FINAL REPORT

Single-inhaler triple therapy for treatment of adult patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

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Drug Assessment Working Group

Therapeutics Initiative

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Single-inhaler triple therapy for treatment of adult patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

Executive Summary

1. Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airway inflammation and airflow limitation that is not fully reversible. It occurs as a consequence of exposure to noxious particles or gases. Exposure to cigarette smoke is the most common risk factor. Drugs to treat COPD are licensed by regulatory authorities based on short-term randomized trials (typically 12 weeks in duration) that show an improvement in the surrogate marker FEV_1 which is the primary outcome measure in most trials. However, the goal of treating COPD is to prevent acute moderate to severe exacerbations, improve quality of life and reduce symptoms such as dyspnea. (1)

The main treatment options for COPD belong to a number of pharmacological classes – bronchodilators (short-acting $beta_2$ agonists [SABA], long-acting $beta_2$ agonists [LABA], short-acting muscarinic antagonists [SAMA], and long-acting muscarinic antagonists [LAMA]), inhaled corticosteroids [ICS], and inhibitors of the enzyme phosphodiesterase-4 [PDE4 inhibitors]. Numerous clinical practice guidelines recommendations involve a stepwise intensification of drug therapy.

Two triple therapy inhalers are approved in Canada to reduce exacerbations and airflow obstruction in patients with COPD not adequately treated by ICS/LABA or LAMA/LABA combinations. (2-5)

- Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol);
- Breztri Aerosphere (budesonide/glycopyrrolate/formoterol fumarate)

For people who experience persistent dyspnea and are at *"high risk"* of exacerbation despite maximal LAMA/LABA therapy, the 2025 BC and 2023 CTS guidelines recommend adding ICS as "step-up" to triple therapy. (7,8) We italicise "*high risk"* within quotations, to remind readers that this categorization can only be applied retrospectively (i.e., prior history of moderate or severe exacerbations). The GOLD 2025 update, published in November 2024, recommends adding ICS only if eosinophils are $\geq$100/uL, **but adds that evidence *"strongly favours use"* only with eosinophils $\geq$300/uL**. (9) For patient convenience, CTS and GOLD recommend a single inhaler. All guidelines emphasize the crucial importance of smoking cessation, appropriate immunizations, maintaining physical fitness, demonstrating and rehearsing effective inhaler technique.

The GOLD 2025 update, published in November 2024, includes a section titled, "Therapeutic interventions that reduce COPD mortality" cites two studies with triple therapy, IMPACT and ETHOS, which are reported to have a mortality benefit compared with dual bronchodilator therapy in patients with a history of exacerbations who were previously receiving maintenance therapy with triple therapy, LABA+ICS or dual long-acting bronchodilator (LABD) therapy (LAMA-LABA). No mortality benefit was seen with triple therapy versus ICS-LABA.

The mortality estimates are from post-hoc analyses which included vital status of patients that were missing from the original manuscripts. Both compared triple therapy with dual long-acting bronchodilator (LABD) (i.e., LAMA-LABA). Mortality was based on "on-treatment" (i.e., per protocol) analysis in IMPACT, whereas ETHOS assessed mortality in the intention-to-treat population.

The GOLD 2025 update reiterates: *"There is no high-quality evidence such as randomized controlled trials to support initial pharmacological treatment strategies in newly diagnosed patients."* Its new *"practical recommendation"* for patients defined as *"high risk"* is to **consider a patient's blood eosinophil count when deciding whether to initiate ICS treatment.** (11) Despite the caveat that *"there are no direct data concerning initiation of triple therapy in newly diagnosed patients,"* GOLD 2025 recommends **considering first-line triple therapy** for patients with eosinophils ≥300/µL. In *"high-risk"* patients already using LAMA/LABA therapy, it recommends escalation to triple therapy if eosinophils are ≥100/µL, but to azithromycin or roflumilast when eosinophils are <100/µL.

However, no RCT has evaluated using blood eosinophil count as a factor when deciding whether to add ICS treatment in patients at any level of severity, including COPD defined as *"high risk."*

In contrast, the Canadian guideline (CTS) recommends first-line triple therapy **for patients with a high symptom burden and severe health impairment** at *"high risk"* of exacerbations, **regardless of eosinophil count**. For people with **persisting dyspnea** at *"high"* or *"low"* risk of exacerbation despite dual LAMA/LABA therapy, CTS recommends escalation to triple therapy. (12)

In 2018, the Ministry of Health's Pharmaceutical, Laboratory & Blood Services Division (PLBSD) requested an evidence review of Trelegy Ellipta, a single dose triple therapy containing fluticasone furoate 100mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg (FF/UMEC/VI), as compared to combination therapy with 2 drugs (UMEC 62.5 mcg/VI 25 mcg or FF 100 mcg/VI 25 mcg or UMEC 62.5 mcg/FF 100 mcg), all administered once daily as a single inhaler, in preventing acute moderate to severe exacerbations, improving quality of life and reducing dyspnea symptoms in adult patients with symptomatic COPD (diagnosed FEV1/FVC <0.70).

The TI report dated September 12, 2018 identified and critically appraised IMPACT 2018, the only study that met the inclusion criteria. (13) IMPACT 2018 randomized 10,355 patients

with symptomatic COPD and a history of exacerbations despite being on triple therapy (38%) and combination therapy with ICS/LABA (29%) or LAMA/LABA (9%) at baseline. This 1-year study compared triple therapy with FF/UMEC/VI (n=4151) with UMEC/VI (n=4134) and FF/VI (n=2070), all administered once daily as a single inhaler. The same drugs and doses of ICS, LABA and LAMA were used in the triple-therapy and comparator groups. No studies were identified that compared FF/UMEC/VI with FF/UMEC.

The review concluded that based on IMPACT 2018 there is insufficient evidence that triple therapy with FF/UMEC/VI provides a therapeutic advantage versus dual therapy (FF/VI or UMEC/VI) in terms mortality, total serious adverse events (which includes all cause hospitalization and hospitalization due to severe exacerbation), moderate exacerbations, total adverse events or withdrawal due to adverse events, COPD symptoms or quality of life.

Since the 2018 TI DAWG review, another single-inhaler triple therapy Breztri Aerosphere (budesonide/glycopyrrolate/formoterol fumarate) has since been licensed in Canada to reduce exacerbations and airflow obstruction in patients with COPD not adequately treated by ICS/LABA or LAMA/LABA combinations. (3,5) Also, recent guidelines added a new recommendation for single-inhaler triple therapy as initial treatment for COPD patients at *"high risk"* of exacerbation. Guidelines assign the term *"high-risk"* to patients who within the last year have experienced at least 2 moderate, or at least 1 severe exacerbation of COPD. A "moderate exacerbation" implies antibiotic or oral corticosteroid treatment, whereas "severe exacerbation" requires an emergency department visit or hospitalization. We italicise "*high risk"* within quotations, to remind readers that this categorization can only be applied retrospectively.

PLBSD requested an updated search of the scientific literature to identify any new RCT evidence published since the completion of the 2018 TI DAWG review.

Requested Research Question

In double blind active controlled parallel group RCTs of at least 24 weeks duration, what are the comparative effects of single-inhaler triple therapy versus corresponding dual therapy (LAMA/LABA or ICS/LABA) on moderate to severe exacerbations, total mortality, quality of life and dyspnea symptoms in COPD patients at "high risk" of exacerbation?

2. Methods

We searched Ovid MEDLINE, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from dates of inception until April 2024. We also searched clinicaltrials.gov, Drugs@FDA, European Medicines Agency public assessment reports and the manufacturer's website for all relevant RCT reports. Outcomes were analyzed in order of clinical importance (i.e., a health outcome hierarchy) recognizing that not all outcomes are of equivalent value and not all evidence has uniform protection against bias. Meta-analysis was carried out whenever possible. Risk of bias was assessed according to the Cochrane Risk of Bias 1.0 tool and helped to inform conclusions.

3. Summary of Available Evidence

No RCT evaluated initiation of single-inhaler triple therapy in newly diagnosed or treatment-naïve COPD patients at "high risk" of exacerbations.

Our updated search identified one new study (ETHOS 2020) that met our inclusion criteria. (14) Therefore, two 52-week double-blind RCTs (IMPACT 2018, ETHOS 2020) evaluated single-inhaler triple therapy versus single-inhaler dual therapy (LAMA/LABA or ICS/LABA) in COPD patients with a moderate to high symptom burden and history of moderate or severe exacerbations in the 12 months prior to study enrolment. (13,14)

Both included RCTs enrolled patients with a mean duration of 8 years since diagnosis of COPD. Their primary outcome was the incidence of moderate or severe exacerbations. At baseline, almost all patients (92-100%) were already receiving inhaler therapy, including 70-80% treated with an inhaler containing ICS (double or triple therapy). Fourty percent of participants were already using triple therapy when randomized to continue triple therapy or step down to dual therapy. Patients with a history of asthma were permitted and 20-30% had bronchodilator reversibility at baseline. Results of these RCTs cannot be extrapolated to naïve patients for whom triple therapy is considered for first-line treatment.

IMPACT 2018 is a double blind RCT in 10,355 patients with symptomatic COPD and a history of exacerbation within a year before enrolment. (13) This study compared triple therapy with FF/UMEC/VI (n=4151) with UMEC/VI (n=4134) and FF/VI (n=2070), all administered once daily as a single inhaler. The same agents and doses of ICS, LABA and LAMA were used in the triple-therapy and comparator groups. No studies were identified that compared FF/UMEC/VI with FF/UMEC.

The mean age of study participants was 65.3 (± 8.3) years, 66% male, and 65% former smokers. Post-bronchodilator FEV_1 was 45.5% of predicted normal value and a mean CAT score of 20.1 (± 6.1) at screening. Fourty-seven percent and 26% had a history of ≥2 moderate COPD exacerbations and ≥1 severe COPD exacerbation, respectively. Patients with a history of asthma were included in the study. Nearly 40% of the patients were receiving triple therapy, and more than 70% were receiving ICS at baseline.

9087 patients (88%) completed the trial and 7991 (77%) completed the trial while receiving randomized therapy. This study used intention to treat to analyze safety and efficacy. Patients who permanently discontinued study treatment did not receive further evaluation but were encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, SAEs and concomitant medications post-treatment. The proportion of patients successfully contacted was not reported. The accuracy and completeness of phone call information was not reported. Vital status was available for 9781 (94.4%) of the total study population at Week 52.

ETHOS 2020 is a double blind RCT in 8,588 patients with symptomatic COPD and a history of exacerbation in the year before screening. (14) This study compared budesonide 320 mcg/glycopyrrolate 18 mcg/ formoterol fumarate 9.6 mcg triple therapy (BGF 320) (n=2157)

with 160 mcg/ glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg triple therapy (BGF 160) (n=2137), glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg (GFF) (n=2143), and budesonide 320 mcg/formoterol fumarate 9.6 mcg (BFF) (n=2151), all delivered twice daily via a single metered-dose Aerosphere inhaler. No studies were identified that compared BGF 320 or BGF 160 with BG.

The mean age of study patients was 64.6 (7.6) years, 60% were males, and 59% were former smokers. Postbronchodilator FEV_1 was 43.4% of predicted normal value and a mean CAT score of 19.1 (6.6) at screening. Fifty six percent and 21% had a history of ≥ 2 moderate or severe COPD exacerbations and ≥ 1 severe COPD exacerbation, respectively. Patients with a history of asthma were included in the study and approximately 30% had bronchodilator reversibility at baseline. Use of specific drugs within the LABA, LAMA and ICS class is not reported. Approximately 40% of the patients were receiving triple therapy, and 80% were receiving ICS at randomization. It is not reported whether dual therapy (LAMA/LABA or LABA/ICS) actually failed in those patients receiving triple therapy at screening.

A total of 7187 patients (83.8%) completed the trial, of whom 6654 (77.6%) completed 52 weeks of treatment (79.4% and 80.4% in the budesonide 320 mcg and budesonide 160 mcg triple-therapy groups, respectively, 74.1% in the GFF group, and 76.6% in the BFF group). This study analyzed safety and efficacy data using a modified intention-to-treat approach. A full intention-to-treat analysis was not performed because patients who permanently discontinued study treatment did not come in for further evaluation. The modified intention-to-treat population included all patients in the intention-to-treat population with post-randomization data obtained before discontinuation of treatment. Any data collected after completion of, or discontinuation of the assigned trial regimen was excluded from the modified intention-to-treat analysis. The safety population included all patients who underwent randomization, received any amount of treatment, and had a post-randomization safety assessment. Time to death was assessed in the intention-to-treat population (all patients who underwent randomization and received any amount of trial treatment) and included all observed data obtained from patients regardless of whether they continued to receive their assigned treatment.

Whether patients were encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, SAEs and concomitant medications post-treatment is unknown. Vital status was known for 8125 of 8509 patients (95.5%) at Week 52.

Total mortality data are from secondary analyses of IMPACT and ETHOS following collection of additional vital status data that were missing from the original study publications. IMPACT 2020 and ETHOS 2021 report vital status data for 99.6% of the intention-to-treat population in both studies (IMPACT n=10,355; ETHOS n=8509). (17,18)

IMPACT 2018 and ETHOS 2020 were judged to have a high risk of bias according to the Cochrane Risk of Bias 1.0 tool with respect to attrition and source of funding. There are also

other biases with respect to study design and presence of confounding that misrepresent the treatment effect.

4. Results and Interpretation

There were no differences in on- and off-treatment total mortality rates between triple therapy with FF/UMEC/VI and either dual combination in the final retrieved dataset of IMPACT 2020 [RR 0.74 (95% CI 0.54, 1.01) vs. UMEC/VI; RR 0.90 (95% CI 0.68, 1.17) vs. FF/VI]. The final retrieved dataset of ETHOS 2020 found a reduction in on-and off-treatment total mortality with BGF 320/18/9.6 triple therapy as compared to LAMA/LABA only (GFF 18/9.6) [RR 0.53 (95% CI 0.34, 0.82); ARR 1.2%; NNT 81 for 1 year] but not ICS/LABA (BFF 320/9.6). There was no difference between the lower dose triple therapy group (BGF 160/18/9.6) and either dual combination.

When the 2 studies were pooled for total mortality (on- and off-treatment), there were fewer deaths with triple therapy (2.0%) compared with LAMA/LABA dual therapy (2.9%) [RR 0.66 (95% CI 0.51, 0.85); ARR 0.9%; NNT 114 for 1 year].

A major study design flaw seriously undermines the validity of IMPACT 2018 and ETHOS 2020: the confounding effect of abrupt withdrawal of ICS at randomization in those patients assigned to dual bronchodilator (LAMA/LABA) therapy. Patients with a history of asthma (who are known to benefit from ICS use) were included in IMPACT and ETHOS. Approximately 70% and 80% were receiving a COPD regimen that included ICS in IMPACT and ETHOS, respectively. Both IMPACT and ETHOS showed an excess of deaths and exacerbations in the LAMA/LABA group – compared with triple therapy - occurred during the first 90 days of follow-up. (19,20) This includes the 30-day interval when biological effects of abrupt corticosteroid withdrawal would be maximal. During the remaining 9 months of follow-up, no benefit of triple therapy was observed. Analyses limited to the subgroup of ICS-naïve patients in IMPACT and ETHOS found no mortality benefit (HR 1.25 (95% CI: 0.60–2.59) in IMPACT and 1.49 (95% CI: 0.49–4.55) in ETHOS). (20) **Thus, the assumed benefit of triple versus dual inhaler therapy is likely due to abrupt ICS withdrawal in the LAMA/LABA group.** This is one reason why the US FDA Advisory Committee specifically rejected a claim that triple therapy reduces mortality, (21,22) and why Canadian triple inhaler monographs (2,3) and Health Canada's regulatory decisions (4,5) also do not suggest a mortality benefit.

Both RCTs showed no difference in total SAEs between triple therapy and either dual combination. Hospitalization due to any cause was not reported in either study.

A serious adverse event of pneumonia occurred in 4%, 4%, and 3% of patients treated with FF/UMEC/VI, FF/VI and UMEC/VI, respectively, in IMPACT. Time-to-first-event analysis reveals that the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with UMEC/VI (HR 1.53; 95% CI, 1.22,1.92). In ETHOS a serious adverse event of pneumonia occurred in 3.0%, 2.5%, 2.4% and 1.3% of patients treated with BGF 320, BGF 160, BFF and GFF, respectively. In both studies there was a significantly higher incidence of

serious pneumonia in the groups that received ICS than in the LAMA/LABA group. There was no significant difference in the risk of pneumonia between triple therapy and ICS/LABA.

The trials report the annual rate of moderate or severe exacerbations (pre-specified primary outcome), which was 0.91 per year with triple therapy versus 1.21 per year with the LAMA/LABA (UMEC/VI) combination in IMPACT and 1.08 per year with triple therapy (BGF 320) versus 1.42 per year with the LAMA/LABA (GFF) combination in ETHOS. The study authors added all the exacerbations that took place in a treatment arm and divided by the number of years in the study. Therefore, they counted multiple exacerbations that occurred in a single patient. They then created rate ratios with triple therapy, 0.75 (95% CI 0.70,0.81); 25% difference in the annual rate; P<0.001 in IMPACT and 0.76 (95% CI 0.69–0.83); 24% difference in the annual rate in ETHOS, versus LAMA/LABA. The rate ratio with triple therapy versus ICS/LABA combination in IMPACT was 0.85 (95% CI 0.80,0.90); 15% difference in the annual rate; P<0.001 and 0.87 (95% 0.79–0.95); 13% difference in the annual rate in ETHOS.

Interpreting a 24-25% and 13-15% reduction in an annual rate is not possible without knowing how to divide the effect among individual people. If this rate reduction was a reduction in the proportion of people who had one or more exacerbation, NNT calculations could be made. With a rate estimate, perhaps this means that a person needs treatment for 4 years with triple therapy to prevent one or more additional moderate to severe exacerbation with LAMA/LABA and 7 years versus ICS/LABA?

The reported rates are also uncertain due to the withdrawal rates in the three groups (IMPACT: 18, 25 and 27% in UMEC/FF/VI, FF/VI and UMEC/VI, respectively; ETHOS: 20, 19, 25, 23 and 27% in BGF 320, BGF 160, BFF and GFF, respectively). Excluding enrolled participants from the analysis in RCTs often results in biased estimates of treatment effects. (23) It is unclear how annual rates of moderate or severe exacerbations were calculated and whether patients who withdrew prematurely were appropriately accounted for in this calculation. In an effort to reduce bias in the safety and efficacy analysis, the IMPACT investigators state they tried to collect post-treatment exacerbations, SAEs and concomitant medications data via telephone contacts on patients who prematurely discontinued assigned treatment during follow-up. The success rate as well as the accuracy and completeness of information from these telephone contacts is not known. This attempt to reduce attrition bias is insufficient without knowing how successful they were at obtaining information via phone contacts. It appears that ETHOS investigators did not attempt to collect post-treatment exacerbations, SAEs and concomitant medications data for patients who discontinued prematurely.

Time-to-first-event analysis reported that triple therapy was associated with a lower risk of moderate or severe exacerbations during treatment than dual therapy. In IMPACT, the hazard ratio (HR) on the reported study sample for triple therapy versus FF/VI was 0.85 (95% CI 0.80 to 0.91; 15% difference; P<0.001), and versus UMEC/VI was 0.84 (95% CI 0.78 to 0.91; 16% difference; P<0.001). In ETHOS, the hazard ratio (HR) on the reported study

sample for triple therapy (BGF 320) versus BFF was 0.89 (95% CI 0.81 to 0.97; 11% difference, and versus GFF was 0.88 (95% CI 0.81 to 0.96; 12% difference. Time-to-first-event analysis is useful only when it is known how many patients had more than one exacerbation throughout the study in the treatment groups. Time-to-first-event analysis is potentially biased by the increase in exacerbations following abrupt withdrawal of ICS in the LAMA/LABA group.

Patients with a history of asthma were included in both studies. In addition, 40% of randomized patients were already receiving triple therapy and more than 70-80% were receiving a COPD regimen that included ICS. Sudden ICS withdrawal at randomization in those patients assigned to dual bronchodilator therapy may explain more rapid increase in exacerbations in these groups as compared to triple therapy during the first month of follow-up. The incidence of moderate or severe exacerbations among the groups was similar during the subsequent 11 months of follow-up.

SGRQ was used to measure health-related quality of life in this study. SGRQ total score ranges from 0 to 100, with lower scores indicating better health-related quality of life. A minimum change in score of 4 points is considered as clinically important (i.e. MCID). Mean change in SGRQ total score was evaluated in 7814 (76%) patients in IMPACT. In this subset of patients there were significant differences between the FF/UMEC/VI group and the FF/VI [-1.8 (95% CI -2.4,-1.1)] and UMEC/VI [-1.8 (95% CI-2.6,-1.0)] groups. In ETHOS, mean change in SGRQ total score was evaluated in 6554 (77%) patients. In this subset of patients there were significant differences between the BGF 320 group and the BFF [-1.5 (95% CI -2.4,-0.5)] and GFF [-1.9 (95% CI-2.8,-0.9)] groups. SGRQ total score was only reported for a subset (76-77%) of patients. The finding of improved quality of life with triple therapy is unreliable because data for 23-24% of patients who withdrew prematurely from the study are missing. Analysis of the effect of treatment on SGRQ total score should be based on all randomized patients rather than incomplete data from a subset of patients.

TDI score was used to measure the severity of dyspnea (breathlessness, shortness of breath) in this study. TDI score ranges from -9 to 9, with a lower score indicating more deterioration in severity of dyspnea. A minimum improvement of 1 point is considered a MCID. The score was only reported In a subset of 5058 (49%) of randomized patients in IMPACT. In ETHOS the TDI score was reported in 95% of randomized patients but only at 24 weeks. There were significant differences between the BGF 320 group and the BFF [0.31 (0.15 to 0.46)] and GFF [0.40 (0.24 to 0.55)] groups but did not the MCID threshold for both comparisons. TDI score was only reported for a subset of 5058 (49%) patients in IMPACT. The finding of symptomatic improvement with triple therapy is unreliable because data for half of randomized patients are missing. Analysis of the effect of treatment on TDI score should be based on all randomized patients rather than incomplete data from 49% of randomized patients. ETHOS only reported TDI score at 24 weeks and MCID was not achieved between triple therapy and either dual combination.

Despite being listed as a protocol-defined endpoint, use of rescue salbutamol was not reported in IMPACT. Use of rescue salbutamol over 24 weeks was only reported in a subset of 5627 (66%) of randomized patients in ETHOS. If triple therapy actually improves TDI score, a significant decrease in use of rescue medication is also expected in this group. The finding of improved quality of life with triple therapy is unreliable because data for 33% of patients are missing. Analysis of the effect of treatment on daily rescue medication should be based on all randomized patients rather than incomplete data from a subset of patients at the midpoint of the study.

COPD related health care utilization, which includes physician visits/ER visits and hospitalizations, is another protocol-defined endpoint that was not reported in the study publication despite being listed as a prespecified study endpoint in the IMPACT protocol. This was not a prespecified outcome of ETHOS.

Adverse events occurred in 64-70% receiving triple therapy, 65-68% receiving ICS/LABA, and 62-69% receiving LAMA/LABA in both studies. There was no difference between triple therapy and dual therapy comparators for total adverse events. A total of 5.5-6%, 6.4-8% and 6.9-9% patients treated with triple therapy, ICS/LABA and LAMA/LABA, respectively, withdrew due to an adverse event in both studies. There was no difference between triple therapy and dual therapy comparators for withdrawal due to adverse events. Overall, 9087 patients (88%) completed the IMPACT trial and 7991 (77%) completed the trial while receiving randomized therapy. This study analyzed harm data using an intention-to-treat approach, however, a full intention-to-treat analysis was not performed because patients who permanently discontinued study treatment did not come in for further evaluation. A total of 7187 patients (83.8%) completed ETHOS, of whom 6654 (77.6%) completed 52 weeks of treatment. This study analyzed safety and efficacy data using a modified intention-to-treat approach. Any data collected after completion of, or discontinuation of the assigned trial regimen was excluded from the modified intention-to-treat analysis.

In IMPACT, of 7916 (76%) patients evaluated, the difference between the triple therapy and FF/VI and UMEC/VI groups in the mean change from baseline in trough FEV_1 was 97 ml (95% CI 85,109) and 54 ml (95% CI 39,69), respectively. FEV_1 was not reported in ETHOS. FEV_1 is a surrogate outcome that has validity in estimating the risk of dying from COPD but little use in assessing the impact of inhaled drug therapy on COPD symptoms. (9)

A recent high quality observational study evaluated the real-world effectiveness of single-inhaler triple therapy with single-inhaler LAMA/LABA therapy amongst nearly 31,000 primary care COPD patients age $\geq$ 40 years in the United Kingdom. (27) From September 15, 2017 (when a triple inhaler first became available in the UK) through 2020, investigators compared 4,106 new users of triple therapy with 29,702 people who were prescribed LAMA/LABA. Patients were naïve to inhaled corticosteroids. During the prior year, 58% had used LAMA, LABA or both; 42% had used no long-acting bronchodilator; 35% had used a systemic corticosteroid. Patients were followed in the UK Clinical Practice Research Datalink database for up to 1 year, with a mean continuous treatment of 6 months in each group. Investigators used adjustment by propensity score weighting to render comparable the two

treatment arms, and reduce the effects of confounding inherent to observational studies although residual confounding cannot be ruled out in any observational study.

Compared with single-inhaler LAMA/LABA, single-inhaler triple therapy including inhaled corticosteroid had a similar risk of the primary outcome, a first moderate or severe exacerbation, adjusted HR 1.08 (95% CI 1.00–1.16). This finding, based on patients not previously treated with an ICS, avoiding the confounding effects of abrupt ICS withdrawal, differs from the reductions in moderate or severe exacerbations reported in IMPACT and ETHOS.

Triple therapy increased all-cause mortality (HR 1.53, 95% CI 1.30-1.79) relative to dual bronchodilators in the observational study of ICS-naïve patients. Although the IMPACT and ETHOS trials reported significant overall reductions in total mortality with triple therapy versus dual bronchodilator therapy, this effect was predominantly in patients who had to abruptly discontinue ICS at randomization. Among patients who were not using ICS prior to randomization, the HRs of total mortality comparing triple therapy with dual LAMA-LABA therapy were 1.25 (95% CI 0.60, 2.59) in IMPACT and 1.49 (95% CI 0.49, 4.55) in ETHOS. (17,18) These estimates are unimpacted by the effect of abrupt ICS withdrawal at randomization and are consistent with the findings of the observational study that excluded patients already treated with ICS.

Triple therapy increased pneumonia requiring hospitalization: adjusted HR 1.50 (95% CI 1.29-1.75). This is consistent with the 65% and 78% increases in serious pneumonias with triple therapy reported in the IMPACT and ETHOS trials, respectively.

Despite the use of propensity score weighting which created groups highly comparable on all available measures of patient characteristics, residual confounding cannot be ruled out in any observational study, including COPD severity.

5. Overall Summary

- Two studies were included: IMPACT 2018 and ETHOS 2020, both double blind RCTs of 52 weeks duration comparing single inhaler triple therapy with LAMA/LABA and ICS/LABA, all administered once daily as a single inhaler, in 18,864 patients with symptomatic COPD and a history of exacerbation within a year before enrolment.
- IMPACT 2018 and ETHOS 2020 are judged to have a high risk of bias according to the Cochrane Risk of Bias 1.0 Tool with respect to attrition and source of funding. Therefore, the overall quality of evidence is low for all outcomes except total mortality.
- Both studies share a major study design flaw that seriously undermines the claimed benefit of reduced mortality with triple therapy. Patients with a history of asthma (who are known to benefit from ICS use) were included and 70-80% were receiving ICS, including 40% already using triple therapy. Abrupt ICS withdrawal at randomization. There was an excess of deaths and exacerbations in the LAMA/LABA group compared with triple therapy during the first 90 days of follow-up when the effects of abrupt corticosteroid withdrawal would be maximal. No benefit of triple therapy was observed during the remaining 9 months of follow-up, Analyses limited to the subgroup of ICS-naive patients in IMPACT and ETHOS

found no mortality benefit. Thus, the claimed benefit of triple versus dual inhaler therapy is likely due to abrupt ICS withdrawal in the LAMA/LABA group.

- There was no reduction in total serious adverse events (which includes all cause hospitalization and hospitalization due to severe exacerbation).
- There was no difference in total adverse events and withdrawal due to adverse events.
- The risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with LAMA/LABA but not with ICS/LABA, although reporting for this outcome is also incomplete.
- The claimed benefit of a reduced rate of moderate to severe exacerbations may be solely due to abrupt ICS or LABA withdrawal and needs to be reported as the proportion of patients with one or more exacerbations.
- There is insufficient evidence whether triple therapy improves quality of life or dyspnea symptoms.
- There is insufficient evidence whether triple therapy reduces use of rescue salbutamol.

6. Conclusion

- First-line triple therapy in treatment-naïve COPD patients, including people deemed at *"high risk"* of exacerbation, has not been studied in RCTs.
- Independent of blood eosinophil count, there is insufficient evidence that escalation to triple therapy – compared with dual bronchodilator therapy - reduces mortality or moderate or severe exacerbations in COPD patients deemed at *"high risk"* of exacerbation.

Single-inhaler triple therapy for treatment of adult patients with moderate-to-severe chronic obstructive pulmonary disease (COPD)

Background

Diagnosis and management of COPD

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airway inflammation and airflow limitation that is not fully reversible. It occurs as a consequence of exposure to noxious particles or gases. Exposure to cigarette smoke is the most common risk factor. Drugs to treat COPD are licensed by regulatory authorities based on short-term randomized trials (typically 12 weeks in duration) that show an improvement in the surrogate marker FEV_1 which is the primary outcome measure in most trials. However, the goal of treating COPD is to prevent acute moderate to severe exacerbations, improve quality of life and reduce symptoms such as dyspnea. (1)

The main treatment options for COPD belong to a number of pharmacological classes – bronchodilators (short-acting $beta_2$ agonists [SABA], long-acting $beta_2$ agonists [LABA], short-acting muscarinic antagonists [SAMA], and long-acting muscarinic antagonists [LAMA]), inhaled corticosteroids [ICS], and inhibitors of the enzyme phosphodiesterase-4 [PDE4 inhibitors]. Numerous clinical practice guidelines recommendations involve a stepwise intensification of drug therapy.

Single-inhaler triple therapy approved in Canada

Two triple therapy inhalers are approved in Canada to reduce exacerbations and airflow obstruction in patients with COPD not adequately treated by ICS/LABA or LAMA/LABA combinations. (2-5)

- Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol);
- Breztri Aerosphere (budesonide/glycopyrrolate/formoterol fumarate)

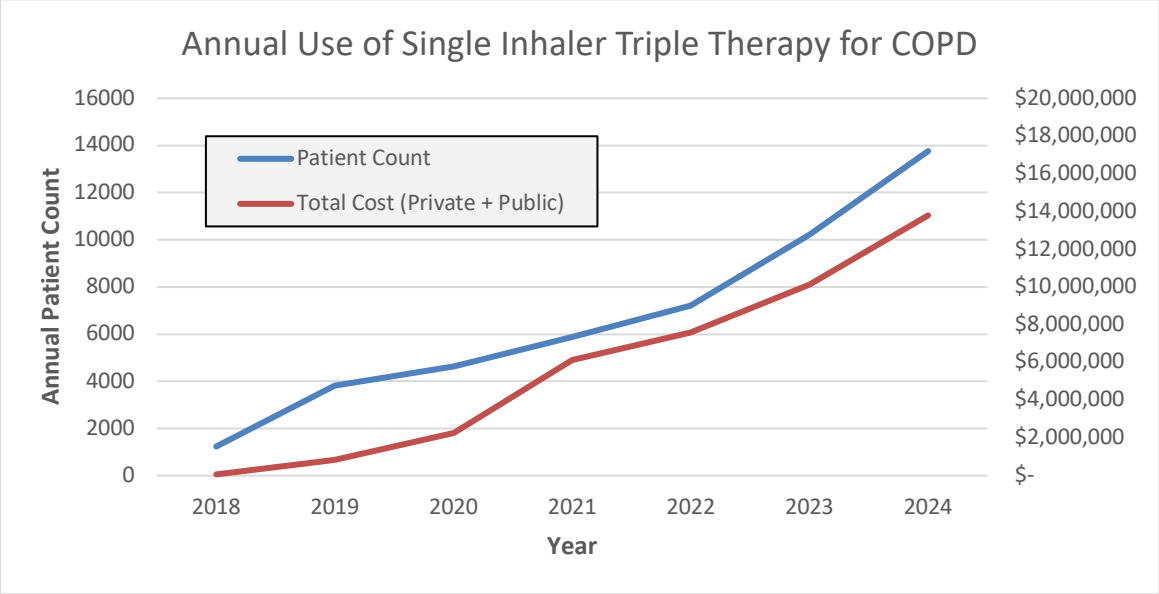
Current annual costs in BC (excluding dispensing fees) are $1,810 for Trelegy Ellipta and $1,670 for Breztri Aerosphere. (6)

For people who experience persistent dyspnea and are at *"high risk"* of exacerbation despite maximal LAMA/LABA therapy, the 2025 BC and 2023 CTS guidelines recommend adding ICS as "step-up" to triple therapy. (7,8) We italicise "*high risk"* within quotations, to remind readers that this categorization can only be applied retrospectively (i.e., prior history of moderate or severe exacerbations). The GOLD 2025 update, published in November 2024, recommends adding ICS only if eosinophils are $\geq$100/uL, **but adds that evidence *"strongly favours use"* only with eosinophils $\geq$300/uL**. (9) For patient convenience, CTS and GOLD recommend a single inhaler. All guidelines emphasize the

crucial importance of smoking cessation, appropriate immunizations, maintaining physical fitness, demonstrating and rehearsing effective inhaler technique.

Since their introduction in 2018, dispensing of triple therapy inhalers for people diagnosed with COPD in BC has increased steadily. (10) (Figure 1) This is probably not limited to people with *"high risk"* COPD. Combined costs for both triple inhalers (without dispensing fees or markups) reached almost $14 million in 2024 for just under 14,000 people. Of this, PharmaCare paid $6.65 million from public funds.

Figure 1: Single-inhaler triple therapy for COPD in BC (2018-2024)



Caption: Annual users and total cost (public plus private) of triple therapy single-inhalers (*Trelegy Ellipta* and *Breztri Aerosphere*) used for COPD in BC. Between 2019 and 2024, usage of these inhalers grew by 23%/year. This may reflect a shift from multi-device triple therapy to single-inhalers.

Recent guideline recommendations for triple therapy

The GOLD 2025 update, published in November 2024, includes a section titled, "Therapeutic interventions that reduce COPD mortality" which cites previous studies (e.g., TORCH, SUMMIT, UPLIFT) that failed to show mortality benefit. Two studies with triple therapy, IMPACT and ETHOS, are reported to have a mortality benefit compared with dual bronchodilator therapy in patients with a history of exacerbations who were previously receiving maintenance therapy with triple therapy, LABA+ICS or dual long-acting bronchodilator (LABD) therapy (LAMA-LABA). No mortality benefit was seen with triple therapy versus ICS-LABA.

The mortality estimates in Figure 2 are not from the original studies, but from post-hoc analyses which included vital status of patients that were missing from the original manuscripts. Both compared triple therapy with dual long-acting bronchodilator (LABD) (i.e., LAMA-LABA).

Mortality was based on "on-treatment" (i.e., per protocol) analysis in IMPACT, whereas ETHOS assessed mortality in the intention-to-treat population.

Figure 2: Evidence supporting a reduction in mortality with pharmacotherapy according to GOLD 2025

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Single inhaler triple therapy compared to dual LABD therapy relative risk reduction: IMPACT: HR 0.72 (95% CI: 0.53, 0.99)[1a] ETHOS: HR 0.51 (95% CI: 0.33, 0.80)[1b]	Symptomatic people with a history of frequent and/or severe exacerbations

The GOLD 2025 update reiterates: *"There is no high-quality evidence such as randomized controlled trials to support initial pharmacological treatment strategies in newly diagnosed patients."* Its new *"practical recommendation"* for patients defined as *"high risk"* is to **consider a patient's blood eosinophil count when deciding whether to initiate ICS treatment.** (11) Despite the caveat that *"there are no direct data concerning initiation of triple therapy in newly diagnosed patients,"* GOLD 2025 recommends **considering first-line triple therapy** for patients with eosinophils ≥300/µL. In *"high-risk"* patients already using LAMA/LABA therapy, it recommends escalation to triple therapy if eosinophils are ≥100/µL, but to azithromycin or roflumilast when eosinophils are <100/µL.

However, no RCT has evaluated using blood eosinophil count as a factor when deciding whether to add ICS treatment in patients at any level of severity, including COPD defined as *"high risk."*

In contrast, the Canadian guideline (CTS) recommends first-line triple therapy **for patients with a high symptom burden and severe health impairment** at *"high risk"* of exacerbations, **regardless of eosinophil count**. For people with **persisting dyspnea** at *"high"* or *"low"* risk of exacerbation despite dual LAMA/LABA therapy, CTS recommends escalation to triple therapy. (12)

2018 TI DAWG review of Trelegy Ellipta

In 2018, the Ministry of Health's Pharmaceutical, Laboratory & Blood Services Division (PLBSD) requested an evidence review of Trelegy Ellipta, a single dose triple therapy containing fluticasone furoate 100mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg (FF/UMEC/VI), as compared to combination therapy with 2 drugs (UMEC 62.5 mcg/VI 25 mcg or FF 100 mcg/VI 25 mcg or UMEC 62.5 mcg/FF 100 mcg), all administered once daily as a single inhaler, in preventing acute moderate to severe exacerbations, improving quality of life and reducing dyspnea symptoms in adult patients with symptomatic COPD (diagnosed FEV1/FVC <0.70).

The TI report dated September 12, 2018 identified and critically appraised IMPACT 2018, the only study that met the inclusion criteria. (13) IMPACT 2018 randomized 10,355 patients with symptomatic COPD and a history of exacerbations despite being on triple therapy (38%) and

combination therapy with ICS/LABA (29%) or LAMA/LABA (9%) at baseline. This 1-year study compared triple therapy with FF/UMEC/VI (n=4151) with UMEC/VI (n=4134) and FF/VI (n=2070), all administered once daily as a single inhaler. The same drugs and doses of ICS, LABA and LAMA were used in the triple-therapy and comparator groups. No studies were identified that compared FF/UMEC/VI with FF/UMEC.

The review concluded that based on IMPACT 2018 there is insufficient evidence that triple therapy with FF/UMEC/VI provides a therapeutic advantage versus dual therapy (FF/VI or UMEC/VI) in terms mortality, total serious adverse events (which includes all cause hospitalization and hospitalization due to severe exacerbation), moderate exacerbations, total adverse events or withdrawal due to adverse events, COPD symptoms or quality of life.

Since the 2018 TI DAWG review, another single-inhaler triple therapy Breztri Aerosphere (budesonide/glycopyrrolate/formoterol fumarate) has since been licensed in Canada to reduce exacerbations and airflow obstruction in patients with COPD not adequately treated by ICS/LABA or LAMA/LABA combinations. (3,5) Also, recent guidelines added a new recommendation for single-inhaler triple therapy as initial treatment for COPD patients at *"high risk"* of exacerbation. Guidelines assign the term *"high-risk"* to patients who within the last year have experienced at least 2 moderate, or at least 1 severe exacerbation of COPD. A "moderate exacerbation" implies antibiotic or oral corticosteroid treatment, whereas "severe exacerbation" requires an emergency department visit or hospitalization. We italicise "*high risk"* within quotations, to remind readers that this categorization can only be applied retrospectively.

PLBSD requested an updated search of the scientific literature to identify any new RCT evidence published since the completion of the 2018 TI DAWG review on the comparative effects of single-inhaler triple therapy versus corresponding dual therapy (LAMA/LABA or ICS/LABA) on moderate to severe exacerbations, total mortality, quality of life and dyspnea symptoms in COPD patients at high risk of exacerbation.

Requested research question

The policy relevant research question, '**What is the evidence to support a mortality benefit of triple inhaler therapy in COPD patients?'** was operationalized for systematic review design using a PICOS approach to research question formulation. Studies were selected for inclusion in the systematic review based on the predetermined selection criteria presented below:

Participants: Adult patients with COPD:
1) who are not adequately treated by ICS/LABA or LAMA/LABA (i.e., at "high risk" of exacerbations, or;
2) who are treatment-naïve and at "high risk" of exacerbations

Intervention: Single-inhaler triple therapy with ICS/LAMA/LABA available in Canada.

Comparators: Corresponding dual therapies (LAMA/LABA or ICS/LABA) (i.e., same drug and dose as triple therapy components).

Outcome hierarchy:

1. Total mortality
2. Total serious adverse events (including total hospitalizations)
3. Number of patients with one or more acute moderate or severe exacerbation
4. Quality of life measured by Saint George Respiratory Questionnaire (SGRQ) total score (≥ 4 point change in total score is considered as minimal clinically important difference in clinical trials; and a mean change in total score from baseline)
5. Time to first moderate or severe exacerbation
6. Improvement in symptoms such as dyspnea measured by Transition Dyspnea Index (TDI) score (≥ 1 point improvement is considered MCID in clinical trials; a mean change in TDI score)
7. Decreased need for rescue medications (an additional measure of symptom improvement)
8. Total adverse events
9. Total withdrawals
10. Withdrawal due to adverse events
11. COPD related health care utilization (physician visits/ER visits and hospitalization)
12. End of study trough FEV_1 (We accept there is an increase in FEV_1 – a surrogate outcome measure. We will provide range of improvement in FEV_1. Meta-analysis of this outcome will not be performed.)

Study design: Double blind randomized active controlled parallel group clinical trial of at least 24 weeks duration. Randomized active controlled clinical trials comparing triple therapy versus 2 drug combinations (LABA/LAMA or LABA/ICS or LAMA/ICS) NOT available in Canada are out of scope. Other study designs are also out of scope.

Methods

Search strategy

We searched Ovid MEDLINE, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from dates of inception until April 2024. We also searched clinicaltrials.gov, Drugs@FDA, European Medicines Agency public assessment reports and the manufacturer's website for all relevant RCT reports.

Study selection

The initial search of all the databases was performed to identify citations of potential relevance. The initial screen of these abstracts excluded articles whose titles and/or abstracts are clearly irrelevant. The full texts of remaining articles were then retrieved (and translated into English where required). Two independent reviewers assessed the eligibility of the trials using a standardized trial selection form. A third reviewer resolved any discrepancies.

Data collection and analysis

Data extraction was done by two independent reviewers. Review Manager 5.4 software of the Cochrane Collaboration was used to meta-analyze data. Results are presented as relative risks (RR) with 95% confidence intervals for dichotomous outcomes and as weighted mean difference (WMD) with 95% confidence interval for continuous outcomes.

Assessment of risk of bias in included studies

Risk of bias for each included trial was assessed using the Cochrane Risk of Bias 1.0 tool which includes seven domains: Randomization; allocation concealment; blinding of participant and physician; blinding of outcome assessor; attrition bias; selective reporting bias; and other bias (e.g., conflict of interest bias - funding of study by the manufacturer or employee of the manufacturer is author of the study). Each domain was assessed as "Low", "Unclear" or "High" risk of bias.

Evaluative framework

Evidence from various sources is organized and situated within a health outcome and evidence hierarchy. The principle is that health outcomes higher on the hierarchy are more important than those lower on the hierarchy. Recognizing that not all outcomes are of equivalent value and not all evidence has uniform protection against bias, the overall framework for the review was based on a hierarchy of outcomes provided in section 2. As much as possible, the hierarchy was completed for each included study.

Results

Findings from the literature

No RCT evaluated initiation of single-inhaler triple therapy in newly diagnosed or treatment-naïve COPD patients at "high risk" of exacerbations.

Our updated search identified one new study (ETHOS 2020) that met our inclusion criteria. (14)

Summary of excluded studies

Reasons for exclusion of the excluded studies are provided in Table 1.

Table 1: Excluded studies

Clinical Study ID/Reference	Reason for Exclusion
KRONOS 2018 (15)	No requirement of a history of exacerbations. Approximately 75% of randomized patients had 0 moderate or severe COPD exacerbations in the past 12 months
TRIBUTE 2018 (16)	Single inhaler triple therapy not available in Canada: Trimbow® (beclomethasone 87 mcg/glycopyrronium 9 mcg/ formoterol 5 mcg) pressurized metered-dose inhaler

Description of included studies

Two 52-week double-blind RCTs (IMPACT 2018, ETHOS 2020) evaluated single-inhaler triple therapy versus single-inhaler dual therapy (LAMA/LABA or ICS/LABA) in COPD patients with a moderate to high symptom burden and history of moderate or severe exacerbations in the 12 months prior to study enrolment. (13,14)

Both included RCTs described in Table 2 enrolled patients with a mean duration of 8 years since diagnosis of COPD. Their primary outcome was the incidence of moderate or severe exacerbations. At baseline, almost all patients (92-100%) were already receiving inhaler therapy, including 70-80% treated with an inhaler containing ICS (double or triple therapy). Fourty percent of participants were already using triple therapy when randomized to continue triple therapy or step down to dual therapy. Patients with a history of asthma were permitted and 20-30% had bronchodilator reversibility at baseline. Results of these RCTs cannot be extrapolated to naïve patients for whom triple therapy is considered for first-line treatment.

Table 2: Double-blind RCTs of single-inhaler triple therapy versus dual therapy

Study, duration	Patient characteristics at baseline	Triple therapy	Dual bronchodilator (LAMA/LABA or ICS/LABA)	Prespecified primary outcome
IMPACT 2018 52-wk DBRCT	N=10,355 with symptomatic COPD. Exacerbations in previous yr: ≥2 moderate (47%), ≥1 severe (26%). Past asthma diagnosis included. **At baseline, 40% on triple therapy, 70% on ICS.**	Trelegy Ellipta Once daily (fluticasone 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg)	LAMA/LABA once daily (umeclidinium 62.5 mcg/ vilanterol 25 mcg) OR ICS/LABA once daily (fluticasone furoate 100 mcg/ vilanterol 25 mcg)	Annual rate of moderate or severe exacerbations
ETHOS 2020 52-wk DBRCT	N=8,509 with symptomatic COPD. Exacerbations in previous yr: ≥2 moderate or severe (56%), ≥1 severe (21%). Past asthma diagnosis included. **At baseline, 40% on triple therapy, 80% on ICS.**	Breztri Aerosphere twice daily (budesonide 320 or 160mcg/glycopyrrolate 18 mcg/formoterol 9.6 mcg	LAMA/LABA twice daily (glycopyrrolate 18 mcg/ formoterol 9.6 mcg) OR ICS/LABA twice daily (budesonide 320 mcg/ formoterol 9.6 mcg)	Annual rate of moderate or severe exacerbations

IMPACT 2018 is a double blind RCT in 10,355 patients with symptomatic COPD and a history of exacerbation within a year before enrolment. (13) This study compared triple therapy with FF/UMEC/VI (n=4151) with UMEC/VI (n=4134) and FF/VI (n=2070), all administered once daily as a single inhaler. The same agents and doses of ICS, LABA and LAMA were used in the triple-

therapy and comparator groups. No studies were identified that compared FF/UMEC/VI with FF/UMEC. A description of the study characteristics is provided in Table 3.

Table 3: IMPACT 2018 study characteristics

Participants	N=10,355 symptomatic COPD (CAT score ≥ 10) patients ≥ 40 years of age with: 1) FEV_1 < 50% of predicted normal value and a history of ≥ 1 moderate or severe exacerbation in previous year; or 2) FEV_1 of 50-80% of predicted normal value and a history of ≥ 2 moderate or 1 severe exacerbation in previous year
Intervention	FF/UMEC/VI (100/62.5/25 mcg) OD administered as single inhaler (n=4151)
Comparators	FF/VI (100/25 mcg) OD administered as single inhaler (n=4134) UMEC/VI (62.5/25 mcg) OD administered as single inhaler (n=2070)
Outcomes	**PRIMARY:** • Annual rate of moderate or severe exacerbations **SECONDARY (prespecified):** • Change from baseline in trough FEV_1 at wk 52 for FF/UMEC/VI vs. FF/VI; Change from baseline in SGRQ total score at wk 52 for FF/UMEC/VI vs. FF/VI; Time to first on-treatment moderate or severe exacerbation comparing FF/UMEC/VI with UMEC/VI and with FF/VI; • Annual rate of on-treatment moderate and severe exacerbations comparing FF/UMEC/VI with UMEC/VI in patients with eosinophil count ≥ 150 cells/µL; • Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with UMEC/VI and with FF/VI
Study Design	Multicentre 3-arm parallel group DBRCT consisting of a 2-week run-in period, up to 52-week treatment period and a 1-week safety follow-up period

There were no significant differences among the 3 treatment groups at baseline with regard to demographics, COPD exacerbations and CAT score (Table 4). The mean age of study patients was 65.3 (8.3) years, 66% were males, and 65% were former smokers. Postbronchodilator FEV_1 was 45.5% of predicted normal value and a mean CAT score of 20.1 (6.1) at screening. Forty seven percent and 26% had a history of ≥ 2 moderate COPD exacerbations and ≥ 1 severe COPD exacerbation, respectively. Patients with a history of asthma were included in the study. Use of specific drugs within the LABA, LAMA and ICS class is not reported. Nearly 40% of the patients were receiving triple therapy, and more than 70% were receiving ICS at randomization. It is not reported whether dual therapy (LAMA/LABA or LABA/ICS) actually failed in those patients receiving triple therapy at screening.

Table 4: IMPACT 2018 baseline characteristics of study participants

	FF/UMEC/VI 100/62.5/25mcg (n=4151)	**FF/VI 100/25mcg (n=4134)**	**UMEC/VI 62.5/25mcg (n=2070)**
Age (years), mean (SD)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)
Female sex	1385 (33%)	1386 (34%)	714 (34%)
Former smokers	2715 (65%)	2711 (66%)	1342 (65%)
Moderate or severe COPD exacerbations in previous year			
0	2 (<1%)	5 (<1%)	9 (<1%)
1	1853 (45%)	1907 (46%)	4691 (45%)
2	1829 (44%)	1768 (43%)	4487 (43%)
≥3	467 (11%)	454 (11%)	1168 (11%)
≥2 moderate COPD exacerbations in previous yr	1967 (47%)	1921 (46%)	989 (48%)
≥1 severe COPD exacerbation in previous yr	1087 (26%)	1069 (26%)	515 (25%)
≥2 severe COPD exacerbations in previous yr	147 (4%)	148 (4%)	76 (4%)
CAT score, mean (SD)	20.1 (6.1)	20.1 (6.1)	20.2 (6.2)
Postbronchodilator FEV_1 (% predicted normal value), mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)
COPD medication taken at screening			
ICS + LABA + LAMA	1396 (34%)	1433 (35%)	734 (35%)
ICS + LABA	1103 (27%)	1067 (26%)	523 (25%)
LABA + LAMA	330 (8%)	308 (7%)	163 (8%)
LAMA	273 (7%)	331 (8%)	140 (7%)
ICS + LABA + LAMA + Xanthine	142 (3%)	88 (2%)	67 (3%)
ICS	109 (3%)	109 (3%)	55 (3%)
ICS + LABA + Xanthine	109 (3%)	103 (2%)	51 (2%)
LABA	98 (2%)	105 (3%)	42 (2%)
ICS + LABA + LAMA + PDE4 inhibitors	39 (<1%)	41 (<1%)	21 (1%)
ICS + LAMA	42 (1%)	36 (<1%)	18 (<1%)
LABA + LAMA + Xanthine	23 (<1%)	16 (<1%)	15 (<1%)

Overall, 9087 patients (88%) completed the trial and 7991 (77%) completed the trial while receiving randomized therapy. This study analyzed safety and efficacy data using an intention-to-treat approach, which is a method designed to overcome loss of information due to premature discontinuation of study treatment. However, a full intention-to-treat analysis was not performed because patients who permanently discontinued study treatment did not come in for further evaluation. Patients were encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, SAEs and concomitant medications post-treatment. However, number of calls completed and the accuracy and completeness of phone call information in those patients who were successfully contacted is unknown. Vital status was available from independent data sources for 9781 (94.4%) of the total study population at Week 52. A summary of patient disposition is provided in Table 5.

Table 5: Patient disposition in IMPACT 2018

	FF/UMEC/VI	FF/VI	UMEC/VI
Randomized	4151	4134	2070
Total withdrawals	758 (18%)	1040 (25%)	566 (27%)
Total adverse events	2897 (70%)	2800 (68%)	1429 (69%)
Withdrawal due to lack of efficacy	163 (4%)	313 (8%)	172 (8%)
Withdrawal due to adverse events	252 (6%)	327 (8%)	187 (9%)
Lost to follow-up	21 (0.5%)	25 (0.6%)	14 (0.7%)

Risk of bias in IMPACT 2018

The Cochrane Risk of Bias tool was used to assess the quality of IMPACT 2018. This appraisal tool highlights both the strengths and weaknesses of included studies. Key elements of trial methodology and reporting are assessed using a standardized set of criteria. If the methods are inadequate there is a "high risk of bias". If the risk of bias is "unclear" usually the trial report did not adequately describe the methods. If the methodology and reporting are adequate there is a low risk of bias. IMPACT 2018 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition, selective reporting and source of funding. (Table 6). There are also other biases with respect to study design and the presence of confounding that misrepresent the treatment effect (see Discussion).

Table 6: Cochrane risk of bias summary for IMPACT 2018

Domain	Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	"Patients will be randomised using the proprietary RandAll software (GlaxoSmithKline), and assigned to treatment using the Randomisation and Medication Ordering System (RAMOS; GlaxoSmithKline)."
Allocation concealment (selection bias)	Low risk	"The study will use site-based randomization to allocate treatments. Once a randomization number is assigned to a subject it cannot be reassigned to any other subject in the study."
Blinding of participants and personnel (performance bias)	Low risk	"Each regimen was administered in a single dry-powder inhaler (DPI) (Ellipta, GlaxoSmithKline)." "Investigational product…will be double-blinded and will be delivered by DPIs that are identical in appearance. Neither the subject nor the Investigator will know which IP the subject is receiving."
Blinding of outcome assessment (detection bias)	Low risk	"Blinded evaluation of exacerbation rates is planned for this study…"

Domain	Judgement	Support for Judgement
		"All reports of serious adverse events and all trial deaths were adjudicated by an independent adjudication committee whose members were unaware of the treatment assignments."
Incomplete outcome data (attrition bias)	High risk	The intent-to-treat (ITT) population will comprise all patients who are randomized to treatment except for those randomised in error. This is the primary analysis population and will be used for safety and efficacy analyses." "Patients who permanently discontinue study treatment will be encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, SAEs and concomitant medications post-treatment." **It is important to know how many were contacted and how missing data were handled (e.g. LOCF analysis) for those who could not be contacted but this information is not reported.** "Of the 8,509 patients in the ETHOS intent-to-treat (ITT) population, 384 (4.5%) patients were missing vital status data at Week 52.." **The high withdrawal rates will lead to attrition bias except for mortality data.**
Selective reporting (reporting bias)	High risk	The study publication does not report all outcomes specified in the protocol (e.g. rescue salbutamol use; health care utilization)
Other bias	High risk	"The trial was designed by academic partners and the sponsor (GlaxoSmithKline), which also paid for editorial support; the lead author is an employee of the sponsor."

Outcomes reported

Results are presented in Table 7 according to the outcome hierarchy described above. Total mortality data are from secondary analyses of IMPACT and ETHOS following collection of additional vital status data that were missing from the original study publications. IMPACT 2020 and ETHOS 2021 report vital status data for 99.6% of the intention-to-treat population in both studies (IMPACT n=10,355; ETHOS n=8509). (17,18)

Table 7: Hierarchy of outcomes in IMPACT 2018

	FF/UMEC/VI (n=4151)	**FF/VI (n=4134)**	**UMEC/VI (n=2070)**
Total mortality (on- and off-treatment) (Final retrieved dataset from IMPACT 2020) Time to 1st event analysis (Final retrieved dataset from IMPACT 2020)	98 (2.4%) RR 0.90(0.68,1.17) vs. FF/VI RR 0.74(0.54,1.01) vs. UMEC/VI HR 0.82(0.60,1.11) p=NS vs. FF/VI HR 0.72(0.53,0.99) p=0.042 vs. UMEC/VI	109 (2.6%)	66 (3.2%)
Total mortality (on-treatment only) from IMPACT 2020 Time to 1st event analysis	50 (1.2%) HR 0.58(0.38,0.88) p=0.01 vs. UMEC/VI	49 (1.2%) HR 0.61(0.40,0.93) p=0.02 vs. UMEC/VI	39 (1.9%)
Total SAEs	895 (22%)	850 (21%)	470 (23%)
Total hospitalizations	NR	NR	NR
Hospitalization due to severe COPD exacerbation	NR	NR	NR
SAE of pneumonia	184 (4%)	152 (4%)	54 (3%)
Prespecified AE of pneumonia	317 (8%) RR 1.63 (1.31,2.03) p<0.0001 vs. UMEC/VI RR 1.08 (0.93,1.26) p=NS vs. FF/VI	292 (7%) RR 1.51(1.21,1.88) p=0.0003 vs. UMEC/VI	97 (5%)
Number of patients with ≥1 moderate or severe COPD exacerbation	NR	NR	NR
Number of patients with ≥1 severe COPD exacerbation	NR	NR	NR
SGRQ total score – based on subset of 7814 (76%) patients Patients evaluated Change from baseline Difference	 3318 (80%) -5.5(-5.9,-5.0) -1.8(-2.4,-1.1) p<0.001 vs. FF/VI	 3026 (73%) -3.7(-4.2,-3.2)	 1470 (71%) -3.7(-4.4,-3.0)

	FF/UMEC/VI (n=4151)	FF/VI (n=4134)	UMEC/VI (n=2070)
Patients with ≥4 point decrease (MCID)	-1.8(-2.6,-1.0) p<0.001 vs. UMEC/VI 1723 (42%) OR 1.41(1.29,1.55) vs. FF/VI OR 1.41(1.26,1.57) vs. UMEC/VI	1390 (34%)	696 (34%)
Time to 1st moderate or severe exacerbation	HR 0.85(0.80, 0.91) p<0.001 vs. FF/VI HR 0.84(0.78, 0.91) p<0.001 vs. UMEC/VI		
Transition Dyspnea Index – based on subset of 5058 (49%) patients Patients with ≥1 unit increase (MCID)	36% OR 1.36 (1.19, 1.55) p<0.001 vs. FF/VI OR 1.33 (1.13, 1.57) p<0.001 vs. UMEC/VI	29%	30%
Use of rescue salbutamol	NR	NR	NR
COPD related health care utilization	NR	NR	NR
Trough FEV_1 – based on subset of 7646 (74%) patients Patients evaluated Change from baseline (mL) Difference	3366 (81%) 94(86,102) 97(85,109) p<0.001 vs. FF/VI 54(39,69) P<0.001 vs. UMEC/VI	3060 (74%) -3(-12,6)	1490 (72%) 40(28,52)

ETHOS 2020 is a double blind RCT in 8,588 patients with symptomatic COPD and a history of exacerbation in the year before screening. (14) This study compared budesonide 320 mcg/glycopyrrolate 18 mcg/ formoterol fumarate 9.6 mcg triple therapy (BGF 320) (n=2157) with 160 mcg/ glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg triple therapy (BGF 160) (n=2137), glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg (GFF) (n=2143), and budesonide 320 mcg/formoterol fumarate 9.6 mcg (BFF) (n=2151), all delivered twice daily via a single metered-dose Aerosphere inhaler. No studies were identified that compared BGF 320 or BGF 160 with BG. A description of the study characteristics is provided in Table 8.

Table 8: ETHOS 2020 study characteristics

Participants	N=8588 patients were 40 to 80 years of age and had symptomatic COPD (defined as a score of ≥10 on the COPD Assessment Test, on which scores range from 0 to 40, with higher scores indicating more symptoms; the minimum clinically important difference is 2 points); were receiving at least two inhaled maintenance therapies at the time of screening; had a postbronchodilator ratio of the forced expiratory volume in 1 second (FEV1) to the forced vital capacity of less than 0.7, with a postbronchodilator FEV1 of 25 to 65% of the predicted normal value; had a smoking history of at least 10 pack-years; and had a documented history of at least one moderate or severe COPD exacerbation (if their FEV1 was <50% of the predicted normal value) or at least two moderate or at least one severe COPD exacerbation (if their FEV1 was ≥50% of the predicted normal value) in the year before screening
Intervention	Budesonide 320 mcg/glycopyrrolate 18 mcg/formoterol 9.6 mcg (n= 2157) Budesonide 160 mcg/glycopyrrolate 18 mcg/formoterol 9.6 mcg (n=2137)
Comparators	Glycopyrrolate 18 mcg/formoterol 9.6 mcg (n=2143) Budesonide 320 mcg/formoterol 9.6 mcg (n=2151)
Outcomes	**PRIMARY:** • **A**nnual rate (the estimated mean number per patient per year) of moderate or severe COPD exacerbations **SECONDARY (prespecified):** • Time to first moderate or severe COPD exacerbation • Change from baseline in average daily use of rescue medication over 24 weeks • Percentage of patients who had a SGRQ response (defined as ≥4 point decrease from baseline in total SGRQ score) • Annual rate of severe COPD exacerbations • Time to death from any cause
Study Design	Randomized, double-blind, multicenter, parallel-group, 52-week study

There were no significant between-group differences at baseline with regard to demographics, COPD exacerbations and CAT score (Table 9). The mean age of study patients was 64.6 (7.6) years, 60% were males, and 59% were former smokers. Postbronchodilator FEV_1 was 43.4% of predicted normal value and a mean CAT score of 19.1 (6.6) at screening. Fifty six percent and 21% had a history of ≥ 2 moderate or severe COPD exacerbations and ≥ 1 severe COPD exacerbation, respectively. Patients with a history of asthma were included in the study and approximately 30% had bronchodilator reversibility at baseline. Use of specific drugs within the LABA, LAMA and ICS class is not reported. Approximately 40% of the patients were receiving triple therapy, and 80% were receiving ICS at randomization. It is not reported whether dual therapy (LAMA/LABA or LABA/ICS) actually failed in those patients receiving triple therapy at screening.

Table 9: ETHOS 2020 baseline characteristics of study participants

Demographic Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population)*

	BGF 320/18/9.6 (n=2137)	**BGF 160 160/18/9.6 (n=2121)**	**GFF 18/9.6 (n=2120)**	**BFF 320/9.6 (n=2131)**
Age (years), mean (SD)	64.6 (7.6)	64.6 (7.6)	64.8 (7.6)	64.6 (7.6)
Male sex	1260 (59.0%)	1298 (61.2%)	1244 (58.7%)	1279 (60.0%)
Current smokers	910 (42.6%)	865 (40.8%)	856 (40.4%)	864 (40.5%)
Moderate or severe COPD exacerbations in previous year				
0 Moderate or severe — no. (%)	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
1 Moderate or severe — no. (%)	940 (44.0)	932 (43.9)	907 (42.8)	912 (42.8)
≥2 Moderate or severe — no. (%)	1195 (55.9)	1187 (56.0)	1211 (57.1)	1217 (57.1)
≥1 Severe — no. (%)	451 (21.1)	463 (21.8)	429 (20.2)	458 (21.5)
Blood eosinophil count				
Median (range) — cells/mm^3	165 (0–2510)	167 (5–1590)	170 (5–2305)	167 (0–2430)
≥150 cells/mm^3 — no. (%)	1277 (59.8)	1258 (59.3)	1272 (60.0)	1294 (60.7)
≥300 cells/mm^3 — no. (%)	310 (14.5)	318 (15.0)	293 (13.8)	333 (15.6)
FEV1 after admin of albuterol % of predicted normal value	43.6 ± 10.3	43.1 ± 10.4	43.5 ± 10.2	43.4 ± 10.4
50 to <80%: moderate COPD — no. (%)	613 (28.7)	604 (28.5)	596 (28.1)	614 (28.8)
30 to <50%: severe COPD — no. (%)	1305 (61.1)	1270 (59.9)	1293 (61.0)	1283 (60.2)
<30%: very severe COPD — no. (%)	217 (10.2)	245 (11.6)	229 (10.8)	233 (10.4)
Change in FEV1 from before to after administration of albuterol — ml	146.3 ± 158.0	144.4 ± 151.7	148.7 ± 151.1	142.3 ± 144.8
Bronchodilator reversibility— no. (%)†	657 (30.7)	631 (29.8)	669 (31.6)	654 (30.7)
Use of inhaled glucocorticoid at screening — no. (%)	1706 (79.8)	1729 (81.5)	1707 (80.5)	1704 (80.0)
COPD Assessment Test score ‡	17.7 ± 6.5	19.6 ± 6.6	19.5 ± 6.6	19.5 ± 6.5

* Plus–minus values are means ± SD. The modified intention-to-treat population included all patients who underwent randomization, received any amount of trial treatment, and had post-randomization data obtained before discontinuation of treatment.

† Bronchodilator reversibility was defined as an increase in FEV1 of at least 12% and at least 200 ml after administration of albuterol.

‡ Scores on the COPD Assessment Test range from 0 to 40, with higher scores indicating more symptoms; the minimum clinically important difference (MCID) in score is 2 points.

A total of 7187 patients (83.8%) completed the trial, of whom 6654 (77.6%) completed 52 weeks of treatment (79.4% and 80.4% in the budesonide 320 mcg and budesonide 160 mcg triple-therapy groups, respectively, 74.1% in the GFF group, and 76.6% in the BFF group). This study analyzed safety and efficacy data using a modified intention-to-treat approach. A full intention-to-treat analysis was not performed because patients who permanently discontinued study treatment did not come in for further evaluation. The modified intention-to-treat population included all patients in the intention-to-treat population with post-randomization data obtained before discontinuation of treatment. Any data collected after completion of, or discontinuation of the assigned trial regimen was excluded from the modified intention-to-treat analysis. The safety population included all patients who underwent randomization, received any amount of treatment, and had a post-randomization safety assessment. Time to death was assessed in the intention-to-treat population (all patients who underwent randomization and received any amount of trial treatment) and included all observed data obtained from patients regardless of whether they continued to receive their assigned treatment.

Whether patients were encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, SAEs and concomitant medications post-treatment is unknown. Vital status was known for 8125 of 8509 patients (95.5%) at Week 52. A summary of patient disposition is provided in Table 10.

Table 10: Patient disposition in ETHOS 2020

	BGF 320 320/18/9.6	**BGF 160 160/18/9.6**	**GFF 18/9.6**	**BFF 320/9.6**
Randomized	2157	2137	2143	2151
Total withdrawals	437 (20.3%)	412 (19.3%)	544 (25.4%)	492 (22.9%)
Total adverse events	1368 (63.8%)	1356 (63.8%)	1312 (61.7%)	1377 (64.5)
Withdrawal due to lack of efficacy	103 (4.8%)	102 (4.8%)	171 (8.0%)	136 (6.3%)
Withdrawal due to adverse events	118 (5.5%)	114 (5.3%)	147 (6.9%)	138 (6.4%)
Lost to follow-up	25 (1.2%)	21 (1.0%)	19(0.9%)	15 (0.7%)

Risk of bias in ETHOS 2020

According to the Cochrane Risk of Bias 1.0 tool ETHOS 2020 is judged to have a high risk of bias with respect to attrition and source of funding. (Table 11). There are also other biases with respect to study design and the presence of confounding that misrepresent the treatment effect (see Discussion).

Table 11: Cochrane risk of bias summary for ETHOS 2020

Domain	Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	"Patients have been randomized 1:1:1:1 using an interactive web response system".
Blinding of participants and personnel (performance bias)	Low risk	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) from NCT02465567
Blinding of outcome assessment (detection bias)	Low risk	"An independent data monitoring committee and an independent clinical end-point committee reviewed safety data throughout the trial, including cardiovascular and cerebrovascular events, pneumonia, and cause-specific deaths"
Incomplete outcome data (attrition bias)	High risk	"Most efficacy analyses were conducted in the modified intention-to-treat population (all patients who underwent randomization, received a trial treatment, and had post-randomization data obtained before discontinuation of treatment) with the use of an efficacy estimand, which included only data obtained from patients while they were receiving a trial treatment." "The analysis was performed in the modified intention-to-treat …included only data obtained from patients while they were receiving a trial treatment." **No attempt was made to obtain data after patients discontinued treatment. It is important to use an intention-to-treat approach, which is a method designed to overcome loss of information due to premature discontinuation of study treatment.** "…vital status is available for 9781 (94.4%) of the total study population at Week 52. Data for the remaining 5.6% of patients are currently being sought." **The high withdrawal rates will lead to attrition bias except for mortality data.**
Selective reporting (reporting bias)	Low risk	All outcomes specified in the protocol are reported.
Other bias	High risk	"The ETHOS study is supported by Pearl – a member of the AstraZeneca Group. The sponsor was involved in the study design; the collection, analysis and interpretation of data;

Domain	Judgement	Support for Judgement
		the writing of the report; and in the decision to submit the article for publication"

Outcomes reported

Results are presented in Table 12 according to the outcome hierarchy described above.

Table 12: Hierarchy of outcomes in ETHOS

	BGF 320/18/9.6 (n=2137)	**BGF 160 160/18/9.6 (n=2121)**	**GFF 18/9.6 (n=2120)**	**BFF 320/9.6 (n=2131)**
Total mortality (on- and off-treatment) (Final retrieved dataset) from ETHOS 2021	30 (1.4%) HR 0.51 (0.33, 0.80) P = 0.0035 vs. GFF HR 0.72 (0.44,1.16) P = 0.1721 vs. BFF	44 (2.1%) HR 0.78 (0.53, 1.16) P = 0.2244 vs. GFF HR 1.10 (0.71,1.68) P = 0.6785 vs. BFF	56 (2.6%)	40 (1.9%)
Total mortality (on-treatment only) (Final retrieved dataset) from ETHOS 2021	25 (1.2%) HR 0.50 (0.30, 0.81) P = 0.0056 vs. GFF HR 0.82 (0.47,1.41) P = 0.4640 vs. BFF	36 (1.7%) HR 0.75 (0.48, 1.16) P = 0.1981 vs. GFF HR 1.23 (0.75,2.02) P = 0.4064 vs. BFF	45 (2.1%)	28 (1.3%)
Time to death (all cause) from ETHOS 2020 appendix Figure S2 Panel B	HR 0.54 (0.34,0.87) vs. GFF HR 0.78 (0.47,1.30) vs. BFF	HR 0.79 (0.52, 1.20) vs. GFF HR 1.13 (0.72,1.80) vs. BFF		
Outcomes from ETHOS 2020	**BGF 320/18/9.6 (n=2144)**	**BGF 160/18/9.6 (n=2124)**	**GFF 18/9.6 (n=2125)**	**BFF 320/19.6 (n=2131)**
Total SAEs from ETHOS 2020 Table 3	426 (19.9%)	445 (21.1%)	433 (20.4%)	426 (19.9%)
Total hospitalizations	NR	NR	NR	NR
Hospitalization due to severe COPD exacerbation	NR	NR	NR	NR
SAE of pneumonia from ETHOS 2020 appendix Table S8	64 (3.0%)	54 (2.5%)	28 (1.3%)	51 (2.4%)
Number of patients with ≥1 moderate or	NR	NR	NR	NR

severe COPD exacerbation Number of patients with ≥1 severe COPD exacerbation	NR	NR	NR	NR
Change from baseline in SGRQ total score over 24 weeks from ETHOS 2020 appendix Table S4 Patients evaluated Change from baseline (mean, 95%CI) Mean difference (95% CI) vs comparators	2076 -6.5 (-6.99, -6.01) –0.34 (–0.99 to 0.30) vs BGF 160 –1.62 (–2.27 to –0.97) vs GFF –1.38 (–2.02 to –0.73) vs BFF	2056 -6.2 (-6.69, -5.71) –1.28 (–1.93 to –0.63) vs GFF –1.04 (–1.68 to –0.39) vs BFF	2017 -4.9 (-5.39, -4.41)	2056 -5.1 (-5.59, -4.61)
Change from baseline in SGRQ total score at 52 weeks from ETHOS 2020 appendix Table S4 Patients evaluated Change from baseline (mean, 95%CI) Mean difference (95% CI) vs comparators	1681 -6.4 (-7.09, -5.71) –0.37 (–1.32 to 0.59) vs BGF 160 –1.88 (–2.84 to –0.91) vs GFF –1.47 (–2.43 to –0.51) vs BFF	1680 -6.0 (-6.7,-5.3) –1.51 (–2.48 to –0.54) vs GFF –1.10 (–2.06 to –0.14) vs BFF	1562 -4.5 (-5.2, -3.8)	1631 -4.9 (-5.6, -4.2)
Time to 1st moderate or severe exacerbation from ETHOS 2020 appendix Figure S2 Panel A	HR 0.88 (0.81,0.96) vs GFF HR 0.89 (0.81,0.97) vs BFF	HR 0.87 (0.79,0.94) vs GFF HR 0.87 (0.80,0.95) vs BFF		
TDI focal score over 24 weeks from ETHOS 2020 appendix Table S4 No. of patients evaluated Mean (95% CI) Mean difference (95% CI) vs comparators	2044 1.30 (1.18,1.42) 0.03 (-0.12,0.19) vs BGF160 0.40 (0.24,0.55) vs GFF	2023 1.30 (1.18,1.42) 0.37 (0.21,0.52) vs GFF 0.27 (0.12, 0.43) vs BFF	1983 0.90 (0.78,1.02)	2021 1.00 (0.88,1.12)

	0.31 (0.15,0.46) vs BFF			
Change from baseline in average daily rescue medication use over 24 weeks from ETHOS 2020 appendix Table S4 No. of patients evaluated Mean (95% CI) Mean (95% CI) comparators	1425 -1.20 (-1.92, -1.08) –0.15 (–0.32, 0.01) vs BGF 160 –0.51 (–0.68, –0.34) vs GFF –0.37 (–0.54, –0.20) vs BFF	1389 -1.00 (-1.14, -0.86) –0.35 (–0.53,–0.18) vs GFF –0.22 (–0.39,–0.05) vs BFF	1387 -0.7 (-0.84, -0.56)	1426 -0.8 (-0.92, -0.68)
Total adverse events from ETHOS 2020 Table 3	1368 (63.8%)	1356 (63.8%)	1312 (61.7%)	1377 (64.5%)
Total withdrawals from ETHOS 2020 Figure 1	437 (20.4%)	412 (19.4%)	544 (25.6%)	492 (23.0%)
WDAEs ETHOS 2020 Figure 1	118 (5.6%)	114 (5.3%)	147 (6.9%)	138 (6.6%)
COPD related health care utilization	NR	NR	NR	NR
Trough FEV_1	NR	NR	NR	NR

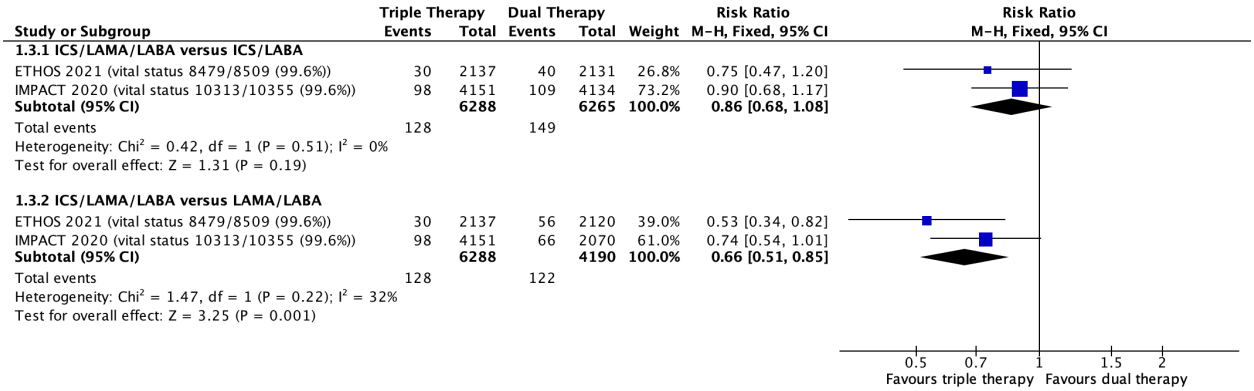
Summary of findings and critical appraisal of included studies

1. Total mortality

There were no differences in on- and off-treatment total mortality rates between triple therapy with FF/UMEC/VI and either dual combination in the final retrieved dataset of IMPACT 2020 [RR 0.74 (95% CI 0.54, 1.01) vs. UMEC/VI; RR 0.90 (95% CI 0.68, 1.17) vs. FF/VI]. The final retrieved dataset of ETHOS 2020 found a reduction in on-and off-treatment total mortality with BGF 320/18/9.6 triple therapy as compared to LAMA/LABA only (GFF 18/9.6) [RR 0.53 (95% CI 0.34, 0.82); ARR 1.2%; NNT 81 for 1 year] but not ICS/LABA (BFF 320/9.6). There was no difference between the lower dose triple therapy group (BGF 160/18/9.6) and either dual combination.

When the 2 studies were pooled for total mortality (on- and off-treatment), there were fewer deaths with triple therapy (2.0%) compared with LAMA/LABA dual therapy (2.9%) [RR 0.66 (95% CI 0.51, 0.85); ARR 0.9%; NNT 114 for 1 year] (Figure 3).

Figure 3: Triple therapy versus dual therapy on total mortality



A major study design flaw seriously undermines the validity of IMPACT 2018 and ETHOS 2020: the confounding effect of abrupt withdrawal of ICS at randomization in those patients assigned to dual bronchodilator (LAMA/LABA) therapy. Patients with a history of asthma (who are known to benefit from ICS use) were included in IMPACT and ETHOS. Approximately 70% and 80% were receiving a COPD regimen that included ICS in IMPACT and ETHOS, respectively. Both IMPACT and ETHOS showed an excess of deaths and exacerbations in the LAMA/LABA group – compared with triple therapy - occurred during the first 90 days of follow-up. (19,20) This includes the 30-day interval when biological effects of abrupt corticosteroid withdrawal would be maximal. During the remaining 9 months of follow-up, no benefit of triple therapy was observed. Analyses limited to the subgroup of ICS-naïve patients in IMPACT and ETHOS found no mortality benefit (HR 1.25 (95% CI: 0.60–2.59) in IMPACT and 1.49 (95% CI: 0.49–4.55) in ETHOS). (20) **Thus, the assumed benefit of triple versus dual inhaler therapy is likely due to abrupt ICS withdrawal in the LAMA/LABA group.** This is one reason why the US FDA Advisory Committee specifically rejected a claim that triple therapy reduces mortality, (21,22) and why Canadian triple inhaler monographs (2,3) and Health Canada's regulatory decisions (4,5) also do not suggest a mortality benefit.

2. SAEs

Both RCTs showed no difference in total SAEs between triple therapy and either dual combination. Hospitalization due to any cause was not reported in either study.

A serious adverse event of pneumonia occurred in 4%, 4%, and 3% of patients treated with FF/UMEC/VI, FF/VI and UMEC/VI, respectively, in IMPACT. Time-to-first-event analysis reveals that the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with UMEC/VI (HR 1.53; 95% CI, 1.22,1.92). In ETHOS a serious adverse event of pneumonia occurred in 3.0%, 2.5%, 2.4% and 1.3% of patients treated with BGF 320, BGF 160, BFF and GFF, respectively. In both studies there was a significantly higher incidence of serious pneumonia in the groups that received ICS than in the LAMA/LABA group. There was no significant difference in the risk of pneumonia between triple therapy and ICS/LABA.

3. Acute moderate or severe COPD exacerbations

a) A moderate exacerbation was defined as an exacerbation leading to treatment with antibiotics and/or systemic glucocorticoids. A severe exacerbation was defined as an exacerbation that required hospitalization or resulted in death.

> **CRITICAL APPRAISAL ISSUE:** Given that these multicenter trials were conducted in 26-37 different countries there will be variability in treatment practices of moderate COPD exacerbations across centers that could bias the study findings**.**

b) The number of patients with one or more acute moderate or severe exacerbations was not reported.

> **CRITICAL APPRAISAL ISSUES:** The trials report the annual rate of moderate or severe exacerbations (pre-specified primary outcome), which was 0.91 per year with triple therapy versus 1.21 per year with the LAMA/LABA (UMEC/VI) combination in IMPACT and 1.08 per year with triple therapy (BGF 320) versus 1.42 per year with the LAMA/LABA (GFF) combination in ETHOS. The study authors added all the exacerbations that took place in a treatment arm and divided by the number of years in the study. Therefore, they counted multiple exacerbations that occurred in a single patient. They then created rate ratios with triple therapy, 0.75 (95% CI 0.70,0.81); 25% difference in the annual rate; P<0.001 in IMPACT and 0.76 (95% CI 0.69–0.83); 24% difference in the annual rate in ETHOS, versus LAMA/LABA. The rate ratio with triple therapy versus ICS/LABA combination in IMPACT was 0.85 (95% CI 0.80,0.90); 15% difference in the annual rate; P<0.001 and 0.87 (95% 0.79–0.95); 13% difference in the annual rate in ETHOS.
>
> Interpreting a 24-25% and 13-15% reduction in an annual rate is not possible without knowing how to divide the effect among individual people. If this rate reduction was a reduction in the proportion of people who had one or more exacerbation, NNT calculations could be made. With a rate estimate, perhaps this means that a person needs treatment for 4 years with triple therapy to prevent one or more additional moderate to severe exacerbation with LAMA/LABA and 7 years versus ICS/LABA?
>
> The reported rates are also uncertain due to the withdrawal rates in the three groups (IMPACT: 18, 25 and 27% in UMEC/FF/VI, FF/VI and UMEC/VI, respectively; ETHOS: 20, 19, 25, 23 and 27% in BGF 320, BGF 160, BFF and GFF, respectively). Excluding enrolled participants from the analysis in RCTs often results in biased estimates of treatment effects. (23) It is unclear how annual rates of moderate or severe exacerbations were calculated and whether patients who withdrew prematurely were appropriately accounted for in this calculation. In an effort to reduce bias in the safety and efficacy analysis, the IMPACT investigators state they tried to collect post-treatment exacerbations, SAEs and concomitant medications data via telephone contacts on patients who prematurely discontinued assigned treatment during follow-up. The success rate as well as the accuracy and completeness of information from these

telephone contacts is not known. This attempt to reduce attrition bias is insufficient without knowing how successful they were at obtaining information via phone contacts. It appears that ETHOS investigators did not attempt to collect post-treatment exacerbations, SAEs and concomitant medications data for patients who discontinued prematurely.

c) Time-to-first-event analysis reported that triple therapy was associated with a lower risk of moderate or severe exacerbations during treatment than dual therapy. In IMPACT, the hazard ratio (HR) on the reported study sample for triple therapy versus FF/VI was 0.85 (95% CI 0.80 to 0.91; 15% difference; P<0.001), and versus UMEC/VI was 0.84 (95% CI 0.78 to 0.91; 16% difference; P<0.001). In ETHOS, the hazard ratio (HR) on the reported study sample for triple therapy (BGF 320) versus BFF was 0.89 (95% CI 0.81 to 0.97); 11% difference, and versus GFF was 0.88 (95% CI 0.81 to 0.96); 12% difference.

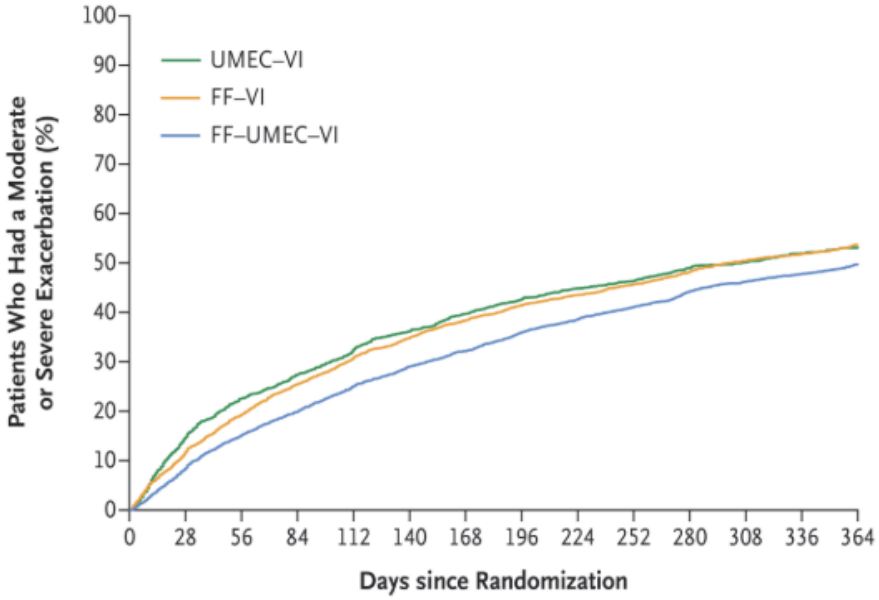
CRITICAL APPRAISAL ISSUE: Time-to-first-event analysis is useful only when it is known how many patients had more than one exacerbation throughout the study in the treatment groups. Time-to-first-event analysis is potentially biased by the increase in exacerbations following abrupt withdrawal of ICS in the LAMA/LABA group.

D) Patients with a history of asthma were included in both studies. In addition, 40% of randomized patients were already receiving triple therapy and more than 70-80% were receiving a COPD regimen that included ICS.

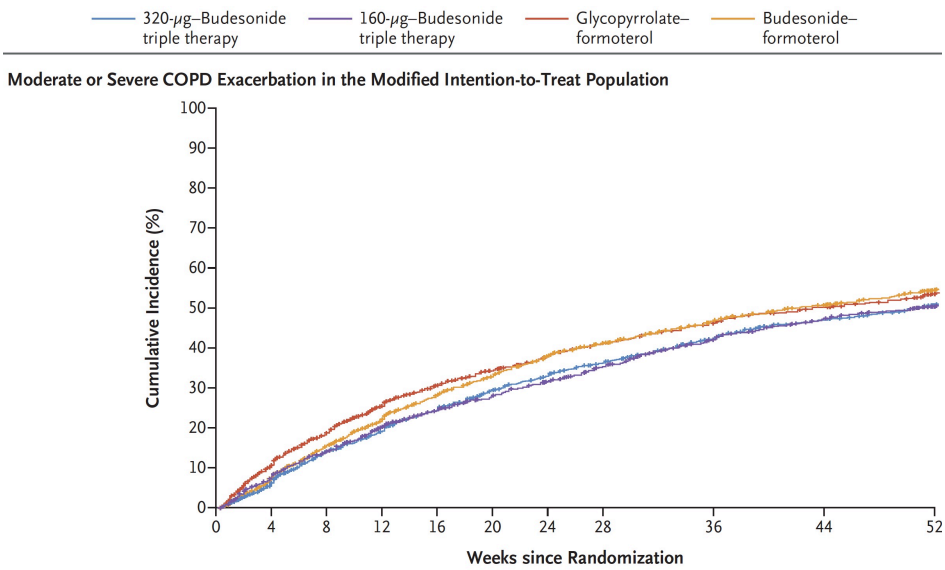
CRITICAL APPRAISAL ISSUE: Sudden ICS withdrawal at randomization in those patients assigned to dual bronchodilator therapy may explain more rapid increase in exacerbations in these group as compared to triple therapy during the first month of follow-up. The incidence of moderate or severe exacerbations among the groups was similar during the subsequent 11 months of follow-up (Figure 4).

Figure 4: Time-to-first-event analysis of moderate or severe COPD exacerbations in IMPACT and ETHOS

A) IMPACT



B) ETHOS



Evidence from double blind, placebo controlled, parallel group RCTs ranging from 26 to 52 weeks duration in patients (N=244-373) with moderate to severe COPD and a history of exacerbations reported that abrupt withdrawal of ICS increased the proportion of patients with one or more severe exacerbations (24,25,26). Of the 244 patients in the 6-month study, 69 (57%) in the placebo (i.e. ICS discontinuation) group and 58 (47%) in the ICS group experienced at least one moderate exacerbation [HR 1.5 (95% CI 1.1,2.1)], defined as worsening of

respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics. (24) In a 1-year pragmatic RCT in 260 primary care COPD patients the relative risk of experiencing a moderate (i.e. requiring oral corticosteroids or antibiotics) or severe exacerbation (i.e. resulting in hospitalization) was greater with placebo versus continued ICS [RR 1.6 (95% CI 1.2,2.2); P<0.001]. (25) The effects of 1-year withdrawal of ICS after a 3-month run-in with ICS/LABA were studied in 373 COPD patients. (26)

4. Health-related quality of life

SGRQ was used to measure health-related quality of life in this study. SGRQ total score ranges from 0 to 100, with lower scores indicating better health-related quality of life. A minimum change in score of 4 points is considered as clinically important (i.e. MCID).

Mean change in SGRQ total score was evaluated in 7814 (76%) patients in IMPACT. In this subset of patients there were significant differences between the FF/UMEC/VI group and the FF/VI [-1.8 (95% CI -2.4,-1.1)] and UMEC/VI [-1.8 (95% CI-2.6,-1.0)] groups. In ETHOS, mean change in SGRQ total score was evaluated in 6554 (77%) patients. In this subset of patients there were significant differences between the BGF 320 group and the BFF [-1.5 (95% CI -2.4,-0.5)] and GFF [-1.9 (95% CI-2.8,-0.9)] groups.

> **CRITICAL APPRAISAL ISSUE:** SGRQ total score was only reported for a subset (76-77%) of patients. The finding of improved quality of life with triple therapy is unreliable because data for 23-24% of patients who withdrew prematurely from the study are missing. Analysis of the effect of treatment on SGRQ total score should be based on all randomized patients rather than incomplete data from a subset of patients.

5. Symptomatic improvement

TDI score was used to measure the severity of dyspnea (breathlessness, shortness of breath) in this study. TDI score ranges from -9 to 9, with a lower score indicating more deterioration in severity of dyspnea. A minimum improvement of 1 point is considered a MCID.

The score was only reported In a subset of 5058 (49%) of randomized patients in IMPACT. In ETHOS the TDI score was reported in 95% of randomized patients but only at 24 weeks. There were significant differences between the BGF 320 group and the BFF [0.31 (0.15 to 0.46)] and GFF [0.40 (0.24 to 0.55)] groups but did not the MCID threshold for both comparisons.

> **CRITICAL APPRAISAL ISSUE:** TDI score was only reported for a subset of 5058 (49%) patients in IMPACT. The finding of symptomatic improvement with triple therapy is unreliable because data for half of randomized patients are missing. Analysis of the effect of treatment on TDI score should be based on all randomized patients rather than incomplete data from 49% of randomized patients. ETHOS only reported TDI score at 24 weeks and MCID was not achieved between triple therapy and either dual combination.

6. **Use of rescue salbutamol**

Despite being listed as a protocol-defined endpoint, use of rescue salbutamol was not reported in IMPACT. Use of rescue salbutamol over 24 weeks was only reported in a subset of 5627 (66%) of randomized patients in ETHOS.

> **CRITICAL APPRAISAL ISSUE**: If triple therapy actually improves TDI score, a significant decrease in use of rescue medication is also expected in this group. The finding of improved quality of life with triple therapy is unreliable because data for 33% of patients are missing. Analysis of the effect of treatment on daily rescue medication should be based on all randomized patients rather than incomplete data from a subset of patients at the midpoint of the study.

7. COPD related health care utilization

This includes physician visits/ER visits and hospitalization. It is another outcome that was not reported in the study publication despite being listed as a prespecified study endpoint in the IMPACT protocol. This was not a prespecified outcome of ETHOS.

8. Adverse events

a. Adverse events occurred in 64-70% receiving triple therapy, 65-68% receiving ICS/LABA, and 62-69% receiving LAMA/LABA in both studies. There was no difference between triple therapy and dual therapy comparators for total adverse events.
b. A total of 5.5-6%, 6.4-8% and 6.9-9% patients treated with triple therapy, ICS/LABA and LAMA/LABA, respectively, withdrew due to an adverse event in both studies. There was no difference between triple therapy and dual therapy comparators for withdrawal due to adverse events.

   CRITICAL APPRAISAL ISSUE: Overall, 9087 patients (88%) completed the IMPACT trial and 7991 (77%) completed the trial while receiving randomized therapy. This study analyzed harm data using an intention-to-treat approach, however, a full intention-to-treat analysis was not performed because patients who permanently discontinued study treatment did not come in for further evaluation. A total of 7187 patients (83.8%) completed ETHOS, of whom 6654 (77.6%) completed 52 weeks of treatment. This study analyzed safety and efficacy data using a modified intention-to-treat approach. Any data collected after completion of, or discontinuation of the assigned trial regimen was excluded from the modified intention-to-treat analysis.

9. FEV_1

In IMPACT, of 7916 (76%) patients evaluated, the difference between the triple therapy and FF/VI and UMEC/VI groups in the mean change from baseline in trough FEV_1 was 97 ml (95% CI 85,109) and 54 ml (95% CI 39,69), respectively. FEV_1 was not reported in ETHOS.

CRITICAL APPRAISAL ISSUE: FEV_1 is a surrogate outcome that has validity in estimating the risk of dying from COPD but little use in assessing the impact of inhaled drug therapy on COPD symptoms. (9)

Observational studies

A recent high quality observational study evaluated the real-world effectiveness of single-inhaler triple therapy with single-inhaler LAMA/LABA therapy amongst nearly 31,000 primary care COPD patients age $\geq$ 40 years in the United Kingdom. (27) From September 15, 2017 (when a triple inhaler first became available in the UK) through 2020, investigators compared 4,106 new users of triple therapy with 29,702 people who were prescribed LAMA/LABA. Patients were naïve to inhaled corticosteroids. During the prior year, 58% had used LAMA, LABA or both; 42% had used no long-acting bronchodilator; 35% had used a systemic corticosteroid. Patients were followed in the UK Clinical Practice Research Datalink database for up to 1 year, with a mean continuous treatment of 6 months in each group. Investigators used adjustment by propensity score weighting to render comparable the two treatment arms, and reduce the effects of confounding inherent to observational studies although residual confounding cannot be ruled out in any observational study.

Compared with single-inhaler LAMA/LABA, single-inhaler triple therapy including inhaled corticosteroid had a similar risk of the primary outcome, a first moderate or severe exacerbation, adjusted HR 1.08 (95% CI 1.00–1.16). This finding, based on patients not previously treated with an ICS, avoiding the confounding effects of abrupt ICS withdrawal, differs from the reductions in moderate or severe exacerbations reported in IMPACT and ETHOS.

Triple therapy increased all-cause mortality (HR 1.53, 95% CI 1.30-1.79) relative to dual bronchodilators in the observational study of ICS-naïve patients. Although the IMPACT and ETHOS trials reported significant overall reductions in total mortality with triple therapy versus dual bronchodilator therapy, this effect was predominantly in patients who had to abruptly discontinue ICS at randomization. Among patients who were not using ICS prior to randomization, the HRs of total mortality comparing triple therapy with dual LAMA-LABA therapy were 1.25 (95% CI 0.60, 2.59) in IMPACT and 1.49 (95% CI 0.49, 4.55) in ETHOS. (17,18) These estimates are unimpacted by the effect of abrupt ICS withdrawal at randomization and are consistent with the findings of the observational study that excluded patients already treated with ICS.

Triple therapy increased pneumonia requiring hospitalization: adjusted HR 1.50 (95% CI 1.29-1.75). This is consistent with the 65% and 78% increases in serious pneumonias with triple therapy reported in the IMPACT and ETHOS trials, respectively.

Despite the use of propensity score weighting which created groups highly comparable on all available measures of patient characteristics, residual confounding cannot be ruled out in any observational study, including COPD severity.

Summary

- GOLD 2025 and CTS 2023 guidelines recommend use of triple therapy inhalers to reduce mortality based on results from the IMPACT 2018 and ETHOS 2020 RCTs.
- IMPACT 2018 and ETHOS 2020 were included in this review. Both are double blind RCTs of 52 weeks duration comparing single inhaler triple therapy with LAMA/LABA and ICS/LABA, all administered once daily as a single inhaler, in 18,864 patients with symptomatic COPD and a history of exacerbation within a year before enrolment.
- IMPACT 2018 and ETHOS 2020 are judged to have a high risk of bias according to the Cochrane Risk of Bias 1.0 Tool with respect to attrition and source of funding. Therefore, the overall quality of evidence is low for all outcomes except total mortality.
- Both studies share a major study design flaw that seriously undermines the claimed benefit of reduced mortality with triple therapy. Patients with a history of asthma (who are known to benefit from ICS use) were included and 70-80% were receiving ICS, including 40% already using triple therapy. Following abrupt ICS withdrawal at randomization. there was an excess of deaths and exacerbations in the LAMA/LABA group compared with triple therapy during the first 90 days of follow-up when the effects of abrupt corticosteroid withdrawal would be maximal. No benefit of triple therapy was observed during the remaining 9 months of follow-up, Analyses limited to the subgroup of ICS-naive patients in IMPACT and ETHOS found no mortality benefit. Thus, the claimed benefit of triple versus dual inhaler therapy is likely due to abrupt ICS withdrawal in the LAMA/LABA group.
- There was no reduction in total serious adverse events (which includes all cause hospitalization and hospitalization due to severe exacerbation).
- There was no difference in total adverse events and withdrawal due to adverse events.
- The risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with LAMA/LABA but not with ICS/LABA, although reporting for this outcome is also incomplete.
- The claimed benefit of a reduced rate of moderate to severe exacerbations may be solely due to abrupt ICS or LABA withdrawal and needs to be reported as the proportion of patients with one or more exacerbations.
- There is insufficient evidence whether triple therapy improves quality of life or dyspnea symptoms.
- There is insufficient evidence whether triple therapy reduces use of rescue salbutamol.

Conclusion

- First-line triple therapy in treatment-naïve COPD patients, including people deemed at *“high risk”* of exacerbation, has not been studied in RCTs.
- Independent of blood eosinophil count, there is insufficient evidence that escalation to triple therapy – compared with dual bronchodilator therapy - reduces mortality or moderate or severe exacerbations in COPD patients deemed at *“high risk”* of exacerbation.

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