UPDATE OF PAD LITERATURE REVIEW:

Inhaled medications for treatment of chronic obstructive pulmonary disease (COPD)

Therapeutics Initiative report

February 28, 2019

Table of Contents

Update of PAD literature review of inhaled therapies for treatment of adult patients with chronic obstructive pulmonary disease (COPD)

Executive Summary

1. Background

Chronic obstructive pulmonary disease (COPD) is a progressive and disabling disease characterized by airway inflammation and airflow limitation that is not fully reversible. Airflow obstruction leads to symptoms of wheezing, shortness of breath, chest tightness, coughing and production of excess mucus.

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]. In Canada, approximately 20 inhaled medications are approved to treat COPD.

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

In Therapeutics Letter #109 published in February 2018 we reported systematic reviews of the clinical efficacy of inhaled LABA drugs licensed for COPD (formoterol, arformoterol and salmeterol) as compared to placebo. We concluded that the 3 inhaled long acting β2 agonists (formoterol, arformoterol and salmeterol) do not prolong survival or reduce the risk of hospitalization (total serious adverse events) in patients with COPD. Evidence for improvement of symptom scores is of low quality and insufficient to justify long-term use. A subset of patients may derive clinically important symptomatic relief. Such patients can be identified on a case-by-case basis using a short therapeutic trial.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report and other clinical practice guidelines recommend stepwise intensification of drug therapy in people with persistent breathlessness or exacerbations.

In 2017, the Provincial Academic Detailing (PAD) service completed a literature review and synopsis of randomized controlled trial (RCT) evidence from 5 Cochrane reviews that address specific GOLD guideline recommendations. The PAD review presents the overall grading of evidence and treatment effect estimates as reported from the Cochrane reviews in summary tables for the following outcomes: all-cause mortality; St. George's Respiratory Questionnaire

(SGRQ) total score, a measure of quality of life; and number of people with 1 or more moderate to severe COPD exacerbation.

2. Pharmaceutical Services Division (PSD) Request

The PAD 2017 review included comparative effectiveness from 5 Cochrane systematic reviews published from 2012 to 2017. These reviews included parallel group design randomized controlled trials from 4 weeks (Horita 2017) to at least 12 weeks duration (Chong 2012; Farne 2015; Welsh 2013) in patients with stable COPD. Nannini 2012 did not specify minimum duration criteria for study inclusion. Any formulation of the drug used within each drug class was included. The reviews also included all doses of drugs within each drug class that were used in clinical trials. For combination therapies treatments could be administered via single combined device or via two separate devices. Participants were allowed ICS and other co-medications provided they were not part of the randomized treatment.

PSD requested an updated search of the scientific literature to identify any new RCT evidence published since the completion of the 2017 PAD literature review on the comparative effects of LAMA and LABA as monotherapy, as well as combination therapies (LAMA+LABA, LABA+ICS, or LAMA+LABA+ICS) on all-cause mortality, change in SGRQ total score, and number of people with 1 or more acute moderate to severe exacerbation. PSD agreed that the PAD literature review update will be limited to RCTs of at least 24 weeks duration and will exclude: 1) studies with comparators not commercialized in Canada; and 2) studies where both comparators are used at non approved dosages in Canada. In addition to adding to the clinical trial evidence summarized by PAD, the TI offered to summarize and critically appraise new RCTs of at least 1 year in duration that evaluated the impact of COPD therapy on outcome measures relevant to PSD funding decisions, including mortality, serious adverse events, all cause hospital admissions (including those due to severe acute exacerbations), and acute moderate to severe exacerbations.

3. Methods

We searched Ovid MEDLINE, MEDLINE In-Process, MEDLINE Ahead of Print, Ovid Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and EBSCO CINAHL from the end dates of the Cochrane reviews included in the PAD literature review until November 7, 2018. We also searched clinicaltrials.gov for all relevant RCT reports. For all newly identified studies data were abstracted for outcomes of interest in the PAD literature review. The summary tables of the PAD review were amended to show the updated estimates of treatment effects that reflect the findings of new RCT evidence. For new studies with a minimum duration of 1 year, data abstraction was performed according to a hierarchy of outcomes developed by the TI and risk of bias was assessed using the Cochrane Risk of Bias Tool and helped to inform conclusions.

4. Summary of Available Evidence

A total of 6 studies evaluating 7 comparisons of interest met the criteria for critical appraisal. The TI previously critically appraised 1 study (IMPACT 2018) evaluating 3

comparisons of interest (LABA+LAMA vs. LABA+ICS; LABA+LAMA+ICS vs. LABA+LAMA; LABA+LAMA+ICS vs. LABA+ICS), which is available in the TI report on Trelegy Ellipta, dated September 12, 2018. Critical appraisal of the 5 remaining studies evaluating LABA vs. LAMA (1 study: INVIGORATE 2013), LABA+LAMA vs. LABA (1 study: Donohue 2016), LABA+LAMA vs. LAMA (2 studies: DYNAGITO 2018; SPARK 2013), and LABA+ICS vs. LAMA (1 study: Sarac 2013) is provided in this report. One additional study (SUMMIT 2016), which is excluded from the PAD literature review update because it uses a LABA comparator (vilanterol 25 mcg) that is not commercialized in Canada, was critically appraised since it is the largest study to date comparing LABA+ICS with LABA.

LABA vs. LAMA: Only INVIGORATE 2013, a double blind RCT in 3444 COPD patients with a documented history of exacerbation within a year before enrolment, met the inclusion criteria for critical appraisal. This study compared indacaterol 150 mcg (n=1721) with tiotropium 18 mcg (n=1718), both administered once daily. The Health Canada recommended dose of indacaterol is 75 mcg inhalation once daily. Patients who had been using a stable dose of inhaled corticosteroid for at least a month before study entry were instructed to continue this regimen for the duration of the study. The mean age of study patients was 64.0 years, 77% were males, and 65% were former smokers. Post-bronchodilator FEV_1 was 40.5% of predicted normal value and a mean SGRQ total score of 48.3 (17.6) at screening. Seventy nine percent had a history of 1 COPD exacerbation in the previous year. Seventy two percent were receiving ICS at randomization. Overall, 2711 patients (79%) completed the trial. This study analyzed 3072 (89.3%) in the per-protocol set for exacerbations and 3013 (87.6%) in the per-protocol set for spirometry. Data for exacerbations and FEV_1 were no longer collected once patients discontinued from the study. Deaths were recorded for all randomized patients during study participation and for 30 days after study drug discontinuation. INVIGORATE 2013 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.

LABA+LAMA vs. LABA: Donohue 2016 is a double blind RCT investigating the long-term safety and tolerability of twice-daily aclidinium/formoterol (ACL/FOR) 400/12 mcg (n=392) versus formoterol (FOR) 12 mcg (n=198) in 590 patients with symptomatic COPD. ICS and oral or parenteral corticosteroids at doses ≤10 mg/day, theophylline and H1-antihistamine were permitted for chronic use provided the dosage was stable for ≥4 weeks prior to screening and throughout the trial. Patients were permitted treatment with albuterol as needed, but not within 6 h before a visit. Chronic use of oxygen therapy was also permitted provided the dosage was stable for ≥4 weeks prior to screening. The mean age of study patients was 64.2 years, 55% were males, 54% were former smokers and 23.9% had ≥1 exacerbation in the previous year. Post-bronchodilator FEV1 was 51.4% of predicted normal value at screening. Fifty two percent and 46% were classified as GOLD Stage II (moderate) and Stage III (severe), respectively. There were no differences in use of concomitant COPD drugs prior to and continuing during study with 38% using drugs from any category and 35% receiving ICS. Only 398 patients (68%) completed the trial. All 590 patients were included in the safety analysis. Patients who discontinued the study prematurely did not come in for further evaluation. The study report does not state if data for exacerbations and other

efficacy outcomes were collected following discontinuation from the study. Vital status was available for the total study population at Week 52. Donohue 2016 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to detection bias, attrition bias and source of funding. There is a high risk of bias related to efficacy outcomes given that this study is likely not blinded for efficacy outcomes and the high withdrawal rates (32%) will lead to attrition bias for exacerbation outcomes. The study is judged to have unclear risk of bias with respect to blinding and selective reporting.

LABA+LAMA vs. LAMA: Two studies (DYNAGITO 2018 and SPARK 2016) were identified in the update search that followed patients for at least a year:

1. DYNAGITO 2018 is a double blind RCT comparing dual bronchodilator therapy with olodaterol/tiotropium (OLO/TIO) 5/5 mcg (n=3939) with tiotropium (TIO) 5 mcg (n=3939), both administered once daily via the Respimat device, in 7880 patients with symptomatic COPD and a history of moderate or severe exacerbation in the preceding year. Patients taking ICS at baseline continued this treatment. Open-label salbutamol was provided for as-needed rescue medication use, but other short-acting beta-agonists, LAMAs and LABAs were not permitted during the study. The mean age of study patients was 66.4 years, 72% were males, and 63% were former smokers. Post-bronchodilator FEV_1 was 44.6% of predicted normal value and a mean SGRQ total score of 47.8 (17.7) at screening. Forty five percent had a history of ≥2 exacerbations or ≥1 severe exacerbation in the preceding year. Nearly 40% of the patients were receiving triple therapy (LABA+LAMA+ICS), and 26% were receiving LABA+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. Overall, 6742 patients (86%) completed the trial. Fewer patients receiving OLO/TIO (12.4%) withdrew from the study as compared to TIO alone (16.5%) [OR 0.72 (95% CI 0.63, 0.81); p<0.00001]. This study analyzed exacerbation data during the "actual treatment period", defined as the time from first dose of medication until 1 day after the last dose of medication. Patients who permanently discontinued study treatment did not come in for further evaluation so there is loss of information on exacerbation events following premature discontinuation of study treatment. Vital status was available for 99.6% of the total study population at the end of the study. Also, the fact that more patients receiving TIO alone withdrew from the study could bias the analysis of exacerbations data.
2. SPARK 2016 is a double blind RCT in 2224 patients with severe and very severe COPD and a history of at least 1 moderate exacerbation in the preceding year. This study compared dual bronchodilator therapy with indacaterol/glycopyrronium (IND/GLY) 110/50 mcg (n=741) with glycopyrronium (GLY) 50 mcg (n=741), both administered once daily via the Breezhaler device. Approximately 75% of patients, with similar proportions across treatment groups, were using ICS either as fixed dose combination or as monotherapy at baseline. Patients using ICS at baseline continued this treatment at the same or equivalent dose and regimen during the study. Salbutamol was permitted as rescue medication use. Long acting bronchodilators were discontinued with a washout of up to 7 days (for theophylline, indacaterol and tiotropium) before screening. The mean age of study patients was 63.1 years, 75% were males, and 62% were former

smokers. Postbronchodilator FEV_1 was 37.2% of predicted normal value and a mean SGRQ total score of 53 (18) at screening. Seventy seven percent and 22% had a history of 1 COPD exacerbation and 2 or more exacerbations, respectively, in the previous year. Seventy five percent were receiving ICS at randomization. Use of other respiratory medications at baseline is not reported. Overall, 1108 patients (75%) completed the trial. A total of 171 (23.1%) patients in the IND/GLY group and 203 (27.4%) in the GLY group permanently discontinued the study. The higher number of withdrawals in the GLY group as compared to IND/GLY was not statistically significant [OR 1.26 (95% CI 0.99, 1.59)]. Data for exacerbations and FEV_1 were no longer collected once patients discontinued from the study. Patients who prematurely discontinued were followed for survival to the end of the study. SPARK 2013 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition and source of funding. Selective reporting is judged to have an unclear risk of bias.

LABA+ICS vs. LABA: SUMMIT 2016 is a double blind RCT in 16,590 patients with symptomatic COPD and a history of cardiovascular disease. This was an event-drive study in which follow-up continued until at least 1000 deaths had occurred (median study exposure was 1.8 years). This study comprised of 4 treatment arms. The comparison of interest for this report is fluticasone furoate/vilanterol (FF/VI) 110/50 mcg (n=4145) versus vilanterol (VI) 25 mcg (n=4146), both administered once daily via the Ellipta device. Vilanterol 25 mcg monotherapy is not commercially available in Canada. **The use of all inhaled corticosteroids and inhaled long acting bronchodilators was discontinued ≤48 hours before study entry**, although other COPD medications such as theophyllines were allowed. The mean age of study patients was 65 years, 75% were males, and 54% were former smokers. Postbronchodilator FEV_1 was 59.7% of predicted normal value at screening. Thirty eight percent had a history of 1 or more COPD exacerbations in the previous year. Approximately 33% were receiving ICS at randomization. Overall, 6250 patients (76%) receiving FF/VI and VI completed the trial. Data for exacerbations and FEV_1 were no longer collected once patients discontinued from the study. Vital status was known for 99.97% of patients in the intention to treat (ITT) population. SUMMIT 2016 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition bias, selective reporting and source of funding. There are also other biases with respect to study design and the presence of confounding that misrepresent the treatment effect.

LABA+ICS vs. LAMA: Only Sarac 2016, a single-centre open RCT was identified. This small study randomized 44 COPD patients with a history of ≥1 exacerbation in the preceding year to twice-daily salmeterol/fluticasone 50/500 mcg (n=22) or once-daily tiotropium 18 mcg (n=22). All long-acting bronchodilators and inhaled steroids were stopped during the washout period and they were only allowed to take short-acting bronchodilators (salbutamol-ipratropium combination MDI). During the treatment period the patients were allowed to use short-acting bronchodilators when needed, but were not allowed to use any other bronchodilators or inhaled steroids. The mean age of study patients was 66.6 years and 91% were males. Smoking status at screening is not reported, CAT score was 9.3 and 39% had ≥2 exacerbations in the previous year. Post-bronchodilator FEV_1 was 65.4% of

predicted normal value at screening. Respiratory medication use at screening is also not reported. All 44 patients completed the trial and no adverse events were reported. According to the Cochrane Risk of Bias Tool, Sarac 2016 is judged to have a high risk of selection bias, allocation bias, performance bias and detection bias, and an unclear risk of selective reporting and source of funding.

5. Results and Interpretation

All studies with a duration of 1 year or longer are judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition. However, vital status was available for >99% of randomized patients in all studies. Therefore the overall quality of evidence is low for all outcomes except mortality.

No study showed a difference in total mortality between any of the comparator groups.

Total SAEs provides the best summary statistic of therapeutic impact accounting for all known and unknown serious impact (benefit and harm) from therapy, and includes outcomes such as fatal COPD exacerbation, hospitalization due to severe exacerbation and hospitalization due to severe pneumonia. No studies showed a difference in total SAEs for any comparison.

The effect of inhaled medications on moderate to severe exacerbations needs to be reported as the proportion of patients with one or more exacerbations. Only 2 studies (Donohue 2016; SPARK 2013) reported the number of patients with 1 or more moderate to severe exacerbation and both studies showed no differences between their respective treatment groups. Other studies reported rate of moderate or severe exacerbation (DYNAGITO 2018; SUMMIT 2016) and time-to-first event analysis of moderate or severe exacerbation (INVIGORATE 2013). DYNAGITO 2018 and SUMMIT 2016 claimed no difference in exacerbation rates between treatment arms. INVIGORATE claimed that time to first moderate or severe exacerbation was longer with tiotropium versus indacaterol [HR 1.20 (95% CI 1.07 to 1.33; p=0.0012)]. Time-to-first-event analysis is useful only when it is known how many patients had more than one exacerbation throughout the study in both treatment groups. Furthermore, the reported events and rates are uncertain due to the high withdrawal rates in the studies and no attempt was made to reduce attrition bias by adequately accounting for the patients who withdrew prematurely in the calculation of event and annual rates of moderate or severe exacerbations.

Two studies (INVIGORATE 2013; SPARK 2013) reported quality of life (SGRQ) and 1 study (INVIGORATE 2013) reported dyspnea symptoms (TDI). Estimates for comparative treatment effects on SGRQ and TDI are uncertain due to the high withdrawal rates in both studies and inadequate accounting of patients who withdrew prematurely. Furthermore, INVIGORATE 2013 reported on a subset (approx. 75%) of total randomized patients. Therefore, the results are not considered valid due to missing data.

There were no differences in total adverse events between any of the comparators in these studies. DYNAGITO 2018 is the only study that demonstrated a difference in withdrawal due

to adverse events between comparator groups with significantly more patients receiving TIO (16.5%) than OLO/TIO (12.4%) who withdrew due to an adverse event (ARI 4.1%, NNH=24 for 1 year).

Reduced need for rescue medication is a marker of improved control of COPD symptoms. Three studies (INVIGORATE 2013; Donohue 2016; SPARK 2013) reported need for rescue salbutamol during the treatment period. Use of rescue treatment did not significantly differ between ACL/FOR and FOR groups in Donohue 2016. INVIGORATE 2013 reported in a subset (91%) of randomized patients that patients in the IND group needed rescue treatment less often as compared to those who received TIO [LS mean difference -0.62 (95% CI -0.79, -0.45); p<0.0001) in daily number of puffs; LS mean difference 8.0% (95% CI 5.9, 10.2); p<0.0001 in proportion of days with no rescue use). This finding is inconsistent with indacaterol showing no difference versus tiotropium for SGRQ total score and TDI score. Also it is difficult to understand how indacaterol reduced the need for rescue medication when time to first event analysis of exacerbation revealed that indacaterol increased the risk of moderate or severe exacerbation during treatment versus tiotropium. SPARK 2013 reported a reduction in daily puffs of rescue salbutamol in the IND/GLY group as compared to GLY group [LS mean difference -0.81; p<0.0001). The clinical relevance of a reduced need of rescue salbutamol is unclear considering the SGRQ effect estimate is uncertain (i.e. at high risk of attrition bias) and TDI score is not reported.

COPD related health care utilization, which includes physician visits/ER visits and hospitalizations, is an endpoint that was not reported in any of the studies. These findings would corroborate the findings of decreased rate of acute moderate to severe exacerbation.

Five studies (Donohue 2016; INVIGORATE 2013; Sarac 2016; SPARK 2013; SUMMIT 2016) reported trough FEV_1, of which 4 studies (Donohue 2016; INVIGORATE 2013; Sarac 2016; SPARK 2013) showed statistically significant but not clinically relevant between-group differences. SUMMIT 2016 did not statistically compare FF/VI and VI groups for on-treatment rate of decline in FEV_1. 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.

6. Conclusion

Based on the newly identified RCTs of at least 1 year duration, there is insufficient scientifically valid evidence that any of these comparisons (LABA vs. LAMA, LABA+LAMA vs. LABA, LABA+LAMA vs. LAMA, and LABA+ICS vs. LAMA) provides a therapeutic advantage in terms of moderate or severe exacerbation, quality of life (SGRQ), reported dyspnea symptoms (TDI), need for rescue medication, and COPD related health care utilization.

Based on the newly identified RCTs of at least 1 year duration, there is sufficient scientifically valid evidence demonstrating that none of these comparisons (LABA vs. LAMA, LABA+LAMA vs. LABA, LABA+LAMA vs. LAMA, and LABA+ICS vs. LAMA) provide a difference in terms of all-cause mortality, total serious adverse events (which includes all cause

hospitalization and hospitalization due to severe exacerbation), and total adverse events in the treatment of COPD.

Update of PAD literature review of inhaled therapies for treatment of adult patients with chronic obstructive pulmonary disease (COPD)

Background

Diagnosis and management of COPD

Chronic obstructive pulmonary disease (COPD) is a progressive and disabling disease characterized by airway inflammation and airflow limitation that is not fully reversible. Airflow obstruction leads to symptoms of wheezing, shortness of breath, chest tightness, coughing and production of excess mucus. COPD 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].

In Canada, approximately 20 inhaled medications are approved to treat COPD (Table 1).

Table 1: COPD Inhaled Medications

Class	**Medication (Brand Name, *Inhaler Device*)**
SABA	salbutamol (Ventolin HFA *MDI*, Airomir *MDI*, Ventolin *Diskus*) terbutaline (Bricanyl *Turbuhaler*)
SAMA	ipratropium (Atrovent HFA *MDI*)
SAMA+SABA	ipratropium + salbutamol (Combivent *Respimat*)
LABA	formoterol (Foradil *Aerolizer*) indacaterol (Onbrez *Breezhaler*) salmeterol (Serevent *Diskus*, Serevent *Diskhaler*)
LAMA	aclidinium (Tudorza *Genuair*) glycopyrronium (Seebri *Breezhaler*) tiotropium (Spiriva *HandiHaler*, Spiriva *Respimat*) umeclidinium (Incruse *Ellipta*)
LAMA+LABA	aclidinium + formoterol (Duaklir *Genuair*) glycopyrronium + indacaterol (Ultibro *Breezhaler*) tiotropium + olodaterol (Inspiolto *Respimat*) umeclidinium + vilanterol (Anoro *Ellipta*)
ICS+LABA	budesonide + formoterol (Symbicort *Turbuhaler*)

Class	Medication (Brand Name, *Inhaler Device*)
	fluticasone furoate + vilanterol (Breo *Ellipta*) fluticasone propionate + salmeterol (Advair *Diskus*)
ICS+LAMA+LABA	fluticasone furoate + umeclidinium + vilanterol (Trelegy *Ellipta*)
SABA short acting beta$_2$ adrenergic agonist; **SAMA** short acting muscarinic antagonist, **LABA** long acting beta$_2$ adrenergic agonist; **LAMA** long acting muscarinic antagonist, **ICS** inhaled corticosteroid	

In Therapeutics Letter #109 published in February 2018 we reported systematic reviews of the clinical efficacy of inhaled LABA drugs licensed for COPD (formoterol, arformoterol and salmeterol) as compared to placebo. (2) We identified 22 RCTs for formoterol and 2 RCTs for arformoterol (N = 13,958), and 17 RCTs for salmeterol (N = 10,115). Duration of formoterol trials ranged from 4-26 weeks (14 RCTs) to 48-52 weeks (8 RCTs). Arformoterol trials ranged from 12 to 52 weeks (2 RCTs). Salmeterol trials ranged from 4-24 weeks (14 RCTs) to 52 weeks (2 RCTs), with a single much longer trial lasting 156 weeks. These trials excluded patients with other concurrent respiratory diseases, including asthma. Most participants were men with a mean age ranging from 60 to 67 years. The doses most studied in COPD clinical trials were formoterol 9 and 12 µg twice daily and salmeterol 50 µg twice daily. Patients were allowed to continue using the following at stable doses throughout the studies: ICS or oral corticosteroids, inhaled SAMAs or LAMAs, PDE4 inhibitors and short-acting salbutamol for rescue therapy. We concluded that, as compared to placebo, the 3 inhaled long acting β2 agonists (formoterol, arformoterol and salmeterol) do not prolong survival or reduce the risk of hospitalization (total serious adverse events) in patients with COPD. Evidence for improvement of symptom scores is of low quality and insufficient to justify long-term use. A subset of patients may derive clinically important symptomatic relief. Such patients can be identified on a case-by-case basis using a short therapeutic trial.

Numerous clinical practice guidelines addressing the management of COPD recommend stepwise intensification of drug therapy in people with persistent breathlessness or exacerbations.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report has provided therapeutic recommendations for patients with COPD based on “ABCD” groups derived exclusively from patient symptoms and their assessment of exacerbation: (3)

1. **Group A** has modified MRC dyspnea scale (mMRC) 0-1, CAT <10 and 0 or 1 exacerbation not leading to hospital admission.
2. **Group B** has mMRC score ≥2, CAT ≥10 and 0 or 1 exacerbation not leading to hospital admission.
3. **Group C** has mMRC 0-1, CAT <10 and ≥2 exacerbation or ≥1 exacerbation leading to hospital admission.
4. **Group D** has mMRC score ≥2, CAT ≥10 and ≥2 exacerbation or ≥1 exacerbation leading to hospital admission.

The GOLD report provides a pharmacological treatment algorithm based on which group the patient belongs:

Group A: Start with a short or long acting bronchodilator; evaluate effect; then continue, stop or try alternate class of bronchodilator. This should be continued if symptomatic benefit is documented.

Group B: Start with a long acting bronchodilator (LABA or LAMA). Long acting bronchodilators are superior to short acting bronchodilators taken as needed. There is no evidence to recommend one class of long acting bronchodilator over another for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on patient's perception of symptom relief.
For patients with persistent breathlessness on monotherapy the use of 2 bronchodilators is recommended (LAMA/LABA). For patients with severe breathlessness initial therapy with 2 bronchodilators may be considered. If addition of the second bronchodilator does not improve symptoms treatment should be stepped down to a single bronchodilator.

Group C: Start with a single long acting bronchodilator. LAMA was superior to LABA regarding exacerbation prevention so start with LAMA in this group.
Patients with persistent exacerbation may benefit from adding a second long acting bronchodilator (LAMA/LABA) or (LABA/ICS). An ICS increases risk of developing pneumonia in some patients so primary choice is LAMA/LABA.

Group D: Start with a LAMA/LABA combination, as it is superior to monotherapy with each class of drug. If single bronchodilator is chosen then LAMA is preferred for exacerbation prevention as compared to LABA.
LAMA/LABA combination was superior to LABA/ICS in preventing exacerbation and other patient reported outcomes. Also Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.
In some patients LABA/ICS may be first choice (history and/or findings of asthma-COPD; or in patients with high eosinophil counts).
In patients who develop further exacerbations on LAMA/LABA therapy then either switch to LABA/ICS or add ICS to LAMA/LABA.
If patients on triple therapy still have exacerbations then:

a. Add roflumilast in patients with FEV_1 <50% predicted value and chronic bronchitis particularly if they experienced at least one hospitalization for an exacerbation in the previous year.
b. Add macrolide (azithromycin)
c. Stop ICS.

In February 10, 2017 the Provincial Academic Detailing (PAD) service completed a literature review and synopsis of randomized controlled trial (RCT) evidence from existing Cochrane reviews that address specific GOLD guideline recommendations. The PAD review presents the overall grading of evidence and treatment effect estimates as reported from the Cochrane reviews as summary tables for the following outcomes: all-cause mortality; St. George's Respiratory Questionnaire (SGRQ) total score, a measure of quality of life; and number of people

with 1 or more acute moderate to severe COPD exacerbation. Findings of the PAD review are summarized below.

LABA vs. Placebo

- **Kew KM et al 2017 Cochrane review summary by PAD:** Evidence is based from 26 RCTs in 14,939 adult patients with COPD; Mortality (Moderate quality evidence 0.90 (0.75, 1.08); 26 RCTs; N=14,179); SGRQ total score (Moderate quality evidence -2.32 (-3.09, -1.54); 17 RCTs; N=11,397); and number of people with 1 or more acute moderate to severe exacerbation (Moderate quality evidence 0.88 (0.76, 1.02); 7 RCTs; N=3,968).
- **The TI letter #109 published in February 2018** (*www.ti.ubc.ca*) on "Inhaled long acting beta2 agonist for COPD" concluded that the four inhaled long acting β2 agonists (indacaterol, formoterol, arformoterol and salmeterol) do not prolong survival or reduce the risk of hospitalization (total serious adverse events) in patients with COPD. Evidence for improvement of symptom scores is of low quality and insufficient to justify long-term use. A subset of patients may derive clinically important symptomatic relief. Such patients can be identified on a case-by-case basis using a short therapeutic trial.

Tiotropium (LAMA) vs. Placebo

- **Karner C et al 2014 Cochrane review summary by PAD:** Evidence is based from 22 RCTs in 23,309 adult patients with COPD; Mortality (Moderate quality evidence 0.98 (0.86, 1.11); 22 RCTs; N=23,309); SGRQ total score (High quality evidence -2.89 (-3.35, -2.44); 9 RCTs; N=13,304); and number of people with 1 or more acute moderate to severe exacerbation (High quality evidence 0.78 (0.70, 0.87); 22 RCTs; N=23,309).
- **TI letter #60 published in September 2006** on "Clinical Pearls from Prescrire" reported in May 2006 that tiotropium is a me-too drug for COPD. For patients with chronic obstructive pulmonary disease, tiotropium has more adverse effects than the bronchodilators with which it has been compared, and it has not been shown to be more effective. Ipratropium seems to be the best choice for patients needing inhaled antimuscarinic therapy.

Tiotropium (LAMA) vs. LABA

- **Chong D et al 2012 Cochrane review summary by PAD:** Evidence is based from 7 RCTs in 12,223 adult patients with COPD; Mortality (Very low quality evidence 0.82 (0.60, 1.13); 6 RCTs; N=12,123); SGRQ total score (ungraded RCTS were not pooled); and number of people with 1 or more acute moderate to severe exacerbation (Moderate quality evidence 0.86 (0.79, 0.93); 6 RCTs; N=12,123).

[Tiotropium (LAMA) + LABA] vs. Tiotropium (LAMA)

- **Farne D et al 2015 Cochrane review summary by PAD:** Evidence is based from 10 RCTs in 10,894 adult patients with COPD; Mortality (Low quality evidence 1.24 (0.81, 1.90); 8 RCTs; N=9,633); SGRQ total score (moderate quality evidence; -1.34 (-1.87 to -0.80); 5 RCTs; N=6,709); and number of people with 1 or more acute moderate to severe exacerbation (Ungraded quality evidence from RCTs were not pooled).

[Tiotropium (LAMA) + LABA] vs. LABA

- **Farne D et al 2015 Cochrane review summary by PAD:** Evidence is based from 4 RCTs in 3,378 adult patients with COPD; Mortality (Low quality evidence 1.15 (0.62, 2.13); 3 RCTs; N=3,514); SGRQ total score (moderate quality evidence; -1.25 (-2.14 to -0.37); 4 RCTs; N=3,378); and number of people with 1 or more acute moderate to severe exacerbation (not reported).

[LABA + ICS] vs. LABA

- **Nannini L et al 2012 Cochrane review summary by PAD:** Evidence is based from 14 RCTs in 11,794 adult patients with COPD; Mortality (Moderate quality evidence 0.92 (0.76, 1.11); 10 RCTs; N=10,618); SGRQ total score (Ungraded quality evidence -1.58 (-2.15, -1.01); 6 RCTs; N=10,681); and number of people with 1 or more acute moderate to severe exacerbation (Moderate quality evidence 0.83 (0.70, 0.98); 6 RCTs; N=3,357).

[LABA + LAMA] vs. [ICS + LABA]

- **Horita N et al 2017 Cochrane review summary by PAD:** Evidence is based from 11 RCTs in 9,839 adult patients with COPD; Mortality (Low quality evidence 1.01 (0.61, 1.67); 8 RCTs; N=8,200); SGRQ total score (Ungraded quality evidence -1.22(-2.52, +0.07); 6 RCTs; N=6,055); and number of people with 1 or more acute moderate to severe exacerbation (Low quality evidence 0.82 (0.70, 0.96); 9 RCTs; N=8,922).

[Tiotropium (LAMA) + LABA + ICS] vs. [Tiotropium (LAMA) + LABA]

Karner C et al 2011 Cochrane review summary by PAD: Evidence is based from 1 RCTs in 293 adult patients with COPD; Mortality (Ungraded quality evidence 1.02 (0.32, 3.24); 1 RCT; N=293); SGRQ total score (Ungraded quality evidence -1.02(-5.10, +3.06); 1 RCT; N=293); and number of people with 1 or more acute moderate to severe exacerbation (Ungraded quality evidence 0.81 (0.51, 1.30); 1 RCT; N=293).

2017 PAD literature review concluded:

1. There is insufficient evidence to estimate the effect of triple therapy (LAMA+LABA+ICS) on health-related quality of life, the risk of exacerbations, or the risk of death.

2. There is absence of high quality evidence regarding the effect of intensifying inhaled therapy (i.e. progressing to LAMA + LABA and LAMA + LABA + ICS) on health-related quality of life and on the risk of exacerbation and death in people with COPD. The true effect cannot be firmly established.

3. Consider risk factors for pneumonia when weighing the suitability of inhaled corticosteroid therapy in people with COPD. These include: COPD exacerbation in the previous year, FEV_1 <50% predicted, prior history of pneumonia, low body mass index, advancing age, and current smoker.

4. In a 2016 comparative effectiveness review of inhaled therapies for COPD, no consistent differences were identified in benefit or harm outcomes within the classes of LABA, LAMA or ICS + LABA therapies.

5. When evaluating patient's symptomatic response to inhaled therapies using a goal-setting approach, give attention to their ability to use inhaled therapy devices.

Pharmaceutical Services Division (PSD) Request

PSD requested an update search of the scientific literature to identify any new RCT evidence published since the completion of the PAD literature review on the comparative effects of LAMA and LABA as monotherapy, as well as combination therapies (LAMA+LABA, LABA+ICS, or LAMA+LABA+ICS) on all-cause mortality, change in SGRQ total score, and number of people with 1 or more acute moderate to severe exacerbation in the treatment of COPD.

The PAD review included comparative effectiveness from 5 Cochrane systematic reviews published from 2012 to 2017. (4-8) These reviews included parallel group design randomised controlled studies from 4 weeks (Horita 2017) to at least 12 weeks duration (Chong 2012; Farne 2015; Welsh 2013) in patients with stable COPD. Nannini 2012 did not specify minimal duration criteria for study inclusion. Any formulation of the drug used within each drug class was allowed. Also the reviews included various range of doses of drugs within each drug class that were used in clinical trials. For combination therapies treatments could be administered via single combined device or via two separate devices. The various doses of drugs within each drug class whether officially indicated or not that were used in clinical trials were included. Participants were allowed ICS and other co-medications provided they were not part of the randomized treatment.

Chong 2012 Cochrane review (LAMA vs LABA): The only LAMA included was tiotropium 18 mcg as Spiriva Handihaler. LABAs included were salmeterol 50 to 100 mcg and indacaterol 150 to 300 mcg. (4)

Farne 2015 Cochrane review (LAMA+LABA vs LAMA): The only LAMA included was tiotropium at doses ranging from 2.5 to 5 mcg as Spiriva Respimat and 18 mcg as Spiriva Handihaler. LABAs included were formoterol 20 to 24 mcg, indacaterol 150 mcg, salmeterol 50 mcg, and olodaterol 5 mcg. (5)

Nannini 2012 Cochrane review (LABA+ICS vs LABA): LABAs included were formoterol 9 to 18 mcg and salmeterol 100 mcg. ICS included were budesonide 160 to 640 mcg and fluticasone 500 to 1000 mcg. (6)

Welsh 2013 Cochrane review (LABA+ICS vs LAMA): The only LAMA included was tiotropium 18 mcg as Spiriva Handihaler. LABA included was salmeterol 100 mcg. ICS included was fluticasone 500 to 1000 mcg. (7)

Horita 2017 Cochrane review (LABA+LAMA vs LABA+ICS): LAMAs included were aclidinium 800 mcg, glycopyrronium 50mcg, tiotropium at doses ranging from 2.5 to 5 mcg as Spiriva Respimat and 18 mcg as Spiriva Handihaler, and umeclidinium 62.5 mcg. LABAs included were formoterol 24 mcg, indacaterol 110 to 150 mcg, olodaterol 5 mcg, salmeterol 100 mcg, and vilanterol 50 mcg. ICS used was fluticasone 500 mcg. (8)

The PSD agreed the PAD literature review update will be limited to RCTs of at least 24 weeks duration and will exclude: 1) studies with comparators not commercialized in Canada; and 2) studies where both comparators are used at non approved dosages in Canada.

The summary tables of the PAD review will be amended to show the updated estimates of treatment effects that reflect the findings of new RCT evidence for all-cause mortality, mean change in SGRQ total score, and number of people with 1 or more acute moderate to severe exacerbation in the treatment of COPD.

In addition to adding to the clinical trial evidence summarized by PAD, the TI offered to summarize and critically appraise new RCTs of at least 1-year in duration that evaluated the impact of COPD therapy on outcome measures relevant to PSD funding decisions, including mortality, serious adverse events, all cause hospital admissions (including those due to severe acute exacerbations), and acute moderate to severe exacerbations. The FDA also recommends minimum 1-year duration studies to support claims of modification or prevention of exacerbation with COPD drugs**.** (9)

Methods

Search strategy

We searched Ovid MEDLINE, MEDLINE In-Process, MEDLINE Ahead of Print, Ovid Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and EBSCO CINAHL from the end dates of the Cochrane reviews included in the PAD literature review until November 7, 2018. We also searched clinicaltrials.gov 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 abstraction was done by two independent reviewers. Review Manager 5.3 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. For all newly identified studies data were abstracted for outcomes of interest in the PAD literature review (all-cause mortality,

change in SGRQ total score, and number of people with 1 or more acute moderate to severe COPD exacerbation). Data abstraction was performed according to a hierarchy of outcomes developed by the TI for studies with a minimum duration of 1 year (see Evaluative framework section below).

Assessment of risk of bias in included studies

Risk of bias for each included trial of at least 1-year duration was assessed using the Cochrane Risk of Bias 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. (10)

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 summary and critical appraisal of new studies with a minimum duration of 1 year was based on a hierarchy of outcomes developed by the TI. As much as possible, the hierarchy was completed for each included RCT with a minimum 1-year duration.

Outcome hierarchy:

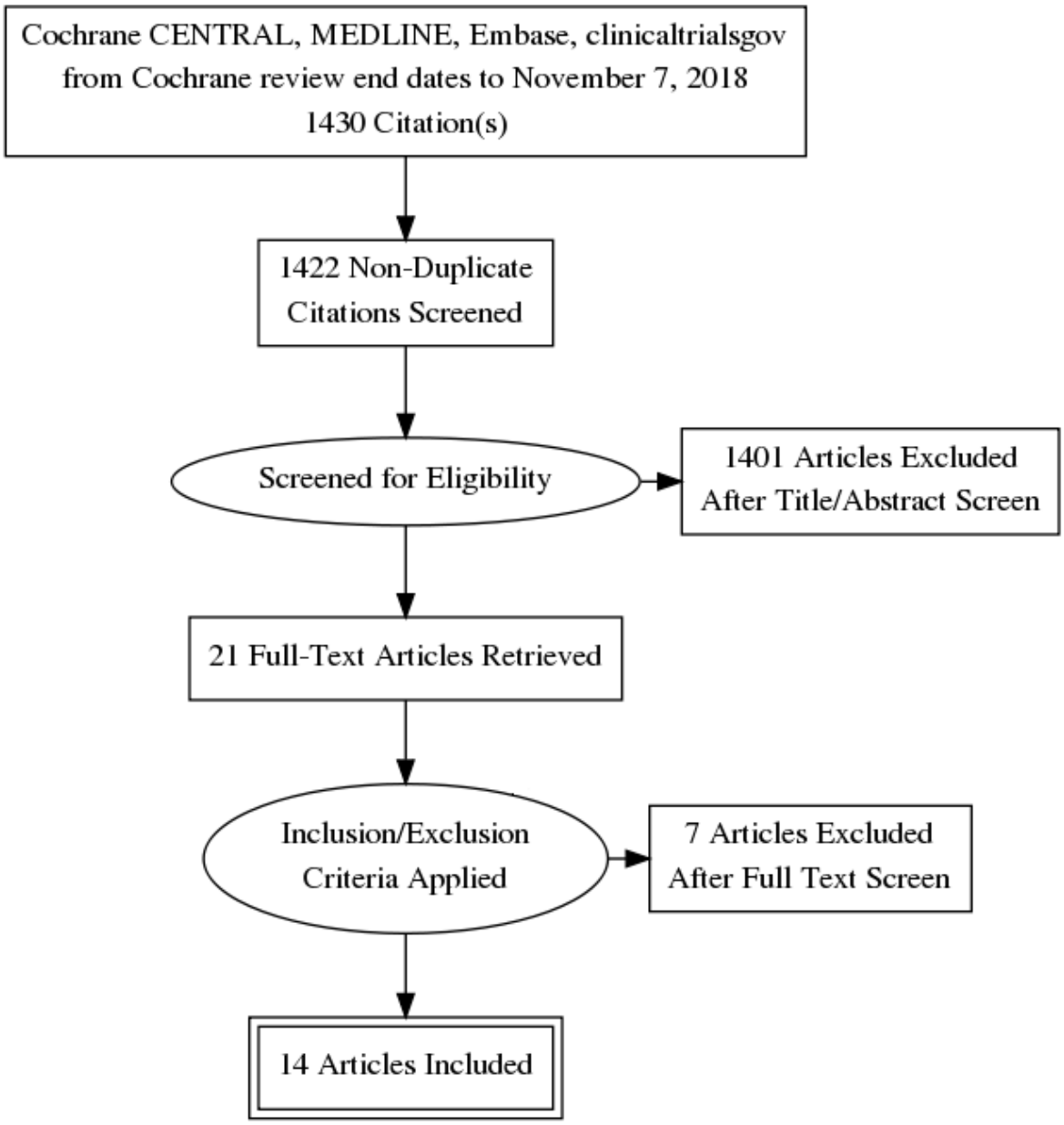
1. Total mortality
2. Total serious adverse events (including total hospitalizations)
3. Number of patients with one or more acute moderate or severe exacerbation
4. Quality of life measured by Saint George's Respiratory Questionnaire (SGRQ) total score (≥ 4 point change in total score is considered a 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.)

Results

Findings from the literature

The sorting and inclusion process is documented using the PRISMA flow diagram (Figure 1).

Figure 1: PRISMA flow diagram of study selection



Summary of excluded studies

Reasons for exclusion of the 6 excluded studies are provided in Table 2.

Table 2: Excluded studies (as requested and agreed by PSD)

Clinical Study ID/Reference	Reason for Exclusion
Buhl 2017 (11)	Already included in Cochrane review (Farne 2015); LABA used as monotherapy is not approved in Canada (olodaterol 5 mcg)
Celli 2014 (12)	LABA used as monotherapy is not approved in Canada (vilanterol 25 mcg)
Donohue 2014 (13)	Compares an unapproved dose of LABA/LAMA combination (vilanterol 25 mcg + umeclidinium 125 mcg) with LAMA monotherapy at an unapproved dose (umeclidinium 125 mcg)
Dransfield 2013 (14)	Compares LABA/ICS combination approved in Canada (vilanterol 25 mcg + fluticasone furoate 100 mcg) with LABA monotherapy not approved in Canada (vilanterol 25 mcg)
Ferguson 2018 (15)	LABA/LAMA combination used as comparator is not approved in Canada (formoterol 9.6 mcg + glycopyrronium 18 mcg)
Sharafkhneh 2012 (16)	All 3 treatment arms use doses of formoterol and budesonide that are not approved in Canada
SUMMIT 2016 (17)	LABA used as monotherapy is not approved in Canada (vilanterol 25 mcg)

Description of included studies

A total of 14 studies met the inclusion criteria for this PAD literature review update. (16-29) Study duration ranged from 24 weeks to 64 weeks. Table 3 lists the newly identified studies according to inhaled COPD treatment comparison. The studies in bold font have a minimum duration of 1 year. A total of 10 studies report SGRQ mean difference, of which only 3 studies of at least 1-year duration report this outcome. Only 3 studies report the number of patients with at least 1 moderate or severe exacerbation. Two of these studies have a minimum 1-year follow-up. All 14 studies report all-cause mortality.

Table 3: New studies according to inhaled COPD treatment comparison

	2017 PAD Review Outcomes of Interest Reported? (Y or N)		
	SGRQ Mean Difference	**Patients with ≥1 Moderate/Severe Exacerbation**	**All-Cause Mortality**
LAMA vs. LABA (4 studies)			
Bateman 2013 (18)	Y	N	Y
D'Urzo 2014 (19)	Y	N	Y
INVIGORATE 2013 (20)	**Y**	**N**	**Y**
Singh 2014 (21)	Y	Y	Y
LABA+LAMA vs. LABA (4 studies)			
Bateman 2013 (18)	Y	N	Y
D'Urzo 2014 (19)	Y	N	Y
Donohue 2016 (22)	**N**	**Y**	**Y**
Singh 2014 (21)	Y	Y	Y
LABA+LAMA vs. LAMA (8 studies)			
Bateman 2013 (18)	Y	N	Y

	2017 PAD Review Outcomes of Interest Reported? (Y or N)		
	SGRQ Mean Difference	**Patients with ≥1 Moderate/Severe Exacerbation**	**All-Cause Mortality**
DYNAGITO 2018 (23)	**N**	**N**	**Y**
D'Urzo 2014 (19)	Y	N	Y
Decramer 2014 (24)	Y	N	Y
Donohue 2013 (25)	Y	N	Y
Maleki-Yazdi 2014 (26)	Y	N	Y
Singh 2014 (21)	Y	Y	Y
SPARK 2013 (27)	**Y**	**Y**	**Y**
LABA+ICS vs. LABA (1 study)			
Ohar 2014 (28)	N	Y	Y
LABA+ICS vs. LAMA (1 study)			
Sarac 2013 (29)	**N**	**N**	**Y**
LABA+LAMA vs. LABA+ICS (1 study)			
IMPACT 2018 (30)	**Y**	**N**	**Y**
LABA+LAMA+ICS vs. LABA+LAMA (1 study)			
IMPACT 2018 (30)	**Y**	**N**	**Y**
LABA+LAMA+ICS vs. LABA+ICS (2 studies)			
FULFIL 2017 (31)	Y	N	Y
IMPACT 2018 (30)	**Y**	**N**	**Y**

New data from the 14 identified studies were incorporated in the data and analyses sections of the corresponding Cochrane reviews. The estimates of treatment effects on all-cause mortality, SGRQ total score and exacerbations were updated to reflect the findings of new evidence. The evidence summary tables and conclusions of the 2017 PAD literature review were amended accordingly and are available as a separate document [PAD 2017 COPD Inhaled Medications BOOKLET (updated February 2019)].

Summary and critical appraisal of 1 year or longer studies

A total of 6 studies evaluating 7 comparisons of interest met the criteria for critical appraisal. The study population consisted of predominantly middle-aged white males. One study (IMPACT 2018) that evaluates 3 comparisons of interest was critically appraised previously as part of a systematic review of Trelegy Ellipta single inhaler triple therapy for treatment of patients with moderate-to-severe COPD. Please see the TI report dated September 12, 2018 for more information on IMPACT 2018.

SUMMIT 2016 is excluded from the PAD literature review update because it uses a LABA comparator (vilanterol 25 mcg) that is not commercialized in Canada. This study is **not** included in the updated PAD summary tables available separately [PAD 2017 COPD Inhaled Medications BOOKLET (updated February 2019)]. However, this is the largest study to date comparing LABA+ICS (vilanterol/fluticasone furoate 25/100 mcg) combination therapy with LABA (vilanterol 25 mcg) so the TI would be remiss not to provide a critical appraisal.

LABA vs. LAMA

Only INVIGORATE 2013, a double blind RCT in 3444 COPD patients with a documented history of exacerbation within a year before enrolment, met the inclusion criteria for critical appraisal. (20) This study compared indacaterol 150 mcg (n=1721) with tiotropium 18 mcg (n=1718), both administered once daily. Patients who had been using a stable dose of inhaled corticosteroid for at least a month before study entry were instructed to continue this regimen for the duration of the study. A description of the study characteristics is provided in Table 4.

Study sample size was based on the key secondary objective of showing non-inferiority of indacaterol to tiotropium in terms of rate of COPD exacerbations over the 52-week treatment period. On the basis of available studies at the time the expected exacerbation rate was 1.1 per year in both groups. The overdispersion factor was estimated to be 1.6. The non-inferiority margin selected was 12% based on half the reduction in exacerbations (20–25%) seen in previous studies of active treatments versus placebo. Using these assumptions the sample size needed was 1750 patients per group for 80% power, including an allowance for dropout.

Table 4: INVIGORATE 2013 study characteristics

Participants	N=3444 COPD patients ≥40 years of age with: 1) smoking history of ≥10 pack-years; 2) post-bronchodilator FEV_1 between 30% and <50% predicted value; 3) post-bronchodilator FEV_1/FVC <0.7; and 4) documented history of ≥1 moderate or severe exacerbation in previous 12 months. **Exclusion criteria:** 1) BMI <15 kg/m2 or >40 kg/m2; 2) respiratory tract infection or COPD exacerbation needing systemic corticosteroids within 6 weeks of screening visit; or 3) history of asthma
Intervention	Indacaterol 150 mcg OD [IND] (n=1721) Available as Onbrez Breezhaler (75 mcg) 1 inhalation OD
Comparator	Tiotropium 18 mcg OD [TIO] (n=1718) Available as Spiriva Handihaler (18 mcg) 1 inhalation OD
Concomitant Medications	Use of inhaled corticosteroid was allowed if a patient's treatment regimen had been stable for at least a month before study entry; patients were instructed to continue this regimen for the duration of the study. Treatments with fixed dose combinations of a LABA plus inhaled corticosteroid were discontinued before the start of the study, as were those with SAMA plus a SABA and those with LABA plus a LAMA. Treatment with a fixed-dose combination of a LABA plus inhaled corticosteroid was replaced by the equivalent monotherapy inhaled corticosteroid for the duration of the trial. All patients were provided with a SABA, salbutamol or albuterol, which they were instructed to use throughout the study as rescue treatment.
Outcomes	**PRIMARY:** • Change from baseline in trough FEV_1 at week 12 (per-protocol analysis) **SECONDARY (pre-specified):** • Rate of exacerbations at week 52 (per-protocol analysis) **OTHER:**

	• Trough FEV_1 values at other time points; FVC at weeks 12, 26 and 52 • SGRQ total score • TDI total score • Change from baseline rescue medication and symptom scores • Proportion of patients who achieved a MCID in SGRQ total score • Proportion of patients who achieved a MCID in TDI total score
Study Design	Multicentre 2-arm parallel group DBRCT consisting of a 52-week treatment period

There were no significant differences between treatment groups at baseline with regard to demographics, COPD exacerbations and SGRQ total score (Table 5). The mean age of study patients was 64.0 years, 77% were males, and 65% were former smokers. Post-bronchodilator FEV_1 was 40.5% of predicted normal value and a mean SGRQ total score of 48.3 (17.6) at screening. Seventy nine percent had a history of 1 COPD exacerbation in the previous year. Use of specific drugs at baseline is not reported. Seventy two percent were receiving ICS at randomization.

Table 5: INVIGORATE 2013 baseline characteristics of study participants

	IND 150 mcg (n=1721)	**TIO 18 mcg (n=1718)**
Age in years, median (range)	64.0 (40-91)	64.0 (40-87)
Males	1344 (78%)	1313 (76%)
White race	1330 (77%)	1324 (77%)
Former smokers	1125 (65%)	1133 (66%)
Number of COPD exacerbations in previous year		
0	6 (<0.5%)	7 (<0.5%)
1	1365 (79%)	1342 (78%)
2	244 (14%)	251 (15%)
3	59 (3%)	69 (4%)
≥4	47 (3%)	49 (3%)
Post-bronchodilator FEV_1, mean % predicted (SD)	40.2 (6.0)	40.7 (6.1)
SGRQ total score Mean (SD)	n=1664 47.9 (17.4)	n=1669 48.7 (17.8)
Baseline Dyspnea Index (BDI) total score Mean (SD)	n=1684 5.9 (2.1)	n=1677 6.0 (2.1)
Daily rescue treatment use Mean number of puffs (SD)	n=1668 3.9 (3.6)	n=1638 3.9 (3.7)
Inhaled corticosteroids use		
Yes	1235 (72%)	1234 (72%)
No	486 (28%)	484 (28%)

Overall, 2711 patients (79%) completed the trial. This study analyzed 3072 (89.3%) in the per-protocol set for exacerbations and 3013 (87.6%) in the per-protocol set for spirometry. Data for

exacerbations and FEV_1 were no longer collected once patients discontinued from the study. Deaths were recorded during study participation and for 30 days after study drug discontinuation. A summary of patient disposition is provided in Table 6.

Table 6: Patient disposition in INVIGORATE 2013

	IND 150 mcg	TIO 18 mcg
Randomized	1721	1718
Total adverse events	1119 (65.0%)	1065 (62.0%)
Total withdrawals	386 (22.4%)	342 (19.9%)
Withdrew consent	105 (6.1%)	108 (6.3%)
Withdrawal due to adverse events	101 (5.9%)	96 (5.6%)
Withdrawal due to lack of efficacy	51 (3.0%)	39 (2.3%)
Lost to follow-up	22 (1.3%)	13 (0.8%)

Risk of bias in INVIGORATE 2013

The Cochrane Risk of Bias Tool was used to assess the quality of INVIGORATE 2013. 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. INVIGORATE 2013 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 7).

Table 7: Cochrane risk of bias summary for INVIGORATE 2013

Domain	Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	"The randomisation sequence was computer-generated by an interactive voice response system (IVRS; Oracle America Inc, Redwood City, CA, USA)... Randomisation was stratified by inhaled corticosteroid use, with balance of treatments maintained at country level. Balance was maintained at the strata level by using randomly permuted blocks."
Allocation concealment (selection bias)	Low risk	"The randomisation sequence was computer-generated by an interactive voice response system (IVRS; Oracle America Inc, Redwood City, CA, USA)..."
Blinding of participants and personnel (performance bias)	Low risk	"Participants, investigators and those assessing the outcomes were masked to treatment intervention. We used a double-dummy design because the identity of the study drugs (indacaterol and tiotropium) could not be disguised due to their different inhaler devices. Patients were dispensed the two devices and their corresponding capsules (either active or

Domain	Judgement	Support for Judgement
		placebo). Drug packs were dispensed by a third party who was not involved in any other aspect of the study."
Blinding of outcome assessment (detection bias)	Low risk	"...those assessing the outcomes were masked to treatment intervention."
Incomplete outcome data (attrition bias)	High risk	3439 patients were randomised. "There were 3419 patients in the FAS population, 3072 (89.3%) in the per-protocol set for exacerbations and 3013 (87.6%) in the per-protocol set for spirometry." "**Analysis for the primary and key secondary endpoints was done in per-protocol populations.** These populations included all randomised patients who received at least one dose of study drug and did not have any major protocol deviations (as pre-defined in the analysis plan) that could affect the analysis of spirometry or exacerbations data. All other analyses of efficacy endpoints were done on the full analysis set (FAS), which consisted of all randomised patients who received at least one dose of study drug." **"Once patients discontinued from the study, either being lost to follow-up or by undertaking a study discontinuation visit, data for FEV_1 and exacerbations were no longer collected."** Deaths were recorded during study participation and for 30 days after study drug discontinuation. **The high withdrawal rates will lead to attrition bias.**
Selective reporting (reporting bias)	Unclear risk	This study is registered with ClinicalTrials.gov, number NCT00845728, and the protocol lists the primary outcome and the pre-specified secondary outcome only. "We recorded adverse events and serious adverse events (including **admissions to hospital** and deaths), along with physical examination measurements, vital signs, laboratory assessments, blood test results, and electrocardiogram readings." **Total hospitalizations are not reported.**
Other bias	High risk	"RC, MS, DL, DY, and DMcB are employees of the trial sponsor (Novartis) and contributed to the design, preparation, and conduct of the

Domain	Judgement	Support for Judgement
		study. They also made substantial contributions to the analysis and interpretation of the study. MD was the principal investigator of the study who critically reviewed the full study report and had the final responsibility for the decision to submit for publication. All authors had full access to the results of pre-specified statistical analyses, were encouraged to suggest appropriate post-hoc analyses, and made substantial contributions to the content of each draft."

Outcomes reported

Results are presented in Table 6 according to the outcome hierarchy described above.

Table 8: Hierarchy of outcomes in INVIGORATE 2013

	IND 150 mcg (n=1721)	TIO 18 mcg (n=1718)
Total mortality	28 (1.6%)	28 (1.6%)
Total SAEs	263 (15%)	255 (15%)
Total hospitalizations	NR	NR
Hospitalization due to severe COPD exacerbation	NR	NR
Worsening of COPD as a SAE	147 (8.5%)	121 (7.0%)
Number of patients with ≥1 moderate or severe COPD exacerbation	NR	NR
Number of patients with ≥1 severe COPD exacerbation	NR	NR
SGRQ total score at Week 52, based on subset of patients		
Patients evaluated	1281 (74.4%)	1325 (77.1%)
Change from baseline, mean (SD)	-4.5 (15.5)	-4.9 (14.8)
Patients evaluated	1273 (74.0%)	1314 (76.5%)
SGRQ total score, mean (SE)	42.3 (0.66)	42.2 (0.65)
LS mean difference	0.2 (95% CI -0.8, 1.2) p=NS	
% Patients with ≥4 point improvement (MCID)	626/1273 (49%) OR 1.03 (95% CI 0.88, 1.21) p=NS	646/1314 (49%)
Time to 1st moderate or severe exacerbation,	1.20 (1.07, 1.33)	

	IND 150 mcg (n=1721)	TIO 18 mcg (n=1718)
HR (95% CI)	p=0.0012	
TDI total score at Week 52, based on subset of patients		
Patients evaluated	1296 (75.3%)	1332 (77.5%)
Change from baseline, mean (SD)	2.22 (3.53)	1.92 (3.56)
Patients evaluated	1288 (74.8%)	1322 (77.0%)
TDI total score, mean (SE)	2.01 (0.17)	1.75 (0.16)
LS mean difference (95% CI)	0.26 (95% CI 0.04, 0.05) p=0.02	
% Patients with ≥1 unit improvement (MCID)	745/1288 (58%) OR 1.12 (95% CI 0.96, 1.31) p=NS	728/1322 (55%)
Rescue treatment over 52 weeks, based on subset of patients		
Patients evaluated	1584 (92.0%)	1561 (90.9%)
Change from baseline in daily number of puffs, mean (SE)	-1.01 (0.11)	-0.39 (0.11)
LS mean difference (95% CI)	-0.62 (-0.79, -0.45) p<0.0001	
Patients evaluated	1561 (90.7%)	1526 (88.8%)
% of days with no rescue use, mean (SE)	42 (1.39)	34 (1.40)
LS mean difference (95% CI)	8.0 (5.9, 10.2) p<0.0001	
Trough FEV_1 based on subset of patients		
Patients evaluated	1324 (76.9%)	1362 (79.3%)
Change from baseline (mL)	73	92
LS mean difference	-20; p=0.022	

1. Total mortality

There was no difference in all-cause mortality between indacaterol and tiotropium groups.

2. SAEs

There were no differences in total SAEs and COPD as a SAE between treatment with indacaterol and tiotropium. All-cause hospitalization was not reported.

3. Acute moderate or severe COPD exacerbations

a. A moderate exacerbation was defined as an exacerbation leading to treatment with antibiotics or systemic corticosteroids. A severe exacerbation was defined as an exacerbation that led to admission to hospital (including a visit to the emergency room for more than 24 h) in addition to treatment with systemic corticosteroids or antibiotics.

CRITICAL APPRAISAL ISSUE: Given that this multicenter trial was conducted in 41 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. Instead time-to-first-event analysis reported that indacaterol was associated with a higher risk of moderate or severe exacerbation during treatment than tiotropium. The hazard ratio (HR) on the reported study sample for indacaterol versus tiotropium was 1.20 (95% CI 1.07 to 1.33; p=0.0012).

CRITICAL APPRAISAL ISSUE: Time-to-first-event analysis is useful only when additional information on the number of patients who had more than one exacerbation throughout the study in both treatment groups is provided. (32)

In fact, attrition bias in this study and lack of data collection on exacerbation either as the first event or total number of exacerbations through out the study period post withdrawal will also affect the analysis.

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 and proportion of patients with a MCID were evaluated in 2606 (76%) patients. In this subset of patients there were no significant differences between the indacaterol group and the tiotropium group for these outcome measures.

CRITICAL APPRAISAL ISSUE: SGRQ total score was only reported for a subset of 2606 (76%) patients. The data for 24% of randomized patients 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.

TDI score and proportion of patients achieving a MCID were only reported in a subset of 2628 (76%) of randomized patients. There were no significant differences between treatment groups.

CRITICAL APPRAISAL ISSUE: TDI score was only reported for a subset of 2626 (76%) patients. The data for 24% 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 76% of randomized patients.

6. **Use of rescue salbutamol**

Reduced need for rescue medication is a marker of improved control of COPD symptoms.

Rescue treatment use, in terms of change in daily number of puffs and proportion of days with no use of rescue medication, was only reported in a subset of 3145 (92%) and 3087 (90%) of randomized patients, respectively. Patients in the indacaterol group needed rescue treatment less often as compared to those who received tiotropium [LS mean difference -0.62 (95% CI -0.79, -0.45); p<0.0001) in daily number of puffs; LS mean difference 8.0% (95% CI 5.9, 10.2); p<0.0001 in proportion of days with no rescue use).

> **CRITICAL APPRAISAL ISSUE**: The clinical importance of a small reduction in the need for rescue treatment is questionable. If indacaterol actually reduces the need for rescue medication, a significant improvement in SGRQ and TDI scores is also expected in this group. However, both SGRQ total score and TDI score were not different from tiotropium group.
>
> As noted by the authors of this study in the time to first event analysis of exacerbation, indacaterol is claimed to be associated with higher risk of moderate or severe exacerbation during treatment versus tiotropium. It is difficult to understand how this would translate into a reduced need for rescue medication.

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.

8. Adverse events

a. Adverse events occurred in 1119 (65%) receiving indacaterol and 1065 (62%) receiving tiotropium. There was no difference between indacaterol and tiotoprium for total adverse events.
b. A total of 101 (5.9%) and 96 (5.6%) patients treated with indacaterol and tiotropium, respectively, withdrew due to an adverse event. There was no between-group difference for withdrawal due to adverse events.

> **CRITICAL APPRAISAL ISSUE**: Overall, 2711 patients (79%) completed the trial. The study report does not provide sufficient information on the analysis of harm data although it does state that patients who permanently discontinued study treatment did not come in for further evaluation. Whether data were collected for adverse events following discontinuation from the study is not reported.

9. FEV_1

In 2686 (78%) patients evaluated, the mean change from baseline in trough FEV_1 in the indacaterol and tiotropium groups was 73 ml and 92 ml, respectively. A statistically significant

but not clinically relevant between-group difference in favour of tiotropium was seen in LS mean trough FEV_1 at study endpoint [-20 ml; p=0.02].

> **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. (3)
>
> **Other critical appraisal issues:**
>
> 1. The dose of indacaterol used in INVIGORATE 2013 is 150 mcg OD when the approved dose by Health Canada is 75 mcg OD.
> 2. The sample size was based on non-inferiority of indacaterol to tiotropium for rate of all exacerbations. The study was not powered to detect a difference between treatment groups in clinically relevant outcomes such as reduction in exacerbation, improvement in quality of life or decrease in mortality or hospitalizations.

LABA+LAMA vs. LABA

Only one study (Donohue 2016) was critically appraised, which is a double blind RCT investigating the long-term safety and tolerability of twice-daily aclidinium/formoterol (ACL/FOR) 400/12 mcg (n=392) versus formoterol (FOR) 12 mcg (n=198) in 590 patients with symptomatic COPD. (22) ICS and oral or parenteral corticosteroids at doses ≤10 mg/day, theophylline and H1-antihistamine were permitted for chronic use provided the dosage was stable for ≥4 weeks prior to screening and throughout the trial. Patients were permitted treatment with albuterol as needed, but not within 6 h before a visit. Chronic use of oxygen therapy was also permitted provided the dosage was stable for ≥4 weeks prior to screening. The study characteristics are provided in Table 9.

The primary objective of this study was long-term safety and tolerability of ACL/FOR 400 mg/12 mg and all efficacy outcomes were pre-defined as additional endpoints. Originally 450 patients were to be randomized as it was considered sufficient to meet the safety objectives of the study and to obtain long-term safety data for regulatory requirements. It was not based on statistical power to meet an efficacy objective.

Table 9: Donohue 2016 study characteristics

Participants	N=590 COPD patients ≥40 years of age with: 1) smoking history of ≥10 pack-years; 2) diagnosis of moderate to severe COPD; 3) post-bronchodilator FEV_1 ≥30% and <80% predicted value; and 4) post-bronchodilator FEV_1/FVC <0.7 **Exclusion criteria:** Any respiratory infection or COPD exacerbation ≤6 weeks before screening; pulmonary rehabilitation within 3 months of screening or an intention to start during the trial; clinically significant cardiovascular conditions, including myocardial infarction ≤6 months; newly diagnosed arrhythmia ≤3 months; unstable angina; unstable arrhythmia that had required changes in pharmacological therapy or other interventions ≤6 months; use of an automated implantable cardioverter-defibrillator; history of thoracic surgery ≤1

	year of screening; hospitalization ≤12 months for heart failure (NYHA class III) or history of thoracic surgery ≤1 year of screening and NYHA class IV; QTcB >470 ms at rest; or BMI ≥40 kg/m^2
Intervention	Aclidinium/formoterol 400/12 mcg BID [ACL/FOR] administered via Genuiar/Presair device (n=392) Available as DuaklirGenuair (400 mcg/12 mcg) 1 inhalation BID
Comparators	Formoterol 12 mcg BID [FOR] administered via Genuiar/Presair device (n=198) Available as Foradil Aerolizer (12 mcg 1-2) inhalations BID
	Patients were permitted treatment with albuterol as needed, but not within 6 h before a visit. ICS and oral or parenteral corticosteroids at doses ≤10 mg/day, theophylline and H1-antihistamine were permitted for chronic use provided the dosage was stable for ≥4 weeks prior to screening and throughout the trial. Chronic use of oxygen therapy was permitted for up to 15 h/day provided the dosage was stable for ≥4 weeks prior to screening. Indacaterol was not allowed within 15 days prior to screening or during the trial. Select β1-blocking agents (atenolol, metoprolol, nebivolol) were permitted for chronic use if the dosage was stable for ≥2 weeks prior to screening.
Outcomes	**PRIMARY:** • Proportion of patients who experienced ≥1 Treatment-Emergent Adverse Event (TEAE) up to week 56 **SECONDARY (prespecified):** • Proportion of patients who experienced any Potentially Clinically Significant (PCS) post-baseline change in clinical laboratory values for hematology, chemistry or urinalysis • Proportion of patients who experienced any PCS post-baseline change in pulse rate, systolic and diastolic blood pressure • Proportion of patients who experienced PCS changes in ECG from baseline **OTHER:** • Change from baseline in trough FEV_1 at 1, 12, 24, 38 and 52 weeks • Change from baseline in trough FVC at 1, 12, 24, 38 and 52 weeks • Change from baseline in total daily rescue medication use over 52 weeks • Rate of COPD exacerbations, defined as an increase in COPD symptoms that required a change in COPD treatment
Study Design	Multicentre 2-arm parallel group DBRCT conducted to fulfill FDA safety requirements and comprised a 2-3-week run-in period, 52-week double-blind treatment period, and a follow-up phone call 4 weeks after last treatment dose

There were no significant differences among the ACL/FOR and FOR treatment groups in baseline characteristics (Table 10). The mean age of study patients was 64.2 (9.3) years, 55% were males, 54% were former smokers and 23.9% had ≥1 exacerbation in the previous year. Post-bronchodilator FEV_1 was 51.4% of predicted normal value at screening. Fifty two percent

and 46% were classified as GOLD Stage II (moderate) and Stage III (severe), respectively. There were no differences in use of concomitant COPD drugs prior to and continuing during study with 38% using drugs from any category and 35% receiving ICS.

Table 10: Donohue 2016 baseline characteristics of study participants

	ACL/FOR 400/12 mcg BID (n=392)	**FOR 12 mcg BID (n=198)**
Age in years, mean (SD)	63.9 (9.3)	64.7 (9.4)
Males	216 (55.1%)	109 (55.1%)
White race	364 (92.9%)	181 (91.4%)
Former smokers	208 (53.1%)	111 (56.1%)
≥1 COPD exacerbation in previous year	89 (22.7%)	52 (26.3%)
Post-bronchodilator FEV_1, mean % predicted (SD)	51.8 (13.0)	50.5 (13.5)
COPD GOLD Stage		
II (Moderate)	207 (52.8%)	102 (51.5%)
III (Severe)	181 (46.2%)	92 (46.5%)
Daily rescue medication use	n=385	n=196
Mean number of puffs (SD)	4.5 (3.7)	4.5 (3.6)
Concomitant medications prior to and continuing during study		
Any category	150 (38.3%)	72 (36.6%)
ICS	138 (35.2%)	68 (34.3%)
LABA	0	0
LABA+ICS	0	1 (0.5%)
LAMA	0	2 (1.0%)
Systemic antihistamines	26 (6.6%)	17 (8.6%)
Theophylline	4 (1.0%)	1 (0.5%)

Only 398 patients (68%) completed the trial. All 590 patients were included in the safety analysis. Patients who discontinued the study prematurely did not come in for further evaluation. The study report does not state if data for exacerbations and other efficacy outcomes were collected following discontinuation from the study. Vital status was available for the total study population at Week 52. A summary of patient disposition is provided in Table 11.

Table 11: Patient disposition in Donohue 2016

	ACL/FOR 400/12 mcg BID	**FOR 12 mcg BID**
Randomized	392	198
Total adverse events	280 (71.4%)	130 (65.7%)
Total withdrawals	127 (32.4%)	65 (32.8%)
Withdrew consent	31 (7.9%)	15 (7.6%)
Withdrawal due to adverse events	26 (6.6%)	13 (6.6%)
Withdrawal due to lack of efficacy	23 (5.9%)	11 (5.6%)
Lost to follow-up	3 (0.8%)	5 (2.5%)

Risk of bias in Donohue 2016

Donohue 2016 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to detection bias, attrition bias and source of funding. The study is judged to have unclear risk of bias with respect to blinding and selective reporting (Table 12). The main concern is the high risk of bias related to efficacy outcomes given that this study is likely not blinded for efficacy outcomes and the high withdrawal rates (32%) will lead to attrition bias for exacerbation outcomes.

Table 12: Cochrane risk of bias summary for Donohue 2016

Domain	Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	"Randomization was carried out by assigning patient identification numbers via an interactive web response system provided by Premier Research Group Limited (East Hartford, Connecticut, USA)."
Allocation concealment (selection bias)	Low risk	"Randomization was carried out by assigning patient identification numbers via an interactive web response system provided by Premier Research Group Limited (East Hartford, Connecticut, USA)."
Blinding of participants and personnel (performance bias)	Unclear risk	Not described in sufficient detail aside from both interventions were administered via "double blind" Genuiar/Presair device.
Blinding of outcome assessment (detection bias)	High risk	"Major adverse cardiac events (MACE) were evaluated and classified according to the criteria prespecified by three blinded independent expert cardiologists not participating in the study." **Likely not blinded for efficacy outcomes.**
Incomplete outcome data (attrition bias)	High risk	All 590 patients were included in the safety analysis. The study report does not state if data for exacerbations were collected in patients who discontinued from the study and subsequently had an exacerbation. **The high withdrawal rates (32%) will lead to attrition bias for exacerbation outcomes but not for safety outcomes.**
Selective reporting (reporting bias)	Unclear risk	This study is registered with ClinicalTrials.gov, number NCT01437540 and the study protocol is provided. The **study publication reports all outcomes specified in the protocol**. Prespecified secondary outcomes are reported in limited detail: "Compared with baseline, no clinically relevant changes in clinical hematology, biochemical and urinalysis parameters, vital signs, or ECGs were attributed

Domain	Judgement	Support for Judgement
		to aclidinium 400 mg/formoterol 12 mg fixed-dose combination." **Other (efficacy) outcomes that were not pre-specified are reported.**
Other bias	High risk	"This study was supported by Forest Laboratories LLC, a wholly owned subsidiary of Allergan plc, and by Almirall S.A. Both funders were involved in the study design, and collection, analysis and interpretation of the data. The development of this manuscript was supported by Forest Laboratories, LLC; the decision to submit the manuscript for publication was made jointly by the funders and authors." "Medical writing and editing was provided by Mary Clare Kane, PhD, and Kristen A. Andersen, PhD, of Prescott Medical Communications Group (Chicago, IL, US), funded by Forest Laboratories LLC, a wholly owned subsidiary of Allergan plc (Jersey City, NJ, USA), and by Richard Knight, PhD, of Complete Medical Communications (Macclesfield, UK), funded by the AstraZeneca group of companies."

Outcomes reported

Results are presented in Table 13 according to the hierarchy of outcomes described above.

Table 13: Hierarchy of outcomes in Donohue 2016

	ACL/FOR 400/12 mcg BID (n=392)	FOR 12 mcg (n=198)
Total mortality	5 (1.3%)	1 (0.5%)
Total SAEs	38 (9.7%)	21 (10.6%)
Total hospitalizations	NR	NR
Hospitalization due to severe COPD exacerbation	NR	NR
Worsening of COPD as a SAE	NR	NR
Number of patients with ≥1 moderate or severe COPD exacerbation	99 (25.3%)	55 (27.8%)
Odds ratio (95% CI)	0.88 (0.60, 1.29) p=NS	
Number of patients with ≥1 severe COPD exacerbation	NR	NR

	ACL/FOR 400/12 mcg BID (n=392)	FOR 12 mcg (n=198)
SGRQ total score at Week 64		
SGRQ total score, mean (SE)	NR	NR
Patients with ≥4 point improvement (MCID)	NR	NR
Rate of moderate to severe COPD exacerbations		
Rate per patient-year (95% CI)	0.52	0.49
Between group difference	p=NS	
Time to 1st moderate or severe exacerbation, HR (95% CI)	NR	NR
Rate of COPD exacerbations leading to hospitalisation	NR	NR
Time to 1st exacerbation leading to hospitalisation, HR (95% CI)	NR	NR
TDI total score	NR	NR
Rescue treatment over 52 weeks, based on ITT population		
Patients evaluated	n=385	n=196
Change from baseline in daily number of puffs, LS mean (SE)	-1.9 (0.10)	-1.6 (0.16)
Trough FEV_1 at week 64		
Change from baseline (mL)	143	62
Mean difference (95% CI)	81.5 (12.5, 150.5) p<0.05	

1. Total mortality

Total mortality did not significantly differ between ACL/FOR and FOR groups.

2. SAEs

There was no significant between-group difference in total SAEs. All-cause hospitalization was not reported.

3. Acute moderate or severe COPD exacerbations

a. The study report does not define a moderate exacerbation or severe exacerbation. It simply states that an exacerbation was defined as an increase in COPD symptoms that required a change in COPD treatment

> **CRITICAL APPRAISAL ISSUE:** Given that this multicenter trial was conducted in 127 centers in the US there will be variability in treatment practices of moderate COPD

exacerbations across centers that could bias the study findings, especially if a moderate exacerbation is not clearly defined**.**

There was no significant difference in the number of patients with one or more acute moderate or severe exacerbations between the 2 treatment arms [OR 0.88 (95% CI 0.60, 1.29)]. The trial also reports the rate of moderate or severe exacerbations, which was 0.52 per patient-year with ACL/FOR versus 0.49 per patient-year with FOR alone (p=NS).

CRITICAL APPRAISAL ISSUE: The reported exacerbation events and rates are also uncertain due to the high withdrawal rates in the study (32 and 33% in ACL/FOR and FOR, respectively). It is unclear whether patients who withdrew prematurely were appropriately accounted for in this study.

4. Health-related quality of life

SGRQ total score was not a prespecified outcome of this study.

5. Symptomatic improvement

TDI score was not a prespecified outcome of this study.

6. **Use of rescue salbutamol**

Use of rescue treatment did not significantly differ between ACL/FOR and FOR groups.

7. COPD related health care utilization

COPD related health care utilization was not a prespecified outcome of this study.

8. Adverse events

a. Adverse events occurred in 280 (71.4%) receiving ACL/FOR and 130 (65.7%) receiving UMEC/VI. There was no between-group difference in total adverse events [OR 1.31 (95% CI 0.91, 1.89)].
b. A total of 26 (6.6%) patients treated with ACL/FOR versus 13 (6.6%) patients treated with FOR alone withdrew due to an adverse event. There was no difference between treatment groups for withdrawal due to adverse events.

9. FEV_1

The difference between ACL/FOR and FOR groups in the mean change from baseline in trough FEV_1 at Week 64 was 143 ml and 62 ml, respectively. The mean difference between groups was statistically significant [81.5 (95% CI 12.5, 150.5); $p<0.05$)] but the clinical relevance of this difference in favour of ACL/FOR is unknown.

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. (3)

Other critical appraisal issues:

1. The sample size was based on treatment emergent adverse events. The study was not powered to detect a difference between treatment groups in clinically relevant outcomes such as reduction in exacerbation, improvement in quality of life or decrease in mortality or hospitalizations.

LABA+LAMA vs. LAMA

Two studies (DYNAGITO 2018 and SPARK 2016) were identified in the update search that followed patients for at least a year.

A. DYNAGITO 2018 is a double blind RCT in 7880 patients with symptomatic COPD and a history of moderate or severe exacerbation in the preceding year. (23) This study compared dual bronchodilator therapy with olodaterol/tiotropium (OLO/TIO) 5/5 mcg (n=3939) with tiotropium (TIO) 5 mcg (n=3939), both administered once daily via the Respimat device. Patients taking ICS at baseline continued this treatment. Open-label salbutamol was provided for as-needed rescue medication use, but other short-acting beta-agonists, LAMAs and LABAs were not permitted during the study. A description of the study characteristics is provided in Table 14.

   A sample size of 3900 patients per group was to provide sufficient power to detect a 12% reduction (based on the results of a previous study) in rate of exacerbations with OLO/TIO compared with TIO. This sample size allowed for 15% loss of data due to patient withdrawals.

Table 14: DYNAGITO 2018 study characteristics

Participants	N=7880 COPD patients ≥40 years of age with: 1) smoking history of >10 pack-years; 2) post-bronchodilator FEV_1 <60% predicted value; 3) post-bronchodilator FEV_1/FVC <0.7; and 4) history of ≥1 moderate or severe exacerbation in preceding year requiring treatment with systemic corticosteroids or antibiotics or both, with or without hospitalisation **Exclusion criteria:** 1) current diagnosis of asthma; 2) severe emphysema requiring endobronchial interventions in the previous 6 months; 3) treatment with antibiotics for any reason within 4 weeks of screening; or 4) PDE-4 inhibitors use within 3 months of screening
Intervention	Olodaterol/tiotropium 5/5 mcg OD [OLO/TIO] via Respimat device (n=3939) Available as Inspiolto Respimat (2.5 mcg/2.5 mcg) 2 inhalations OD
Comparator	Tiotropium 5 mcg OD [TIO] via Respimat device (n=3941) Available as Spiriva Respimat (2.5 mcg) 1 inhalations OD
Concomitant Medications	Patients taking ICS at baseline continued this treatment; those receiving ICS in a fixed-dose combination with a LABA were switched to an equivalent corticosteroid monotherapy. Open-label salbutamol was provided for as-needed rescue medication use, but other short-acting beta-agonists, LAMAs and LABAs (other than the study medication) were not permitted during the

	study.
Outcomes	**PRIMARY:** • Rate of moderate to severe COPD exacerbations during the "actual treatment period", defined as the time from the first dose of medication until 1 day after last drug administration **SECONDARY (pre-specified):** • Number of patients with ≥1 moderate to severe COPD exacerbation during the "actual treatment period" • Number of patients with ≥1 COPD exacerbation leading to hospitalization during the "actual treatment period" • Rate of COPD exacerbations leading to hospitalisation during the "actual treatment period" • All-cause mortality during the "actual treatment period" **OTHER (not pre-specified):** • Time to all-cause mortality during the "on-treatment period", defined as the time from first dose of medication until 21 days after last dose • Time to first actual treatment moderate or severe COPD exacerbation • Time to first actual treatment COPD exacerbation leading to hospitalisation • Rate of actual treatment COPD exacerbations treated with antibiotics Rate of actual treatment COPD exacerbations treated with corticosteroids and antibiotics
Study Design	Multicentre 2-arm parallel group DBRCT consisting of a 52-week treatment period

There were no significant baseline differences between OLO/TIO and TIO groups in terms of demographics, COPD exacerbations and SGRQ total score (Table 15). The mean age of study patients was 66.4 (8.5) years, 72% were males, and 63% were former smokers. Post-bronchodilator FEV_1 was 44.6% of predicted normal value and a mean SGRQ total score of 47.8 (17.7) at screening. Forty five percent had a history of ≥2 exacerbations or ≥1 severe exacerbation in the preceding year. Nearly 40% of the patients were receiving triple therapy (LABA+LAMA+ICS), and 26% were receiving LABA+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 15: DYNAGITO 2018 baseline characteristics of study participants

	OLO/TIO 5/5 mcg (n=3939)	**TIO 5 mcg (n=3941)**
Age in years, mean (SD)	66.5 (8.4)	66.3 (8.5)
Males	2785 (71%)	2841 (72%)
White race	3134 (80%)	3113 (79%)
Former smokers	2505 (64%)	2462 (62%)
Patients with ≥2 COPD exacerbations or ≥1 severe	1754 (45%)	1733 (44%)

	OLO/TIO 5/5 mcg (n=3939)	TIO 5 mcg (n=3941)
exacerbation in previous year		
Post-bronchodilator FEV_1, mean % predicted (SD)	44.6 (37.5)	44.5 (11.5)
SGRQ total score, mean (SD)	48.1 (17.7)	47.4 (17.7)
GOLD class		
A	260 (7%)	308 (8%)
B	1922 (49%)	1895 (48%)
C	176 (4%)	176 (4%)
D	1569 (40%)	1547 (39%)
Missing	12 (<1%)	15 (<1%)
Respiratory medication		
LABA only	122 (3%)	135 (3%)
LAMA only	365 (9%)	350 (9%)
ICS only	107 (3%)	93 (2%)
LABA+ICS	1031 (26%)	1005 (26%)
LAMA+ICS	78 (2%)	88 (2%)
LAMA+LABA	461 (12%)	478 (12%)
LAMA+LABA+ICS	1555 (39%)	1577 (40%)
Neither	220 (6%)	215 (5%)

Overall, 6742 patients (86%) completed the trial. Fewer patients receiving OLO/TIO (12.4%) withdrew from the study as compared to TIO alone (16.5%) [OR 0.72 (95% CI 0.63, 0.81); p<0.00001]. This study analyzed exacerbation data during the "actual treatment period", defined as the time from first dose of medication until 1 day after the last dose of medication. Patients who permanently discontinued study treatment did not come in for further evaluation so there is loss of information on exacerbation events following premature discontinuation of study treatment. Vital status was available for 99.6% of the total study population at the end of the study. Table 16 provides a summary of patient disposition.

Table 16: Patient disposition in DYNAGITO 2018

	OLO/TIO 5/5 mcg	TIO 5 mcg
Randomized	3939	3941
Total adverse events	1119 (65.0%)	1065 (62.0%)
Total withdrawals	488 (12.4%)	650 (16.5%)
Withdrew consent	131 (3.3%)	184 (4.7%)
Withdrawal due to adverse events	259 (6.6%)	348 (8.8%)
Withdrawal due to lack of efficacy	37 (0.9%)	59 (1.5%)
Lost to follow-up	131 (3.3%)	184 (4.7%)

Risk of bias in DYNAGITO 2018

The Cochrane Risk of Bias Tool was used to assess the quality of DYNAGITO 2018. This study is judged to have a high risk of bias with respect to attrition, selective reporting and source of funding (Table 17). In particular, analysis of exacerbation endpoints was done on events that occurred during the "actual treatment period". Patients who withdrew prematurely and

subsequently had an exacerbation outside the “actual treatment period” are not accounted for in the analysis. The fact that more patients receiving tiotropium alone withdrew from the study could bias the analysis of exacerbations data.

Table 17: Cochrane risk of bias summary for DYNAGITO 2018

Domain	Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	"An interactive response technology system was used for randomisation and allocation of trial medication. The randomisation scheme used a randomised block design (block size 4) and was generated using validated randomisation software by Boehringer Ingelheim, which also prepared and coded the medications to maintain the double-blind."
Allocation concealment (selection bias)	Low risk	"An interactive response technology system was used for randomisation and allocation of trial medication. The randomisation scheme used a randomised block design (block size 4) and was generated using validated randomisation software by Boehringer Ingelheim, which also prepared and coded the medications to maintain the double-blind."
Blinding of participants and personnel (performance bias)	Low risk	"As both treatments (tiotropium and tiotropium-olodaterol) were delivered via identical Respimat devices, treatment was masked to patients, investigators, and everyone involved in analysing the trial data. No dummy devices were required."
Blinding of outcome assessment (detection bias)	Low risk	"As both treatments (tiotropium and tiotropium-olodaterol) were delivered via identical Respimat devices, treatment was masked to patients, investigators, and everyone involved in analysing the trial data. No dummy devices were required."
Incomplete outcome data (attrition bias)	High risk	“The primary analysis was done on the treated set (all randomly assigned patients who received any dose of study medication and were not from a site excluded due to on-site protocol violations.” “The primary endpoint was analyzed during the “actual treatment period”, defined as the time from first dose of medication until 1 day after the last dose of medication. This was also the period used for exacerbation and other endpoints.” “All adverse events were collected during the

Domain	Judgement	Support for Judgement
		on-treatment period, defined as up to 21 days after the last dose (appendix p 1)." "At the end of the planned study period (360 plus 21 days after first dose), data on vital status were available from 99.6% of patients." **Analysis for the primary and secondary endpoints was done on events that occurred during the "actual treatment period".** Patients who permanently discontinued study treatment and had an exacerbation outside the "actual treatment period" are not accounted for in the analysis and **this information is not reported.** This could affect the analysis of exacerbations data considering more patients receiving tiotropium alone withdrew from the study, which **could lead to attrition bias except for mortality data.**
Selective reporting (reporting bias)	High risk	This study is registered with ClinicalTrials.gov, number NCT02296138 and the study protocol is provided. The **study publication does not report all outcomes specified in the protocol** (e.g. number of patients with ≥1 moderate to severe exacerbation during the "actual treatment period"; number of patients with ≥1 exacerbation leading to hospitalization during the "actual treatment period") **Other outcomes that were not pre-specified are reported.**
Other bias	High risk	"RC, MS, DL, DY, and DMcB are employees of the trial sponsor (Novartis) and contributed to the design, preparation, and conduct of the study. They also made substantial contributions to the analysis and interpretation of the study. MD was the principal investigator of the study who critically reviewed the full study report and had the final responsibility for the decision to submit for publication. All authors had full access to the results of pre-specified statistical analyses, were encouraged to suggest appropriate post-hoc analyses, and made substantial contributions to the content of each draft."

Outcomes reported

Results are presented in Table 6 according to the outcome hierarchy described above.

Table 18: Hierarchy of outcomes in DYNAGITO 2018

	OLO/TIO 5/5 mcg (n=3939)	TIO 5 mcg (n=3941)
Total mortality	110 (2.8%)	123 (3.1%)
Total SAEs	810 (21%)	862 (22%)
Total hospitalizations	NR	NR
Hospitalization due to severe COPD exacerbation	NR	NR
Worsening of COPD as a SAE	NR	NR
Number of patients with ≥1 moderate or severe COPD exacerbation	NR	NR
Number of patients with ≥1 severe COPD exacerbation	NR	NR
SGRQ total score	NR	NR
Rate of moderate to severe COPD exacerbations		
Adjusted rate per patient-year	0.90 (0.84, 0.96)	0.97 (0.90, 1.03)
Rate ratio (95% CI)	0.93 (0.85, 1.02) p=NS	
Time to 1st moderate or severe exacerbation, HR (99% CI)	0.95 (0.87, 1.03) p=NS	
Rate of COPD exacerbations leading to hospitalisation		
Adjusted rate per patient-year	0.18 (0.16, 0.20)	0.20 (0.18, 0.22)
Rate ratio (95% CI)	0.89 (0.76, 1.03) p=NS	
Time to 1st exacerbation leading to hospitalisation, HR (95% CI)	0.93 (0.82, 1.06) p=NS	
TDI total score	NR	NR
Use of rescue treatment	NR	NR
Trough FEV_1	NR	NR

1. Total mortality

There was no difference in total mortality with OLO/TIO combination versus TIO alone.

2. SAEs

There was no difference in total SAEs between dual therapy with OLO/TIO and TIO. Hospitalization due to any cause was not reported.

3. Acute moderate or severe COPD exacerbations

a. A moderate exacerbation was defined as an exacerbation requiring treatment with oral corticosteroids or antibiotics or both. A severe exacerbation was defined as an exacerbation that required hospitalization or an emergency room visit.

   CRITICAL APPRAISAL ISSUE: Given that this multicenter trial was conducted in 51 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. Instead the trial reports the annual rate of moderate or severe exacerbations during the "actual treatment period" (pre-specified primary outcome), which was 0.90 per year with dual OLO/TIO therapy versus 0.97 per year with TIO alone. The rate ratio with dual OLO/TIO therapy versus TIO, 0.93 (95% CI 0.85, 1.02) was not statistically significant.

   CRITICAL APPRAISAL ISSUES: The trial reports the annual rate of moderate or severe exacerbations during the "actual treatment period", which was calculated by added all the exacerbations that took place in a treatment arm divided by the study duration. Therefore, multiple exacerbations that occurred in a single patient are counted. Interpretation of an annual rate is not possible without knowing how to divide the effect among individual people. If there was a reduction in the proportion of people who had one or more exacerbation, NNT calculations could be made and the treatment effect, if any, could be easily interpreted.

   The reported rates are also uncertain due to the imbalance in withdrawal rates among the treatment arms (12.4 and 16.5% in OLO/TIO and TIO, respectively) and no attempt was made to reduce attrition bias. Patients who withdrew prematurely were not adequately accounted for in the calculation of annual rates of moderate or severe exacerbations.

c. Time-to-first-event analysis reported no difference in the risk of moderate or severe exacerbations during treatment with OLO/TIO versus TIO alone [HR 0.95 (99% CI 0.87, 1.03); p=NS].

   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. (32)

4. Health-related quality of life

SGRQ total score was not a prespecified outcome of this study.

5. Symptomatic improvement

TDI score was not a prespecified outcome of this study.

6. **Use of rescue salbutamol**

Rescue treatment use was not a prespecified outcome of this study.

7. COPD related health care utilization

COPD related health care utilization, which includes physician visits/ER visits and hospitalization, was not a prespecified outcome.

8. Adverse events

a. Adverse events occurred in 1119 (65%) receiving OLO/TIO and 1065 (62%) receiving TIO. There was no difference between treatment arms for total adverse events.
b. Significantly more patients receiving TIO (16.5%) than OLO/TIO (12.4%) withdrew due to an adverse event (ARI 4.1%, NNH=24 for 1 year).

9. FEV_1

Trough FEV_1 was not a prespecified outcome of this study.

B. SPARK 2016 is a double blind RCT in 2224 patients with severe and very severe COPD and a history of at least 1 moderate exacerbation in the preceding year. (27) This study compared dual bronchodilator therapy with indacaterol/glycopyrronium (IND/GLY) 110/50 mcg (n=741) with glycopyrronium (GLY) 50 mcg (n=741), both administered once daily via the Breezhaler device. A third treatment arm received open-label tiotropum 18 mcg (n=742) via the Handihaler device was excluded. Approximately 75% of patients, with similar proportions across treatment groups, were using ICS either as fixed dose combination or as monotherapy at baseline. Patients using ICS at baseline continued this treatment at the same or equivalent dose and regimen during the study. Salbutamol was permitted as rescue medication use. Long acting bronchodilators were discontinued with a washout of up to 7 days (for theophylline, indacaterol and tiotropium) before screening. Study characteristics are provided in Table 19.

   Sample size was calculated in terms of the number of patient-years needed to detect a 20% reduction in the rate of COPD exacerbations (on the assumption of a constant rate during the treatment period) in the IND/GLY group compared with the GLY group. Reassessment of sample size and statistical power within the first 5 months of the study indicated that the study was underpowered for its primary endpoint. To ensure that the study had sufficient power (≥80%) the sample size was increased by 200 patients and the study duration was increased to a minimum of 15 months, with an allowance for additional variable exposure to treatment up to a maximum of 18 months. Assuming an average exposure treatment per patient of approximately 17 months, a total of 2198 patients randomly assigned to the three treatment groups would give a power of 84%.

Table 19: SPARK 2013 study characteristics

Participants	N=2224 COPD patients ≥40 years of age at risk of exacerbations, defined as patients with severe to very severe airflow limitation (Stage III or IV according to GOLD 2008 criteria), with: 1) smoking history of ≥10 pack-years; 2) post-bronchodilator FEV_1 <50% predicted value; 3) post-bronchodilator FEV_1/FVC

	<0.7; and 4) history of ≥1 moderate or severe exacerbation in preceding year requiring treatment with systemic corticosteroids or antibiotics or both **Exclusion criteria:** 1) any history of asthma; 2) treatment with antibiotics, systemic corticosteroids (oral or intravenous), or hospitalisation for COPD exacerbation within 6 weeks before prescreening or during screening; 3) developed a COPD exacerbation during prescreening or screening; or 4) had a respiratory tract infection within 4 weeks before prescreening
Intervention	Indacaterol/glycopyrronium 110/50 mcg OD [IND/GLY] administered via Breezhaler device (n=741) Available as Ultibro Breezhaler (110mcg/50mcg) 1 inhalation OD
Comparators	Glycopyrronium 50 mcg OD [GLY] administered via Breezhaler device (n=741) Available as Seebri Breezhaler (50 mcg) 1 inhalation OD Tiotropium 18 mcg OD [TIO] administered via open-label Handihaler device (n=742) Available as Spiriva Handhaler (18 mcg) 1 inhalation OD
Concomitant Medications	Patients receiving inhaled corticosteroids at baseline continued treatment (or the inhaled corticosteroid component alone if taken as a fixed combination with a bronchodilator) at the same or equivalent dose and regimen during the study. Long acting bronchodilators were discontinued with a washout of up to 7 days (for theophylline, indacaterol, and tiotropium) before screening.
Outcomes	**PRIMARY:** • Rate of moderate to severe COPD exacerbations at week 64 for IND/GLY vs. GLY **SECONDARY (prespecified):** • Rate of moderate to severe COPD exacerbations at week 76 for IND/GLY vs. TIO • Time to first moderate to severe COPD exacerbation at week 64 for IND/GLY vs. GLY vs. TIO • Rate of moderate to severe COPD exacerbations requiring use of both systemic glucocorticoids and antibiotics at week 64 • Number of days with moderate or severe exacerbation that required treatment with systemic glucocorticoids and antibiotics at week 64 • Time to study withdrawal or premature discontinuation for any reason • Proportion of patients with study withdrawal or premature discontinuation for any reason • Cumulative rates of moderate or severe exacerbations for multiple COPD exacerbation at 26, 52, 64, and 76 weeks • Trough FEV_1 at 4, 12, 26, 38, 52 and 64 weeks • Trough FVC at 4, 12, 26, 38, 52 and 64 weeks • Change from baseline of % of days without rescue therapy use • SGRQ total score at 12, 26, 38, 52 and 64 weeks
Study Design	Multicentre 3-arm parallel group DBRCT consisting of a 2-week run-in period, 64-week double-blind treatment period, and option to extend double-blind

	treatment period to a total of 76 weeks to ensure study achieved exacerbation rate prespecified for analysis

There were no significant differences between treatment groups at baseline with regard to demographics, COPD exacerbations and SGRQ total score (Table 20). The mean age of study patients was 63.1 years, 75% were males, and 62% were former smokers. Post-bronchodilator FEV_1 was 37.2% of predicted normal value and a mean SGRQ total score of 53 (18) at screening. Seventy seven percent and 22% had a history of 1 COPD exacerbation and 2 or more exacerbations, respectively, in the previous year. Seventy five percent were receiving ICS at randomization. Use of other respiratory medications at baseline is not reported.

Table 20: SPARK 2013 baseline characteristics of study participants

	IND/GLY 110/50 mcg (n=729)	**GLY 50 mcg (n=740)**
Age in years, mean (SD)	63.1 (8.1)	63.1 (8.0)
Males	556 (76%)	542 (73%)
White race	594 (81%)	605 (82%)
Former smokers	452 (62%)	457 (62%)
Number of COPD exacerbations in previous year 0 1 ≥2	 8 (1%) 557 (76%) 164 (22%)	 13 (2%) 572 (77%) 155 (21%)
Post-bronchodilator FEV_1, mean % predicted (SD)	37.0 (8.1)	37.3 (8.1)
SGRQ total score Mean (SD)	n=727 53 (18)	n=733 52 (18)
Daily rescue treatment use Mean number of puffs (SD)	n=716 5.7 (4.6)	n=737 5.7 (5.0)
Inhaled corticosteroids use	546 (75%)	557 (75%)
Other respiratory medication use	NR	NR

Overall, 1108 patients (75%) completed the trial. A total of 171 (23.1%) patients in the IND/GLY group and 203 (27.4%) in the GLY group permanently discontinued the study. The higher number of withdrawals in the GLY group as compared to IND/GLY was not statistically significant [OR 1.26 (95% CI 0.99, 1.59)]. Data for exacerbations and FEV_1 were no longer collected once patients discontinued from the study. Patients who prematurely discontinued were followed for survival to the end of the study. A summary of patient disposition is provided in Table 21.

Table 21: Patient disposition in SPARK 2013

	IND/GLY 110/50 mcg	**GLY 50 mcg**
Randomized	741	741
Total adverse events	678 (93.0%)	694 (93.8%)
Total withdrawals	171 (23.1%)	203 (27.4%)

	IND/GLY 110/50 mcg	GLY 50 mcg
Withdrew consent	33 (4.5%)	50 (6.8%)
Withdrawal due to adverse events	59 (8.0%)	67 (9.0%)
Withdrawal due to lack of efficacy	18 (2.4%)	32 (4.3%)
Lost to follow-up	5 (0.7%)	6 (0.8%)

Risk of bias in SPARK 2013

SPARK 2013 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition and source of funding. Selective reporting is judged to have an unclear risk of bias (Table 22).

Table 22: Cochrane risk of bias summary for SPARK 2013

Domain	Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	"Investigators contacted an interactive voice response system or web system, which generated a randomisation number (not communicated to the caller) that linked the patient to a treatment group. Patients randomly allocated to open-label tiotropium were not assigned a medication number because this treatment was supplied locally. Randomisation was stratified by current or ex-smoker status and inhaled corticosteroid use."
Allocation concealment (selection bias)	Low risk	"Investigators contacted an interactive voice response system or web system, which generated a randomisation number (not communicated to the caller) that linked the patient to a treatment group. Patients randomly allocated to open-label tiotropium were not assigned a medication number because this treatment was supplied locally."
Blinding of participants and personnel (performance bias)	Low risk	"Patients, investigator staff, people performing assessments, and data analysts were masked to treatment (QVA149 or glycopyrronium) from randomisation until database lock." "The double-blind study drugs were identical in packaging, labelling, schedule of administration, appearance, taste, and odour. Unmasking occurred in the case of emergencies and at conclusion of the study."
Blinding of outcome assessment (detection bias)	Low risk	"Patients, investigator staff, people performing assessments, and data analysts were masked to treatment (QVA149 or glycopyrronium) from randomisation until database lock."
Incomplete outcome data (attrition bias)	High risk	"Patients were followed up for serious adverse events up to 30 days after their last study

Domain	Judgement	Support for Judgement
		dose." "Patients who prematurely discontinued were followed for survival to the end of the study." “Efficacy variables were analysed for all patients randomly assigned to treatment groups who received at least one dose of study drug, analysed according to the treatment they were randomly assigned to receive (the full analysis set)…” “Exacerbation rates during treatment were analysed with the negative binomial model. Because this model includes the length of time the patient was in the study as an off set variable, which automatically accounts for patients who discontinued prematurely, the primary analysis was done without imputation.” The study report does not state if data for exacerbations were collected in patients who discontinued from the study and subsequently had an exacerbation. **The high withdrawal rates, with more patients receiving glycopyrronium alone withdrawing from the study, will lead to attrition bias except for mortality data.**
Selective reporting (reporting bias)	Unclear risk	This study is registered with ClinicalTrials.gov, number NCT01120691 and the study protocol is provided. The **study publication does not report all outcomes specified in the protocol** (e.g. time to first moderate to severe COPD exacerbation; number of days with moderate or severe exacerbation that required treatment with systemic glucocorticoids and antibiotics at week 64; change from baseline of % of days without rescue therapy use)
Other bias	High risk	"AFT, PD, CA, HC, and DB, as employees of the sponsor (Novartis Pharma AG), contributed to the design and preparation, conduct, analysis, and interpretation of the study. JAW and DEN contributed to the design of the study. DB was the responsible medical officer for the sponsor. JAW was the principal investigator of the study, read and commented on the full study report, and had final responsibility for the decision to submit for publication. All authors had full access to raw data, contributed to the writing of each draft of the report, and were

Domain	Judgement	Support for Judgement
		responsible for the decision to submit for publication. No restrictions were placed on authors regarding the statements made in the report." "Symptoms constituting an exacerbation were identified…based on the presence of two major symptoms (dyspnoea, sputum volume, sputum purulence) for at least 2 consecutive days or a worsening of one major symptom together with an increase in any one minor symptom (sore throat, cold, fever without other cause, cough, wheeze) for at least 2 consecutive days." Definition of exacerbation is not specific to COPD.

Outcomes reported

Results are presented in Table 23 according to the outcome hierarchy described above.

Table 23: Hierarchy of outcomes in SPARK 2013

	IND/GLY 110/50 mcg (n=729)	GLY 50 mcg (n=740)
Total mortality	23 (3%)	22 (3%)
Total SAEs	167 (23%)	179 (24%)
Total hospitalizations	NR	NR
Hospitalization due to severe COPD exacerbation	NR	NR
Worsening of COPD as a SAE	107 (15%)	116 (16%)
Number of patients with ≥1 moderate or severe COPD exacerbation	419 (57.5%)	426 (57.7%)
Odds ratio (95% CI)	0.96 (0.78, 1.18)	
Number of patients with ≥1 severe COPD exacerbation	95 (13.0%)	108 (14.6%)
SGRQ total score at Week 64		
SGRQ total score, mean (SE)	43.4 (0.8)	45.5 (0.8)
Change from baseline, mean	-9.2	-7.1
LS mean difference	-2.1 p=0.0067	
Patients with ≥4 point improvement (MCID)	56.7%	51.5%
Odds ratio (95% CI)	1.28 (0.99, 1.66) p=NS	
Rate of moderate to severe COPD exacerbations		

	IND/GLY 110/50 mcg (n=729)	GLY 50 mcg (n=740)
Adjusted rate per patient-year (95% CI) Rate ratio (95% CI)	0.84 (0.75, 0.94) 0.88 (0.77, 0.99) p=0.038	0.95 (0.85, 1.06)
Time to 1st moderate or severe exacerbation, HR (95% CI)	NR	NR
Rate of COPD exacerbations leading to hospitalisation		
Adjusted rate per patient-year Rate ratio (95% CI)	0.09 (0.07, 0.13) 0.81 (0.60, 1.10) p=NS	0.12 (0.09, 0.16)
Time to 1st exacerbation leading to hospitalisation, HR (95% CI)	0.79 (0.60, 1.05) p=NS	
TDI total score	NR	NR
Rescue salbutamol over treatment period Change from baseline in daily number of puffs, mean (SE) LS mean difference	 -2.3 (0.13) -0.81 p<0.0001	 -1.5 (0.13)
Trough FEV_1 at week 64 Change from baseline (mL) Mean difference	 151 70; p<0.0001	 81

1. Total mortality

There was no between-group difference in all-cause mortality.

2. SAEs

There were no differences in total SAEs and COPD as a SAE between treatment with IND/GLY and GLY alone. All-cause hospitalization was not reported.

3. Acute moderate or severe COPD exacerbations

a. A moderate exacerbation was defined as an exacerbation leading to treatment with antibiotics or systemic corticosteroids or both. A severe exacerbation was defined as an exacerbation that required hospital admission or emergency treatment.

   CRITICAL APPRAISAL ISSUE: Given that this multicenter trial was conducted in 27 countries there will be variability in treatment practices of moderate COPD exacerbations across centers that could bias the study findings**.**

b. IND/GLY and GLY groups showed no significant difference in the number of patients with one or more acute moderate or severe exacerbation [OR 0.96 (95% CI 0.78, 1.18)]. The study also reports the number of patients with one or more severe exacerbation and there was no difference between treatment groups. As compared to GLY alone, there is a

significant reduction with dual IND/GLY therapy in the rate of moderate or severe exacerbations therapy [rate ratio 0.88 (95% CI 0.77,0.99); p=0.038] but not in the rate of severe COPD exacerbations leading to hospitalization.

> **CRITICAL APPRAISAL ISSUE:** The reported exacerbation events and rates are uncertain due to the high withdrawal rates in the study (23 and 27% in IND/GLY and GLY, respectively). Patients who withdrew prematurely were not adequately accounted for in this study.

4. Health-related quality of life

Mean change in SGRQ total score and proportion of patients with a MCID were evaluated in this study. There was no significant difference between the IND/GLY and GLY alone for the proportion of patients who achieved a MCID. Change from baseline in SGRQ total score was greater in the IND/GLY group as compared to those who received GLY alone [LS mean difference -2.1; p<0.0067].

> **CRITICAL APPRAISAL ISSUE:** Estimates for mean change in SGRQ total score and proportion of patients with a MCID are uncertain due to the high withdrawal rates in the study (23 and 27% in IND/GLY and GLY, respectively). Patients who withdrew prematurely were not adequately accounted for in this study.

5. Symptomatic improvement

TDI score was not a prespecified outcome of this study.

6. **Use of rescue salbutamol**

Reduced need for rescue medication is a marker of improved control of COPD symptoms.

Change in the daily number of puffs of rescue medication was reported and patients in the IND/GLY group required less daily puffs of rescue salbutamol as compared to GLY group [LS mean difference -0.81; p<0.0001).

> **CRITICAL APPRAISAL ISSUE**: The clinical relevance of a reduced need of rescue salbutamol by less than 1 daily puff is unclear, especially considering the SGRQ effect estimate is uncertain (i.e. at high risk of attrition bias) and TDI score is not reported.

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.

8. Adverse events

a. Adverse events occurred in 678 (93%) receiving IND/GLY and 694 (94%) receiving GLY. There was no difference between treatment groups for total adverse events.

b. A total of 59 (8%) and 67 (9%) patients treated with IND/GLY and GLY, respectively, withdrew due to an adverse event. There was no between-group difference for withdrawal due to adverse events.

> **CRITICAL APPRAISAL ISSUE**: Overall, 1108 patients (75%) completed the trial. The study report does not provide sufficient information on the analysis of harm data although it does state that information about adverse events was collected at clinic visits and patients were followed up for SAEs up to 30 days after their last study dose. Whether data were collected for adverse events following discontinuation from the study is not reported.

9. FEV_1

For the IND/GLY and GLY groups the mean change from baseline in trough FEV_1 was 151 ml and 81 ml, respectively. A statistically significant but not clinically relevant between-group difference in favour of IND/GLY was seen [LS mean difference 70 ml; $p<0.0001$].

> **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. (3)

LABA+ICS vs. LABA

SUMMIT 2016 is a double blind RCT in 16,590 patients with symptomatic COPD and a history of cardiovascular disease. (17) This was an event-drive study in which follow-up continued until at least 1000 deaths had occurred (median study exposure was 1.8 years). This study comprised of 4 treatment arms. The comparison of interest for this report is fluticasone furoate/vilanterol (FF/VI) 110/50 mcg (n=4145) versus vilanterol (VI) 25 mcg (n=4146), both administered once daily via the Ellipta device. (The study also randomized patients to fluticasone furoate (FF) 100 mcg OD as well as placebo. The results for the FF treatment arm are not included in this report since the comparison with ICS is out of scope for this literature review update. The results for the placebo arm are included for informational purposes only.) **The use of all inhaled corticosteroids and inhaled long acting bronchodilators was discontinued ≤48 hours before study entry**, although other COPD medications such as theophyllines were allowed. A description of the study characteristics is provided in Table 24.

The study was designed to have 90% power to detect a 30% reduction in all-cause mortality (hazard ratio=0.70) on combination therapy compared with placebo. To control for multiplicity of testing of combination treatment versus placebo across endpoints, a closed testing procedure (gatekeeper) approach was planned. The hierarchy was the primary endpoint followed by the rate of decline in FEV_1 followed by the composite cardiovascular endpoint. If significance at the 5% level was not achieved for the primary endpoint for the comparison of combination treatment with placebo, then the tests for the secondary and other efficacy endpoints would be interpreted as descriptive only.

Table 24: SUMMIT 2016 study characteristics

Participants	N=16,590 COPD patients aged 40-80 years with: 1) smoking history of ≥10 pack-years; 2) post-bronchodilator FEV_1 50-70% predicted value; 3) post-bronchodilator FEV_1/FVC ≤0.7; 4) score of ≥2 on mMRC dyspnoea scale; and 5) history of cardiovascular disease (CVD), defined as coronary artery disease, peripheral arterial disease, stroke, MI or diabetes mellitus with target organ disease, or at increased CVD risk, defined as aged ≥60 years and receiving medications for >2 of the following: hypercholesterolaemia, hypertension, diabetes mellitus, or peripheral arterial disease **Exclusion criteria:** 1) respiratory disorders other than COPD; 2) lung reduction surgery; 3) receiving long-term oxygen, or oral corticosteroid therapy; 4) severe heart failure (NYHA Class IV) or ejection fraction <30%; 5) life expectancy less than 3 years; or 6) end-stage chronic renal disease
Intervention	Fluticasone furoate/vilanterol 100/25 mcg OD [FF/VI] administered via dry powder inhaler (Ellipta) device (n=4145) Available as Breo Ellipta (100mcg/25mcg) 1 inhalation OD
Comparators	Vilanterol 25 mcg OD [VI] administered via Ellipta device (n=4146) Vilanterol monotherapy not available in Canada Fluticasone furoate 100 mcg OD [FF] administered via Ellipta device (n=4158) Not indicated for COPD patients. Available as Arnuity Ellipta (at 100mcg or 200 mcg) for use in asthma patients. Placebo [PBO] (n=4141)
Concomitant Medications	The use of all inhaled corticosteroids and inhaled long acting bronchodilators was discontinued ≤48 hours before study entry, although other COPD medications such as theophyllines were allowed. Patients unable to tolerate withdrawal of therapy were excluded from study entry.
Outcomes	**PRIMARY:** • Time to all-cause mortality **SECONDARY (prespecified):** • On-treatment rate of decline in FEV_1 for FF/VI vs. PBO • On-treatment composite cardiovascular endpoint of cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischaemic attack for FF/VI vs. PBO **OTHER (prespecified):** • All primary, secondary, exploratory and other end-points for FF/VI vs. FF, FF/VI vs. VI, FF vs. PBO, and VI vs. PBO • Rate of moderate to severe COPD exacerbations for FF/VI vs. PBO • COPD-related mortality for FF/VI vs. PBO • Arterial stiffness in a subset of subjects for FF/VI vs. PBO • Health-related quality of life measured with the SGRQ-C in a subset of subjects for FF/VI vs. PBO • Quality-adjusted life years by treatment group using health status data

	collected from EuroQol Questionnaire in a subset of subjects • Healthcare resource utilisation (measured by number of days hospitalised for COPD) for FF/VI vs. PBO
Study Design	Multicentre 4-arm parallel group DBRCT consisting of a 4-10 day run-in period, median 1.8 years double-blind treatment phase (maximum 4 years follow-up), and 1-week follow-up phase. This was an event-driven study in which follow-up continued until at least 1000 deaths had occurred.

There were no significant differences between treatment groups at baseline with regard to demographics, COPD exacerbations, pre-study COPD therapy and cardiovascular disease or cardiovascular risk (Table 25). The mean age of study patients was 65 years, 75% were males, and 54% were former smokers. Post-bronchodilator FEV_1 was 59.7% of predicted normal value at screening. Thirty eight percent had a history of 1 or more COPD exacerbations in the previous year. There is no between-group difference in use of cardiovascular therapy at baseline. Approximately 33% were receiving ICS at randomization.

Table 25: SUMMIT 2016 baseline characteristics of study participants (ITT population)

	FF/VI 100/25 mcg (n=4121)	**VI 25 mcg (n=4118)**	**PBO (n=4111)**
Age (years), mean (SD)	65 (8)	65 (8)	65 (8)
Males	3112 (76%)	3053 (74%)	3071 (75%)
White race	3332 (81%)	3339 (81%)	3328 (81%)
Former smokers	2253 (55%)	2189 (53%)	2175 (53%)
Pre-study exacerbations in previous year			
0	2528 (61%)	2500 (61%)	2447 (60%)
1	998 (24%)	988 (24%)	1044 (25%)
≥2	595 (14%)	630 (15%)	620 (15%)
Pre-study COPD therapy			
LABA	1456 (35%)	1464 (36%)	1417 (34%)
LAMA	638 (15%)	634 (15%)	659 (16%)
ICS	1394 (34%)	1374 (33%)	1349 (33%)
Postbronchodilator FEV_1 (% predicted normal value), mean (SD)	59.7 (6.1)	59.7 (6.1)	59.7 (6.1)
Cardiovascular disease			
Coronary artery disease	2113 (51%)	2044 (50%)	2103 (51%)
Peripheral arterial disease	807 (20%)	817 (20%)	766 (19%)
Previous stroke	386 (9%)	387 (9%)	404 (10%)
Previous MI	730 (18%)	722 (18%)	658 (16%)
Diabetes with target organ disease	397 (10%)	377 (9%)	374 (9%)
At cardiovascular risk			
Hypercholesterolaemia	2125 (66%)	2191 (67%)	2112 (66%)
Hypertension	2882 (90%)	2900 (89%)	2861 (89%)
Diabetes mellitus	886 (28%)	874 (27%)	850 (27%)

	FF/VI 100/25 mcg (n=4121)	VI 25 mcg (n=4118)	PBO (n=4111)
Peripheral arterial disease	310 (10%)	301 (9%)	279 (9%)
Baseline cardiovascular therapy			
Any	4021 (98%)	3996 (97%)	3996 (97%)
Antithrombotic medication	2384 (58%)	2295 (56%)	2292 (56%)
Lipid-lowering medication	2829 (69%)	2797 (68%)	2751 (67%)
RAAS inhibitor therapy	2932 (71%)	2862 (69%)	2887 (70%)
Beta blockers	1444 (35%)	1376 (33%)	1389 (34%)
Calcium channel blockers	1593 (39%)	1569 (38%)	1551 (38%)
Nitrates	556 (13%)	569 (14%)	613 (15%)
Diuretics	1550 (38%)	1549 (38%)	1508 (37%)

Overall, 6250 patients (76%) receiving FF/VI and VI completed the trial. Data for exacerbations and FEV_1 were no longer collected once patients discontinued from the study. Vital status was known for 99.97% of patients in the intention to treat (ITT) population. A summary of patient disposition is provided in Table 26.

Table 26: Patient disposition in SUMMIT 2016

	FF/VI	VI	PBO
Randomized (ITT population)	4121	4118	4111
Total adverse events	2780 (67%)	2809 (68%)	2782 (67%)
Total withdrawals	950 (23%)	1039 (25%)	1192 (29%)
Withdrawal due to lack of efficacy	46 (1.2%)	65 (1.6%)	98 (2.4%)
Withdrawal due to adverse events	329 (8.0%)	366 (8.9%)	387 (9.4%)
Lost to follow-up	0	1	0

Risk of bias in SUMMIT 2016

SUMMIT 2016 is judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition bias, selective reporting and source of funding, and unclear risk of bias with respect to blinding (Table 27). The study report does not state if data for exacerbations and other efficacy outcomes were collected in patients who discontinued from the study and subsequently had an exacerbation. The high withdrawal rates (23-29%) across treatment groups will lead to attrition bias for all efficacy outcomes including exacerbations but not for mortality. There are also other biases with respect to study design and the presence of confounding that misrepresent the treatment effect (see Results and Critical Appraisal following Table 28).

Table 27: Cochrane risk of bias summary for SUMMIT 2016

Domain	Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned (1:1:1:1) through a centralised randomisation service

Domain	Judgement	Support for Judgement
		in permuted blocks to receive either placebo, fluticasone furoate, vilanterol, or the combination of fluticasone furoate and vilanterol. The randomisation schedule was generated using the GSK validated randomisation software RANDALL. A separate randomisation schedule was produced for each country."
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned (1:1:1:1) through a centralised randomisation service in permuted blocks to receive either placebo, fluticasone furoate, vilanterol, or the combination of fluticasone furoate and vilanterol. The randomisation schedule was generated using the GSK validated randomisation software RANDALL. A separate randomisation schedule was produced for each country." "…with only the database administrators having knowledge of treatment assignment."
Blinding of participants and personnel (performance bias)	Unclear risk	"Treatment was double blind (masking was achieved with Ellipta inhalers of identical appearance) with only the database administrators having knowledge of treatment assignment." Dysphonia is a common local side effect of ICS. Withdrawal of ICS may lead to unblinding in patients who were previously on ICS then randomized to non-ICS treatment in the study. Success of blinding was not reported.
Blinding of outcome assessment (detection bias)	Low risk	"Treatment was double blind (masking was achieved with Ellipta inhalers of identical appearance) with only the database administrators having knowledge of treatment assignment."
Incomplete outcome data (attrition bias)	High risk	"16 590 underwent randomisation…Of these, 22 participants never took study medication and the safety population therefore consists of 16 568 patients [4131 in the placebo group, 4157 in the fluticasone furoate group, 4140 in the vilanterol group, and 4140 in the combination group]. Data from five centres (83 patients) were excluded from the efficacy analysis because of failure to meet the standards of Good Clinical Practice and ethical

Domain	Judgement	Support for Judgement
		practice, and were closed before the study ended. Thus, a total of 16 485 patients were included in the intention-to-treat efficacy (ITT) population; 4111 in the placebo group, 4135 in the fluticasone furoate group, 4118 in the vilanterol group, and 4121 in the combination group (table 1)." "After randomisation, patients were seen every 3 months to confirm vital status and record adverse events. Postbronchodilator spirometry was done every 3 months and health status was assessed at 3 months then every 6 months. An independent data monitoring committee undertook safety reviews every 6 months, and one predefined interim efficacy analysis was done after about 500 deaths had occurred." "To ensure no bias in the ascertainment of survival status, a "common end date" was determined several months in advance. This common end date was selected so that there would be at least 1000 deaths by this date. The common end date was set at Jan 25, 2015, and sites were required to ascertain the survival status of their patients on or after this date." "Quality of life questionnaires were collected in a subset of patients (4443 [27%])." "More patients withdrew from study medication in the placebo group (29%) than in the three other groups: the lowest withdrawal rates were seen with combination therapy (23%)." "Vital status was known for 16 480 (99.97%) of 16 485 patients in the ITT population." "Patients with worsening COPD status or progressive CVD while on study treatment can receive other medications, or be withdrawn if in the investigator's opinion the patient's deterioration prevents ongoing participation. The reason for withdrawal will be recorded and patients will be followed up until study termination." The study report does not state if data for exacerbations were collected in patients who discontinued from the study and subsequently had an exacerbation.

Domain	Judgement	Support for Judgement
		The high withdrawal rates (23-29%) across treatment groups, with more patients in the placebo group withdrawing from the study, will lead to attrition bias except for mortality data. Also timing of withdrawal in different treatment groups and how many days they were followed following withdrawal in each treatment group, to record subsequent outcomes need to be reported.
Selective reporting (reporting bias)	High risk	This study is registered with ClinicalTrials.gov, number NCT013130676 and the study protocol was published previously. The **study publication does not report all outcomes specified in the protocol** (e.g. COPD-related mortality; health-related quality of life measured with the SGRQ-C in a subset of subjects; quality-adjusted life years by treatment group using health status data collected from EuroQol Questionnaire in a subset of subjects; healthcare resource utilisation [measured by number of days hospitalised for COPD]). Quality of life outcome was collected only in 27% of total randomised patients.
Other bias	High risk	"The study was designed by the funder (GlaxoSmithKline) in collaboration with the academic members of the steering committee. The sponsor was responsible for the running of the trial, data collection, and statistical analysis. Statistical analyses were done by a contract research organisation (Veramed Ltd, Twickenham, UK; funded by GSK) on behalf of, and with oversight from, employees of the funder. The first draft of the report was written by the primary academic author, and all the authors worked collaboratively to prepare the final content. All authors made the decision to submit the manuscript for publication. All the authors had full access to the data and vouch for the accuracy and completeness of all data and analyses, and for the fidelity of the study to the protocol. The corresponding author had access to all the data and had final responsibility for the decision to submit for publication." Exacerbation definition did not include specific

Domain	Judgement	Support for Judgement
		symptoms (no pre-defined clinical criteria); temporal independence of exacerbation events was not established; no blinded adjudication of exacerbation events. "About a third of patients stopped inhaled corticosteroids before study entry, with a similar proportion stopping long-acting β agonists. 6464 (39%) patients reported having had a COPD exacerbation in the year before entry." **Abrupt withdrawal of ICS may lead to increase in exacerbations post randomization. The number of patients with ≥1 exacerbation has not been reported in this study.**

Outcomes reported

In this study publication statistical analysis of mortality and all efficacy endpoints was in comparison with placebo. However, the study protocol does specify that comparisons of FF/VI and VI will be performed for all primary, secondary, exploratory and other end-points but these data are not reported. If study endpoint data were available in the publication, comparisons of FF/VI versus VI were done using Cochrane's Review Manager 5.3 software and presented as odds ratios (italicized) in Table 28.

Results are presented in Table 28 according to the outcome hierarchy described above.

Table 28: Hierarchy of outcomes in SUMMIT 2016

	FF/VI (n=4121)	VI (n=4118)	PBO (n=4111)
Total mortality	275 (6.7%)	265 (6.4%)	246 (6.0%)
P value vs. PBO	NS	NS	
Odds ratio (95% CI) vs. VI [calculated in RevMan]	*1.04 (0.87, 1.24)*		
Time to 1st event analysis	HR 0.88 (0.74, 1.04)	HR 0.96 (0.81, 1.14)	
P value vs. PBO	NS	NS	
P value vs. VI	NR		
Total SAEs	961 (23%)	972 (23%)	918 (22%)
Total hospitalizations	NR	NR	NR
Hospitalization due to severe	NR	NR	NR

	FF/VI (n=4121)	VI (n=4118)	PBO (n=4111)
COPD exacerbation			
SAE of pneumonia	NR	NR	NR
AE of pneumonia	237 (6%)	163 (4%)	214 (5%)
P value vs. PBO	NS	NS	
Odds ratio (95% CI) vs. VI [calculated in RevMan]	*1.48 (1.21, 1.82)*		
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 4443 (27%) patients	NR	NR	NR
Annual rate of moderate to severe exacerbation	0.25	0.31	0.35
P value vs. PBO	<0.0001	0.017	
P value vs. VI	NR		
Annual rate of severe exacerbation	0.05	0.06	0.07
P value vs. PBO	0.0004	0.013	
P value vs. VI	NR		
Transition Dyspnea Index	NR	NR	NR
Use of rescue salbutamol	NR	NR	NR
COPD related health care utilization	NR	NR	NR
On-treatment rate of decline in FEV_1 (mL/year), mean (SE)	38 (2.4)	47 (2.4)	46 (2.5)
Difference (95% CI)	8 (1, 15)	-2 (-8, 5)	
P value vs. PBO	0.019	NS	
P value vs. VI	NR		

1. Total mortality

There was no difference in total mortality between FF/VI combination therapy and VI alone.

2. SAEs

There was no difference in total SAEs between dual therapy with FF/VI and VI monotherapy. All-cause hospitalization was not reported.

3. Acute moderate or severe COPD exacerbations

a. A moderate exacerbation was defined as an exacerbation leading to treatment with antibiotics or systemic corticosteroids. A severe exacerbation was defined as an exacerbation that required hospitalization.

   CRITICAL APPRAISAL ISSUE: Given that this multicenter trial was conducted in 43 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 trial reports the annual rate of moderate or severe exacerbations, which was 0.25 per year with dual FF/VI therapy versus 0.31 per year with VI alone. The annual rates of severe exacerbation were 0.05 per year and 0.06 per year with FF/VI and VI, respectively. The rates were not statistically compared (i.e. rate ratio) between FF/VI and VI groups. Rates were calculated by adding all the exacerbations that took place in a treatment arm divided by the duration of the study. Therefore, multiple exacerbations that occurred in a single patient are counted.

   Interpreting a difference between treatment groups 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.

   Also the reported rates are uncertain due to the withdrawal rates in the FF/VI (23%) and VI (25%) groups. 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.

c. Thirty five percent, 34% and 15% of randomized patients were already receiving LABA, ICS and LAMA at screening and were required to discontinue these medications ≤48 hours before study entry.

   CRITICAL APPRAISAL ISSUE: Sudden ICS or LAMA withdrawal or both at randomization in those patients assigned to VI monotherapy may explain the numerically higher rate of exacerbations in this group as compared to dual therapy (although the two treatment groups were not statistically compared).

   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 (33-35). 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. (33) 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]. (34) The effects of 1-year withdrawal of ICS after a 3-month run-in with ICS/LABA were studied in 373 COPD patients. (35)

4. Health-related quality of life

Health-related quality of life measured with the SGRQ-C was not reported in the study publication despite being listed as a prespecified study endpoint in the protocol.

5. Symptomatic improvement

TDI score was not a prespecified outcome of this study.

6. **Use of rescue salbutamol**

Use of rescue medication was not a prespecified outcome of this study.

7. COPD related health care utilization

Health care resource utilization, measured by number of days hospitalised for COPD, is another outcome that was not reported in the study publication despite being listed as a prespecified study endpoint in the protocol. However, this study endpoint does not capture physician visits and ER visits.

8. Adverse events

a. Adverse events occurred in 2780 (67%) receiving dual therapy with FF/VI and 2809 (68%) receiving VI alone. There was no difference between FF/VI and VI comparator groups for total adverse events. Significantly more patients who received FF/VI (6%) versus VI alone (4%) had an AE of pneumonia [OR 1.48 (95% CI 1.21, 1.82)].
b. A total of 329 (8%) and 366 (9%) patients treated with FF/VI and VI, respectively, withdrew due to an adverse event. There was no between-group difference for withdrawal due to adverse events.

CRITICAL APPRAISAL ISSUE: Overall, 5589 (68%) patients receiving FF/VI or VI completed the trial. Information on adverse events may be incomplete given that patients who permanently discontinued study treatment did not come in for further evaluation.

9. FEV_1

On-treatment rate of decline in FEV_1 is reported but the difference of 10 ml/year between FF/VI and VI groups is not statistically compared.

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. (3)

LABA+ICS vs. LAMA

Only Sarac 2016, a single-centre open RCT was identified. (29) This small study randomized 44 COPD patients with a history of ≥1 exacerbation in the preceding year to twice-daily salmeterol/fluticasone 50/500 mcg (n=22) or once-daily tiotropium 18 mcg (n=22). All long-acting bronchodilators and inhaled steroids were stopped during the washout period and they were only allowed to take short-acting bronchodilators (salbutamol-ipratropium combination MDI). During the treatment period the patients were allowed to use short-acting bronchodilators when needed, but were not allowed to use any other bronchodilators or inhaled steroids. The study characteristics are provided in Table 29.

With a sample size of only 44 patients this study was not powered to detect a difference between treatment groups in clinically relevant outcomes such as reduction in exacerbation, improvement in quality of life or decrease in mortality or hospitalizations.

Table 29: Sarac 2016 study characteristics

Participants	N=44 moderate COPD patients aged 35-80 years with: 1) smoking history of ≥10 pack-years; 2) FEV_1 50-80% predicted value; and 3) history of ≥1 exacerbation in preceding year **Exclusion criteria:** 1) prior diagnosis of asthma; 2) previous documentation of bronchial hyperreactivity; 3) history of allergy and/or atopy; or 4) presence of congestive heart failure or any other cardiopulmonary disease that might interfere with patients' follow-up
Intervention	Salmeterol/fluticasone 50/500 mcg BID [SF] via Diskus inhaler (n=22)
Comparator	Tiotropium 18 mcg OD [TIO] via Handihaler device (n=22)
Concomitant Medications	All long-acting bronchodilators and inhaled steroids were stopped during the washout period and they were only allowed to take short-acting bronchodilators (salbutamol-ipratropium combination MDI). During the treatment period the patients were allowed to use short-acting bronchodilators when needed, but were not allowed to use any other bronchodilators or inhaled steroids.
Outcomes	**PRIMARY:** • Rate of COPD exacerbations **OTHER:** • Rate of COPD exacerbations leading to hospitalization • Post-bronchodilator spirometry and lung volumes • COPD Assessment Test (CAT) score • Arterial blood gas analysis • BODE index • Six-minute walk distance

Study Design	Single centre 2-arm parallel group open RCT consisting of a 2-week washout period followed 52-week open-label treatment period

The mean age of study patients was 66.6 (10.2) years and 91% were males (Table 30). Smoking status at screening is not reported, CAT score was 9.3 and 39% had ≥2 exacerbations in the previous year. Post-bronchodilator FEV_1 was 65.4% of predicted normal value at screening. Respiratory medication use at screening is also not reported.

Table 30: Sarac 2016 baseline characteristics of study participants

	SF 50/500 mcg (n=22)	**TIO 18 mcg (n=22)**
Age in years, mean (SD)	65.7 (10.6)	67.4 (9.7)
Males	20 (91%)	20 (91%)
White race	NR	NR
Former smokers	NR	NR
Patients with ≥2 exacerbations in previous year	9 (41%)	8 (36%)
No. of exacerbations in previous year, mean (SD)	2.2 (2.1)	1.9 (1.4)
Post-bronchodilator FEV_1, mean % predicted (SD)	63.5 (9.5)	67.2 (9.1)
SGRQ total score, mean (SD)	NR	NR
CAT score	8.7 (5.5)	9.6 (7.2)
Respiratory medication use	NR	NR

All 44 patients completed the trial and no adverse events were reported (Table 31).

Table 31: Patient disposition in Sarac 2016

	OLO/TIO 5/5 mcg	**TIO 5 mcg**
Randomized	22	22
Total adverse events	0	0
Total withdrawals	0	0

Risk of bias in Sarac 2016

According to the Cochrane Risk of Bias Tool, Sarac 2016 is judged to have a high risk of selection bias, allocation bias, performance bias and detection bias, and an unclear risk of selective reporting and source of funding (Table 32).

Table 32: Cochrane risk of bias summary for Sarac 2016

Domain	**Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	High risk	"The randomizaton was done according to a list prepared prior to the initiation of the study."
Allocation concealment (selection bias)	High risk	"The randomizaton was done according to a list prepared prior to the initiation of the study."
Blinding of participants and	High risk	Open trial

Domain	Judgement	Support for Judgement
personnel (performance bias)		
Blinding of outcome assessment (detection bias)	High risk	Open trial
Incomplete outcome data (attrition bias)	Low risk	"All patients completed the study."
Selective reporting (reporting bias)	Unclear risk	This study is not registered with ClinicalTrials.gov. A study protocol was not found so it is unknown if the study publication reports all outcomes specified in the protocol. Other outcomes that were not pre-specified may be reported.
Other bias	Unclear risk	"The study medications were kindly provided by Glaxo Smith Kline and Boehringer Ingelheim companies. These companies had no other involvement in the planning, design and execution of the study and in the analysis of the data." Source of funding is not reported.

Outcomes reported

Results are presented in Table 33 according to the outcome hierarchy described above.

Table 33: Hierarchy of outcomes in Sarac 2016

	SF 50/500 mcg (n=22)	TIO 18 mcg (n=22)
Total mortality	0	0
Total SAEs	NR	NR
Total hospitalizations	NR	NR
Hospitalization due to severe COPD exacerbation	NR	NR
Worsening of COPD as a SAE	NR	NR
Number of patients with ≥1 moderate or severe COPD exacerbation	NR	NR
Number of patients with ≥1 severe COPD exacerbation	NR	NR
SGRQ total score	NR	NR
Rate of moderate to severe COPD exacerbations Adjusted rate per patient-year Rate ratio (95% CI)	NR	NR

	SF 50/500 mcg (n=22)	TIO 18 mcg (n=22)
Time to 1st moderate or severe exacerbation, HR (99% CI)	NR	NR
Rate of COPD exacerbations leading to hospitalisation		
Rate per patient-year	0.6 (1.0)	1.1 (1.4)
Rate ratio (95% CI)	p=NS	
Time to 1st exacerbation leading to hospitalisation, HR (95% CI)	NR	NR
TDI total score	NR	NR
Use of rescue treatment	NR	NR
Change from baseline in FEV_1 (ml)	34.8; p=NS	16.1; p=NS

Sarac 2016 does not report any outcomes listed in the outcome hierarchy other than that no deaths occurred in either treatment group and there was no difference between groups in change from baseline in FEV_1. Several outcome measures including rate of COPD exacerbations leading to hospitalization and CAT score were not reported despite being mentioned in the Methods section.

LABA+LAMA vs. LABA+ICS

IMPACT 2018 was critically appraised previously. Please see TI report on Trelegy Ellipta dated September 12, 2018.

LABA+LAMA+ICS vs. LABA+LAMA

IMPACT 2018 was critically appraised previously. Please see TI report on Trelegy Ellipta dated September 12, 2018.

LABA+LAMA+ICS vs. LABA+ICS

IMPACT 2018 was critically appraised previously. Please see TI report on Trelegy Ellipta dated September 12, 2018.

Summary

A total of 6 studies evaluating 7 comparisons of interest met the criteria for critical appraisal. The TI previously critically appraised 1 study (IMPACT 2018) evaluating 3 comparisons of interest (LABA+LAMA vs. LABA+ICS; LABA+LAMA+ICS vs. LABA+LAMA; LABA+LAMA+ICS vs. LABA+ICS), which is available in the TI report on Trelegy Ellipta, dated September 12, 2018. Critical appraisal of the 5 remaining studies evaluating LABA vs. LAMA (1 study: INVIGORATE 2013), LABA+LAMA vs. LABA (1 study: Donohue 2016), LABA+LAMA vs. LAMA (2 studies: DYNAGITO 2018; SPARK 2013), and LABA+ICS vs. LAMA (1 study: Sarac 2013) is provided in this report. One additional

study (SUMMIT 2016), which is excluded from the PAD literature review update because it uses a LABA comparator (vilanterol 25 mcg) that is not commercialized in Canada, was critically appraised since it is the largest study to date comparing LABA+ICS with LABA.

All studies with a duration of 1 year or longer are judged to have a high risk of bias according to the Cochrane Risk of Bias Tool with respect to attrition. However, vital status was available for >99% of randomized patients in all studies. Therefore the overall quality of evidence is low for all outcomes except mortality.

No study showed a difference in total mortality between any of the comparator groups.

Total SAEs provides the best summary statistic of therapeutic impact accounting for all known and unknown serious impact (benefit and harm) from therapy. No studies showed a difference in total SAEs (which includes all cause hospitalization and hospitalization due to severe exacerbation) for any comparison.

The effect of inhaled medications on moderate to severe exacerbations needs to be reported as the proportion of patients with one or more exacerbations. Only 2 studies (Donohue 2016; SPARK 2013) reported the number of patients with 1 or more moderate to severe exacerbation and both studies showed no differences between their respective treatment groups. Other studies reported rate of moderate or severe exacerbation (DYNAGITO 2018; SUMMIT 2016) and time-to-first event analysis of moderate or severe exacerbation (INVIGORATE 2013). DYNAGITO 2018 and SUMMIT 2016 claimed no difference in exacerbation rates between treatment arms. INVIGORATE claimed that time to first moderate or severe exacerbation was longer with tiotropium versus indacaterol [HR 1.20 (95% CI 1.07 to 1.33; p=0.0012)]. Time-to-first-event analysis is useful only when it is known how many patients had more than one exacerbation throughout the study in both treatment groups. Furthermore, the reported events and rates are uncertain due to the high withdrawal rates in the studies and no attempt was made to reduce attrition bias by adequately accounting for the patients who withdrew prematurely in the calculation of event and annual rates of moderate or severe exacerbations.

Two studies (INVIGORATE 2013; SPARK 2013) reported quality of life (SGRQ) and 1 study (INVIGORATE 2013) reported dyspnea symptoms (TDI). Estimates for comparative treatment effects on SGRQ and TDI are uncertain due to the high withdrawal rates in both studies and inadequate accounting of patients who withdrew prematurely. Furthermore, INVIGORATE 2013 reported on a subset (approx. 75%) of total randomized patients. Therefore, the results are not considered valid due to missing data.

There were no differences in total adverse events between any of the comparators in these studies. DYNAGITO 2018 is the only study that demonstrated a difference in withdrawal due to adverse events between comparator groups with significantly more patients receiving TIO (16.5%) than OLO/TIO (12.4%) who withdrew due to an adverse event (ARI 4.1%, NNH=24 for 1 year).

Reduced need for rescue medication is a marker of improved control of COPD symptoms. Three studies (INVIGORATE 2013; Donohue 2016; SPARK 2013) reported need for rescue salbutamol

during the treatment period. Use of rescue treatment did not significantly differ between ACL/FOR and FOR groups in Donohue 2016. INVIGORATE 2013 reported in a subset (91%) of randomized patients that patients in the IND group needed rescue treatment less often as compared to those who received TIO [LS mean difference -0.62 (95% CI -0.79, -0.45); p<0.0001) in daily number of puffs; LS mean difference 8.0% (95% CI 5.9, 10.2); p<0.0001 in proportion of days with no rescue use). This finding is inconsistent with indacaterol showing no difference versus tiotropium for SGRQ total score and TDI score. Also it is difficult to understand how indacaterol reduced the need for rescue medication when time to first event analysis of exacerbation revealed that indacaterol increased the risk of moderate or severe exacerbation during treatment versus tiotropium. SPARK 2013 reported a reduction in daily puffs of rescue salbutamol in the IND/GLY group as compared to GLY group [LS mean difference -0.81; p<0.0001). The clinical relevance of a reduced need of rescue salbutamol is unclear considering the SGRQ effect estimate is uncertain (i.e. at high risk of attrition bias) and TDI score is not reported.

COPD related health care utilization, which includes physician visits/ER visits and hospitalizations, is an endpoint that was not reported in any of the studies. These findings would corroborate the findings of decreased rate of acute moderate to severe exacerbation.

Five studies (Donohue 2016; INVIGORATE 2013; Sarac 2016; SPARK 2013; SUMMIT 2016) reported trough FEV_1, of which 4 studies (Donohue 2016; INVIGORATE 2013; Sarac 2016; SPARK 2013) showed statistically significant but not clinically relevant between-group differences. SUMMIT 2016 did not statistically compare FF/VI and VI groups for on-treatment rate of decline in FEV_1. 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.

Conclusion

Based on the newly identified RCTs of at least 1 year duration, there is insufficient scientifically valid evidence that any of these comparisons (LABA vs. LAMA, LABA+LAMA vs. LABA, LABA+LAMA vs. LAMA, and LABA+ICS vs. LAMA) provides a therapeutic advantage in terms of moderate or severe exacerbation, quality of life (SGRQ), reported dyspnea symptoms (TDI), need for rescue medication, and COPD related health care utilization.

Based on the newly identified RCTs of at least 1 year duration, there is sufficient scientifically valid evidence demonstrating that none of these comparisons (LABA vs. LAMA, LABA+LAMA vs. LABA, LABA+LAMA vs. LAMA, and LABA+ICS vs. LAMA) provide a difference in terms of all-cause mortality, total serious adverse events (which includes all cause hospitalization and hospitalization due to severe exacerbation), and total adverse events in the treatment of COPD.

References

1. Therapeutics Initiative. Indacaterol for chronic obstructive pulmonary disease. Therapeutics Letter. 2016 Sept-Oct;102:1-2. URL: http://ti.ubc.ca/letter102.
2. Therapeutic Initiative. Inhaled long acting beta2 agonists for COPD. Therapeutics Letter. 2018 Feb;109:1-2. URL: http://ti.ubc.ca/letter109.
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2018 Edition. Available www.goldcopd.org.
4. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD009157.
5. Farne HA, Cates CJ. Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD008989.
6. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD006829.
7. Welsh EJ, Cates CJ, Poole P. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive lung disease. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.:CD007891.
8. Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, Kaneko T. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012066.
9. Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment Guidance for Industry DRAFT GUIDANCE. May 13, 2016 Clinical/Medical Revision 1. URL: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or http://www.regulations.gov
10. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.
11. Buhl R, Magder S, Bothner U, Tetzlaff K, Vob F, Loaiza L, Vogelmeier CF, McGarvey L. Long-term general and cardiovascular safety of tiotropium/olodaterol in patients with moderate to very severe chronic obstructive pulmonary disease. Respiratory Medicine. 2017;122:58-66.
12. Celli B, Crater G, Kilbride S, Mehta R, Tabberer M, Kalberg CJ, Church A. Once-daily umeclidinium/vilanterol 125/25 mcg therapy in COPD: A randomized, controlled study. Chest. 2014;145(5):981-91.
13. Donohue JF, Niewoehner D, Brooks J, O'Dell D, Church A. Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. Respiratory Research. 2014;15:78.

14. Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, Wachtel A, Martinez FJ, Barnhart F, Sanford L, Lettis S, Crim C, Calverley PMA. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respiratory Medicine. 2013;1:210-23.
15. Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M, Bourne E, Ballal S, Darken P, DeAngelis K, Aurivillius M, Dorinsky P, Reisner C. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. Lancet Respiratory Medicine. 2018;6:747-58.
16. Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: A double-blind, randomized study. Respiratory Medicine. 2012;106:257-68.
17. Vestbo J, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, Martinez F, Yates J, Newby DE. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet. 2016;387:1817-26.
18. Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, Banerji D. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. European Respiratory Journal. 2013;42:1484-94.
19. D'Urzo AD, Rennard SI, Kerwin EM, Mergel V, Leselbaum AR, Caracta CF. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. Respiratory Research. 2014;15:123.
20. Decramer ML, Chapman KR, Dahl R, Frith P, Devouassoux G, Fritscher C, Cameron R, Shoaib M, Lawrence D, Young D, McBryan. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded parallel-group study. 2013;1:524-33.
21. Singh D, Jones PW, Bateman ED, Korn S, Serra C, Molins E, Caracta C, Gil EG, Leselbaum A. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. 2014;14:178.
22. Donohue JF, Soong W, Wu X, Shrestha P, Lei A. Long-term safety of aclidinium bromide/formoterol fumarate fixed-dose combination: Results of a randomized 1-year trial in patients with COPD. 2016;116:41-8.
23. Calverley PMA, Anzueto AR, Carter K, Gronke L, Hallmann C, Jenkins C, Wedzicha J, Rabe KF. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. 2018;6:337-44.
24. Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G, Tabberer M, Harris S, Church A. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. 2014;2:472-86.

25. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respiratory Medicine. 2013;107:1538-46.
26. Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M, Church A. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: Results of a 24-week, randomized, controlled study. Respiratory Medicine. 2014;108:1752-60.
27. Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandstrom T, Taylor AF, D'Andrea P, Arrasate C, Chen H, Banerji D. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respiratory Medicine. 2013;1:199-209.
28. Ohar JA, Crater GD, Emmett A, Ferro TJ, Morris AN, Raphiou I, Sriram PS, Dransfield MT. Fluticasone propionate/salmeterol 250/50 mcg versus salmeterol 50 mcg after chronic obstructive pulmonary disease exacerbation. Respiratory Research. 2014;15:105.
29. Sarac P, Sayiner A, Compare the efficacy and safety of long-acting anticholinergic and a combination of inhaled steroids and long-acting beta-2 agonist in moderate chronic obstructive pulmonary disease. Tuberk Toraks. 2016;64(2):112-8.
30. Lipson DA, Barnhart F, Brealey N et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. New England Journal of Medicine. 2018;378(18):1671-80.
31. Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu CQ, Pascoe SJ. FULFIL Trial: Once-daily triple therapy for patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2017;196(4):438-46.
32. Aaron SD, Fergusson D, Marks GB, Suissa S, Vandemheen KL, Doucette S, Maltais F, Bourbeau JF, Goldstein RS, Balter M, O'Donnell D, FitzGerald M, for the Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. Thorax. 2008;63:122-8.
33. van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. American Journal of Respiratory and Critical Care Medicine. 2002;166:1358-63.
34. Choudhury AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha JA, Feder GS, Griffiths CJ. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respiratory Research. 2007;8:93.
35. Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, Pasma HR, Hensing CAJ, Creutzberg EC. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax. 2005;60:480-7.