Adv Ther (2021) 38:3089–3112
https://doi.org/10.1007/s12325-021-01703-z

ORIGINAL RESEARCH

Efficacy and Safety of Budesonide/Glycopyrronium/Formoterol Fumarate versus Other Triple Combinations in COPD: A Systematic Literature Review and Network Meta-analysis

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Received: January 22, 2021 / Accepted: March 10, 2021 / Published online: April 30, 2021

ABSTRACT

In patients with chronic obstructive pulmonary disease (COPD) who experience further exacerbations or symptoms, despite being prescribed dual long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) or inhaled corticosteroid (ICS)/LABA therapies, triple ICS/LAMA/LABA therapy is recommended. A previous network meta-analysis showed comparable efficacy of the ICS/LAMA/LABA, budesonide/glycopyrronium bromide/formoterol fumarate (BUD/GLY/FOR) 320/18/9.6 μg, to other fixed-dose and open combination triple therapies at 24 weeks in COPD. Subsequently, the ETHOS study was published, including data for 8509 patients, assessing the efficacy and safety of BUD/GLY/FOR over 52 weeks. This network meta-analysis (NMA) was conducted to compare the relative efficacy, safety, and tolerability of BUD/GLY/FOR 320/18/9.6 μg with other fixed-dose and open combination triple therapies in COPD over 52 weeks, including data from ETHOS. A systematic literature review was conducted to identify ≥ 10-week randomized controlled trials, including ≥ 1 fixed-dose or open

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-021-01703-z.

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combination triple-therapy arm, in patients with moderate-to-very severe COPD. The methodologic quality and risk of bias of included studies were assessed. Study results were combined using a three-level hierarchical Bayesian NMA model to assess efficacy and safety outcomes at or over 24 and 52 weeks. Meta-regression and sensitivity analyses were used to assess heterogeneity across studies. Nineteen studies (n = 37,741 patients) met the inclusion criteria of the review; 15 contributed to the base case network. LAMA/LABA dual combinations were combined as a single treatment group to create a connected network. Across all outcomes for exacerbations, lung function, symptoms, health-related quality of life, safety, and tolerability, the efficacy and safety of BUD/GLY/FOR were comparable to those of other triple ICS/LAMA/LABA fixed-dose (fluticasone furoate/umeclidinium/vilanterol and beclomethasone dipropionate/glycopyrronium bromide/formoterol fumarate) and open combinations at or over 24 and 52 weeks. Sensitivity analyses and meta-regression results for exacerbation outcomes were broadly in line with the base case NMA. In this NMA, BUD/GLY/FOR 320/18/9.6 μg showed comparable efficacy versus other ICS/LAMA/LABA fixed-dose or open combination therapies in terms of reducing exacerbation rates and improving lung function, symptoms and health-related quality of life in patients with moderate-to-very-severe COPD, in line with previously published meta-analysis results of triple combinations in COPD. The safety and tolerability profile of BUD/GLY/FOR was also found to be comparable to other triple combination therapies.

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; Safety; Triple therapy

Key Summary Points

In patients with chronic obstructive pulmonary disease (COPD) who experience further exacerbations or symptoms, despite being prescribed dual long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) or inhaled corticosteroid (ICS)/LABA therapies, triple ICS/LAMA/LABA therapy is recommended

The clinical efficacy, safety and tolerability of budesonide/glycopyrronium bromide/formoterol fumarate (BUD/GLY/FOR), delivered via metered dose Aerosphere inhaler, was compared with other triple ICS/LAMA/LABA therapies (in available open or fixed-dose combinations) over 52 weeks in patients with moderate-to-very-severe COPD

BUD/GLY/FOR 320/18/9.6 μg showed comparable efficacy versus other ICS/LAMA/LABA open or fixed-dose combination therapies in terms of reducing exacerbation rates and improving lung function, symptoms and health-related quality of life in patients with moderate-to-very severe COPD, in line with previously published meta-analysis results of triple combinations in COPD

The safety and tolerability profile of BUD/GLY/FOR 320/18/9.6 μg was also comparable to other triple combination therapies

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14186543.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease that leads to airflow limitation and persistent respiratory symptoms and is characterized by exacerbations and commonly presents with multiple comorbidities [1]. The goals of pharmacologic treatments in COPD include reducing symptoms, lowering the risk of exacerbations and reducing the impact an exacerbation might have on a patient with COPD [1]. Patients who have eosinophil counts $\geq$ 100 cells/μl, continuing exacerbations or remain symptomatic despite treatment with dual bronchodilator (long-acting β_2-agonist [LABA]/long-acting muscarinic antagonist [LAMA]) or inhaled corticosteroid (ICS)/LABA combinations, are recommended by the Global Initiative for Obstructive Lung Disease (GOLD) to step up to triple therapy (ICS/LAMA/LABA) [1]. The component parts of triple therapy may be delivered as an 'open' combination in separate devices [2–4] or as a fixed-dose combination (FDC) within a single inhaler [5–8]. To date, there are no head-to-head randomized controlled trials (RCTs) of their relative efficacy in patients with COPD.

In lieu of head-to-head evidence, network meta-analyses (NMA) comparing the efficacy of triple therapy as a class with LAMA/LABA dual therapy or bronchodilator monotherapy have previously been presented [9–11]. Additionally, pairwise meta-analyses have compared triple therapies with ICS/LABA [12, 13] or LAMA/LABA therapies [13].

The ICS/LAMA/LABA budesonide/glycopyrronium bromide/formoterol fumarate (BUD/GLY/FOR), delivered via a metered dose Aerosphere inhaler, is a triple FDC that has been approved for the maintenance treatment of COPD in the US, Europe, China and Japan [14–17]. In the Phase III ETHOS (NCT02465567) and KRONOS (NCT02497001) studies, BUD/GLY/FOR showed benefits in reducing COPD exacerbations and improving lung function and symptoms versus dual LAMA/LABA and ICS/LABA therapies [18, 19]. A recent NMA showed that BUD/GLY/FOR had similar efficacy to other ICS/LAMA/LABA fixed-dose and open combination therapies in reducing exacerbation rates, and improving lung function and symptoms at 24 weeks, in patients with moderate-to-very-severe COPD [20]. Subsequently, the recent ETHOS study has provided a large body of evidence regarding the efficacy and safety of BUD/GLY/FOR over 52 weeks [19], allowing for comparisons with other triple therapies that have been assessed in 1-year studies.

Therefore, the objective of this systematic literature review and NMA was to compare the relative clinical efficacy, safety and tolerability of BUD/GLY/FOR with other triple ICS/LAMA/LABA therapies over 52 weeks in patients with moderate-to-very-severe COPD, including data from the recent ETHOS study.

METHODS

Systematic Literature Review

A systematic literature review was conducted to identify evidence on the efficacy, safety and tolerability of triple ICS/LAMA/LABA open or FDC therapies in patients with moderate-to-very-severe COPD. Open combinations were included as they are a widely available treatment option, and patients currently receiving open triple therapy may be candidates to switch to a triple FDC. The systematic literature review was conducted 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 June 2020. 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 2017 to retrieve studies that have not yet been published in full-text articles or abstracts reporting supplementary results of previously published studies.

Primary eligibility criteria were RCTs of duration $\geq$ 10 weeks, assessing patients

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

Studies to include	
Study designs	Randomized controlled trials (including crossover studies up to the time of crossover)
Population	Age: adults (≥ 40 years old)
	Gender: any
	Race: any
	Disease: moderate-to-very-severe COPD
Interventions	Triple therapies (ICS + LAMA + LABA, both open and fixed combinations including BUD/GLY/FOR, BDP/GLY/FOR, FF/UMEC/VIL and other open triple combinations)
Comparators	Any included intervention
	Dual therapies (ICS + LABA or LAMA + LABA in both open and closed combinations)
	Monotherapies (ICS, LAMA or LABA)
	Placebo/best supportive care/observation
Outcomes	Efficacy and quality of life outcomes
	Lung function (post-bronchodilator FEV_1, trough FEV_1, AUC FEV_1)
	Symptoms/dyspnea (TDI focal score, use of rescue medication)
	Exacerbations (moderate-to-severe or severe)
	HRQoL measurements (SGRQ, EQ-5D-5L)
	Safety outcomes
	Any adverse events
	Any serious adverse events
	Any treatment-related adverse events
	Pneumonia
	Upper respiratory tract infections
	Tolerability outcomes
	All withdrawals
	Withdrawal due to death
	Withdrawal due to adverse events
	Withdrawal due to lack of efficacy
Language	English language studies
Publication timeframe	Database: March 2017 to July 2020

Table 1 continued

Data sources	
Databases	Embase®
	MEDLINE®
	MEDLINE® In-Process
	CENTRAL
Conference search	American Thoracic Society
	European Respiratory Society
	American College of Chest Physicians
Other sources	ClinicalTrials.gov of the US National Institute of Health
	Bibliographic searching using the relevant systematic literature reviews

AUC area under the curve, *CENTRAL* Cochrane Central Register of Controlled Trials, *COPD* chronic obstructive pulmonary disease, *Embase* Excerpta Medica Database, *EQ-5D-5L* 5-level EuroQol 5-dimensional questionnaire, FEV_1 forced expiratory volume in 1 s, *HRQoL* health-related quality of life, *ICS* inhaled corticosteroids, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *MEDLINE* Medical Literature Analysis and Retrieval System Online

≥ 40 years of age with a clinical diagnosis of moderate-to-severe COPD (Table 1). Additionally, for inclusion, studies were required to compare one of the interventions with at least one of the comparators listed in Table 1.

The titles and abstracts of the publications identified in the search were screened, full-text copies of articles judged to be potentially relevant were reviewed, and data for eligible studies were 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.

The methodologic quality of the 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 [21]. The risk of bias was assessed with respect to method of randomization and allocation concealment, comparability of baseline characteristics, blinding, balance of withdrawals between groups, outcomes reporting and statistical analysis.

Network Meta-analysis

The relevant study results were combined using a three-level hierarchical Bayesian NMA, as previously described in Ferguson et al. [20]. For convenience, the methods are summarized here. The methods followed the recommended best practice of the NICE Decision Support Unit for evidence synthesis [22, 23]. The NMA was conducted using WinBUGS (a Markov chain Monte Carlo simulation-based software for Bayesian inference) version 1.4.3. The code was based on that recommended by the NICE Decision Support Unit [24]. The relevant study results were combined using a three-level hierarchical Bayesian NMA model that accounted for the exchangeability between treatments

within the same class [25–27]. Individual treatments were classified under different classes as: LAMA monotherapy, ICS + LABA therapy, triple therapy (ICS/LAMA/LABA) and LAMA + LABA (reference treatment). The base case NMA included only double-blind studies.

Underlying treatment effects within each class were assumed to follow a normal distribution with class-specific mean and variance to account for the exchangeability of treatment effects within the same class. An additional scenario analysis was conducted using an independent treatment effect model, wherein the treatment effect is drawn from a treatment-specific underlying distribution.

Results were generated using both random- and fixed-effects models and were compared for goodness of fit to the data, calculated as the overall mean residual deviance. 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.

One of the prerequisites for conducting an NMA is the assumption of consistency between direct and indirect evidence. Inconsistencies between direct and indirect estimates were checked for all outcomes whose networks included closed loops.

A separate NMA was performed for each of the following outcomes: rate of moderate-to-severe exacerbations, rate of severe exacerbations, change from baseline in trough forced expiratory volume in 1 second (FEV_1) at 24 and 52 weeks, change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at 24 and 52 weeks, proportion of SGRQ responders (patients who experienced an improvement in SGRQ total score that met or exceeded the minimum clinically important difference of $\geq$ 4 units) at 24 and 52 weeks, Transition Dyspnea Index (TDI) focal score at 24 and 52 weeks, change from baseline in daily rescue medication use over 52 weeks, adverse events (AEs) (any AEs, serious AEs, upper respiratory tract infections [URTIs] and cases of pneumonia over 52 weeks) and withdrawals (all-cause and due to AE) over 52 weeks.

The NMA model estimated mean differences (MDs) for FEV_1, SGRQ, TDI and rescue medication change from baseline, rate ratios (RRs) for exacerbation outcomes and odds ratios (ORs) for SGRQ responders (defined as improvement in SGRQ score $\geq$ 4 units) and safety/tolerability outcomes. For pneumonia, the NMA was conducted using a risk difference (RD) model in the base case rather than the odds ratio due to the low event rates observed. The number needed to benefit (NNTB; number needed to treat for 1 year to prevent one moderate/severe exacerbation) and the number needed to harm (NNTH; number needed to treat for 1 year for there to be one extra patient with pneumonia) were calculated using the absolute RD between the event or incidence rates in the control group (LAMA/LABA) and the active treatment group (ICS/LAMA/LABA).

For triple combinations where more than one dose level has been studied, results are presented for the dose(s) currently approved and licensed (as a triple FDC or as dual therapy plus monotherapy that can be prescribed as open triple therapy). Studies reporting data at 20–28 weeks were included in the 24-week analyses and those reporting data at 48–-56 weeks were included in the 52-week analyses. For the exacerbation rates, all studies > 10 weeks were included.

Meta-regression and sensitivity analyses account for heterogeneity across studies. A sensitivity analysis was undertaken by adding open-label studies to the base case network of double-blind studies. Sensitivity analyses were also conducted using subgroups according to the following factors: symptomatic population (excluding studies with no requirement for patients to be symptomatic), exacerbation history (excluding studies not requiring prior exacerbation history) and trial duration (excluding studies < 24 weeks). A univariate meta-regression analysis (using age, gender, body mass index (BMI), smoking status, COPD severity and exacerbation history) was performed for exacerbation outcomes.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with

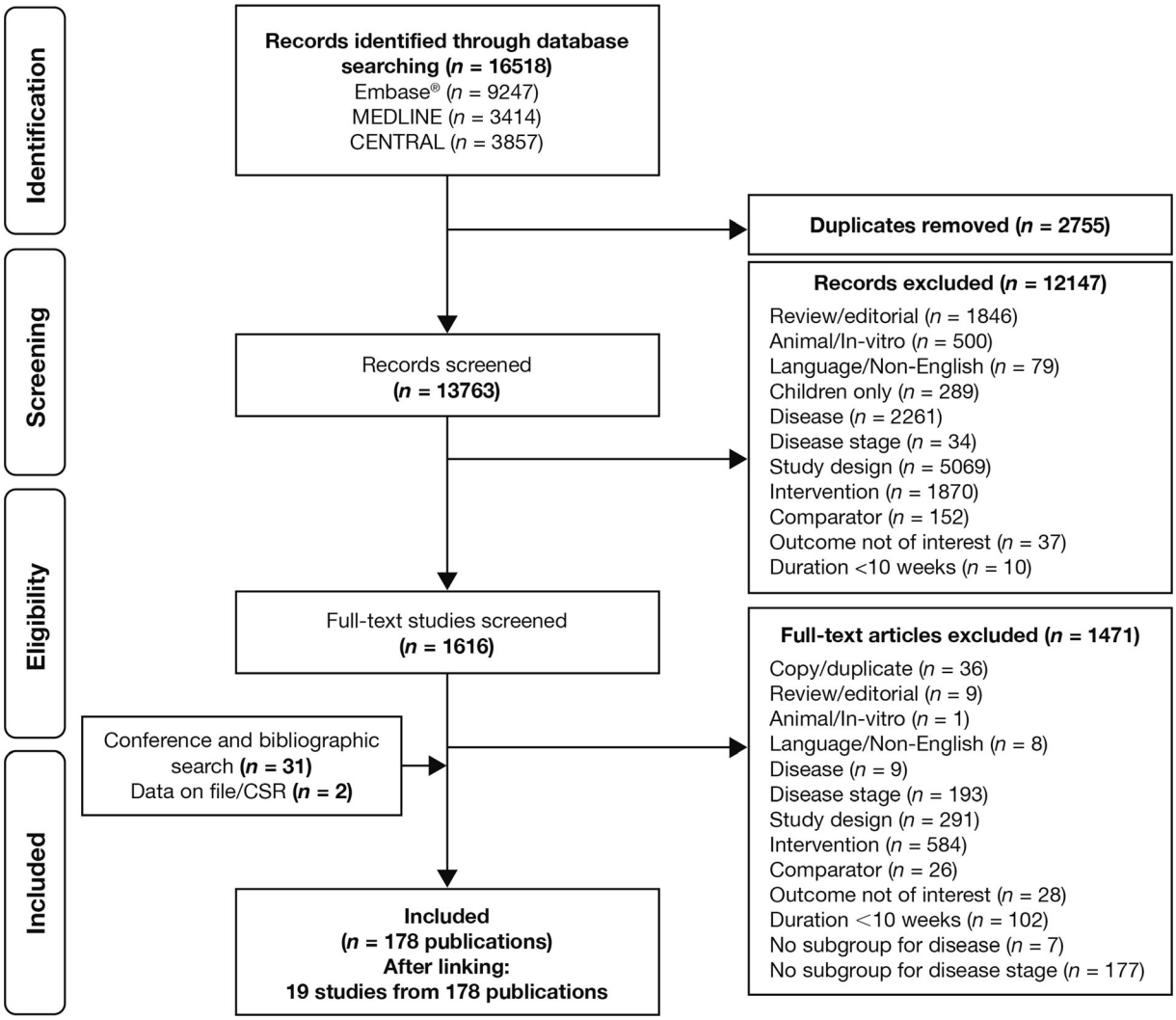

Fig. 1 PRISMA flowchart of study screening process. *CSR* clinical study report

human participants or animals performed by any of the authors.

RESULTS

Study Selection

The systematic literature review process is shown in Fig. 1. Initial database searches identified 16,518 publications, with 2755 removed because of duplication across databases searched. Initial screening reduced eligible publications to 1616, which were subject to full-text review. A further 33 citations were identified from the conference proceedings and bibliographies of identified publications, together with two clinical study reports for BUD/GLY/FOR RCTs. A total of 19 studies from 178 publications met the inclusion criteria of the review. Of these, two studies by Siler et al. [28] met the inclusion criteria; however, they could not be connected in the base-case network, omitting them from the NMA. Additionally, two studies were excluded from the base case (but included in sensitivity analyses) as they were open label [2, 4], leaving a total of 15 double-blind studies that contributed to the base-case network.

Table 2 Study characteristics

Study	Treatment	Patient number	Study duration (weeks)	Primary endpoint	Publication type	Study phase	Blinding	Study setting
Aaron 2007 [41] ISRCTN29870041	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] [42] NCT02729051	FF/UMEC/VIL (FF 100 μg + UMEC 62.5 μg + VIL 25 μg) OD	527	24	Change from baseline in trough FEV_1 at Week 24	Journal article	III	Double-blind	Multicenter
	FF/VIL (FF 100 μg + VIL 25 μg) OD + UMEC 62.5 μg OD	528						
ETHOS [19] NCT02465567	BUD/GLY/FOR (BUD 320 μg + GLY 18 μg + FOR 9.6 μg) BID	2137	52	Annual rate of moderate-to-severe COPD exacerbations	Journal article	III	Double-blind	Multicenter
	BUD/GLY/FOR (BUD 160 μg + GLY 18 μg + FOR 9.6 μg) BID	2121						
	GLY/FOR (GLY 18 μg + FOR 9.6 μg) BID	2120						
	BUD/FOR MDI (BUD 320 μg + FOR 9.6 μg) BID	2131						
FULFIL[a] [43] NCT02345161	FF/UMEC/VIL (FF 100 μg + UMEC 62.5 μg + VIL 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 DPI (BUD 320 μg + FOR 9 μg) BID	899						
Hanania 2012[a] [44] NCT00784550	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] [6] NCT02164513	FF/UMEC/VIL (FF 100 μg + UMEC 62.5 μg + VIL 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/VIL (FF 100 μg + VIL 25 μg) OD	4139						
	UMEC/VIL (UMEC 62.5 μg + VIL 25 μg) OD	2073						

Table 2 continued

Study	Treatment	Patient number	Study duration (weeks)	Primary endpoint	Publication type	Study phase	Blinding	Study setting
KRONOS[a] [18] NCT02497001	BUD/GLY/FOR (BUD 320 μg + GLY 18 μg + FOR 9.6 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 $AUC_{0–4}$ h 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 (GLY 18 μg + FOR 9.6 μg) BID	627						
	BUD/FOR MDI (BUD 320 μg + FOR 9.6 μg) BID	316						
	BUD/FOR DPI (BUD 320 μg + FOR 9 μg) BID	319						
Study 200109[a] [3] NCT01957163	FF/VIL (FF 100 μg + VIL 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/VIL (FF 100 μg + VIL 25 μg) OD + UMEC 62.5 μg OD	206						
	FF/VIL (FF 100 μg + VIL 25 μg) OD	206						
Study 200110[a] [3] NCT02119286	FF/VIL (FF 100 μg + VIL 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/VIL (FF 100 μg + VIL 25 μg) OD + UMEC 62.5 μg OD	206						
	FF/VIL (FF 100 μg + VIL 25 μg) OD	206						
SUNSET[a] [45] NCT02603393	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 54 μg + IND 85 μg) OD	527						
TRIBUTE[a] [8] NCT02579850	BDP/GLY/FOR (BDP 174 μg + GLY 18 μg + FOR 10 μg) BID	764	52	Annual rate of moderate-to-severe COPD exacerbations over 52 weeks	Journal article	III	Double-blind	Multicenter international
	GLY/IND (GLY 54 μg + IND 85 μg) OD	768						
TRILOGY[a] [5] NCT01917331	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						

Table 2 continued

Study	Treatment	Patient number	Study duration (weeks)	Primary endpoint	Publication type	Study phase	Blinding	Study setting
TRINITY[a] [46] NCT01911364	BDP/GLY/FOR (BDP 200 μg + GLY 25 μg + FOR 12 μg) BID	1078	52	Moderate-to-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 [47] NCT00496470	BUD/FOR DPI (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 [48] NCT00975195	FP 500 μg BID + SAL 50 μg BID + TIO 18 μg OD	1244	52	Time to the first moderate-to-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						
Not included in the base case network								
Jung 2012 [2]	FP/SAL (FP 250 μg + SAL 50 μg) BID + TIO 18 μg OD	237	24	Change from baseline in pre-bronchodilator FEV_1 at Week 24	Journal article	IV	Open- label	Multicenter
	TIO 18 μg OD	242						
Lee 2016 [4] NCT01397890	BUD/FOR DPI (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] [28] NCT01772134	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] [28]	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
NCT01772147	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						

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; *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 bromide, *IND* indacaterol, *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, *VIL* vilanterol trifenatate

[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) [48]

Study Characteristics

All 19 studies identified in the systematic literature review were multicenter, the majority were phase III, two were open label, and the remainder were double blind; the majority were 24 or 52 weeks in duration (Table 2; Table S2).

The majority of studies included in the NMA were adjudged to pose a low risk of bias with respect to randomization, baseline characteristics, balance of withdrawals between groups and statistical methodology (Table S3). The two open-label studies, which were excluded from the base case, were associated with a high risk of performance and detection bias [2, 4].

Analysis Assumptions

Comparison of triple therapies using all treatments as reported was not possible because of the absence of a common comparator between treatments of interest, which prevented the formation of an interlinking network (Fig. 2a). To resolve the disconnected network, LAMA/LABA combinations were grouped into a single treatment node on the assumption that each has a comparable efficacy in moderate-to-severe COPD, as supported by multiple, previously published meta-analyses [29–32], allowing an interlinked network to be created (Fig. 2b).

Patient Baseline Clinical Characteristics

A total of 37,741 evaluable patients contributed to the NMA. Average patient characteristics of the included double-blind studies were similar in terms of age, gender, BMI, smoking status and disease duration, but differences were noted in race (likely as a result of different regional recruitment), symptom burden, COPD severity and exacerbation history. The patient characteristics of two open-label studies differed from double-blind studies in terms of gender, disease duration, race and BMI parameters (Table 3).

Adjustment for differences in important treatment effect modifiers using meta-regression was carried out for exacerbation endpoints, as the number of studies contributing to each NMA was limited for other outcomes. Twelve of

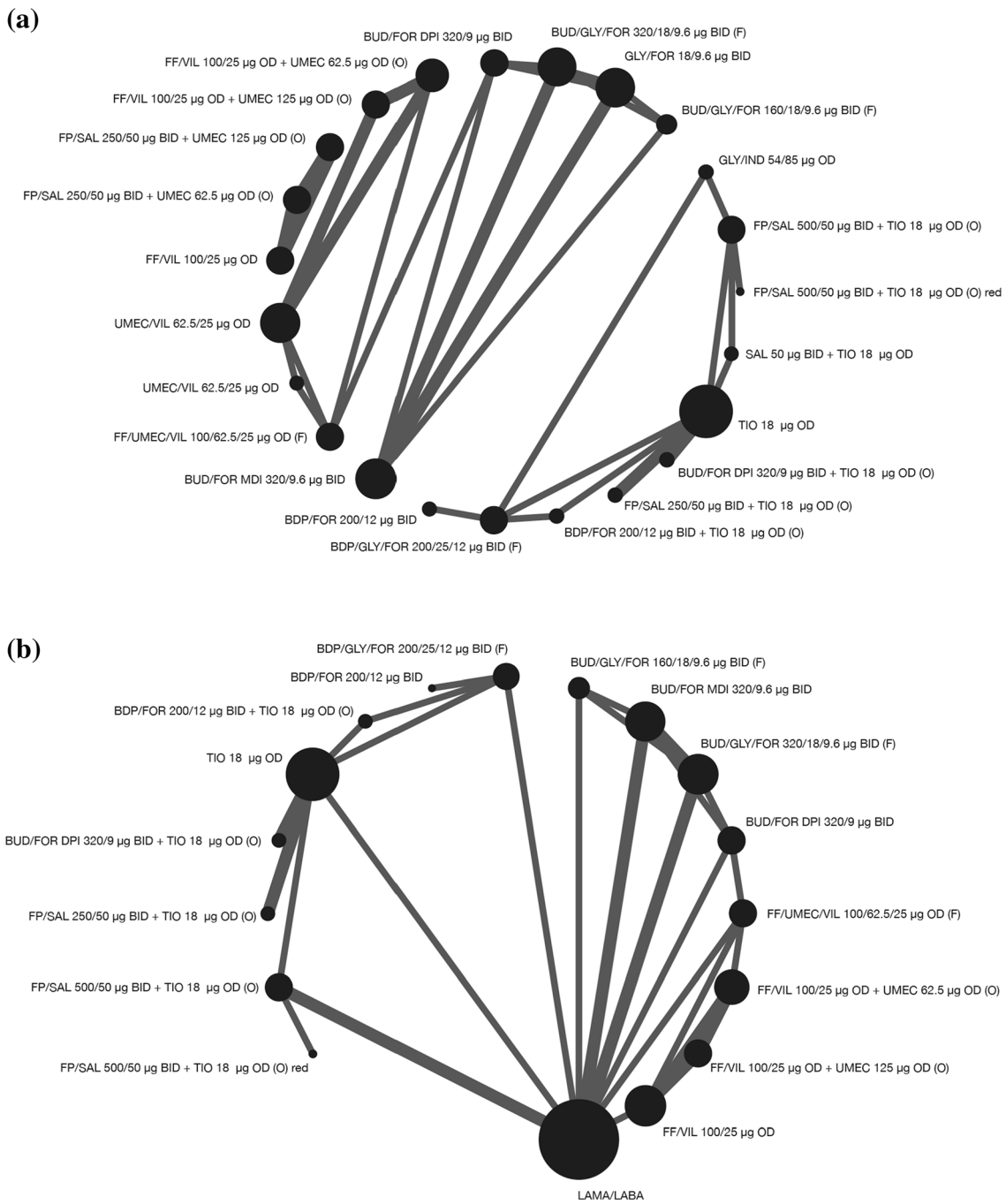

Fig. 2 Networks using treatments as reported (**a**) and using all LAMA/LABA treatments as a single treatment group (**b**). *BDP* beclomethasone dipropionate, *BID* twice daily, *BUD* budesonide, *DPI* dry powder inhaler, *F* fixed-dose combination triple therapy, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium bromide, *IND* indacaterol, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *MDI* metered dose inhaler, *O* open triple therapy, *OD* once daily, *red* reducing dose of fluticasone, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VIL* vilanterol trifenatate

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-to-severe exacerbation history, ≥ 1 exacerbations (%)	Mean CAT score	Mean mMRC score
Aaron 2007 [41]	68	56	98	NR	28	28	NR	100	NR	NR
Bremner 2018[a] [42]	66	75	NR	NR	38	NR	< 1/35/49/15	100	19.9	NR
FULFIL[a] [43]	64	74	85	NR	44	27	< 1/33/54/13	65	19.1	NR
ETHOS [19]	65	60	85	8	41	27	NA/29/61/11	100	19.6	NR
Hanania 2012[a] [44]	61	47	96	7	58	27	NA/68/32/NA	29[b]	NR	2.5
IMPACT[a] [6]	65	66	78	NR	35	27	< 1/36/48/16	100	20.1	NR
KRONOS[a] [18]	65	71	50	7	40	26	< 1/49/43/8	26	18.3	NR
Study 200109[a] [3]	64	66	98	NR	42	28	NA/40/46/14	15[b]	16.6	2.5
Study 200110[a] [3]	63	63	86	NR	57	27	NA/48/41/11	14[b]	17.6	2.3
SUNSET[a] [45]	65	71	100	8	42	28	NA/70/30/NA	34	NR	NR
TRIBUTE[a] [8]	64	72	92	8	45	26	NA/NA/79/20	100	21.2[c]	NR
TRILOGY[a] [5]	64	76	100	8	47	26	NA/NA/77/23	100	20.8	NR
TRINITY[a] [46]	63	76	99	8	48	26	NA/NA/79/21	100	21.6	NR
Welte 2009 [47]	62	75	NR	6[d]	44	26	NA/25/64/11	100	NR	NR
WISDOM [48]	64	82	81	8	33	25	< 1/< 1/61/38	100	NR	1.8
Not included in the base-case network										
Jung 2012 [2]	67	98	NR	NR	NR	22	NA/58/38/3	NR	NR	NR
Lee 2016 [4]	67	96	NR	5	NR	21	NA/8/74/18	100	NR	NR
Study AC4116135[a] [28]	63	66	88	NR	54	28	NA/46/44/11	21[b]	18.2	2.4
Study AC4116136[a] [28]	65	63	82	NR	38	27	NA/40/48/12	31[b]	17.7	2.4

Baseline characteristics were obtained from publicly available clinical study reports when not available in the primary publication
BMI body mass index, *CAT* COPD assessment test; *COPD* chronic obstructive pulmonary disease, *GOLD* Global Initiative for Obstructive Lung 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-to-severe not reported)
[c] Reported in [49]
[d] Median (mean not reported)

the 17 included studies enrolled only symptomatic patients, and for 10 of the 17 included studies, all enrolled patients had a history of moderate-to-severe exacerbations in the previous year. Subgroup analyses were carried out in both of these subsets.

Efficacy

For each outcome, the findings are presented for all comparisons with data available within the network. The primary objective was to compare BUD/GLY/FOR to other triple combination therapies, but the results for BUD/GLY/FOR versus dual therapies are also provided in the supplementary information.

Exacerbation Rates

Moderate-to-severe and severe exacerbations were reported in 14 and 13 studies, respectively (networks shown in Fig. S1). BUD/GLY/FOR 320/18/9.6 μg showed comparable reductions to two other triple ICS/LAMA/LABA fixed-dose combinations—(beclomethasone dipropionate/glycopyrronium bromide/formoterol fumarate [BDP/GLY/FOR 200/25/12 μg twice daily (BID)] and fluticasone furoate/umeclidinium/vilanterol [FF/UMEC/VIL 100/62.5/25 μg once daily (OD)])—and six open triple combinations for both moderate-to-severe and severe exacerbations (Fig. 3A and B). BUD/GLY/FOR 320/18/9.6 μg significantly reduced moderate-to-severe exacerbation rates versus all dual combination therapies in the network and severe exacerbation rates versus LAMA/LABA (Table S4).

Lung Function

Changes from baseline in trough FEV_1 at 52 weeks were reported in eight studies, respectively (networks shown in Fig. S2). At 52 weeks, BUD/GLY/FOR 320/18/9.6 μg showed comparable improvement in trough FEV_1 to FF/UMEC/VIL, BDP/GLY/FOR and three open triple combinations (Fig. 4).

Similar results were observed for trough FEV_1 at 24 weeks (Figs. S3 and S4). Lung function outcomes for BUD/GLY/FOR 320/18/9.6 μg versus dual combination therapies at 24 and 52 weeks are shown in Table S4. BUD/GLY/FOR 320/18/9.6 μg showed significant improvements in trough FEV_1 versus all dual therapy comparators at both 24 and 52 weeks (Table S4).

Quality of Life and Symptoms

Changes from baseline in total SGRQ score at 52 weeks were reported in eight studies (networks shown in Fig. S5). At 52 weeks, BUD/GLY/FOR 320/18/9.6 μg showed comparable improvement in the total SGRQ score to FF/UMEC/VIL, BDP/GLY/FOR and three open triple combinations (Fig. 5a).

SGRQ responders at Week 52 were reported in six studies. At 52 weeks, BUD/GLY/FOR 320/18/9.6 μg showed a comparable SGRQ responder rate to FF/UMEC/VIL, BDP/GLY/FOR and the open triple therapy comprising tiotropium + beclomethasone dipropionate + formoterol fumarate (BDP/FOR 200/12 μg BID + TIO 18 μg OD; Fig. 5b).

Changes at Week 52 in TDI focal score were reported in four studies. At 52 weeks, BUD/GLY/FOR 320/18/9.6 μg showed comparable improvements in TDI focal score to FF/UMEC/VIL and an open triple combination fluticasone propionate (FP)/salmeterol (SAL) 500/50 μg BID + TIO 18 μg OD (Fig. 5c).

Rescue medication use over 52 weeks was reported in six studies. Over 52 weeks, BUD/GLY/FOR showed comparable reduction in mean puffs per day of rescue medication to FF/UMEC/VIL, BDP/GLY/FOR and the open triple combination BDP/FOR 200/12 μg BID + TIO 18 μg OD (Fig. 5d).

The results for quality of life and symptom outcomes at 24 weeks were similar to the 52-week findings (Figs. S6 and S7). Quality of life and symptom outcomes for BUD/GLY/FOR 320/18/9.6 μg versus dual combination therapies at 24 and 52 weeks are shown in Table S4. BUD/GLY/FOR 320/18/9.6 μg showed significant improvements in SGRQ outcomes and comparable or greater improvements in TDI score and rescue medication versus all dual therapy comparators (Table S4).

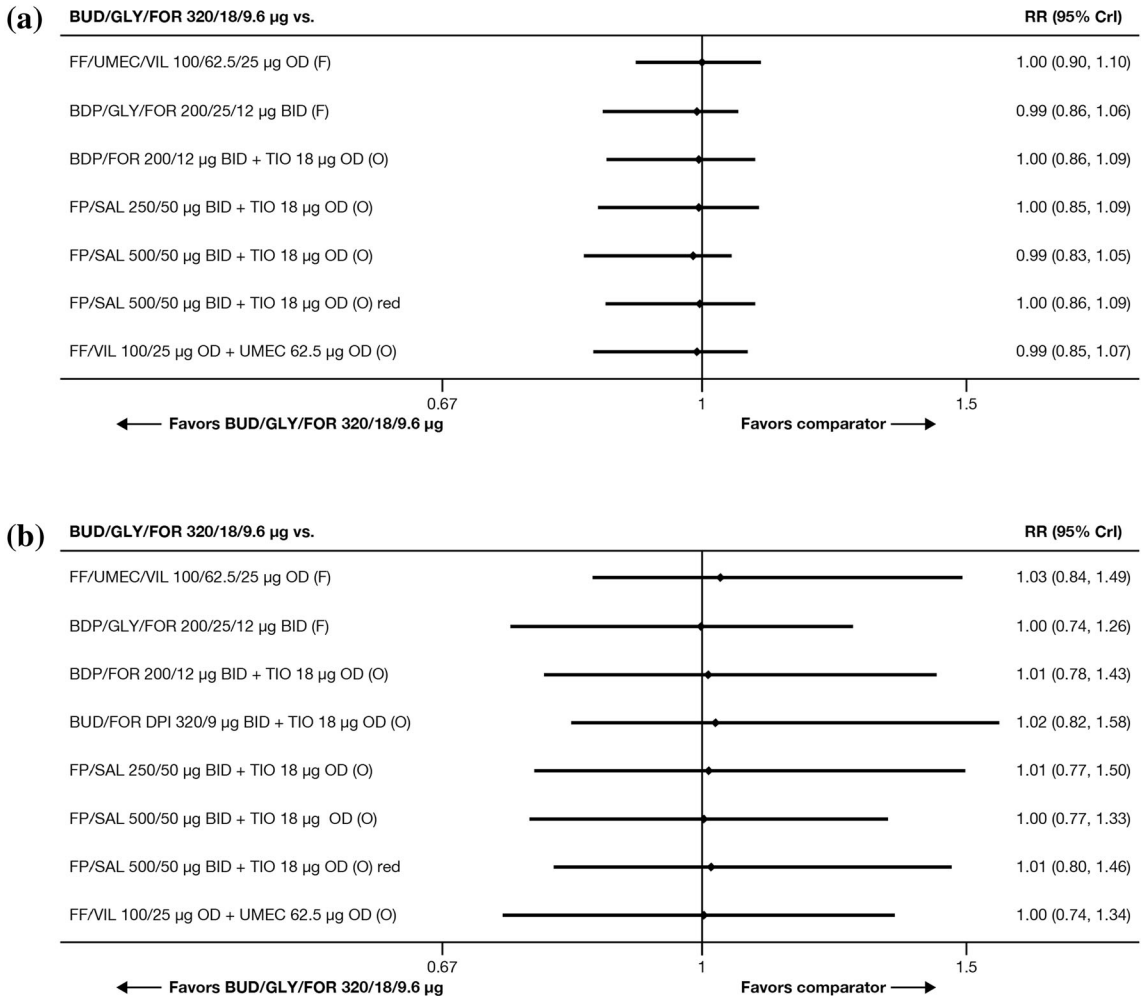

Fig. 3 Rate ratio of moderate-to-severe (**a**) and severe (**b**) exacerbations. Data from REM. *BDP* beclomethasone dipropionate, *BID* twice daily, *BUD* budesonide, *CrI* credible interval, *DPI* dry powder inhaler, *F* fixed-dose combination triple therapy, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium bromide, *O* open triple therapy, *OD* once daily, *red* reducing dose of fluticasone, *REM* random effects model, *RR* rate ratio, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VIL* vilanterol trifenatate

Safety and Tolerability

Networks for safety outcomes are shown in Fig. S8. A total of eight studies presented results for any AE, serious AE and pneumonia (any grade) outcomes, respectively, over 52 weeks. A total of three studies presented results for URTIs over 52 weeks (networks shown in Fig. S8). A comparable safety profile in terms of any AEs, serious AEs, pneumonia and URTIs was observed among BUD/GLY/FOR, FF/UMEC/VIL, BDP/GLY/FOR and all triple combinations, with data available within the network for each of these outcomes (Fig. 6a–d).

A total of eight studies presented results for all withdrawals and withdrawals due to AEs, respectively, at 52 weeks (networks shown in Fig. S9). BUD/GLY/FOR 320/18/9.6 µg showed a comparable tolerability profile to FF/UMEC/VIL, BDP/GLY/FOR and open triple combinations in terms of all-cause withdrawals and withdrawals due to AEs (Fig. 7).

Comparisons of BUD/GLY/FOR 320/18/9.6 µg to dual therapies for safety and

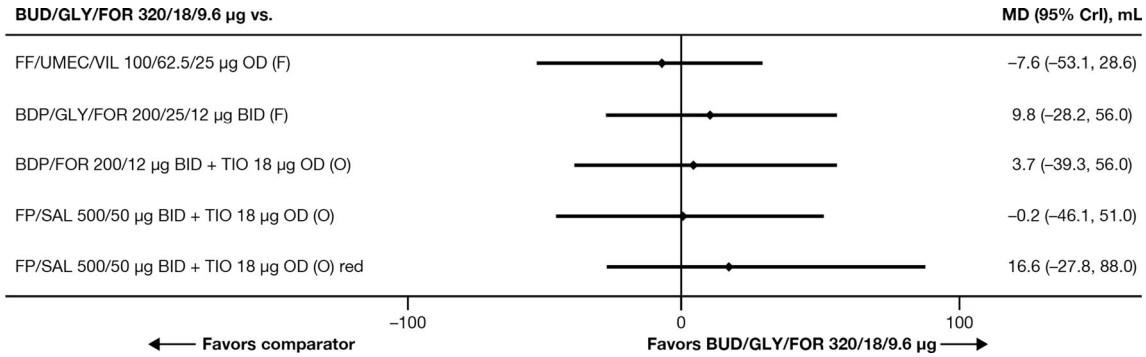

Fig. 4 Change from baseline in trough FEV_1 at 52 weeks. *BDP* beclomethasone dipropionate, *BID* twice daily, *BUD* budesonide, *CrI* credible interval, *F* fixed-dose combination triple therapy, *FEV_1* forced expiratory volume in 1 s, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium bromide, *MD* mean difference, *O* open triple therapy, *OD* once daily, *red* reducing dose of fluticasone, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VIL* vilanterol trifenatate

tolerability outcomes are shown in Table S4. BUD/GLY/FOR 320/18/9.6 µg showed a comparable safety profile to all dual therapy comparators, with the exception of a slightly higher risk of pneumonia and a lower risk of withdrawals and AE withdrawals versus LAMA/LABA (Table S4).

Statistical Heterogeneity and Inconsistency

For the majority of outcomes at 52 weeks, no inconsistency was observed; statistical heterogeneity assessments were not possible because of the limited number of studies. For moderate-to-severe and severe exacerbations, the results of the consistency assessment showed inconsistency and heterogeneity (I^2: 0–92% for moderate-to-severe exacerbations and 0–83% for severe exacerbations). A sensitivity analysis was conducted by excluding studies not requiring prior exacerbation history from the base case network, which removed the inconsistency and heterogeneity and produced comparable conclusions (Tables S5 and S6).

Sensitivity Analyses and Meta-regression

The results of sensitivity analyses were in line with the base-case results for all outcomes (Tables S5–S7). Analyses of lung function and symptom outcomes, including open-label studies, produced results in line with the base-case model, which only included double-blind studies. For exacerbation outcomes, sensitivity analyses and meta-regression findings (including the analysis of exacerbations excluding studies < 24 weeks) were aligned with the base-case model (Tables S5 and S8, respectively). In addition to the base-case class effect models, all outcomes were also analyzed using independent treatment effect models, and the results were generally in line with the base-case analyses for all triple comparisons (Tables S9 and S10).

DISCUSSION

The primary analysis of this systematic literature review and NMA compared the efficacy, safety and tolerability of BUD/GLY/FOR with other triple ICS/LAMA/LABA open or fixed-dose combinations in the treatment of moderate-to-very-severe COPD. Secondary analyses compared BUD/GLY/FOR with dual therapies. NMAs provide important evidence for developing healthcare guidelines and are useful where direct head-to-head trials are lacking [33, 34]; to date, there are no head-to-head trials of triple FDCs. In evaluating the current evidence regarding triple therapies in COPD, this NMA

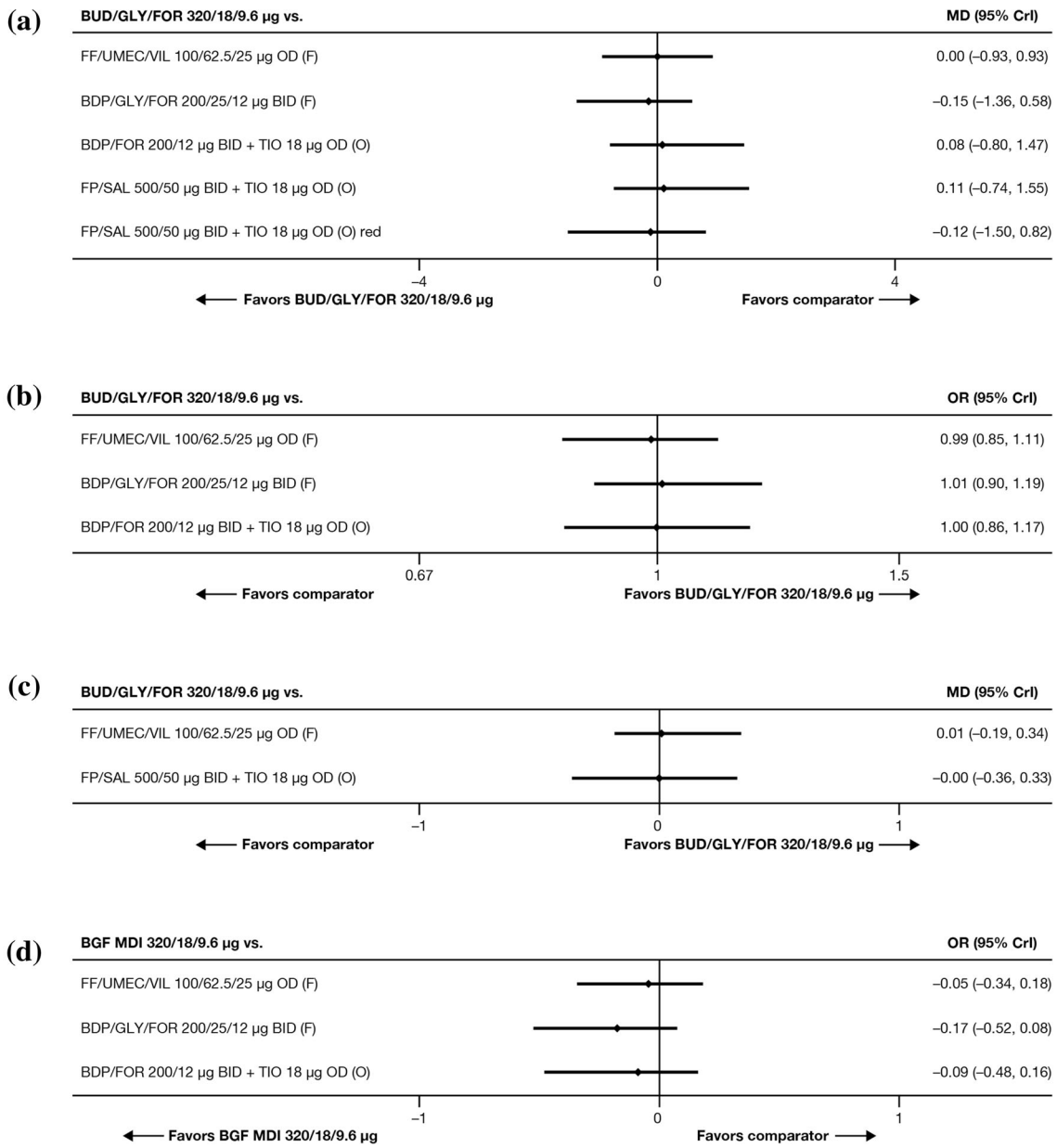

Fig. 5 HRQoL and symptom endpoints. Change from baseline in SGRQ total score (**a**), SGRQ responders (**b**) and TDI focal score (**c**) at 52 weeks; change from baseline in daily rescue medication use over 52 weeks (**d**). *BDP* beclomethasone dipropionate, *BID* twice daily, *BUD* budesonide, *CrI* credible interval, *F* fixed-dose combination triple therapy, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium bromide, *HRQoL* health-related quality of life, *MD* mean difference, *O* open triple therapy, *OD* once daily, *OR* odds ratio, *red* reducing dose of fluticasone, *SAL* salmeterol, *SGRQ* St George's Respiratory Questionnaire, *TIO* tiotropium, *UMEC* umeclidinium, *VIL* vilanterol trifenatate

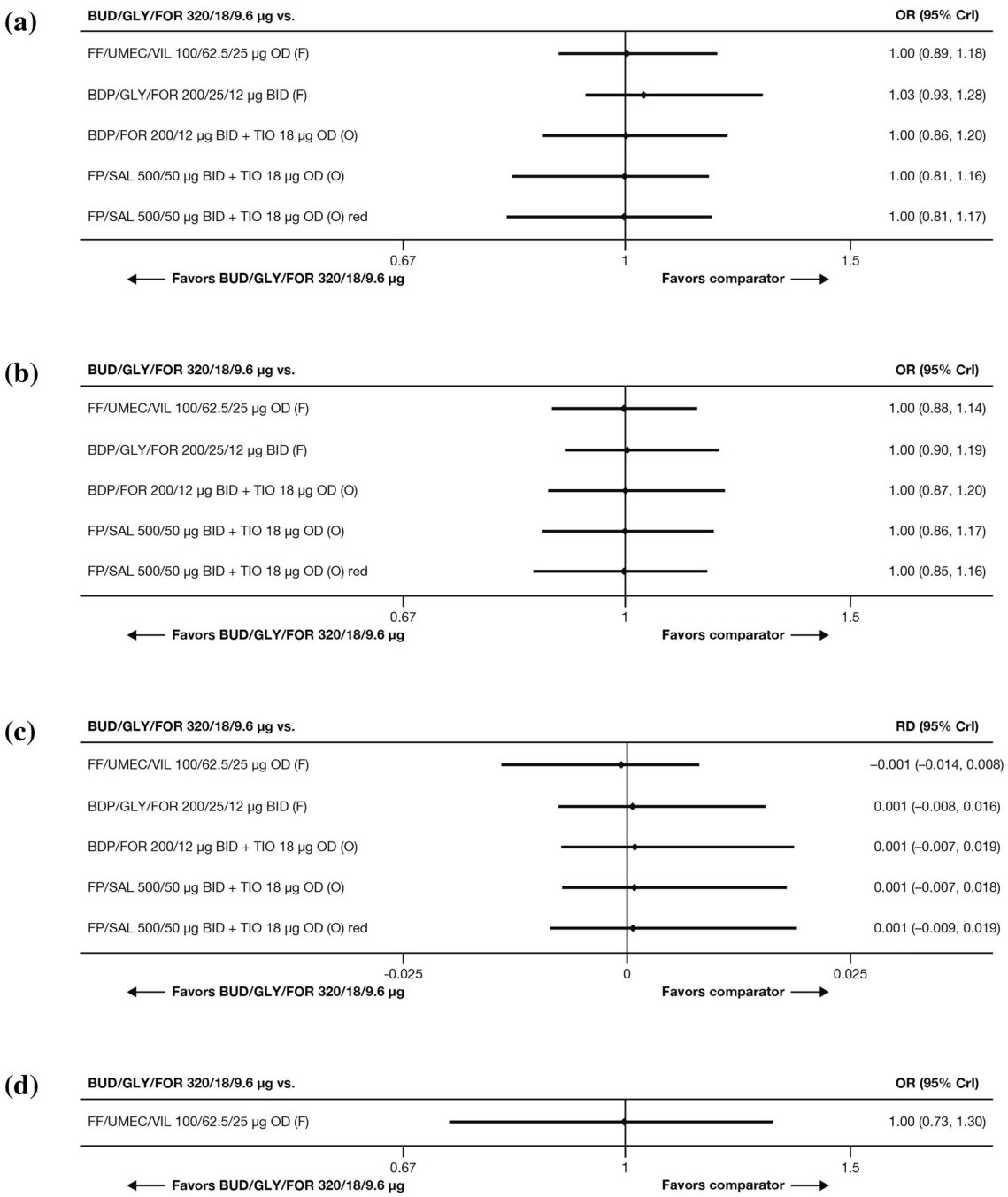

Fig. 6 Safety endpoints. AEs (**a**), SAEs (**b**), pneumonia (any grade) (**c**) and URTI (any grade) (**d**) at 52 weeks. *AEs* adverse events, *BDP* beclomethasone dipropionate, *BID* twice daily, *BUD* budesonide, *CrI* credible interval, *F* fixed-dose combination triple therapy, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium bromide, *O* open triple therapy, *OD* once daily, *OR* odds ratio, *RD* risk difference, *red* reducing dose of fluticasone, *SAEs* serious adverse events *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *URTI* upper respiratory tract infection, *VIL* vilanterol trifenatate

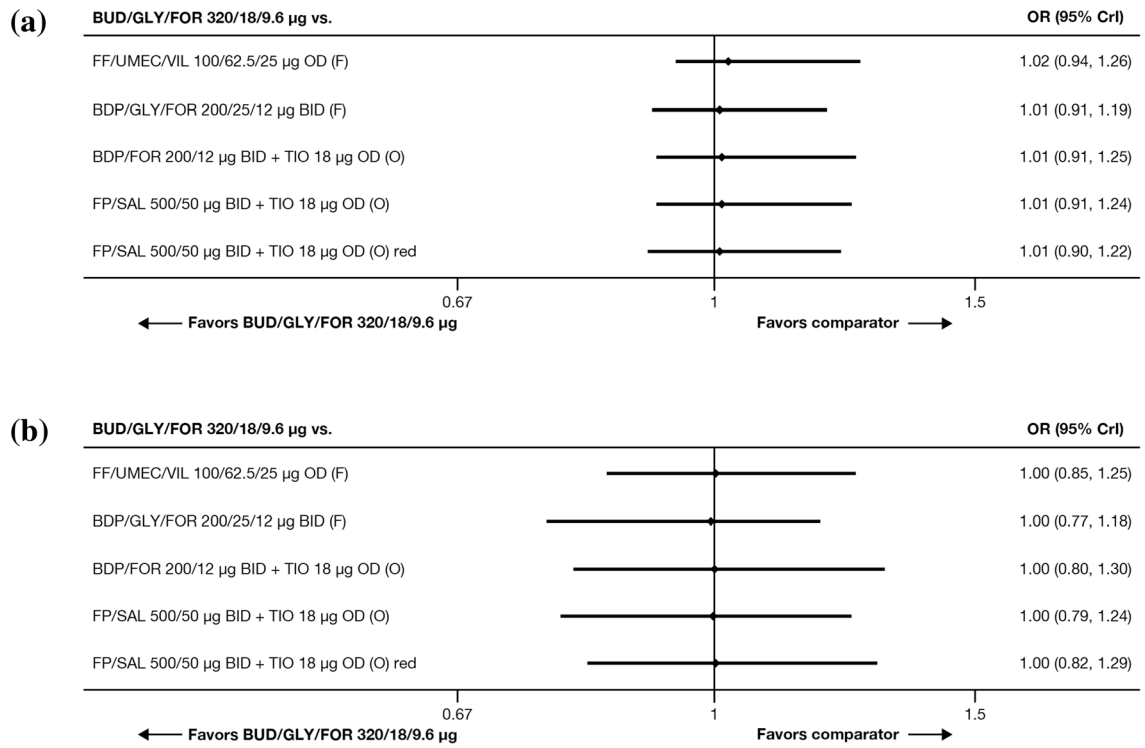

Fig. 7 Tolerability endpoints. All withdrawals (**a**) and withdrawals due to an AE (**b**) at 52 weeks. *AE* adverse event, *BDP* beclomethasone dipropionate, *BID* twice daily, *BUD* budesonide, *F* fixed-dose combination triple therapy, *FF* fluticasone furoate, *FP* fluticasone propionate, *FOR* formoterol, *GLY* glycopyrronium bromide, *O* open triple therapy, *OD* once daily, *OR* odds ratio, *red* reducing dose of fluticasone, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VIL* vilanterol trifenatate

provides important context for healthcare providers and payers.

The findings of this NMA suggested that the efficacy of BUD/GLY/FOR was comparable to all other fixed-dose (FF/UMEC/VIL and BDP/GLY/FOR) and open triple ICS/LAMA/LABA combination therapies with respect to reducing exacerbation rates and rescue medication use and improving lung function, quality of life and symptoms at/over 52 weeks. The addition of the ETHOS study results ($n = 8509$) continued to support the previous findings of Ferguson and colleagues, who found that all fixed-dose and open combinations showed comparable efficacy in reducing exacerbation rates, and improving lung function and symptoms in patients with moderate-to-very-severe COPD at/over 24 weeks [20]. In addition, this was the first NMA to assess tolerability outcomes associated with different triple therapy FDCs. It was shown that BUD/GLY/FOR 320/18/9.6 µg had comparable safety and tolerability profiles to FF/UMEC/VIL and BDP/GLY/FOR, in addition to several available open triple combinations.

Given the similarity of the triple combinations in our NMA, we subsequently calculated the NNTB and NNTH for the triple combinations compared with LAMA/LABA for exacerbation and pneumonia outcomes, as this is a key area of interest for ICS-containing therapies in COPD (Table S11). All fixed-dose and open triple combinations were more effective than LAMA/LABA in reducing moderate-to-severe exacerbations, each with an NNTB of 3–4 (Table S11). BUD/GLY/FOR and FF/UMEC/VIL FDCs were more effective than LAMA/LABA in reducing severe exacerbations, each indicating a NNTB of 3 (Table S11). All fixed-dose and open triple combinations were associated with higher risk of pneumonia compared with LAMA/LABA,

with a comparable NNTH of 61–75 for one extra patient with pneumonia (Table S11). However, these NNT analyses should be interpreted with caution as these were a function of baseline risk, which could vary across trials. It should be noted that when there is no statistically significant difference between treatment groups, the credibility interval contains the potential for both benefit and harm.

The comparability of BUD/GLY/FOR with other fixed-dose and open triple combinations in clinical well-controlled, randomized study settings raises the importance of other factors, such as inhaler device, patient preferences and therapeutic education [1]. While we did not observe any meaningful differences between fixed and open triple combinations in the NMA, a retrospective observational study of patients with COPD who were receiving LAMA, LABA and/or ICS therapy in either single or multiple inhalers showed higher adherence to therapy when delivered via a single inhaler compared with therapy delivered via multiple inhalers [35]. This evidence suggests that triple therapy FDCs may result in better patient outcomes compared with open triple combinations in real-world use. Poor inhaler technique has also been associated with poor disease outcomes in COPD [36], and therefore it is important to ensure that patients are prescribed appropriate inhalers that take into account their preferences, disease characteristics and handling abilities. In a patient survey study, patients forced to switch from a metered dose inhaler (MDI) to a dry powder inhaler (DPI) therapy for non-therapeutic reasons, due to formulary changes, reported substantial morbidity, suggesting that unfamiliarity with a new device may have a negative impact on symptoms and quality of life [37]. Overall, both patient education and familiarity with a device continue to be important aspects in maintaining treatment adherence and positive clinical outcomes in a real-world setting.

An NMA allows many treatments to be connected without the requirement of head-to-head comparisons between treatments required by pairwise analyses [38]; however, several limitations of the NMA methodology should be acknowledged. Different LAMA/LABA combinations were grouped under a single treatment class to resolve the disconnected network. While this approach has been used in previous meta-analyses [4, 5], and differentiating between distinct LAMA/LABAs was not an objective of this NMA, it means that intra-class differences among LAMA/LABA would not have been captured within the analyses. However, numerous previous NMAs have shown no significant differences among the LAMA/LABA class [29–32, 39], particularly with respect to exacerbations or symptom outcomes, suggesting that the assumption of similar efficacy is reasonable. While the studies included in this NMA were broadly similar, there were some differences in study design and patient populations across studies, including symptom requirements and exacerbation history. Potential sources of clinical heterogeneity were explored in sensitivity analyses and meta-regression where possible. Sensitivity analyses excluding studies that did not require a specific symptom burden or previous exacerbation history from the base-case network were in line with the overall findings for exacerbation outcomes. In addition to the base-case class effect models, all outcomes were also analyzed using independent treatment effect models and the results were generally in line with the base-case analyses for all triple comparisons. The study populations were similar across studies (moderate-to-very-severe COPD), and the studies included in the NMA were generally considered to have a low risk of bias. Finally, more data are needed to evaluate the relative efficacy of triple combinations in reducing mortality as the currently available network is sparse and the incidence of fatal events is low in most COPD studies. There are also differences in death reporting across studies; for example, some report mortality as time to event endpoint, while others report data for the proportion of patients who died, making comparison difficult and requiring strong assumptions to perform a network meta-analysis.

CONCLUSION

In conclusion, this NMA showed BUD/GLY/FOR 320/18/9.6 μg to have comparable efficacy to

other ICS/LAMA/LABA open and FDC therapies in terms of reducing exacerbation rates and improving lung function, symptoms and health-related quality of life when studied in RCTs of patients with moderate-to-very-severe COPD. In addition, this NMA was the first to assess safety and tolerability outcomes associated with different triple therapy FDCs and showed BUD/GLY/FOR 320/18/9.6 μg to have a comparable safety and tolerability profile to other ICS/LAMA/LABA open and FDC therapies. Consistent with head-to-head trial data, BUD/GLY/FOR 320/18/9.6 μg showed a significantly better efficacy profile versus dual combinations. The findings of this NMA are aligned with the findings of previously published meta-analysis results of triple combinations in COPD.

ACKNOWLEDGEMENTS

We thank Akanksha Sharma of Parexel International for her valuable contributions to the study.

Funding. This study was supported by AstraZeneca. The sponsor funded the journal's Rapid Service and Open Access fees.

Medical Writing and Editorial Assistance. Medical writing support, under the direction of the authors, was provided by Jake Casson, PhD, of CMC Connect, McCann Health Medical Communications, funded by AstraZeneca in accordance with Good Publication Practice (GPP3) guidelines [40].

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Ulf Holmgren, Mario Ouwens, Martin Jenkins, and Enrico De Nigris made substantial contributions to the conception and design of the study. Barinder Singh and Mohd Kashif Siddiqui performed the meta-analysis. All authors contributed to the interpretation of the data, critically revised the manuscript, approved the final version to be submitted, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures. Arnaud Bourdin reports grants, personal fees, non-financial support, and other from AstraZeneca; grants, personal fees, non-financial support, and other from Boehringer Ingelheim; grants, personal fees, non-financial support, and other from GlaxoSmithKline; personal fees, non-financial support, and other from Novartis; personal fees and non-financial support from Teva; personal fees, non-financial support, and other from Regeneron; personal fees, non-financial support, and other from Chiesi Farmaceutici; grants, personal fees, non-financial support, and other from Actelion; personal fees from Gilead; non-financial support and other from Roche; other from Nuvaira, from null, outside of the submitted work. Nicolas Molinari reports grants and personal fees from AstraZeneca outside the submitted work. Gary T. Ferguson reports grants, personal fees, and non-financial support from AstraZeneca during the conduct of the study; grants, personal fees, and non-financial support from AstraZeneca, Boehringer Ingelheim, Novartis, Pearl – a member of the AstraZeneca Group, and Sunovion; grants and personal fees from Theravance; personal fees from Circassia, GlaxoSmithKline, Innoviva, Mylan, and Verona, outside of the submitted work. Ulf Holmgren, Mario Ouwens, Martin Jenkins and Enrico De Nigris are employees of AstraZeneca and hold stock and/or stock options in the company. Mohd Kashif Siddiqui is an employee of Parexel International. Barinder Singh is a former employee of Parexel International.

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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