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[Intervention Review]

Once daily long-acting beta2-agonists and long-acting muscarinic antagonists in a combined inhaler versus placebo for chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is a respiratory condition causing accumulation of mucus in the airways, cough, and breathlessness; the disease is progressive and is the fourth most common cause of death worldwide. Current treatment strategies for COPD are multi-modal and aim to reduce morbidity and mortality and increase patients' quality of life by slowing disease progression and preventing exacerbations. Fixed-dose combinations (FDCs) of a long-acting beta$_2$-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) delivered via a single inhaler are approved by regulatory authorities in the USA, Europe, and Japan for the treatment of COPD. Several LABA/LAMA FDCs are available and recent meta-analyses have clarified their utility versus their mono-components in COPD. Evaluation of the efficacy and safety of once-daily LABA/LAMA FDCs versus placebo will facilitate the comparison of different FDCs in future network meta-analyses.

Objectives

We assessed the evidence for once-daily LABA/LAMA combinations (delivered in a single inhaler) versus placebo on clinically meaningful outcomes in patients with stable COPD.

Search methods

We identified trials from Cochrane Airways' Specialised Register (CASR) and also conducted a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch). We searched CASR and trial registries from their inception to 3 December 2018; we imposed no restriction on language of publication.

Selection criteria

We included parallel-group and cross-over randomised controlled trials (RCTs) comparing once-daily LABA/LAMA FDC versus placebo. We included studies reported as full-text, those published as abstract only, and unpublished data. We excluded very short-term trials with a duration of less than 3 weeks. We included adults (≥ 40 years old) with a diagnosis of stable COPD. We included studies that allowed participants to continue using their ICS during the trial as long as the ICS was not part of the randomised treatment.

Data collection and analysis

Two review authors independently screened the search results to determine included studies, extracted data on prespecified outcomes of interest, and assessed the risk of bias of included studies; we resolved disagreements by discussion with a third review author. Where possible, we used a random-effects model to meta-analyse extracted data. We rated all outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system and presented results in 'Summary of findings' tables.

Main results

We identified and included 22 RCTs randomly assigning 8641 people with COPD to either once-daily LABA/LAMA FDC (6252 participants) or placebo (3819 participants); nine studies had a cross-over design. Studies had a duration of between three and 52 weeks (median 12 weeks). The mean age of participants across the included studies ranged from 59 to 65 years and in 21 of 22 studies, participants had GOLD stage II or III COPD. Concomitant inhaled corticosteroid (ICS) use was permitted in all of the included studies (where stated); across the included studies, between 28% to 58% of participants were using ICS at baseline. Six studies evaluated the once-daily combination of IND/GLY (110/50 μg), seven studies evaluated TIO/OLO (2.5/5 or 5/5 μg), eight studies evaluated UMEC/VI (62.5/5, 125/25 or 500/25 μg) and one study evaluated ACD/FOR (200/6, 200/12 or 200/18 μg); all LABA/LAMA combinations were compared with placebo.

The risk of bias was generally considered to be low or unknown (insufficient detail provided), with only one study per domain considered to have a high risk of bias except for the domain 'other bias' which was determined to be at high risk of bias in four studies (in three studies, disease severity was greater at baseline in participants receiving LABA/LAMA compared with participants receiving placebo, which would be expected to shift the treatment effect in favour of placebo).

Compared to the placebo, the pooled results for the primary outcomes for the once-daily LABA/LAMA arm were as follows: all-cause mortality, OR 1.88 (95% CI 0.81 to 4.36, low-certainty evidence); all-cause serious adverse events (SAEs), OR 1.06 (95% CI 0.88 to 1.28, high-certainty evidence); acute exacerbations of COPD (AECOPD), OR 0.53 (95% CI 0.36 to 0.78, moderate-certainty evidence); adjusted St George's Respiratory Questionnaire (SGRQ) score, MD -4.08 (95% CI -4.80 to -3.36, high-certainty evidence); proportion of SGRQ responders, OR 1.75 (95% CI 1.54 to 1.99). Compared with placebo, the pooled results for the secondary outcomes for the once-daily LABA/LAMA arm were as follows: adjusted trough forced expiratory volume in one second (FEV1), MD 0.20 L (95% CI 0.19 to 0.21, moderate-certainty evidence); adjusted peak FEV1, MD 0.31 L (95% CI 0.29 to 0.32, moderate-certainty evidence); and all-cause AEs, OR 0.95 (95% CI 0.86 to 1.04; high-certainty evidence). No studies reported data for the 6-minute walk test. The results were generally consistent across subgroups for different LABA/LAMA combinations and doses.

Authors' conclusions

Compared with placebo, once-daily LABA/LAMA (either IND/GLY, UMEC/VI or TIO/OLO) via a combination inhaler is associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild-to-moderate COPD; UMEC/VI appears to reduce the rate of exacerbations in this population. These conclusions are supported by moderate or high certainty evidence based on studies with an observation period of up to one year.

PLAIN LANGUAGE SUMMARY

Once daily long-acting beta2-agonists and long-acting muscarinic antagonists in a combined inhaler versus placebo for COPD

We wanted to know whether once-daily treatment with a fixed-dose combination of a long-acting beta2 agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) delivered via a single inhaler is better than treatment with a dummy inhaler (placebo) for people with chronic obstructive pulmonary disease (COPD).

Background to the review

COPD is a disease of the lungs and is the fourth most common cause of death worldwide. People with COPD experience symptoms of cough, breathlessness and a build up of mucus, which become worse over time. Current treatments for COPD aim to manage these symptoms and improve the quality of life of people with the disease.

A combination of a LABA plus a LAMA taken once-daily in a single inhaler (LABA/LAMA) has been shown to be more effective than taking each separately in individual inhalers. Several different combinations of inhaled LABA and LAMA are available (e.g. indacaterol/glycopyrronium, olodaterol/tiotropium, formoterol/aclidinium, and vilanterol/umeclidinium) and are used for the treatment of COPD. By gathering information from clinical trials that compare once-daily LABA/LAMA with placebo in a dummy inhaler we will provide information to help future research decide which combination is best for treating people with COPD.

What did we find?

Twenty-two studies (including 8641 people with COPD) compared once-daily LABA/LAMA in a single inhaler with a dummy inhaler. People were allowed to continue to use their inhaled corticosteroids (ICS) during the studies; approximately a third to a half of people were using their ICS at the beginning of each study. The evidence presented in this review is current up to December 2018. The majority of people who took part in the studies had mild-to-moderate COPD and the average age of people in each study ranged from 59 to 65 years. Six studies evaluated the once-daily combination of indacaterol/glycopyrronium, seven studies evaluated tiotropium/olodaterol, eight studies evaluated umeclidinium/vilanterol and one study evaluated aclidinium/formoterol.

People who took once-daily LABA/LAMA using a single inhaler showed a greater improvement in quality of life than those taking placebo in a dummy inhaler; lung function was also improved in people taking once-daily LABA/LAMA. People taking umeclidinium/vilanterol had fewer flare-ups (exacerbations). There was no significant difference between groups (LABA/LAMA versus placebo) in the number of people who died, or in the number of people who experienced serious adverse events or any adverse event. The results were similar for the different LABA/LAMA combinations and doses that we evaluated.

The included studies were generally well designed and well reported. People in the studies and those performing the research did not know which treatment people were receiving, which ensures a fair evaluation of the treatments.

In three of the studies, people who were taking once-daily LABA/LAMA had more severe COPD at the start of the study than people taking dummy inhalers; this could have reduced the treatment effect seen with LABA/LAMA in these studies so we can be confident that our findings do not overestimate the effect seen with once-daily LABA/LAMA. One of the outcomes of interest (how far a person is able to walk in six minutes) was not reported by any of the included studies. Overall, we can be confident in the conclusions of this review.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Once daily LABA/LAMA in a combined inhaler compared with placebo in adults with COPD

Patient or population: Adults with COPD
Setting: Clinical practice (primary care/secondary care/academic centres)
Intervention: Once-daily LABA/LAMA in a combined inhaler
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with once daily LABA/LAMA in a combined inhaler				
All-cause mortality (3-week to 1-year follow-up)	1 per 1,000	2 per 1,000 (1 to 4)	OR 1.88 (0.81 to 4.36)	8752 (18 RCTs)	⊕⊕◯◯ LOW [1,2]	
Serious adverse events (3-week to 1-year follow-up)	47 per 1,000	50 per 1,000 (42 to 59)	OR 1.06 (0.88 to 1.28)	10536 (22 RCTs)	⊕⊕⊕⊕ HIGH	
Acute exacerbations of COPD (4-week to 24-week follow-up)	136 per 1,000	77 per 1,000 (53 to 109)	OR 0.53 (0.36 to 0.78)	1127 (3 RCTs)	⊕⊕⊕◯ MODERATE [3]	Data limited to UMEC/VI versus placebo comparison
Difference vs placebo in adjusted SGRQ score (HRQoL) Scale 0-100, lower on the scale is better. (12-week to 1-year follow-up)	Mean change from baseline in SGRQ score with placebo ranged from 6.39 lower to 0.12 higher	MD 4.08 points lower (4.8 lower to 3.36 lower)	-	4952 (8 RCTs)	⊕⊕⊕⊕ HIGH	MD exceeded MCID (4 points).

Difference vs placebo in adjusted trough FEV1 at EOT (3-week to 1-year follow-up)	Mean change from baseline in trough FEV1 with placebo ranged from 0.08 L lower to 0.01 L higher	MD 0.20 L higher (0.19 higher to 0.21 higher)	-	6598 (13 RCTs)	⊕⊕⊕◯ MODERATE [4]	MD exceeded MCID.
Difference vs placebo in adjusted peak FEV1 (3-week to 6-month follow-up)	Mean change from baseline in peak FEV1 with placebo ranged from 0.04 to 0.1 L higher	MD 0.31 L higher (0.29 higher to 0.32 higher)	-	4188 (7 RCTs)	⊕⊕⊕◯ MODERATE [4]	
Adverse events (3-week to 1-year follow-up)	448 per 1,000	435 per 1,000 (411 to 458)	OR 0.95 (0.86 to 1.04)	8235 (17 RCTs)	⊕⊕⊕⊕ HIGH	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

COPD: chronic obstructive pulmonary disease; **CI:** confidence interval; **EOT**: end of treatment; **FEV1:** forced expiratory volume in 1 second; **HRQoL:** health-related quality of life; **LABA:** long-acting beta-adrenoceptor agonist; **LAMA:** long-acting muscarinic antagonist; **MCID:** minimum clinically important difference; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SGRQ:** St George's Respiratory Questionnaire; **UMEC:** umeclidinium; **VI:** vilanterol.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once for indirectness; duration of treatment varied widely: maximum duration 52 weeks, n = 3 studies duration < 6 weeks.
[2] Downgraded once for imprecision; wide 95% confidence intervals due to low number of events - confidence intervals encompassed no effect, benefit, and risk.
[3] Downgraded once for indirectness as all studies examined UMEC/VI.
[4] Downgraded once for inconsistency; significant heterogeneity (overall $I^2 \geq 68\%$), noting that effect sizes were similar between studies with the exception of ACLID/FORM.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a progressive condition resulting from the complex interplay between environmental exposures (e.g. cigarette smoke) and genetic factors (Barnes 2015). The disease is characterised by a chronic limitation of airflow, which is not fully reversible, and intermittent exacerbations during which symptoms increase in severity. Symptoms include shortness of breath, increased sputum production and cough. The condition is diagnosed objectively by spirometric evaluation, with a post bronchodilator forced expiratory volume in one second/forced vital capacity (FEV1/FVC) < 0.70 confirming the presence of airflow limitation. COPD severity is graded by the extent of airflow limitation according to international guideline criteria (GOLD 2017).

COPD is the fourth most common cause of death worldwide (WHO 2015), and has an estimated prevalence of 6.4%; the burden on worldwide healthcare services is significant (CDC 2016; GOLD 2017).

Current treatment strategies are multi-modal and aim to reduce morbidity and mortality and increase patients' quality of life by slowing disease progression and preventing exacerbations. Interventions include cessation of smoking and pulmonary rehabilitation, vaccination against influenza and pneumonia, and the use of inhaled corticosteroids (ICS) and bronchodilators (GOLD 2017). Supplemental oxygen is a life-prolonging option in hypoxaemic patients. Although treatment is not curative, patients may occasionally be candidates for lung transplantation (GOLD 2017).

Description of the intervention

Long-acting beta$_2$-agonists (LABA) and long-acting anticholinergics (LAMA) are commonly used in patients with COPD as recommended by COPD guidelines (GOLD 2017; Wedzicha 2017). Each bronchodilator can be taken individually or in combination using either two separate inhalers or a single inhaler in a fixed-dose combination (FDC; denoted herein by LABA/LAMA). Evidence suggests that combination of a LABA and tiotropium in individual inhalers offers benefits over the use of either component alone, in terms of lung function and quality of life (Farne 2015). The need for single-inhaler fixed-dose combinations arose for several reasons including the underwhelming efficacy of salmeterol and tiotropium administered via separate devices (Aaron 2007) and potential advantages in terms of convenience and adherence (Bangalore 2007). This review has synthesised the evidence for the safety and efficacy of once-daily LABA/LAMA FDCs versus placebo in patients with COPD.

How the intervention might work

The co-administration of LABA/LAMA in COPD has beneficial effects on lung function, dyspnoea scores, health-related quality of life, and possibly in preventing acute exacerbations of COPD (AECOPD) (Calzetta 2016; Wedzicha 2014). Bronchodilation is thought to form the foundation of these benefits, but a reduction in hyperinflation, modulation of mucous production and clearance, and potentially anti-inflammatory effects are theorised to contribute as well (Beeh 2016). In terms of bronchodilation, use of LABA and LAMA together is more effective compared to either agent alone (Singh 2014a; Van Noord 2005), but the nature of this interaction is not entirely clear, with in vitro and clinical studies suggesting that there is a synergistic rather than additive effect (Cazzola 2015). The mechanism of increased bronchodilation has mainly been attributed to the activation of presynaptic beta$_2$-receptors, which attenuates the release of junctional acetylcholine (Calzetta 2015). In addition, airway smooth muscle relaxation achieved by a LABA (via increased cyclic adenosine monophosphate) is amplified by the blockade of acetylcholine by inhibition of M3 muscarinic receptors (Cazzola 2010), and there is evidence to suggest that M2 receptors interact with adenyl cyclase as well (Beeh 2016).

Why it is important to do this review

Fixed-dose combinations (FDCs) of a long-acting beta$_2$-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) delivered via a single inhaler are approved by regulatory authorities in the USA, Europe, and Japan for the treatment of COPD . The introduction of these inhalers follow guideline-based recommendations to optimise inhaled bronchodilator use (Quaseem 2011; Vestbo 2013). Recent meta-analyses have clarified the utility of LABA/LAMA combination inhalers compared to their mono-components in COPD, particularly with respect to trough FEV$_1$, transitional dyspnoea index (TDI), St. George's Respiratory Questionnaire (SGRQ) and safety (Calzetta 2016; Calzetta 2017). They found statistically and clinically significant improvements in trough FEV1 for all fixed-dose combinations (FDC) compared with their mono-components. Though there were statistically significant improvements in TDI and SGRQ, these fell below previously established minimal clinically important differences (MCIDs), and thus the clinical meaning of this benefit is unclear. Side effects, including cardiac events, were no greater in those taking LABA/LAMA. There were no significant differences between different FDCs for the outcomes examined (Calzetta 2016; Calzetta 2017). Individual clinical trials have demonstrated a reduction in AECOPD with LABA/LAMA versus mono-components and versus placebo (Bateman 2015; Wedzicha 2017). Unfortunately, the benefits of LABA/LAMA on AECOPD were not included in the meta-analyses, and thus remain to be clarified. Evaluation of the efficacy and safety of once-daily LABA/LAMA

fixed-dose combinations versus placebo will facilitate the comparison of different FDCs in future network meta-analyses.

OBJECTIVES

To assess the effects of single-inhaler LABA/LAMA combinations versus placebo on clinically meaningful outcomes in patients with stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group and cross-over randomised controlled trials (RCTs). We included studies reported as full-text, those published as abstract only, and unpublished data. We excluded very short-term trials (i.e. ≤ three weeks in duration).

Types of participants

We included adults (≥ 40 years old) with a diagnosis of stable COPD. We recorded study authors' definition of stable COPD. We did not exclude participants with comorbidities.

Types of interventions

We included trials comparing once-daily LABA/LAMA in a single inhaler (i.e. fixed dose combination) versus placebo.

We included studies that allowed participants to continue using their ICS during the trial as long as the ICS was not part of the randomised treatment; if ICS was administered in combination with LABA prior to the trial, participants should be transitioned to the equivalent ICS monotherapy prior to study start. The effect of continued ICS use was planned to be examined by subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Serious Adverse Events (SAE) of any cause.
3. Acute Exacerbations of COPD (AECOPD).
4. Respiratory Health-related Quality of Life (HRQoL), as measured by the
    i) St. George's Respiratory Questionnaire (SGRQ).
    ii) Chronic Respiratory Questionnaire (CRQ).

Comments about primary outcomes

Serious adverse events

SAEs can include death, life-threatening adverse reaction, hospitalisation or increased length of hospital stay, disability, and birth defects. We recorded each study's definition of an SAE if it varied from our definition.

Respiratory health-related quality of life

CRQ and SGRQ are widely-used, reliable and valid measures of patient-reported health status in COPD (Guyatt 1987; Jones 1992). SGRQ scores three domains of health status (symptoms, patient activity, and disease impact), and reports scores ranging from zero (best) to 100 (worst). The Minimally Clinical Important Difference (MCID) is approximately four (Schunemann 2003). That is, a clinically meaningful change in health status is equal to a change of about four points on SGRQ. CRQ scores four domains (shortness of breath, fatigue, emotional function, and mastery), reports scores ranging from one (worst) to seven (best), and has an MCID of 0.5 (Schunemann 2005). While CRQ and SGRQ provide very similar information and are highly correlated, SGRQ is less responsive; it was shown to underestimate treatment effects when compared to CRQ in identical populations (Puhan 2006). Thus, pooling SGRQ data with CRQ data may spuriously suggest heterogeneity of treatment effect. Therefore, SGRQ and CRQ were considered as separate outcomes; this approach agrees with the recommendations of Puhan 2006, who suggest that mean differences for SGRQ and CRQ should be reported separately.

Acute exacerbations of COPD

We included AECOPD as a main outcome because exacerbations are consistently linked to mortality, morbidity, and costly hospitalisations. Since a consensus definition and standard reporting criteria do not exist for AECOPD (Cazzola 2008), we performed a meta-analysis of AECOPD data only when study authors used one of the following definitions: increase in symptoms precipitating the use of antibiotics; increase in symptoms precipitating the use of systemic steroids; increase in symptoms precipitating emergency room visit; or hospitalisation. The MCID for AECOPD outcomes is not established: Calverley 2005 estimated an MCID of 20% to 25% using a crude anchor-based approach, while Chapman 2013 used an expert consensus process to estimate an MCID of 11%.

Secondary outcomes

1. Trough (pre-dose) Forced Expiratory Volume in One Second (FEV1).
2. Peak (post-dose) FEV1.
3. Six-minute walking test (6MWT).
4. Adverse effects.

Comments about secondary outcomes

Forced expiratory volume

FEV1 is the volume of air forcibly exhaled one second after maximum inhalation. FEV1 is often used for staging COPD (GOLD 2017): FEV1 is 20% lower than normal for patients with mild COPD and 70% lower than normal for patients with very severe COPD. FEV1 is also used to assess treatment effect. However, the MCID for FEV1 has not been quantitatively established (expert opinion proposes an MCID of 100 mL to 140 mL) (Cazzola 2008). Moreover, FEV1 is an intermediate endpoint, representing airflow as a surrogate for clinically important outcomes. Surrogate outcomes are not patient-centred. Nevertheless, we included trough FEV1 because one meta-analysis points to a modest correlation between increased trough FEV1 and improved SGRQ (Westwood 2011). For the purpose of this review we will consider the MCID for FEV1 to be 100 mL (Donohue 2005).

Six-minute walking test

In the ECLIPSE study (a non-interventional cohort study of treated COPD patients), one-year change in 6MWT predicted death in the subsequent 12 months. The mean between-group change between survivors and non-survivors was 30 metres (95% CI 26 to 34). Using these results, Polkey 2013 proposed an MCID of about 30 metres.

Adverse effects

We analysed all-cause adverse effects and serious adverse events reported in studies of LABA or LAMA.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Trials Register on 3 December 2018. The Cochrane Airways Trials Register is maintained by the Information Specialist for the Group and contains studies identified from several sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies - CRS Web;
2. Weekly searches of MEDLINE Ovid SP;
3. Weekly searches of Embase Ovid SP;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register were identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We searched the following trials registries on 3 December 2018:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We searched the Cochrane Airways Trials Register and additional sources from inception, with no restriction on language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' web sites for trial information.

We searched for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and reported the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (DE, UM, RW, or TH) independently screened each title and abstract for inclusion of all the potential studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications that appeared eligible and two review authors (DE, UM, TH, or RW) independently screened each full-text paper and identified studies for inclusion, or identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third person (DE, UM, RW, or TH). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table.

Data extraction and management

We used a data collection form for study characteristics and outcome data which had been piloted on at least one study in the review. Two review authors (DE, UM, RW, or TH) extracted study characteristics from each included study. We extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.

2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.

3. Interventions: intervention, comparison, concomitant medications, and excluded medications.

4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.

5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (DE, UM, RW, or TH) independently extracted outcome data from each included study. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third person (DE, UM, RW, or TH). One review author (DE) transferred data into the Review Manager file. We double-checked that data have been entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (RW) spot-checked study characteristics for accuracy against the trial report.

Trials may report continuous outcomes as change scores (i.e. change from baseline) or final values. As per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we presented mean differences in change scores in one subgroup, mean differences in final values in another, and pooled both subgroups for an overall analysis.

Where multiple time points were reported for outcomes, we chose the time point that maximised length of follow-up for the randomised treatment period.

Assessment of risk of bias in included studies

Two review authors (DE, KP, or FE) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving a third author (DE, KP, or FE). We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes, where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios and continuous data as mean differences or standardised mean differences. We entered data presented as a scale with a consistent direction of effect.

We performed meta-analyses only where this was meaningful, i.e. if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

We narratively described skewed data reported as medians and interquartile ranges.

Where multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we halved the control group to avoid double-counting.

Unit of analysis issues

We analysed dichotomous data using participants as the unit of analysis (rather than events) to avoid counting the same participant more than once. Paired data from each participant in cross-over trials were analysed using the Generic Inverse Variance method.

Dealing with missing data

We contacted investigators or study sponsors in order to obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). That is, if study authors did not report true intention-to-treat (ITT) data, we attempted an available case analysis by including data for all participants for whom outcome data were collected (whether the participants completed or did not complete the trial). Please note that a case analysis is not a true ITT analysis, nor a per-protocol analysis.

If we could not obtain missing data from study authors, we planned to:

1. compare our available case analysis with an imputed, true ITT analysis (see Sensitivity Analyses);

2. use an average standard deviation (SD) borrowed from other studies included in our meta-analysis if the SD for a mean difference was unavailable (or incalculable);

3. use final values instead of the change-from-baseline values if the standard deviation for a change score was missing.

If the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (i.e. I^2 greater than 30%) we reported it and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we were able to pool more than 10 trials, we planned to create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We used a fixed-effect model and performed a sensitivity analysis with a random-effects model. Where study authors reported exacerbation rate, we meta-analysed rate data when study authors accounted for duration of follow-up and inter-patient variability (Aaron 2008). The odds ratio was our primary summary statistic. Where possible, we also reported AECOPD as the percentage of participants experiencing at least one exacerbation. This way, AECOPD could be presented as a dichotomous outcome, and a patient-based number needed to treat for an additional beneficial outcome (NNTB) could be reported. When possible, we also reported SGRQ and CRQ as dichotomous outcomes (i.e. participants who reached the MCID versus participants who did not).

Summary of findings table

We created a 'Summary of findings' table using the seven primary and secondary outcomes identified above; for health-related quality of life, SGRQ was reported in the 'summary of findings' table. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it related to the studies which contributed data to the meta-analyses for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software. We justified all decisions to downgrade or upgrade the certainty of the evidence using footnotes and we made comments to aid reader's understanding of the review, where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

1. participants with ICS use during the trial versus participants without ICS use during the trial;
2. different LABA/LAMA combinations (IND/GLY; UMEC/VI; TIO/OLO; ACM/FOR);
3. length of follow-up (less than six months versus six months or longer);
4. baseline COPD severity (mild or moderate disease versus severe disease, according to GOLD criteria).

We used our primary outcomes in subgroup analyses.

We used the formal test for subgroup interactions in Review Manager.

Sensitivity analysis

We planned to carry out the following sensitivity analyses:

1. a comparison of available case analysis to true ITT analyses, where the ITT analyses were imputed with best-case and worse-case outcome data;
2. a comparison of results from fixed-effect models with results from random-effects models;
3. a comparison based on our 'risk of bias' assessments (i.e. exclusion of studies with a high risk of bias).

RESULTS

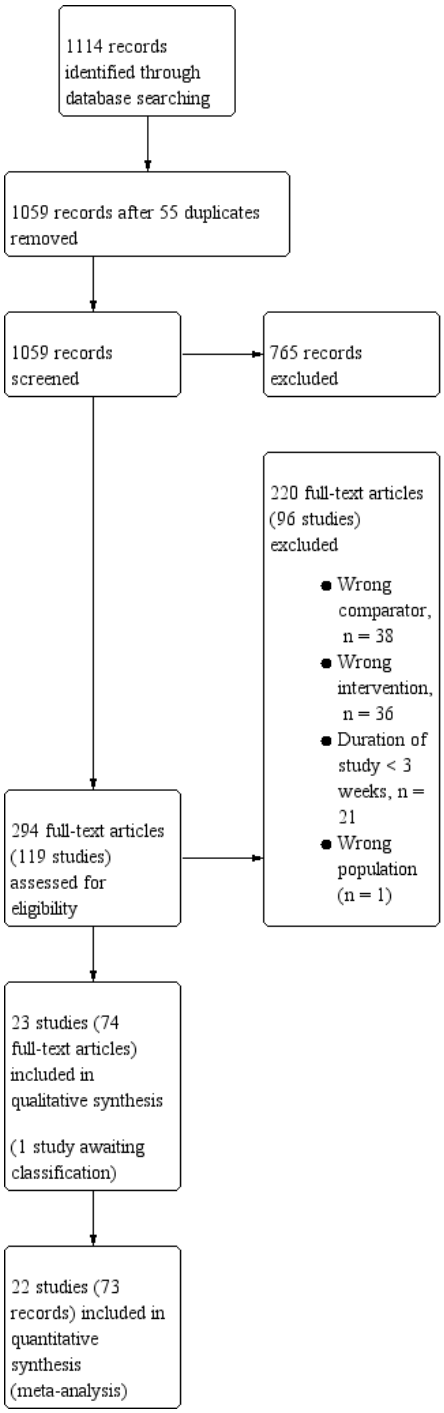
Description of studies

The Characteristics of included studies tables presents details of the included studies; a summary table is also provided (Table 1). In the Characteristics of excluded studies table, we reported reasons for the exclusion of studies considered during review of full-text articles.

Results of the search

We identified 1114 records by performing electronic searches of bibliographic databases . Of a total of 1059 records (55 duplicates removed), we excluded 765 upon screening titles and abstracts. We examined full-text articles of the remaining 294 records and excluded 220 records (reporting 96 studies; see Excluded studies). The remaining 74 records reported the findings of 23 studies, which we included in this review (studies included in quantitative analyses, n = 22; studies awaiting classification, n = 1). Figure 1 depicts the flow of information through the different stages of this systematic review.

Figure 1. Study flow diagram.



Included studies

Of the 23 studies that met the inclusion criteria, there were twenty-two included studies (Bateman 2013; Beeh 2014; Beeh 2015; Celli 2014; Dahl 2013; Donohue 2013; Feldman 2012; Larbig 2015; Mahler 2014; Maltais 2014b; Maltais 2014c; Maltais 2014; NCT00626522; NCT02275052; O'Donnell 2015a; O'Donnell 2015b; Siler 2016; Singh 2016a; Singh 2016b; Troosters 2016; Watz 2016; Zheng 2014) and one study awaiting classification (NCT02233543 2014). A majority of included studies were reported as full peer-reviewed articles, with the exception of those reported as abstract only (Larbig 2015) or trial registry only (NCT00626522 and NCT02275052).

Methods

Of the included studies, 13 had a parallel-group design and nine had a cross-over design; all 22 studies were described as double-blind (blinding of participants and staff occurred in 15 studies and was unclear in seven studies; blinding of outcome assessors occurred in six studies and was unclear in 16 studies). Studies had a randomly assigned treatment period ranging from three weeks to 52 weeks (mean 11 weeks; median 12 weeks; mode 12 weeks); a minority of studies had a duration of six months or longer (6 months, n = 4; 12 months, n = 2). All studies were multicentre studies; 19 of 22 studies were international, with the exception of trials performed solely in Germany (Watz 2016) or the USA (Feldman 2012; NCT02275052). Overall, there was good geographical coverage; the majority of studies (16/22) enrolled participants from both Europe and North America and studies also enrolled a proportion of participants from China and Asia (Bateman 2013; Dahl 2013; Donohue 2013; Larbig 2015; Siler 2016), Oceania (O'Donnell 2015a; O'Donnell 2015b; Singh 2016a; Singh 2016b; Troosters 2016), Russia (Maltais 2014c; NCT00626522; O'Donnell 2015a; O'Donnell 2015b; Siler 2016) and South Africa (Dahl 2013; Maltais 2014b; Singh 2016a; Singh 2016b). Study setting was poorly reported, but appeared to represent a mix of academic/clinical research centres and primary or secondary care units.

Participants

The twenty-two included studies randomised a total of 8641 participants (Table 1). Baseline characteristics were generally consistent across studies. Inclusion criteria for the majority of studies (n = 21/22) specified either GOLD stage II/III, or criteria aligned with this disease severity (i.e. post-bronchodilator FEV1 < 70% or 80%; post-bronchodilator FVC/FEV1 < 70%; MRC dyspnoea score $\geq$ 2); Beeh 2015 permitted inclusion of participants with GOLD stage II to IV. The mean ages of participants across the relevant arms of all included studies ranged from 59 to 65 years; the proportion of current smokers generally ranged from 40% to 55% (n = 20; two outliers: 25% (Zheng 2014) and 78% (Feldman 2012)). In each trial, a majority of participants were male (range across studies 53% to 82%; one outlier, 92% to 94% (Zheng 2014)). Where reported, post-bronchodilator percent predicted FEV1 ranged from 47% to 62% (median ~58%); Zheng 2014 did not report % predicted FEV1, but pre-bronchodilator FEV1 was 1.2 L to 1.3 L; Larbig 2015, NCT00626522, NCT02275052 and Troosters 2016 did not report baseline lung-function (abstract or trial registry only). Concomitant inhaled corticosteroid (ICS) use was permitted in all of the included studies (where stated); across the included studies, between 28% to 58% of participants were using ICS at baseline.

Intervention

Of the 8641 randomised participants across the 22 studies, and accounting for the enrolment in multiple arms of cross-over studies, a total of 6252 participants were randomised to receive once-daily LABA/LAMA via a combined inhaler, and 3819 participants were randomised to receive placebo. In the subgroup of parallel-group trials, 4124 participants were randomised to receive once-daily LABA/LAMA via a combined inhaler and 2520 participants were randomised to receive placebo. Across the 22 studies, six studies evaluated the once-daily combination of IND/GLY (110/50 μg), seven studies evaluated TIO/OLO (2.5/5 or 5/5 μg), eight studies evaluated UMEC/VI (62.5/5, 125/25 or 500/25 μg) and one study evaluated ACD/FOR (200/6, 200/12 or 200/18 μg); all LABA/LAMA combinations were compared with placebo. Where reported, concomitant treatment with ICS was permitted by all studies with various restrictions relating to prior use and stable dose for a prespecified time prior to study initiation; whether concomitant ICS was permitted was not reported for one study (Troosters 2016).

Outcomes

With the exception of the 6MWT (secondary outcome), all of the prespecified outcomes were reported by at least three of the included studies. All-cause mortality was reported by 18 studies, SAEs, by all 22 studies, AECOPD by three studies, difference versus placebo in adjusted trough FEV1 by 13 studies, difference versus placebo in adjusted peak FEV1 by seven studies, difference versus placebo in adjusted SGRQ score by eight studies, and all-cause AEs by 18 studies (Summary of findings for the main comparison). 6MWT was not reported by any of the included studies.

Excluded studies

Ninety-six studies were excluded, primarily because either the intervention did not meet the inclusion criteria (i.e. the LAMA and LABA were not administered once-daily in a fixed dose combination, or the combination was administered twice daily; n = 36 studies) or because the study did not include a placebo arm (n = 38). It was often difficult to ascertain from the abstract whether the LAMA and LABA were administered as a fixed-dose combination and from the clinical trial record headers it was not always possible to identify whether a placebo group was included; this resulted in a high rate of exclusions at full-text review stage. Other reasons for exclusion at this stage included 'duration < 3 weeks' (n = 21), 'wrong participant population' (healthy volunteers; n = 1).

Risk of bias in included studies

Please refer to the Characteristics of included studies tables for details on risk of bias and for supporting evidence for each study. Figure 2 provides a summary of 'risk of bias' judgements, presented by study and domain (sequence generation, allocation concealment, blinding, incomplete data, selective reporting and 'other'). Figure 3 depicts the risk of bias for each domain, presented as percentages across all included studies. Across 198 assessments (22 studies, nine risk of bias domains), 146 were considered to be at a low risk of bias, seven at a high risk of bias and 45 to have an unclear risk of bias.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

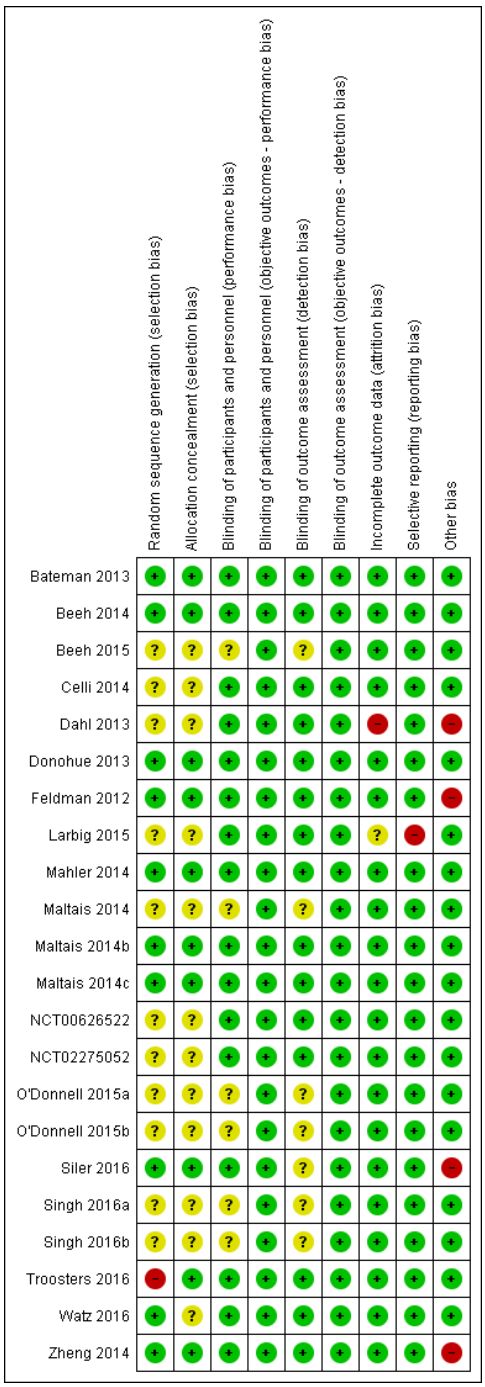
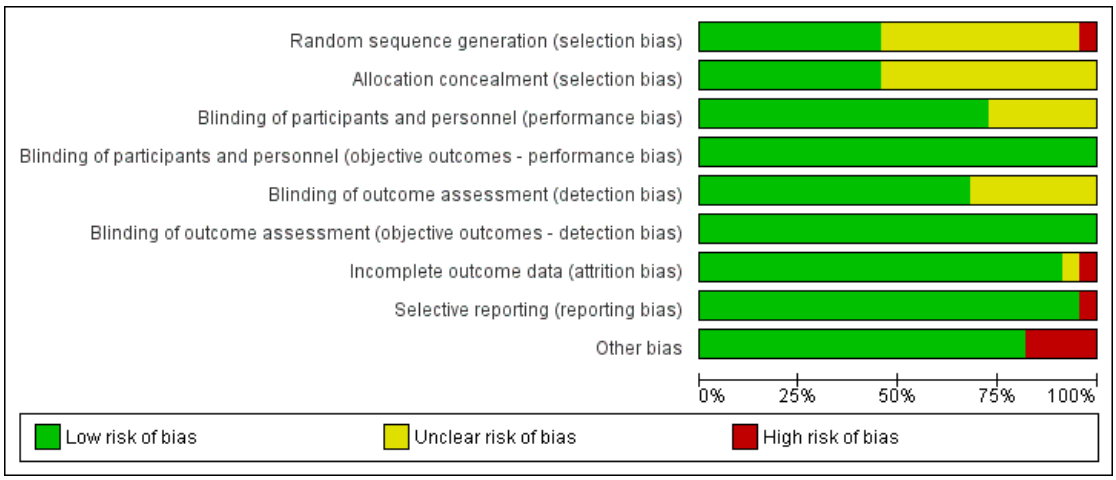


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

More than half of the included studies provided insufficient information regarding methods of random sequence generation (11 of 22 studies) and concealment of treatment allocation (12 of 22 studies) to allow a judgement on risk of bias; the risk of bias for these studies was rated as unclear. Ten studies employed adequate methods of random sequence generation and were considered to be at low risk of bias. (Bateman 2013; Beeh 2014; Donohue 2013; Feldman 2012; Mahler 2014; Maltais 2014b; Maltais 2014c; Siler 2016; Watz 2016; Zheng 2014) or adequate methods of allocation concealment (Bateman 2013; Beeh 2014; Donohue 2013; Feldman 2012; Mahler 2014; Maltais 2014b; Maltais 2014c; Siler 2016; Troosters 2016; Zheng 2014). Inadequate methods of random sequence generation (pseudo-random number generator and block randomisation) were employed in one study (Troosters 2016), which was considered to be at high risk of bias.

Blinding

We considered the risk of performance and detection bias separately for objective and subjective outcomes. For objective outcomes (all-cause mortality, SAEs, AECOPD, lung function and AEs) we considered that a lack of blinding would not result in a risk of detection or performance bias; therefore all studies were considered to be at low risk of bias with respect to these outcomes. The only subjective outcome relevant to this review was HRQoL based on assessment by SGRQ; sixteen studies were considered to be at a low risk of performance bias (Bateman 2013; Beeh 2014; Celli 2014; Dahl 2013; Donohue 2013; Feldman 2012; Larbig 2015; Mahler 2014; Maltais 2014b; Maltais 2014c; NCT00626522; NCT02275052; Siler 2016; Troosters 2016; Watz 2016; Zheng 2014); and the risk of performance bias was unclear for the remaining six studies (Beeh 2015; Maltais 2014; O'Donnell 2015a; O'Donnell 2015b; Singh 2016a; Singh 2016b). For HRQoL, the risk of detection bias was considered low for fifteen studies (Bateman 2013; Beeh 2014; Celli 2014; Dahl 2013; Donohue 2013; Feldman 2012; Larbig 2015; Maltais 2014b; Maltais 2014c; Mahler 2014; NCT00626522; NCT02275052; Watz 2016; Troosters 2016; Zheng 2014) and unclear in seven studies (Beeh 2015; Maltais 2014; O'Donnell 2015a; O'Donnell 2015b; Siler 2016; Singh 2016a; Singh 2016b).

Incomplete outcome data

We considered 20 of 22 studies to be at low risk of attrition bias on the basis of low and balanced rates of participant withdrawal, which were adequately documented in the trial reports. One study (Dahl 2013) was considered to be at high risk for attrition bias based on a greater than 20% rate of attrition in the placebo arm versus < 15% in the IND/GLY arm; insufficient information was reported by one study (Larbig 2015), resulting in a rating of unclear

risk of attrition bias.

Selective reporting

We considered 21 of 22 studies to be at low risk of reporting bias. One study (Larbig 2015) was considered to be at high risk for reporting bias as the abstract (abstract only) did not report key prespecified outcomes (as reported on the trial registry site).

Other potential sources of bias

We considered there to be potential sources of bias present in four of the studies. In Dahl 2013, more participants in the QVA149 group had severe COPD versus those in the placebo group; however, this would likely skew treatment effect in favour of placebo. An imbalance in baseline characteristics in Feldman 2012 suggested that randomisation was not robust, although the limited sample size of the placebo group could also account for imbalance in baseline characteristics. In Siler 2016, a greater proportion of participants with GOLD category D were enrolled in the active treatment group, possibly favouring placebo and underestimation of the treatment effect. In Zheng 2014, a higher proportion of participants with GOLD Stage IV were enrolled in the UMEC/VI 62.5/25 µg group compared with placebo and could potentially skew the treatment effect in favour of placebo. These four studies were considered to be at high risk of 'other' bias; however, we noted that in three cases, the issue would tend to skew the results in favour or placebo, resulting in a potential underestimation of the treatment effect.

Effects of interventions

See: **Summary of findings for the main comparison** Once-daily LABA/LAMA in a combined inhaler compared with placebo in adults with COPD

Structure of the meta-analysis

As per the protocol, we elected to perform a meta-analysis only when interventions and outcomes were sufficiently similar for pooling of the data. We subgrouped the data in the forest plots according to the type and dose of LABA/LAMA combination. However, some comparisons (stated below) should be interpreted with caution because of the relatively small number of trials for each subgrouping, heterogeneity in study design (i.e. length, inclusion and exclusion criteria), and the low number of events for all-cause mortality and SAEs.

Structure of the narrative synthesis

In the following sections, we present a narrative summary of study results according to the prespecified outcomes. We present primary outcomes (all-cause mortality, SAEs, AECOPD, respiratory HRQoL) followed by secondary outcomes (trough FEV1, peak FEV1, 6MWT, AEs). For each outcome, we describe the overall effect of the intervention irrespective of LABA/LAMA type or dose, followed by the effect of the intervention in subgroups according to LABA/LAMA type and dose.

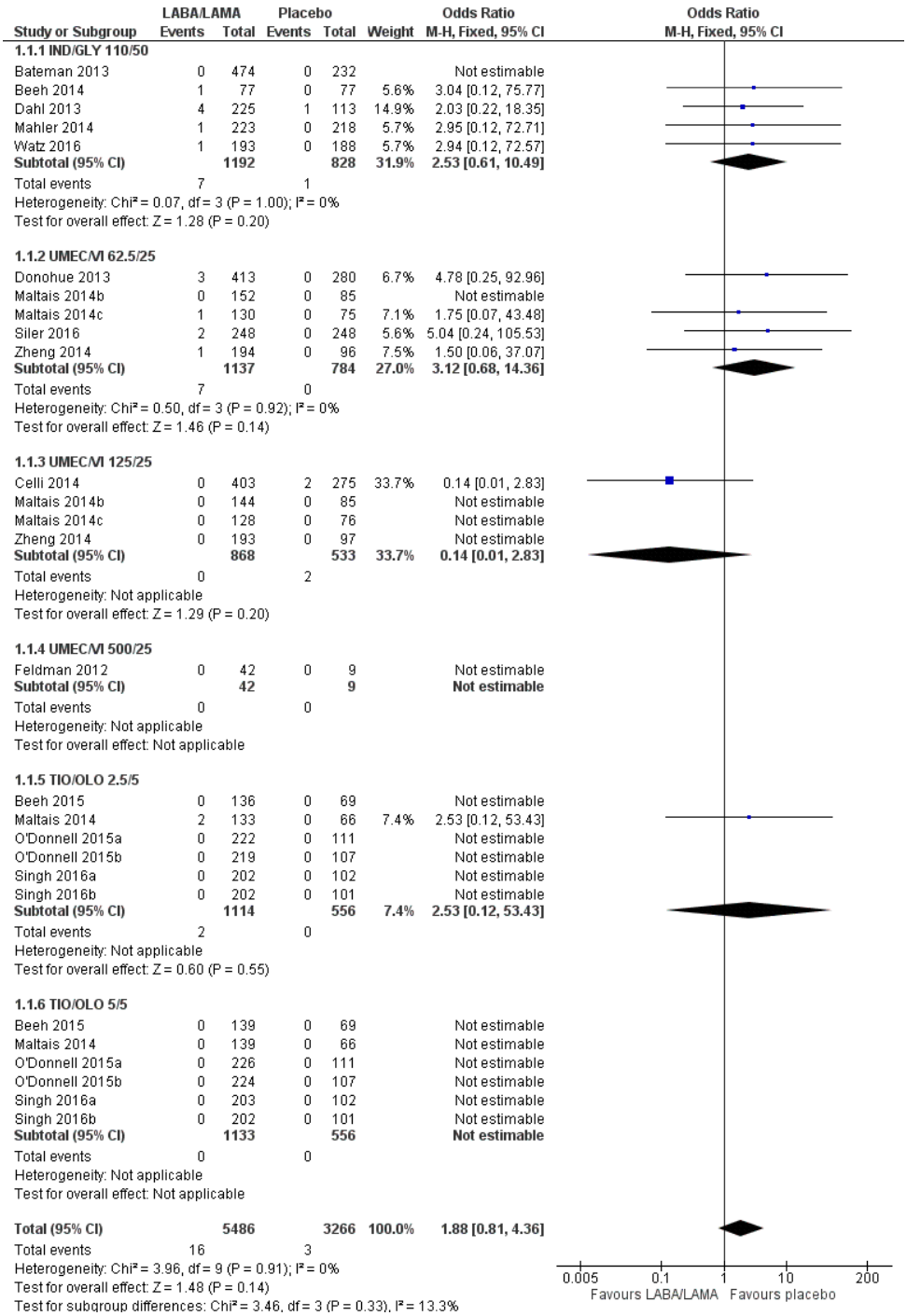
Primary outcomes

All-cause mortality

Eighteen studies (8752 participants) reported all-cause mortality, although the number of reported deaths was low. There was no significant difference in the number of deaths reported in participants receiving a once-daily LABA/LAMA fixed-dose combination compared with those receiving placebo (OR 1.88, 95% CI 0.81 to 4.36; I^2 = 0%; Analysis 1.1). The overall certainty of the evidence for this outcome was rated as low, having been downgraded once for indirectness (duration of studies varied widely from six weeks to 52 weeks) and once for imprecision (wide confidence intervals due to a low number of events).

The results were generally consistent (i.e. overlapping CIs) across subgroups for different LABA/LAMA combinations and doses, with ORs ranging from 1.88 with UMEC/VI 500/25 μg to 3.12 with UMEC/VI 62.5/25 μg (Figure 4); the only exception was the UMEC/VI 125/25 μg subgroup with two deaths reported in the placebo arm of one of four studies and no other deaths reported in the remaining three studies, resulting in an OR of 0.14 (95% CI 0.01 to 2.83).

Figure 4. Forest plot of comparison: 1 LABA/LAMA versus placebo, outcome: 1.1 All-cause mortality.

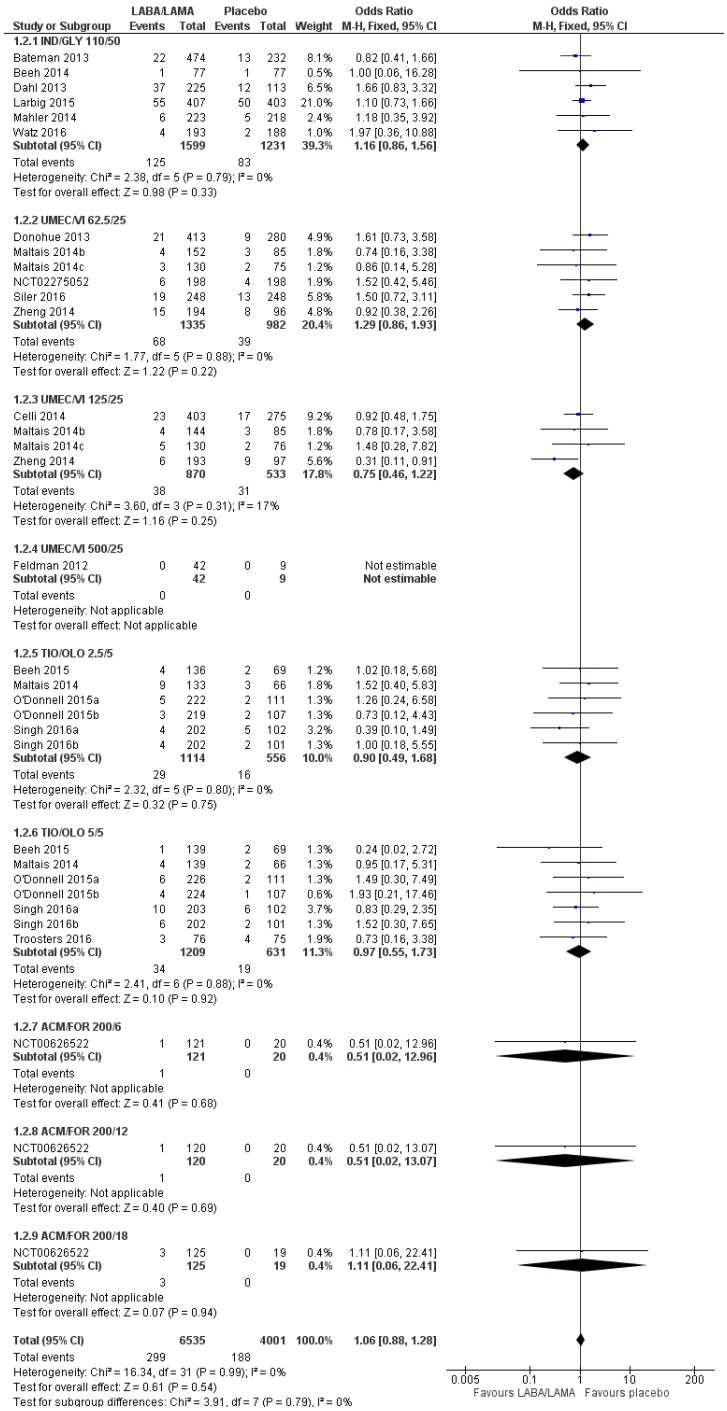


Serious adverse events

Twenty-two studies (10,536 participants) reported the number of participants experiencing serious, but non-fatal adverse events during the study period, for which there was no statistically significant difference (OR 1.06, 95% CI 0.88 to 1.28; I^2 = 0%; Analysis 1.2). Compared with taking placebo, we estimated that taking once-daily LABA/LAMA in a combined inhaler would result in three more people per 1000 experiencing a SAE, but the confidence intervals ranged from five fewer to nine more people per 1000. The overall certainty of the evidence for this outcome was rated as high.

The results were generally consistent across subgroups for different LABA/LAMA combinations and doses, with ORs ranging from 0.75 with UMEC/VI 125/25 μg to 1.29 with UMEC/VI 62.5/25 μg (Figure 5). The only exceptions were the ACM/FOR 200/6 μg and 200/12 μg subgroups, where the ORs were 0.51 (95% CI 0.02 to 12.96) and 0.51 (95% CI 0.02 to 13.07), respectively; however, these results should be interpreted cautiously as they were based on a small sample size from a single study, resulting in wide confidence intervals.

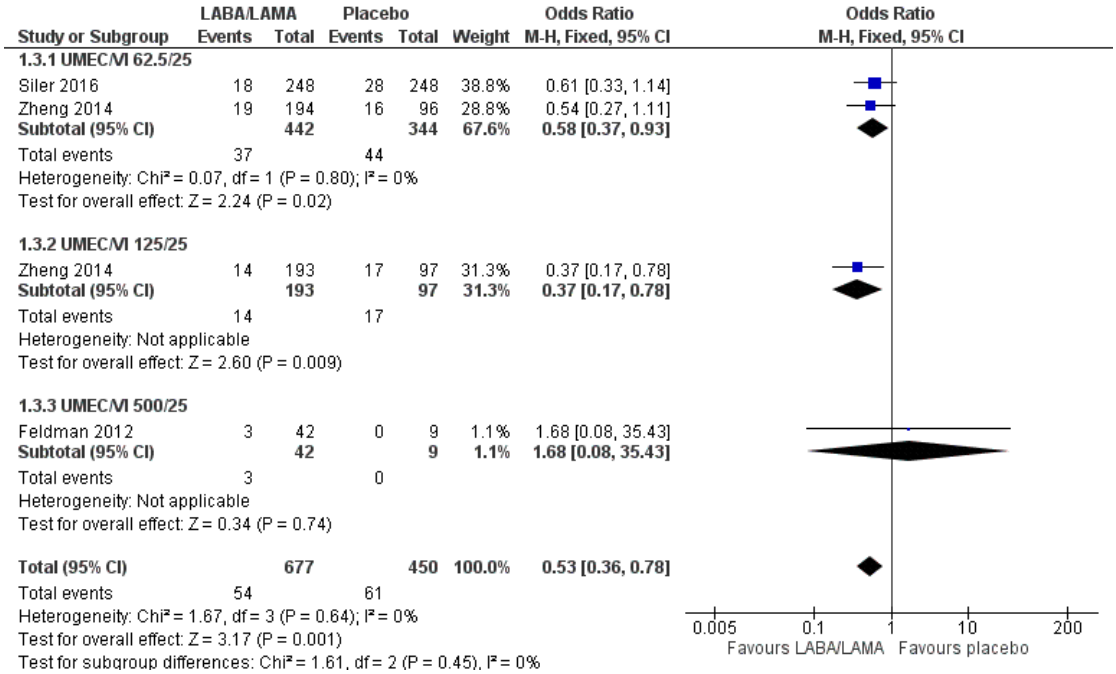
Figure 5. Forest plot of comparison: 1 LABA/LAMA versus placebo, outcome: 1.2 SAEs.



AECOPD

Three studies (1127 participants) reported the number of participants experiencing an AECOPD; all three studies examined UMEC/VI versus placebo. Significantly fewer people receiving once-daily LABA/LAMA in a combined inhaler experienced an AECOPD compared with those receiving placebo (OR 0.53, 95% CI 0.36 to 0.78; I^2 = 0%; Analysis 1.3; Figure 6). Compared with taking placebo, we estimated that taking once-daily LABA/LAMA in a combined inhaler would result in 59 fewer people per 1000 experiencing an AECOPD, with the confidence intervals ranging from 27 to 83 fewer people per 1000. The overall certainty of the evidence for this outcome was rated as moderate, having been downgraded once for indirectness (all studies related to UMEC/VI). The results were consistent for two of three UMEC/VI doses examined, with ORs of 0.58 (95% CI 0.37 to 0.93) and 0.37 (0.17 to 0.78) for the 62.5/25 μg and 125/25 μg groups, respectively; the OR for the 500/25 μg dose was 1.68 (0.08 to 35.43) but was based on data from a small sample size (n = 51 participants).

Figure 6. Forest plot of comparison: 1 LABA/LAMA versus placebo, outcome: 1.3 AECOPD.



Two studies (1371 participants), reported the time to first AECOPD; both studies examined UMEC/VI 125/25 μg versus placebo. The mean time to first AECOPD was statistically significantly longer in people receiving once-daily LABA/LAMA in a combined inhaler compared with those receiving placebo (Hazard Ratio 0.44, 95% CI 0.31 to 0.63; Analysis 1.4).

Health-related quality of life

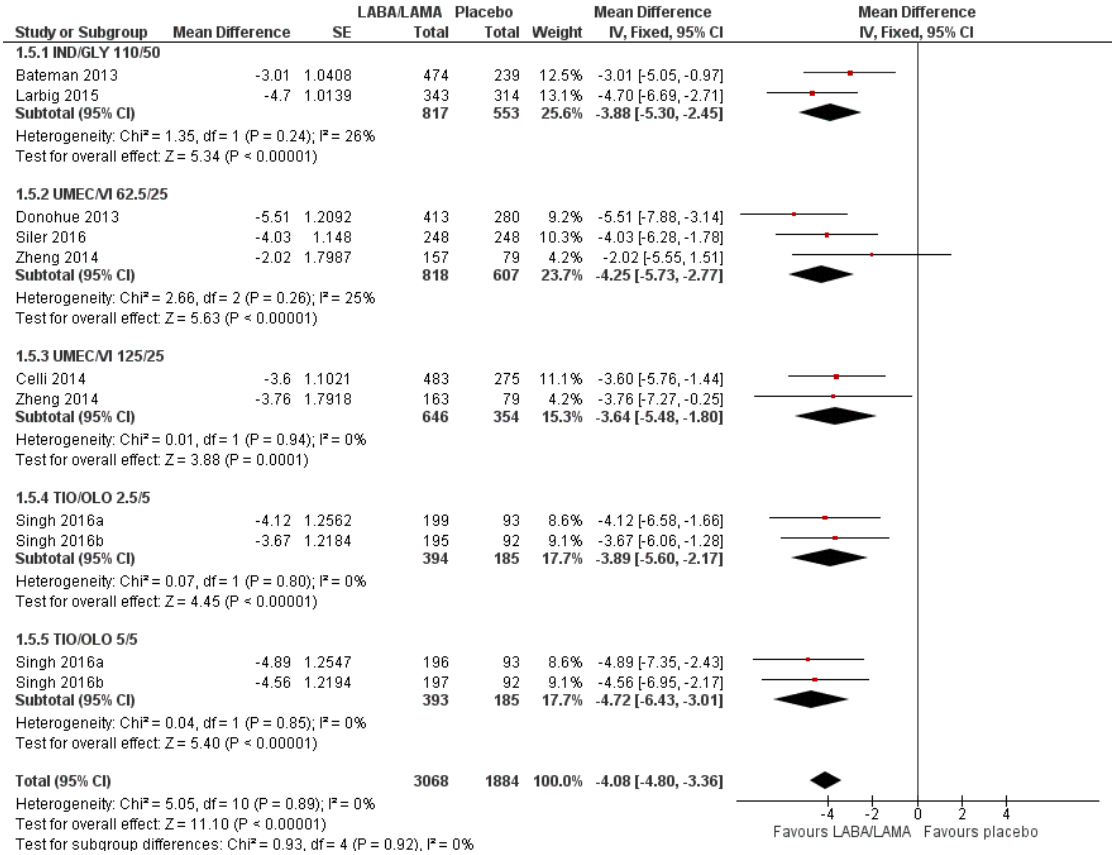
SGRQ

Eight studies (4952 participants) reported health-related quality of life as assessed using the SGRQ, at the end of treatment. A decrease in SGRQ represents an improvement in quality of life and the MCID is considered to be a change of four units (SGRQ-C Manual). At the end of treatment in participants receiving once-daily LABA/LAMA in a combined inhaler, the mean improvement versus placebo in adjusted SGRQ score was -4.08 (95% CI -4.80 to -3.36; Analysis 1.5), which was statistically significant and

clinically relevant, exceeding the MCID. The overall certainty of the evidence for this outcome was rated as high.

The results were generally consistent across subgroups for different LABA/LAMA combinations and doses, with mean differences versus placebo ranging from -3.64 with UMEC/VI 125/25 μg to -4.72 with TIO/OLO 5/5 μg (Figure 7). The mean difference in SGRQ score versus placebo was statistically significant for all LABA/LAMA combinations and doses for which data were available (IND/GLY 110/50 μg; UMEC/VI 125/25 μg; UMEC/VI 62.5/25 μg; TIO/OLO 2.5/5 μg; TIO/OLO 5/5 μg); however, the MCID (4.00) was only exceeded with UMEC/VI 62.5/25 μg, TIO/OLO 2.5 μg and TIO/OLO 5/5 μg.

Figure 7. Forest plot of comparison: 1 LABA/LAMA versus placebo, outcome: 1.5 Difference vs placebo in adjusted SGRQ score (HRQoL).



Seven studies (4258 participants) reported SGRQ responder status (i.e. the proportion of participants who achieved a $\geq$ 4 point improvement from baseline in SGRQ total score) at the end of treatment. Compared with placebo, a greater proportion of participants receiving once-daily LABA/LAMA were responders (OR 1.75, 95% CI 1.54 to 1.99; I^2 = 0%; Analysis 1.6) and this difference was statistically significant. Compared with taking placebo,

we estimated that taking a once-daily LABA/LAMA in a combined inhaler would result in 138 more people per 1000 achieving a clinically meaningful improvement in quality of life, with the confidence intervals ranging from 106 to 170 more people per 1000. This finding is in agreement with the mean improvement in SGRQ total score for LABA/LAMA versus placebo, as reported above. The results were generally consistent across subgroups for different LABA/LAMA combinations and doses, with ORs versus placebo ranging from 1.70 with UMEC/VI 62.52/5 μg to 2.35 with TIO/OLO 5/5 μg; the exception was IND/GLY 110/50 μg for which the OR (95% CI) versus placebo was 1.35 (0.98 to 1.86), thus narrowly missing out on statistical significance. We note that the latter result was based on a single study, for which data were presented as percentages and extrapolated to participant numbers; given uncertainty around the precise raw data, this finding should be interpreted cautiously.

Secondary outcomes

Trough FEV1

Adjusted difference versus placebo in trough FEV1 at end of treatment

Thirteen studies (6598 participants) reported adjusted trough FEV1 at the end of treatment (i.e. change from baseline in FEV1). In participants receiving once-daily LABA/LAMA in a combined inhaler, the mean difference versus placebo in adjusted trough FEV1 was 0.20 L (95% CI 0.19 to 0.21; Analysis 1.7), which was statistically significant and clinically relevant, exceeding the MCID of 100 mL (Donohue 2005). The overall certainty of the evidence for this outcome was rated as moderate, having been downgraded once for inconsistency (significant heterogeneity, I^2= 71%), noting that heterogeneity was due to a different magnitude of treatment effect in a single study (NCT00626522; see below). The results were generally consistent (i.e. overlapping CIs) across subgroups for different LABA/LAMA combinations and doses, with mean differences versus placebo ranging from 0.18 L with UMEC/VI 62.5/25 μg to 0.25 L with IND/GLY 110/50 μg; the exception was the results for ACLID/FORM, which were based on a single study (NCT00626522); mean differences were 0.07, 0.12 and 0.07 L for the 200/6, 200/12 and 200/18 μg subgroups, respectively. The MCID (0.1 L) was exceeded with IND/GLY 110/50 μg, UMEC/VI 62.5/25 μg, UMEC/VI 125/25 μg, TIO/OLO 2.5 μg, and TIO/OLO 5/5 μg.

Unadjusted difference versus placebo in trough FEV1 at end of treatment

Five studies (2330 participants) reported trough FEV1 at the end of treatment (i.e. not adjusted for baseline values). In participants receiving once-daily LABA/LAMA in a combined inhaler, the mean difference versus placebo in trough FEV1 was 0.18 L (95% CI 0.16 to 0.20; Analysis 1.8), which was statistically significant and clinically relevant, exceeding the MCID of 100 mL (Donohue 2005). The overall certainty of the evidence for this outcome was rated as high.

The results were consistent across subgroups for different LABA/LAMA combinations and doses, with mean differences versus placebo ranging from 0.16 L with TIO/OLO (2.5/5 and 5/5 μg doses) to 0.20 L with IND/GLY 110/50 μg. The MCID (0.1L) was exceeded with all LABA/LAMA combinations/doses for which data were available (IND/GLY 110/50 μg; TIO/OLO 2.5/5 μg; TIO/OLO 5/5 μg).

Pooled analyses for trough FEV1

When the adjusted and unadjusted data for trough FEV1 were pooled, there was no appreciable change in the overall mean difference (adjusted: MD 0.20 L, 95% CI 0.19 to 0.21; unadjusted: 0.18 L, 95% CI 0.16 to 0.20; pooled: MD 0.20 L, 95% CI 0.19 to 0.20 Analysis 1.9).

Adjusted peak FEV1

Seven studies (4188 participants) reported peak FEV1 at the end of treatment (i.e. peak FEV1 was explicitly specified, rather than 1-hour FEV1, 2-hour FEV1, etc). In participants receiving once-daily LABA/LAMA in a combined inhaler, the mean difference versus placebo in peak FEV1 was 0.31 L (95% CI 0.29 to 0.32; Analysis 1.10), which was statistically significant. The overall certainty of the evidence for this outcome was rated as moderate, having been downgraded once for inconsistency (significant heterogeneity, I^2= 68%).

The results were consistent across subgroups for different LABA/LAMA combinations and doses, with mean differences versus placebo ranging from 0.22 L with UMEC/VI 62.52/5 μg to 0.35 L with IND/GLY 110/50 μg.

6MWT

No studies reported data for this outcome.

Adverse events

Seventeen studies (8235 participants) reported the number of participants experiencing adverse events during the study period, for which there was no statistically significant difference (OR 0.95, 95% CI 0.86 to 1.04; I^2 = 0%; Analysis 1.11). Compared with taking placebo, we estimated that taking once-daily LABA/LAMA in a combined inhaler would result in 13 fewer people per 1000 experiencing a AE, with the confidence intervals ranging from 37

fewer to 10 more people per 1000. The overall certainty of the evidence for this outcome was rated as high.

The results were generally consistent across subgroups for different LABA/LAMA combinations and doses, with ORs ranging from 0.78 with TIO/OLO 5/5 μg to 1.08 with UMEC/VI 125/25 μg (Figure 5). The only exception was the UMEC/VI 500/25 μg subgroup (OR 2.84, 95% CI 0.32 to 25.36; participants = 51); however, these results should be interpreted cautiously as they were based on a small sample size from a single study, resulting in wide confidence intervals.

Subgroup analyses

Participants with ICS use during the trial versus participants without ICS use during the trial

All studies permitted the use of ICS during the trial, provided that participants had used ICS prior to the trial, and, in some cases, that the dose was stable prior to study initiation. Therefore, no subgroup analysis was performed.

Different LABA/LAMA combinations

The main analyses were split out by different LABA/LAMA combinations; please see the main results section above for a summary of different LABA/LAMA combinations.

Length of follow-up (less than six months versus six months or longer)

Three studies had a duration of six months or longer (Bateman 2013; Dahl 2013; Larbig 2015) and all evaluated IND/GLY 110/50 versus placebo. This subanalysis was only relevant for three of the four primary outcomes as no studies evaluating IND/GLY contributed data to the meta-analyses for AECOPD.

For all-cause mortality, no significant difference between LABA/LAMA and placebo groups was identified, regardless of study duration (overall: < 6 months, OR 1.86, 95% CI 0.75 to 4.60 (25 studies); ≥ 6 months, OR 2.03, 95% CI 0.22 to 18.35 (2 studies); IND/GLY: < 6 months, OR 2.97, 95% CI 0.47 to 18.97 (3 studies); ≥ 6 months, OR 2.03, 95% CI 0.22 to 18.35 (2 studies)) (Analysis 2.1; Analysis 3.1).

For SAEs, there was no statistically significant difference in the number of participants experiencing serious, but non-fatal, adverse events during the study period, regardless of study duration (overall: < 6 months, OR 1.02, 95% CI 0.80 to 1.29 (19 studies); ≥ 6 months, OR 1.14, 95% CI 0.83 to 1.56 (3 studies); IND/GLY: < 6 months, OR 1.35, 95% CI 0.54 to 3.40 (3 studies); ≥ 6 months, OR 1.14, 95% CI 0.83 to 1.56 (3 studies)) (Analysis 2.2; Analysis 3.2).

For HRQoL, a statistically significant and clinically relevant improvement (i.e. exceeding MCID) in SGRQ score was observed with LABA/LAMA compared with placebo based on studies with a duration of < 6 months (MD -4.15, 95% CI -4.99 to -3.32; 9 studies). Three studies with a duration of ≥ 6 months reported SGRQ score and all evaluated IND/GLY 110/50 μg. As in the primary analyses, a statistically significant improvement was observed but did not exceed the MCID (MD -3.88, 95% CI -5.30 to -2.45; 2 studies).

For each outcome (all-cause mortality, SAEs, and HRQoL), given the overlapping confidence intervals for the < 6-month versus ≥ 6-month comparison, we concluded that study duration had no statistically significant effect on the results.

Baseline COPD severity

All of the included studies that contributed data to the quantitative analyses enrolled a majority (> 97%) of participants with GOLD Stage II/III COPD. Therefore, subanalyses based on baseline disease severity were not performed.

Sensitivity analyses

The following sensitivity analyses were performed for the primary outcomes.

Available case analysis versus true ITT analysis

All included studies claimed to analyse the ITT population or 'full analysis set'; however, in the majority of studies it was not possible to determine whether missing values were imputed. Therefore, this sensitivity analysis was not performed.

Fixed- versus random-effect models

The results were consistent regardless of choice of analysis model (fixed- versus random-effects model) (Table 2).

Risk of bias assessments

The results were consistent regardless of the inclusion of studies with a high risk of bias for one or more domains (i.e. any risk of bias versus low/unclear risk of bias) (Table 3).

DISCUSSION

Summary of main results

We included twenty-two studies (13 parallel-group designs and nine cross-over designs), which randomised a total of 8461 participants. All studies were RCTs that compared once-daily LABA/LAMA via combination inhaler (n = 6252) with placebo (n = 3819). Most participants were adults with GOLD stage II/III

COPD and between 28% to 58% of participants were using ICS at baseline. The duration of treatment ranged from three to 52 weeks (mean = 11 weeks; median = 12 weeks) and only three studies had a duration of six months or longer. All studies were performed at multiple centres and 19 of 22 studies were international. Most studies were well designed and considered to be at low risk of bias. Compared to placebo, once-daily LABA/LAMA in a combined inhaler resulted in an improvement in HRQoL (measured using the SGRQ) and lung function and a decrease in AECOPD. Generally, the safety and tolerability of once-daily LABA/LAMA appeared comparable to that observed in placebo-treated participants, with similar rates of AEs and SAEs observed in each group. There was no significant difference in the number of deaths reported in participants receiving a once-daily LABA/LAMA fixed-dose combination (one per 1000) compared with those receiving placebo (2 per 1000); we assessed the certainty of the evidence to be low having been downgraded for imprecision and indirectness. Treatment effects were generally consistent across different LABA/LAMA combinations and doses. Improvements in HRQoL that statistically significantly exceeded the MCID were achieved with UMEC/VI 62.5/25 μg and TIO/OLO (2.5/5 and 5/5 μg) but not with IND/GLY 110/50 μg or UMEC/VI 125/25 μg. Improvements in lung function (trough FEV1 and peak FEV1) that statistically significantly exceeded the MCID were achieved with IND/GLY 110/50 μg, UMEC/VI (62.5/25 and 125/25 μg) and TIO/OLO (2.5/5 and 5/5 μg); these findings should be interpreted cautiously given the uncertainty around the MCID for FEV1 (see Types of outcome measures). A clinically significant improvement in peak FEV1, but not trough FEV1, was observed with ACLID/FORM, although the evidence for this combination was based only on a single study with a relatively small sample size. A statistically significant reduction in both the time to first AECOPD and rate of AECOPD was observed with UMEC/VI; data for these AECOPD outcomes were not available for other combinations.

Overall completeness and applicability of evidence

Demographics across the 8641 randomised participants were representative of patients with COPD (GOLD 2017). For example, participants had a mean age of around 60 to 65 years, were more often male and the majority either currently smoked or had a history of smoking. The inclusion criteria for 21 of 22 included studies specified either GOLD stage II/III, or criteria aligned with this disease severity; only one of the included studies permitted the enrolment of individuals with moderate-to-severe COPD. Therefore, the evidence synthesised herein is applicable to individuals with mild-to-moderate COPD. All prespecified outcomes, except for the 6MWT, were well reported across the 22 studies, although reporting of the number of participants experiencing AECOPD was based on only three studies and time to first AECOPD on only two studies; this was taken into account when evaluating the strength of the evidence for these outcomes. Six studies evaluated the once-daily combination of IND/GLY (110/50 μg), seven studies evaluated TIO/OLO (2.5/5 or 5/5 μg), eight studies evaluated UMEC/VI (62.5/5 μg, 125/25 or 500/25 μg) and one study evaluated ACD/FOR (200/6, 200/12 or 200/18 μg). Subgrouping of studies by LABA/LAMA combination and dose had the effect of reducing the sample size for each comparison; in particular, only one study with a short duration examined the ACLID/FORM combination so we can be less certain of how the overall findings apply to the ACLID/FORM combination. The median study duration was 12 weeks; only three studies had a duration of six months or longer and all evaluated ING/GLY 110/50 μg. In these studies with a duration of six months or longer, the results of meta-analyses for all-cause mortality, SAEs, and HRQoL were consistent with those based on studies with a duration of less than six months.

Quality of the evidence

The certainty of the evidence was generally considered to be moderate or high with the exception of all-cause mortality, which we considered to be low, having downgraded it once for indirectness and once for imprecision due to a low number of events. We considered the certainty of the evidence for SAEs, HRQoL, and AEs to be high. The certainty of the evidence for lung function (trough and peak FEV1) was considered to be moderate having been downgraded for inconsistency due to significant heterogeneity. The certainty of the evidence for AECOPD was considered moderate having been downgraded once for indirectness as the evidence related only to UMEC/VI. We could not rule out the possibility of publication bias for this outcome but were unable to demonstrate conclusively that publication bias existed, due to the low number of studies reporting this outcome (i.e. the validity of a funnel plot is limited when based on fewer than ten studies). Additionally, selective reporting for this outcome in studies of other LABA/LAMA combinations did not occur based on comparison of primary reports with trial registry entries.

Risk of bias in the included studies was generally considered to be low or was unclear due to the lack of necessary information provided in the study reports. Across 198 assessments (22 studies, nine domains each), over three-quarters were considered to be at a low risk of bias, and only seven were considered to be at a high risk of bias. Risk of bias was considered unclear in the remaining 37 assessments. Four studies were considered to be at high risk for 'other' bias, in three cases, due to greater disease severity in the LABA/LAMA group compared with the placebo group; this problem would tend to skew the results in favour or placebo, resulting in a potential underestimation of the treatment effect. However, the results were robust to the removal of studies with any domain considered to be at high risk of bias and no downgrading

of the strength of the evidence (by GRADE) was performed on the basis of risk of bias.

Potential biases in the review process

The review was conducted to the standards set by MECIR (MECIR 2018) and in accordance with the published protocol. In particular, two authors independently screened the search results, determined studies for inclusion, assessed the risk of bias, extracted the relevant data, and performed the GRADE assessment (i.e. all steps involving subjective decisions). There were several minor deviations from the protocol (see Differences between protocol and review). It is unlikely that any relevant studies were missed, as a skilled information specialist conducted the main electronic searches. Additionally, the main searches were supplemented by manual searches of reference lists of associated studies and reviews. Finally, this review has undergone editorial and peer review and thus considers the opinions of independent external experts. In summary, the review was conducted in a manner that should ensure that our conclusions fairly and accurately represent the results synthesised during the review process.

Agreements and disagreements with other studies or reviews

The majority of relevant systematic reviews compared LABA/LAMA FDCs with their mono-components (Calzetta 2016; Calzetta 2017). However, our findings are consistent with those of a recent network meta-analysis of LABA/LAMA versus their mono-components and placebo (Oba 2016). For example, LABA/LAMA combinations demonstrated a mean improvement in trough FEV1 over placebo of 0.21 (95% CI 0.19, 0.23), 0.20 L (95% CI 0.17 to 0.23) and 0.24 L (95% CI 0.14 to 0.35) at three, six, and 12 months, respectively, agreeing with the 0.20 L reported herein. Clinically significant improvements in HRQoL were also seen with LABA/LAMA over placebo, with a mean change from baseline in SGRQ score of -4.6 (-5.9, -3.3) at three months and -4.1 (-5.9, -2.3) at six months, agreeing with the 4.08 point improvement reported herein. Furthermore and in agreement with our findings, no significant differences in mortality or total SAEs were observed between LABA/LAMA and placebo (Oba 2016).

AUTHORS' CONCLUSIONS

Implications for practice

Compared with placebo, once-daily LABA/LAMA (either IND/GLY, UMEC/VI or TIO/OLO) via a combination inhaler is associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild-to-moderate COPD; in addition, UMEC/VI appears to reduce the rate of exacerbations in this population. These conclusions are supported by moderate- or high-certainty evidence from studies with an observation period of up to one year.

Implications for research

Prespecified outcomes of interest for this review were generally well evaluated by the included studies, with the exception of the 6MWT, which was not evaluated by any of the studies. The 6MWT requires large sample sizes or large treatment effects to detect a statistically significant signal and thus may not be the most appropriate test for evaluating new interventions; alternative outcomes for assessing functional exercise capacity include the incremental shuttle walk test and the endurance shuttle walk test (Singh 2014b). Future research should focus on establishing the relative net clinical benefit (i.e. considering both efficacy and safety) for the different LABA/LAMA combinations; the findings of this review (relative to placebo) should facilitate this work.

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The Background and Methods section of the protocol were based on a standard template used by Cochrane Airways Group. Some of the content from an earlier Cochrane protocol has been used verbatim and modified after the original author team stepped down from the review (Sarai 2014).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bateman 2013

Methods	**Study ID and dates performed:** NCT01202188 (SHINE); September 2010 to February 2012. **Study design:** Randomised, double-blind, parallel-group, placebo and active controlled study **Duration of study:** Pre-randomisation period (pre-screening + run-in): 3 weeks; treatment period: 26 weeks **Study setting, location, number of centres:** 166 academic and clinical research centres in Europe, North America, South America, Asia (Philippines, Japan, India), Australia, China, Taiwan. and South Africa **Key inclusion criteria:** Adults aged ≥ 40 years; signed consent; symptomatic moderate-to-severe stable COPD (GOLD 2008 Stage II or III); current or ex-smokers (≥ 10 pack years); post-BD FEV1 ≥ 30% and < 80% predicted normal AND post-BD FEV1/FVC < 0.7 at visit 2 (day 14) **Key exclusion criteria:** Pregnant or women of child bearing potential; concomitant pulmonary disease; history of asthma; lung cancer or history of lung cancer; history of long QT syndrome; Type I or uncontrolled Type II diabetes; contraindication to or hypersensitive to anticholinergics, LABA, sympathomimetic amines, or lactose **Concomitant medications:** Permitted: SSRI stable regimen ≥ 1 month prior to screening or during study; inactivated vaccine (not within 48 hours of study visit); ICS (constant doses and dose regimens of ≥ 1 month); H1 antagonists (constant doses and dose regimens). Excluded: long term O_2 therapy.
Participants	**N randomised:** IND/GLY 110/50 µg: 475; placebo: 234. **N analysed:** IND/GLY 110/50 µg: 474; placebo: 232. **Mean age (SD), years:** IND/GLY 110/50 µg: 64.0 (8.9); placebo: 64.4 (8.6). **Gender male, n/N (%):** IND/GLY 110/50 µg: 362/474 (76.4); placebo: 169/232 (72.8). **Baseline lung function - mean (SD) post-BD % predicted FEV1, %:** IND/GLY 110/50 µg: 55.7 (13.2); placebo: 55.2 (12.7). **Smoking status (current), n/N (%):** IND/GLY 110/50 µg: 192/474 (40.5); placebo: 93/232 (40.1).
Interventions	**Intervention:** Once-daily QVA149 (IND/GLY 110/50 µg). **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes:** Primary: Trough FEV1 at week 26. Secondary: SGRQ score (week 26); SGRQ score week 12 and week 26; and number of participants with a MCID (4 units) improvement from baseline in SGRQ score (week 26); rate of moderate or severe COPD exacerbation; percentage of participants with ≥ 1 moderate or severe COPD exacerbation (26 weeks); AEs; SAEs **Reported outcomes:** all prespecified outcomes reported.

Notes	**Funding for trial; notable author COIs:** The study was funded by Novartis Pharma AG. Authors were employed by Novartis or had received remuneration from Novartis for advisory boards/lectures

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were assigned a randomisation number via IRT system, linking the patient to a treatment arm and specific unique medication number for the study drug. The randomisation number was not communicated to the investigator contacting the IRT
Allocation concealment (selection bias)	Low risk	See random sequence generation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants, investigator staff, personnel performing assessments and data analysts was maintained by ensuring randomisation data remained strictly confidential and inaccessible to anyone involved in the study until the time of unblinding. In addition, the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, and schedule of administration, appearance, taste, and odour
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of personnel performing assessments and data analysts was maintained by ensuring randomisation data remained strictly confidential and inaccessible to anyone involved in the study until the time of unblinding. In addition, the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, and schedule of administration, appearance, taste, and odour
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation

Bateman 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and consistent between treatment arms.
Selective reporting (reporting bias)	Low risk	Comparison of trial registration and published report information performed. Prespecified outcomes were well reported
Other bias	Low risk	None identified.

Beeh 2014

Methods	**Study ID and dates performed:** NCT01294787 (BRIGHT); study dates not reported. **Study design:** Multicentre, randomised, double-blind, double-dummy, placebo-controlled, three-period cross-over study **Duration of study:** 18-25 day run-in period; 3 x 3-week treatment period, 21-day washout period between treatments **Study setting, location, number of centres:** Not reported. **Key inclusion criteria:** Participants ≥ 40 years of age; moderate-to-severe COPD (Stage II or III according to GOLD 2008 criteria); smoking history of ≥ 10 pack years (current or ex-smokers); post-bronchodilator FEV1 of ≥ 40% and < 70% **Key exclusion criteria:** Pregnant women or nursing mothers; women of child-bearing potential; contraindication for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs or drugs of a similar class: anticholinergic agents, long and short acting beta-2 agonists, sympathomimetic amines, lactose or any of the other excipients; a history of long QT syndrome or whose QTc measured at screening (Fridericia method) is prolonged (> 450 ms for males and females) as confirmed by the central ECG assessor; a clinically significant abnormality on the screening ECG; Type I or uncontrolled Type II diabetes; W_{max} value < 20 W (as determined by the incremental cycle endurance test) at visit 2); body mass index < 15 or > 40 kg/m^2; contraindication to cardiopulmonary exercise testing; resting (5 min) oxygen SaO_2 saturation on room air of < 85%; participants who do not maintain regular day/night, waking/sleeping cycles (e.g. night shift workers); participants whose endurance in the exercise test is limited by non-respiratory conditions e.g. by neurologic, orthopaedic, or other disorders, narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention; a history of malignancy of any organ system (including lung cancer); clinically relevant laboratory abnormality or a clinically significant condition **Concomitant medications:** Short-acting bronchodilators (salbutamol or albuterol) were provided for rescue use throughout the study but were not permitted within 6 hours of each visit. Prior ICS use permitted
Participants	**Note: cross-over study therefore participant data reported for whole cohort** **N randomised:** 85 **N analysed:** 77 **Mean age (SD), years:** 62.1 (8.11) **Gender - male, n/N (%):** 53/84 (63.1) **Baseline lung function - post-bronchodilator % predicted FEV1:** 46.5 (10.30) **Smoking status, current smoker, n/N (%):** 45 (53.6)

Interventions	**Intervention:** Once-daily IND/GLY (QVA149) 110/50 µg **Comparator:** Once-daily placebo
Outcomes	**Prespecified outcomes:** Primary: exercise tolerance comparison between QVA149 and placebo groups at 3 weeks. Secondary (all QVA149 vs placebo): dynamic inspiratory capacity at 3 weeks; trough 24-hour post-dose inspiratory capacity at 3 weeks; trough 24-hour post-dose FEV1 at 3 weeks; residual volume, slow vital capacity, specific airway conductance and functional residual capacity, each on day 1 and day 21, at 5 min and 15 min post-dose as determined by body plethysmography; dynamic inspiratory capacity post-dose pre-exercise after three weeks of treatment; exertional dyspnoea (Borg CR10 Scale) at 3 weeks; leg discomfort (Borg CR10 Scale) during submaximal constant load cycle ergometry test after three weeks treatment; exercise endurance time during submaximal constant load cycle ergometry test cycle exercise test on day 1 **Reported outcomes:** prespecified outcomes well reported.
Notes	**Funding for trial; notable author COIs:** Novartis Pharma AG funded this study. All authors had relevant conflicts of interest relating to funding or employment provided by Novartis Pharma AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	IRT system was used to assign randomisation.
Allocation concealment (selection bias)	Low risk	IRT system was used to assign randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Personal communication from Dr Beeh (7 August 2018) confirmed that personnel and participants were blinded to treatment
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Personal communication from Dr Beeh (7 August 2018) confirmed that personnel and participants were blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Personal communication from Dr Beeh (7 August 2018) confirmed that outcome assessors were blinded to treatment
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Personal communication from Dr Beeh (7 August 2018) confirmed that outcome assessors were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rate was low (~15%) and similar between QVA149 and placebo arms

Beeh 2014 (*Continued*)

Selective reporting (reporting bias)	Low risk	Prespecified outcomes were generally well reported.
Other bias	Low risk	Safety results were analysed according to treatment received. No other issues identified

Beeh 2015

Methods	**Study ID and dates performed:** NCT01559116; VIVACITO; dates not reported. **Study design:** Double-blind, placebo-controlled, multicentre, Phase III, incomplete cross-over study **Duration of study:** 38-42 weeks including 2-6 week run-in period. Each treatment given for 6 weeks **Study setting, location, number of centres:** 29 centres in seven countries (Belgium, Canada, Denmark, Germany, Hungary, The Netherlands, and the USA) **Key inclusion criteria:** A diagnosis of COPD; aged ≥ 40 years; smoking history of ≥ 10 pack-years; relatively stable airway obstruction with a post-bronchodilator FEV1 < 80% of predicted normal (in German sites only, FEV1 ≥ 30%) and FEV1/FVC < 70% of predicted normal **Key exclusion criteria:** History of asthma or significant disease other than COPD; unstable or life-threatening cardiac arrhythmia; hospitalisation for heart failure within the past year; history of myocardial infarction within 1 year of screening or a history of life-threatening pulmonary obstruction **Concomitant medications:** Participants could continue on inhaled corticosteroids during treatment periods (if taken as maintenance treatment at study entry) but not anticholinergics or LABAs. Short-acting anticholinergics were permitted during screening and the washout periods, but had to be stopped 8 h before pulmonary function test at the first visit of the next treatment period. LAMAs and LABAs were not permitted during washout or screening periods. Open-label salbutamol was provided to participants as rescue medication to be used at baseline and during screening, treatment, washout, and follow-up periods
Participants	**Note: incomplete cross-over study therefore participant data reported for whole cohort** **N randomised:** N = 219 **N analysed:** TIO/OLO 2.5/5 µg: n = 135 ; TIO/OLO 5/5 µg: n = 138 ; placebo: n = 130 **Mean age (SD), years:** 61.1 (7.7) **Gender - male, n/N (%):** 129 (58.9%) **Baseline lung function - mean (SD) pre-bronchodilator FEV1, L:** 1.361 (0.471) **Smoking status, current smoker, n/N (%):** 137/219 (62.6)
Interventions	**Intervention:** Once-daily TIO/OLO 2.5/5 µg; once-daily TIO/OLO 5/5 µg. **Comparator:** Once-daily placebo.

Outcomes	**Prespecified outcomes: Primary:** FEV1 AUC 0-24 h response after 6 weeks treatment. **Secondary (each after 6 weeks of treatment):** FEV1 AUC 0-12h response; FEV1 AUC 12-24 h response; trough FEV1 response; peak (0-3 h) FEV1 response; FVC AUC 0-24 h response; FVC AUC 0-12 h response; FVC AUC 12-24h response; trough FVC response; peak (0-3h) FVC response; safety **Reported outcomes:** All prespecified outcomes were reported, plus functional residual capacity, residual volume, inspiratory capacity, and total lung capacity
Notes	**Funding for trial; notable author COIs:** This study was funded by Boehringer Ingelheim Pharma GmbH & co. KG. Three of seven authors were employees of the company that funded the study; the remaining authors received no compensation in relation to development of the manuscript (no COIs provided)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided ('double-blind' stated but did not specify participant, personnel or outcome assessor)
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided ('double-blind' stated but did not specify participant, personnel or outcome assessor)
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and consistent between the groups, with the highest group dropout acknowledged as 5.8%
Selective reporting (reporting bias)	Low risk	Comparison of trial registration and published report information performed. Prespecified outcomes were well reported
Other bias	Low risk	None identified.

Celli 2014

Methods	**Study ID and dates performed:** NCT01313637; March 22, 2011 to April 19, 2012. **Study design:** Multicentre, randomised, placebo-controlled, double-blind, parallel-group study **Duration of study:** 24 weeks. **Study setting, location, number of centres:** 153 centres in 14 countries. **Key inclusion criteria:** Aged ≥ 40 years; history of COPD (ATS/ERS); current or former smoker with a history of ≥10 pack-years; post-albuterol (salbutamol) FEV1/FVC ratio < 0.70, FEV1 ≤ 70% predicted normal; a score of ≥ 2 on modified MRC dyspnoea scale at screening **Key exclusion criteria:** Not reported. **Concomitant medications:** Not reported.
Participants	**N randomised:** UMEC/VI 125/25 µg: n = 403 ; placebo: n = 275. **N analysed:** UMEC/VI 125/25 µg: 403/403 (100; ITT) ; placebo: 275/275 (100; ITT) **Mean age (SD), years:** UMEC/VI 125/25 µg: 63.4 (8.08); placebo: 62.2 (8.53). **Gender - male, n/N (%):** UMEC/VI 125/25 µg: 264/403 (66); placebo: 175/275 (64) . **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** UMEC/VI 125/25 µg: 47.7 (12.53); placebo: 47.6 (12.47). **Smoking status, current smoker, n/N (%):** UMEC/VI 125/25 µg: 200/403 (50); placebo: 143/275 (52).
Interventions	**Intervention:** Once-daily UMEC/VI 125/25 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Change from baseline in trough FEV1 on day 169 (week 24). **Secondary:** Mean transition dyspnoea index focal score at day 168 (week 24); change from baseline in weighted mean 0-6 hour FEV1 obtained post-dose at day 168; safety. **Other:** change from baseline in the mean Shortness of Breath with Daily Activities score for week 24 **Reported outcomes:** All prespecified outcomes were reported, plus: the proportion of participants achieving an increase in FEV1 of ≥ 12% and ≥ 0.200 L above baseline at any time during 0-6 hours post-dose on day 1; the proportion of participants achieving an increase of ≥ 0.100 L above baseline in trough FEV1, LSM peak FEV1, serial FEV1 and serial and trough FVC; SGRQ score and time to first COPD exacerbation. Serial FVC 0-24 h post-dose was obtained in a subset of participants
Notes	**Funding for trial; notable author COIs:** GSK funded the design/conduct of the study and manuscript development. All authors had received funding from, or were past or present employees, of GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.

Celli 2014 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking quadruple (participants, care provider, investigator, outcome assessor)
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking quadruple (participants, care provider, investigator, outcome assessor)
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were high and unbalanced between groups; however, ITT analysis performed
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified.

Dahl 2013

Methods	**Study ID and dates performed:** NCT01120717 (ENLIGHTEN); study dates not reported. **Study design:** Multicentre, randomised, double-blind, parallel-group, placebo-controlled study **Duration of study:** 55 weeks (7-day pre-screening; 14-day run-in period; 52-week treatment period) **Study setting, location, number of centres:** Academic and clinical research centres in Europe, Canada, Asia (India, Korea) and South Africa **Key inclusion criteria:** Aged ≥ 40 years of age; moderate-to-severe COPD (Stage II or III according to the GOLD 2008 criteria); smoking history of ≥ 10 pack-years; post-bronchodilator FEV1 of ≥ 30% and < 80% of the predicted normal and post-bronchodilator FEV1/FVC < 0.70 at screening; total daily symptom score of ≥ 1 (obtained by adding the scores for the morning and evening symptoms (i.e. cough, wheezing, sputum production/colour, shortness of breath)) on 4 of the last 7 days prior to randomisation **Key exclusion criteria:** COPD exacerbations that required treatment with antibiotics or oral steroids or hospitalisation in the 6 weeks prior to screening or between screening and randomisation; respiratory tract infection 4 weeks before or during screening; history of asthma; a clinically significant ECG abnormality **Concomitant medications:** No participants received placebo treatment in isolation at any time during the study: placebo was included in participants' established background COPD therapy (e.g. daily ICS). The short-acting bronchodilator salbutamol (albuterol) was provided for rescue use throughout the study. participants were not permitted to use short-acting (LAMAs, LABAs, theophylline) before the screening period (for at least 7 days for LAMAs and theophylline; 48 h for LABA and LABA/ICS combinations) or during the study. ICS use was maintained (i.e. participants taking combined LABA/ICS at screening were transitioned to the equivalent ICS monotherapy)
Participants	**N randomised:** IND/GLY 110/50 µg: n = 226; placebo: n = 113. **N analysed, n/N (%):** IND/GLY 110/50 µg: 194/226 (85.8); placebo: 89/113 (78.8). **Mean age (SD), years:** IND/GLY 110/50 µg: 62.5 (8.81); placebo: 62.9 (8.14). **Gender - male, n/N (%):** IND/GLY 110/50 µg: 174/225 (77.3); placebo: 86/113 (76.1). **Baseline lung function - post-bronchodilator % predicted FEV1:** IND/GLY 110/50 µg: 56.39 (13.27); placebo: 59.43 (12.50). **Smoking status, current smoker, n/N (%):** IND/GLY 110/50 µg: 102/225 (45.3); placebo: 51/113 (45.1).
Interventions	**Intervention:** Once-daily IND/GLY 110/50 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Number of participants with AEs, SAEs or death. **Secondary:** Pre-dose FEV1 at 52 weeks; number of participants with newly occurring or worsening clinically notable haematology values at any time point over the whole treatment period; number of participants with newly occurring or worsening clinically notable biochemistry values at any time point over the whole treatment period; number of participants with newly occurring or worsening clinically notable vital signs values at any time point over the whole treatment period; number of participants with notable change from baseline in Fridericia's QTc values at any time point over the whole treatment period

	Reported outcomes: All prespecified outcomes (see above) reported.
Notes	**Funding for trial; notable author COIs:** The study was funded by Novartis Pharma AG. All authors had previously received funding/compensation from Novartis or were employees of Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking quadruple (participants, care provider, investigator, outcome assessor)
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking quadruple (participants, care provider, investigator, outcome assessor)
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	High rates of attrition (> 20%) noted in placebo arm (versus < 15% in QVA149 arm). mITT analysis performed based on full analysis set (all participants randomised to treatment and who received at least one dose)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	High risk	More participants in the QVA149 group had severe COPD versus those in the placebo group (note: this would likely skew treatment effect in favour of placebo)

Donohue 2013

Methods	**Study ID and dates performed:** NCT01313650. 30 March 2011 to 5 April 2012. **Study design:** Randomised, double-blind, placebo-controlled, multicentre, parallel-group study **Duration of study:** 24 weeks. **Study setting, location, number of centres:** 163 centres in 13 countries. **Key inclusion criteria:** Current or former cigarette smokers; aged > 40 years; clinically established history of COPD characterised by airflow limitation that is not fully reversible (ATS/ERS criteria) and documented based on a smoking history of ≥ 10 pack years; post-salbutamol FEV1/FVC ratio < 0.70; post-salbutamol FEV1 of ≤ 70% of predicted normal values; dyspnoea score ≥ 2 on modified MRC dyspnoea scale **Key exclusion criteria:** Current diagnosis of asthma or other known respiratory disorder; abnormal or clinically significant electrocardiogram or 24-hour Holter ECG; clinically significant clinical laboratory finding **Concomitant medications:** Permitted: Inhaled salbutamol as rescue medication; ICS at a stable dose of ≤ 1000 µg/day fluticasone propionate or equivalent from 30 days prior to screening onward
Participants	**N randomised:** UMEC/VI 62.5/25 µg: N = 413; placebo: N = 280. **N analysed, n/N (%):** UMEC/VI 62.5/25 µg: 413/413 (100); placebo: 280/280 (100) . **Mean age (SD), years:** UMEC/VI 62.5/25 µg: 63.1 (8.71); placebo: 62.2 (9.04). **Gender - male, n/N (%):** UMEC/VI 62.5/25 µg: 305/413 (74); placebo: 195/280 (70) . **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** UMEC/VI 62.5/25 µg: 47.8 (13.19); placebo:46.7 (12.71). **Smoking status, current smoker, n/N (%):** UMEC/VI 62.5/25 µg: 203/413 (49); placebo: 150/280 (54).
Interventions	**Intervention:** Once-daily UMEC/VI 62.5/25 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary endpoint:** Pre-dose trough FEV1 on day 169. **Secondary lung function endpoints:** Mean TDI focal score at day 168 (week 24); change from baseline in weighted mean 0-6 hour FEV1 obtained post-dose at day 168 baseline and day 168. **Other outcomes:** Change from baseline in the mean Shortness of Breath With Daily Activities (SOBDA) score for (baseline and week 24) **Reported outcomes:** Pre-dose trough FEV1 on treatment day 169, defined as the mean of FEV1 values obtained 23 h and 24 h after dosing on day 168 (week 24 visit). Secondary and additional lung function endpoints: weighted mean FEV1 over 0-6 h post-dose on day 168; trough and 0-6 h weighted mean FEV1 at other visits, serial FEV1 assessments, time to onset during 0-6 h post-dose on day 1, proportion of participants achieving an increase in FEV1 of ≥ 12% and ≥ 0.2 L above baseline at any time during 0-6 h post-dose on day 1, proportion of participants achieving an increase of ≥ 0.1 L above baseline in trough FEV1, peak FEV1 and serial and trough FVC. Serial FEV1 over 0-24 h post-dose was obtained in a subset of participants to characterise changes in lung function over the dosing interval
Notes	**Funding for trial; notable author COIs:** The design, concept and conduct of the study and development of the manuscript was funded by GSK. Both external authors had

	acted as consultants and received research grants from GSK. All other co-authors were GSK employees

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation was performed centrally through a validated computerised system and an interactive voice response system was then used to communicate the randomisation to the study team
Allocation concealment (selection bias)	Low risk	Participants were randomised using an automated, interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking quadruple (participants, care provider, investigator, outcome assessor)
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking quadruple (participants, care provider, investigator, outcome assessor)
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced across treatment groups; ITT analysis performed
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified.

Feldman 2012

Methods	**Study ID and dates performed:** NCT01039675; 14 January 2010 to 20 April 2010. **Study design:** Multicentre, randomised, placebo-controlled, double-blind, parallel-group study **Duration of study:** Run-in period 5-8 days; 4-week treatment period; 7-day follow-up **Study setting, location, number of centres:** 4 centres in the USA. **Key inclusion criteria:** Males and females aged ≥ 40 years with an established clinical history of COPD under the ATS/ERS standards; a history of at least 10 pack-years of cigarette smoking; a post-albuterol/salbutamol FEV1/FVC ≤ 0.70 and a post-albuterol/salbutamol FEV1 of ≤ 80% of predicted normal values calculated using NHANES III **Key exclusion criteria:** Current diagnosis of asthma, alpha1-antitrypsin deficiency; use of OCS, antibiotics, or had been hospitalised due to exacerbation of COPD or a lower respiratory tract infection within 3 months prior to screening; abnormal 12-lead ECG that resulted in an active medical problem or had clinically significant abnormalities from 24-h Holter ECG monitoring at screening; prior evidence of pathological QT waves on ECG at least 12 months prior to screening that were unchanged at screening were not exclusionary; use of ICS at a dose > 1000 µg/day of FP or equivalent within 30 days prior to screening or initiation or termination of ICS use within 30 days prior to screening; use of long-term oxygen therapy; regular use of short-acting bronchodilators, including nebulised therapy **Concomitant medications: Permitted concomitant medications:** ICS ≤ 1000 µg/day of FP or equivalent) provided the dose remained constant for 30 days prior to the screening visit and throughout the study; antibiotics that were not strong inhibitors of cytochrome P450 3A4 for short-term treatment (≤ 14 days) of acute non-respiratory tract infections provided that the infection did not meet the criteria for a COPD exacerbation. **Medications not permitted during study:** systemic beta-receptor antagonists (ophthalmic preparations were allowed); tricyclic antidepressants; monoamine oxidase inhibitors; anticonvulsants (such as barbiturates); and phenothiazines
Participants	**N randomised:** UMEC/VI 500/25 µg: N = 42; placebo: N = 9. **N analysed, n/N (%):** UMEC/VI 500/25 µg: 42/42 (100); placebo: 9/9 (100). **Mean age (range), years:** UMEC/VI 500/25 µg: 59.2 (40-83); placebo: 58.7 (42-69). **Gender - male, n/N (%):** UMEC/VI 500/25 µg: 24/42 (57.1); placebo: 7/9 (78). **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** UMEC/VI 500/25 µg: 48.37 (15.376); placebo: 50.58 (15.609). **Smoking status, current smoker, n/N (%):** UMEC/VI 500/25 µg: 24/42 (57); placebo: 7/9 (78).
Interventions	**Intervention:** Once-daily UMEC/VI 500/25 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Change from baseline in weighted mean pulse rate over 0 to 6 hours post-dose at day 28 (baseline and day 28). **Secondary:** change from baseline in weighted mean pulse rate over 0 to 6 hours post-dose at day 1 and day 14; change from baseline in maximum and minimum pulse rate 0 to 6 hours post-dose on days 1, 14, and 28 **Reported outcomes: Prespecified primary and secondary outcomes well reported; Other:** weighted mean systolic and diastolic blood pressure 0-6 h post-dose on days 1, 14, and 28; maximum systolic and minimum diastolic blood pressure on days 1, 14, and 28; 24-h Holter ECG parameters at screening and day 28; maximum QTc with interval corrected by Fridericia's method; (during 0-6 h post-dose) on days 1, 14, and

	28 (measured using 12-lead ECG); changes in haematological and clinical chemistry parameters from baseline on days 14 and 29; incidence of AEs and SAEs throughout the 28-day treatment period and follow-up; incidence of COPD exacerbations; and plasma concentrations and derived PK Cmax, tmax, AUC for UMEC and VI parameters, and trough FEV1 on day 29
Notes	**Funding for trial; notable author COIs:** The study was sponsored by GSK and administered by Greenville Pharmaceutical Research. All authors received funding from, or were employees of, GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation schedule was generated by the sponsor using a validated computerised system (RandAll)
Allocation concealment (selection bias)	Low risk	Centralised system used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to treatment allocation
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants for subjective outcomes were the outcome assessors; therefore, low risk of bias
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Differential withdrawal rates noted between UMEC/VI and placebo groups; however, ITT analysis performed
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	High risk	Imbalance in baseline characteristics suggested that randomisation was not robust; limited sample size of placebo group could also account for imbalance in baseline characteristics

Larbig 2015

Methods	**Study ID and dates performed:** NCT01610037 (RADIATE); October 2012-February 2015; abstract only; additional info/data sourced from clinicaltrials.gov **Study design:** Multicentre, double-blind (participant & investigator), parallel-group, placebo- and active-controlled study **Duration of study:** 52 weeks. **Study setting, location, number of centres:** 116 locations - international. **Key inclusion criteria:** Male and female adults aged ≥ 40 years; stable COPD according to GOLD strategy (GOLD 2011); airflow limitation indicated by a post-bronchodilator FEV1 ≥ 30% and < 80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70; current or ex-smokers with a smoking history of at least 10 pack years; participants with an mMRC ≥ grade 2 **Key exclusion criteria:** History of long QT syndrome or prolonged QTc; COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalisation in the 6 weeks prior to visit 1; type I or uncontrolled type II diabetes; history of asthma or have concomitant pulmonary disease; paroxysmal (e.g. intermittent) atrial fibrillation (only patients with persistent atrial fibrillation and controlled with a rate control strategy for at least six months could be eligible); clinically significant renal, cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or haematological abnormalities which could interfere with the assessment of safety **Concomitant medications:** Not reported.
Participants	**N randomised:** IND/GLY 110/50 µg: N = 407; placebo: N = 404. **N analysed, n/N (%):** IND/GLY 110/50 µg: 407/407 (100); placebo: 403/404 (99.8). **Mean age (SD), years:** IND/GLY 110/50 µg: 64.6 (7.89); placebo: 64.9 (7.95). **Gender - male, n/N (%):** IND/GLY 110/50 µg: 288/407; placebo: 310/404. **Baseline lung function - post-bronchodilator % predicted FEV1:** Not reported. **Smoking status, current smoker, n/N (%):** Not reported.
Interventions	**Intervention:** Once-daily IND/GLY 110/50 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Number of participants with SAEs during study. **Secondary:** Percentage of participants with composite endpoint of all-cause mortality, and serious cardio- and cerebrovascular events; post hoc analysis: percentage of participants with composite endpoint of cardiovascular death and MACE change from baseline in pre-dose FEV1 (days 22, 43, 85, 183, 274, and 364); change from baseline at day 364 in health status as measured by SGRQ for COPD participants; change from baseline at week 52 in daily, morning, and evening symptom scores; change from baseline at week 52 in percentage of nights with no night-time awakenings; change from baseline at week 52 in percentage of no daytime symptoms; change from baseline at week 52 in percentage of days able to perform usual daily activities; change from baseline in 1 hour post-dose FVC measurements (days 1, 22, 43, 85, 183, 274, and 364); time to premature discontinuation; change from baseline in 1 hour post-dose FEV1 measurements (days 1, 22, 43, 85, 183, 274, and 364) **Reported outcomes:** Prespecified outcome (see above) well reported.
Notes	**Funding for trial; notable author COIs:** The study was funded by Novartis Pharmaceuticals.

Larbig 2015 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided (abstract only).
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided (abstract only).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinical trial registry states that 'participant and investigators' were blinded to treatment allocation
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Clinical trial registry states that 'participant and investigators' were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants for subjective outcomes were the outcome assessors; therefore, low risk of bias
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided (abstract only).
Selective reporting (reporting bias)	High risk	Abstract did not report key prespecified outcomes.
Other bias	Low risk	None identified.

Mahler 2014

Methods	**Study ID and dates performed:** NCT01490125 (BLAZE); October 26, 2011 to August 29, 2012. **Study design:** Randomised, placebo-controlled, multicentre, blinded, double-dummy, three-period cross-over study **Duration of study:** 22 weeks (2-week screening period; 3 X 6-week treatment periods with 2-week washouts) **Study setting, location, number of centres:** 42 centres in 5 countries: Belgium, Canada, Germany, Spain, and the United Kingdom. "Data were collected in a clinical setting." **Key inclusion criteria:** Aged ≥ 40 years; moderate-to-severe stable COPD (stage II or III according to the 2009 GOLD criteria); were either current smokers or ex-smokers, with a smoking history of ≥ 10 pack-years; post-bronchodilator FEV1 of ≥ 30% and < 80% of predicted normal; post-bronchodilator FEV1/FVC < 0.70 at screening (visit 2, day 14); modified MRC dyspnoea scale grade of ≥ 2 at visit 2 **Key exclusion criteria:** Participants were excluded if they: required long-term oxygen therapy; had a COPD exacerbation (requiring antibiotics, systemic steroids, or hospitalisation) in the 6 weeks before screening, or between screening and randomisation; had a respiratory tract infection in the weeks before or during screening; had concomitant pulmonary disease or had undergone a lung lobectomy, volume reduction or transplantation; had asthma, eczema, known high IgE levels, blood eosinophil count > 600/mm^3 at screening, or a known positive skin prick test in the previous 5 years; had allergic rhinitis and used an H_1 antagonist or intra-nasal corticosteroids; or if they had α-1 antitrypsin deficiency **Concomitant medications:** Participants were requested not to take short-acting bronchodilators in the 6 hours prior to the start of each visit
Participants	**Note: cross-over study therefore participant data reported for whole cohort.** **N randomised:** 247. **N analysed:** 218. **Mean age (SD), years:** 62.8 (8.2). **Gender - male, n/N (%):** 173/246 (70.3). **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** 56.1 (12.3). **Smoking status, current smoker, n/N (%):** 112/246 (45.5).
Interventions	**Intervention:** Once-daily IND/GLY 110/50 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Total Transient Dyspnea Index score after 6 weeks of treatment (QVA149 versus placebo). **Secondary:** Total Transient Dyspnea Index score after 6 weeks of treatment (QVA149 versus tiotropium); standardized FEV1 AUC 5min-4h after first dose and 6 weeks of treatment (QVA149 vs placebo and tiotropium); standardised FVC AUC 5 min-4 hrs after first dose and 6 weeks of treatment (QVA149 vs placebo and tiotropium); change from baseline in the Capacity of Daily Living during the Morning (CDLM) score averaged over 6 weeks of treatment; change from baseline in the mean daily number of puffs of rescue medication used over the 6 weeks of treatment; safety **Reported outcomes:** All prespecified outcomes (see above) were reported.

Notes	**Funding for trial; notable author COIs:** The study was funded by Novartis Pharma AG. Author disclosures not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Investigators used an automated, interactive response technology. Randomisation numbers generated using this procedure ensured that treatment assignment was unbiased and concealed from participants and investigators
Allocation concealment (selection bias)	Low risk	Investigators used an automated, interactive response technology. Randomisation numbers generated using this procedure ensured that treatment assignment was unbiased and concealed from participants and investigators. See supplemental section of Mahler 2014 for details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants, investigator staff, personnel performing assessments and data analysts was maintained. Treatment allocation was blinded by the use of identical packaging, labelling, schedule of administration, appearance, taste, and colour
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Blinding of participants, investigator staff, personnel performing assessments and data analysts was maintained. Treatment allocation was blinded by the use of identical packaging, labelling, schedule of administration, appearance, taste, and colour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants, investigator staff, personnel performing assessments and data analysts was maintained. Treatment allocation was blinded by the use of identical packaging, labelling, schedule of administration, appearance, taste, and colour
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Blinding of participants, investigator staff, personnel performing assessments and data analysts was maintained. Treatment allocation was blinded by the use of identical packaging, labelling, schedule of adminis-

Mahler 2014 (*Continued*)

		tration, appearance, taste, and colour
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate was relatively high at ~23%; however, a modified ITT was used whereby attrition rate was effective ~10-15% across treatment groups
Selective reporting (reporting bias)	Low risk	Key, prespecified primary and secondary endpoints were reported as per trial registry. Slight difference versus prespecified time points for FEV/FVC noted
Other bias	Low risk	None identified.

Maltais 2014

Methods	**Study ID and dates performed:** NCT01525615 (TORRACTO); study dates not reported. **Study design:** Multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group trial **Duration of study:** 1-week run-in, 12-week treatment period, 3-week follow-up. **Study setting, location, number of centres:** 58 centres in 10 countries. **Key inclusion criteria:** Aged 40-75 years; clinical diagnosis of COPD and stable airway obstruction; post-bronchodilator FEV1/FVC < 70% and post-bronchodilator FEV1 < 80% and ≥ 30% predicted normal; current or ex-smokers with a smoking history of > 10 pack-years **Key exclusion criteria:** Significant disease other than COPD; a history of asthma, myocardial infarction in the previous year; unstable or life-threatening cardiac arrhythmia, or hospitalisation for heart failure within the previous year; a recognised contraindication to exercise; participated in a pulmonary rehabilitation program within the 6 weeks prior to the screening visit; an exercise limitation other than leg fatigue or exertional dyspnoea (e.g. arthritis in the leg or morbid obesity) **Concomitant medications:** Participants continued with inhaled corticosteroids if taken at baseline. Open-label salbutamol (albuterol) was provided as rescue medication throughout the study
Participants	**N randomised:** TIO/OLO 2.5/5 µg: N = 133; TIO/OLO 5/5 µg: N = 139; placebo: N = 132 **N analysed, n/N:** TIO/OLO 2.5/5 µg: 129/133 ; TIO/OLO 5/5 µg: n = 135/139; placebo: n = 121/132 **Mean age (SD), years:** TIO/OLO 2.5/5 µg: 61.9 (7.3); TIO/OLO 5/5 µg: 63.1 (7.5); placebo: 60.8 (7.6) **Gender - male, n/N (%):** TIO/OLO 2.5/5 µg: 87 (65.4); TIO/OLO 5/5 µg: 95 (68.3); placebo: 87 (65.9) **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** Not reported. **Smoking status, current smoker, n/N (%):** Not reported.

Interventions	**Intervention:** Once-daily TIO/OLO 2.5/5 µg; once-daily TIO/OLO 5/5 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Adjusted mean endurance time during constant work rate cycle ergometry after 12 weeks. **Secondary:** Adjusted mean endurance time during endurance shuttle walk test after 12 weeks; adjusted mean inspiratory capacity at pre-exercise after 12 weeks; adjusted mean endurance time during constant work rate cycle ergometry on day 1, after 6 weeks treatment; adjusted mean inspiratory capacity at pre-exercise after 1 day and 6 weeks; adjusted mean slope of the intensity of breathing discomfort on day 1 and after weeks 6 and 12; adjusted mean 1-hour, post-dose FEV1 on day 1, and after 6 and 12 weeks **Reported outcomes:** The majority of prespecified outcomes (see above) were reported although no data provided for FEV1-related outcomes
Notes	**Funding for trial; notable author COIs:** The study was sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG. All authors except JBGI were either employees of BI or had received research funding/honoraria from BI

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	According to clinicaltrials.gov results tab, noncompletion < 20% in each arm (in fact < 11%) and reasonably balanced across arms

Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified.

Maltais 2014b

Methods	**Study ID and dates performed:** NCT01323660 (Study 417). **Study design:** Two multicentre, double-blind, randomised cross-over studies (incomplete treatment block) **Duration of study:** 12-21-day run-in period; two 12-week treatment periods separated by a 14-day washout period **Study setting, location, number of centres:** 31 centres in 6 countries. **Key inclusion criteria:** Current or former smokers; ≤ 40 years of age; smoking history of ≥ 10 pack-years; clinical diagnosis of moderate-to-severe stable COPD (post-bronchodilator FEV1/FVC < 70% and FEV1 ≥ 35% and ≤ 70% predicted); score of ≥ 2 on the mMRC Dyspnoea Scale at visit 1; resting FRC ≥ 120% of predicted (to ensure participants were hyperinflated, as hyperinflation is associated with exercise intolerance) **Key exclusion criteria:** Comorbid conditions or current diagnosis of asthma. **Concomitant medications:** All participants were provided with salbutamol for use on an 'as-needed' basis throughout the run-in, washout, and treatment periods. Stable/regular doses of ICS were permitted
Participants	**Note: cross-over study therefore participant data reported for whole cohort.** **N randomised:** N = 349. **N analysed, n/N:** 341/349. **Mean age (SD), years:** 61.6 (8.3). **Gender - male, n/N (%):** 195/348 (56.0). **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** 51.3 (9.8). **Smoking status, current smoker, n/N (%):** 220/348 (63.2).
Interventions	**Intervention:** Once-daily UMEC/VI 62.5/25 µg; once-daily UMEC/VI 125/25 µg **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Change from baseline in exercise endurance time post-dose at week 12 of each treatment period; change from baseline in trough FEV1 at week 12 of each treatment period. **Secondary:** Change from baseline in inspiratory capacity (trough and 3 hours post-dose) at week 12 of each treatment period; change from baseline in functional residual capacity (trough and 3 hours post-dose) at week 12 of each treatment period; change from baseline in residual volume (trough and 3 hours post-dose) at week 12 of each treatment period; change from baseline in 3 hours post-dose FEV1 at week 12 of each treatment period **Reported outcomes:** All prespecified outcomes (see above) plus safety were reported
Notes	**Funding for trial; notable author COIs:** The studies were sponsored by GSK; all authors were employees of, or had received honoraria/research funding from, GSK

Maltais 2014b (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Simple randomisation was performed through a validated computerised system, then communicated to the study team via an IVRS
Allocation concealment (selection bias)	Low risk	Allocation of treatments was controlled by RAMOS, a telephone-based IRVS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial registry states that participants and investigators were blinded to treatment allocation. All six treatments options were administered in a 'double-blind fashion' via the same model of inhaler
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Trial registry states that participants and investigators were blinded to treatment allocation. All six treatments options were administered in a 'double-blind fashion' via the same model of inhaler
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants for subjective outcomes were the outcome assessors; therefore, low risk of bias
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes (including a co-primary endpoint of exercise tolerance time) would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and comparable attrition in UME/VI and placebo arms.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified.

Maltais 2014c

Methods	**Study ID and dates performed:** NCT01328444 (Study 418). **Study design:** Two multicentre, double-blind, randomised cross-over studies (incomplete treatment block) **Duration of study:** 12-21-day run-in period; two 12-week treatment periods separated by a 14-day washout period **Study setting, location, number of centres:** 31 centres in 6 countries. **Key inclusion criteria:** Current or former smokers; ≤ 40 years of age; smoking history of ≥ 10 pack-years; clinical diagnosis of moderate-to-severe stable COPD (post-bronchodilator FEV1/FVC < 70% and FEV1 ≥ 35% and ≤ 70% predicted); score of ≥ 2 on the mMRC Dyspnoea Scale at visit 1; resting FRC ≥ 120% of predicted (to ensure participants were hyperinflated, as hyperinflation is associated with exercise intolerance) **Key exclusion criteria:** Comorbid conditions or current diagnosis of asthma. **Concomitant medications:** All participants were provided with salbutamol for use on an 'as-needed' basis throughout the run-in, washout, and treatment periods. Stable/regular doses of ICS were permitted
Participants	**Note: cross-over study therefore participant data reported for whole cohort** **N randomised:** N = 308. **N analysed, n/N:** 307/308. **Mean age (SD), years:** 62.6 (7.9). **Gender - male, n/N (%):** 168/307 (54.7). **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** 51.3 (10.0). **Smoking status, current smoker, n/N (%):** 186/307 (60.6).
Interventions	**Intervention:** Once-daily UMEC/VI 62.5/25 µg; once-daily UMEC/VI 125/25 µg **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Change from baseline in exercise endurance time post-dose at week 12 of each treatment period; change from baseline in trough FEV1 at week 12 of each treatment period. **Secondary:** Change from baseline in inspiratory capacity (trough and 3 hours post-dose) at week 12 of each treatment period; change from baseline in functional residual capacity (trough and 3 hours post-dose) at week 12 of each treatment period; change from baseline in residual volume (trough and 3 hours post-dose) at week 12 of each treatment period; change from baseline in 3 hours post-dose FEV1 at week 12 of each treatment period **Reported outcomes:** All prespecified outcomes (see above) plus safety were reported
Notes	**Funding for trial; notable author COIs:** The studies were sponsored by GSK; all authors were employees of, or had received honoraria/research funding from, GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation was performed through a validated computerised system, then communicated to the study team via an IVRS

Maltais 2014c (*Continued*)

Allocation concealment (selection bias)	Low risk	Allocation of treatments was controlled by RAMOS, a telephone-based IVRS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial registry states that participants and investigators were blinded to treatment allocation. All six treatments options were administered in a 'double-blind fashion' via the same model of inhaler
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Trial registry states that participants and investigators were blinded to treatment allocation. All six treatments options were administered in a 'double-blind fashion' via the same model of inhaler
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants for subjective outcomes were the outcome assessors; therefore, low risk of bias
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes (including a co-primary endpoint of exercise tolerance time) would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and comparable attrition in UME/VI and placebo arms.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified.

NCT00626522

Methods	**Study ID and dates performed:** NCT00626522; not published (source clinicaltrials.gov); study completed 2008 **Study design:** Randomised, 4-week, placebo-controlled, double-blind, 6-arm parallel-group, dose-finding trial **Duration of study:** 4-week treatment period. **Study setting, location, number of centres:** 11 sites in 4 countries. **Key inclusion criteria:** Aged 40-85 years; clinical diagnosis of stable moderate-to-severe COPD (GOLD 2006 stages II-III); current or ex-cigarette smoker with a smoking history of ≥ 10 pack-years; FEV1 at screening measured between 30-45 minutes post-inhalation of 400 μg of salbutamol was 30% ≤ FEV1 < 80% of the predicted normal value; FEV1/FVC at screening measured between 30- 45 minutes post inhalation of 400 μg of salbutamol was < 70% **Key exclusion criteria:** History or current diagnosis of asthma, allergic rhinitis or atopy, or exercise-induced bronchospasm; clinically significant respiratory conditions at the time of screening visit; hospitalisation due to COPD exacerbation within 3 months prior to screening; signs of COPD exacerbation or respiratory infection up to 6 weeks prior to screening visit; clinically significant cardiovascular conditions **Concomitant medications:** Not reported.
Participants	**N randomised:** ACL/FOR 200/6 µg: n = 121; ACL/FOR 200/12 µg: n = 120; ACL/FOR 200/18 µg: n = 125; placebo: n = 59 **N analysed:** ACL/FOR 200/6 µg: 121/121 (100); ACL/FOR 200/12 µg: 120/120 (100) ; ACL/FOR 200/18 µg: 125/125 (100); placebo: 59/59 (100) **Mean age (SD), years:** ACL/FOR 200/6 µg: 62.9 (9.0); ACL/FOR 200/12 µg: 63.6 (8.9); ACL/FOR 200/18 µg: 63.9 (8.1); placebo: 60.7 (7.8) **Gender - male, n/N:** ACL/FOR 200/6 µg: 91/121; ACL/FOR 200/12 µg: 98/120; ACL/FOR 200/18 µg: 96/125; placebo: 44/59 **Baseline lung function - post-bronchodilator % predicted FEV1:** Not reported. **Smoking status, current smoker, n/N (%):** Not reported.
Interventions	**Intervention:** Once-daily ACL/FOR 200/6 µg; once-daily ACL/FOR 200/12 µg; once-daily ACL/FOR 200/18 µg **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Change from baseline in normalised FEV1 AUC for 0-12 hr at week 4. **Secondary:** Change from baseline in trough FEV1 at week 4; change from baseline in peak FEV1 at week 4; change from baseline in normalised FEV1 AUC 0-3 hours at week 4; change from baseline in normalised FEV1 AUC 0-6 hours at week 4 **Reported outcomes:** All of the prespecified outcomes (see above) plus safety were reported on the clinicaltrials.gov site
Notes	**Funding for trial; notable author COIs:** The study was sponsored by AstraZeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement

NCT00626522 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient information provided (trial registry only).
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided (trial registry only).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded.
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Participants and investigators blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants for subjective outcomes were the outcome assessors; therefore, low risk of bias
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were low and balanced between treatment groups
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified.

NCT02275052

Methods	**Study ID and dates performed:** NCT02275052 **Study design:** A multicenter, randomised, double-blind, placebo-controlled, 2-period, complete block design cross-over study **Duration of study:** 2 x 12-week treatment periods with washout of 12-17 days. Run in period 12-25 days. Total duration approximately 30 weeks including follow up **Study setting, location, number of centres:** United States of America. **Key inclusion criteria:** Aged ≥ 40 years; diagnosis of COPD (ATS/ERS); current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years; pre- and post-albuterol FEV1/FVC < 0.70 and a post-albuterol FEV1 of ≥ 30% and ≤ 70% of predicted normal value; dyspnoea score of ≥ 2 on the mMRC scale at visit 1; a resting FRC of ≥ 120% of predicted normal FRC at visit 1 **Key exclusion criteria:** Pregnancy; current diagnosis of asthma; other respiratory disorders; known alpha-1 antitrypsin deficiency; active lung infections (such as tuberculosis) , and lung cancer in remission for < 5 years **Concomitant medications: Permitted:** All participants were provided with albuterol for use on an 'as needed' basis throughout the run-in, washout, and study treatment periods while on investigational product. Use of the following medications according to the following defined time intervals prior to visit 1: Depot corticosteroids (12 weeks), systemic, oral or parenteral corticosteroids (Intra-articular and epidural corticosteroid injections were permitted) (6 weeks), antibiotics (for lower respiratory tract infection and/or COPD exacerbation) (6 weeks), long-acting beta agonist (LABA)/inhaled corticosteroid (ICS) combination products if LABA/ICS therapy was discontinued completely (30 days), LABA/ICS combination products only if discontinuing LABA therapy and switching to ICS monotherapy (dose of ICS that is switched to must not exceed 1000 µg of fluticasone propionate or equivalent) (48 hours for the salmeterol or formoterol component, 14 days for the vilanterol component), use of ICS at a dose > 1000 μg/day of fluticasone propionate or equivalent (use of ICS was permitted provided the dose did not exceed 1000 μg of fluticasone propionate or equivalent; ICS use not to be initiated or discontinued within 30 days prior to visit 1 except for participants on LABA/ICS therapy who may discontinue LABA/ICS therapy as indicated and switch to ICS monotherapy) (30 days), initiation or discontinuation of ICS use (30 days), PDE4 inhibitor (roflumilast) (14 days), Inhaled LABA: salmeterol, formoterol (48 hours); olodaterol, indacaterol (14 days), LAMA (tiotropium, aclidinium, glycopyrronium, umeclidinium) (7 days) , LABA/LAMA combination products (whichever mono component had the longest washout), theophyllines (48 hours), oral beta2-agonists (long-acting (48 hours), short-acting (12 hours), inhaled SABA (study provided prn albuterol was permitted during the study, except in the 4-hour period prior to spirometry testing) (4 hours), inhaled short-acting anticholinergics (permitted during the run-in period between visits 1 and 4 and washout period between visits 7 and 9. **Restricted/non-permitted:** Participants must discontinue use of short-acting anticholinergics at least 4 hours before visit 4 and visit 9. Participants should not use short acting anticholinergics during the double-blind treatment periods (4 hours), inhaled short-acting anticholinergic/SABA combination products (4 hours), and any other investigational medication (30 days or within 5 drug half-lives (whichever was longer))
Participants	**Note: cross-over study therefore participant data reported for whole cohort.** **N randomised:** N = 99. **N analysed, n/N:** UMEC/VI 62.5/25 µg: 93/99; placebo: 90/99. **Mean age (SD), years:** 60.7 (9.47). **Gender - male, n/N (%):** 104/198 (52.5).

NCT02275052 (*Continued*)

	Baseline lung function - post-bronchodilator % predicted FEV1: Not reported. **Smoking status, current smoker, n/N (%):** Not reported.
Interventions	**Intervention:** Once-daily UMEC/VI 62.5/25 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary outcome:** change from baseline in exercise endurance time post-dose at week 12 of each treatment period. **Secondary outcome:** change from baseline in trough FEV1 at week 12 of each treatment period; change from baseline in FRC 3 hours post-dose at week 12 of each treatment period; change from baseline in IC 3 hours post-dose at week 12 of each treatment period **Reported outcomes:** All of the prespecified outcomes (see above) plus safety were reported on the clinicaltrials.gov site
Notes	**Funding for trial; notable author COIs:** Study sponsored by GlaxoSmithKline.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided (trial registry only).
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided (trial registry only).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to treatment allocation
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Participants and investigators were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants for subjective outcomes were the outcome assessors; therefore, low risk of bias
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate < 20% and balanced between treatment arms.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported

NCT02275052 (*Continued*)

Other bias	Low risk	None identified.

O'Donnell 2015a

Methods	**Study ID and dates performed:** NCT01533922 (MORACTO-1); study dates not stated. **Study design:** Double-blind, 6-week incomplete cross-over study. **Duration of study:** 38-40 weeks, including a 2-4 week run-in period. **Study setting, location, number of centres:** 82 investigational sites in 13 countries. **Key inclusion criteria:** Aged 40-75 years; post-bronchodilator (400 μg salbutamol) FEV1/FVC < 70%; post-bronchodilator FEV1 $\geq$ 30% and < 80% of predicted normal (GOLD 2-3); current or ex-smokers with a smoking history of > 10 pack-years **Key exclusion criteria:** Significant disease other than COPD; unstable or life-threatening cardiac arrhythmia; hospitalisation for heart failure or myocardial infarction within the past year; regular use of daytime oxygen therapy for > 1 h per day; history of asthma and contraindications to exercise as per the ERS guidelines **Concomitant medications: Permitted:** Participants continued with inhaled corticosteroids if taken at baseline; open-label salbutamol (albuterol) was provided as rescue medication throughout the study. **Restricted/not permitted:** LABA or LAMA (other than study medication) during the baseline, treatment, and washout periods; short-acting muscarinic antagonists during the treatment periods (permitted only during baseline and washout periods, with an 8-h washout prior to assessments)
Participants	**Note: cross-over study therefore participant data reported for whole cohort; baseline characteristics and participant flow reported for combined studies (MORACTO-1 and MORACTO-2).** **N randomised:** N = 586. **N analysed, n/N:** TIO/OLO 2.5/5 µg: 424/442; TIO/OLO 5/5µg: 428/450; placebo: 413/438 **Mean age (SD), years:** 61.7 (7.7). **Gender - male, n/N (%):** 417/586 (71.2). **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** 58 (13) . **Smoking status, current smoker, n/N (%):** 229/586 (39.1).
Interventions	**Intervention:** Once-daily TIO/OLO 2.5/5 µg; once-daily TIO/OLO 5/5 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Inspiratory capacity at rest immediately before constant work rate cycle ergometry (assessed at 6 weeks); endurance time during constant work rate cycle ergometry. **Secondary:** Slope of the intensity of breathing discomfort during constant work rate cycle ergometry (assessed at 6 weeks); 1-hour post-dose FEV1 (assessed at 6 weeks) **Reported outcomes:** All prespecified outcomes (see above) plus FVC and safety and tolerability

Notes	**Funding for trial; notable author COIs:** This work was funded by BI Pharma GmbH & Co. All authors were either employees of BI or had received research funding or honoraria from BI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar attrition with similar reasons for combined treatment arm and placebo arm; discontinuation rates < 5%
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified.

O'Donnell 2015b

Methods	**Study ID and dates performed:** NCT01533935 (MORACTO-2); study dates not stated. **Study design:** Double-blind, 6-week incomplete cross-over study. **Duration of study:** 38-40 weeks, including a 2-4 week run-in period. **Study setting, location, number of centres:** 82 investigational sites in 13 countries. **Key inclusion criteria:** Aged 40-75 years; post-bronchodilator (400 μg salbutamol) FEV1/FVC < 70%; post-bronchodilator FEV1 ≥ 30% and < 80% of predicted normal (GOLD 2-3); current or ex-smokers with a smoking history of > 10 pack-years **Key exclusion criteria:** Significant disease other than COPD; unstable or life-threatening cardiac arrhythmia; hospitalisation for heart failure or myocardial infarction within the past year; regular use of daytime oxygen therapy for > 1 h per day; history of asthma and contraindications to exercise as per the ERS guidelines **Concomitant medications: Permitted:** Participants continued with inhaled corticosteroids if taken at baseline; open-label salbutamol (albuterol) was provided as rescue medication throughout the study. **Restricted/not permitted:** LABA or LAMA (other than study medication) during the baseline, treatment, and washout periods; short-acting muscarinic antagonists during the treatment periods (permitted only during baseline and washout periods, with an 8-h washout prior to assessments)
Participants	**Note: cross-over study therefore participant data reported for whole cohort; baseline characteristics and participant flow reported for combined studies (MORACTO-1 and MORACTO-2).** **N randomised:** N = 586. **N analysed, n/N:** TIO/OLO 2.5/5 µg: 424/442; TIO/OLO 5/5µg: 28/450; placebo: 413/438 **Mean age (SD), years:** 61.7 (7.7). **Gender - male, n/N (%):** 417/586 (71.2). **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** 58 (13) . **Smoking status, current smoker, n/N (%):** 229/586 (39.1).
Interventions	**Intervention:** Once-daily TIO/OLO 2.5/5 µg; once-daily TIO/OLO 5/5µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Inspiratory capacity at rest immediately before constant work rate cycle ergometry (assessed at 6 weeks); endurance time during constant work rate cycle ergometry. **Secondary:** Slope of the intensity of breathing discomfort during constant work rate cycle ergometry (assessed at 6 weeks); 1-hour post-dose FEV1 (assessed at 6 weeks) **Reported outcomes:** All prespecified outcomes (see above) plus FVC and safety and tolerability
Notes	**Funding for trial; notable author COIs:** This work was funded by BI Pharma GmbH & Co. All authors were either employees of BI or had received research funding or honoraria from BI

Risk of bias

Bias	Authors' judgement	Support for judgement

O'Donnell 2015b (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar attrition with similar reasons for combined treatment arm and placebo arm; discontinuation rates < 5%
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified.

Siler 2016

Methods	**Study ID and dates performed:** NCT02152605; September 2014 to March 2015. **Study design:** Multicentre, randomised, double-blind, parallel-group, placebo-controlled study **Duration of study:** 7-14 day run-in period; 12-week treatment period. **Study setting, location, number of centres:** 55 centres in Bulgaria, Germany, Hungary, Romania, Russian Federation, Ukraine, and US **Key inclusion criteria:** ≥ 40 years of age; diagnosis of COPD; current or prior history of ≥ 10 pack-years of cigarette smoking at screening; a pre- and post-albuterol (salbutamol) FEV1/FVC < 0.70 and a post-albuterol FEV1 ≤ 70% of predicted normal values at screening (based on NHANES III reference equations; a score ≥ 2 on the mMRC Dyspnoea Scale at screening **Key exclusion criteria:** Current diagnosis of asthma or other known respiratory conditions (α1-antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases, or other active pulmonary diseases); hospitalisation for COPD or pneumonia within 12 weeks prior to visit 1; lung volume reduction surgery within the 12 months prior to visit 1; use of long-term oxygen therapy (prescribed for > 12 h/day); severe hepatic impairment; any rapidly progressing disease or immediate life-threatening illness (e.g. cancer); any condition that was likely to affect respiratory function (e.g. neurological condition); abnormal, clinically significant electrocardiogram finding at screening (atrial fibrillation with rapid ventricular rate > 120 bpm; sustained or nonsustained ventricular tachycardia; second-degree heart block Mobitz type II, and third-degree heart block (unless pacemaker or defibrillator had been inserted)) **Concomitant medications:** Use of study-provided albuterol was permitted, except in the 4-hour period prior to spirometry testing. Excluded medications prior to visit 1: depot corticosteroids; systemic, oral or parenteral corticosteroids; ICS/LABA combination products; ICS at a dose > 1000 µg/day of FP or equivalent; initiation or discontinuation of ICS use; PDE4 inhibitors; LAMAs, inhaled LABAs, LABA/LAMA combination products; theophyllines; oral beta2-agonists; inhaled SABA or inhaled short-acting anticholinergics, or any combination of the two
Participants	**N randomised:** UMEC/VI 62.5/25 µg: n = 249; placebo: n = 249. **N analysed, n/N:** UMEC/VI 62.5/25 µg: 248/249; placebo: 248/249. **Mean age (SD), years:** UMEC/VI 62.5/25 µg: 64.1 (8.70); placebo: 62.6 (8.23). **Gender - male, n/N (%):** UMEC/VI 62.5/25 µg: 144/248 (58); placebo: 149/248 (60) . **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** UMEC/VI 62.5/25 µg: 46.5 (12.81); placebo: 48.4 (14.06). **Smoking status, current smoker, n/N (%):** UMEC/VI 62.5/25 µg: 137/248 (55); placebo: 129/248 (52).
Interventions	**Intervention:** Once-daily UMEC/VI 62.5/25 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Change from baseline in mean SGRQ total score at day 84**. Secondary:** Change from baseline in trough FEV1 at day 84; change from baseline in mean number of puffs of rescue medication per day used over weeks 1-12 **Reported outcomes:** plus the proportion of SGRQ responders at days 28, 56, and 84; SGRQ total score at days 28 and 56 (SGRQ responders were defined as having a total score ≥ 4 units below baseline); percentage of rescue-free days; trough FEV1 at days 28

	and 56; trough FVC at days 28, 56, and 84; safety
Notes	**Funding for trial; notable author COIs:** The study was funded by GSK. Lead author had received research funding from GSK. All other authors were employees of GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised IRVS system used for randomisation.
Allocation concealment (selection bias)	Low risk	Centralised IRVS system used for randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to treatment (see clinicaltrial.gov)
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Participants and investigators were blinded to treatment (see clinicaltrial.gov)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar loss in both arms (treatment and placebo) for similar reasons and loss < 10%
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	High risk	Greater proportion of participants with GOLD category D in the active treatment group; favoured placebo and underestimation of treatment effect

Singh 2016a

Methods	**Study ID and dates performed:** NCT01964352 (OTEMTO 1). **Study design:** A multinational, double-blind, parallel-group, placebo-controlled study **Duration of study:** 2-week run-in period; 12-week treatment period; 3-week follow-up **Study setting, location, number of centres:** Not stated. **Key inclusion criteria:** Participants aged ≥ 40 years with moderate to severe COPD (GOLD 2-3); post-bronchodilator FEV1 ≥ 30% and < 80% of predicted normal), FEV1/FVC < 70% predicted and a smoking history of > 10 pack-years **Key exclusion criteria:** A history of asthma, another significant disease, COPD exacerbation or symptoms of lower respiratory tract infection within the previous 3 months; unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure within the past year; a history of myocardial infarction within 1 year of screening; a history of life-threatening pulmonary obstruction **Concomitant medications:** Participants were allowed to continue their ICS therapy (if they were on a stable dose for 6 weeks prior to screening). LAMAs or LABAs other than study medication were prohibited; short-acting muscarinic antagonists were permitted only during the screening period. Open-label salbutamol was provided as rescue medication for use throughout the study
Participants	**N randomised:** TIO/OLO 2.5/5 µg: n = 202; TIO/OLO 5/5 µg: n = 204; placebo: n = 204 **N analysed, n/N (%):** TIO/OLO 2.5/5 µg: 196/202 (97.0); TIO/OLO 5/5 µg: 195/204 (96.1); placebo: 178/204 (87.3) **Mean age (SD), years:** TIO/OLO 2.5/5 µg: 64.7 (8.2); TIO/OLO 5/5 µg: 64.7 (8.9); placebo: 65.1 (8.3) **Gender - male, n/N (%):** TIO/OLO 2.5/5 µg: 116 (57.4); TIO/OLO 5/5 µg: 114 (56.2); placebo: 127 (62.3) **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** TIO/OLO 2.5/5 µg: 55.5 (13.7); TIO/OLO 5/5 µg: 54.9 (12.0); placebo: 56.3 (12.8) **Smoking status, current smoker, n/N (%):** TIO/OLO 2.5/5 µg: 98/202 (48.5); TIO/OLO 5/5 µg: 111/203 (54.7); placebo: 88/204 (43.1)
Interventions	**Intervention:** Once-daily TIO/OLO 2.5/5 µg; once-daily TIO/OLO 5/5 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** FEV1 AUC 0-3 h response at 12 weeks; trough FEV1 response at 12 weeks; SGRQ total score at 12 weeks. **Secondary:** trough FVC response (change from baseline) at 12 weeks; TDI focal score at 12 weeks; FVC AUC 0-3 h response (change from baseline) at 12 weeks **Reported outcomes:** All prespecified outcomes (see above) were reported.
Notes	**Funding for trial; notable author COIs:** This study was funded by Boehringer Ingelheim Pharma GmbH & Co. KG. Seven of nine authors were employees of, or had received funding/honoraria from, BI. Two authors disclosed no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement

Singh 2016a (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate was < 15% in placebo and combined LABA/LAMA arms
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified. Note slightly higher rates of discontinuation in placebo arm - likely accounted for due to the most severely ill participants dropping out. Potential positive placebo treatment effect not observed

Singh 2016b

Methods	**Study ID and dates performed:** NCT02006732 (OTEMTO 2). **Study design:** One of two multinational, double-blind, parallel-group, placebo-controlled studies **Duration of study:** 2-week run-in period; 12-week treatment period; 3-week follow-up **Study setting, location, number of centres:** Not stated. **Key inclusion criteria:** Participants aged ≥ 40 years with moderate to severe COPD (GOLD 2-3); post-bronchodilator FEV1 ≥ 30% and < 80% of predicted normal), FEV1/FVC < 70% predicted and a smoking history of > 10 pack-years **Key exclusion criteria:** A history of asthma, another significant disease, COPD exacerbation or symptoms of lower respiratory tract infection within the previous 3 months; unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure within the past year; a history of myocardial infarction within 1 year of screening; a history of life-threatening pulmonary obstruction **Concomitant medications:** Participants were allowed to continue their ICS therapy (if they were on a stable dose for 6 weeks prior to screening). LAMAs or LABAs other than study medication were prohibited; short-acting muscarinic antagonists were permitted only during the screening period. Open-label salbutamol was provided as rescue medication for use throughout the study
Participants	**N randomised:** TIO/OLO 2.5/5 µg: n = 202; TIO/OLO 5/5 µg: n = 202; placebo: n = 202 **N analysed, n/N:** TIO/OLO 2.5/5 µg: 193/202; TIO/OLO 5/5 µg: 198/202; placebo: 182/202 **Mean age (SD), years:** TIO/OLO 2.5/5 µg: 64.4 (8.6); TIO/OLO 5/5 µg: 65.2 (8.5); placebo: 64.0 (8.3) **Gender - male, n/N (%):** TIO/OLO 2.5/5 µg: 126 (62.4); TIO/OLO 5/5 µg: 133 (65.8); placebo: 117 (57.9) **Baseline lung function - mean (SD) post-bronchodilator % predicted FEV1:** TIO/OLO 2.5/5 µg: 54.5 (12.7); TIO/OLO 5/5 µg: 54.8 (12.8); placebo: 54.3 (13.4) **Smoking status, current smoker, n/N (%):** TIO/OLO 2.5/5 µg: 90/202 (44.6) ; TIO/OLO 5/5 µg: 92/202 (45.5); placebo: 95/202 (47.0)
Interventions	**Intervention:** Once-daily TIO/OLO 2.5/5 µg; once-daily TIO/OLO 5/5 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** FEV1 AUC 0-3 h response at 12 weeks; trough FEV1 response at 12 weeks; SGRQ total score at 12 weeks. **Secondary:** trough FVC response (change from baseline) at 12 weeks; TDI focal score at 12 weeks; FVC AUC 0-3 h response (change from baseline) at 12 weeks **Reported outcomes:** All prespecified outcomes (see above) were reported.
Notes	**Funding for trial; notable author COIs:** This study was funded by Boehringer Ingelheim Pharma GmbH & Co. KG. Seven of nine authors were employees of, or had received funding/honoraria from, BI. Two authors disclosed no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement

Singh 2016b (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided.
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate was < 15% in placebo and combined LABA/LAMA arms
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	None identified. Note slightly higher rates of discontinuation in placebo arm - likely accounted for due to the most severely ill participants dropping out. Potential positive placebo treatment effect not observed

Troosters 2016

Methods	**Study ID and dates performed:** NCT02085161; PHYSACTO; dates not reported. **Study design:** Randomised, partially double-blinded, placebo-controlled, parallel-group trial **Duration of study:** 19 weeks (4-week run-in; 12-week treatment period; 3-week follow-up) **Study setting, location, number of centres:** 34 sites in Australia, New Zealand, USA, Canada, Europe (17 academic centres, 15 secondary care and 5 primary care centres) **Key inclusion criteria:** COPD; aged ≥ 40 years and ≤ 75 years; smoking history of > 10 pack-years; post-bronchodilator FEV1 ≥ 30% and < 80% of predicted normal (GOLD 2-3) and no acute exacerbations in the month prior to the study; post-bronchodilator FEV1/FVC < 70% **Key exclusion criteria:** Significant disease other than COPD; history of asthma; clinically relevant abnormal baseline haematology, blood chemistry or urinalysis; conditions excluding participants from exercise **Concomitant medications:** Not reported.
Participants	**N randomised:** TIO/OLO 5/5 µg: n = 76; placebo: n = 76. **N analysed, n/N:** TIO/OLO 5/5 µg: 72/76; placebo: 65/76. **Mean age (SD), years:** TIO/OLO 5/5 µg: 65.0 (6.9); placebo: 64.4 (6.6). **Gender - male, n/N (%):** TIO/OLO 5/5 µg: 48/76 (63.2); placebo: 52/75 (69.3). **Baseline lung function - post-bronchodilator % predicted FEV1:** Not reported. **Smoking status, current smoker, n/N (%):** Not reported.
Interventions	**Intervention:** Once-daily TIO/OLO 5/5 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Endurance time during endurance shuttle walk test (to symptom limitation) after 8 weeks. **Secondary:** average daily walking time measured by the activity monitor in the week prior to week 12; average daily walking intensity measured by the activity monitor in the week prior to 12 weeks of treatment; perceived difficulties as evaluated with functional performance inventory-short form (FPI-SF) total score at week 12; endurance time during endurance shuttle walk test (to symptom limitation) after 12 weeks; one-hour, post-dose FEV1 after 8 weeks of treatment; one-hour, post-dose FVC after 8 weeks of treatment; resting inspiratory capacity measured at 1.5 hours post-dose after 8 weeks of treatment **Reported outcomes:** Prespecified outcomes (clinicaltrials.gov) were well reported
Notes	**Funding for trial; notable author COIs:** Study sponsored by BI. Authors had received funding or honoraria from BI, or were employees of BI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Randomisation is performed using a pseudo-random number generator and block randomisation is used to achieve balanced allocation"

Troosters 2016 (*Continued*)

Allocation concealment (selection bias)	Low risk	Web-based and telephone-based response system used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Partially double-blind' as it was not possible to blind participants and personnel to the receipt of exercise training or behavioural modifications. However; the groups of interest (TIO/OLO and placebo) received treatments in double-blind fashion (participants and personnel were blinded)
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Knowledge of treatment allocation by participant or personnel would be unlikely to influence objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants for subjective outcomes were the outcome assessors; therefore, low risk of bias
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate was < 20% and the difference in attrition rates between relevant treatment groups was < 10%
Selective reporting (reporting bias)	Low risk	Data presented on clinicaltrials.gov website appeared in line with protocol
Other bias	Low risk	None identified.

Watz 2016

Methods	**Study ID and dates performed:** ; NCT01996319 (MOVE); study dates not reported. **Study design:** Randomised, placebo-controlled, double-blind, multicentre, cross-over study **Duration of study:** Flexible run-in period (duration dependent on COPD medication at baseline; two 21-day treatment periods separated by a 14-day washout **Study setting, location, number of centres:** Multicentre, randomised, double-blind, placebo-controlled cross-over study, conducted at 30 secondary care (pulmonology) practices in Germany **Key inclusion criteria:** Stable COPD according to the current GOLD guidelines (GOLD 2013); current or ex-smokers; smoking history of ≥ 10 pack years; airflow limitation indicated by a post-bronchodilator FEV1 ≥ 40% and < 80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70 **Key exclusion criteria:** Concomitant pulmonary disease, history of asthma, onset of respiratory symptoms prior to age 40 years, blood eosinophil count > 600/mm^3 during run-in, or a clinically significant abnormality that could interfere with the assessment of efficacy or safety of the study; COPD exacerbation in the 6 weeks prior to screening or during the run-in period; respiratory tract infection within 4 weeks prior to screening or during the run-in period **Concomitant medications:** The following COPD medication was prohibited from the indicated time prior to visit 2 and for the duration of the study: LAMAs (7 days); LABAs (48 h; 7 days for indacaterol); xanthines and oral phosphodiesterase IV inhibitors (7 days) . ICS were permitted, at a stable dose throughout the study (participants on a LABA/ICS combination were to be switched to the nearest equivalent dose of ICS monotherapy at least 48 h prior to visit 2)
Participants	**Note: cross-over study therefore participant data reported for whole cohort.** **N randomised:** N = 194. **N analysed:** N = 194. **Mean age (SD), years:** 62.8 (7.9). **Gender - male, n/N (%):** 127/194 (65.5). **Baseline lung function - mean (SD), post-bronchodilator % predicted FEV1:** 61.6 (10.7). **Smoking status, current smoker, n/N (%):** 110/194 (56.7).
Interventions	**Intervention:** Once-daily IND/GLY 110/50 µg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Change from baseline in peak IC (IND/GLY versus placebo); change from baseline in average physical activity level (IND/GLY versus placebo). **Secondary:** Average number of steps per day; change in the duration of at least moderate activity per day; change from baseline in peak IC; change from baseline in the trough IC; peak FEV1 at day 1; trough FEV1 comparison after 22 days **Reported outcomes:** Prespecified outcomes (clinicaltrials.gov) were well reported
Notes	**Funding for trial; notable author COIs:** This study was funded by Novartis Pharma. All authors were employees of Novartis, or received research funding/honoraria from Novartis

Risk of bias

Watz 2016 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random number sequence was generated by the sponsor using a validated automated system
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, staff, persons performing the assessments, sponsor, and data analysts were blinded to treatment
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Participants, staff, persons performing the assessments, sponsor, and data analysts were blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Persons performing the assessments were blinded to treatment
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Persons performing the assessments were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants received at least one dose of allocated treatment and were included in the full analysis set
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	Low risk	Cross-over design may not be appropriate for a study that examines physical activity end points, which require a change in lifestyle - washout periods may be insufficient. However, physical activity end points were not included in the present meta-analyses

Zheng 2014

Methods	**Study ID and dates performed:** NCT01636713; dates not reported. **Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group study **Duration of study:** 7-14 day run-in; 24-week treatment period. **Study setting, location, number of centres:** People's Republic of China, Philippines, South Korea, Taiwan, Thailand **Key inclusion criteria:** Aged ≥ 40 years at screening; established clinical history of COPD (ATS/ERS criteria); current or former smokers with a smoking history ≥ 10 pack-years; post-albuterol FEV1/FVC < 0.70 and a post-albuterol FEV1 ≤ 70% of predicted normal values (NHANES III reference equations at visit 1); dyspnoea score of ≥ 2 on the mMRC Dyspnea Scale at screening **Key exclusion criteria:** Current diagnosis of asthma or any other known respiratory disorder, including α1-anti-trypsin deficiency or active lung infection, e.g. tuberculosis, lung cancer, clinically significant bronchiectasis, pulmonary hypertension, sarcoidosis, or interstitial lung disease; previous history or current evidence of clinically significant or uncontrolled cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine, or haematological abnormalities **Concomitant medications: Permitted:** Supplemental albuterol as rescue medication; ICS < 1000 µg/day of FP or equivalent; ICS not initiated or discontinued within 30 days prior to study entry
Participants	**N randomised:** UMEC/VI 62.5/25 µg: n = 194; UMEC/VI 125/25 µg: n = 193; placebo: n = 193 **N analysed, n/N (100):** UMEC/VI 62.5/25 µg: 194/194 (100); UMEC/VI 125/25 µg: 193/193 (100); placebo: 193/193 (100) **Mean age (SD), years:** UMEC/VI 62.5/25 µg: 64.0 (8.71); UMEC/VI 125/25 µg: 63.7 (8.26); placebo: 64.3 (8.78) **Gender - male, n (%):** UMEC/VI 62.5/25 µg: 183 (94); UMEC/VI 125/25 µg: 182 (94); placebo: 177 (92) **Baseline lung function - mean (SD) post-bronchodilator FEV1, L:** UMEC/VI 62.5/25 µg: 1.131 (0.3965); UMEC/VI 125/25 µg: 1.195 (0.3889); placebo: 1.168 (0.3708) **Smoking status, current smoker, n/N (%):** UMEC/VI 62.5/25 µg: 56/194 (29); UMEC/VI 125/25 µg: 48/193 (25); placebo: 65/193 (34)
Interventions	**Intervention:** Once-daily UMEC/VI 62.5/25 µg; once-daily UMEC/VI 125/25 µg **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Change from baseline in trough FEV1 on day 169 (week 24). **Secondary:** Transition Dyspnea Index (TDI) Focal Score at day 168 (week 24); change from baseline weighted mean 0-6 hour FEV1 obtained post-dose at day 1 **Reported outcomes:** Prespecified outcomes (clinicaltrials.gov) were well reported, plus trough FEV1 at other time points; serial FEV1 over 0-6 hours post-dose at day 1; the proportion of participants achieving an increase in FEV1 of ≥ 12% and ≥ 0.200 L above baseline at any time 0-6 hours post-dose on day 1; the proportion of participants achieving an increase of ≥ 0.100 L above baseline in trough FEV1; and trough and serial FVC and time to onset 0-6 hours post-dose at day 1; TDI focal score recorded at other time points; proportion of TDI responders (a responder to TDI was defined as a participant who reported a TDI score of ≥ 1 unit); rescue-albuterol use (percentage of rescue-free days and puffs/day) and time to first COPD exacerbation (defined as an acute

	worsening of symptoms of COPD requiring the use of rescue albuterol or any treatment beyond study medication); safety
Notes	**Funding for trial; notable author COIs:** GSK funded this study. Lead author has received lecture fees from GSK. 3 of 4 co-authors are employees of GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation schedule was generated by GSK using the validated computerised system RandAll version 2.5
Allocation concealment (selection bias)	Low risk	Used the sponsors formal system for randomisation so although concealment not specifically stated, it seems likely that this was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to treatment allocation
Blinding of participants and personnel (objective outcomes - performance bias) Objective outcomes	Low risk	Participants and investigators were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants for subjective outcomes were the outcome assessors; therefore, low risk of bias
Blinding of outcome assessment (objective outcomes - detection bias) All outcomes	Low risk	Assessment of objective outcomes would be unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition based on completion rates < 20% across arms. Data reported for ITT population
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (clinicaltrials.gov) were well reported
Other bias	High risk	Higher proportion of participants with GOLD Stage IV in the UMEC/VI 62.5/25 µg group compared with placebo; may skew the treatment effect in favour of placebo. Lower proportion of current smokers than comparable studies

AE: adverse event; AUC: area under the curve; ATS: American Thoracic Society; BD: bronchodilator; bpm: beats per minute; CDLM: capacity of daily living during the morning; COI: conflict of interest; COPD: chronic obstructive pulmonary disease; CR10: category ratio 10; ECG: echocardiogram; ERS: European Respiratory Society; FEV1: forced expiratory volume in 1 second; FP: fluticasone propionate; FPI-SF: functional performance inventory-short-form; FRC: functional residual capacity; FVC: forced vital capacity; GOLD: Global Initiative for chronic obstructive pulmonary disease; H1: histamine 1; IC: inspiratory capacity; ICS: inhaled corticosteroid; IgE: immunoglobulin E; IND: indacaterol; IRT: interactive voice response system; ITT: intent to treat; IVRS: interactive voice response system; LABA: long-acting beta-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; LSM: least squares mean; MACE: major adverse cardiovascular event; MCID: minimally clinically important difference; mITT: modified intent-to-treat; mMRC: modified Medical Research Council; MRC: Medical Research Council; N: number; $O_{2:oxygen;}$ OCS: oral corticosteroids; OLO: olodaterol; PDE4: phosphodiesterase 4; PK Cmax: pharmacokinetic maximum plasma concentration; prn: pro re nata (as needed); QT: Q-T interval; RAMOS: registration and medical ordering system; SABA: short-acting beta-adrenoceptor agonist; SAE: serious adverse event; SaO2: oxygen saturation; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire; SOBDA: shortness of breath with daily activities; SpO2: peripheral capillary oxygen saturation; SSRI: selective serotonin reuptake inhibitor; TDI: transition dyspnoea index; TIO: tiotropium; tmax:time to maximum plasma concentration; UMEC: umeclidinium; VI: vilanterol; W: Watt.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aalbers 2015	Wrong intervention (combination inhaler not used)
Asai 2013	Wrong comparator (different LABA used in control arm)
Berton 2009	Wrong intervention (LABA/LAMA not administered in combined inhaler)
Buhl 2011 INTENSITY	Wrong intervention (LABA/LAMA combination not evaluated)
Buhl 2015 TONADO	2nd Round: Wrong comparator (no placebo)
D'Urzo 2014 AUGMENT	2nd ROUND: Wrong intervention - LAMA/LABA administered twice daily
Decramer 2014	2nd Round: Wrong comparator (no placebo)
Di Marco 2005	Duration of treatment < 3 weeks
Donohue 2013b	2nd ROUND: Wrong intervention - LAMA/LABA administered twice daily
Donohue 2016	Duration of treatment < 3 weeks
Donohue 2016b	2nd Round: Wrong comparator (no placebo)
EUCTR2007-003648-31	Duration of treatment < 3 weeks
EUCTR2007-004435-30	Wrong intervention (combination inhaler not used)
EUCTR2009-015901-38	Duration of treatment < 3 weeks

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Evdokimov 2015	2nd Round: Wrong comparator (no placebo)
Evdokimov 2015b	2nd Round: Wrong comparator (no placebo)
Ferguson 2015	Wrong comparator (dose of indacaterol in the control group was greater than that in combination arm)
Fogarty 2014	Duration of treatment < 3 weeks
Hanania 2016	2nd Round: Wrong comparator (no placebo)
Hoshino 2014	Wrong intervention (combination inhaler not used)
Ichinose 2016	No placebo group
Ichinose 2017	2nd Round: Wrong comparator (no placebo)
Imran 2015	Duration of treatment < 3 weeks
Jones 2010	Combined inhaler not used (LAMA plus LABA in individual inhalers)
Mahler 2015	2nd ROUND: Wrong intervention - LAMA/LABA administered twice daily
Maltais 2010	2nd Round: Wrong comparator (no placebo)
NCT00308191 2006	Wrong intervention (combination inhaler not used)
NCT00424528 2006	Wrong intervention (combination inhaler not used)
NCT00696020 2008	2nd Round: Wrong comparator (no placebo)
NCT00720499 2008	Wrong comparator (no placebo)
NCT00845728 2009	Wrong intervention (LABA/LAMA combination not evaluated)
NCT00846586 2009	Wrong intervention (combination inhaler not used)
NCT00877383 2009	Wrong intervention (combination inhaler not used)
NCT01040689 2010	Wrong intervention (LABA/LAMA combination not evaluated)
NCT01040728 2010	Wrong intervention (LABA/LAMA combination not evaluated)
NCT01049360 2009	Treatment duration < 3 weeks
NCT01437540 2011	2nd Round: Wrong comparator (no placebo)
NCT01476813 2012	Wrong intervention (LABA/LAMA combination not evaluated)

(*Continued*)

NCT01491802 2012	2nd Round: Wrong comparator (no placebo)
NCT01529632 2012	Wrong comparator (both individual LAMA and LABA received)
NCT01536262 2012	2nd Round: Wrong comparator (no placebo)
NCT01551888 2012	Treatment duration < 3 weeks
NCT01574651 2012	Wrong comparator (Indaceterol or glycopyrronium (i.e. FDC evaluated in intervention arm) not evaluated in comparator arm)
NCT01682863 2012	Wrong comparator (indacaterol dose in control arm different than used in FDC in intervention arm)
NCT01697696 2012	Wrong intervention (LABA/LAMA combination not evaluated)
NCT01703845 2012	Wrong comparator (no LAMA or LABA alone, or placebo)
NCT01817764 2013	Wrong comparator (no single agent, or placebo)
NCT01985334 2014	Wrong comparator (individual LAMA or LABA could be used based on prior treatment)
NCT02030535 2014	Wrong study design (single-dose study)
NCT02059434 2013	Treatment duration < 3 weeks (single ascending-dose study)
NCT02196714 2014	Wrong patient population (healthy volunteers)
NCT02231177 2008	2nd Round: Wrong comparator (no placebo)
NCT02296138 2015	No placebo group
NCT02343458 2015	LAMA/LABA administered twice daily
NCT02429765 2015	LAMA/LABA administered twice daily
NCT02442206 2015	Treatment duration < 3 weeks
NCT02465567 2015	Wrong comparator (no single agent, or placebo)
NCT02487446 2015	Wrong comparator (no single agent, or placebo)
NCT02487498 2015	Wrong comparator (no single agent, or placebo)
NCT02579850 2015	Wrong comparator (no single agent, or placebo)
NCT02643082 2015	Treatment duration < 3 weeks

(*Continued*)

NCT02796677 2016	LAMA/LABA administered twice daily
NCT02845752 2016	Treatment duration < 3 weeks
NCT02937584 2016	Wrong intervention (LABA/LAMA combination not evaluated)
NCT02988869 2016	No placebo group
NCT03022097 2017	LAMA/LABA administered twice daily
NCT03024346 2016	Duration of treatment < 3 weeks
NCT03034915 2017	No placebo group
Orevillo 2016	Duration of treatment < 3 weeks
Rabe 2015	2nd ROUND: Wrong intervention - LAMA/LABA administered twice daily
Reisner 2011	Duration of treatment < 3 weeks
Reisner 2013	Duration of treatment < 3 weeks
Reisner 2016	2nd ROUND: Wrong intervention - LAMA/LABA administered twice daily
Reisner 2017	Duration of treatment < 3 weeks
Reisner 2017b	2nd Round: Wrong comparator (no placebo)
Sadigov 2014	2nd Round: Wrong comparator (no placebo)
Salomon 2017	Wrong intervention (LABA/LAMA not administered in combined inhaler)
Setoguchi 2015	2nd Round: Wrong comparator (no placebo)
Singh 2014	2nd ROUND: Wrong intervention - LAMA/LABA administered twice daily
Sliwinski 2010	Wrong intervention (LABA/LAMA not administered in combined inhaler)
Tanaka 2015	2nd Round: Wrong comparator (no placebo)
Tashkin 2007	Wrong intervention (LABA/LAMA not administered in combined inhaler)
Tashkin 2016	Duration of treatment < 3 weeks
Ulubay 2005	2nd Round: Wrong comparator (no placebo)
Van de Maele 2010	Duration of treatment < 3 weeks

(*Continued*)

Van Noord 2005	Wrong intervention (LABA/LAMA not administered in combined inhaler)
Van Noord 2010	Duration of treatment < 3 weeks
Velazquez-Uncal 2016	Wrong intervention (LABA/LAMA not evaluated)
Vincken 2013	Wrong intervention (LABA/LAMA not administered in combined inhaler)
Vogelmeier 2008	Wrong intervention (LABA/LAMA not administered in combined inhaler)
Vogelmeier 2013	Wrong comparator (LABA/LAMA vs LABA steroids)
Watz 2017	2nd ROUND: Wrong intervention - LAMA/LABA administered twice daily
Webb 2015	2nd Round: Wrong comparator (no placebo)
Wedzicha 2013	2nd Round: Wrong comparator (no placebo)
Yosuke 2014	2nd Round: Wrong comparator (no placebo)
ZuWallack 2014	Wrong intervention (LABA/LAMA not administered in combined inhaler)

FDC:

LABA:

LAMA:

tobecompleted

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT02233543 2014

Methods	**Study ID and dates performed:** NCT02233543; Nov 2014 to June 2016; trial registry entry only (clinicaltrials.gov); no data submitted **Study design:** Randomised, placebo-controlled, cross-over trial. **Duration of study:** 12 weeks (4 weeks per treatment, 2-week washout). **Study setting, location, number of centres:** Not reported. **Key inclusion criteria:** Aged ≥ 40 years; clinical diagnosis of COPD (according to GOLD guidelines, updated 2014) with a post-bronchodilator FEV1/FVC < 0.70; post-bronchodilator FEV1 ≥ 30% and < 60% of the predicted normal value; resting daytime oxygen saturation levels measured by pulse oximetry of ≤ 95% SpO2; smoking history of at least 10 pack years (ten pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years) **Key exclusion criteria:** An exacerbation of COPD (treatment with oral or parenteral antibiotics and/or glucocorticosteroids and/or hospitalisation related to COPD) within 4 weeks prior to screening or during the run-in period; diagnosed asthma; participants receiving regular long-term oxygen therapy; ongoing/planned rehabilitation during the study period; three or more awakenings during the night leading to toilet visit or other reasons for exiting the bed during the last week prior to the screening visit due to non-COPD reasons **Concomitant medications:** Not reported.
Participants	**Note: cross-over study therefore participant data reported for whole cohort; no data posted.** **N randomised:** No data posted to trial registry site; no report available. **N analysed:** No data posted to trial registry site; no report available. **Mean age (SD), years:** No data posted to trial registry site; no report available. **Gender - male, n/N (%):** No data posted to trial registry site; no report available. **Baseline lung function - post-bronchodilator % predicted FEV1:** No data posted to trial registry site; no report available. **Smoking status, current smoker, n/N (%):** No data posted to trial registry site; no report available.
Interventions	**Intervention:** Once-daily IND/GLY 85/43 μg. **Comparator:** Once-daily placebo.
Outcomes	**Prespecified outcomes: Primary:** Mean night-time blood oxygenation at 4 weeks.**Secondary:** Time during the night spent below 90% in blood oxygen saturation at 4 weeks **Reported outcomes:** No result posted.
Notes	**Funding for trial; notable author COIs:** Study sponsored by Novartis Pharmaceuticals.

AE, adverse event; BD, bronchodilator; COI: conflict of interest; COPD: chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GLY: glycopyrrolate; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; IND: indacaterol; IRT, Interactive Response Technology; MCID, minimum clinically important difference; SAE, serious adverse event; SD, standard deviation; SGRQ, St George's Respiratory Questionaire; SpO2: oxygen saturation; SSRI, selective serotonin reuptake inhibitor.

DATA AND ANALYSES

Comparison 1. LABA/LAMA versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	18	8752	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.81, 4.36]
1.1 IND/GLY 110/50	5	2020	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [0.61, 10.49]
1.2 UMEC/VI 62.5/25	5	1921	Odds Ratio (M-H, Fixed, 95% CI)	3.12 [0.68, 14.36]
1.3 UMEC/VI 125/25	4	1401	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.83]
1.4 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 TIO/OLO 2.5/5	6	1670	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [0.12, 53.43]
1.6 TIO/OLO 5/5	6	1689	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 SAEs	22	10536	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.88, 1.28]
2.1 IND/GLY 110/50	6	2830	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.86, 1.56]
2.2 UMEC/VI 62.5/25	6	2317	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.86, 1.93]
2.3 UMEC/VI 125/25	4	1403	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.46, 1.22]
2.4 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 TIO/OLO 2.5/5	6	1670	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.68]
2.6 TIO/OLO 5/5	7	1840	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.55, 1.73]
2.7 ACM/FOR 200/6	1	141	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.02, 12.96]
2.8 ACM/FOR 200/12	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.02, 13.07]
2.9 ACM/FOR 200/18	1	144	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.06, 22.41]
3 AECOPD	3	1127	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.36, 0.78]
3.1 UMEC/VI 62.5/25	2	786	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.37, 0.93]
3.2 UMEC/VI 125/25	1	290	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.17, 0.78]
3.3 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [0.08, 35.43]
4 Time to first AECOPD	2	1371	Hazard Ratio (Fixed, 95% CI)	0.44 [0.31, 0.63]
4.1 UMEC/VI 125/25	2	1371	Hazard Ratio (Fixed, 95% CI)	0.44 [0.31, 0.63]
5 Difference vs placebo in adjusted SGRQ score (HRQoL)	8	4952	Mean Difference (Fixed, 95% CI)	-4.08 [-4.80, -3.36]
5.1 IND/GLY 110/50	2	1370	Mean Difference (Fixed, 95% CI)	-3.88 [-5.30, -2.45]
5.2 UMEC/VI 62.5/25	3	1425	Mean Difference (Fixed, 95% CI)	-4.25 [-5.73, -2.77]
5.3 UMEC/VI 125/25	2	1000	Mean Difference (Fixed, 95% CI)	-3.64 [-5.48, -1.80]
5.4 TIO/OLO 2.5/5	2	579	Mean Difference (Fixed, 95% CI)	-3.89 [-5.60, -2.17]
5.5 TIO/OLO 5/5	2	578	Mean Difference (Fixed, 95% CI)	-4.72 [-6.43, -3.01]
6 SGRQ responder analysis	7	4258	Odds Ratio (M-H, Fixed, 95% CI)	1.75 [1.54, 1.99]
6.1 IND/GLY 110/50	1	706	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.98, 1.86]
6.2 TIO/OLO 2.5/5	2	579	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [1.30, 2.70]
6.3 TIO/OLO 5/5	2	578	Odds Ratio (M-H, Fixed, 95% CI)	2.35 [1.63, 3.40]
6.4 UMEC/VI 62.5/25	3	1441	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [1.37, 2.12]
6.5 UMEC/VI 125/25	2	954	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [1.35, 2.34]
7 Difference vs placebo in adjusted trough FEV1 at EOT	13	6598	Mean Difference (Fixed, 95% CI)	0.20 [0.19, 0.21]
7.1 IND/GLY 110/50	2	1018	Mean Difference (Fixed, 95% CI)	0.25 [0.22, 0.28]
7.2 UMEC/VI 62.5/25	6	2158	Mean Difference (Fixed, 95% CI)	0.18 [0.17, 0.20]
7.3 UMEC/VI 125/25	4	1304	Mean Difference (Fixed, 95% CI)	0.22 [0.20, 0.25]
7.4 TIO/OLO 2.5/5	3	845	Mean Difference (Fixed, 95% CI)	0.18 [0.15, 0.20]
7.5 TIO/OLO 5/5	3	859	Mean Difference (Fixed, 95% CI)	0.21 [0.18, 0.23]

7.6 ACLID/FORM 200/6	1	137	Mean Difference (Fixed, 95% CI)	0.07 [-0.04, 0.18]
7.7 ACLID/FORM 200/12	1	137	Mean Difference (Fixed, 95% CI)	0.12 [0.01, 0.22]
7.8 ACLID/FORM 200/18	1	140	Mean Difference (Fixed, 95% CI)	0.08 [-0.04, 0.19]
8 Difference vs placebo in trough FEV1 at EOT	5	2330	Mean Difference (Fixed, 95% CI)	0.18 [0.16, 0.20]
8.1 IND/GLY 110/50	3	1139	Mean Difference (Fixed, 95% CI)	0.20 [0.17, 0.22]
8.2 TIO/OLO 2.5/5	2	596	Mean Difference (Fixed, 95% CI)	0.16 [0.13, 0.19]
8.3 TIO/OLO 5/5	2	595	Mean Difference (Fixed, 95% CI)	0.16 [0.13, 0.20]
9 Difference vs placebo in trough FEV1 - pooled adjusted and EOT analyses	18		Mean Difference (Fixed, 95% CI)	0.20 [0.19, 0.20]
9.1 IND/GLY 110/50	5		Mean Difference (Fixed, 95% CI)	0.22 [0.21, 0.24]
9.2 UMEC/VI 125/25	4		Mean Difference (Fixed, 95% CI)	0.22 [0.20, 0.25]
9.3 UMEC/VI 62.5/25	6		Mean Difference (Fixed, 95% CI)	0.18 [0.17, 0.20]
9.4 TIO/OLO 2.5/5	5		Mean Difference (Fixed, 95% CI)	0.17 [0.15, 0.19]
9.5 TIO/OLO 5/5	5		Mean Difference (Fixed, 95% CI)	0.19 [0.17, 0.21]
9.6 ACLID/FORM 200/6	1		Mean Difference (Fixed, 95% CI)	0.07 [-0.04, 0.18]
9.7 ACLID/FORM 200/12	1		Mean Difference (Fixed, 95% CI)	0.12 [0.01, 0.22]
9.8 ACLID/FORM 200/18	1		Mean Difference (Fixed, 95% CI)	0.08 [-0.04, 0.19]
10 Difference vs placebo in adjusted peak FEV1	7	4188	Mean Difference (Fixed, 95% CI)	0.31 [0.29, 0.32]
10.1 IND/GLY 110/50	2	1094	Mean Difference (Fixed, 95% CI)	0.35 [0.32, 0.38]
10.2 UMEC/VI 62.5/25	1	693	Mean Difference (Fixed, 95% CI)	0.22 [0.18, 0.27]
10.3 UMEC/VI 125/25	1	678	Mean Difference (Fixed, 95% CI)	0.28 [0.24, 0.32]
10.4 TIO/OLO 2.5/5	2	644	Mean Difference (Fixed, 95% CI)	0.29 [0.27, 0.32]
10.5 TIO/OLO 5/5	2	656	Mean Difference (Fixed, 95% CI)	0.33 [0.30, 0.35]
10.6 ACLID/FORM 200/6	1	140	Mean Difference (Fixed, 95% CI)	0.25 [0.13, 0.37]
10.7 ACLID/FORM 200/12	1	139	Mean Difference (Fixed, 95% CI)	0.31 [0.20, 0.43]
10.8 ACLID/FORM 200/18	1	144	Mean Difference (Fixed, 95% CI)	0.31 [0.19, 0.42]
11 AEs	17	8235	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.86, 1.04]
11.1 IND/GLY 110/50	6	2830	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.07]
11.2 UMEC/VI 62.5/25	5	1921	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.29]
11.3 UMEC/VI 125/25	4	1401	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.86, 1.34]
11.4 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Fixed, 95% CI)	2.84 [0.32, 25.36]
11.5 TIO/OLO 2.5/5	4	1011	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.11]
11.6 TIO/OLO 5/5	4	1021	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.60, 1.01]

Comparison 2. LABA/LAMA versus placebo < 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	16	7708	Odds Ratio (M-H, Fixed, 95% CI)	1.86 [0.75, 4.60]
1.1 IND/GLY 110/50	3	976	Odds Ratio (M-H, Fixed, 95% CI)	2.97 [0.47, 18.97]
1.2 UMEC/VI 62.5/25	5	1921	Odds Ratio (M-H, Fixed, 95% CI)	3.12 [0.68, 14.36]
1.3 UMEC/VI 125/25	4	1401	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.83]
1.4 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 TIO/OLO 2.5/5	6	1670	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [0.12, 53.43]
1.6 TIO/OLO 5/5	6	1689	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 SAEs	19	8682	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.80, 1.29]

2.1 IND/GLY 110/50	3	976	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.54, 3.40]
2.2 UMEC/VI 62.5/25	6	2317	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.86, 1.93]
2.3 UMEC/VI 125/25	4	1403	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.46, 1.22]
2.4 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 TIO/OLO 2.5/5	6	1670	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.68]
2.6 TIO/OLO 5/5	7	1840	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.55, 1.73]
2.7 ACM/FOR 200/6	1	141	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.02, 12.96]
2.8 ACM/FOR 200/12	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.02, 13.07]
2.9 ACM/FOR 200/18	1	144	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.06, 22.41]
3 AECOPD	3	1127	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.36, 0.78]
3.1 UMEC/VI 62.5/25	2	786	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.37, 0.93]
3.2 UMEC/VI 125/25	1	290	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.17, 0.78]
3.3 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [0.08, 35.43]
4 Time to first AECOPD	2		Hazard Ratio (Fixed, 95% CI)	0.44 [0.31, 0.63]
4.1 UMEC/VI 125/25	2		Hazard Ratio (Fixed, 95% CI)	0.44 [0.31, 0.63]
5 Difference vs placebo in adjusted SGRQ score (HRQoL)	6		Mean Difference (Fixed, 95% CI)	-4.15 [-4.99, -3.32]
5.1 UMEC/VI 62.5/25	3		Mean Difference (Fixed, 95% CI)	-4.25 [-5.73, -2.77]
5.2 UMEC/VI 125/25	2		Mean Difference (Fixed, 95% CI)	-3.64 [-5.48, -1.80]
5.3 TIO/OLO 2.5/5	2		Mean Difference (Fixed, 95% CI)	-3.89 [-5.60, -2.17]
5.4 TIO/OLO 5/5	2		Mean Difference (Fixed, 95% CI)	-4.72 [-6.43, -3.01]
6 SGRQ responder analysis	6	3552	Odds Ratio (M-H, Fixed, 95% CI)	1.84 [1.59, 2.12]
6.1 TIO/OLO 2.5/5	2	579	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [1.30, 2.70]
6.2 TIO/OLO 5/5	2	578	Odds Ratio (M-H, Fixed, 95% CI)	2.35 [1.63, 3.40]
6.3 UMEC/VI 62.5/25	3	1441	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [1.37, 2.12]
6.4 UMEC/VI 125/25	2	954	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [1.35, 2.34]

Comparison 3. LABA/LAMA versus placebo ≥ 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	1044	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [0.22, 18.35]
1.1 IND/GLY 110/50	2	1044	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [0.22, 18.35]
2 SAEs	3	1854	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.83, 1.56]
2.1 IND/GLY 110/50	3	1854	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.83, 1.56]
3 Difference vs placebo in adjusted SGRQ score (HRQoL)	2		Mean Difference (Fixed, 95% CI)	-3.88 [-5.30, -2.45]
3.1 IND/GLY 110/50	2		Mean Difference (Fixed, 95% CI)	-3.88 [-5.30, -2.45]
4 SGRQ responder analysis	1	706	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.98, 1.86]
4.1 IND/GLY 110/50	1	706	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.98, 1.86]

Comparison 4. Sensitivity analysis - random-effects model

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	18	8752	Odds Ratio (M-H, Random, 95% CI)	2.02 [0.79, 5.17]
1.1 IND/GLY 110/50	5	2020	Odds Ratio (M-H, Random, 95% CI)	2.54 [0.61, 10.48]
1.2 TIO/OLO 2.5/5	6	1670	Odds Ratio (M-H, Random, 95% CI)	2.53 [0.12, 53.43]
1.3 TIO/OLO 5/5	6	1689	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 UMEC/VI 62.5/25	5	1921	Odds Ratio (M-H, Random, 95% CI)	2.92 [0.62, 13.79]
1.5 UMEC/VI 125/25	4	1401	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.83]
1.6 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 SAEs	22	10536	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.87, 1.27]
2.1 IND/GLY 110/50	6	2830	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.85, 1.55]
2.2 TIO/OLO 2.5/5	6	1670	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.47, 1.68]
2.3 TIO/OLO 5/5	7	1840	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.53, 1.74]
2.4 UMEC/VI 62.5/25	6	2317	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.85, 1.92]
2.5 UMEC/VI 125/25	4	1403	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.41, 1.30]
2.6 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.7 ACM/FOR 200/6	1	141	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.02, 12.96]
2.8 ACM/FOR 200/12	1	140	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.02, 13.07]
2.9 ACM/FOR 200/18	1	144	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.06, 22.41]
3 AECOPD	3	1127	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.35, 0.78]
3.1 UMEC/VI 62.5/25	2	786	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.36, 0.93]
3.2 UMEC/VI 125/25	1	290	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.17, 0.78]
3.3 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Random, 95% CI)	1.68 [0.08, 35.43]
4 Time to first AECOPD	2		Hazard Ratio (Random, 95% CI)	0.44 [0.31, 0.63]
4.1 UMEC/VI 125/25	2		Hazard Ratio (Random, 95% CI)	0.44 [0.31, 0.63]
5 Difference vs placebo in adjusted SGRQ score (HRQoL)	8		Mean Difference (Random, 95% CI)	-4.08 [-4.80, -3.36]
5.1 IND/GLY 110/50	2		Mean Difference (Random, 95% CI)	-3.87 [-5.53, -2.22]
5.2 UMEC/VI 125/25	2		Mean Difference (Random, 95% CI)	-3.64 [-5.48, -1.80]
5.3 UMEC/VI 62.5/25	3		Mean Difference (Random, 95% CI)	-4.18 [-5.92, -2.44]
5.4 TIO/OLO 2.5/5	2		Mean Difference (Random, 95% CI)	-3.89 [-5.60, -2.17]
5.5 TIO/OLO 5/5	2		Mean Difference (Random, 95% CI)	-4.72 [-6.43, -3.01]
6 SGRQ responder analysis	7	4258	Odds Ratio (M-H, Random, 95% CI)	1.74 [1.53, 1.99]
6.1 IND/GLY 110/50	1	706	Odds Ratio (M-H, Random, 95% CI)	1.35 [0.98, 1.86]
6.2 TIO/OLO 2.5/5	2	579	Odds Ratio (M-H, Random, 95% CI)	1.87 [1.30, 2.70]
6.3 TIO/OLO 5/5	2	578	Odds Ratio (M-H, Random, 95% CI)	2.35 [1.63, 3.40]
6.4 UMEC/VI 62.5/25	3	1441	Odds Ratio (M-H, Random, 95% CI)	1.70 [1.37, 2.12]
6.5 UMEC/VI 125/25	2	954	Odds Ratio (M-H, Random, 95% CI)	1.78 [1.35, 2.34]
7 Difference vs placebo in adjusted trough FEV1 at EOT	13		Mean Difference (Random, 95% CI)	0.20 [0.18, 0.21]
7.1 IND/GLY 110/50	2		Mean Difference (Random, 95% CI)	0.25 [0.20, 0.30]
7.2 UMEC/VI 125/25	4		Mean Difference (Random, 95% CI)	0.22 [0.18, 0.26]
7.3 UMEC/VI 62.5/25	6		Mean Difference (Random, 95% CI)	0.18 [0.15, 0.22]
7.4 TIO/OLO 2.5/5	3		Mean Difference (Random, 95% CI)	0.18 [0.15, 0.20]
7.5 TIO/OLO 5/5	3		Mean Difference (Random, 95% CI)	0.21 [0.18, 0.23]
7.6 ACLID/FORM 200/6	1		Mean Difference (Random, 95% CI)	0.07 [-0.04, 0.18]
7.7 ACLID/FORM 200/12	1		Mean Difference (Random, 95% CI)	0.12 [0.01, 0.22]
7.8 ACLID/FORM 200/18	1		Mean Difference (Random, 95% CI)	0.08 [-0.04, 0.19]

8 Difference vs placebo in trough FEV1 at EOT	5		Mean Difference (Random, 95% CI)	0.18 [0.16, 0.20]
8.1 IND/GLY 110/50	3		Mean Difference (Random, 95% CI)	0.20 [0.17, 0.22]
8.2 TIO/OLO 2.5/5	2		Mean Difference (Random, 95% CI)	0.16 [0.13, 0.19]
8.3 TIO/OLO 5/5	2		Mean Difference (Random, 95% CI)	0.16 [0.13, 0.20]
9 Difference vs placebo in adjusted peak FEV1	7		Mean Difference (Random, 95% CI)	0.30 [0.28, 0.33]
9.1 IND/GLY 110/50	2		Mean Difference (Random, 95% CI)	0.35 [0.31, 0.39]
9.2 UMEC/VI 125/25	1		Mean Difference (Random, 95% CI)	0.28 [0.24, 0.32]
9.3 UMEC/VI 62.5/25	1		Mean Difference (Random, 95% CI)	0.22 [0.18, 0.27]
9.4 TIO/OLO 2.5/5	2		Mean Difference (Random, 95% CI)	0.29 [0.27, 0.32]
9.5 TIO/OLO 5/5	2		Mean Difference (Random, 95% CI)	0.33 [0.30, 0.35]
9.6 ACLID/FORM 200/6	1		Mean Difference (Random, 95% CI)	0.25 [0.13, 0.37]
9.7 ACLID/FORM 200/12	1		Mean Difference (Random, 95% CI)	0.31 [0.20, 0.43]
9.8 ACLID/FORM 200/18	1		Mean Difference (Random, 95% CI)	0.31 [0.19, 0.42]
10 AEs	17	8235	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.04]
10.1 IND/GLY 110/50	6	2830	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.07]
10.2 TIO/OLO 2.5/5	4	1011	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.11]
10.3 TIO/OLO 5/5	4	1021	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.01]
10.4 UMEC/VI 62.5/25	5	1921	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.88, 1.29]
10.5 UMEC/VI 125/25	4	1401	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.86, 1.34]
10.6 UMEC/VI 500/25	1	51	Odds Ratio (M-H, Random, 95% CI)	2.84 [0.32, 25.36]
11 Difference vs placebo in trough FEV1 - pooled adjusted and EOT analyses	18		Mean Difference (Random, 95% CI)	0.20 [0.19, 0.21]
11.1 IND/GLY 110/50	5		Mean Difference (Random, 95% CI)	0.22 [0.19, 0.26]
11.2 UMEC/VI 125/25	4		Mean Difference (Random, 95% CI)	0.22 [0.18, 0.26]
11.3 UMEC/VI 62.5/25	6		Mean Difference (Random, 95% CI)	0.18 [0.15, 0.22]
11.4 TIO/OLO 2.5/5	5		Mean Difference (Random, 95% CI)	0.18 [0.15, 0.20]
11.5 TIO/OLO 5/5	5		Mean Difference (Random, 95% CI)	0.20 [0.18, 0.21]
11.6 ACLID/FORM 200/6	1		Mean Difference (Random, 95% CI)	0.07 [-0.04, 0.18]
11.7 ACLID/FORM 200/12	1		Mean Difference (Random, 95% CI)	0.12 [0.01, 0.22]
11.8 ACLID/FORM 200/18	1		Mean Difference (Random, 95% CI)	0.08 [-0.04, 0.19]

Comparison 5. Sensitivity analysis - RoB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	14	7287	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [0.60, 4.50]
1.1 IND/GLY 110/50	4	1682	Odds Ratio (M-H, Fixed, 95% CI)	2.97 [0.47, 18.97]
1.2 TIO/OLO 2.5/5	6	1670	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [0.12, 53.43]
1.3 TIO/OLO 5/5	6	1689	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 UMEC/VI 62.5/25	3	1135	Odds Ratio (M-H, Fixed, 95% CI)	3.22 [0.38, 27.52]
1.5 UMEC/VI 125/25	3	1111	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.83]
2 SAEs	17	8448	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.86, 1.40]
2.1 IND/GLY 110/50	5	2020	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.79, 1.89]
2.2 TIO/OLO 2.5/5	6	1670	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.68]
2.3 TIO/OLO 5/5	6	1689	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.54, 1.91]
2.4 UMEC/VI 62.5/25	4	1531	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.75, 2.40]

2.5 UMEC/VI 125/25	3	1113	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.55, 1.66]
2.6 ACM/FOR 200/6	1	141	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.02, 12.96]
2.7 ACM/FOR 200/12	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.02, 13.07]
2.8 ACM/FOR 200/18	1	144	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.06, 22.41]
3 Time to first AECOPD	2		Hazard Ratio (Fixed, 95% CI)	0.44 [0.31, 0.63]
3.1 UMEC/VI 125/25	2		Hazard Ratio (Fixed, 95% CI)	0.44 [0.31, 0.63]
4 Difference vs placebo in adjusted SGRQ score (HRQoL)	5		Mean Difference (Fixed, 95% CI)	-4.12 [-4.99, -3.24]
4.1 IND/GLY 110/50	1		Mean Difference (Fixed, 95% CI)	-3.01 [-5.05, -0.97]
4.2 UMEC/VI 125/25	1		Mean Difference (Fixed, 95% CI)	-3.60 [-5.76, -1.44]
4.3 UMEC/VI 62.5/25	1		Mean Difference (Fixed, 95% CI)	-5.51 [-7.88, -3.14]
4.4 TIO/OLO 2.5/5	2		Mean Difference (Fixed, 95% CI)	-3.89 [-5.60, -2.17]
4.5 TIO/OLO 5/5	2		Mean Difference (Fixed, 95% CI)	-4.72 [-6.43, -3.01]
5 SGRQ responder analysis	5	3234	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.56, 2.10]
5.1 IND/GLY 110/50	1	706	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.98, 1.86]
5.2 TIO/OLO 2.5/5	2	579	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [1.30, 2.70]
5.3 TIO/OLO 5/5	2	578	Odds Ratio (M-H, Fixed, 95% CI)	2.35 [1.63, 3.40]
5.4 UMEC/VI 62.5/25	1	693	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [1.37, 2.59]
5.5 UMEC/VI 125/25	1	678	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [1.32, 2.54]
6 Difference vs placebo in adjusted trough FEV1 at EOT	10		Mean Difference (Fixed, 95% CI)	0.20 [0.19, 0.22]
6.1 IND/GLY 110/50	1		Mean Difference (Fixed, 95% CI)	0.28 [0.24, 0.32]
6.2 UMEC/VI 125/25	3		Mean Difference (Fixed, 95% CI)	0.22 [0.20, 0.25]
6.3 UMEC/VI 62.5/25	4		Mean Difference (Fixed, 95% CI)	0.20 [0.18, 0.22]
6.4 TIO/OLO 2.5/5	3		Mean Difference (Fixed, 95% CI)	0.18 [0.15, 0.20]
6.5 TIO/OLO 5/5	3		Mean Difference (Fixed, 95% CI)	0.21 [0.18, 0.23]
6.6 ACLID/FORM 200/6	1		Mean Difference (Fixed, 95% CI)	0.07 [-0.04, 0.18]
6.7 ACLID/FORM 200/12	1		Mean Difference (Fixed, 95% CI)	0.12 [0.01, 0.22]
6.8 ACLID/FORM 200/18	1		Mean Difference (Fixed, 95% CI)	0.08 [-0.04, 0.19]
7 Difference vs placebo in trough FEV1 at EOT	4		Mean Difference (Fixed, 95% CI)	0.18 [0.16, 0.20]
7.1 IND/GLY 110/50	2		Mean Difference (Fixed, 95% CI)	0.2 [0.17, 0.23]
7.2 TIO/OLO 2.5/5	2		Mean Difference (Fixed, 95% CI)	0.16 [0.13, 0.19]
7.3 TIO/OLO 5/5	2		Mean Difference (Fixed, 95% CI)	0.16 [0.13, 0.20]
8 Difference vs placebo in adjusted peak FEV1	7		Mean Difference (Fixed, 95% CI)	0.31 [0.29, 0.32]
8.1 IND/GLY 110/50	2		Mean Difference (Fixed, 95% CI)	0.35 [0.32, 0.38]
8.2 UMEC/VI 125/25	1		Mean Difference (Fixed, 95% CI)	0.28 [0.24, 0.32]
8.3 UMEC/VI 62.5/25	1		Mean Difference (Fixed, 95% CI)	0.22 [0.18, 0.27]
8.4 TIO/OLO 2.5/5	2		Mean Difference (Fixed, 95% CI)	0.29 [0.27, 0.32]
8.5 TIO/OLO 5/5	2		Mean Difference (Fixed, 95% CI)	0.33 [0.30, 0.35]
8.6 ACLID/FORM 200/6	1		Mean Difference (Fixed, 95% CI)	0.25 [0.13, 0.37]
8.7 ACLID/FORM 200/12	1		Mean Difference (Fixed, 95% CI)	0.31 [0.20, 0.43]
8.8 ACLID/FORM 200/18	1		Mean Difference (Fixed, 95% CI)	0.31 [0.19, 0.42]
9 AEs	11	5579	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.08]
9.1 IND/GLY 110/50	3	1301	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.70, 1.19]
9.2 TIO/OLO 2.5/5	4	1011	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.11]
9.3 TIO/OLO 5/5	4	1021	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.60, 1.01]
9.4 UMEC/VI 62.5/25	3	1135	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.89, 1.46]
9.5 UMEC/VI 125/25	3	1111	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.90, 1.48]