Efficacy and Safety of Aclidinium/Formoterol versus Tiotropium in COPD: Results of an Indirect Treatment Comparison

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ABSTRACT

Introduction: The objective of this study was to estimate the relative efficacy and safety of fixed-dose combination aclidinium/formoterol 400/12 μg twice daily compared to tiotropium 18 μg once daily in adult patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).

Methods: A systematic literature review performed in March 2014, using a predefined search strategy in MEDLINE, EMBASE and Cochrane Library, identified 17 randomized placebo-controlled trials, (tiotropium \( n = 15 \); aclidinium/formoterol \( n = 2 \)). Outcomes of interest were: bronchodilation (peak and trough forced expiratory volume in 1 s (FEV\(_1\))), COPD symptoms [Transition Dyspnea Index (TDI) focal score and % of responders (>1 unit improvement)] and Health Related Quality of Life (HRQoL) [St. George’s Respiratory Questionnaire (SGRQ) total score and % responders (>4 unit improvement)], % of patients with ≥1 exacerbations, adverse events (AE), serious adverse events (SAE), hospitalization and mortality, all at 24 weeks. In the absence of head-to-head trials between aclidinium/formoterol and tiotropium, a Bayesian indirect treatment comparison (ITC) was used with placebo as common control.

Results: Regarding bronchodilation, aclidinium/formoterol was found to be more efficacious than tiotropium at peak FEV\(_1\), with mean difference in change from baseline (DCFb) 143 mL [95% credible interval (CrI): 112, 174] and at trough FEV\(_1\) [DCFb 26 mL (95% CrI -2, 55)]. Aclidinium/formoterol is expected to be more efficacious than tiotropium in improving dyspnea symptoms measured by TDI [DCFb 0.54 points (95% CrI 0.09, 0.99); odds ratio (OR) of responders 1.51 (95% CrI 1.11, 2.06)]. SGRQ results are comparable for aclidinium/formoterol versus tiotropium [DCFb -0.52 (95% CrI -2.21, 1.17); OR of responders...
1.16 (95% CrI 0.47, 2.87)]. The ITC results suggest similar safety profiles regarding AEs, SAEs and hospitalization.

**Conclusion:** Based on the ITC, aclidinium/formoterol is expected to be more efficacious than tiotropium in terms of lung function and symptom control while providing comparable HRQoL results and safety profile.

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**Keywords:** Aclidinium; Formoterol; Indirect treatment comparison; Literature review; Tiotropium

**INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is a disorder characterized by the progressive development of airway obstruction, which manifests as an accelerated decline in lung function, with symptoms such as breathlessness on physical exertion, deteriorating health status and exacerbations [1].

Currently COPD is the fourth leading cause of death globally [2], a major cause of morbidity and mortality, projected to become the world’s third leading cause of mortality by 2020 [3]. Characterized by progressive airflow limitation, COPD also has a major economic impact [4].

According to the COPD Guidelines from 2011, which were updated in 2015, it is recommended to combine two long-acting bronchodilators in moderate-to-severe COPD patient groups [5]. The combination of two bronchodilators with different mechanisms of action, such as long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs), are a successful treatment option for patients with COPD. Compared to single bronchodilators, the combination of LAMAs and LABAs demonstrates significant improvements in lung function without increasing the risk for adverse events [5–8]. The use of fixed-dose combinations (FDCs) of LABAs and LAMAs provide the opportunity to improve the accessibility and conformity compared to separate inhalers. Also, the dose of each substance used in the combination can be enhanced. An objection related to the development of an FDC is the arrangement of improved bronchodilation over monotherapy segments, while adjusting the associated adverse effects with efficacy [9]. The safety and efficacy profiles of both LAMAs and LABAs are well accepted. However, it is important to recognize both the similarities and differences in both efficacy and safety, when combining two substances.

A new LABA/LAMA FDC, aclidinium/formoterol 400/12 µg twice-daily (BD), has recently been introduced in the management of COPD. The FDC, aclidinium/formoterol, is compared to placebo and aclidinium and formoterol as monotherapies in two pivotal, randomized, placebo-controlled studies [ACLIFORM (ClinicalTrials.gov identifier NCT01462942) and AUGMENT (Clinicaltrials.gov identifier NCT01437397)] [10, 11]. Results from both studies show a significant improvement in 24 h symptom control compared with placebo and aclidinium and formoterol monotherapies. Furthermore, in the aclidinium/formoterol group, the frequency of exacerbations is also reduced compared to placebo [6].

Tiotropium 18 µg is a once-daily treatment and has been the first and most widely prescribed LAMA for COPD, considered as the standard of care in many countries [12]. Based on the outcomes of the AUGMENT and ACLIFORM studies, it is expected that an FDC of aclidinium/formoterol will be more efficient on key COPD outcomes, compared to LAMA
monotherapies. As there are no published direct head-to-head comparisons on the clinical efficacy and safety between FDC aclidinium/formoterol and tiotropium, alternative methodologies need to be employed to inform health-care practitioners.

For this reason, a systematic literature review and Bayesian indirect treatment comparison (ITC) were undertaken to assess the relative efficacy and safety of aclidinium/formoterol 400/12 µg BD versus tiotropium 18 µg once daily (OD) for the treatment of adult patients with moderate-to-severe COPD.

METHODS

Data Sources

A systematic literature review was performed to identify randomized placebo-controlled trials (RCTs) reporting the safety and efficacy of aclidinium/formoterol 400/12 µg and tiotropium 18 µg compared to each other or placebo. Using a predefined strategy, MEDLINE®, MEDLINE in-process and EMBASE® databases were searched simultaneously through the OVID platform, while the Cochrane Central Register of Controlled Trials was searched separately. The American Thoracic Society International Conference (2013) and European Respiratory Society International Congress (2013) were hand-searched for relevant abstracts. In addition, the search was also performed in ClinicalTrials.gov website. The searches were performed on March 24, 2014, for studies in English language with a time restriction from the year 1989 to March 2014. The predefined search strategies used were tailored for each database and are presented in Supplementary Table 1. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Study Selection Process

The relevance of each citation identified was assessed according to predefined abstract selection criteria (Supplementary Table S2). First, titles and abstracts were screened for eligibility, and then full texts of the selected articles were assessed by one researcher and checked against the original study by another. Those that met the inclusion criteria were included for data extraction.

The studies of interest were RCTs with duration of 22–26 weeks, including adults with moderate-to-severe COPD, reporting on aclidinium/formoterol 400/12 µg BD (using the Genuair® device [AstraZeneca AB, Södertälje, Sweden]) or tiotropium 18 µg OD (using the Handihaler® device [Boehringer Ingelheim, Ridgefield, USA]) compared with each other or placebo. The efficacy outcomes of interest were: trough forced expiratory volume in 1 s (FEV$_1$) (pre-bronchodilatory), peak FEV$_1$ (post-bronchodilatory), St. George’s Respiratory Questionnaire (SGRQ) score, Transition Dyspnea Index (TDI) focal score and the % of patients with ≥1 exacerbations. The safety outcomes of interest were: adverse events, serious adverse events, hospitalization and mortality. In all cases, outcomes reported in the range of 22–26 weeks were grouped as 24 weeks.

Data Abstraction and Quality Assessment

For the studies identified that met the inclusion criteria, details were extracted on population characteristics, interventions, outcomes and the study design of interest at 24 weeks.
| Author, Year and study acronym | Compared treatment | Randomized | Trial design | Centers/countries | Inclusion criteria | Background treatment | Trial duration | Run-in period |
|--------------------------------|-------------------|------------|--------------|-------------------|--------------------|---------------------|---------------|--------------|
| Chan 2007 [19] BI trial: 205,259 [20] | Tiotropium 18 µg OD | 608        | RCT, PC, DB, MC, PG | 101 centers/Canada | ≥40 years old; ≥10 pack-years; FEV1 ≤65%; FEV1/FVC ≤70%; included if ≥1 exacerbation in the previous year, but not in the prior 6 weeks (later amended to incl 1 exacerbation in the past 2 years) | Allowed: s dose oral corticosteroids, ICS, theophylline preparations, mucolytic preparations (not containing bronchodilators), LABAs | 48 weeks | N/A |
| Tonnell 2008 (TIPHON) [21] | Tiotropium 18 µg OD | 266        | RCT, PC, DB, MC | 123 centers/France | ≥40 years old; >10 pack-years; FEV1 20–70%; FEV1/FVC ≤70% | Allowed: stable doses of theophylline preparations (excluding 24 h preparations), mucolytics, ICS and oral steroids | 36 weeks | N/A |
| Tashkin et al. 2008 (UPLIFT) [12] | Tiotropium 18 µg OD | 2987       | RCT, PC, DB, MC, PG | 490 centers/37 countries | ≥40 years old; >10 pack-years; FEV1 ≤70%; FEV1/FVC ≤70%; excluded if exacerbation in prior 4 weeks | Allowed: all respiratory medications, except other inhaled anticholinergic drugs | 4 years | N/A |
| Celli et al. 2009 [22] | Formoterol 10 µg BID + Tiotropium 18 µg OD | 207        | RCT, PC, DB (TIO was OL), MC | 86 centers in Germany, Italy, Netherlands, Russian Federation, Poland, Czech Republic, Spain and Hungary | FEV1 <70%, FEV1/FVC <70%; stable COPD; aged 40 years at COPD onset; smoking history of 10 pack-years | Allowed: salbutamol, ICS monotherapy | 24 weeks | N/A |
| Vogelmeier 2008 [23] | Formoterol 10 µg BID | 210        | RCT, PC, DB | 26 centers/USA | ≥40 years old; ≥10 pack-years; FEV1 ≤60%; FEV1/FVC ≤70%; excluded if not recovered from exacerbation ≥30 days prior | Allowed: all other respiratory medications (including ICS and LABAs) | 6 months | N/A |
| Niewoehner et al. 2005 [24] | Placebo | 209        | | | | Not allowed: open-label anticholinergic bronchodilator | |
| Brusasco 2003 [25] | Tiotropium 18 µg OD | 402        | RCT, PC, DB, MC, DD, PG | # Centers NR/18 countries | ≥40 years old; >10 pack-years; FEV1 ≤65%; FEV1/FVC ≤70% | NR | 24 weeks | N/A |
| | Salmeterol 50 µg BID | 405        | | | | | |
| | Placebo | 400        | | | | | |
| Author, Year and study acronym | Compared treatment | Randomized | Trial design | Centers/countries | Inclusion criteria | Background treatment | Trial duration | Run-in period |
|--------------------------------|--------------------|------------|--------------|------------------|-------------------|---------------------|---------------|--------------|
| Donohue et al. 2002 [26]       | Tiotropium 18 µg OD | 209 RCT, PC, DB, MC, DD, PG | 39 countries/12 countries | ≥40 years old; >10 pack-years; FEV1 ≤60%; FEV1/FVC ≤70%; | Allowed: usual ICS and oral steroids; Not allowed: inhaled anticholinergic LABAs | 24 weeks | N/A |
| Donohue et al. 2003 [27]       | Salmeterol 50 µg BID | 213 Placebo | 201 | | | | |
| Casaburi 2002 [28]             | Tiotropium 18 µg OD | 550 Two RCTs, PC, DB, MC | 50 centers, countries NR | ≥40 years old; ≥10 pack-years; FEV1 ≤65%; FEV1/FVC ≤70%; | Allowed: stable doses of theophylline, ICS, oral prednisone | 56 weeks | N/A |
| Placebo                        | 371 | | | | | |
| Donohue 2010 [29]              | Indacaterol 150 µg OD | 420 RCT, PC, DB (except for tiotropium arm), MC, DD; adaptive seamless | # Centers NR/USA, Sweden, Turkey, Germany | ≥40 years old; ≥20 pack-years; FEV1 peak <80% (predicted); 30% ≥FEV1/FVC <70%; | Allowed: continue ICS monotherapy if stable for 1 month before screening; albuterol (as needed) | 26 weeks | N/A |
| Indacaterol 300 µg OD          | 418 | | | | | |
| Tiotropium 18 µg OD            | 420 | | | | | |
| Placebo                        | 425 | | | | | |
| Bateman et al. 2013 [8]        | QVA 149 110/50 µg OD | 475 RCT, MC, DB, PG, PC, active controlled trial | 301 sites in 27 countries: Argentina; Australia; Bulgaria; Canada; China; Finland; France; Germany; Guatemala; Hungary; India; Japan; Mexico; Netherlands; Panama; Philippines; Poland; Romania; Russia; Slovakia; South Africa; Spain; Switzerland; Taiwan; Turkey; UK; USA | ≥40 years; moderate-to-severe stable COPD, smoking history of ≥10 pack-years, peak FEV1 ≥30% and <80% of predicted normal and post-bronchodilator FEV1/FVC <0.70 | Allowed: selective serotonin reuptake inhibitors; inactivated vaccine; ICS; intranasal CS; H1 antagonists | 26 weeks | 2 weeks |
| Frith et al. 2013 [30]         | Indacaterol 150 µg OD | 477 | | | | |
| SHINE CSR data (by Novartis)   | Glycopyrronium 50 µg OD | 475 | | | | |
| Placebo                        | 483 | | | | | |
| Bateman et al. 2013 [8]        | QVA 149 110/50 µg OD | 475 RCT, MC, DB, PG, PC, active controlled trial | 301 sites in 27 countries: Argentina; Australia; Bulgaria; Canada; China; Finland; France; Germany; Guatemala; Hungary; India; Japan; Mexico; Netherlands; Panama; Philippines; Poland; Romania; Russia; Slovakia; South Africa; Spain; Switzerland; Taiwan; Turkey; UK; USA | ≥40 years; moderate-to-severe stable COPD, smoking history of ≥10 pack-years, peak FEV1 ≥30% and <80% of predicted normal and post-bronchodilator FEV1/FVC <0.70 | Allowed: selective serotonin reuptake inhibitors; inactivated vaccine; ICS; intranasal CS; H1 antagonists | 26 weeks | 2 weeks |
| Author, Year and study acronym | Compared treatment | Randomized | Trial design | Centers/countries | Inclusion criteria | Background treatment | Trial duration | Run-in period |
|--------------------------------|-------------------|------------|-------------|------------------|-------------------|---------------------|-----------------|--------------|
| Ambrosino et al. 2008 [31]    | Tiotropium 18 µg OD | 117        | RCT, MC, DB, PC, PG | 12 sites in Italy | ≥40 years old; ≥10 pack-years; FEV1 predicted ≤60%; FEV1/FVC ≤70% | Excluded: anti-arrhythmic drugs; other β2-agonists (long and short acting) and inhaled anticholinergic medications (other than study drugs) | 25 weeks | 4 weeks |
| Kerwin et al. 2012 [32] (GLOW2 study) | NVA237 50 µg OD | 529 | RCT, DB, MC, PC, PG | NR | ≥40 years old; ≥10 pack-years; FEV1 peak ≥30% and <80% of the predicted normal; FEV1/FVC <70%; moderate-to-severe stable COPD | Allowed: inhaled or intranasal CS and H1-antagonists; salbutamol/albuterol as rescue medication | 52 weeks | 2 weeks |
| Cooper et al. 2012 [33]       | Tiotropium 18 µg OD | 260 | RCT, DB, MC, PC, PG | NR | ≥40 years old; ≥10 pack-years; moderate-to-severe stable COPD; FEV1 peak ≤65% predicted; trough FEV1 ≤60%; FEV1/FVC <70%; Medical Research Council dyspnea score ≥2 (based on a 1–5 scale) | Excluded: inhaled anticholinergics during a screening visit | 96 weeks | 2 weeks |
| Author, Year and study acronym | Compared treatment | Randomized | Trial design | Centers/countries | Inclusion criteria | Background treatment | Trial duration | Run-in period |
|--------------------------------|--------------------|------------|-------------|------------------|-------------------|---------------------|---------------|--------------|
| CSR: M/40464/30R [34]         | Aclidinium/        | 385        | RCT, PG, DB, PC, MC, multinational, phase III | 193 centers in 22 countries: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Slovakia, South Africa, South Korea, Spain, Sweden, Ukraine, UK | ≥40 years; smoking history of ≥10 pack-years; FEV1/FVC <70%; with a diagnosis of moderate-to-severe COPD. Peak FEV1 30% ≤FEV1 <80% of the predicted normal value | Excluded concomitant drugs: anticholinergic drugs; β2-agonists; terbutaline or metaproterenol; formoterol, salmeterol, indacaterol; combination of SABA and an anticholinergic agent (e.g., Combivent); inhaled fixed-dose combinations of LABAs and corticosteroids (e.g., Symbicort, Advair); corticosteroid drugs; cromolyn sodium, nedocromil; leukotriene modifiers; methyl-xanthines; phosphodiesterase 4 inhibitors; β1-blocking agents | 24 weeks | 2–3 weeks |
|                               | Formoterol 400/12 µg BID | 381        | PC, MC, multinational, phase III | | | | | |
|                               | Aclidinium 400 µg BID | 385        | | | | | | |
|                               | Formoterol 12 µg BID | 384        | | | | | | |
|                               | Placebo            | 194        | | | | | | |
| Author, Year and study acronym | Compared treatment | Randomized | Trial design | Centers/countries | Inclusion criteria | Background treatment | Trial duration | Run-in period |
|-------------------------------|-------------------|------------|-------------|-------------------|-------------------|---------------------|---------------|---------------|
| CSR: LAC-MD-31 [35]           | Aclidinium/ Formoterol 400/12 µg BID | 338        | RCT, DB, PC, PG, MC, active controlled, multinational | A total of 222 study centers located in the USA (193 centers), Canada (10 centers), Australia (11 centers), and New Zealand (8 centers) screened patients for the study. | ≥ 40 years, moderate-to-severe stable COPD, smoking history of >10 pack-years, peak FEV1 ≥30% and <80% of predicted normal and post bronchodilator FEV1/FVC <0.70 | Allowed: ICS, systemic corticosteroids (oral or parenteral corticosteroids), oxygen, SABAs and methylxanthines | 24 weeks | 2–3 weeks |
|                               | Aclidinium/ Formoterol 400/6 µg BID | 338        |             |                   |                   |                     |               |               |
|                               | Aclidinium 400 µg BID | 340        |             |                   |                   |                     |               |               |
|                               | Formoterol 12 µg BID | 339        |             |                   |                   |                     |               |               |
|                               | Placebo            | 337        |             |                   |                   |                     |               |               |

BID twice daily, COPD chronic obstructive pulmonary disease, CS corticosteroid, CSR clinical study reports, DB double blind, DD double dummy, FEV1 forced expiratory volume in 1 s, FVC forced vital capacity, ICS inhaled corticosteroids, LABA long-acting β2-agonists, MC multicenter, NR not reported, OD once daily, OL open label, PC placebo controlled, PG parallel group, RCT randomized controlled trial, SABA short-acting beta agonists, SD standard deviation, TIO tiotropium, USA United States of America. Arms in gray are not of interest for this study.
Table 2  Key patient characteristics at baseline for included studies (only arms of interest)

| Author, year and study acronym | Treatment | Randomized Male (%) | Age (SD) (years) | Current smoker | ICS use | Duration COPD (SD) (years) | Pack-years (SD) | FEV<sub>1</sub> mean (SD) (liters) | FEV<sub>1</sub>% pred. (SD) | % FEV<sub>1</sub>/FVC (SD) | FVC mean (SD) (liters) |
|-------------------------------|-----------|---------------------|-----------------|----------------|---------|--------------------------|----------------|----------------------------------|------------------|---------------------|-------------------------|
| Chan 2007 [19] BI trial: 205.259 [20] | Tiotropium 18 µg OD | 608 59 | 67.0 (8.7) | 32% | 66% | 9.9 (8.1) | 50.2 (22.6) | 0.97 (0.39) | 39.4 (13.0) | 46.4 (12.0) | 2.11 (0.76) |
| Placebo | 305 61 | 67.0 (9.1) | 30% | 71% | 9.9 (7.9) | 51.0 (26.3) | 0.96 (0.38) | 39.3 (14.0) | 46.3 (12.0) | 2.11 (0.73) |
| Tonnell 2008 (TIPHON) [21] | Tiotropium 18 µg OD | 266 87 | 65.0 (9.7) | 24% | 38% | 7.9 (7.6) | 44.4 (21.3) | 1.38 (0.44) | 47.5 (13.3) | 55.3 (11.3) | 2.50 (0.68) |
| Placebo | 288 85 | 64.0 (10.1) | 30% | 36% | 8.0 (7.9) | 43.0 (22.5) | 1.35 (0.46) | 46.2 (12.4) | 54.6 (11.3) | 2.49 (0.75) |
| Tashkin et al. 2008 (UPLIFT) [12] | Tiotropium 18 µg OD | 2987 75 | 65.0 (8.4) | 29% | 62% | 9.9 (7.6) | 49.0 (28.0) | 1.10 (0.40) | 39.5 (12.0) | 42.4 (11.0) | 2.63 (0.81) |
| Placebo | 3006 74 | 65.0 (8.5) | 30% | 62% | 9.7 (7.4) | 48.4 (27.9) | 1.09 (0.40) | 39.3 (12.0) | 42.1 (11.0) | 2.63 (0.83) |
| Vogelmeier 2008 [23] | Tiotropium 18 µg OD | 221 79 | 63.4 (9.5) | NR | NR | 6.9 (6.3) | 38.6 (19.3) | 1.50 (0.39) | 51.6 (11.2) | 54.4 (9.6) | 50.1 (NR) |
| Placebo | 209 78 | 62.5 (8.6) | NR | NR | 6.7 (6.1) | 40.1 (22.8) | 1.50 (0.39) | 51.1 (11.0) | 53.5 (10.0) | NR (NR) |
| Niewoehner et al. 2005 [24] | Tiotropium 18 µg OD | 914 98 | 67.6 (8.7) | 29% | 61% | 12.2 (10.4) | 67.4 (35.4) | 1.04 (0.40) | 35.6 (12.6) | 47.9 (11.5) | NR (NR) |
| Placebo | 915 99 | 68.1 (8.5) | 30% | 58% | 11.9 (10.5) | 69.4 (36.6) | 1.04 (0.40) | 35.6 (12.6) | 47.7 (11.1) | NR (NR) |
| Author, year and study acronym | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo |
|-------------------------------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| Brusasco 2003 [25] | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo |
| Donohue et al. 2002 [26] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Donohue et al. 2003 [27] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Casaburi 2002 [28] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Donohue 2010 [29] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Bateman et al. 2013 [30] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Frith et al. 2013 [31] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| SHINE CSR data (by Novartis) [36] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |

| Author, year and study acronym | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo | Tiotropium | Placebo |
|-------------------------------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| Brusasco 2003 [25] | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Donohue et al. 2002 [26] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Donohue et al. 2003 [27] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Casaburi 2002 [28] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Donohue 2010 [29] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Bateman et al. 2013 [30] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Frith et al. 2013 [31] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| SHINE CSR data (by Novartis) [36] | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD | Placebo | 18 Hg OD |
| Author, year and study acronym | Treatment | Randomized Male (%) | Age (SD) (years) | Current smoker | ICS use | Duration COPD (SD) (years) | Pack-years COPD (SD) | FEV$_1$ mean (SD) (liters) | FEV$_1$% pred. (SD) | % FEV$_1$/FVC (SD) | FVC mean (SD) (liters) |
|-------------------------------|-----------|---------------------|-----------------|----------------|---------|--------------------------|---------------------|--------------------------|----------------|-----------------|-------------------------|
| Ambrosino et al. 2008 [31]    | Tiotropium 18 µg OD | 117 | 83 | 67.8 (7.8) | NR | 42% | 10.9 (9.8) | 38.3 (25.2) | 1.10 (0.40) | 42.5 (13.3) | 47.3 (11.8) | 2.40 (0.70) |
|                               | Placebo   | 117 | 85 | 66.9 (7.3) | NR | 52% | 11.3 (9.5) | 35.0 (22.4) | 1.10 (0.40) | 40.3 (12.6) | 45.2 (10.4) | 2.50 (0.80) |
| Kerwin et al. 2012 [32]       | Tiotropium 18 µg OD | 267 | 63 | 63.9 (8.2) | 44% | 52% | 7.5 (6.6) | 50.2 (28.0) | Trough: 1.30 (0.50)* | Peak: 1.50 (0.50)** |
|                               | Placebo   | 268 | 65 | 63.6 (9.1) | 46% | 51% | 7.4 (6.6) | 48.0 (24.0) | Trough: 1.40 (0.50)* | Peak: 1.50 (0.50)** |
| Cooper et al. 2012 [33]       | Tiotropium 18 µg OD | 260 | 77 | 64.7 (8.2) | 35% | 61% | NR | 52.2 (29.0) | 1.25 (0.41) | 44.5 (11.7) | 46.7 (11.8) | 2.75 (0.84) |
|                               | Placebo   | 259 | 78 | 64.5 (8.5) | 33% | 59% | NR | 51.0 (26.3) | 1.25 (0.42) | 44.2 (12.1) | 46.7 (11.1) | 2.72 (0.80) |
| Author, year and study acronym | Treatment | Randomized Male (%) | Age (SD) (years) | Current smoker | ICS use | Duration COPD (SD) (years) | Pack-years (SD) | FEV₁ mean (SD) (liters) | FEV₁% pred. (SD) | % FEV₁/FVC (SD) | FVC mean (SD) (liters) |
|-------------------------------|-----------|---------------------|-----------------|---------------|---------|--------------------------|----------------|------------------------|----------------|-------------|------------------|
| CSR: M/40464/30 R [34]        | Aclidinium/Formoterol 400/12 µg BID | 385             | 68              | 62.7 (8.1)    | 47%     | 22%                       | 8.5 (6.3)      | 40.8 (21.5)           | 1.42 (0.49)    | 50.1 (14.3)   | 48.1 (10.4)       | 3.00 (0.87)       |
| Placebo                       |           | 194                | 71              | 64.2 (8.0)    | 49%     | 20%                       | 8.6 (6.2)      | 41.9 (21.0)           | 1.42 (0.54)    | 50.1 (13.7)   | 47.8 (10.4)       | 3.03 (0.94)       |
| CSR: LAC-MD-31 [35]           | Aclidinium/Formoterol 400/12 µg BID | 335             | 50              | 64.2 (8.9)    | 52%     | 9%                        | 8.8 (6.4)      | 53.3 (27.2)           | 1.33 (0.53)*   | 46.4 (13.9)*   | 50.6 (10.9)       | 2.69 (0.85)*       |
| Placebo                       |           | 332                | 53              | 63.5 (8.9)    | 51%     | 7%                        | 8.4 (6.3)      | 53.3 (28.5)           | 1.34 (0.54)**  | 45.5 (13.4)** | 50.2 (11.1)       | 2.75 (0.91)*       |

* Trough FEV₁ (Pre-bronchodilatory)
** Peak FEV₁ (post-bronchodilatory)

BID twice daily, COPD chronic obstructive pulmonary disease, CSR clinical study report, FEV₁ forced expiratory volume in 1 s, FVC forced vital capacity, ICS Inhaled corticosteroids, NR not reported, OD once daily, SD standard deviation
Data abstraction was performed by one researcher and verified against the original study publication by another. Data of interest presented in graphs were extracted using DigitizeIT version 4.1 software (DigitizeIT, Braunschweig, Germany).

For continuous outcomes, the change from baseline (CFB) and the associated sampling variance were extracted or calculated based on the available data. For dichotomous outcomes, the number of patients experiencing an event was extracted or estimated based on the reported percentages and intention to treat population, and the total patient-years of follow-up were calculated.

The validity of each trial used in the ITC was assessed using the National Institute of Health and Clinical Excellence (NICE) checklist. The results of this assessment were not explicitly used in the ITC, but serve as additional information to determine the quality of the evidence base when interpreting the results (Supplementary Table S3).

Data Synthesis: Indirect Treatment Comparison

The existence of a connection between the treatments of interest via a common control (placebo), as well as the study design and patient characteristics of the identified studies, was used to assess the feasibility of a valid ITC [13]. Subsequently, the identified evidence was used to perform an ITC within a Bayesian framework to simultaneously synthesize the results of the included studies and obtain relative treatment effects [14, 15]. A linear model with normal likelihood distribution was used for continuous outcomes, and a Poisson likelihood with a log link for the dichotomous outcomes [16]. Flat (non-informative) prior distributions, normal with zero mean and variance of 10,000, were assumed for the relative treatment effects of all outcomes. A uniform distribution with range 0–5 was used as the prior of the between-study standard deviation.

For each outcome, a fixed and a random effects model was evaluated. The goodness of fit of each model to the data was assessed using the deviance information criterion [17]. The posterior densities were estimated using the Markov chain Monte Carlo (MCMC) simulations based on 80,000 iterations on three chains, with a burn-in of 20,000 iterations. Convergence assessment was based on visual inspection of trace plots and accuracy of the posterior estimates using the Monte Carlo error for each parameter. WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) statistical software was used for the analyses and the models were based on those defined by Dias et al. [18]. The posterior distributions were summarized with the median to reflect the most likely value of the estimate, and the 2.5th and 97.5th percentile to capture the 95% credible interval (CrI). For each end point, the probability that each treatment was better than a certain comparator was established.

RESULTS

Search and Selection Results

After searching, a total of 2401 abstracts from the databases and 88 clinical trials from ClinicalTrials.gov were identified (Fig. 1). Following the abstracts and full-text publication screening stages, 17 full-text publications [8, 12, 19–33] were identified and
3 clinical study reports [34–36] were provided by AstraZeneca. In total, the evidence base comprised 15 different studies; 13 studies [8, 12, 19–33, 36] compared tiotropium 18 μg to placebo (14,697 patients) and two studies [34, 35] compared aclidinium/formoterol 400/12 μg to placebo (1246 patients).

**Study Characteristics**

An overview of the study characteristics is presented in Table 1. All studies were multicenter, placebo-controlled RCTs. Twelve studies [8, 12, 19–22, 24–28, 30, 31, 33, 36] were double-blind and three [23, 29, 32] included tiotropium as an open-label arm. The included studies varied in terms of the number of patients randomized to each treatment, ranging from 117 [31] to 3006 [12, 22]. The trial duration varied from 96 weeks [33] to 24 weeks [23–27, 34, 35]. The use of ICS (inhaled corticosteroids) as a background treatment was allowed in all studies and patients were permitted a short-acting beta-agonist as rescue medication (salbutamol or albuterol). The studies were of comparable quality, according to the results of the assessment using NICE questionnaire

Fig. 1 Flowchart of the study selection process. ATS American Thoracic Society, CSR clinical study report, ERS European Respiratory Society
In general, the method of randomization and concealment of treatment allocation was well reported.

**Patient Characteristics**

An overview of the main patient characteristics is provided in Table 2. The enrolled patients were adults with a COPD diagnosis. The studies included a predominantly male population, ranging from 50% [35] to 99% [24], while in three studies [21, 24, 31] more than 80% of the included patients were male in both arms. The patients' average age across all the studies was similar (range 63–68 years). Overall, spirometry measures were fairly consistent at baseline. According to the inclusion criteria, most studies required an FEV₁/forced vital capacity (FVC) of less than or equal to 0.70 and an FEV₁% predicted range between 30% and 80%. The mean FEV₁% predicted at baseline ranged between 35.6% and 56.4%. FEV₁ at baseline ranged from 0.96 liter (L) to 1.55 L. The FEV₁/FVC at baseline was reported to be between 41.3% and 55.3%. Across all the included studies, the percentage of patients per arm that used ICS at baseline ranged between 7% and 71%. The percentage was lower in both aclidinium/formoterol trials (7% to 9% for LAC-MD-31 and 19–22% for M/40464/30R) than in the other studies (35–71%). Furthermore, all studies included patients who were current or ex-smokers. In studies where the percentage of current smokers was reported, it ranged from 40% to 53%. Six studies (reported in 7 publications: [23, 25–29, 31]) did not report the percentage of current smokers. The mean number of pack-years ranged from 35.0 to 69.4 years.

**Indirect Treatment Comparison**

Despite some differences identified across the studies in terms of study design and patient characteristics, the 15 RCTs (reported in 20 publications) are considered to be broadly comparable and the ITC was feasible [13]. The diagram of the trials included in the ITC is shown in Fig. 2.

**Efficacy Outcomes**

Individual study results for efficacy outcomes are presented in Supplementary Table S5, where data not reported but estimated are denoted by an asterisk. The results of the ITC analysis are presented in Table 3. Regarding lung function, for both outcomes considered in this study, i.e., peak and trough FEV₁, aclidinium/formoterol 400/12 μg appeared to be more efficacious compared to tiotropium 18 μg at 24 weeks.

Regarding health-related quality of life, as measured by SGRQ total score, the individual study results for aclidinium/formoterol demonstrate high variation between the M/40464/30R and LAC-MD-31 studies. The cause of this variation is unknown and cannot be explained by differences in study design or patient characteristics. The heterogeneity is reflected in the results of the ITC by means of wide credible intervals with a difference in CFB of −0.52 (95% CrI −2.21, 1.17). Similarly, for the % of responders (patients with ≥4 units reduction), the relative effect is heterogeneous with variation between M/40464/30R and LAC-MD-31 studies with an odds ratio (OR) 1.16 [95% CrI (0.47, 2.87)]. Due to this high variation, the results should be interpreted with
Table 3 ITC results for aclidinium/formoterol versus tiotropium at 24 weeks

| Outcome                                      | Mean       | 95% CrI            | Prob. better (%) |
|----------------------------------------------|------------|--------------------|------------------|
| **Efficacy**                                 |            |                    |                  |
| Peak FEV₁ (DCFB, mL)                         | 143.2      | (112.00, 174.50)   | >99              |
| Trough FEV₁ (DCFB, mL)                       | 26.21      | (−2.31, 54.72)     | 96               |
| SGRQ total score (DCFB, units)               | −0.52      | (−2.21, 1.17)      | 73               |
| SGRQ responders (OR, ≥4 units improvement)   | 1.16       | (0.47, 2.87)       | 68               |
| TDI focal score (difference vs. comparator)  | 0.54       | (0.09, 0.99)       | >99              |
| TDI responders (OR, ≥1 points improvement)   | 1.51       | (1.11, 2.06)       | >99              |
| Patients with at least 1 exacerbation (OR)    | 1.03       | (0.73, 1.47)       | 43               |
| **Safety**                                   |            |                    |                  |
| Adverse events (OR)                          | 1.16       | (0.86, 1.55)       | 17               |
| Serious adverse events (OR)                  | 1.22       | (0.71, 2.16)       | 24               |
| Hospitalization                              | 1.03       | (0.37, 2.90)       | 48               |

CrI credible interval, DCFB difference in change from baseline, FEV₁ forced expiratory volume in 1 s, mL milliliters, OR odds ratio, Prob. better probability of aclidinium/formoterol being a better treatment than tiotropium for this outcome, SGRQ St. George’s Research Questionnaire, TDI Transitional Dyspnea Index.

cautions; aclidinium/formoterol appeared to be comparable to tiotropium for both SGRQ total score and % responders.

Aclidinium/formoterol was more efficacious than tiotropium in improving breathlessness measured by TDI and % responders (i.e., patients with >1 point increase from baseline).

With regard to the percentage of patients with at least one exacerbation, aclidinium/formoterol was likely to be better compared to placebo with OR of 0.78 [95% CrI (0.56, 1.08)] and comparable to tiotropium with OR 1.03 (95% CrI [0.73, 1.47]). For this outcome, the time period of 24 weeks is relatively short, as the results are heavily dependent on the recent history of the patients recruited (e.g., if they had an exacerbation within the last months before recruitment, see inclusion/exclusion criteria in Table 1). Furthermore, the percentage of patients with at least one exacerbation in the placebo arm is almost 3.5 times higher in Donohue et al. 2002 and 2003 [26, 27] (45.8%) than in M/40464/30R (13.4%) [34], suggesting differences in COPD severity, in exacerbation-related study inclusion criteria or in the way the exacerbations were defined/reported. For these reasons, the results of the ITC shall be interpreted with caution.

Safety Outcomes

For the safety outcomes, the individual study results are presented as: number of patients with an event (n); number of patients included in the analysis (N); and proportion of patients with an event per treatment arm (Supplementary Table S6). Compared to placebo, aclidinium/formoterol [OR 1.19; 95% CrI (0.95, 1.49)], and tiotropium [OR 1.03; 95% CrI (0.85, 1.24)] resulted in a mean OR above 1, suggesting an advantage for placebo, although
not a significant one as the CrI included 1 in all cases. In both cases, the results of this analysis should be interpreted with extreme caution, first due to the limited number of studies, the time of assessment (24 weeks is a rather short period for safety outcomes) and potential differences in the way this outcome is reported in each study.

In the results of the ITC for serious adverse events for active treatments compared to placebo, the median OR for all active treatments was above 1 suggesting an advantage for placebo, but in all cases the credible intervals included 1; thus, the difference cannot be considered as significant. In line with this in pairwise comparisons between the active treatments, the CrI include 1 in all cases. Regarding AEs, the results of this analysis should be interpreted with extreme caution, due to the limited number of studies and the time of assessment (24 weeks is a rather short period for safety outcomes).

The results of the ITC regarding the proportion of patients with hospitalization within 24 weeks are uncertain for aclidinium/formoterol versus placebo with an OR 0.65 [95% CrI (0.22, 1.64)], mainly due to the lack of data, while for tiotropium the OR was 0.59 [95% CrI (0.46, 0.74)] versus placebo. Similarly, aclidinium/formoterol was comparable to tiotropium with OR 1.03 [95% CrI (0.37, 2.90)], but with high uncertainty.

The ITC for mortality was not (computationally) feasible, as the majority of the studies reported zero events (deaths) which lead the algorithm (MCMC) to numerical overflow, even when applying a continuity correction of 0.5. With such a large proportion of trials with zero events, estimation of a treatment effect and its variance becomes practically impossible. The individual study results for mortality are presented in Supplementary Table S6.

**DISCUSSION**

Based on the results of the ITC, aclidinium/formoterol is expected to be more efficacious than tiotropium in terms of peak FEV₁, TDI focal score and TDI responders. Regarding trough FEV₁, aclidinium/formoterol is expected to be favorable compared to tiotropium. In all other efficacy and safety end points, aclidinium/formoterol and tiotropium are expected to result in similar (comparable) outcomes. The analysis for mortality was not feasible because the majority of the studies reported zero events.

A few other studies compared LABA/LAMA combinations versus tiotropium in a head-to-head trial. Both the SHINE study (ClinicalTrials.gov identifier, NCT01202188) [8] and SPARK study (ClinicalTrials.gov identifier, NCT01120691) [37] compared QVA149 (indacaterol 110 mg/glycopyrronium 50 mg) to tiotropium. The SHINE study reports comparable results to our study with superior improvements in lung function for the QVA149 group compared to tiotropium. The safety results are comparable to placebo and with no additional safety signal compared to tiotropium [8]. The SPARK study also shows similar results, with a significant reduction in the rate of all exacerbations, and a significant improvement in trough FEV₁ and health status favoring the dual LABA/LAMA bronchodilator QVA149 versus tiotropium. Furthermore, no safety differences between the dual LABA/LAMA bronchodilator and tiotropium are found [37]. Decramer et al. [38] and Maleki-Yazdi et al. [39] both compared umeclidinium plus vilanterol versus tiotropium. Both studies report a
significant improvement in lung function compared to tiotropium, and no safety differences are found between the groups.

It is challenging to demonstrate the relevance of the end points on COPD studies comparing combination therapy to monotherapy. To determine the clinical effectiveness, the minimum clinically important difference (MCID) is often used to acknowledge a clinically significant effect. This measure is however focused on the comparison of a monotherapy versus placebo. When comparing a combination therapy to a monotherapy, uncertainty has occurred if the MCID is a valid measure, because the differences in effects tend to be smaller since both arms receive active therapy. Jones et al. [40] discuss this issue and have introduced the ‘minimum worthwhile incremental advantage’ which can be used to describe the percentage of patients experiencing improvement at or above MCID when adding active treatment on top of another active treatment or when comparing two active treatments to each other [6, 40].

Furthermore, there are a number of other potential limitations to this analysis. First, as for any meta-analysis, inherent limitations are related to the potential for within-study bias and publication bias. Furthermore, there are differences in the definitions of exacerbations and in study methodology, populations that could introduce bias. For example, across all the included studies, the percentage of patients per arm that used ICS at baseline ranged between 7% and 71%. The percentage was lower in both aclidinium/formoterol trials (7–9% for LAC-MD-31 and 19–22% for M/40464/30R) than in the other studies (35–71%). Also, for the SGRQ total score outcome, the CFB versus placebo reported for aclidinium/formoterol 400/12 demonstrated high variation between the M/40464/30R and LAC-MD-31 studies. The cause of this variation is unknown and cannot be explained by the study designs or patient characteristics.

In addition, bias could be introduced due to the imbalances in potential treatment effect modifiers (e.g., FEV\textsubscript{1} predicted at baseline) and differences in the background medications. Due to the lack of access to individual patient data and the low number of studies (especially for aclidinium/formoterol), it was not feasible to further explore these differences.

Furthermore, it is considered complicated to include safety in indirect comparisons, since this is not a straightforward approach. However, we decided to include safety next to efficacy outcomes, since a benefit–risk assessment will add important data about the intervention.

CONCLUSION

The results of this analysis suggest that aclidinium/formoterol is more efficacious with a similar safety profile compared to tiotropium.

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criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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