Dual bronchodilation in COPD: lung function and patient-reported outcomes – a review

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Abstract: Several fixed-dose combinations (FDCs) of long-acting bronchodilators (a long-acting muscarinic antagonist [LAMA] plus a long-acting β2-agonist [LABA]) are available for the treatment of COPD. Studies of these FDCs have demonstrated substantial improvements in lung function (forced expiratory volume in 1 second) in comparison with their respective constituent monocomponents. Improvements in patient-reported outcomes (PROs), such as symptoms and health status, as well as exacerbation rates, have been reported compared with a LABA or LAMA alone, but results are less consistent. The inconsistencies may in part be owing to differences in study design, methods used to assess study end points, and patient populations. Nevertheless, these observations tend to support an association between improvements in forced expiratory volume in 1 second and improvements in symptom-based outcomes. In order to assess the effects of FDCs on PROs and evaluate relationships between PROs and changes in lung function, we performed a systematic literature search of publications reporting randomized controlled trials of FDCs. Results of this literature search were independently assessed by two reviewers, with a third reviewer resolving any conflicting results. In total, 22 Phase III randomized controlled trials of FDC bronchodilators in COPD were identified, with an additional study including a post-literature search (ten for indacaterol–glycopyrronium once daily, eight for umeclidinium–vilanterol once daily, three for tiotropium–olodaterol once daily, and two for aclidinium–formoterol twice daily). Results from these studies demonstrated that the LAMA–LABA FDCs significantly improved lung function compared with their component monotherapies or other single-agent treatments. Furthermore, LABA–LAMA combinations also generally improved symptoms and health status versus monotherapies, although some discrepancies between lung function and PROs were observed. Overall, the safety profiles of the FDCs were similar to placebo. Further research is required to examine more closely any relationship between lung function and PROs in patients receiving LABA–LAMA combinations.

Keywords: chronic obstructive pulmonary disease, combination therapy, dyspnea, forced expiratory volume, health status, spirometry

Introduction

Appropriate pharmacological management of COPD involves treatment with inhaled bronchodilators to reduce airflow limitation and hyperinflation. Most patient groups identified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy can be managed using long-acting inhaled bronchodilators (long-acting muscarinic antagonists [LAMAs] and long-acting β2-agonists [LABAs]), with or without inhaled corticosteroids.1 Fixed dose combinations (FDCs) provide potent bronchodilation versus single agents,2 with some advantage in terms of convenience and simplicity compared with combinations administered via separate inhalers. Beta agonists (BAs) and muscarinic antagonists (MAs) target different pathways to promote smooth-muscle relaxation and...
inhibit pulmonary constriction. Combining bronchodilators with different modes of action appears to be additive, providing greater efficacy versus component monotherapies. Randomized controlled trials (RCTs) of LABA–LAMA combinations via separate inhalers have generally shown improved lung function versus component monotherapies.

COPD is characterized by persistent airflow limitation, with forced expiratory volume in 1 second ($FEV_1$) to forced vital capacity ratio and percentage predicted $FEV_1$ widely used as pathophysiological markers. However, COPD is multidimensional, with pulmonary, extrapulmonary, and systemic effects. Outcomes in addition to $FEV_1$ are needed to assess disease burden and treatment efficacy. Spirometry is central to COPD diagnosis, but does not measure COPD burden in terms of health status. Spirometry is not always performed, and symptoms and exacerbation history can play important roles in treatment initiation and management. It is therefore important that spirometry is accompanied by assessments using patient-reported outcome (PRO) measures, such as breathlessness, physical functioning, and health status. Additionally, spirometry is often weak, particularly for LAMAs and LABA–LAMA combinations. Here, we examine the evidence for the use of FDC bronchodilators in COPD, assess effects on PROs, and evaluate relationships between PROs and changes in lung function.

**Materials and methods**

This systematic literature search (not registered) was performed in accordance with the general principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The literature search identified primary, English-language, RCT publications of fixed-combination bronchodilators reporting treatment effects on lung function and/or PROs in COPD. The relationship between these efficacy measures is often weak, particularly for LAMAs and LABA–LAMA combinations. Here, we examine the evidence for the use of FDC bronchodilators in COPD, assess effects on PROs, and evaluate relationships between PROs and changes in lung function.

Following the publication-database searches and during preparation of this manuscript (August 2015 onward), additional relevant articles became available, and thus these were added to the literature-search results.

All search results were extracted and gathered by a single party. Titles and abstracts were then scrutinized in parallel by two independent reviewers, and papers were categorized as relevant (where both reviewers categorized a paper as “relevant”), not relevant (where both reviewers judged a paper as “not relevant”), or potentially relevant (where one reviewer judged a paper as “relevant” and the other judged the same paper as “not relevant”). Irrelevant publications/studies comprised review papers, unapproved treatment doses, nonclinical trials, incorrect drug, or incorrect disease. Conflicting results were resolved by a third reviewer, who provided input as to whether the abstract was of potential relevance based on the same criteria as the first reviewers. To reduce the risk of omitting relevant studies/papers, all relevant and potentially relevant results were subsequently reviewed by the authors, who had the final decision regarding which publications to take to the next review level. Where relevance was not discernible from abstracts, full copies of author-confirmed relevant/potentially relevant articles were further assessed by two reviewers and conflicts resolved by a third reviewer. Data from the literature describing treatment differences with the FDC and comparator are summarized – according to end point – using least-squares mean (LSM) and 95% confidence interval (95% CI), odds ratio (OR), rate ratio, or hazard ratio (HR).

**Results**

**Systematic literature-search results**

The searches yielded 729 records, from which 35 primary publications were relevant (Figure 1). Literature searches were supplemented with information from ClinicalTrials.gov, and author expertise/knowledge (eg, if authors were aware that important publications were missing from search results). Between the time of the predefined search end (July 2014 for published manuscripts and May 2015 for congress abstracts) and the drafting of this manuscript (August 2015 onwards), additional FDC studies were being published, and are thus included in this review.

**Trials of fixed-dose dual-combination bronchodilators**

FDC bronchodilators approved or in advanced clinical development for COPD include: indacaterol–glycopyrronium once daily (OD; QVA149; Ultibro® Breezhaler®; Novartis.
International AG, Basel, Switzerland), umeclidinium–vilanterol 110/50 µg OD (Laventair/Anoro® Ellipta®; GlaxoSmithKline PLC, London, UK), tiotropium–olodaterol OD (Spiolto® Respimat®; Boehringer Ingelheim, Ingelheim, Germany), aclidinium–formoterol twice daily (bis in die [BID]; Duaklir® Genuair®; AstraZeneca PLC, London, UK) and glycopyrrolate–formoterol (PT003; AstraZeneca). Indacaterol–glycopyrronium OD is approved in >70 countries. Of 13 large Phase III trials of indacaterol–glycopyrronium, publications are available for ten (SHINE, ILLUMINATE, BRIGHT, ENLIGHTEN, SPARK, BLAZE, BEACON, LANTERN, QUANTIFY, and FLAME), all of which report lung function and PRO data and are included in this review (Table 1). These active-comparator and placebo-controlled trials ranged from 3 to 64 weeks in duration.

Umeclidinium–vilanterol 62.5/25 µg OD is approved in the US and EU (higher doses are not reviewed here). Findings from 12 Phase III trials had been reported in publications or conference abstracts at the time of the literature search, including: five 24-week studies; seven 12-week studies; and one 52-week safety study (125/25 µg). Lung-function and PRO data have been fully reported for six of the eight trials listed in Table 1.

Tiotropium–olodaterol (5/5 µg; lower doses are not reviewed) OD has been approved in more than 20 European countries, the US, Canada, and Australia since May 2015. Results from two 1-year studies with tiotropium–olodaterol 5/5 µg (included in this review; Table 1) have been reported and include data on lung function and health status versus the monocomponents. Results from an additional Phase III trial evaluating lung function and volume (VIVACITO) have been published (Table 1). two Phase III trials have been presented as abstracts, one further Phase III study has been completed (ClinicalTrials.gov NCT01536262) and four are ongoing (ClinicalTrials.gov NCT02006732, NCT01964352, NCT01969721, and NCT02085161). Acidium–formoterol (400/12 µg BID) is approved in the EU. Findings from two of four Phase III trials have been fully reported comparing the combination therapy versus monocomponents or placebo, and are included in this paper (Table 1). Results from a 24-week Phase III study comparing acidinium–formoterol with salmeterol–fluticasone combination (SFC) BID had been published in abstract form at the time of the literature search. For glycopyrrolate–formoterol (in late-stage development), only Phase II congress abstracts are available. Three Phase III studies are ongoing (ClinicalTrials.gov NCT01854645, NCT01854658, and NCT01970878).

In this review, we focus on the 23 aforementioned published Phase III RCTs and listed in Table 1 (supplemented with results presented at major respiratory congresses, where applicable): ten with indacaterol–glycopyrronium OD, eight with acidinium–vilanterol OD, three with tiotropium–olodaterol OD, and two with acidinium–formoterol BID. The remaining primary publications from the literature search were excluded, due to duplicate publications of the same results (eg, where a primary publication superseded several congress abstracts).

Patient population and study design
Patient populations, inclusion criteria, treatment blinding, and other characteristics differed between trials (Table 1). The majority of indacaterol–glycopyrronium OD studies enrolled symptomatic patients with moderate-to-severe airflow limitation (GOLD 2008, 2009, or 2010 classification), except for SPARK and FLAME, which enrolled patients with severe-to-very-severe or moderate-to-very-severe disease, respectively, and one or more exacerbations in the past year. The eight umeclidinium–vilanterol OD trials enrolled patients with moderate-to-severe or moderate-to-very-severe COPD who were symptomatic Patients in the tiotropium–olodaterol OD studies had moderate-to-very-severe COPD. The acidinium–formoterol BID studies were conducted in patients with moderate-to-severe COPD.
## Table 1: Clinical trials of FDC bronchodilator therapies evaluating treatment effects on lung function and/or patient-reported outcome

| Reference and study | Design | Duration | Patients, n | Patient population | Mean FEV₁ % predicted (GOLD stage) | Treatment | Primary and other efficacy outcomes |
|---------------------|--------|----------|-------------|--------------------|-----------------------------------|-----------|-----------------------------------|
| **Published Phase III clinical trials** | | | | | | | |
| **IND–GLY** (SHINE) | MC, R, DB | 26 weeks | 2,144 | Moderate-to-severe COPD (FEV₁ ≥30% and <80% predicted) and symptomatic (total daily symptom score ≥1 on ≥4 of the 7 days prior to randomization); 75% had no reports of exacerbations in the previous year | 55 (II or III) | IND–GLY 110/50 µg Indacaterol 150 µg Glycopyrronium 50 µg Tiotropium 18 µg OL Placebo | Trough FEV₁ at week 26 (primary) Dyspnea (TDI) Health status (SGRQ) Rescue-medication use Symptoms (diary) |
| **Dahl et al³⁶** (ENLIGHTEN) | MC, R, DB | 52 weeks | 339 | Moderate-to-severe COPD (FEV₁ ≥30% and <80% predicted) and symptomatic (total daily symptom score ≥1 on ≥4 of the 7 days prior to randomization); excluded patients who had an exacerbation requiring antibiotics, oral steroids, or hospitalization, within 6 weeks prior to screening or between screening and randomization | 57 (II or III) | IND–GLY 110/50 µg Placebo | Safety (primary) Rescue-medication use Symptoms (diary) Trough FEV₁ |
| **Dahl et al³⁷** (BEACON) | MC, R, DB | 4 weeks | 193 | Moderate-to-severe COPD (FEV₁ ≥30% and <80% predicted) and symptomatic (total daily symptom score ≥1 on ≥3 days prior to randomization); excluded patients who had an exacerbation requiring treatment with antibiotics and/or oral corticosteroids and/or hospitalization ≤6 weeks prior to visit 1 | 54 (II or III) | IND–GLY 110/50 µg Indacaterol 150 µg + glycopyrronium 50 µg | Trough FEV₁ at week 4 (noninferiority; primary) Rescue-medication use Symptoms (diary) |
| **Mahler et al³⁸** (BLAZE) | MC, R, B, DD, XO | 6 weeks | 247 | Moderate-to-severe COPD (FEV₁ ≥30% and <80% predicted) with mMRC grade ≥2; 70% of patients had no history of exacerbations in the previous year | 56 (II or III) | IND–GLY 110/50 µg Placebo Tiotropium 18 µg | Dyspnea at week 6 (TDI-SAC; primary) FEV₁, AUC₀–₁₄h Rescue-medication use Symptoms (diary) |
| Study                  | Authors | Duration | Patients | Inclusion Criteria                                                                                      | Treatment | Outcomes                                                                 |
|-----------------------|---------|----------|----------|-------------------------------------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------|
| Vogelmeier et al      | MC, R, DB, DD | 26 weeks | 523      | Moderate-to-severe COPD (FEV<sub>1</sub> 40% and <80% predicted) and symptomatic (total daily symptom score ≥1 on ≥4 of the 7 days prior to randomization); excluded patients with exacerbations requiring treatment with antibiotics, systemic corticosteroids, and/or hospitalization in the previous year | IND–GLY 1 10/50 µg SFC 50/500 µg BID | Dyspnea (TDI), FEV<sub>1</sub> and FVC, Health status (SGRQ), Rescue-medication use, Symptoms (diary) |
| Wedzicha et al        | MC, R, DB | 64 weeks | 2,224    | Severe-to-very-severe COPD (FEV<sub>1</sub> <50% predicted) with ≥1 COPD exacerbation requiring treatment with systemic corticosteroids and/or antibiotics in the previous year | IND–GLY 1 10/50 µg Glycopyrronium 50 µg Tiotropium 18 µg OL | Exacerbations (primary), Health status (SGRQ), Rescue-medication use, Trough FEV<sub>1</sub> |
| Beeh et al            | MC, R, DB, DD, XO | 3 weeks | 85       | Moderate-to-severe COPD (FEV<sub>1</sub> 40% and <70% predicted), 83% of patients had no history of exacerbation in the previous year | IND–GLY 1 10/50 µg Tiotropium 18 µg + Placebo | Exercise endurance time at week 3 (primary), Dyspnea and leg discomfort (Borg), Lung function, Rescue-medication use, Symptoms (diary) |
| Buhl et al            | DB, TD   | 26 weeks | 934      | Moderate-to-severe COPD (FEV<sub>1</sub> ≥30%−80% predicted; postbronchodilator FEV<sub>1</sub> to FVC ratio <0.7 at screening), current or ex-smoker (≥10 pack-years); no COPD exacerbation within 6 weeks of prescreening or prior to randomization | IND–GLY 1 10/50 µg Tiotropium 18 µg + Formoterol 12 µg BID | Health status (SGRQ-C; primary), Dyspnea (TDI), Symptoms (SGRQ-C), FEV<sub>1</sub> and FVC, Exacerbations |
| Zhong et al           | MC, R, DB, DD | 26 weeks | 744      | Moderate-to-severe COPD (FEV<sub>1</sub> ≥30%−80% predicted; postbronchodilator FEV<sub>1</sub> to FVC ratio <0.7 at screening), current or ex-smoker (≥10 pack-years); mMRC grade ≥2; ≤1 COPD exacerbation within 12 months of screening/randomization | IND–GLY 1 10/50 µg SFC 50/500 µg BID | Trough FEV<sub>1</sub>, at week 26 (primary), Other FEV<sub>1</sub>, FVC, Dyspnea (TDI), Health status (SGRQ and CAT), Rescue-medication use, Symptoms (diary), Exacerbations |

(Continued)
| Reference and study | Design | Duration | Patients, n | Patient population | Mean FEV₁, % predicted (GOLD stage) | Treatment | Primary and other efficacy outcomes |
|---------------------|--------|----------|-------------|--------------------|------------------------------------|-----------|-----------------------------------|
| Wedzicha et al²⁶ (FLAME) | MC, R, DB, DD, NI | 52 weeks | 3,362 | Moderate-to-very-severe COPD (FEV₁ ≥25%–<60% predicted; postbronchodilator FEV₁ to FVC ratio <0.7 at screening); mMRC grade ≥2; a documented history of ≥1 COPD exacerbation requiring treatment with systemic corticosteroids and/or antibiotics in the previous 1 year | 44 (II–IV) | IND–GLY 110/50 µg SFC 50/500 µg BID | Exacerbations (primary) Other exacerbation end points Trough FEV₁ and FEV₁ AUC₀–₁₂h Health status (SGRQ-C) Rescue-medications use |
| Maleki-Yazdi et al²² | MC, R, DB | 24 weeks | 905 | Moderate-to-very-severe COPD (FEV₁ ≥70% predicted) and mMRC grade ≥2; exacerbation history not stated | 46 (II–IV) | UMEC–VI 62.5/25 µg Tiotropium 18 µg Umeclidinium 125 µg | Trough FEV₁ at week 24 (primary) Dyspnea (TDI, SOBDA) Exacerbations Other FEV₁, FVC Health status (SGRQ) Rescue-medications use |
| Study | Authors | Duration | Number | COPD Severity | Inclusion Criteria | Intervention | Comparison | Outcomes | Notes |
|-------|---------|----------|--------|---------------|--------------------|--------------|------------|----------|-------|
| Maltais et al\(\textsuperscript{23}\) (study 1 \[417\]) | MC, R, DB, XO | 12 weeks | 349 | Moderate-to-severe COPD (FEV\(_1\) \(\leq 35\%\) and \(\geq 70\%\) predicted), mMRC grade \(\geq 2\) and FRC \(\geq 120\%\) (hyperinflated); exacerbation history not stated | 51 (II or III) | UMEC–VI 125/25 or 62.5/25 \(\mu g\) Umclidinium \(62.5\) or 125 \(\mu g\) Vilanterol \(25\) \(\mu g\) Placebo | Exercise-endurance time at week 12 (co-primary) | Trough FEV\(_1\) at week 12 (co-primary) | Lung function | Lung volume |
| Maltais et al\(\textsuperscript{23}\) (study 2 [418]) | MC, R, DB, XO | 12 weeks | 308 | Moderate-to-severe COPD (FEV\(_1\) \(\leq 35\%\) and \(\geq 70\%\) predicted), mMRC grade \(\geq 2\) and FRC \(\geq 120\%\) (hyperinflated); exacerbation history not stated | 51 (II or III) | UMEC–VI 125/25 or 62.5/25 \(\mu g\) Umclidinium \(62.5\) or 125 \(\mu g\) Vilanterol \(25\) \(\mu g\) Placebo | Exercise-endurance time at week 12 (coprimary) | Trough FEV\(_1\) at week 12 (coprimary) | Lung function | Lung volume |
| Donohue et al\(\textsuperscript{27}\) (study 2114930) | MC, R, DB, DD | 12 weeks | 707 | Moderate-to-severe COPD; (FEV\(_1\) \(\leq 30\%\) and \(\geq 70\%\) predicted); no exacerbations in past year | 49–50 (II or III) | UMEC–VI 62.5/25 \(\mu g\) SFC 50/250 \(\mu g\) | FEV\(_1\) \(0–24\) hours at week 12 (primary) | Other FEV\(_1\), FVC IC Dyspnea (TDI) Health status (EuroQol 5D, SGRQ, and CAT) Rescue-medication use Symptoms (diary) |
| Donohue et al\(\textsuperscript{27}\) (study 2114951) | MC, R, DB, DD | 12 weeks | 700 | Moderate-to-severe COPD; (FEV\(_1\) \(\leq 30\%\) and \(\geq 70\%\) predicted); no exacerbations in past year | 49–50 (II or III) | UMEC–VI 62.5/25 \(\mu g\) SFC 50/250 \(\mu g\) | FEV\(_1\) \(0–24\) hours at week 12 (primary) | Other FEV\(_1\), FVC Dyspnea (TDI) Health status (EuroQol 5D, SGRQ, and CAT) Rescue-medication use Symptoms (diary) |
| TIO–OLO | Buhl et al\(\textsuperscript{30}\) (replicate studies 1237.5 and 1237.6) | MC, R, DB | 52 weeks \((\times 2)\) | 2,624 | Moderate-to-severe COPD (GOLD stage II–III); FEV\(_1\) \(\leq 30\%\) and \(\geq 80\%\) predicted; exacerbation history not stated | 49–50 (I–IV) | Olodaterol 5 \(\mu g\) Tiotropium 2.5 \(\mu g\) Tiotropium 5 \(\mu g\) TIO–OLO 2.5/5 \(\mu g\) TIO–OLO 5/5 \(\mu g\) Placebo | FEV\(_1\) AUC \(0–24\) h at week 6 (primary) | Other FEV\(_1\), FVC Dyspnea (TDI) Residual volume |
| Beeh et al\(\textsuperscript{31}\) (VIVACITO) | MC, R, DB, IN, XO | 6 weeks | 219 | Moderate-to-very-severe COPD (GOLD stage II–IV); FEV\(_1\) \(< 80\%\) predicted \((\geq 30\%\) for certain sites); exacerbation history not stated | | Olodaterol 5 \(\mu g\) Tiotropium 2.5 \(\mu g\) Tiotropium 5 \(\mu g\) TIO–OLO 2.5/5 \(\mu g\) TIO–OLO 5/5 \(\mu g\) Placebo | FEV\(_1\), FVC, FRC Residual volume |

(Continued)
| Reference and study | Design | Duration | Patients, n | Patient population | Mean FEV₁% predicted (GOLD stage) | Treatment | Primary and other efficacy outcomes |
|---------------------|--------|----------|-------------|--------------------|---------------------------------|----------|-------------------------------------|
| **ACL–FORM**        |        |          |             |                    |                                 |          |                                     |
| Singh et al<sup>38</sup> (ACLIFORM-COPD) | MC, R, DB | 24 weeks | 1,729 | Moderate-to-severe COPD (FEV₁ ≥30%, but <80% predicted); exacerbation history not stated | 54 (III–IV) | Placebo, ACL–FORM, 400/12 µg BID, ACL–FORM 400/6 µg BID, Aclidinium 400 µg BID, Formoterol 12 µg BID | FEV₁, 1 hour postdose (co-primary) Trough FEV₁ (co-primary) Dyspnea (TDI) Symptoms (diary) Daytime symptoms (EXACT) Respiratory symptoms (E-RS) Night and early morning symptoms (questionnaire) Exacerbations (HCRU) |
| D’Urzo et al<sup>39</sup> (AUGMENT) | MC, R, DB | 24 weeks | 1,692 | Moderate-to-severe COPD (FEV₁ ≥30% and <80% predicted); excluded patients with exacerbations ≤6 weeks (≤3 months if hospitalized for exacerbation) before screening | 53–55 (III–IV) | Placebo, ACL–FORM, 400/12 µg BID, ACL–FORM 400/6 µg BID, Aclidinium 400 µg BID, Formoterol 12 µg BID | FEV₁, 1 hour postdose (co-primary) Trough FEV₁ (co-primary) Dyspnea (TDI) Health status (SGRQ) |
| **Studies reported in abstract form** |         |          |             |                    |                                 |          |                                     |
| IND–GLY             |        |          |             |                    |                                 |          |                                     |
| Asai et al<sup>40</sup> (ARISE) | MC, R, OL | 52 weeks | 160 | NR (II or III) | IND–GLY 110/50 µg Tiotropium 18 µg OL | Safety (primary) Lung function Health status (SGRQ) Symptoms (diary) |
| UMEC–VI             |        |          |             |                    |                                 |          |                                     |
| Donohue et al<sup>41</sup> (study 1) | MC, R, DB, XO | 12 weeks | 207 | NR (NR)<sup>4</sup> | UMEC–VI 62.5/25 µg Umeclidinium 62.5 µg Vilanterol 25 µg | FEV₁, at week 2 |
| Donohue et al<sup>41</sup> (study 2) | MC, R, DB, XO | 12 weeks | 182 | NR (NR)<sup>4</sup> | UMEC–VI 62.5/25 µg Umeclidinium 62.5 µg Vilanterol 25 µg | FEV₁, at week 12 |
| Singh et al<sup>42</sup> | MC, R, DB, DD | 12 weeks | 716 | NR (II or III) | UMEC–VI 62.5/25 µg SFC 500/50 µg BID | FEV₁, at week 12 (primary) Dyspnea (TDI) Health status (SGRQ) |
| TIO–OLO             |        |          |             |                    |                                 |          |                                     |
| Maltais et al<sup>43</sup> (TORRACTO) | DB, PG | 12 weeks | 404 | NR (II–III) | TIO–OLO 5/5 µg TIO–OLO 2.5/5 µg | Exercise-endurance time at week 12 |
| Study | Authors | Randomization | Duration | N | FEV1 | FEV1/FVC | Intervention | Comparator | Endpoints |
|-------|---------|---------------|----------|---|------|----------|--------------|------------|-----------|
| O'Donnell et al<sup>34</sup> (MORACTO 1 and 2) | DB, PG, IN, XO | 6 weeks | 586 | 58.6 (II–III) | TIO–OLO 5/5 µg | Exercise endurance (coprimary) | Breathing discomfort during exercise testing |
| ACL–FORM | D'Urzo et al<sup>35</sup> (AUGMENT extension) | R, DB, AC extension | 52 weeks | 1,668 | NR (NR) | ACL–FORM 400/12 µg BID | Postdose and trough FEV<sub>1</sub> | Dyspnea (TDI) and responders |
| Donohue et al<sup>36</sup> | R, DB, PG | 52 weeks | 581 | NR (II–III) | ACL–FORM 400/12 µg BID | Trough FEV<sub>1</sub> | Rescue-medications use Safety |
| Vogelmeier et al<sup>37</sup> | R, DB, DD, AC | 24 weeks | 933 | 53.2 (NR) | ACL–FORM 400/12 µg BID | Peak FEV<sub>1</sub> at week 24 (primary) | Peak FEV<sub>1</sub> at other visits, TDI, CAT score, exacerbations |
| GFF | Reisner et al<sup>38</sup> | R, DB, XO Phase IIB | 7 days | 118 | NR (II–IV) | GFF 72/9.6 µg BID | Trough FEV<sub>1</sub> | Lung function Mean PEFR Rescue use |
| Reisner et al<sup>39</sup> | R, DB, XO Phase IIB | 7 days | NR | NR (II–IV) | GFF 72/9.6 µg BID | Lung function Mean PEFR Rescue use |

**Notes:** Treatment was once daily unless stated otherwise. <sup>a</sup>patients randomized to treatment; <sup>b</sup>investigator-blinded only; <sup>c</sup>inclusion criteria: FEV<sub>1</sub> ≤ 70% predicted and FEV<sub>1</sub>/FVC 0.7.

**Abbreviations:** ACL–FORM, aclidinium–formoterol; AUC<sub>0–4 h</sub>, area under the (plasma concentration–time) curve from 0 to 4 hours; AUC<sub>0–12 h</sub>, area under the (plasma concentration–time) curve from 0 to 12 hours; AUC<sub>0–24 h</sub>, area under the (plasma concentration–time) curve from 0 to 24 hours; B, blinded; BID, bis in die (twice daily); CAT, COPD Assessment Test; DB, double-blind; DD, double-dummy; DPI, dry-powder inhaler; e-RS, evaluating Respiratory Symptoms; eXACT, eXAcerbations of COPD Tool; FEV<sub>1</sub>, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; GFF, glycopyrrolate–formoterol fumarate; GOLD, Global Initiative For Chronic Obstructive Lung Disease; HCRU, health-care-resource utilization; IC, inspiratory capacity; IN, incomplete; IND–GLY, indacaterol–glycopyrronium; MC, multicenter; MDI, metered-dose inhaler; mMRC, modified Medical Research Council; NL, noninferiority; NR, not reported; OL, open-label; PEFR, peak expiratory flow rate; R, randomized; SFC, salmeterol–fluticasone combination; SGRQ–C, St George's Respiratory Questionnaire – COPD; TD, triple-dummy; TDI-SAC, transition dyspnea index – self-administered, computerized; TIO–OLO, tiotropium–olodaterol; UMEC–VI, umeclidinium–vilanterol; XO, crossover.
Lung function
Across eight trials (3–64 weeks), indacaterol–glycopyrronium OD provided significant LSM treatment differences in trough FEV₁ of 60–80 mL versus tiotropium 18 µg, 70–80 mL versus indacaterol 150 µg or glycopyrronium 50 µg alone, 68 mL versus tiotropium + formoterol 18/12 µg, 62–72 mL versus SFC 50/500 µg BID, and 189–200 mL versus placebo (Table 2).2,24–26,35,36,39,40 Preliminary data suggest that the extent of FEV₁ improvement may vary: in a post hoc analysis of SHINE, data from patients in the spirometry subset who received indacaterol–glycopyrronium OD (n=399) showed that 39.8% had an increase in FEV₁ of ≥200 mL between baseline and week 26, 23.8% achieved ≥300 mL, and 13.1% had an increase of ≥400 mL.51

In three Phase III studies, LSM treatment differences in trough FEV₁ change from baseline to week 24 with umeclidinium–vilanterol 62.5/25 µg OD were 60–112 mL versus tiotropium 18 µg, 52 mL versus umeclidinium 62.5 µg, 22 mL versus umeclidinium 125 µg (not statistically significant), 90–95 mL versus vilanterol 25 µg, and 167 mL versus placebo.23,32,41 In two 12-week studies, umeclidinium–vilanterol 62.5/25 µg produced greater increases in trough FEV₁ versus individual components.33 In another two 12-week studies, umeclidinium–vilanterol 62.5/25 µg resulted in

Table 2 Lung function: margin of efficacy of fixed combinations versus comparators in fully published studies

| Reference and study | Duration | Treatment | Trough FEV₁, LSM (95% CI) treatment difference at end point, mL | Other lung-function parameters |
|---------------------|----------|-----------|---------------------------------------------------------------|--------------------------------|
| **IND–GLY**         |          |           |                                                               |                                |
| Bateman et al (SHINE) | 26 weeks | IND–GLY 110/50 µg OD vs Indacaterol 150 µg OD and Glycopyrronium 50 µg OD Placebo | 70 (NR)                          | FEV₁, AUC₀–₄ h and peak FEV₁ compared with placebo, glycopyrronium, and tiotropium (all P<0.01) |
| Dahl et al (ENLIGHTEN) | 52 weeks | IND–GLY 110/50 µg OD vs placebo | 189 (NR)                        | FEV₁ at 60 minutes postdose significantly greater with IND–GLY than placebo throughout the 52-week treatment period (P<0.001 at all time points); IND–GLY improved FVC versus placebo over the 52-week treatment period (P<0.001 at all time points) |
| Dahl et al (BEACON)  | 4 weeks  | IND–GLY 110/50 µg OD vs indacaterol 150 µg OD + glycopyrronium 50 µg OD Placebo | 5 (NR; NS for superiority) | FEV₁, AUC₀–₄ h (day 1 and week 4) similar between treatment groups |
| Mahler et al (BLAZE) | 6 weeks  | IND–GLY 110/50 µg OD vs Placebo and Tiotropium 18 µg OD Placebo | 330 (0.31–0.36)a,b 110 (0.08–0.13)a,b | FEV₁, AUC₀–₄₄ h, postdose significantly higher for IND–GLY vs tiotropium and placebo at day 1 and week 6 (all P<0.001) |
| Vogelmeier et al (ILLUMINATE) | 26 weeks | IND–GLY 110/50 µg OD vs SFC 50/500 µg BID Placebo | 103 (65–141) | Week 26 FEV₁, AUC₀–₁₂₅ h, significantly higher with IND–GLY than with SFC (treatment difference 138 mL, 95% CI 0.1–0.176; P<0.0001) |
| Wedzicha et al (SPARK) | 64 weeks | IND–GLY 110/50 µg OD vs Glycopyrronium 50 µg OD and Tiotropium 18 µg OD Placebo | Weeks 4–64: 70–80 (NR) 60–80 (NR) | NR |
| Beeh et al (BRIGHT)  | 3 weeks  | IND–GLY 110/50 µg OD vs Tiotropium 18 µg OD Placebo | 100 (50–150) 200 (150–260) | At day 21, mean treatment differences in trough IC, FEV₁, and FVC significantly higher for IND–GLY vs Placebo (190, 200, and 280 mL, respectively) and vs tiotropium (150, 100, and 110 mL, respectively) |
| Buhl et al (QUANTIFY) | 26 weeks | IND/GLY 110/50 µg OD vs Tiotropium 18 µg OD + formoterol 12 µg BID | 68 (37–100) | IND–GLY increased predose FVC vs tiotropium + formoterol at week 26 (74 mL, 95% CI: 24–125 mL; P<0.004) |

(Continued)
| Reference and study | Duration | Treatment | Trough FEV$_1$ (95% CI) treatment difference at end point, mL | Other lung-function parameters |
|---------------------|----------|-----------|-------------------------------------------------------------|---------------------------------|
| Zhong et al$^{a4}$ (LANTERN) | 26 weeks | IND–GLY 110/50 µg OD vs SFC 50/500 µg BID | 72* (40–104) | Improvements in trough FEV$_1$ with IND–GLY vs SFC observed at day 1 ($\Delta=43$ mL) and reaching steady state by week 12 ($\Delta=78$ mL, both $P<0.001$). Improvements in FEV$_1$, AUC$_{0-6h}$ at day 1/week 26 with IND–GLY vs SFC ($\Delta=65/122$ mL, respectively). Peak FEV$_1$ higher at day 1/week 26 with IND–GLY vs SFC ($P<0.001$). Trough FVC higher for IND–GLY vs SFC ($P<0.001$). Improvements in peak FVC (over the first 4 hours) with IND–GLY vs SFC at day 1/week 26 (all $P<0.001$) |
| Wedzicha et al$^{a6}$ (FLAME) | 52 weeks | IND–GLY 110/50 µg OD vs SFC 50/500 µg BID | 62* (NR) | Change from baseline in FEV$_1$, AUC$_{0-6h}$ (measured in a subgroup of 556 patients) was significantly greater with IND–GLY vs SFC at week 52 ($\Delta=110$ mL, $P<0.001$) |
| **UMEC–VI** | | | | |
| Donohue et al$^{a1}$ | 24 weeks | UMEC–VI 62.5/25 µg OD vs Umeclidinium 62.5 µg OD, Vilanterol 25 µg OD, Placebo | Change from baseline: 52* (17–87) 95* (60–130) 167* (128–207) | Improvements in trough FVC change from baseline observed at day 169 for UMEC–VI 62.5/25 µg, UMEC 62.5 µg, and VI 25 µg vs placebo (248 mL, 175 mL, and 105 mL; all $P<0.002$) |
| Decramer et al$^{a2}$ (study 1) | 24 weeks | UMEC–VI 125/25 µg OD$^+$ UMEC–VI 62.5/25 µg OD vs Tiotropium 18 µg OD, Vilanterol 25 µg OD | Change from baseline: 90* (39–141) 90* (39–142) | Mean 0- to 6-hour FEV$_1$, on day 168 for UMEC–VI (both doses) significantly improved vs tiotropium 18 µg |
| Decramer et al$^{a2}$ (study 2) | 24 weeks | UMEC–VI 125/25 µg OD$^+$ UMEC–VI 62.5/25 µg OD vs Tiotropium 18 µg OD, Umeclidinium 125 µg OD | Change from baseline: 60* (10–109) 22* (–27 to 72) | Mean 0- to 6-hour FEV$_1$, on day 168 for both doses of UMEC/VI improved vs tiotropium 18 µg (nominal $P$-values) |
| Maleki-Yazdi et al$^{a3}$ | 24 weeks | UMEC–VI 62.5/25 µg OD vs tiotropium 18 µg OD | Change from baseline: 112* (81–144) | Weighted mean FEV$_1$ over 0–6 hours postdose at day 168 improved for UMEC–VI vs tiotropium (105 mL, 95% CI 0.071–0.14; $P<0.001$) |
| Maltais et al$^{a1}$ (study 417) | 12 weeks | UMEC–VI 125/25 µg OD$^+$ UMEC–VI 62.5/25 µg OD, Umeclidinium 62.5 µg OD, Umeclidinium 125 µg OD, Vilanterol 25 µg OD | Change from baseline vs placebo: 211* (172–249) 87* (30–143) 140* (84–96) 99* (50–148) | Trough FEV$_1$, numerically improved with UMEC–VI 125/25 µg and UMEC–VI 62.5/25 µg compared with placebo from day 2 to week 12 |
| Maltais et al$^{a1}$ (study 418) | 12 weeks | UMEC–VI 125/25 µg OD$^+$ UMEC–VI 62.5/25 µg OD, Umeclidinium 62.5 µg OD, Umeclidinium 125 µg OD, Vilanterol 25 µg OD | Change from baseline vs placebo: 243* (202–284) 144* (86–203) 255* (193–318) 112* (61–163) | Trough FEV$_1$, improved with UMEC–VI 125/25 µg and UMEC–VI 62.5/25 µg compared with placebo ($P<0.001$) from day 2 to week 12 |
| Donohue et al$^{a7}$ (study 2114930) | 12 weeks | UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID | Change from baseline: 74* (38–110) | FEV$_1$ significantly improved for UMEC–VI vs SFC at all time points on day 84 (except 18 hours); significantly greater improvement in LSM trough FEV$_1$, from baseline for UMEC–VI vs SFC on day 85 (treatment difference 82 mL, $P<0.001$) |

*(Continued)*
significant improvements in FEV₁ 0–24 hours and trough FEV₁ compared with 50/250 µg BID.²⁷

At week 24 of the two 1-year studies, tiotropium–olodaterol 5/5 µg OD increased trough FEV₁ by 82–88 mL versus olodaterol 5 µg and by 50–71 mL versus tiotropium 5 µg.³⁰ A 6-week incomplete crossover study showed improvements in 24-hour lung function with tiotropium–olodaterol 5/5 µg versus components or placebo.³¹

Acridinium–formoterol (400/12 µg BID) increased week 24 trough FEV₁ significantly versus placebo (143 mL) and formoterol (85 mL) in the ACLIFORM study, but the smaller difference (~25 mL) versus aclidinium BID was not statistically significant.³² Similar results were observed in the AUGMENT trial, with a significant difference for the combination versus formoterol (45 mL), but not aclidinium (28 mL).²⁹

### Table 2 (Continued)

| Reference and study        | Duration | Treatment                        | Trough FEV₁, LSM (95% CI) treatment difference at end point, mL | Other lung-function parameters                     |
|-----------------------------|----------|----------------------------------|---------------------------------------------------------------|---------------------------------------------------|
| Donohue et al²² (study 2114951) | 12 weeks | UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID | Change from baseline: 10¹ (63–139)                          | FEV₁ significantly improved for UMEC–VI vs SFC at all time points on day 84; significantly greater improvement in LSM trough FEV₁ from baseline for UMEC–VI vs SFC on day 85 (treatment difference 98 mL, P<0.001) |

**TIO–OLO**

| Reference and study        | Duration | Treatment                        | Trough FEV₁, LSM (95% CI) treatment difference at end point, mL | Other lung-function parameters                     |
|-----------------------------|----------|----------------------------------|---------------------------------------------------------------|---------------------------------------------------|
| Buhl et al²³ (study 1237.5) | 52 weeks | TIO–OLO 2.5/5 µg OD¹  | Change from baseline at week 24: 82¹ (59–106)                  | Improvements observed for FEV₁ values on all test days over each of the 52-week studies; responses in trough FVC and FVC were similar for both TIO–OLO doses vs placebo and monotherapies at 6 weeks; similar pattern of response for FVC, FRC, and residual volume |
|                             |          | TIO–OLO 5/5 µg OD               | 71¹ (47–94)                                                  |                                                   |
|                             |          | Olodaterol 5 µg OD              |                                                              |                                                   |
|                             |          | Tiotropium 5 µg OD              |                                                              |                                                   |
|                             |          | Tiotropium 2.5 µg OD            |                                                              |                                                   |
|                             |          | Placebo                         |                                                              |                                                   |

**ACL–FORM**

| Reference and study        | Duration | Treatment                        | Trough FEV₁, LSM (95% CI) treatment difference at end point, mL | Other lung-function parameters                     |
|-----------------------------|----------|----------------------------------|---------------------------------------------------------------|---------------------------------------------------|
| Singh et al²⁴ (ACLIFORM-COPD) | 24 weeks | ACL–FORM 400/6 µg BID²  | Change from baseline at week 24: 85² (63–113)                  | Fast onset of action of both ACL–FORM doses on day 1, with significant improvements in bronchodilation vs placebo at 5 minutes postdose |
|                             |          | ACL–FORM 400/12 µg BID vs       | 79² (NR)                                                      |                                                   |
|                             |          | Formoterol 12 µg BID            |                                                              |                                                   |
|                             |          | Aclidinium 400 µg BID           |                                                              |                                                   |
|                             |          | Placebo                         |                                                              |                                                   |

**D’Urzo et al²⁵ (AUGMENT)**

| Reference and study        | Duration | Treatment                        | Trough FEV₁, LSM (95% CI) treatment difference at end point, mL | Other lung-function parameters                     |
|-----------------------------|----------|----------------------------------|---------------------------------------------------------------|---------------------------------------------------|
|                             | 24 weeks | ACL–FORM 400/6 µg BID²  | Change from baseline at week 24: 45² (63–113)                  | ACL–FORM (both doses) associated with significant changes from baseline in peak FEV₁ at day 1 and week 24 (P<0.0001 all comparisons); rapid bronchodilation occurred with significant FEV₁ improvements 5 minutes postdose (P<0.0001) |
|                             |          | ACL–FORM 400/12 µg BID vs       | 28                                                            |                                                   |
|                             |          | Formoterol 12 µg BID            |                                                              |                                                   |
|                             |          | Aclidinium 400 µg BID           |                                                              |                                                   |
|                             |          | Placebo                         |                                                              |                                                   |

**Notes:** Treatment once daily unless stated otherwise. "Significant treatment difference; ‘FEV₁, AUC₀–₄₄₄₄’; ¹dose not approved for use (ACL–FORM, dose not approved in EU); ²estimated from figure.

**Abbreviations:** ACL–FORM, aclidinium–formoterol; AUC₀–₄₄₄₄, area under the plasma concentration-time curve from 0 to 4 hours; AUC₀–₂₄₄₄, area under the (plasma concentration-time) curve from 0 to 24 hours; BID, once daily; OL, open-label; SFC, salmeterol/fluticasone combination; TIO–OLO, tiotropium–olodaterol; UMEC–VI, umeclidinium–vilanterol.
Symptoms
Improvements in dyspnea and other symptoms were seen with fixed-dose LABA–LAMA therapies versus monotherapies and for indacaterol–glycopyrronium OD versus SFC.\textsuperscript{2,25,26,27} Indacaterol–glycopyrronium significantly improved transition dyspnea index (TDI) scores in SHINE and ILLUMINATE versus placebo, open-label tiotropium, and SFC.\textsuperscript{2,38} In BLAZE, indacaterol–glycopyrronium significantly improved self-administered computerized total TDI score versus placebo (LSM treatment difference 1.37, $P<0.001$) and blinded tiotropium (LSM treatment difference: 0.49, $P=0.021$).\textsuperscript{38} The proportion of patients achieving the MCID ($\geq 1$-point) for TDI score was also significantly increased versus blinded

Table 3 Symptoms: margin of efficacy of fixed combinations versus comparators in published studies

| Reference and study | Duration | Treatment | Treatment difference at end point | Other |
|---------------------|----------|-----------|-----------------------------------|-------|
|                      |          |           | TDI total score, % TDI responders* | OR    |
| IND–GLY             |          |           | LSM (95% CI)                       |       |
| Bateman et al\textsuperscript{2} (SHINE) | 26 weeks | IND–GLY 110/50 \(\mu\) OD vs placebo | 0.25 (NR) | 3.5 (NR) |
|                     |          | Indacaterol 150 \(\mu\) OD |                        |       |
|                     |          | Glycopyrronium 50 \(\mu\) OD |                        |       |
|                     |          | Tiotropium 18 \(\mu\) OD OL |                        |       |
|                     |          | Placebo | 1.09 (0.61–1.57) | 10.6 (NR) |
|                     |          |          | Diary data (values vs placebo): % days with no daytime symptoms, +3.05%; % days able to perform usual daily activities, +11.48%; % nights without awakenings, +10.01\textsuperscript{bc} |
| Dahl et al\textsuperscript{24} (ENLIGHTEN) | 52 weeks | IND–GLY 110/50 \(\mu\) OD vs Placebo | NR | NR | Diary data: Total daily symptom score, −0.573; % days with no daytime symptoms, +5.3; % days able to perform usual daily activities, +8.1; % nights without awakenings, +6.3 |
| Dahl et al\textsuperscript{27} (BEACON) | 4 weeks | IND–GLY 110/50 \(\mu\) OD vs indacaterol 150 \(\mu\) OD + glycopyrronium 50 \(\mu\) OD | NR | NR | Diary data: Total daily symptom score, 0.07 (−0.24, 0.39) |
| Mahler et al\textsuperscript{19} (BLAZE) | 6 weeks | IND–GLY 110/50 \(\mu\) OD vs tiotropium 18 \(\mu\) OD placebo | SAC TDI: 0.49 (0.07, 0.91) | SAC TDI: 1.15 (2.78) |
|                     |          | Placebo | 1.37 (0.95, 1.79) | 17.8 (1.78) | Diary data (vs placebo and tiotropium): Total daily symptom score, −0.72$\pm$ and −0.03; % days with no daytime symptoms, +3.5$\pm$ and +1.5; % nights with no awakenings, 5.6$\pm$ and 2.6; days able to perform usual activities, 8.8$\pm$ and −0.4 |
| Vogelmeier et al\textsuperscript{20} (ILLUMINATE) | 26 weeks | IND–GLY 110/50 \(\mu\) OD vs SFC 50/500 \(\mu\) BID | 0.76 (0.26, 1.26) | 10.7 (1.56) | Diary data: Differences in scores for most symptoms NS between treatment groups % days with no daytime symptoms, +2.50\textsuperscript{b} |
| Beih et al\textsuperscript{22} (BRIGHT) | 3 weeks | IND–GLY 110/50 \(\mu\) OD vs tiotropium 18 \(\mu\) OD placebo | NR | NR | Diary data, mean daily symptom score vs baseline: IND–GLY −0.64, tiotropium −0.43, placebo −0.19 |
| Buhl et al\textsuperscript{23} (QUANTIFY) | 26 weeks | IND–GLY 110/50 \(\mu\) OD vs tiotropium 18 \(\mu\) OD + formoterol 12 \(\mu\) BID | 0.38 (−0.06, 0.82) | 7.2 (1.17 risk ratio)$^b$ | LSM treatment difference in SGRQ–C symptom score IND–GLY vs tiotropium + formoterol (−1.31 [95% CI −3.49, 0.86]) |
| Zhong et al\textsuperscript{25} (LANTERN) | 26 weeks | IND–GLY 110/50 \(\mu\) OD vs SFC 50/500 \(\mu\) BID | 0.25 (−0.09, 0.59) | NR | Improvements in TDI focal score at weeks 12 and 26 similar between IND–GLY and SFC. Similar improvement in SGRQ total score between IND–GLY and SFC at weeks 12 and 26. Symptoms, rescue medication use and total COPD assessment test scores at week 26 comparable for IND–GLY and SFC |
| UMEC–VI |          |          |                                  |       |
| Donohue et al\textsuperscript{26} | 24 weeks | UMEC–VI 62.5/25 \(\mu\) OD vs Placebo | 0.3 (−0.2, 0.7) | 5.0 (NR) |
|                     |          | Umeclidinium 62.5 \(\mu\) OD |                        |       |
|                     |          | Vilanterol 25 \(\mu\) OD |                        |       |
|                     |          | Placebo | 1.2 (0.7, 1.7) | 17.0 (2.0) |
Table 3 (Continued)

| Reference and study | Duration | Treatment | TDI total score, % TDI responders (OR) | Other |
|---------------------|----------|-----------|---------------------------------------|-------|
| Decramer et al\(^2\) (study 1) | 24 weeks | UMEC–VI 125/25 µg OD\(^1\) UMEC–VI 62.5/25 µg OD vs | | |
|                     |          | tiotropium 18 µg OD | –0.1 (–0.7, 0.5) | 5 (0.9) | NR |
|                     |          | Vilanterol 25 µg OD | 0.2 (–0.4, 0.8) | 6 (1.4) | NR |
| Decramer et al\(^2\) (study 2) | 24 weeks | UMEC–VI 125/25 µg OD\(^1\) UMEC–VI 62.5/25 µg OD vs | | |
|                     |          | tiotropium 18 µg OD | 0.2 (–0.5, 0.9) | 6 (1.3) | NR |
|                     |          | Umeclidinium 125 µg OD | 0.4 (–0.3, 1.1) | 7 (1.3) | NR |
| Donohue et al\(^2\) (study 2114930) | 12 weeks | UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID | | |
|                     |          | Tiotropium 5 µg OD | 0.3 (–0.2, 0.7) | NR | NR |
| Donohue et al\(^2\) (study 2114951) | 12 weeks | UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID | | |
|                     |          | Tiotropium 5 µg OD | 0.3 (–0.1, 0.8) | NR | NR |
| Maltas et al\(^2\) (study 417) | 12 weeks | UMEC–VI 125/25 µg OD\(^1\) UMEC–VI 62.5/25 µg OD | | |
|                     |          | Umeclidinium 62.5 µg OD | NR | NR | 0.39 (0.91 to 0.79) |
|                     |          | Umeclidinium 125 µg OD | NR | NR | |
|                     |          | Vilanterol 25 µg OD | NR | NR | |
| Maltas et al\(^2\) (study 418) | 12 weeks | UMEC–VI 125/25 µg OD\(^1\) UMEC–VI 62.5/25 µg OD | | |
|                     |          | Umeclidinium 62.5 µg OD | NR | NR | 0.36 (0.76 to 0.03) |
|                     |          | Umeclidinium 125 µg OD | NR | NR | 0.66 (1.14 to –0.18) |
|                     |          | Vilanterol 25 µg OD | NR | NR | |
| TIO–OLO             |          | TIO–OLO 2.5/25 µg OD vs TIO–OLO 5/5 µg OD | | |
| Buhl et al\(^10\) (studies 1237.5 and 1237.6 combined) | 52 weeks | Olodaterol 5 µg OD | 0.420 (0.155–0.684) | NR | NR |
|                     |          | Tiotropium 5 µg OD | 0.356 (0.092–0.619) | NR | NR |
| ACL–FORM            |          | ACL–FORM 400/6 µg BID\(^1\) ACL–FORM 400/12 µg BID vs | | E-RS changes from baseline: |
| Singh et al\(^2\) (ACLFORM COPD) | 24 weeks | Placebo | 1.29 (0.73–1.86) | 19.3 (2.54) | –0.82 (–8.2)\(^d\) |
|                     |          | ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID | 0.45 (0–0.9) | 3.5 (1.19) | –0.69 (–6.2)\(^b\) |
|                     |          | Acldinium 400 µg BID | 0.40 (–0.05 to 0.85) | 8.3 (1.42) | –0.89 (–8.4)\(^b\) |
|                     |          | Placebo | 1.29 (0.73–1.86) | 19.3 (2.54) | –0.82 (–8.2)\(^d\) |
|                     |          | Formoterol 12 µg BID | NR | NR | –0.04 (–4.2) |
|                     |          | Acldinium 400 µg BID | NR | NR | –0.09 (–10.5) |
|                     |          | Placebo | NR | NR | –0.07 (–8)\(^d\) |
|                     |          | ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID | NR | NR | –0.04 (–3.7) |
|                     |          | ACL 400 µg BID | NR | NR | –0.08 (–7.5)\(^h\) |
|                     |          | Placebo | NR | NR | –0.09 (–8.1)\(^h\) |
|                     |          | ACL–FORM 400/6 µg BID\(^1\) ACL–FORM 400/12 µg BID vs | Early morning symptoms, change from baseline: |
| D’Urzo et al\(^15\) (AUGMENT) | 24 weeks | Placebo | 1.44\(^a\) | 21.5 (2.8)\(^a\) | –1.36 (–10.8)\(^d\) |
|                     |          | Formoterol 12 µg BID | 0.5 | 6.4 | –0.48 (–3.4) |
|                     |          | Acldinium 400 µg BID | 0.46 | 3.3 | –0.32 (–1.7) |
| (Continued)
tiotropium in BLAZE (OR 1.78, P<0.05) and versus SFC in ILLUMINATE (OR 1.56, P<0.05; Figure 2). In QUANTIFY, a similar reduction in dyspnea was observed with indacaterol–glycopyrronium versus tiotropium + formoterol, and significantly more patients achieved clinically relevant improvements in TDI total score with indacaterol–glycopyrronium (49.6%) versus tiotropium + formoterol (42.4%, P=0.033).25

In LANTERN, a comparable improvement with indacaterol–glycopyrronium OD and SFC BID was demonstrated for TDI focal score and St George’s Respiratory Questionnaire (SGRQ) total score from baseline after 26 weeks; the percentage of patients achieving the MCID for both end points was higher with indacaterol–glycopyrronium versus SFC.24 Compared with its component monotherapies, indacaterol–glycopyrronium was associated with numerical improvements in TDI score and percentage of TDI responders at week 26 in SHINE.2 At week 12, improvement in TDI score with indacaterol–glycopyrronium was significantly greater than with glycopyrronium (LSM treatment difference 0.41, P=0.03).

Three indacaterol–glycopyrronium OD studies evaluated patient-diary data and reported significantly improved symptom scores versus indacaterol, glycopyrronium, tiotropium, or placebo (Table 3).26,36,38 In the shorter BRIGHT trial, change in mean daily symptom score from baseline to week 3 was numerically greater for indacaterol–glycopyrronium versus tiotropium and placebo.35 In ILLUMINATE, differences in scores for most symptoms were comparable for indacaterol–glycopyrronium and SFC BID.99

In three 24-week studies, umeclidinium–vilanterol 62.5/25 µg OD significantly improved TDI focal and Shortness of Breath with Daily Activity (SOBDA) scores versus placebo, with numerical improvements versus monocomponents and tiotropium.33,41 The proportion of patients achieving the MCID for TDI score was significantly increased in patients receiving umeclidinium–vilanterol versus placebo (OR 2, P<0.001) and vilanterol (OR 1.4, P<0.05) in one study (Figure 2).33 LSM changes from baseline to week 24 in SOBDA scores were clinically significant (≥0.1 unit) for umeclidinium–vilanterol, vilanterol 25 µg, umeclidinium 62.5 and 125 µg, and tiotropium 18 µg.33,41 SOBDA responder rates were reported for one trial, and were significantly higher for umeclidinium–vilanterol (OR 1.8, P<0.01) and its monocomponents (umeclidinium 52.5 µg OR 1.7, P<0.01; vilanterol 25 µg OR 1.6, P<0.05) versus placebo. In two 12-week studies, there was no significant difference in TDI focal scores between umeclidinium–vilanterol 62.5/25 µg and salmeterol–fluticasone propionate 50/250 µg.27 Exercise-associated dyspnea (Borg) was reduced with umeclidinium–vilanterol 62.5/25 µg compared with placebo in one of two studies; active–placebo differences were not significant for the individual components.31 In combined results from two 1-year studies, tiotropium–olodaterol OD increased TDI total score versus monocomponents (week 24) by approximately 0.4 points with the higher dose and by a similar margin (0.3–0.4 points) with the lower dose.30

Symptoms were evaluated using a number of end points in the two 24-week aclidinium–formoterol BID studies.28,29 For TDI total score, aclidinium–formoterol 400/12 µg

### Table 3 (Continued)

| Reference and study | Duration | Treatment | TDI total score, % TDI responders* (OR) | Other |
|---------------------|----------|-----------|---------------------------------------|-------|
| ACL–FORM 400/6 µg BID^ | -2,39 | **TDI total score, % TDI responders** (OR) | Night-time symptoms, change from baseline vs: |
| ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID | NR | NR | −0.05 (−2.4) |
| Acclidinium 400 µg BID | NR | NR | −0.08 (−5.3) |
| Placebo | NR | NR | −0.12 (−9.3)^h |
| ACL–FORM 400/6 µg BID^ | -2,39 | Early-morning symptoms, change from baseline vs: |
| ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID | NR | NR | −0.06 (−4.6) |
| Acclidinium 400 µg BID | NR | NR | −0.09 (−7.4)^h |
| Placebo | NR | NR | −0.13 (−9.8)^h |

Notes: Treatment once daily unless stated otherwise. *TDI responders had improvement ≥1 unit in TDI score. Significant treatment difference versus ‘indacaterol, ’glycopyrronium or ‘tiotropium (values NR).’ Dose not approved for use (ACL–FORM, dose not approved in EU). Values in parentheses are differences expressed in percentage points (not percentage differences). Abbreviations: ACL–FORM, aclidinium–formoterol; BID, bis in die (twice daily); CI, confidence interval; E-RS, Evaluating Respiratory Symptoms; IND–GLY, indacaterol–glycopyrronium; LSM, least-squares mean; NR, not reported; NS, not significant; OR, odds ratio; SAC, self-administered computerized; SFC, salmeterol–fluticasone combination; SGRQ-C, St George’s Respiratory Questionnaire – COPD; TIO–OLO, tiotropium–olodaterol; TDI, transition dyspnea index; UMeC–vI, umeclidinium–vilanterol.
Figure 2 Differences between monotherapy and combination bronchodilators or placebo in TDI patient-response rates in published studies.

Notes: (A) Indacaterol–glycopyrronium; (B) umeclidinium–vilanterol 62.5/25 µg; (C) aclidinium–formoterol 400/12 µg BID. TDI response was defined as improvement of ≥1 unit in TDI score. All treatments were once daily unless stated otherwise. *Significant treatment difference. 

Abbreviations: BID, bis in die (twice daily); SFC, salmeterol–fluticasone propionate; TDI, transition dyspnea index.

BID achieved a significant, >1-point improvement versus placebo (and a higher proportion of TDI responders), but the differences versus the monotherapies were not significant. For Evaluating Respiratory Symptoms (E-RS) score, the combination was significantly better than placebo (both studies) and the monotherapies (one study). Aclidinium–formoterol 400/12 µg improved nighttime symptom scores versus placebo (one study) or aclidinium BID (one study); early morning symptom scores were improved versus placebo and aclidinium (both studies), assessed by questionnaires for both.28,29
Rescue-medication use
Rescue-medication usage provides a surrogate measure of symptom control, and was reported in most of the published indacaterol–glycopyrronium OD and umeclidinium–vilanterol OD Phase III trials (Table 4). Indacaterol–glycopyrronium treatment consistently led to significantly less rescue-medication use per day than LABA or LAMA monotherapy or LABA–inhaled corticosteroids in each trial with active comparators.\textsuperscript{2,26,35,38–40} In LANTERN, rescue-medication use was comparable between the indacaterol–glycopyrronium and SFC BID groups.\textsuperscript{24} Daily rescue-medication use was similar or numerically slightly lower with umeclidinium–vilanterol versus either umeclidinium or vilanterol monotherapy, significantly lower versus tiotropium in two of three trials, and significantly lower versus SFC in one of two trials.\textsuperscript{23,27,32,33,41} Rescue-medication use remained at approximately two puffs/day with tiotropium–olodaterol OD over the course of 52 weeks; at the

| Reference and study | Duration | Treatment | Rescue albuterol/salbutamol puffs/day change from baseline, LSM (95% CI) treatment difference at end point |
|---------------------|----------|-----------|--------------------------------------------------------------------------------------------------|
| **IND–GLY**         |          |           |                                                                                                  |
| Bateman et al\textsuperscript{a} (SHINE) | 26 weeks | IND–GLY 110/50 µg OD vs Placebo | \textsuperscript{a}0.31 (NR) |
| Dahl et al\textsuperscript{a} (ENLIGHTEN) | 52 weeks | IND–GLY 110/50 µg OD vs Placebo | \textsuperscript{a}0.73 (NR) |
| Dahl et al\textsuperscript{a} (BEACON) | 4 weeks | IND–GLY 110/50 µg OD vs Placebo | \textsuperscript{a}0.04 (0.35 to 0.28) |
| Mahler et al\textsuperscript{a} (BLAZE) | 6 weeks | IND–GLY 110/50 µg OD vs Placebo | \textsuperscript{a}−1.43 (−1.72 to −1.13) |
| Vogelmeier et al\textsuperscript{a} (ILLUMINATE) | 26 weeks | IND–GLY 110/50 µg OD vs SFC 50/500 µg BID | \textsuperscript{a}−0.39 (−0.71 to −0.06) |
| Wedzicha et al\textsuperscript{a} (SPARK) | 64 weeks | IND–GLY 110/50 µg OD vs Placebo | \textsuperscript{a}−0.81 (NR) |
| Beeh et al\textsuperscript{a} (BRIGHT) | 3 weeks | IND–GLY 110/50 µg OD vs Placebo | \textsuperscript{a}−1.08 (NR) |
| Zhong et al\textsuperscript{a} (LANTERN) | 26 weeks | IND–GLY 110/50 µg OD vs SFC 50/500 µg BID | \textsuperscript{a}−0.03 (−0.26 to 0.21) |
| Wedzicha et al\textsuperscript{a} (FLAME) | 52 weeks | IND–GLY 110/50 µg OD vs SFC 50/500 µg BID | \textsuperscript{a}−0.25 (−0.38 to −0.12) |
| **UMEC–VI**         |          |           |                                                                                                  |
| Donohue et al\textsuperscript{a} | 24 weeks | UMEC–VI 62.5/25 µg OD vs Placebo | \textsuperscript{a}−0.6 (−1.0 to −0.1) |
| Decramer et al\textsuperscript{a} (study 1) | 24 weeks | UMEC–VI 125/25 µg OD vs Placebo | \textsuperscript{a}−0.7 (−1.2 to −0.1) |
| Decramer et al\textsuperscript{a} (study 2) | 24 weeks | UMEC–VI 125/25 µg OD vs Placebo | \textsuperscript{a}−0.6 (−1.2 to 0) |
| Maleki-Yazdi et al\textsuperscript{a} | 24 weeks | UMEC–VI 62.5/25 µg OD vs Placebo | \textsuperscript{a}−0.5 (−0.7 to −0.2) |

(Continued)
end of the studies, this was 0.3–0.4 puffs/day less than with olodaterol and 0.7–0.8 puffs/day less than with tiotropium.30 In the two 24-week studies with aclidinium–formoterol 400/12 µg BID, rescue-medication use was significantly lower compared with placebo and aclidinium BID, but not compared with formoterol.28,29

### Exacerbations

The effects of FDC therapy on exacerbation rates and time to first exacerbation are summarized in Table 5.

The effect of indacaterol–glycopyrronium OD on exacerbation rate was examined as the primary end point in both SPARK and FLAME, and exacerbation rates have also been reported from ILLUMINATE, LANTERN, and QUANTIFY.24,26,39,40,52 In SPARK, indacaterol–glycopyrronium significantly reduced rates of moderate-to-severe (primary end point, rate ratio 0.88; P=0.038) and all exacerbations (LSM treatment difference 0.85, P<0.01) versus glycopyrronium.40 Compared with open-label tiotropium, rates of moderate-to-severe exacerbations were 10% lower with indacaterol–glycopyrronium (P=0.096), and rates of all exacerbations were 14% lower (P<0.01). In comparison with SFC BID in a post hoc analysis of data from ILLUMINATE, rates of moderate-to-severe exacerbations (rate ratio 0.8, not significant [NS]) and all exacerbations (rate ratio 0.69, NS) were numerically lower with indacaterol–glycopyrronium.52 In LANTERN, indacaterol–glycopyrronium significantly reduced the rate of moderate or severe exacerbations by 31% (P=0.048) over SFC.24 Furthermore, in the recent FLAME study, indacaterol–glycopyrronium significantly

### Table 4 (Continued)

| Reference and study | Duration | Treatment | Rescue albuterol/salbutamol puffs/day change from baseline, LSM (95% CI) treatment difference at end point |
|---------------------|----------|-----------|---------------------------------------------------------------|
| Maltais et al33 (study 417) | 12 weeks | UMEC–VI 125/25 µg OD<sup>a</sup>  
UMEC–VI 62.5/25 µg OD  
Umecilinum 62.5 µg OD  
Umecilinum 125 µg OD  
Vilanterol 25 µg OD | Differences from placebo:  
-0.6<sup>b</sup> (−0.8 to −0.3)  
-0.2 (−0.6 to 0.1)  
-0.6<sup>b</sup> (−1 to −0.2)  
-0.4<sup>b</sup> (−0.7 to 0) |
| Maltais et al33 (study 418) | 12 weeks | UMEC–VI 125/25 µg OD<sup>a</sup>  
UMEC–VI 62.5/25 µg OD  
Umecilinum 62.5 µg OD  
Umecilinum 125 µg OD  
Vilanterol 25 µg OD | Differences from placebo:  
-1.2<sup>b</sup> (−1.5 to −0.8)  
-0.7<sup>b</sup> (−1.3 to −0.2)  
-1.0<sup>b</sup> (−1.5 to −0.4)  
-0.8<sup>b</sup> (−1.2 to −0.3) |
| Donohue et al37 (study 2114930) | 12 weeks | UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID | 0 (−0.3 to 0.2) |
| Donohue et al37 (study 2114951) | 12 weeks | UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID | −0.3<sup>c</sup> (−0.6 to −0.1) |

**TIO–OLO**

Buhl et al27 (studies 1237.5 and 1237.6 combined) | 52 weeks | TIO–OLO 2.5/5 µg OD<sup>a</sup>  
TIO–OLO 5/5 µg OD vs Olodaterol 5 µg OD  
Tirotropium 5 µg OD | −0.4<sup>c</sup>  
Value NR<sup>a</sup>  
−0.8<sup>c</sup> |

**ACL–FORM**

Singh et al26 (ACLFORM-COPD) | 24 weeks | ACL–FORM 400/6 µg BID<sup>a</sup>  
ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID  
Acclidinium 400 µg BID Placebo | NS  
Value NR<sup>a</sup>  
−0.6<sup>c</sup> |

D’Urzo et al37 (AUGMENT) | 24 weeks | ACL–FORM 400/6 µg BID<sup>a</sup>  
ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID  
Acclidinium 400 µg BID Placebo | 0.21  
Value NR<sup>a</sup> |

**Notes:** Treatment once daily unless stated otherwise. *Significant treatment difference; †dose not approved for use; ‡estimated from figure. Statistical analysis not reported.**

**Abbreviations:** ACL–FORM, aclidinium–formoterol; BID, bis in die (twice daily); CI, confidence interval; IND–GLY, indacaterol–glycopyrronium; LSM, least-squares mean; NR, not reported; NS, not significant; OL, open-label; SFC, salmeterol–fluticasone combination; TIO–OLO, tiotropium–olodaterol; UMEC–VI, umeclidinium–vilanterol.
Table 5: Exacerbations: margin of efficacy of fixed combinations versus comparators in published studies that included exacerbations as an efficacy outcome

| Reference and study | Duration | Treatment | Exacerbation definition | Treatment difference at end point |
|---------------------|----------|-----------|-------------------------|----------------------------------|
| **IND–GLY**         |          |           |                         |                                  |
| Wedzicha et al (SPARK) | 64 weeks | IND–GLY 110/50 µg OD vs Glycopyrronium 50 µg OD Tiotropium 18 µg OD QD | Presence of two major symptoms (dyspnea, sputum volume, sputum purulence) for ≥2 consecutive days or worsening of one major symptom plus increase in one minor symptom (sore throat, colds, fever without other cause, cough, wheeze) for ≥2 consecutive days | 0.85 (0.77–0.94) 0.86 (0.78–0.94) |
| Buhl et al (QUANTIFY) | 26 weeks | IND–GLY 110/50 µg OD vs Tiotropium 18 µg OD & formoterol 12 µg BID | Moderate exacerbations were those managed with antibiotics and/or systemic corticosteroids; severe exacerbations were those that resulted in hospitalization. | 0.85 (0.62–1.17) NR |
| Zhong et al (LANTERN) | 26 weeks | IND–GLY 110/50 µg OD vs SFC 50/500 µg BID | An exacerbation was considered moderate if patients were treated with systemic corticosteroids, antibiotics, or both. Exacerbations were considered severe if patients were hospitalized or experienced an emergency room visit ≥24 hours | 0.69 (0.48–1) 0.32 (0.12–0.88) |
| Wedzicha et al (FLAME) | 52 weeks | IND–GLY 110/50 µg OD vs SFC 50/500 µg BID | COPD exacerbations were categorized as mild (involving worsening of symptoms for ≥2 consecutive days, but not leading to treatment with systemic glucocorticoids or antibiotics), moderate (leading to treatment with systemic glucocorticoids, antibiotics, or both), or severe (leading to hospital admission or a visit to the ER that lasted ≥24 hours in addition to treatment with systemic glucocorticoids, antibiotics, or both) | 0.89 (0.83–0.96) 0.84 (0.78–0.91) |
| **UMEC–VI**         |          |           |                         |                                  |
| Donohue et al | 24 weeks | UMEC–VI 62.5/25 µg OD vs Umeclidinium 62.5 µg OD Vilanterol 25 µg OD Placebo | Acute worsening of COPD symptoms requiring emergency treatment, hospitalization, or use of additional pharmacotherapy beyond study drug or rescue salbutamol (eg, oral steroids and antibiotics) | NR NR NR 0.5 (0.3–0.8) |
| Decramer et al (study 1) | 24 weeks | UMEC–VI 125/25 µg OD | Acute worsening of COPD symptoms requiring use of any treatment other than study drug or rescue salbutamol | NR NR 1.2 (0.5–2.6) 0.7 (0.4–1.5) |
| Decramer et al (study 2) | 24 weeks | UMEC–VI 125/25 µg OD | Acute worsening of COPD symptoms requiring use of any treatment other than study drug or rescue salbutamol | NR NR 1.9 (1–3.6) 1 (0.6–1.8) |

(Continued)
| Reference and study | Duration | Treatment | Exacerbation definition | Treatment difference at end point |
|---------------------|----------|-----------|-------------------------|-------------------------------------|
|                      |          |           |                         | Exacerbation rate, RR (95% CI)     |
| Maleki-Yazdi et al<sup>12</sup> | 24 weeks | UMEC–VI 62.5/25 µg OD vs tiotropium 18 µg OD | Acute worsening of COPD symptoms requiring use of any treatment other than study drug or rescue albuterol/salbutamol | NR |
|                      |          |           |                         | Time to first exacerbation, HR (95% CI) | 0.5<sup>a</sup> (0.3–1) |

**TIO–OLO**

Buhl et al<sup>19</sup> (studies 1237.5 and 1237.6 combined) | 52 weeks | TIO–OLO 2.5/5 µg OD<sup>d</sup> TIO–OLO 5/5 µg OD vs Olodaterol 5 µg OD Tiotropium 5 µg OD | “Moderate/severe” (not defined) | Kaplan–Meier plot shows descending probability in the following order: olodaterol 5 µg; tiotropium 2.5 µg; tiotropium 5 µg; TIO–OLO 5/5 µg; TIO–OLO 2.5/5 µg (statistical analysis NR) |

**ACL–FORM**

Singh et al<sup>20</sup> (ACLIFORM-COPD) | 24 weeks | ACL–FORM 400/6 µg BID<sup>l</sup> ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID Aclidinium 400 µg BID Placebo | HCRU: an increase of COPD symptoms during ≥2 consecutive days that requires a change in COPD treatment | NR |

|                      |          |           |                         | 0.64 (0.4–1) |
|                      |          |           |                         | 0.89 (0.6–1.4) |
|                      |          |           |                         | 0.73 (0.4–1.2) |

|                      |          |           |                         | EXACT: an increase from baseline in total EXACT score ≥9 points for ≥3 days or ≥12 points for ≥2 days<sup>e</sup> | NR |
|                      |          |           |                         | 0.86 (0.7–1.1) |
|                      |          |           |                         | 0.78 (0.6–1) |
|                      |          |           |                         | 0.71<sup>a</sup> (0.5–0.9) |

**Notes:** Treatment once daily unless stated otherwise. <sup>a</sup>Significant treatment difference; <sup>b</sup>data reported for all exacerbations; <sup>c</sup>includes only severe exacerbations requiring hospitalization/emergency room treatment for ≥24 hours; <sup>d</sup>dose not approved for use (ACL–FORM dose not approved in EU); <sup>e</sup>the EXACT instrument assesses patients’ breathlessness, cough and sputum, chest symptoms, difficulty bringing up sputum, feeling tired or weak, sleep disturbance, and feeling scared or worried about their condition with a 14-item questionnaire.

**Abbreviations:** ACL–FORM, aclidinium–formoterol; BID, bis in die (twice daily); CI, confidence interval; EXACT, EXAcerbations of COPD Tool; HCRU, health care-resource utilization; HR, hazard ratio; IND–GLY, indacaterol–glycopyrronium; NR, not reported; OL, open-label; RR, rate ratio; TIO–OLO, tiotropium–olodaterol; UMEC–VI, umeclidinium–vilanterol.
reduced the rates of all exacerbations (primary end point) by 11% (P=0.003) and of moderate-to-severe exacerbations by 17% (P<0.001) compared with SFC; findings were consistently in favor of indacaterol–glycopyrronium when patients were analyzed according to their baseline disease characteristics, including baseline eosinophil count (<2% or ≥2%).26 This study also found that compared with SFC, indacaterol–glycopyrronium was associated with longer times to first exacerbation, representing reduced risks of 16% for all exacerbations (P<0.001), 22% for moderate-to-severe exacerbations (P<0.001), and 19% for severe exacerbations (P=0.046). Finally, QUANTIFY showed a comparable percentage of patients experiencing at least one moderate or severe exacerbation and a comparable time to first moderate or severe exacerbation between the two treatment groups (indacaterol–glycopyrronium vs tiotropium + formoterol).29

Currently, there are no studies evaluating exacerbation risk as a primary end point in patients receiving umeclidinium–vilanterol OD. The data available from analysis of secondary end points indicate that umeclidinium–vilanterol significantly increased time to first exacerbation versus placebo (HR 0.5, P<0.001),21 but not compared with vilanterol 25 µg (HR 0.7, NS) or umeclidinium 125 µg (HR 1, NS).23

Time to first exacerbation was comparable for combination therapy versus tiotropium alone in two trials23 and significantly greater in a third study (HR 0.5, P=0.044).22 In the combined results of the two 52-week studies with tiotropium–olodaterol OD, there was only a “trend” for improvement in exacerbations with both doses of the combination versus the monotherapy components.30 Over the 24 weeks of the ACLIFORM study, using the health care resource-utilization definition of exacerbations, aclidinium–formoterol BID 400/12 µg was not significantly different from placebo or its separate components; with the EXACT (EXAcerbations of COPD Tool) definition, a significant difference was demonstrated versus placebo, but not compared with the components.28

Exacerbations were not reported as an efficacy outcome in the AUGMENT study.29

### Health status

Indacaterol–glycopyrronium OD significantly improved health status, assessed using the SGRQ (Table 6). In SPARK, Table 6 Health status: margin of efficacy of fixed combinations versus comparators in published studies

| Reference and study | Duration | Treatment | Change from baseline: | Treatment difference at end point |
|---------------------|----------|-----------|-----------------------|----------------------------------|
| **IND–GLY**         | 26 weeks | IND–GLY 110/50 µg OD vs tiotropium 18 µg OD OL | Change from baseline: | SGRQ total score, LSM (95% CI) | % SGRQ responders (OR) |
| Bateman et al22 (SHINE) | 24 weeks | IND–GLY 110/50 µg OD vs tiotropium 18 µg OD OL | 0.32 (−1.41 to 1.07) | 2.23 (−0.48 to 5.01) | 7.1 (NR) |
| Vogelmeier et al23 (ILLUMINATE) | 26 weeks | IND–GLY 110/50 µg OD vs tiotropium 18 µg OD OL | 0.57 (−1.37 to 2.49) | 0.57 (−1.87 to 2.15) | 0.57 (−1.37 to 2.49) |
| Wedzicha et al24 (SPARK) | 64 weeks | IND–GLY 110/50 µg OD vs tiotropium 18 µg OD OL | 0.57 (−1.37 to 2.49) | 0.57 (−1.87 to 2.15) | 0.57 (−1.37 to 2.49) |
| Buhl et al25 (QUANTIFY) | 26 weeks | IND–GLY 110/50 µg OD vs tiotropium 18 µg OD OL | 0.57 (−1.37 to 2.49) | 0.57 (−1.87 to 2.15) | 0.57 (−1.37 to 2.49) |
| Zhong et al26 (LANTERN) | 26 weeks | IND–GLY 110/50 µg OD vs tiotropium 18 µg OD OL | 0.57 (−1.37 to 2.49) | 0.57 (−1.87 to 2.15) | 0.57 (−1.37 to 2.49) |
| Wedzicha et al27 (FLAME) | 52 weeks | IND–GLY 110/50 µg OD vs tiotropium 18 µg OD OL | 0.57 (−1.37 to 2.49) | 0.57 (−1.87 to 2.15) | 0.57 (−1.37 to 2.49) |
| **UMEC–VI**         | 12 weeks | UMEC–VI 62.5/25 µg OD vs tiotropium 18 µg OD OL | Change from baseline: | SGRQ total score, LSM (95% CI) | % SGRQ responders (OR) |
| Donohue et al28 (study 1) | 24 weeks | UMEC–VI 62.5/25 µg OD vs tiotropium 18 µg OD OL | Change from baseline: | 0.75 (NR) | 3 (0.9) |
| Decramer et al29 (study 2) | 24 weeks | UMEC–VI 62.5/25 µg OD vs tiotropium 18 µg OD OL | Change from baseline: | 1.42 (NR) | 3 (0.8) |

(Continued)
Table 6 (Continued)

| Reference and study | Duration | Treatment | SGRQ total score, LSM (95% CI) | % SGRQ responders (OR) |
|----------------------|----------|-----------|--------------------------------|-----------------------|
| Decramer et al<sup>23</sup> (study 2) | 24 weeks | UMEC–VI 125/25 µg OD<sup>#</sup> | Change from baseline: |          |
| | | UMEC–VI 62.5/25 µg OD vs Tiotropium 18 µg OD | |          |
| | | Umeclidinium 125 µg OD | –0.17<sup>c</sup> (NR) | 1 (1) |
| Maleki-Yazdi et al<sup>22</sup> | 24 weeks | UMEC–VI 62.5/25 µg vs tiotropium 18 µg | Change from baseline: |          |
| | | | | –2.1<sup>c</sup> (–3.61 to –0.59) |
| Donohue et al<sup>27</sup> (study 2114930) | 12 weeks | UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID | 0.47 (–1.36 to 2.29) | NR |
| Donohue et al<sup>27</sup> (study 2114951) | 12 weeks | UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID | –1.55 (–3.63 to 0.53) | NR |

**TIO–OLO**

| Reference and study | Duration | Treatment | SGRQ total score, LSM (95% CI) | % SGRQ responders (OR) |
|----------------------|----------|-----------|--------------------------------|-----------------------|
| Buhl et al<sup>19</sup> (studies 1237.5 and 1237.6 combined) | 52 weeks | TIO–OLO 2.5/5 µg OD<sup>f</sup> | At 24 weeks: |          |
| | | TIO–OLO 5/5 µg OD vs Olopatadine 5 µg OD | –1.693<sup>a,b</sup> | 12.7<sup>a</sup> |
| | | Tiotropium 5 µg OD | –1.233<sup>a</sup> | 8.8<sup>a</sup> |

**ACL–FORM**

| Reference and study | Duration | Treatment | SGRQ total score, LSM (95% CI) | % SGRQ responders (OR) |
|----------------------|----------|-----------|--------------------------------|-----------------------|
| Singh et al<sup>18</sup> (ACLFORM-COPD) | 24 weeks | ACL–FORM 400/6 µg BID<sup>c</sup> | Change from baseline: |          |
| | | ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID | |          |
| | | Aclidinium 400 µg BID | –1.59 (–3.52 to 0.35) | NR |
| | | Placebo | –1.36 (–3.3 to 0.58) | NR |
| | | | –0.65 (–3.08 to 1.78) | NR |
| D’Urzo et al<sup>17</sup> (AUGMENT) | 24 weeks | ACL–FORM 400/6 µg BID<sup>c</sup> | Change from baseline: |          |
| | | ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID | |          |
| | | Aclidinium 400 µg BID | –1.87 | 5.8 |
| | | Placebo | –0.13 | 3.7 |
| | | | –4.36<sup>f</sup> | 19.5 (2.3)<sup>f</sup> |

**Notes:** Treatment once daily unless stated otherwise. SGRQ responder = SGRQ total score ≤4 units versus baseline. *Significant treatment difference; 8*range of LSM differences in scores for weeks 12, 24, 38, 52, and 64 (95% CI not reported); 9differences in LSM change from baseline to week 24; 9dose not approved for use (ACL–FORM dose not approved in EU); 9*95% CI not reported; OR not reported.

**Abbreviations:** ACL–FORM, aclidinium-formoterol; BID, bis in die (twice daily); CI, confidence interval; IND–GLY, indacaterol–glycopyrronium; LSM, least-squares mean; NR, not reported; OL, open-label; OR, odds ratio; SFC, salmeterol–fluticasone combination; SGRQ, St George’s Respiratory Questionnaire; TIO–OLO, tiotropium–olodaterol; UMEC–VI, umeclidinium–vilanterol.

Indacaterol–glycopyrronium improved SGRQ total score versus glycopyrronium (all P<0.01) and open-label tiotropium (all P<0.05; 12–64 weeks).<sup>40</sup> In SHINE, improvement in SGRQ with indacaterol–glycopyrronium was superior to open-label tiotropium (P=0.009) and placebo (P=0.002) and comparable to component monotherapies. In a 26-week study, indacaterol–glycopyrronium and SFC BID provided similar improvements in health status. However, in FLAME, significant improvements over time in SGRQ total score were observed for indacaterol–glycopyrronium compared with SFC, with treatment differences that ranged from –1.2 points to –1.8 points over the time points measured between weeks 12 and 52 (all P<0.01).<sup>26</sup> The SGRQ responder rate for the MCID (reduction of ≤4 units from baseline)<sup>35</sup> was also significantly greater with indacaterol–glycopyrronium versus SFC in FLAME (OR 1.3, P<0.001)<sup>26</sup> and versus glycopyrronium (OR 1.62, P=0.00013) and open-label tiotropium (OR 1.48, P=0.0017) at all time points except week 64 in SPARK.<sup>40</sup> In QUANTIFY, indacaterol–glycopyrronium was noninferior to tiotropium + formoterol for improvement in SGRQ score; the percentage of patients achieving a MCID was significantly in favor of indacaterol–glycopyrronium (50.1% vs 42.5%, P=0.038) in the per-protocol set.<sup>25</sup> Similarly, in LANTERN comparable improvements with indacaterol–glycopyrronium versus SFC were observed for all SGRQ analyses (weeks 12 and 26).<sup>24</sup> Significant improvements in SGRQ total score mean change from baseline (P≤0.001) and percentages of SGRQ responders (OR 2, P≤0.001) were reported for umeclidinium–vilanterol 62.5/25 µg OD versus placebo in three 24-week studies.<sup>41</sup> Across three of four trials, health-status improvement was not significantly different for umeclidinium–vilanterol versus monotherapy with tiotropium, vilanterol, or umeclidinium (SGRQ total scores or percentage of SGRQ responders).<sup>23,41</sup> The fourth trial reported significant improvement in SGRQ total score from baseline (P<0.006) and percentage of SGRQ responders (OR 1.4, P=0.022) for umeclidinium–vilanterol versus
tiotropium. Improvements in SGRQ from baseline were not significantly different between umeclidinium–vilanterol 62.5/25 µg and salmeterol–fluticasone propionate 50/250 µg in two 12-week studies.27

In combined results from two 1-year studies, tiotropium–olodaterol 5/5 µg OD significantly improved SGRQ total score at week 24 by 1.2 and 1.7 units versus its respective components. Proportions of SGRQ responders were significantly increased for all the combination-versus-component comparisons, apart from tiotropium–olodaterol 2.5/5 µg versus tiotropium 2.5 µg. In the 24-week ACLIFORM and AUGMENT studies, aclidinium–formoterol BID improved SGRQ total score and percentage of responders significantly compared with placebo in one study, but did not achieve significant differences against its components in either study.28,29

Safety
To date, the most extensive safety data available for FDC bronchodilators comes from indacaterol–glycopyrronium OD trials. Overall, indacaterol–glycopyrronium was well tolerated across the studies, and had a similar safety profile to placebo in individual trials and analyses of pooled data.23,26,39,40,54–56 The incidence of adverse events (AEs) and serious AEs (SAEs) reported with indacaterol–glycopyrronium treatment was comparable to that of placebo, indacaterol, glycopyrronium, tiotropium (± formoterol) or SFC BID.2,24–26,39,40 Interestingly, the FLAME trial reported a significant reduction in the incidence of pneumonia with indacaterol–glycopyrronium compared with SFC (3.2% vs 4.8%, respectively; P=0.02).20 In an analysis of pooled data from 11,404 patients, the HR for indacaterol–glycopyrronium versus placebo showed no significant increase in the overall risk for death (HR [95% CI] 0.93 [0.34–2.54]), cardiocerebrovascular events (0.6 [0.29–1.24]), major adverse cardiovascular events (MACEs; 1.04 [0.45–2.42]), pneumonia (1.1 [0.54–2.25]), COPD exacerbations (0.6 [0.4–0.91]), or atrial flutter/fibrillation (1.03 [0.49–2.18]).44

Over 24 weeks, umeclidinium–vilanterol 62.5/25 µg OD was well tolerated, and the incidence of AEs and serious AEs was similar for combination therapy versus placebo and monocomponents.41,57 The rate of class-effect AEs associated with anticholinergic (eg, dry mouth) and BA (eg, tachycardia) agents was similar to that observed for placebo.41,57 In two 12-week studies, umeclidinium–vilanterol 62.5/25 µg and SFC 250/50 µg were both well tolerated and had similar AE profiles.27 In a pooled analysis of data from eight trials of umeclidinium–vilanterol 62.5/25 µg and 125/25 µg, no increased risk of MACE was observed with active treatment versus placebo.58 Small numerical imbalances in cardiac ischemia were reported in some studies, but not others. As the imbalances were not dose-related, they were not considered drug-related. The incidence of cardiovascular AEs of special interest was comparable for umeclidinium–vilanterol, monocomponents, and placebo.

In the two 1-year tiotropium–olodaterol OD studies, the frequency of AEs was largely comparable between the combination- and individual component-treatment groups. The rates of MACE and cardiac events did not differ significantly between the combination and the individual component groups.30 Similarly, AE reporting (including MACE and Holter monitoring) in the two aclidinium–formoterol BID studies was generally comparable across all treatment groups.28,29

In a 2013 preliminary report from a retrospective cohort study of mortality in more than 5,000 patients with COPD, LAMA–LABA combination therapy reduced both all-cause (HR 0.53 [95% CI 0.34–0.84]) and cardiovascular mortality (HR 0.39 [95% CI 0.17–0.9]).59 Reductions in both mortality types were also observed with LAMA–LABA–inhaled corticosteroids, LABA–inhaled corticosteroids, and LAMA-only treatment.

Discussion
We identified 23 published Phase III RCTs of FDC bronchodilators in COPD. The data demonstrated that fixed-dose LAMA–LABA combinations significantly improved lung function compared with component monotherapies or single agents.2,23,30–32,35,36,39–41 Indacaterol–glycopyrronium OD, umeclidinium–vilanterol OD, and tiotropium–olodaterol OD also provided significant improvements over component monotherapies and/or tiotropium in several PROs.2,23,30,32,35,38,40,41 Compared with its components, aclidinium–formoterol BID improved symptoms (one study),28 but did not improve health status.28,29 Indacaterol–glycopyrronium and umeclidinium–vilanterol significantly improved lung function compared with SFC BID.26,27,39 Indacaterol–glycopyrronium also improved exacerbation rates in LANTERN and FLAME (Table 6), reduced dyspnea in ILLUMINATE, and led to reductions in use of rescue medication in ILLUMINATE and FLAME compared with SFC.24,26,27,39 The safety profiles of the FDC agents were similar to placebo and incidence of pneumonia significantly reduced with indacaterol–glycopyrronium versus SFC in FLAME.2,23,26,30,32,36,39–41,54,56

Several studies have examined the relationship between improvements in lung function following LABA or LAMA monotherapy and improvements in other outcomes,
such as SGRQ total score, TDI, exacerbation rate, and rescue-medication use. However, although significant or clinically relevant correlations appear at group levels, they tend to be only moderate, weak, or too weak to be useful at individual levels.\textsuperscript{16–19,21} This may be because some patients have very poor health despite only mild lung-function impairments or vice versa.\textsuperscript{17} Indeed, the health impact of COPD is not necessarily mediated entirely through expiratory airflow limitation; a better correlate may instead be exercise performance.\textsuperscript{17} The analyzed studies may also have been too short in duration to capture meaningful changes in exacerbations or health status, and only a few studies were available for some outcomes.\textsuperscript{18} Finally, the Hawthorne effect may also have played a role, as changes in FEV\textsubscript{1} of 0 still resulted in a 2.5-point reduction in SGRQ score in some cases.\textsuperscript{18}

Likewise, in trials of combination-bronchodilator therapy versus components, improvement in FEV\textsubscript{1} was not always mirrored by improved PROs. For example, significant improvement in dyspnea for umeclidinium–vilanterol OD versus monocomponents occurred only for vilanterol (in one of three trials), despite improvements in FEV\textsubscript{1}.\textsuperscript{23,41} Possible reasons for this include insufficient sensitivity/specificity in instruments assessing PROs. Additionally, such measurements as inspiratory capacity may be more strongly related to dyspnea and COPD pathophysiology than FEV\textsubscript{1}.\textsuperscript{60} Therefore, it may be useful to examine correlations between other outcomes instead, in larger sample sizes or longer-duration studies. Findings may still be somewhat limited though, as these end points are often only secondary, meaning power may be lacking.

Patient-selection criteria represent an important limitation of RCTs. Most trials recruit subjects from highly selective populations likely to represent less than 5% of “real-life” patients. As such, the extrapolation of RCT data is limited.\textsuperscript{64} Populations are generally chosen to demonstrate the primary end point (usually lung function). Clinical trial participants tend to be less symptomatic than general patient populations, and clinical trials may exclude patients likely to benefit the most from treatment (as a maximum level of benefit may be reached sooner). Additionally, the most symptomatic patients in control arms may discontinue study treatment to obtain greater symptom relief. In contrast, real-life studies are likely to involve broader populations and treat each study arm to a similar level. Roche et al suggested a new framework to categorize the approach taken in clinical trials from highly controlled efficacy RCT management to usual clinical care.\textsuperscript{61} The positioning of studies on this scale can be useful as a descriptive classification.\textsuperscript{61} Future COPD trials may need to include more real-life patient populations and ecology of care. In addition, composite end points, such as lack of exacerbations and improved health status, may provide greater insight into the true benefits of treatment.

Additional studies of fixed-combination bronchodilators are needed to characterize further the relationship between FEV\textsubscript{1} and PROs with these agents, as well as defining optimal strategies for their use in clinical practice. Should therapy be initiated with a single bronchodilator and then stepped up to a LABA–LAMA combination and/or triple therapy with LABA–LAMA plus another agent as needed, or should treatment commence with a LABA–LAMA in certain patients?

In conclusion, our review of a systematic literature search indicates that fixed-dose LABA–LAMA combinations significantly improved lung function compared with their component monotherapies. In general, LABA–LAMA combinations also improved other outcomes, including symptoms and health status, compared with the monotherapies, although some discrepancies between lung function and PROs were apparent. Further research is needed to explore the relationship between lung-function outcomes and PROs in patients receiving LABA–LAMA combinations.

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**Author contributions**

All authors contributed to the concept and objectives of the review and provided guidance on the literature search, presentation, and discussion of the findings, as well as critically reviewing the article. In addition, all authors reviewed and approved the final manuscript.

**Disclosure**

AO has received payment for lectures/speaking from Boehringer Ingelheim, GlaxoSmithKline, Meda, Sandoz, and Pfizer. He has advisory board membership with Boehringer Ingelheim, Novartis and Teva. DP has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, Teva...
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## Supplementary materials

### Table S1 Search strategy and results for published manuscripts and congress abstracts

| Search number | Search terms                                                                 | Number of records |
|---------------|------------------------------------------------------------------------------|-------------------|
| S1            | MeSH.EXACT.EXPLODE ("Bronchodilator Agents") AND MeSH.EXACT.EXPLODE ("Drug Combinations") | 821a              |
| S2            | "Fixed-dose combination" OR "Fixed dose combination" OR "Fixed-dose long-acting combination" OR "Fixed dose long-acting combination" OR "Fixed-dose combinations" OR "Fixed dose combinations" OR "Fixed-dose long-acting combinations" OR "Fixed dose long-acting combinations" OR "fixed combination" OR "fixed combinations" OR "LABA/LAMA" OR "LAMA/LABA" OR "dual bronchodilator" OR "dual bronchodilator" OR "dual bronchodilators" OR "dual bronchodilators" OR "dual-acting bronchodilator" OR "dual-acting bronchodilators" OR "dual-acting bronchodilator" OR "QVA149" OR "QVA-149" OR "QVA 149" OR "glycopyrronium/indacaterol" OR "indacaterol/glycopyrronium" OR "Anoro" OR "umeclidinium/vilanterol" OR Embase:EXACT ("glycopyrronium bromide plus indacaterol") | 6,959b            |
| S3            | MeSH.EXACT.EXPLODE ("Pulmonary Disease, Chronic Obstructive") OR "chronic obstructive pulmonary disease" OR "COPD" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Airway Disease" | 90,402b           |
| S4            | (S1 OR S2) AND S3                                                           | 444a              |

**Notes:**
- a Duplicate citations removed from result count; result count includes duplicate citations. ProQuest search, including Biosis, Biosis previews, Embase, and Medline databases. Searches were limited to publications from January 1, 2006 to July 31, 2014 and English-language articles.
- b Result count includes duplicate citations.

**Abbreviations:** EXACT, EXAcerbations of COPD Tool; EXPLODE, terms indexed as subterms included; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; MeSH, Medical Subject Headings.

### Table S2 Congress abstract search strategy and results

| Congress abstracts searched                                                                 | Search terms                                                                 | Number of records |
|-----------------------------------|------------------------------------------------------------------------------|-------------------|
| Annual Congress of the European Respiratory Society                                     | "Fixed-dose combination" OR "Fixed dose combination" OR "Fixed-dose long-acting combination" OR "Fixed dose long-acting combination" OR "Fixed dose long-acting combinations" OR "Fixed dose combinations" OR "Fixed-dose long-acting combinations" OR "Fixed dose long-acting combinations" OR "fixed combination" OR "fixed combinations" OR "LABA/LAMA" OR "LAMA/LABA" OR "dual bronchodilator" OR "dual bronchodilator" OR "dual bronchodilators" OR "dual bronchodilators" OR "dual-acting bronchodilator" OR "dual-acting bronchodilators" OR "dual-acting bronchodilator" OR "QVA149" OR "QVA-149" OR "QVA 149" OR "glycopyrronium/indacaterol" OR "indacaterol/glycopyrronium" OR "Anoro" OR "umeclidinium/vilanterol" OR Embase:EXACT ("glycopyrronium bromide plus indacaterol") | 285               |
| Annual International Conference of the American Thoracic Society                      |                                                                               |                   |
| Annual Winter Meeting of the British Thoracic Society                                 |                                                                               |                   |
| Biennial International Multidisciplinary Conference on Chronic Obstructive Pulmonary Disease |                                                                               |                   |
| Biennial World Conference of the International Primary Care Respiratory Group         |                                                                               |                   |
| CHEST                                                                               |                                                                               |                   |
| Annual Congress of the Asian Pacific Society of Respirology                          |                                                                               |                   |

**Note:** Available abstracts from January 1, 2009 to May 20, 2015 were included in the literature search.