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ORIGINAL RESEARCH

Efficacy of Budesonide/Glycopyrronium/Formoterol Fumarate Metered Dose Inhaler (BGF MDI) Versus Other Inhaled Corticosteroid/Long-Acting Muscarinic Antagonist/Long-Acting β_2-Agonist (ICS/LAMA/LABA) Triple Combinations in COPD: A Systematic Literature Review and Network Meta-analysis

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ABSTRACT

Introduction: Triple inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist (ICS/LAMA/LABA) combination therapy is recommended for patients with chronic obstructive pulmonary disease (COPD) who experience further exacerbations/symptoms on dual LAMA/LABA or ICS/LABA therapy. The relative efficacy of budesonide/glycopyrronium/formoterol fumarate metered dose inhaler 320/18/9.6 μg (BGF MDI) in COPD was compared with other ICS/LAMA/LABA fixed-dose and open combination therapies in a network meta-analysis (NMA).

Methods: A systematic literature review was conducted to identify randomized controlled trials of at least 10-week duration, including at least one fixed-dose or open combination triple therapy arm, in patients with moderate to very severe COPD. Studies were assessed for methodological quality and risk of bias. A three-level hierarchical Bayesian NMA model was used to determine the exacerbation rate per patient per year as well as the following outcomes at week 24: changes from baseline in pre-dose trough forced expiratory volume in 1 s (FEV_1), post-dose peak FEV_1, and St. George's Respiratory Questionnaire (SGRQ) total score; proportion of SGRQ responders; and Transition Dyspnea Index focal score. Change from baseline in rescue medication use over weeks 12–24 was also analyzed. Meta-regression and sensitivity analyses were used to assess heterogeneity across studies.

Results: Eighteen studies (n = 29,232 patients) contributed to the NMA. ICS/LABA dual combinations were combined as a single treatment group to create a connected network. Across all outcomes, there were no statistically significant differences between BGF MDI and other triple ICS/LAMA/LABA fixed-dose (fluticasone furoate/umeclidinium/vilanterol and beclomethasone dipropionate/glycopyrronium/formoterol

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fumarate) and open combinations with data available within the network. Results from sensitivity analyses and meta-regression were consistent with the base-case scenario.
Conclusion: This NMA suggested that BGF MDI has comparable efficacy to other ICS/LAMA/LABA fixed-dose and open triple combination therapies in reducing exacerbations and improving lung function and symptoms in patients with moderate to very severe COPD. Further research is warranted as additional evidence regarding triple therapies, especially fixed-dose combinations, becomes available.

Keywords: Chronic obstructive pulmonary disease; Exacerbations; Inhaled corticosteroid; Long-acting muscarinic antagonist; Long-acting β_2-agonist; Lung function; Network meta-analysis; Patient-reported outcomes; Triple therapy

Key Summary Points

Why carry out this study?

Budesonide/glycopyrronium/formoterol fumarate metered dose inhaler (BGF MDI) is a triple fixed-dose combination therapy for chronic obstructive pulmonary disease (COPD).

Given the relatively recent introduction of fixed-dose triple therapies for COPD, there are no head-to-head randomized controlled trials of their relative efficacy.

We performed a network meta-analysis to compare the relative efficacy of BGF MDI versus other triple therapies (in fixed-dose or open combination) in patients with moderate to very severe COPD.

What was learned from the study?

On the basis of evidence from 18 studies, BGF MDI was found to have similar efficacy to other fixed-dose and open triple combination therapies in reducing exacerbations and improving lung function and symptoms in patients with moderate to very severe COPD.

The results of this network meta-analysis provide important context for healthcare providers and payers in evaluating the current evidence regarding triple therapies in COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease that causes symptoms including dyspnea, sputum production, and chronic cough, and can be associated with significant comorbidities [1]. COPD is associated with significant morbidity and mortality: it was reported to be the third leading cause of death in 2016, causing an estimated 3.0 million deaths globally [2].

A range of pharmacological treatment options exists for COPD, with the key treatment goals being to reduce symptoms, decrease the risk of exacerbations, and minimize the impact of exacerbations if they occur [1]. Patients with a high symptom burden and a history of exacerbations may be treated with dual bronchodilator therapy [long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA)], or for patients who also have elevated eosinophil levels, inhaled corticosteroid (ICS)/LABA therapy is a recommended initial treatment option [1]. Escalation to ICS/LAMA/LABA triple therapy is recommended for patients who continue to experience symptoms such as breathlessness or difficulty with physical activity while on ICS/LABA treatment, or for patients on LAMA/LABA therapy who continue to have exacerbations and who have eosinophil counts of at least 100 cells/μL [1]. Notably, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 report includes, for the first time, a specific treatment pathway for the management of exacerbations, indicating the clinical importance of preventing their occurrence [3].

Combination therapies may be delivered via separate inhalers (in "open" combination) [4–6] or within a single inhaler (in fixed-dose combination) [7–10]. Given the relatively recent

introduction of fixed-dose triple therapies, there are no head-to-head randomized controlled trials (RCTs) of their relative efficacy in COPD. In the absence of head-to-head data, network meta-analysis (NMA) can be used to compare multiple interventions by combining direct and indirect evidence, adjusting with the use of common comparators [11]. NMA techniques have been applied to compare the efficacy of triple therapy as a class with LAMA/LABA dual therapy or bronchodilator monotherapy [12], and two pairwise meta-analyses have provided comparisons of triple therapies with ICS/LABA [13, 14] or LAMA/LABA [14].

Budesonide/glycopyrronium/formoterol fumarate metered dose inhaler (BGF MDI), formulated with co-suspension delivery technology (AEROSPHERE®, AstraZeneca), is a triple ICS/LAMA/LABA fixed-dose combination that has recently been approved in Japan and China for the treatment of COPD [15, 16]. In the phase III KRONOS study, BGF MDI showed benefits in improving lung function and symptoms and reducing COPD exacerbations versus dual LAMA/LABA and ICS/LABA therapies [10]. We performed a systematic literature review (SLR) and NMA to compare the relative clinical efficacy of BGF MDI versus other triple ICS/LAMA/LABA therapies (in fixed-dose or open combination) in patients with moderate to very severe COPD. To our knowledge, this is the first NMA to assess the relative efficacy of triple therapies in COPD. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

METHODS

Systematic Literature Review

An SLR was conducted to identify evidence on the efficacy of triple ICS/LAMA/LABA fixed-dose or open combination therapies in patients with moderate to very severe COPD, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Searches of Embase®, MEDLINE®, MEDLINE® In-Process, and the Cochrane Central Register of Controlled Trials (CENTRAL) were run from database inception to October 2019. Only articles published in English were included. The search strategies are shown in Table S1. Abstracts from the American Thoracic Society, European Respiratory Society, and American College of Chest Physicians conference proceedings were hand-searched from September 2015 to August 2019 to retrieve studies that had not yet been published in full-text articles or abstracts reporting supplementary results of previously published studies. Additionally, the following trial registries were searched to capture unpublished clinical trials: ClinicalTrials.gov of the US National Institute of Health and the World Health Organization International Clinical Trials Registry Platform.

To be included in the SLR, studies had to meet pre-defined eligibility criteria: the primary criteria were RCTs with a duration of at least 10 weeks, assessing patients of at least 40 years of age with moderate to very severe COPD, published in English, and including at least one treatment arm with fixed-dose or open combination triple therapy (Table 1). Titles and abstracts of publications identified in the search were screened, full-text copies of articles judged to be potentially relevant reviewed, and data for eligible studies extracted using a pre-defined extraction grid, which included details on trial design, inclusion criteria, study population characteristics, interventions, outcome measures, and length of follow-up. Screening, review, and data extraction were conducted by two independent reviewers, with results checked and reconciled by a third independent reviewer. Where a single study was described by more than one publication, the data were compiled into a single entry in the data extraction sheet to avoid duplication, with all publications referenced.

The methodological quality of included studies was assessed using the concise critical appraisal checklists provided by the National Institute for Health and Care Excellence (NICE) in the Single Technology Appraisal user guide [17]. The risk of bias was assessed with respect to the method of randomization and allocation concealment, comparability of baseline characteristics, blinding, the balance of withdrawals

Table 1 Population, interventions, comparators, outcomes, and study design criteria for inclusion in the network meta-analysis

Population	Adult patients (≥ 40 years of age) of any gender or race with moderate to very severe COPD (predicted $FEV_1 \leq 80\%$)
Interventions	Triple therapies (ICS + LAMA + LABA, both fixed-dose and open combinations)
Comparators	Any included intervention
	Dual therapies (ICS + LABA or LAMA + LABA both fixed-dose and open combinations)
	Monotherapies (ICS/LAMA/LABA)
	Placebo
Outcomes	Efficacy outcomes
	Exacerbations (severe only, moderate to severe)
	Lung function (peak FEV_1, trough FEV_1)
	SGRQ total score and SGRQ responders
	TDI focal score
	Use of rescue medication
Study designs	Randomized controlled trials of ≥ 10 weeks duration

COPD chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume in 1 s, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *SGRQ* St. George's Respiratory Questionnaire, *TDI* Transition Dyspnea Index

between groups, outcomes reporting, and statistical analysis.

Network Meta-analysis

The NMA followed the recommended best practice of the NICE Decision Support Unit for evidence synthesis [18, 19]. Relevant results were combined using a three-level hierarchical Bayesian NMA model, which assumes exchangeability between treatments within the same class, i.e., that all studies measure the same underlying relative treatment effects [20, 21]. This model accounted for the exchangeability between interventions of the same class (i.e., LAMA monotherapy, ICS/LABA dual combinations, ICS/LAMA/LABA triple combinations) by assuming that underlying treatment effects within each class followed a normal distribution with class-specific mean and variance. Thus, estimates of treatment effects and their uncertainty are affected by both the evidence propagated through the network, as well as the borrowed strength between treatments in the same class. The synthesis was conducted from a Bayesian perspective, using WinBUGS (a Markov chain Monte Carlo simulation-based software for Bayesian inference) version 1.4.3. The NMA WinBUGS code, developed initially by Dias et al. [22], was adapted to incorporate a three-level hierarchical class-effect model [20, 21, 23]. Results were generated using both random- and fixed-effects models and compared for goodness-of-fit to the data, calculated as the overall mean residual deviance. The goodness of fit was assessed using the Deviance Information Criterion (DIC); the model with the lowest DIC was considered the model with the best fit to the data. If DIC and residual deviance were comparable between models, a random-effects model was preferred as it takes into account additional heterogeneity in the network, but a fixed-effects model was used when the number of contributing studies was five or fewer. Results are presented as posterior median effect estimates with 95% credible limits: rate ratios for counts outcomes modeled with a Poisson model (exacerbations), mean differences for continuous outcomes [forced expiratory volume in 1 s (FEV_1), St. George's Respiratory Questionnaire (SGRQ), Transition Dyspnea Index (TDI), and rescue medication use], and odds ratios for binary outcomes (SGRQ responders). No type I error control was performed, as is common with other studies of this nature using a Bayesian framework [24]. For continuous outcomes, results were considered non-significant if the credible interval (CrI) contained the null value; for Poisson/binomial outcomes, results were considered non-significant if the CrI contained 1. Inconsistencies between direct and indirect estimates were

checked, where appropriate, for outcomes where both direct and indirect data were available for the comparison of interest (further details are provided in the Supplementary methods).

A separate NMA was performed for each of the outcomes of interest. Exacerbations were assessed as the mean rate of exacerbations per patient per year (moderate/severe and severe exacerbations, analyzed as relative ratios for BGF MDI vs comparators). Lung function endpoints were the change from baseline in trough FEV_1 and the change from baseline in peak FEV_1, both at week 24. The following patient-reported outcomes were assessed: change from baseline in SGRQ total score at 24 weeks, proportion of SGRQ responders (patients who experienced an improvement that met or exceeded the minimum clinically important difference of at least 4 units [25]) at 24 weeks, TDI focal score at 24 weeks, and change from baseline in rescue medication use over 12–24 weeks. Analysis of TDI responders could not be performed because of variation between studies in the reporting of this outcome.

Studies reporting data between 22 and 26 weeks were considered for inclusion in the 24-week analyses. For the exacerbation outcomes, there was no limit applied on the basis of maximum trial duration, as the treatments were compared using rates (events per patient-year). Networks were presented graphically with a "node" representing each intervention and an "edge" representing the comparison between them. Each node was weighted according to the number of patients receiving that intervention, and each edge was weighted according to the number of studies included for the comparison.

Several sensitivity analyses were undertaken. The base-case scenario included only double-blind studies; therefore, a sensitivity analysis was performed, including both double-blind and open-label studies in one network. A sensitivity analysis was also performed, including only studies in which the majority of the patient population was symptomatic (defined as a COPD assessment test (CAT) score of at least 10 or a modified Medical Research Council (mMRC) dyspnea scale score of at least 2).

Additionally, a meta-regression analysis was conducted for the efficacy outcomes with at least 10 studies to account for differences in selected baseline patient characteristics that could be acting as the key effect modifiers.

RESULTS

Study Selection

The SLR process is shown in Fig. 1. Initial database searches identified 15,542 publications, with 2742 removed owing to duplication across databases searched. Initial screening of the 12,800 remaining records (based on titles and abstracts) reduced eligible publications to 1589, which were subject to full-text review. A further 32 citations were identified from conference proceedings and bibliographies of identified publications, including a clinical study report for an RCT with BGF MDI. Following full-text review, a total of 23 studies from 165 publications met the inclusion criteria of the SLR. Five studies did not report any efficacy outcome of interest at specified time points, thus leaving 18 studies [4–10, 26–34] that contributed to the NMA (Table 2; Table S2).

Study Characteristics

All 18 of the studies included were multicenter, the majority were phase III, two were open-label, and the remainder were double-blind (Table 2). All studies included in the NMA were adjudged to pose a low risk of bias with respect to randomization and allocation concealment, baseline characteristics, the balance of withdrawals between groups, and statistical analysis (Table S3). High risk of bias in blinding was associated with two open-label studies [4, 5], and one study was considered to have a high risk of bias with respect to outcome selection and reporting [31].

Analysis Assumptions

When all treatments reported in the included studies were considered, there was no

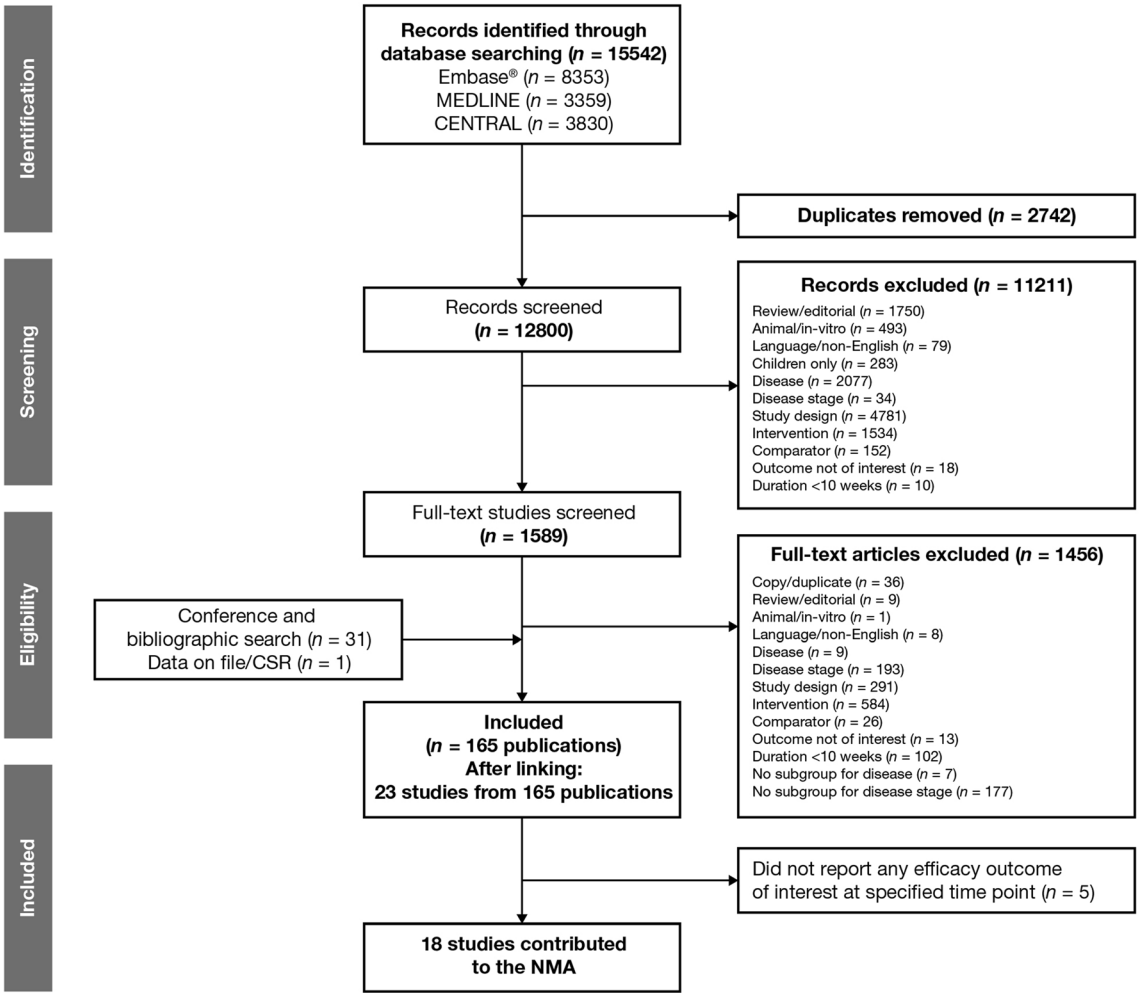

Fig. 1 PRISMA flowchart. *CSR* clinical study report, *NMA* network meta-analysis

interlinked network allowing comparison of BGF MDI with other triple therapies in the base-case analysis, which included only double-blind studies ($n = 16$; Fig. 2a). Therefore, to create an interlinked network, all ICS/LABA dual combinations were considered as a single treatment group (Fig. 2b). The networks of evidence for each outcome varied according to the endpoints available from each study (Figs. S1–S3).

Patient Baseline Clinical Characteristics

A total of 29,232 evaluable patients contributed to the NMA. Patient characteristics were generally similar in terms of age, gender, body mass index, and smoking status, but differences were noted in disease duration, race, symptom burden, COPD severity, and exacerbation history (Table 3). These potential differences in key effect modifiers could not be adjusted in a meta-regression model because of the limited number of studies contributing to the NMA, except for moderate/severe exacerbations and severe exacerbations. For these outcomes, meta-regression was feasible for prior exacerbation history, smoking status, BMI, and disease severity, as classified by GOLD (III or IV). Thirteen of the 18 studies included enrolled only symptomatic patients, while the remainder did not describe any inclusion criteria regarding symptom burden.

Table 2 Study characteristics

Study	Treatment	Patient number	Study duration (weeks)	Primary endpoint	Publication type	Study phase	Blinding	Study setting
Aaron 2007 [26]	FP/SAL (FP 500 μg + SAL 50 μg) BID + TIO 18 μg OD	145	52	Proportion of patients who experienced a COPD exacerbation that required treatment with systemic steroids or antibiotics within 52 weeks of randomization	Journal article	Unclear	Double-blind	Multicenter
	TIO 18 μg OD + SAL 50 μg BID	148						
	TIO 18 μg OD	156						
Bremner 2018[a] [27]	FF/UMEC/VI (FF 100 μg + UMEC 62.5 μg + VI 25 μg) OD	527	24	Change from baseline in trough FEV_1 at week 24	Journal article	III	Double-blind	Multicenter
	FF/VI (FF 100 μg + VI 25 μg) OD + UMEC 62.5 μg OD	528						
FULFIL[a] [28]	FF/UMEC/VI (FF 100 μg + UMEC 62.5 μg + VI 25 μg) OD	911	24	Change from baseline in trough FEV_1 at week 24, change from baseline in SGRQ total score at week 24	Journal article/ CSR	III	Double-blind	Multicenter international
	BUD/FOR (BUD 320 μg + FOR 9 μg) BID	899						
Hanania 2012[a] [29]	FP/SAL (FP 250 μg + SAL 50 μg) BID + TIO 18 μg OD	173	24	Change from baseline in morning pre-dose FEV_1 at week 24	Journal article	IV	Double-blind	Multicenter
	TIO 18 μg OD	169						
IMPACT[a] [8]	FF/UMEC/VI (FF 100 μg + UMEC 62.5 μg + VI 25 μg) OD	4155	52	Annual rate of moderate or severe COPD exacerbations over 52 weeks	Journal article/ CSR	III	Double-blind	Multicenter international
	FF/VI (FF 100 μg + VI 25 μg) OD	4139						
	UMEC/VI (UMEC 62.5 μg + VI 25 μg) OD	2073						
Jung 2012 [4]	FP/SAL (FP 250 μg + SAL 50 μg) BID + TIO 18 μg OD	237	24	Change from baseline in prebronchodilator FEV_1 at week 24	Journal article	IV	Open-label	Multicenter
	TIO 18 μg OD	242						

Table 2 continued

Study	Treatment	Patient number	Study duration (weeks)	Primary endpoint	Publication type	Study phase	Blinding	Study setting
KRONOS[a] [10]	BUD/GLY/FOR (BGF MDI; BUD 320 μg + GLY 14.4 μg + FOR 10 μg) BID	640	24	*Japan/China* Change from baseline in morning pre-dose trough FEV_1 over weeks 12–24 *EU/Canada* Change from baseline in morning pre-dose trough FEV_1 over 24 weeks, FEV_1 $AUC_{0–4}$ over 24 weeks *USA* FEV_1 $AUC_{0–4}$ at week 24, change from baseline in morning pre-dose trough FEV_1 at week 24	Journal article/ CSR	III	Double-blind	Multicenter international
	GLY/FOR (GFF MDI; GLY 14.4 μg + FOR 10 μg) BID	627						
	BUD/FOR (BFF MDI; BUD 320 μg + FOR 10 μg) BID	316						
	BUD/FOR (BUD/FOR DPI; BUD 320 μg + FOR 9 μg) BID	319						
Lee 2016 [5]	BUD/FOR (BUD 320 μg + FOR 9 μg) BID + TIO 18 μg OD	287	12	Change from baseline in pre-bronchodilator FEV_1 at weeks 1, 6, and 12	Journal article	IV	Open-label	Multicenter international
	TIO 18 μg OD	291						
Study AC4116135[a] [33]	FP/SAL (FP 250 μg + SAL 50 μg) BID + UMEC 125 μg OD	205	12	Change from baseline in trough FEV_1 at day 85 (week 12)	Journal article	III	Double-blind	Multicenter international
	FP/SAL (FP 250 μg + SAL 50 μg) BID + UMEC 62.5 μg OD	204						
	FP/SAL (FP 250 μg + SAL 50 μg) BID	205						

Table 2 continued

Study	Treatment	Patient number	Study duration (weeks)	Primary endpoint	Publication type	Study phase	Blinding	Study setting
Study AC4116136[a] [33]	FP/SAL (FP 250 μg + SAL 50 μg) BID + UMEC 125 μg OD	202	12	Change from baseline in trough FEV_1 at day 85 (week 12)	Journal article	III	Double-blind	Multicenter international
	FP/SAL (FP 250 μg + SAL 50 μg) BID + UMEC 62.5 μg OD	203						
	FP/SAL (FP 250 μg + SAL 50 μg) BID	201						
Study 200109[a] [6]	FF/VI (FF 100 μg + VI 25 μg) OD + UMEC 125 μg OD	207	12	Change from baseline in trough FEV_1 at day 85 (week 12)	Journal article	III	Double-blind	Multicenter international
	FF/VI (FF 100 μg + VI 25 μg) OD + UMEC 62.5 μg OD	206						
	FF/VI (FF 100 μg + VI 25 μg) OD	206						
Study 200110[a] [6]	FF/VI (FF 100 μg + VI 25 μg) OD + UMEC 125 μg OD	207	12	Change from baseline in trough FEV_1 at day 85 (week 12)	Journal article	III	Double-blind	Multicenter international
	FF/VI (FF 100 μg + VI 25 μg) OD + UMEC 62.5 μg OD	206						
	FF/VI (FF 100 μg + VI 25 μg) OD	206						
SUNSET[a] [30]	FP/SAL (FP 500 μg + SAL 50 μg) BID + TIO 18 μg OD	526	26	Change from baseline in post-dose trough FEV_1 at week 26	Journal article	IV	Double-blind	Multicenter international
	GLY/IND (GLY 43 μg + IND 85 μg) OD	527						
TRIBUTE[a] [9]	BDP/GLY/FOR (BDP 174 μg + GLY 18 μg + FOR 10 μg) BID	764	52	Annual rate of moderate/severe COPD exacerbations over 52 weeks	Journal article	III	Double-blind	Multicenter international
	GLY/IND (GLY 43 μg + IND 85 μg) OD	768						

Table 2 continued

Study	Treatment	Patient number	Study duration (weeks)	Primary endpoint	Publication type	Study phase	Blinding	Study setting
TRILOGY[a] [7]	BDP/GLY/FOR (BDP 200 μg + GLY 25 μg + FOR 12 μg) BID	687	52	Change from baseline in pre-dose (morning) FEV_1, change from baseline in 2-h post-dose FEV_1, and TDI focal score at week 26	Journal article	III	Double-blind	Multicenter international
	BDP/FOR (BDP 200 μg + FOR 12 μg) BID	681						
TRINITY[a] [34]	BDP/GLY/FOR (BDP 200 μg + GLY 25 μg + FOR 12 μg) BID	1078	52	Moderate/severe COPD exacerbation rate for 52 weeks of treatment	Journal article	III	Double-blind	Multicenter international
	BDP/FOR (BDP 200 μg + FOR 12 μg) BID + TIO 18 μg OD	538						
	TIO 18 μg OD	1075						
Welte 2009 [31]	BUD/FOR (BUD 320 μg + FOR 9 μg) BID + TIO 18 μg OD	329	12	Change in pre-dose FEV_1 from randomization (week 0) to the full treatment period (mean FEV_1 at weeks 1, 6, and 12 of treatment)	Journal article	IV	Double-blind	Multicenter international
	TIO 18 μg OD	331						
WISDOM [32]	FP 500 μg BID + SAL 50 μg BID + TIO 18 μg OD	1244	52	Time to the first moderate/severe COPD exacerbation	Journal article	IV	Double-blind	Multicenter international
	FP 500 μg BID (reducing[b]) + SAL 50 μg BID + TIO 18 μg OD	1244						

Doses represent the total amount per administered dose, which may be the sum of two actuations. Fixed-dose combinations are represented with "/" between components; open combinations are represented with "+" between components

AUC_{0-4} area under the curve from 0 to 4 h, *BDP* beclomethasone dipropionate, *BFF* budesonide/formoterol fumarate, *BGF* budesonide/glycopyrronium/formoterol fumarate, *BID* twice daily, *BUD* budesonide, *CAT* COPD Assessment Test, *COPD* chronic obstructive pulmonary disease, *CSR* clinical study report, *DPI* dry powder inhaler, *FEV_1* forced expiratory volume in 1 s, *FF* fluticasone furoate, *FP* fluticasone propionate, *FOR* formoterol, *GLY* glycopyrronium, *IND* indacaterol, *ITT* intent-to-treat, *MDI* metered dose inhaler, *mMRC* modified Medical Research Council dyspnea scale, *OD* once daily, *SAL* salmeterol, *SGRQ* St. George's Respiratory Questionnaire, *TDI* Transition Dyspnea Index, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

[a] A majority of the patient population was classified as symptomatic at baseline (based on CAT ≥ 10 or mMRC ≥ 2)

[b] The BID dose of FP was reduced every 6 weeks in a stepwise withdrawal, from 500 to 250 μg, then to 100 μg, and finally to 0 μg (placebo) [32]

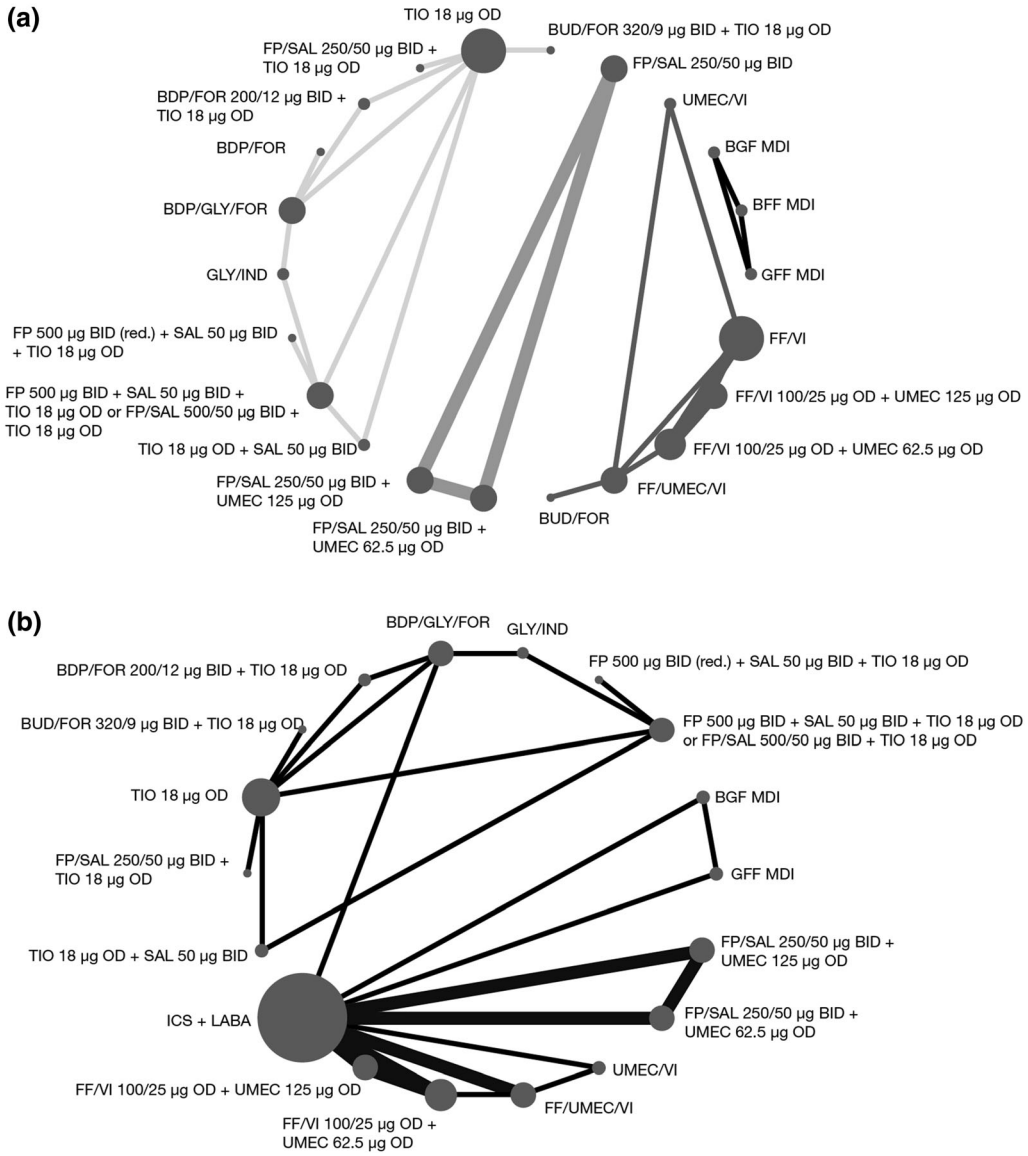

Fig. 2 Networks using treatments as reported (**a**), and using all ICS/LABA treatments as a single treatment group (**b**). Fixed-dose combinations are represented with "/" between components; open combinations are represented with "+" between components. *BDP* beclomethasone dipropionate, *BFF* budesonide/formoterol fumarate, *BGF* budesonide/glycopyrronium/formoterol fumarate, *BID* twice daily, *BUD* budesonide, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GFF* glycopyrronium/formoterol fumarate, *GLY* glycopyrronium, *ICS* inhaled corticosteroid, *IND* indacaterol, *LABA* long-acting β_2-agonist, *MDI* metered dose inhaler, *OD* once daily, red. reducing, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

Efficacy

For each outcome, findings are presented for all comparisons with data available within the network.

Exacerbations

Moderate/severe and severe exacerbations were reported in 15 and 12 studies, respectively, with one study excluded from the severe exacerbations analysis as no events were reported

Table 3 Patient baseline clinical characteristics

Study	Mean age (years)	Male (%)	Race (% white)	Disease duration (years)	Current smoker (%)	BMI (kg/m^2)	COPD severity (%; GOLD 1/2/3/4)	Moderate/severe exacerbation history, ≥ 1 exacerbations (%)	Mean CAT score	Mean mMRC score
Aaron 2007 [26]	68	56	98	NR	28	28	NR	100	NR	NR
Bremner 2018[a] [27]	66	75	NR	NR	38	NR	< 1/35/49/15	100	19.9	NR
FULFIL[a] [28]	64	74	85	NR	44	27	< 1/33/54/13	65	19.1	NR
Hanania 2012[a] [29]	61	47	96	7	58	27	NA/68/32/NA	29[b]	NR	2.5
IMPACT[a] [8]	65	66	78	NR	35	27	< 1/36/48/16	100	20.1	NR
Jung 2012 [4]	67	98	NR	NR	NR	22	NA/58/38/3	NR	NR	NR
KRONOS[a] [10]	65	71	50	7	40	26	< 1/49/43/8	26	18.3	NR
Lee 2016 [5]	67	96	NR	5	NR	21	NA/8/74/18	100	NR	NR
Study AC4116135[a] [33]	63	66	88	NR	54	28	NA/46/44/11	21[b]	18.2	2.4
Study AC4116136[a] [33]	65	63	82	NR	38	27	NA/40/48/12	31[b]	17.7	2.4
Study 200109[a] [6]	64	66	98	NR	42	28	NA/40/46/14	15[b]	16.6	2.5
Study 200110[a] [6]	63	63	86	NR	57	27	NA/48/41/11	14[b]	17.6	2.3
SUNSET[a] [30]	65	71	100	8	42	28	NA/70/30/NA	34	NR	NR
TRIBUTE[a] [9]	64	72	92	8	45	26	NA/NA/79/20	100	21.2[c]	NR
TRILOGY[a] [7]	64	76	100	8	47	26	NA/NA/77/23	100	20.8	NR
TRINITY[a] [34]	63	76	99	8	48	26	NA/NA/79/21	100	21.6	NR
Welte 2009 [31]	62	75	NR	6[d]	44	26	NA/25/64/11	100	NR	NR
WISDOM [32]	64	82	81	8	33	25	< 1/< 1/61/38	100	NR	1.8

Baseline characteristics were obtained from publically available clinical study reports when not available in the primary publication

BMI body mass index, *CAT* COPD Assessment Test, *COPD* chronic obstructive pulmonary disease, *mMRC* Modified Medical Research Council, *NA* not applicable, *NR* not reported

[a] A majority of the patient population was classified as symptomatic at baseline (based on CAT ≥ 10 or mMRC ≥ 2)

[b] Moderate exacerbation history (moderate/severe not reported)

[c] Reported in [47]

[d] Median (mean not reported)

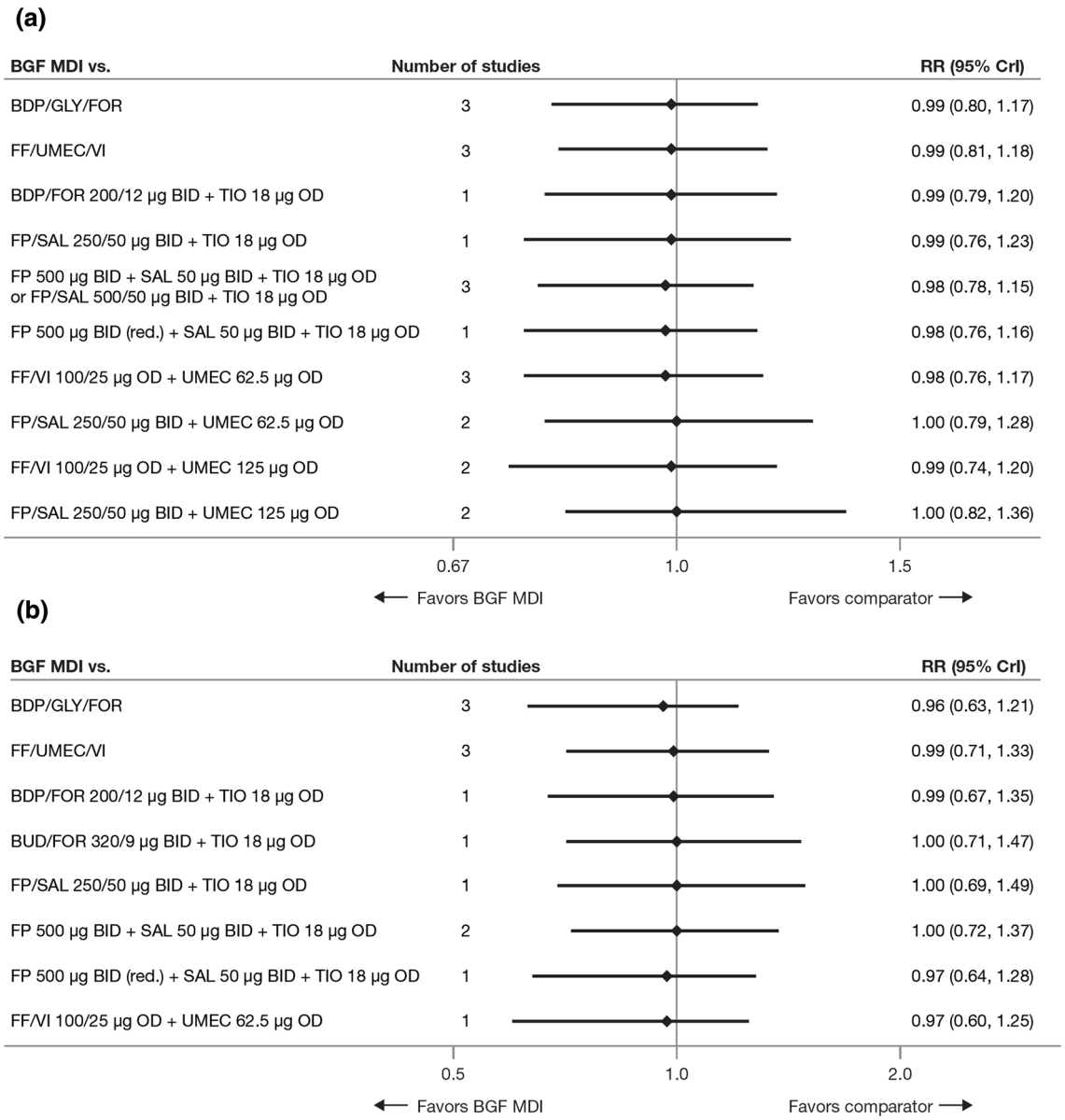

Fig. 3 Rate ratio of (**a**) moderate/severe exacerbations and (**b**) severe exacerbations. Fixed-dose combinations are represented with "/" between components; open combinations are represented with "+" between components. *BDP* beclomethasone dipropionate, *BGF* budesonide/glycopyrronium/formoterol fumarate, *BUD* budesonide, *CrI* credible interval, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium, *MDI* metered dose inhaler, red. reducing, *RR* rate ratio, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

(networks shown in Fig. S1). The definitions of moderate and severe exacerbations were broadly similar among the included studies. BGF MDI 320/18/9.6 µg twice daily (BID) showed comparable reductions in moderate/severe exacerbations to two other triple ICS/LAMA/LABA fixed-dose combinations [beclomethasone dipropionate/glycopyrronium/formoterol fumarate (BDP/GLY/FOR 100/6/12.5 BID) and fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI 100/62.5/25 µg once daily (OD))] and eight open triple

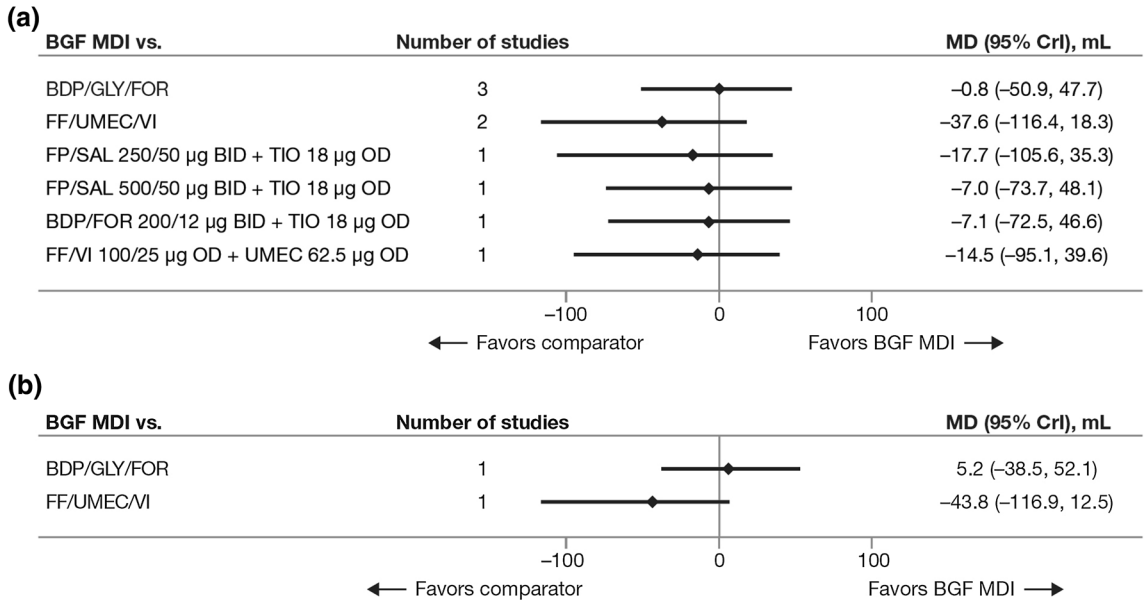

Fig. 4 Lung function endpoints at 24 weeks. Change from baseline in (**a**) trough FEV_1 and (**b**) peak FEV_1. Fixed-dose combinations are represented with "/" between components; open combinations are represented with "+" between components. *BDP* beclomethasone dipropionate, *BGF* budesonide/glycopyrronium/formoterol fumarate, *CrI* credible interval, *FEV_1* forced expiratory volume in 1 s, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium, *MD* mean difference, *MDI* metered dose inhaler, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

combinations (Fig. 3a). BGF MDI also showed a comparable reduction in severe exacerbations to FF/UMEC/VI, BDP/GLY/FOR, and six open triple combinations (Fig. 3b).

Lung Function

Changes from baseline in trough and peak FEV_1 at 24 weeks were reported in nine and four studies, respectively (networks shown in Fig. S2). At 24 weeks, BGF MDI showed comparable effect on trough FEV_1 to BDP/GLY/FOR, FF/UMEC/VI, and four open triple combinations [fluticasone propionate + tiotropium + salmeterol (FP/SAL 250/50 µg BID + TIO 18 µg OD and FP/SAL 500/50 µg BID + TIO 18 µg OD), beclomethasone dipropionate + tiotropium + formoterol (BDP/FOR 200/12 µg BID + TIO 18 µg OD), and fluticasone furoate + umeclidinium + vilanterol (FF/VI 100/25 µg OD + UMEC 62.5 µg OD)] (Fig. 4a).

At 24 weeks, BGF MDI showed comparable improvement in peak FEV_1 to BDP/GLY/FOR and FF/UMEC/VI (Fig. 4b).

Quality of Life and Symptoms

Changes from baseline in SGRQ total score at 24 weeks were reported in eight studies (network shown in Fig. S3a). At 24 weeks, BGF MDI showed comparable improvement in SGRQ total score to BDP/GLY/FOR, FF/UMEC/VI, and three open triple combinations (BDP/FOR 200/12 µg BID + TIO 18 µg OD, FP/SAL 500/50 µg BID + TIO 18 µg OD, and FF/VI 100/25 µg OD + UMEC 62.5 µg OD) (Fig. 5a).

Changes at week 24 in TDI focal score were reported in five studies (network shown in Fig. S3b). At 24 weeks, BGF MDI showed comparable improvements in TDI focal score to BDP/GLY/FOR, FF/UMEC/VI, and an open triple combination (FF/VI 100/25 µg OD + UMEC 62.5 µg OD) (Fig. 5b).

Rescue medication use over 12–24 weeks was reported in six studies (network shown in Fig. S3c). Over 12–24 weeks, BGF MDI showed a comparable reduction in mean puffs per day of rescue medication versus BDP/GLY/FOR, FF/UMEC/VI, and an open triple combination (BDP/FOR 200/12 µg BID + TIO 18 µg OD) (Fig. 5c).

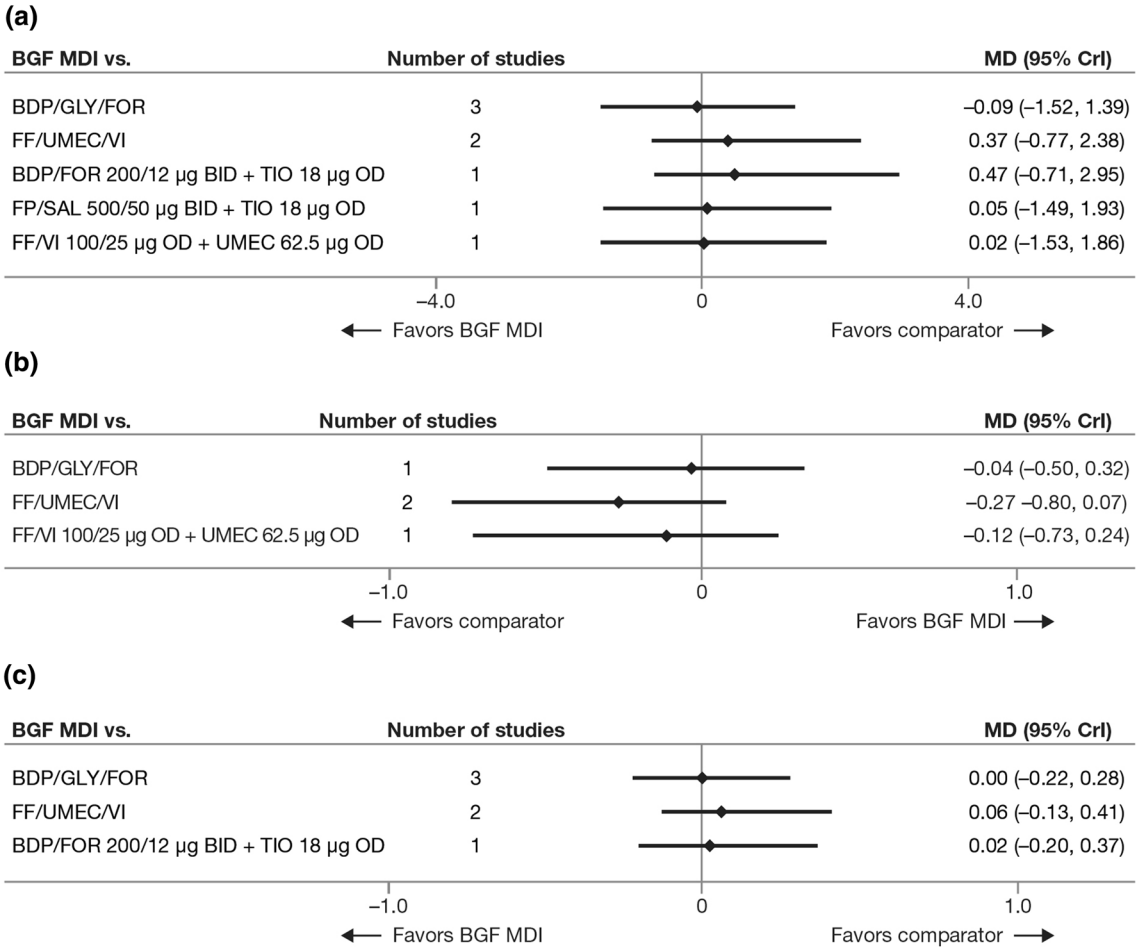

Fig. 5 Health-related quality of life and symptom endpoints. (**a**) Change from baseline in SGRQ total score at 24 weeks, (**b**) TDI focal score at 24 weeks, and (**c**) change from baseline in daily rescue medication use over 12–24 weeks. Fixed-dose combinations are represented with "/" between components; open combinations are represented with "+" between components. *BDP* beclomethasone dipropionate, *BGF* budesonide/glycopyrronium/formoterol fumarate, *CrI* credible interval, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium, *MD* mean difference, *MDI* metered dose inhaler, *SAL* salmeterol, *SGRQ* St. George's Respiratory Questionnaire, *TDI* Transition Dyspnea Index, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

Inconsistency Testing

Where feasible, assessments of inconsistency were performed. For the majority of outcomes, no direct comparisons were available, so statistical inconsistency checks between direct and indirect comparisons were not possible. For moderate/severe exacerbations, the results of the consistency assessment indicated no inconsistency between direct and indirect estimates for all comparisons, i.e., the 95% confidence intervals for the inconsistency estimates contained 0.

Sensitivity Analyses and Meta-Regression

Meta-regression and sensitivity analyses were conducted to examine the impact of heterogeneity across the studies included in the NMA. Analyses of lung function, symptom, and exacerbation outcomes, including open-label studies produced results in line with the base-

case model, which only included double-blind studies (Table S4). The studies included in the base-case were conducted entirely in symptomatic patients, with the exception of one study that assessed the open combination budesonide (BUD)/FOR + TIO [31] and two studies that assessed open combinations of FP, SAL, and TIO [26, 32]. Sensitivity analyses excluding these studies produced findings in line with the base-case model for all comparisons (Table S4). There was no statistically significant association between the covariates assessed in the meta-regression and treatment effects on severe exacerbations, which indicated that no linear relationship could be demonstrated between these covariates and treatment effect size (Table S5). For moderate/severe exacerbations, there were no significant associations with BMI, disease severity, or prior exacerbation history, but there was a significant negative association with current smokers at baseline (Table S5). For both endpoints, results from the meta-regression were broadly similar to the base-case NMA. None of the covariate-adjusted models offered notable improvement in between-study variability compared to 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.

DISCUSSION

This SLR and NMA compared the efficacy of BGF MDI with other triple ICS/LAMA/LABA fixed-dose or open combinations in the treatment of mostly symptomatic patients with moderate to very severe COPD. NMAs are increasingly recognized as an essential form of evidence in developing healthcare guidelines, especially in areas of clinical practice where direct head-to-head trials are lacking [35, 36]. To date, three triple fixed-dose combinations have been developed and, as yet, no head-to-head trials of these therapies have been performed. Therefore, this NMA provides important context for healthcare providers and payers in evaluating the current evidence regarding triple therapies in COPD. Our findings suggested that the efficacy of BGF MDI is comparable with all other fixed-dose (BDP/GLY/FOR and FF/UMEC/VI) and open triple ICS/LAMA/LABA combination therapies with respect to reducing exacerbation rates and improving lung function, quality of life, and symptoms.

Exacerbations of COPD are associated with significant morbidity and mortality, and reducing the risk of future exacerbations is a key goal of treatment [1, 37]. Reductions in moderate/severe exacerbations and severe exacerbations with BGF MDI were comparable to BDP/GLY/FOR, FF/UMEC/VI, and all open triple combinations evaluated. The effect of BGF MDI in reducing exacerbations in a patient population with high exacerbation risk has been investigated in the phase III ETHOS study, which reported topline results for more than 8500 patients in August 2019 [38]. This study will provide a more considerable body of evidence to evaluate the efficacy and safety profiles of two different doses of BGF MDI (160/18/9.6 μg and 320/18/9.6 μg) and will allow for more precise estimates of the comparison between triple therapies with regard to exacerbation rates [39].

When the relative efficacy of different treatments is comparable, other factors should be considered in choosing the right inhaler for individual patients. COPD medications are available in a variety of device types, including MDIs, dry powder inhalers, smooth mist inhalers, and nebulizers. Each device has advantages and disadvantages; the optimal inhaler for each patient depends on their preferences (e.g., device familiarity, ease of use, size, cost), disease characteristics (e.g., inspiratory flow), and abilities (e.g., hand–breath coordination, grip strength, and dexterity) [1, 40–42]. While this NMA suggests comparable efficacy with fixed-dose and open triple combinations in RCTs conducted in highly controlled settings, real-world studies have reported higher medication adherence and persistence in patients with COPD using fewer inhalers [43–45]. A 12-month retrospective cohort study found higher adherence to triple therapy in patients with COPD who were using two inhalers versus three inhalers [43]. Similarly, a retrospective

observational study of patients with COPD who were receiving LAMA, LABA, and/or ICS therapy in single or multiple inhalers showed that the proportion of adherent patients was higher for single-inhaler users versus multiple inhaler users [44]. Persistence was also higher for single versus multiple inhalers, with a significantly higher risk of discontinuation in users of multiple inhalers [44]. The use of a dual combination inhaler versus two individual inhalers has also been associated with a lower risk of respiratory-related hospitalization and reduced healthcare costs [45]. Together, these studies suggest that in real-world use, fixed-dose combination triple therapies may result in better patient outcomes than open triple therapy with multiple inhalers despite comparable efficacy, owing to improved adherence and persistence. However, to our knowledge, specific comparisons of adherence and persistence for fixed-dose triple therapies versus open triple therapies in real-world use have not yet been reported.

Several limitations of the NMA methodology should be acknowledged. Different ICS/LABAs were grouped under a single treatment class to resolve the disconnected network. While this approach has been used in previous meta-analyses [12, 13], it means that intra-class differences among ICS/LABAs would not have been captured within the analyses. However, intra-class differences in dual therapies were beyond the objective of this NMA.

NMAs and traditional pairwise meta-analyses depend upon an assumption of similarity between the included studies, including in their patient populations, study design, and outcome measures [11]. While the studies included in this NMA were broadly similar, there were some differences in study design and patient populations across studies, including disease severity and exacerbation history. While statistical inconsistency checks were not possible for most outcomes because of the lack of direct comparisons available within the networks, for the one outcome with direct comparisons available (moderate/severe exacerbations), no inconsistency was identified. Potential sources of clinical heterogeneity were explored in sensitivity analyses and meta-regression where possible, and the results were consistent with the base-case scenario. While some outcomes could not be assessed with meta-regression because of a smaller number of studies reporting data, the study populations were broadly similar across studies (moderate to very severe COPD), and the majority of studies included in the NMA were considered to have a low risk of bias. Further research is warranted as additional evidence regarding triple therapies, especially fixed-dose combinations, becomes available.

In conclusion, this NMA of 18 studies suggests that BGF MDI has similar efficacy to other ICS/LAMA/LABA fixed-dose and open combination therapies in reducing exacerbation rates and improving lung function and symptoms in patients with moderate to very severe COPD.

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

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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