Drug Use Research & Management Program
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Abbreviated Class Update: COPD

Month/Year of Review: November 2013 **End date of literature search: August 2013**
New Drug: fluticasone furoate/vilanterol trifenatate inhaled **Brand Name (Manufacturer): Breo® Ellipta® (GSK)**

Current Status of PDL Class:

- **Preferred Agents:** IPRATROPIUM BROMIDE HFA AER AD, IPRATROPIUM BROMIDE SOLUTION, IPRATROPIUM/ALBUTEROL SULFATE AMPUL-NEB, TIOTROPIUM BROMIDE(SPIRIVA®) CAP W/DEV,
- **Non-Preferred Agents:** AFORMOTEROL (BROVANA®), FORMOTEROL (PERFOROMIST), IPRATROPIUM/ALBUTEROL (COMBIVENT®) RESPIMAT, ROFLUMILAST (DALIRESP®), INDACATEROL (ARCAPTA®) NEOHALER, ACLIDINIUM (TUDORZA®) PRESSAIR

Current PA Criteria: Prior Authorization (PA) criteria is in place for combination long-acting beta(2)-agonists (LABAs) and inhaled corticosteroid (ICS) inhalers (Appendix 2) to ensure that they are being prescribed for appropriate diagnoses and therapy. requires a PA to ensure appropriate therapy for patients with severe Chronic Obstructive Pulmonary Disease (COPD) with a history of chronic exacerbations or prior exacerbations while being treated with a long-acting bronchodilator.

Research Questions:

- Is there new comparative evidence of a meaningful difference between LABAs, long-acting antimuscarinic agents (LAMAs), and ICSs or combinations thereof in long term clinical outcomes or safety in the treatment of COPD that could justify changes in current PDL management?
- Is there any evidence that fluticasone/vilanterol is more effective or safer than other LABA/ICS combination products in adults with COPD?
- Are there subgroups of patients in which fluticasone/vilanterol is more effective or safer than other available treatments for the treatment of COPD in adults?

Conclusions:

- Published trials use the surrogate marker of change in FEV1 to evaluate the efficacy of fluticasone/vilanterol, while mortality remains most desired clinical outcome. There remains insufficient evidence to determine its effects on mortality and other patient-related outcomes.
- There is moderate quality evidence that once daily fluticasone/vilanterol is effective at improving lung function in patients with moderate to severe COPD, as measured by the weighted mean FEV1 (0-4 h post-dose) after 24 weeks of treatment compared to placebo (173 ml, $p<0.001$). Trials have been short-term, and the long-term safety and efficacy of fluticasone/vilanterol is unknown.

- Serious adverse events were similar among treatment groups versus placebo. The most common adverse events are pneumonia, decrease in bone mineral density, nasopharyngitis, upper respiratory tract infection, oral candidiasis and headache (all seen in ≥5% of patients).
- There is insufficient evidence for differences in subpopulations in which fluticasone/vilanterol is more effective or safer.
- There is moderate quality evidence that fluticasone/vilanterol is non-inferior to fluticasone/salmeterol 250/50 ug after 12 weeks of therapy in change in FEV1 after 12 weeks.
- There is no evidence demonstrating clinical superiority of aclidinium bromide over tiotropium, and limited long term effectiveness or safety evidence of aclidinium bromide compared to tiotropium.
- There is evidence of no difference between tiotropium and LABAs in mortality, quality of life, and overall hospitalizations and insufficient evidence to compare the combination of tiotropium plus LABA with tiotropium alone.
- There is insufficient comparative effectiveness evidence between inhaled corticosteroids and long acting agents. Choice of agent should be based on availability, cost of medication and the patient's response.

Recommendations:

- Due to no evidence demonstrating clinical superiority of fluticasone/vilanterol over current agents, recommend comparing costs in executive session.
- Recommend adding LABA/ICS prior authorization criteria to fluticasone/vilaterol and also limit to use in patients who have COPD.
- Recommend comparing costs of agents for any further additions or eliminations to preferred products.

Previous Conclusions and Recommendations:

- There is insufficient comparative effectiveness evidence between inhaled corticosteroids and inhaled anticholinergics.
- There is no evidence demonstrating clinical superiority of aclidinium bromide over tiotropium, recommend making it non-preferred.
- There is moderate quality evidence that ipratropium bromide/albuterol Respimat inhaler is non-inferior to ipratropium bromide/albuterol MDI on lung function in the treatment of moderate to severe COPD.
- Due to limited long term effectiveness or safety evidence compared to multiple alternatives, recommend making indacaterol a nonpreferred LABA.
- Recommend maintaining roflumilast as a non-preferred agent and include clinical PA criteria necessary for approval to ensure it is only used in the appropriate patient population:
    - Patient has severe or very severe COPD with chronic bronchitis and frequent exacerbation
    - Patient has documented failure with an ICS or ICS combination product or tiotropium
    - Patient is on a concurrent long acting controller medication (LABA or LAMA) as monotherapy or in combination with other therapies.

Background:

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.[1] COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[2] The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema); the degree to which each type of structural changes contributes to disease varies in each individual. Chronic inflammation causes structural changes and narrowing of the small airways.[1] COPD is the result of cumulative exposures over decades. The most common risk factor for COPD is tobacco smoking. Other risk factors include indoor air pollution, occupational dusts and chemicals, outdoor air pollution, and factors that affect lung growth during gestation and childhood. COPD results from a gene-environment interaction. The

genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin, a circulating inhibitor of serine proteases. COPD has a higher prevalence among men and prevalence increases with age.[2]

COPD is defined as a FEV1/FVC< 0.70 based on a post-bronchodilator FEV1. Patients are stratified into groups (A-D) based on their symptoms and future risk of exacerbations.[2] Many trials for COPD use a surrogate endpoint of change in FEV1 because it is highly reproducible in a majority of patients. However, FEV1 measurements do not always correlate with clinically relevant outcomes such as dyspnea, health status, exercise capacity, quality of life or exacerbations and hospitalization, and changes in lung volume can occur without concomitant changes in FEV1.[3] A change of 5-10% from baseline values is considered to be clinically important when taking into consideration the values that would be considered clinically meaningful by regulators. The American Thoracic Society/European Respiratory Society (ATS/ERS) recommends the change in FEV1 should be ≥20% in short-term trials and ≥15% in long-term trials (≥1 year) to be confident that a clinically meaningful change has occurred. ATS/ERS suggests a minimally important difference of 100-140 ml is an appropriate value, although this value remains poorly defined in COPD patients.[4]

Both pharmacological and non-pharmacological treatment options exist for COPD. Smoking cessation is one of the most effective interventions. Other non-pharmacological options are modification of occupational exposure, reducing or avoiding indoor air pollution, and participating in physical exercise. There are several drug classes available for the relief of airflow obstruction in patients with COPD and to reduce the frequency and severity of COPD exacerbations. These include short- and long-acting beta-2 adrenergic agonists, short- and long-acting anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents (both short-acting and long-acting), combination of LABAs and ICS, as well as methylxanthines and phosphodiesterase-4 (PDE4) inhibitors. There are a small number of drug classes available for reducing COPD exacerbations. These include long-acting anticholinergic agents, combination products containing LABA and ICS, and PDE inhibitors. With the exception of methylxanthines and PDE4 inhibitors, all products are inhaled. Adjunctive therapies include systemic steroids, vaccines, alpha-1 antitrypsin augmentation therapy, antibiotics, mucolytic agents, antitussives and vasodilators. Optimal therapy must factor in the severity of disease, comorbidities, frequency and severity of exacerbations, cost, and general health status.[2,5]

Combination therapy with ICS and long acting agents appears to reduce the risk of exacerbation and improve lung function and health status in patients with moderate to severe COPD. Based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, patients who are in Group A (and low risk of exacerbation) should be managed by short or long acting agents, patients in Group B should be on a long acting agent [LABA or long-acting anticholinergic (LAMA)], and patients in Group C and D should be on an ICS and a long acting agent. Drug therapy can be escalated based on patient response and deterioration in lung capacity.[2] The NICE guidelines recommend adding therapy based on an algorithm of breathless ness and FEV1. If patients have intermittent breathlessness, they should use a short-acting agent. Patients with exacerbations or persistent breathlessness should be on a long-acting agent. These guidelines recommend adding an ICS to a long acting agent when a patient's FEV1 is less than 50% predicted or in patients with an FEV1 greater than 50% predicted who remain breathless or have exacerbations despite maintenance therapy with a LABA.[6]

Fluticasone/vilanterol is a new combination inhalation product comprised of a LABA and an ICS and is delivered with the dry powder inhaler Ellipta. Neither component is currently marketed as a single-ingredient inhalation product. Fluticasone furoate is marketed as an intranasal formulation for the treatment of allergic rhinitis. Vilanterol is a new molecular entity and not marketed for any indication. This is the first LABA/ICS product that is approved for once daily dosing. Only one strength is approved (fluticasone/vilanterol 100/25 ug) for the treatment of COPD. It is not approved for use in patients with asthma and carries a safety warning in patients with asthma, as LABAs increase the risk of asthma-related death.[6] Two other combination LABA/ICS products are on the market, fluticasone/salmeterol (Advair®) and budesonide/formoterol (Symbicort®).

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Methods:
A Medline literature search ending July 2013 for new systematic reviews and randomized controlled trials (RCT's) comparing ipratropium, tiotropium, beclomethasone, ciclesonide, fluticasone, salmeterol, formoterol,budesonide, mometasone, aformoterol, roflumilast, indacaterol, and aclidinium . The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.[7],[8] The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials (RCTs) will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, seven systematic reviews, one guideline update, three head to head RCTs, and one new drug were identified.

Systematic reviews:
A recently published high quality systematic review published by the Cochrane Collaboration by Cheyne et al[9] compared the effect of tiotropium to ipratropium in patients with COPD. Two good quality studies with 1,073 participants were included. Both studies used a similar design and inclusion criteria and were of at least 12 weeks duration. One study used tiotropium via the HandiHaler for 12 months and the other studied the Respimat device for 12 weeks. For primary outcomes, this review found that FEV1 increased significantly with tiotropium compared to ipratropium at 3 months (mean difference 109 mL; 95% Confidence Interval (CI) 81 to 137, moderate quality evidence). Fewer people experienced non-fatal serious adverse events on tiotropium compared to ipratropium (odds ratio (OR) 0.5; 95% CI 0.34 to 0.73, high quality evidence). This represents an absolute risk reduction from 176 50 97 per 1000 people over 3 to 12 months. The tiotropium group was also less likely to experience a COPD-related serious adverse event when compared to ipratropium (OR 0.59; 95% CI 0.41 to 0.85, moderate quality evidence). This review shows that tiotropium treatment, when compared with ipratropium, was associated with improved lung function, fewer hospital admissions, fewer exacerbations of COPD and improved quality of life.

A new high quality Cochrane Collaboration systematic review by Chong et al[10] evaluated the use of tiotropium versus LABAs. This review included seven randomized trials with 12,223 participants. All studies were of good methodological quality. However, there was a high amount of heterogeneity among the trials. The primary objective was to compare the relative clinical effects of tiotropium alone versus a LABA alone in quality of life, exacerbations, and lung function in people with chronic stable COPD. Results from six studies showed tiotropium reduced the number of participants experiencing one or more exacerbations compared to the LABA (OR 0.86, 95% CI 0.79 to 0.93). There was no difference seen among the different LABAs. Tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalization compared to LABA treatment (OR 0.87; 95% CI 0.77 to 0.99), but there was no difference in overall hospitalizations (OR 0.93; 95% CI 0.57 to 1.54) or mortality (OR 0.82; 95% CI 0.60 to 1.13). Due to the high level of heterogeneity in the quality of life data, the authors did not feel it was appropriate to pool the data. Symptom improvement and changes in lung function were similar between the two groups. Overall, there was insignificant evidence to conclude whether tiotropium or LABAs result in improved quality of life. However, it appears tiotropium may be superior in preventing exacerbations than LABAs (NNT 29; 95% CI 19 to 59). Tiotropium and LABAs appear to be similar in improving lung function, symptom relief, and mortality.

Cope at al[11] evaluated the use of indacaterol 75 µg versus fixed-dose combinations of an ICS and LABA for the treatment of COPD. Fifteen randomized, placebo-controlled trials including COPD patients were evaluated. In the indacaterol studies, patients were allowed to continue receiving inhaled corticosteroids, which was not the case in the ICS/LABA studies. Only a subgroup of patients in the indacaterol studies who did not receive concurrent ICS was included in this analysis,

and the number of those in the subgroup was not reported. All trials were analyzed simultaneously using a Bayesian network meta-analysis and relative treatment effects between all regimens were obtained. Outcomes of interest were trough FEV_1 and transitional dyspnea index at 12 weeks. Indacaterol resulted in greater improvement in FEV_1 at 12 weeks compared with budesonide/formoterol 160/9 ug (change from baseline 0.09L; 95% CI 0.04 to 0.13), budesonide/formoterol 320/9 ug (change from baseline 0.07L; 95% CI 0.03 to 0.11), fluticasone/salmeterol 250/50 ug (change from baseline 0.00L; 95% CI -0.07 to 0.07), and fluticasone/salmeterol 500/50 ug (change from baseline 0.01L; 95% CI -0.04 to 0.05). Based on the results of a network meta-analysis with and without covariates, indacaterol 75 µg is expected to be at least as efficacious to budesonide/formoterol and comparable to fluticasone/salmeterol with respect to lung function, but the results of effects on dypsnea are inconclusive with available data.

A review by Dong et al[12] evaluated the overall safety and cardiovascular death for inhaled medications in patients with COPD. Forty-two trials with 52,516 subjects were included. The Cochrane risk of bias tool was used to assess quality of individual trials and two investigators (one pharmacist and one physician) independently evaluated each trial. A mixed-treatment comparison meta-analysis with a fixed effect model indicated tiotropium Soft Mist Inhaler was associated with a universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at higher daily doses. This outcome may be due to severe disease or comorbidities. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium Handihaler or LABA. However, cardiovascular death was a rare, non-predefined outcome in many trials and did not have a consistent definition in clinical trials.

A recent high quality systematic review from the Cochrane Collaboration[13] evaluated the use of LABA and tiotropium combination therapy versus either tiotropium or a LABA therapy alone. A total of five trials were included in the analysis; four studies comparing tiotropium plus LABA to tiotropium alone and one trial comparing to LABA alone. Two studies (moderate quality evidence) used the LABA indacaterol, two used formoterol and one used salmeterol. Results demonstrated moderate quality evidence of improvement in quality of life (as measured by the St. George's Respiratory Questionnaire) with LABA plus tiotropium vs. tiotropium alone (MD -1.61; 95% CI -2.93 to -0.29). Although this was statistically significant, the mean difference is smaller than what is considered a clinically important difference. There was low quality evidence of no significant difference in hospital admission (OR 1.01; 95% CI 0.63-1.61) or mortality (OR 1.56; 95% CI 0.56-4.33). The secondary outcome of pre-bronchodilator FEV(1) showed a small mean increase with the addition of LABA (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and LABA compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. There was no difference in other outcomes of interest, such as mortality and hospital admissions. There is insufficient data to compare tiotropium plus LABA to LABA alone.

Another high quality Cochrane Collaboration review[14] evaluated the efficacy of ICS and LABA in a single inhaler with mono-component LABA alone. Fourteen studies were included, randomizing 11,794 people with COPD. Ten studies assessed fluticasone plus salmeterol and four assessed budesonide plus formoterol. All studies were well designed with a low risk for bias for randomization and blinding, but had high rates of attrition. There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomized 9921 participants (rate ratio 0.76; 95% CI 0.68 to 0.84). This corresponds to one exacerbation per person per year on LABA and 0.76 exacerbations per person per year on ICS/LABA. When analyzed as the number of people experiencing one or more exacerbations over the course of the study, fluticasone/salmeterol lowered the odds of an exacerbation with an odds ratio (OR) of 0.83 (95% CI 0.70 to 0.98, 6 studies, 3357 participants). With a risk of an exacerbation of 47% in the LABA group over one year, 42% of people treated with LABA/ICS would be expected to experience an exacerbation. There was no significant difference in the rate of

hospitalizations (rate ratio 0.79; 95% CI 0.55 to 1.13, very low quality evidence). There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, moderate quality evidence). Pneumonia occurred more commonly in people randomized to combined inhalers, from 12 studies with 11,076 participants (OR 1.55; 95% CI 1.20 to 2.01, moderate quality evidence) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of inhaled corticosteroid. Data were inconclusive as to the superiority of ICS/LABA over LABA alone in preventing COPD exacerbations.

Rodrigo et al[15] explored the efficacy and safety of indacaterol in comparison with tiotropium or twice-daily dosed LABAs for the treatment of moderate to severe COPD. Five trials were included in this systematic review. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea (43% greater likelihood of achieving a minimal clinically important difference [MCID] in the transitional dyspnea index [TDI]; number needed to treat (NNT) = 10). Additionally, the MCID in health status was more likely to be achieved with indacaterol than with tiotropium (OR = 1.43; 95% CI, 1.22–1.68; P = .00001; NNT = 10). Trough FEV1 was statistically significantly higher at the end of treatment with indacaterol than with TD-LABAs (80 mL, p = .00001). Similarly, indacaterol significantly improved dyspnea (61% greater likelihood of achieving an MCID in TDI, p = .008) and health status (21% greater likelihood of achieving an MCID in St. George's Respiratory Questionnaire, p = .04) than TD-LABA. Indacaterol showed similar levels of safety and tolerability to both comparators. There was moderate quality evidence showing indacaterol may be a useful alternative to tiotropium or twice-daily dosed LABAs.

Rodrigo et al[16] evaluated the use of tiotropium plus a LABA ("dual" therapy), LABA/ICS ("combined" therapy), tiotropium plus a LABA/ICS ("triple" therapy), and tiotropium monotherapy in the maintenance treatment of moderate to severe COPD. This was a medium quality systematic review. Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in FEV1, health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV1, HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to harm = 20; 95% CI: 11-119). Finally, "triple therapy" increased FEV1, improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, p = 0.21). While treatments with tiotropium plus a LABA and tiotropium plus a LABA/ICS look promising, there is no data to support a recommendation of either therapy over the other. More studies are needed to examine long-term safety and efficacy of these combinations.

New FDA Safety Alerts:
None.

New Guidelines:
An update to the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines was released in 2013.[2] Recommendations were based on evidence and expert opinion. Levels of evidence were given based on the source of evidence (Evidence A being RCT, B from limited RCTs, C from observational studies, and D from consensus judgement). This update redefines COPD as a mixture of airflow obstruction, alveolar destruction and chronic inflammation. Previous GOLD guidelines classified COPD severity by post-bronchodilator FEV1 alone. Grading was updated to include grades A-D based upon a combination of clinical symptoms, most notably dypsnea, FEV1 and number of yearly exacerbations. Drug therapy options for COPD were addressed. Indacaterol was included as a therapeutic option superior to salmeterol and formeterol, with similar efficacy to tiotropium (level A evidence). Roflumilast was included in the 2011

guidelines, but was again supported with level A evidence for its proven efficacy in reducing exacerbations in patients with severe COPD. Although aclidinium was approved at the time of publication, tiotropium is the only recommended long-acting anticholinergic agent; this may be due to the larger body of evidence on tiotropium. Main recommendations are as followed:

- For group A patients (few symptoms, low risk of exacerbations), a short-acting bronchodilator is recommended as first choice. Alternatively, a long-acting bronchodilator may be used (weak evidence for this recommendation).
- For Group B patients (many symptoms, low risk of exacerbations), long-acting bronchodilators are recommended over short-acting bronchodilators. For patients with severe breathlessness, a combination of long –acting bronchodilators can be used (weak evidence for this recommendation).
- For Group C patients (few symptoms, high risk of exacerbations), the first choice is a ICS/LABA combination or a LAMA. Alternatively, a combination of two long-acting bronchodilators or the combination of ICS/LAMA can be used (based on expert opinion).
- For Group D patients (many symptoms, high risk of exacerbations), the first choice of therapy is an ICS plus a LABA or LAMA, with some evidence of triple therapy with one medication from all three classes (Evidence B).
- Within a class, guidelines do not prefer one agent over another and rather recommend the choice be based on availability, cost of medication, and the patient's response.
- Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators (Evidence A).

Randomized Controlled Trials

A total of six RCT's were identified in the literature search. Of these, there are three potentially relevant head to head clinical trials. Abstracts of these trials are located in Appendix 4.

Study	Comparison	Population	Primary Outcome	Results
Fuhr et al[17]	Aclidinium 400 ug BID with placebo and tiotropium (1:1:1)	Moderate to severe COPD N=30	Mean change from baseline in FEV1 AUC on day 15	Mean change from baseline in FEV1 at day 15 was significantly greater for aclidinium and tiotropium over placebo (p<0.0001)
Sharafkheneh et al[18]	BID budesonide/formoterol pMDI 320/9 ug, budesonide/formoterol pMDI 160/9 ug, or formoterol dry powder inhaler 9 ug (1:1:1)	COPD patients aged >= 40 years with an exacerbation history discontinued medications except ICSs N=1219	Exacerbation rates (number per patient-treatment year)	Budesonide/formoterol 320/9 ug and 160/9 ug reduced exacerbation rates by 34.6% and 25.9%, respectively, versus formoterol (p<= 0.002
Zhong et al[19]	Budesonide/formoterol 320/9 ug BID or budesonide 400 ug BID	Moderate to very severe COPD in Chinese population	FEV1 change from baseline after 24 weeks	Budesonide/formoterol FEV1 improved by 0.18L vs 0.03L in budesonide

		N=308		alone group (p<0.001)

New Drug:

FDA Approved Indication:

Fluticasone/vilanterol is indicated for the long-term, once daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.[20]

Clinical Efficacy:

In trials with an increase in treatment comparisons, even when there are no differences between treatments, there is an increase in expected significance due to chance. Evaluated studies of fluticasone/vilanterol used a pre-specified testing hierarchy to control for this. Level 1 of the hierarchy comprised comparisons of the primary endpoint(s) at the highest dose tested in the study. Significance with a p-value <0.05 was required for these comparisons to allow statistical significance to be inferred for differences with p-value <0.05 for the primary endpoint(s) of lower fluticasone/vilanterol strengths. Inferences could only be made for secondary endpoints if primary endpoints were significant as shown with p-value <0.05. In studies where the highest strength of fluticasone/vilanterol was not statistically significant, the magnitude of effect of subsequent doses cannot be inferred even where information is available.[21–23]

Two similarly designed phase 3, double-blind, double-dummy, multicenter trials were completed (study 2206, study 2207)[21,22] in patients with moderate to severe COPD aged 40 or older. No prior history of COPD exacerbations was required for eligibility. Both studies compared the combination of fluticasone furoate (FF) and vilanterol (VI) to each component and placebo. Of the 2,254 subjects in these trials, 70% were male and 84% were Caucasian. They had an average smoking history of 44 pack years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV1 was 48%, the mean postbronchodilator FEV1/FVC ratio was 47%, and the mean percent reversibility was 14%.[20]

Study 2206 was a fair quality study that included 1030 patients. Patients were randomized to FF/VI 100/25 ug, FF/VI 50/25 ug, VI 25 ug, FF 100 ug, or placebo for 24 weeks. For the co-primary endpoint of mean change in weighted mean (0-4 h post-dose) on day 168, FF/VI 100/25ug, and VI 25 ug were statistically better than placebo; treatment differences were clinically significant at 173 ml and 103 ml, respectively (p <0.001 for both). The FF/VI 50/25 ug arm of the trial is unable to be regarded as statically significant due to the hierarchy employed. When compared to FF alone, the combination of FF/VI resulted in statistically significant changes (120 ml; 95% CI 0.07, 0.17, p-value <0.001). When compared to VI alone, no statistical difference was found for either the higher (70ml; 95% CI 0.021, 0.121, p-value >0.082) or lower strength (90 ml; 95% CI 0.039, 0.140, p-value >0.082) of the combination product. Descriptive differences in symptomatic endpoints such as rescue inhaler use showed a benefit for the higher strength of the combination product, but any symptomatic benefit of adding FF to VI will require further assessment. The primary effect of the ICS component of combination therapy is to reduce COPD exacerbations and control symptoms and generally requires a length of study of one year or more. While COPD exacerbation data was provided for this study, it was not powered or designed to examine exacerbations from an efficacy perspective. Due to the statistical hierarchy, no significance could be inferred for the secondary outcomes. However, no clinically meaningful difference was observed for dyspnea between any active therapy and placebo (as measured by the CRQ-SAS dyspnea domain).[21]

Study 2207 was a fair quality study that randomized 1124 patients to FF/VI 200/25 ug, FF/VI 100/25 ug, VI 25 ug, FF 200 ug, FF 100 ug, and placebo for 24 weeks. For the co-primary endpoint of mean change in weighted mean FEV1 (0-4 h post-dose) on day 168, FF/VI 200/25ug vs placebo (209 ml; 95% CI 0.157, 0.261; p-

value <0.001), FF/VI 200/25 ug vs FF 200 ug (168 ml; 95% CI 0.117, 0.219; p-value <0.001), and VI 25 ug vs placebo (185 ml; 95% CI 0.133, 0.237; p-value <0.001) comparisons were all statistically significant. Due to the pre-defined statistical testing hierarchy, no inference can be drawn for comparisons of lower strengths of FF/VI with placebo or its components as there was no significant difference in the change in lung function between VI and the highest strength of FF/VI (24 ml; 95% CI -0.027, 0.075). Although the number of exacerbations in the corticosteroid-containing regimens was fewer, this study was not designed or powered to examine the impact of fluticasone furoate when added to vilanterol on acute exacerbations. There was a lack of a clinically important change in the dyspnea domain of the CRQ-SAS despite notable improvements in lung function and further study should be done in order to understand the relationship between improvement in the surrogate endpoint FEV1 and improvement in COPD disease state.[22]

Three head-to-head phase 3b, double-blind, double-dummy, multicenter trials compared FF/VI 100/25 ug to salmeterol/fluticasone (Advair®) 250/50 ug for 12 weeks in patients 40 years or older with moderate to severe COPD.[24] None of these studies have been published and therefore could not be assessed for quality. The primary outcome in all three trials was the change from baseline in 0-24 hour weighted mean serial FEV1 on day 84. During study 2352, 511 subjects were randomized and included in the ITT population. The LS mean difference between FF/VI and fluticasone/salmeterol was 29 ml (95% CI -22, 80; p-value = 0.267). 519 subjects were randomized in study 3109. The LS mean difference between treatment groups was 80 ml (95% CI 37,124; p-value <0.001). This difference may be statistically significant, but it is not clinically significant according to consensus expert opinion on the minimal important difference.[5] In study 6974, 828 patients were randomized. The LS mean difference between treatment groups was 0.025 ml (95% CI -0.008, 0.59; p-value = 0.137). Therefore, FF/VI 100/25 ug should be considered non-inferior to fluticasone/salmeterol 250/50 ug after 12 weeks of therapy.

Two year-long studies (2871, 2970) evaluated the rate of exacerbations.[23] Eligible patients entered a 4-week open-label salmeterol/fluticasone (Advair®) 250/50 twice daily treatment phase followed by a 52-week double-blind treatment period with three doses of FF/VI or VI. To account for multiplicity across treatment comparison a step-down procedure was used with testing for high dose combination first, followed by low dose combination, and then other variables. In order to make inferences on secondary endpoints at a given strength, statistical significance at the 5% level had to have been demonstrated at the primary efficacy endpoint for that combination strength; this demonstration also needed to occur in order to make inferences of primary endpoints at a lower strength.[24] COPD exacerbations were defined as worsening of two or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any one major symptom together with any one of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least two consecutive days.[25] COPD exacerbations were considered to be of moderate severity if treatment with systemic corticosteroids and/or antibiotics were required and were considered to be severe if hospitalization was required.[24]

In study 2871, FF/VI 200/25 did not show a statistically significant difference from VI 25 ug alone (LS mean annual rate ratio 0.85; 95% CI 0.70, 1.04; p-value 0.109). The pre-specified statistical analysis plan required statistical significance of the higher dose prior to testing the lower dose which this study failed to accomplish, and therefore we cannot determine the statistical significance of the magnitude of effect of the FF/VI 100/25 ug or FF/VI 50/25 ug doses from this study. The rate of serious adverse events was similar across all treatment groups as was the rate of withdrawal due to adverse events.[23]

Study 2970 showed a statistically significant reduction in exacerbation rates of three doses of FF/VI when compared to vilanterol alone. FF/VI 200/25 ug showed the highest reduction in exacerbation rate compared to VI 25 ug, (LS mean annual rate ratio vs VI 25ug: 0.69; 95% CI 0.56, 0.85; p-value <0.001) followed by FF/VI 100/25 ug (LS mean annual rate ratio vs. VI 25 ug: 0.79; 95% CI 0.64, 0.97; p-value 0.024)and FF/VI 50/25 ug (LS mean annual rate ratio vs. VI 25 ug: 0.81; 95% CI 0.66, 0.99; p-value 0.04). Over half of the subjects in each treatment group did not experience on-treatment exacerbations. The number of subjects with one or more exacerbations was lowest for the FF/VI 100/25 ug and 200/25 ug groups (177 [44%] and 160 [39%] respectively) followed by VI 25ug and FF/VI

50/25 ug (197 [48%] and 198 [48%]).[25] The majority of moderate/sever exacerbations were moderate in intensity (90% in VI 25 ug group and 87-90% in the FF/VI groups). Serious adverse events were similar across all treatments as were withdrawals due to adverse events.

Clinical Safety:

Overall, the most common adverse events seen in trials are pneumonia, decrease in bone mineral density, nasopharyngitis, upper respiratory tract infection, oral candidiasis and headache (all ≥5% of patients). The total incidence of adverse events was comparable across treatment group and respiratory events were the most commonly reported. Rates of patients discontinuing due to an adverse event was also comparable across treatment groups.[20] Two safety findings of interest for inhaled doses of ICS are pneumonia and bone fractures, and both have been seen in previous LABA/ICS combination product development programs for COPD.[25]

An increase in pneumonia was seen in trials, as well as an increased incidence of pneumonias resulting in hospitalization. In two 52-week studies in 3,255 subjects with COPD who had a COPD exacerbation in the prior year, there was a higher incidence of pneumonia reported in subjects receiving FF/VI than subjects receiving vilanterol alone. One subject receiving FF/VI 100/25 ug and six subjects receiving FF/VI 200/25 ug had fatal pneumonia (less than 1% for each treatment group). There were no cases of fatal pneumonia in groups receiving VI 25 ug or FF/VI 50/25 ug.[24,25]

In the same two 52-week studies, an increased risk of fractures was seen with FF/VI compared to VI alone. 15 patients in the FF/VI 50/25 ug arm, 19 in the FF/VI 100/25 ug arm, 13 patients in the FF/VI 200/25 ug arm, and 8 in the VI arm developed fractures.[24, 25]

Due to the LABA component of this combination product, the FDA has issued a safety warning for its use in patients with asthma, as LABAs have been shown to increase asthma exacerbation and asthma-related death. Since COPD is a disease that occurs only in adults, FF/VI has not been specifically studied in the pediatric population, and as such no safety data for this population is available.[25]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Rate of exacerbations
3) Health-related quality of life
4) Dyspnea

Primary Study Endpoint:

1) Mean change from baseline in weighted mean (wm) FEV1 (0-4 h post-dose) on day 168
2) LS mean annual rate of moderate to severe exacerbation

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

Study 2206 Kerwin et al[21,25] 24-week, Phase III, DB, PC, RCT, MC	FV100: FF/VI 100/25 mcg FV50: FF/VI 50/25 mcg V: VI 25 mcg F: FF 100 mcg P: Placebo	Demographics: 221 centers in 9 countries US, EU, other (39% US) Average age: 62.6 yrs Inclusion Criteria: Age ≥ 40 yrs, clinical diagnosis of COPD, smoking hx ≥10 pack yrs, FEV1/FVC ratio ≤ 0.70, post-bronchodilator FEV1 ≤ 70% predicted, score of ≥2 on Modified Medical Research Counil Dyspnea Scale (mMRC) Exclusion Criteria: Diagnosis of non-COPD respiratory disorder, lung volume reduction surgery within 12 months of enrollment, acute worsening of COPD requiring steroid or antibiotics within 6 weeks hospitalization due to poorly controlled COPD within 12 weeks, Lower RTI requiring use of antibiotics within 6 weeks need for long-term oxyge therapy or nocturnal oxygen therapy (≥12 hr/day)	ITT: FV100: 206 FV50: 206 V: 205 F: 206 P: 207 Total Attrition FV100: 55 (26.7%). FV50: 60 (29.1%) V: 62 (30.2%) F: 61 (29.6%) P: 69 (33.3%) Loss to f/u: FV100: 3 (1.4%) FV50: 1 (0.5%) V: 2 (1.0%) F: 0 (0.0%) P: 4 (1.9%)	Mean change from baseline wm FEV1 (0-4 h post-dose) on day 168* FV100 diff from P: 0.17L; 95% CI: (0.12, 0.22) p –value: <0.001 FV50 diff from P: 0.19L; 95% CI: (0.14, 0.24) V diff from P: 0.10L; 95% CI: (0.05, 0.15) F diff from P: 0.05L; 95% CI: (0.00, 0.10) *No significance could be inferred for primary endpoints because of the pre specified statistical hierarch	N/A N/A N/A N/A	Total AEs: FV100: 111 (54%) p-value: 0.279 RR: 1.146 (95% CI: 0.942-1.393) FV50: 114 (55%) p-value: 0.168 V: 111 (54%) p-value: 0.239 F: 123 (60%) p-value: 0.023 P: 100 (48%) SAEs: FV100: 11 (5%) p-value: 1.0 RR: 1.005 95% CI: 0.414, 0.523 FV50: 6 (3%) p-value: 0.322 V: 15 (7%) p-value: 0.425 F: 16 (8%) p-value: 0.328 P: 11 (5%) COPD exacerbations FV100: 19 (9.2%) p –value: 0.868 RR: 0.909 95% CI: 0.481, 1.712 FV50: 12 (6%) p –value: 0.146 V: 22 (10.7%) p –value: 0.873 F: 26 (12.6%) p –value: 0.536 P: 21 (10.1%)	FV100 vs P: ARR: 7.0% NNH: 14 NS NS	**Quality Rating:** Fair **Internal Validity Review of Bias:** Selection: Randomization occurred via computerized system, which was used to register and randomize patients and receive medication assignment information Performance: All groups received medication via identical dry powder inhalers Detection: Patients, investigators, and outcome assessors were all blinded. Attrition: 33.3% P, 30.2% V, 29.6% F, 29.1% FV50, 26.7% FV100. The majority of patients withdrew due to adverse events, lack of efficacy or withdrawn consent. **External Validity Review of Bias:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a two-week run in period, and a the study was conducted in an outpatient setting Outcomes: The accepted surrogate outcome o FEV1 was used for efficacy measure. No clinically important outcomes measured, including mortality, hospitalizations, and quality of life.

Study 2207 Martinez et al[22,25] 24-week, Phase III, DB, PC, RCT, MC	FV200: FF/VI 200/25 mcg FV100: FF/VI 100/25 mcg V: VI 25 mcg F200: FF 200 mcg F100: FF 100 mcg P: Placebo	Demographics: US, EU, Other (25% US) Average age: 61.6 years Inclusion Criteria: Clinica diagnosis of COPD, age ≥ 40 yrs, smoking hx ≥10 pack yrs, FEV1/FVC ratio ≤ 0.70, post-bronchodilator FEV1 ≤ 70% predicted, score of ≥2 on mMRC Exclusion Criteria: Diagnosis of non-COPD respiratory disorder, lung volume reduction surgery within 12 months of enrollment, acute worsening of COPD within 6 weeks, hospitalization due to poorly controlled COPD within 12 weeks, lower RTI requiring use of antibiotics within 6 weeks need for long-term oxyge therapy or nocturnal oxygen therapy (≥12 hr/day)	ITT: FV200: 205 FV100: 204 V: 203 F200: 203 F100: 204 P: 205 Total Attrition FV200: 50 (24.4%). FV100: 64 (31.4%) V: 50 (24.6%) F200: (23.1%) F100: 53 (30.0%) P: 61 (29.7%) Loss to f/u: FV200: 1 (0.5%) FV100: 2 (1.0%) V: 0 (0.0%) F200: 0 (0.0%) F100: 2 (1.0%) P: 3 (1.5%)	Mean change from baseline in weighted mean (wm) FEV1 (0-4 h post-dose) on day 168 FV200 diff from P: 0.21L; 95% CI: (0.16, 0.26) p <0.001 FV100 diff from P: 0.21L; 95% CI: (0.16, 0.27) V diff from P: 0.19L; 95% CI: (0.13, 0.24) p <0.001 F200 d iff from P: 0.04L; 95% CI: (-0.01, 0.09) F100 diff from P: 0.05L; 95% CI: (-0.01, 0.10)	 N/A N/A N/A N/A	Total AEs: FV200: 93 (45%) p-value: 0.843 FV100: 92 (45%) p-value: 0.766 RR: 0.958 95% CI: 0.768, 1.195 V: 85 (42%) p-value: 0.321 F200: 96 (47%) p-value: 1.0 F100: 78 (38%) p-value: 0.089 P: 96 (47%) SAEs: FV200: 15 (7%) p-value: 0.410 FV100: 12 (6%) p-value: 0.669 RR: 1.2 95% CI: 0.0.494, 2.941 V: 16 (8%) p-value: 0.231 F200: 10 (5%) p-value: 1.0 F100:6 (3%) p-value: 0.445 P: 10 (5%) COPD exacerbations FV200: 14 (6.8%) p-value: 0.289 FV100: 13 (6.4%) p-value: 0.209 V: 18 (8.9%) p-value: 0.737 F200: 10 (4.9%) p-value: 0.060 F100: 4 (2.0%) p-value: 0.001 P: 21 (10.2%)	 NS NS	**Quality Rating: Fair** **Internal Validity Review of Bias:** Selection: Randomization occurred via computerized system, which was used to register and randomize patients and receive medication assignment information Performance: All groups received medication via identical dry powder inhalers Detection: Patients, investigators, and outcome assessors were all blinded. Attrition: 29.7% P, 24.6% V, 30.0% F100, 23.1% F200, 31.4% FV100, 24.4% FV200. High attrition was similar across all groups and included withdrawal due to adverse events, lack of efficacy, protocol stopping criteria, or withdrawn consent. **External Validity Review of Bias:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a two-week run in period, and a the study was conducted in an outpatient setting Outcomes: The accepted surrogate outcome o FEV1 was used for efficacy measure.

Study 2871 Dransfield et al[23,25] 52-week, Phase III, DB, PC, RCT, MC	FV 200: FF/VI 200/25 ug FV100: FF/VI 100/25 ug FV50: FF/VI 50/25 ug V: VI 25 ug	Demographics: US, EU, Canada, S Africa, Australia, Other (33% US Average age: 63.6 years Inclusion Criteria: Clinica diagnosis of COPD, age ≥ 40 yrs, current smoker or hx ≥10 pack yrs of smoking, FEV1/FVC ratio ≤ 0.70, post-bronchodilator FEV1 ≤ 70% predicted, documented hx of at least 1 COPD exacerbation in 12 months before screening Exclusion Criteria: Diagnosis of non-COPD respiratory disorder, lung volume reduction surgery within 12 months of enrollment, acute worsening of COPD within 6 weeks, hospitalization due to poorly controlled COPD within 12 weeks, lower RTI requiring use of antibiotics within 6 weeks need for long-term oxygen therapy or nocturnal oxygen therapy (≥12 hr/day), subjects at risk of noncompliance, women who are pregnant or breast-feeding or at risk o becoming pregnant during trial, historical or current evidence of uncontrolled or clinically significant disease states	ITT: FV200: 402 FV100: 403 FV50: 408 V: 409 Total Attrition FV200: 101 (25%) FV100: 91 (23 FV50:93 (23%) V: 115 (28%) Loss to f/u: FV200: 5 (1%) FV100:6 (1%) FV50: 7 (2%) V: 11 (3%)	LS mean annual rate of moderate to severe exacerbation FV200: 0.90 FV100: 0.70 FV50: 0.92 V: 1.05 Ratio vs. V* FV200: 0.85 (95% CI 0.70, 1.04; p-value 0.109) FV100: 0.66 (95% CI 0.54, 0.81) FV50: 0.87 (95% CI 0.72,1.0) *No significance could be inferred for primary endpoints for FV100 or FV50 because of the pre-specified statistical hierarch		Total AEs: FV200: 288 (72%) FV100: 301 (75%) p-value: 0.052 RR: 1.090 95% CI: 0.996, 1.190 FV50: 304 (75%) V: 281 (69%) SAEs: FV200: 63 (16%) FV100: 56 (14%) p-value: 0.764 RR: 0.947 95% CI: 0.665, 1.348 FV50: 65 (16%) V: 60 (15%) Death: FV200: 13 (3%) FV100:5 (1%) FV50: 7 (2%) V: 4 (1%)	FV100 vs V: ARR: 6.2% NNH: 16 NS	**Quality Rating:** Fair **Internal Validity Review of Bias:** Selection: Randomization occurred via computerized system, which was used to register and randomize patients and receive medication assignment information Performance: All groups received medication via identical dry powder inhalers Detection: Patients, investigators, and outcome assessors were all blinded. Attrition: 28% P, 23% FV50, 23% FV100, 25% FV200. Attrition was similar across all groups and due to adverse events, withdrawn consent, lack of efficacy, or protocol deviation. Patients in the FV 200 and V groups also had high rates of attrition due to exacerbations. **External Validity Review of Bias:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a four week run in period and the study was conducted in an outpatient setting. Outcomes: Efficacy and safety of patients were evaluated at study visits at weeks 2, 4, 8 12, 20, 28, 36, 44, and 52.

Study 2970 Dransfield et al[23,25] 52-week, Phase III, DB, PC, RCT, MC	FV 200: FF/VI 200/25 ug FV100: FF/VI 100/25 ug FV50: FF/VI 50/25 ug V: VI 25 ug	Demographics: US, EU, Canada, S Africa, Australia, Other (36% US Average age: 63.7 years Inclusion Criteria: Clinica diagnosis of COPD, age ≥ 40 yrs, current smoker or hx ≥10 pack yrs of smoking, FEV1/FVC ratio ≤ 0.70, post-bronchodilator FEV1 ≤ 70% predicted, documented hx of at least 1 COPD exacerbation in 12 months before screening Exclusion Criteria: Diagnosis of non-COPD respiratory disorder, lung volume reduction surgery within 12 months of enrollment, acute worsening of COPD within 6 weeks, hospitalization due to poorly controlled COPD within 12 weeks, lower RTI requiring use of antibiotics within 6 weeks need for long-term oxygen therapy or nocturnal oxygen therapy (≥12 hr/day), subjects at risk of noncompliance, women who are pregnant or breast-feeding or at risk o becoming pregnant during trial, historical or current evidence of uncontrolled or clinically significant disease states	ITT: FV200: 409 FV100: 403 FV50: 412 V: 409 Total Attrition FV200: 103 (25%) FV100: 112 (28%) FV50:109 (26%) V: 125 (31%) Loss to f/u: FV200: 10 (2%) FV100:6 (1%) FV50: 8 (2%) V: 6 (1%)	LS mean annual rate of moderate to severe exacerbation FV200: 0.79 FV100: 0.90 FV50: 0.92 V: 1.14 Ratio vs. V FV200: 0.69 (95% CI 0.56, 0.85; p-value <0.001) FV100: 0.79 (95% CI 0.64, 0.97; p-value 0.024) FV50: 0.81 (95% CI 0.66,0.99; p-value 0.04)		Total AEs: FV200: 334 (82%) FV100: 320 (79%) p-value: 0.014 RR: 1.105 95% CI: 1.018, 1.196 FV50: 316 (77%) V: 294 (72%) SAEs: FV200: 61 (15%) FV100: 67 (17%) p-value: 0.924 RR: 1.030 95% CI: 0.744, 1.426 FV50: 71 (17%) V: 66 (16%) Death: FV200: 0 FV100:3 (<1%) FV50: 7 (2%) V: 4 (<1%)	FV100 vs V: ARR: 7.5% NNH: 13 NS	**Quality Rating:** Fair **Internal Validity Review of Bias:** Selection: Randomization occurred via computerized system, which was used to register and randomize patients and receive medication assignment information Performance: All groups received medication via identical dry powder inhalers Detection: Patients, investigators, and outcome assessors were all blinded. Attrition: 31% P, 26% FV50, 28% FV100, 25% FV200. Attrition was similar across all groups and due to adverse events, withdrawn consent, lack of efficacy, protocol deviation, or subject reached protocol defined stopping criteria. **External Validity Review of Bias:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a four week run in period and the study was conducted in an outpatient setting. Outcomes: Efficacy and safety of patients were evaluated at study visits at weeks 2, 4, 8 12, 20, 28, 36, 44, and 52.

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Fluticasone furoate /vilanterol is a combination of an ICS/LABA. Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. It has been shown to bind to the human glucofcorticoid receptor, with approximately 29.9 times more binding affinity than that of dexamethasone and 1.7 times that of fluticasone propionate. The precise mechanism through which fluticasone furoate affects COPD symptoms is unknown. Cortidcosteroids have shown a wide range of actions on multiple cell types (e.g. mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

Vilanterol is a LABA. The pharmacologic effects of beta$_2$-agonists are at least in part to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially mast cells.

PHARMACOKINETICS

Parameter	Result
Bioavailability	15.2% (fluticasone furoate) 27.3% (vilanterol)
Protein Binding	99% (fluticasone furoate) 94% (vilanterol)
Elimination	Via feces 101% and 90% (fluticasone furoate and vilanterol, respectively)
Half-Life	24 hours (fluticasone furoate) 21.3 hours (vilanterol)
Metabolism	Hepatic via CYP3A4 and p-glycoprotein (fluticasone furoate and vilaterol)

DOSE & AVAILABILITY

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
FF 100/ VI 25 ug	Inh	Q Daily	1 puff	None	None. Monitor for corticosteroid-related side effects	Not indicated	No adjustment	

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning: May cause an increase in asthma-related death, which is considered a class effect of LABA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with fluticasone furoate /vilanterol has been conducted.

Contraindications: Patients with severe hypersensitivity to milk proteins or hypersensitivity to fluticasone foroate, vilanterol or any component of the product.

REMS: none

Warnings and Precautions:

- Should not be initiated in patients during rapidly deteriorating exacerbations.
- Should not be used as a rescue inhaler
- Should not be used more often than recommended, as an overdose may result
- Should not use with any other LABA-containing medication
- May cause thrush; patients should rinse mouth after use
- May cause an increase of pneumonias
- May increase risk of serious infections such as chickenpox, measles, tuberculosis
- Caution should be exercised when considering the coadministration of fluticasone furoate /vilanterol with known strong CYP3A4 inhibitors because increased systemic corticosteroid and increased cardiovascular adverse events may occur
- May cause paradoxical bronchospasm
- May produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and cardiac arrhythmias
- Decreases in bone mineral density have been observed with long-term administration of products containing inhaled corticosteroids
- Glaucoma and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids
- May cause significant hypokalemia in patients

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Fluticasone furoate may be confused with fluticasone furoate nasal (Veramyst®), fluticasone propionate
Ellipta may be confused with Ella®, Ellence®, eletriptan

Adverse Reactions Table

Adverse Reaction	Placebo (n= 412)	Drug (n=410)	
Infections and infestations			
Nasopharyngitis	8 (1.9%)	9 (2.2%)	
Upper respiratory tract infection	3 (0.7%)	7 (1.7%)	
Oropharyngeal candidiasis	2 (0.5%)	5 (1.2%)	
Headache	5 (1.2%)	7 (1.7%)	

Author: Amanda Meeker, Pharm.D.

Allergies/Interactions: Breo Ellipta contains lactose, so patients with hypersensitivity to milk proteins should not use this product.

Interactions:

- Inhibitors of CYP3A4
- Monoamine Oxidase Inhibitors and Tricyclic Antidepressants
- Beta blockers
- Non-potassium-sparing diuretics

Author: Amanda Meeker, Pharm.D.

Current PA with Proposed Changes (Appendix 2):

LABA/ICS Inhalers

Goal(s):

- Approve LABA/ICS only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication).
- LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists).

Initiative:

- LABA/ICS Step Therapy

Length of Authorization:

Up to 12 months

Requires PA:

- All combination inhaled corticosteroid/long-acting beta-agonist inhalers

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Step Therapy Required Prior to Coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at (www.orpdl.org)

COPD: short and long-acting beta-agonist inhalers, anticholinergics and inhaled corticosteroids (see preferred drug list options at www.orpdl.org), DO NOT require prior authorization

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to ~~3~~ **2**	**No:** Go to ~~3~~ **4**
2. Is the medication for Breo Ellipta (fluticasone furoate/vilanterol)	**Yes: Pass to RPH; Deny (Medical appropriateness)**	**No:** Go to **3**
~~2~~3. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Had ≥2 exacerbations requiring oral systemic corticosteroids in the past year, OR • Is there documentation of step 3 asthma or higher OR • Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 60 days?	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	**No**: **PASS TO RPH** **DENY (Medical Appropriateness).**

Author: Amanda Meeker, Pharm.D.

~~3~~4. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.) and/or emphysema (492.xx)?	**Yes:** Approve for 12 months.	**NO: PASS TO RPH** **DENY (Medical Appropriateness).** Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.

Appendix 3:

Combination Short Acting Bronchodilator Inhalers

Goal(s):

- *Promote preferred drugs that are selected based on evidence based reviews.*
- *To ensure appropriate drug use .*

Initiative: Short Acting Bronchodilator Step Therapy

Length of Authorization: 1 year

Covered alternatives that DO NOT require a PA:
See PDL list at http://www.orpdl.org/

Step Therapy Required prior to coverage:

Requires PA: non-preferred combination short acting bronchodilators

Approval Criteria		
1. What diagnosis is being treated?	**Record ICD9 code**	
2. Does the patient have COPD (ICD-9 496)?	**Yes**: Go to #3	**No**: Pass to RPh; Deny (Medical Appropriateness).
3. Will the prescriber change to a preferred product?	**Yes:** Inform provider of covered alternatives in class	**NO:** Go to #4
4. Has patient failed an inhaled Short acting beta agonist (albuterol) OR An inhaled short acting anticholinergic agent (ipratropium)?	**Yes:** Approve for one year	**No:** Pass to RPh, Deny (medical appropriateness)

P&T/DUR Action: 1/31/2013 (MH)
Revision(s): 7/1/2013
Initiated: 9/1/2013

Appendix 4:

Author: Amanda Meeker, Pharm.D.

Roflumilast

Goal(s):

- Decrease the number of COPD exacerbations in patients with severe COPD and chronic bronchitis and a history of prior exacerbations.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	**Yes:** Go to #4	**No:** Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	**Yes:** Go to #5	**No:** Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	**Yes:** Go to #6	**No:** Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient tried an inhaled corticosteroid (ICS), and ICS combination, or tiotropium (LAMA)?	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred long-acting ICS or LAMA

Appendix 5: RCT Abstracts

Furh, R., H. Magnussen, et al. (2012). "Efficacy of aclidinimium bromide 400 ug twice daily compared with placebo and tiotropium in patients with moderate to severe COPD." Chest **141**(3): 745-752.

Author: Amanda Meeker, Pharm.D.

BACKGROUND: The efficacy and safety of aclidinium bromide bid, a novel, long-acting, muscarinic antagonist, was assessed in patients with moderate to severe COPD.

METHODS: In this phase IIa randomized, double-blind, double-dummy, crossover trial, patients with moderate to severe COPD received aclidinium 400 ug bid, tiotropium 8 ug once daily, and placebo for 15 days, with a 9- to 15-day washout between treatment periods. Treatments were administered through the Genuair or HandiHaler dry powder inhalers. The primary end point was mean change from baseline in FEV(1) AUC(0-12 /12h)(area under the curve where the numbers represent the time period for which data were collected divided by the number of hours over which the data are averaged [eg, 0-12 h postdose divided by 12h]) on day 15. Secondary end points were changes from baseline in FEV(1) AUC(12-24/12h), FEV(1) AUC(0-24/24h), morning predose FEV(1), peak FEV(1), and COPD symptom scores.

RESULTS: Thirty patients with COPD were randomized, and 27 completed the study. Mean change from baseline in FEV(1) AUC(12-24/12h) at day 15 was significantly greater for aclidinium and tiotropium over placebo (P < .0001). Mean changes from baseline in FEV(1) AUC(12-24/12h), FEV(1) AUC(0-24/24h), morning predose FEV(1), and peak FEV(1) at day 15 were significantly greater for aclidinium and tiotropium over placebo (P < .0001 for all except P <.001 for FEV(1) AUC(12-24/12h) tiotropium vs placebo). Improvements were significantly greater with aclidinium vs tiotropium on day 1 for all of the normalized AUC values of FEV(1) as well as on day 15 for FEV(1) AUC(12-24/12h) (P < .05 for all). COPD symptoms were significantly improved from baseline with aclidinium vs placebo (P < .05) but not with tiotropium.

CONCLUSIONS: In patients with COPD, aclidinium 400 ug bid compared with placebo provided clinically meaningful improvements in 24-h bronchodilation that generally were comparable to tiotropium 18 ug daily but with significant differences in favor of aclidinium observed in the average nighttime period. Larger studies with longer treatment duration are ongoing to confirm the efficacy of aclidinium 400 ug bid on bronchodilation and COPD symptoms. Trial registry: ClinicalTrials.gov; No.: NCT00868231; URL: www.clinicaltrials.gov.

Sharafkhaneh, A., J. G. Southard, et al. (2012). "Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study." Respiratory Medicine **106**(2):257-268.

BACKGROUND: Treatment of an inhaled corticosteroid (ICS) and long-acting bronchodilator is recommended for severe/very severe chronic obstructive pulmonary disease (COPD) patients with repeated exacerbations This randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study evaluated the effect of budesonide/formoterol pressurized metered-dose inhaler (pMDI) on COPD exacerbations.

METHODS: Following a 2-week run-in during which COPD patients aged >=40 years with an exacerbation history discontinued medications except ICSs, 1219 patients were randomized 1:1:1 to twice-daily budesonide/formoterol pMDI 320/9 ug, budesonide/formoterol 160/9 ug, or formoterol dry powder inhaler 9 ug. An exacerbation was defined as COPD worsening requiring oral corticosteroids and/or hospitalization. A post hoc analysis, with antibiotic treatment added to the exacerbation definition, was also performed.

RESULTS: Budesonide/formoterol 320/9 and 160/9 rediced exacerbation rates (number per patient-treatment year) by 34.6% and 25.9%, respectively, versus formoterol (p ,= 0.002). Budesonide/formoterol320/9 prolonged time to first exacerbation versus formoterol, corresponding to a 21.2% reduction in hazard ration (0.788 [95% CI: 0.639, 0.972]; p = 0.026). Exacerbation rates (number per patient-treatment year) including antibiotic treatment (post hoc analysis) were reduced by 25.9% and 18.7% with budesonide/formoterol 320/9 and 160/9, respectively, versus formoterol (p <= 0.023). Both budesonide/formoterol 320/9, 160/9 and formoterol groups.

CONCLUSIONS: Over 12 months, both budesonide/formoterol doses reduced the exacerbation rate (defined with or without antibiotic treatment) versus formoterol. Budesonide/formoterol pMDI is an appropriate treatment for reducing exacerbations in COPD patients with a history of exacerbations. (NTC00419744).

Zhong, N., J. Zheng, et al. (2012). "Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronicobstructive pulmonary disease. Current Medical Research & Opinion 28**(2):** 257-265**.**

OBJECTIVE: To evaluate the efficacy and safety of budesonide (BUD)/formoterol (FORM) compared with BUD, both administered by way of a dry powder inhaler (Turbuhaler).

METHODS: This was a 6-month, multicenter, randomized, parallel-group, double-blind, double-dummy design study (NCT 00421122). Patients were randomized to either BUD/FORM 160/9 twice daily or BUD 400 ug, twice daily. Improvement of lung function, daily symptoms, reliever use and health-related quality-of-life (St. George's Respiratory Questionaire [SGRQ] score) were compared between the two treatment groups.

RESULTS: A total of 308 patients with moderate to very severe COPD from 12 centers in China were randomized to BUD/FORM (n=156) or BUD (n=152). The primary endpoint, 1-hour post-dose forced expiratory volume in 1 second (FEV1), in the BUD/FORM group improved by 0.18L (from 0.83L at baseline to 1.01L) and this was significantly

better (p<0.001) than the small increase (0.03L) observed in the BUD group after 24 weeks' treatment. Increases in pre-dose and 15-min post-does FEV(1) together with 1-hour post-dose forced vital capacity were also significantly larger with BUD/FORM than BUD (p<0.001 for all). Compared with BUD alone, BUD/FORM improved COPD total symptom scores (-1.04+/-0.16 vs -0.55+/-0.17; p=0.03), reduced reliever use (-0.85+/-0.16 puffs/day vs -0.31+/-0.16 puffs/day; p=0.012) and improved health-related quality-of-life (mean change of total SGRQ score -4.5 points (p=0182). Overall, both treatment groups were well tolerated.

CONCLUSIONS: In Chinese patients with moderate to very severe COPD, fixed combination treatments with BUD/FORM resulted in clinically meaningful improvements in lung function, health-related quality-of-life, COPD symptoms and a reduction in reliever use, compared with BUD use alone and both treatments were well tolerated. Treatment of BNUD/FORM for milder patients with COPD and head to head comparison of Chinese and Caucasians in future studies will be helpful to expand upon the findings of the current clinical trial.

Appendix 6: Abstracts of Meta Analyses

Cheyne L, Irvin-Sellers MJ, White J. "Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews 2013, 9. Art. No.: CD009552.

BACKGROUND: Tiotropium and ipratropium bromide are both recognised treatments in the management of people with stable chronic obstructive pulmonary disease (COPD). There are new studies which have compared tiotropium with ipratropium bromide, making an update necessary.

OBJECTIVES: To compare the relative effects of tiotropium to ipratropium bromide on markers of quality of life, exacerbations, symptoms, lung function and serious adverse events in patients with COPD using available randomised controlled trial (RCT) data.

SEARCH METHODS: We identified RCTs from the Cochrane Airways Group Specialised Register of trials (CAGR) and ClinicalTrials.gov up to November 2012.

SELECTION CRITERIA: We included parallel group RCTs of 12 weeks duration or longer comparing treatment with tiotropium with ipratropium bromide for patients with stable COPD.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed studies for inclusion and then extracted data on study quality and outcome results. We contacted trial sponsors for additional information. We analysed the data using Cochrane Review Manager (RevMan 5.2).

MAIN RESULTS: This review included two studies of good methodological quality that enrolled 1073 participants with COPD. The studies used a similar design and inclusion criteria and were of at least 12 weeks duration; the participants had a mean forced expiratory volume in one second (FEV_1) of 40% predicted value at baseline. One study used tiotropium via the HandiHaler (18 µg) for 12 months and the other via the Respimat device (5 µg and 10 µg) for 12 weeks. In general, the treatment groups were well matched at baseline but not all outcomes were reported for both studies. Overall the risk of bias across the included RCTs was low.

For primary outcomes this review found that at the three months trough (the lowest level measured before treatment) FEV_1 significantly increased with tiotropium compared to ipratropium bromide (mean difference (MD) 109 mL; 95% confidence interval (CI) 81 to 137, moderate quality evidence, I^2 = 62%). There were fewer people experiencing one or more non-fatal serious adverse events on tiotropium compared to ipratropium (odds ratio (OR) 0.5; 95% CI 0.34 to 0.73, high quality evidence). This represents an absolute reduction in risk from 176 to 97 per 1000 people over three to 12 months. Concerning disease specific adverse events, the tiotropium group were also less likely to experience a COPD-related serious adverse event when compared to ipratropium bromide (OR 0.59; 95% CI 0.41 to 0.85, moderate quality evidence).

For secondary outcomes, both studies reported fewer hospital admissions in the tiotropium group (OR 0.34; 95% CI 0.15 to 0.70, moderate quality evidence); as well as fewer patients experiencing one or more exacerbations leading to hospitalisation in the people on tiotropium in both studies (OR 0.56; 95% CI 0.31 to 0.99, moderate quality evidence). There was no significant difference in mortality between the treatments (OR 1.39; 95% CI 0.44 to 4.39, moderate quality evidence). One study measured quality of life using the St George's Respiratory Questionnaire (SGRQ); the mean SGRQ score at 52 weeks was lower in the tiotropium group than the ipratropium group (lower on the scale is favourable) (MD -3.30; 95% CI -5.63 to -0.97, moderate quality evidence). There were fewer participants suffering one of more exacerbations in the tiotropium arm (OR 0.71; 95% CI 0.52 to 0.95, high quality evidence) and there was also a reported difference in the mean number of

exacerbations per person per year which reached statistical significance (MD -0.23; 95% CI -0.39 to -0.07, P = 0.006, moderate quality evidence). From the 1073 participants there were significantly fewer withdrawals from the tiotropium group (OR 0.58; 95% CI 0.41 to 0.83, high quality evidence).

AUTHORS' CONCLUSIONS: This review shows that tiotropium treatment, when compared with ipratropium bromide, was associated with improved lung function, fewer hospital admissions (including those for exacerbations of COPD), fewer exacerbations of COPD and improved quality of life. There were both fewer serious adverse events and disease specific events in the tiotropium group, but no significant difference in deaths with ipratropium bromide when compared to tiotropium. Thus, tiotropium appears to be a reasonable choice (instead of ipratropium bromide) for patients with stable COPD, as proposed in guidelines. We would advise some caution with tiotropium via the Respimat inhaler and suggest waiting for further information from an ongoing head-to-head trial comparing mortality in relation to tiotropium delivery devices and doses.

Chong M. J., C. Karner, et al. (2102). "Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease." ¨Cochrane Database of Systemic Reviews 2012 9: CD009157.

BACKGROUND: Tiotropium and long-acting beta(2)-agonists (LABAs) are both accepted in the routine management for people with stable chronic obstructive pulmonary disease (COPD). There are new studies which have compared tiotropium with LABAs, including some that have evaluated recently introduced LABAs.

OBJECTIVES: To compare the relative clinical effects of tiotropium bromide alone versus LABA alone, upon measures of quality of life, exacerbations, lung function and serious adverse events, in people with stable COPD. To critically appraise and summarize current evidence on the costs and cost-effectiveness with tiotropium compared to LABA in people with COPD.

SEARCH METHODS: We identified randomized controlled trials (RCTs) from the Cochrane Airwasys Group Specialised Register of trials and economic evaluations from searching NHS EED and HEED (date of last search February 2012). We found additional trials from web-based clinical trial registers.

SELECTION CRITERIA: We included RCTs and full economic evaluations if they compared effects of tiotropium alone with LABAs alone in people with COPD. We allowed co-administration of standard COPD therapy.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed studies for inclusion, then extracted data on study quality and outcomes .We contacted study authors and trial sponsors for additional information. We analyzed data using the Cochrane Review Manager (RevMan 5.1) software.

MAIN RESULTS: Seven clinical studies totaling 12,223 participants with COPD were included in the review. The studies used similar designs and were generally of good methodological quality. Inclusion criteria for RCTs were similar across the included studies, although studies varied in terms of smoking history and COPD severity of participants. They compared tiotropium (which was delivered by HandiHaler in all studies) with salmeterol (four studies, 8936 participants), formoterol (one study, 431 participants) and indacaterol (two studies, 2856 participants). All participants were instructed to discontinue anticholinergic or LABA bronchodilators during treatment, but could receive inhaled corticosteroids (ICS) at a stable dose. Study duration ranged from 3 to 12 months. We extracted data for 11,223 participants. In general, the treatment groups were well matched at baseline. Overall, the risk of bias across the included RCTs was low. In the analysis of the primary outcomes in this review, a high level of heterogenicity amongst studies meant that we did not pool data for St. George's Respiratory Questionnaire quality of life score. Subgroup analyses based on the type of LABA found statistically significant differences among effects on quality of life depending on whether tiopropium was compared with salmeterol, formoterol, or indacaterol. Tiotropium reduced the number of participants experiencing one or more exacerbations compared with LABA (odds ratio (OR) 0.86; 95% confidence interval (CI) 0.79 to 0.93). For this outcome, there was no difference seen among the different types of LABA. There was no statistical difference in mortality observed between the treatment groups. For secondary outcomes, tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalisation compared with LABA treatment (OR 0.87; 95% CI 0.77 to 0.99), but not in the overall rate of all-cause hospitalizations. There was no statistically significant difference in forced expiratory volume in one second FEV(!) or symptom score between tiotropium and LABA-treated participants. There was a lower rate of non-fatal serious adverse events recorded with tiotropium compared with LABA (OR 0.88; 95% CI 0.78 to 0.99). The tiotropium group was also associated with a lower rate of study withdrawals (OR 0.89; 95% CI 0.81 to 0.99). We identified six full economic evaluations assessing the cost and cost-effectiveness of tiotropium and salmeterol. The studies were based on an economic model or empirical analysis of clinical data from RCTs. They all looked at maintenance costs and the costs for COPD exacerbations, including respiratory medications and hospitalizations. The setting for the evaluations was primary and secondary care in the UK, Greece, Netherlands,

Spain and US> All the studies estimated tiotropium to be superior to salmeterol based on better clinical outcomes (exacerbations or quality of life_ and/or lower total costs. However, the authors of all evaluations reported there was substantial uncertainty around the results.

AUTHORS' CONCLUSIONS: In people with COPD, the evidence is equivocal as to whether or not tiotropium offers greater benefit than LABAs in improving quality of life; however, this is complicated by differences in effect among the LABA types. Tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations, although there were no statistical differences between groups in overall hospitalization rates or mortality during the study periods. There were fewer serious adverse events and study withdrawals recorded with tiotropium compared with LABAs. Symptom improvement and changes in lung function were similar between the treatment groups. Given the small number of studies to date, with high levels of heterogeneity among them, one approach may be to give a COPD patient a substantial trial of tiotropium, followed by a LABA (or vice-versa), then to continue prescribing the long-acting bronchodilator that the patient prefers. Further studies are needed to compare tiotropium with different LABAs, which are currently ongoing. The available economic evidence indicates that tiotropium may be cost-effective compared with salmeterol in several specific setting, but there is considerable uncertainty around this finding.

Cope, S., M. Kraemer, et al. (2012). "Efficacy of indacaterol 75 ug versusfixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis." International Journal of Copd 7: 415-420.

BACKGROUND: The purpose of this study was to update our network meta-analysis in order to compare the efficacy of indacaterol 75 µg with that of a fixed-dose combination of formoterol and budesonide (FOR/BUD) and a fixed-dose combination salmeterol and fluticasone (SAL/FP) for the treatment of chronic obstructive pulmonary disease (COPD) based on evidence identified previously in addition to two new randomized clinical trials.

METHODS: Fifteen randomized, placebo-controlled clinical trials including COPD patients were evaluated: indacaterol 75 µg once daily (n = 2 studies), indacaterol 150 µg once daily (n = 5), indacaterol 300 µg once daily (n = 4), FOR/BUD 9/160 µg twice daily (n = 2), FOR/BUD 9/320 µg twice daily (n = 2), SAL/FP 50/500 µg twice daily (n = 4), and SAL/FP 50/250 µg twice daily (n = 1). All trials were analyzed simultaneously using a Bayesian network meta-analysis and relative treatment effects between all regimens were obtained. Treatment-by-covariate interactions were included where possible to improve the similarity of the trials. Outcomes of interest were trough forced expiratory volume in 1 second (FEV(1)) and transitional dyspnea index at 12 weeks.

RESULTS: Based on the results without adjustment for covariates, indacaterol 75 µg resulted in a greater improvement in FEV(1) at 12 weeks compared with FOR/BUD 9/160 µg (difference in change from baseline 0.09 L [95% credible interval 0.04-0.13]) and FOR/BUD 9/320 µg (0.07 L [0.03-0.11]) and was comparable with SAL/FP 50/250 µg (0.00 L [-0.07-0.07]) and SAL/FP 50/500 µg (0.01 L [-0.04-0.05]). For transitional dyspnea index, data was available only for indacaterol 75 µg versus SAL/FP 50/500 µg (-0.49 points [-1.87-0.89]).

CONCLUSION: Based on results of a network meta-analysis with and without covariates, indacaterol 75 µg is expected to be at least as efficacious as FOR/BUD (9/320 µg and 9/160 µg) and comparable with SAL/FP (50/250 µg and 50/500 µg) in terms of lung function. In terms of breathlessness (transitional dyspnea index) at 12 weeks, the results are inconclusive given the limited data.

Dong, Y.. –H., H.-H. Lin, et al. (2013). "Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomized controlled trials." ¨Thorax 65(1): 48-56.

BACKGROUND: The active-treatment comparative safety information for all inhaled medications in patients with chronic obstructive pulmonary disease (COPD) is limited. We aimed to compare the risk of overall and cardiovascular death for inhaled medications in patients with COPD.

METHODS: Through systematic database searching, we identified randomised controlled trials of tiotropium Soft Mist Inhaler, tiotropium HandiHaler, long-acting β2 agonists (LABAs), inhaled corticosteroids (ICS), and LABA-ICS combination with at least a 6-month treatment duration. Direct comparison and mixed treatment comparison (MTC) meta-analyses were conducted to estimate the pooled ORs of death for each comparison.

RESULTS: 42 trials with 52 516 subjects were included. The MTC meta-analysis with the fixed effect model indicated tiotropium Soft Mist Inhaler was associated with an universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at a higher daily

dose. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium HandiHaler or LABA. The results were similar for MTC and direct comparison meta-analyses, with less precision in the random effects model.

CONCLUSION: Our study provided a comparative safety spectrum for each category of inhaled medications. Tiotropium Soft Mist Inhaler had a higher risk of mortality and should be used with caution.

Karner, C. & Cates, C. J. "LABAin addition to tiotropium versus either tiotropium or LABAalone for chronic obstructive pulmonary disease." Cochrane Database Syst Rev 4, CD008989 (2012).

BACKGROUND: Long-acting bronchodilators comprising long-acting beta(2)-agonists and the anticholinergic agent tiotropium are commonly used for managing persistent symptoms of chronic obstructive pulmonary disease. Combining these treatments, which have different mechanisms of action, may be more effective than the individual components. However, the benefits and risks of combining tiotropium and long-acting beta(2)-agonists for the treatment of chronic obstructive pulmonary (COPD) disease are unclear.

OBJECTIVES: To assess the relative effects of treatment with tiotropium in addition to LABA compared to tiotropium or LABA alone in patients with chronic obstructive pulmonary disease.

SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials and clinicaltrials.gov up to January 2012.

SELECTION CRITERIA: We included parallel group, randomised controlled trials of three months or longer comparing treatment with tiotropium in addition to LABA against tiotropium or LABA alone for patients with chronic obstructive pulmonary disease.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trials for inclusion and then extracted data on trial quality and the outcome results. We contacted study authors for additional information. We collected information on adverse effects from the trials.

MAIN RESULTS: Five trials were included in this review, mostly recruiting participants with moderate or severe chronic obstructive pulmonary disease. All of them compared tiotropium in addition to LABA to tiotropium alone, but only one trial additionally compared a combination of the two types of bronchodilator with LABA (formoterol) alone. Two studies used the LABA indacaterol, two used formoterol and one used salmeterol. Compared to tiotropium alone (3263 patients), treatment with tiotropium plus LABA resulted in a slightly larger improvement in the mean health-related quality of life (St George's Respiratory Questionnaire (SGRQ) MD -1.61; 95% CI -2.93 to -0.29). In the control arm, tiotropium alone, the SGRQ improved by falling 4.5 units from baseline and with both treatments the improvement was a fall of 6.1 units from baseline (on average). High withdrawal rates in the trials increased the uncertainty in this result, and the GRADE assessment for this outcome was therefore moderate. There were no significant differences in the other primary outcomes (hospital admission or mortality).The secondary outcome of pre-bronchodilator FEV(1) showed a small mean increase with the addition of LABA (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. There were wide confidence intervals around these outcomes and moderate heterogeneity for both exacerbations and withdrawals. The results from the one trial comparing the combination of tiotropium and LABA to LABA alone (417 participants) were insufficient to draw firm conclusions for this comparison.

AUTHORS' CONCLUSIONS: The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and LABA compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta(2)-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus LABA compared to LABA alone. There were insufficient data to make comparisons between the different long-acting beta(2)-agonists when used in addition to tiotropium.

Nannin, L. J., T. J. Lasserson, et al. (2012). "Combined corticosteroid and LABA in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews **9: CD006829.**

BACKGROUND: Both inhaled steroids (ICS) and long-acting beta(2)-agonists (LABA) are used in the management of chronic obstructive pulmonary disease (COPD). This updated review compared compound LABA plus ICS therapy (LABA/ICS) with the LABA component drug given alone.

OBJECTIVES: To assess the efficacy of ICS and LABA in a single inhaler with mono-component LABA alone in adults with COPD.

SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials. The date of the most recent search was November 2011.

SELECTION CRITERIA: We included randomised, double-blind controlled trials. We included trials comparing compound ICS and LABA preparations with their component LABA preparations in people with COPD.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed study risk of bias and extracted data. The primary outcomes were exacerbations, mortality and pneumonia, while secondary outcomes were health-related quality of life (measured by validated scales), lung function, withdrawals due to lack of efficacy, withdrawals due to adverse events and side-effects. Dichotomous data were analysed as random-effects model odds ratios or rate ratios with 95% confidence intervals (CIs), and continuous data as mean differences and 95% CIs. We rated the quality of evidence for exacerbations, mortality and pneumonia according to recommendations made by the GRADE working group.

MAIN RESULTS: Fourteen studies met the inclusion criteria, randomising 11,794 people with severe COPD. We looked at any LABA plus ICS inhaler (LABA/ICS) versus the same LABA component alone, and then we looked at the 10 studies which assessed fluticasone plus salmeterol (FPS) and the four studies assessing budesonide plus formoterol (BDF) separately. The studies were well-designed with low risk of bias for randomisation and blinding but they had high rates of attrition, which reduced our confidence in the results for outcomes other than mortality. Primary outcomes There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomised 9921 participants (rate ratio 0.76; 95% CI 0.68 to 0.84). This corresponds to one exacerbation per person per year on LABA and 0.76 exacerbations per person per year on ICS/LABA. Our confidence in this effect was limited by statistical heterogeneity between the results of the studies (I(2) = 68%) and a risk of bias from the high withdrawal rates across the studies. When analysed as the number of people experiencing one or more exacerbations over the course of the study, FPS lowered the odds of an exacerbation with an odds ratio (OR) of 0.83 (95% CI 0.70 to 0.98, 6 studies, 3357 participants). With a risk of an exacerbation of 47% in the LABA group over one year, 42% of people treated with LABA/ICS would be expected to experience an exacerbation. Concerns over the effect of reporting biases led us to downgrade the quality of evidence for this effect from high to moderate. There was no significant difference in the rate of hospitalisations (rate ratio 0.79; 95% CI 0.55 to 1.13, very low quality evidence due to risk of bias, statistical imprecision and inconsistency). There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, downgraded to moderate quality evidence due to statistical imprecision). Pneumonia occurred more commonly in people randomised to combined inhalers, from 12 studies with 11,076 participants (OR 1.55; 95% CI 1.20 to 2.01, moderate quality evidence due to risk of bias in relation to attrition) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of inhaled corticosteroid. Secondary outcomes ICS/LABA was more effective than LABA alone in improving health-related quality of life measured by the St George's Respiratory Questionnaire (1.58 units lower with FPS; 2.69 units lower with BDF), dyspnoea (0.09 units lower with FPS), symptoms (0.07 units lower with BDF), rescue medication (0.38 puffs per day fewer with FPS, 0.33 puffs per day fewer with BDF), and forced expiratory volume in one second (FEV(1)) (70 mL higher with FPS, 50 mL higher with BDF). Candidiasis (OR 3.75) and upper respiratory infection (OR 1.32) occurred more frequently with FPS than SAL. We did not combine adverse event data relating to candidiasis for BDF studies as the results were very inconsistent.

AUTHORS' CONCLUSIONS: Concerns over the analysis and availability of data from the studies bring into question the superiority of ICS/LABA over LABA alone in preventing exacerbations. The effects on hospitalisations were inconsistent and require further exploration. There was moderate quality evidence of an increased risk of pneumonia with ICS/LABA. There was moderate quality evidence that treatments had similar effects on mortality. Quality of life, symptoms score, rescue medication use and FEV(1) improved more on ICS/LABA than on LABA, but the average differences were probably not clinically significant for these outcomes. To an individual patient the increased risk of pneumonia needs to be balanced against the possible reduction in exacerbations. More information would be useful on the relative benefits and adverse event rates with combination inhalers using different doses of inhaled corticosteroids. Evidence from head-to-head comparisons is needed to assess the comparative risks and benefits of the different combination inhalers.

Rodrigo, G.J. and H. Neffen (2012). “Comparison of indacaterol with tiotropium or twice-daily long-acting beta-agonists for stale COPD: a systematic review.” Chest 142(5) 1104-1110.

BACKGROUND: Bronchodilators are central to the symptomatic management of patients with COPD. Previous data have shown that inhaled indacaterol improved numerous clinical outcomes over placebo.

METHODS: This systematic review explored the efficacy and safety of indacaterol in comparison with tiotropium or bid long-acting β 2 -agonists (TD-LABAs) for treatment of moderate to severe COPD. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.

RESULTS: Five trials (5,920 participants) were included. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea(43% greater likelihood of achieving a minimal clinically important difference [MCID] in the transitional dyspnea index [TDI]; number needed to treat for benefit [NNTB] 5 10). Additionally, the MCID in health status was more likely to be achieved with indacaterol than with tiotropium (OR = 1.43; 95% CI, 1.22–1.68; P = .00001; [NNTB]= 10). Trough FEV 1 was significantly higher at the end of treatment with indacaterol than with TD-LABAs (80 mL, P = .00001). Similarly, indacaterol significantly improved dyspnea (61% greater likelihood of achieving an MCID in TDI, P = .008) and health status (21% greater likelihood of achieving an MCID in St. George's Respiratory Questionnaire, P 5 .04) than TD-LABA. Indacaterol showed similar levels of safety and tolerability to both comparators.

CONCLUSIONS: Available evidence suggests that indacaterol may prove useful as an alternative to tiotropium or TD-LABA due to its effects on health status, dyspnea, and pulmonary function.

Rodrigo, G. J., Plaza, V. & Castro-Rodríguez, J. A. "Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review." Pulm Pharmacol Ther **25,** 40–47 (2012).

BACKGROUND: Guidelines recommend the use of inhaled long-acting bronchodilators, inhaled corticosteroids (ICS) and their combinations for maintenance treatment of moderate to severe COPD. However, there are limited data supporting combination therapy.

METHODS: This systematic review assessed the efficacy of three therapeutic approaches: tiotropium plus long-acting beta2-agonist (LABA) ("dual" therapy), LABA/ICS ("combined" therapy), and tiotropium plus LABA/ICS ("triple" therapy), all compared with tiotropium monotherapy. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.

RESULTS: Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in forced volume in the first second (FEV(1)), health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV(1), HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to treat for harm [NNTH] = 20; 95% CI: 11-119). Finally, "triple therapy" increased FEV(1), improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, p = 0.21).

CONCLUSIONS: "Dual" and "triple" therapy seem like the most promising for patients with moderate to very severe COPD. However, data are still scarce and studies too short to generate a strong recommendation. Future studies should examine long-term efficacy and safety**.**