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Combined acclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD) (Review)

Ni H, Moe S, Soe Z, Myint KT, Viswanathan KN

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Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD011594.

DOI: [10.1002/14651858.CD011594.pub2](https://doi.org/10.1002/14651858.CD011594.pub2).

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**Combined acclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD)
(Review)**

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[Intervention Review]

Combined acclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD)

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Editorial group: Cochrane Airways Group.

Publication status and date: New, published in Issue 12, 2018.

Citation: Ni H, Moe S, Soe Z, Myint KT, Viswanathan KN. Combined acclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews* 2018, Issue 12. Art. No.: CD011594. DOI: [10.1002/14651858.CD011594.pub2](https://doi.org/10.1002/14651858.CD011594.pub2).

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ABSTRACT

Background

Several dual bronchodilator combinations of long-acting beta₂-agonist (LABA) and long-acting muscarinic antagonist (LAMA) have been approved for treatment of stable chronic obstructive pulmonary disease (COPD). The current GOLD (Global Initiative for Chronic Obstructive Lung Disease) recommendations suggest the use of LABA/LAMA combinations in people with group B COPD with persistent symptoms, group C COPD with further exacerbations on LAMA therapy alone and group D COPD with or without inhaled corticosteroids (ICS). Fixed-dose combination (FDC) of acclidinium/formoterol is one of the approved LABA/LAMA therapies for people with stable COPD.

Objectives

To assess the efficacy and safety of combined acclidinium bromide and long-acting beta₂-agonists in stable COPD.

Search methods

We searched the Cochrane Airways Group Specialised Register (CAGR), ClinicalTrials.gov, World Health Organization (WHO) trials portal, United States Food and Drug Administration (FDA) and manufacturers' websites as well as the reference list of published trials up to 12 October 2018.

Selection criteria

Parallel-group randomised controlled trials (RCTs) assessing combined acclidinium bromide and LABAs in people with stable COPD.

Data collection and analysis

We used standard methodological procedures expected by Cochrane for data collection and analysis. The primary outcomes were exacerbations requiring a short course of an oral steroid or antibiotic, or both; quality of life measured by a validated scale and non-fatal serious adverse events (SAEs). Where the outcome or study details were not reported, we contacted the study investigators or pharmaceutical company trial co-ordinators (or both) for missing data.

Main results

We identified RCTs comparing acclidinium/formoterol FDC versus acclidinium, formoterol or placebo only. We included seven multicentre trials of four to 52 weeks' duration conducted in outpatient settings. There were 5921 participants, whose mean age ranged from 60.7 to 64.7 years, mostly men with a mean smoking pack-years of 46.4 to 61.3 of which 43.9% to 63.4% were current smokers. They had a

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moderate-to-severe degree of COPD with a mean postbronchodilator forced expiratory volume in one second (FEV₁) between 50.5% and 61% of predicted normal and the baseline mean FEV₁ of 1.23 L to 1.43 L. We assessed performance and detection biases as low for all studies whereas selection, attrition and reporting biases were either low or unclear.

FDC versus acclidinium

There was no evidence of a difference between FDC and acclidinium for exacerbations requiring steroids or antibiotics, or both (OR 0.95, 95% CI 0.71 to 1.27; 2 trials, 2156 participants; moderate-certainty evidence); quality of life measured by St George's Respiratory Questionnaire (SGRQ) total score (MD -0.92, 95% CI -2.15 to 0.30); participants with significant improvement in SGRQ score (OR 1.17, 95% CI 0.97 to 1.41; 2 trials, 2002 participants; moderate-certainty evidence); non-fatal SAE (OR 1.19, 95% CI 0.79 to 1.80; 3 trials, 2473 participants; moderate-certainty evidence); hospital admissions due to severe exacerbations (OR 0.62, 95% CI 0.29 to 1.29; 2 trials, 2156 participants; moderate-certainty evidence) or adverse events (OR 0.95, 95% CI 0.76 to 1.18; 3 trials, 2473 participants; moderate-certainty evidence). Compared with acclidinium, FDC improved symptoms (Transitional Dyspnoea Index (TDI) focal score: MD 0.37, 95% CI 0.07 to 0.68; 2 trials, 2013 participants) with a higher chance of achieving a minimal clinically important difference (MCID) of at least one unit improvement (OR 1.34, 95% CI 1.11 to 1.62; high-certainty evidence); the number needed to treat for an additional beneficial outcome (NNTB) being 14 (95% CI 9 to 39).

FDC versus formoterol

When compared to formoterol, combination therapy reduced exacerbations requiring steroids or antibiotics, or both (OR 0.78, 95% CI 0.62 to 0.99; 3 trials, 2694 participants; high-certainty evidence); may decrease SGRQ total score (MD -1.88, 95% CI -3.10 to -0.65; 2 trials, 2002 participants; low-certainty evidence; MCID for SGRQ is 4 units); increased TDI focal score (MD 0.42, 95% CI 0.11 to 0.72; 2 trials, 2010 participants) with more participants attaining an MCID (OR 1.30, 95% CI 1.07 to 1.56; high-certainty evidence) and an NNTB of 16 (95% CI 10 to 60). FDC lowered the risk of adverse events compared to formoterol (OR 0.78, 95% CI 0.65 to 0.93; 5 trials, 3140 participants; high-certainty evidence; NNTB 22). However, there was no difference between FDC and formoterol for hospital admissions, all-cause mortality and non-fatal SAEs.

FDC versus placebo

Compared with placebo, FDC demonstrated no evidence of a difference in exacerbations requiring steroids or antibiotics, or both (OR 0.82, 95% CI 0.60 to 1.12; 2 trials, 1960 participants; moderate-certainty evidence) or hospital admissions due to severe exacerbations (OR 0.55, 95% CI 0.25 to 1.18; 2 trials, 1960 participants; moderate-certainty evidence), although estimates were uncertain. Quality of life measure by SGRQ total score was significantly better with FDC compared to placebo (MD -2.91, 95% CI -4.33 to -1.50; 2 trials, 1823 participants) resulting in a corresponding increase in SGRQ responders who achieved at least four units decrease in SGRQ total score (OR 1.72, 95% CI 1.39 to 2.13; high-certainty evidence) with an NNTB of 7 (95% CI 5 to 12). FDC also improved symptoms measured by TDI focal score (MD 1.32, 95% CI 0.96 to 1.69; 2 studies, 1832 participants) with more participants attaining at least one unit improvement in TDI focal score (OR 2.51, 95% CI 2.02 to 3.11; high-certainty evidence; NNTB 4). There were no differences in non-fatal SAEs, adverse events and all-cause mortality between FDC and placebo.

Combination therapy significantly improved trough FEV₁ compared to acclidinium, formoterol or placebo.

Authors' conclusions

FDC improved dyspnoea and lung function compared to acclidinium, formoterol or placebo, and this translated into an increase in the number of responders on combination treatment. Quality of life was better with combination compared to formoterol or placebo. There was no evidence of a difference between FDC and monotherapy or placebo for exacerbations, hospital admissions, mortality, non-fatal SAEs or adverse events. Studies reported a lower risk of moderate exacerbations and adverse events with FDC compared to formoterol; however, larger studies would yield a more precise estimate for these outcomes.

PLAIN LANGUAGE SUMMARY

Are combined acclidinium and long-acting beta₂-agonist inhalers effective and safe for people with stable COPD?

Background

Chronic obstructive pulmonary disease (COPD) is a disease of the lungs that causes airways to narrow. As a result, people with COPD experience symptoms of breathlessness and cough with sputum production which worsen over time. It is mainly caused by smoking or inhaling dust. In people with COPD, inhalers that contain medicines to widen the airways are generally given to relieve symptoms. Long-acting medicines whose action lasts for at least half a day or one day are preferred. Acclidinium and formoterol (a long-acting beta₂-agonist medicine) are such inhalers. We wanted to find out how a combination of acclidinium and long-acting beta₂-agonist fare against either inhaler alone and dummy (placebo) inhaler.

Study characteristics

We could only identify studies on acclidinium and formoterol combination and included seven studies involving 5921 people with COPD which ranged from four weeks to one year long. Most participants were men in their 60s, moderate-to-heavy smokers, around half of whom were current smokers. They had moderate-to-severe symptoms of COPD when they started treatment. People in the studies took either combined inhalers containing acclidinium and formoterol or acclidinium or formoterol or placebo through a similar inhaler. Both people doing the research and people in the study did not know which treatment participants were getting. The conclusions of this review are current to October 2018.

Key results

People taking combined inhaler and acclidinium inhaler were not different in terms of flare-ups that need additional medicines, quality of life, hospitalisations, side effects or serious side effects. However, they were less breathless than those taking acclidinium inhaler. Fourteen people with COPD would need to be treated with combined inhalers to have one additional person with a clinically significant improvement in breathlessness.

People on combined inhalers were likely to have fewer flare-ups, side effects and symptoms and a better quality of life compared to those taking formoterol inhaler. But, there was little or no difference in hospital admissions due to severe flare-ups, serious side effects or the risk of dying.

When compared to dummy inhalers, people taking combined inhalers experienced less breathlessness and better quality of life. Seven people with COPD would need to be treated with combined inhaler to achieve a significant improvement in quality of life than dummy inhaler. For flare-ups, hospital admissions, side effects, serious side effects and death, there was no difference between combined and dummy inhalers.

The lungs worked better in people taking combined inhalers than those taking only one drug or dummy inhaler.

Quality of the evidence

We had to interpret the results carefully as all the included studies were sponsored by pharmaceutical companies, which could have led to bias. However, the included studies were generally conducted in a systematic and acceptable manner. We are confident that combined inhalers are more effective than single or dummy inhalers at improving breathlessness and lung function. However, we are less certain about its effects on flare-ups, hospital admissions, quality of life and side effects.

Conclusion

Combined inhalers are more effective than individual or dummy inhalers for relieving breathlessness and improving lung performance. They also lead to better quality of life than formoterol or dummy inhalers. However, they are not different from individual or dummy inhalers in terms of flare-ups or hospital admissions. These combined inhalers have similar safety profiles as individual or dummy inhalers in terms of death, side effects or serious side effects. Combined inhalers probably had lesser side effects and moderate flare-ups than formoterol, but further studies are needed to confidently support this finding. In summary, the combined inhalers are an effective option for treatment of COPD and appear to have a similar safety profile to individual or dummy inhalers.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Fixed-dose combination acclidinium/formoterol compared to acclidinium alone for chronic obstructive pulmonary disease (COPD)

Fixed-dose combination acclidinium/formoterol compared to acclidinium for chronic obstructive pulmonary disease (COPD)

Patient or population: people with COPD
Setting: community
Intervention: FDC acclidinium/formoterol
Comparison: acclidinium

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with acclidinium	Risk with FDC acclidinium/formoterol				
Exacerbations requiring steroids or antibiotics or both: number of participants Follow-up: 24 weeks	105 per 1000	101 per 1000 (77 to 130)	OR 0.95 (0.71 to 1.27)	2156 (2 RCTs)	⊕⊕⊕⊖ Moderate^a	—
Quality of life: number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score Follow-up: 24 weeks	541 per 1000	579 per 1000 (533 to 624)	OR 1.17 (0.97 to 1.41)	2002 (2 RCTs)	⊕⊕⊕⊖ Moderate^a	The mean quality of life: change from baseline in SGRQ total score was 0.92 lower (2.15 lower to 0.3 higher) in FDC group (2002 participants, 2 RCTs)
Non-fatal serious adverse events Follow-up: 4–24 weeks	41 per 1000	49 per 1000 (33 to 72)	OR 1.19 (0.79 to 1.80)	2473 (3 RCTs)	⊕⊕⊕⊖ Moderate^a	—
Hospital admissions due to exacerbations: number of participants Follow-up: 24 weeks	18 per 1000	11 per 1000 (5 to 23)	OR 0.62 (0.29 to 1.29)	2156 (2 RCTs)	⊕⊕⊕⊖ Moderate^a	—
Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit) Follow-up: 24 weeks	557 per 1000	627 per 1000 (582 to 671)	OR 1.34 (1.11 to 1.62)	2013 (2 RCTs)	⊕⊕⊕⊕ High	The mean improvement in symptoms: change from baseline in TDI focal score was 0.37 higher (0.07 higher to 0.68 higher) in

FDC group (2013 participants, 2 RCTs).

Change in lung function: from baseline in trough FEV₁ (L) Follow-up: 4–24 weeks	Mean change from baseline in trough FEV ₁ (L) across aclidinium group ranged from – 0.017 to 0.066	Mean change from baseline in trough FEV ₁ (L) in the FDC group was 0.02 higher (0 to 0.04 higher)	—	2333 (3 RCTs)	⊕⊕⊕⊕ High	—
Adverse events (not including serious adverse events): number of participants Follow-up: 4–24 weeks	194 per 1000	186 per 1000 (155 to 221)	OR 0.95 (0.76 to 1.18)	2473 (3 RCTs)	⊕⊕⊕⊖ Moderate^a	—

*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).

CI: confidence interval; **COPD:** chronic obstructive pulmonary disease; **FDC:** fixed-dose combination; **FEV₁:** forced expiratory volume in 1 second; **OR:** odds ratio; **RCT:** randomised controlled trial; **SGRQ:** St George's Respiratory Questionnaire; **TDI:** Transitional Dyspnoea Index.

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.

^aDowngraded one level for serious imprecision: the CIs included a potential for appreciable benefit or harm.

Summary of findings 2. Fixed-dose combination aclidinium/formoterol compared to formoterol for chronic obstructive pulmonary disease (COPD)

Fixed-dose combination aclidinium/ formoterol compared to formoterol for chronic obstructive pulmonary disease (COPD)

Patient or population: people with COPD

Setting: community

Intervention: FDC aclidinium/formoterol

Comparison: formoterol

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with formoterol	Risk with FDC aclidinium/formoterol				
Exacerbations requiring steroids or antibiotics or both: number of participants Follow-up: 24 weeks	154 per 1000	124 per 1000 (101 to 152)	OR 0.78 (0.62 to 0.99)	2694 (3 RCTs)	⊕⊕⊕⊕ High	—
Quality of life: number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score Follow-up: 24 weeks	524 per 1000	559 per 1000 (495 to 623)	OR 1.15 (0.89 to 1.50)	1000 (1 RCT)	⊕⊕⊕⊖ Low ^{a,b}	The mean quality of life: change from baseline in SGRQ total score was 1.88 lower (3.1 lower to 0.65 lower) in FDC group (2002 participants, 2 RCTs).
Non-fatal serious adverse events Follow-up: 4–52 weeks	50 per 1000	58 per 1000 (42 to 79)	OR 1.15 (0.82 to 1.61)	3140 (5 RCTs)	⊕⊕⊕⊖ Moderate ^a	—
Hospital admissions due to exacerbations: number of participants Follow-up: 24–52 weeks	27 per 1000	20 per 1000 (12 to 34)	OR 0.76 (0.45 to 1.28)	2694 (3 RCTs)	⊕⊕⊕⊖ Moderate ^a	—
Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit) Follow-up: 24 weeks	565 per 1000	628 per 1000 (582 to 670)	OR 1.30 (1.07 to 1.56)	2010 (2 RCTs)	⊕⊕⊕⊕ High	The mean improvement in symptoms: change from baseline in TDI focal score was 0.42 higher (0.11 higher to 0.72 higher) in FDC group (2010 participants, 2 RCTs).
Change in lung function: from baseline in trough FEV₁ (L) Follow-up: 4–24 weeks	Mean change from baseline in trough FEV ₁ (L) across formoterol group ranged from – 0.002 to 0.118	Mean change from baseline in trough FEV ₁ (L) in the FDC group was 0.04 higher (0.03 higher to 0.06 higher)	—	2411 (4 RCTs)	⊕⊕⊕⊕ High	—
Adverse events (not including serious adverse events): number of participants Follow-up: 4–52 weeks	271 per 1000	225 per 1000 (195 to 257)	OR 0.78 (0.65 to 0.93)	3140 (5 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).

CI: confidence interval; **COPD:** chronic obstructive pulmonary disease; **FDC:** fixed-dose combination; **FEV₁:** forced expiratory volume in 1 second; **OR:** odds ratio; **RCT:** randomised controlled trial; **SGRQ:** St George's Respiratory Questionnaire; **TDI:** Transitional Dyspnoea Index.

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.

^aDowngraded one level for serious imprecision: CIs included a potential for appreciable benefit or harm.

^bDowngraded one level as [ACLIFORM COPD](#) did not report the SGRQ responders for formoterol arm in the published articles.

Summary of findings 3. Fixed-dose combination acclidinium/formoterol compared to placebo for chronic obstructive pulmonary disease (COPD)

Fixed dose combination acclidinium/formoterol compared to placebo for chronic obstructive pulmonary disease (COPD)

Patient or population: people with chronic obstructive pulmonary disease (COPD)

Setting: community

Intervention: FDC acclidinium/formoterol

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with FDC acclidinium/formoterol				
Exacerbations requiring steroids or antibiotics or both: number of participants Follow-up: 24 weeks	129 per 1000	109 per 1000 (82 to 143)	OR 0.82 (0.60 to 1.12)	1960 (2 RCTs)	⊕⊕⊕⊖ Moderate^a	—
Quality of life: number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score Follow-up: 24 weeks	433 per 1000	568 per 1000 (515 to 619)	OR 1.72 (1.39 to 2.13)	1823 (2 RCTs)	⊕⊕⊕⊕ High	The mean quality of life: change from baseline in SGRQ total score was 2.91 lower (4.33 lower to 1.5 lower) in FDC group (1823 participants, 2 RCTs).
Non-fatal serious adverse events Follow-up: 4–24 weeks	38 per 1000	42 per 1000 (27 to 64)	OR 1.12 (0.72 to 1.74)	2527 (4 RCTs)	⊕⊕⊕⊖ Moderate^a	—

Hospital admissions due to exacerbations: number of participants Follow-up: 24 weeks	21 per 1000	12 per 1000 (5 to 25)	OR 0.55 (0.25 to 1.18)	1960 (2 RCTs)	⊕⊕⊕⊖ Moderate^a	—
Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit) Follow-up: 24 weeks	394 per 1000	620 per 1000 (568 to 669)	OR 2.51 (2.02 to 3.11)	1832 (2 RCTs)	⊕⊕⊕⊕ High	The mean improvement in symptoms: change from baseline in TDI focal score was 1.32 higher (0.96 higher to 1.69 higher) in FDC group (1832 participants, 2 RCTs).
Change in lung function: from baseline in trough FEV₁ (L) Follow-up: 4–24 weeks	Mean change from baseline in trough FEV ₁ (L) across placebo group ranged from –0.061 to –0.031	Mean change from baseline in trough FEV ₁ (L) in the FDC group was 0.12 higher (0.10 higher to 0.14 higher)	—	2137 (3 RCTs)	⊕⊕⊕⊕ High	—
Adverse events (not including serious adverse events): number of participants Follow-up: 4–24 weeks	175 per 1000	171 per 1000 (139 to 206)	OR 0.97 (0.76 to 1.22)	2527 (4 RCTs)	⊕⊕⊕⊖ Moderate^a	—

***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).

CI: confidence interval; **COPD:** chronic obstructive pulmonary disease; **FDC:** fixed-dose combination; **FEV₁:** forced expiratory volume in 1 second; **OR:** odds ratio; **RCT:** randomised controlled trial; **SGRQ:** St George's Respiratory Questionnaire; **TDI:** Transitional Dyspnoea Index.

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.

^aDowngraded one level for serious imprecision: the CIs included a potential for appreciable benefit or harm.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is characterised by slowly progressive airflow limitation that is not fully reversible and is associated with enhanced inflammatory response of the airways and destruction of lung parenchyma (Barnes 2000; Criner 2015; GOLD 2018). It is the fourth leading cause of death in Canada and the third in the US, with 12.7 million adults in the US estimated to have COPD in 2011 (Criner 2015). As the result of continued exposure to smoking and environmental pollution, COPD is projected to become the third leading cause of death worldwide by 2020 (Chapman 2006; GOLD 2018; Raherison 2009). Well-described COPD prevalence of approximately 15% among smokers is considered to be an underestimate caused by underdiagnosis (Rennard 2006), and is noted to be as high as 50% among heavy smokers according to current criteria (Mannino 2007). Active smoking remains the major risk factor for COPD, posing a serious health threat to more than 1.1 billion smokers worldwide (Bauer 2013). However, non-smokers are also affected by COPD, with a prevalence of 3% to 11% reported among never-smokers (GOLD 2018). In one population-based study of lifelong never-smokers, risk of COPD was independently associated with passive smoking or environmental tobacco smoke (Hagstad 2014). Other factors such as exposure to biomass fuels and indoor air pollution are important causes of COPD in low- to middle-income countries (Bruce 2000; Rivera 2008).

The chronic airflow limitation in COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) (GOLD 2018). Destruction of alveoli and lung parenchyma by inflammatory infiltrates results in enlargement of air spaces, thus reducing the elastic pressure that generates expiratory flow (Cosio 2009; GOLD 2018). Onset of symptoms usually occurs when forced expiratory volume in one second (FEV₁) has fallen to approximately 50% of predicted normal value (Sutherland 2004).

Exacerbations of COPD are a major cause of morbidity and mortality; an exacerbation is defined as "an acute event characterised by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication" (GOLD 2018). Respiratory viral and bacterial infections mainly precipitate exacerbations, which are associated with worsened quality of life, increased healthcare costs, accelerated decline in lung function and reduced survival (Bauer 2013; Marchetti 2013; Mullerova 2015). Exacerbations may occur at any stage of COPD; however, the frequency of exacerbations correlates with the severity of airflow limitation, with a mean rate of 1.34 events/year in people with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 3 disease and 2.00 events/year in people with GOLD stage 4 disease (Marchetti 2013). One three-year prospective observational study including 2138 participants reported severe exacerbations requiring hospital admission in about 30% of participants, causing a substantial economic burden (Mullerova 2015). The long-term prognosis of people with exacerbation-related hospitalisations is poor, with mortality rates of 26% at two years and 55% at five years (Marchetti 2013; Mullerova 2015).

The major goals of treatment in stable COPD are to relieve symptoms, reduce exacerbations, and improve quality of life and

exercise tolerance (ATS/ERS 2011; GOLD 2018; Sutherland 2004; TSANZ 2018). Bronchodilators are the cornerstone for symptomatic treatment of stable COPD (Tashkin 2004); inhaled long-acting bronchodilators (both beta₂-agonists and anticholinergics) are more effective than short-acting bronchodilators in sustaining symptom relief (GOLD 2018). Some evidence suggests that early initiation of long-acting bronchodilator therapy in mild-to-moderate cases of stable COPD may impact lung function decline and health-related quality of life (HRQoL) (Welte 2015). However, inhaled corticosteroids (ICSs) in early disease have no impact on lung function (Welte 2015), and long-term monotherapy is not recommended for stable COPD (GOLD 2018). ICSs are indicated as long-term therapy only for people with severe-to-very severe airflow limitation who experience frequent exacerbations despite using long-acting bronchodilators (GOLD 2018; TSANZ 2018). Current guidelines recommend combination therapy of inhaled long-acting beta₂-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) as an alternative choice for people with moderate-to-severe stable COPD if no symptomatic improvement is seen with use of a single agent (GOLD 2018). As the result of complementary and independent mechanisms for bronchodilation, combined LAMA/LABA therapy provides significantly greater improvement in lung function compared with LAMA or LABA monotherapy in people with moderate-to-severe COPD (Cazzola 2010; Tashkin 2008; van der Molen 2012); however, impact on patient-reported outcomes is limited (GOLD 2018).

Description of the intervention

Acclidinium bromide

Acclidinium bromide is a long-acting anticholinergic that blocks the action of the neurotransmitter acetylcholine. It has potent antagonistic effects on all muscarinic acetylcholine receptor subtypes (M1 to M5) (Ulrik 2012); however, only M2 and M3 subtypes are present on airway smooth muscles (Moulton 2011). Acetylcholine-induced bronchoconstriction is mediated mainly by M3 receptors and indirectly by M2 receptors, which prevent beta₂-adrenergic receptor-mediated bronchial relaxation through inhibition of adenylate cyclase (Moulton 2011). M2 receptors also mediate feedback inhibition of acetylcholine release at the cholinergic nerve endings (Karakiulakis 2012; Sims 2011). Acclidinium dissociates more slowly from the M3 receptor than from the M2 receptor because of its approximately six-fold kinetic selectivity for the M3 compared with the M2 subtype, leading to more effective bronchodilator action with lesser M2-mediated cardiac adverse effects (Maltais 2012; Sims 2011).

Acclidinium has been approved as twice-daily maintenance therapy in stable COPD (FDA 2012). In one Cochrane Review (Ni 2014), acclidinium reduced the number of participants with exacerbation-related hospitalisations compared with placebo (odds ratio (OR) 0.64, 95% confidence interval (CI) 0.46 to 0.88). Within the same review, acclidinium was also associated with significant benefit over placebo in HRQoL, breathlessness and lung function indices. Acclidinium produced no significant reduction in exacerbations requiring a short course of an oral steroid or antibiotic, or both. However, there was no strong evidence to support the superiority of acclidinium over the current standard of care, tiotropium or LABAs (Ni 2014).

Long-acting beta₂-agonists

Inhaled LABAs are widely used as maintenance therapy for people with COPD with moderate-to-severe airflow limitation and as an alternative therapy for people with mild disease (GOLD 2018). Twice-daily salmeterol and formoterol have been in clinical use since the late 1990s, and once-daily preparations of LABAs with an even longer duration of action have become available to improve adherence (Zafar 2014). Indacaterol is the first once-daily LABA approved for clinical use by the US Food and Drug Administration (FDA) and it was approved in July 2011 (FDA 2011). This was followed by approvals of combined preparations of once-daily LABA with ICS or LAMA. The FDA-approved the vilanterol-fluticasone furoate combination in May 2013 (FDA 2013a), and the vilanterol-umeclidinium combination in December 2013 (FDA 2013b), as once-daily, long-term maintenance treatment of people with stable COPD.

Beta₂-receptors are located mainly in bronchial smooth muscle, while beta₁-receptors are situated predominantly in the heart. However, beta₂-receptors in the heart account for approximately 10% to 50% of the total beta-receptors of the heart, and this results in the likelihood of cardiac adverse effects, even with highly selective beta₂-agonists (Karner 2012). All inhaled beta₂-agonists cause bronchodilation through a cascade of reactions by activating beta₂-receptors on airway smooth muscle cells, which vary in exact mechanisms of action among different LABAs (Kew 2013). Formoterol is a rapidly acting highly selective LABA with minimal affinity for beta₁- and alpha-adrenergic receptors that causes bronchial relaxation by progressively leaking out from a cell membrane depot to interact with the active site of the beta₂-receptor (Berger 2008; Johnson 1998). Salmeterol has a slower onset of action than formoterol, whereby the side chain of salmeterol binds with the beta₂-adrenoceptor, but the head continually engages and disengages the active site of the receptor (Johnson 1998; Karner 2012). Indacaterol has a very quick onset of action of less than five minutes (Zafar 2014), and its affinity to lipid domains within the membrane is greater than that of salmeterol, resulting in its longer duration of action (Beier 2011; Karner 2012). One short-term unblinded exploratory study found that indacaterol produced significantly greater improvement in inspiratory capacity (Beier 2009).

Current guidelines advocate LABAs as first-line therapy for people with stable COPD, as they reduce exacerbations including those requiring hospitalisations, while improving quality of life and lung function (Kew 2013). Addition of regular ICS therapy is recommended only for people with frequent exacerbations (GOLD 2018; Spencer 2011). Combined therapy of LABA/ICS in one inhaler is associated with a reduction in exacerbations compared with placebo, LABA alone or ICS alone; however, it increases the risk of pneumonia (Nannini 2012; Nannini 2013a; Nannini 2013b). LABAs have similar efficacy compared with tiotropium for symptom improvement (Appleton 2006; Chong 2012).

Reported adverse effects of LABAs include cardiac events such as arrhythmias, heart failure and acute coronary syndrome; tremors; cough; dry mouth and headache (Berger 2008; Gershon 2013), as well as possibly increased risk of cardiovascular death, especially among people with asthma (Hanania 2013). However, there is no strong evidence indicating significant differences in mortality or

cardiovascular complications between salmeterol or formoterol and placebo in people with COPD (Ferguson 2003; Rodrigo 2008).

How the intervention might work

LABAs and acclidinium result in bronchial smooth muscle relaxation through two different pathways: sympathetic (LABA) and parasympathetic (acclidinium) systems. It is postulated that the activity of the sympathetic system is more prominent in the daytime, whereas the parasympathetic system plays a more important role during the night (Cazzola 2010). A combination of these two medications has the potential to maximise bronchodilation and overcome interpatient and inpatient variability of bronchomotor tone associated with COPD (Cazzola 2010; de Miguel-Diez 2014; Tashkin 2013). Cross-activity of acetylcholine on the sympathetic system and of adrenergic catecholamines on the parasympathetic system has been reported in preclinical models (Matera 2014). Acetylcholine-mediated bronchoconstriction is known to occur primarily via muscarinic receptors of the M3 subtype and is also regulated by prejunctional beta₂-adrenoceptors (Tashkin 2013). Similarly, a beta-receptor-mediated increase in cyclic adenosine monophosphate (cAMP) causing bronchial smooth muscle relaxation is also affected by M2 receptors that functionally oppose by coupling with adenylate cyclase via an inhibitory G protein (Matera 2014).

When LABA/LAMA combined therapy is used, bronchodilation is attained both directly and indirectly. Combining a LABA with acclidinium amplifies the action of acclidinium via modulation of cholinergic neurotransmission by prejunctional beta₂-adrenoceptors, in addition to its direct stimulation of smooth muscle beta₂-adrenoceptors (Cazzola 2013; van der Molen 2012). Likewise, acclidinium augments beta₂-agonist-stimulated bronchial relaxation by decreasing the bronchoconstrictor effects of acetylcholine (Tashkin 2013). Thus, combined acclidinium bromide and LABA is expected to produce more effective bronchodilation than is produced by the individual components alone.

Why it is important to do this review

GOLD 2018 suggests the use of LAMA/LABA dual therapy as a treatment alternative for people in GOLD groups B (high symptoms/low risk), C (low symptoms/high risk) and D (high symptoms/high risk). Data from trials on LABA/LAMA combination therapies using a well-established LAMA, tiotropium, demonstrated greater improvement in patient-centred outcomes such as dyspnoea, symptoms, rescue medication use and HRQoL than is seen with individual drugs alone (van der Molen 2012). One Cochrane Review reported a slight clinically insignificant improvement in HRQoL with combined LABA and tiotropium compared with tiotropium alone in people with moderate-to-severe COPD (Karner 2012).

Acclidinium was approved in 2012 for use in people with moderate-to-severe COPD; a considerable number of randomised controlled trials (RCTs) have looked at the benefits and risks of combined acclidinium bromide and LABA compared with placebo or individual inhaled therapies. However, for patients or for clinicians facing patients, the question of how effective and safe this combination is remains unanswered, thus we aimed to fill this gap in evidence by conducting this review.

OBJECTIVES

To assess the efficacy and safety of combined acclidinium bromide and long-acting beta₂-agonists in stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs of parallel-group design. We included both open-label and blinded trials. We excluded cross-over and cluster-randomised trials.

Types of participants

We included adults over 18 years of age with a diagnosis of COPD according to the criteria of GOLD ([GOLD 2018](#)), the American Thoracic Society (ATS), the European Respiratory Society (ERS) ([ATS/ERS 2011](#)), the Thoracic Society of Australia and New Zealand (TSANZ) ([TSANZ 2018](#)), the UK National Institute for Health and Care Excellence ([NICE 2010](#)), or the World Health Organization ([WHO](#)). Participants had evidence of airway obstruction (postbronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) ratio less than 70%) with symptoms of dyspnoea, chronic cough or sputum production with or without a history of smoking. We excluded studies that enrolled participants with bronchial asthma, bronchiectasis, cystic fibrosis or other chronic lung diseases.

Types of interventions

We included trials comparing acclidinium bromide/LABA versus placebo, acclidinium bromide, LABA or LAMA. LABA and LAMA must have been part of the randomly assigned treatments in the included studies. The minimum duration of trials was four weeks. We planned to study the following comparisons.

- Acclidinium bromide/LABA free combination in separate inhalers:
  - * versus acclidinium bromide;
  - * versus the same LABA;
  - * versus LAMA; or
  - * versus placebo.
- Acclidinium bromide/LABA fixed-dose combination (FDC) in one inhaler:
  - * versus acclidinium bromide;
  - * versus the same LABA;
  - * versus LAMA; or
  - * versus placebo.

We included the following cointerventions provided they are not part of the randomised treatment: salbutamol or albuterol as rescue medication, oral sustained-release theophylline, ICSs or systemic corticosteroids (oral or parenteral) at stable doses and oxygen therapy of less than 15 hours/day.

Types of outcome measures

Primary outcomes

- Exacerbations requiring a short course of an oral steroid or antibiotic, or both.

- Quality of life as measured by a validated scale, St George's Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Disease Questionnaire (CRQ).
- Non-fatal serious adverse events (SAE) such as any adverse event that is life-threatening or places the participant at immediate risk of death; requires in-patient hospitalisation or prolongs hospitalisation; causes persistent or significant disability/incapacity (i.e. a substantial disruption in an individual's ability to conduct normal life functions); results in congenital anomalies or birth defects; or other medically important conditions which investigators judge to represent significant hazards

Secondary outcomes

- Mortality (all-cause and respiratory).
- Hospital admissions due to exacerbations.
- Improvement in symptoms as measured by the Transitional Dyspnoea Index (TDI).
- Change in lung function.
- Adverse events not including SAEs.

Reporting in the trial of one of more of the outcomes listed here was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Trials Register up to 12 October 2018 with no restrictions on language or type of publication. The Cochrane Airways Trials Register is maintained by the information specialist for Cochrane Airways and contains studies identified from the following sources:

- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS);
- weekly searches of MEDLINE Ovid;
- weekly searches of Embase Ovid;
- monthly searches of PsycINFO Ovid;
- monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
- monthly searches of AMED EBSCO (Allied and Complementary Medicine);
- handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are 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 also conducted a search of [www.ClinicalTrials.gov](#) ([Appendix 3](#)) and the WHO trials portal ([WHO ICTRP](#)) up to 12 October 2018.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites ([Forest Pharmaceuticals](#), [Almirall](#), and [AstraZeneca](#)) and the US FDA website ([FDA](#)) for trial information. We also searched

for errata or retractions from included studies published as full-text articles on [PubMed](#) and reported within the review the date this was done. We planned to translate trials published in a language other than English. The date of the last search was 12 October 2018.

Data collection and analysis

Selection of studies

Two review authors (HN and KTM) independently screened titles and abstracts for inclusion of all potential studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve.' Two review authors (SM and KTM) independently screened the full-text articles, identified studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion, or, if required, we consulted a third review author (ZS). 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 a [Characteristics of excluded studies](#) table.

Data extraction and management

We used a data collection form that was piloted on at least one study in the review to document study characteristics and outcome data. One review author (SM) extracted the following characteristics from included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals and date of study.
- Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected and time points reported.
- Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (HN and KTM) independently extracted outcome data from included studies. 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 consultation with a third review author (KNV). One review author (HN) transferred data into Review Manager 5 ([Review Manager 2014](#)). We double-checked that data were entered correctly by comparing the data presented in the systematic review versus those provided in the study reports. A second review author (KTM) spot-checked study characteristics for accuracy against those provided in the trial report.

Assessment of risk of bias in included studies

Two review authors (HN and SM) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved disagreements by discussion or by consultation with another review author (ZS). We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- 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 risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale). When 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 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 the published protocol and reported 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 (OR), and continuous data as mean differences (MD) if studies used the same measurement scale or standardised mean differences (SMD) if studies used different scale measurements, with 95% confidence intervals (CI). We entered data presented as a scale with a consistent direction of effect. We applied Peto OR, with 95% CI for rare events.

We undertook meta-analyses only when this was meaningful (i.e. if 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. When multiple trial arms were reported in a single trial, we included only the relevant arms in the analysis and reported the other treatment arms in the [Characteristics of included studies](#) table. When 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 the number of participants instead of the number of events for outcomes that may have occurred more than once, such as exacerbations, hospital admissions and adverse events. For exacerbation rates, we planned to analyse the data as rate ratios, transformed them into log rate ratios and combined them across studies using the generic inverse variance method.

To prevent unit of analysis error In studies with multiple intervention arms, for dichotomous data, we divided up both the number of participants and the number of events according to the number of interventions in the study. For continuous data, we only divided the total number of participants and the means and

standard deviations remained unchanged. If we needed to combine groups, we summed both sample sizes and the numbers of people with events for dichotomous outcomes. For continuous outcomes, we used the formula described in Table 7.7a in Section 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* to combine means and standard deviations (Higgins 2011).

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as an abstract only). When this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by performing 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^2 greater than 50%), we reported this and explored possible causes by performing prespecified subgroup analysis.

Assessment of reporting biases

If we had been 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 random-effects model and performed a sensitivity analysis using a fixed-effect model. We applied a fixed-effect model if the I^2 statistic showed homogeneous results, and a random-effects model for data synthesis when there was significant heterogeneity (I^2 greater than 50%) that could not be explained by subgroup analyses.

We combined dichotomous outcome variables using a Mantel-Haenszel OR with 95% CIs. For continuous outcomes, we analysed data as MDs with 95% CIs. We calculated the number needed to treat for an additional beneficial outcome (NNTB) from the pooled OR and assumed control risk using the formula described in Section 12.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

'Summary of findings' tables

We created 'Summary of findings' tables using the following outcomes.

- Exacerbations requiring a short course of an oral steroid or antibiotic, or both.
- Quality of life.
- Non-fatal SAEs.
- Hospital admissions due to exacerbations.
- Improvement in symptoms.
- Change in lung function (trough FEV₁).
- Adverse events not including SAEs.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it related to the studies that contributed data to the meta-analyses for prespecified

outcomes. We applied 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 studies by using footnotes, and we made comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

- Dose of LABAs (e.g. formoterol 6 µg, formoterol 12 µg, formoterol 18 µg).
- Different LABAs (e.g. formoterol, salmeterol, indacaterol).
- Concurrent use of ICS (dichotomised as yes/no).

We planned to use the following outcomes in subgroup analyses.

- Exacerbations requiring a short course of an oral steroid or antibiotic, or both.
- Quality of life.
- Non-fatal SAEs.
- Improvement in symptoms.

We used the formal test for subgroup interactions provided in Review Manager 5 (Review Manager 2014).

Sensitivity analysis

We planned to carry out the following sensitivity analyses.

- Repeating the meta-analysis after exclusion of trials with high risk of bias or unclear methodological data.
- Performing the meta-analysis by using both a random-effects model and a fixed-effect model.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#) tables for detailed description.

Results of the search

We conducted the initial search of the Cochrane Airways Group Specialised Register of trials (CAGR) on 11 March 2015 and the search of other sources (www.clinicaltrials.gov; WHO ICTRP; Almirall) on 13 March 2015, 29 March 2015 and 1 April 2015, respectively with no restriction on language. Updated search was performed in August 2017 for CAGR and September 2017 for other sources. Since the aclidinium trials had been taken over by AstraZeneca, we searched their website (AstraZeneca) in 2017. A prepublication literature search update was done on 12 October 2018.

We identified 384 (132 plus 178 plus 74) records from the CAGR, 104 (89 plus 15) from WHO ICTRP, 43 (21 plus 22) from www.clinicaltrials.gov, 25 (two plus 23) from Almirall and AstraZeneca clinical trial registry, and one from a reference list. After removal of duplicates, we screened the titles and abstracts of 387 records for eligibility and excluded 323 reports as obviously irrelevant based on title and abstract. We thoroughly studied the remaining 64 references for further assessment, retrieving full-

text articles where applicable. From our search, we excluded 23 references for 13 studies with complete agreement between the review authors. Details of studies that failed to meet the inclusion criteria were recorded in the [Characteristics of excluded studies](#) table. We identified seven studies reported in 38 references that

were eligible for inclusion. There was one ongoing study with estimated completion date in 2018 ([AVANT](#)). We identified one study with two references that had completed recently with no published results for further classification ([AMPLIFY](#)). For details of the search results, see [Figure 1](#).

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

See [Table 1](#) for an overview of the included studies.

Study design, duration and setting

All the included trials were double-blind, randomised, parallel-group studies, assessing combined acclidinium bromide/formoterol as FDC in one inhaler. Four trials were active comparator (acclidinium/formoterol) and placebo controlled ([ACLIFORM COPD](#); [AUGMENT COPD](#); [D'Urzo 2017a](#); [Sliwinski 2010](#)), two trials compared FDC with formoterol ([Donohue 2016](#); [NCT00706914](#)), and one trial assessed FDC versus placebo ([ACTIVATE](#)). Four trials were phase three studies ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Donohue 2016](#); [D'Urzo 2017a](#)), two were phase two studies ([NCT00706914](#); [Sliwinski 2010](#)), and one was a phase four study ([ACTIVATE](#)). [D'Urzo 2017a](#) was the 28-week extension study of [AUGMENT COPD](#), in which the participants who agreed for this extension study were kept on the same treatment and placebo arms as in the primary study.

The total duration of studies ranged from four to 52 weeks, with a mean of 20.6 weeks. Four of the included trials were of long duration with two studies of 24 weeks ([ACLIFORM COPD](#); [AUGMENT COPD](#)), one study of 28 weeks ([D'Urzo 2017a](#)), and one study of 52 weeks ([Donohue 2016](#)). The remaining studies were of four weeks' ([NCT00706914](#); [Sliwinski 2010](#)) and eight weeks' duration ([ACTIVATE](#)).

Most of the studies were based in the US ([AUGMENT COPD](#); [D'Urzo 2017a](#); [Donohue 2016](#); [NCT00706914](#)), Canada ([ACTIVATE](#); [AUGMENT COPD](#); [D'Urzo 2017a](#)), Europe ([ACLIFORM COPD](#); [ACTIVATE](#); [Sliwinski 2010](#)), and Australia and New Zealand ([AUGMENT COPD](#); [Sliwinski 2010](#)). Other study locations were South Africa ([ACLIFORM COPD](#)), and Asian countries of South Korea ([ACLIFORM COPD](#)), and India, Malaysia and Taiwan ([Sliwinski 2010](#)).

Participants

The seven eligible studies randomised 5921 participants. [ACLIFORM COPD](#) was the largest trial with 1729 participants, while [NCT00706914](#) had the least number of participants with only 156. The number of participants of other studies ranged from 267 to 1692.

The participants men and women aged 40 years or older, who were current or former cigarette smokers with a smoking history of 10 or more pack-years and diagnosed with stable moderate-to-severe airway obstruction according to GOLD criteria (postbronchodilator FEV₁/FVC ratio less than 70% and FEV₁ 30% or greater but less than 80% of predicted normal value). The mean age of participants ranged from 60.7 to 64.7 years, with more men (3555) than women (2366). More than 90% of the participants were white in three studies ([ACLIFORM COPD](#); [AUGMENT COPD](#); [D'Urzo 2017a](#)); the

other studies did not specify the race of the participants. The percentage of current smokers ranged from 43.9% to 63.4%, with mean smoking of 46.4 pack-years to 61.3 pack-years. Participants had moderate-to-severe COPD according to GOLD criteria though [Sliwinski 2010](#) did not mention the specific criteria used for severity assessment. The participants' mean postbronchodilator FEV₁ was between 50.5% and 61% of predicted normal with their baseline mean FEV₁ ranging from 1.23 L to 1.43 L.

Interventions

All included trials assessed the efficacy and safety of combined acclidinium bromide/formoterol as FDC in one inhaler and we found no trials assessing the combination of acclidinium with other LABAs or in separate inhalers. The participants underwent a two-to three-week run-in period for disease stability and washout of disallowed medications in three trials ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Donohue 2016](#)), while the duration of run-in and screening period was 11 to 17 days in [ACTIVATE](#). Six trials had a treatment arm of FDC of acclidinium 400 µg plus formoterol 12 µg (FDC 400/12 µg) ([ACLIFORM COPD](#); [ACTIVATE](#); [AUGMENT COPD](#); [D'Urzo 2017a](#); [Donohue 2016](#); [NCT00706914](#)), and three studies assessed acclidinium/formoterol FDC 400/6 µg ([ACLIFORM COPD](#); [AUGMENT COPD](#); [D'Urzo 2017a](#)). Dose of acclidinium in FDC investigated in the initial phases of clinical development was 200 µg, which was later proved to be suboptimal ([Sliwinski 2010](#)).

Three main studies assessed two doses of FDC (400/6 µg, 400/12 µg) ([ACLIFORM COPD](#); [AUGMENT COPD](#); [D'Urzo 2017a](#)), and one study assessed three doses of FDC (200/6 µg, 200/12 µg, 200/18 µg) ([Sliwinski 2010](#)), in comparison to acclidinium monotherapy, formoterol monotherapy and placebo. [D'Urzo 2017a](#) was the extension of [AUGMENT COPD](#) in which consented participants who completed the primary study remained on the same intervention arm in a double-blind method for another 28 weeks. Two studies compared FDC 400/12 µg to formoterol ([Donohue 2016](#); [NCT00706914](#)), and one study compared FDC 400/12 µg versus placebo ([ACTIVATE](#)).

Three trials delivered FDC, acclidinium monotherapy, formoterol monotherapy and placebo twice daily via Genuair inhaler ([ACLIFORM COPD](#); [AUGMENT COPD](#); [D'Urzo 2017a](#)), and one trial delivered them once daily ([Sliwinski 2010](#)). One trial administered FDC 400/12 µg and formoterol 12 µg twice daily ([Donohue 2016](#)). One trial studied twice-daily FDC 400/12 µg versus placebo ([ACTIVATE](#)). One trial allocated participants into three arms, both intervention arms received FDC 200/12 µg once daily in the morning with placebo in the evening in one arm and formoterol in the evening in the other arm; along with the comparator arm of formoterol 12 µg twice daily, all delivered via Genuair inhaler ([NCT00706914](#)).

Concomitant medications

Five studies with full-text publications stated that participants were permitted to continue ICSs, oral or parenteral corticosteroids at doses equivalent to prednisolone of 10 mg/day or less or 20 mg every other day, oxygen therapy for less than 15 hours per day, provided treatment was stable for at least four weeks prescreening as well as the use of albuterol/salbutamol as rescue medication ([ACLIFORM COPD](#); [ACTIVATE](#); [AUGMENT COPD](#); [D'Urzo 2017a](#); [Donohue 2016](#)). Four trials permitted oral sustained-release methylxanthines ([ACLIFORM COPD](#); [AUGMENT COPD](#); [D'Urzo 2017a](#); [Donohue 2016](#)), though one trial prohibited it ([ACTIVATE](#)). Four trials did not permit any bronchodilator treatment other than the investigative and rescue medications ([ACTIVATE](#); [AUGMENT COPD](#); [D'Urzo 2017a](#); [Donohue 2016](#)). The remaining two studies were in abstract form and there was no detailed description with respect to concomitant medications ([NCT00706914](#); [Sliwinski 2010](#)).

Outcomes

The primary outcomes of the included studies and our review's primary outcomes were not the same since most of the individual trials assessed lung function as the primary outcome. Change from baseline in trough FEV₁ ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Donohue 2016](#); [Sliwinski 2010](#)) and one-hour postmorning dose FEV₁ ([ACLIFORM COPD](#); [AUGMENT COPD](#)) were the primary outcomes in individual trials which were analysed as secondary outcomes in our review. Other lung function parameters such as change from baseline in trough functional residual capacity ([ACTIVATE](#)), normalised FEV₁ area under the curve, peak FEV₁ ([Sliwinski 2010](#)) were also studied as primary outcomes whereas lung function tests with no further specification were the secondary outcomes for [NCT00706914](#).

Quality of life measured by the SGRQ total score, one of the primary outcomes of our review, was studied in the two pivotal trials as secondary outcome ([ACLIFORM COPD](#); [AUGMENT COPD](#)), and we analysed as both change from the baseline and percentage of

participants with at least four unit decrease (minimal clinically important difference).

The safety data on adverse events not including SAEs, non-fatal SAEs and mortality of all cause were studied as primary ([Donohue 2016](#); [D'Urzo 2017a](#)) and secondary outcomes ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Sliwinski 2010](#)), and well reported in the full-text publications as well as in the European Public Assessment Report (EPAR). Though it is unlikely that a 24-week study is long enough to demonstrate a clinically meaningful effect on exacerbations, necessary information regarding the number of participants with hospital admissions due to exacerbations and exacerbations who required a short course of oral steroids or antibiotics, or both were provided by the study sponsors. Improvement in symptoms measured in TDI score was studied as secondary outcome in [ACLIFORM COPD](#) and [AUGMENT COPD](#), reported in the respective publications. Data in the format required for the meta-analysis of some of the outcomes, especially SGRQ and TDI score, were kindly provided on request.

Funding

All studies were sponsored by Almirall (SA, Barcelona, Spain) and Forest Laboratories, Inc (New York, USA) or Menarini Group through its affiliate Berlin-Chemie and AstraZeneca.

Excluded studies

Thirteen trials did not meet our eligibility criteria, seven were of cross-over study design, four studied aclidinium bromide/formoterol fumarate combination with no comparator arm according to our review, one assessed the preference between Genuair and HandiHaler inhalers, and one was withdrawn prior to enrolment ([ASTUTE](#)) (see [Characteristics of excluded studies](#) table for details).

Risk of bias in included studies

Assessments of risk of bias in included studies are presented in detail in the [Characteristics of included studies](#) table and [Figure 2](#).

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ACLIFORM COPD	+	+	+	+	+	?	+
ACTIVATE	?	?	+	+	+	+	+
AUGMENT COPD	+	+	+	+	?	+	+
D'Urzo 2017a	+	+	+	+	?	+	+
Donohue 2016	+	+	+	+	?	+	+
NCT00706914	?	?	+	+	+	+	+
Sliwinski 2010	?	?	+	+	+	+	+

Allocation

The published article on [ACLIFORM COPD](#) mentioned allocation using a centralised interactive voice response system with stratification by smoking status (smoker or ex-smoker) in detail. The study concealed treatment identity with identical packaging/appearance and no odour or colour. [AUGMENT COPD](#) and its extension study [D'Urzo 2017a](#) generated randomisation codes by

statistical programming and implemented by an interactive web response system. [Donohue 2016](#) used a similar interactive web response system provided by Premier Research Group Limited (East Hartford, CT, USA) to assign patient identification numbers. Thus, the risk of bias for selection and allocation was low for these studies. However, the remaining trials were at unclear risk as they did not mention random sequence generation and allocation details ([ACTIVATE](#); [NCT00706914](#); [Sliwinski 2010](#)).

Blinding

All the included trials were double blind where investigators, participants and carers were unaware of the intervention received. Therefore, we judged these studies at low risk of bias. Investigators administered the study drugs in a double-blind pattern where neither the attending physician nor the participant knew which intervention arm a particular participant was in. Furthermore, the study medications were in identical packaging or of appearance and delivered by a similar inhaler device. All inhalers were identical from an external perspective where the only difference between them was that placebo did not contain active ingredient. The active ingredients had no perceptible taste, appearance, odour or colour that could unmask the blinding. Independent adjudication committee members who were not participating in the study and were blinded to treatment evaluated outcomes. For safety outcomes, blinded independent expert cardiologists not participating in the study performed the assessment of major adverse cardiac events (D'Urzo 2017a; Donohue 2016).

Incomplete outcome data

All included studies reported with reasons the total number of withdrawals for each study arm in full-text articles (ACLIFORM COPD; ACTIVATE; AUGMENT COPD; D'Urzo 2017a; Donohue 2016) or the study results from the clinicaltrials.gov (NCT00706914; Sliwinski 2010). The withdrawal rates were relatively low with similar reasons across the study arms in four trials (ACLIFORM COPD; ACTIVATE; NCT00706914; Sliwinski 2010), thus the risk of attrition bias for these studies was low. We assessed the attrition bias for the remaining three studies as unclear because the dropout rates were high even though they were relatively similar among the study arms (AUGMENT COPD; D'Urzo 2017a; Donohue 2016). All studies performed efficacy by intention to treat and safety analysis in the safety population, which was defined as all randomised participants who had received at least one dose of study medication.

Selective reporting

Both full-text publications and clinical study synopses described the results of all prespecified outcomes for all included studies, without obvious reporting bias. Moreover, trial result summaries for those started in late 2015 and beyond were available on the AstraZeneca website regardless of the positive or negative effects of the study medication which made reporting bias very unlikely. However, ACLIFORM COPD did not report data on the percentage of participants with clinically significant improvement in SGRQ total score of at least four units for FDC compared to formoterol in any of the published texts despite reporting the absolute change of SGRQ score for these arms, thus this study was at unclear risk of reporting bias.

Other potential sources of bias

Almirall funded the initial six trials (ACLIFORM COPD; AUGMENT COPD; D'Urzo 2017a; Donohue 2016; NCT00706914; Sliwinski 2010) and AstraZeneca sponsored the latest trial (ACTIVATE) following the agreement between Almirall and AstraZeneca on the transition of the Almirall respiratory studies. Study authors disclosed any possible conflicts of interest, both financial and non-financial, in the published articles, thus we detected no other possible sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Fixed-dose combination acclidinium/formoterol compared to acclidinium alone for chronic obstructive pulmonary disease (COPD); [Summary of findings 2](#) Fixed-dose combination acclidinium/formoterol compared to formoterol for chronic obstructive pulmonary disease (COPD); [Summary of findings 3](#) Fixed-dose combination acclidinium/formoterol compared to placebo for chronic obstructive pulmonary disease (COPD)

We only identified trials on combined acclidinium bromide and formoterol in FDC and included data from all studies except D'Urzo 2017a for quantitative synthesis (meta-analysis). We compared FDC of acclidinium bromide/formoterol versus acclidinium, formoterol and placebo. None of the seven studies were designed to enrol people with exacerbation-prone COPD. None of the included studies required participants to have at least two prior year exacerbations or at least one prior year hospitalisation. Therefore, there were no currently published studies of acclidinium/formoterol specifically designed or powered to look for benefits on COPD exacerbation endpoints for dual therapy versus monotherapy.

1. Fixed-dose combination acclidinium/formoterol versus acclidinium alone

Primary outcomes

Exacerbations requiring a short course of an oral steroid or antibiotic, or both

Analysis of 2156 participants from two trials found no evidence of a difference between FDC acclidinium/formoterol and acclidinium alone for the number of participants experiencing at least one exacerbation requiring a short course of oral steroids or antibiotics, or both over 24 weeks (OR 0.95, 95% CI 0.71 to 1.27; moderate-certainty evidence; [Analysis 1.1](#)) (ACLIFORM COPD; AUGMENT COPD). Published articles did not report this outcome, however, the sponsors provided the data necessary for this analysis. Subgroup analysis for the FDC doses of formoterol 12 µg (OR 0.91, 95% CI 0.60 to 1.39; 2 trials, 1080 participants) and 6 µg (OR 0.99, 95% CI 0.65 to 1.49; 2 trials, 1076 participants) demonstrated a similar result with no evidence of a difference between the subgroups (test for subgroup differences: $P = 0.80$).

Quality of life

Two trials studied quality of life as change from baseline in SGRQ total score as well as the number of participants who attained a minimal clinically significant reduction of at least four units (ACLIFORM COPD; AUGMENT COPD). From the meta-analysis of 2002 participants, there was no evidence of a difference in change from baseline of mean SGRQ total score with FDC acclidinium/formoterol compared to acclidinium alone (MD -0.92, 95% CI -2.15 to 0.30; [Analysis 1.2](#)). There was no evidence of a difference over acclidinium monotherapy for FDC doses using formoterol 12 µg (MD -0.77, 95% CI -2.51 to 0.96; 2 trials, 1004 participants) and 6 µg (MD -1.08, 95% CI -2.81 to 0.65; 2 trials, 998 participants) (test for subgroup differences: $P = 0.81$).

This translated into no evidence of a difference in the number of participants who achieved a minimal clinically important improvement of SGRQ total score reduction of at least four units over 24 weeks between FDC acclidinium/formoterol and acclidinium alone (OR 1.17, 95% CI 0.97 to 1.41; 2 trials, 2002 participants;

Analysis 1.3). In absolute terms, 579/1000 participants (95% CI 533/1000 to 624/1000) treated with FDC acclidinium/formoterol reported a clinically important improvement in quality of life while 541/1000 participants taking acclidinium alone experienced the same improvement (moderate-certainty evidence; [Summary of findings for the main comparison](#)). Neither of the FDC doses containing formoterol 12 µg (OR 1.12, 95% CI 0.86 to 1.45; 2 trials, 1004 participants) nor 6 µg (OR 1.22, 95% CI 0.93 to 1.59; 2 trials, 998 participants) demonstrated a significant improvement over acclidinium (test for subgroup differences: $P = 0.65$).

Non-fatal serious adverse events

The pooled analysis of data from three studies revealed no evidence of a difference in non-fatal SAEs between FDC acclidinium/formoterol and acclidinium alone groups (OR 1.19, 95% CI 0.79 to 1.80; 2473 participants; moderate-certainty evidence; [Analysis 1.4](#)) ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Sliwinski 2010](#)). In 1000 participants, 49 (95% CI 33 to 72) in the FDC acclidinium/formoterol group developed non-fatal SAEs compared to 41 in the acclidinium alone group ([Summary of findings for the main comparison](#)). Subgroup analysis showed no evidence of a difference between the FDC dose of formoterol 12 µg (OR 1.32, 95% CI 0.74 to 2.36; 3 trials, 1238 participants) and 6 µg (OR 1.07, 95% CI 0.60 to 1.92; 3 trials, 1235 participants) (test for subgroup differences: $P = 0.62$).

Secondary outcomes

Mortality

Three trials reported the total number of deaths. There were no deaths in either FDC acclidinium/formoterol and acclidinium alone arms in [Sliwinski 2010](#) during the four-week study period ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Sliwinski 2010](#)). The total number of deaths due to all causes was not significantly different between FDC acclidinium/formoterol-treated and acclidinium-treated participants (Peto OR 0.66, 95% CI 0.14 to 3.16; 3 trials, 2473 participants; [Analysis 1.5](#)).

Hospital admissions due to exacerbations

Meta-analysis of data from two studies demonstrated no evidence of a difference in the number of participants who required at

least one hospital admission due to severe exacerbations between FDC acclidinium/formoterol and acclidinium alone (OR 0.62, 95% CI 0.29 to 1.29; 2156 participants; moderate-certainty evidence; [Analysis 1.6](#)) ([ACLIFORM COPD](#); [AUGMENT COPD](#)). Neither FDC with formoterol 12 µg (OR 0.58, 95% CI 0.19 to 1.74; 2 trials, 1080 participants) nor FDC with formoterol 6 µg (OR 0.65, 95% CI 0.24 to 1.75; 2 trials, 1076 participants) were associated with a significant reduction in hospitalisations compared to acclidinium monotherapy (test for subgroup differences: $P = 0.88$). Among 1000 participants, 11 (95% CI 5 to 23) in the FDC acclidinium/formoterol group and 18 in the acclidinium alone group experienced at least one severe COPD exacerbation necessitating hospital admission ([Summary of findings for the main comparison](#)).

Improvement in symptoms

Two studies assessed symptomatic improvement in dyspnoea by TDI focal score as the change from baseline in mean value to the end of the study over 24 weeks as well as the number of participants with at least one unit increment which was of minimal clinically important difference ([ACLIFORM COPD](#); [AUGMENT COPD](#)). Overall, FDC acclidinium/formoterol significantly increased TDI focal score from baseline with an MD of 0.37 units compared to acclidinium (95% CI 0.07 to 0.68; 2013 participants; [Analysis 1.7](#); [Figure 3](#)). Similarly, FDC acclidinium/formoterol was associated with a statistically significant difference in the number of participants with at least one unit improvement in TDI focal score compared to acclidinium alone (OR 1.34, 95% CI 1.11 to 1.62; 2013 participants; [Analysis 1.8](#)). In absolute terms, 627/1000 (95% CI 582 to 671) participants receiving FDC acclidinium/formoterol reported a clinically significant symptomatic improvement compared to 557/1000 participants given acclidinium alone, indicating 70 more (25 more to 114 more) participants attained this improvement. Thus, for every 14 participants given FDC acclidinium/formoterol, one more person experienced a clinically important improvement of at least one unit increase in TDI focal score (95% CI 9 to 39, high-certainty evidence; [Summary of findings for the main comparison](#)).

Figure 3. Forest plot of comparison: 1 Fixed-dose combination (FDC) acclidinium and formoterol versus acclidinium, Outcome: 1.7 Improvement in symptoms: change from baseline in Transitional Dyspnoea Index (TDI) focal score.

Upon subgroup analyses, both FDC doses containing formoterol 12 µg (MD 0.42, 95% CI -0.01 to 0.85; 2 trials, 1012 participants) and formoterol 6 µg (MD 0.33, 95% CI -0.10 to 0.76; 2 trials, 1001 participants) showed no significant change from baseline TDI focal score (test for subgroup differences: $P = 0.76$; [Analysis 1.7](#)). Likewise, there was no evidence of a difference between FDC containing formoterol 12 µg (OR 1.28, 95% CI 0.98 to 1.67; 2 trials, 1012 participants) and formoterol 6 µg (OR 1.40, 95% CI 1.08 to 1.84; 2 trials, 1001 participants) in the proportion of participants with clinically important symptomatic improvement of at least one unit change in TDI focal score (test for subgroup differences: $P = 0.62$; [Analysis 1.8](#)).

Change in lung function

Three trials assessed trough FEV₁ ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Sliwinski 2010](#)), two of which also reported one-hour postmorning dose FEV₁ as the change from baseline in mean value at the end of the study ([ACLIFORM COPD](#); [AUGMENT COPD](#)). From the meta-analysis of these data, we observed that FDC acclidinium/formoterol compared to acclidinium alone significantly improved both trough FEV₁ (MD 0.02, 95% CI 0.00 to 0.04; 3 trials, 2333 participants; high-certainty evidence; [Analysis 1.9](#); [Summary of findings for the main comparison](#)) and postmorning dose FEV₁ (MD 0.10, 95% CI 0.08 to 0.12; 2 trials, 2018 participants; [Analysis 1.10](#)). Subgroup analysis for trough FEV₁ demonstrated a significant improvement compared to acclidinium alone with FDC

dose containing formoterol 12 µg (MD 0.04, 95% CI 0.01 to 0.06; 3 trials, 1171 participants) and a non-significant difference for FDC dose containing formoterol 6 µg (MD 0.01, 95% CI -0.02 to 0.04; 3 trials, 1162 participants). However, there was no evidence of a difference between the two doses of formoterol (test for subgroup differences: $P = 0.16$; [Analysis 1.9](#)). For postmorning dose FEV₁, both FDC containing formoterol 12 µg (MD 0.12, 95% CI 0.09 to 0.15; 2 trials, 1013 participants) and formoterol 6 µg (MD 0.08, 95% CI 0.05 to 0.11; 2 trials, 1005 participants) produced a significant improvement compared with acclidinium alone (test for subgroup differences: $P = 0.09$; [Analysis 1.10](#)).

Adverse events not including SAEs

From the pooled analysis of data of three trials, there was no evidence of a difference between FDC acclidinium/formoterol and acclidinium alone for the number of participants experiencing adverse events, not including SAEs (OR 0.95, 95% CI 0.76 to 1.18; 2473 participants; [Analysis 1.11](#)) ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Sliwinski 2010](#)). Both doses of formoterol 12 µg (OR 0.93, 95% CI 0.68 to 1.27; 3 trials, 1238 participants) and 6 µg (OR 0.97, 95% CI 0.71 to 1.31; 3 trials, 1235 participants) showed similar results (test for subgroup differences: $P = 0.85$, [Figure 4](#)). In absolute terms, 186/1000 participants (95% CI 155 to 221) in the FDC acclidinium/formoterol group had adverse events compared with 194/1000 in the acclidinium alone group (moderate-certainty evidence; [Summary of findings for the main comparison](#)).

Figure 4. Forest plot of comparison: 1 Fixed-dose combination (FDC) acclidinium and formoterol versus acclidinium, Outcome: 1.11 Number of participants with adverse events (not including serious adverse events).

2. Fixed-dose combination acclidinium/formoterol versus formoterol alone

Primary outcomes

Exacerbations requiring a short course of an oral steroid or antibiotic, or both

Three trials reported exacerbations requiring a short course of an oral steroid or antibiotic, or both (ACLIFORM COPD; AUGMENT COPD; Donohue 2016). Overall analysis of data from these trials demonstrated a statistically significant reduction in the number of participants experiencing at least one exacerbation requiring a short course of an oral steroid or antibiotic, or both, with FDC acclidinium/formoterol compared to formoterol alone (OR 0.78, 95%

CI 0.62 to 0.99; 3 trials, 2694 participants; high-certainty evidence; Analysis 2.1). In absolute terms, 124/1000 participants (95% CI 101 to 152) receiving FDC acclidinium/formoterol had at least one exacerbation compared to 154/1000 participants receiving formoterol alone; thus FDC acclidinium/formoterol resulted in 30 fewer (2 to 53 fewer) participants with a moderate exacerbation than formoterol alone (Summary of findings 2). Subgroup analysis showed that the difference between formoterol 12 µg (OR 0.75, 95% CI 0.56 to 1.00; 3 trials, 1622 participants) and formoterol 6 µg (OR 0.85, 95% CI 0.57 to 1.26; 2 trials, 1072 participants) was not statistically significant (test for subgroup differences: $P = 0.64$, Figure 5).

Figure 5. Forest plot of comparison: 2 Fixed-dose combination (FDC) acclidinium and formoterol versus formoterol, Outcome: 2.1 Number of participants with exacerbations requiring steroids or antibiotics or both.

Quality of life

Two trials assessed quality of life reported as the change in mean SGRQ total score from baseline towards the end of the study (24 weeks) (ACLIFORM COPD; AUGMENT COPD); however, ACLIFORM COPD did not report the proportion of participants who attained a minimal clinically important difference of at least four units' reduction in the score. FDC acclidinium/formoterol revealed a statistically significant improvement in change from baseline in mean SGRQ total score with a mean difference of -1.88 compared to formoterol alone (95% CI -3.10 to -0.65 ; 2 trials, 2002 participants; Analysis 2.2); however, it found no significant improvement in the number of participants achieving at least four units reduction (OR 1.15, 95% CI 0.89 to 1.50; 1 trial, 1000 participants; Analysis 2.3). Further subgroup analysis indicated no significant improvement with formoterol 12 µg (MD -1.72 , 95% CI -3.45 to 0.02 ; 2 trials, 1005 participants) and a significant reduction for FDC with formoterol 6 µg (MD -2.03 , 95% CI -3.76 to -0.30 ; 2 trials, 997 participants); however, the difference was not significant between the two groups (test for subgroup differences: $P = 0.80$; Analysis 2.2). In a population of 1000, 559 (95% CI 495 to 623) participants taking FDC had at

least a four-unit reduction in SGRQ total score compared with 524 participants taking formoterol alone (low-certainty evidence, Summary of findings 2).

Non-fatal serious adverse events

Five trials reported participants with non-fatal SAEs for FDC acclidinium/formoterol and formoterol alone, the pooled analysis of which showed no evidence of a difference between them (OR 1.15, 95% CI 0.82 to 1.61; 5 trials, 3140 participants; Analysis 2.4) (ACLIFORM COPD; AUGMENT COPD; Donohue 2016; NCT00706914; Sliwinski 2010). In a population of 1000, 58 (95% CI 42 to 79) participants in the FDC acclidinium/formoterol group and 50 participants in the formoterol alone group had a non-fatal SAE (moderate-certainty evidence; Summary of findings 2). The difference between FDCs containing formoterol 12 µg (OR 1.13, 95% CI 0.76 to 1.70; 5 trials, 1914 participants) and formoterol 6 µg (OR 1.20, 95% CI 0.65 to 2.20; 3 trials, 1226 participants) were not statistically significant (test for subgroup differences: $P = 0.88$).

Secondary outcomes

Mortality

Five trials stated the number of deaths in published articles (ACLIFORM COPD; AUGMENT COPD; Donohue 2016; NCT00706914; Sliwinski 2010); however, two of them reported no death during the study period (NCT00706914; Sliwinski 2010). There was no evidence of a difference between FDC aclidinium/formoterol and formoterol alone for the all-cause mortality (Peto OR 1.46, 95% CI 0.44 to 4.87; 5 trials, 3140 participants; Analysis 2.5).

Hospital admissions due to exacerbations

Three trials assessed the number of participants with severe exacerbations requiring hospital admissions and the meta-analysis found no difference between FDC aclidinium/formoterol and formoterol alone (OR 0.76, 95% CI 0.45 to 1.28; 2694 participants; Analysis 2.6) (ACLIFORM COPD; AUGMENT COPD; Donohue 2016). In a total of 1000 participants receiving FDC aclidinium/formoterol, 20 (95% CI 12 to 34) would require admission compared to 27 from the formoterol alone group (moderate-certainty evidence; Summary of findings 2). Subgroup analysis showed no difference between an FDC formoterol dose of 12 µg (OR 0.69, 95% CI 0.38 to 1.25; 3 trials, 1622 participants) and formoterol 6 µg (OR 1.06, 95% CI 0.34 to 3.28; 2 trials, 1072 participants) (test for subgroup differences: $P = 0.51$).

Improvement in symptoms

Two trials studied symptomatic improvement in terms of TDI focal score as change from baseline to the end of the study (24 weeks) as well as the percentage of participants who achieved a minimal clinically important difference of one unit improvement in the score (ACLIFORM COPD; AUGMENT COPD). Overall, FDC aclidinium/formoterol was associated with a significant improvement in TDI focal score change from baseline compared with formoterol alone (MD 0.42, 95% CI 0.11 to 0.72; 2 trials, 2010 participants; Analysis 2.7). Subgroup analysis of the FDC formoterol dose of 12 µg found significant improvement (MD 0.47, 95% CI 0.03 to 0.90; 2 trials, 1011 participants) while formoterol 6 µg showed no significance (MD 0.37, 95% CI -0.06 to 0.80; 2 trials, 999 participants); however, test for subgroup differences was not significant ($P = 0.76$).

Similarly, FDC aclidinium/formoterol was significantly associated with a higher number of participants achieving a clinically important improvement in TDI focal score (OR 1.30, 95% CI 1.07 to 1.56; 2 trials, 2010 participants; Analysis 2.8). In absolute terms, for every 1000 participants, 628 (95% CI 582 to 670; 17 more to 105 more) taking FDC aclidinium/formoterol and 565 taking formoterol alone attained a clinically significant symptomatic improvement (high-certainty evidence, Summary of findings 2). Thus, for every 16 (95% CI 10 to 60) participants treated with FDC aclidinium/formoterol, one additional participant would attain the clinically important improvement of TDI focal score. Subgroup analysis of the dosage revealed no evidence of a difference between the subgroups ($P = 0.57$) of formoterol 12 µg (OR 1.23, 95% CI 0.94 to 1.60; 2 trials, 1011 participants) and formoterol 6 µg (OR 1.37, 95% CI 1.05 to 1.79; 2 trials, 999 participants).

Change in lung function

Four trials reported change from baseline in trough FEV₁ (ACLIFORM COPD; AUGMENT COPD; NCT00706914; Sliwinski 2010), and two trials reported one-hour postmorning dose FEV₁ (ACLIFORM COPD; AUGMENT COPD). There was a significant

improvement in trough FEV₁ change from baseline with FDC aclidinium/formoterol compared to formoterol alone (MD 0.04, 95% CI 0.03 to 0.06; 4 trials, 2411 participants; high-certainty evidence; Analysis 2.9; Summary of findings 2). Both FDC formoterol dose of 12 µg (MD 0.05, 95% CI 0.03 to 0.08; 4 trials, 1254 participants) and formoterol 6 µg (MD 0.04, 95% CI 0.01 to 0.07; 3 trials, 1157 participants) had a statistically significant result with no difference between the two doses (test for subgroup differences: $P = 0.52$).

FDC aclidinium/formoterol also resulted in a significant improvement of one-hour postmorning dose FEV₁ compared with formoterol alone (MD 0.09, 95% CI 0.07 to 0.11; 2 trials, 2021 participants; Analysis 2.10). There was similar improvement for FDC dose of formoterol 12 µg (MD 0.11, 95% CI 0.08 to 0.14; 2 trials, 1015 participants) and formoterol 6 µg (MD 0.07, 95% CI 0.04 to 0.10; 2 trials, 1006 participants) with no evidence of a difference between the two doses (test for subgroup differences: $P = 0.09$).

Adverse events not including SAEs

Analysis of data from five trials found significantly fewer adverse events (not including SAEs) with FDC aclidinium/formoterol compared to formoterol (OR 0.78, 95% CI 0.65 to 0.93; 5 trials, 3140 participants; Analysis 2.11) (ACLIFORM COPD; AUGMENT COPD; Donohue 2016; NCT00706914; Sliwinski 2010). Upon subgroup analysis, there was no evidence of a difference between FDC dose of formoterol 12 µg (OR 0.79, 95% CI 0.63 to 0.99; 5 trials, 1914 participants) and formoterol 6 µg (OR 0.76, 95% CI 0.56 to 1.02; 3 trials, 1226 participants) with no evidence of a difference between the two doses (test for subgroup differences: $P = 0.81$). In a group of 1000 participants, 46 (95% CI 14 to 76 lower) fewer participants experienced adverse events if they received FDC aclidinium/formoterol compared to participants receiving formoterol alone (high-certainty evidence; Summary of findings 2). Thus, to achieve an additional person with no adverse events, 22 (95% CI 13 to 71) participants need to be treated with FDC aclidinium/formoterol.

3. Fixed-dose combination aclidinium/formoterol versus placebo

Primary outcomes

Exacerbations requiring a short course of an oral steroid or antibiotic, or both

According to the analysis of data from two trials, FDC aclidinium/formoterol was not associated with significant reduction in the number of participants with exacerbations which required a short course of an oral steroid or antibiotic, or both, compared to placebo over the period of 24 weeks (moderate-certainty evidence, OR 0.82, 95% CI 0.60 to 1.12; 2 trials, 1960 participants; Analysis 3.1) (ACLIFORM COPD; AUGMENT COPD). Both FDCs containing formoterol 12 µg (OR 0.82, 95% CI 0.52 to 1.28; 2 trials; 983 participants) and formoterol 6 µg showed no significance over placebo (OR 0.82, 95% CI 0.53 to 1.27; 2 trials, 977 participants), with no difference among the doses (test for subgroup differences: $P = 0.99$). In absolute terms, among 1000 participants, FDC caused 20 fewer (47 lower to 14 higher) participants with moderate exacerbation requiring steroids or antibiotics, or both, than placebo (Summary of findings 3).

Quality of life

FDC acclidinium/formoterol produced a significant improvement in quality of life in terms of change from baseline in SGRQ total score (MD -2.91, 95% CI -4.33 to -1.50; 2 trials, 1823 participants; [Analysis 3.2](#)) as well as the number of participants with clinically important improvement of at least four units (OR 1.72, 95% CI 1.39 to 2.13; 2

trials, 1823 participants; [Analysis 3.3](#)) compared to placebo in two trials over 24 weeks ([ACLIFORM COPD](#); [AUGMENT COPD](#)). Both FDCs containing formoterol 12 µg (MD -2.86, 95% CI -4.87 to -0.85; 2 trials, 915 participants) and formoterol 6 µg (MD -2.97, 95% CI -4.97 to -0.96; 2 trials, 908 participants) showed significant improvement in SGRQ total score over placebo, with no difference among the doses (test for subgroup differences: $P = 0.94$, [Figure 6](#)).

Figure 6. Forest plot of comparison: 3 Fixed-dose combination (FDC) acclidinium and formoterol versus placebo, Outcome: 3.2 Quality of life: change from baseline in St George's Respiratory Questionnaire (SGRQ) total score.

Both FDCs with formoterol 12 µg (OR 1.69, 95% CI 1.26 to 2.28; 2 trials, 915 participants) and formoterol 6 µg (OR 1.75, 95% CI 1.29 to 2.36; 2 trials, 908 participants) revealed a significant number of participants with SGRQ total score of at least four units' improvement (test for subgroup differences: $P = 0.89$). Among a population of 1000 participants, 568 taking FDC had a clinically important improvement in SGRQ total score of more than four units whereas only 433 of those given placebo resulted in similar response (difference 135, 95% CI 82 to 186 more). Thus, for every seven (95% CI five to 12) participants treated with FDC acclidinium/formoterol, one extra person would achieve a clinically important improvement in quality of life compared to placebo (high-certainty evidence; [Summary of findings 3](#)).

Non-fatal serious adverse events

Four trials reported the number of participants with non-fatal SAEs ([ACLIFORM COPD](#); [ACTIVATE](#); [AUGMENT COPD](#); [Sliwinski 2010](#)). There was no evidence of a difference between FDC acclidinium/formoterol and placebo (OR 1.12, 95% CI 0.72 to 1.74; 4 trials, 2527 participants; moderate-certainty evidence; [Analysis 3.4](#)). There was no difference between FDCs with formoterol 12 µg (OR 1.15, 95% CI 0.63 to 2.10; 4 trials, 1399 participants) and formoterol 6 µg (OR 1.09, 95% CI 0.56 to 2.09; 3 trials, 1128 participants), with no evidence of a difference between the subgroups ($P = 0.90$). In a group of 1000 participants, 42 (95% CI 27 to 64) receiving FDC acclidinium/formoterol and 38 receiving placebo experienced a non-fatal SAE ([Summary of findings 3](#)).

Secondary outcomes

Mortality

Three studies found no difference in the number of deaths between FDC acclidinium/formoterol and placebo (Peto OR 3.79, 95% CI 0.37

to 39.13; 3 trials, 2260 participants; [Analysis 3.5](#)) ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Sliwinski 2010](#)). There were no reported deaths in [Sliwinski 2010](#), which was a short duration study of four weeks.

Hospital admissions due to exacerbations

Two studies reported hospital admissions due to exacerbations ([ACLIFORM COPD](#); [AUGMENT COPD](#)). There was no evidence of a difference in the number of participants with severe exacerbations who required hospital admissions between FDC acclidinium/formoterol and placebo (OR 0.55, 95% CI 0.25 to 1.18; 1960 participants; [Analysis 3.6](#)). Both FDCs with formoterol 12 µg (OR 0.49, 95% CI 0.15 to 1.60; 2 trials, 983 participants) and formoterol 6 µg (OR 0.59, 95% CI 0.21 to 1.65; 2 trials, 977 participants) revealed similar results, with no evidence of a difference between the subgroups ($P = 0.83$). In absolute terms, for a group of 1000 participants, 12 (95% CI 5 to 25) from the FDC acclidinium/formoterol group required hospitalisation due to exacerbations compared with 21 from the placebo group (moderate-certainty evidence; [Summary of findings 3](#)).

Improvement in symptoms

Two studies reported improvement in symptoms ([ACLIFORM COPD](#); [AUGMENT COPD](#)). Compared to placebo, FDC acclidinium/formoterol showed significant improvement in terms of TDI focal score change from baseline over 24 weeks (MD 1.32, 95% CI 0.96 to 1.69; 1832 participants; [Analysis 3.7](#)). Both doses of FDC formoterol 12 µg (MD 1.37, 95% CI 0.85 to 1.88; 2 trials; 922 participants) and formoterol 6 µg (MD 1.28, 95% CI 0.77 to 1.80; 2 trials, 910 participants) showed significance over placebo with no difference between the two subgroups ($P = 0.82$).

Likewise, FDC acclidinium/formoterol was associated with a significantly higher number of participants with a minimal clinically

significant improvement of TDI focal score one unit or more when compared with placebo (OR 2.51, 95% CI 2.02 to 3.11; 2 trials, 1832 participants; [Analysis 3.8](#)). This significant improvement was observed with FDCs containing formoterol 12 µg (OR 2.37, 95% CI 1.75 to 3.22; 2 trials, 922 participants) and formoterol 6 µg (OR 2.65, 95% CI 1.96 to 3.60; 2 trials, 910 participants). There was no difference between the subgroups ($P = 0.61$). In a group of 1000 participants, 620 (95% CI 568 to 669) taking FDC aclidinium/formoterol had at least one unit increment in TDI focal score compared with 394 for placebo group over 24 weeks' duration (high-certainty evidence; [Summary of findings 3](#)). One additional participant would achieve a minimal clinically significant increment of at least one unit in TDI focal score for every four (95% CI four to six) participants treated with FDC aclidinium/formoterol compared to placebo.

Change in lung function

Three trials studied change from baseline in trough FEV₁ ([ACLIFORM COPD](#); [AUGMENT COPD](#); [Sliwinski 2010](#)), while two studies reported change from baseline in one-hour post morning dose FEV₁ ([ACLIFORM COPD](#); [AUGMENT COPD](#)). FDC aclidinium/formoterol significantly improved trough FEV₁ change from baseline compared with placebo (MD 0.12, 95% CI 0.10 to 0.14; 3 trials, 2137 participants; high-certainty evidence; [Analysis 3.9](#); [Summary of findings 3](#)). There was no difference between FDCs with formoterol 12 µg (MD 0.13, 95% CI 0.10 to 0.16; 3 trials, 1073 participants) and formoterol 6 µg (MD 0.11, 95% CI 0.07 to 0.14; 3 trials, 1064 participants; test for subgroup differences: $P = 0.25$).

FDC aclidinium/formoterol also demonstrated a significant improvement in one-hour postmorning dose FEV₁ change from baseline compared to placebo (MD 0.27, 95% CI 0.25 to 0.30; 2 trials, 1842 participants; [Analysis 3.10](#)) with no difference between FDCs with formoterol 12 µg (MD 0.29, 95% CI 0.25 to 0.33; 2 trials, 925 participants) and formoterol 6 µg (MD 0.25, 95% CI 0.22 to 0.29; 2 trials, 917 participants; test for subgroup differences: $P = 0.17$).

Adverse events not including SAEs

Four trials reported the number of participants experiencing adverse events not including SAEs ([ACLIFORM COPD](#); [ACTIVATE](#); [AUGMENT COPD](#); [Sliwinski 2010](#)). There was no difference between FDC aclidinium/formoterol and placebo (OR 0.97, 95% CI 0.76 to 1.22; 2527 participants, moderate-certainty evidence; [Analysis 3.11](#)). Both FDCs with formoterol 12 µg (OR 0.89, 95% CI 0.65 to 1.22; 4 trials, 1399 participants) and formoterol 6 µg (OR 1.07, 95% CI 0.75 to 1.53; 3 trials, 1128 participants) resulted in the similar response compared to placebo with no difference between the subgroups ($P = 0.44$). Out of 1000 participants, 171 (95% CI 139 to 206) in the FDC aclidinium/formoterol group would experience at least one adverse event compared with 175 for placebo group over a period of four to 24 weeks ([Summary of findings 3](#)).

DISCUSSION

Summary of main results

We could only identify trials assessing a combination therapy of aclidinium/formoterol in a single inhaler as an FDC with the dose of formoterol either 12 µg or 6 µg. Compared to aclidinium alone, FDC aclidinium/formoterol significantly improved symptoms as TDI focal score was increased by 0.37 units (from 0.07 to 0.68 higher) although this mean improvement did not reach the

accepted threshold of one unit for a clinically important difference. Correspondingly, there was a significantly higher number of TDI responders with FDC aclidinium/formoterol than aclidinium alone, with an NNTB of 14. FDC aclidinium/formoterol also improved lung function, both trough FEV₁ and one-hour postmorning dose FEV₁, but there were no differences in terms of exacerbations requiring steroids, or antibiotics, or both; quality of life; hospital admissions due to severe exacerbations; all-cause mortality; non-fatal SAEs and other adverse events compared with aclidinium.

When compared to formoterol alone, FDC aclidinium/formoterol demonstrated a significant improvement in symptoms; lung function; quality of life; reduction in exacerbations requiring a short course of steroids or antibiotics, or both and adverse events (not including SAEs). FDC aclidinium/formoterol was associated with a mean increase in TDI focal score of 0.42 units (from 0.11 to 0.72 higher) as well as a greater TDI responders than formoterol (NNTB 16). Combination therapy also lowered SGRQ total score by 1.88 units (from 3.10 to 0.65 lower) compared with formoterol, although this mean improvement did not reach clinical significance of four units. However, there was no difference for hospital admissions, all-cause mortality and non-fatal SAEs.

In comparison with placebo, combination therapy significantly improved quality of life, symptoms and lung function. FDC aclidinium/formoterol demonstrated a clinically significant reduction of 2.91 units (from 4.33 to 1.50 lower) in SGRQ total score with an NNTB of seven. Participants treated with FDC aclidinium/formoterol experienced clinically significantly greater improvements in dyspnoea with a TDI focal score change from baseline of 1.32 units (95% CI 0.96 to 1.69 units) compared to placebo. To attain one additional person with at least one unit increase in TDI focal score, four participants need to be treated. There were no differences between combination therapy and placebo in terms of moderate exacerbations requiring steroids or antibiotics, or both; hospital admissions due to severe exacerbations; all-cause mortality; adverse events and non-fatal SAEs.

Overall completeness and applicability of evidence

The latest COPD guidelines recommend the use of combined LABA and LAMA as an alternative for people with group B and C COPD with persistent symptoms or further exacerbations and as a first line for people with group D COPD ([GOLD 2018](#)). An FDC of aclidinium 400 µg and formoterol 12 µg as Duaklir Genuair was approved by the European Medicines Agency in November 2014 for people with COPD. The evidence from this review arose from the meta-analysis of six trials of moderate-to-high methodological standard, thus providing a better estimate of treatment effects on the risks and benefits of combination therapy than any of the studies alone. One of the included studies ([D'Urzo 2017a](#)) was the extension study of [AUGMENT COPD](#), and we included only the data of the primary study as the extension period was not a truly randomised comparison with substantial withdrawals. Some of the data required for the meta-analysis were not reported in the published articles for which we contacted the manufacturers who were helpful in providing additional information. Most of the data in the published articles reported the difference in treatment effects versus monotherapies or placebo rather than the individual arms. Thus, we requested for exact values, which were provided for two studies ([ACLIFORM COPD](#); [AUGMENT COPD](#)), or used the data provided by the ClinicalTrials website or participant level data

from the AztraZeneca database for other trials to maximise the accuracy of our evidence. Clinical characteristics of the participants recruited into the trials, baseline severity of the disease and prior medications were similar between the trial arms. There was little or no heterogeneity for most of the summary estimates, except for the total number of deaths compared to acclidinium as there were more deaths among the FDC group; however, none of these was considered to be related to study medication as all these participants had multiple underlying comorbidities. In most of the studies, formoterol was delivered in Genuair inhaler to maintain blindness, which is not an ideal device and might affect the outcome measures for comparison with formoterol. In this review, subgroup analysis was performed for the dose of formoterol in the FDC, 12 µg or 6 µg, for most of the outcomes; however, there was no evidence of a difference between the subgroups.

Generally, the evidence from this review supported the effectiveness of combination therapy compared to monotherapies and placebo for improving lung function and reducing dyspnoea for people with stable COPD which is in accordance with the updated GOLD recommendations (GOLD 2018). Based on the evidence from this review, acclidinium/formoterol combination therapy showed no difference in reducing exacerbations, either moderate exacerbations requiring short course of steroids or antibiotics, or both, or severe exacerbations requiring hospital admissions. There was a possibility of better reduction in moderate exacerbations which necessitated the use of steroids or antibiotics, or both, with FDC compared to formoterol, though the summary estimates may not be clinically significant. It could be due to power effect as the analysis involved three trials with more participants. For other comparisons, the data contributing to the exacerbation outcome came from only two trials of 24 weeks' duration and we strongly believe further inclusion of longer studies will alter this evidence. There was no difference in all-cause mortality, adverse events and non-fatal SAEs indicating the safety of this combination treatment. There were statistically fewer adverse events with FDC acclidinium/formoterol when compared to formoterol alone. Overall, the evidence from our review indicated that combination treatment was an effective and safe option for treating people with stable COPD.

Quality of the evidence

We evaluated the quality of evidence for the review's outcomes with GRADE assessment (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3), which ranged from low to high. All the seven included studies in this review were industry sponsored and were conducted according to similar prespecified protocols with generally limited potential for significant bias. The meta-analyses of most of the outcomes of this review were mainly contributed by two trials (ACLIFORM COPD; AUGMENT COPD), and occasionally by other four trials. The studies providing data to this review were large and we judged them to be at low or unclear for overall risk of bias. All the comparisons for the outcomes were direct and there was no significant heterogeneity for most of the outcomes. In a few select instances for the comparison with formoterol alone, moderate statistical heterogeneity detected was difficult to explain, with trials having similar inclusion and exclusion criteria, enrolling participants with similar severity of disease and using similar methodology and statistical approaches. Most of the pooled effect estimates were not precise which led to downgrading

of the evidence in our review. Improvement in symptoms and lung function were graded as high-certainty evidence for all comparisons and we are confident that the true effect lies close to the effect estimate. We rated the certainty of evidence for improvement in SGRQ total score as high for the comparison of FDC acclidinium/formoterol with placebo, moderate for acclidinium and low for formoterol. In primary studies, some predefined endpoints especially exacerbations were not published specifically as moderate and severe exacerbations, although these outcomes of interest were made available by the manufacturer. However, we are less confident and certain about exacerbation and hospital admission outcomes for all comparisons. As these are relatively infrequent events for the current included trials of relatively short duration, additional information from future trials might alter our confidence in these results and provide new evidence for clinical practice.

Potential biases in the review process

We made every effort to obtain grey literature to minimise bias in the review process. In addition to the Cochrane Airways Group's systematic electronic search, we performed a comprehensive search of other sources including manufacturers' websites and trial registries. We also contacted the trial authors for missing data and were provided access to participant level data of the individual trials concerned. Two review authors independently determined inclusion and exclusion of trials, extracted data and judged risk of bias to minimise error. Most of the data were consistent throughout the published trials and ClinicalTrials.gov website except for the outcome for SGRQ responders in ACLIFORM COPD. We noted an inconsistency in the reporting of SGRQ responders as the number of responders did not appear to be compatible with the finding of overall improvement in SGRQ total score for formoterol and FDC acclidinium/formoterol arms. Inclusion of only seven studies in this review limited the use of a funnel plot for proper publication bias assessment.

Most reported data were obtained from methodologically robust RCTs, and the potential for introduction of significant systematic biases in these trials is generally considered to be low. Clinical characteristics of the participants recruited into the trials and baseline disease severity were similar across the trials. Rates of attrition were generally between 10% and 20%, with higher rates in AUGMENT COPD and Donohue 2016. There was slightly greater loss of participants from placebo than experimental arms in AUGMENT COPD and in Donohue 2016, both FDC acclidinium/formoterol and formoterol alone arms had high withdrawal rates. Loss to follow-up was most commonly due to unsatisfactory therapeutic effect or to adverse events or withdrawal of consent. Therefore, it is possible that unmatched attrition between placebo and experimental arms may have introduced some bias, and such bias would most likely lead to underestimation of the treatment effects of FDC. However, the overall impact of such bias was likely to be low as the analyses were based on the ITT population.

Concomitant use of ICSs and methylxanthines may impact outcomes; however, inclusion of only the participants who had already achieved a stable state with these medications for at least four weeks prior to screening would have little influence on the overall effect estimates. It is also supported by the findings from a subgroup analysis of pooled data from ACLIFORM COPD and AUGMENT COPD according to concomitant ICS use, in which acclidinium/formoterol 400/12 µg improved lung function

compared with placebo and monotherapies regardless of ICS use (D'Urzo 2017b). In addition, prior use of LABAs, LAMAs, ICSs or combinations of any of these could also introduce bias; however, we noted no obvious differences between the proportions of participants treated with either of these agents in the intervention and control arms of included studies. Thus, we assume there will not be a significant change in the findings of our review.

Agreements and disagreements with other studies or reviews

There has been increasing evidence that LABA/LAMA combination therapy is more efficacious than monotherapies or placebo for improving symptoms, lung function and quality of life, and reducing exacerbations. To date, despite a considerable number of meta-analyses and systematic reviews on combined LABA/LAMA therapy, those focusing specifically on aclidinium and formoterol are limited. In one systematic review of an indirect comparison between aclidinium/formoterol and tiotropium (Medic 2016), combined therapy was more effective than tiotropium alone in improving FEV₁ and dyspnoea with correspondingly higher number of TDI responders. There was no difference for quality of life, hospitalisations, adverse events and SAEs. Bateman 2015 and Di Marco 2017 reported that FDC aclidinium/formoterol 400/12 µg therapy significantly improved TDI focal score compared to monotherapies and placebo with the potential to control symptoms throughout the 24 hours, which was similar to our findings. That review also revealed a significant reduction in moderate-to-severe exacerbations versus placebo but not the monotherapies, a finding our review did not demonstrate. Our review's finding of FEV₁ improvement and dyspnoea reduction by FDC aclidinium/formoterol also supports the 2018 updated GOLD guidance (GOLD 2018).

Current evidence suggests that LABA/LAMA therapy was more effective than monotherapy in terms of symptoms, quality of life and lung function (Calzetta 2017a; Lal 2017; Oba 2016; Rodrigo 2017), though our review did not show an improvement in HRQoL versus aclidinium. In another meta-analysis, LABA/LAMA combinations were significantly more effective than LABA or LAMA alone in terms of improvement in endurance time and inspiratory capacity (Calzetta 2017b), though the studies particularly comparing FDC aclidinium/formoterol with monotherapy were not included in that analysis. In our review, people taking FDC aclidinium/formoterol had fewer exacerbations requiring steroids or antibiotics, or both than formoterol alone but not when compared with aclidinium alone, which is a comparable finding as in the network meta-analysis by Oba 2016. Variable degree of symptoms at baseline possibly could affect our findings of lung function and symptomatic improvement; however, the baseline characteristics of participants are comparable among the groups. One post hoc pooled analysis of ACLIFORM COPD and AUGMENT COPD categorised by symptom status demonstrated a similar magnitude of postdose FEV₁ improvements regardless of the baseline symptoms. Not surprisingly, greater improvement in trough FEV₁ from baseline and dyspnoea was observed in more symptomatic participants (Miravittles 2016). According to the long-term studies over a five-year period conducted in Scotland (Ramos 2016) and Spain (Capel 2018), combined therapy of FDC aclidinium/formoterol 400/12 µg can be considered a cost-effective option compared to aclidinium 400 µg alone or tiotropium/olodaterol in

people with moderate-to-severe COPD though our review did not assess the cost of these medications.

AUTHORS' CONCLUSIONS

Implications for practice

Combination treatment with aclidinium/formoterol provides improvements in lung function and dyspnoea across all comparisons with aclidinium, formoterol or placebo as well as a better health-related quality of life than formoterol or placebo. However, some uncertainty remains regarding its superiority over aclidinium alone for improvement in quality of life. Therefore, combined therapy is an appropriate treatment for people with confirmed symptomatic stable chronic obstructive pulmonary disease (COPD). Current evidence is insufficient to confirm the effects of aclidinium/formoterol combination on the chances of experiencing an exacerbation or hospital admissions for exacerbations. As there is no evidence of a difference in mortality or non-fatal serious adverse events compared with monotherapies or placebo, fixed-dose combination of aclidinium/formoterol could be considered a relatively safe option for treating people with stable COPD.

Implications for research

Further research is indicated to clarify potential differences in efficacy between aclidinium/formoterol and alternative LABA/LAMA combinations, particularly with respect to quality of life, dyspnoea and exacerbations. Trialists should define and report exacerbations consistently and, if possible, provide disaggregated data for participants in different COPD severity groups. Longer-term follow-up data would be beneficial, especially to identify any impact of combined aclidinium/formoterol on exacerbations, hospital admissions, serious adverse events and mortality. Further trials examining the efficacy and safety of aclidinium/formoterol with participant-related outcomes as primary endpoints rather than lung function improvement would be more appropriate for applicability to clinical practice in people with COPD. Studies on cost-effectiveness comparing aclidinium/formoterol with other available combinations of LABA/LAMA are also anticipated.

ACKNOWLEDGEMENTS

We would like to thank the editors and staff of the Cochrane Airways Review Group and Cochrane, especially Managing Editor Dr Emma Dennett for their utmost help and support, feedback, suggestions and advice provided regarding preparation of the manuscript.

We are very grateful to Ms Liz Stovold, Information Specialist, for designing and running the search strategy. We are also grateful to the authoritative people of respective institutions for their support.

Chris Cates was the Editor for this review and commented critically on the review and assisted with signing off the review for publication.

The 'Background' and 'Methods' sections of this review are based on a standard template used by the Cochrane Airways Group. Parts of the review use similar wording to our related reviews (Ni 2014; Ni 2017)

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the

Cochrane Airways Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those

of the Systematic Reviews Programme, NIHR, NHS (National Health Service) or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ACLIFORM COPD

Methods	Study design: randomised, double-blind, active- and placebo-controlled, parallel group, phase III study
	Total duration of study: 24 weeks
	Run-in period: 2-3 weeks
	Follow-up: 2 weeks after the last dose
	Study setting: multicentre trial, clinic patients
	Number of study centres and location: 193 centres in 22 countries: Austria (2), Belgium (2), Bulgaria (5), Croatia (2), Czech Republic (12), Denmark (4), Finland (5), France (7), Germany (28), Hungary (15), Italy (4), the Netherlands (7), Poland (20), Romania (12), Russia (5), Slovakia (7), South Africa (9), South Korea (8), Spain (7), Sweden (5), Ukraine (11), UK (16). In addition, 4 centres screened but did not randomise any participants: Hungary (1), the Netherlands (1), South Korea (1), and Spain (1)
	Date of study: 26 October 2011 to 4 January 2013

ACLIFORM COPD (Continued)

Withdrawals: stated

Participants	Number screened: 2443 Number randomised: 1729 ITT population: 1726 Number in treatment group: 381 (FDC aclidinium/formoterol 400/6 µg), 385 (FDC aclidinium/formoterol 400/12 µg) Number in control group: 385 (aclidinium 400 µg), 384 (formoterol 12 µg), 194 (placebo) Number of withdrawals: 40 (FDC 400/6 µg), 34 (FDC 400/12 µg), 50 (aclidinium 400 µg), 45 (formoterol 12 µg), 34 (placebo) Number completing trial: 341 (FDC 400/6 µg), 351 (FDC 400/12 µg), 335 (aclidinium 400 µg), 339 (formoterol 12 µg), 160 (placebo) Mean age (years): 62.9 (FDC 400/6 µg), 62.7 (FDC 400/12 µg), 63.1 (aclidinium 400 µg), 63.4 (formoterol 12 µg), 64.2 (placebo) Gender (men/women): 259/122 (FDC 400/6 µg), 261/124 (FDC 400/12 µg), 256/129 (aclidinium 400 µg), 255/129 (formoterol 12 µg), 138/56 (placebo) Caucasian (%): 96.1 (FDC 400/6 µg), 95.3 (FDC 400/12 µg), 94.3 (aclidinium 400 µg), 94.3 (formoterol 12 µg), 94.3 (placebo) Severity of condition: moderate to severe Diagnostic criteria: GOLD 2010 Baseline mean FEV₁ (L): 1.41 (FDC 400/6 µg), 1.42 (FDC 400/12 µg), 1.40 (aclidinium 400 µg), 1.40 (formoterol 12 µg), 1.42 (placebo) Baseline mean postbronchodilator FEV₁ (% of predicted): 54.1 (FDC 400/6 µg), 54.6 (FDC 400/12 µg), 53.6 (aclidinium 400 µg), 54.5 (formoterol 12 µg), 55.0 (placebo) Current smoker (number/%): 182/47.8 (FDC 400/6 µg), 181/47.0 (FDC 400/12 µg), 182/47.3 (aclidinium 400 µg), 179/46.6 (formoterol 12 µg), 94/48.5 (placebo) Inclusion criteria: men and women aged ≥ 40 years who were current or former cigarette smokers with a smoking history of ≥ 10 pack-years and diagnosed with stable moderate-to-severe COPD according to GOLD 2010 criteria (postbronchodilator FEV₁/FVC < 70% and FEV₁ ≥ 30% but < 80% of predicted normal value) Exclusion criteria: history/current diagnosis of asthma; respiratory tract infection or COPD exacerbation within 6 weeks (3 months if hospitalisation required) prescreening; clinically relevant respiratory conditions other than COPD; clinically significant cardiovascular conditions and contraindications to anticholinergics
Interventions	Intervention: inhaled FDC aclidinium/formoterol 400/6 µg twice daily, inhaled FDC aclidinium/formoterol 400/12 µg twice daily Comparison: inhaled aclidinium 400 µg twice daily, inhaled formoterol 12 µg twice daily, inhaled placebo twice daily Concomitant medications: inhaled salbutamol (100 µg/puff) as needed, but discontinued 6 hours before planned study visits; ICS provided treatment was stable ≥ 4 weeks prescreening; oral sustained-release methylxanthines; oxygen therapy (< 15 hours/day) and oral or parenteral corticosteroids equivalent to ≤ 10 mg/day of prednisone or 20 mg every other day, provided treatment was stable ≥ 4 weeks prescreening were permitted. Prior medications:

ACLIFORM COPD (Continued)

ICS: 72 (FDC 400/6 µg), 85 (FDC 400/12 µg), 79 (aclidinium 400 µg), 68 (formoterol 12 µg), 39 (placebo)

LABA: 69 (FDC 400/6 µg), 79 (FDC 400/12 µg), 78 (aclidinium 400 µg), 80 (formoterol 12 µg), 38 (placebo)

LAMA: 122 (FDC 400/6 µg), 118 (FDC 400/12 µg), 107 (aclidinium 400 µg), 110 (formoterol 12 µg), 60 (placebo)

LABA + ICS: 128 (FDC 400/6 µg), 118 (FDC 400/12 µg), 121 (aclidinium 400 µg), 119 (formoterol 12 µg), 63 (placebo)

Outcomes	Primary outcomes: change from baseline in morning predose (trough) FEV₁ and 1-hour postmorning dose FEV₁ at week 24 Secondary outcomes: change from baseline in TDI focal score and SGRQ total score at week 24
Notes	Full-text publication Funding: Almirall SA, Barcelona, Spain, and Forest Laboratories LLC, a subsidiary of Actavis, New York, NY, USA Study number: ClinicalTrials.gov NCT01462942 Authors reported and declared possible conflicts of interest. Sponsors placed no restriction on statements made in final version of the manuscript for publication and all authors had full access to the data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from text): "randomisation was performed using a centralised interactive voice response system on day 1 (visit 1), with stratification by smoking status (smoker or ex-smoker)."
Allocation concealment (selection bias)	Low risk	Quote (from text): "treatment identity was concealed with identical packaging/appearance and no odour or colour."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participant and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from text): "evaluated and classified by an independent, blinded adjudication committee."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (from text): "three patients were excluded from ITT population due to missing FEV₁ data. Efficacy analyses, with the exception of exacerbation rate, were performed on the ITT population (patients who took ≥ one dose of study medication and had a baseline and ≥ one postbaseline FEV₁ assessment). Exacerbations and safety outcomes were assessed in the safety population (patients who received ≥ one dose of study medication)." Comment: overall withdrawal rates were relatively low and balanced across the study arms; 10.5% (FDC 400/6 µg), 8.8% (FDC 400/12 µg), 13% (aclidinium 400 µg), 11.7% (formoterol 12 µg), 17.5% (placebo).
Selective reporting (reporting bias)	Unclear risk	Comment: study protocol was not available, but all the prespecified outcomes in the method section were reported in the result section and the additional

ACLIFORM COPD (Continued)

file of the full-text publication except for the SGRQ responders compared to formoterol though the mean improvement for that outcome was reported.

Other bias	Low risk	Comment: no apparent source of bias was observed.

ACTIVATE

Methods	Study design: randomised, double-blind, placebo-controlled, parallel group, phase IV study Total duration of study: 8 weeks Run-in and screening period: 11–17 days Follow-up: 2 weeks after the final treatment Number of study centres and location: 26 sites in 4 countries (15 in Germany, 4 in Hungary, 3 in Spain and 4 in Canada) Date of study: April 2015 to July 2016 Withdrawals: stated
Participants	Number screened: 335 Number randomised: 267 ITT population: 267 Number in treatment group: 134 (FDC aclidinium/formoterol 400/12 µg) Number in control group: 133 (placebo) Number of withdrawals: 7 (FDC 400/12 µg), 10 (placebo) Number completing trial: 127 (FDC 400/12 µg), 123 (placebo) Mean age (years): 62.6 (FDC 400/12 µg), 62.1 (placebo) Gender (men/women): 81/53 (FDC 400/12 µg), 79/54 (placebo) Severity of condition: moderate to severe Diagnostic criteria: GOLD 2014 Baseline mean postbronchodilator FEV₁ (% of predicted): 60.3 (FDC 400/12 µg), 61.0 (placebo) Baseline mean smoking pack-years: 48.4 (FDC 400/12 µg), 46.4 (placebo) Current smoker (number/%): 85/63.4 (FDC 400/12 µg), 83/62.4 (placebo) Inclusion criteria: men and women aged ≥ 40 years, current or former cigarette smokers with smoking history ≥ 10 pack-years with a clinical diagnosis of moderate-to-severe COPD according to GOLD 2014 criteria with FRC ≥ 120% of predicted value, postbronchodilator FEV₁ ≥ 40% and < 80% of the predicted value, FEV₁/FVC < 70% and mMRC dyspnoea scale score ≥ 2 Exclusion criteria: history or current diagnosis of asthma; any respiratory tract infection (including upper respiratory tract) or COPD exacerbation within 6 weeks prior to screening or during the run-in period; hospitalised for COPD exacerbation within 3 months prior to screening and during the run-in period; clinically significant respiratory conditions other than COPD; use of long-term oxygen therapy (≥ 15 hours/day); oxygen saturation ≤ 85% during exercise testing at visit 1, 2 or 3 prior to randomisation; body mass index ≥ 40 kg/m²; pulmonary rehabilitation during the study or within 3 months prior to screening, or both; clinically significant cardiovascular conditions; clinically relevant abnormalities

ACTIVATE (Continued)

in the results of blood pressure, electrocardiogram or physical examination at visit 1; conditions other than COPD that may have contributed to dyspnoea and exercise limitation or with contraindications to clinical exercise testing according to American Thoracic Society recommendations for cardiopulmonary exercise testing; people who cycled < 2 minutes or > 15 minutes during the constant work rate exercise tests conducted at visit 2 (run-in visit) or at visit 3 even after adjustment of the work load.

Interventions	Intervention: inhaled FDC aclidinium/formoterol 400/12 µg twice daily Comparison: inhaled placebo twice daily Concomitant medications: participants were allowed to continue ICS therapy, oral or parenteral corticosteroids at a dose equivalent to 10 mg of prednisone per day or 20 mg every other day, and oxygen therapy < 15 hours/day if the administration had been stable for ≥ 4 weeks. Prohibited medications: any bronchodilator treatment (with the exception of salbutamol used as rescue medication), methylxanthines and phosphodiesterase type 4 inhibitors Number of participants with prior medications ICS: 2 (FDC 400/12 µg), 8 (placebo) LABA: 16 (FDC 400/12 µg), 11 (placebo) LAMA: 24 (FDC 400/12 µg), 23 (placebo) LAMA/LABA: 34 (FDC 400/12 µg), 40 (placebo) LABA/ICS: 17 (FDC 400/12 µg), 14 (placebo) LAMA/ICS: 2 (FDC 400/12 µg), 1 (placebo) LAMA/LABA/ICS: 11 (FDC 400/12 µg), 5 (placebo)
Outcomes	Primary outcome: change from baseline in trough FRC at week 4 Secondary outcomes: change from baseline in EET during constant work rate cycle ergometry to symptom limitation at 75% of peak work rate (W_{max}) after 8 weeks; percentage of inactive participants (< 6000 steps/day) after 8 weeks Other outcome measures: percentage of inactive participants (< 6000 steps/day) after 4 weeks; change from baseline in physical activity parameters after 4 and 8 weeks; IC during constant work rate cycle ergometry; change from baseline in D-PPAC questionnaire scores (total, amount and difficulty) after 4 and 8 weeks; pulmonary function variables after 4 weeks of treatment (predose FEV₁ and FVC, post-dose FRC, pre- and postdose specific airway conductance and residual volume)
Notes	Full-text publication Funding: Menarini Group through its affiliate Berlin-Chemie and AstraZeneca Study number: ClinicalTrials.gov NCT02424344 Authors reported and declared possible conflicts of interest. Menarini Group and AstraZeneca were also involved in the development and review of the manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (from text): "patients were randomised (1:1) to receive AB/FF [aclidinium bromide/formoterol fumarate] 400/12 µg or placebo bid via a multidose dry powder inhaler."

ACTIVATE (Continued)

		Comment: insufficient information about the sequence generation process although it was a randomised trial.
Allocation concealment (selection bias)	Unclear risk	Quote (from text): "patients were randomised (1:1) to receive AB/FF 400/12 µg or placebo bid via a multidose dry powder inhaler." Comment: no details were provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: double-blind study including blinding of investigator and participant and used a placebo dry powder which is identical in taste and appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (from text): "The safety population (used for adverse event analyses) and the intent-to-treat (ITT) population (used for efficacy analyses) were both defined as all randomised patients who took at least one dose of study medication." Comment: withdrawal rates were relatively low with similar reasons across the study arms; 5.2% (FDC 400/12 µg), 7.5% (placebo).
Selective reporting (reporting bias)	Low risk	Comment: study protocol not available, but all the prespecified outcomes in the method section were reported in the result section.
Other bias	Low risk	Comment: the authors disclosed both financial and non-financial support with no other conflicts of interest in this work. No apparent source of bias observed.

AUGMENT COPD

Methods	Study design: randomised, double-blind, placebo-controlled, parallel group, phase III study Total duration of study: 24 weeks Run-in period: 2–3 weeks Follow-up: 2 weeks after the last dose Study setting: multicentre trial, clinic patients Number of study centres and location: 222 study sites (193 sites in the US, 11 in Australia, 10 in Canada and 8 in New Zealand) Date of study: 4 October 2011 to 6 February 2013 Withdrawals: stated
Participants	Number screened: 3260 Number randomised: 1692 ITT population: 1668 Number in treatment group: 338 (FDC aclidinium/formoterol 400/6 µg), 338 (FDC aclidinium/formoterol 400/12 µg) Number in control group: 340 (aclidinium 400 µg), 339 (formoterol 12 µg), 337 (placebo)

AUGMENT COPD (Continued)

Number in efficacy analysis: 333 (FDC 400/6 µg), 335 (FDC 400/12 µg), 337 (aclidinium 400 µg), 332 (formoterol 12 µg), 331 (placebo)

Number of withdrawals: 62 (FDC 400/6 µg), 66 (FDC 400/12 µg), 72 (aclidinium 400 µg), 69 (formoterol 12 µg), 101 (placebo)

Number completing trial: 276 (FDC 400/6 µg), 272 (FDC 400/12 µg), 268 (aclidinium 400 µg), 270 (formoterol 12 µg), 236 (placebo)

Mean age (years): 63.9 (FDC 400/6 µg), 64.2 (FDC 400/12 µg), 64.4 (aclidinium 400 µg), 63.7 (formoterol 12 µg), 63.5 (placebo)

Gender (men/women): 187/151 (FDC 400/6 µg), 168/170 (FDC 400/12 µg), 188/152 (aclidinium 400 µg), 169/170 (formoterol 12 µg), 175/162 (placebo)

Caucasian (%): 92.8 (FDC 400/6 µg), 91.0 (FDC 400/12 µg), 93.2 (aclidinium 400 µg), 93.7 (formoterol 12 µg), 95.5 (placebo)

Severity of condition: moderate to severe

Diagnostic criteria: GOLD 2010

Baseline mean FEV₁ (L): 1.40 (FDC 400/6 µg), 1.34 (FDC 400/12 µg), 1.34 (aclidinium 400 µg), 1.37 (formoterol 12 µg), 1.35 (placebo)

Baseline mean postbronchodilator FEV₁ (% of predicted): 54.7 (FDC 400/6 µg), 53.2 (FDC 400/12 µg), 53.0 (aclidinium 400 µg), 53.9 (formoterol 12 µg), 52.6 (placebo)

Baseline mean smoking pack-years: 52.1 (FDC 400/6 µg), 53.3 (FDC 400/12 µg), 52.0 (aclidinium 400 µg), 52.5 (formoterol 12 µg), 53.3 (placebo)

Current smoker (number/%): 176/52.9 (FDC 400/6 µg), 173/51.6 (FDC 400/12 µg), 171/50.7 (aclidinium 400 µg), 171/51.5 (formoterol 12 µg), 169/50.9 (placebo)

Inclusion criteria: men and women aged ≥ 40 years, current or former smokers (≥ 10 pack-years) and diagnosed with stable, moderate-to-severe expiratory airflow obstruction according to GOLD guidelines (postbronchodilator FEV₁/FVC < 70% and FEV₁ ≥ 30% and < 80% predicted)

Exclusion criteria: COPD exacerbation or respiratory tract infection ≤ 6 weeks (≤ 3 months if hospitalised for exacerbation) before screening; clinically significant respiratory conditions (including asthma); clinically significant cardiovascular conditions including myocardial infarction within the previous 6 months; unstable angina; unstable arrhythmia that required changes in pharmacological therapy or other intervention within the previous 6 months.

Interventions

Intervention: inhaled FDC aclidinium/formoterol 400/6 µg twice daily, inhaled FDC aclidinium/formoterol 400/12 µg twice daily.

Comparison: inhaled aclidinium 400 µg twice daily, inhaled formoterol 12 µg twice daily, inhaled placebo twice daily.

Concomitant medications: theophylline, ICS, oral or parenteral corticosteroids (≤ 10 mg/day or 20 mg every other day of prednisone) were allowed if stable for ≥ 4 weeks prior to screening. Use of albuterol/salbutamol as rescue medication was permitted.

Excluded medications: long-acting bronchodilators other than investigative treatment were not permitted.

Outcomes

Primary outcomes: change from baseline in morning predose (trough) FEV₁ and 1-hour postdose FEV₁ at week 24

Secondary outcomes: change from baseline in SGRQ total score and improvement in TDI score at week 24

AUGMENT COPD (Continued)

Other outcome measures: rescue medication use; onset of action of bronchodilation; daily COPD symptoms assessed by the E-RS score; night-time symptoms by Nighttime Symptoms of COPD Instrument and early morning symptoms by Early Morning Symptoms of COPD Instrument respectively; adverse events

Notes	Full-text publication Funding: Almirall SA, Barcelona, Spain, and Forest Laboratories LLC, a subsidiary of Actavis plc (New York, NY, USA) Study number: ClinicalTrials.gov NCT01437397 Authors reported and declared possible conflicts of interest. The sponsors did not place any restriction on authors about the statements made in the final paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from text of extension study): "Randomisation was carried out at the start of the 24-week lead-in study. A list of patient randomisation codes was generated by Statistical Programming at Forest Research Institute and implemented by using an interactive web response system."
Allocation concealment (selection bias)	Low risk	Quote (from text of extension study): "Randomisation was carried out at the start of the 24-week lead-in study. A list of patient randomisation codes was generated by Statistical Programming at Forest Research Institute and implemented by using an interactive web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: double-blind study including blinding of participant, investigator and career for all outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: double-blind study including blinding of outcomes assessor. Quote (from text): "major adverse cardiovascular events (MACE) were evaluated and classified by an adjudication committee of independent cardiologists who were not participating in the study and were blinded to treatment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (from text): "All efficacy analyses with the exception of E-RS were based on the ITT population, defined as all randomised patients who took $\geq$ one dose of study medication and had a baseline and at least one post baseline FEV₁ assessment. E-RS data were analysed for the ITT-Exacerbation population, which included all patients in the randomised population who took at least one dose of double-blind investigational product. Safety results, were based on the safety population, defined as all randomised patients who took $\geq$ one dose of study medication. A total of 5.9% of patients in the placebo group discontinued due to insufficient therapeutic response. Among the active treatment groups, discontinuations due to insufficient response were 2.9% for formoterol, 2.4% for aclidinium, and 1.5% and 1.2% for the aclidinium/formoterol FDC 400/12 μg and 400/6 μg groups." Comment: overall withdrawal rates were balanced across study arms, 18% (FDC 400/6 μg), 20% (FDC 400/12 μg), 21% (aclidinium 400 μg), 20% (formoterol 12 μg), 30% (placebo), but the rates were high.
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but all the prespecified outcomes in the method section were reported in the result section.

AUGMENT COPD (Continued)

Other bias	Low risk	Comment: no apparent source of bias was observed.

D'Urzo 2017a

Methods	Study design: randomised, double-blind, placebo-controlled, parallel group, phase III, long-term extension study of AUGMENT COPD (NCT01437397) Study duration: 28 weeks Follow-up: 4 weeks Setting: multicentre trial Number of study centres and location: 169 centres in USA (160) and Canada (9) Date of study: April 2012 to June 2013 Withdrawals: stated
Participants	Number enrolled in extension: 921 Number in treatment group: 205 (FDC aclidinium/formoterol 400/6 µg), 184 (FDC aclidinium/formoterol 400/12 µg) Number in control group: 194 (aclidinium 400 µg), 192 (formoterol 12 µg) or 146 (placebo) Number of withdrawals: 26 (FDC 400/6 µg), 29 (FDC 400/12 µg), 29 (aclidinium 400 µg), 32 (formoterol 12 µg) or 25 (placebo) Number completing trial: 179 (FDC 400/6 µg), 155 (FDC 400/12 µg), 165 (aclidinium 400 µg), 160 (formoterol 12 µg) or 121 (placebo) Mean age (years): 63.6 (FDC 400/6 µg), 63.7 (FDC 400/12 µg), 62.9 (aclidinium 400 µg), 62.8 (formoterol 12 µg), 63.2 (placebo) Gender (men/women): 120/85 (FDC 400/6 µg), 88/96 (FDC 400/12 µg), 104/90 (aclidinium 400 µg), 90/102 (formoterol 12 µg), 81/65 (placebo) Caucasian (%): 91.2 (FDC 400/6 µg), 89.6 (FDC 400/12 µg), 91.8 (aclidinium 400 µg), 93.2 (formoterol 12 µg), 94.5 (placebo) Severity of condition: moderate to severe Diagnostic criteria: GOLD 2011 Baseline mean FEV₁ (L): 1.42 (FDC 400/6 µg), 1.30 (FDC 400/12 µg), 1.33 (aclidinium 400 µg), 1.39 (formoterol 12 µg), 1.43 (placebo) Baseline mean postbronchodilator FEV₁ (% of predicted): 55.1 (FDC 400/6 µg), 52.1 (FDC 400/12 µg), 52.7 (aclidinium 400 µg), 55.1 (formoterol 12 µg), 53.2 (placebo) Baseline mean smoking pack-years: 53.7 (FDC 400/6 µg), 53.3 (FDC 400/12 µg), 52.3 (aclidinium 400 µg), 53.1 (formoterol 12 µg), 54.5 (placebo) Current smoker (number/%): 111/54.4 (FDC 400/6 µg), 98/53.8 (FDC 400/12 µg), 115/59.3 (aclidinium 400 µg), 103/53.6 (formoterol 12 µg), 77/52.7 (placebo) Inclusion criteria: participants who completed the treatment phase of the lead-in study, LAC-MD-31 (AUGMENT COPD) with no medical contraindication; compliance with LAC-MD-31 (AUGMENT COPD) study procedures and IP dosing; agreed to participate in this extension study.

D'Urzo 2017a (Continued)

Exclusion criteria: exclusion criteria same as lead-in study (AUGMENT COPD)

Interventions	Intervention: inhaled FDC aclidinium/formoterol 400/6 µg twice daily, inhaled FDC aclidinium/formoterol 400/12 µg twice daily Comparison: inhaled aclidinium 400 µg twice daily, inhaled formoterol 12 µg twice daily, inhaled placebo twice daily Concomitant medications: theophylline, ICS, oral or parenteral corticosteroids (≤ 10 mg/day or 20 mg every other day prednisone) were allowed if treatment was stable within 4 weeks of the lead-in trial start. Albuterol (108 µg/puff) or salbutamol (100 µg/puff) were the only rescue medications permitted during the study. Excluded medications: long-acting bronchodilators other than the investigative treatment were not permitted.
Outcomes	Primary outcomes: safety and tolerability, adverse events, clinical laboratory parameters, vital sign measurement, and electrocardiogram parameters at week 28
Notes	Full-text publication Funding: Almirall SA, Barcelona, Spain, and Forest Laboratories LLC, a wholly owned subsidiary of Allergan plc, New York, NY, USA Study number: ClinicalTrials.gov NCT01572792

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from text): "Randomisation was carried out at the start of the 24-week lead-in study. A list of patient randomisation codes was generated by Statistical Programming at Forest Research Institute and implemented by using an interactive web response system."
Allocation concealment (selection bias)	Low risk	Quote (from text): "Randomisation was carried out at the start of the 24-week lead-in study. A list of patient randomisation codes was generated by Statistical Programming at Forest Research Institute and implemented by using an interactive web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (from text): "Almirall, study personnel and study patients were blinded as to which treatment patients were receiving. All inhalers were identical from an external perspective; the only difference between them was that placebo did not contain active ingredient. Active ingredients had no perceptible taste, appearance, odour, or colour that could unmask the blinded design." Comment: double blind (participant, career and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from text): "Major adverse cardiovascular events (MACE), defined in accordance with Food and Drug Administration guidance (cardiovascular death, myocardial infarction and stroke) were adjudicated by a clinical outcomes committee of independent cardiologists." Comment: double blind including blinding of outcomes assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (from text): "safety outcomes were analysed using descriptive statistics based on the extension safety population (all patients enrolled in the extension study and who took one dose of double-blind treatment in the extension study). Efficacy analyses were based on the combined intent-to-treat (ITT) population (all patients randomised in the lead-in study who took at least one

D'Urzo 2017a (Continued)

dose of double-blind investigational product and who had a baseline and one post baseline FEV₁ assessment in the lead-in study)."

Comment: withdrawal rates and reasons for dropout were relatively even across the groups (FDC 400/12 µg 28.1%; FDC 400/6 µg 26.0%; aclidinium 29.7%; formoterol 29.8%; placebo 37.4%) but high

Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but all the prespecified outcomes in the method section were reported in the result section.
Other bias	Low risk	Comment: no apparent source of bias was observed.

Donohue 2016

Methods	Study design: randomised, double-blind, parallel-group, phase III study Total duration of study: 52 weeks Run-in period: 2–3 weeks Follow-up: 4 weeks after the last dose Number of study centres and location: 135 centres in the US Date of study: September 2011 to March 2013 Withdrawals: stated
Participants	Number screened: 1063 Number randomised: 590 ITT population: 581 Number in treatment group: 392 (FDC aclidinium/formoterol 400/12 µg) Number in control group: 198 (formoterol 12 µg) Number of withdrawals: 127 (FDC 400/12 µg), 65 (formoterol 12 µg) Number completing trial: 265 (FDC 400/12 µg), 133 (formoterol 12 µg) Mean age (years): 63.9 (FDC 400/12 µg), 64.7 (formoterol 12 µg) Gender (men/women): 216/176 (FDC 400/12 µg), 109/89 (formoterol 12 µg) Severity of condition: moderate to severe Diagnostic criteria: GOLD Baseline mean postbronchodilator FEV₁ (% of predicted): 51.8 (FDC 400/12 µg), 50.5 (formoterol 12 µg) Baseline mean smoking pack-years: 50.9 (FDC 400/12 µg), 52.6 (formoterol 12 µg) Current smoker (number/%): 184/46.9 (FDC 400/12 µg), 87/43.9 (formoterol 12 µg) Inclusion criteria: men and women, current or former smokers (history ≥ 10 pack-years) aged ≥ 40 years with a diagnosis of stable moderate-to-severe COPD according to GOLD guidelines: postbronchodilator FEV₁/FVC < 70% and FEV₁ ≥ 30% and < 80% predicted Exclusion criteria: any respiratory infection or COPD exacerbation ≤ 6 weeks before screening; pulmonary rehabilitation

Donohue 2016 (Continued)

within 3 months of screening or an intention to start during the trial; clinically significant cardiovascular conditions, including myocardial infarction ≤ 6 months; newly diagnosed arrhythmia ≤ 3 months; unstable angina; unstable arrhythmia that had required changes in pharmacological therapy or other interventions ≤ 6 months; use of an automated implantable cardioverter-defibrillator; history of thoracic surgery ≤ 1 year of screening; hospitalisation ≤ 12 months for heart failure (NYHA class III) or history of thoracic surgery ≤ 1 year of screening and NYHA class IV; QTcB > 470 ms at rest; or body mass index ≥ 40 kg/m².

Interventions	Intervention: inhaled FDC aclidinium/formoterol 400/12 µg twice daily Comparison: inhaled formoterol 12 µg twice daily Concomitant medications: albuterol as needed, but not within 6 hours before a visit; ICS and oral or parenteral corticosteroids at doses ≤ 10 mg/day; theophylline and H1 antihistamine at stable dosage for 4 weeks prior to screening and throughout the trial; chronic use of oxygen therapy up to 15 hours/day provided the dosage was stable for 4 weeks prior to screening; selective beta₁ antagonists (atenolol, metoprolol, nebivolol) for chronic use if the dosage was stable for 2 weeks prior to screening were permitted. Excluded medications: indacaterol was not allowed within 15 days prior to screening or during the trial. People taking concomitant medications prior to and continuing during study ICS: 138 (FDC 400/12 µg), 68 (formoterol 12 µg) LABA: 0 (FDC 400/12 µg), 0 (formoterol 12 µg) LAMA: 0 (FDC 400/12 µg), 2 (formoterol 12 µg) LABA + ICS: 0 (FDC 400/12 µg), 1 (formoterol 12 µg) Theophylline: 4 (FDC 400/12 µg), 1 (formoterol 12 µg)
Outcomes	Primary outcomes: change from baseline in morning predose (trough) FEV₁ at weeks 1, 12, 24, 38 and 52; mean daily total rescue medication use; adverse events Secondary outcomes: not specified
Notes	Source of support: Forest Laboratories LLC, a wholly owned subsidiary of Allergan plc, New York, NY, USA, and by Almirall SA, Barcelona, Spain. Study number: ClinicalTrials.gov NCT01437540

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from text): "Randomization was carried out by assigning patient identification numbers via an interactive web response system provided by Premier Research Group Limited (East Hartford, Connecticut, USA)."
Allocation concealment (selection bias)	Low risk	Quote (from text): "Randomization was carried out by assigning patient identification numbers via an interactive web response system provided by Premier Research Group Limited (East Hartford, Connecticut, USA)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: double-blind study including blinding of investigator, participant and career.
Blinding of outcome assessment (detection bias)	Low risk	Comment: double-blind study including blinding of outcomes assessor.

Combined aclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD) (Review)

Donohue 2016 (Continued)

All outcomes

Quote (from text): "major adverse cardiac events (MACE) were evaluated by three blinded independent expert cardiologists not participating in the study."

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (from text): "lung function and rescue medication use were analysed in the intent-to-treat (ITT) population (all randomised patients who received $\geq$ one dose of study medication and had a baseline and $\geq$ one post-baseline FEV assessment). Exacerbation rate was analysed in the ITT-exacerbation population (all randomised patients who took $\geq$ one dose of study medication)." Comment: withdrawal rates were relatively balanced between treatment (FDC 400/12 μ g 32.4%) and control groups (formoterol 32.8%) with similar reasons. However, the rates were high.
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the published report included all prespecified outcomes.
Other bias	Low risk	Comment: no apparent source of bias was observed. Participant level data was provided upon request.

NCT00706914

Methods	Study design: randomised, double-blind, parallel group, phase II study Total duration of study: 4 weeks Follow-up: 7 days after the last inhalation Number of study centres and location: 31 centres in the US Date of study: March 2008 to February 2009 Withdrawals: stated
Participants	Number screened: 264 Number randomised: 156 Number in treatment group: 63 (FDC aclidinium/formoterol 200/12 μ g once daily + placebo in the evening), 62 (FDC aclidinium/formoterol 200/12 μ g once daily + formoterol in the evening) Number in control group: 31 (formoterol 12 μ g twice daily) Number of withdrawals: 6 (FDC + placebo), 4 (FDC + formoterol), 1 (formoterol 12 μ g) Number completing trial: 57 (FDC + placebo), 58 (FDC + formoterol), 30 (formoterol 12 μ g) Mean age (years): 63.0 (FDC + placebo), 63.9 (FDC + formoterol), 62.2 (formoterol 12 μ g) Gender (men/women): 35/28 (FDC + placebo), 37/25 (FDC + formoterol), 16/15 (formoterol 12 μ g) Severity of condition: moderate to severe Diagnostic criteria: GOLD Baseline mean smoking pack-years: 61.3 (FDC + placebo), 61.0 (FDC + formoterol), 50.8 (formoterol 12 μ g) Baseline mean FEV ₁ (L): 1.29 (FDC + placebo), 1.33 (FDC + formoterol), 1.23 (formoterol 12 μ g) Inclusion criteria: men and women aged 40–80 years inclusive; current or ex-smokers of ≥ 10 packyear with a clinical diagnosis of moderate to severe stable COPD

NCT00706914 (Continued)

Exclusion criteria: history or current diagnosis of asthma, allergic rhinitis or exercise-induced bronchospasm, COPD exacerbation or respiratory tract infection ≤ 6 weeks (≤ 3 months if hospitalised for exacerbation) before screening; eosinophil count ≥ 600 cells/mm³; long-term oxygen therapy > 15 hours/day

Interventions	Intervention: inhaled FDC aclidinium/formoterol 200/12 µg once daily in the morning and placebo once daily in the evening via Genuair, inhaled FDC aclidinium/formoterol 200/12 µg once daily in the morning and formoterol 12 µg once daily in the evening via Genuair Comparison: inhaled formoterol 12 µg twice daily via Genuair
Outcomes	Primary outcomes: improvement in symptoms at week 4 Secondary outcomes: change from baseline in lung function tests (trough FEV ₁ , peak FEV ₁ , FEV ₁ AUC _{0-3/3h}) at week 4
Notes	Source of support: Almirall SA, Barcelona, Spain, and Forest Laboratories, Inc, New York, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information on methods of randomisation though it was a randomised trial
Allocation concealment (selection bias)	Unclear risk	Comment: no details provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participant, investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (from text): "analysis includes the number of patients in the randomised population with available analysis value at both baseline and a specific time point. Randomised population is defined as all patients in the screened population who were randomised to a treatment group in the study." Comment: withdrawal rates were relatively low across the study arms; 9.5% (FDC + placebo), 6.5% (FDC + formoterol), 3.3% (formoterol 12 µg).
Selective reporting (reporting bias)	Low risk	Comment: no published report available, but results for all specified outcomes were reported in the synopsis.
Other bias	Low risk	Comment: synopsis was available from the ClinicalTrials.gov; no other apparent source of bias was observed.

Sliwinski 2010

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group, phase II study Study duration: 4 weeks

Sliwinski 2010 (Continued)

Date of study: February 2008 to November 2008

Follow-up: 7 days after the last dose

Number of study centres and location: 81 centres (21 in Russia, 13 in Poland, 8 in India, 8 in Romania, 6 in Australia, 5 in Taiwan, 5 in the Czech Republic, 5 in New Zealand, 4 in Hungary, 3 in Malaysia and 3 in Slovakia)

Withdrawals: stated

Participants	Number screened: 808 Number randomised: 566 ITT population: 563 Number in treatment group: 121 (FDC aclidinium/formoterol 200/6 µg once daily), 120 (FDC aclidinium/formoterol 200/12 µg once daily), 125 (aclidinium/formoterol FDC 200/18 µg once daily) Number in control group: 76 (aclidinium 200 µg once daily), 65 (formoterol 12 µg once daily) or 59 (placebo) Number of withdrawals: 6 (FDC 200/6 µg), 7 (FDC 200/12 µg), 8 (FDC 200/18 µg), 2 (aclidinium 200 µg), 7 (formoterol 12 µg), 2 (placebo) Number completing trial: 115 (FDC 200/6 µg), 113 (FDC 200/12 µg), 117 (FDC 200/18 µg), 74 (aclidinium 200 µg), 58 (formoterol 12 µg), 57 (placebo) Mean age (years): 62.9 (FDC 200/6 µg), 63.6 (FDC 200/12 µg), 63.9 (FDC 200/18 µg), 63.7 (aclidinium 200 µg), 64.0 (formoterol 12 µg), 60.7 (placebo) Gender (men/women): 91/30 (FDC 200/6 µg), 98/22 (FDC 200/12 µg), 96/29 (FDC 200/18 µg), 60/16 (aclidinium 200 µg), 54/11 (formoterol 12 µg), 44/15 (placebo) Inclusion criteria: men and women aged 40–80 years inclusive, current or exsmokers of ≥10 packyear with a clinical diagnosis of moderate to severe stable COPD Exclusion criteria: history or current diagnosis of asthma, allergic rhinitis or atopy; COPD exacerbation or respiratory tract infection ≤ 6 weeks (≤ 3 months if hospitalised for exacerbation) before screening; contraindication to anticholinergic drugs
Interventions	Intervention: aclidinium 200 µg + formoterol 6 µg or, 12 µg or 18 µg once daily via the Genuair, multi-dose dry powder inhaler Comparison: aclidinium 200 µg, formoterol 12 µg or placebo once daily via the Genuair inhaler
Outcomes	Primary outcomes: change from baseline in normalised FEV₁ AUC over 12 hours (AUC_{0–12h/12h}) at week 4, changes from baseline in trough FEV₁, peak FEV₁, FEV₁ AUC_{0–3/3h} and FEV₁ AUC_{0–6/6h} at week 4 Secondary outcomes: pharmacokinetics and safety
Notes	Trial was available as abstract only. Source of support: Almirall SA, Barcelona, Spain, and Forest Laboratories, Inc, New York, USA Study number: EUCTR2007-004435-30-CZ, NCT00626522

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information on methods of randomisation though it was a randomised trial.

Sliwinski 2010 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: no details were provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (from text): "ITT population is defined as all randomised patients who took at least one dose of investigational medicinal product and had at least the baseline and one post-baseline efficacy assessments." Comment: withdrawal rates were low and reasons for dropout were relatively even across the groups (FDC 200/6 µg 4.9%; FDC 200/12 µg 5.8%; FDC 200/18 µg 6.4%; aclidinium 2.6%; formoterol 10.8%; placebo 3.4%)
Selective reporting (reporting bias)	Low risk	Comment: no published report available, but results for all specified outcomes were reported in the synopsis.
Other bias	Low risk	Comment: synopsis was available from the ClinicalTrials.gov; no other apparent source of bias was observed.

AUC: area under the curve; COPD: chronic obstructive pulmonary disease; D-PPAC: Daily PROactive Physical Activity in COPD; EET: exercise endurance time; E-RS: EXACT-Respiratory Symptoms; EXACT: Exacerbations of Chronic Pulmonary Disease Tool; FDC: fixed-dose combination; FEV₁: forced expiratory volume in one second; FF: formoterol fumarate; FRC: functional residual capacity; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IC: inspiratory capacity; ICS: inhaled corticosteroid; IP: investigational product; ITT: intention-to-treat analysis; LABA: long-acting beta₂-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council; NYHA: New York Heart Association; SAE: serious adverse event; SGRQ: St George's Respiratory Questionnaire; TDI: Transitional Dyspnoea Index.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
ALIGHT-COPD	Cross-over trial
ASTUTE	Study withdrawn prior to enrolment
EUCTR2007-003648-31-DE	Cross-over trial
Fogarty 2014	Cross-over trial
ISRCTN11017699	Study of aclidinium bromide/formoterol vs triple therapy (aclidinium/formoterol/budesonide), with no aclidinium, formoterol monotherapy or placebo arms
Kerwin 2013	Cross-over trial
MUSIC	Study of aclidinium bromide/formoterol fumarate combination vs triple therapies, with no aclidinium, formoterol monotherapy or placebo arms
NCT02429765	Cross-over trial

Study	Reason for exclusion
NCT03104634	Cross-over trial
NCT03275116	Cross-over trial
NCT03276078	Study of acclidinium bromide/formoterol fumarate combination with no comparison
van der Palen 2013	Preference study of Genuair vs HandiHaler inhalers
Vogelmeier 2015	Study of acclidinium bromide/formoterol fumarate combination vs salmeterol/fluticasone

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

AMPLIFY

Methods	Study design: randomised, double-blind, parallel group, phase III study Study duration: 24 weeks Date of study: 5 July 2016 to 9 June 2017
Participants	Enrolment: 1595 Inclusion criteria: men and non-pregnant, non-lactating women aged ≥ 40 years; current or former smokers with smoking history ≥ 10 pack-years; diagnosis of moderate-to-very severe stable COPD with postbronchodilator $FEV_1 < 80\%$ of the predicted normal and postbronchodilator $FEV_1/FVC < 70\%$ at screening visit; symptomatic people with a CAT score ≥ 10 at screening and randomisation visit; able to perform repeatable pulmonary function testing for FEV_1 according to the American Thoracic Society /European Respiratory Society 2005 criteria at screening. Exclusion criteria: history or current diagnosis of asthma, any respiratory tract infection or COPD exacerbation ≤ 6 weeks (≤ 3 months if hospitalised for exacerbation) before screening; clinically significant cardiovascular, medical and other respiratory conditions; long-term oxygen therapy ≥ 15 hours/day; clinically significant abnormalities in the laboratory tests, ECG parameters or in the physical examination at screening.
Interventions	Interventions: inhaled FDC acclidinium/formoterol 400/12 μg twice daily via Pressair/Genuair inhaler Comparisons: inhaled acclidinium bromide 400 μg twice daily via Pressair/Genuair inhaler, inhaled formoterol fumarate 12 μg twice daily via Pressair/Genuair inhaler, inhaled tiotropium 18 μg once daily via HandiHaler, inhaled placebo
Outcomes	Primary outcomes: change from baseline in 1-hour morning postdose FEV_1 of FDC 400/12 μg compared to acclidinium 400 μg at week 24. Change from baseline in morning predose (trough) FEV_1 of FDC 400/12 μg compared to formoterol 12 μg at week 24. Change from baseline in morning predose (trough) FEV_1 of acclidinium 400 μg compared to tiotropium 18 μg at week 24 Secondary outcomes: change from baseline in normalised $AUC_{0-3h} FEV_1$ St George's Respiratory Questionnaire total score responders
Notes	Study number: ClinicalTrials.gov NCT02796677

AMPLIFY (Continued)

Source of support: AstraZeneca

This study has been completed but the results not published yet.

AUC: area under the curve; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; FDC: fixed-dose combination; FEV₁: forced expiratory volume in one second.

Characteristics of ongoing studies [ordered by study ID]

AVANT

Trial name or title	Study to patients with stable COPD to assess the efficacy and safety of acclidinium bromide/formoterol fumarate (DUAKLIR).
Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group, phase III study Study duration: 24 weeks Setting: multicentre trial (80 study locations)
Participants	Estimated enrolment: 1060 Inclusion criteria: men and non-pregnant, non-lactating women aged ≥ 40 years; current or former smokers with smoking history of ≥ 10 pack-years; diagnosis of stable COPD according to GOLD 2015 guidelines for ≥ 6 months prior to screening with moderate-to-severe stable COPD (Stage II or Stage III, according to GOLD 2015): postbronchodilator FEV₁ $\geq 30\%$ and $< 80\%$ and postbronchodilator FEV₁/FVC ratio $< 70\%$; able to perform repeatable pulmonary function testing for FEV₁ according to the American Thoracic Society/European Respiratory Society 2005 criteria at screening. Exclusion criteria: history or current diagnosis of asthma; any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation (including the mild COPD exacerbation) within 6 weeks prior to screening or during the run-in period; hospitalised for COPD exacerbation (emergency department visit for > 24 hours will be considered a hospitalisation) within 3 months prior to screening and during the run-in period; clinically significant respiratory conditions other than COPD; people who need to start a pulmonary rehabilitation programme during the study or people who started/finished it within 3 months prior to screening; use of long-term oxygen therapy (≥ 15 hours/day); clinically significant cardiovascular conditions; QT corrected interval (QTc) > 470 msec-onds at screening; malignancy and clinically significant medical illnesses; clinically significant abnormalities in the laboratory tests, ECG parameters (other than QTc) or in the physical examination at screening; history of hypersensitivity to inhaled anticholinergics
Interventions	Intervention: inhaled FDC acclidinium bromide 400 μg/formoterol fumarate 12 μg twice daily via Genuair Comparison: inhaled acclidinium bromide 400 μg twice daily via Genuair, inhaled formoterol fumarate 12 μg twice daily via Turbuhaler, Inhaled placebo twice daily via Genuair or via Turbuhaler
Outcomes	Primary outcomes: Change from baseline in 1-hour morning postdose FEV₁ of FDC 400/12 μg compared to acclidinium bromide at week 24. Change from baseline in morning predose (trough) FEV₁ of FDC 400/12 μg compared to formoterol fumarate at week 24. Change from baseline in trough FEV₁ of acclidinium bromide 400 μg compared to placebo at week 24. Secondary outcomes:

AVANT (Continued)

Change from baseline in peak FEV₁ of aclidinium bromide 400 µg compared to placebo at week 24.

Improvements TDI focal score of FDC 400/12 µg and aclidinium bromide 400 µg compared to placebo at week 24.

Change from baseline in SGRQ total score of FDC 400/12 µg and aclidinium bromide 400 µg compared to placebo at week 24

Starting date	24 January 2017
Contact information	AstraZeneca Clinical Study Information Center tel: 1-877-240-9479 information.center@astrazeneca.com
Notes	Estimated study completion date: 12 December 2018 Study number: ClinicalTrials.gov NCT03022097 Source of support: AstraZeneca and PAREXEL

COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; FDC: fixed-dose combination; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; SGRQ: St George's Respiratory Questionnaire; TDI: Transitional Dyspnoea Index.

DATA AND ANALYSES

Comparison 1. Fixed-dose combination (FDC) aclidinium/formoterol versus aclidinium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring steroids or antibiotics or both: number of participants	2	2156	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.71, 1.27]
1.1 Formoterol 12 µg	2	1080	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.60, 1.39]
1.2 Formoterol 6 µg	2	1076	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.65, 1.49]
2 Quality of life: change from baseline in St George's Respiratory Questionnaire (SGRQ) total score	2	2002	Mean Difference (IV, Fixed, 95% CI)	-0.92 [-2.15, 0.30]
2.1 Formoterol 12 µg	2	1004	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-2.51, 0.96]
2.2 Formoterol 6 µg	2	998	Mean Difference (IV, Fixed, 95% CI)	-1.08 [-2.81, 0.65]
3 Quality of life: number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score	2	2002	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.97, 1.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Formoterol 12 µg	2	1004	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.86, 1.45]
3.2 Formoterol 6 µg	2	998	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.93, 1.59]
4 Non-fatal serious adverse events	3	2473	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.79, 1.80]
4.1 Formoterol 12 µg	3	1238	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.74, 2.36]
4.2 Formoterol 6 µg	3	1235	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.60, 1.92]
5 Total number of deaths	3	2473	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.14, 3.16]
6 Hospital admissions due to exacerbations: number of participants	2	2156	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.29, 1.29]
6.1 Formoterol 12 µg	2	1080	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.19, 1.74]
6.2 Formoterol 6 µg	2	1076	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.24, 1.75]
7 Improvement in symptoms: change from baseline in Transitional Dyspnoea Index (TDI) focal score	2	2013	Mean Difference (IV, Fixed, 95% CI)	0.37 [0.07, 0.68]
7.1 Formoterol 12 µg	2	1012	Mean Difference (IV, Fixed, 95% CI)	0.42 [-0.01, 0.85]
7.2 Formoterol 6 µg	2	1001	Mean Difference (IV, Fixed, 95% CI)	0.33 [-0.10, 0.76]
8 Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit)	2	2013	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [1.11, 1.62]
8.1 Formoterol 12 µg	2	1012	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.98, 1.67]
8.2 Formoterol 6 µg	2	1001	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [1.08, 1.84]
9 Change in lung function: from baseline in trough forced expiratory volume in 1 second (FEV ₁) (L)	3	2333	Mean Difference (IV, Fixed, 95% CI)	0.02 [0.00, 0.04]
9.1 Formoterol 12 µg	3	1171	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.01, 0.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Formoterol 6 µg	3	1162	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.02, 0.04]
10 Change in lung function: from baseline in 1-hour postmorning dose FEV ₁ (L)	2	2018	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.08, 0.12]
10.1 Formoterol 12 µg	2	1013	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.09, 0.15]
10.2 Formoterol 6 µg	2	1005	Mean Difference (IV, Fixed, 95% CI)	0.08 [0.05, 0.11]
11 Adverse events (not including serious adverse events): number of participants	3	2473	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.18]
11.1 Formoterol 12 µg	3	1238	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.68, 1.27]
11.2 Formoterol 6 µg	3	1235	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.71, 1.31]

Analysis 1.1. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 1 Exacerbations requiring steroids or antibiotics or both: number of participants.

Analysis 1.2. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 2 Quality of life: change from baseline in St George's Respiratory Questionnaire (SGRQ) total score.

Analysis 1.3. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 3 Quality of life: number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score.

Analysis 1.4. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 4 Non-fatal serious adverse events.

Analysis 1.5. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 5 Total number of deaths.

Analysis 1.6. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 6 Hospital admissions due to exacerbations: number of participants.

Analysis 1.7. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 7 Improvement in symptoms: change from baseline in Transitional Dyspnoea Index (TDI) focal score.

Study or subgroup	FDC		Acclidinium		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Test for subgroup differences: $\chi^2=0.09$, $df=1$ ($P=0.76$), $I^2=0\%$

Favours acclidinium   -2   -1   0   1   2   Favours FDC

Analysis 1.8. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 8 Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit).

Study or subgroup	FDC		Acclidinium		Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
	n/N		n/N				

1.8.1 Formoterol 12 μ g

ACLIFORM COPD	223/344		93/165			23.89%	1.43[0.98,2.08]
AUGMENT COPD	195/335		92/168			27.67%	1.15[0.79,1.67]
Subtotal (95% CI)	679		333			51.55%	1.28[0.98,1.67]

Total events: 418 (FDC), 185 (Acclidinium)
Heterogeneity: $\tau^2=0$; $\chi^2=0.63$, $df=1$ ($P=0.43$); $I^2=0\%$
Test for overall effect: $Z=1.81$ ($P=0.07$)

1.8.2 Formoterol 6 μ g

ACLIFORM COPD	212/333		94/166			24.63%	1.34[0.92,1.96]
AUGMENT COPD	214/333		93/169			23.82%	1.47[1.01,2.14]
Subtotal (95% CI)	666		335			48.45%	1.4[1.08,1.84]

Total events: 426 (FDC), 187 (Acclidinium)
Heterogeneity: $\tau^2=0$; $\chi^2=0.11$, $df=1$ ($P=0.74$); $I^2=0\%$
Test for overall effect: $Z=2.49$ ($P=0.01$)

Total (95% CI)

	1345		668			100%	1.34[1.11,1.62]

Total events: 844 (FDC), 372 (Acclidinium)
Heterogeneity: $\tau^2=0$; $\chi^2=0.98$, $df=3$ ($P=0.81$); $I^2=0\%$
Test for overall effect: $Z=3.04$ ($P=0$)
Test for subgroup differences: $\chi^2=0.24$, $df=1$ ($P=0.62$), $I^2=0\%$

Favours acclidinium   0.5   0.7   1   1.5   2   Favours FDC

Analysis 1.9. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 9 Change in lung function: from baseline in trough forced expiratory volume in 1 second (FEV₁) (L).

Study or subgroup	FDC		Acclidinium		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

1.9.1 Formoterol 12 μ g

ACLIFORM COPD	349	0.1 (0.2)	166	0.1 (0.2)		22.4%	0.03[-0.01,0.07]
AUGMENT COPD	335	0.1 (0.2)	168	0.1 (0.2)		22.36%	0.03[-0.01,0.07]
Sliwinski 2010	117	0.1 (0.2)	36	-0 (0.2)		5.14%	0.1[0.02,0.19]
Subtotal ***	801		370			49.9%	0.04[0.01,0.06]

Heterogeneity: $\tau^2=0$; $\chi^2=2.61$, $df=2$ ($P=0.27$); $I^2=23.44\%$
Test for overall effect: $Z=2.56$ ($P=0.01$)

1.9.2 Formoterol 6 μ g

Favours acclidinium   -0.1   -0.05   0   0.05   0.1   Favours FDC

Analysis 1.10. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 10 Change in lung function: from baseline in 1-hour postmorning dose FEV₁ (L).

Analysis 1.11. Comparison 1 Fixed-dose combination (FDC) acclidinium/formoterol versus acclidinium, Outcome 11 Adverse events (not including serious adverse events): number of participants.

Comparison 2. Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring steroids or antibiotics or both: number of participants	3	2694	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.62, 0.99]
1.1 Formoterol 12 µg	3	1622	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.56, 1.00]
1.2 Formoterol 6 µg	2	1072	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.26]
2 Quality of life: change from baseline in St George's Respiratory Questionnaire (SGRQ) total score	2	2002	Mean Difference (IV, Fixed, 95% CI)	-1.88 [-3.10, -0.65]
2.1 Formoterol 12 µg	2	1005	Mean Difference (IV, Fixed, 95% CI)	-1.72 [-3.45, 0.02]
2.2 Formoterol 6 µg	2	997	Mean Difference (IV, Fixed, 95% CI)	-2.03 [-3.76, -0.30]
3 Quality of life: Number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score	1	1000	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.89, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Formoterol 12 µg	1	501	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.87, 1.84]
3.2 Formoterol 6 µg	1	499	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.73, 1.53]
4 Non-fatal serious adverse events	5	3140	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.82, 1.61]
4.1 Formoterol 12 µg	5	1914	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.76, 1.70]
4.2 Formoterol 6 µg	3	1226	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.65, 2.20]
5 Total number of deaths	5	3140	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.44, 4.87]
6 Hospital admissions due to exacerbations: number of participants	3	2694	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.45, 1.28]
6.1 Formoterol 12 µg	3	1622	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.38, 1.25]
6.2 Formoterol 6 µg	2	1072	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.34, 3.28]
7 Improvement in symptoms: change from baseline in Transitional Dyspnoea Index (TDI) focal score	2	2010	Mean Difference (IV, Fixed, 95% CI)	0.42 [0.11, 0.72]
7.1 Formoterol 12 µg	2	1011	Mean Difference (IV, Fixed, 95% CI)	0.47 [0.03, 0.90]
7.2 Formoterol 6 µg	2	999	Mean Difference (IV, Fixed, 95% CI)	0.37 [-0.06, 0.80]
8 Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit)	2	2010	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [1.07, 1.56]
8.1 Formoterol 12 µg	2	1011	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.94, 1.60]
8.2 Formoterol 6 µg	2	999	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [1.05, 1.79]
9 Change in lung function: from baseline in trough forced expiratory volume in 1 second (FEV ₁) (L)	4	2411	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.03, 0.06]
9.1 Formoterol 12 µg	4	1254	Mean Difference (IV, Fixed, 95% CI)	0.05 [0.03, 0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Formoterol 6 µg	3	1157	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.01, 0.07]
10 Change lung function: from baseline in 1-hour postmorning dose FEV ₁ (L)	2	2021	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.07, 0.11]
10.1 Formoterol 12 µg	2	1015	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.08, 0.14]
10.2 Formoterol 6 µg	2	1006	Mean Difference (IV, Fixed, 95% CI)	0.07 [0.04, 0.10]
11 Adverse events (not including serious adverse events): number of participants	5	3140	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.65, 0.93]
11.1 Formoterol 12 µg	5	1914	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.63, 0.99]
11.2 Formoterol 6 µg	3	1226	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.56, 1.02]

Analysis 2.1. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 1 Exacerbations requiring steroids or antibiotics or both: number of participants.

Study or subgroup	FDC n/N	Formoterol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Test for subgroup differences: $\chi^2=0.22$, $df=1$ ($P=0.64$), $I^2=0\%$					
			Favours FDC 0.1 0.2 0.5 1 2 5 10 Favours formoterol		

Analysis 2.2. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 2 Quality of life: change from baseline in St George's Respiratory Questionnaire (SGRQ) total score.

Study or subgroup	FDC		Formoterol		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
2.2.1 Formoterol 12 µg							
ACLIFORM COPD	338	-7.2 (12.9)	166	-5.6 (12.9)		26.21%	-1.58[-3.98,0.81]
AUGMENT COPD	335	-6.6 (13.5)	166	-4.7 (13.5)		23.7%	-1.87[-4.38,0.65]
Subtotal ***	673		332			49.91%	-1.72[-3.45,0.02]
Heterogeneity: $\tau^2=0$; $\chi^2=0.03$, $df=1$ ($P=0.87$); $I^2=0\%$							
Test for overall effect: $Z=1.94$ ($P=0.05$)							
2.2.2 Formoterol 6 µg							
ACLIFORM COPD	332	-8.3 (12.9)	166	-5.6 (12.9)		26.13%	-2.76[-5.16,-0.36]
AUGMENT COPD	333	-5.9 (13.3)	166	-4.7 (13.5)		23.96%	-1.24[-3.74,1.26]
Subtotal ***	665		332			50.09%	-2.03[-3.76,-0.3]
Heterogeneity: $\tau^2=0$; $\chi^2=0.74$, $df=1$ ($P=0.39$); $I^2=0\%$							
Test for overall effect: $Z=2.3$ ($P=0.02$)							
Total ***	1338		664			100%	-1.88[-3.1,-0.65]
Heterogeneity: $\tau^2=0$; $\chi^2=0.83$, $df=3$ ($P=0.84$); $I^2=0\%$							
Test for overall effect: $Z=3$ ($P=0$)							
Test for subgroup differences: $\chi^2=0.06$, $df=1$ ($P=0.8$), $I^2=0\%$							
					Favours FDC -10 -5 0 5 10 Favours formoterol		

Analysis 2.3. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 3 Quality of life: Number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score.

Study or subgroup	Favours for- moterol n/N	Formoterol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Formoterol 12 µg					
AUGMENT COPD	195/335	87/166		47.52%	1.26[0.87,1.84]
Subtotal (95% CI)	335	166		47.52%	1.26[0.87,1.84]
Total events: 195 (Favours formoterol), 87 (Formoterol)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=1.23$ ($P=0.22$)					
2.3.2 Formoterol 6 µg					
AUGMENT COPD	179/333	87/166		52.48%	1.06[0.73,1.53]
Subtotal (95% CI)	333	166		52.48%	1.06[0.73,1.53]
Total events: 179 (Favours formoterol), 87 (Formoterol)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.28$ ($P=0.78$)					
			Favours formoterol 0.2 0.5 1 2 5 Favours FDC		

Analysis 2.4. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 4 Non-fatal serious adverse events.

Analysis 2.5. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 5 Total number of deaths.

Analysis 2.6. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 6 Hospital admissions due to exacerbations: number of participants.

Analysis 2.7. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 7 Improvement in symptoms: change from baseline in Transitional Dyspnoea Index (TDI) focal score.

Analysis 2.8. Comparison 2 Fixed-dose combination (FDC) acclidinium/ formoterol versus formoterol, Outcome 8 Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit).

Analysis 2.9. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 9 Change in lung function: from baseline in trough forced expiratory volume in 1 second (FEV₁) (L).

Analysis 2.10. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 10 Change lung function: from baseline in 1-hour postmorning dose FEV₁ (L).

Analysis 2.11. Comparison 2 Fixed-dose combination (FDC) acclidinium/formoterol versus formoterol, Outcome 11 Adverse events (not including serious adverse events): number of participants.

Comparison 3. Fixed-dose combination (FDC) acclidinium and formoterol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring steroids or antibiotics or both: number of participants	2	1960	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.60, 1.12]
1.1 Formoterol 12 µg	2	983	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.52, 1.28]
1.2 Formoterol 6 µg	2	977	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.53, 1.27]
2 Quality of life: change from baseline in St George's Respiratory Questionnaire (SGRQ) total score	2	1823	Mean Difference (IV, Fixed, 95% CI)	-2.91 [-4.33, -1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Formoterol 12 µg	2	915	Mean Difference (IV, Fixed, 95% CI)	-2.86 [-4.87, -0.85]
2.2 Formoterol 6 µg	2	908	Mean Difference (IV, Fixed, 95% CI)	-2.97 [-4.97, -0.96]
3 Quality of life: Number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score	2	1823	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [1.39, 2.13]
3.1 Formoterol 12 µg	2	915	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [1.26, 2.28]
3.2 Formoterol 6 µg	2	908	Odds Ratio (M-H, Fixed, 95% CI)	1.75 [1.29, 2.36]
4 Non-fatal serious adverse events	4	2527	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.72, 1.74]
4.1 Formoterol 12 µg	4	1399	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.63, 2.10]
4.2 Formoterol 6 µg	3	1128	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.56, 2.09]
5 Total number of deaths	3	2260	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.79 [0.37, 39.13]
6 Hospital admissions due to exacerbations: number of participants	2	1960	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.18]
6.1 Formoterol 12 µg	2	983	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.15, 1.60]
6.2 Formoterol 6 µg	2	977	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.21, 1.65]
7 Improvement in symptoms: change from baseline in Transitional Dyspnoea Index (TDI) focal score	2	1832	Mean Difference (IV, Fixed, 95% CI)	1.32 [0.96, 1.69]
7.1 Formoterol 12 µg	2	922	Mean Difference (IV, Fixed, 95% CI)	1.37 [0.85, 1.88]
7.2 Formoterol 6 µg	2	910	Mean Difference (IV, Fixed, 95% CI)	1.28 [0.77, 1.80]
8 Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit)	2	1832	Odds Ratio (M-H, Fixed, 95% CI)	2.51 [2.02, 3.11]
8.1 Formoterol 12 µg	2	922	Odds Ratio (M-H, Fixed, 95% CI)	2.37 [1.75, 3.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Formoterol 6 µg	2	910	Odds Ratio (M-H, Fixed, 95% CI)	2.65 [1.96, 3.60]
9 Change in lung function: from base-line in trough forced expiratory volume in 1 second (FEV ₁) (L)	3	2137	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.10, 0.14]
9.1 Formoterol 12 µg	3	1073	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.10, 0.16]
9.2 Formoterol 6 µg	3	1064	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.07, 0.14]
10 Change lung function: from base-line in 1-hour postmorning dose FEV ₁ (L)	2	1842	Mean Difference (IV, Fixed, 95% CI)	0.27 [0.25, 0.30]
10.1 Formoterol 12 µg	2	925	Mean Difference (IV, Fixed, 95% CI)	0.29 [0.25, 0.33]
10.2 Formoterol 6 µg	2	917	Mean Difference (IV, Fixed, 95% CI)	0.25 [0.22, 0.29]
11 Adverse events (not including serious adverse events): number of participants	4	2527	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.76, 1.22]
11.1 Formoterol 12 µg	4	1399	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.22]
11.2 Formoterol 6 µg	3	1128	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.75, 1.53]

Analysis 3.1. Comparison 3 Fixed-dose combination (FDC) acclidinium and formoterol versus placebo, Outcome 1 Exacerbations requiring steroids or antibiotics or both: number of participants.

Analysis 3.2. Comparison 3 Fixed-dose combination (FDC) acclidinium and formoterol versus placebo, Outcome 2 Quality of life: change from baseline in St George's Respiratory Questionnaire (SGRQ) total score.

Analysis 3.3. Comparison 3 Fixed-dose combination (FDC) acclidinium and formoterol versus placebo, Outcome 3 Quality of life: Number of participants with clinically significant improvement (≥ 4 units) in SGRQ total score.

Analysis 3.4. Comparison 3 Fixed-dose combination (FDC) acclidinium and formoterol versus placebo, Outcome 4 Non-fatal serious adverse events.

Analysis 3.5. Comparison 3 Fixed-dose combination (FDC) aclidinium and formoterol versus placebo, Outcome 5 Total number of deaths. **Analysis 3.6. Comparison 3 Fixed-dose combination (FDC) aclidinium and formoterol versus placebo, Outcome 6 Hospital admissions due to exacerbations: number of participants.** **Analysis 3.7. Comparison 3 Fixed-dose combination (FDC) aclidinium and formoterol versus placebo, Outcome 7 Improvement in symptoms: change from baseline in Transitional Dyspnoea Index (TDI) focal score.**

Analysis 3.8. Comparison 3 Fixed-dose combination (FDC) acclidinium and formoterol versus placebo, Outcome 8 Improvement in symptoms: number of participants with clinically significant improvement: using TDI focal score (≥ 1 unit).

Analysis 3.9. Comparison 3 Fixed-dose combination (FDC) acclidinium and formoterol versus placebo, Outcome 9 Change in lung function: from baseline in trough forced expiratory volume in 1 second (FEV₁) (L).

Analysis 3.10. Comparison 3 Fixed-dose combination (FDC) acclidinium and formoterol versus placebo, Outcome 10 Change lung function: from baseline in 1-hour postmorning dose FEV₁ (L).

Analysis 3.11. Comparison 3 Fixed-dose combination (FDC) aclidinium and formoterol versus placebo, Outcome 11 Adverse events (not including serious adverse events): number of participants.

ADDITIONAL TABLES

Table 1. Overview of included studies

Study	Duration of study	Number randomised	Intervention	Comparison
ACLIFORM COPD	24 weeks	1729	Inhaled FDC aclidinium/formoterol 400/6 µg twice daily	Inhaled aclidinium 400 µg twice daily
			Inhaled FDC aclidinium/formoterol 400/12 µg twice daily	Inhaled formoterol 12 µg twice daily
				Inhaled placebo twice daily
ACTIVATE	8 weeks	267	Inhaled FDC aclidinium/formoterol 400/12 µg twice daily	Inhaled placebo twice daily
AUGMENT COPD	24 weeks	1692	Inhaled FDC aclidinium/formoterol 400/6 µg twice daily	Inhaled aclidinium 400 µg twice daily

Table 1. Overview of included studies (Continued)

			Inhaled FDC aclidinium/formoterol 400/12 µg twice daily	Inhaled formoterol 12 µg twice daily Inhaled placebo twice daily
D'Urzo 2017a	28 weeks	921	Inhaled FDC aclidinium/formoterol 400/6 µg twice daily Inhaled FDC aclidinium/formoterol 400/12 µg twice daily	Inhaled aclidinium 400 µg twice daily Inhaled formoterol 12 µg twice daily Inhaled placebo twice daily
Donohue 2016	52 weeks	590	Inhaled FDC aclidinium/formoterol 400/12 µg twice daily	Inhaled formoterol 12 µg twice daily
NCT00706914	4 weeks	156	Inhaled FDC aclidinium/formoterol 200/12 µg once daily in the morning and placebo once daily in the evening Inhaled FDC aclidinium/formoterol 200/12 µg once daily in the morning and formoterol 12 µg once daily in the evening	Inhaled formoterol 12 µg twice daily
Sliwinski 2010	4 weeks	566	Inhaled FDC aclidinium/formoterol 400/6 µg once daily Inhaled FDC aclidinium/formoterol 400/12 µg once daily Inhaled FDC aclidinium/formoterol 400/18 µg once daily	Inhaled aclidinium 200 µg once daily Inhaled formoterol 12 µg once daily Inhaled placebo once daily

FDC: fixed-dose combination.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Review Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via Cochrane Register of Studies)	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly

(Continued)

AMED (EBSCO)

From inception

Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respiriology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema\$.mp.
4. (chronic\$ adj3 bronchiti\$).mp.
5. (obstruct\$ adj3 (pulmonary or lung\$ or airway\$ or airflow\$ or bronch\$ or respirat\$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify randomised controlled trials

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.

6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and the RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant trials from the CAGR

- #1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
- #2 MeSH DESCRIPTOR Bronchitis, Chronic
- #3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
- #4 COPD:MISC1
- #5 (COPD OR COAD OR COBD):TI,AB,KW
- #6 #1 OR #2 OR #3 OR #4 OR #5
- #7 aclidinium*
- #8 LAS34273
- #9 Tudorza
- #10 Eklira
- #11 Genuair
- #12 Pressair
- #13 LAMA
- #14 Muscarinic* NEXT Antagonist*
- #15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
- #16 formoterol
- #17 salmeterol
- #18 indacaterol
- #19 QAB149
- #20 LABA:ti,ab
- #21 long* NEAR beta* NEAR agonist*
- #22 long NEAR beta* NEAR adrenergic*
- #23 #16 or #17 or #18 or #19 or #20 or #21 or #22
- #24 #6 AND #15 and #23

[Note: In search line #4, MISC2 denotes the field in which the reference has been coded for condition, in this case, COPD]

Appendix 3. Search strategy for ClinicalTrials.gov

Search terms: "combined acclidinium and long acting beta agonists" OR "combined acclidinium bromide and long acting beta agonists" OR "combined acclidinium and formoterol" OR "combined acclidinium and salmeterol" OR "combined acclidinium and indacaterol" OR "fixed dose combination of acclidinium and formoterol"

Condition: COPD, or chronic obstructive pulmonary disease

Study type: interventional studies

CONTRIBUTIONS OF AUTHORS

HN and KNV wrote the protocol with suggestions and input on the background from ZS and on the methods from KTM and SM.

For the review:

SM performed the search of additional resources.

HN and KTM screened search results and identified full-text articles to be retrieved.

SM and KTM screened those full-text articles and selected studies for inclusion.

HN contacted trial authors and the manufacturer of acclidinium/formoterol ([AstraZeneca](#)) for any unpublished data.

SM and HN independently assessed risk of bias of included studies.

SM extracted the characteristics of studies while HN and KTM extracted outcome data for meta-analysis.

HN performed data entry, which was checked by KTM and also conducted data analysis with statistical expertise and input obtained from SM.

HN and KTM drafted the manuscript with statistical input from SM.

If there were disagreements at any stage during this review process, we consulted ZS and KNV for their expert opinion.

All review authors checked, revised and agreed on the full review manuscript before submission for editorial review.

DECLARATIONS OF INTEREST

HN: none known.

SM: none known.

ZS: none known.

KTM: none known.

KNV: none known.

We conducted this systematic review for academic purposes.

SOURCES OF SUPPORT

Internal sources

- The review authors declared that they received no funding for this systematic review, Malaysia.

External sources

- The review authors declared that they received no funding for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review strictly followed the prespecified protocol. A funnel plot to explore reporting bias was not applicable to our review, as the meta-analysis included only six trials. We could only identify trials on acclidinium/formoterol combination, thus the planned subgroup analysis on different LABAs was not possible. Similarly, subgroup analysis on concurrent use of ICS was not done because of the insufficient information.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-2 Receptor Agonists [*therapeutic use]; Bronchodilator Agents [therapeutic use]; Disease Progression; Drug Therapy, Combination [methods]; Dyspnea [drug therapy]; Forced Expiratory Volume; Formoterol Fumarate [therapeutic use]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Quality of Life; Randomized Controlled Trials as Topic; Tropanes [*therapeutic use]

MeSH check words

Female; Humans; Male; Middle Aged