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Double or Triple Therapy in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Although the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy recommends triple therapy involving long-acting muscarinic antagonists (LAMAs), long-acting β_2-agonists (LABAs) and inhaled corticosteroids (ICS) only for further advanced patients, particularly for those at a high risk for exacerbation (GOLD D), triple therapy is widely prescribed in real-life management of chronic obstructive pulmonary disease (COPD), even in patients with mild or moderate COPD severity, likely because physicians prefer to prescribe a full treatment to ensure the best care to their patients. While the available clinical evidence on triple therapy has greatly increased in recent years, there is still no solid evidence to indicate whether and when addition of an ICS to the LABA/LAMA combination provides additional clinical value. Therefore, a strong recommendation can still not be generated but the results of four recent pivotal triple therapy studies support the possibility that this treatment option should be considered also for GOLD B patients. **(BRN Rev. 2018;4(4):287-303)**

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INTRODUCTION

The Global Initiative for Obstructive Lung Disease (GOLD) strategy recommends treating patients at lower risk of exacerbations (group B) with a long-acting bronchodilator, escalating to dual bronchodilation if symptoms persist, but dual bronchodilation is the first-choice initial treatment for patients of GOLD D, i.e. patients with COPD assessment test (CAT) ≥ 10 units plus ≥ 2 moderate exacerbations and/or ≥ 1 severe exacerbation in the previous year[1]. Actually, all long-acting muscarinic receptor antagonist (LAMA)/long-acting β_2-agonist (LABA) combinations are always more effective than the LAMA or LABA alone in terms of improvement in trough forced expiratory volume in one second (FEV_1), Transition Dyspnoea Index (TDI) and St. George's Respiratory Questionnaire (SGRQ) scores[2]. There is also some evidence that LAMA/LABA combinations result in fewer acute exacerbations of COPD (AECOPDs) and pneumonia, and larger improvement in FEV_1 than LABA/inhaled corticosteroid (ICS) combinations[3].

The GOLD strategy also recommends an escalation to a triple therapy, which adds ICS to dual-bronchodilator therapy or a LAMA to existing LABA/ICS, only after having maximised bronchodilator treatment with LAMA/LABA regimens and be limited to patients with more symptomatic GOLD D, because there is no conclusive evidence on the superiority of triple therapy over other therapeutic options, particularly in patients at low risk of exacerbations[1].

Nevertheless, triple therapy is widely prescribed in real-life management of COPD, even in patients with mild or moderate COPD severity, as demonstrated by retrospective observational studies in the United States[4] (US) and United Kingdom (UK)[5,6].

Several independent factors, such as being older, having undergone pulmonary or spirometry evaluation or having been placed on LABA/ICS fixed-dose combination (FDC) therapy at diagnosis, the presence of comorbid asthma and the possibility of a better control of symptoms can predict prescriptions of triple therapy in clinical practice regardless of the severity of airflow limitation[7,8]. However, there is also real-world evidence that patients with COPD are more likely to initiate open-triple therapy following initiation with LAMA monotherapy, compared with LABA/ICS therapy[9]. It has been speculated that, at least in Sweden, the widespread use of triple therapy is due to the chronic characteristics of the disease, with a documented high proportion of persistent breathlessness in spite of maximum optimised treatment[10]. Other potential explanations may be increased availability of inhaled therapy in different devices and combinations, overtreatment due to heavy marketing from pharmaceutical companies, and increased awareness and implementation of GOLD ABCD recommendations.

In any case, the use of triple therapy is not only a practice of general practitioners; also pulmonologists often prefer to use triple therapy, even in patients who are not suffering from severe COPD[11]. The Adelphi Respiratory Disease Specific Programme documented that considerable proportions of patients in the low risk groups (GOLD A and B) were currently receiving LABA/ICS, either alone or in combination with a LAMA[12]. Actually, the percentage of 3813 patients with COPD recruited

in the survey by an equal number of primary care physicians and pulmonologists working in the US and five European countries (France, Germany, Italy, Spain and the UK) who were receiving LABA/ICS + LAMA or LABA + ICS + LAMA, was 11.8% in patients with GOLD A and 23.8% in those with GOLD B. This prescriptive behaviour is likely due to the confidence that physicians have in starting a full treatment to ensure the best care to their patients[13].

TRIPLE THERAPY ADMINISTERED USING MULTIPLE INHALERS

The confidence of physicians that triple therapy provides the best care to their patients should be based on personal clinical experience but, above all, on scientific evidence. Meta-analyses of published data (Table 1) or observational studies are useful to help in understanding the real role of triple therapy in COPD.

In 2011, a Cochrane review[14] was able to examine only three studies, two lasting three months and the third one year[17]. Heterogeneity and wide confidence intervals did not draw any conclusions from the outcomes except for an improvement in the health-related quality of life (HRQoL) scores and lung function for triple therapy versus tiotropium alone. However, the Canadian Optimal Therapy of COPD (OPTIMAL) study showed that the free LAMA + LABA/ICS combination, compared with LAMA alone or LABA/ICS, caused the greatest reduction in hospitalisations due to AECOPD[17].

A second Cochrane review published in 2016[18] added other three studies, one lasting three months[19] and the other two six months[20,21]. This review showed an evidence of moderate quality that combining tiotropium + LABA/ICS compared with tiotropium monotherapy was able to decrease hospital admission. Lung function was slightly, but significantly, better in the combined therapy group, but the improvement in HRQoL with combined therapy was of low-quality evidence. Evidence was also insufficient to support the benefit of tiotropium + LABA/ICS for mortality and exacerbations (moderate- and low-quality evidence, respectively).

The Italian observational study Long-term outcomes and adverse events of therapy with inhaled corticosteroids, long-acting β_2-agonists and anticholinergic drugs in hospitalised patients with COPD (OUTPUL) documented that tiotropium + LABA/ICS did not reduce AECOPDs within a one-year follow-up period compared with LABA/ICS alone among patients discharged after a COPD exacerbation, although it was more effective in preventing moderate exacerbations compared to LABA/ICS in frequent exacerbators[22]. Also a retrospective cohort study using a National Health Service (NHS) database of UK patients with COPD supported the signal indicating that tiotropium + LABA/ICS may confer benefits in reducing all-cause mortality, exacerbations requiring oral glucocorticoids (–29%), and hospital admissions (–15%) compared with LABA/ICS[23].

The only information derived from the Cochrane reviews and pooled analysis of the UK primary data was the possible advantage of adding tiotropium in patients on regular treatment with LABA/ICS. However, a post hoc analysis of pooled data from four 12-week

Table 1. Trials with triple therapy administered using multiple inhalers

Study	Patients	Study design	Therapy	Key findings
Cazzola et al.[15]	90 patients with well-controlled COPD	Randomised, double-blind, double-dummy, parallel-group trial over 12 weeks	SFC 50/500 µg twice daily TIO 18 µg once daily SFC 50/500 µg twice daily + TIO 18 µg once daily	Significant ($p < 0.05$) improvements in trough FEV_1 above baseline (140 mL in the SFC group, 141 mL in the TIO group, and 186 mL in SFC + TIO group Greater improvements in dyspnoea with TIO and SFC+TIO (VAS scores decreased by –2.31, and –2.34, respectively), than SFC (–2.00 but differences between the three treatments statistically not significant ($p > 0.05$)
Welte et al.[16]	660 patients with severe or very severe COPD and a history of exacerbations requiring systemic steroids and/or antibiotics	Randomised, double-blind, parallel-group, multi-centre trial over 12 weeks	TIO 18 µg once daily + FF/BUD 9/320 µg 1 twice daily TIO 18 µg once daily	Triple therapy significantly improved pre-dose FEV_1 compared with TIO (6% increase [65 mL]; $p < 0.001$) Triple therapy significantly improved post-dose FEV_1 (11% increase [123 and 131 mL at 5 and 60 min post-dose, respectively]; both $p < 0.001$) and reduced exacerbation rate versus TIO (rate ratio, 0.38; 95% CI: 0.25–0.57; $p < 0.001$) Triple therapy significantly improved SGRQ total score (mean difference: –2.3 units; $p = 0.023$) and symptoms (as measured by GCSQ [mean difference in scores for chest tightness and breathlessness ranging from –0.104 to –0.185 at 5 min and 15 min post-dose; all $p < 0.05$] and COPD symptoms rating scale [mean difference in scores ranging from –0.142 to –0.161 for breathlessness, chest tightness, night-time awakenings and cough; all $p < 0.001$]) versus TIO
Aaron et al.[17]	449 patients with a clinical history of moderate or severe COPD	Randomised, double-blind, placebo-controlled, parallel-group trial over 52 weeks	TIO 18 µg once daily + SFC 50/500 µg twice daily TIO 18 µg once daily + salmeterol 50 µg twice daily TIO 18 µg once daily	No significant difference in the rate of patients who experienced ≥ 1 COPD exacerbation (60.0%, 64.8% and 62.8% of patients in SFC + TIO, TIO + SAL and TIO groups, respectively) No significant difference in TDI total score (mean scores 1.84, 1.40 and 1.78 units, respectively), rate of exacerbations (mean exacerbations per patient year 1.37, 1.75 and 1.61, respectively) or time-to-first exacerbation (217, 128 and 130 days, respectively) Triple therapy, compared with TIO, significantly improved pre-bronchodilator FEV_1 (increase of 86 mL versus 27 mL; $p = 0.049$) and SGRQ total score (change in score –8.6 units vs. –4.5 units; $p = 0.01$)
Hoshino et al.[19]	36 patients	Open, randomised, parallel-group study over 12 weeks	SFC 50/250 µg twice daily + TIO 18 µg once daily TIO 18 µg once daily	Triple therapy significantly decreased airway wall area corrected for body surface area; percentage wall area and absolute wall thickness ($p < 0.05$; $p < 0.01$ and $p < 0.01$, respectively) and increased luminal area corrected for body surface area ($p < 0.01$) Triple therapy significantly improved SGRQ total score versus TIO
Hanania et al.[20]	342 patients with a clinical history of moderate-to-severe COPD	Randomised, double-blind, parallel-group, multi-centre study over 24 weeks	SFC 50/250 µg twice daily + TIO 18 µg once daily TIO 18 µg once daily	Triple therapy significantly improved pre-dose FEV_1 compared with TIO (LSM difference: 115 mL; $p < 0.001$) Triple therapy significantly improved rescue medication use compared with TIO (LSM difference: –0.6 [SE 0.24]; $p = 0.01$) There were no significant differences in health status (LSM differences in CRQ-SAS domain scores ranging from 0.02 to 0.2) or exacerbation rate (0.14 versus 0.17 for SFC + TIO and TIO, respectively
Jung et al.[21]	479 patients with COPD	Randomised, open-label, multi-centre, two-arm, parallel study over 24 weeks	SFC 50/250 µg twice daily + TIO 18 µg once daily TIO 18 µg once daily	Triple therapy significantly improved pre-bronchodilator FEV_1 versus TIO (90 mL versus 38 mL; $p = 0.005$) Triple therapy significantly improved SGRQ-C scores versus TIO (mean change in score: –6.6 units versus –1.5 units; $p = 0.001$)
Vincken et al.[26]	280 patients	Multicentre, double-blind, parallel group study over 12 weeks	GB 50 µg + IND 150 µg + ICS IND 150 µg + ICS	Compared to free combination of IND + ICS, free combination of GB + IND + ICS significantly improved trough FEV_1 (MTD 64 mL; $p = 0.021$), FEV_1 $AUC_{0\text{-}4\,h}$ (MTD 118 mL; $p < 0.001$) and dyspnoea in terms of TDI score (MTD 0.7; $p = 0.041$)

$AUC_{0\text{-}4h}$: area under the curve from 0 to 4h; BUD: budesonide; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CRQ-SAS: Chronic Respiratory Disease Questionnaire-Self-Administered Standardised; FEV_1: forced expiratory volume in one second; FF: formoterol fumarate; GB: glycopyrronium bromide; GCSQ: global chest symptoms questionnaire; ICS: inhaled corticosteroid; IND: indacaterol; LSM: least squares mean; MTD: mean treatment difference; SAL: salmeterol; SE: standard error; SFC: salmeterol/fluticasone propionate combination; SGRQ: St George's Respiratory Questionnaire; SGRQ-C: St George's Respiratory Questionnaire for COPD patients; TDI: Transition Dispnoea Index; TIO: tiotropium; VAS: visual analogue scale.

randomised controlled trials (RCTs) confirmed that in GOLD D patients, adding umeclidinium (UMEC) 62.5 µg to LABA/ICS (vilanterol [VI]/fluticasone furoate [FF] 25/100 µg or salmeterol/fluticasone propionate 50/250 µg) resulted in clinically important (> 100 mL) improvements in lung function, reduced rescue medication use, reduced the risk of moderate-to-severe AECOPDs, and improved the SGRQ total score compared with placebo + LABA/ICS[24]. When analysing GOLD B and GOLB D patients, improvements in lung function with UMEC 62.5 µg + LABA/ICS versus placebo + LABA/ICS were numerically greater in patients with better lung function at study entry, i.e. patients with GOLD B versus those with GOLD D.

The introduction of double bronchodilation has offered an alternative: LAMA/LABA FDCs to combine with an ICS in another inhaler. Although a network meta-analysis of 23 RCTs reported that indacaterol (IND) + tiotropium is expected to be comparable to triple therapies when focused on FEV_1 after 12-week treatment[25], a post hoc analysis from the GLycopyrronium bromide in COPD airWays clinical study 6 (GLOW6) study showed that over 12 weeks, the free triple combination with glycopyrronium bromide (GB) + IND + ICS induced significantly better improvements in lung function and dyspnoea compared to the free double combination (IND + ICS) in symptomatic patients with moderate-to-severe COPD[26].

This is interesting information for the treatment of patients with COPD, to whom we must guarantee mainly appropriate administration of the bronchodilators, with a more controversial role for ICS. For this reason, as rightly pointed out by Lopez-Campos et al.[27], due to the lack of specific clinical trials, it seems more reasonable to use the combination of LAMA/LABA + ICS in COPD than to add a LAMA to LABA/ICS. Actually, a Scottish real-life retrospective analysis showed that in patients exposed to ICS, concomitant use of LAMA alone as dual therapy or in combination with LABA as triple therapy was associated with reductions in all-cause mortality, while concomitant use of LABA without LAMA conferred no reduction[28]. Moreover, only triple therapy was found to confer benefits on cardiovascular mortality. On the other side, in the Withdrawal of inhaled glucocorticoids and exacerbations of COPD (WISDOM) study, although the withdrawal of ICS induced a trend toward an increased risk for severe exacerbations, this did not reach significant levels[29].

In 2015, a systematic review and a meta-analysis that compared triple therapy versus dual bronchodilator therapy[30] could include only two studies: the OPTIMAL trial[17], and the WISDOM study[29]. There was no difference in all-cause mortality, all-cause admission, exacerbation, adverse effect, and serious adverse effect between the dual-bronchodilator and the triple therapy arms. The triple therapy was slightly associated with favourable impacts on both the FEV_1 and the SGRQ total score in both studies, although the observed difference did not reach the minimum clinically important difference (MCID) in either (i.e. 50 mL for FEV_1 and four points for the total SGRQ score).

PHARMACOLOGICAL RATIONALE FOR TRIPLE INHALED THERAPY

The favourable pharmacological interaction between inhaled β_2-agonists and corticosteroids

in COPD is a concept that has been developed for a long time[31]. We documented that combining beclometasone dipropionate (BDP) with formoterol furoate (FF) at 100:6 concentration-ratio not only improved the effectiveness of FF, but also elicited a synergistic bronchorelaxant effect in both medium and small airways[32]. Multiple mechanisms could account for the clinical efficacy of LABA/ICS combination therapies[33]. In particular, glucocorticoids increase the numbers of β_2-adrenoceptors and β_2-agonists induce direct bronchodilation, and act on glucocorticoid receptors to increase the anti-inflammatory effects of glucocorticoids[33]. The exact effect of LABAs on ICS is uncertain, but a synergistic interaction may likely exist[31]. While the molecular basis of synergy remains unclear, it is probable that mechanistic interpretations must accommodate gene-specific regulation[34]. In any case, we strongly believe that mechanisms affecting airway obstruction, inflammation, structural changes, and mucociliary dysfunction could all together account for the clinical efficacy of LABA/ICS combination therapies[31].

Our group has repeatedly described the strong pharmacological rationale that supports the use of double bronchodilation[35,36], and has also widely documented with translational studies that the combination of a LABA with a LAMA leads to a synergistic release of the airway smooth muscle (ASM)[37,38].

We have also demonstrated that the acute administration of BDP and GB induces a significant relaxation of passively sensitised ASM pre-contracted with histamine, by causing submaximal/maximal inhibition of the contractile tone in both medium bronchi and bronchioles[39]. However, the LAMA/ICS combination synergistically enhanced only the relaxation of passively sensitised medium and small bronchi. These pre-clinical findings may suggest that there is no advantage in combining a LAMA and an ICS in COPD patients.

The evidence of a true pharmacological advantage deriving from the combination of LAMA + LABA + ICS is still absent, but it could be supposed that the possible synergism of action with the LABA + ICS might be added to the well-documented synergistic effect of the LAMA + LABA combinations. Unfortunately, so far there is no study evaluating the in vitro pharmacological interactions of triple therapy.

TRIPLE THERAPIES UNDER DEVELOPMENT

Although the reviewed evidence is not solid enough to support the regular use of triple therapy in COPD, it is likely that the usual prescriptive behaviour of physicians that favours the triple therapy even in those patients with COPD whose airflow limitation is not severe is the main reason why the pharmaceutical industry has interest in developing LAMA/LABA/ICS FDC.

Triohale (tiotropium 18 µg + FF 12 µg + ciclesonide 400 µg) was the first triple combination to enter the market, at least in India. A 24-week, open-label, prospective, non-comparative, multicentre, real-world study, which enrolled patients with COPD requiring triple therapy as assessed by physician, documented that lung function and symptoms significantly

Table 2. Pharmacological characteristics of long-acting β_2 (LABAs) and long-acting muscarinic antagonists (LAMAs) versus inhaled corticosteroids (ICS) included in triple combinations under development[36,65]

LABAs						
	β_2-AR				β_1-AR	β_2/β_1 ratio
	pKi	IA (% isoprenaline)	Onset of action ($t_{1/2}$, min)	Duration of action (h)		
Formoterol	8.06	95.0	5.9	0.93	6.10	130
Vilanterol	9.42	70.0	3.45	NA	NA	2400

LAMAs									
	M_3 mAChR				M_1 mAChR		M_2 mAChR		M^3/M^2 ratio
	pKi	K_{off} (h^{-1})	Onset of action ($t_{1/2}$, min)	Duration of action (h)	pKi	K_{off} (h^{-1})	pKi	K_{off} (h^{-1})	
Glycopyrronium	9.28	0.11	8.72	6.1	9.77	NA	9.09	1.84	16.5
Umeclidinium	9.80	0.53	9.0	1.37	9.80	NA	9.82	4.44	8.7

ICS							
	Relative glucocorticoid receptor binding affinity*	Lipophilicity (log P**)	Aqueous solubility (μg ml^{-1})	PPB (%)	Vss l	CL (h^{-1})	F (%)
Beclometasone dipropionate	53 (1345)	4.59 (3.27)	0.13 (15.5)	95.9	424	120	62^{CFC} 82^{HFA} 41^{oral}
Budesonide	935	2.32	16	91.4	180	84	39^{DPI} 11^{oral}
Fluticasone furoate	2989	4.17	0.03	99.7	608	65	15^{DPI} 1^{oral}

*Glucocorticoid receptor binding affinity is relative to dexamethasone where dexamethasone affinity = 100.
**Log P values are defined as the $\log_{10}$ of the octanol/water partition coefficient.
β_2-AR: β_2-adrenergic receptors; CFC: chlorofluorocarbon; CL: plasma clearance; DPI: dry powder inhaler; F: absolute bioavailability determined in healthy subjects; HFA: hydrofluoroalkane; IA: intrinsic activity; K_{off}: dissociation rate; NA: not available in human tissue; M_3 mAChR: M_3 muscarinic acetylcholine receptor; pKi: the negative logarithm to base 10 of the equilibrium dissociation constant of a ligand determined in inhibition studies; PPB: plasma protein binding; $t_{1/2}$: residence half-life; Vss: volume of distribution at steady state.

improved in patients with COPD, independent of their smoking history[40].

There is much more information on three other triple combinations that are still under development. Detailed pharmacological characteristics of LAMAs, LABAs and ICS included in these FDCs are reported in table 2. Table 3 describes the main trials already published.

a. Glycopyrronium bromide/formoterol fumarate/beclometasone dipropionate combination

A GB/FF/BDP FDC is under clinical development as a hydrofluoroalkane (HFA) solution delivered via a pressurised metered dose inhaler (pMDI) with a nominal dose per actuation of 12.5, 6, and 100 μg of GB, FF, and BDP,

Table 3. Trials with triple therapy administered in a single inhaler

Study	Patients	Study design	Therapy	Key findings
Glycopyrronium bromide/formoterol fumarate/beclometasone dipropionate				
Singh et al. (TRIDENT)[41]	178 patients with moderate-to-severe COPD	Multicentre, double-blind, randomised, active- and placebo-controlled, four-way crossover study over seven days	GB 12.5, 25 or 50 µg twice daily added to regular FF/BDP 12/200 µg twice daily	Mean FEV_1 $AUC_{0–12}$ significantly higher ($p < 0.001$) for all GB doses plus FF/BDP compared to FF/BDP alone, with the difference for the 25 and 50 µg doses being clinically relevant (≥ 100 mL)
Singh et al. (TRILOGY)[42]	1368 patients with a post-bronchodilator $FEV_1 < 50\%$, ≥ 1 moderate-to-severe COPD exacerbation in the previous 12 months, CAT total score ≥ 10, and a BDI focal score ≤ 10	Multicentre, randomised, parallel group, double blind, active-controlled study over 52 weeks	GB/FF/BDP 25/12/200 µg twice daily FF/BDP 12/200 µg twice daily	Triple therapy significantly improved pre-dose FEV_1 (adjusted mean difference: 81 mL; $p < 0.001$) and 2-hour post-dose FEV_1 (adjusted mean difference: 117 mL; $p < 0.001$) compared with FF/BDP Triple therapy did not significantly improve TDI total score compared with FF/BDP (mean treatment difference: 0.21 units) Triple therapy significantly improved SGRQ total score at Weeks 4, 12 and 52 versus FF/BDP (mean treatment difference at week 52: –1.69 units; $p = 0.029$) Triple therapy significantly reduced the rate of moderate-to-severe exacerbations versus FF/BDP (rate ratio 0.77; 95% CI: 0.65 to 0.92; $p = 0.005$) In patients with > 1 exacerbation, triple therapy significantly reduced the rate of moderate-to-severe exacerbation versus FF/BDP (rate ratio 0.67; 95% CI: 0.48 to 0.94; $p = 0.019$)
Vestbo et al. (TRINITY)[43]	2691 patients with a post-bronchodilator $FEV_1 < 50\%$, ≥ 1 moderate-to-severe COPD exacerbation in the previous 12 months, CAT total score ≥ 10	Multicentre, randomised, parallel group, double-blind, double-dummy, active-controlled trial over 52 weeks	GB/FF/BDP 25/12/200 µg twice daily TIO 18 µg once daily FF/BDP 12/200 µg twice daily + TIO 18 µg once daily	GB/FF/BDP significantly reduced the rate of moderate or severe exacerbations compared with TIO (rate ratio 0.80; 95% CI: 0.69 to 0.92; $p = 0.0025$) GB/FF/BDP significantly improved pre-dose FEV_1 compared with TIO (mean difference 61 mL; $p < 0.001$) GB/FF/BDP was non-inferior to FF/BDP + TIO in terms of lung function (adjusted mean difference –3 mL) GB/FF/BDP significantly improved SGRQ total score compared with TIO at all time-points except week 26 GB/FF/BDP and FF/BDP + TIO resulted in similar rates of moderate or severe exacerbations (rate ratio 1.01; 95% CI 0.85 to 1.21) and provided a similar mean change from baseline in SGRQ total score at all time-points except weeks 26 and 52
Papi et al. (TRIBUTE)[44]	1532 patients with a post-bronchodilator $FEV_1 < 50\%$, ≥ 1 moderate-to-severe COPD exacerbation in the previous 12 months, CAT total score ≥ 10 and, who had used LABA/ICS, LAMA/ICS, LAMA/LABA, or LAMA monotherapy, but not triple therapy, for at least 2 months before screening	Multicentre, randomised, parallel-group, double-blind, double-dummy study over 52 weeks	GB/FF/BDP 25/12/200 µg twice daily GB/IND 43/85 µg once daily	Moderate-to-severe exacerbation rates were 0.50 per patient per year (95% CI 0.45 to 0.57) for GB/FF/BDP and 0.59 per patient per year (95% CI 0.53 to 0.67) for GB/IND GB/FF/BDP significantly reduced the rate of moderate or severe exacerbations compared with GB/IND (0.848 (95% CI 0.723 to 0.995; $p = 0.043$) The time to first moderate or severe exacerbation and the time to the first severe exacerbation were similar between the two treatment groups (hazard ratio 0.901, 95% CI 0.763 to 1.064, $p = 0.219$; and 0.864, 95% CI 0.613 to 1.219, $p = 0.405$. respectively) Change in FEV_1 and improvement in mean SGRQ total score from baseline were significantly better with GB/FF/BDP than with GB/IND Pneumonia occurred in 28 (4%) patients receiving GB/FF/BDP versus 27 (4%) patients receiving GB/IND

(continued)

Table 3. Trials with triple therapy administered in a single inhaler *(continuation)*

Study	Patients	Study design	Therapy	Key findings
Umeclidinium/vilanterol/fluticasone furoate				
Siler et al.[46]	727 patients with a post-bronchodilator $FEV_1 \leq 0.70$ and a mMRC dyspnea scale score ≥ 2	Two replicate, multicentre, randomised, double-blind, placebo-controlled parallel-group studies over 12 weeks	VI/FLF 25/100 µg + UMEC 62.5 µg VI/FLF 25/100 µg + UMEC 125 µg VI/FLF 25/100 µg	Statistically significant ($p < 0.001$) and clinically meaningful improvements in trough FEV_1 with VI/FLF + UMEC 62.5 µg (122-124 mL) and VI/FLF + UMEC 125 µg (111-128 mL) versus VI/FLF SGRQ results were inconsistent, with statistically significant improvements with VI/FLF + UMEC versus VI/FLF in one study only and with UMEC 62.5 µg only (difference in SGRQ total score from baseline between treatments: –2.16, $p < 0.05$)
Lips et al. (FULFIL)[47]	1810 patients defined as GOLD D (FEV_1 < 50% and CAT ≥ 10, or patients with FEV_1 ≥ 50–< 80% and CAT ≥ 10, and either ≥ 2 moderate exacerbations in the past year or ≥ 1 severe exacerbation in the past year), who had used daily maintenance therapy for at least 3 months before screening	Multicentre, randomised, double-blind, double-dummy study over 24 weeks	UMEC/VI/FLF 62.5/25/100 µg once daily FF/BUD 12/400 µg twice daily	At Week 24, triple therapy significantly improved trough FEV_1 (between- treatment difference: 171 mL; $p < 0.001$) and SGRQ total score (between-treatment difference: –2.2 units; $p < 0.001$) compared with FF/BUD At Week 52, triple therapy significantly improved trough FEV_1 compared with FF/BUD (between treatment difference: 179 mL; $p < 0.001$) No significant difference in SGRQ total score at week 52 (between-treatment difference: –2.7 units) Triple significantly reduced the rate of moderate or severe exacerbations (up to 24 weeks and 52 weeks) compared with FF/BUD (35% reduction in rate; $p = 0.002$ and 44% reduction in rate $p = 0.006$, respectively)
Bremner et al.[49]	1311 patients defined as GOLD D (FEV_1 < 50% and CAT ≥ 10, or patients with FEV_1 ≥ 50–< 80% and CAT ≥ 10, and either ≥ 2 moderate exacerbations in the past year or ≥ 1 severe exacerbation in the past year)	Multicentre, randomised, double-blind, parallel group, multicenter non-inferiority study over 2 weeks	UMEC/VI/FLF 62.5/25/100 µg once daily VI/FLF 25/100 µg + UMEC 62.5 µg once daily	Mean change from baseline in trough FEV_1 was 113 mL (95% CI 91 to 135) for UMEC/VI/FLF and 95 mL (95% CI 72 to 117) for VI/FLF + UMEC The proportion of responders based on SGRQ Total score was 50% (UMEC/VI/FLF) and 51% (VI/FLF + UMEC); the proportion of responders based on the TDI focal score was similar (56% both groups) The proportion of patients experienced a moderate/severe exacerbation in the UMEC/VI/FLF (24%) and VI/FLF + UMEC (27%) was similar The incidence of pneumonia (UMEC/VI/FLF, 3%; VI/FLF + UMEC, 4%) was similar
Lipson et al. (IMPACT)[50]	10,355 patients with FEV_1 < 50% and CAT ≥ 10 and ≥ 1 moderate or severe exacerbation in the previous year, or patients with FEV_1 ≥ 50–< 80% and CAT ≥ 10, and ≥ 2 moderate exacerbations in the past year or ≥ 1 severe exacerbation in the previous year	Multicentre, randomised, double-blind, parallel-group, trial over 52 weeks	UMEC/VI/FLF 62.5/25/100 µg once daily UMEC/VI 62.5/25 µg once daily VI/FLF 25/100 µg once daily	Moderate-to-severe exacerbation rates were 0.91 per patient per year for UMEC/VI/FLF, 1.07 per patient per year for VI/FLF (rate ratio with triple therapy, 0.85; 95% CI 0.80 to 0.90; 15% difference; $p < 0.001$), and 1.21 per patient per year for UMEC/VI (rate ratio with triple therapy, 0.75; 95% CI 0.70 to 0.81; 25% difference; $p < 0.001$) The annual rate of moderate or severe exacerbations was lower with triple therapy than with either dual-therapy combination, regardless of eosinophil level The annual rate of severe exacerbations was not significantly lower with UMEC/VI/FLF than with VI/FLF but was significantly lower with triple therapy than with UMEC/VI Change in FEV_1 and improvement in mean SGRQ total score from baseline were significantly better with UMEC/VI/FLF than with either dual-therapy combination The risk of clinician-diagnosed pneumonia was significantly higher with UMEC/VI/FLF than with UMEC/VI, as assessed in a time-to-first event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; $p < 0.001$) but not with VI/FLF (hazard ratio, 1.02; 95% CI, 0.87 to 1.19; $p = 0.85$)

(continued)

Table 3. Trials with triple therapy administered in a single inhaler *(continuation)*

Study	Patients	Study design	Therapy	Key findings
Glycopyrronium bromide/formoterol fumarate/budesonide				
Darken et al.[52]	84 healthy volunteers	Randomised, Phase I, single-dose, six-treatment, four-period, crossover study	GB/FF/BUD (14.4/10/320 µg (equivalent to GB/FF/BUD 18/9.6/320 µg), 14.4/10/160 µg and 14.4/10/80 FF/BUD 9/320 µg and 9/160 µg GB/FF 14.4/10 µg	SGB/FF/BUD 14.4/10/320 µg was bioequivalent to FF/BUD 320/9 µg for BUD for C_{max}, AUC_{0-12} and AUC_{0-t} Dose proportionality was observed for the BUD component between GB/FF/BUD 14.4/10/80 µg and GB/FF/BUD 14.4/10/160 µg, and between GB/FF/BUD 14.4/10/160 µg and GB/FF/BUD 14.4/10/320 Systemic exposure to GB and FF after GB/FF/BUD 14.4/10/320 µg treatment was similar to GB/FF/BUD 14.4/10/320 The rate of adverse events was 3.7-17.9% across treatments without any serious adverse events

AUC_{0-12}: area under the plasma concentration-time curve from 0 to 12 h; AUC_{0-t}: area under the plasma concentration-time curve up to the last measurable concentration; BDP: beclometasone dipropionate; BUD: budesonide; CAT: COPD assessment test; CI: confidence interval; C_{max}: maximum plasma concentration; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FF: formoterol fumarate; FLF: fluticasone furoate; GB: glycopyrronium bromide; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol.

respectively. It has an extrafine formulation and is administered twice-daily.

An initial Phase II study (Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial [TRIDENT]) showed the potential benefits on lung function of stepping-up to triple therapy through the addition of GB for patients already on FF/BDP[41]. Afterwards, three pivotal Phase III studies (Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for COPD [TRILOGY][42], Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for COPD [TRINITY][43] and Extrafine inhaled triple therapy versus dual bronchodilator therapy in COPD [TRIBUTE][44]) have provided precious information on the therapeutic value of this triple combination.

The TRILOGY study compared GB/FF/BDP with FF/BDP in COPD patients with severe or very severe airflow limitation, symptoms, and an exacerbation history[42]. After 26-week treatment, triple therapy significantly improved pre-dose FEV_1 (+81 mL) and two-hour post-dose FEV_1 (+117 mL), but there were no significant improvements in TDI. The adjusted annual rate of moderate-to-severe exacerbations was 0.41 for GB/FF/BDP and 0.53 for FF/BDP. A rate ratio of 0.77 indicated a 23% reduction with GB/FF/BDP.

In the TRINITY study, GB/FF/BDP was compared with FF/BDP + tiotropium (open triple) and with tiotropium alone in a 52-week study[43]. The inclusion criteria were very similar to those of TRILOGY. Triple therapy improved pre-dose FEV_1 (+61 mL) compared with tiotropium, but there was no difference between fixed and ex-temporary triple combination (–3 mL). The adjusted annual rate of moderate-to-severe exacerbations was 0.46 for GB/FF/BDP and 0.57 for tiotropium, with a rate ratio of 0.80, indicating a 20% reduction with GB/FF/BDP. No difference was observed between fixed and ex-temporary triple combination either in adjusted annual rate of moderate-to-severe exacerbations (0.46 versus 0.45).

In the TRIBUTE study, GB/FF/BDP was compared with GB/IND in terms of the rate of moderate-to-severe AECOPDs over 52 weeks of treatment[44]. Moderate-to-severe exacerbation rates were 0.50 per patient per year for GB/FF/BDP and 0.59 per patient per year for GB/IND, with a rate ratio of 0.85, indicating a 15% reduction with BDP/FF/GB. Change in FEV_1 and improvement in mean SGRQ total score from baseline were significantly better with GB/FF/BDP than with GB/IND.

b. Umeclidinium/vilanterol/fluticasone furoate combination

Umeclidinium/vilanterol/fluticasone furoate is another triple FDC under clinical development. In a Phase I study, systemic exposure to all three components of this FDC following single-dose delivery in healthy volunteers was similar to that seen with VI/FLF and UMEC/VI[45].

Two RCTs demonstrated that UMEC (62.5 µg and 125 µg + VI/FLF (25/100 µg) provides statistically significant and clinically meaningful improvements in lung function compared with placebo + VI/FLF 25/100 µg in COPD patients (difference in trough FEV_1 versus placebo + VI/FLF at day 85: +124 mL with UMEC 62.5 µg + VI/FLF, and +122 mL with UMEC 125 µg + VI/FF)[46]. However, statistically significant improvements in HRQoL with UMEC+VI/FLF versus placebo+VI/FLF were reported in one study only.

The Lung function and quality of life assessment in COPD with closed triple therapy (FULFIL) trial compared 24 weeks of UMEC/VI/FLF 62.5/25/100 µg with FF/budesonide (BUD) 12/400 µg in GOLD D patients[47]. At week 24, the difference between UMEC/VI/FLF and FF/BUD in trough FEV_1 (171 mL) was statistically significant. The mean annualised rate of moderate/severe exacerbations was 0.22 and 0.34 for UMEC/VI/FF and FF/BUD, respectively, indicating a significant 35% reduction in the annualised rate with triple therapy compared with LABA/ICS. Umeclidinium/vilanterol/fluticasone furoate also improved symptoms and HRQoL compared with twice-daily FF/BUD[48].

A large RCT has evaluated the non-inferiority of single-inhaler UMEC/VI/FLF versus VI/FLF + UMEC using two inhalers and has shown that single-inhaler triple therapy with UMEC/VI/FLF offers similar efficacy, HRQoL, and safety benefits as the same triple therapy administered using two inhalers[49].

The Informing the Pathway of COPD Treatment (IMPACT) trial has been a Phase III, randomised, double-blind, three-arm, parallel-group, global multicentre study comparing the rate of moderate and severe exacerbations between UMEC/VI/FLF and VI/FLF or UMEC/VI in 10,355 patients with COPD over a 52-week treatment period[50]. Patients had to have either a FEV_1 less than 50% of the predicted normal value and a history of at least one moderate or severe exacerbation in the previous year, or an FEV_1 of 50 to 80% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year. There was a significant reduction in moderate-to-severe exacerbation rate with triple therapy (–15% versus VI/FLF and –25% versus UMEC/VI). The rate of moderate or severe exacerbations in the UMEC/VI/FLF group was 0.91 per year, as compared with 1.07 per year in

the VI/FLF group (rate ratio, 0.85) and 1.21 per year in the UMEC/VI group (rate ratio, 0.75). Triple therapy significantly reduced also the annual rate of severe exacerbations compared to UMEC/VI (rate ratio, 0.66; 34% difference), but not to VI/FLF (rate ratio, 0.87; 13% difference).

Umeclidinium/vilanterol/fluticasone furoate was more effective than the other two treatments in improving the trough FEV_1 at week 52 (+97 mL versus VI/FF, and +54 mL versus UMEC/VI). It was also significantly better than the other two treatments with respect to the impact on SGRQ total score and in the percentage of patients who had a response as defined by a decrease in the SGRQ total score of at least 4 points. Furthermore, in a subset of 5058 patients, the percentage of patients who had a response as defined by an increase in the TDI of at least one unit was higher with triple therapy than with either dual therapy. The risk of clinician-diagnosed pneumonia was significantly higher with UMEC/VI/FLF than UMEC/VI as assessed in a time-to-first-event analysis (hazard ratio [HR] 1.53), but not than VI/FLF (HR 1.02).

c. Glycopyrronium bromide/formoterol fumarate/budesonide combination

Glycopyrronium bromide/budesonide/formoterol fumarate FDC is the third triple therapy under clinical development. It uses Aerosphere Delivery Technology (ADT), which provides a stable, uniform, and easily dispersed MDI suspension formulation when combined with one or multiple types of drug crystals[51]. A Phase I trial documented no drug-drug interaction when comparing pharmacokinetics of GB/FF/BUD 14.4/9.6/320 µg to GB[52]. Systemic exposure to BUD following administration of GB/FF/BUD was slightly higher but bioequivalent to FF/BUD pMDI 9/320 µg. No pharmacokinetic drug-drug interactions were observed when BUD was added to GB and FF.

ATHENA is a Phase III clinical trial programme for GB/FF/BUD FDC, which will include more than 15,500 patients globally across 11 trials. Top-line results from the Phase III Study to Assess the Efficacy and Safety of PT010, PT003, and PT009 Compared With Symbicort® Turbuhaler® in Subjects with Moderate-to-Very-Severe COPD (KRONOS) trial have been announced[53]. The latter study is a randomised, double-blind, parallel-group, 24-week, chronic-dosing, multi-centre trial to assess the efficacy and safety of GB/FF/BUD FDC. The trial compared GB/FF/BUD FDC to GB/FF 14.4/9.6 µg using ADT, FF/BUD 12/400 µg Turbuhaler and FF/BUD 9.6/320 µg using ADT. Triple combination demonstrated a statistically significant improvement compared with dual combination therapies in six out of seven lung function primary endpoints based on FEV_1 assessments in patients with moderate-to-very-severe COPD. In total, eight of the nine primary endpoints in the KRONOS trial were met, including two non-inferiority endpoints to qualify FF/BUD 9.6/320 µg delivered using ADT.

The Study to Assess the Efficacy and Safety of PT009 (budesonide and formoterol fumarate MDI) Compared to PT005 (formoterol fumarate MDI) on COPD Exacerbations Over a 52-Week Period in Subjects With Moderate-to-Very-Severe COPD (SOPHOS) assesses

the efficacy and safety of GB/FF/BUD FDC compared to FF/BUD 9.6/320 µg and FF 9.6 µg (ClinicalTrials.gov Identifier: 02727660). The Study to Assess the Efficacy and Safety of PT010 Relative to PT003 (glycopyrronium and formoterol fumarate MDI) and PT009 in Subjects With Moderate-to-Very-Severe COPD (ETHOS) is a randomised, double-blind, multicentre, parallel-group study that is assessing the efficacy and safety of GB/FF/BUD FDC relative to GB/FF 14.4/9.6 µg and FF/BUD 9.6/320 µg on AECOPDs over a 52-week treatment period in approximately 8000 patients (ClinicalTrials.gov Identifier: NCT02465567).

WHAT DOES NEW EVIDENCE TELL US?

Nowadays, we have evidence that LAMA/LABA FDCs may be more effective than LABA/ICS in reducing the risk of exacerbations[54] and this finding raises the fundamental question of whether the potential benefit gained by adding ICS to the dual-bronchodilator therapy actually overcomes the risk of adverse effects and the increased cost of triple therapy[30].

The TRIBUTE study demonstrated a 15% reduction in exacerbations with triple therapy compared with dual bronchodilation[44]. However, TRIBUTE, as well as TRILOGY[42] and TRINITY[43] studies, was not focused on frequent exacerbators and, consequently, the annual rate of exacerbations was too low to evaluate the true value of this reduction. Therefore, it is difficult to draw firm conclusions on this finding. Likely, it would be preferable to calculate how many exacerbations requiring medical intervention would be prevented for every 100 patients treated for one year with GB/FF/BDP versus GB/IND therapy. In any case, the rates of moderate and severe exacerbations analysed separately were not significantly different between GB/FF/BDP and GB/IND. Also the time to first moderate or severe exacerbation was similar between the two treatment groups. All these findings suggest that either the triple therapy is actually not more effective than double bronchodilation in reducing the risk of exacerbations, or/and the study has been not sufficiently well designed. Also the results of the FULFIL study are not very useful because it was a 24-week trial, but, due to seasonal variation, an evaluation of exacerbation frequency requires a period of ≥ 1 year and, furthermore, the timing of the study treatment may prove important (e.g. capturing winter cold season in the majority of patients)[55].

The 2018 GOLD strategy suggests for patients with GOLD D escalation from dual bronchodilation to LAMA/LABA/ICS, and when LABA/ICS therapy does not positively impact exacerbations/symptoms, a LAMA can be added[1]. Regrettably, there is still no solid evidence of a real clinical advantage when performing such an escalation. Suissa and Drazen[56], while editorialising the IMPACT study data, highlighted that although this trial has addressed the possibility of a step-up approach from a dual long-acting bronchodilator regimen to triple therapy, the results of the study were probably artificially inflated because the majority of the enrolled patients were already treated with ICSs and some of them had a history of asthma. For this reason, they think that the IMPACT trial falls short of providing the anticipated strong evidence to better understand the potential for stepping-up to single inhaler triple therapy in clinical practice. Umeclidinium/vilanterol/fluticasone furoate

and VI/FLF also showed a signal toward lower all-cause mortality during treatment than UMEC/VI[50]. However, we do not believe that it is an outcome endowed with consistency, and not only because it contradicts the results of the Study to Understand Mortality and Morbidity in COPD (SUMMIT) study that was powered to evaluate all-cause mortality and did not show a significant effect for VI/FLF[57], but also, and mainly because death from any cause during treatment was not a pre-specified primary and secondary outcome. This means that the study was not appropriately powered to assess effects on mortality.

At this point in time, we are waiting for the results of the ETHOS study, mainly because of the number of patients involved. However, we must highlight that the step-up approach from dual bronchodilation to triple therapy takes no account of the critical differences in COPD exacerbations (they differ in aetiology, severity, and biological substrate), and thus it is not designed on the patient's specific needs to be treated[58].

In any case, we fully agree that the available evidence does support the current recommendation of triple therapy for GOLD D patients, but it only suggests triple therapy is effective in GOLD B patients (i.e. highly symptomatic but at low risk of exacerbations)[59]. Therefore, the current GOLD strategy recommendations should be revisited and studies with triple therapy in GOLD B patients should be conducted with the aim of testing its effect on hospitalisations and survival[59]. However, Suissa and Drazen[56] have invoked caution in using the single-inhaler triple therapy in treating COPD because any potential benefit could be lost and potential undue harm induced if triple therapy is expanded to GOLD A, B, and C patients.

Now we must establish whether and when addition of an ICS to the LAMA/LABA combination provides real additional clinical value, regardless of a preventive effect on exacerbations, and determine what kind of benefit it is, or whether LAMA/LABA combination therapy is preferred over triple therapy also because of the cost differences of the two treatments in real-life. It has been suggested that baseline blood eosinophil levels may represent an informative marker for exacerbation reduction with LABA/ICS in patients with COPD and a history of moderate-to-severe exacerbations[60]. Nonetheless, prospective analyses of data from the Effect of Indacaterol Glycopyronium versus Fluticasone Salmeterol on COPD Exacerbations (FLAME) trial indicate that dual bronchodilation provides superior or similar benefits over LABA/ICS regardless of blood eosinophil levels in patients with COPD[61]. In the TRIBUTE trial, the relative effect of GB/FF/BDP versus GB/IND on moderate-to-severe exacerbations was greater in patients with eosinophils > 2%, but the effect of the two treatments was not significantly different when an eosinophil threshold of 200 cells per µL was used[44]. However, in the IMPACT study, the annual rate of moderate-to-severe exacerbations was lower with triple therapy regardless of eosinophil level[50]. Therefore, it is obvious that at the present time blood eosinophil counts cannot be recommended as an unquestionable biomarker for the management of individual patients with COPD[62].

In any case, we agree that it can be difficult to discern whether an individual who continues to experience exacerbations following the

addition of an ICS would have experienced a similar number or more of these events without this addition[63].

Also the evaluation of possible risk of adverse events is central to the choice of therapy. The overall incidence of pneumonia in the IMPACT study was 50% higher in patients treated with UMEC/VI/FLF than in the UMEC/VI group[50], whereas in the TRIBUTE trial the addition of BDP did not increase the risk of pneumonia[44].

CONCLUSIONS

Although the available information has greatly increased in recent years, there is still no solid evidence to state whether and when addition of an ICS to the LAMA/LABA combination provides additional clinical value. Therefore, a strong recommendation cannot be generated as yet. However, it is likely that the fundamental question in the next paradigm for the treatment of COPD will no longer be whether and/or when it is appropriate to switch patients with COPD from a LABA/ICS regimen to a LAMA/LABA one, but rather in which patients and when we can add an ICS to the dual bronchodilation.

We strongly believe that maximising the treatment in patients with a degree of clinical instability by including an ICS in the therapeutic regimen is useful to control the disease but may not be needed during periods of clinical stability. However, it is always better to avoid a therapeutic step-up progression when it is not needed rather than being forced subsequently into a step-down approach in which the outcome is always unpredictable[64].

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CONFLICTS OF INTEREST

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