LABA/LAMA Fixed Dose Combination in Chronic Obstructive Pulmonary Disease: The Impact on Health-Related Quality of Life

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Keywords

Chronic obstructive pulmonary disease treatment · Long-acting beta 2-agonists /long-acting muscarinic antagonists fixed dose combinations · Randomized controlled trials · Health-related quality of life · Patient reported outcomes

Abstract

Background: While fixed dose combinations (FDCs) of long-acting beta 2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are increasingly tested on their efficacy in improving lung function, their effectiveness on Patient Reported Outcomes (PROs) such as Health Related Quality of Life (HRQoL) and Health Status (HS) deserve more attention. **Objectives:** To review current available evidence about the treatment effect of fixed LABA/LAMA FDCs on HRQoL. **Methods:** A systematic literature search for randomized controlled trials (RCTs) about the impact of LABA/LAMA FDCs

versus placebo, LABA or LAMA or LABA/ICS on HRQoL in Chronic obstructive pulmonary disease (COPD) patients has been performed. **Results:** Twenty-eight RCTs ($n = 32$, 165 COPD patients) investigating the impact of fixed LABA/LAMA combinations on HRQoL were included. Using the St George's Respiratory Questionnaire, 27 out of 28 trials assessed HRQoL. LABA/LAMA FDCs significantly improved HRQoL versus placebo in 9 out of 11 trials, while change when compared to other LABA or LAMA monocomponents was significantly better in 11 out of 24. In 5 out of 6 RCTs having LABA/ICS as comparators, LABA/LAMA FDC had a similar effect and only 1 showed significant improvement in HRQoL compared to LABA/ICS FDC. **Conclusion:** LABA/LAMA FDCs may be helpful in improving HRQoL, but because of the heterogeneity of performed trials, strong conclusions cannot be drawn. Moreover, due to the different molecule properties,

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treatment schedule, and device characteristics of each FDC, a generalized judgment seems inappropriate. Pragmatic trials powered to detect real-life differences in HRQoL and head-to-head comparison are needed to guide clinical practice in terms of PROs.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disorder that requires long-term, regular use of inhaled medications to control symptoms. Maintenance therapy with long-acting bronchodilators is the cornerstone of therapy for GOLD groups B, C and D [1] patients. Both long-acting beta 2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) are effective as monotherapies and have acceptable safety profiles [2, 3]. They also significantly improve Health Related Quality of Life (HRQoL) and Health Status (HS), but in many cases, this change is below the Minimally Important Difference (MID) [4]. Symptomatic, not adequately controlled patients on a single long-acting bronchodilator, may benefit from the treatment of the combined use of 2 bronchodilators (LABA/LAMA) with distinct mechanisms of action. Therefore, combining these 2 drugs into a single inhaler, LABA/LAMA fixed dose combination (FDC) is the preferred next step in COPD treatment [1]. It has been demonstrated that they provide superior bronchodilation and reduce hyperinflation compared with the individual drugs, with a lower risk of side effects than any increased dose of either single drug [1, 5–7]. Furthermore, LABAs might enhance the bronchodilator effect of LAMAs through decreasing the release of acetylcholine, thereby enhancing the bronchial smooth muscle relaxation induced by LAMA, while LAMAs might amplify the direct stimulatory effect of LABAs on smooth muscle by reducing bronchoconstriction effects of acetylcholine [8, 9]. So far, 5 LABA/LAMA FDCs are available in Europe (Glycopyrronium/Indacaterol, Umeclidinium/Vilanterol, Tiotropium/Olodaterol, Aclidinium/Formoterol, Glycopyrrolate/Formoterol). Step-up on a LABA/LAMA FDC is now an important therapeutic option, providing patients more efficient drug delivery, thus improving adherence [1]. Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment versus LABA treatment [10, 11] LABA/LAMA combination provided improvements in lung function, lower use of rescue medication, better HS, and less COPD symptoms [11–13]. Previous studies with LABA/LAMA fo-

cused primarily on the improvement in lung function, and less attention has been paid to HRQoL and HS [14–16]. However, lung function improvement does not correlate strongly with HRQoL and HS, although functional improvement of clinical parameters implies such a relationship [4]. Patient Reported Outcomes (PROs) [17], such as HRQoL and HS, represent the patient perspective and therefore a relevant outcome. Furthermore, the first head-to-head comparison trial of 2 different LABA/LAMA FDCs showed that different compounds can have a different impact on HRQoL [17]. In this light, the aim of this systematic review was to examine and summarize current available evidence about the treatment effect of fixed LABA/LAMA FDCs on HRQoL.

Methods

A comprehensive literature search for randomized controlled trials (RCTs) published in English and looking at the impact of LABA/LAMA FDCs in patients with COPD. The search was performed in PubMed, Embase, Scopus and Google Scholar through to December 2017. The terms “aclidinium,” “formoterol,” “glycopyrronium,” “glycopyrrolate,” “indacaterol,” “olodaterol,” “salmeterol,” “tiotropium,” “umeclidinium,” and “vilanterol” were searched for the FDCs, and the terms “chronic obstructive pulmonary disease” OR “COPD” were searched for the disease. Studies reporting the impact of LABA/LAMA FDCs versus LABAs or LAMAs or LABA/inhaled corticosteroid (ICS) FDCs on quality of life/health status were included in this systematic review. Two reviewers independently checked the relevant studies identified from literature searches and databases. The evaluated LABA/LAMA FDCs were as follows: Aclidinium/Formoterol (ACL/FOR) 400/12 µg twice daily, Indacaterol/Glycopyrronium (IND/GLY) 110/50 µg once daily or Indacaterol/Glycopyrrolate 27.5/15.6 µg twice daily, Glycopyrrolate/Formoterol (GLY/FOR) 8/9.6 µg (2 inhalations twice daily), Tiotropium/Olodaterol (TIO/OLO) 5/5 µg once daily, Umeclidinium/Vilanterol (UME/VIL) 62.5/25 µg once daily. For each study, the following issues were considered:

- Changes in HRQoL/HS total scores from baseline to the end of the study in each group;
- Differences in HRQoL/HS score changes between the study treatment and comparators;
- Percentage of patients who achieved the MID at the end of the study in each group;
- Change in HRQoL/HS factorial scores from baseline to the end of the study in the active group.

Results

A total of 22 articles reporting 28 RCTs evaluated the impact of fixed LABA/LAMA combinations on HRQoL by means of validated questionnaires: 4 with ACL/FOR,

Table 1. Characteristics of the tools that were used in the selected RCTs

Questionnaire	Number of items	Dimensions	Scoring	MID
St. George's Respiratory Questionnaire (SGRQ) [19, 20]	50	Symptoms Activity Impact	Total and factorial scores range from 0 to 100, with higher scores indicating more limitations	≥4 [21]
COPD Assessment TEST (CAT) [43, 44]	8	Impact	Range of CAT scores from 0–40. Higher scores denote a more severe impact of COPD on a patient's life. Scores of 0–10, 11–20, 21–30 and 31–40 represent mild, moderate, severe or very severe clinical impact [4]	≥2 [45]
EuroQoL-5D (EQ-5D) [46]	5 questions + 1 VAS	Mobility, self-care, usual activities, pain/discomfort anxiety/depression	Three possible answers for each item (1 = no problem, 2 = moderate problem, 3 = severe problem) A summary index with a maximum score of 1 (indicates full health) can be derived from the five dimensions. The VAS indicates the general health status on a continuous scale with 100 indicating the best health status	0.108 [47]

MID, minimally important difference; VAS, Visual Analogue Scale.

3 with GLY/FOR, 8 RCTs with IND/GLY, 4 with TIO/OLO, and 9 with UME/VIL. One study used the only the CAT to assess HRQoL [18], while the St George's Respiratory Questionnaire (SGRQ) [19–21] was used in 27 RCTs [22–42]. Three RCTs [23, 29, 37] also used the COPD Assessment Test (CAT) [43–45], and 2 papers [38, 39] used the EQ-5D [46, 47]. Table 1 reports the characteristics of the tools that were used in the selected RCTs. An overall population of 32,165 patients were randomized and 20,414 completed the studies. The duration of the studies ranged from 8 to 64 weeks. The characteristics of the selected trials are described in Table 2. The change in SGRQ total score from baseline to the end of the study in each arm of the studies, the difference in SGRQ total score for LABA/LAMA and comparators, the percentage of patients who achieved the MID in each arm, and the change in SGRQ factorial scores are shown in Table 3. Figure 1 reports the number of trials in which the differences between LABA/LAMA and each comparator were significant and not significant.

Here below, we report the key results of the data shown in Table 2 and 3. ACL/FOR 400/12 significantly improved SGRQ when compared to placebo in the AUGMENT [25] study and in its extension [22] in patients with moderate to severe COPD according to GOLD 2014, 40 years old or older. On the contrary, in the

ACLIFORM-COPD study, enrolling patients with moderate severe COPD according to GOLD 2010, no differences in HRQoL scores were found after 24 weeks of treatment with ACL/FOR 400/12 or placebo [24]. Improvement of SGRQ after treatment with ACL/FOR 400/12 was never found superior to those with monotherapies [22, 25] or to other ACL/FOR dosages [24]. The percentage of patients who reached the MID with ACL/FOR 400/12 treatment was significantly higher than placebo in the study of D'Urzo et al. [25] but was not higher than comparators or placebo in the other studies. In addition to SGRQ, CAT has been used in the study of Vogelmeier et al. [23] in which the MID was achieved in both ACL/FOR 400/12 and in SAL/FLU 50/500 at the end of the study, without any significant differences between groups enrolled with a CAT score ≥10.

GLY/FOR was superior to monotherapy with GLY [26, 27] and to placebo [26] but never superior to FOR in 2 studies including moderate to severe COPD patients according to ATS guidelines [26, 27]. The percentage of them who reached the MID with GLY/FOR was significantly higher compared to placebo [26] or GLY [26, 27].

IND/GLY was superior to monotherapy with GLY [32, 30], TIO [31, 32, 37], placebo [30, 31, 37] but not superior to IND [30, 31] in patients with moderate COPD according to ATS guidelines 2014 (FEV1 – 50–70% predicted) and MRC ≥1 [37] or moderate/severe COPD according to

Table 2. Studies characteristics

Notes	Study, reference, and year	Trial Number Identifier	Study duration, weeks	Randomized patients (patients who completed the study)	FDCs, µg	Comparators, µg (vs. LABA or LAMA; vs. ICS/LABA)	SGRQ	CAT	Primary endpoint
6-month AUGMENT extension study	D'Urzo et al. [22], 2017	NCT01572792	28	921 (780)	ACL/FOR 400/12	ACL/FOR 400/6, ACL 400, FOR 12, Placebo	X		No
AFFIRM	Vogelmeier et al. [23], 2016	NCT01908140	24	933 (788)	ACL/FOR 400/12	SAL/FLU 50/500	X	X	No
ACLIFORM-COPD	Singh et al. [24], 2014	NCT01462942	24	1,729 (1,526)	ACL/FOR 400/12	ACL/FOR 400/6, ACL 400, FOR 12, Placebo	X		No
AUGMENT COPD	D'Urzo et al. [25], 2014	NCT01437397	24	1,692 (1,322)	ACL/FOR 400/12	ACL/FOR 400/6, ACL 400, FOR 12, placebo	X		No
Pinnacle 1	Martinez et al. [26], 2017	NCT01854645,	24	2,013 (1,695)	GLY/FOR 18/9.6	GLY 18, FOR 9.6, TIO 18 placebo	X		No
Pinnacle 2		NCT01854658	24	1,615 (1,308)	GLY/FOR 18/9.6	GLY 18, FOR 9.6, placebo	X		No
Pinnacle 3: 28-weeks Pinnacle 1 and 2 extension study	Hanania et al. [27], 2017	NCT01970878	52	892 (778)	GLY/FOR 18/9.6	GLY 18, FOR 9.6, TIO 18	X		No
Notes	Study, reference, and year	Trial Number Identifier	Study duration, weeks	Randomized patients (patients who completed the study)	FDCs, µg	Comparators, µg (vs. LABA or LAMA; vs. ICS/LABA)	Quality of life (SGRQ)	CAT	Primary endpoint
FLAME	Wedzicha et al. [28], 2016	NCT01782326	52	3,362 (2,760)	IND/GLY 110/50	SAL/FLU 50/500	X		No
LANTERN	Zhong et al. [29], 2015	NCT01709903	26	744 (676)	IND/GLY 110/50	SAL/FLU 50/500	X	X	No
FLIGHT1 and FLIGHT2	Mahler et al. [30], 2015	NCT01727141, NCT01712516	12	1,042 (951) 1,001 (934)	IND/GLY 27.5/15.6	IND 27.5, GLY 15.6, Placebo	X		No
SHINE	Bateman et al. [31], 2013	NCT01202188	26	2,144 (,1910)	IND/GLY 110/50	GLY 50, IND 150, TIO 18, Placebo	X		No
SPARK	Wedzicha et al. [32], 2013	NCT01120691	64	2,224 (1,667)	IND/GLY 110/50	GLY 50, TIO 18	X		No
ILLUMINATE	Vogelmeier et al. [33], 2013	NCT01315249	26	523 (432)	IND/GLY 110/50	SAL/FLU 50/500	X		No
–	Molino et al. [34], 2017		52	40 (35)	IND/GLY 110/50	TIO 2.5	X		No
Notes	Study, reference, and year	Trial Number Identifier	Study duration, weeks		FDCs, µg	Comparators, µg	Quality of life (SGRQ)	CAT	Primary endpoint
OTEMTO	Buhl et al. [35], 2015	NCT01431274, NCT01431287	52 52	2,624 (2,262)	TIO/OLO 5/5	TIO/OLO 2.5/5, TIO 5, TIO 2.5, OLO 5	X		No
–	Singh et al. [36], 2015	NCT01964352, NCT02006732	12 12	814 (761) 809 (764)	TIO/OLO 5/5	TIO 5, TIO/OLO 2.5/5, Placebo	X		yes
–	Kerwin et al. [37], 2017	NCT01899742	12	494 (461)	UME/VIL 62.5/25	TIO 18	X	X	No

Table 2. (continued)

Notes	Study, reference, and year	Trial Number Identifier	Study duration, weeks		FDCs, µg	Comparators, µg	Quality of life (SGRQ)	CAT	Primary endpoint
–	Singh et al. [38], 2015	NCT01822899	12	717 (674)	UME/VIL 62.5/25	SAL/FLU 50/500	X	X (EQ-5D)	No
–	Donohue et al. [39], 2015	NCT01817764, NCT01879410	12 12	707 (634) 700 (638)	UME/VIL 62.5/25	SAL/FLU 25/250	X	X (EQ-5D)	No
–	Decramer et al., 2014 [40]	NCT01316900, NCT01316913	24	846 (696) 872 (670)	UME/VIL 62.5/25	UME/VIL 125/25, VIL 25, TIO 18	X		No
–	Maleki-Yazdi et al. [41], 2014	NCT01777334	24	905 (789)	UME/VIL 62.5/25	TIO 18	X		No
–	Donohue et al. [42], 2013	NCT01313650	24	1,536 (1,178)	UME/VIL 62.5/25	UME 62.5, VIL 25, placebo	X		No
–	Feldman et al. [18], 2017	NCT02799784	8	236 (225)	UMEC/VI (62.5/25 lg)	TIO/OLO (5/5 lg)		X	No

ACL, aclidinium bromide; FDC, fixed-dose combination; FLU, fluticasone fumarate; FOR, formoterol fumarate; GLY, glycopyrronium or glycopyrrolate; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; OLO, olodaterol; SAL, salmeterol; SGRQ, St. George's Respiratory Questionnaire; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

GOLD 2011 [30] or 2008 [31]. Of note, another study showed no significant difference compared to TIO [34]. IND/GLY was superior to SAL/FLU 50/500 in the study of Wedzicha et al. [28] enrolling COPD patients with mMRC >2 and FEV₁ 25–60% predicted but not in the studies performed by Vogelmeier et al. [33] and Zhong et al. [29] including, respectively, COPD patients stages 2–3 according GOLD 2009 and stages 2–3 GOLD 2010 and MRC ≥ 2 . The percentage of patients who reached the MID with GLY/IND was significantly higher compared to that of the placebo [30], GLY [30, 36], SAL/FLU 50/500 [28] or TIO [31]. The use of CAT as secondary outcome measure to assess HRQoL [29] showed no difference in patients treated with IND/GLY 110/50 and SAL/FLU 50/500.

TIO/OLO significantly improved SGRQ when compared to monotherapies [35, 36] and placebo [36], but no differences emerged in comparison with its different dosages [35, 36] in patients with COPD stages 2–4 according GOLD 2006. A significantly higher percentage of patients treated with TIO/OLO compared to monotherapies with LABA or LAMA [35, 36] and placebo [35, 36] achieved MID, whereas no differences emerged in comparison to TIO/OLO 2.5/5 [35, 36].

UME/VIL was never found to be superior to comparators in patients with COPD according to ATS 2004, MRC >1 , FEV₁ 20–70% predicted [37], COPD with FEV₁ – 30–70% predicted, MRC ≥ 2 , [38], and COPD

Fig. 1. HRQoL differences between LAMA/LABA versus comparators.

with FEV₁ 30–70%, MRC ≥ 2 [39, 42] and at least 1 exacerbation in the previous year [42], (both in improving SGRQ scores and in percentage of patients who achieved the MID) [37–40], except for TIO [41] and placebo [39]. The studies of Kerwin [37] and Feldman [18] evaluated HRQoL using the CAT. At the end of the study, no significant difference was found between UME/VIL and TIO [37], TIO/OLO [18] in CAT change or in the percentage of patients who achieved MID. Moreover, the assessment of HRQoL by means of EQ-5D [46], did not detect a superiority of UME/VIL compared to SAL/FLU 25/500 [38–39].

Table 3. Changes in SGRQ scores

Study, reference and year	Changes in SGRQ scores from baseline to the end of the study in each group	Differences in SGRQ score changes between the study treatment and comparators	Percentage of patients who achieved the MID at the end of the study in each group	Change in SGRQ factorial scores from baseline to the end of the study in the active group
D'Urzo et al. [22], 2017	ACL/FOR 400/12 ACL/FOR 400/6 FOR/12 ACL/400 Placebo	Data not available Data not available Data not available Data not available Data not available	-3.67 vs. placebo ($p = 0.0034$) ACL/FOR 400/12 ACL/FOR 400/6 FOR/12 ACL/400 Placebo	57.8 51.5 53.5 49.3 47.0 Data not available
Vogelmeier et al. [23], 2016	ACL/FOR 400/12 SAL/FLU 50/500	1 ($p = 0.27$) -4.7 -5.7	ACL/FOR 400/12 SAL/FLU 50/500	52.6 55.8 Data not available
Singh et al. [24], 2014	ACL/FOR 400/12 ACL/FOR 400/6 FOR/12 ACL/400 Placebo	-7.16 (mean) -8.34 (mean) -5.80 (mean) -5.58 (mean) -6.51 (mean)	-0.65 vs. placebo (ns) -1.36 vs. ACL/400 (ns) -1.59 vs. FOR/12 (ns) Data not available Data not available 53.2 ($p < 0.05$ vs. ACL/FOR 400/6)	55.3 (ns difference vs. placebo) 64.2 Data not available Data not available Data not available
D'Urzo et al. [25], 2014	ACL/FOR 400/12 ACL/FOR 400/6 FOR/12 ACL/400 Placebo	-6.57 (mean) -5.94 (mean) -6.44 (mean) -4.70 (mean) -2.21 (mean)	-4.6 vs. placebo ($p < 0.01$) ACL/FOR 400/12 ACL/FOR 400/6 FOR/12 ACL/400 Placebo	58.2 (vs. placebo $p < 0.01$) 53.6 54.5 52.4 38.7 Data not available
Martinez et al. [26], 2017 Pinnacle 1	GLY/FOR 18/9/6 GLY/18 FOR/9/6 TIO 18 Placebo	-3.3 (least squares mean) -1 (least squares mean) -2.7 (least squares mean) -2.6 (least squares mean) -0.8 (least squares mean)	-2.52 vs. placebo ($p < 0.05$) ACL/FOR 400/12 ACL/FOR 400/6 FOR/12 ACL/400 Placebo	37.1 (OR 1.49 vs. placebo, $p < 0.5$; OR 1.39 vs. GLY/18, $p < 0.05$) 29.8 34.7 38.5 28.4 Data not available
Martinez et al. [26], 2017 Pinnacle 2	GLY/FOR 18/9/6 GLY/18 FOR/9/6 Placebo	-3.0 (least squares mean) -2.2 (least squares mean) -2.3 (least squares mean) -1.2 (least squares mean)	-1.72 vs. placebo (ns) GLY/FOR 18/9/6 GLY/18 FOR/9/6 Placebo	39.4 (OR ns compared to placebo and other treatments) 34.7 33.5 33.1 Data not available
Hanania et al. [27], 2017 Pinnacle 3	GLY/FOR 18/9/6 GLY/18 FOR/9/6 TIO 18	Data not available Data not available Data not available Data not available	-1.39 (least squares mean) vs. GLY/18 ($p = 0.0066$) -0.90 (least squares mean) vs. FOR/9/6 ($p = 0.07$) -1.68 (least squares mean) vs. TIO 18 ($p = 0.49$) GLY/18 FOR/9/6 TIO 18	41.3 (OR 1.27 vs. GLY, $p = 0.0140$) 35.6 37.2 43.8 Data not available
Wedzicha et al. [28], 2016	IND/GLY 110/50 SAL/FLU 50/500	-3.1 (least squares mean) -1.9 (least squares mean)	-1.3 (least squares mean) ($p = 0.03$) IND/GLY 110/50 SAL/FLU 50/500	49.2% (OR 1.3, $p < 0.001$) 43.7% Data not available

Table 3. (continued)

Study, reference and year	Changes in SGRQ scores from baseline to the end of the study in each group	Differences in SGRQ score changes between the study treatment and comparators	Percentage of patients who achieved the MID at the end of the study in each group	Change in SGRQ factorial scores from baseline to the end of the study in the active group
Zhong [29], 2015	IND/GLY 110/50 SAL/FLU 50/500 -7.51 (mean) -6.38 (mean)	0.69 (least squares mean; ns)	IND/GLY 110/50 SAL/FLU 50/500 Data not available. No significant difference between the 2 groups has been reported	
Mahler et al. [30], 2015 FLIGHT 1	IND/GLY 27.5/15 Data not available	-1.9 (least squares mean) vs. IND 27.5 (ns) -1.7 (least squares mean) vs. GLY 15.6 ($p < 0.05$) -3.8 (least squares mean) vs. placebo ($p < 0.001$)	IND/GLY 27.5/15 Data not available OR 1.53 vs. IND 27.5 ($p < 0.05$) OR 1.60 vs. GLY 15.6 ($p < 0.05$) OR 2.20 vs. placebo ($p < 0.05$)	Data not available
	IND 27.5, GLY 15.6 Placebo Data not available Data not available Data not available		IND 27.5, GLY 15.6 Placebo Data not available	
Mahler et al. [30], 2015 FLIGHT 2	IND/GLY 27.5/15 Data not available	-1.5 (least squares mean) vs. IND 27.5 (ns) -1.4 (least squares mean) vs. GLY 15.6 (ns) -36.4 (least squares mean) vs. placebo ($p < 0.001$)	IND/GLY 27.5/15 OR 1.13 vs. IND 27.5 (ns) OR 1.40 vs. GLY 15.6 (ns) OR 2.85 vs. placebo ($p < 0.001$)	Data not available
	IND 27.5, GLY 15.6 Placebo Data not available Data not available Data not available		IND 27.5, GLY 15.6 Placebo	
Bateman et al. [31], 2013	IND/GLY 110/50 GLY 50 -8.91 (mean) IND 150 TIO 18 -8.59 (mean) -7.69 (mean) -6.39 (mean)	-3.01 (least squares mean) vs. placebo ($p = 0.002$) -2.13 (least squares mean) vs. TIO 18 ($p = 0.009$)	IND/GLY 110/50 GLY 50 63.7 (significant difference compared to TIO 18 ($p = 0.047$)) 63 IND 150 TIO 18 60.5 56.4 56.6	Not available
Wedzicha et al. [32], 2013	IND/GLY 110/50 GLY 50 TIO 18 Data not available Data not available Data not available	Notes: significant lower scores (= better HRQoL) have been shown in IND/GLY 110/50 vs. GLY 50 ($p = 0.0066$) and vs. TIO 18 ($p = 0.00037$)	Data not available ORs associated with % of patients achieving the MID in SGRQ total score: IND/GLY 110/50 vs. GLY 50: 1.28 ($p = 0.055$) IND/GLY 110/50 vs. TIO 18: 1.29 ($p = 0.051$)	SGRQ component scores (symptoms, activity, impacts) during study treatment. At the end of the study, differences between IND/GLY 110/50 and GKY 50, and between IND/GLY 110/50 and TIO 18 were not significant (least squares means)

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Table 3. (continued)

Study, reference and year	Changes in SGRQ scores from baseline to the end of the study in each group	Differences in SGRQ score changes between the study treatment and comparators	Percentage of patients who achieved the MID at the end of the study in each group	Change in SGRQ factorial scores from baseline to the end of the study in the active group
Singh et al. [38], 2015	UME/VIL 62.5/25 SAL/FLU 50/500	-5.1 (least squares means) -5.64 (least squares means) Differences between the 2 groups: ns ($p = 0.545$)	UME/VIL 62.5/25 SAL/FLU 50/500	Data not available
Donohue et al. [39], 2015 DB2114930	UME/VIL 62.5/25 SAL/FLU 25/250	-6.33 (least squares means) -6.79 (least squares means) Differences between the 2 groups: ns ($p = 0.616$)	UME/VIL 62.5/25 SAL/FLU 25/250	Data not available
Donohue et al. [39], 2015 DB2114951	UME/VIL 62.5/25 SAL/FLU 25/250	-7.23 (least squares means) -5.67 (least squares means) Differences between the 2 groups: ns ($p = 0.143$)	UME/VIL 62.5/25 SAL/FLU 25/250	Data not available
Decramer et al. [40], 2014 NCT01316900	UME/VIL 62.5/25 UME/VIL 125/25 VIL 25 TIO18	-9.03 (least squares means) -6.87 (least squares means) -8.29 (least squares means) -7.62 (least squares means) No significant differences among treatment groups	UME/VIL 62.5/25 UME/VIL 125/25 VIL 25 TIO18	Data not available
Decramer et al. [40], 2014 NCT01316913	UME/VIL 62.5/25 UME/VIL 125/25 VIL 25 TIO18	-10.52 (least squares means) -9.95 (least squares means) -8.49 (least squares means) -9.78 (least squares means) No significant differences among treatment groups	UME/VIL 62.5/25 UME/VIL 125/25 VIL 25 TIO18	Data not available
Maleki-Yazdi et al. [41], 2014	UME/VIL 62.5/25 TIO18	-7.27 (least squares means) -5.17 (least squares means) Differences between the 2 groups: $p = 0.006$	UME/VIL 62.5/25 TIO18	Symptoms domain: -15.18 Activity domain: -6.49 Impact domain: -4.55 (significance non reported) Symptoms domain: -11.48 Activity domain: -4.37 Impact domain: -2.57 (significance non reported)
Donohue et al. [42], 2013	UME/VIL 62.5/25 UME 62.5 VIL 25 Placebo	-8.07 (mean) -7.25 (mean) -7.75 (mean) -2.56 (mean) Difference vs. placebo ($p < 0.001$)	UME/VIL 62.5/25 UME 62.5 VIL 25 Placebo	49 OR vs. placebo: 2 ($p < 0.001$) 44 48 34 Data not available

Discussion

In this review, we analyzed 22 articles, reporting 28 RCTs. A consistent improvement in HRQoL with LABA/LAMA FDC when compared to placebo has been shown, while the average change when compared to LAMA or LABA monocomponents was significantly better in 11 out of 24. Interestingly, of 6 RCTs having LABA/ICS as comparators, only 1 (IND/GLY) showed a significant improvement in HRQoL. Three out of four studies with ACL/FOR used placebo as one of the comparators with 1/3 showing no significant difference, and the remaining showing significantly better results with the difference reaching MID [25]. Two (out of 3) RCTs with GLY/FOR compared the combination with placebo showing a significantly better improvement in one (Pinnacle 1) with a difference not reaching MID [26] and no significant difference in the other (Pinnacle 2) [26]. For the IND/GLY combination 3 papers (out of 8) reported results compared to placebo arm and all of them showed a significantly better SGRQ scores for the combination. However, the average difference did not reach MID in any of the 3 studies. For TIO/OLO, 2 (out of 3) reported significantly better SGRQ scores, reaching MID in both cases. For the UME/VIL combination, out of 9 RCTs, only one had a placebo arm, reporting a significantly better improvement (reaching MID) for the combination. Only 6 studies used other HRQoL questionnaires (EQ-5D and/or CAT) and no one detected significant differences. Reported studies show significant methodological heterogeneity, in terms of duration, number of treatment arms, and comparators. Although in all but one studies SGRQ was used as the measure of HRQoL, a significant heterogeneity exists in reporting the outcomes for HRQoL measures, with only 2 papers reporting SGRQ component analysis. In 9 out of 12 trials, the improvement from baseline until the end of trial exceeded the MID. Several problems were found in interpreting the published results. In 7 articles, data were not available in the source materials and only the % of patients exceeding MID, or ORs for exceeding MID were published, although these data support the previous conclusion. This could be the consequence of HRQoL not being the primary outcome in these studies, but even in the single study where HRQoL was the primary outcome, data about the change in SGRQ from baseline until the end of trial were not available [36]. Although a weak association ($R^2 = 0.21$) exists between the level of bronchodilation and HRQoL/HS outcomes [17], it could be expected that less hyperinflation, lower level of symptoms and dyspnea, comparable incidence of adverse events, and dosing from

a single device could provide such a consistent effect for different LABA/LAMA FDCs. Furthermore, there is a significant heterogeneity regarding the duration of trials, ranging from 8 to 64 weeks, although changes in HRQoL after initial improvement with long-acting bronchodilators show a stable effect. Based on the published RCTs, it is not possible to compare the results of different LABA/LAMA combinations. The only head-to-head comparison between UME/VIL and TIO/OLO fixed combinations showed a significantly better improvement in HRQoL (measured by CAT) for UME/VIL after 4 weeks but not after 8 weeks, suggesting possible marginal difference in the effect on the HRQoL with the stabilization of the effect after 8 weeks of treatment [18]. Although data when analyzed together and despite the significant heterogeneity of the studies do point in the same direction, toward improvement in HRQoL outcomes with LABA/LAMA FDCs versus comparators, there are some interesting differences that should be mentioned. These differences could point into some clinical aspects that could be relevant for some patient groups (phenotypes) and could lead the treatment decisions. This is especially relevant in the light of discordant results for different facets (lung function, exacerbations, PROs) of the disease [17]. The first one of clinical interest is the finding that when LAMA was the comparator to LABA/LAMA FDCs in 10 out of 19 RCTs the combination showed a significant improvement in HRQoL, while when LABA was a comparator the odds were the opposite. Only in 1 out of 13 RCTs, the combination showed a significant improvement in HRQoL. The same odds were seen with LABA/ICS as a comparator. We can only speculate that the second finding could be the consequence of LABA being the part of the combination or that it was associated also with ICS. However, these findings could point out that if the primary goal of treatment change in a patient with COPD is to improve HRQoL change from LABA or LABA/ICS to LABA/LAMA FDC would probably not be beneficial. This speculation certainly deserves well-designed RCTs. Other recently published reviews on the efficacy of LABA/LAMA FDCs [15, 16, 48, 49] were not specifically focused on HRQoL and HS but also analyzed these outcomes. The results of our review and the other recent reviews [15, 48] show that studies powered to detect differences in HRQoL/HS as primary outcome are needed. More head-to-head comparisons of LABA/LAMA products would improve clinical relevant insights as well. Additionally, current data depend on the quality of the used instruments to assess PROs. Commonly used instruments, like SGRQ, CAT, or Transition Dyspnea Index, lack certain domains of great

importance to patients with COPD, such as mobility, fatigue, anxiety, depression, social functioning, and sleep. We pointed out this aspect in a previous review about HRQoL/HS outcomes with long-acting bronchodilators in COPD, but the goal still needs to be reached [4]. This issue could be solved by the usage of a standardized set of tools to assess also these important PROs domains. Furthermore, to allow proper meta-analyses and give researchers the right opportunity to pull up and analyze the data and reduce heterogeneity, a standardized set and format of data should be proposed and agreed upon (at least for the supplementary set of data that is published online). All this will give us reassurance that we will have

enough high-quality scientific data to better assess and understand outcomes that are of primary concern for patients.

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Disclosure Statement

The authors report no conflicts of interest.

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