LMMG New Medicine Recommendation

Fluticasone furoate/vilanterol (Relvar Ellipta®▼) combination inhaler

Chronic obstructive pulmonary disease in adults

Recommendation:

Fluticasone furoate/vilanterol (Relvar Ellipta) combination inhaler is not recommended for the treatment of adults with chronic obstructive pulmonary disease (COPD). **BLACK**

Summary of supporting evidence:

- Relvar Ellipta is a once-daily dry-powder inhaler licensed for symptomatic treatment of adults with COPD with a FEV_1 less than 70% predicted normal (post-bronchodilator), and an exacerbation history despite regular bronchodilator therapy. It contains fluticasone furoate, an inhaled corticosteroid (ICS), and vilanterol, a long-acting beta-2 agonist (LABA). It is available in two strengths, 92/22 micrograms and 184/22 micrograms, but only the lower strength is licensed for COPD.

- In two pivotal 24-week studies, fluticasone furoate/vilanterol 92/22 micrograms produced clinically important improvements in lung function compared with placebo in patients with moderate to very severe COPD, as shown by increases in post-dose weighted mean (wm) FEV_1 and trough FEV_1. In a pooled analysis of two pivotal 52-week studies in patients with a history of COPD exacerbations, fluticasone furoate/vilanterol 92/22 micrograms produced a clinically and statistically significant decrease in mean yearly rate of moderate and severe exacerbations compared with vilanterol 22 micrograms alone (rate ratio 0.7 [95% CI, 0.6 to 0.8]; p<0.0001). There was a similar reduction in mean yearly rate of exacerbations in people with a history of frequent exacerbations (two or more in the previous year). It did not reduce mean yearly rate of severe exacerbations requiring hospitalisation compared with vilanterol 22 micrograms alone; this was thought to be due to the small number of severe exacerbations, and has previously been reported with other ICS/LABA combination inhalers. Compared with vilanterol 22 micrograms alone, fluticasone furoate/vilanterol 92/22 micrograms produced statistically significant improvements in night-time awakenings and dyspnoea.

- The comparator in the pivotal studies was not an established ICS/LABA combination therapy or monotherapy licensed for use in COPD. The only trials comparing Relvar Ellipta with an ICS/LABA combination inhaler licensed for treatment of patients with COPD are relatively short-term and measure a disease-orientated outcome rather than a patient-orientated outcome such as exacerbation rate. This limits the conclusions that can be drawn from them. In a published 12-week study comparing the effect on lung function of fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 500/50 micrograms (Seretide 500 Accuhaler) twice daily, there was no significant difference between groups in mean change from baseline in 0-24 hour

wmFEV_1. Symptoms, assessed as a secondary outcome using St George's Respiratory Questionnaire, improved from baseline with both treatments. There was no difference between groups in compliance with treatment.

- No studies have measured the effect of Relvar Ellipta on mortality or been powered to adequately assess quality of life.

- The most common adverse events with Relvar Ellipta in patients with COPD are headache, nasopharyngitis and upper respiratory tract infection. Its safety profile in patients with COPD is similar to that in patients with asthma, except for a higher incidence of fracture and pneumonia in patients with COPD. Adrenal suppression is a potential risk although data on the effects of Relvar Ellipta on cortisol excretion are inconsistent.

- Pooled trial data shows the incidence of pneumonia is 6% with fluticasone furoate/vilanterol, 3% with vilanterol alone, and less than 1% with placebo. When Relvar Ellipta 92/22 micrograms was compared with fluticasone propionate/salmeterol 500/50 micrograms twice daily in a 12-week study, the overall incidence of pneumonia was less than 1% in both groups. Relvar Ellipta 184/22 micrograms is not recommended for use in patients with COPD because no additional benefit is seen compared with the lower dose, and there is an increased risk of systemic corticosteroid-related adverse reactions. Risk factors for pneumonia include current smoking, history of prior pneumonia, body mass index less than 25kg/m^2, an FEV_1 less than 50% predicted and a history of COPD exacerbations.

- There is a risk that patients may mistakenly use Relvar Ellipta on an 'as needed' basis because it has a grey and blue cover, and patients in the UK are educated that blue inhalers are relievers, and the name 'Relvar' sounds similar to 'reliever'. Patients should be given clear advice that Relvar Ellipta must be used regularly and not 'as needed'.

- Relvar Ellipta is the only ICS/LABA combination inhaler licensed for once daily administration. It might be an option for patients unable to adhere to treatment with twice daily ICS/LABA inhalers, although there are no data to show adherence is improved.

- At current prices, Relvar Ellipta 92/22 micrograms inhaler is less expensive than other ICS/LABA combination inhalers licensed to treat patients with COPD.

Details of Review

Name of medicine (generic & brand name) **[manufacturer]:**

Fluticasone furoate and vilanterol (Relvar Ellipta®▼) combination inhaler [GlaxoSmithKline]

Strength(s) and form(s):

One strength is licensed for use in chronic obstructive pulmonary disease:

- fluticasone furoate 92 micrograms plus vilanterol (as trifenatate) 22 micrograms (the delivered dose leaving the mouthpiece).

Doses are administered using the multi-dose, dry-powder Ellipta inhalation device. The inhaler is light grey with a blue mouthpiece.

Dose and administration:

One inhalation once a day.

BNF therapeutic class / mode of action

3.2 Corticosteroids / 3.1.1.1 Selective beta$_2$ agonists

Licensed indication(s):

Symptomatic treatment of adults with chronic obstructive pulmonary disease with a FEV_1 <70% predicted normal (post-bronchodilator), and an exacerbation history despite regular bronchodilator therapy.

Course and cost:

The cost of 30 days' treatment is £27.80 and the annual cost is £333.60.

Current standard of care/comparator therapies:

Three other ICS/LABA combination inhalers are licensed in the UK for treating COPD:

- Fostair inhaler – beclometasone/formoterol 100/6 metered-dose inhaler
- Seretide Accuhaler – fluticasone propionate/salmeterol 500/50 dry-powder inhaler
- Symbicort Turbohaler – budesonide/formoterol 200/6 and 400/12 dry-powder inhalers.

Relevant NICE guidance:

- National Institute for Health and Clinical Excellence (2010) Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). NICE clinical guideline 101

Background and context

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease characterised by airflow obstruction that is not fully reversible [1]. It is diagnosed according to signs and symptoms (e.g. exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze), supported by measurement of forced expiratory volume in one second (FEV_1) using spirometry. Severity of airflow obstruction is classed as mild (FEV_1 ≥80% predicted), moderate (FEV_1 50-79% predicted), severe (FEV_1 30-49% predicted) or very severe (FEV_1 <30% predicted, or FEV_1 <50% predicted with respiratory failure). Exacerbations often occur, where there is rapid and sustained worsening of symptoms beyond normal day-to-day variation.

The National Institute for Health and Care Excellence (NICE) recommends that people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, should be offered as maintenance therapy [1]:

- if FEV_1 is 50% predicted or more: a long-acting $beta_2$ agonist (LABA) or a long-acting muscarinic antagonist (LAMA)
- if FEV_1 is less than 50% predicted: a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA.

In people with stable COPD and an FEV_1 of 50% predicted or more, who remain breathless or have exacerbations despite maintenance therapy with a LABA:

- consider an ICS/LABA combination inhaler
- consider a LAMA plus a LABA where an ICS is declined or not tolerated.

Offer a LAMA plus a LABA and an ICS to people with COPD who remain breathless or have exacerbations despite using an ICS/LABA, irrespective of their FEV_1. Consider an ICS/LABA combination inhaler in addition to a LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with a LAMA, irrespective of their FEV_1.

Three twice-daily ICS/LABA combination inhalers are licensed in the UK for treating COPD [2]:

- Fostair inhaler – beclometasone/formoterol 100/6 metered-dose inhaler – in adults with a FEV_1 <50% predicted normal.
- Seretide Accuhaler – fluticasone propionate/salmeterol (FP/SM) 500/50 dry-powder inhaler – in adults with a FEV_1 <60% predicted normal.
- Symbicort Turbohaler – budesonide/formoterol 200/6 and 400/12 dry-powder inhalers – in adults with a FEV_1 <50% predicted normal.

Other ICS/LABA combination inhalers are licensed for use in asthma but not COPD [3].

Relvar Ellipta is a once-daily dry-powder inhaler [4] containing fluticasone furoate (FF), a novel ICS with greater affinity for glucocorticoid receptors and longer retention in respiratory tissues than FP [5], and vilanterol (VI), a novel LABA which is more selective for beta-2 receptors than beta-1 or beta-3 receptors [6]. It is licensed for symptomatic treatment of adults with COPD with a FEV_1 <70% predicted normal (post-bronchodilator), and an exacerbation history despite regular bronchodilator therapy [4]. It is available in two strengths, but only the lower dose is licensed for use in COPD [4]:

- fluticasone furoate 92 micrograms plus vilanterol (as trifenatate) 22 micrograms, and
- fluticasone furoate 184 micrograms plus vilanterol (as trifenatate) 22 micrograms.

In patients with asthma, FF 92 micrograms once daily is approximately equivalent to FP 250 micrograms twice daily [4]; equivalent doses in patients with COPD have not been established.

Explanation of terms (used in the text and Table of trials):

[a]**Modified Medical Research Council Dyspnoea Scale (mMRC)**: a simple questionnaire for assessing severity of breathlessness, that relates well to other measures of health status and predicts future mortality risk. Patients select one from five grades of breathlessness [13].

[b]**Chronic Respiratory Disease Questionnaire, self-administered standardised (CRQ-SAS)**: The CRQ-SAS is a questionnaire based on the original CRQ but is self-administered and contains standardised dyspnoea questions. The CRQ is a validated measure of health-related quality of life in patients with chronic airflow limitation. It consists of 20 questions scored on a 7-point scale in four domains: dyspnoea, fatigue, emotional function and mastery [14]. The suggested clinically important difference is an improvement of 0.5 points or more [7].

[c]**Moderate exacerbation**: worsening symptoms of COPD (≥ two consecutive days) needing treatment with oral corticosteroids and/or antibiotics but not hospital admission [6].

[d]**Severe exacerbation**: worsening symptoms of COPD (≥ two consecutive days) needing treatment with oral corticosteroids and/or antibiotics and hospital admission [6].

[e]**St. George's Respiratory Questionnaire (SGRQ)**: a 50-item survey asking about symptoms, and activities with social or psychological impact. Total scores range from 0 (best) to 100 (worst). The suggested clinically important difference is an improvement of four or more units [15].

Summary of evidence

Summary of efficacy data in proposed use:

Four pivotal studies and five supportive studies were submitted in support of a license for Relvar Ellipta for treating patients with COPD [7].

Pivotal studies (see also Table of trials)

The four pivotal studies were centrally randomised, double-blind studies involving adults aged 40 years and over with moderate to very severe COPD (post bronchodilator FEV_1 ≤70% predicted, and FEV_1/forced vital capacity {FVC} ratio ≤0.7) [6,8,9]. Those with poorly controlled COPD or other causes of chronic airflow limitation were excluded. All patients had a smoking history of at least ten pack-years. In two studies patients had to have a score of at least two on the *Modified Medical Research Council Dyspnoea Scale (mMRC)*[a] [8,9]. Each study had a two to four-week run-in period to check compliance with treatment and confirm stable disease by assessing symptoms and use of rescue medicines; in two studies all patients received open-label inhaled FP/SM 250/50 micrograms twice daily during this period [6] and in the other two, they were given placebo [8,9]. Rescue use of salbutamol was allowed throughout the studies. Power calculations were done in all four studies to ensure at least 90% power to detect important differences between FF/VI and VI alone for the primary outcome(s). All analyses were done on intention-to-treat (ITT) populations, and were stratified by smoking status. To account for multiplicity because

of the large number of arms in all studies and avoid spurious statistically significant findings arising through chance, statistical analyses followed a step-down, closed-testing procedure in which analysis of subsequent outcomes was only done if the difference between arms for the previous outcome in the hierarchy was significant (except for pooled analyses).

Study one [8] Kerwin et al. 2013

- This 24-week study compared the effects on lung function of two strengths of FF/VI (46/22 micrograms and 92/22 micrograms) with the individual components and placebo in 1,030 adults (mean age 63 years; mean post bronchodilator FEV_1 range 46.9% to 49.9%). Patients were randomised to five treatments, taken once daily in the morning using the dry-powder Ellipta inhaler:
  - FF/VI 46/22 micrograms,
  - FF/VI 92/22 micrograms,
  - FF 92 micrograms,
  - VI 22 micrograms, or
  - placebo.

  The two co-primary outcomes were weighted mean (wm) FEV_1 (0 to 4 hours post-dose) (chosen to assess the contribution of VI within the combination product) on day 168, and change from baseline in trough FEV_1 (23–24 hours post-dose) (chosen to assess the contribution of FF) on day 169. No previous history of COPD exacerbations was needed but about a quarter of patients had at least one moderate exacerbation and 7% had at least one severe exacerbation in the year before trial entry.

  FF/VI 92/22 micrograms significantly increased post-dose $wmFEV_1$ by 173 mL ([95% confidence interval {CI} 123 to 224]; p<0.001) and trough FEV_1 by 115 mL ([60 to 169]; p<0.001) compared with placebo after 24 weeks' treatment; these differences were clinically important (>100mL [10]). However, there was no statistically significant difference between FF/VI 92/22 micrograms and VI 22 micrograms in trough FEV_1 (48 mL [-6.0 to 102]; p=0.082). Because of this non-significant result, no formal statistical testing was performed on secondary and additional outcomes, including changes in *CRQ-SAS dyspnoea score*[b], night-time awakenings and other symptom-related outcomes. No clinically important differences were seen in *CRQ-SAS dyspnoea score*[b] between FF/VI and placebo (i.e. >0.5 points) [7].

Study two [9] Martinez et al. 2013

This 24-week study was similarly designed to study one but compared FF/VI 184/22 micrograms and FF/VI 92/22 micrograms with their individual components and placebo. It involved 1,224 adults with moderate to very severe COPD (mean age 62 years; mean percentage predicted post bronchodilator FEV_1 range 47.1 to 48.5%; 25% with at least one *moderate*[c] exacerbation and 10% with at least one *severe*[d] exacerbation in the previous year). The first analysis involved FF/VI 184/22 micrograms which significantly increased post-dose $wmFEV_1$ (209 mL [157 to 261]; p<0.001) and trough FEV_1 (131 mL [80 to 183]; p<0.001) compared with placebo; these differences were clinically important (>100mL). However, there was no statistically significant difference between FF/VI 184/22 micrograms and VI 22 micrograms in trough FEV_1 (32 mL [-19.0 to 83]; p=0.224). Because of this non-significant result, no formal statistical testing was performed for the lower dose

of FF/VI 92/22 micrograms.

Studies three and four [6] Dransfield et al. 2013

- These were two 52-week identical studies that investigated whether FF/VI (three different doses of FF) would prevent more exacerbations than VI alone. 1,622 adults were involved in the first study and 1,633 adults in the second study. The two studies were analysed separately and in a pre-defined pooled analysis, based on the ITT population. Patients in the pooled population had a mean age of 64 years, a mean predicted post-bronchodilator FEV_1 range of 44.3% to 46.4%, and a history of at least one *moderate*[c] or *severe*[d] COPD exacerbation in the previous year (about 40% with at least two *moderate exacerbations*[c] and about 8% with at least one *severe exacerbation*[d]). Patients were randomised to one of four treatments taken once daily:
    - FF/VI 44/22 micrograms,
    - FF/VI 92/22 micrograms,
    - FF/VI 184/22 micrograms, or
    - VI 22 micrograms.

  The primary outcome was yearly rate of *moderate*[c] and *severe*[d] COPD exacerbations. Secondary and additional outcomes included time to first *moderate*[c] or *severe*[d] exacerbation, yearly rate of *severe*[d] exacerbations, number of night-time awakenings due to symptoms, dyspnoea score and change from baseline in trough FEV_1.

  In the pooled analysis, mean yearly rate of *moderate*[c] and *severe*[d] exacerbations with FF/VI 92/22 micrograms was 0.81 compared with 1.11 for VI 22 micrograms (rate ratio 0.7 [0.6 to 0.8]; p<0.0001). This was similar in people with a history of frequent exacerbations; defined as at least two *moderate*[c] or s*evere*[d] exacerbations in the previous year (0.7 [0.6 to 0.9]; p=0.0005). This relative reduction of 30% is considered clinically important (≥20% [10]). The absolute difference between the groups was 7% (42% of patients had at least one exacerbation in both Relvar Ellipta groups and 49% in the VI group). It should be noted that analysis of data from only the first study showed there was no significant difference in exacerbation rate between the FF/VI 184/22 microgram group and the VI group (rate ratio 0.9 [0.7 to 1.0]; p=0.1093), so no statistical analysis of the 92/22 microgram group was performed.

  In the pooled analysis, FF/VI 92/22 micrograms also increased the time to first *moderate*[c] or *severe*[d] exacerbation compared with VI 22 micrograms (hazard ratio 0.8 [0.7 to 0.9]; p=0.0002). However, it did not reduce the mean yearly rate of *severe*[d] exacerbations compared with VI 22 micrograms (rate ratio 0.9 [0.6 to 1.4]; p=0.695) [6]. Compared with VI 22 micrograms, FF/VI 92/22 micrograms produced statistically significant improvements in night-time awakenings (mean difference −0.08 [−0.12 to −0.03]; p=0.0012) and dyspnoea (mean difference −0.09 [−0.014 to −0.05]; p<0.0001, on a scale of −2 to +2, with −2 indicating 'much less than usual' and +2 indicating 'much more than usual') [3].

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) considered these four studies to be well designed and conducted [7]. In the two 24-week studies, improvements in wmFEV_1 (0 to 4 hours post-dose) and trough FEV_1 with Relvar Ellipta compared with placebo were clinically important (>100mL). The lack of a significant difference between FF/VI and VI alone may reflect the small contribution corticosteroids have on lung function when given with a LABA. There were no clinically important differences between FF/VI and placebo in mean *CRQ-SAS dyspnoea score*[b] in both studies [7], but a responder analysis showed the odds of being a responder was between 1.67 and 2.03 times greater with FF/VI 92/22 micrograms than with placebo.

In the 52-week studies, Relvar Ellipta 92/22 micrograms once daily produced a clinically significant (although small) improvement in annual rate of *moderate*[c] and *severe*[d] exacerbations compared with VI alone (7% absolute difference). No significant effect on rate of *severe*[d] exacerbations was seen, and this was thought to be due to the small number of events (11 to 14% of exacerbations) and has previously been reported with other ICS/LABA combination inhalers, e.g. in the TRISTAN and TORCH studies with FP/SM [7]. There was no evidence of a dose-response effect on lung function between the three doses of FF studied, and no additional benefit from the higher 184/22 microgram dose in reducing exacerbation rates. The CHMP considered it acceptable that Relvar Ellipta had been compared with VI, rather than a LABA licensed for use in patients with COPD, because the improvements seen in lung function are similar to that seen in studies of other LABAs (between 40 to 92mL change in trough FEV_1).

Supportive studies

Study five [11] Agusti et al. 2014

- This 12-week superiority study compared the effect on lung function of FF/VI 92/22 micrograms once daily and FP/SM 500/50 micrograms (Seretide 500 Accuhaler) twice daily over 12 weeks in 528 adults with COPD who had been treated with oral corticosteroids or antibiotics for an exacerbation within three years prior to screening. There was no significant difference between the two groups – least squares mean (LSM) change from baseline in 0-24 hour wmFEV_1 was 130mL [standard deviation ± 222] with FF/VI 92/22 micrograms and 108mL [± 221] with FP/SM 500/50 micrograms (LSM difference 22 [-18 to 63]; p=0.282). As in the pivotal studies, failure to achieve a significant difference for this outcome meant that no further statistical testing could be done for any other outcomes, including *St George's Respiratory Questionnaire (SGRQ)*[e]. *SGRQ*[e] total scores after 12 weeks improved in both groups – change from baseline was -4.3 [± 11.8] in the FF/VI 92/22 group and -3.0 [± 11.8] in the FP/SM 500/50 group. The authors note that the change with FF/VI, but not FP/SM, is clinically important (≥four units [10]) but the difference is change from baseline and not a comparison with change from baseline with placebo. This could have exaggerated the result. Mean compliance in both groups was 97.5%.

Studies six to nine [7,12]

- Of the four remaining studies, three are currently unpublished – two are 12-week superiority studies with a similar design to study five but compare FF/VI 92/22 micrograms once daily with FP/SM 250/50 micrograms twice daily [7]. Results are conflicting, with one study showing a significant difference between groups in LSM change from baseline in 0-24 hour wmFEV_1 between groups (174mL vs. 94mL, respectively; LSM difference 80mL [37 to 124]; p<0.001) and the other showing no significant difference (LSM difference 29mL [-22 to 80]; p=0.267). The other two supportive studies lasted only four weeks and are not described here [7,12].

Summary of safety data:

The most common adverse events with Relvar Ellipta in patients with COPD are headache, nasopharyngitis and upper respiratory tract infection [7]. Its safety profile in patients with COPD is similar to that in patients with asthma, except for a higher incidence of fracture and pneumonia (including those resulting in hospitalisation) in patients with COPD [4]. In the pooled analysis of 52-week exacerbation studies, 7.7% of patients receiving FF/VI 92/22 micrograms experienced an adverse event leading to discontinuation or study withdrawal (mostly due to an exacerbation or pneumonia), compared with 5.5% of those receiving VI 22 micrograms [6].

Pneumonia

In an analysis of data from 5,880 patients with COPD (including the four pivotal studies), the incidence of pneumonia was about 6% across the FF/VI groups compared with 3% in the VI group, and less than 1% in the placebo and FF groups [7]. When these data were adjusted for exposure, the rate of pneumonia was 76.7 per 1,000 treatment-years in the FF/VI 184/22 microgram group compared with 68.2 in the 92/22 microgram group and 18 in the placebo group; rates of fatal pneumonia were 7.8, 1.2 and zero per 1,000 treatment-years, respectively [7]. In the pooled analysis of two 52-week exacerbation studies, 3.1% of patients in the FF/VI 92/22 microgram group had pneumonia needing admission to hospital compared with 0.98% of patients in the VI 22 microgram group [6]. When compared with FP/SM in 12-week studies, the overall incidence of pneumonia was less than 1% in the FF/VI 92/22 microgram group and in the FP/SM 500/50 group [7]. Relvar Ellipta 184/22 micrograms is not recommended for use in patients with COPD because no additional benefit is seen compared with the lower dose, and there is an increased risk of systemic corticosteroid-related adverse reactions [4]. Risk factors for pneumonia include current smoking, history of prior pneumonia, body mass index less than 25kg/m^2, an FEV_1 less than 50% predicted [4] and a history of COPD exacerbations [7].

Fracture

In the 52-week studies, there were six non-traumatic fractures in the FF/VI 92/22 microgram group (0.74%) compared with two in the VI group (0.24%) (pooled data) [7]. In one of these studies, which measured markers of bone formation, patients in the FF/VI 184/22 microgram group had a statistically significant decrease of 9% in osteocalcin (p=0.047) [6,7]; the manufacturer considered this to be clinically insignificant but the CHMP has included fracture as a risk in the Summary of Product Characteristics [4].

Cardiovascular (CV) events, adrenal suppression and local adverse events

The incidence of CV events, adjusted by exposure, in patients with COPD was not higher in the FF/VI groups (range 130 to 160 per 1,000 subject-years) than in the placebo (319) and FF (range 223 to 251) groups [7]. When compared with FP/SM 500/50 microgram, more patients experienced CV events with FF/VI 92/22 micrograms (nine vs. one) [11]. The manufacturer advises that Relvar Ellipta should be used with caution in patients with severe CV disease [4].

Adrenal suppression is a potential risk although data on the effects of Relvar Ellipta on cortisol excretion are inconsistent [7]. Oral candidiasis was common with rates of 7% with FF/VI 92/22 micrograms compared with 4% (VI), 2% (FF 92 or 184 micrograms) and <1% (placebo) in studies involving a total of 5,880 patients [7]. Local steroid effects (candidiasis and dysphonia) were more common with FP/SM 500/50 micrograms twice daily than with FF/VI 92/22 micrograms once daily (10 vs. three) [11].

Strengths and limitations of the evidence:

Overall study design

- All pivotal studies were sufficiently long in duration to demonstrate effects on lung function and symptoms (12 to 24 weeks), and on exacerbations (52 weeks) [16].
- The rationale for conducting two identical pivotal exacerbation studies simultaneously in a large number of centres (350), each recruiting only a small number of patients with a common disease, is unclear [3].
- The 52-week exacerbation studies, although each adequately powered for the primary outcome, were pooled to provide greater precision for effect sizes and allow pre-specified subgroup analysis, including the effects in patients with a history of frequent exacerbations (at least two *moderate*[c] or *severe*[d] exacerbations in the previous year) [6].

Population

- Relvar Ellipta is licensed for use in patients with an exacerbation history despite regular bronchodilator therapy, but only a quarter of the population in the two pivotal 24-week studies had had an exacerbation in the last year [8,9].
- In the two 52-week exacerbation studies, two thirds of patients were using ICS on study entry, so patients in the VI group were likely to have experienced ICS withdrawal which can lead to exacerbations [6]. Commentators have called for the data to be stratified by previous ICS use [17], but the authors have explained that this cannot be done because all patients enrolled in the studies were given FP during the four-week run-in period [18]. About a quarter of patients in the 24-week studies had previously been using ICS [8,9].
- All studies required patients to complete a run-in period where adherence to treatment was assessed, and only patients adhering to treatment were randomised [6,7,8,9,11]. Therefore, efficacy of Relvar Ellipta may be less in clinical practice than in the studies.

Intervention

- Selecting an ICS dose for treatment of COPD is challenging because of their lack of efficacy when used as a single agent. Therefore, multiple doses have to be assessed in exacerbation studies [19].

Comparator

- The comparator in the pivotal studies was placebo or VI 22 micrograms, and not an established ICS/LABA combination therapy or monotherapy licensed for use in COPD.
- The only trials comparing Relvar Ellipta with an ICS/LABA combination inhaler licensed for treatment of patients with COPD are relatively short-term (12 weeks) and measure a disease-orientated outcome (24-hour spirometric effect [FEV_1]) rather than a patient-orientated outcome such as exacerbation rate. This limits the conclusions that can be drawn from them. Only one of these studies has been published in full [11]. The doses of FP/SM used in these studies include 500/50 micrograms (the dose licensed for COPD) and 250/50 micrograms twice daily.

Outcomes

- The 24-week pivotal studies were not adequately powered to measure effect on patients' symptoms. The primary outcome in both studies was FEV_1, a measure of the obstructive element of COPD. However, if FEV_1 is the primary outcome, there should be a co-primary outcome which is symptom-based or patient-related [16].
- The two 24-week studies showed that FF/VI 92/22 micrograms produced clinically significant increases in mean trough FEV_1 compared with placebo. However, the lower limit of the 95% CIs for the difference in both trials was below the 100mL difference considered clinically important [10].
- In the 52-week exacerbation studies, the primary outcome depended in part on local practice (whether or not to start systemic corticosteroids or antibiotics, or admit to hospital) and this may have varied between sites [3]. Exacerbation rates were lower than expected.
- The statistical hierarchy method used in the pivotal studies, although a robust way of reducing the risk of false-positive results arising from chance after repeated analyses, limited the opportunities for analysis of secondary outcomes in some cases.
- No studies measured effect on mortality or were powered to adequately assess effect on quality of life.

Summary of evidence on cost effectiveness:

The Scottish Medicines Consortium accepted FF/VI (Relvar Ellipta®) for restricted use within NHS Scotland on 07 April 2014 for patients with severe COPD (FEV_1 <50% predicted normal) [20].

Their review included the following analysis of comparative health economic evidence [20]:

> The company submitted a cost-minimisation analysis of fluticasone furoate/vilanterol for the symptomatic treatment of adults with COPD with a FEV_1 <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. The comparators included fluticasone propionate/salmeterol and budesonide/formoterol fumarate dihydrate (which have both been accepted for use by SMC in COPD (FEV_1 <50% predicted normal). The time horizon for the analysis was five years.
>
> The data to support comparable efficacy were based on Bayesian mixed treatment comparisons assessing the probability of non-inferiority of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol and budesonide/formoterol fumarate dihydrate. A 12-week study directly compared fluticasone furoate/vilanterol with fluticasone propionate/salmeterol, however the purpose of this study was to demonstrate superiority and the primary superiority endpoint was not met. There were no direct clinical data versus budesonide/formoterol fumarate dihydrate.
>
> Only drug costs were included in the analysis. Costs were presented over one to five years. The results showed that the cost of fluticasone furoate/vilanterol is £338 in year one and £1,645 over a five year time horizon compared with a cost in year one of £498 for fluticasone propionate/salmeterol and £2,422 over a five year time horizon and compared with a cost of £462 in year one for budesonide/formoterol fumarate dihydrate and £2,249 over a five year time horizon. Fluticasone furoate/vilanterol is therefore associated with cost savings of £160 and £124 in year one compared with fluticasone propionate/salmeterol and budesonide/formoterol fumarate dihydrate, respectively, and £777 and £604 over a five year time horizon compared with fluticasone propionate/salmeterol and budesonide/formoterol fumarate dihydrate, respectively. Fluticasone furoate/vilanterol would therefore be the preferred treatment on cost-minimisation grounds.
>
> The economic case has been demonstrated for patients with an FEV_1 <50% predicted normal. However, as the comparators are not in routine use for COPD patients with FEV_1 50% to <70% predicted normal, the case has not been demonstrated in the group of patients with less severe disease.

Prescribing and risk management issues:

- Some respiratory experts have warned that there is a risk that patients with COPD may mistakenly use Relvar Ellipta on an 'as needed' basis because it has a grey and blue cover, and patients in the UK are educated that blue inhalers are relievers [21]. In addition, the name 'Relvar' sounds similar to 'reliever'. The Midlands Therapeutics Review and Advisory Committee have also expressed concern over a safety risk in patients with COPD because of the similarity of the colour of Relvar Ellipta to reliever inhalers [22]. The colour of alternative ICS/LABA combination inhalers licensed for treating COPD are pink (Fostair), purple (Seretide Accuhaler) and white/red (Symbicort Turbohaler) [23,24,25,26]. Patients will have to be given clear advice that Relvar Ellipta must be used regularly and not 'as needed'. UK Medicines Information has produced a safety assessment report for Relvar Ellipta listing recommendations for the manufacturer, NHS organisations, prescribers and patients [27].
- There are differences between the three ICS/LABA combination inhalers available for patients with COPD in their licensed indications. All are licensed for patients with COPD and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy, but Relvar is recommended for patients with a FEV_1 <70% of predicted [4], Seretide for patients with a FEV_1 <60% of predicted [24], and Fostair and Symbicort for patients with severe COPD (FEV_1 <50% of predicted) [23,26].
- Clinically significant drug interactions are unlikely but use of Relvar Ellipta should be avoided in patients taking strong CYP3A4 inhibitors which may increase systemic exposure to FF and VI [4].
- Patients should rinse their mouth without swallowing, after using Relvar Ellipta [4].

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per 30 days (ex VAT)
Relvar Ellipta dry-powder inhaler	92/22 micrograms 1 inhalation once a day	£27.80 30-dose unit	£27.80
Fostair metered-dose inhaler	100/6 micrograms 2 puffs twice a day	£29.32 120-dose unit	£29.32
Seretide Accuhaler dry-powder inhaler	500/50 1 inhalation twice a day	£40.92 60-dose unit	£40.92
Symbicort Turbohaler dry-powder inhaler	200/6 micrograms 2 inhalations twice a day	£38.00 120-dose unit	£38.00
	400/12 micrograms 1 inhalation twice a day	£38.00 60-dose unit	£38.00
Costs based on MIMS list prices May 2014. This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

None.

Productivity, service delivery, implementation:

Not applicable.

Anticipated patient numbers and net budget impact:

An estimated 3 million people have COPD in the UK – about 900,000 have been diagnosed and two million remain undiagnosed [1]. This is equivalent to approximately 1,500 people diagnosed with COPD per 100,000 people and 3,000 undiagnosed per 100,000 population.

The manufacturer expects FF/VI to be used in patients new to this class of drugs or in patients on existing treatments who are symptomatic on their current regimen and may benefit from a once-daily product [3]. NICE calculated in 2011 that 12.2% of patients with COPD receive an ICS/LABA combination inhaler in primary care, and a further 1.2% of patients receive separate ICS and LABA inhalers (total 13.4%) [28]. 12.8% of patients receive triple therapy with an ICS and a LABA and a LAMA.

Assuming 393 patients per 100,000 population diagnosed with COPD are eligible for ICS/LABA combination therapy (as dual therapy, or triple therapy with a LAMA), the annual cost of Relvar Ellipta 92/22 micrograms once daily per 100,000 people is about £131,000. This compares to an annual cost per 100,000 population of £138,000 with Fostair 200/12 micrograms twice daily, £193,000 with Seretide Accuhaler 500/50 micrograms twice daily, and £179,000 with Symbicort Turbohaler 400/12 micrograms twice daily.

Innovation, need, equity:

Not applicable.

References

1. National Institute for Health and Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). NICE clinical guideline 101. 2010. Accessed 03 March 2014 at: http://guidance.nice.org.uk/CG101/NICEGuidance/pdf/English.
2. Joint Formulary Committee. British National Formulary 63 ed. London: BMJ Group and the Royal Pharmaceutical Society of Great Britain; 2012. Accessed 03 March 2014 at: www.bnf.org/bnf/index.htm.
3. National Institute for Health and Care Excellence. ESNM21: Chronic obstructive pulmonary disease: fluticasone furoate plus vilanterol. June 2013. Accessed 03 March 2014 at: www.nice.org.uk/mpc/evidencesummariesnewmedicines/ESNM21.jsp.
4. GlaxoSmithKline UK. Summaries of Product Characteristics Relvar Ellipta 184/22 micrograms and 92/22 micrograms inhalation powder, pre-dispensed. November 2013. Accessed 03 March 2014 at: www.medicines.org.uk/emc/medicine/28496/SPC/.
5. O'Byrne PM, Bleecker ER, Bateman ED et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Euro Respir J 2014; 43: 773-782.
6. Dransfield MT, Bourbeau J, Jones PW et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: Two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respir Med 2013; 1: 210-223.
7. European Medicines Agency. Relvar Ellipta – Assessment Report; September 2013. Accessed 03 March 2014 at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002673/WC500157635.pdf.
8. Kerwin EM, Scott-Wilson C, Sanford L et al. A randomised trial of fluticasone furoate/vilanterol (50/25 microgram; 100/25 microgram) on lung function in COPD. Respir Med 2013; 107: 560-9.
9. Martinez FJ, Boscia J, Feldman G et al. Fluticasone furoate/vilanterol (100/25 microgram; 200/25 microgram) improves lung function in COPD: a randomised trial. Respir Med 2013; 107: 550-9.
10. National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. October 2010. Accessed 07 April 2014 at: http://guidance.nice.org.uk/CG101/Guidance/pdf/English.
11. Agusti A, de Teresa L, De Backer W et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J 2014; 43: 763-772.
12. Boscia JA, Pudi KK, Zvarich MT et al. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. Clinical Therapeutics 2012; 34: 1655-66.
13. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. January 2014. Accessed 07 April 2014 at: www.goldcopd.org.
14. McMaster University. Available questionnaires. Accessed 07 April 2014 at: http://milo.mcmaster.ca/questionnaires/questionnaires.
15. American Thoracic Society. St. George's Respiratory Questionnaire (SGRQ). 2014. Accessed 07 April 2014 at: www.thoracic.org/assemblies/srn/questionaires/sgrq.php.
16. European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease. June 2012. Accessed 03 March 2014 at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500144964.pdf.
17. Morjaria JB and Morice AH. Fluticasone furoate and vilanterol for COPD. Lancet Respir Med 2013; 1(5): e21.
18. Dransfield MT, Lettis S, Barnhart F, Crim C and Calverley PMA. Author's reply. Lancet Respir Med 2013; 1(5): e21-22.
19. Center for Drug Evaulation and Research. Application number: 204275Orig1s000. Summary review. Accessed 03 March 2014 at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM347929.pdf.
20. Scottish Medicines Consortium. Fluticasone furoate/vilanterol 92/22 micrograms inhalation powder (Relvar Ellipta). SMC No. (953/14). Accessed 07 April 2014 at: www.scottishmedicines.org.uk/files/advice/M__Scottish_Medicine_Consortium_Web_Data_Audit_advice_Advice_by_Year_2014_No.4_-

_April_2014_fluticasone_furoate_vilanterol__Relvar__FINAL_March_2014_Amended_03.04.14_for_website.pdf.
21. Capstick TGD, Khachi H, Murphy A et al. Our concerns with Relvar Ellipta. Pharm J 2014. Accessed on 25 February 2014 at: www.pjonline.com/letters/our_concerns_with_relvar_ellipta.
22. Midlands Therapeutics Review and Advisory Committee. Commissioning support: Fluticasone furoate/vilanterol (Relvar Ellipta) for the treatment of chronic obstructive pulmonary disease. March 2014. Accessed 20 March 2014 at: http://centreformedicinesoptimisation.co.uk/download/e92adb5a1de0ad47177fe75a517f456e/Fluticasone-furoate-vilanterol-inhaler-final.pdf.
23. Chiesi Ltd. Summary of Product Characteristics Fostair 100/6 inhalation solution. March 2014. Accessed 27 May 2014 at: http://www.medicines.org.uk/emc/medicine/21006/SPC/
24. Allen and Hanburys Ltd. Summary of Product Characteristics Seretide 100, 250, 500 Accuhaler. September 2013. Accessed 25 March 2014 at: www.medicines.org.uk/emc/medicine/2317/SPC/
25. Health.GSK. Seretide. Accessed 08 April 2014 at: http://public.gsk.co.uk/products/seretide.html.
26. AstraZeneca. Summary of Product Characteristics. Symbicort Turbohaler 200/6 inhalation powder and Symbicort Turbohaler 400/12 inhalation powder. February 2013. Accessed 25 March 2014 at: www.medicines.org.uk/emc/searchresults.aspx?term=symbicort&searchtype=QuickSearch.
27. UK Medicines Information. In use product safety assessment report for Relvar Ellipta (fluticasone furoate/vilanterol inhalation powder). April 2014. Accessed 09 April at: www.ukmi.nhs.uk/filestore/ukmiaps/ProductsafetyassessmentforFluticasonevilanterol.docx.
28. National Institute for Health and Clinical Excellence. Chronic obstructive pulmonary disease (update): costing report. February 2011. Accessed 10 April 2014 at: www.nice.org.uk/nicemedia/live/13029/53292/53292.pdf.

Table of trials: Summary of pivotal Relvar Ellipta RCTs relevant to use in COPD

Ref	Trial design	Trial population and treatment	Efficacy results	FF/VI 92/22	FF 92	VI 22	Placebo	Grading of evidence (SORT criteria)*
7,8	24-week, randomised, multicentre (221), double-blind, parallel-group study. The study consisted of: • A 2-week run-in period, • A 24-week treatment period with patients randomised centrally (1:1:1:1:1) to FF/VI 46/22*, or FF/VI 92/22, or FF 92, or VI 22, or placebo, all once daily. Stratified by smoking status. **Inclusion criteria:** • Outpatients aged ≥40 years with COPD. • History of cigarette smoking ≥10 pk-yrs. • Post-BD FEV_1/FVC ratio ≤0.70. • Post-BD FEV_1 ≤70%. • mMRC score ≥2. **Exclusion criteria:** • Asthma, alpha-1-antitrypsin deficiency, other non-COPD respiratory disorder. • Lung volume reduction surgery in the last year, or clinically significant chest X-ray abnormality. • Poorly controlled COPD (acute worsening treated with antibiotics or CS) or lower respiratory tract infection requiring antibiotics in last 6 weeks. • Hospitalisation for poorly controlled COPD in last 12 weeks. • Long-term oxygen ≥12 hours daily. • Other clinically significant diseases.	1,030 patients randomised; 70% completed the study. ITT population, n=1,030. • 67% men. • 72% white. • Mean age 63 years. • Mean BMI 26 kg/m^2. • 52% diagnosed ≥5 years ago. • 25% ≥1 exacerbation needing CS or antibiotics in last 12 months. • 54% current smoker. **Screening data** Indicate moderate to very severe COPD. • Mean post-BD predicted FEV_1 48% (range 17-72). • Mean FEV_1/FVC ratio 0.48 (range 0.18-0.74). • Mean % reversibility 16%.	**Co-primary outcomes**					3
			0-4 hour post-dose $wmFEV_1$ (mL)					
			Baseline (day 1), LSM (± SE)	1,392 (528)	1,169 (450)	1,442 (526)	1,255 (459)	
			Change from baseline to day 168, LSM (± SE)	200 (18)	80 (18)	129 (18)	26 (18)	
			Treatment difference, mean [95% CI]					
			vs. placebo	**173* [123-224]**	**53*** [3-104]**	**103* [52-153]**	-	
			vs. FF 92	**120* [70-170]**	-	-	-	
			vs. VI 22	**71*** [21-121]**	-	-	-	
			Trough FEV_1 (mL)					
			Baseline (day 1), LSM (± SE)	1,379 (515)	1,191 (441)	1,399 (520)	1,251 (454)	
			Change from baseline to day 169, LSM (± SE)	151 (19)	70 (20)	103 (20)	37 (20)	
			Treatment difference, mean [95% CI]					
			vs. placebo	**115* [60-169]**	33 [-22-88]	**67** [12-121]**	-	
			vs. FF 92	**82*** [28-136]**	-	-	-	
			vs. VI 22	48 [-6-102]	-	-	-	
			Secondary outcome (see note 2)					
			CRQ-SAS dyspnoea domain					
			Change from baseline to day 168, LSM (± SE)	0.53 (0.085)	0.29 (0.086)	0.37 (0.086)	0.23 (0.088)	
			Treatment difference, mean [95% CI]					
			vs. placebo	0.30 [0.06-0.5]	0.06 [-0.2-0.3]	0.14 [-0.1-0.4]	-	
			vs. FF 92	0.24 [0.01-0.5]	-	-	-	
			vs. VI 22	0.16 [-0.08-0.4]	-	-	-	

Statistical significance: *p<0.001; **p=0.017; ***p<0.05. ***Abbreviations***: CI confidence interval; CRQ-SAS Chronic Respiratory Disease Questionnaire, self-administered standardised; CS corticosteroid; FF/VI fluticasone furoate/vilanterol; FVC forced vital capacity; ITT intention-to-treat; LSM least squares mean; mMRC modified Medical Research Council Dyspnoea Scale; pk pack; post-BD post-bronchodilator; SE standard error; Trough FEV_1 pre-bronchodilator and pre-dose forced expiratory volume in 1 second; $wmFEV_1$ weighted mean forced expiratory volume in 1 second. ***Note 1***: All doses in micrograms. ***Note 2***: Failure to achieve p<0.05 for the comparison of FF/VI 92/22 vs. VI 22 for a primary outcome meant significance could not be inferred from further analyses.

Ref	Trial design	Trial population and treatment	Efficacy results	FF/VI 92/22	FF/VI 184/22	FF 92	FF 184	VI 22	Placebo	Grading of evidence (SORT criteria)*
7,9	24-week, randomised, multicentre, double-blind, parallel-group study. The study consisted of: • A 2-week run-in period, • A 24-week treatment period with patients randomised centrally (1:1:1:1:1:1) to FF/VI 92/22, or FF/VI 184/22, or FF 92, or FF 184, or VI 22, or placebo, all once daily. Stratified by smoking status. **Inclusion and exclusion criteria:** • As in the study above.	1,224 patients randomised; 75% completed the study. ITT population, n=1,224. • 72% men. • 94% white. • Mean age 62 years. • Mean BMI 27 kg/m^2. • 52% diagnosed ≥5 years ago. • 25% ≥1 exacerbation needing CS or antibiotics in last 12 months. • 54% current smoker. **Screening data** Indicate moderate to very severe COPD. • Mean post-BD predicted FEV$_1$ 48% (range 14-87). • Mean FEV$_1$/FVC ratio 0.47 (range 0.17-0.88). • Mean % reversibility 12%.	**Co-primary outcomes** (see note 2)							
			0-4hour post-dose wmFEV$_1$ (mL)							
			Baseline (day 1), LSM (± SE)	1,529 (579)	1,490 (562)	1,438 (500)	1,347 (493)	1,535 (499)	1,365 (493)	
			Change from baseline to day 168, LSM (± SE)	202 (19)	197 (18)	34 (19)	29 (19)	173 (18)	-12 (19)	
			Treatment difference, mean [95% CI]							
			vs. placebo	214 [161-266]	**209 [157-261]***	46 [-6-98]	41 [-11-93]	**185 [133-237]***	-	
			vs. FF 92 or 182 (respectively)	168 [116-220]	**168 [117-219]***	-	-	-	-	
			vs. VI 22	29 [-23-81]	24 [-27-75]	-	-	-	-	
			Trough FEV$_1$ (mL)							
			Baseline (day 1), LSM (± SE)	1,495 (567)	1,444 (543)	1,438 (505)	1,323 (472)	1,488 (520)	1,345 (477)	
			Change from baseline to day 169, LSM (± SE)	148 (19)	135 (19)	48 (19)	12 (19)	103 (19)	4 (19)	
			Treatment difference, mean [95% CI]							
			vs. placebo	144 [91-197]	**131 [80-183]***	44 [-8-97]	8 [-44-60]	**100 [48-151]***	-	3
			vs. FF 92 or 182 (respectively)	100 [47-152]	**123 [72-174]***	-	-	-	-	
			vs. VI 22	45 [-8-97]	32 [-19-83]	-	-	-	-	
			Secondary outcomes (see note 2)							
			CRQ-SAS dyspnoea domain							
			Change from baseline to day 168, LSM (± SE)	0.45 (0.08)	0.31 (0.08)	0.10 (0.08)	0.21 (0.08)	0.28 (0.08)	0.21 (0.08)	
			Treatment difference, mean [95% CI]							
			vs. placebo	0.24 [0.02-0.5]	0.10 [-0.1-0.3]	-0.12 [-0.3-0.1]	-0.01 [-0.2-0.2]	0.07 [-0.1-0.3]	-	
			vs. FF 92 or 182 (respectively)	0.36 [0.1-0.6]	0.10 [-0.1-0.3]	-	-	-	-	
			vs. VI 22	0.17 [-0.04-0.4]	0.03 [-0.2-0.2]	-	-	-	-	

Statistical significance: *p<0.001. ***Abbreviations***: CI confidence interval; CRQ-SAS Chronic Respiratory Disease Questionnaire, self-administered standardised; CS corticosteroid; FF/VI fluticasone furoate/vilanterol; FVC forced vital capacity; ITT intention-to-treat; LSM least squares mean; post-BD post-bronchodilator; SE standard error; Trough FEV$_1$ pre-bronchodilator and pre-dose forced expiratory volume in 1 second; wmFEV$_1$ weighted mean forced expiratory volume in 1 second. ***Note 1***: All doses in micrograms. ***Note 2***: Failure to achieve p<0.05 for the comparison of FF/VI 184/22 vs. VI 22 for the primary outcomes meant significance could not be inferred from further analyses including primary outcomes for FF/VI 92/22.

Ref	Trial design	Trial population and treatment	Efficacy results				Grading of evidence (SORT criteria)*
				FF/VI 92/22	FF/VI 184/22	VI 22	
6,7	Two 52-week, randomised, multicentre (350), double-blind, parallel-group studies. The study consisted of: • A 4-week run-in period during which all patients received open-label FP/SM 250/50 twice daily, • A 52-week treatment period with patients randomised centrally (1:1:1:1) to FF/VI 46/22, or FF/VI 92/22, or FF/VI 184/22 or VI 22, all once daily. Stratified by smoking status. **Inclusion criteria:** • Outpatients aged ≥40 years with COPD. • History of cigarette smoking ≥10 pk-yrs. • Post-BD FEV_1/FVC ratio ≤0.70. • Post-BD FEV_1 ≤70%. • At least one COPD exacerbation needing systemic CS, antibiotics or hospitalisation in the last year. **Exclusion criteria:** • Asthma, alpha-1-antitrypsin deficiency, other non-COPD respiratory disorder. • Lung volume reduction surgery in the last year, or clinically significant chest X-ray abnormality. • Immunosuppression or other risk factors for pneumonia. • Moderate or severe COPD exacerbation not resolved at least 14 days prior to screening. • Long-term oxygen ≥12 hours daily. • Other clinically significant diseases.	1,622 patients randomised in the first study; 1,633 patients randomised in the second study. 75% and 73% completed the studies, respectively. ITT populations, n=1,622 and 1,633. • 41% and 45% women. • 82% and 88% white. • Mean age 64 years in both studies. • Mean BMI 27 kg/m^2 in both studies. • 31% and 32% diagnosed ≥5 to 10 years ago. • 93% and 92% ≥1 (37% and 41% ≥2) exacerbation(s) needing CS or antibiotics in the last year. • 42% and 46% current smoker. • Mean % reversibility 29% and 31%. **Screening data** Indicate mild to very severe COPD – overall, mean post-BD predicted FEV_1 45% (range 12-92) (4 patients with predicted FEV_1 >70%).	**Primary outcome (pre-defined pooled analysis of the two studies)**				1
			Moderate and severe exacerbations (see note 2) LSM yearly rate LSM yearly rate ratio for moderate and severe exacerbations vs. VI 22 [95% CI]	**0.81** **0.73 [0.63 to 0.84]; p<0.0001**	**0.85** **0.77 [0.66 to 0.88]; p=0.0003**	1.11 -	
			Selected secondary and additional outcomes (pre-defined pooled analysis of the two studies)				
			Time to first moderate or severe exacerbation compared with VI 22 (see note 2) Hazard ratio [95% CI]	**0.76 [0.7 to 0.9]; p=0.0002**	**0.75 [0.7 to 0.9]; p=0.0001**	-	
			Severe exacerbations LSM yearly rate LSM yearly rate ratio for severe exacerbations vs. VI 22 [95% CI]	0.09 0.9 [0.6 to 1.4]; p=0.695	0.08 0.8 [0.5 to 1.2]; p=0.280	0.10 -	
			Night-time awakenings LSM difference vs. VI 22 [95% CI]	**−0.08 [−0.12 to −0.03]; p=0.001**	**−0.07 [−0.12 to −0.03]; p=0.002**	-	
			Dyspnoea score (see note 3) LSM difference vs. VI 22 [95% CI]	**−0.09 [−0.014 to −0.05]; p<0.0001**	**−0.11 [−0.16 to −0.07]; p<0.0001**	-	
			Trough FEV_1 (mL) Change from baseline to week 52, LSM (± SE) Treatment difference vs. VI 22, mean [95% CI]	**10** **40 [20 to 60]; p=0.0003**	**20** **50 [23 to 70]; p<0.0001**	-30 -	

Abbreviations: CI confidence interval; CS corticosteroid; FF/VI fluticasone furoate/vilanterol; FP/SM fluticasone propionate/salmeterol; FVC forced vital capacity; ITT intention-to-treat; LSM least squares mean; pk pack; post-BD post-bronchodilator; SE standard error; Trough FEV_1 pre-bronchodilator and pre-dose forced expiratory volume in 1 second. ***Note 1***: All doses in micrograms. ***Note 2***: Exacerbations were not centrally adjudged. Moderate exacerbation defined as worsening COPD symptoms ≥2 consecutive days needing oral CS or antibiotics; severe exacerbation defined as for moderate exacerbation but needing hospitalisation. ***Note 3***: Dyspnoea was scored on a scale of −2 to +2, with −2 indicating 'much less than usual' and +2 indicating 'much more than usual'.

Grading of evidence (based on SORT criteria):

Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies
Level 3	Disease-oriented evidence or evidence from: • consensus guidelines • expert opinion • case series

Midlands and Lancashire Commissioning Support Unit,
Jubilee House**,** Lancashire Business Park, Leyland, PR26 6TR
Tel: 01772 644 400 | www.staffordshirelancashirecsu.nhs.uk