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Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting β2-agonists: a systematic review and network meta-analysis

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Abstract

Background: A number of long-acting muscarinic antagonist (LAMA)/long-acting β2-agonist (LABA) fixed-dose combinations (FDCs) for treatment of moderate-to-very severe chronic obstructive pulmonary disease (COPD) have recently become available, but none have been directly compared in head-to-head randomized controlled trials (RCTs). The purpose of this study was to assess the relative clinical benefit of all currently available LAMA/LABA FDCs using a Bayesian network meta-analysis (NMA).

Methods: A systematic literature review identified RCTs investigating the efficacy, safety and quality of life associated with licensed LAMA/LABA FDCs for the treatment of moderate-to-very severe COPD. RCTs were screened for inclusion in the NMA using prespecified eligibility criteria. Data were extracted for outcomes of interest, including change in trough forced expiratory volume in 1 second ($tFEV_1$) from baseline, St. George Respiratory Questionnaire (SGRQ) percentage of responders, Transition Dyspnea Index (TDI) percentage of responders, change in SGRQ score from baseline, change in TDI focal score from baseline, moderate-to-severe exacerbations, all-cause discontinuation, and discontinuation due to adverse events.

Results: Following screening, a total of 27 trials from 26 publications with 30,361 subjects were eligible for inclusion in the NMA. Nonsignificant results were seen in most analyses comparing efficacy, exacerbations and discontinuation rates of included LAMA/LABA FDCs (i.e. aclidinium/formoterol 400/12 µg, glycopyrronium/indacaterol 110/50 µg, tiotropium + olodaterol 5/5 µg, umeclidinium/vilanterol 62.5/25 µg). Meta-regression controlling for post-bronchodilator percentage of $tFEV_1$ predicted at baseline as well as meta-regression adjusting for concomitant use of inhaled corticosteroids at baseline was performed to assess the magnitude of effect modification and produced similar results as observed in the base case analysis.

Conclusion: All LAMA/LABA FDCs were found to have similar efficacy and safety. Definitive assessment of the relative efficacy of different treatments can only be performed through direct comparison in head-to-head RCTs. In the absence of such data, this indirect comparison may be of value in clinical and health economic decision-making.

Keywords: aclidinium/formoterol, chronic obstructive pulmonary disease, glycopyrronium/indacaterol, network meta-analysis, tiotropium/olodaterol, umeclidinium/vilanterol

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Background

Chronic obstructive pulmonary disease (COPD) continues to be a major cause of morbidity, mortality, and impaired quality of life. The prevalence of COPD was estimated to be 7.6% by a systematic review from 2006 of studies across 28 countries [Halbert *et al.* 2006]. According to WHO estimates, 65 million people have moderate-to-very

severe COPD, and it is predicted that COPD will become the third leading cause of death worldwide by 2030 [Halbert *et al.* 2006; World Health Organization, 2014].

COPD is a chronic disease characterized by a progressive decline in lung function and accompanied by respiratory symptoms such as dyspnea, cough, and sputum production [Global Initiative for Chronic Obstructive Lung Disease, 2015). Given the progressive nature of COPD, treatment is aimed at reducing symptoms and exacerbations, thereby improving functional status and health-related quality of life [Mosenifar, 2015].

Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs), are the cornerstone of maintenance therapy for moderate-to-very severe COPD [Global Initiative for Chronic Obstructive Lung Disease, 2015]. LAMAs can be combined with LABAs, resulting in enhanced bronchodilation. Combinations of bronchodilators as well as long-acting bronchodilators with a 24-hour duration of action and a once-daily dosing regimen are an emerging area of clinical research and development [Fuso *et al.* 2013; Malerba *et al.* 2012, 2014].

Tiotropium is an established once-daily LAMA that improves a range of functional and patient-reported outcomes in COPD [Tashkin *et al.* 2008], decreases moderate and severe exacerbations and has shown a positive effect on mortality [Decramer *et al.* 2009; Troosters *et al.* 2010, 2014]. Olodaterol, a novel once-daily LABA which was specifically designed as combination partner to tiotropium, has shown 24-hour bronchodilation [Feldman *et al.* 2013; Ferguson *et al.* 2013; Koch *et al.* 2013b; Lange *et al.* 2013], symptomatic benefits [Koch *et al.* 2013a] and improvement in exercise capacity [Maltais *et al.* 2013]. Tiotropium and olodaterol have complementary pharmacokinetic and pharmacodynamic profiles [Aalbers *et al.* 2012; Maltais *et al.* 2010].

A once-daily fixed-dose combination (FDC) of tiotropium + olodaterol in the Respimat® Soft Mist™ Inhaler as a maintenance bronchodilator treatment for patients with COPD was assessed in the randomized, double-blind, parallel group phase III trials TONADO I [ClinicalTrials.gov identifier: NCT01431274] and TONADO II [ClinicalTrials.gov identifier: NCT01431287], which compared the FDC (2.5/5 μg or 5/5 μg) with monotherapy with each of the individual components (tiotropium 2.5 μg or 5 μg, olodaterol 5 μg), also once daily and delivered by the Respimat® inhaler [Buhl *et al.* 2015].

A number of other LAMA/LABA FDCs for treatment of moderate-to-very severe COPD have also recently become available, but none have been directly compared in head-to-head randomized controlled trials (RCTs). In the absence of comparative trials, indirect comparisons enable the relative effects of treatments to be compared against a common comparator to facilitate indirect comparisons between interventions of interest.

The purpose of this study was to assess the relative clinical benefit of all currently available LAMA/LABA FDCs using a Bayesian network meta-analysis (NMA) which included RCTs investigating the efficacy, safety and quality of life associated with licensed LAMA/LABA FDCs for the treatment of moderate-to-very severe COPD as identified in a systematic literature review.

Methods

Identification of trials

Relevant publications were identified through a systematic literature review performed in July–August 2013 and updated in September 2014. Inclusion criteria are shown in Table 1. The review was designed to capture both LAMA/LABA and LABA/ICS studies, but the latter were removed at screening stage for the purposes of this analysis as the intention was to focus on LAMA/LABA FDCs.

The databases searched were MEDLINE, MEDLINE-IN-PROCESS, EMBASE, the Cochrane CENTRAL Register, NHS EED (Economic Evaluation Database), the HTA Database and MEDMEME1. Searches were run from database inception to 11 September 2014. Only articles published in English were included. To capture clinical trials not yet published, additional hand searches were conducted of the abstracts of five major conferences, the ClinicalTrials.gov registry, and websites of four HTA bodies (England, France, Germany, Canada), the European Medicines Agency and the US FDA's Pulmonary Allergy Drugs Advisory Committee (PADAC). Studies retrieved were screened by two independent reviewers according to pre-specified eligibility criteria and any

Table 1. PICOS framework for inclusion in the systematic literature review.

Population	Patients with COPD
Interventions	• Tiotropium + olodaterol • Glycopyrronium + indacaterol • Umeclidinium + vilanterol • Aclidinium+formoterol • Beclometasone dipropionate+formoterol (± LAMA*) • Budesonide+formoterol (± LAMA*) • Fluticasone propionate+salmeterol (± LAMA*) • Fluticasone furoate +vilanterol (± LAMA*) • Free-dose combination of tiotropium+ salmeterol • Free-dose combination of tiotropium+ olodaterol • Tiotropium†
Comparison	Any of the interventions above Placebo†
Outcomes of interest	• Spirometric indices of lung function (trough FEV_1, AUC FEV_1)‡ • Transitional Dyspnoea Index (TDI) focal score and proportion of responders • Hospitalizations‡ • COPD exacerbations (all exacerbations, moderate+severe exacerbations, severe exacerbations) • Discontinuations (all-cause, due to AEs, due to worsening of the disease)‡ • Health-related quality of life (HRQoL): SGRQ (St. George's Respiratory Questionnaire) total score and proportion of responders
Study type	• Randomised controlled trials • Systematic literature reviews (with or without a meta-analysis)

*LAMA: tiotropium, aclidinium, glycopyrronium and umeclidinium.
†Included only to allow formation of networks.
‡AUC FEV_1, hospitalizations and discontinuation due to worsening of the disease were not included as outcomes of interest for the purpose of this analysis.

discrepancies were resolved by discussion. Data extraction was conducted by two separate reviewers and quality checked by a third. Some data not available as text were extracted from graphs using Plot Digitizer software version 2.6.6. Study quality was assessed using the National Institute for Health and Clinical Excellence (NICE) quality checklist [National Institute for Health and Care Excellence, 2013].

Eligibility criteria for study inclusion in the NMA included reporting of results for outcomes of interest within time ranges around 6 and 12 months (i.e. 20–28 weeks and 48–52 weeks); this was to allow inclusion of studies reporting at slightly different time points whilst mitigating heterogeneity due to modifying effects of time. Ranges around 6 and 12 months were chosen because most COPD trials last 24/26 or 48/52 weeks. Studies with comparator set treatments (i.e. tiotropium and placebo) that allowed use of concomitant LABA were removed, since studies of the main comparators of interest (LAMA/LABA FDCs) by definition would not allow concomitant LABA given that it was a component of the FDC being investigated. As concomitant LABA is likely to be an impactful effect modifier, and inclusion of comparator set treatments allowing use of concomitant LABA would have resulted in systematic differences between studies of decision and comparator set treatments, it was therefore deemed not appropriate to link the network with studies allowing concomitant LABA.

Network meta-analysis

Due to the complexity of the evidence networks and the fact that there were multiple studies per comparison and at least one closed loop caused by a multi-arm trial, a NMA was deemed to be the most appropriate method for evidence synthesis. The outcomes evaluated in the NMA were change in $tFEV_1$ from baseline, SGRQ percentage of responders and change in SGRQ score from baseline, TDI percentage of responders and change in TDI focal score from baseline, all-cause discontinuation, discontinuation due to adverse events, and moderate-to-severe exacerbations

(see the online supplement for definitions). FEV_1 area under the curve (AUC) and peak FEV_1 were unfeasible to be included as outcomes of interest as there was no sufficiently consistent definition used across included studies [Amaris, 2013].

The analysis was conducted using WinBUGS version 1.4.3 [Lunn *et al.* 2000]. All baseline and intervention effect parameters were given flat (uninformative) normal (0, 1000) priors and the between-study standard deviation was given a flat uniform distribution with an appropriately large range. A binomial likelihood with logit link function was used for binary data, and a normal likelihood, with identity link, for continuous data. WinBUGS code was based on the NICE Decision Support Unit (DSU) Technical Support Guidance [Dias *et al.* 2011a], and the methodology followed guidance from the ISPOR Task Force on Indirect Treatment Comparisons [Hoaglin *et al.* 2011; Jansen *et al.* 2011]. Results were expressed as odds ratios for binary outcomes and treatment difference in change from baseline for continuous outcomes, given as median values with the associated standard deviation and 95% credible intervals (CrIs) in each case. Due to skewness of the odds ratios pertaining to binary outcomes, median values are presented as for skewed distributions they represent a better measure of centrality than mean values. We note that as this analysis was conducted in a Bayesian framework, formal significance testing was not conducted. However, we describe results as statistically significant or meaningful wherever 95% CrIs did not cross the null value (zero for differences, one for odds ratios).

Both fixed and random effects models were fitted. Fixed effects models make the assumption that each study is estimating the same treatment effect, with variability induced by sampling error alone. A random effects model assumes that the trial-specific treatment effects come from a common distribution and thus takes into account between-study heterogeneity, resulting in wider credible intervals. Model fit was assessed using the Deviance Information Criterion (DIC) and the total residual deviance. For the majority of outcomes, the fixed effects model yielded a lower DIC than the random effects model. Model fit, as measured by the difference between the total residual deviance, was generally similar between fixed and random effects models. This could be interpreted as the fixed effects model being the more parsimonious model and the model of choice. However, current ISPOR guidance recommends reporting results using random effects models [Jansen *et al.* 2014] and therefore for completeness, both fixed and random effect model results were reported.

Meta-regression was performed for the outcome $tFEV_1$ to assess the impact on treatment effect sizes of use of concomitant inhaled corticosteroids (ICS) and of disease severity (measured as post-bronchodilator $\%FEV_1$ predicted) at baseline. Only a random effects model was used, as the aim of the meta-regression is to assess the extent to which between-study heterogeneity affects observed treatment effects.

Convergence was assessed by visual inspection of density, history and autocorrelation plots. If autocorrelation was observed, chains were thinned until autocorrelation was no longer present. In all cases a burn-in of at least 50,000 simulations was discarded. All results are presented based on a further sample of at least 50,000 simulations or until convergence was achieved. Lastly, the Monte Carlo error, which reflects both the number of simulations and the degree of autocorrelation, was examined. This should be no more than 5% of the posterior standard deviation of the parameters of interest [Welton *et al.* 2009].

For the base case analysis, data for the tiotropium 5 μg and 18 μg doses were grouped to enable connected networks to be created for all outcomes of interest. This approach was deemed justifiable given that a large-scale RCT found no significant difference in treatment effect between these doses [Wise *et al.* 2013]. In addition, the combined node approach was used in the base case since the studies allowing a split of tiotropium doses required data to be extracted from graphs. A sensitivity analysis for the outcome $tFEV_1$ explored the impact of analysing the tiotropium 5 μg and 18 μg doses separately, in order to test the assumption that they were equivalent. The only studies meeting the inclusion criteria and reporting results separately for both tiotropium dose were from Bateman and colleagues [Bateman *et al.* 2010a, 2010b]. Data from these publications were extracted from graphs to enable conducting the sensitivity analysis.

Analysis assumptions

Given the focus on fixed dose combinations, the only monotherapies considered for the NMA

were tiotropium and placebo in order to allow connected networks. This approach was based on NICE DSU guidance for defining decision and comparator sets [Dias *et al.* 2011a] where it is recommended that all studies conducted in treatments required to provide a connected network are included in the NMA. Results were only reported for treatments in the decision set (LAMA/LABA FDCs), and were not reported for unlicensed doses (i.e. TIO + OLO 2.5 μg/5 μg, TIO 2.5 μg, UMEC/VI 125 μg/25 μg, ACL/FM 400 μg/6 μg).

There were marked differences between studies in the definition of exacerbations, including time of assessment and exacerbation measures reported. A few studies did not define moderate and severe exacerbations. For this reason, studies were only included if they broadly followed the modified Anthonisen definition [Seemungal *et al.* 2000] of COPD exacerbations (i.e. worsening of two or more major respiratory symptoms [dyspnea, cough, sputum, chest tightness, or wheezing] with a duration of ⩾3 days requiring specified treatment changes) and had sufficiently similar classification of moderate (i.e. requiring additional treatment with antibiotics, systemic glucocorticoids, or both) and severe exacerbations (i.e. requiring hospitalization). Removing studies with no, or different, definition of COPD exacerbations and those reporting data at a time point outside the range of interest resulted in exclusion of approximately 40% of studies reporting moderate-to-severe exacerbations. This approach was nonetheless deemed justifiable given that heterogeneity of endpoint definition cannot be adjusted for and would render the outputs difficult to interpret.

To enable comparison of moderate-to-severe exacerbations across major studies of FDCs and dual treatments, studies reporting results at different time points were included in the same network. Whilst this approach carries the limitation of having to assume a constant relative risk independent of the observational period, it was the only way a connected network including the tiotropium + olodaterol FDC could be created.

Data on missing standard errors associated with the change in continuous outcomes from baseline were imputed using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Higgins and Green, 2011].

Results

Study selection

The electronic database search identified a total of 2538 citations. A further 582 publications were identified through other sources. After removal of duplicates, the titles and abstracts of a total of 2059 citations were screened. After abstract screening, full texts of the remaining 372 publications were retrieved and reviewed. In total, 145 studies met the prespecified inclusion criteria as shown in Figure 1, of which 120 were discarded from the NMA on grounds of (a) pertaining to LABA/ICS rather than LAMA/LABA FDCs, (b) reporting results outside the time ranges of interest specified above, or (c) permitting concomitant LABA. Following study screening for eligibility, a total of 27 trials from 26 publications (the publication by Decramer *et al.* [2014] included results from two trials) with 30,361 subjects were eligible for inclusion in the NMA. Key study and patient baseline characteristics of included studies are provided in Table 2. The majority were found to be associated with low or unclear risk of bias. Some were associated with a high risk of bias in terms of allocation concealment and blinding, which can largely be explained by the high number of studies including open-label tiotropium.

Assessment of effect modification

In line with best practice in evidence synthesis and NMA [Jansen *et al.* 2014], studies included in the NMA were first assessed for presence and extent of effect modification, which may occur due to imbalances of effect modifiers across studies (heterogeneity) or across comparisons (inconsistency) [Jansen and Naci, 2013]. The main effect modifiers considered were disease severity, use of concomitant ICS, and history of exacerbations.

Disease severity at baseline is thought to be an effect modifier, with lung function effect sizes decreasing with increased severity. The average post-bronchodilator %FEV_1 predicted across all studies included for the tFEV_1 outcome analysis was 50.9% ranging from 65.7% [Troosters *et al.* 2014] to 37.2% [Wedzicha, 2013]. The average distribution by GOLD stages across all included studies was 51% for GOLD stage II (moderate COPD), 41.9% for GOLD stage III (severe COPD), and 6.8% for GOLD stage IV (very severe COPD). Notably, the SPARK study [Wedzicha, 2013] was conducted in patients with

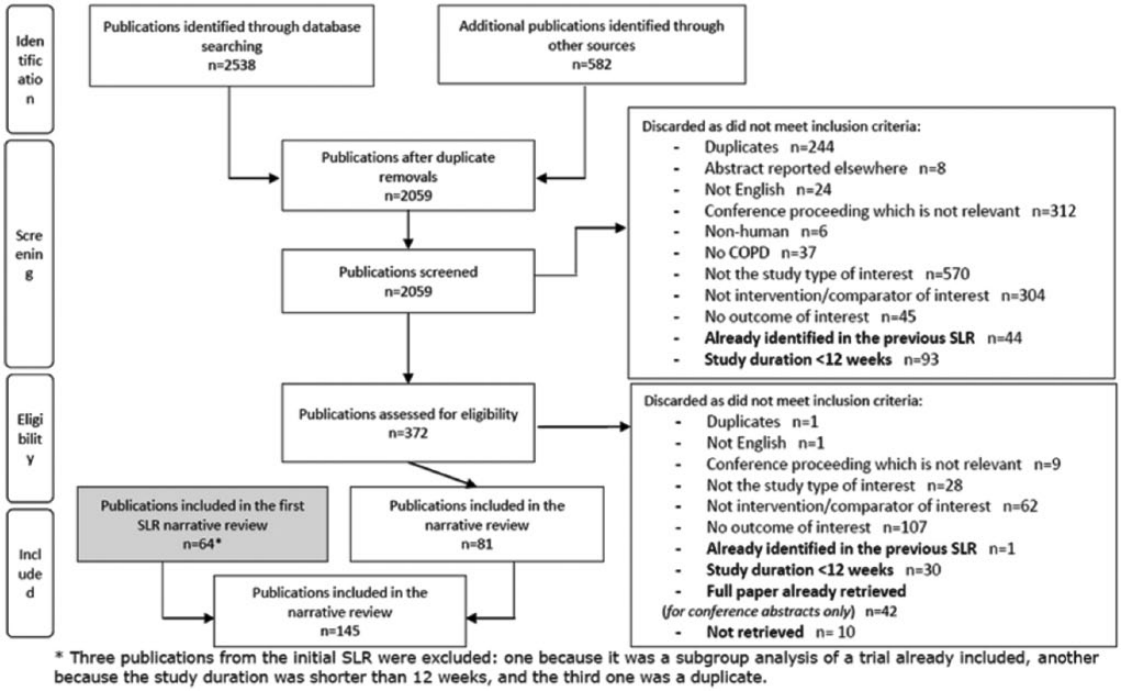

Figure 1. Summary of study selection process.

GOLD stages III and IV only. Conversely, other studies of the glycopyrronium/indacaterol FDC were conducted in populations almost exclusively consisting of GOLD stage II and III patients only. Given the wide distribution across studies, meta-regression controlling for post-bronchodilator % FEV_1 predicted at baseline was performed.

It is thought that use of concomitant ICS is assumed to increase observed treatment effects and hence to be an effect modifier. The average across all studies included for the $tFEV_1$ outcome analysis was 48.2%, and substantial variation was observed in the distribution of use of concomitant ICS at baseline across included studies. The high proportion of concomitant ICS use in the SPARK study [Wedzicha, 2013] is likely due to the fact that this study was conducted in patients with severe and very severe COPD only. It should be noted, however, that whilst concomitant medication may increase overall treatment effects it may also be positively correlated with severity, therefore potentially rendering adjustments less meaningful. Overall the distribution of the use of concomitant ICS may pose challenges for meaningful interpretation. To assess the magnitude of effect modification, meta-regression controlling for concomitant ICS use at baseline was performed.

Finally, exacerbation history may be an effect modifier, with effect sizes likely to decrease with higher incidence of exacerbations prior to study enrolment and randomization to treatment. The average distribution across studies was 59.1% for patients with no exacerbations in the 12 months prior to study enrolment, and 40.8% for patients with at least one exacerbation in the previous year. Notably, virtually all patients in the SPARK study [Wedzicha, 2013] had experienced at least on exacerbation in the 12 months prior to study enrolment.

As part of the assessment of effect modification, Bucher comparisons were conducted for all networks containing closed loops that did not contain multi-arm trials [Dias *et al.* 2011b] in order to assess whether there is evidence of a conflict between direct and indirect evidence within each network which would likely be caused by an imbalance of effect modifiers across included trials. For the outcome 'change in SGRQ score from baseline at 24/26 weeks' a significant value was found for omega (3.73, $p < 0.05$), indicating potential inconsistency in this network caused by the umeclidinium/vilanterol trials [Decramer *et al.* 2014; Donohue *et al.* 2013]. Notably, the direction of results differed in these trials, but the assessment of study level effect modifiers in the

Table 2. Study and patient baseline characteristics of included trials.

Study	Number of patients	Treatment duration (weeks)	Treatment comparisons of interest	Baseline characteristics				GOLD stage distribution				Quality assessment		
				Mean age	Male (%)	Baseline FEV_1 % pred	Baseline FEV_1 (L)	I (%)	II (%)	III (%)	IV (%)	Allocation concealm.	ITT analysis	Blinding
Anzueto *et al.* [2013]	410	24	UMEC/VI 62.5/25µg qdTIO 18µg qd	63	69	NR	NR	NR	NR	NR	NR	Yes	Yes	Yes
Bateman *et al.* [2010a]	1990	48	TIO (SMI) 10µg qdTIO (SMI) 5µg qdPLB	65	74.2	37.7†	1.28‡	NR	NR	NR	NR	Unclear	Unclear	Yes
Bateman *et al.* [2010b]	3917	48	TIO (SMI) 5µg qdPLB	64.8	77.6	45.3‡	1.24‡	NR	NR	NR	NR	Yes	Yes	Yes
Bateman *et al.* [2013]	1192	26	QVA149 110/50µg qdTIO (DPI) 18µg qdPLB	64	74.7	55.3‡	1.5‡	0	65.1	34.9	0	No	Yes	No*
Boehringer Ingelheim International GmbH, [2005]	914	48	TIO (DPI) 18µg qdPLB	66.8	59.8	39.3†	0.97†	NR	NR	NR	NR	Yes	Yes	Yes
Buhl *et al.* [2015]	2062	52	TIO/OLO 5/5µg qd TIO (SMI) 5µg qd	63.9	72.2	49.5‡	1.19†	0.1	49.4	38.6	12	Yes	Yes	Yes
Casaburi *et al.* [2002]	921	52	TIO (DPI) 18µg qdPLB	65	64.7	38.6†	1.02†	NR	NR	NR	NR	Unclear	Yes	Yes
Dahl *et al.* [2013]	339	52	QVA149 110/50µg qdPLB	62.7	76.7	57.9‡	1.66‡	0	74.5	24.9	0.5	Unclear	Yes	Yes
Decramer *et al.* [2014]	854	24	UMEC/VI 62.5/25µg qdTIO (DPI) 18µg qd	64	68.3	47.7‡	NR	0	48	39.8	11.5	Unclear	Yes	Unclear
Decramer *et al.* [2013a]	432	24	UMEC/VI 62.5/25µg qd TIO (DPI) 18µg qd	65.1	68	47.6‡	1.33‡	NR	NR	NR	NR	Unclear	Yes	Yes
Donohue *et al.* [2013]	693	24	UMEC/VI 62.5/25µg qdPLB	62.7	72	47.3‡	NR	0	46	44	10.5	Yes	Yes	Yes
Donohue *et al.* [2010]	845	26	TIO (DPI) 18µg qdPLB	63.8	62.9	55‡	1.48‡	NR	NR	NR	NR	No	Yes	No*
Donohue *et al.* [2003]Δ	410	24	TIO (DPI) 18µg qdPLB	65.1	74.5	NR	1.09†	NR	NR	NR	NR	Yes	Unclear	Unclear
D'Urzo *et al.* [2014a]§,#	675	24	ACL/FM 400/12µg bidPLB	63.9	51.4	52.9‡	1.35†	NR	54.9	43.8	NR	Yes	Yes	Yes
Dusser *et al.* [2006]	1010	52	TIO (DPI) 18µg qdPLB	64.8	88	47.9†	1.37†	NR	NR	NR	NR	Unclear	Yes	Yes
Hodder *et al.* [2007]	788	24	TIO (DPI) 18µg qdPLB	64.3	76	40.5†	1.11†	NR	NR	NR	NR	Yes	No	Yes
Kerwin *et al.* [2012]	537	52	TIO (DPI) 18µg qdPLB	63.8	63.8	56.2‡	1.5‡	0	64.7	34.8	0.4	Yes	Yes	Yes
Maleki-Yazdi *et al.* [2014]	905	24	UMEC/VI 62.5/25µg qdTIO (DPI) 18µg qd	62.3	67.5	46.4‡	1.41‡	0	41.5	46	13	Yes	Yes	Yes
Niewoehner *et al.* [2005]	1829	26	TIO (DPI) 18µg qdPLB	67.9	98.5	NR	1.04†	NR	NR	NR	NR	Yes	Yes	Yes
Powrie *et al.* [2007]	142	52	TIO (DPI) 18µg qdPLB	66.4	62.9	50.1†	1.29†	NR	NR	NR	NR	Unclear	Yes	Yes
Singh *et al.* [2014]#	579	24	ACL/FM 400/12µg bidPLB	63.5	69.5	54.8‡	1.42†	0	59.8	40.2	0	Yes	Yes	Yes
Tashkin *et al.* [2008]	5993	208	TIO (DPI) 18µg qdPLB	64.5	74.7	39.4†	1.33‡	NR	45.5	44	8.5	Yes	Unclear	Yes
Tonnel *et al.* [2008]	554	39	TIO (DPI) 18µg qdPLB	64.2	86.1	46.8†	1.37†	NR	NR	NR	NR	Unclear	Yes	Unclear
Troosters *et al.* [2014]	457	24	TIO (DPI) 18µg qdPLB	61.8	68.4	65.7‡	1.93‡	NR	NR	NR	NR	Unclear	Yes	Yes
Vogelmeier *et al.* [2008]	430	24	TIO (DPI) 18µg qdPLB	63	78.4	51.4‡	1.5‡	NR	NR	NR	NR	No	Yes	No*
Wedzicha *et al.* [2013c]¶	1483	64	QVA149 110/50µg qdTIO (DPI) 18µg qd	63.4	75.5	37.2‡	1.04‡	0	0	79	21	No	Yes	No*

ACL, aclidinium; bid, twice daily; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FM, formoterol; GOLD, Global Initiative for Chronic Obstructive Disease; ITT, intention to treat; NR, not reported; OLO, olodaterol; PLB, placebo; qd, once daily; QVA, glycopyrronium + vilanterol; SMI, soft mist inhaler; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol

*Tiotropium was administered open-label.

†Pre-bronchodilator.

‡Post-bronchodilator.

ΔSecondary reference from study based on the same trial was included [Donohue *et al.* 2002].

§Includes secondary references [D'Urzo *et al.* 2013, 2014a, 2014b].

#Includes secondary reference [European Medicines Agency, 2014].

¶Includes secondary references [Decramer *et al.* 2013b, 2013c, 2013d; Ficker *et al.* 2013a, 2013b; Wedzicha *et al.* 2013a, 2013b; Wedzicha, 2013].

umeclidinium/vilanterol trials did not reveal any differences in either severity or concomitant medication that would cause substantial effect modification. A lack of reporting of baseline SGRQ values in these studies precluded establishing the association between baseline values and change in SGRQ score, thus rendering unfeasible a definitive assessment of the reasons for the conflict between direct and indirect evidence. Results for comparisons with umeclidinium/vilanterol for this outcome should therefore be interpreted with caution.

Results for outcomes of interest

In the main section of the paper we report results for $tFEV_1$ and meta-regression, SGRQ percentage of responders, TDI percentage of responders, and the sensitivity analysis for $tFEV_1$ splitting the tiotropium doses, all at 24/26 weeks. Results for the other outcomes are reported in the online supplement. Results are shown for all comparisons of decision set treatments included in a given outcome.

The network of studies for change in $tFEV_1$ from baseline at 24/26 weeks included 11 studies [Bateman *et al.* 2013; Buhl *et al.* 2015; D'Urzo *et al.* 2014a; Dahl *et al.* 2013; Decramer *et al.* 2014; Donohue *et al.* 2013; Kerwin *et al.* 2012; Maleki-Yazdi *et al.* 2014; Singh *et al.* 2014; Troosters *et al.* 2014; Wedzicha *et al.* 2013c], SGRQ percentage of responders included 10 studies [Bateman *et al.* 2013; Buhl *et al.* 2015; D'Urzo *et al.* 2014a; Decramer *et al.* 2014; Donohue *et al.* 2002, 2013; Maleki-Yazdi *et al.* 2014; Singh *et al.* 2014; Tonnel *et al.* 2008; Wedzicha *et al.* 2013c], and TDI percentage of responders included 9 studies [Bateman *et al.* 2013; Buhl *et al.* 2015; D'Urzo *et al.* 2014a; Decramer *et al.* 2014; Donohue *et al.* 2002, 2010, 2013; Kerwin *et al.* 2012; Singh *et al.* 2014].

Change in $tFEV_1$ from baseline

In the analysis of $tFEV_1$ at 24/26 weeks, TIO/OLO 5/5 µg was associated with a 0.039 ml (95% CrI 0.002–0.075) increase in $tFEV_1$ compared to ACL/FF 400/12 µg when using a fixed effects model, and this result was statistically significant. Similarly, QVA149 110/50 µg was found to be associated with a 0.042 ml (95% CrI 0.007–0.077) increase in $tFEV_1$ compared with ACL/FF 400/12 µg when using a fixed effects model. Favourable and statistically significant results were also observed for UMEC/VI 62.5/25 µg compared with ACL 400/12 µg when using either a fixed or random effects model. All other comparisons yielded nonsignificant results (see Table 3).

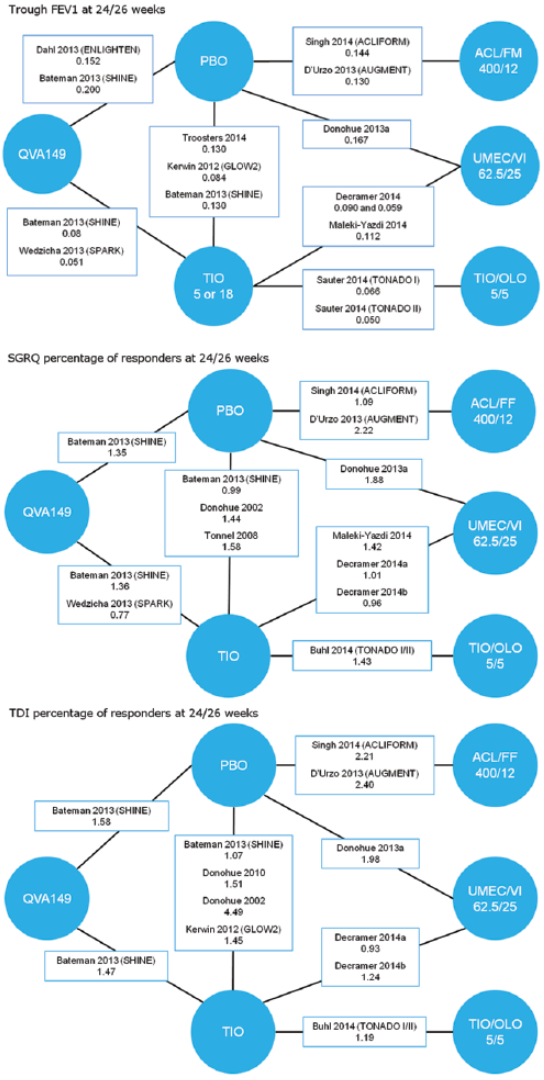

Figure 2. Network diagrams for $tFEV_1$, SGRQ percentage of responders, TDI percentage of responders.

Results of the meta-regressions on baseline severity and concomitant use of ICS for the outcome of change in $tFEV_1$ from baseline are shown in Tables 4 and 5, respectively. Meta-regression adjusting for post-bronchodilator percentage of FEV_1 predicted at baseline yielded similar results as in the base case analysis, with slightly smaller effect sizes. The only statistically significant result observed in this analysis suggested a 0.062 ml (95% CrI 0.020–0.103) increase in $tFEV_1$ for UMEC/VI 62.5/25 µg compared with ACL/FF 400/12 µg.

Table 3. Change in $tFEV_1$ from baseline (24/26 weeks).

	ACL/FF 400/12 µg	QVA149 110/50 µg	TIO/OLO 5/5 µg	UMEC/VI 62.5/25 µg
Fixed effects*				
ACL/FF 400/12 µg		−0.042 [−0.077,−0.007]	−0.039 [−0.075,−0.002]	−0.064 [−0.099,−0.028]
QVA149 110/50 µg	0.042 [0.007,0.077]		0.003 [−0.024,0.031]	−0.022 [−0.050,0.007]
TIO/OLO 5/5 µg	0.039 [0.002,0.075]	−0.003 [−0.031,0.024]		−0.025 [−0.052,0.002]
UMEC/VI 62.5/25 µg	0.064 [0.028,0.099]	0.022 [−0.007,0.050]	0.025 [−0.002,0.052]	
Total residual deviance		35.24 [24.90,50.75]		
DIC		−177.79		
Random effects*				
ACL/FF 400/12 µg		−0.041 [−0.084,0.003]	−0.037 [−0.082,0.011]	−0.061 [−0.103,−0.018]
QVA149 110/50 µg	0.041 [−0.003,0.084]		0.004 [−0.032,0.042]	−0.020 [−0.055,0.015]
TIO/OLO 5/5 µg	0.037 [−0.011,0.082]	−0.004 [−0.042,0.032]		−0.024 [−0.059,0.011]
UMEC/VI 62.5/25 µg	0.061 [0.018,0.103]	0.020 [−0.015,0.055]	0.024 [−0.011,0.059]	
Total residual deviance		32.81 [20.36,49.15]		
SD		0.01 [0.0004,0.03]		
DIC		−176.76		

*Values >0 denote favourable results.
$tFEV_1$, trough forced expiratory volume in 1 second; DIC, Deviance Information Criterion; SD, standard deviation; ACL/FF, aclidinium/formoterol; QVA149, indacaterol/glycopyrronium bromide; TIO/OLO, tiotropium + olodaterol; UMEC/VI, umeclidinium/vilanterol.

Meta-regression adjusting for concomitant ICS use at baseline again produced similar results to the base case analysis, with the notable exception that a change in the direction of results was observed in the comparisons of TIO/OLO 5/5 µg and ACL/FF 400/12 µg as well as ACL/FF 400/12 µg and QVA149 110/50 µg, compared with base case results presented in Table 3. Nonsignificant results favouring ACL/FF 400/12 µg in these comparisons were due to the small proportion of patients using concomitant ICS in the only study of ACL/FF 400/12 µg included in the meta-regression [Singh *et al.* 2014], relative to the studies of TIO/OLO 5/5 µg and QVA149 110/50 µg. None of the treatment comparisons in the meta-regression controlling for concomitant ICS use produced statistically meaningful results.

Results from the sensitivity analysis on tiotropium dose as presented in Table 6 were similar to the base case results, except that a change in the direction of results was observed for the comparison of TIO/OLO 5/5 µg and QVA149 110/50 µg. This was due to a higher effect size in the only included study comparing tiotropium 5 µg with placebo [Bateman *et al.* 2010a], as compared with the pooled estimate of studies comparing tiotropium 18 µg with placebo [Bateman *et al.* 2013; Kerwin *et al.* 2012; Troosters *et al.* 2014]. Overall, results of the sensitivity analysis indicate that the findings of the $tFEV_1$ base case analysis were not meaningfully sensitive to the pooling of the tiotropium 5 µg and 18 µg doses.

SGRQ percentage of responders at 24/26 weeks

For the analysis of SGRQ percentage of responders at 24/26 weeks, no statistically significant results were seen in any of the LAMA/LABA FDC treatment comparisons. Results are presented in Table 7.

TDI percentage of responders at 24/26 weeks

The analysis of TDI percentage of responders at 24/26 weeks suggested no significant relative treatment differences for any LAMA/LABA FDC treatment comparisons. Results are presented in Table 8.

Discussion

No data are available from RCTs on the relative efficacy and safety of the TIO/OLO 5/5 µg FDC in relation to the main comparators in the treatment of COPD. In the absence of head-to-head data, we performed a NMA to assess its efficacy relative to other LAMA/LABA FDCs that are available to COPD patients. This study builds on previous network meta-analyses examining LAMA/LABA FDCs [Huisman *et al.* 2015; Oba *et al.* 2015] and to the best of the authors' knowledge is

Table 4. Change in $tFEV_1$ from baseline (24/26 weeks): meta-regression adjusting for post-bronchodilator percentage $tFEV_1$ predicted at baseline.

Random effects*				
	ACL/FF 400/12µg	QVA149 110/50µg	TIO/OLO 5/5µg	UMEC/VI 62.5/25µg
ACL/FF 400/12 µg		−0.032 [−0.077,0.013]	−0.032 [−0.077,0.014]	−0.062 [−0.103,−0.020]
QVA149 110/50 µg	0.032 [−0.013,0.077]		−0.00003 [−0.035,0.036]	−0.031 [−0.067,0.007]
TIO/OLO 5/5 µg	0.032 [−0.014,0.077]	0.00003 [−0.036,0.035]		−0.031 [−0.065,0.004]
UMEC/VI 62.5/25 µg	0.062 [0.020,0.103]	0.031 [−0.007,0.067]	0.031 [−0.004,0.065]	
B	0.19 [−0.17,0.54]			
Total residual deviance	32.10 [20.35,48.59]			
SD	0.01 [0.0003,0.02]			
DIC	26.3			

*Values >0 denote favourable results.
$tFEV_1$, trough forced expiratory volume in 1 second; DIC, Deviance Information Criterion; SD, standard deviation; ACL/FF, aclidinium/formoterol; QVA149, indacaterol/glycopyrronium bromide; TIO/OLO, tiotropium + olodaterol; UMEC/VI, umeclidinium/vilanterol.

Table 5. Change in $tFEV_1$ from baseline (24/26 weeks): meta-regression adjusting for concomitant ICS use at baseline.

Random effects				
	ACL/FF 400/12 µg	QVA149 110/50 µg	TIO/OLO 5/5 µg	UMEC/VI 62.5/25 µg
ACL/FF 400/12 µg		0.023 [−0.133,0.175]	0.024 [−0.128,0.175]	−0.005 [−0.151,0.140]
QVA149 110/50 µg	−0.023 [−0.175,0.133]		0.001 [−0.038,0.043]	−0.028 [−0.066,0.014]
TIO/OLO 5/5 µg	−0.024 [−0.175,0.128]	−0.001 [−0.043,0.038]		−0.029 [−0.066,0.009]
UMEC/VI 62.5/25 µg	0.005 [−0.140,0.151]	0.028 [−0.014,0.066]	0.029 [−0.009,0.066]	
B	0.15 [−0.31,0.59]			
Total residual deviance	29.06 [17.63,45.14]			
SD	0.01 [0.001,0.03]			
DIC	24.61			

*Values >0 denote favourable results.
$tFEV_1$, trough forced expiratory volume in 1 second; ICS, inhaled corticosteroids; DIC, Deviance Information Criterion; SD, standard deviation; ACL/FF, aclidinium/formoterol; QVA149, indacaterol/glycopyrronium bromide; TIO/OLO, tiotropium + olodaterol; UMEC/VI, umeclidinium/vilanterol.

the first published NMA investigating the relative efficacy of all currently available LAMA/LABA FDCs against one another.

Overall, nonsignificant results were seen in almost all analyses comparing efficacy, exacerbations and discontinuation rates of TIO/OLO 5/5 µg FDC with those of other LAMA/LABA FDCs, suggesting that TIO/OLO 5/5 µg FDC has similar efficacy and safety relative to other LAMA/LABA FDCs (see the online supplement).

Few analyses produced statistically significant results. In the base case analysis, results for $tFEV_1$ at 24/26 weeks suggest significant improvements with TIO/OLO 5/5 µg compared with ACL/FF 400/12 µg and for QVA149 110/50 µg compared with ACL/FF 400/12 µg when using a fixed effects model, and for UMEC/VI 62.5/25 µg compared with ACL/FF 400/12 µg irrespective of model choice.

We assessed the impact of concomitant ICS use and baseline disease severity on the treatment effect sizes observed for the outcome $tFEV_1$ using meta-regression. Whilst results generally were similar to the base case analysis, relative effect sizes were lower in all comparisons despite the

Table 6. Change in $tFEV_1$ from baseline (24/26 weeks): sensitivity analysis splitting TIO 5 and 18 µg doses.

	ACL/FF 400/12 µg	QVA149 110/50 µg	TIO/OLO 5/5 µg	UMEC/VI 62.5/25 µg
Fixed effects*				
ACL/FF 400/12 µg		−0.042 [−0.077,−0.007]	−0.046 [−0.079,−0.014]	−0.064 [−0.099,−0.029]
QVA149 110/50 µg	0.042 [0.007,0.077]		−0.004 [−0.033,0.025]	−0.022 [−0.050,0.006]
TIO/OLO 5/5 µg	0.046 [0.014,0.079]	0.004 [−0.025,0.033]		−0.018 [−0.047,0.012]
UMEC/VI 62.5/25 µg	0.064 [0.029,0.099]	0.022 [−0.006,0.050]	0.018 [−0.012,0.047]	
Total residual deviance		37.30 [26.36,53.35]		
DIC		−194.91		
Random effects*				
ACL/FF 400/12µg		−0.041 [−0.084,0.003]	−0.046 [−0.093,0.003]	−0.061 [−0.103,−0.017]
QVA149 110/50µg	0.041 [−0.003,0.084]		−0.005 [−0.051,0.041]	−0.021 [−0.055,0.015]
TIO/OLO 5/5µg	0.046 [−0.003,0.093]	0.005 [−0.041,0.051]		−0.016 [−0.059,0.031]
UMEC/VI 62.5/25µg	0.061 [0.017,0.103]	0.021 [−0.015,0.055]	0.016 [−0.031,0.059]	
Total residual deviance		35.06 [22.14,52.15]		
SD		0.01 [0.0004,0.03]		
DIC		−193.64		

*Values >0 denote favourable results.
$tFEV_1$, trough forced expiratory volume in 1 second; DIC, Deviance Information Criterion; SD, standard deviation; ACL/FF, aclidinium/formoterol; QVA149, indacaterol/glycopyrronium bromide; TIO/OLO, tiotropium + olodaterol; UMEC/VI, umeclidinium/vilanterol.

fact that rates of concomitant ICS use in the TONADO I and TONADO II trials were lower than the average rates of use in the QVA149 110/50 µg and UMEC/VI 62.5/25 µg studies included in the analysis. This was because two studies [D'Urzo *et al.* 2013; Troosters *et al.* 2014] included in the base case analysis were discarded from the meta-regression as they did not report rates of concomitant ICS use; the removal of the study by Troosters and colleagues [Troosters *et al.* 2014] resulted in a decrease in the effect size of tiotropium *versus* placebo, which also affected the effect size relative to the QVA149 110/50 µg and UMEC/VI 62.5/25 µg FDCs.

Similarly, meta-regression on disease severity produced smaller relative effect sizes in the majority of comparisons. Notably, adjusting for severity produced a result for the comparison of TIO/OLO 5/5 µg with QVA149 110/50 µg that was very similar to the base case analysis. The result therefore supports the validity of including the SHINE [Bateman *et al.* 2013] and ENLIGHTEN [Dahl *et al.* 2013] studies on the one hand and the SPARK [Wedzicha *et al.* 2013c] study on the other hand despite the former being conducted in moderate and severe (GOLD stage II and III) patients only and the latter in severe and very severe (GOLD stage III and IV) patients only.

No significant treatment differences were observed for any treatment comparisons in the outcome analysis of the percentage of SGRQ and TDI responders at week 24/26. Similarly, the analysis of change in SGRQ total score and change in TDI focal score from baseline did not produce statistically significant results for any treatment comparisons of LAMA/LABA FDCs except when using a fixed effects model for the comparison of QVA 100/50 µg and TIO/OLO 5/5 µg in the analysis of SGRQ total score at 48/52 weeks (see online supplement). In addition, results for the analysis of SGRQ total score at 24/26 weeks should be treated with caution given a potential inconsistency caused by the umeclidinium/vilanterol trials for this outcome.

For the analysis of moderate-to-severe exacerbations, again no significant results were observed for any treatment comparisons (see the online supplement). Of note, the studies on TIO/OLO 5/5 µg FDC were not designed to assess the impact of treatment on COPD exacerbations [Buhl *et al.* 2015]. The analysis of all-cause discontinuation at week 24/26 suggested a significantly lower

Table 7. SGRQ percentage of responders (24/26 weeks).

	ACL/FF 400/12 µg	QVA149 110/50 µg	TIO/OLO 5/5 µg	UMEC/VI 62.5/25 µg
Fixed effects*				
ACL/FF 400/12 µg		0.926 [0.680,1.257]	0.817 [0.588,1.138]	0.931 [0.692,1.252]
QVA149 110/50 µg	1.080 [0.795,1.470]		0.883 [0.696,1.120]	1.006 [0.804,1.258]
TIO/OLO 5/5 µg	1.224 [0.879,1.702]	1.132 [0.893,1.437]		1.139 [0.892,1.455]
UMEC/VI 62.5/25 µg	1.074 [0.799,1.446]	0.994 [0.795,1.244]	0.878 [0.687,1.121]	
Total residual deviance		39.89 [30.43,54.49]		
DIC		404.53		
Random effects*				
ACL/FF 400/12 µg		0.925 [0.528,1.620]	0.800 [0.399,1.577]	0.935 [0.562,1.558]
QVA149 110/50 µg	1.081 [0.617,1.893]		0.866 [0.466,1.562]	1.011 [0.654,1.566]
TIO/OLO 5/5 µg	1.250 [0.634,2.509]	1.155 [0.640,2.145]		1.167 [0.667,2.102]
UMEC/VI 62.5/25 µg	1.070 [0.642,1.780]	0.990 [0.639,1.529]	0.857 [0.476,1.498]	
Total residual deviance		29.10 [16.38,46.50]		
SD		0.19 [0.05,0.42]		
DIC		400.05		

*Values >1 denote favourable results.
SGRQ, St George Respiratory Questionnaire; DIC, Deviance Information Criterion; SD, standard deviation; ACL/FF, aclidinium/formoterol; QVA149, indacaterol/glycopyrronium bromide; TIO/OLO, tiotropium + olodaterol; UMEC/VI, umeclidinium/vilanterol.

Table 8. TDI percentage of responders (24/26 weeks).

	ACL/FF 400/12 µg	QVA149 110/50 µg	TIO/OLO 5/5 µg	UMEC/VI 62.5/25 µg
Fixed effects*				
ACL/FF 400/12 µg		1.165 [0.818,1.650]	1.273 [0.919,1.765]	1.263 [0.924,1.727]
QVA149 110/50 µg	0.859 [0.606,1.223]		1.093 [0.807,1.489]	1.085 [0.792,1.490]
TIO/OLO 5/5 µg	0.786 [0.567,1.088]	0.915 [0.672,1.239]		0.993 [0.752,1.307]
UMEC/VI 62.5/25 µg	0.792 [0.579,1.082]	0.922 [0.671,1.263]	1.008 [0.765,1.330]	
Total residual deviance		33.81 [24.68,47.95]		
DIC		522.61		
Random effects*				
ACL/FF 400/12 µg		1.174 [0.646,2.147]	1.241 [0.636,2.325]	1.247 [0.749,2.059]
QVA149 110/50 µg	0.852 [0.466,1.549]		1.059 [0.533,1.997]	1.065 [0.613,1.804]
TIO/OLO 5/5 µg	0.806 [0.430,1.572]	0.945 [0.501,1.877]		1.005 [0.571,1.808]
UMEC/VI 62.5/25 µg	0.802 [0.486,1.336]	0.939 [0.554,1.631]	0.995 [0.553,1.750]	
Total residual deviance		27.68 [15.38,43.78]		
SD		0.17 [0.01,0.43]		
DIC		521.37		

*Values >1 denote favourable results.
TDI, Transition Dyspnea Index; DIC, Deviance Information Criterion; SD, standard deviation; ACL/FF, aclidinium/formoterol; QVA149, indacaterol/glycopyrronium bromide; TIO/OLO, tiotropium + olodaterol; UMEC/VI, umeclidinium/vilanterol.

probability of treatment discontinuation due to all causes in TIO/OLO 5/5 µg compared with UMEC/VI 62.5/25 µg when using either a fixed or random effects model.

A number of indirect comparisons have been conducted in COPD to inform the relative efficacy of treatments that have not been directly compared in an RCT. The evidence base in COPD is heterogeneous, however, rendering indirect comparisons problematic. Some issues that have been identified in previous NMAs in COPD are inconsistent reporting across trials, correlation between outcomes, diverse compounds being grouped

into the same class, and differing trial durations and levels of background treatment. This NMA addressed some of these issues by focusing on LAMA/LABA FDCs only, by only including studies reporting results at broadly consistent time points, by removing studies of tiotropium *versus* placebo permitting concomitant LABA, and by assessing the impact of concomitant medication and disease severity at baseline by means of meta-regression.

Our NMA has a number of potential limitations. First, between-study heterogeneity may have been present. In particular, the QVA149 110/50 μg FDC studies SHINE and ENLIGHTEN [Bateman *et al.* 2013; Dahl *et al.* 2013] were conducted in patients with GOLD stage II and III only whereas the SPARK study [Wedzicha *et al.* 2013c] had been conducted in patients with GOLD stage III and IV only. These studies were included in the LAMA/LABA networks to allow the comparison with the QVA149 110/50 μg FDC. The average distribution of patients across GOLD stages among the SPARK, SHINE and ENLIGHTEN studies overall was very similar to that in the TONADO I and TONADO II studies. Furthermore, our meta-regression on baseline post-bronchodilator $\%FEV_1$ (predicted) found that controlling for COPD severity had virtually no impact on results and did not change their direction.

A further limitation for the analysis of moderate-to-severe exacerbations was the inclusion of studies reporting data from different time points in the same network. This approach assumes a constant relative risk of having at least one exacerbation independent of the observational period. Following a feasibility assessment, however, this approach was the only means of creating a connected network that allowed comparison of the TIO/OLO 5/5 μg FDC with other LAMA/LABA FDCs. Notably, the network also included the SPARK study which comprised a substantially higher proportion of patients with a history of at least one exacerbation in the 12 months prior to study enrolment, relative to other studies included in the network.

In conclusion, this study is the first published NMA investigating the relative efficacy of all currently available LAMA/LABA FDCs, and sought to establish the relative efficacy and safety of these treatments for the management of moderate to very severe COPD given the lack of head-to-head RCTs. Our analysis suggests that TIO/OLO 5/5 μg FDC, the latest LAMA/LABA FDC to become available, has similar efficacy and safety to other LAMA/LABA FDCs. Definitive assessment of the relative efficacy of different treatments can only be performed through direct comparison in head-to-head RCTs. However, in the absence of such data, this indirect comparison may be of value in clinical and health economic decision-making.

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