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ORIGINAL RESEARCH

Comparative efficacy of combination bronchodilator therapies in COPD: a network meta-analysis

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Background: Several new fixed-dose combination bronchodilators have been recently launched, and assessing their efficacy relative to each other, and with open dual combinations is desirable. This network meta-analysis (NMA) assessed the efficacy of umeclidinium and vilanterol (UMEC/VI) with that of available dual bronchodilators in single/separate inhalers.

Methods: A systematic literature review identified randomized controlled trials of ≥10 weeks among chronic obstructive pulmonary disease patients (≥40 years), assessing the efficacy of combination bronchodilators in single or separate inhalers. Comparative assessment was conducted on change from baseline in trough forced expiratory volume in 1 second (FEV_1), St George's Respiratory Questionnaire (SGRQ) total scores, transitional dyspnea index (TDI) focal scores, and rescue medication use at 12 weeks and 24 weeks using an NMA within a Bayesian framework.

Results: A systematic literature review identified 77 articles of 26 trials comparing UMEC/VI, indacaterol/glycopyrronium (QVA149), formoterol plus tiotropium (TIO) 18 µg, salmeterol plus TIO, or indacaterol plus TIO, with TIO and placebo as common comparators at 12 weeks and approximately 24 weeks. The NMA showed that at 24 weeks, efficacy of UMEC/VI was not significantly different compared with QVA149 on trough FEV_1 (14.1 mL [95% credible interval: −14.2, 42.3]), SGRQ total score (0.18 [−1.28, 1.63]), TDI focal score (−0.30 [−0.73, 0.13]), and rescue medication use (0.02 [−0.27, 0.32]); compared with salmeterol plus TIO on trough FEV_1 (67.4 mL [−25.3, 159.4]), SGRQ total score (−0.11 [−1.84, 1.61]), and TDI focal score (0.58 [−0.33, 1.50]); and compared with formoterol plus TIO 18 µg on SGRQ total score (−0.68 [−1.77, 0.39]). Results at week 12 were consistent with week 24 outcomes. Due to lack of availability of evidence, no comparison was made with formoterol plus TIO on FEV_1 or TDI at 24 weeks.

Conclusion: UMEC/VI has comparable efficacy to other dual-bronchodilator combinations on available efficacy endpoints.

Keywords: LABA/LAMA, UMEC/VI, QVA149, fomoterol, tiotropium, glycopyrronium, indacaterol, umeclidinium

Introduction

Recommendations for COPD treatment are primarily based on the burden of symptoms, categorized using the modified Medical Research Council and COPD assessment test questionnaires, and on risks, assessed based on severity of airflow limitation and history of exacerbations.[1] Studies have shown that coadministration of long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs) is more effective than treatment with either drug class alone in stable COPD as the combination offers improvement in airflow obstruction, dynamic hyperinflation, reduction in rescue medication, and a safety profile that is similar to the components.[2–4]

LABA/LAMA combinations evaluated in clinical studies include open combinations of a LABA such as formoterol (FOR), salmeterol (SAL), or indacaterol (IND)

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and of a LAMA such as tiotropium (TIO), glycopyrronium (GLY), or aclidinium, and newer once-daily (OD), fixed-dose combinations such as umeclidinium and vilanterol (UMEC/VI, Anoro® Ellipta®) and IND/GLY (QVA149, Ultibro® Breezhaler®). Studies have shown that UMEC/VI is well tolerated and offers greater improvements in lung function, health status, and dyspnea scores compared with placebo and better lung function compared with its monotherapy components and TIO.[5–9] UMEC/VI administration in a single inhaler (Anoro® Ellipta®) has been approved by the US Food and Drug Administration and the European Medicines Agency as a OD maintenance treatment for airflow obstruction in patients with COPD.[10] The nominal dose of UMEC/VI is 62.5/25 µg OD per the US label, whereas the actual dose delivered is 55/22 µg mentioned in the European Union label. Similarly, several studies have evaluated the safety and efficacy of other open-combination dual bronchodilators with a variety of dosing regimens, such as FOR + TIO (12 µg metered dose/10 µg delivered dose twice daily (bid) +18 µg OD), SAL + TIO (50 µg bid +18 µg OD), IND + TIO (150 µg +18 µg OD), and QVA149 (nominal dose, 110/50 µg OD; delivered dose, 85/43 µg OD) in patients with moderate-to-very severe COPD.[11–21]

With the recent introduction of a new class of fixed-dose combination bronchodilators (UMEC/VI and QVA149)[22,23] and several others under development, assessing their efficacy relative to each other and with open dual combinations is desirable. Therefore, this study aimed to perform a systematic literature review (SLR) and to synthesize, by means of a Bayesian network meta-analysis (NMA), the published evidence on the efficacy of the fixed combination of UMEC/VI (55/22 µg OD) with that of all available dual-bronchodilator combinations in single or separate inhalers. The relative efficacy of the treatments was assessed at 12 weeks and 24 weeks by means of difference in change from baseline (CFB) on lung function (trough forced expiratory volume in 1 second [FEV_1]), health status (St George's Respiratory Questionnaire [SGRQ] total score), difference in transitional dyspnea index (TDI) focal score, and difference in rescue medication use.

Methods

Data sources

The study protocol was approved by GSK internal protocol review committee. Since the study was based on data extracted from published literature, it was exempt from human subjects review.

An SLR was conducted to identify randomized controlled trials (RCTs) comparing UMEC/VI with alternative LABA/LAMA open and fixed combinations, using appropriate databases and registries from their inception up to April 16, 2014. RCTs in English language were included. A broad search strategy was employed to cover the entire range of available LABA, LAMA, or LABA/LAMA comparators. Details of the databases, selection criteria, and the search strategies are presented in Tables S1 and S2, respectively.

Inclusion criteria and study selection process

Identified abstracts were independently assessed by two reviewers as per predefined selection criteria: patient population – adult COPD patients (age ≥40 years of any race and sex); interventions – UMEC/VI; comparators – LABA/LAMA, placebo, TIO 18 µg (henceforth, TIO = TIO 18 µg); outcomes – FEV_1, SGRQ total scores, TDI focal scores, and rescue medication use; study design – RCTs of ≥10-week duration.

Studies were included in the SLR if they compared interventions of interest in the analysis with each other or with placebo. During the SLR protocol development, it was known that three of UMEC/VI RCTs (clinical study reports provided by GlaxoSmithKline) had TIO as comparator. Due to this, we decided to include TIO as one of the comparators in the selection criteria. Because both TIO and placebo were selected as potential common comparators, studies comparing TIO with placebo were also of interest to strengthen the network.

Data abstraction and quality assessment

For studies that met the selection criteria, the following information was extracted: study design, patient characteristics, types of intervention and comparators, outcomes of interest, and patient withdrawals with reasons for withdrawal.

For each trial, the mean difference in CFB between the arms of interest (or least square mean) and the 95% confidence interval (95% CI), standard error (SE), or standard deviation (SD) were abstracted, where available. If not reported, the difference in CFB was calculated based on the CFB (or least square mean) per treatment arm. If not reported, the SE was imputed using the uncertainty of other trials in the network. A checklist for RCTs based on the guidance by the Institute for Quality and Efficiency in Health Care was used for risk of bias assessment.[24]

An effect modifier is a study or patient characteristic that influences the treatment effect. Because of the randomization process, potential effect modifiers are expectedly balanced between treatment arms within an RCT. However, an NMA involves different trials comparing different interventions. Therefore, the distribution of effect modifiers not only varies

across studies for a particular comparison (heterogeneity) but also between comparisons (inconsistency). Although slight variations in patient characteristics across studies are always expected, an NMA is only valid when no imbalances exist in effect modifiers across comparisons. To reduce the risk of biased outcomes in the NMA, data from only studies that are similar with respect to patient populations and study designs should be compared.[25,26]

The similarity of studies was assessed by evaluating the distribution of patient characteristics and study design across the direct comparisons in the network. If major imbalances in patient or study characteristics were detected that could influence the treatment effect, scenario analysis was used to explore the inhomogeneity. Meta-regression techniques could not be used to adjust for variations due to the limited number of studies available in the network.

Data synthesis

The identified trial evidence was used to perform an NMA within a Bayesian framework to simultaneously synthesize the results of the included studies and to obtain relative treatment effects. A linear model with normal likelihood distribution was used with flat (noninformative) prior distributions assumed for all outcomes. Prior distributions of the relative treatment effects were normal, with zero mean and a variance of 10,000. A uniform distribution ranging from zero to five was used as the prior of the interstudy SD.

For each outcome, fixed- and random-effects models were evaluated. The goodness of fit of each model to the data was assessed using the Deviance Information Criterion. The posterior densities for the outcomes of interest were estimated using the Markov Chain Monte Carlo simulations for each model. The results were based on 80,000 iterations on three chains, with a burn-in of 20,000 iterations. Convergence assessment was based on visual inspection of trace plots. Accuracy of the posterior estimates was assessed using the Monte Carlo error for each parameter (Monte Carlo error $<1\%$ of the posterior SD). The models used in this study were based on those defined by Dias et al[27] and were implemented using WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

The posterior distributions were summarized with the corresponding median values to reflect the most likely value of the estimate, and the 2.5 and 97.5 percentile to capture the 95% credible interval (95% CrI), which represents the range of true underlying effects with 95% probability. Pairwise comparisons for all treatments included in the network were calculated, including the relative effectiveness and the probability of each treatment being better than each of the rest. If studies reported mean values without any measure of uncertainty (SE, SD, 95% CI), scenario analyses were performed excluding this study because of the lack of data; however, such studies were included with the reported mean value and an imputation for the SE.

The feasibility of an NMA to compare LABA/LAMA treatments with each other or with placebo was assessed. Considering the lack of placebo-controlled LABA/LAMA studies, TIO was included in the network to allow indirect comparisons with more treatments of interest. Extending the network by including TIO does have potential advantages such as strengthening inference and producing a more robust analysis. Two sets of analyses were performed, one including only LABA/LAMA treatments and placebo in the network (data not shown) and the other including LABA/LAMA treatments, TIO, and placebo in the network. The second analysis (including TIO) allowed for indirect comparisons with more relevant open and closed dual comparators because many studies lacked a placebo arm.

Results

Search and selection results

In total, 3,006 abstracts were identified, of which, 309 (10.3%) abstracts were of interest based on predefined selection criteria, and full-text articles were obtained (Figure 1). Of the 4,720 identified registries, 159 were included. The registry screening results were merged with the abstracts and were screened against full-text selection criteria. The final NMA evidence base comprised 77 articles relating to 26 trials. These trials represented RCTs comparing LABA/LAMA combinations approved as of April 16, 2014 and TIO with each other or with placebo. The efficacy parameters shared between trials included lung function, defined as a difference in CFB in trough FEV_1 and patient-reported outcomes, such as mean CFB in SGRQ total scores, difference in mean TDI focal scores, and change in rescue medication use estimated as mean number of puffs per day. Changes in efficacy parameters were compared at the 3-month (12-week) and 6-month time points (range, 24–26 weeks), to correspond to the duration of the UMEC/VI comparator trials (Table 1).

An overview of the study design, inclusion criteria, and background treatments of these trials is presented in Table 1. Study participants included individuals aged $\geq$40 years with an established diagnosis of COPD and a smoking history of $\geq$10 pack-years. Patients with moderate-to-very severe (GOLD stages II–IV) COPD, with an FEV_1 of $\leq$70% of predicted normal value, and no inclusion criterion related to the number of exacerbations in the previous year were considered[21]; potential exceptions were the SPARK study,

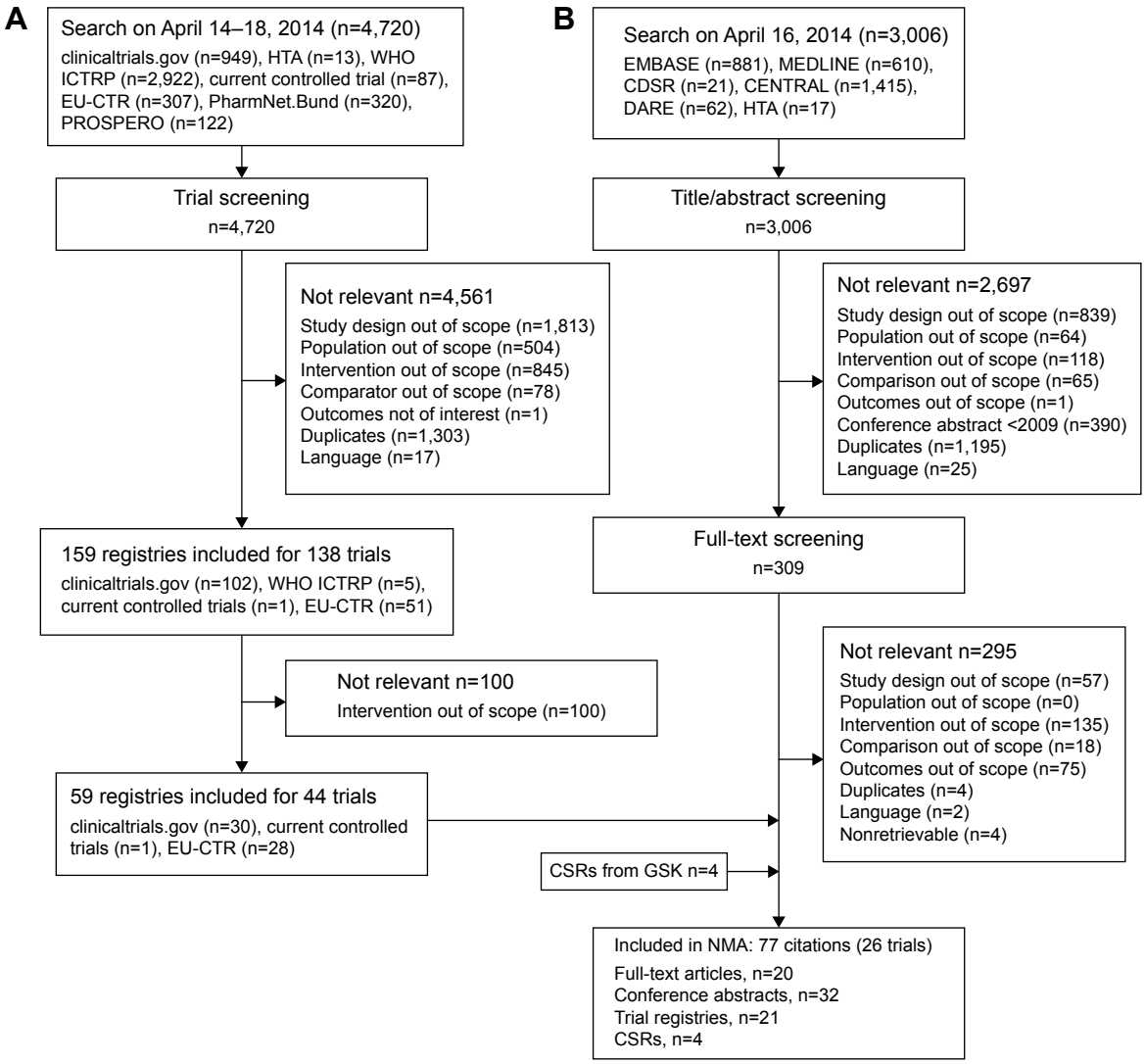

Figure 1 Summary of study-flow (**A**) registries (**B**) study selection.
Abbreviations: CDSR, Cochrane Database of Systematic Review; CSR, clinical study report; DARE, Database of Abstracts of Reviews of Effects; EMBASE, Excerpta Medica dataBASE; EU-CTR, European Union Clinical Trials Register; HTA, Health Technology Assessment Database; GSK, GlaxoSmithKline; MEDLINE, Medical Literature Analysis and Retrieval System Online; NMA, network meta-analysis; PROSPERO, international prospective register of systematic review; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

which included no patients with moderate COPD, but only patients with a history of >1 moderate or severe exacerbation during the past year,[16] and the UMEC/VI studies, all of which included patients who had breathlessness (modified Medical Research Council scale ≥2).[6,9,28] Regarding the background treatments, most of the studies allowed the use of inhaled corticosteroids (ICSs), while the use of LAMAs, LABAs, or LABA/ICS was not allowed.

Table 2 presents an overview of the primary patient characteristics (and potential treatment effect modifiers in COPD), including age, sex, smoking status, ICS use, COPD duration, number of pack-years, predicted FEV_1, and proportion of patients with severe or very severe disease. The patients were primarily male (49%–99%), with a mean age above 60 years (60–68 years) and heavy smokers (36–69.2 pack-years). Some variation in ICS use was detected (25%–76%), with Aaron et al[20] and Tashkin et al[18] reporting that <30% of patients used ICS at baseline in at least one of the treatment arms.

Overall, patient characteristics were comparable between UMEC/VI and other dual-bronchodilator trials. No major imbalances in the study and patient characteristics were observed between direct comparisons in the network that could act as effect modifiers of the relative treatment effects; therefore, an NMA was deemed to be feasible.[26] The results of the risk of bias assessment at study level for all studies included in the NMA are summarized in Table S3.

Table 1 Key study characteristics for all studies included in the NMA (only arms of interest)

Study	Study design	Treatment	Trial duration	Inclusion criteria	Background treatment
Decramer et al[9] (DB2113360)	Phase III multicenter, randomized, double-blind, double-dummy, parallel-group study	Tiotropium 18 μg OD Vilanterol 22 μg/ umeclidinium 55 μg OD	24 weeks	Outpatient; age ≥40 years; diagnosed with COPD; post-salbutamol FEV_1 ≤70% and post-salbutamol FEV_1/FVC ratio <0.7; smoking history ≥10 pack-years	Allowed: ICS at a dose of up to 1,000 μg/day of FP or equivalent, salbutamol/albuterol as rescue medication Not allowed: LABAs, SABAs, short-acting anticholinergics, and SABA/ICS combination products
Decramer et al[9] (DB2113374)	Phase III multicenter, randomized, double-blind, double-dummy, parallel-group study	Tiotropium 18 μg OD Vilanterol 22 μg/ umeclidinium 55 μg OD	24 weeks	Outpatient; age ≥40 years; diagnosed with COPD; post-salbutamol FEV_1/FVC ratio <0.70 and post-salbutamol FEV_1 ≤70%; smoking history ≥10 pack-years	Allowed: ICS at a dose of up to 1,000 μg/day of FP or equivalent, salbutamol/albuterol as rescue medication Not allowed: LABAs, oral SABAs and LABAs, inhaled SABAs, inhaled short-acting anticholinergics, and SABA/ICS combination products
Donohue et al[6] (DB2113373)	Phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Placebo Vilanterol 22 μg/ umeclidinium 55 μg OD	24 weeks	Outpatient; age ≥40 years; diagnosed with COPD; post-salbutamol FEV_1/FVC ratio <0.70 and post-salbutamol FEV_1 ≤70%; smoking history ≥10 pack-years	Allowed: ICS at a dose of up to 1,000 μg/day of FP or equivalent, salbutamol/albuterol as rescue medication Not allowed: LABAs, LABA/ICS combination products, SABAs, short-acting anticholinergics, and SABA/ICS combination products
Maleki-Yazdi et al[28] (ZEP117115)	Phase III multicenter, randomized, double-blind, double-dummy, parallel-group study	Tiotropium 18 μg OD Vilanterol 22 μg/ umeclidinium 55 μg OD	24 weeks	Outpatient; age ≥40 years; diagnosed with COPD; post-salbutamol FEV_1/FVC ratio <0.70 and post-salbutamol FEV_1 ≤70%; smoking history ≥10 pack-years	Allowed: ICS at a dose of up to 1,000 μg/day of FP or equivalent, salbutamol/albuterol as rescue medication Not allowed: LABAs, LABA/ICS combination products, oral SABAs and LABAs, inhaled SABAs, inhaled short-acting anticholinergics, and SABA/ICS combination products
INTRUST 1 (Mahler et al[17])	Randomized, double-blind, controlled, parallel-group study	Tiotropium 18 μg OD Indacaterol 150 μg + tiotropium 18 μg OD	12 weeks	Age ≥40 years; post-bronchodilator FEV_1 ≤65% and ≥30%; post-bronchodilator FEV_1/FVC <70%; smoking history ≥10 pack-years	Allowed: ICS monotherapy, salbutamol/albuterol as rescue medication Not allowed: LABAs, SABAs (except those prescribed in the study), theophylline, and anticholinergics
INTRUST 2 (Mahler et al[17])	Randomized, double-blind, controlled, parallel-group study	Tiotropium 18 μg OD Indacaterol 150 μg + tiotropium 18 μg OD	12 weeks	Age ≥40 years; post-bronchodilator FEV_1 ≤65% and ≥30%; post-bronchodilator FEV_1/FVC <70%; smoking history ≥10 pack-years	Allowed: ICS monotherapy, salbutamol/albuterol as rescue medication Not allowed: LABAs, SABA (except those prescribed in the study), theophylline, and anticholinergics
Aaron et al[20]	Randomized, double-blind, placebo-controlled study	Tiotropium 18 μg OD + salmeterol 25 μg 2 puffs bid Tiotropium 18 μg OD + placebo 2 puffs bid Tiotropium 18 μg OD + fluticasone 250 μg/ salmeterol 25 μg 2 puffs bid	52 weeks	Age ≥35 years; diagnosed with moderate or severe COPD; ≥1 exacerbation of COPD requiring systemic steroids or antibiotics in previous 12 months; smoking history ≥10 pack-years; post-bronchodilator FEV_1 ≤65%; FEV_1/FVC <70%.	Allowed: albuterol for relief of symptoms Not allowed: ICS, LABAs, and anticholinergics
ENLIGHTEN (Dahl et al[13])	Multicenter, randomized, double-blind, parallel-group, placebo-controlled study	Placebo QVA149 (indacaterol 110 μg/glycopyrronium 50 μg) OD	52 weeks	Age ≥40 years; diagnosed with moderate or severe COPD (stage II or III according to GOLD 2008 criteria); post-bronchodilator FEV_1 <80% and ≥30%; post-bronchodilator FEV_1/FVC <0.70; smoking history ≥10 pack-years	Allowed: albuterol as rescue medication, ICS monotherapy Not allowed: long-acting bronchodilators (LABAs, LAMAs, theophylline) and short-acting muscarinic antagonists

(*Continued*)

Table 1 (*Continued*)

Study	Study design	Treatment	Trial duration	Inclusion criteria	Background treatment
SPARK (Wedzicha et al[16])	Multicenter, randomized, double-blind, parallel-group, active-controlled study	Tiotropium 18 µg OD QVA149 (indacaterol 110 µg/glycopyrronium 50 µg) OD	64 weeks	Age ≥40 years; diagnosed with severe or very severe COPD (stage III or IV according to GOLD 2008 criteria); post-bronchodilator FEV_1 <50%; FEV_1/FVC <0.70; ≥1 exacerbation in the previous 12 months requiring systemic corticosteroids or antibiotics; smoking history ≥10 pack-years	Allowed: salbutamol, stable dose of ICS Not allowed: long-acting bronchodilators
SHINE (Bateman et al[11])	Multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled (open-label) study	Placebo Tiotropium 18 µg OD QVA149 (indacaterol 110 µg/glycopyrronium 50 µg) OD	26 weeks	Age ≥40 years; diagnosed with moderate or severe COPD (stage II or III according to GOLD 2008 criteria); post-bronchodilator FEV_1 <80% and ≥30%; post-bronchodilator FEV_1/FVC <0.70; smoking history ≥10 pack-years	Allowed: salbutamol/albuterol as rescue medication, inhaled or intranasal corticosteroids in constant doses Not allowed: LABAs, LAMAs, and LABA/ICS
Vogelmeier et al[19]	Randomized, partially blinded, placebo-controlled study	Formoterol 10 µg bid + tiotropium 18 µg OD Tiotropium 18 µg OD Placebo	24 weeks	Diagnosed with stable COPD; age ≥40 years at COPD onset; smoking history ≥10 pack-years; FEV_1 <70% of patient's predicted normal value (and ≥1.00 L); FEV_1/FVC <70%	Allowed: salbutamol, ICS monotherapy
Tashkin et al[18]	Active-controlled, double-blind, multicenter study	Tiotropium 18 µg OD + formoterol 12 µg bid Tiotropium 18 µg OD + placebo bid	12 weeks	Age ≥40 years; post-bronchodilator FEV_1 <70% and >30% of the predicted normal value or >0.75 L, whichever was lesser at run-in; FEV_1/FVC <0.70	Continued use of prior stable ICS regimens and systemic corticosteroids for the treatment of exacerbations was permitted throughout the study. All patients were provided with albuterol inhalers for use as rescue medication.
Chan et al[36] BI trial: 205.259	Randomized, double-blind, parallel-group study	Tiotropium 18 µg OD Placebo	48 weeks	Age ≥40 years; smoking history ≥10 pack-years; FEV_1 ≤65%; FEV_1/FVC ≤70%; included if ≥1 exacerbation noted during the previous year, but not within 6 weeks prior to treatment (later amended to include 1 exacerbation in past 2 years)	Allowed: stable dose of oral corticosteroids, ICS, theophylline preparations, mucolytic preparations (not containing bronchodilators), LABAs
TIPHON (Tonnel et al[37])	Randomized, double-blind, multicenter study	Tiotropium 18 µg OD Placebo	36 weeks	Age ≥40 years; smoking history >10 pack-years; FEV_1 20%–70%; FEV_1/FVC ≤70%;	Allowed: stable doses of theophylline preparations (excluding 24-hour preparations), mucolytics, ICS, and oral steroids
UPLIFT (Tashkin et al[38] and Celli et al[39])	Placebo-controlled study and randomized, double-blind study	Tiotropium 18 µg OD Placebo	4 years	Age ≥40 years; smoking history >10 pack-years; FEV_1 ≤70%; FEV_1/FVC ≤70%; excluded if exacerbation observed 4 weeks prior	Allowed: all respiratory medications, except other inhaled anticholinergic drugs
Niewoehner et al[40]	Randomized, double-blind study	Tiotropium 18 µg OD Placebo	6 months	Age ≥40 years; smoking history ≥10 pack-years; FEV_1 ≤60%; FEV_1/FVC ≤70%; excluded if no recovery from exacerbation ≥30 days prior	Allowed: all other respiratory medications (including ICS and LABAs) Not allowed: open-label anticholinergic bronchodilators
Brusasco et al[41]	Randomized, placebo-controlled, double-blind, double-dummy study	Tiotropium 18 µg OD Placebo	24 weeks	Age >40 years; smoking history >10 pack-years; FEV_1 ≤65%; FEV_1/FVC ≤70%	NR

Donohue et al[29]	Randomized, placebo-controlled, double-blind, double-dummy, parallel-group study	Tiotropium 18 μg OD Placebo	24 weeks	Age ≥40 years; smoking history >10 pack-years; FEV_1 ≤60%; FEV_1/FVC ≤70%	Allowed: regular ICS and oral steroids Not allowed: inhaled anticholinergic LABAs
Casaburi et al[42]	Randomized, double-blind placebo-controlled study	Tiotropium 18 μg OD Placebo	56 weeks	Age ≥40 years; smoking history ≥10 pack-years; FEV_1 ≤65%; FEV_1/FVC ≤70%	Allowed: stable doses of theophylline, ICS, and oral prednisone
Donohue et al[43]	Randomized, double-blind study	Tiotropium 18 μg OD Placebo	26 weeks	Patients aged ≥40 years; smoking history ≥20 pack-years; diagnosed with moderate-to-severe COPD (GOLD criteria) were enrolled. Post-bronchodilator (within 30 minutes of inhaling albuterol 360 μg) FEV_1 <80% and ≥30% of the predicted normal value; FEV_1/FVC <70%	Patients could continue ICS monotherapy if stable for 1 month before screening; dose and regimen were kept stable throughout the study. Before the start of the run-in period, treatment with anticholinergic bronchodilators or with β2-agonists was discontinued with appropriate washout, and patients receiving fixed-combination β2-agonists/ICS were switched to ICS monotherapy at an equivalent dose. All patients were provided albuterol for use as needed
GLOW 2 (Kerwin et al[44])	Randomized, placebo-controlled study	Tiotropium 18 μg OD Placebo	52 weeks	Patients aged ≥40 years; any sex; smoking history ≥10 pack-years; diagnosed with moderate-to-severe stable COPD; post-bronchodilator FEV_1 ≥30% and <80% of the predicted normal value; post-bronchodilator FEV_1/FVC <0.70 were enrolled	Allowed: inhaled or intranasal corticosteroids and H1 antagonists, salbutamol/albuterol as rescue medication Not allowed: LAMAs (at least 7 days before run-in), LABAs or LABA/ICS combinations (at least 48 hours before run-in)
Verkindre et al[45]	Randomized, placebo-controlled study	Tiotropium 18 μg OD Placebo	12 weeks	FEV_1 ≤50%; FEV_1/FVC ≤70%; residual volume ≥125%; excluded if unstable doses of oral corticosteroids received 6 weeks prior	Allowed: stable-dose oral corticosteroids, ICS, theophylline preparations, mucolytic agents Not allowed: SABAs, oral β2-agonists, or LABAs
Casaburi et al[46]	Randomized, double-blind, placebo-controlled, multicenter study	Tiotropium 18 μg OD Placebo	13 weeks	Age ≥40 years; diagnosed with COPD defined by ATS; smoking history >10 pack-years; FEV_1 ≤65%; FEV_1/FVC ≤70%	Allowed: stable doses of theophylline, ICS, oral prednisone Not allowed: other inhaled or oral bronchodilators
Covelli et al[47]	Randomized, double-blind, placebo-controlled, parallel-group study	Tiotropium 18 μg OD Placebo	12 weeks	FEV_1 ≤60%; FEV_1/FVC ≤70%; excluded if exacerbation during 6 weeks prior	Allowed: ICS, LABAs, and theophyllines Not allowed: cromones, leukotriene antagonists, and inhaled anticholinergics
Garcia et al[48]	Randomized, double-blind, placebo-controlled study	Tiotropium 18 μg OD Placebo	12 weeks	Ambulatory patients of either sex; age >40 years; diagnosed with COPD (FEV_1 <60% of the predicted value and FEV_1/FVC <70%); smokers or ex-smokers with smoking history ≥10 pack-years	NR
Moita et al[49]	Randomized, double-blind, placebo-controlled study	Tiotropium 18 μg OD Placebo	12 weeks	FEV_1 ≤70%; FEV_1/FVC ≤70%; excluded if ≥3 exacerbations during the previous year or an exacerbation 6 weeks prior	Allowed: LABAs, theophylline, mucolytics, ICS, stable-dose oral corticosteroids; temporary increases in theophylline or oral steroids for exacerbations Not allowed: 24-hour preparations of theophylline

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced expiratory vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; NMA, network meta-analysis; OD, once daily; QVA149, indacaterol/glycopyrronium; NR, not reported; SABA, short-acting β2-agonist.

Table 2 Key patient characteristics at baseline for all studies included in the NMA (only arms of interest)

Studies included in the NMA	Treatment	ITT (n)	Male (%)	Age (SD) in years	Current smokers (%)	Severe or very severe (%)	ICS usage (%)	COPD duration mean (SD) in years	Pack-years (SD)	FEV_1% predicted (SD)
Decramer et al[9]	Tiotropium 18 µg OD	208	67	62.6 (9.39)	48	53	45	NR	41.9 (24.44)	47.8 (13.36)
(DB2113360)	Vilanterol 22 µg/umeclidinium 55 µg OD	212	70	63 (8.67)	46	50	44	NR	44.8 (27.65)	48.0 (12.94)
Decramer et al[9]	Tiotropium 18 µg OD	215	71	65.2 (8.3)	47	52	53	NR	54.0 (31.59)	47.4 (13.10)
(DB2113374)	Vilanterol 22 µg/umeclidinium 55 µg OD	217	65	65 (8.62)	42	51	47	NR	47.8 (26.13)	47.7 (13.55)
Donohue et al[6]	Placebo	280	70	62.2 (9.04)	54	58	49	NR	47.2 (27.21)	46.7 (12.71)
(DB2113373)	Vilanterol 22 µg/umeclidinium 55 µg OD	413	74	63.1 (8.71)	49	51	51	NR	46.5 (25.80)	47.8 (13.19)
Maleki-Yazdi et al[28]	Tiotropium 18 µg OD	451	67	62.7 (8.50)	54	58	53	NR	44.4 (25.03)	46.5 (12.76)
(ZEP117115)	Vilanterol 22 µg/umeclidinium 55 µg OD	454	68	61.9 (8.41)	59	60	54	NR	44.1 (24.44)	46.2 (13.02)
INTRUST 1	Tiotropium 18 µg OD	564	67	63.4 (9.22)	36	53	52	6.6 (6.45)	47.2 (26.58)	48.9 (11.46)
(Mahler et al[17])	Indacaterol 150 µg OD + tiotropium 18 µg OD	570	70	64.0 (9.07)	40	53	52	7.1 (6.12)	47.2 (25.86)	48.3 (9.70)
INTRUST 2	Tiotropium 18 µg OD	570	68	62.8 (8.98)	43	54	51	7.1 (6.26)	46.3 (24.64)	48.6 (9.76)
(Mahler et al[17])	Indacaterol 150 µg OD + tiotropium 18 µg OD	572	63	63.1 (8.83)	38	54	57	7.3 (6.48)	46.2 (25.52)	48.6 (9.74)
Aaron et al[20]	Tiotropium 18 µg OD	156	53.8	68.1 (8.9)	27	NR	25	11.3 (8.8)[a]	51.8 (28.0)	42.1 (13.5)
	Tiotropium 18 µg OD + salmeterol 25 µg 2 puffs bid	148	57.4	67.6 (8.2)	24.3	NR	34.9	NR	48.7 (27.1)	41.2 (13.0)
ENLIGHTEN	Placebo	113[b]	76.1	62.9 (8.14)	45	19	39	5.46 (5.1)	38.1 (15.93)	59.43 (12.5)
(Dahl et al[13])	QVA149 (indacaterol 110 µg/glycopyrronium 50 µg) OD	226[b]	77.3	62.5 (8.81)	45	31	46	5.82 (5.74)	36.3 (16.01)	56.39 (13.27)
SPARK	Tiotropium 18 µg OD	742[b]	75	63.6 (7.8)	37	100	76	7.2 (5.5)	47 (28)	37.4 (8.1)
(Wedzicha et al[16])	QVA149 (indacaterol 110 µg/glycopyrronium 50 µg) OD	741[b]	76	63.1 (8.1)	38	100	75	7.2 (5.8)	45 (23)	37.0 (8.1)
SHINE	Placebo	234[b]	72.8	64.4 (8.6)	40	32	58	6.4 (5.7)	NR	55.2 (12.7)
(Bateman et al[11])	Tiotropium 18 µg OD	483[b]	75.0	63.5 (8.7)	39	38	59	6.1 (5.5)	NR	55.1 (13.5)
	QVA149 (indacaterol 110 µg/glycopyrronium 50 µg) OD	475[b]	76.4	64.0 (8.9)	40	34	56	6.0 (5.5)	NR	55.7 (13.2)
Vogelmeier et al[19]	Tiotropium 18 µg OD	221	79.2	63.4 (9.5)	NR	NR	NR	6.9 (6.3)	38.6 (19.3)	51.6 (11.2)
	Formoterol 10 µg bid + tiotropium 18 µg OD	207	79.2	62.6 (8.8)	NR	NR	NR	7.2 (7.0)	37.9 (18.2)	50.4 (10.5)
	Placebo	209	77.5	62.5 (8.6)	NR	NR	NR	6.7 (6.1)	40.1 (22.8)	51.1 (11)
Tashkin et al[18]	Tiotropium 18 µg OD + formoterol 12 µg bid	124	65	63.8 (8.7)	49	NR	27	NR	NR	NR
	Tiotropium 18 µg OD + placebo bid	131	68	63.9 (8.5)	46	NR	27	NR	NR	NR
Chan et al[36]	Tiotropium 18 µg OD	608	59	67.0 (8.7)	32	NR	66	9.9 (8.1)	50.2 (22.6)	39 (13)
BI trial: 205.259	Placebo	305	61	67.0 (9.1)	30	NR	71	9.9 (7.9)	51.0 (26.3)	39 (14)
TIPHON	Tiotropium 18 µg OD	266	87	65.0 (9.7)	24	57	38	7.9 (7.6)	44.4 (21.3)	47 (13)
(Tonnel et al[37])	Placebo	288	85	64.0 (10.1)	30	62	36	8.0 (7.9)	43.0 (22.5)	46 (12)
UPLIFT (Tashkin et al[38] and Celli et al[39])	Tiotropium 18 µg OD	2,987	75	65.0 (8.4)	29	52	62	9.9 (7.6)	49.0 (28.0)	40 (12)
	Placebo	3,006	74	65.0 (8.5)	30	53	62	9.7 (7.4)	48.4 (27.9)	39 (12)
Niewoehner et al[40]	Tiotropium 18 µg OD	914	98	67.6 (8.7)	29	NR	61	12.2 (10.4)	67.4 (35.4)	36 (13)
	Placebo	915	99	68.1 (8.5)	30	NR	58	11.9 (10.5)	69.4 (36.6)	36 (13)
Brusasco et al[41]	Tiotropium 18 µg OD	402	77	63.8 (8.0)	NR	NR	NR	9.0 (7.3)	44.1 (22.9)	39 (12)
	Placebo	400	76	64.6 (8.6)	NR	NR	NR	9.8 (7.4)	42.4 (22.7)	39 (12)

Donohue et al[29]	Tiotropium 18 µg OD	209	74	64.5 (7.9)	NR	NR	66	9.2 (7.8)	47.0 (25.0)	41 (NR)
	Placebo	201	75	65.6 (7.8)	NR	NR	66	9.7 (7.9)	46.0 (24.0)	41 (NR)
Casaburi et al[42]	Tiotropium 18 µg OD	550	67	65.0 (9.0)	NR	NR	44	8.6 (7.4)	63.0 (31.0)	39 (14)
	Placebo	371	63	65.0 (9.0)	NR	NR	40	8.1 (6.8)	59.0 (30.0)	38 (14)
Donohue et al[43]	Tiotropium 18 µg OD	420	65	64 (8.8)	NR	NR	35	NR	50.0 (25.1)	54 (16)
	Placebo	425	61	63.6 (8.9)	NR	NR	40	NR	49.7 (23.9)	56 (14)
GLOW 2 (Kerwin et al[44])	Tiotropium 18 µg OD	267	63	63.9 (8.2)	44	NR	52	7.5 (6.6)	50.2 (28.0)	56 (13)
	Placebo	268	65	63.6 (9.1)	46	NR	51	7.4 (6.6)	48.0 (24.0)	56 (14)
Verkindre et al[45]	Tiotropium 18 µg OD	46	94	61.0 (9.5)	24	NR	NR	9.7 (6.9)	45.6 (23.1)	35 (9)
	Placebo	54	94	60.0 (10.2)	33	NR	NR	8.8 (6.6)	41.8 (18.0)	36 (9)
Casaburi et al[46]	Tiotropium 18 µg OD	276	67	65.0 (8.6)	NR	NR	NR	9.3 (8.0)	64.5 (33.1)	39 (14)
	Placebo	188	63	65.0 (9.0)	NR	NR	NR	8.6 (6.9)	60.5 (30.2)	38 (14)
Covelli et al[47]	Tiotropium 18 µg OD	94	66	66.0 (8.9)	40	NR	54	10.1 (8.1)	66 (35.6)	40 (13)
	Placebo	84	49	63.0 (9.2)	37	NR	58	10.4 (7.7)	65 (31.2)	39 (14)
Garcia et al[48]	Tiotropium 18 µg OD	123	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	125	NR	NR	NR	NR	NR	NR	NR	NR
Moita et al[49]	Tiotropium 18 µg OD	147	NR	NR	28	NR	NR	NR	NR	NR
	Placebo	164	NR	NR	25	NR	NR	NR	NR	NR

Notes: [a]Duration of reported dyspnea. [b]Randomized population.

Abbreviations: bid, twice daily; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate; ICS, inhaled corticosteroid; ITT, intent-to-treat; NMA, network meta-analysis; NR, not reported; OD, once daily; QVAI 49, indacaterol/glycopyrronium; SD, standard deviation.

Bayesian NMA

Figure 2 presents the overall network of studies in the analysis. These studies were identified in the SLR comparing QVA149, FOR + TIO, SAL + TIO, IND + TIO, or UMEC/VI with TIO OD or placebo as common comparators. The common endpoints in the identified studies were trough FEV_1, SGRQ total scores, TDI focal scores, and rescue medication use at 24 weeks and within the time margins around these time points.

Trough FEV_1

In total, 14 studies were included for the FEV_1 endpoint (Figure 2 and Table 3). Combination therapies of UMEC/VI, QVA149, and TIO + SAL were more efficacious than placebo, and UMEC/VI and QVA149 were more efficacious than TIO monotherapy as indicated by CFB in mean trough FEV_1 at 24 weeks. The difference in CFB in mean trough FEV_1 numerically favored UMEC/VI in comparison to both QVA149 (estimated difference [ED], 14.14 mL; 95% CrI: −14.18, 42.25) and TIO + SAL (ED, 67.40 mL; 95% CrI: −25.25, 159.40), although no statistically or clinically significant differences were observed between the LABA/LAMA combinations (Figure 3A and Table 4).

SGRQ total scores

Fourteen studies were included in the analysis of SGRQ total scores (Figure 2 and Table 3). All the combination therapies, including UMEC/VI, QVA149, TIO + SAL, and TIO + FOR, demonstrated significantly higher efficacy in CFB in SGRQ total scores compared with placebo and TIO at 24 weeks. UMEC/VI was not significantly different from QVA149 (ED, 0.18; 95% CrI: −1.28, 1.63), TIO + SAL (ED, −0.11; 95% CrI: −1.84, 1.61), and TIO + FOR (ED, −0.68; 95% CrI: −1.77, 0.40) (Figure 3B and Table 4). As a scenario analysis, SE was imputed for the study by Donohue et al (TIO vs placebo),[29] and this study was included in the network, having marginal impact on the results.

TDI focal scores

In total, ten studies were included in the TDI analysis (Figure 2 and Table 3). Combination therapies of UMEC/VI and QVA149 were more efficacious than placebo, and QVA149 was more efficacious than TIO monotherapy in TDI focal score at 24 weeks. UMEC/VI was not significantly different from QVA149 (ED, −0.30; 95% CrI: −0.73, 0.13) and TIO + SAL (ED, 0.58; 95% CrI: −0.33, 1.50) (Figure 3C and Table 4). The addition of imputed evidence from the Donohue et al study[29] had marginal impact on the results.

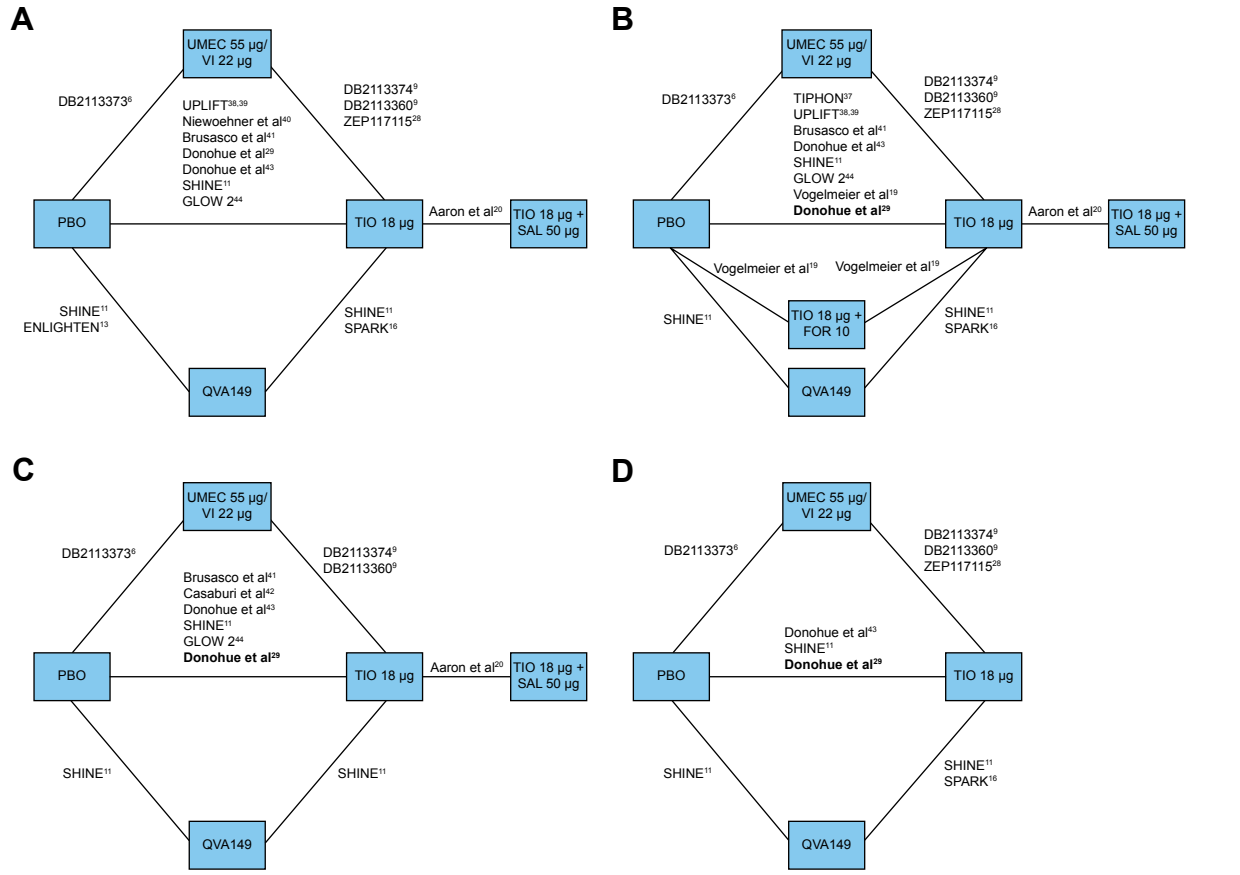

Figure 2 Overall network of studies in the NMA analysis of UMEC/VI versus LABA/LAMA combination therapies evaluated at 24 weeks for (**A**) trough FEV_1, (**B**) SGRQ total score, (**C**) TDI focal score, and (**D**) rescue medication use.

Notes: Studies in bold represent those that report only mean values without reporting SE, SD, and 95% CI. Studies DB2113360 and DB2113374 from Decramer et al.[9] Study DB2113373 from Donohue et al.[6] Study ZEP117115 from Maleki-Yazdi et al.[28]

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FOR, formoterol; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; NMA, network meta-analysis; PBO, placebo; QVA149, indacaterol/glycopyrronium; SAL, salmeterol; SD, standard deviation; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnoea index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Rescue medication use

In total, seven studies were included in the rescue medication use network (Figure 2 and Table 3). For rescue medication use at 24 weeks, the combination therapies of UMEC/VI and QVA149 were more efficacious than placebo and TIO. No significant difference was observed between UMEC/VI and QVA149 (ED, 0.02; 95% CrI: −0.27, 0.32) (Figure 3D and Table 4) with imputed evidence from the Donohue et al[29] study having marginal impact.

Discussion

This study evaluated the comparative efficacy of UMEC/VI 55/22 µg with all the available open and closed dual-combination bronchodilators in patients with moderate-to-very severe COPD who were eligible to receive maintenance bronchodilator therapy. Four endpoints, including mean CFB in trough FEV_1, CFB in SGRQ total scores, TDI focal scores, and CFB in rescue medication use, were selected and analyzed because they were consistently reported across all the studies and deemed as important endpoints in clinical practice. The Bayesian NMA showed that for each endpoint, UMEC/VI was similar to all the other dual fixed or open LABA/LAMA combination bronchodilators (IND + TIO, TIO + SAL, TIO + FOR, and QVA149) available at the time of this analysis. Indirect treatment comparison within a frequentist framework by using Bucher's method also showed consistent results for all the aforementioned efficacy parameters (data not shown).[30] This suggests that combination therapies of LABA/LAMA are broadly comparable across the most common endpoints evaluated in RCT settings. These aforementioned observations are consistent with two other recent NMAs, which suggested that bronchodilator monotherapies are broadly similar across a range of clinical endpoints.[31] One NMA, however, showed that newer OD LABAs were likely to be more effective compared with bid LABAs at improving FEV_1 and SGRQ scores.[32] The NMA focused on four most commonly

Table 3 Individual study results at 12 weeks and 24 weeks for trough FEV_1, SGRQ total scores, TDI focal scores, and rescue medication use (puffs/day)

Study	Treatment	Weeks	Trough FEV_1 in mL (difference in CFB), mean (SE)	SGRQ total score (difference in CFB), mean (SE)	TDI focal score (difference in TDI), mean (SE)	Rescue medication use (difference in puffs/day vs placebo), mean (SE)
Donohue et al[6] (DB2113373)	Vilanterol 22 µg/umeclidinium 55 µg OD vs placebo	12	195.00 (17.86)	−4.72 (1.06)	1.30 (0.23)	−1.00 (0.24)
		24	167.00 (20.15)	−5.51 (1.21)	1.20 (0.26)	−0.80 (0.26)
Decramer et al[9] (DB2113360)	Vilanterol 22 µg/umeclidinium 55 µg OD vs tiotropium 18 µg OD	12	95.00 (21.94)	−2.01 (1.26)	0.70 (0.31)	−0.51 (0.32)
		24	60.00 (25.26)	−0.17 (1.37)	0.20 (0.36)	−0.60 (0.31)
Decramer et al[9] (DB2113374)	Vilanterol 22 µg/umeclidinium 55 µg OD vs tiotropium 18 µg OD	12	80.00 (24.49)	−0.23 (1.29)	0.20 (0.26)	−0.78 (0.30)
		24	90.00 (26.02)	0.75 (1.47)	−0.10 (0.31)	−0.70 (0.28)
Maleki-Yazdi et al[28] (ZEP117115)	Vilanterol 22 µg/umeclidinium 55 µg OD vs tiotropium 18 µg OD	12	109.00 (15.82)	−2.08 (0.70)		−0.50 (0.10)
		24	112.00 (16.07)	−2.10 (0.77)		−0.50 (0.13)
SHINE[11]	QVA149 (indacaterol 110 µg/glycopyrronium 50 µg) OD vs placebo	12	230.00 (17.86)	−3.99 (0.87*)	1.22 (0.26)	
		24	200.00 (17.86)	−3.01 (1.04)	1.09 (0.24)	−0.96 (0.17)
SHINE[11]	Tiotropium 18 µg OD vs placebo	12	130.00 (17.86)	−2.37 (0.87*)	0.59 (0.27)	
		24	130.00 (17.86)	−0.88 (1.04)	0.58 (0.24)	−0.41 (0.17)
SPARK[16]	QVA149 (indacaterol 110 µg/glycopyrronium 50 µg) OD vs tiotropium 18 µg OD	12	70.00 (13.79)	−3.00 (0.88)		
		24	70.00 (13.79)	−1.60 (0.92)		
ENLIGHTEN[13]	QVA149 (indacaterol 110 µg/glycopyrronium 50 µg) OD vs placebo	12	163.00 (32.02)			
		24	152.00 (35.36)			
Niewoehner et al[40]	Tiotropium 18 µg OD vs placebo	12	100.00 (10.00)			
		24	100.00 (13.00)			
Donohue et al[43]	Tiotropium 18 µg OD vs placebo	12	140.00 (20.41)	−1.10 (0.87)	0.75 (0.22)	
		24	140.00 (20.41)	−1.00 (0.92)	0.87 (0.23)	−0.60 (0.19)
GLOW 2[44]	Tiotropium 18 µg OD vs placebo	12	83.00 (19.00)	−2.84 (0.97)	0.26 (0.30)	
		24	84.00 (21.60)	−2.52 (1.11)	0.94 (0.30)	
TIPHON[37]	Tiotropium 18 µg OD vs placebo	12		−3.59 (1.22)		
		24		−3.51 (0.65)		
Casaburi et al[42]	Tiotropium 18 µg OD vs placebo	12			0.95 (0.18)	
		24			0.85 (0.19)	
INTRUST 1[17]	Indacaterol 150 µg OD + tiotropium 18 µg OD vs tiotropium 18 µg OD	12	80.00 (12.76)			−1.10 (0.18)
INTRUST 2[17]	Indacaterol 150 µg OD + tiotropium 18 µg OD vs tiotropium 18 µg OD	12	70.00 (10.20)			−0.70 (0.15)
Tashkin et al[18]	Tiotropium 18 µg OD + formoterol 12 µg bid vs tiotropium 18 µg OD	12	90.00 (28.06)	−1.01 (1.68*)	0.07 (0.39)	−0.25 (0.35*)
Chan et al[36]	Tiotropium 18 µg OD vs placebo	12	100.00 (15.00)			
Niewoehner et al[40]	Tiotropium 18 µg OD vs placebo	12	100.00 (10.00)			
Verkindre et al[45]	Tiotropium 18 µg OD vs placebo	12	110.00 (40.00)	−6.50 (2.90)	1.28 (0.89)	−0.13 (0.25)
Casaburi et al[46]	Tiotropium 18 µg OD vs placebo	12	150.00 (14.00)			

(Continued)

Table 3 (*Continued*)

Study	Treatment	Weeks	Trough FEV_1 in mL (difference in CFB), mean (SE)	SGRQ total score (difference in CFB), mean (SE)	TDI focal score (difference in TDI), mean (SE)	Rescue medication use (difference in puffs/day vs placebo), mean (SE)
Covelli et al[47]	Tiotropium 18 μg OD vs placebo	12	184.00 (37.00)			
Moita et al[49]	Tiotropium 18 μg OD vs placebo	12	102.00 (31.38)			
Aaron et al[20]	Tiotropium 18 μg OD + salmeterol 50 μg vs tiotropium 18 μg OD	24	18.49 (45.46)	–1.47 (0.69)	–0.42 (0.43)	
UPLIFT[38,39]	Tiotropium 18 μg OD vs placebo	24	100.00 (7.00)	–2.5 (0.36)		
Brusasco et al[41]	Tiotropium 18 μg OD vs placebo	24	120.00 (100.00)	–2.7 (0.99)	1.10 (0.30)	
Donohue et al[29]	Tiotropium 18 μg OD vs placebo	24	137.00 (20.00)	–2.71 (0.99*)	1.02 (0.25*)	–1.45 (0.26*)
Vogelmeier et al[19]	Tiotropium 18 μg OD + formoterol 10 μg bid vs placebo	24		–2.93 (1.33)		
Vogelmeier et al[19]	Tiotropium 18 μg OD + formoterol 10 μg bid vs tiotropium 18 μg OD	24		–0.88 (1.84)		
Vogelmeier et al[19]	Tiotropium 18 μg OD vs placebo	24		–2.05 (1.27)		

Notes: *Imputed value. Blank spaces in the table indicate not applicable.
Abbreviations: bid, twice daily; CFB, change from baseline; FEV_1, forced expiratory volume in 1 second; OD, once daily; QVA149, indacaterol/glycopyrronium; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index.

reported endpoints in RCTs of bronchodilators. Endpoints such as adverse events, exercise tolerance, and exacerbations were excluded. Our feasibility assessment suggested that the definitions of adverse events, exacerbations, and exercise tolerance tests used in manufacturer-conducted trials differed significantly across various LABA and/or LAMA treatments, preventing robust comparison. The patients assessed in most trials reported a limited history of exacerbations and in those trials enriched for patients with exacerbations; no placebo comparisons were included. Moreover, exacerbation was not a key endpoint in most selected studies, including the UMEC/VI studies. Patients with exacerbations were withdrawn from UMEC/VI studies at the first event,[6,9,28] thereby limiting the available evidence to the risk of a first event but providing no data on exacerbation rates. Other trials designed to examine exacerbations included the SPARK study,[16] in which the LABA/LAMA combination (QVA149) was compared with two LAMAs and was reported to provide superior reductions in the rate of moderate or severe exacerbations versus GLY but not versus TIO. This benefit of QVA149 was also entirely confined to patients using concurrent corticosteroids.[16] Similarly, Aaron et al[20] reported no exacerbation benefit with TIO + SAL versus TIO in patients not using corticosteroids. In the UMEC/VI studies, approximately 50% of patients used corticosteroids and a superior exacerbation benefit was observed on the time to the first exacerbation with UMEC/VI versus placebo[6] and versus TIO but only in the largest of three similar 6-month trials.[28] Consequently, uncertainty still exists on this endpoint, which is out of scope for this NMA.

These meta-analyses also demonstrated that monobronchodilators when compared with placebo generally failed to improve total SGRQ scores by ≥4 units and TDI focal scores by ≥1 unit at 6 months, which are the minimal clinically important differences for each of these commonly used patient-reported outcomes, even when the trough FEV_1 improved by at least 100 mL compared with placebo.[32] In the current analysis, we observed that UMEC/VI consistently demonstrated clinically important benefits versus placebo and statistically significant benefits versus TIO at 6 months, which were broadly comparable to any alternative dual-bronchodilator combinations. These findings highlight that LAMA or LABA monotherapy alone may not always provide all patients with sustained benefits enabling freedom from recurrence of COPD symptoms.[33] Dual bronchodilators, which are sparingly used in current clinical practice, may provide optimal symptom control in addition to maximum bronchodilation to appropriate COPD patients.[34] Overall, both QVA149 and UMEC/VI demonstrated beneficial effects compared with monotherapy at 24 weeks,

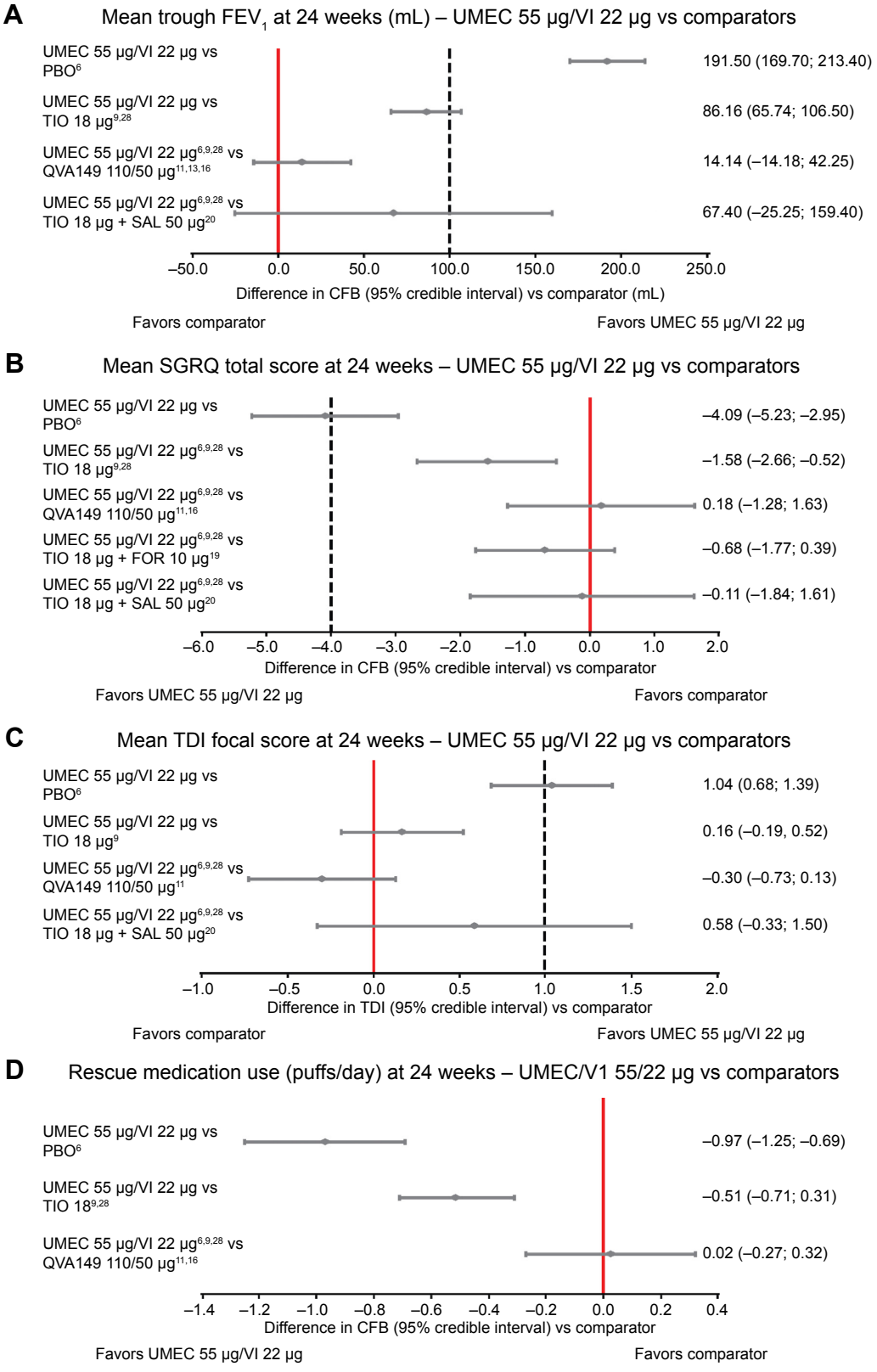

Figure 3 Forest plot for (**A**) mean trough FEV_1, (**B**) mean SGRQ total scores, (**C**) mean TDI focal scores, and (**D**) mean rescue medication use of UMEC 55 µg/VI 22 µg versus comparators at 24 weeks.

Notes: Dotted lines included in panels (**A**–**C**) indicate the MCIDs versus placebo if these have been defined: these have been included in the graph for reference purpose only. The values shown on the right of each figure represent mean (95% CI).

Abbreviations: CFB, change from baseline; FEV_1, forced expiratory volume in 1 second; FOR, formoterol; MCID, minimal clinically important difference; PBO, placebo; QVA149, indacaterol/glycopyrronium; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Table 4 Results of the NMA

Intervention	Weeks		Comparator						
			Placebo	Tiotropium 18 µg	QVA149 (indacaterol 110 µg/glycopyrronium 50 µg)	Tiotropium 18 µg + salmeterol 50 µg	Tiotropium 18 µg + formoterol 10 µg	Tiotropium 18 µg + formoterol 12 µg	Tiotropium 18 µg + indacaterol 150 µg
CFB in trough FEV_1									
Tiotropium 18 µg	12	Estimate	114.50						
		95% CrI	103.60, 125.30						
		P (better)	>99%						
	24	Estimate	105.40						
		95% CrI	95.10, 115.90						
		P (better)	>99%						
QVA149 (indacaterol 110 µg/glycopyrronium 50 µg)	12	Estimate	198.70	84.20					
		95% CrI	178.50, 218.70	65.58, 102.90					
		P (better)	>99%	>99%					
	24	Estimate	177.50	72.01					
		95% CrI	157.30, 197.80	53.74, 90.75					
		P (better)	>99%	>99%					
Vilanterol 22 µg/umeclidinium 55 µg	12	Estimate	208.10	93.65	9.41			3.86	19.80
		95% CrI	187.90, 228.40	74.53, 112.60	−16.96, 35.77			−54.14, 62.18	−4.90, 44.40
		P (better)	>99%	>99%	76%			55%	94%
	24	Estimate	191.50	86.16	14.14	67.40			
		95% CrI	169.70, 213.40	65.74, 106.50	−14.18, 42.25	−25.25, 159.40			
		P (better)	>99%	>99%	84%	92%			
Formoterol 12 µg + tiotropium 18 µg	12	Estimate	204.30	89.78	5.56				
		95% CrI	148.30, 260.00	34.82, 144.50	−52.53, 63.42				
		P (better)	>99%	>99%	57%				
Indacaterol 150 µg + tiotropium 18 µg	12	Estimate	188.30	73.85	−10.32			−15.94	
		95% CrI	169.30, 207.40	58.21, 89.46	−34.82, 13.93			−72.84, 41.26	
		P (better)	>99%	>99%	20%			29%	
Tiotropium 18 µg + salmeterol 50 µg	24	Estimate	124.50	19.18	−53.00				
		95% CrI	33.98, 214.20	−71.35, 108.70	−146.80, 38.38				
		P (better)	>99%	65%	13%				
SGRQ total score									
Tiotropium 18 µg	12	Estimate	−2.52						
		95% CrI	−3.51, −1.53						
		P (better)	>99%						
	24	Estimate	−2.50						
		95% CrI	−3.01, −2.01						
		P (better)	>99%						

QVA149 (indacaterol 110 µg/glycopyrronium 50 µg)	12	Estimate	−5.52	−3.00				
		95% CrI	−7.50, −3.52	−4.72, −1.28				
		P (better)	>99%	>99%				
	24	Estimate	−4.27	−1.77				
		95% CrI	−5.34, −3.20	−2.75, −0.78				
		P (better)	>99%	>99%				
Vilanterol 22 µg/ umeclidinium 55 µg	12	Estimate	−4.35	−1.83	1.17			
		95% CrI	−5.58, −3.11	−2.81, −0.84	−0.81, 3.15			
		P (better)	>99%	>99%	12%			
	24	Estimate	−4.09	−1.58	0.18	−0.11	−0.68	
		95% CrI	−5.23, −2.95	−2.66, −0.52	−1.28, 1.63	−1.84, 1.61	−1.77, 0.39	
		P (better)	>99%	>99%	41%	55%	89%	
Tiotropium 18 µg + formoterol 10 µg	24	Estimate	−3.41	−0.90	0.86			
		95% CrI	−3.95, −2.86	−1.06, −0.74	−0.13, 1.86			
		P (better)	>99%	>99%	4%			
Tiotropium 18 µg + salmeterol 50 µg	24	Estimate	−3.98	−1.47	0.29		−0.57	
		95% CrI	−5.42, −2.53	−2.83, −0.12	−1.38,1.96		−1.93, 0.79	
		P (better)	>99%	98%	37%		80%	
TDI focal score								
Tiotropium 18 µg	12	Estimate	0.76					
		95% CrI	0.55, 0.97					
		P (better)	>99%					
	24	Estimate	0.87					
		95% CrI	0.67, 1.07					
		P (better)	>99%					
QVA149 (indacaterol 110 µg/glycopyrronium 50 µg)	12	Estimate	1.33	0.57				
		95% CrI	0.92, 1.73	0.18, 0.96				
		P (better)	>99%	>99%				
	24	Estimate	1.34	0.46				
		95% CrI	1.03, 1.64	0.21, 0.72				
		P (better)	>99%	>99%				
Vilanterol 22 µg/ umeclidinium 55 µg	12	Estimate	1.22	0.46	−0.10			0.39
		95% CrI	0.90, 1.54	0.16, 0.77	−0.59, 0.38			−0.43, 1.22
		P (better)	>99%	>99%	34%			83%
	24	Estimate	1.04	0.16	−0.30	0.58		
		95% CrI	0.68, 1.39	−0.19, 0.52	−0.73, 0.13	−0.33, 1.50		
		P (better)	>99%	82%	9%	90%		
Tiotropium 18 µg + formoterol 12 µg	12	Estimate	0.83	0.07	−0.50			
		95% CrI	0.03, 1.62	−0.70, 0.83	−1.36, 0.36			
		P (better)	0.98	57%	13%			

(*Continued*)

Table 4 (*Continued*)

Intervention	Weeks		Comparator						
			Placebo	Tiotropium 18 µg	QVA149 (indacaterol 110 µg/ glycopyrronium 50 µg)	Tiotropium 18 µg + salmeterol 50 µg	Tiotropium 18 µg + formoterol 10 µg	Tiotropium 18 µg + formoterol 12 µg	Tiotropium 18 µg + indacaterol 150 µg
Tiotropium 18 µg + salmeterol 50 µg	24	Estimate	0.45	–0.42	–0.89				
		95% CrI	–0.42, 1.31	–1.26, 0.42	–1.77, –0.01				
		P (better)	0.85	16%	2%				
Rescue medication use									
Tiotropium 18 µg	12	Estimate	–0.21						
		95% CrI	–0.60, 0.18						
		P (better)	0.86						
	24	Estimate	–0.46						
		95% CrI	–0.68, –0.23						
		P (better)	>99%						
Vilanterol 22 µg/ umeclidinium 55 µg	12	Estimate	–0.93	–0.71					0.15
		95% CrI	–1.31, –0.55	–1.08, –0.35					–0.28, 0.58
		P (better)	>99%	>99%					25%
	24	Estimate	–0.97	–0.51	0.02				
		95% CrI	–1.25, –0.69	–0.71, –0.31	–0.27, 0.32				
		P (better)	>99%	>99%	43%				
Indacaterol 150 µg + tiotropium 18 µg	12	Estimate	–1.08	–0.86					
		95% CrI	–1.53, –0.63	–1.09, –0.64					
		P (better)	>99%	>99%					
QVA149 (indacaterol 110 µg/glycopyrronium 50 µg)	24	Estimate	–0.99	–0.54					
		95% CrI	–1.27, –0.72	–0.77, –0.31					
		P (better)	>99%	>99%					

Notes: Differences in intervention versus the comparator for CFB in trough FEV_1 (mL), SGRQ total scores, TDI focal scores, and rescue medication use at 12 weeks and 24 weeks, 95% CrI, and probability (*P*) that the intervention is better than the comparator. Blank spaces in the table indicate not applicable.

Abbreviations: CFB, change from baseline; CrI, credible interval; FEV_1, forced expiratory volume in 1 second; NMA, network meta-analysis; OD, once daily; QVA149, indacaterol/glycopyrronium; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index.

and these findings were further corroborated by the supplementary analysis performed at 12 weeks. This NMA also revealed comparable efficacy of UMEC/VI to open dual-combination bronchodilators. However, caution is needed in this regard, as the advantage of combining two long-acting bronchodilators in a single inhaler in terms of improved medication adherence leading to potentially better outcomes may become evident only in studies of a less controlled nature.

Limitations

A potential limitation of this analysis is the low number of studies for some of the treatments (eg, TIO18 + SAL50) and the absence of direct evidence with other active treatments of interest. The fact that for these treatments only indirect comparison (via TIO or placebo) was available is reflected in the uncertainty of the relative efficacy results (ie, wide CIs).

An additional limitation is that studies reporting data for aclidinium/FOR were not identified.

A further limitation of the analysis, as with all meta-analyses, is the potential influence of confounders. A meta-regression to adjust for possible confounders was not feasible because of the limited number of studies included in each analysis. Although two studies[18,20] reported lower ICS use at baseline, it was not possible to design scenario analyses excluding these studies. In both cases, it would result in the loss of a comparator in the network and would not affect the other relative efficacy estimates due to the shape of the network. Because recent NMAs[31,32,35] evaluating long-acting bronchodilators in COPD did not suggest the relative efficacy estimates to be greatly affected by this and other potential effect modifiers, the impact of this imbalance was not believed to be a likely source of bias. Although the studies were similar enough to be included in an NMA, residual confounding may exist in these aggregated data.

Conclusion

Based on the results of this 6-month NMA of the available RCTs reporting on efficacy outcomes in terms of trough FEV_1, SGRQ total scores, TDI focal scores, and rescue medication use, UMEC/VI is comparable to QVA149 and is expected to be at least comparable to the remaining dual-bronchodilator combinations.

Statement of originality/clinical relevance

With the recent introduction of a new class of fixed-dose combination bronchodilators (UMEC/VI and QVA149) and several others under development, assessing their efficacy relative to each other and with open dual combinations is desirable. Therefore, this study aimed to perform an SLR and to synthesize, by means of a Bayesian NMA, the published evidence on the efficacy of the fixed combination of UMEC/VI (55/22 µg OD) with that of all available dual-bronchodilator combinations in single or separate inhalers. The analysis was conducted with TIO and placebo as common comparators. The relative efficacy of the treatments was assessed at 12 weeks and 24 weeks in terms of lung function (trough FEV_1), health status (SGRQ total scores), TDI focal scores, and rescue medication use. To our knowledge, this is the first study to compare fixed-dose combination bronchodilators with other such fixed-dose and open combinations and to provide valuable evidence for clinicians and payers to choose the most optimal medication for their patients.

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Author contributions

All authors contributed to the conception and design of the study. AK and ELH contributed to data acquisition, and all five authors contributed to data analysis and interpretation, drafting and critically revising the paper, and agree to be accountable for all aspects of the work.

Disclosure

SMC, ASI, and YSP are employees of GlaxoSmithKline and hold stocks at GlaxoSmithKline. AK and ELH are employees of Mapi Group and were consultants to GlaxoSmithKline on this study. The authors report no conflicts of interest in this work.

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