Adv Ther (2022) 39:4961–5010
https://doi.org/10.1007/s12325-022-02234-x

ORIGINAL RESEARCH

Comparative Efficacy of Umeclidinium/Vilanterol Versus Other Bronchodilators for the Treatment of Chronic Obstructive Pulmonary Disease: A Network Meta-Analysis

Afisi S. Ismaila · Katrin Haeussler · Alexandrosz Czira · Vanita Tongbram · Mia Malmenäs · Jatin Agarwal · Maria Nassim · Marija Živković-Gojović · Yunrong Shen · Xinzhe Dong · Maria Duarte · Chris Compton · Claus F. Vogelmeier · David M. G. Halpin

Received: April 22, 2022 / Accepted: June 17, 2022 / Published online: July 20, 2022

ABSTRACT

Introduction: Few randomised controlled trials (RCTs) have directly compared long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) dual maintenance therapies for patients with chronic obstructive pulmonary disease (COPD). This systematic literature review and network meta-analysis (NMA) compared the efficacy of umeclidinium/vilanterol (UMEC/VI) versus other dual and mono-bronchodilator therapies in symptomatic patients with COPD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-022-02234-x.

A. S. Ismaila
R&D Global Medical, GSK, Collegeville, PA, USA

A. S. Ismaila
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada

K. Haeussler · M. Nassim
ICON Plc, München, Germany

A. Czira · M. Duarte · C. Compton
R&D Global Medical, GSK, Brentford, Middlesex, UK

V. Tongbram
ICON Plc, North Wales, PA, USA

M. Malmenäs
ICON Plc, Stockholm, Sweden

J. Agarwal
ICON Plc, Bengaluru, Karnataka, India

M. Živković-Gojović
ICON Plc, Burlington, ON, Canada

Y. Shen
ICON Plc, Cambridge, MA, USA

X. Dong
ICON Plc, Vancouver, BC, Canada

C. F. Vogelmeier
Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-Universität Marburg, Member of the German Center for Lung Research (DZL), Marburg, Germany

D. M. G. Halpin
University of Exeter Medical School, College of Medicine and Health, University of Exeter, Exeter, UK

A. S. Ismaila (✉)
Value Evidence and Outcomes, GSK, 1250 South Collegeville Road, Collegeville, PA 19426-0989, USA
e-mail: afisi.s.ismaila@gsk.com

Methods: A systematic literature review (October 2015–November 2020) was performed to identify RCTs ≥ 8 weeks long in adult patients with COPD that compared LAMA/LABA combinations against any long-acting bronchodilator-containing dual therapy or monotherapy. Data extracted on changes from baseline in trough forced expiratory volume in 1 s (FEV_1), St George's Respiratory Questionnaire (SGRQ) total score, Transitional Dyspnoea Index (TDI) focal score, rescue medication use and moderate/severe exacerbation rate were analysed using an NMA in a frequentist framework. The primary comparison was at 24 weeks. Fixed effects model results are presented.

Results: The NMA included 69 full-length publications (including 10 GSK clinical study reports) reporting 49 studies. At 24 weeks, UMEC/VI provided statistically significant greater improvements in FEV_1 versus all dual therapy and monotherapy comparators. UMEC/VI provided similar improvements in SGRQ total score compared with all other LAMA/LABAs, and significantly greater improvements versus UMEC 125 μg, glycopyrronium 50 μg, glycopyrronium 18 μg, tiotropium 18 μg and salmeterol 50 μg. UMEC/VI also provided significantly better outcomes versus some comparators for TDI focal score, rescue medication use, annualised moderate/severe exacerbation rate, and time to first moderate/severe exacerbation.

Conclusion: UMEC/VI provided generally better outcomes compared with LAMA or LABA monotherapies, and consistent improvements in lung function (measured by change from baseline in trough FEV_1 at 24 weeks) versus dual therapies. Treatment with UMEC/VI may improve outcomes for symptomatic patients with COPD compared with alternative maintenance treatments.

Keywords: Dual bronchodilators; Dual inhaler therapy; COPD; LABA; LAMA; Network meta-analysis

PLAIN LANGUAGE SUMMARY

Bronchodilators are medicines that open the airways, allowing patients with chronic obstructive pulmonary disease (COPD) to breathe more easily. There are two different types of bronchodilators, namely long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), which can be used on their own or combined (LAMA/LABAs). Only a few clinical trials have compared different LAMA/LABA combinations with each other, so it is unclear which LAMA/LABA combination provides the greatest benefits for patients.

In this study, we used network meta-analysis to compare a LAMA/LABA combination medicine called umeclidinium and vilanterol (UMEC/VI) with other LAMAs and LABAs used alone or in combination to treat patients with COPD. Network meta-analysis is a way of comparing two or more medicines by analysing data from many studies. We systematically searched for evidence from clinical trials in adult patients with COPD that were at least 8 weeks long and that compared LAMA/LABA combinations with a LAMA, a LABA, or another LAMA/LABA combination. We analysed data from 49 clinical trials that met these criteria.

We found that patients treated with UMEC/VI had better lung function than patients treated with alternative LAMA/LABA combinations or bronchodilators used on their own. Patients treated with UMEC/VI had better quality of life than those receiving some other treatments, but not all. All the medicines we compared had similar side effects.

Our results suggest that treating patients with COPD with UMEC/VI might improve their lung function and quality of life more than alternative bronchodilators.

Key Summary Points

Why carry out this study?

Long-acting bronchodilators are the mainstay of maintenance therapy for patients with chronic obstructive pulmonary disease (COPD), but there is no consensus on the timing of treatment initiation with dual therapy with a long-acting muscarinic antagonist and a long-acting β_2-agonist (LAMA/LABA) combination versus monotherapy with a LAMA or a LABA.

Several dual bronchodilator therapies are available for COPD treatment; however, only a few head-to-head randomised controlled trials have compared outcomes between dual bronchodilator therapies, and these may have been affected by differences in inhaler devices.

This network meta-analysis investigated the relative efficacy of umeclidinium/vilanterol (UMEC/VI) versus other dual bronchodilator combinations and LAMA and LABA monotherapies with reduced confounding due to inhaler device differences.

What was learned from the study?

UMEC/VI dual therapy provided better outcomes in terms of lung function (as measured by change from baseline in trough FEV_1) compared with alternative dual therapies and monotherapies, as well as improvements in health-related quality of life, symptoms, rescue medication use, moderate/severe exacerbation rates, and time to first moderate/severe exacerbation compared with monotherapies.

These results suggest that treatment with UMEC/VI may improve outcomes for symptomatic patients with COPD compared with alternative dual and monotherapies.

INTRODUCTION

Long-acting bronchodilators are the mainstay of maintenance therapy for patients with chronic obstructive pulmonary disease (COPD). However, treatment guidelines provide different recommendations on when to initiate long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) dual therapy rather than LAMA or LABA monotherapy. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report typically recommends a stepwise approach with escalation to LAMA/LABA dual therapy for patients who have persistent dyspnoea or exacerbations on LAMA or LABA monotherapy, although LAMA/LABA dual therapy can also be considered as an initial maintenance therapy option for patients with severe symptoms [1]. In contrast, the American Thoracic Society (ATS) and the UK National Institute for Health and Care Excellence (NICE) guidelines recommend initiating treatment with LAMA/LABA dual therapy for all patients with dyspnoea [2, 3].

Previous meta-analyses of clinical trial data comparing dual and mono-bronchodilator therapies have shown that treatment with LAMA/LABA combinations provide better outcomes for patients than LAMA or LABA monotherapy [4–9]. All currently available LAMA/LABA combinations provided greater improvements in lung function, health status and breathlessness compared with monotherapies [4–6, 9]. However, further evidence from large randomised controlled trials (RCTs) evaluating efficacy and safety of LAMA/LABA dual therapy versus monotherapy is now available, so there is a need for updated analyses to incorporate these findings.

The relative differences in safety and efficacy between available LAMA/LABA treatments within the dual bronchodilator class also remain unclear. There is a need to identify whether there is a difference between bronchodilators in the benefits they produce across different outcomes to help guide treatment decisions. Previous meta-analyses showed a gradient of effectiveness between LAMA/LABA fixed-dose combinations in patients with

moderate-to-severe COPD based on the evidence available in 2015 [4, 6]. Although within-class RCTs comparing outcomes between LAMA/LABA dual therapies remain limited, recent evidence may help to clarify the relative benefits of different LAMA/LABA combinations.

An updated synthesis of recent and previously available evidence is therefore needed to understand the potential advantages of starting treatment with LAMA/LABA dual therapy versus LABA or LAMA monotherapy, and which treatments provide the best outcomes within the LAMA/LABA dual therapy class. The aim of this network meta-analysis (NMA) was to investigate whether treatment with umeclidinium/vilanterol (UMEC/VI) provides better outcomes than (a) monotherapy with LABA or LAMA, and (b) other dual bronchodilator combinations in symptomatic patients with moderate-to-severe COPD.

METHODS

Systematic Literature Review Rationale

The systematic literature review (SLR) methodology was consistent with recommendations published in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, as well as guidance provided by the Centre for Reviews and Dissemination and the Cochrane Collaboration [10, 11].

A previously published SLR identified publications up to October 2015 reporting RCTs in patients with COPD that compared selected maintenance therapies, including LAMA and LABA monotherapies and LAMA/LABA dual therapies, to inform an NMA [6]. An update to this search was conducted to identify publications between October 2015 and November 2020 reporting studies in which any LAMA, LABA or LABA/LAMA either as a monotherapy or as a combination with inhaled corticosteroids (ICS; dual therapy) were compared with LABA/LAMA dual therapy (fixed-dose or open combination). Studies with an ICS/LABA treatment arm were used to construct the networks, but were excluded from the comparisons.

Search Strategy

The systematic bibliographic searches were conducted between 2 October 2015 and 19 November 2020 using the Ovid Platform in the following databases: MEDLINE and MEDLINE In-Process, EMBASE, The Cochrane Library: Cochrane Database of Systematic Review (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) websites, HTA database and the National Institute for Health Research (NIHR). To complement the evidence from the bibliographic databases, a secondary systematic searches were performed in clinical trial registries including Clinicaltrials.gov (https://clinicaltrials.gov/ct2/search/advanced), the US National Institutes of Health clinical trial register; World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; http://apps.wo.int/trialsearch/AdvSearch.aspx); ISRCTN registry Clinical Trials Register (ISRCTN; http://www.controlled-trials.com/editAdvancedSearch); Klinische Prüfungen PharmNet.Bund (http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm); the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/#searchadvanced); National Institute for Health Research—Health Technology Assessment (NIHR HTA; http://www.nets.nihr.ac.uk/projects) and EU Clinical Trials Register (EU-CTR; www.clinicaltrialsregister.eu). The search was restricted to articles written in English or German.

Inclusion Criteria and Study Selection Process

The outcomes included in the SLR are listed in Table 1. For all outcomes evaluated at 12 and 24 weeks, an extended margin of time was permitted to strengthen the networks. If the endpoint of interest was not reported at 12 or 24 weeks, but instead between 8 and 16 weeks and 20 and 28 weeks, the proxy outcome was reported. The primary outcome was trough FEV_1 at 24 weeks.

Table 1 PICOS criteria

Population	**Adult patients with COPD**
Intervention	Dual therapies: • UMEC/VI 62.5/25 μg OD • ACL/FOR 400/12 μg or 400/6 μg • GLY/FOR 18/9.6 μg • IND/GLY 27.5/15.6 μg or 110/50 μg or 150/50 μg • TIO/OLO 2.5/5 μg or 5/5 μg • TIO 18 μg + FOR 10 μg or TIO 18 μg + FOR 12 μg • TIO 18 μg + IND 150 μg • Any other combination of a LABA and LAMA LAMA monotherapies: • UMEC 62.5 μg or 125 μg OD • ACL 400 μg BID • TIO 5 μg or 18 μg OD • GLY 15.6 μg or 18 μg or 50 μg OD LABA monotherapies: • SAL 50 μg BID • FOR 9.6 μg or 10 μg or 12 μg BID • IND 25.5 μg or 75 μg or 150 μg or 300 μg OD • OLO 5 μg or 10 μg OD
Comparator	Any comparison between the interventions of interest (including combination therapies) or of those interventions with placebo, as long as one arm receiving a LABA/LAMA dual therapy was included in the study
Outcomes	• Trough FEV_1 • Post-bronchodilator FEV_1 • SGRQ total score • Proportion of patients with an improvement of at least 4 units in SGRQ total score (responder analysis) • TDI focal score • Proportion of patients with an improvement of at least 1 unit in TDI score (responder analysis) • Rescue medication use (including SABAs and ICS) • Rate of exacerbations per patient-year over the trial period across definitions • Proportion of patients experiencing at least one exacerbation (across definitions) at the end of the study • Time to first moderate/severe exacerbation
Study design	RCTs with a duration ≥ 8 weeks

ACL aclidinium; *BID* twice daily; *COPD* chronic obstructive pulmonary disease; *FEV_1* forced expiratory volume in 1 s; *FOR* formoterol; *ICS* inhaled corticosteroid; *IND* indacaterol; *GLY* glycopyrronium; *LABA* long-acting β_2-agonist; *LAMA* long-acting muscarinic antagonist; *OD* once daily; *OLO* olodaterol; *PICOS* population, intervention, comparator, outcomes, and study design; *RCT* randomised controlled trial; *SABA* short-acting β_2-agonist; *SAL* salmeterol; *SGRQ* St George's Respiratory Questionnaire; *TDI* Transitional Dyspnoea Index; *TIO* tiotropium; *UMEC* umeclidinium; *VI* vilanterol

All abstracts and full articles were reviewed against the eligibility criteria by two systematic reviewers; disagreements were referred to a third reviewer and an agreement was reached. A PRISMA flow diagram, indicating the numbers of studies included and excluded at each stage of the review, is shown in Fig. 1.

Quality Assessment

The Cochrane Collaboration's tool was used to assess risk of bias at study level. The scored items were extracted in the data extraction form.

Network Meta-Analysis

In traditional pairwise meta-analysis, all included studies compare the same intervention with the same comparator. NMA is an extension of this approach that includes multiple different pairwise comparisons across a range of different interventions (Supplementary Methods) [12–14]. For the current study, all analyses were conducted using a frequentist weighted regression-based approach as previously described [15]. The efficacy outcomes were lung function (trough forced expiratory volume in 1 s [FEV_1]), health-related quality of life (HRQoL; St George's Respiratory Questionnaire [SGRQ] total score), breathlessness (Transitional Dyspnoea Index [TDI] focal score), rescue medication use, moderate/severe exacerbation rate and time to first moderate/severe exacerbation. For safety outcomes, analyses were not feasible because of differences in outcome definitions. Both fixed effects (FE) and random effects (RE) models were used; in the absence of heterogeneity, results from both models were identical. Where heterogeneity was present, the RE models automatically accounted for this; RE model results are presented in the supplementary material. Networks were stratified by observation time horizon (12 and 24 weeks) depending on data availability and the primary comparison was at 24 weeks. Results from the frequentist approach are presented as point estimates with a 95% confidence interval (CI). Point estimates and 95% CIs are presented in figures and tables; only statistically significant results at 24 weeks have been reported in the text. The frequentist regression-based NMA was conducted using R v4.1.2 (www.r-project.org), using the netmeta package [16]. Further details are provided in the Supplementary Methods.

Compliance with Ethics Guidelines

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

RESULTS

Studies and Patient Characteristics

In the SLR and its update, a total of 6847 abstracts were reviewed following the removal of duplicates. Of those, 753 full length publications were assessed for inclusion and data were extracted from 83 publications and 13 GSK clinical study reports (CSRs). In total, 96 publications reporting 61 studies were included in the SLR. Following assessment of the feasibility of including studies identified in the SLR, the NMA included 69 publications (including 10 GSK CSRs) reporting 49 different studies (Fig. 1).

The characteristics of the studies included in the NMA are shown in Table 2; the characteristics of patients included in these studies are shown in Table 3.

Lung Function

Trough FEV_1 data were available from 22 and 44 studies at 24 and 12 weeks, respectively (Supplementary Fig. S1). Not all comparators had data available at 24 weeks, including tiotropium/olodaterol (TIO/OLO) fixed-dose and open combinations. The networks of evidence showed that the TONADO 1 and TONADO 2 studies formed a disconnected network at 24 weeks (Supplementary Fig. S1A). In the FE model at 24 weeks, change from baseline in trough FEV_1 was statistically significant in favour of UMEC/VI versus all comparators,

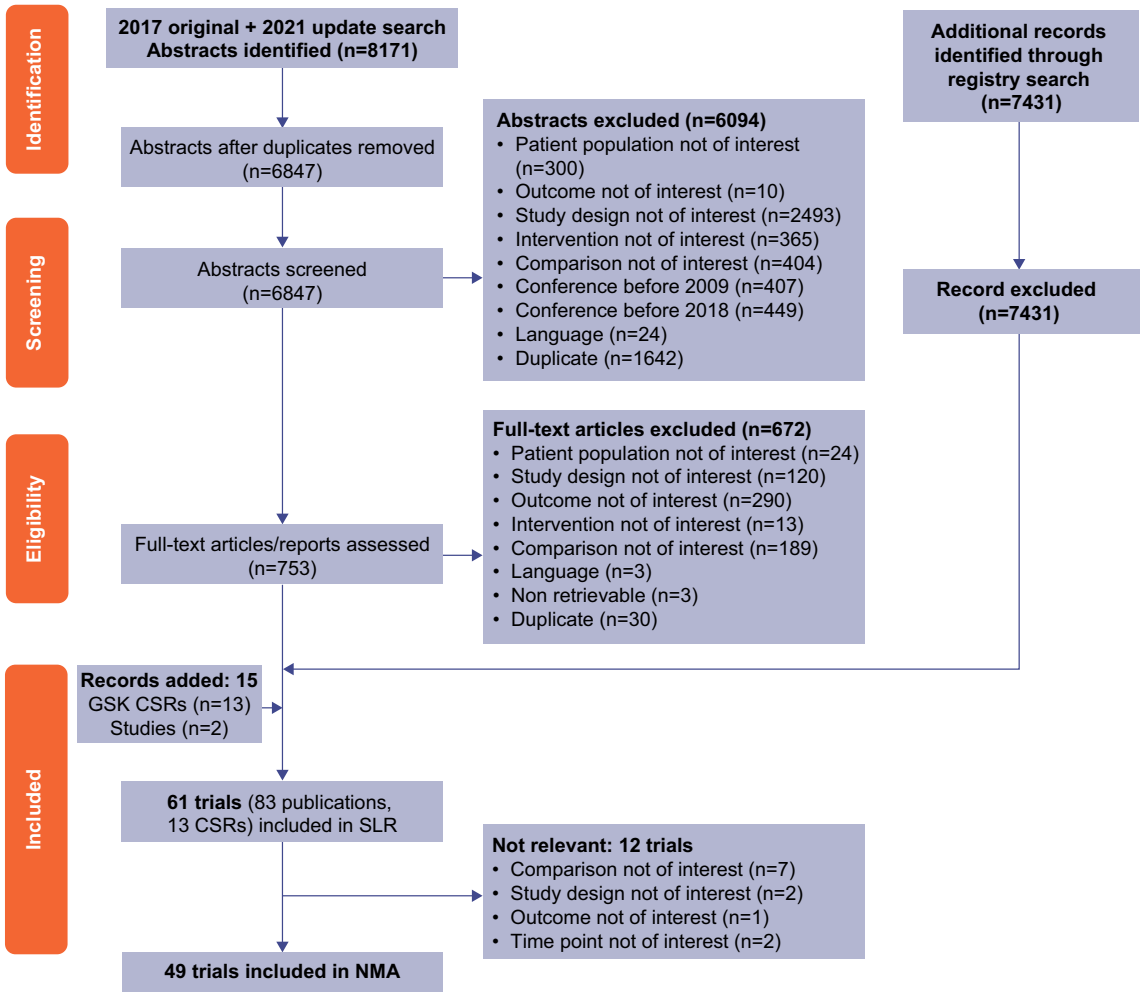

Fig. 1 PRISMA flow diagram of study selection process. *CSR* clinical study report, *NMA* network meta-analysis, *SLR* systematic literature review

including dual therapies (Fig. 2a) and monotherapies (Fig. 2b). Mean difference in change from baseline in trough FEV_1(95% CI) versus dual therapies was 108.87 ml (79.27, 138.47) versus aclidinium/formoterol (ACL/FOR) 400/6 µg, 97.50 ml (72.89, 122.11) versus ACL/FOR 400/12 µg, 74.19 ml (55.06, 93.31) versus glycopyrronium (GLY)/FOR 18/9.6 µg, 39.43 ml (19.56, 59.30) versus indacaterol (IND)/GLY 110/50 µg, and 107.43 ml (70.18, 144.67) versus TIO 18 µg + FOR 12 µg. UMEC/VI showed clinically meaningful improvements (treatment difference ≥ 100 ml) [17] compared with ACL/FOR 400/6 µg and TIO 18 µg + FOR 12 µg dual therapies. At 12 weeks, UMEC/VI provided statistically significantly greater improvements in trough FEV_1 than all dual therapies, with the exception of GLY/IND (Supplementary Fig. S2A), and provided greater improvements than all monotherapies and placebo (Supplementary Fig. S2B). All therapies were significantly more effective than placebo in increasing trough FEV_1, with UMEC/VI providing the largest improvements at both time points (Supplementary Figs. S3 and S4). The RE model produced consistent results (Supplementary Tables S1 and S2).

Table 2 Study characteristics of the trials included in the NMA

Author, year	Study name, NCT number	Treatment	ITT/study duration, weeks	Study design	Study phase	Crossover
Lipworth, 2018 [30]	PINNACLE-4, NCT02343458	GLY/FOR (MDI) 18/9.6	24	RCT, MC, DB, PG, PC	3	No
		GLY 18				
		FOR 9.6				
		PBO				
Singh, 2015 [31]	OTEMTO 1, NCT01964352	TIO/OLO 5/5	12	RCT, MC, DB, PC	3	No
		TIO/OLO 2.5/5				
		TIO 5				
		PBO				
Singh, 2015 [31]	OTEMTO 2, NCT02006732	TIO/OLO 5/5	12	RCT, MC, DB, PC	3	No
		TIO/OLO 2.5/5				
		TIO 5				
		PBO				
Vogelmeier, 2008 [32]	NCT00134979	FOR 10	24	RCT, MC, DB (TIO open label), AC	4	No
		TIO 18				
		TIO 18 + FOR 10				
		PBO				
Maleki-Yazdi, 2014 [33]	ZEP117115, NCT01777334	UMEC/VI 62.5/25	24	RCT, MC, DB, DD, PG	3	No
		TIO 18				
Calverley, 2018 [34]	DYNAGITO, NCT02296138	TIO/OLO 5/5	52	RCT, MC, MN, DB, PG, AC	3	No
		TIO 5				
Kerwin, 2017 [35]	A2349, NCT02487446	IND/GLY 27.5/15.6 BID	12	RCT, MC, DB, DD, AC, 2-period crossover	3	Yes, at 12 weeks
Kerwin, 2017 [35]	A2350, NCT02487498	IND/GLY 27.5/15.6 BID	12	RCT, MC, DB, DD, AC, 2-period crossover	3	Yes, at 12 weeks
		UMEC/VI 62.5/25				

Table 2 continued

Author, year	Study name, NCT number	Treatment	ITT/study duration, weeks	Study design	Study phase	Crossover
Maltais, 2019 [22]	EMAX, NCT03034915	UMEC/VI 62.5/25 UMEC 62.5 SAL 50	24	RCT, MC, MN, DB, DD, PG	3	No
Feldman, 2017 [25]	GSK 204990, NCT02799784	UMEC/VI 62.5/25 TIO/OLO 5/5	8	RCT, MC, open label, two-period crossover study	4	Yes, at 8 weeks
Kalberg, 2016 [36]	GSK 116961, NCT02257385	UMEC/VI 62.5/25 TIO 18 + IND 150	12	RCT, MC, DB, triple dummy	3	No
Riley, 2018 [37]	GSK 201317, NCT02275052	UMEC/VI 62.5/25 PBO	12	RCT, MC, DB, PC, crossover	4	Yes, at 12 weeks
Mahler, 2012 [38]	INTRUST-1, NCT00846586	TIO 18 + IND 150 TIO 18	12	RCT, MC, DB, PG	3	No
Mahler, 2012 [38]	INTRUST-2, NCT00877383	TIO 18 + IND 150 TIO 18	12	RCT, MC, DB, PG	3	No
Vincken, 2014 [39]	GLOW6, NCT01604278	IND 150 + GLY 50 IND 150	12	RCT, MC, DB, PG	3	No
Wedzicha, 2013 [40]	SPARK, NCT01120691	IND/GLY 110/50 GLY 50 TIO 18	64	RCT, MC, DB, PG	3	No
GSK CSR[a]	DB2113374, NCT01316913	UMEC 125 UMEC/VI 62.5/25 UMEC/VI 125/25 TIO 18	24	RCT, MC, DB, DD, PG	3	No
GSK CSR[a]	DB2113360, NCT01316900	UMEC 125 UMEC/VI 62.5/25 UMEC/VI 125/25 TIO 18	24	RCT, MC, DB, DD, PG	3	No

Table 2 continued

Author, year	Study name, NCT number	Treatment	ITT/study duration, weeks	Study design	Study phase	Crossover
GSK CSR[a]	DB2113373, NCT01313650	UMEC 125 UMEC/VI 62.5/25 UMEC/VI 125/25 TIO 18	24	RCT, MC, DB, PC	3	No
Vogelmeier, 2016 [41]	AFFIRM, NCT01908140	ACL/FOR 400/12 SAL/FP 50/500	24	RCT, MC, DB	3b	No
Wedzicha, 2016 [42]	FLAME, NCT01782326	IND/GLY 110/50 SAL/FF 50/500	52	RCT, MC, DB	3	No
Maltais, 2019 [24]	AERISTO, NCT03162055	GLY/FOR 18/9.6 UMEC/VI 62.5/25	24	RCT, MC, DB, double dummy	3b	No
Sethi, 2019 [43]	AMPLIFY, NCT02796677	ACL/FOR 400/12 ACL 400 FOR 12 TIO 18	24	RCT, DB, DD, PG	3	No
D'Urzo, 2014 [44]	AUGMENT, NCT01437397	ACL/FOR 400/12 ACL/FOR 400/6 ACL 400 FOR 12 PBO	24	RCT, MC, DB, PC	3	No
D'Urzo, 2017 [45][b]	AUGMENT EXTENSION, NCT01572792	ACL/FOR 400/12 ACL/FOR 400/6 ACL 400 FOR 12 PBO	28	RCT, MC, DB, PC, long-term extension	3	No

Table 2 continued

Author, year	Study name, NCT number	Treatment	ITT/study duration, weeks	Study design	Study phase	Crossover
Ferguson, 2016 [46]	FLIGHT3, NCT01682863	IND/GLY 27.5/15.6 BID	52	RCT, MC, DB	3	No
		IND/GLY 27.5/31.2 BID				
		IND 75				
Mahler, 2015 [47]	FLIGHT1, NCT01727141	IND/GLY 27.5/15.6 BID	12	RCT, MC, DB, PC, PG	3	No
		IND 27.5				
		GLY 15.6				
		PBO				
Mahler, 2015 [47]	FLIGHT2, NCT0171251	IND/GLY 27.5/15.6 BID	12	RCT, MC, DB, PC, PG	3	No
		IND 27.5				
		GLY 15.6				
		PBO				
Siler, 2016 [48]	201211, NCT02152605	UMEC/VI 62.5/25	12	RCT, MC, DB, PC	3	No
		PBO				
Kerwin, 2017 [49]	DB2116960, NCT01899742	UMEC/VI 62.5/25	12	RCT, MC, DB, DD	3	No
Donohue, 2016 [50]	NCT01437540	ACL/FOR 400/12	52	RCT, MC, DB, AC	3	No
		FOR 12				
Martinez, 2017 [51]	PINNACLE-1, NCT01854645	GLY/FOR 18/9.6	24	RCT, MC, DB, PC	3	No
		GLY 18				
		FOR 9.6				
		PBO				
		TIO 18				

Table 2 continued

Author, year	Study name, NCT number	Treatment	ITT/study duration, weeks	Study design	Study phase	Crossover
Martinez, 2017 [51]	PINNACLE-2, NCT01854658	GLY/FOR 18/9.6	24	RCT, MC, DB, PC	3	No
		GLY 18				
		FOR 9.6				
		PBO				
		TIO 18				
Bateman, 2013 [18]	SHINE, NCT01202188	IND/GLY 110/50	26	RCT, MC, DB, PG, PC, AC	3	No
Buhl, 2015 [52]	QUANTIFY, NCT01120717	IND/GLY 110/50	26	RCT, MC, DB, AC, PG, triple dummy	3	No
		TIO 18 + FOR 12				
Tashkin, 2009 [53]	NR	TIO 18 + FOR 12	12	RCT, MC, DB (TIO open label), AC	NR	No
		TIO 18				
Frith, 2018 [54]	FLASH, NCT02516592	IND/GLY 110/50	12	RCT, MC, DB, DD, AC	4	No
		SAL/FF 50/500				
Celli, 2014 [55]	NCT01313637	UMEC/VI 125/25	24	RCT, MC, DB, AC, PC	3	No
		VI 25				
		UMEC 125				
		PBO				
Singh, 2015 [56]	DB2116134, NCT01822899	UMEC/VI 62.5/25	12	RCT, MC, DB, PC	3b	No
		SAL/FP 50/500				
Donohue, 2015 [57]	DB2114930, NCT01817764	UMEC/VI 62.5/25	12	RCT, MC, DB, DD	3	No
		SAL/FP 50/250				
Donohue, 2015 [57]	DB2114951, NCT01879410	UMEC/VI 62.5/25	12	RCT, MC, DB, DD	3	No
		SAL/FP 50/250				
Vogelmeier, 2013 [58]	ILLUMINATE NCT01315249	IND/GLY 110/50	26	RCT, MC, DB, PC	3	No
		SAL/FF 50/500				
Zhong, 2015 [59]	LANTERN, NCT01709903	IND/GLY 110/50	26	RCT, MC, DB, DD	3	No

Table 2 continued

Author, year	Study name, NCT number	Treatment	ITT/study duration, weeks	Study design	Study phase	Crossover
Hoshino, 2015 [60]	NR	TIO 18 + IND 150	16	RCT, open label	_	No
		SAL/FF 50/250				
Singh, 2014 [61]	ACLIFORM-COPD, NCT01462942	ACL/FOR 400/12	24	RCT, MC, DB, PG	3	No
		ACL/FOR 400/6				
		ACL 400				
		FOR 12				
		PBO				
ZuWallack, 2014 [62]	ANHELTO 1, NCT01694771	TIO 18	12	RCT, MC, DB, AC, PG	3	No
		TIO 18 + OLO 5				
ZuWallack, 2014 [62]	ANHELTO 2, NCT01696058	TIO 18	12	RCT, MC, DB, AC, PG	3	No
		TIO 18 + OLO 5				
Dahl, 2013 [63]	ENLIGHTEN, NCT01120717	IND/GLY 110/50	52	RCT, MC, DB, PC	3	No
		PBO				
Buhl, 2015b [19]	TONADO 1, NCT01431274	OLO 5	52	RCT, MC, DB, PG	3	No
		TIO 2.5				
		TIO 5				
		TIO/OLO 2.5/5				
		TIO/OLO 5/5				
Buhl, 2015b [19]	TONADO 2, NCT01431287	OLO 5	52	RCT, MC, DB, PG	3	No
		TIO 2.5				
		TIO 5				
		TIO/OLO 2.5/5				
		TIO/OLO 5/5				

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
Lipworth, 2018 [30]	Age ≥ 40 years; FEV $_1$/FVC < 0.70 predicted and FEV_1 of ≤ 80%; diagnosed with COPD; smoking history of > 10 pack-years	FEV_1	Sponsor-provided ipratropium bromide (administered four times daily) and albuterol sulfate (as rescue), ICS monotherapy	Oral β_2-agonists, LABAs, cromoglycate or nedocromil inhalers, leukotriene antagonists, ketotifen (except as eye drops), and LAMAs	Yes
Singh, 2015 [31]	Age ≥ 40 years; moderate-to-severe COPD (GOLD stage 2–3); post-bronchodilator FEV_1 ≥ 30% and < 80% predicted; FEV_1/FVC < 70% predicted; smoking history of > 10 pack-years	SGRQ	Open-label salbutamol (as rescue); continued ICS therapy if patients were on a stable dose for 6 weeks prior to screening	LAMAs or LABAs other than study medication SAMAs were permitted only during the screening period	Yes
Singh, 2015 [31]	Age ≥ 40 years; moderate-to-severe COPD (GOLD stage 2–3); post-bronchodilator FEV_1 ≥ 30% and < 80% predicted; FEV_1/FVC < 70% predicted; smoking history of > 10 pack-years	SGRQ	Open-label salbutamol (as rescue); continued ICS therapy if patients were on a stable dose for 6 weeks prior to screening	LAMAs or LABAs other than study medication; SAMAs were permitted only during the screening period	Yes
Vogelmeier, 2008 [32]	Age ≥ 40 years at COPD onset; stable COPD; FEV_1 < 70% of patient's predicted normal value (and ≥ 1.00 L); FEV_1/FVC < 70%; smoking history ≥ 10 pack-years	FEV_1	Salbutamol (as rescue), ICS monotherapy	Not specified	Yes
Maleki-Yazdi, 2014 [33]	Outpatient; ≥ 40 years of age; diagnosed with COPD, post-salbutamol FEV_1 ≤ 70% and post-salbutamol FEV_1/FVC ratio < 0.7. Smoking history ≥ 10 pack-years	FEV_1	ICS (dose ≤ 1000 μg/day of FP or equivalent), salbutamol (as rescue)	LABAs, ICS/LABA combination products, oral SABAs and LABAs, inhaled SABAs, inhaled short-acting anticholinergics, and ICS/SABA combinations	Yes
Calverley, 2018 [34]	Age ≥ 40 years; postbronchodilator FEV_1/FVC < 0.70 and postbronchodilator FEV_1 ≤ 60% predicted; history of at least one moderate or severe exacerbation in the preceding year requiring treatment with systemic corticosteroids or antibiotics or both, with or without hospitalisation; smoking history of > 10 pack-years	COPD exacerbations rate	ICS monotherapy, open-label salbutamol (as rescue)	Other short-acting β_2-agonists, LAMAs, and LABAs (other than the study medication)	Yes
Kerwin, 2017 [35]	Age ≥ 40 years; diagnosis of COPD (according to the GOLD 2015 criteria); moderate-to-severe airflow limitation; smoking history of > 10 pack-years	FEV_1	ICS monotherapy, albuterol (as rescue)	ICS/LABA	Yes

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
Kerwin, 2017 [35]	Age ≥ 40 years; diagnosis of COPD (according to the GOLD 2015 criteria); moderate-to-severe airflow limitation; smoking history of > 10 pack-years	FEV_1	ICS monotherapy, albuterol (as rescue)	ICS/LABA	Yes
Maltais, 2019 [22]	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post-salbutamol FEV_1/FVC ratio < 0.7, post-salbutamol FEV_1 of ≥ 30 to ≤ 80% predicted, CAT score ≥ 10, with ≤ 1 moderate exacerbation and no severe exacerbations in the previous year; smoking history of > 10 pack-years	FEV_1	Before screening and during the 4-week run-in period, bronchodilator maintenance therapy was limited to a LAMA or LABA; as-needed salbutamol was allowed throughout all study phases	All patients were required to be ICS and ICS/LABA free for ≥ 6 weeks and LAMA/LABA free for ≥ 2 weeks prior to run-in	No
Feldman, 2017 [25]	Age ≥ 40 years; diagnosis of COPD (ATS/ERS definition), pre- and post-albuterol/salbutamol FEV_1/FVC ratio < 0.70, post albuterol ≤ 70% and ≥ 50% predicted; mMRC grade scale score ≥ 2; smoking history of > 10 pack-years	FEV_1	Albuterol (as rescue), short-acting inhaled muscarinic antagonists, mucolytics, rhinitis medications, influenza vaccine, pneumonia vaccine, antibiotics, systemic corticosteroids, oxygen, localised corticosteroid injections, immunotherapy injections, topical or ophthalmic corticosteroids	Not specified	No
Kalberg, 2016 [36]	Age ≥ 40 years; established COPD (in accordance with the ATS/ERS criteria); pre- and post-bronchodilator FEV_1/FVC ratio < 0.7 and a post-bronchodilator FEV_1 ≤ 70% predicted; mMRC grade scale score ≥ 2; smoking history of > 10 pack-years	FEV_1	ICS monotherapy, albuterol (as rescue)	ICS/LABAs, PDE4 inhibitors, theophyllines, oral β_2-agonists, LAMAs, LABAs, and LAMA/LABA combinations (other than those under study)	No
Riley, 2018 [37]	Age ≥ 40 years; diagnosis of COPD (according to ATS/ERS); FEV_1/FVC ratio < 0.7 and a post-bronchodilator FEV_1 30–70% predicted; resting FRC ≥ 120% predicted; mMRC grade scale score ≥ 2; smoking history of > 10 pack-years	Exercise endurance time	During the washout period: short-acting anticholinergic medications, salbutamol (as rescue)	Not specified	No
Mahler, 2012 [38]	Age ≥ 40 years; post-bronchodilator FEV_1 ≤ 65% and ≥ 30%; post-bronchodilator FEV_1/FVC < 70%; smoking history ≥ 10 pack-years	FEV_1	ICS monotherapy, salbutamol/albuterol (as rescue)	LABAs, short-acting β_2-agonists (except those prescribed in the study), theophylline, anticholinergics	Yes

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
Mahler, 2012 [38]	Age ≥ 40 years; post-bronchodilator FEV_1 ≤ 65% and ≥ 30%; post-bronchodilator FEV_1/FVC < 70%; smoking history ≥ 10 pack-years	FEV_1	ICS monotherapy, salbutamol/albuterol (as rescue)	LABAs, short-acting β_2-agonists (except those prescribed in the study), theophylline, anticholinergics	Yes
Vincken, 2014 [39]	Diagnosed with moderate to severe stable COPD (stage II or III according to GOLD criteria); FEV_1 ≥ 30% and/or < 80% predicted, a post-bronchodilator FEV_1/FVC < 0.70; symptomatic patients (according to daily diary data); smoking history ≥ 10 pack-years	FEV_1	ICS monotherapy, salbutamol (as rescue)	Long-acting bronchodilators before starting the run-in period (≥ 7 days for LAMAs and the LABA indacaterol, and ≥ 48 h for other LABAs or ICS/LABA)	Yes
Wedzicha, 2013 [40]	Age ≥ 40 years; 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	COPD exacerbations rate	Stable dose of ICS, salbutamol (as rescue)	Long-acting bronchodilators	Yes
GSK CSR[a]	Outpatient; ≥ 40 years of age; diagnosis of COPD, post-salbutamol FEV_1 ≤ 70% and post-salbutamol FEV_1/FVC ratio < 0.7. Smoking history ≥ 10 pack-years	FEV_1	ICS (dose ≤ 1000 µg/day of FP or equivalent), salbutamol/albuterol (as rescue)	LABAs, oral SABAs and LABAs, inhaled SABAs, inhaled short-acting anticholinergics, and SABA/ICS combination products	Yes
GSK CSR[a]	Outpatient; ≥ 40 years of age; diagnosed with COPD, post-salbutamol FEV_1 ≤ 70% and post-salbutamol FEV_1/FVC ratio < 0.7. Smoking history ≥ 10 pack-years	FEV_1	ICS (dose ≤ 1000 µg/day of FP or equivalent), salbutamol/albuterol (as rescue)	LABAs, short-acting β_2-agonists, short-acting anticholinergics and SABA/ICS combination products	Yes

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
GSK CSR[a]	Outpatient; ≥ 40 years of age; diagnosed with COPD; post-salbutamol FEV_1/FVC ratio of < 0.70 and a post-salbutamol FEV_1 of ≤ 70%; smoking history ≥ 10 pack-years	FEV_1	ICS (dose ≤ 1000 µg/day of FP or equivalent), salbutamol/albuterol (as rescue)	LABAs, ICS/LABA combination products, SABAs, short-acting anticholinergics, and ICS/SABA combination products	Yes
Vogelmeier, 2016 [41]	Age ≥ 40 years; diagnosed with moderate-to-severe COPD (stage II or III according to GOLD 2013 criteria); post-bronchodilator FEV_1/FVC < 70% and FEV_1 < 80% predicted; symptomatic patients; CAT score ≥ 10; smoking history ≥ 10 pack-years	FEV_1	Salbutamol (as rescue)	Use of triple therapy (LAMA/LABA/ICS) within 4 weeks of the screening visit; patients discontinued all bronchodilator and ICS medication the night before the randomisation visit (visit 2)	NR
Wedzicha, 2016 [42]	Age ≥ 40 years; diagnosed with stable COPD (according to GOLD 2011 criteria); post-bronchodilator FEV_1/FVC < 0.70%; post-bronchodilator FEV_1 ≥ 25 and < 60% predicted; symptomatic patients; documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics; mMRC grade scale score ≥ 2; smoking history ≥ 10 pack-years	COPD exacerbation rate	Open-label salbutamol (as rescue)	Pre-existing LABA, LAMA, ICS, and LABA/ICS fixed-combination therapies were discontinued prior to run-in; ICS and bronchodilators (apart from study medications) were prohibited during the run-in and treatment periods	NR
Maltais, 2019 [24]	Age ≥ 40 years; post-bronchodilator FEV_1/FVC < 0.7 and FEV_1 < 80% predicted; smoking history ≥ 10 pack-years	FEV_1	Patients prescribed only rescue medication or maintenance monotherapy before the study were required to be symptomatic (CAT score 10) at screening, whereas there was no symptom requirement at screening for patients prescribed dual maintenance therapy (ICS/LABA or LAMA/LABA) before the study	Not specified	No
Sethi, 2019 [43]	Age ≥ 40 years; diagnosed with moderate-to-severe COPD; post-bronchodilator FEV_1/FVC < 70% and FEV_1 < 80% predicted; CAT score ≥ 10; smoking history ≥ 10 pack-years	FEV_1	Inhaled, oral, or parenteral corticosteroids (dose equivalent to ≤ 10 mg/day prednisone); oxygen therapy (< 15 h/day); oral sustained-release theophylline, selective β-blocking agents (e.g. atenolol, metoprolol, nebivolol; stable administration for ≥ 2 weeks)	LABAs, LAMAs, SABAs (except albuterol/salbutamol, which were permitted as needed throughout all study periods), SAMAs (except ipratropium, during washout and screening only), methylxanthines, leukotriene modifiers, PDE4 inhibitors, or non-selective beta-blocking agents	Yes

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
D'Urzo, 2014 [44]	Age ≥ 40 years; FEV_1 < 80% and ≥ 30% predicted; post-bronchodilator FEV_1/FVC < 70; smoking history ≥ 10 pack-years	FEV_1	Albuterol/salbutamol (as rescue); other COPD medications such as theophylline, ICS, oral or parenteral corticosteroids (≤ 10 mg/day or 20 mg every other day of prednisone) were allowed if treatment was stable ≥ 4 weeks prior to screening	LABAs other than investigational treatment	Yes
D'Urzo, 2017 [45][b]	Age ≥ 40 years; FEV_1 < 80% and ≥ 30% predicted; post-bronchodilator FEV_1/FVC < 70; smoking history ≥ 10 pack-years	Safety	Theophylline, ICS, oral or parenteral corticosteroids (≤ 10 mg/day or 20 mg every other day of prednisone), albuterol/salbutamol (as rescue)	Long-acting bronchodilators other than the investigative treatment	Yes
Ferguson, 2016 [46]	Age ≥ 40 years; diagnosed with stable COPD (according to GOLD 2011 criteria); moderate-to-severe airflow limitation; post-bronchodilator FEV_1/FVC < 70% and FEV_1 ≥ 30% and < 80% predicted; symptomatic patients (defined by mMRC grade ≥ 2); smoking history ≥ 10 pack-years	Safety and tolerability	Salbutamol/albuterol (as rescue)	Nebulized salbutamol/albuterol, non-potassium-sparing diuretics, non-selective beta-blocking agents, cardiac antiarrhythmics class Ia and III, drugs with QT prolongation potential, tricyclic antidepressants, antipsychotic agents, LAMA, ICS/LABA, SAMA, SABA, SABA/SAMA; patients receiving selective serotonin reuptake inhibitors, ICS, intranasal steroids, H_1-antagonists, inactivated influenza, pneumococcal or any other inactivated vaccine were excluded unless on stable dose	No
Mahler, 2015 [47]	Age ≥ 40 years; stable COPD (according to GOLD 2011 guidelines); post-bronchodilator FEV_1 ≥ 30% and < 80% predicted; post-bronchodilator FEV_1/FVC < 0.70 at run-in; mMRC grade ≥ 2 at run-in; smoking history ≥ 10 pack-years	FEV_1	ICS	COPD-related medications other than investigational therapy (LAMAs, SAMAs, ICS/LABA combinations, SABA, SAMA/SABA combinations, etc.); patients receiving SSRIs, ICS, intranasal steroids, H_1-antagonists, or inactivated influenza, pneumococcal or any other inactivated vaccines should be excluded unless on stable dose	Yes

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
Mahler, 2015 [47]	Age ≥ 40 years; stable COPD (according to GOLD 2011 guidelines); post-bronchodilator FEV_1 ≥ 30% and < 80% predicted; post-bronchodilator FEV_1/FVC < 0.70 at run-in; mMRC grade ≥ 2 at run-in; smoking history ≥ 10 pack-years	FEV_1	ICS	COPD-related medications other than investigational therapy (LAMAs, SAMAs, ICS/LABA combinations, SABA, SAMA/SABA combinations, etc.); patients receiving SSRIs, ICS, intranasal steroids, H_1-antagonists, or inactivated influenza, pneumococcal or any other inactivated vaccines should be excluded unless on stable dose	Yes
Siler, 2016 [48]	Age ≥ 40 years; diagnosed with stable COPD; moderate-to-severe airflow limitation; pre- and post-albuterol FEV_1/FVC < 0.70 and post-albuterol FEV_1 ≤ 70% predicted; symptomatic patients (defined by mMRC grade ≥ 2); mMRC grade scale score ≥ 2; smoking history ≥ 10 pack-years	SGRQ	Albuterol (as rescue)	Depot corticosteroids, systemic, oral or parenteral corticosteroids, ICS/LABA combination products, ICS (dose > 1000 μg/day of FP or equivalent), initiation or discontinuation of ICS use, PDE4 inhibitors (roflumilast), LAMAs, inhaled LABAs, LAMA/LABA combination, theophyllines, oral β_2-agonists, inhaled SABAs, inhaled short-acting anticholinergics, inhaled short-acting anticholinergic/SABA combination products	No
Kerwin, 2017 [49]	Age ≥ 40 years; diagnosed with stable COPD (according to ATS/ERS); post-bronchodilator FEV_1 ≤ 70% and ≥ 50% predicted; mMRC grade scale score ≥ 1; smoking history ≥ 10 pack-year	FEV_1	Albuterol (as rescue)	Not specified	No
Donohue, 2016 [50]	Age ≥ 40 years; diagnosed with moderate to severe COPD; FEV_1/FVC ratio < 70%; post-bronchodilator FEV_1 30% and < 80% predicted; smoking history ≥ 10 pack-year	Safety	Albuterol (as rescue but not within 6 h before a visit), ICS and oral or parenteral corticosteroids at doses ≤ 10 mg/day, theophylline and H_1-antihistamine (dosage was stable for ≥ 4 weeks prior to screening and throughout the trial), chronic use of oxygen therapy (up to 15 h/day provided the dosage was stable for ≥ 4 weeks prior to screening), select β1-blocking agents (atenolol, metoprolol, nebivolol; stable dosage for ≥ 2 weeks prior to screening)	Indacaterol within 15 days prior to screening or during the trial; select β1-blocking agents (atenolol, metoprolol, nebivolol) were permitted for chronic use if the dosage was stable for ≥ 2 weeks prior to screening	Yes

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
Martinez, 2017 [51]	Age ≥ 40 years; diagnosed with moderate-to-very severe COPD (according to ATS/ERS); FEV_1/FVC ratio < 0.70 and FEV_1 < 80% predicted; FEV_1 < 30% predicted were required to have postbronchodilator FEV_1 ≥ 750 mL; smoking history ≥ 10 pack-year	FEV_1	Albuterol (as rescue), oral corticosteroid (stable dose equivalent to ≤ 5 mg/day or ≤ 10 mg every other day), prednisone, ICS and/or PDE4 inhibitors; if ICS was administered as part of an FDC, this was discontinued and substituted with an ICS single agent (fluticasone, mometasone, or budesonide) at the equivalent dose	Theophylline (> 400 mg/day), leukotriene antagonists, mast-cell stabilisers, non-selective β-blockers, antiarrhythmic agents, antipsychotics and antidepressants (except selective serotonin [or serotonin–norepinephrine] reuptake inhibitors)	Yes
Martinez, 2017 [51]	Age ≥ 40 years; diagnosed with moderate-to-very severe COPD (according to ATS/ERS); FEV_1/FVC ratio < 0.70 and FEV_1 < 80% predicted; FEV_1 < 30% predicted were required to have postbronchodilator FEV_1 ≥ 750 mL; smoking history ≥ 10 pack-year	FEV_1	Albuterol (as rescue), oral corticosteroid (stable dose equivalent to ≤ 5 mg/day or ≤ 10 mg every other day), prednisone, ICS and/or PDE4 inhibitors; if ICS was administered as part of an FDC, this was discontinued and substituted with an ICS single agent (fluticasone, mometasone, or budesonide) at the equivalent dose	Theophylline (> 400 mg/day), leukotriene antagonists, mast-cell stabilisers, non-selective β-blockers, antiarrhythmic agents, antipsychotics and antidepressants (except selective serotonin [or serotonin–norepinephrine] reuptake inhibitors)	Yes
Bateman, 2013 [18]	Age ≥ 40 years; 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	FEV_1	Salbutamol/albuterol (as rescue), inhaled or intranasal corticosteroids (at constant doses)	LABAs, LAMAs, and ICS/LABA	Yes
Buhl, 2015 [52]	Age ≥ 40 years; moderate-to-severe stable COPD (GOLD stage 2–3); post-bronchodilator FEV_1 ≥ 30% and < 80% predicted; post-bronchodilator FEV_1/FVC < 0.7; smoking history of ≥ 10 pack-years	SGRQ	Salbutamol (as rescue), SSRI, H_1-antagonists (except mizolastine or terfenadine), inactivated influenza, pneumococcal or any other inactivated vaccine if not administered within 48 h before the study visit; patients receiving ICS at baseline continued treatment at the same or equivalent dose and regimen	Not specified	Yes

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
Tashkin, 2009 [53]	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	FEV_1	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	Following screening, prohibited medications (i.e. β-agonists, β-blockers, cromolyn sodium, ipratropium bromide, leukotriene antagonists, cytotoxic agents, and theophylline) were withdrawn	Yes
Frith, 2018 [54]	Age ≥ 40 years; post-bronchodilator FEV_1/FVC < 70%; post-bronchodilator FEV_1 ≤ 70% predicted; post-bronchodilator FEV_1 ≥ 30% and < 80% predicted; mMRC grade scale score ≥ 2; treated with SFC 50/500 µg BID for ≥ 3 months prior to screening; CAT score of ≥ 10; smoking history of ≥ 10 pack-years	FEV_1	Pre-randomisation maintenance therapy with salmeterol/fluticasone, SABA (salbutamol or albuterol) for use as a rescue inhaler on an 'as-needed' basis throughout the study	LAMA monotherapy, SABA (except when used as a rescue medication), SAMA, SABA/SAMA, LABA monotherapy, oral PDE4 inhibitor, xanthines, parenteral or oral corticosteroids (except as allowed for treating COPD exacerbations) and intramuscular depot corticosteroids	No
Celli, 2014 [55]	Age ≥ 40 years; diagnosed with established COPD; post-bronchodilator FEV_1/FVC < 70%; post-salbutamol FEV_1 ≤ 70% predicted; mMRC grade scale score ≥ 2; smoking history of ≥ 10 pack-years	FEV_1	Albuterol (as rescue)	Depot corticosteroids; systemic, oral, or parenteral corticosteroids; antibiotics (for lower respiratory tract infection); cytochrome P450 3A4 strong inhibitors; LABA/ICS combination products; ICS > 1000 µg/day; PDE4 inhibitor (e.g. roflumilast); TIO; theophyllines; oral leukotriene inhibitors; oral β_2-agonists; inhaled LABA; inhaled sodium cromoglycate or nedocromil sodium; inhaled SABAs; inhaled short-acting anticholinergics; inhaled short-acting anticholinergic/short-acting β_2-agonist combination products	NR

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
Singh, 2015 [56]	Age ≥ 40 years; diagnosed with established COPD; post-bronchodilator $FEV_1/FVC < 0.7$; a post-salbutamol $FEV_1 \geq 30\%$ and $< 70\%$ predicted; mMRC grade scale score ≥ 2; smoking history of ≥ 10 pack-years	FEV_1	Salbutamol (as rescue)	Depot corticosteroids, antibiotics for lower respiratory tract infection, ICS/LABA products, PDE4 inhibitors, long-acting anticholinergics, xanthines, oral leukotriene inhibitors, nedocromil sodium, SABAs, short-acting anticholinergics, SABA combination products, herbal medications potentially containing oral or systemic steroids, any other investigational medication for COPD	NR
Donohue, 2015 [57]	Age ≥ 40 years; diagnosed with established COPD; post-bronchodilator $FEV_1 \geq 30\%$ and $< 70\%$ predicted; post-bronchodilator $FEV_1/FVC < 0.7$; mMRC grade scale score ≥ 2; smoking history of ≥ 10 pack-years	FEV_1	Albuterol (as rescue)	Depot corticosteroids, systemic, oral or parenteral corticosteroids, antibiotics, cytochrome inhibitors, herbal medications potentially containing steroids, ICS, ICS/LABA, PDE4 inhibitors, olodaterol, indacaterol, inhaled long-acting anticholinergics, xanthines, oral leukotriene inhibitors, oral beta-agonists, SAL and FOR, inhaled sodium cromoglycate or nedocromil sodium, inhaled SABAs, inhaled short-acting anticholinergics, inhaled short-acting anticholinergic/SABA combination products, investigational medication	No
Donohue, 2015 [57]	Age ≥ 40 years; diagnosed with established COPD; post-bronchodilator $FEV_1 \geq 30\%$ and $< 70\%$ predicted; post-bronchodilator $FEV_1/FVC < 0.7$; mMRC grade scale score ≥ 2; smoking history of ≥ 10 pack-years	FEV_1	Albuterol (as rescue)	Depot corticosteroids, systemic, oral or parenteral corticosteroids, antibiotics, cytochrome inhibitors, herbal medications potentially containing steroids, ICS, ICS/LABA, PDE4 inhibitors, olodaterol, indacaterol, inhaled long-acting anticholinergics, xanthines, oral leukotriene inhibitors, oral beta-agonists, SAL and FOR, inhaled sodium cromoglycate or nedocromil sodium, inhaled SABAs, inhaled short-acting anticholinergics, inhaled short-acting anticholinergic/SABA combination products, investigational medication	No

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
Vogelmeier, 2013 [58]	Age ≥ 40 years; diagnosed with moderate-to-severe stable COPD (stage II or stage III; according to GOLD guideline); post-bronchodilator FEV_1 ≥ 40% and < 80% predicted; post-bronchodilator FEV_1/FVC < 0.7; symptomatic patients (mMRC grade score 1); smoking history of ≥ 10 pack-years	FEV_1	Salbutamol (as rescue), selective serotonin reuptake inhibitors (stable treatment regimen for ≥ 1 month prior to screening visit and during the study screening normal ECG), inactivated vaccine (not administered < 48 h prior to a study visit), intranasal corticosteroids (constant doses and dose regimens for ≥ 5 days prior to screening), H_1-antagonists (in constant doses and dose regimens for ≥ 5 days prior to screening)	Not specified	NR
Zhong, 2015 [59]	Age ≥ 40 years; diagnosed with moderate-to-severe stable COPD (stage II or stage III; according to GOLD 2010 guideline); post-bronchodilator FEV_1 ≥ 30% and < 80% predicted; post-bronchodilator FEV_1/FVC < 0.7; mMRC grade score ≥ 2; smoking history of ≥ 10 pack-years	FEV_1	Selective serotonin reuptake inhibitors (stable dose for ≥ 1 month prior to visit 1 and during the study), intranasal corticosteroids (stable dose for ≥ 30 days prior to visit 1), H_1-antagonists (stable dose for ≥ 30 days prior to visit 1), inactivated influenza, pneumococcal or any other inactivated vaccine (not administered < 48 h prior to a study visit)	Not specified	Yes
Hoshino, 2015 [60]	Age ≥ 40 years; FEV_1 < 80% and ≥ 30% predicted; post-bronchodilator FEV_1/FVC < 70%; smoking history of ≥ 10 pack-years	Airway dimensions	Salbutamol (as rescue)	Antibiotics, systemic glucocorticosteroids	No
Singh, 2014 [61]	Age ≥ 40 years; FEV_1 < 80% and ≥ 30% predicted; post-bronchodilator FEV_1/FVC < 70%; smoking history of ≥ 10 pack-years	FEV_1	Albuterol/salbutamol (as rescue); other COPD medications, e.g. theophylline, ICS, oral or parenteral corticosteroids (≤ 10 mg/day or 20 mg every other day of prednisone) were allowed if treatment was stable ≥ 4 weeks prior to screening	LABAs other than investigational treatment	Yes, provided treatment was stable ≥ 4 weeks pre-screening

Table 2 continued

Author, year	Simplified inclusion criteria	Primary outcomes	Permitted background treatments	Prohibited background treatments	ICS allowed
ZuWallack, 2014 [62]	Age ≥ 40 years; post-bronchodilator FEV_1 ≥ 30% and < 80% of predicted normal; post-bronchodilator FEV_1/FVC < 70% (GOLD stage 2–3); smoking history of > 10 pack-years	FEV_1	ICS, oral (≤ 10 mg prednisone per day, or equivalent) and injected steroids; cromolyn sodium/nedocromil sodium; antihistamines; antileukotrienes; methylxanthines; mucolytics; theophyllines; albuterol permitted as rescue medication only	Concurrent ICS in fixed combination with LABA, ICS/SABA combinations, SAMA/SABA combinations or PDE4 inhibitors	Yes
ZuWallack, 2014 [62]	Age ≥ 40 years; post-bronchodilator FEV_1 ≥ 30% and < 80% of predicted normal; post-bronchodilator FEV_1/FVC < 70% (GOLD stage 2–3); smoking history of > 10 pack-years	FEV_1	ICS, oral (≤ 10 mg prednisone per day, or equivalent) and injected steroids; cromolyn sodium/nedocromil sodium; antihistamines; antileukotrienes; methylxanthines; mucolytics; theophyllines; albuterol permitted as rescue medication only	Concurrent ICS in fixed combination with LABA, ICS/SABA combinations, SAMA/SABA combinations or PDE4 inhibitors	Yes
Dahl, 2013 [63]	Age ≥ 40 years; 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	Safety and tolerability	Albuterol (as rescue), ICS monotherapy	Long-acting bronchodilators (LABAs, LAMAs, theophylline) and short-acting muscarinic antagonists	Yes
Buhl, 2015b [19]	Outpatient; age ≥ 40 years; smoking history of > 10 pack-years; moderate-to-very-severe COPD (GOLD stage 2–4); post-bronchodilator FEV_1 < 80% predicted; post-bronchodilator FEV_1/FVC < 70%	FEV_1	ICS	Oxygen	Yes

Table 2 continued

Author, year	Study name, NCT number	Treatment	ITT/study duration, weeks	Study design	Study phase
Crossover					
	Buhl, 2015b [19]	Outpatient;	age ≥ 40 years; smoking history of > 10 pack-years; moderate-to-very-severe COPD (GOLD stage 2–4); post-bronchodilator FEV_1 < 80% predicted; post-bronchodilator FEV_1/FVC < 70%	FEV_1	ICS
Oxygen	Yes				

AC active-controlled, *ACL* aclidinium, *ATS* American Thoracic Society, *CAT* COPD Assessment Test, *COPD* chronic obstructive pulmonary disease, *CSR* clinical study report, *DB* double blind, *DD* double dummy, *ECG* electrocardiogram, *ERS* European Respiratory Society, FEV_1 forced expiratory volume in 1 s, *FOR* formoterol fumarate, *FP* fluticasone propionate, *FRC* functional residual capacity, *FVC* forced vital capacity, *ICS* inhaled corticosteroid, *GLY* glycopyrronium, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *IND* indacaterol, *ITT* intent-to-treat, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *MC* multicentred, *MDI* metered dose inhaler, *mMRC* modified Medical Research Council, *NMA* network meta-analysis, *NR* not reported, *OLO* olodaterol, *PBO* placebo, *PC* placebo controlled, *PDE* phosphodiesterase, *PG* parallel group, *RCT* randomised controlled trial, *SAL* salmeterol, *SABA* short-acting β_2-agonist, *SAMA* short-acting muscarinic antagonist, *SGRQ* St George's Respiratory Questionnaire, *SSRI* selective serotonin reuptake inhibitor, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

[a]CSRs are available from clinicalstudydatarequest.com

[b]The extension trial AUGMENT EXTENSION was not counted as a unique trial but secondary publication to main trial

Health-Related Quality of Life

SGRQ total score was available in 17 studies at 24 weeks (Supplementary Fig. S5) and 20 studies at 12 weeks. In the FE model at 24 weeks, there was no evidence of any statistically significant differences in SGRQ total score with UMEC/VI compared with all other LAMA/LABAs (Fig. 3a), whereas UMEC/VI provided statistically significantly greater improvements versus UMEC 125 µg (mean difference in change from baseline [95% CI] − 1.89 [− 3.49, − 0.30), GLY 18 µg (− 2.12 [− 3.61, − 0.62]), GLY 50 µg (− 1.43 [− 2.67, − 0.18]), TIO 18 µg (− 1.37 [− 2.42, − 0.32]), and salmeterol (SAL) 50 µg (− 1.79 [− 3.04, − 0.54]), but not versus other monotherapies (Fig. 3b). At 12 weeks, improvements in SGRQ total score with UMEC/VI were not statistically significant compared with other LAMA/LABA combinations; statistically significant improvements were seen for IND/GLY 110/50 µg and TIO 18 µg + IND 150 µg compared with UMEC/VI (Supplementary Table S2). UMEC/VI provided statistically significantly greater improvements in SGRQ total score at 12 weeks than TIO 18 µg and SAL 50 µg, but not compared with the other monotherapies (Supplementary Table S2). In the FE model, all treatments provided statistically significant improvements in SGRQ total score versus placebo, with the exception of UMEC 125 µg at 24 and 12 weeks and SAL 50 µg and IND 150 µg at 24 weeks (Supplementary Tables S3 and S4).

SGRQ responder analyses were available in 14 and 12 studies at 24 (Supplementary Fig. S6) and 12 weeks, respectively. At 24 weeks, UMEC/VI was associated with a statistically significantly greater proportion of SGRQ responders compared with UMEC 62.5 µg (SGRQ responders odds ratio [95% CI] 1.19 [1.02, 1.40]), GLY 18 µg (1.54 [1.22, 1.95]), TIO 18 µg (1.18 [1.00, 1.39]), FOR 9.6 µg (1.36 [1.08, 1.72]) and SAL 50 µg (1.47 [1.22, 1.78]) (Supplementary Fig. S7). At 12 weeks, the odds of being a responder were significantly greater with UMEC/VI versus UMEC 62.5 µg, ACL 400 µg and SAL 50 µg (Supplementary Table S2). All treatments provided statistically significantly greater proportion of SGRQ responders compared with placebo, with the exception of

Table 3 Baselines characteristics of patients in the studies included in the NMA

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Lipworth, 2018 [30]	GLY/FOR (MDI) 18/9.6	551	74.0	64.7	45.7	Severe: 34.8 Very severe: 4.2	30.7	6.2	45.9	NR	NR	NR	53.9
	GLY 18	474	73.0	64.0	44.1	Severe: 35.4 Very severe: 3.0	30.2	6.2	44.8	NR	NR	NR	54.8
	FOR 9.6	480	76.0	64.1	43.3	Severe: 35.6 Very severe: 2.9	29.6	6.1	46.9	NR	NR	NR	53.9
	PBO	235	72.8	63.9	48.1	Severe: 36.6 Very severe: 2.6	33.6	6.1	45.7	NR	NR	NR	54.4

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Singh, 2015 [31] (OTEMTO 1)	TIO + OLO 5/5	203	56.2	64.7	54.7	GOLD 3: 36.0 GOLD 4: 0	41.9	NR	NR	1.3	1.5	NR	54.9
	TIO + OLO 2.5/5	202	57.4	64.7	48.5	GOLD 3: 34.2 GOLD 4: 0.5	38.6	NR	NR	1.3	1.5	NR	55.5
	TIO 5	203	61.1	64.9	48.3	GOLD 3: 36.0 GOLD 4: 1.0	37.9	NR	NR	1.3	1.5	NR	54.7
	PBO	204	62.3	65.1	43.1	GOLD 3: 36.0 GOLD 4: 0.5	34.8	NR	NR	1.4	1.6	NR	56.3

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Singh, 2015 [31] (OTEMTO 2)	TIO + OLO 5/5	202	65.8	65.2	45.5	GOLD 3: 38.1 GOLD 4: 0	35.6	NR	NR	1.4	1.6	NR	54.8
	TIO + OLO 2.5/5	202	62.4	64.4	44.6	GOLD 3: 34.7 GOLD 4: 1.5	41.1	NR	NR	1.3	1.5	NR	54.5
	TIO 5	203	64.0	64.7	44.8	GOLD 3: 32.5 GOLD 4: 0	35.0	NR	NR	1.4	1.6	NR	55.9
	PBO	202	57.9	64.0	47.0	GOLD 3: 39.1 GOLD 4: 0.5	35.1	NR	NR	1.3	1.5	NR	54.3
Vogelmeier, 2008 [32]	FOR 10	210	75.7	61.8	NR	NR	NR	7	35.4	1.5	NR	51.6	NR
	TIO 18	221	79.2	63.4	NR	NR	NR	6.9	38.6	1.5	NR	51.6	NR
	TIO 18 + FOR 10	207	79.2	62.6	NR	NR	NR	7.2 (7.0)	37.9	1.5	NR	50.4	NR
	PBO	209	77.5	62.5	NR	NR	NR	6.7	40.1	1.5	NR	51.1	NR

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Maleki-Yazdi, 2014 [33]	UMEC/VI 62.5/25	454	68.0	61.9	59.0	60.0	54.0	NR	44.1	1.3	Post salbutamol: 1.4 Post ipratropium: 1.5	NR	46.2
	TIO 18	451	67.0	62.7	54.0	58.0	53.0	NR	44.4	1.3	Post salbutamol: 1.4 Post ipratropium: 1.5	NR	46.5
Calverley, 2018 [34]	TIO/OLO 5/5	3939	71.0	66.5	36.0	GOLD C: 4.0 GOLD D: 40	ICS only: 3 LABA–ICS: 26 LAMA–ICS: 2 LAMA–LABA–ICS: 39	NR	44.8	NR	1.2	NR	44.6
	TIO 5	3941	72.0	66.3	36.0	GOLD C: 4.0 GOLD D: 39	ICS only: 2 LABA–ICS: 26 LAMA–ICS: 2 LAMA–LABA–ICS: 40	NR	44.7	NR	1.2	NR	44.5
Kerwin, 2017 [49] (A2349)	IND/GLY 27.5/15.6 BID and UMEC/VI 62.5/25	357	52.1	64.1	56.9	GOLD 3: 35.6	36.1	8.1	52.3	1.2	1.5	NR	54.0
Kerwin, 2017 [49] (A2350)	IND/GLY 27.5/15.6 BID and UMEC/VI 62.5/25	355	54.1	63.9	57.2	GOLD 3: 37.5	36.1	8.4	54.0	1.3	1.6	NR	54.6

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Maltais, 2019 [22]	UMEC/VI 62.5/25	812	61.0	64.6	49	GOLD 3: 36.0	NR	8.8	49.4	1.5	1.6	NR	54.9
	UMEC 62.5	804	59.0	64.9	49	GOLD 3: 34.0	NR	7.8	47.6	1.5	1.6	NR	55.9
	SAL 50	809	58.0	64.4	51	GOLD 3: 35.0	NR	8.3	48.1	1.5	1.6	NR	55.6
Feldman, 2017 [25]	UMEC/VI 62.5/25	236	60.0	64.4	53	5.0	4	NR	50.2	NR	1.7	NR	59.6
	TIO/OLO 5/5	236	60.0	64.4	53	5.0	4	NR	50.2	NR	1.7	NR	59.6
Kalberg, 2016 [36]	UMEC/VI 62.5/25	482	74.0	64.0	41.0	56.0	56.0	NR	43.2	NR	1.4	NR	NR
	TIO 18 + IND 150	479	71.0	64.0	46.0	58.0	51.0	NR	42.3	NR	1.4	NR	NR
Riley, 2018 [37]	UMEC/VI 62.5/25	198	53.0	60.7	64.0	46.0	28.0	NR	52.2	1.4	1.5	NR	50.5
	PBO	198	53.0	60.7	64.0	46.0	28.0	NR	52.2	1.4	1.5	NR	50.5
Mahler, 2012 [38] (INTRUST-1)	TIO 18 + IND 150	570	70.0	64.0	40.0	53.0	52.0	7.1	47.2	Pre salbutamol: 1.2 Pre ipratropium: 1.2	Post salbutamol: 1.3 Post ipratropium: 1.4	NR	48.3
	TIO 18	561	67.0	63.4	36.0	53.0	52.0	6.6	47.2	Pre salbutamol: 1.2 Pre ipratropium: 1.2	Post salbutamol: 1.3 Post ipratropium: 1.4	NR	48.9

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Mahler, 2012 [38] (INTRUST-2)	TIO 18 + IND 150	572	63.0	63.1	38.0	54.0	57.0	7.3	46.2	Pre salbutamol: 1.1 Pre ipratropium: 1.2	Post salbutamol: 1.3 Post ipratropium: 1.3	NR	48.6
	TIO 18	570	68.0	62.8	43.0	54.0	51.0	7.1	46.3	Pre salbutamol: 1.2 Pre ipratropium: 1.2	Post salbutamol: 1.3 Post ipratropium: 1.4	NR	48.6
Vincken, 2014 [39]	IND 150 + GYL 50	226	79.6	63.4	42.5	38.5	61.1	7.1	44.5	NR	1.5	54.2	NR
	IND 150	223	84.2	64.1	41.6	33.0	64.3	7.2	44.4	NR	1.6	55.5	NR
Wedzicha, 2013 [40]	IND/GLY 110/50	729	76.0	63.1	38.0	Severe: 79.0 Very severe: 21	75.0	7.2	45.0	0.9	1.0	NR	37.0
	GLY 50	740	73.0	63.1	38.0	Severe: 79.0 Very severe: 21.0	75.0	7.1	44.0	0.9	1.0	NR	37.3
	TIO 18	737	75.0	63.6	37.0	Severe: 79.0 Very severe: 21.0	76.0	7.2	47.0	0.9	1.0	NR	37.4

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
GSK CSR[b] (DB2113374)	UMEC 125	222	67.0	64.5	44.0	61.0	56.0	NR	47.6	NR	1.1	NR	46.2
	UMEC/VI 62.5/25	217	65.0	65.0	42.0	51.0	47.0	NR	47.8	NR	1.2	NR	47.7
	UMEC/VI 125/25	215	69.0	63.8	45.0	59.0	53.0	NR	46.9	NR	1.2	NR	47.1
	TIO 18	215	71.0	65.2	47.0	52.0	53.0	NR	54.0	NR	1.2	NR	47.4
GSK CSR[b] (DB2113360)	UMEC/VI 125/25	214	71.0	62.9	58.0	53.0	48.0	NR	43.5	NR	1.3	NR	47.2
	UMEC/VI 62.5/25	212	70.0	63.0	46.0	50.0	44.0	NR	44.8	NR	1.3	NR	48
	VI 25	209	68.0	63.2	51.0	54.0	40.0	NR	41.6	NR	1.3	NR	47.7
	TIO 18	208	67.0	62.6	48.0	53.0	45.0	NR	41.9	NR	1.3	NR	47.8
GSK CSR[b] (DB2113373)	UMEC 62.5	418	71.0	64.0	50.0	54.0	52.0	NR	46.8	1.2	1.3	NR	46.8
	VI 25	421	68.0	62.7	47.0	53.0	50.0	NR	44.7	1.2	1.4	NR	48.2
	UMEC/VI 62.5/25	413	74.0	63.1	49.0	51.0	51.0	NR	46.5	1.3	1.4	NR	47.8
	PBO	280	70.0	62.2	54.0	58.0	49.0	NR	47.2	1.2	1.4	NR	46.7
Vogelmeier, 2016 [41]	ACL/FOR 400/12	468	65.7	63.5	NR	GOLD D: 43.5	37.7	NR	41.6	NR	1.4	NR	53.3
	SAL/FP 50/500	466	64.4	63.3	NR	GOLD D: 44.8	39.1	NR	42.6	NR	1.4	NR	53.2
Wedzicha, 2016 [42]	IND/GLY 110/50	1680	77.3	64.6	40.0	57.9	56.8	7.2	NR	1.0	1.2	NR	44.0
	SAL/FF 50/500	1682	74.8	64.5	40.0	58.3	55.8	7.3	NR	1.0	1.2	NR	44.1
Maltais 2019 [24]	GLY/FOR 18/9.6	552.0	74.3	64.3	52.7	53.5	53.3	8.1	39.5	NR	NR	NR	48.5
	UMEC/VI 62.5/25	552.0	71.0	63.8	54.3	52.6	52.7	8.0	38.7	NR	NR	NR	48.9

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Sethi, 2019 [43]	ACL/FOR 400/12	314	61.5	64.4	52.2	47.5	33.1	NR	46.2	1.3	NR	NR	50.9
	ACL 400	475	64.0	64.4	52.2	51.4	32.4	NR	45.4	1.3	NR	NR	49.6
	FOR 12	319	59.6	64.7	51.1	53.6	34.2	NR	45.2	1.3	NR	NR	49.6
	TIO 18	475	58.1	64.0	52.6	45.7	29.9	NR	46.4	1.3	NR	NR	51.2
D'Urzo, 2014 [44]	ACL/FOR 400/12	335	50.1	64.2	51.6	42.4	NR	NR	53.3	1.3	NR	NR	53.2
	ACL/FOR 400/6	333	56.2	63.9	52.9	38.1	NR	NR	52.1	1.4	NR	NR	54.7
	ACL 400	337	55.8	64.4	50.7	43.6	NR	NR	52.0	1.3	NR	NR	53
	FOR 12	332	50.9	63.7	51.5	39.5	NR	NR	52.5	1.4	NR	NR	53.9
	PBO	332	52.7	63.5	50.9	45.2	NR	NR	53.3	1.4	NR	NR	52.6
D'Urzo, 2017 [45][c]	ACL/FOR 400/12	182	48.4	63.7	53.8	44.0	NR	NR	53.3	1.3	NR	NR	52.1
	ACL/FOR 400/6	204	58.8	63.6	54.4	36.8	NR	NR	53.7	1.4	NR	NR	55.1
	ACL 400	194	53.6	62.9	59.3	45.4	NR	NR	52.3	1.3	NR	NR	52.7
	FOR 12	192	46.9	62.8	53.6	37.0	NR	NR	53.1	1.4	NR	NR	55.1
	PBO	146	55.5	63.2	52.7	45.2	NR	NR	54.5	1.4	NR	NR	53.2
Ferguson, 2016 [46]	IND/GLY 27.5/15.6 BID	204	64.2	64.0	49.5	35.8	46.6	6.7	NR	1.3	1.5	NR	55
	IND/GLY 27.5/31.2 BID	204	60.3	63.9	51.5	38.2	48.5	6.8	NR	1.2	1.5	NR	54.2
	IND 75	207	72.0	62.8	51.7	35.7	48.8	6.6	NR	1.3	1.6	NR	53.9

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Mahler, 2015 [47] (FLIGHT1 & FLIGHT2, pooled)	IND/GLY 27.5/15.6 BID	508	63.4	63.4	50.4	37.8	45.9	7.1	NR	1.3	1.5	NR	54.9
	IND 27.5	511	65.8	63.7	52.1	39.9	48.9	7	NR	1.3	1.5	NR	54.4
	GLY 15.6	511	63.8	63.4	52.3	37.4	42.9	7	NR	1.3	1.5	NR	54.6
	PBO	508	60.2	63.2	51.6	39.2	45.5	7.1	NR	1.3	1.5	NR	54.4
Siler, 2016 [48]	UMEC/VI 62.5/25	248	58.0	64.1	55.0	GOLD D: 64	45.0	NR	38.8	NR	NR	NR	46.5
	PBO	248	60.0	62.6	52.0	GOLD D: 56	50.0	NR	38.4	NR	NR	NR	48.4
Kerwin, 2017 [49]	UMEC/VI 62.5/25	247	66.0	64.5	52.0	0.0	NR	NR	38.6	NR	1.8	NR	59.8
	TIO 18	247	65.0	64.3	48.0	0.0	NR	NR	40.4	NR	1.8	NR	59.4
Donohue, 2016 [50]	ACL/FOR 400/12	392	55.1	63.9	46.9	46.2	35.2	NR	50.9	1.3	NR	NR	51.8
	FOR 12	198	55.1	64.7	43.9	46.5	ICS: 34.3 ICS + LABA: 0.6	NR	52.6	1.3	NR	NR	50.5
Martinez, 2017 [51] (PINNACLE-1)	GLY/FOR 18/9.6	526	55.1	62.6	53.4	46.0	33.7	NR	50.9	NR	1.5	NR	51.4
	GLY 18	451	56.5	62.9	54.3	47.0	35.9	NR	50.4	NR	1.5	NR	50.7
	FOR 9.6	449	54.8	63.0	54.3	47.0	36.7	NR	52.9	NR	1.5	NR	51.2
	PBO	219	55.7	62.5	57.5	47.0	35.2	NR	50.8	NR	1.5	NR	50.6
	TIO 18	451	59.6	63.0	52.8	47.0	36.4	NR	53.0	NR	1.5	NR	51.4
Martinez, 2017 [51] (PINNACLE-2)	GLY/FOR 18/9.6	510	53.3	62.8	52.5	47.7	37.6	NR	50.5	NR	1.5	NR	52.1
	GLY 18	439	55.1	62.8	51.5	46.2	39.2	NR	50.4	NR	1.5	NR	51.5
	FOR 9.6	437	56.5	62.6	57.7	47.1	35.9	NR	50.6	NR	1.5	NR	51.9
	PBO	223	56.1	64.2	49.3	47.5	39.9	NR	53.2	NR	1.5	NR	52.5

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Bateman, 2013 [18]	IND/GLY 110/50	475	76.4	64.0	40.5	Severe: 34.0	57.0	6.0	NR	1.3	1.5	NR	55.7
	IND 150	477	74.4	63.6	38.7	Severe: 38.2	57.0	6.3	NR	1.3	1.5	NR	54.9
	GLY 50	475	77.2	64.3	40.0	Severe: 36.6	58.0	6.5	NR	1.3	1.5	NR	55.1
	TIO 18	483	75.0	63.5	39.4	Severe: 38.3	59.0	6.1	NR	1.3	1.5	NR	55.1
	PBO	234	72.8	64.4	40.1	Severe: 32.3	58.0	6.4	NR	1.3	1.5	NR	55.2
Buhl, 2015 [52]	IND/GLY 110/50	476	66.6	62.6	49.2	41.7	42.0	6.5	41.1	1.3	1.6	53.3	NR
	TIO 18 + FOR 12	458	65.1	63.1	48.9	43	40.0	6.8	41.8	1.3	1.5	53.0	NR
Tashkin, 2009 [53]	TIO 18 + FOR 12	124	65.0	63.8	49.0	NR	27.0	NR	NR	NR	NR	NR	NR
	TIO 18	131	68.0	63.9	46.0	NR	27.0	NR	NR	NR	NR	NR	NR
Frith, 2018 [54]	IND/GLY 110/50	248	88.7	65.0	36.7	46.0	100.0	6.4	44.3	NR	NR	NR	51.3
	SAL/FF 50/500	250	89.6	65.1	38.0	46.6	100.0	6.4	45.3	NR	NR	NR	51.7

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Celli, 2014 [55]	UMEC 125	407	66.0	63.1	53.0	GOLD 3: 44.0 GOLD 4: 8.0	47.0	NR	44.0	NR	NR	NR	48.8
	VI 25	404	66.0	62.8	52.0	GOLD 3: 40.0 GOLD 4: 9.0	47.0	NR	42.8	NR	NR	NR	48.5
	UMEC/VI 125/25	403	66.0	63.4	50.0	GOLD 3: 47.0 GOLD 4: 9.0	44.0	NR	45.4	NR	NR	NR	47.7
	PBO	275	64.0	62.2	52.0	GOLD 3: 48.0 GOLD 4: 8.0	50.0	NR	43.6	NR	NR	NR	47.6
Singh, 2015 [56]	UMEC/VI 62.5/25	358	73.0	61.8	57.0	GOLD D: 46.0	NR	6.6	40.7	1.4	1.6	NR	50.2
	SAL/FP 50/500	358	71.0	61.4	61.0	GOLD D: 44.0	NR	6.6	39.4	1.5	1.6	NR	51.1
Donohue, 2015 [57] (DB2114930)	UMEC/VI 62.5/25	353	72.0	62.5	45.0	52.0	NR	–[d]	43.2	1.3	1.4	NR	49.2
	SAL/FP 50/250	353	69.0	63.0	41.0	50.0	NR	–[d]	41.7	1.3	1.5	NR	49.6
Donohue, 2015 [57] (DB2114951)	UMEC/VI 62.5/25	349	76.0	63.2	51.0	50.0	NR	–[d]	43.8	1.3	1.5	NR	49.4
	SAL/FP 50/250	348	76.0	64.0	53.0	50.0	NR	–[d]	44.5	1.3	1.5	NR	49.5
Vogelmeier, 2013 [58]	IND/GLY 110/50	258	70.2	63.2	47.7	19.8	32.9	6.4	40.7	1.5	1.7	51.1	60.5
	SAL/FF 50/500	264	71.6	63.4	48.1	19.7	37.1	7.5	39.6	1.4	1.7	50.7	60.0

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Zhong, 2015 [59]	IND/GLY 110/50	372	91.7	64.8	26.0	47.0	55.4	5.2	NR	1.3	1.3	NR	51.6
	SAL/FF 50/500	369	89.7	65.3	26.0	45.8	54.2	5.1	NR	1.2	1.3	NR	52.0
Hoshino, 2015 [60]	TIO 18 + IND 150	22	81.8	72.0	NR	NR	NR	NR	56.2	1.4	NR	61.9	NR
	SAL/FF 50/250	21	85.7	69.0	NR	NR	NR	NR	60.4	1.4	NR	60.8	NR
Singh, 2014 [61]	ACL/FOR 400/12	385	67.8	62.7	47.0	40.5	22.1	NR	NR	1.4	NR	NR	54.6
	ACL/FOR 400/6	381	68.0	62.9	47.8	39.6	18.9	NR	NR	1.4	NR	NR	54.1
	ACL 400	385	66.5	63.1	47.3	40.9	20.5	NR	NR	1.4	NR	NR	53.6
	PBO	194	71.1	64.2	48.5	39.9	20.1	NR	NR	1.4	NR	NR	55.0
	FOR 12	384	66.4	63.4	46.6	37.6	17.7	NR	NR	1.4	NR	NR	54.5
ZuWallack, 2014 [62] (ANHELTO 1)	TIO 18	565	50.4	64.8	52.2	40.2	37.9	7.9	52.7	1.3	1.5	NR	53.9
	TIO 18 + OLO 5	567	49.2	64.3	49.7	39.5	35.8	8.5	54.0	1.2	1.5	NR	54.2
ZuWallack, 2014 [62] (ANHELTO 2)	TIO 18	569	53.3	63.6	48.2	44.3	37.8	7.1	51.4	1.3	1.4	NR	53.0
	TIO 18 + OLO 5	566	53.9	64.6	45.8	40.3	37.6	8.2	53.9	1.3	1.5	NR	53.6
Dahl, 2013 [63]	IND/GLY 110/50	225	77.3	62.5	45.3	31.1	45.8	5.8	36.3	1.4	1.6	NR	56.4
	PBO	113	76.1	62.9	45.1	19.5	38.9	5.5	38.1	1.5	1.7	NR	59.4

Table 3 continued

Author & year	Treatment	ITT population, *n*	Male, %	Age, years	Current smokers, %	Severe or very severe COPD, %	Concomitant ICS, %	Mean/median duration of COPD, years[a]	Smoking history, pack-years	Trough mean/median pre-bronchodilator FEV_1, L[a]	Mean/median post-bronchodilator FEV_1, L[a]	Pre-bronchodilator FEV_1% predicted	Post-bronchodilator FEV_1% predicted
Buhl, 2015b [19] (TONADO 1)	OLO 5	528	73.1	63.7	37.1	51.3	47.2	NR	NR	1.2	1.4	49.9	NR
	TIO 2.5	525	74.7	64.2	41.0	48.6	46.5	NR	NR	1.3	1.4	50.9	NR
	TIO 5	527	72.7	64.2	35.7	50.1	45.0	NR	NR	1.2	1.4	49.7	NR
	TIO/OLO 2.5/5	522	74.5	64.1	37.5	48.5	49.8	NR	NR	1.2	1.4	50.5	NR
	TIO/OLO 5/5	522	73.6	64.8	36.2	50.6	51.7	NR	NR	1.2	1.3	49.5	NR
Buhl, 2015b [19] (TONADO 2)	OLO 5	510	74.1	64.7	35.7	46.0	50.2	NR	NR	1.2	1.4	50.7	NR
	TIO 2.5	507	71.2	63.9	34.1	50.7	45.8	NR	NR	1.2	1.4	49.7	NR
	TIO 5	506	73.5	63.5	36.0	49.6	45.3	NR	NR	1.2	1.4	49.7	NR
	TIO/OLO 2.5/5	508	72.4	64.1	34.6	50.6	45.9	NR	NR	1.2	1.4	50.0	NR
	TIO/OLO 5/5	507	68.8	62.7	41.6	51.8	46.5	NR	NR	1.2	1.4	49.1	NR

ACL aclidinium, *COPD* chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume in 1 s, *FOR* formoterol fumarate, *FP* fluticasone propionate, *GLY* glycopyrronium, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *ICS* inhaled corticosteroid, *IND* indacaterol, *ITT* intent-to-treat, *LABA* long-acting β_2-agonist, *MDI* metered dose inhaler, *NMA* network meta-analysis, *NR* not reported, *OLO* olodaterol, *PBO* placebo, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

[a]Reported data are mean or median, as reported in the corresponding study. If both the mean and median were reported, the mean is presented

[b]Available from clinicalstudydatarequest.com

[c]The extension trial AUGMENT EXTENSION was not counted as a unique trial but secondary publication to main trial

[d]Duration of COPD reported by category (< 1 year, ≥ 1 to < 5 years, ≥ 5 to < 10 years and ≥ 10 years)

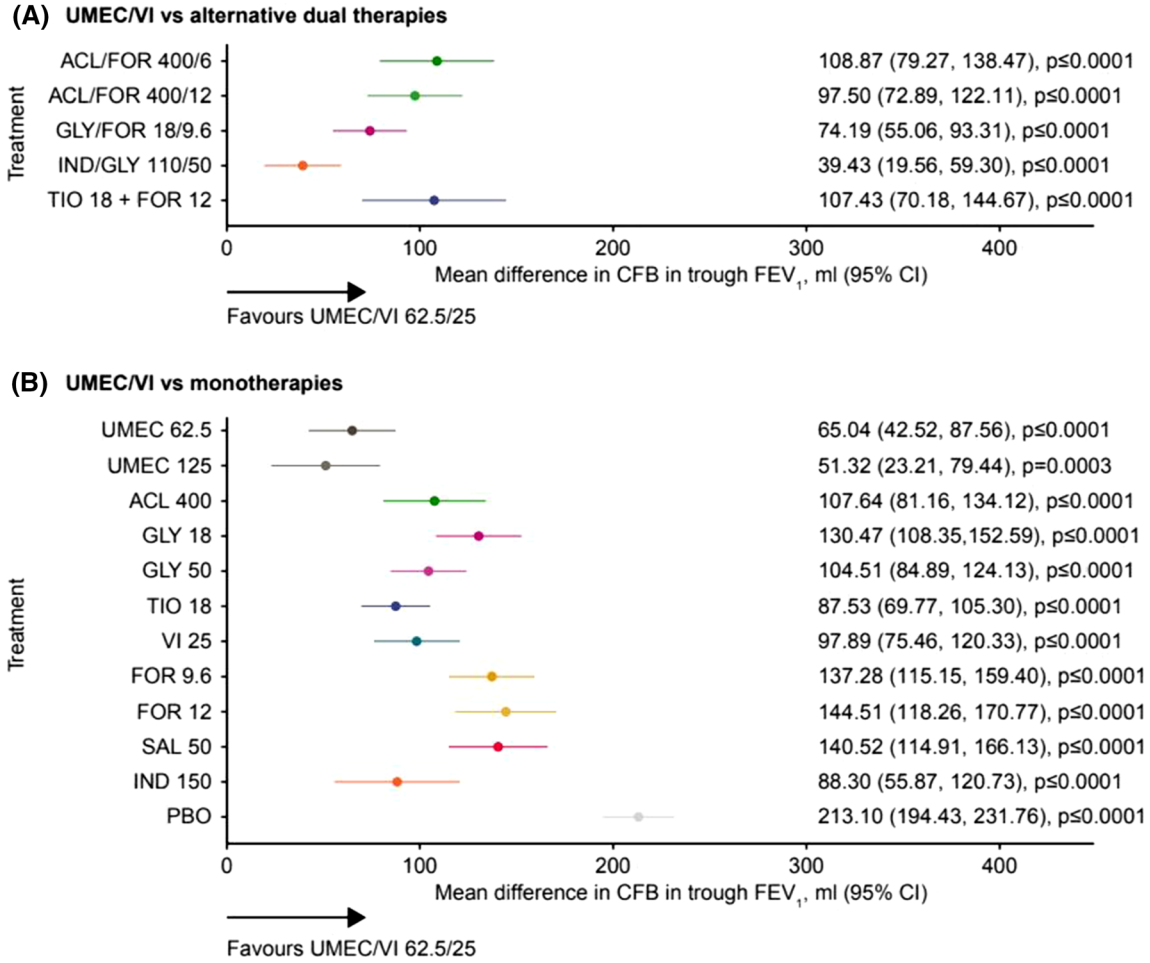

Fig. 2 Fixed effects model of mean difference in change from baseline in trough FEV_1 of UMEC/VI versus **a** dual therapy and **b** monotherapy at 24 weeks. Assessment of heterogeneity/inconsistency: $I^2 = 35.33\%$; $Q = 44.84$, $p = 0.0305$. *ACL* aclidinium, *CFB* change from baseline, *CI* confidence interval, *FEV_1* forced expiratory volume in 1 s, *FOR* formoterol fumarate, *FP* fluticasone propionate, *GLY* glycopyrronium, *IND* indacaterol, *PBO* placebo, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

GLY 18 µg at 24 weeks; ACL 400 µg and FOR 12 µg at 12 weeks; and SAL 50 µg at both time points (Supplementary Tables S3 and S4).

The RE model produced consistent results (Supplementary Tables S1–S4).

Breathlessness

Breathlessness as measured by TDI focal score was available in 14 studies at 24 weeks (Supplementary Fig. S8) and 21 studies at 12 weeks. In the FE model at 24 weeks, TDI focal score was statistically significant in favour of UMEC/VI versus GLY/FOR 18/9.6 µg (mean difference in change from baseline [95% CI] 0.33 [0.13, 0.52]), UMEC 62.5 µg (0.32 [0.08, 0.57]), UMEC 125 µg (0.55 [0.16, 0.93]), GLY 18 µg (0.68 [0.32, 1.04]), TIO 18 µg (0.34 [0.03, 0.64)], VI 25 µg (0.42 [0.13, 0.71]), FOR 9.6 µg (0.48 [0.11, 0.84]) and SAL 50 µg (0.43 [0.14, 0.72]) (Fig. 4). At 12 weeks, UMEC/VI provided statistically significantly greater improvements in TDI focal score than UMEC 62.5 µg, UMEC 125 µg, TIO 18 µg, VI 25 µg and SAL 50 µg; IND/GLY 27.5/15.6 µg, TIO/OLO 2.5/5 µg and TIO/OLO 5/5 µg provided statistically significantly greater

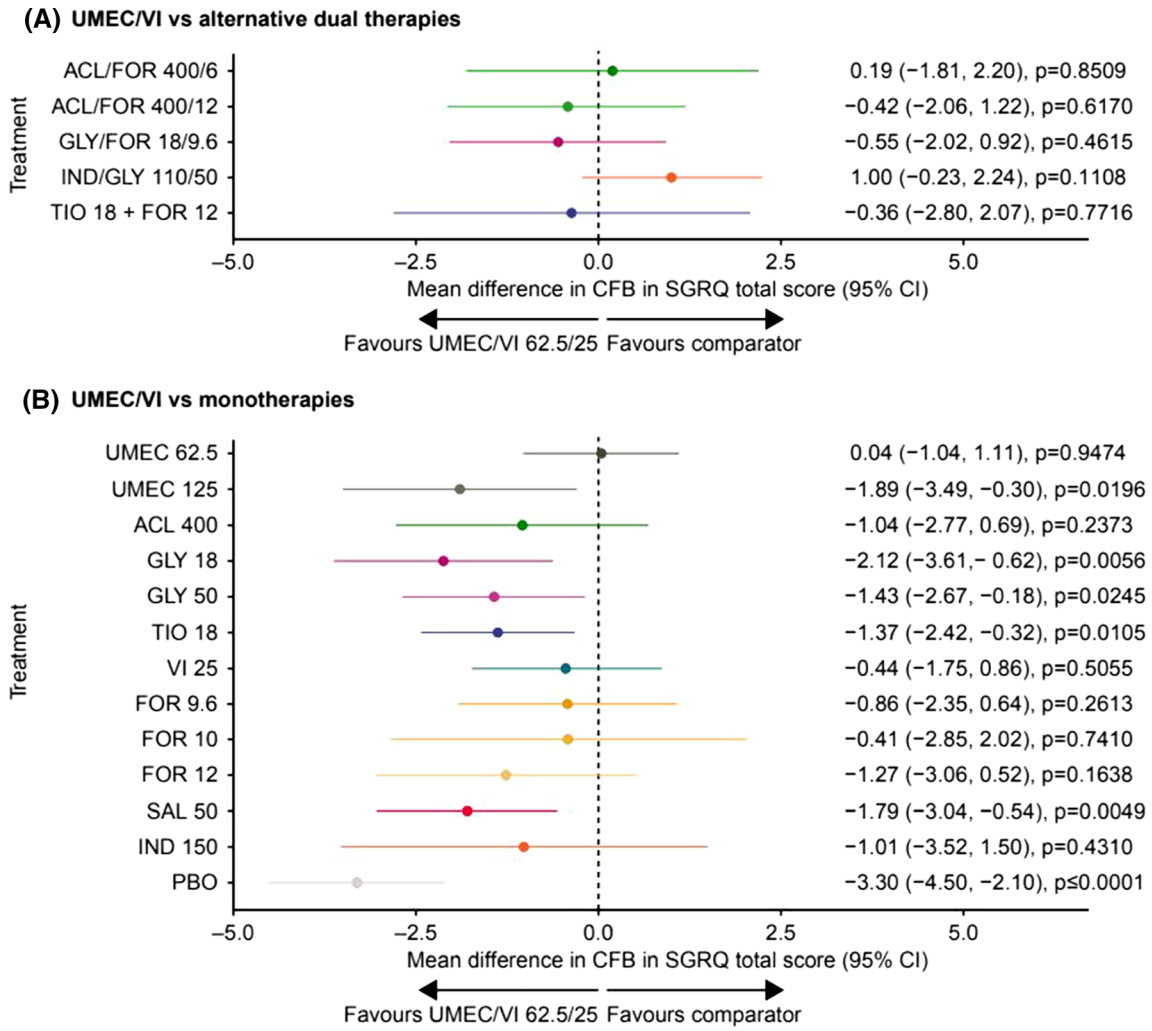

Fig. 3 Fixed effects model of mean difference in change from baseline in SGRQ total score of UMEC/VI versus **a** dual therapy and **b** monotherapy at 24 weeks. Assessment of heterogeneity/inconsistency: I^2 = 22.49%; Q = 32.25; p = 0.1508. *ACL* aclidinium, *CFB* change from baseline, *CI* confidence interval, *FOR* formoterol fumarate, *FP* fluticasone propionate, *GLY* glycopyrronium, *IND* indacaterol, *PBO* placebo, *SAL* salmeterol, *SGRQ* St George's Respiratory Questionnaire, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

improvements in TDI focal score than UMEC/VI (Supplementary Table S2). At both time points, all therapies provided statistically significantly greater improvements than placebo, with the exception of TIO 18 µg + FOR 12 µg at 12 weeks (Supplementary Tables S3 and S4).

TDI responder analyses were available for 10 and 11 studies at 24 (Supplementary Fig. S9) and 12 weeks, respectively. In the FE model, the odds of being a responder were statistically significantly greater with UMEC/VI versus GLY 15.6 µg and TIO 18 µg at 12 weeks, and versus UMEC 62.5 µg, VI 25 µg and SAL 50 µg at both 24 and 12 weeks (TDI responders odds ratio at 24 weeks [95% CI]; UMEC 62.5 µg: 1.33 [1.14, 1.56]; VI 25 µg: 1.38 [1.14, 1.67]; SAL 50 µg: 1.41 [1.17, 1.70]) (Supplementary Fig. S10; Supplementary Table S2). At both time points, all therapies provided statistically significantly greater proportion of TDI responders than placebo, with the exception of TIO 18 µg + FOR 12 µg at 24 weeks (Supplementary Tables S3 and S4).

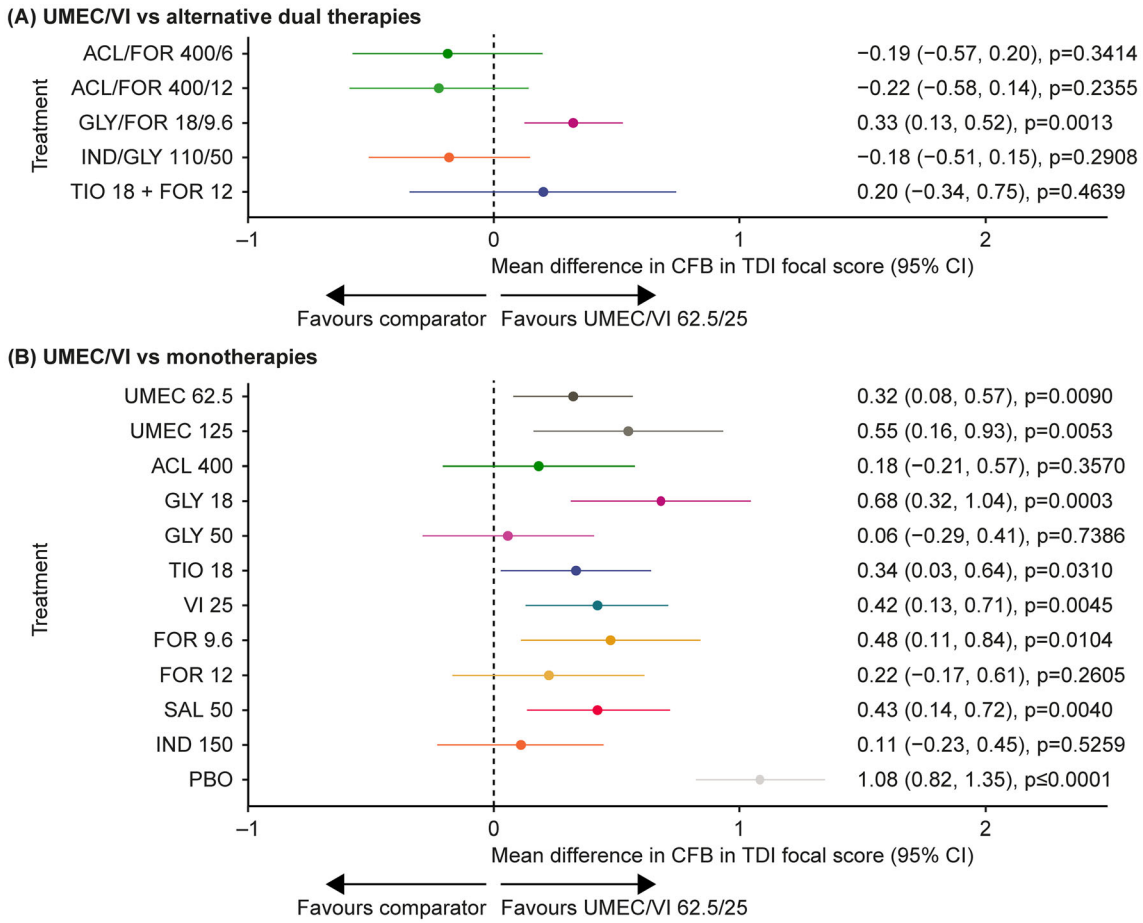

Fig. 4 Fixed effects model of mean difference in change from baseline in TDI focal score of UMEC/VI versus **a** dual therapy and **b** monotherapy at 24 weeks. Assessment of heterogeneity/inconsistency: I^2 = 0%; Q = 12.60; p = 0.4793. *ACL* aclidinium, *CFB* change from baseline, *CI* confidence interval, *FOR* formoterol fumarate, *FP* fluticasone propionate, *GLY* glycopyrronium, *IND* indacaterol, *PBO* placebo, *SAL* salmeterol, *TDI* Transitional Dyspnoea Index, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

The RE model produced consistent results (Supplementary Tables S1–4).

Rescue Medication Use

Rescue medication use data were available in 14 studies at 24 weeks and 15 studies at 12 weeks. At 24 weeks, the ILLUMINATE study was disconnected from the network (Supplementary Fig. S11). In the FE model at 24 weeks, change from baseline in rescue medication use was statistically significant in favour of UMEC/VI versus ACL/FOR 400/12 µg (mean difference in change from baseline [95% CI] − 0.46 [− 0.66, − 0.25]) and all monotherapies (mean difference in change from baseline [95% CI]; UMEC 62.5 µg: − 0.33 [− 0.48, − 0.18]; UMEC 125 µg: − 0.36 [− 0.72, − 0.01]; ACL 400 µg: − 0.37 [− 0.61, − 0.12]; GLY 18 µg: − 0.58 [− 0.80, − 0.37]; GLY 50 µg: − 0.86 [− 1.24, − 0.48]; TIO 18 µg: − 0.50 [− 0.51, − 0.49]; FOR 9.6 µg: − 0.27 [− 0.49, − 0.06]; FOR 12 µg: − 0.27 [− 0.53, 0.00]; SAL 50 µg: − 0.28 [− 0.43, − 0.13]; IND 150 µg: − 0.51 [− 0.89, − 0.13]), with the exception of VI 25 µg: − 0.29 (− 0.64, 0.06) (Fig. 5). At 12 weeks, UMEC/VI provided statistically significantly greater improvements in rescue medication use than TIO/OLO 5/5 µg, UMEC 62.5 µg, TIO 18 µg and SAL 50 µg;

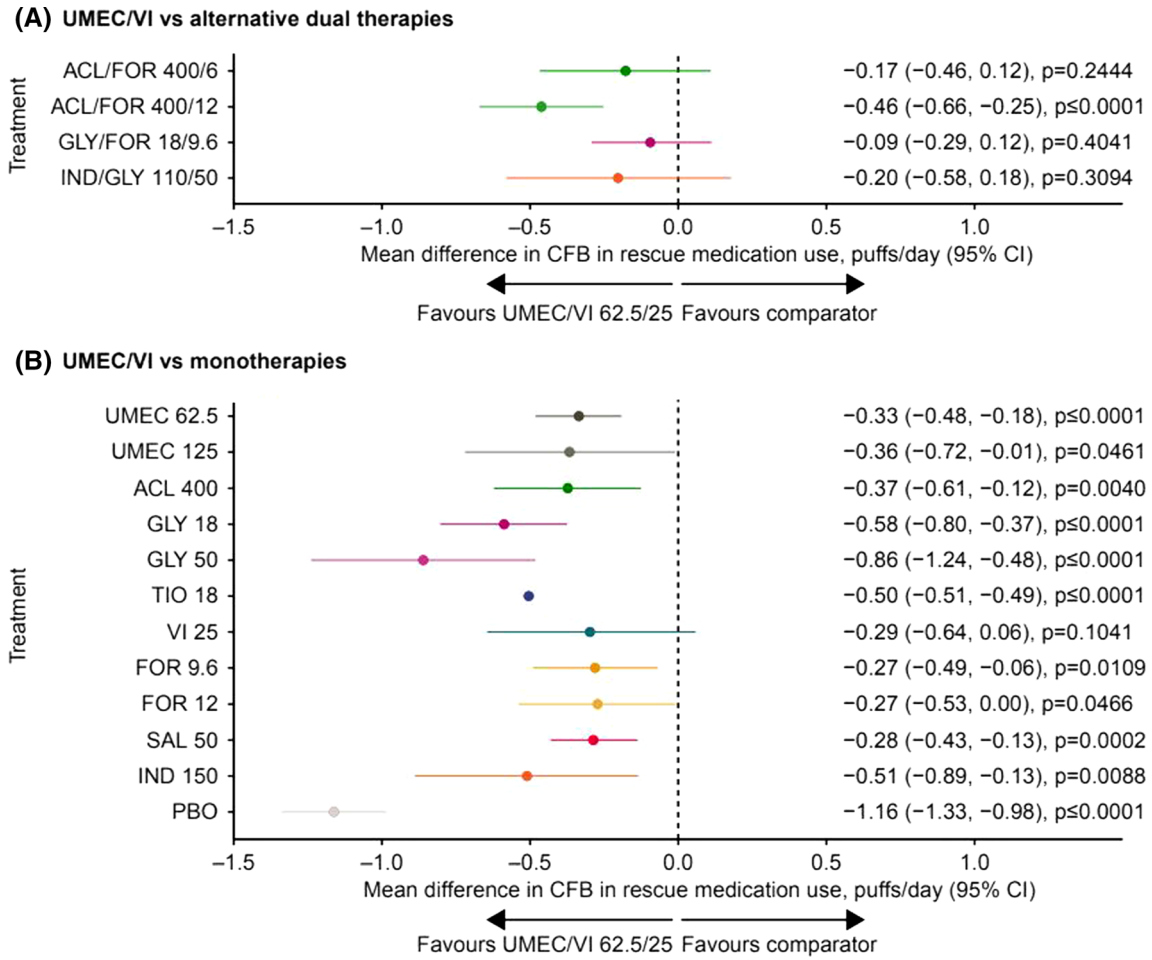

Fig. 5 Fixed effects model of mean difference in change from baseline in rescue medication use of UMEC/VI versus **a** dual therapy and **b** monotherapy at 24 weeks. Assessment of heterogeneity/inconsistency: I^2 = 49.21%; Q = 33.47; p = 0.0098. *ACL* aclidinium, *CFB* change from baseline, *CI* confidence interval, *FOR* formoterol fumarate, *FP* fluticasone propionate, *GLY* glycopyrronium, *IND* indacaterol, *PBO* placebo, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

IND/GLY 27.5/15.6 µg and TIO 18 µg + IND 150 µg provided statistically significantly greater improvements in rescue medication use than UMEC/VI (Supplementary Table S2). All treatments provided statistically significantly greater improvements in rescue medication use compared with placebo, with the exception of GLY 50 µg at 24 weeks and UMEC 125 µg at 12 weeks (Supplementary Tables S3 and S4).

Some differences were observed in the findings of the RE model for rescue medication use. At 24 weeks, change from baseline in rescue medication use was statistically significant in favour of UMEC/VI versus ACL/FOR 400/12 µg, ACL 400 µg, GLY 18 µg, GLY 50 µg and TIO 18 µg (Supplementary Table S1). At 12 weeks, UMEC/VI provided statistically significantly greater improvements versus TIO 18 µg only (Supplementary Table S2).

Annualised Moderate/Severe Exacerbations Rates

Moderate/severe exacerbation data were available in nine studies (Supplementary Fig. S12). In the FE model, UMEC/VI provided statistically

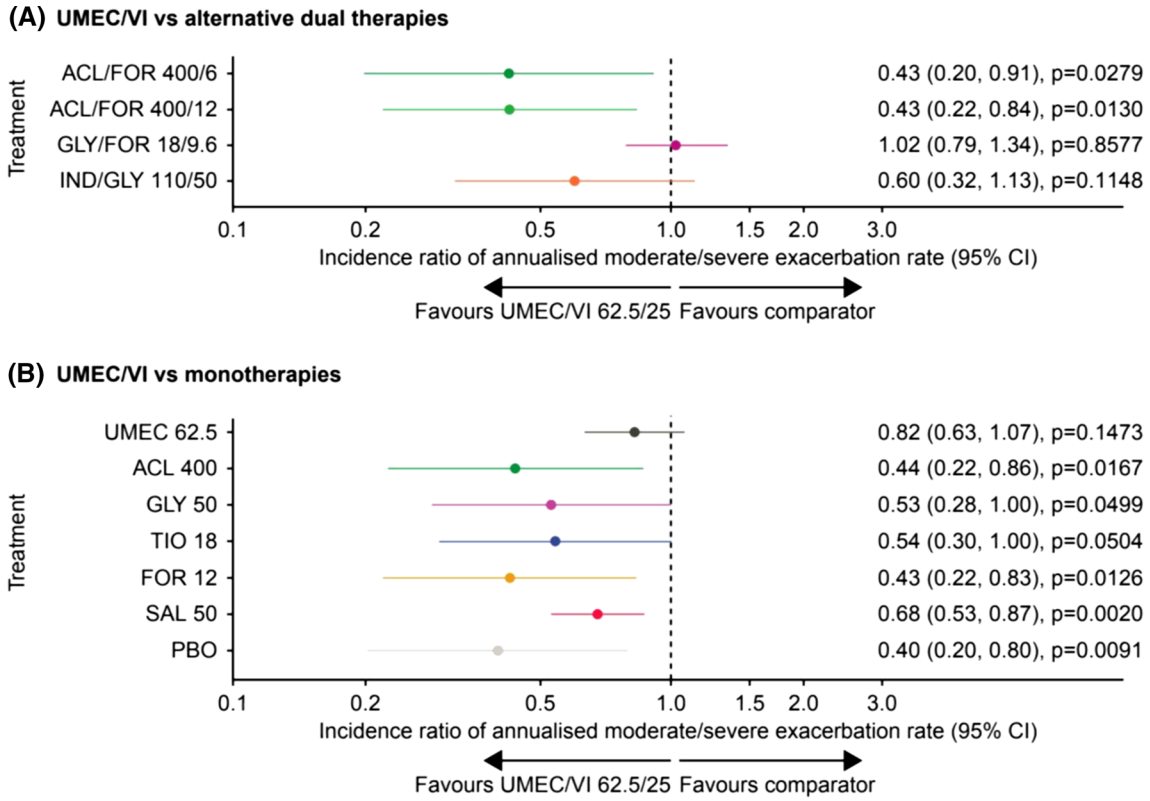

Fig. 6 Fixed effects model of incidence ratio of annualised moderate/severe exacerbations rates of UMEC/VI versus **a** dual therapy and **b** monotherapy at 24 weeks. Assessment of heterogeneity / inconsistency: I^2 = 38.86%; Q = 6.54; p = 0.1622. *ACL* aclidinium, *CFB* change from baseline, *CI* confidence interval, *FOR* formoterol fumarate, *FP* fluticasone propionate, *GLY* glycopyrronium, *IND* indacaterol, *PBO* placebo, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

significantly lower annualised rates of moderate/severe exacerbations versus ACL/FOR 400/6 µg (incidence rate ratio [95% CI] 0.43 [0.20, 0.91]) and ACL/FOR 400/12 µg (0.43 [0.22, 0.84]), and versus all monotherapies with the exception of UMEC 62.5 µg and TIO 18 µg (Fig. 6). Only UMEC/VI 62.5/25 µg, GLY/FOR 18/9.6 µg and IND/GLY 110/50 µg provided statistically significantly lower annualised rates of moderate/severe exacerbations versus placebo, with IND/GLY 110/50 µg providing statistically significant improvements only in the RE model (Supplementary Table S3).

Time to First Exacerbation

In total, 12 studies had data available for time to first exacerbation (Supplementary Fig. S13). In the FE model, hazard of a first exacerbation was statistically significantly lower with UMEC/VI versus SAL 50 µg (hazard ratio [95% CI] 0.64 [0.50, 0.81]) and placebo (0.47 [0.32, 0.67]) (Fig. 7), which was consistent with the RE model (Supplementary Table S1). In the FE model, among dual therapies, UMEC/VI 62.5/25 µg, IND/GLY 110/50 µg and GLY/FOR 18/9.6 µg provided statistically significantly lower hazard of a first exacerbation than placebo, with IND/GLY 110/50 µg only providing statistically significant improvements versus placebo in the RE model (Supplementary Table S3). UMEC 62.5 µg, UMEC 125 µg and TIO 18 µg monotherapies provided statistically significant reductions in hazard of a first exacerbation versus placebo; results from the RE model were similar (Supplementary Table S3).

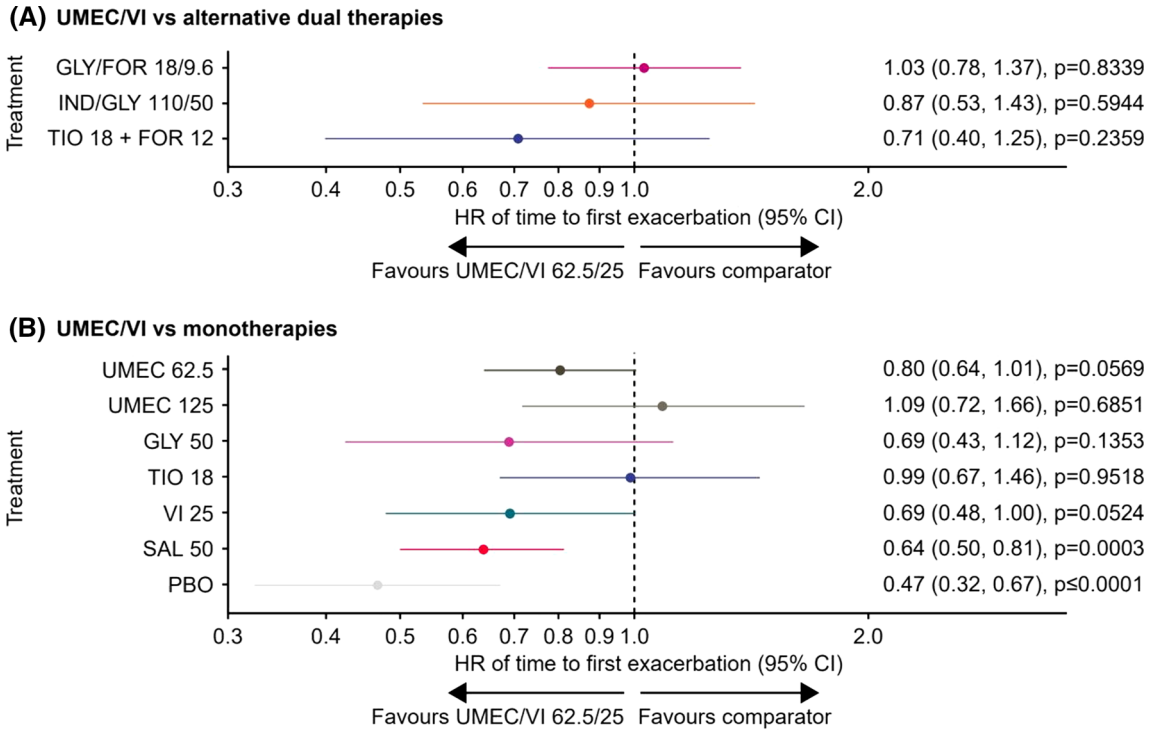

Fig. 7 Fixed effects model of hazard ratio of time to first exacerbation of UMEC/VI versus **a** dual therapy and **b** monotherapy at 24 weeks. Assessment of heterogeneity/inconsistency: I^2 = 35.54%; Q = 10.86; p = 0.1448. *CI* confidence interval, *FOR* formoterol fumarate, *FP* fluticasone propionate, *GLY* glycopyrronium, *HR* hazard ratio, *IND* indacaterol, *PBO* placebo, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium, *VI* vilanterol

Safety Overview

Safety outcomes were not analysed in the NMA, but are summarised for the included studies in Supplementary Table S5. Briefly, the percentage of patients with ≥1 adverse event (AE) ranged from 21% to 94%, and the percentage with ≥1 serious AE from 0.6% to 24.0%. Pneumonia was reported in 0–16.0% of patients. In total, 0.2–33.0% of patients withdrew, and 0.5–10.6% of early withdrawals were due to AEs. On-treatment mortality was reported for 0–3.1% of patients.

DISCUSSION

This study evaluated the comparative efficacy of UMEC/VI dual therapy versus other mono and dual therapies in symptomatic patients with COPD at 24 and 12 weeks. Treatment with dual therapy resulted in greater improvements in lung function as measured by trough FEV_1 compared with LABA or LAMA monotherapy, with improvements in HRQoL, symptoms, rescue medication use and moderate/severe exacerbation rates seen in some comparisons; AEs were also summarised and showed a similar safety profile across the treatments of interest.

At both time points, all treatments provided greater improvements in lung function compared with placebo; the two UMEC formulations performed better than other monotherapies, and the twice-daily LABAs (SAL 50 μg; FOR 12 μg and FOR 9.6 μg) performed worse than other LABAs. Treatment with UMEC/VI resulted in significant improvements in lung function as measured by trough FEV_1 compared with all LAMA and LABA monotherapies. These findings support existing evidence from clinical trials that dual therapy provides greater improvements than monotherapies

[18–22], and suggest that starting treatment with dual therapy may improve outcomes for many symptomatic patients compared with a stepwise approach to treatment escalation [1]. The non-interventional prospective DETECT study in 3653 patients showed improvements in lung function, QoL and morning symptoms in the year following a switch from prior treatment (most commonly bronchodilator monotherapy) to fixed-dose ACL/FOR, GLY/IND or UMEC/VI [23]. Previous NMAs have also demonstrated that LAMA/LABA dual therapy is more effective than LAMA or LABA monotherapy in terms of lung function improvement [4, 5, 8]. Notably, while many trials comparing dual bronchodilator therapies with monotherapy are likely to have been affected by the confounding effects of concomitant ICS use, the EMAX trial has demonstrated that UMEC/VI provides better outcomes than UMEC and SAL in symptomatic patients at low exacerbations risk not taking concomitant ICS [22]. Taken together, this evidence suggests that dual therapy may be an appropriate initial maintenance therapy in this patient population, as recommended by the ATS and NICE guidelines [2, 3]. However, it should be noted that the present study also supported the efficacy of LAMA and LABA monotherapies compared with placebo.

At both time points, UMEC/VI demonstrated larger improvements in lung function than other dual therapies. The smallest treatment differences were seen with UMEC/VI versus IND/GLY formulations, while the other dual therapies performed similarly; clinically meaningful differences (based on a mean difference in change from baseline of $\geq$ 100 ml) [17] were seen with UMEC/VI versus some dual therapies at 24 weeks. Treatment effects on SGRQ total score, TDI focal score, rescue medication use and moderate/severe exacerbations were less clear. The results of this updated NMA are consistent with head-to-head trials. The AERISTO trial in 1119 symptomatic patients with moderate-to-very severe COPD found that GLY/FOR was non-inferior to UMEC/VI when comparing treatment effects on peak FEV_1, but was inferior when comparing the co-primary endpoint of trough FEV_1 [24]. UMEC/VI provided numerical improvements compared with GLY/FOR on symptoms outcomes (TDI focal score and COPD Assessment Test score) in the AERISTO trial, although these were not considered clinically significant [24]. Another head-to-head study showed that UMEC/VI provided statistically significant increases in lung function-related outcomes compared with TIO/OLO in 236 symptomatic patients [25]. Results for patient-reported outcomes (PRO) were less clear; while UMEC/VI provided a significantly greater reduction in rescue medication use during the study and a significant decrease in CAT score at week 4 versus TIO/OLO, there were no consistent treatment differences on exacerbations or other symptoms outcomes, although the study was not powered to demonstrate treatment effects on these measures [25].

Despite the efficacy gradient suggested by the findings of head-to-head trials, previous NMAs have shown mixed results when comparing treatments within the LAMA/LABA class. An NMA of studies in moderate-to-very severe patients with COPD found that TIO/OLO 5/5 μg was ranked highest on efficacy and cardiovascular safety when compared with alternative LAMA/LABAs, including UMEC/VI 62.5/25 μg; however, SGRQ and TDI response rates, rescue medication use, and moderate/severe exacerbations were not included in the analysis [26]. Another previous NMA including RCTs of patients with stable COPD compared six LAMA/LABA dual therapies, and reported that UMEC/VI reduced total exacerbation events compared with alternative LAMA/LABAs (with the exception of GLY/FOR) in one network, although no statistically significant differences were seen in an alternative network [19]. Similarly, the current updated NMA found that UMEC/VI reduced the rate of moderate/severe exacerbations versus two formulations of ACL/FOR, but not GLY/FOR 18/9.6 μg or IND/GLY 110/50 μg. Taken together, the evidence from head-to-head trials and NMAs generally supports a gradient of effectiveness within the LAMA/LABA class, with UMEC/VI providing greater improvements in lung function compared with other LAMA/LABAs, and improvements in other outcomes including exacerbations and PROs in some analyses. The relationship between improvement in lung function and PROs remains unclear; a

pooled analysis of 23 clinical trials in COPD found a correlation between improvement in lung function and PRO improvements [27], but disparities have been noted in other studies [28, 29]. This dissociation may be related to factors such as study design, patient population, and statistical power.

This NMA is an updated extension of our original NMA comparing the efficacy of UMEC/VI with fixed-dose and open LAMA/LABA combinations, with TIO, and with placebo [6]. In the present study we have used well-established frequentist NMA approach to compare UMEC/VI with dual therapies and monotherapies, and we have incorporated a larger number of studies, with an additional five RCTs included in the updated NMA. The updated NMA also included additional outcomes such as the rate of moderate/severe exacerbations, time to first moderate/severe exacerbation, and responder analyses for symptoms and health status outcomes. Similar to our original NMA [6] and to a previous NMA that compared RCTs of patients with COPD comparing five combinations of LAMA/LABA dual therapies [4], the present study also found evidence for a potential gradient of effectiveness in treatment effects within the LAMA/LABA class. However, this updated NMA did not analyse certain outcomes relevant to patients with COPD, such as exercise capacity, because of lack of sufficient clinical trial data to construct networks.

A general strength of NMA approaches is the inclusion of a broader population than individual RCTs; specific strengths of this study include the greater number of studies available for inclusion in the NMA compared with similar previous analyses, which allowed for a better estimation of relative treatment effects. Potential general limitations of NMA approaches include a risk of unknown imbalances in effect modifiers and residual confounding bias. Only RCTs were included in this study, eliminating the risk of bias due to imbalanced effect modifiers within the trials as a result of randomisation. However, randomisation does not control for known treatment effect modifiers across studies, and unknown treatment effect modifiers could still bias the results. Another potential general limitation of NMA approaches is the risk of violation of the three assumptions of similarity, consistency and transitivity. In this study, the similarity assumption (i.e. the comparability of baseline characteristics) and consistency assumption (tested through heterogeneity statistics such as I^2, the Q statistic and the corresponding p value) were deemed to hold, providing certainty that the transitivity assumption also holds. This study was also limited by the availability of data for inclusion in the NMA, which in some cases included relatively small sample sizes and sparse networks of evidence. This resulted in wide CIs which in some cases covered the decision threshold, raising the possibility that potential differences between interventions were not identified.

CONCLUSION

The findings of this SLR and NMA suggest that UMEC/VI provides better outcomes in terms of lung function (as measured by change from baseline in trough FEV_1) with a similar safety profile compared with LAMA and LABA monotherapies and other LAMA/LABA dual therapies. UMEC/VI also provided additional benefits on HRQoL, symptoms, rescue medication use and moderate/severe exacerbations compared with some monotherapies. These results suggest that treatment with UMEC/VI dual therapy may improve outcomes for symptomatic patients with COPD.

ACKNOWLEDGEMENTS

Funding. This study/analysis was funded by GSK (GSK study 214886). GSK-affiliated authors had a role in study design, data analysis, data interpretation, and writing of the report, and GSK funded the journal's Rapid Service and Open Access Fees.

Medical Writing, Editorial and Other Assistance. Editorial support (in the form of writing assistance during development of the initial draft, assembling tables and figures, collating authors comments, grammatical editing,

and referencing) was provided by Maria Guillermina Casabona, PhD, and Mark Condon, DPhil, of Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK.

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

Author Contributions. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. ASI, KH, AC, VT, MM and MN were involved in the conception and design of the study, the acquisition of data, and data analysis and interpretation. JA, MZ-G, YS and XD were involved in the acquisition of data and data analysis and interpretation. MD and CC were involved in the conception and design of the study, and in data analysis and interpretation. CFV and DMGH were involved in the data analysis and interpretation. All authors contributed to the writing and reviewing of the manuscript, and have approved the final manuscript.

Prior Presentation. An abstract reporting some of the data included in this manuscript was presented at the 2022 American Thoracic Society international conference.

Disclosures. Afisi S. Ismaila, Alexandrosz Czira, Maria Duarte and Chris Compton are employees of GSK and hold stock and shares at GSK. Afisi S. Ismaila is also a part-time member of the McMaster University faculty. Katrin Haeussler, Vanita Tongbram, Mia Malmenäs, Jatin Agarwal, Maria Nassin, Marija Živković-Gojović, Yunrong Shen and Xinzhe Dong are employees of ICON (or were at the time of the study), which received funding from GSK to conduct the study. Claus F. Vogelmeier has received grants from AstraZeneca, Boehringer Ingelheim, GSK, Grifols and Novartis, and has received lecturing and personal fees from AstraZeneca, Boehringer Ingelheim, Berlin Chemie/Menarini, Chiesi, CSL Behring, GSK, Grifols, MedUpdate, Novartis, Aerogen and Nuvaira. David M.G. Halpin has received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer and Sanofi, and non-financial support from Boehringer Ingelheim and Novartis.

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

Data Availability. Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com. Extracted data summaries are available upon request to the authors.

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