at week 24. LAMA/LABA FDCs *versus* placebo and GFF/MDI *versus* other LAMA/LABA FDCs for change from baseline in (a) trough FEV_1, (b) peak FEV_1, and (c) FEV_1 $AUC_{0–4}$.
ACL, aclidinium; AUC, area under the curve; CrI, credible interval; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 s; FOR, formoterol; GFF MDI, glycopyrrolate/formoterol fumarate metered dose inhaler; GLY, glycopyrrolate; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; OLO, olodaterol; TIO, tiotropium; UMEC, umeclidinium; VIL, vilanterol.

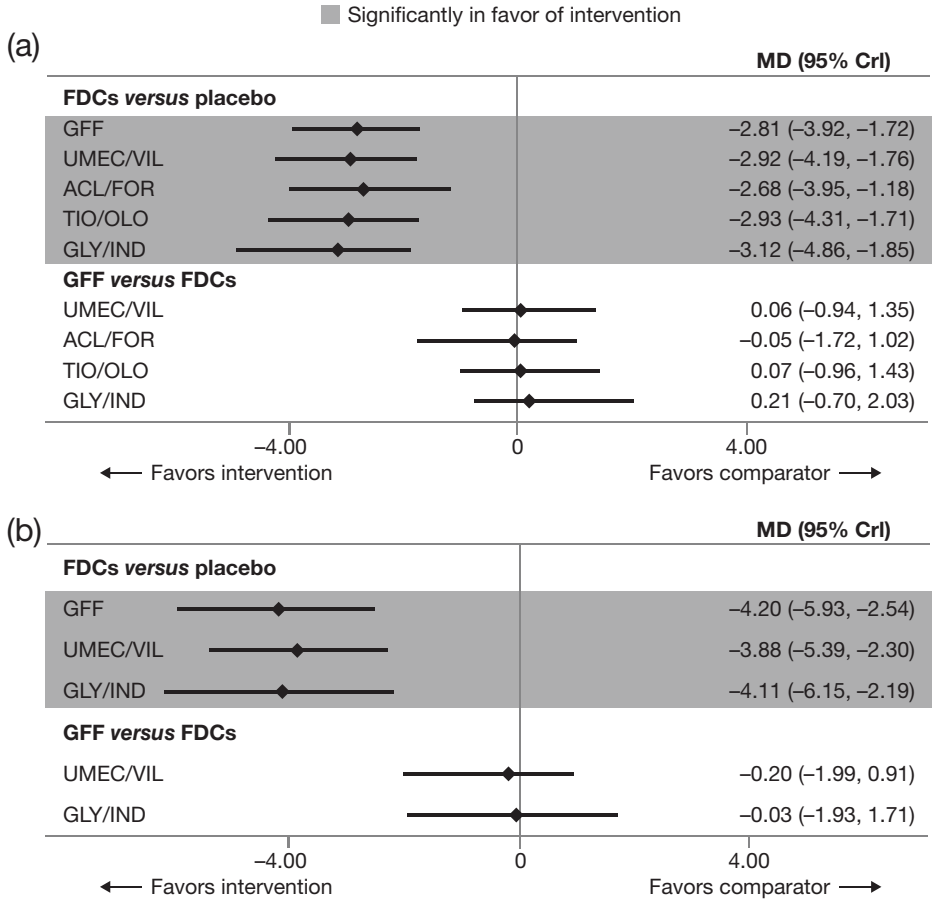

Figure 4. Quality of life at week 24. LAMA/LABA FDCs *versus* placebo and GFF MDI *versus* other LAMA/LABA FDCs for change from baseline in SGRQ total score in (a) the overall population and (b) the symptomatic population.

ACL, aclidinium; CrI, credible interval; FDC, fixed-dose combination; FOR, formoterol; GFF MDI, glycopyrrolate/formoterol fumarate metered dose inhaler; GLY, glycopyrrolate; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; OLO, olodaterol; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium; UMEC, umeclidinium; VIL, vilanterol.

patients meeting SGRQ and TDI response criteria, all LAMA/LABA FDC treatment groups had significantly more responders than the respective placebo groups and GFF MDI was not significantly different from the other analyzable LAMA/LABA FDCs (Supplementary Figure S2b and 2d).

Use of rescue medication

A total of 14 studies[6–8,10,13,14,18,21,37–39,47] examined the change in daily rescue medication use over 24 weeks. All LAMA/LABA FDCs significantly reduced the use of daily rescue medication compared with placebo (Supplementary Figure S3). No differences were observed between GFF MDI and other analyzable LAMA/LABA FDCs in terms of this outcome, although no comparison *versus* TIO/OLO could be made.

Exacerbations

Seven studies reported the effects of LAMA/LABA FDCs on moderate-to-severe exacerbations, which were defined using conventional criteria that were largely consistent across studies (Supplementary Figure S4).[8,10,18,21,36,38] All studies in the analysis of moderate-to-severe exacerbations were of at least 24 weeks' duration. GFF MDI, UMEC/VIL, and GLY/IND significantly reduced the rate of moderate-to-severe exacerbations compared with placebo, and the effects of GFF MDI were not significantly different to those of UMEC/VIL or GLY/IND (Figure 6a). No comparisons

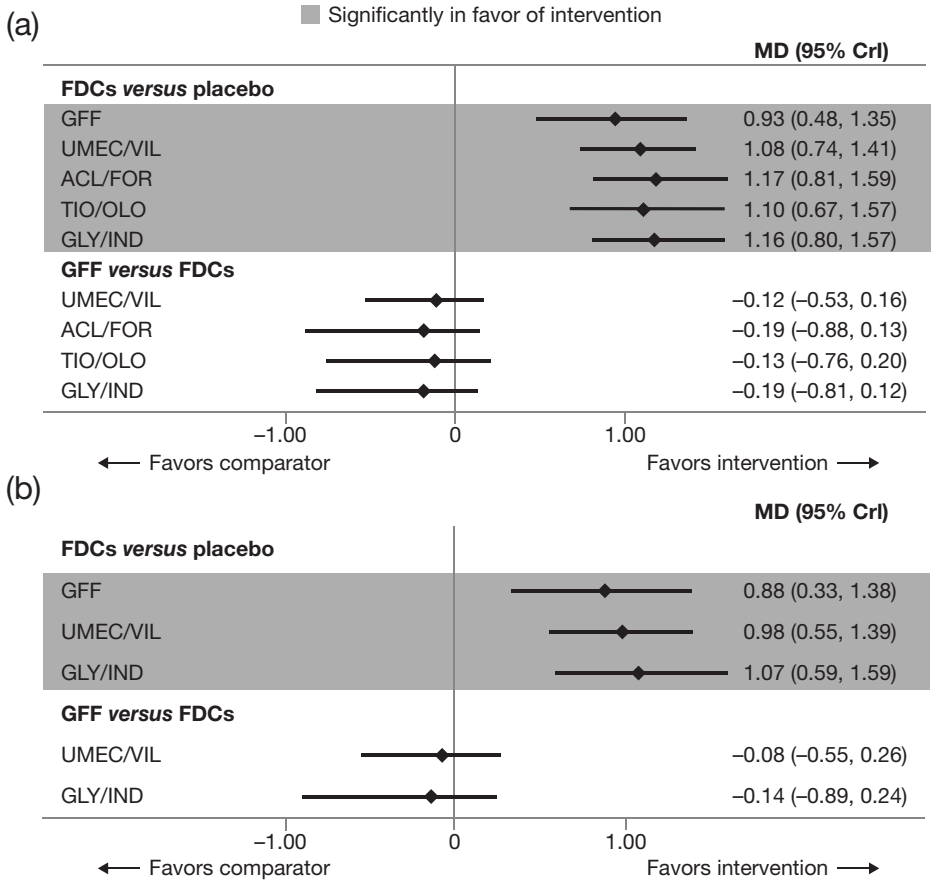

Figure 5. Symptoms at week 24. LAMA/LABA FDCs *versus* placebo and GFF MDI *versus* other LAMA/LABA FDCs for TDI focal score in (a) the overall population and (b) the symptomatic population.
ACL, aclidinium; CrI, credible interval; FDC, fixed-dose combination; FOR, formoterol; GFF MDI, glycopyrrolate/formoterol fumarate metered dose inhaler; GLY, glycopyrrolate; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; OLO, olodaterol; TDI, transition dyspnea index; TIO, tiotropium; UMEC, umeclidinium; VIL, vilanterol.

could be made for TIO/OLO or ACL/FOR with respect to moderate-to-severe exacerbations. Additionally, GFF MDI was not significantly different to the other analyzable LABA/LAMA FDCs or placebo in reducing the number of severe exacerbations (Supplementary Figure S5), as reported in a total of seven studies,[8,14,18,42] although these comparisons are based upon only a small number of severe exacerbations, given that such events are rare. Two studies of less than 24 weeks' duration (Studies 114930 and 114951)[42] were included in the analysis of severe exacerbations. The evidence network for severe exacerbations was considerably sparse, and the comparison was limited to a single LAMA/LABA FDC (UMEC/VIL).

Exacerbations in symptomatic patients. In total, five studies (including the pooled PINNACLE studies) presented data for the effects of LAMA/LABA FDCs on moderate-to-severe exacerbations in symptomatic patients.[10,21,36,38,49] GFF MDI, UMEC/VIL, and GLY/IND significantly reduced the rate of moderate-to-severe exacerbations compared with placebo, and the efficacy of GFF MDI was not significantly different to that of UMEC/VIL or GLY/IND with respect to risk of moderate-to-severe exacerbation (Figure 6b).

Safety

In total, 17 studies contributed to the NMA of any AE (Supplementary Figure S6), any SAE, and all-cause withdrawals following 24 weeks of treatment with LAMA/LABA FDCs. For TIO/OLO, 24-week safety data were not available, precluding the inclusion of this FDC in the safety NMA. No significant differences were observed between any LAMA/LABA FDC and placebo in

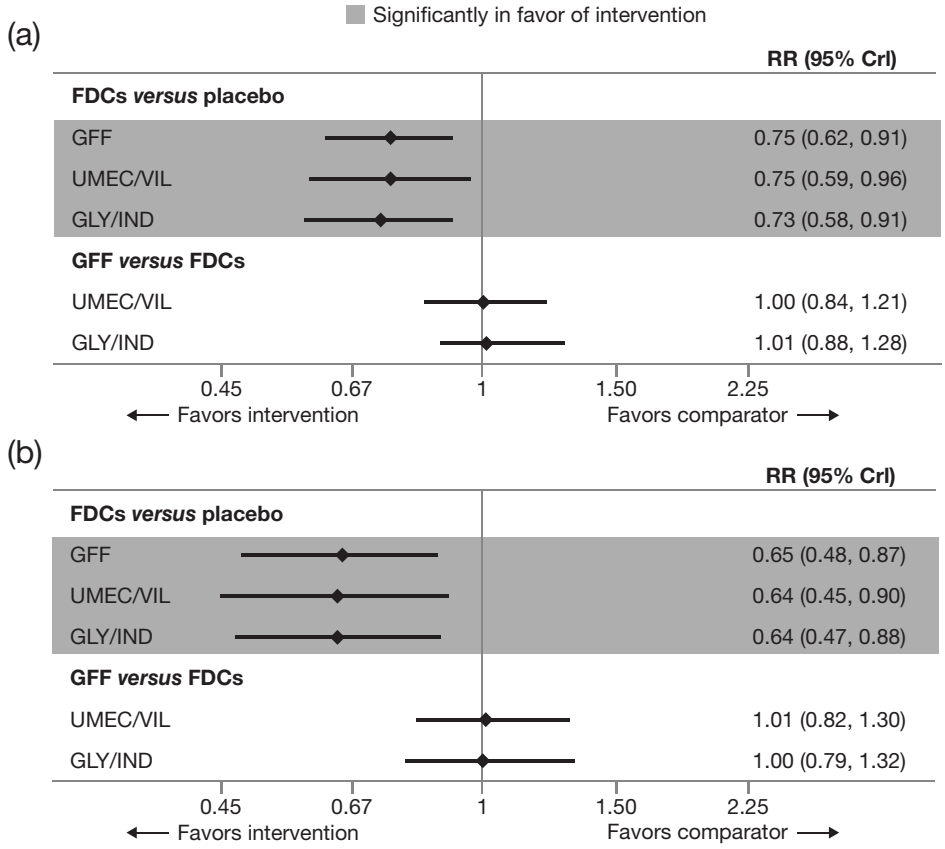

Figure 6. Moderate-to-severe exacerbations. LAMA/LABA FDCs *versus* placebo and GFF MDI *versus* other LAMA/LABA FDCs in (a) the overall population and (b) the symptomatic population.
CrI, credible interval; FDC, fixed-dose combination; GFF MDI, glycopyrrolate/formoterol fumarate metered dose inhaler; GLY, glycopyrrolate; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; RR, rate ratio; UMEC, umeclidinium; VIL, vilanterol.

terms of the incidence of any AE or SAE (Figure 7a). All LAMA/LABA FDCs were associated with a significantly lower likelihood of treatment withdrawal for all causes, compared with placebo (Figure 7b). No significant differences were noted between GFF MDI and the other analyzable LAMA/LABA FDCs with respect to these safety outcomes. The incidence of specific AEs including cough, dyspnea, headache, and upper respiratory tract infection was similar to placebo for all LAMA/LABA FDCs, with no significant differences between GFF MDI and other analyzable dual therapies (data not shown).

Meta-regression and sensitivity analyses

Meta-regression and sensitivity analyses were conducted to account for heterogeneity across the studies included in the NMA. There was no statistically significant association between the covariates assessed in the meta-regression (FEV_1 percentage predicted, SGRQ total score, and ICS use at baseline) and treatment effects on trough FEV_1, peak FEV_1, SGRQ responders, TDI score, or TDI responders at week 24, or daily rescue medication use over 24 weeks, which indicated that no linear relationship could be demonstrated between these covariates and treatment effect size. For SGRQ total score at week 24, there was no significant association between treatment effect and baseline FEV_1 percentage predicted or SGRQ covariates, but there was a significant negative association with ICS use at baseline. For each of these endpoints, results from the meta-regression were similar to the base case NMA. None of the covariate-adjusted models offered notable improvement in between-study variability (SD) compared with unadjusted models. The meta-regression results should be interpreted with caution, as the analyses were based on aggregate data, to allow for accurate modeling of the effect of covariates on the treatment effect.

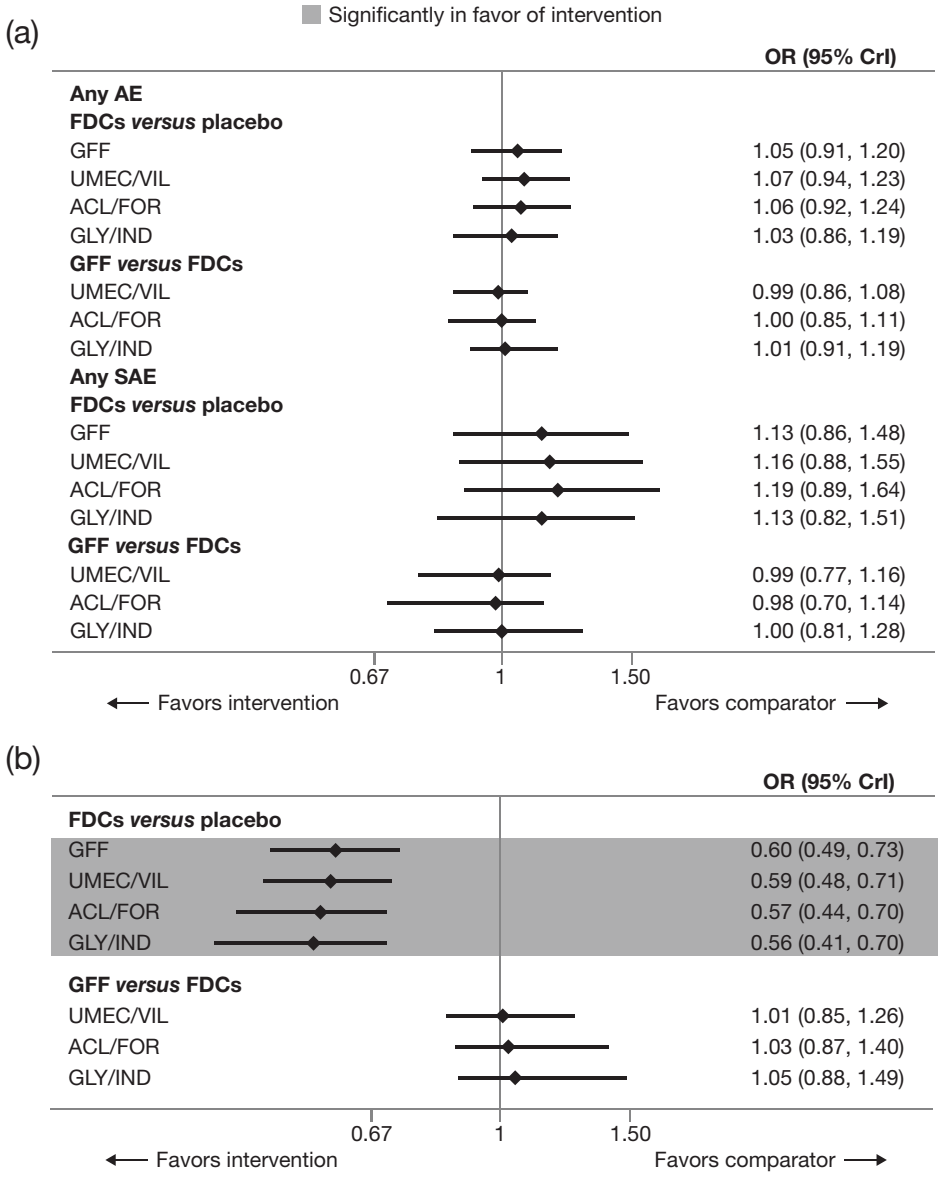

Figure 7. Safety. LAMA/LABA FDCs *versus* placebo and GFF MDI *versus* other LAMA/LABA FDCs for (a) any AE or any SAE and (b) all-cause withdrawals.
ACL, aclidinium; AE, adverse event; CrI, credible interval; FDC, fixed-dose combination; FOR, formoterol; GFF MDI, glycopyrrolate/formoterol fumarate metered dose inhaler; GLY, glycopyrrolate; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OR, odds ratio; SAE, serious adverse event; UMEC, umeclidinium; VIL, vilanterol.

Sensitivity analyses after exclusion of open-label arms/studies were conducted to account for heterogeneity in the NMA. After the exclusion of open-label studies, the results obtained for trough FEV_1, peak FEV_1, SGRQ total score, SGRQ responders, TDI focal score or TDI responders at week 24, or daily rescue medication use over 24 weeks, were consistent with the base case results.

Discussion

In this NMA we considered extensive up-to-date evidence surrounding the use of LAMA/LABA FDCs, including GFF MDI 18/9.6 µg, for the management of moderate-to-very severe COPD. In contrast to other published analyses of a similar nature,[22–26] the current study included both recently published pivotal trial data and phase IIIb head-to-head comparative data surrounding

GFF MDI.[8,18,21] The NMA demonstrated that GFF MDI and all other LAMA/LABA FDCs showed significant benefits with respect to improvements in lung function, quality of life, symptom control, and exacerbation parameters, compared with placebo. Where data were available for indirect comparisons, differences between GFF MDI and other approved LAMA/LABA FDCs were small relative to established margins of clinical relevance and generally not statistically significant. The efficacy findings were supported by the meta-regression analysis, which demonstrated similar outcomes to the base case analysis when selected baseline patient characteristics were accounted for. The safety and tolerability profile of GFF MDI was also found to be comparable to that of the other LAMA/LABA FDCs examined.

Our findings are consistent with previous NMAs that have examined LAMA/LABA FDCs but did not include GFF MDI, in that the LAMA/LABA FDCs analyzed generally showed similar efficacy,[22–25] and safety profiles.[22,23,25] Considering the totality of available FEV_1 data within these publications, NMAs have largely shown the efficacy of LAMA/LABA FDCs in improving lung function to be comparable, although some differences in trough FEV_1 outcomes have been noted but were unlikely to be of clinical relevance and, in some instances, were dependent upon the type of statistical model used in the analysis.[22,25]

Similarities in efficacy between GFF MDI and the other LAMA/LABA FDCs with regards to symptom and quality of life outcomes are noteworthy, given that these outcomes, along with exacerbations, are likely to be of greater importance to the patient than FEV_1, which does not fully reflect the burden of COPD.[48,50] Indeed, GOLD recommendations identify the main treatment goals for the management of patients with COPD as reducing symptoms and future risk of exacerbations.[2] Consistent with the findings of previous NMAs, in this study no statistically or clinically significant differences were observed between LAMA/LABA FDCs, in terms of improvement in TDI or SGRQ scores, or the percentage of TDI or SGRQ responders at 24 weeks.[22–25]

Considering that COPD exacerbations are responsible for the majority of the burden inflicted on healthcare systems by the disease,[51] understanding the impact of LAMA/LABA FDCs on COPD exacerbations is particularly important from a health economics perspective. Although the present study found similar efficacy between LAMA/LABA FDCs in reducing the rate of moderate-to-severe exacerbations *versus* placebo, these findings must be prefaced by the fact that few studies in the NMA reported rates of severe exacerbations. In addition, it should be noted that several large studies of triple ICS/LAMA/LABA FDCs included a LAMA/LABA group,[52–54] but were not captured by the SLR criteria as they did not include another LAMA/LABA comparator or a placebo or monotherapy arm, which would have been required to connect them to the network. In contrast to studies of LAMA/LABA FDCs, which tend to focus on lung function and symptoms outcomes, studies of triple ICS/LAMA/FDCs usually include exacerbations outcomes as the primary endpoint, and therefore typically enroll populations with high exacerbation risk.

Given the apparent similarities between LAMA/LABA FDCs in terms of their efficacy and safety profiles in this NMA of clinical studies in patients with COPD, it will be interesting to note the real-world impact and importance of other factors that influence treatment choice within the class, such as patient preference and ability to handle the device correctly.[16,55,56]

To date, only four direct head-to-head comparisons of LAMA/LABA FDCs in patients with COPD have been published [UMEC/VIL *versus* OLO/TIO, UMEC/VIL *versus* GLY/IND (two studies), and GFF MDI *versus* UMEC/VIL], and the primary endpoints of these studies varied.[19–21] Feldman and colleagues found that UMEC/VIL was superior to TIO/OLO for the change from baseline in trough FEV_1 at week 8,[20] and Kerwin and colleagues reported two similar trials which showed that GLY/IND was not noninferior to UMEC/VIL for the change from baseline in $FEV_1AUC_{0\text{-}24}$ at week 12, although small noninferiority margins of –20 mL were used.[19] Due to the short study durations of only 8 or 12 weeks, as well as the US-only dosing regimen used by Kerwin and colleagues, these three studies were not included in the week 24 efficacy analyses presented in this manuscript. The AERISTO study showed that, over 24 weeks of treatment, GFF MDI was noninferior to UMEC/VIL for change from baseline in peak FEV_1, but not for change from baseline in morning predose trough FEV_1.[21] Due to the differences in study duration, primary endpoint, and patient populations enrolled, it is difficult to

directly compare findings across these studies. The results of AERISTO for lung function were in contrast to the findings of this NMA, which found no difference between GFF MDI and UMEC/VIL for trough FEV_1 and a small difference in favor of GFF MDI for peak FEV_1. In line with the findings of this NMA, there were no clinically meaningful differences between UMEC/VIL and GFF MDI in terms of symptom endpoints.

Given the shortage of head-to-head trials comparing all available LAMA/LABA FDCs, NMAs provide a useful indicator of clinical effects based on both direct and indirect evidence. Since, in general, previous meta-analyses have not shown statistically significant or clinically meaningful differences between LAMA/LABA FDCs within the drug class,[22–26] and there is currently no inclass differentiation in the clinical guidance regarding the value of LAMA/LABA FDCs for COPD,[2] a Bayesian three-level hierarchical model was applied to the NMA. This approach assumes that treatment effects within each class follow a normal distribution with class-specific mean and common variance, thus making better use of information from within the class, increasing the precision of estimates, while maintaining the interpretability of individual treatment-effect estimates. A noted strength of this NMA was that it included data pertaining to all five FDCs currently approved for the maintenance treatment of patients with COPD.[2] A further positive aspect was the subgroup analysis of SGRQ and TDI in a symptomatic subpopulation of patients with COPD. As some of the studies included in the NMA recruited only patients above a certain symptom threshold, and symptomatic status can be a key effect modifier, this subgroup analysis was valuable in its confirmation of the results from the overall population.

However, due to the inherent limitations of an NMA, the findings from this study should be interpreted with a degree of caution. As the number of interventions and trials within each class can vary substantially, in particular for classes in which there are few available interventions and a small evidence base, estimates will remain fairly uncertain. As with traditional meta-analyses, NMAs are dependent on the similarity of studies to generate exchangeable treatment effects. We explored potential sources of heterogeneity in a sensitivity analysis by excluding open-label arms/studies, conducting meta-regression, and conducting a subgroup analysis in the symptomatic population, and the results generated were consistent with those reported for the base case.

Conclusion

Compared with placebo, all LAMA/LABA FDCs exhibited statistically significantly greater improvement in FEV_1 (trough, peak, and $AUC_{0–4}$), SGRQ total score, TDI score, and reduced rates of moderate-to-severe exacerbations over 24 weeks of treatment in patients with moderate-to-very severe COPD. The efficacy of GFF MDI was comparable to that of other LAMA/LABA FDCs in terms of improvements in lung function, quality of life, symptom control, and reduction of moderate-to-severe exacerbation rates. Similarly, the safety and tolerability profile of GFF MDI resembled that of other LAMA/LABA FDCs and placebo. This indirect comparison strengthens the existing evidence base and may be important in understanding the health and economic consequences of using different LAMA/LABA FDCs. Given that efficacy and tolerability outcomes between LAMA/LABA FDCs appear comparable, personalization of COPD treatment within the class on the basis of other factors, including patient preference and device choice, may be appropriate.

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Conflict of interest statement

MKS is an employee of Parexel, and PS is a former employee of Parexel, the organization that received funding from AstraZeneca to perform the systematic literature review and network meta-analysis.

MJ, MO, DG, PD, and MB are employees of AstraZeneca.

MJ, DG, and PD hold stock or stock options in AstraZeneca.

Supplemental material

Supplemental material for this article is available online.

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