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REVIEW

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 β_2-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 β_2-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

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inhibit pulmonary constriction. Combining bronchodilators with different modes of action appears to be additive, providing greater efficacy versus component monotherapies.[3] Randomized controlled trials (RCTs) of LABA–LAMA combinations via separate inhalers have generally shown improved lung function versus component monotherapies.[4–12]

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.[1] 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.[13] Spirometry is central to COPD diagnosis, but does not measure COPD burden in terms of health status.[14] Additionally, spirometry is not always performed, and symptoms and exacerbation history can play important roles in treatment initiation and management.[15] It is therefore important that spirometry is accompanied by assessments using patient-reported outcome (PRO) measures, such as breathlessness, physical functioning, and health status.[14] Minimal clinically important differences (MCIDs) for these assessments and other COPD outcomes have been reviewed by Jones et al.[14] Although a few studies and reports have examined associations between improved lung function (mainly FEV_1) and PROs in COPD,[16–21] 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.

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).[22] The literature search identified primary, English-language, RCT publications of fixed-combination bronchodilators reporting treatment effects on lung function and/or PROs in comparison with placebo, bronchodilator monotherapy, or inhaled corticosteroid–LABA combinations in patients with COPD (Table S1). Data sources included a ProQuest search of Biosis, Biosis previews, Embase and Medline databases (January 1, 2006 to July 31, 2014), and abstracts from principal respiratory congresses (January 1, 2009 to May 20, 2015; Table S2). These selected search dates ensured that all relevant publications on fixed-combination bronchodilators were captured. 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).[23] 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.[23–34]

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

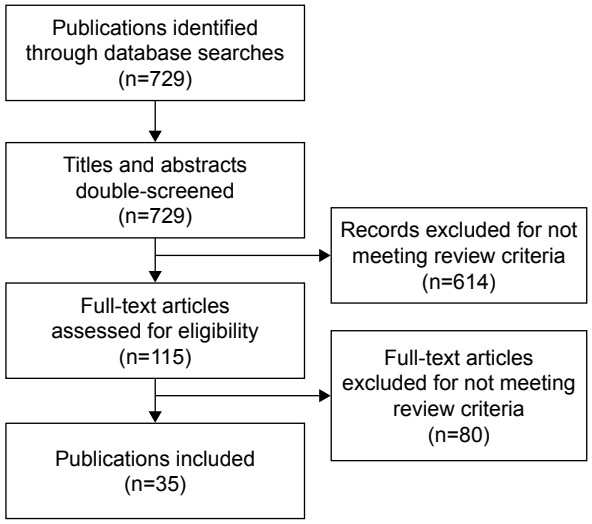

Figure 1 Flowchart of systematic literature search.
Notes: Reasons for exclusion comprised: not a primary publication or not containing novel data from clinical studies, non-COPD study, data not from a randomized clinical study, medication not combination LABA–LAMA bronchodilator treatment, and unapproved dose for a licensed combination therapy.
Abbreviations: LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.

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).[2,24–26,35–40] 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,[23,32,41] seven 12-week studies,[27,33,42,43] and one 52-week safety study (125/25 µg).[45] Lung-function and PRO data have been fully reported for six of the eight trials listed in Table 1.[23,27,32,41]

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.[30] Results from an additional Phase III trial evaluating lung function and volume (VIVACITO) have been published (Table 1),[31] two Phase III trials have been presented as abstracts,[34,45] one further Phase III study has been completed (ClinicalTrials.gov NCT01536262) and four are ongoing (ClinicalTrials.gov NCT02006732, NCT01964352, NCT01969721, and NCT02085161).

Aclidinium–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).[28,29,46] Results from a 24-week Phase III study comparing aclidinium–formoterol with salmeterol–fluticasone combination (SFC) BID had been published in abstract form at the time of the literature search.[47] For glycopyrrolate–formoterol (in late-stage development), only Phase II congress abstracts are available.[48–50] 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 umeclidinium–vilanterol OD, three with tiotropium–olodaterol OD, and two with aclidinium–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.[2,24,26,35–40] The eight umeclidinium–vilanterol OD trials enrolled patients with moderate-to-severe or moderate-to-very-severe COPD who were symptomatic.[23,27,32,41] Patients in the tiotropium–olodaterol OD studies had moderate-to-very-severe COPD.[30,31] The aclidinium–formoterol BID studies were conducted in patients with moderate-to-severe COPD.[28,29]

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[a]	Patient population	Mean FEV_1% predicted (GOLD stage)	Treatment	Primary and other efficacy outcomes
Published Phase III clinical trials							
IND–GLY							
Bateman et al[2] (SHINE)	MC, R, DB	26 weeks	2,144	Moderate-to-severe COPD (FEV_1 ≥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 FEV_1 at week 26 (primary) Dyspnea (TDI) Health status (SGRQ) Rescue-medication use Symptoms (diary)
Dahl et al[36] (ENLIGHTEN)	MC, R, DB	52 weeks	339	Moderate-to-severe COPD (FEV_1 ≥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 FEV_1
Dahl et al[37] (BEACON)	MC, R, DB	4 weeks	193	Moderate-to-severe COPD (FEV_1 ≥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 FEV_1 at week 4 (noninferiority; primary) Rescue-medication use Symptoms (diary)
Mahler et al[38] (BLAZE)	MC, R, B, DD, XO	6 weeks	247	Moderate-to-severe COPD (FEV_1 ≥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) FEV_1 $AUC_{0–4\,h}$ Rescue-medication use Symptoms (diary)

Vogelmeier et al[39] (ILLUMINATE)	MC, R, DB, DD	26 weeks	523	Moderate-to-severe COPD (FEV_1 ≥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	60 (II or III)	IND–GLY 110/50 µg SFC 50/500 µg BID	FEV_1 $AUC_{0–12\ h}$ at week 26 (primary) Dyspnea (TDI) FEV_1 and FVC Health status (SGRQ) Rescue-medication use Symptoms (diary)
Wedzicha et al[40] (SPARK)	MC, R, DB	64 weeks	2,224	Severe-to-very-severe COPD (FEV_1 <50% predicted) with ≥1 COPD exacerbation requiring treatment with systemic corticosteroids and/or antibiotics in the previous year	37 (III or IV)	IND–GLY 110/50 µg Glycopyrronium 50 µg Tiotropium 18 µg OL	Exacerbations (primary) Health status (SGRQ) Rescue-medication use Trough FEV_1
Beeh et al[35] (BRIGHT)	MC, R, DB, DD, XO	3 weeks	85	Moderate-to-severe COPD (FEV_1 ≥40% and <70% predicted); 83% of patients had no history of exacerbation in the previous year	56 (II or III)	IND–GLY 110/50 µg Tiotropium 18 µg[b] Placebo	Exercise endurance time at week 3 (primary) Dyspnea and leg discomfort (Borg) Lung function Rescue-medication use Symptoms (diary)
Buhl et al[25] (QUANTIFY)	DB, TD	26 weeks	934	Moderate-to-severe COPD (FEV_1 ≥30%–<80% predicted; postbronchodilator FEV_1 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	53 (II or III)	IND–GLY 110/50 µg Tiotropium 18 µg + formoterol 12 µg BID	Health status (SGRQ-C; primary) Dyspnea (TDI) Symptoms (SGRQ-C) FEV_1 and FVC Exacerbations
Zhong et al[24] (LANTERN)	MC, R, DB, DD	26 weeks	744	Moderate-to-severe COPD (FEV_1 ≥30%–<80% predicted; postbronchodilator FEV_1 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	52 (II or III)	IND–GLY 110/50 µg SFC 50/500 µg BID	Trough FEV_1 at week 26 (primary) Other FEV_1, FVC Dyspnea (TDI) Health status (SGRQ and CAT) Rescue-medication use Symptoms (diary) Exacerbations

(*Continued*)

Table 1 (*Continued*)

Reference and study	Design	Duration	Patients, n[a]	Patient population	Mean FEV_1% predicted (GOLD stage)	Treatment	Primary and other efficacy outcomes
Wedzicha et al[26] (FLAME)	MC, R, DB, DD, NI	52 weeks	3,362	Moderate-to-very-severe COPD (FEV_1 ≥25%–<60% predicted; postbronchodilator FEV_1 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 FEV_1 and FEV_1 $AUC_{0–12\ h}$ Health status (SGRQ-C) Rescue-medication use
UMEC–VI							
Donohue et al[41]	MC, R, DB	24 weeks	1,536	Moderate-to-very-severe COPD (FEV_1 ≤70% predicted) and mMRC grade ≥2; exacerbation history not stated	47 (II–IV)	UMEC–VI 62.5/25 μg Umeclidinium 62.5 μg Vilanterol 25 μg Placebo	Trough FEV_1 at week 24 (primary) Dyspnea (TDI, SOBDA) Exacerbations Other FEV_1, FVC Health status (SGRQ) Rescue-medication use
Decramer et al[23] (study 1)	MC, R, B, DD	24 weeks	843	Moderate-to-very-severe COPD (FEV_1 ≤70% predicted) and mMRC grade ≥2; 53% of patients experienced an exacerbation in the previous year	48 (II–IV)	UMEC–VI 125/25 μg UMEC–VI 62.5/25 μg Tiotropium 18 μg Vilanterol 25 μg	Trough FEV_1 at week 24 (primary) Dyspnea (TDI, SOBDA) Exacerbations Health status (SGRQ) Other FEV_1, FVC Rescue-medication use
Decramer et al[23] (study 2)	MC, R, B, DD	24 weeks	869	Moderate-to-very-severe COPD (FEV_1 ≤70% predicted) and mMRC grade ≥2; 38% of patients had experienced an exacerbation in the previous year	47 (II–IV)	UMEC–VI 125/25 μg UMEC–VI 62.5/25 μg Tiotropium 18 μg Umeclidinium 125 μg	Trough FEV_1 at week 24 (primary) Dyspnea (TDI, SOBDA) Exacerbations Health status (SGRQ) Other FEV_1, FVC Rescue-medication use
Maleki-Yazdi et al[32]	MC, R, B, DD	24 weeks	905	Moderate-to-very-severe COPD (FEV_1 ≤70% predicted) and mMRC grade ≥2; exacerbation history not stated	46 (II–IV)	UMEC–VI 62.5/25 μg Tiotropium 18 μg	Trough FEV_1 at week 24 (primary) Exacerbations Health status (SGRQ) Other FEV_1, FVC Rescue-medication use

Maltais et al[33] (study 1 [417])	MC, R, DB, XO	12 weeks	349	Moderate-to-severe COPD (FEV_1 ≥35% and ≤70% predicted), mMRC grade ≥2 and FRC ≥120% (hyperinflated); exacerbation history not stated	51 (II or III)	UMEC–VI 125/25 or 62.5/25 μg Umeclidinium 62.5 or 125 μg Vilanterol 25 μg Placebo	Exercise-endurance time at week 12 (co-primary) Trough FEV_1 at week 12 (co-primary) Lung function Lung volume
Maltais et al[33] (study 2 [418])	MC, R, DB, XO	12 weeks	308	Moderate-to-severe COPD (FEV_1 ≥35% and ≤70% predicted), mMRC grade ≥2 and FRC ≥120% (hyperinflated); exacerbation history not stated	51 (II or III)	UMEC–VI 125/25 or 62.5/25 μg Umeclidinium 62.5 or 125 μg Vilanterol 25 μg Placebo	Exercise-endurance time at week 12 (coprimary) Trough FEV_1 at week 12 (coprimary) Lung function Lung volume
Donohue et al[27] (study 2114930)	MC, R, DB, DD	12 weeks	707	Moderate-to-severe COPD; (FEV_1 ≥30% and ≤70% predicted); no exacerbations in past year	49–50 (II or III)	UMEC–VI 62.5/25 μg SFC 50/250 μg	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[27] (study 2114951)	MC, R, DB, DD	12 weeks	700	Moderate-to-severe COPD; (FEV_1 ≥30% and ≤70% predicted); no exacerbations in past year	49–50 (II or III)	UMEC–VI 62.5/25 μg SFC 50/250 μg	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[30] (replicate studies 1237.5 and 1237.6)	MC, R, DB	52 weeks (×2)	2,624	Moderate-to-severe COPD (GOLD stage II–III); FEV_1 ≥30% and <80% predicted; exacerbation history not stated	49–50 (I–IV)	Olodaterol 5 μg Tiotropium 2.5 μg Tiotropium 5 μg TIO–OLO 2.5/5 μg TIO–OLO 5/5 μg	FEV_1 0–3 hours, trough FEV_1 and health status (SGRQ total score) at week 24 (joint primary) Dyspnea (TDI)
Beeh et al[31] (VIVACITO)	MC, R, DB, IN, XO	6 weeks	219	Moderate-to-very-severe COPD (GOLD stage II–IV); FEV_1 <80% predicted (≥30% for certain sites); exacerbation history not stated		Olodaterol 5 μg Tiotropium 2.5 μg Tiotropium 5 μg TIO–OLO 2.5/5 μg TIO–OLO 5/5 μg Placebo	FEV_1 $AUC_{0–24\ h}$ at week 6 (primary) Other FEV_1, FVC FRC Residual volume

(*Continued*)

Table 1 (*Continued*)

Reference and study	Design	Duration	Patients, n[a]	Patient population	Mean FEV_1% predicted (GOLD stage)	Treatment	Primary and other efficacy outcomes
ACL–FORM							
Singh et al[28] (ACLIFORM-COPD)	MC, R, DB	24 weeks	1,729	Moderate-to-severe COPD (FEV_1 ≥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	FEV_1 1 hour postdose (co-primary) Trough FEV_1 (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[29] (AUGMENT)	MC, R, DB	24 weeks	1,692	Moderate-to-severe COPD (FEV_1 ≥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	FEV_1 1 hour postdose (coprimary) Trough FEV_1 (coprimary) Dyspnea (TDI) Health status (SGRQ)

Reference and study	Design	Duration	Patients, n[a]	Mean FEV_1% predicted (GOLD stage)	Treatment	Primary and other efficacy outcomes
Studies reported in abstract form						
IND–GLY						
Asai et al[62] (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[42] (study 1)	MC, R, DB, XO	12 weeks	207	NR (NR)[c]	UMEC–VI 62.5/25 μg Umeclidinium 62.5 μg Vilanterol 25 μg	FEV_1 at week 2
Donohue et al[42] (study 2)	MC, R, DB, XO	12 weeks	182	NR (NR)[c]	UMEC–VI 62.5/25 μg Umeclidinium 62.5 μg Vilanterol 25 μg	FEV_1 at week 12
Singh et al[43]	MC, R, DB, DD	12 weeks	716	NR (II or III)	UMEC–VI 62.5/25 μg SFC 500/50 μg BID	FEV_1 at week 12 (primary) Dyspnea (TDI) Health status (SGRQ)
TIO-OLO						
Maltais et al[45] (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

O'Donnell et al[34] (MORACTO 1 and 2)	DB, PG, IN, XO	6 weeks	586	58.6 (II–III)	TIO–OLO 5/5 μg TIO–OLO 2.5/5 μg Tiotropium 5 μg Olodaterol 5 μg Placebo	IC at rest (coprimary) Exercise endurance (coprimary) Breathing discomfort during exercise testing
ACL–FORM						
D'Urzo et al[63] (AUGMENT extension)	R, DB, AC extension	52 weeks	1,668	NR (NR)	ACL–FORM 400/12 μg BID ACL–FORM 400/6 μg BID Aclidinium 400 μg BID Formoterol 12 μg BID Placebo	Postdose and trough FEV_1 Dyspnea (TDI) and responders
Donohue et al[46]	R, DB, PG	52 weeks	581	NR (II–III)	ACL–FORM 400/12 μg BID Formoterol 12 μg BID	Trough FEV_1 Rescue-medication use Safety
Vogelmeier et al[47]	R, DB, DD, AC	24 weeks	933	53.2 (NR)	ACL–FORM 400/12 μg BID SFC 50/500 μg	Peak FEV_1 at week 24 (primary) Peak FEV_1 at other visits, TDI, CAT score, exacerbations
GFF						
Reisner et al[48]	R, DB, XO Phase IIB	7 days	118	NR (II–IV)	GFF 72/9.6 μg BID GFF 36/9.6 μg BID Tiotropium 18 μg BID Placebo	Trough FEV_1 IC
Reisner et al[49]	R, DB, XO Phase IIB	7 days	NR	NR (II–IV)	GFF 72/9.6 μg BID GFF 36/9.6 μg BID Glycopyrrolate MDI 36 μg BID Formoterol MDI 9.6 μg BID Formoterol MDI 7.2 μg BID Tiotropium 18 μg Formoterol DPI 12 μg BID Placebo	Lung function Mean PEFR Rescue use

Notes: Treatment was once daily unless stated otherwise. [a]Patients randomized to treatment; [b]investigator-blinded only; [c]inclusion criteria: FEV_1 ≤70% predicted and FEV_1/FVC 0.7.

Abbreviations: ACL–FORM, aclidinium–formoterol; $AUC_{0-4\,h}$, area under the (plasma concentration–time) curve from 0 to 4 hours; $AUC_{0-12\,h}$, area under the (plasma concentration–time) curve from 0 to 12 hours; $AUC_{0-24\,h}$, 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_1, 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; NI, noninferiority; NR, not reported; OL, open-label; PEFR, peak expiratory flow rate; R, randomized; SFC, salmeterol–fluticasone combination; SOBDA, Shortness Of Breath with Daily Activity; 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 FEV_1 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 FEV_1 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 FEV_1 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-FEV_1 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 FEV_1 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 FEV_1 LSM (95% CI) treatment difference at end point, mL	Other lung-function parameters
IND–GLY				
Bateman et al[2] (SHINE)	26 weeks	IND–GLY 110/50 µg OD vs Indacaterol 150 µg OD Glycopyrronium 50 µg OD Tiotropium 18 µg OD OL Placebo	 70[a] (NR) 80[a] (NR) 70[a] (NR) 200[a] (170–240)	IND–GLY provided significantly higher FEV_1 $AUC_{0-4\,h}$ and peak FEV_1 compared with placebo, glycopyrronium, and tiotropium (all $P<0.01$)
Dahl et al[36] (ENLIGHTEN)	52 weeks	IND–GLY 110/50 µg OD vs placebo	189[a] (NR)	FEV_1 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[37] (BEACON)	4 weeks	IND–GLY 110/50 µg OD vs indacaterol 150 µg OD + glycopyrronium 50 µg OD	5 (NR; NS for superiority)	FEV_1 $AUC_{0-4\,h}$ (day 1 and week 4) similar between treatment groups
Mahler et al[38] (BLAZE)	6 weeks	IND–GLY 110/50 µg OD vs Placebo Tiotropium 18 µg OD	 330 (0.31–0.36)[a,b] 110 (0.08–0.13)[a,b]	FEV_1 $AUC_{0-4\,h}$ postdose significantly higher for IND–GLY vs tiotropium and placebo at day 1 and week 6 (all $P<0.001$)
Vogelmeier et al[39] (ILLUMINATE)	26 weeks	IND–GLY 110/50 µg OD vs SFC 50/500 µg BID	103[a] (65–141)	Week 26 FEV_1 $AUC_{0-12\,h}$ significantly higher with IND–GLY than with SFC (treatment difference 138 mL, 95% CI 0.1–0.176; $P<0.0001$)
Wedzicha et al[40] (SPARK)	64 weeks	IND–GLY 110/50 µg OD vs Glycopyrronium 50 µg OD Tiotropium 18 µg OD OL	Weeks 4–64: 70–80[a] (NR) 60–80[a] (NR)	NR
Beeh et al[35] (BRIGHT)	3 weeks	IND–GLY 110/50 µg OD vs Tiotropium 18 µg OD[a] Placebo	 100[a] (50–150) 200[a] (150–260)	At day 21, mean treatment differences in trough IC, FEV_1, 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[25] (QUANTIFY)	26 weeks	IND/GLY 110/50 µg OD vs tiotropium 18 µg OD + formoterol 12 µg BID	68[a] (37–100)	IND–GLY increased predose FVC vs tiotropium + formoterol at week 26 (74 mL, 95% CI: 24–125 mL; $P=0.004$)

(*Continued*)

Table 2 (*Continued*)

Reference and study	Duration	Treatment	Trough FEV_1 LSM (95% CI) treatment difference at end point, mL	Other lung-function parameters
Zhong et al[24] (LANTERN)	26 weeks	IND–GLY 110/50 µg OD vs SFC 50/500 µg BID	72[a] (40–104)	Improvements in trough FEV_1 with IND–GLY vs SFC observed at day 1 (Δ=43 mL) and reaching steady state by week 12 (Δ=78 mL, both $P<0.001$). Improvements in FEV_1 $AUC_{0–4\,h}$ at day 1/ week 26 with IND–GLY vs SFC (Δ=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[26] (FLAME)	52 weeks	IND–GLY 110/50 µg OD vs SFC 50/500 µg BID	62[a] (NR)	Change from baseline in FEV_1 $AUC_{0–12h}$ (measured in a subgroup of 556 patients) was significantly greater with IND–GLY vs SFC at week 52 (Δ=110 mL, $P<0.001$)
UMEC–VI				
Donohue et al[41]	24 weeks	UMEC–VI 62.5/25 µg OD vs Umeclidinium 62.5 µg OD Vilanterol 25 µg OD Placebo	Change from baseline: 52[a] (17–87) 95[a] (60–130) 167[a] (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[23] (study 1)	24 weeks	UMEC–VI 125/25 µg OD[c] UMEC–VI 62.5/25 µg OD vs Tiotropium 18 µg OD Vilanterol 25 µg OD	Change from baseline: 90[a] (39–141) 90[a] (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[23] (study 2)	24 weeks	UMEC–VI 125/25 µg OD[c] UMEC–VI 62.5/25 µg OD vs Tiotropium 18 µg OD Umeclidinium 125 µg OD	Change from baseline: 60[a] (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[32]	24 weeks	UMEC–VI 62.5/25 µg OD vs tiotropium 18 µg OD	Change from baseline: 112[a] (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[33] (study 417)	12 weeks	UMEC–VI 125/25 µg OD[c] 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[a] (172–249) 87[a] (30–143) 140[a] (84–96) 99[a] (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[33] (study 418)	12 weeks	UMEC–VI 125/25 µg OD[c] 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[a] (202–284) 144[a] (86–203) 255[a] (193–318) 112[a] (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[27] (study 2114930)	12 weeks	UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID	Change from baseline: 74[a] (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*)

Table 2 (*Continued*)

Reference and study	Duration	Treatment	Trough FEV_1 LSM (95% CI) treatment difference at end point, mL	Other lung-function parameters
Donohue et al[27] (study 2114951)	12 weeks	UMEC–VI 62.5/25 µg OD vs SFC 50/250 µg BID	Change from baseline: 101[a] (63–139)	FEV_1 significantly improved for UMEC–VI vs SFC at all time points on day 84; significantly greater improvement in LSM trough FEV_1 from baseline for UMEC–VI vs SFC on day 85 (treatment difference 98 mL, $P<0.001$)
TIO–OLO				
Buhl et al[30] (study 1237.5)	52 weeks	TIO–OLO 2.5/5 µg OD[c] TIO–OLO 5/5 µg OD vs Olodaterol 5 µg OD Tiotropium 5 µg OD Tiotropium 2.5 µg OD	Change from baseline at week 24: 82[a] (59–106) 71[a] (47–94) NR	Improvements observed for FEV_1 values on all test days over each of the 52-week studies; responses in trough FVC and FVC $AUC_{0-3\ h}$ over 24 weeks consistent with the primary end points
Buhl et al[30] (study 1237.6)	52 weeks	TIO–OLO 2.5/5 µg OD[c] TIO–OLO 5/5 µg OD vs Olodaterol 5 µg OD Tiotropium 5 µg OD Tiotropium 2.5 µg OD	Change from baseline at week 24: 88[a] (63–113) 50[a] (24–75) NR	Improvements observed for FEV_1 values on all test days over each of the 52-week studies; responses in trough FVC and FVC $AUC_{0-3\ h}$ over 24 weeks consistent with the primary end points
Beeh et al[31] (VIVACITO)	6 weeks	TIO–OLO 2.5/5 µg OD[c] TIO–OLO 5/5 µg OD vs Olodaterol 5 µg OD Tiotropium 5 µg OD Tiotropium 2.5 µg OD Placebo	Adjusted mean difference: 92[a] (NR) 79[a] (NR) NR 207[a] (NR)	Significant improvement in FEV_1 $AUC_{0-24\ h}$ and greater improvement in 24-hour FEV_1 profile for both TIO–OLO doses vs placebo and monotherapies at 6 weeks; similar pattern of response for FVC, FRC, and residual volume
ACL–FORM				
Singh et al[28] (ACLIFORM-COPD)	24 weeks	ACL–FORM 400/6 µg BID[c] ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID Aclidinium 400 µg BID Placebo	Change from baseline at week 24: 85[a] ~25[d] 143[a]	Fast onset of action of both ACL–FORM doses on day 1, with significant improvements in bronchodilation vs placebo at 5 minutes postdose
D'Urzo et al[29] (AUGMENT)	24 weeks	ACL–FORM 400/6 µg BID[c] ACL–FORM 400/12 µg BID vs Formoterol 12 µg BID Aclidinium 400 µg BID Placebo	Change from baseline at week 24: 45[a] 28 129[a]	ACL–FORM (both doses) associated with significant changes from baseline in peak FEV_1 at day 1 and week 24 ($P<0.0001$ all comparisons); rapid bronchodilation occurred with significant FEV_1 improvements 5 minutes postdose ($P<0.0001$)

Notes: Treatment once daily unless stated otherwise. [a]Significant treatment difference; [b]FEV_1 $AUC_{0-4\ h}$; [c]dose not approved for use (ACL–FORM, dose not approved in EU); [d]estimated from figure.

Abbreviations: ACL–FORM, aclidinium–formoterol; $AUC_{0-3\ h}$, area under the plasma concentration-time curve from 0 to 3 hours; $AUC_{0-4\ h}$, area under the (plasma concentration–time) curve from 0 to 4 hours; $AUC_{0-12\ h}$, area under the (plasma concentration–time) curve from 0 to 12 hours; $AUC_{0-24\ h}$, area under the (plasma concentration–time) curve from 0 to 24 hours; BID, bis in die (twice daily); CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; IC, inspiratory capacity; IND–GLY, indacaterol–glycopyrronium; LSM, least-squares mean; NR, not reported; NS, not significant; OD, once daily; OL, open-label; SFC, salmeterol/fluticasone combination; TIO–OLO, tiotropium–olodaterol; UMEC–VI, umeclidinium–vilanterol.

significant improvements in FEV_1 0–24 hours and trough FEV_1 compared with 50/250 µg BID.[27]

At week 24 of the two 1-year studies, tiotropium–olodaterol 5/5 µg OD increased trough FEV_1 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]

Aclidinium–formoterol (400/12 µg BID) increased week 24 trough FEV_1 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.[28] 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]

Symptoms

Improvements in dyspnea and other symptoms were seen with fixed-dose LABA–LAMA therapies versus monotherapies and for indacaterol–glycopyrronium OD versus SFC BID. (Table 3, Figure 2).[2,24,25,38,39] Indacaterol–glycopyrronium significantly improved transition dyspnea index (TDI) scores in SHINE and ILLUMINATE versus placebo, open-label tiotropium, and SFC.[2,39] 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, $P=0.021$).[38] The proportion of patients achieving the MCID (≥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		
			TDI total score, LSM (95% CI)	% TDI responders[a] (OR)	Other
IND–GLY					
Bateman et al[2] (SHINE)	26 weeks	IND–GLY 110/50 µg OD vs Indacaterol 150 µg OD Glycopyrronium 50 µg OD Tiotropium 18 µg OD OL Placebo	 0.25 (NR) 0.20 (NR) 0.51[b] (NR) 1.09[b] (0.61–1.57)	 3.5 (NR) 4.4 (NR) 8.9[b] (NR) 10.6[b] (NR)	Diary data (values vs placebo): % days with no daytime symptoms, +3.05[b]; % days able to perform usual daily activities, +11.48[b–e]; % nights without awakenings, +10.01[b,c]
Dahl et al[36] (ENLIGHTEN)	52 weeks	IND–GLY 110/50 µg OD vs Placebo	 NR	 NR	Diary data: Total daily symptom score, −0.573[b]; % days with no daytime symptoms, +5.3[b], % days able to perform usual daily activities, +8.1[b]; % nights without awakenings, +6.3
Dahl et al[37] (BEACON)	4 weeks	IND–GLY 110/50 µg OD vs indacaterol 150 µg OD + glycopyrronium 50 µg OD	 NR	 NR	Diary data: Total daily symptom score, 0.07 (−0.24, 0.39)
Mahler et al[38] (BLAZE)	6 weeks	IND–GLY 110/50 µg OD vs tiotropium 18 µg OD Placebo	SAC TDI: 0.49[b] (0.07, 0.91) 1.37[b] (0.95, 1.79)	SAC TDI: 11.5[b] (2.78) 17.8[b] (1.78)	Diary data (vs placebo and tiotropium): Total daily symptom score, −0.72[b] and −0.03; % days with no daytime symptoms, +3.5[b] and +1.5; % nights with no awakenings, 5.6[b] and 2.6; days able to perform usual activities, 8.8[b] and −0.4
Vogelmeier et al[39] (ILLUMINATE)	26 weeks	IND–GLY 110/50 µg OD vs SFC 50/500 µg BID	0.76[b] (0.26, 1.26)	10.7[b] (1.56)	Diary data: Differences in scores for most symptoms NS between treatment groups % days with no daytime symptoms, +2.50[b]
Beeh et al[35] (BRIGHT)	3 weeks	IND–GLY 110/50 µg OD vs tiotropium 18 µg OD Placebo	 NR NR	 NR NR	Diary data, mean daily symptom score vs baseline: IND–GLY −0.64, tiotropium −0.43, placebo −0.19
Buhl et al[25] (QUANTIFY)	26 weeks	IND–GLY 110/50 µg OD vs tiotropium 18 µg OD + formoterol 12 µg 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[24] (LANTERN)	26 weeks	IND–GLY 110/50 µg OD vs SFC 50/500 µg 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[41]	24 weeks	UMEC–VI 62.5/25 µg OD vs umeclidinium 62.5 µg OD Vilanterol 25 µg OD Placebo	 0.3 (−0.2, 0.7) 0.4 (−1.0, 0.8) 1.2[b] (0.7, 1.7)	 5.0 (NR) 7.0[b] (1.4) 17.0[b] (2.0)	NR

(*Continued*)

Table 3 (*Continued*)

Reference and study	Duration	Treatment	TDI total score, LSM (95% CI)	% TDI responders[a] (OR)	Other
Decramer et al[23] (study 1)	24 weeks	UMEC–VI 125/25 μg OD[f]			
		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)	
Decramer et al[23] (study 2)	24 weeks	UMEC–VI 125/25 μg OD[f]			
		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)	
Donohue et al[27] (study 2114930)	12 weeks	UMEC–VI 62.5/25 μg OD vs SFC 50/250 μg BID	0.3 (−0.2, 0.7)	NR	NR
Donohue et al[27] (study 2114951)	12 weeks	UMEC–VI 62.5/25 μg OD vs SFC 50/250 μg BID	0.3 (−0.1, 0.8)	NR	NR
Maltais et al[33] (study 417)	12 weeks				Exercise dyspnea scale (Borg), changes from baseline vs placebo:
		UMEC–VI 125/25 μg OD[f]			−0.25 (−0.57 to 0.07)[f]
		UMEC–VI 62.5/25 μg OD			−0.05 (−0.37 to 0.27)
		Umeclidinium 62.5 μg OD	NR	NR	−0.16 (−0.61 to 0.3)
		Umeclidinium 125 μg OD	NR	NR	−0.13 (−0.58 to 0.33)
		Vilanterol 25 μg OD	NR	NR	0.39 (−0.01 to 0.79)
Maltais et al[33] (study 418)	12 weeks				Exercise dyspnea scale (Borg), change from baseline vs placebo:
		UMEC–VI 125/25 μg OD[f]			−0.34 (−0.76 to 0.03)[f]
		UMEC–VI 62.5/25 μg OD			−0.36 (0.67 to −0.05)[b]
		Umeclidinium 62.5 μg OD	NR	NR	−0.32 (−0.78 to 0.13)
		Umeclidinium 125 μg OD	NR	NR	−0.66 (−1.14 to −0.18)
		Vilanterol 25 μg OD	NR	NR	−0.36 (−0.76 to 0.03)
TIO–OLO					
Buhl et al[30] (studies 1237.5 and 1237.6 combined)	52 weeks	TIO–OLO 2.5/5 μg OD[f]	(At week 24):		
		TIO–OLO 5/5 μg OD vs			
		Olodaterol 5 μg OD	0.420[b] (0.155–0.684)	NR	NR
		Tiotropium 5 μg OD	0.356[b] (0.092–0.619)	NR	NR
ACL–FORM					
Singh et al[28] (ACLIFORM-COPD)	24 weeks	ACL–FORM 400/6 μg BID[f]			E-RS changes from baseline:
		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]
		Aclidinium 400 μg BID	0.40 (−0.05 to 0.85)	8.3 (1.42)	−0.89 (−8.4)[b]
		Placebo	1.29[b] (0.73–1.86)	19.3 (2.54)[b]	−0.82 (−8.2)[b,g]
		ACL–FORM 400/12 μg BID vs			Nighttime symptoms, change from baseline:
		Formoterol 12 μg BID	NR	NR	−0.04 (−4.2)
		Aclidinium 400 μg BID	NR	NR	−0.09[b] (−10.5)
		Placebo	NR	NR	−0.07 (−8)[g]
		ACL–FORM 400/12 μg BID vs			Early morning symptoms, change from baseline vs:
		Formoterol 12 μg BID	NR	NR	−0.04 (−3.7)
		ACL 400 μg BID	NR	NR	−0.08 (−7.5)[b]
		Placebo	NR	NR	−0.09 (−8.1)[b,g]
D'Urzo et al[29] (AUGMENT)	24 weeks	ACL–FORM 400/6 μg BID[f]			E-RS changes from baseline:
		ACL–FORM 400/12 μg BID vs			
		Formoterol 12 μg BID	0.5	6.4	−0.48 (−3.4)
		Aclidinium 400 μg BID	0.46	3.3	−0.32 (−1.7)
		Placebo	1.44[b]	21.5 (2.8)[b]	−1.36 (−10.8)[b,g]

(*Continued*)

Table 3 (*Continued*)

Reference and study	Duration	Treatment	TDI total score, LSM (95% CI)	% TDI responders[a] (OR)	Other
		ACL–FORM 400/6 μg BID[f] ACL–FORM 400/12 μg BID vs			Night-time symptoms, change from baseline vs:
		Formoterol 12 μg BID	NR	NR	−0.05 (−2.4)
		Aclidinium 400 μg BID	NR	NR	−0.08 (−5.3)
		Placebo	NR	NR	−0.12 (−9.3)[b,g]
		ACL–FORM 400/6 μg BID[f] ACL–FORM 400/12 μg BID vs			Early-morning symptoms, change from baseline vs:
		Formoterol 12 μg BID	NR	NR	−0.06 (−4.6)
		Aclidinium 400 μg BID	NR	NR	−0.09 (−7.4)[b]
		Placebo	NR	NR	−0.13 (−9.8)[b,g]

Notes: Treatment once daily unless stated otherwise. [a]TDI responders had improvement ≥1 unit in TDI score. [b]Significant treatment difference. Significant treatment difference versus [c]indacaterol, [d]glycopyrronium or [e]tiotropium (values NR). [f]Dose not approved for use (ACL–FORM, dose not approved in EU). [g]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.

tiotropium in BLAZE (OR 1.78, $P<0.05$) and versus SFC in ILLUMINATE (OR 1.56, $P<0.05$; Figure 2).[2,39] 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).[2,36,38] 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.[39]

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.[23,41] 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, $P<0.05$)[41] in one study (Figure 2).[23] 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.[23,41] 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.[33] 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

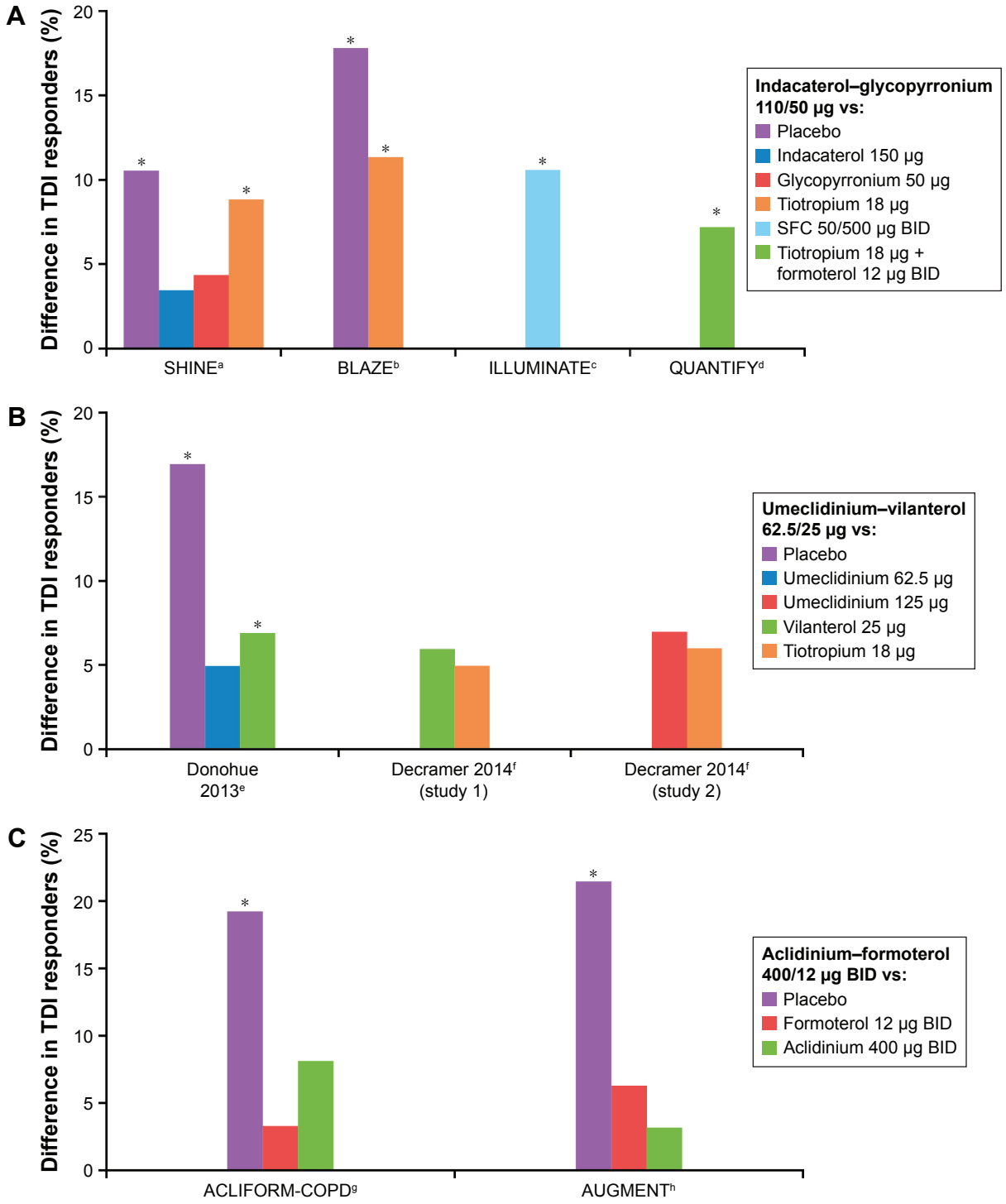

Figure 2 Differences between monotherapy and combination bronchodilators or placebo in TDI patient-response rates in published studies.
Notes: (**A**) Indacaterol–glycopyrronium; (**B**) umeclidinium–vilanterol 62.5/25 µg; (**C**) aclidinium–formoterol 400/12 µg BID. TDI response was defined as improvement of ≥1 unit in TDI score. All treatments were once daily unless stated otherwise. *Significant treatment difference. [a]Bateman et al;[2] [b]self-administered computerized TDI;[38] [c]Vogelmeier et al;[39] [d]Buhl et al;[25] [e]Donohue et al;[41] [f]Decramer et al;[23] [g]Singh et al;[28] [h]D'Urzo et al.[29]
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.[2,26,35,38–40] In LANTERN, rescue-medication use was comparable between the indacaterol–glycopyrronium and SFC BID groups.[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.[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

Table 4 Rescue-medication use: margin of efficacy of fixed combinations versus comparators in published studies

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[2] (SHINE)	26 weeks	IND–GLY 110/50 µg OD vs	
		Indacaterol 150 µg OD	–0.31[a] (NR)
		Glycopyrronium 50 µg OD	–0.66[a] (NR)
		Tiotropium 18 µg OD OL	–0.55[a] (NR)
		Placebo	–0.96[a] (–1.29 to –0.62)
Dahl et al[36] (ENLIGHTEN)	52 weeks	IND–GLY 110/50 µg OD vs	
		Placebo	–0.73[a] (NR)
Dahl et al[37] (BEACON)	4 weeks	IND–GLY 110/50 µg OD vs	
		Indacaterol 150 µg OD + glycopyrronium 50 µg OD	–0.04 (–0.35 to 0.28)
Mahler et al[38] (BLAZE)	6 weeks	IND–GLY 110/50 µg OD vs	
		Placebo	–1.43[a] (–1.72 to –1.13)
		Tiotropium 18 µg OD	–0.45[a] (–0.74 to –0.16)
Vogelmeier et al[39] (ILLUMINATE)	26 weeks	IND–GLY 110/50 µg OD vs	
		SFC 50/500 µg BID	–0.39[a] (–0.71 to –0.06)
Wedzicha et al[40] (SPARK)	64 weeks	IND–GLY 110/50 µg OD vs	
		Glycopyrronium 50 µg OD	–0.81[a] (NR)
		Tiotropium 18 µg OD OL	–0.76[a] (NR)
Beeh et al[35] (BRIGHT)	3 weeks	IND–GLY 110/50 µg OD vs	
		Tiotropium 18 µg[a] OD	–1.08[a] (NR)
		Placebo	–1.23[a] (NR)
Zhong et al[24] (LANTERN)	26 weeks	IND–GLY 110/50 µg OD vs	
		SFC 50/500 µg BID	–0.03 (–0.26 to 0.21)
Wedzicha et al[26] (FLAME)	52 weeks	IND–GLY 110/50 µg OD vs	
		SFC 50/500 µg BID	–0.25[a] (–0.38 to –0.12)
UMEC–VI			
Donohue et al[41]	24 weeks	UMEC–VI 62.5/25 µg OD vs	
		Umeclidinium 62.5 µg OD	–0.6[a] (–1.0 to –0.1)
		Vilanterol 25 µg OD	0.1 (–0.3 to 0.5)
		Placebo	–0.8[a] (–1.3 to –0.3)
Decramer et al[23] (study 1)	24 weeks	UMEC–VI 125/25 µg OD[b]	
		UMEC–VI 62.5/25 µg OD vs	
		Tiotropium 18 µg OD	–0.7[a] (–1.2 to –0.1)
		Vilanterol 25 µg OD	–0.3 (–0.8 to 0.3)
Decramer et al[23] (study 2)	24 weeks	UMEC–VI 125/25 µg OD[b]	
		UMEC–VI 62.5/25 µg OD vs	
		Tiotropium 18 µg OD	–0.6 (–1.2 to 0)
		Umeclidinium 125 µg OD	–0.6 (–1.2 to 0)
Maleki-Yazdi et al[32]	24 weeks	UMEC–VI 62.5/25 µg OD vs	
		Tiotropium 18 µg OD	–0.5[a] (–0.7 to –0.2)

(*Continued*)

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 al[33] (study 417)	12 weeks	UMEC–VI 125/25 μg OD[b]	Differences from placebo:
		UMEC–VI 62.5/25 μg OD	–0.6[a] (–0.8 to –0.3)
		Umeclidinium 62.5 μg OD	–0.2 (–0.6 to 0.1)
		Umeclidinium 125 μg OD	–0.6[a] (–1 to –0.2)
		Vilanterol 25 μg OD	–0.4[a] (–0.7 to 0)
Maltais et al[33] (study 418)	12 weeks	UMEC–VI 125/25 μg OD[b]	Differences from placebo:
		UMEC–VI 62.5/25 μg OD	–1.2[a] (–1.5 to –0.8)
		Umeclidinium 62.5 μg OD	–0.7[a] (–1.3 to –0.2)
		Umeclidinium 125 μg OD	–1.0[a] (–1.5 to –0.4)
		Vilanterol 25 μg OD	–0.8[a] (–1.2 to –0.3)
Donohue et al[27] (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 al[27] (study 2114951)	12 weeks	UMEC–VI 62.5/25 μg OD vs	
		SFC 50/250 μg BID	–0.3[a] (–0.6 to –0.1)
TIO–OLO			
Buhl et al[30] (studies 1237.5 and 1237.6 combined)	52 weeks	TIO–OLO 2.5/5 μg OD[b]	
		TIO–OLO 5/5 μg OD vs	
		Olodaterol 5 μg OD	~ –0.4[c]
		Tiotropium 5 μg OD	~ –0.8[c]
ACL–FORM			
Singh et al[28] (ACLIFORM-COPD)	24 weeks	ACL–FORM 400/6 μg BID[b]	
		ACL–FORM 400/12 μg BID vs	
		Formoterol 12 μg BID	NS
		Aclidinium 400 μg BID	Value NR[a]
		Placebo	–0.66[a]
D'Urzo et al[29] (AUGMENT)	24 weeks	ACL–FORM 400/6 μg BID[b]	
		ACL–FORM 400/12 μg BID vs	
		Formoterol 12 μg BID	0.21
		Aclidinium 400 μg BID	0.43[a]
		Placebo	Value NR[a]

Notes: Treatment once daily unless stated otherwise. [a]Significant treatment difference; [b]dose not approved for use; [c]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.

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 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	
				Exacerbation rate, RR (95% CI)	Time to first exacerbation, HR (95% CI)
IND–GLY					
Wedzicha et al[40] (SPARK)	64 weeks	IND–GLY 110/50 μg OD vs Glycopyrronium 50 μg OD Tiotropium 18 μg OD OL	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[a,b] (0.77–0.94) 0.86[a,b] (0.78–0.94)	0.79[c] (0.60–1.05) 1.13[c] (0.83–1.53)
Buhl et al[25] (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[24] (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[a] (0.48–1)	0.32 (0.12–0.88)
Wedzicha et al[26] (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[a,b] (0.83–0.96)	0.84[a,b] (0.78–0.91)
UMEC–VI					
Donohue et al[41]	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	NR NR 0.5[a] (0.3–0.8)
Decramer et al[23] (study 1)	24 weeks	UMEC–VI 125/25 μg OD[d] UMEC–VI 62.5/25 μg OD vs Tiotropium 18 μg OD Vilanterol 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[23] (study 2)	24 weeks	UMEC–VI 125/25 μg OD[d] UMEC–VI 62.5/25 μg OD vs Tiotropium 18 μg OD Umeclidinium 125 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*)

Table 5 (*Continued*)

Reference and study	Duration	Treatment	Exacerbation definition	Treatment difference at end point	
				Exacerbation rate, RR (95% CI)	Time to first exacerbation, HR (95% CI)
Maleki-Yazdi et al[32]	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	0.5[a] (0.3–1)
TIO–OLO					
Buhl et al[30] (studies 1237.5 and 1237.6 combined)	52 weeks	TIO–OLO 2.5/5 μg OD[d] TIO–OLO 5/5 μg OD vs Olodaterol 5 μg OD Tiotropium 5 μg OD	"Moderate/severe" (not defined)	 NR NR	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[28] (ACLIFORM-COPD)	24 weeks	ACL–FORM 400/6 μg BID[d] 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	 0.64 (0.4–1) 0.89 (0.6–1.4) 0.73 (0.4–1.2)	 NR NR NR
		ACL–FORM 400/6 μg BID[d] ACL–FORM 400/12 μg BID vs Formoterol 12 μg BID Aclidinium 400 μg BID Placebo	EXACT: an increase from baseline in total EXACT score ≥9 points for ≥3 days or ≥12 points for ≥2 days[e]	 0.86 (0.7–1.1) 0.78 (0.6–1) 0.71[a] (0.5–0.9)	 NR NR NR

Notes: Treatment once daily unless stated otherwise. [a]Significant treatment difference; [b]data reported for all exacerbations; [c]includes only severe exacerbations requiring hospitalization/emergency room treatment for ≥24 hours; [d]dose not approved for use (ACL–FORM dose not approved in EU); [e]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).[25]

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),[41] 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 trials[23] and significantly greater in a third study (HR 0.5, P=0.044).[32] 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	Treatment difference at end point	
			SGRQ total score, LSM (95% CI)	% SGRQ responders (OR)
IND–GLY				
Bateman et al[2] (SHINE)	26 weeks	IND–GLY 110/50 µg OD vs		
		Indacaterol 150 µg OD	−1.09 (NR)	0.7 (NR)
		Glycopyrronium 50 µg OD	−1.18 (NR)	3.2 (NR)
		Tiotropium 18 µg OD OL	−2.13[a] (NR)	7.3[a] (NR)
		Placebo	−3.01[a] (−5.05 to −0.97)	7.1 (NR)
Vogelmeier et al[39] (ILLUMINATE)	26 weeks	IND–GLY 110/50 µg OD vs		
		SFC 50/500 µg BID	−1.24 (−3.33 to 0.85)	6.4 (1.32)
Wedzicha et al[40] (SPARK)	64 weeks	IND–GLY 110/50 µg OD vs		
		Glycopyrronium 50 µg OD	−1.9 to −2.8[b] (NR); all P<0.01	NR (1.28)
		Tiotropium 18 µg OD OL	−1.7 to −3.1[b] (NR); all P<0.05	NR (1.29)
Buhl et al[25] (QUANTIFY)	26 weeks	IND–GLY 110/50 µg OD vs tiotropium 18 µg OD + formoterol 12 µg BID	−0.69 (−2.31 to 0.92)	4.5 (risk ratio 1.11)
Zhong et al[24] (LANTERN)	26 weeks	IND–GLY 110/50 µg OD vs SFC 50/500 µg BID	−0.69 (−2.38 to 1)	NR
Wedzicha et al[26] (FLAME)	52 weeks	IND–GLY 110/50 µg OD vs SFC 50/500 µg BID	−1.8[a] (NR)	1.3[a] (NR)
UMEC–VI				
Donohue et al[41]	24 weeks	UMEC–VI 62.5/25 µg OD vs	Change from baseline:	
		Umeclidinium 62.5 µg OD	−0.82[c] (−2.90 to 1.27)	5 (NR)
		Vilanterol 25 µg OD	−0.32[c] (−2.41 to 1.78)	1 (NR)
		Placebo	−5.51[a,c] (−7.88 to −3.13)	15 (2)[a]
Decramer et al[23] (study 1)	24 weeks	UMEC–VI 125/25 µg OD[d]	Change from baseline:	
		UMEC–VI 62.5/25 µg OD vs		
		Tiotropium 18 µg OD	0.75[c] (NR)	3 (0.9)
		Vilanterol 25 µg OD	1.42[c] (NR)	3 (0.8)

(*Continued*)

Table 6 (*Continued*)

Reference and study	Duration	Treatment	Treatment difference at end point	
			SGRQ total score, LSM (95% CI)	% SGRQ responders (OR)
Decramer et al[23] (study 2)	24 weeks	UMEC–VI 125/25 μg OD[d]	Change from baseline:	
		UMEC–VI 62.5/25 μg OD vs		
		Tiotropium 18 μg OD	–0.17[c] (NR)	1 (1)
		Umeclidinium 125 μg OD	–1.55[c] (NR)	6 (1.3)
Maleki-Yazdi et al[32]	24 weeks	UMEC–VI 62.5/25 μg vs	Change from baseline:	
		tiotropium 18 μg	–2.1[a] (–3.61 to –0.59)	7[a] (1.4)
Donohue et al[27] (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[27] (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				
Buhl et al[30] (studies 1237.5 and 1237.6 combined)	52 weeks	TIO–OLO 2.5/5 μg OD[d]	At 24 weeks:	At 24 weeks:[f]
		TIO–OLO 5/5 μg OD vs		
		Olodaterol 5 μg OD	–1.693[a,e]	12.7[a]
		Tiotropium 5 μg OD	–1.233[a]	8.8[a]
ACL–FORM				
Singh et al[28] (ACLIFORM-COPD)	24 weeks	ACL–FORM 400/6 μg BID[d]	Change from baseline:	
		ACL–FORM 400/12 μg BID vs		
		Formoterol 12 μg BID	–1.59 (–3.52 to 0.35)	NR
		Aclidinium 400 μg BID	–1.36 (–3.3 to 0.58)	NR
		Placebo	–0.65 (–3.08 to 1.78)	NR
D'Urzo et al[29] (AUGMENT)	24 weeks	ACL–FORM 400/6 μg BID[d]	Change from baseline:	
		ACL–FORM 400/12 μg BID vs		
		Formoterol 12 μg BID	–1.87	5.8
		Aclidinium 400 μg BID	–0.13	3.7
		Placebo	–4.36[a]	19.5 (2.3)[a]

Notes: Treatment once daily unless stated otherwise. SGRQ response = SGRQ total score ≤4 units versus baseline. [a]Significant treatment difference; [b]range of LSM differences in scores for weeks 12, 24, 38, 52, and 64 (95% CI not reported); [c]differences in LSM change from baseline to week 24; [d]dose not approved for use (ACL–FORM dose not approved in EU); [e]95% CI not reported; [f]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).[40] 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.[2] In a 26-week study, indacaterol–glycopyrronium and SFC BID provided similar improvements in health status.[39] 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 $P<0.01$).[26] The SGRQ responder rate for the MCID (reduction of ≤4 units from baseline)[53] was also significantly greater with indacaterol–glycopyrronium versus SFC in FLAME (OR 1.3, $P<0.001$)[26] 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.[40] 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.[25] Similarly, in LANTERN comparable improvements with indacaterol–glycopyrronium versus SFC were observed for all SGRQ analyses (weeks 12 and 26).[24]

Significant improvements in SGRQ total score mean change from baseline ($P\leq0.001$) and percentages of SGRQ responders (OR 2, $P\leq0.001$) were reported for umeclidinium–vilanterol 62.5/25 μg OD versus placebo in three 24-week studies.[41] 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).[23,41] 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.[32] 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.[2,36,39,40,54–56] 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.[2,24–26,36,39,40] 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).[26] 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]).[54]

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.[16–19,21] This may be because some patients have very poor health despite only mild lung-function impairments or vice versa.[17] Indeed, the health impact of COPD is not necessarily mediated entirely through expiratory airflow limitation; a better correlate may instead be exercise performance.[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.[18] Finally, the Hawthorne effect may also have played a role, as changes in FEV_1 of 0 still resulted in a 2.5-point reduction in SGRQ score in some cases.[18]

Likewise, in trials of combination-bronchodilator therapy versus components, improvement in FEV_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_1.[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_1.[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.[61] 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.[61] The positioning of studies on this scale can be useful as a descriptive classification.[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_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.

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AØ 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")	821[a]
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 bronchodilators" OR "dual bronchodilation" OR "dual-acting bronchodilator" OR "dual-acting bronchodilators" OR "dual-acting bronchodilation" 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")	6,959[b]
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"	90,402[b]
S4	(S1 OR S2) AND S3	444[a]

Notes: [a]Duplicate citations removed from result count; [b]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.
Abbreviations: EXACT, EXAcerbations of COPD Tool; EXPLODE, terms indexed as subterms included; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MeSH, Medical Subject Headings.

Table S2 Congress abstract search strategy and results

Congress abstracts searched	• Annual Congress of the European Respiratory Society • 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
Search terms	"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-bronchodilation" OR "dual bronchodilators" OR "dual bronchodilation" OR "dual-acting bronchodilator" OR "dual-acting bronchodilators" OR "dual-acting bronchodilation" OR "dual acting bronchodilator" OR "dual acting bronchodilators" OR "dual acting bronchodilation" OR "QVA149" OR "QVA-149" OR "QVA 149" OR "glycopyrronium/indacaterol" OR "indacaterol/glycopyrronium" OR "Anoro" OR "umeclidinium/vilanterol" OR "glycopyrronium bromide plus indacaterol" OR "glycopyrronium plus indacaterol"
Number of records	285

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