Relvar Ellipta (fluticasone furoate/vilanterol [as trifenate]) for the treatment of patients with asthma

Evidence Summary to support formulary decision making and guideline development

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This document has been designed to allow you to quickly access the information that you require. It may be used in a linear manner by scrolling through the content, or by navigating straight to the section of interest using the links contained within the document.

There are six key sections where diverse information has been included – these are accessible via the toolbar, which is located at the top of every page. Please see the illustration of the toolbar here:

Clicking on the relevant button in the toolbar will take you straight to the first page of that section; from there you will be able to navigate within that section.

In certain sections, for example the Clinical Information section, a summary has been provided on the first page of that section and is followed by more detailed information.

If at any time you wish to return to your previous page after following a link, you can press Alt + the back arrow key on your keyboard (Alt + ←); this will return you to your original place in the document.

If in doubt, the Home button in the toolbar will take you back to the main homepage where all information can be accessed.

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Date of preparation: February 2019
The **Medicine Details** section provides details of Relvar Ellipta, including:

- Disease area and licensed indication
- Brand and generic name
- Drug class and treatment type
- Strength and dosing
- Manufacturer
- Device

The **Licensing Information** section provides basic licensing information for Relvar Ellipta, including:

- Status of marketing authorisation
- HTA body information

The **Formulary Implications** section provides information that may be of use when considering a formulary application, including:

- Potential place in therapy
- Place in therapy as recommended by HTA bodies
- Place in therapy as recommended by clinical guidelines

The **Clinical Information** section provides information on the clinical trial outcomes for Relvar Ellipta, including:

- Efficacy data
- Dose-ranging information
- Safety data
- Effectiveness data

The **Patient Factors & Ellipta Device** section provides information on factors associated with the use of Relvar Ellipta, including:

- Device
- Inhaler errors
- Patient preference
- Ease-of-use

The **Financial & Environmental Implications** section provides financial information for the medicine, including:

- Cost
- Budget impact
- Environmental considerations

Date of preparation: February 2019
## Medicine Details

<table>
<thead>
<tr>
<th>Disease area</th>
<th>Asthma(^1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Relvar Ellipta(^1,2)</td>
</tr>
<tr>
<td>Generic name</td>
<td>Fluticasone furoate (FF, inhaled corticosteroid [ICS]) and vilanterol as trifenate (VI, long-acting (\beta_2) agonist [LABA]) combination(^1,2)</td>
</tr>
<tr>
<td>Drug class</td>
<td>Respiratory systems; corticosteroids; compound preparations(^3)</td>
</tr>
<tr>
<td>Strength</td>
<td>92/22 mcg or 184/22 mcg(^1,2)</td>
</tr>
<tr>
<td>Dose</td>
<td>One inhalation once daily(^1,2)</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Glaxo Group Limited(^1,2)</td>
</tr>
<tr>
<td>Treatment type</td>
<td>Long term(^1,2)</td>
</tr>
</tbody>
</table>

### Licensed indication(s)

Relvar Ellipta is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting \(\beta_2\) agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting \(\beta_2\) agonists.
- patients already adequately controlled on both inhaled corticosteroid and long-acting \(\beta_2\) agonist \(^1,2\)

Furthermore, section 4.2 of the Relvar Ellipta 92/22 mcg and 184/22 mcg SPCs state:

- “A starting dose of Relvar Ellipta 92/22 mcg should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting \(\beta_2\) agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 mcg, the dose can be increased to 184/22 mcg, which may provide additional improvement in asthma control.”\(^1\)
- “Relvar Ellipta 184/22 mcg should be considered for adults and adolescents 12 years and over who require a higher dose of inhaled corticosteroid in combination with a long-acting \(\beta_2\) agonist.”\(^1,2\)

### Device

The Ellipta device is a multi-dose dry powder inhaler (DPI). The inhaler consists of a light grey body, a yellow mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant packet. The tray is sealed with a peelable foil lid\(^1,2\).
### Licensing Information

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does Relvar Ellipta have UK/EU marketing authorisation?</td>
<td>Marketing authorisation (MA) nos. 92/22 mcg 1x30 doses [EU/1/13/886/002]; 184/22 mcg 1x30 doses [EU/1/13/886/005]$^{1,2,4}$</td>
</tr>
<tr>
<td>NICE MTA recommendation</td>
<td>The National Institute for Health and Care Excellence (NICE) did not consider Relvar for a NICE technology appraisal$^6$</td>
</tr>
<tr>
<td>SMC number</td>
<td>SMC Drug ID: 966/14$^6$</td>
</tr>
<tr>
<td>AWMSG reference</td>
<td>Ref: 1216$^7$</td>
</tr>
</tbody>
</table>
Formulary Implications

Proposed place in therapy

The clinical trial data for fluticasone furoate/vilanterol (FF/VI; Relvar Ellipta) has been assessed and approved by the European Medicines Agency (EMA). This is reflected in the license for Relvar Ellipta 92/22 mcg.

Section 4.2 of the Relvar Ellipta 92/22 mcg and 184/22 mcg prescribing information states: “A starting dose of Relvar Ellipta 92/22 mcg should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting β2 agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 mcg, the dose can be increased to 184/22 mcg, which may provide additional improvement in asthma control. Relvar Ellipta 184/22 mcg should be considered for adults and adolescents 12 years and over who require a higher dose of inhaled corticosteroid in combination with a long-acting β2 agonist.”

Please note: FF is not licensed as a monotherapy for the treatment of asthma in the UK.

Place in therapy recommended by relevant bodies

<table>
<thead>
<tr>
<th>NICE</th>
<th>NICE did not consider Relvar Ellipta for a NICE technology appraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWMSG</td>
<td>AWMSG advice recommends Relvar Ellipta for the treatment of asthma:</td>
</tr>
<tr>
<td></td>
<td>• “Fluticasone furoate/vilanterol (Relvar Ellipta) is recommended as an option for use within NHS Wales for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting β2 agonist and inhaled corticosteroid) is appropriate: patients not adequately controlled with inhaled corticosteroids and ‘as needed’ inhaled short-acting β2 agonists.”</td>
</tr>
<tr>
<td></td>
<td>• In March 2018 the marketing authorisation for fluticasone furoate/vilanterol (Relvar Ellipta) was extended to include use in <strong>patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist</strong>. This change was not assessed by AWMSG. Relvar Ellipta has been included in the AWMSG ‘excluded medicines report’.</td>
</tr>
<tr>
<td>SMC</td>
<td>The SMC advice accepts the use of Relvar Ellipta for use within NHS Scotland:</td>
</tr>
<tr>
<td></td>
<td>• “Indication under review: the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting β2 agonist and inhaled corticosteroid) is appropriate in patients not adequately controlled with inhaled corticosteroids and ‘as needed’ inhaled short acting β2 agonists.</td>
</tr>
<tr>
<td></td>
<td>• There was no statistically significant difference between fluticasone furoate/vilanterol 92/22 mcg daily and another inhaled corticosteroid/long acting β2 agonist combination (ICS/LABA) inhaler for 0 to 24 hour serial weighted mean forced expiratory volume in one second, at 24 weeks.</td>
</tr>
<tr>
<td></td>
<td>• Some alternative ICS/LABA combination inhalers are available at a lower daily cost.”</td>
</tr>
<tr>
<td></td>
<td>• In March 2018 the marketing authorisation for fluticasone furoate/vilanterol (Relvar Ellipta) was extended to include use in <strong>patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist</strong>. This change will not be assessed by SMC.</td>
</tr>
</tbody>
</table>
Place in therapy recommended by clinical practice guidelines

**BTS/SIGN**
Relvar Ellipta 92/22 mcg is positioned as a low to medium dose ICS/LABA in The British Guideline on the management of asthma:9
- Relvar Ellipta 92/22 mcg is the only ICS/LABA to span both the low & medium dose columns for the treatment of adults and adolescents over 12 years (Relvar Ellipta fills half of the low, and the whole of the medium dose column) in the BTS/SIGN Asthma Guideline. Relvar Ellipta 184/22 mcg is positioned as a high dose ICS/LABA (see ‘Table 9’ and ‘Figure 2’ from The British Guideline on the management of asthma below):9

**GINA**
FF 92 mcg is positioned as a low dose ICS in the ‘Global Strategy for Asthma Management and Prevention’10
- GINA (Global Initiative for Asthma) position FF 92 mcg as a low dose ICS and FF 184 mcg as a high dose ICS for the treatment of adults and adolescents (12 years and older) in the ‘Global Strategy for Asthma Management and Prevention’ (Box 3-6, p44).10

Please note: FF is not licensed as a monotherapy for the treatment of asthma in the UK.

### Table 9: Categorisation of inhaled corticosteroids by dose – adults* (see also Figure 2)9

<table>
<thead>
<tr>
<th>ICS</th>
<th>Dose</th>
<th>Low dose</th>
<th>Medium dose</th>
<th>High dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate (extrafine) with formoterol</td>
<td>100/6 one puff twice a day</td>
<td>100/6 two puffs twice a day</td>
<td>200/6 two puffs twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100/6 one puff twice a day</td>
<td>100/6 two puffs twice a day</td>
<td>200/6 two puffs twice a day</td>
<td></td>
</tr>
<tr>
<td>Budesonide with formoterol</td>
<td>200/6 one puff twice a day</td>
<td>200/6 two puffs twice a day</td>
<td>400/12 two puffs twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400/12 one puff twice a day</td>
<td>400/12 two puffs twice a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate with formoterol</td>
<td>250/10 two puffs twice a day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate with salmeterol</td>
<td>250/50 one puff twice a day</td>
<td>250/50 one puff twice a day</td>
<td>500/50 one puff twice a day</td>
<td></td>
</tr>
<tr>
<td>Seretide Accuhaler</td>
<td>50/25 two puffs twice a day</td>
<td>125/25 two puffs twice a day</td>
<td>250/25 two puffs twice a day</td>
<td></td>
</tr>
<tr>
<td>Seretide Evohaler</td>
<td>100/50 one puff twice a day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone furoate with vilanterol</td>
<td>92/22 one puff once a day</td>
<td>184/22 one puff once a day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Different products and doses are licensed for different age groups and some may be applicable to older children. Prior to prescribing, the relevant summary of product characteristics should be checked (www.medicines.org.uk/emc)

* High doses (shaded boxes) should only be used after referring patient to secondary care

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GSK fully supports the positioning of Relvar Ellipta 92/22 mcg as a low to medium strength ICS/LABA in the BTS/SIGN Asthma Guideline, as GSK believes this appropriately reflects the evidence base for Relvar Ellipta.\(^4,9\) In terms of lung function efficacy, Relvar Ellipta 92/22 mcg is similar to a medium dose ICS/LABA, whilst the impact on the hypothalamic pituitary axis is more consistent with a low dose ICS/LABA.\(^11-14\)

**Figure 2: Summary of management in adults (see also Table 9)**

<table>
<thead>
<tr>
<th>Asthma - suspected</th>
<th>Asthma - diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis and assessment</td>
<td>Evaluation: • assess symptoms, measure lung function, check inhaler technique and adherence • adjust dose • update self-management plan • move up and down as appropriate</td>
</tr>
</tbody>
</table>

Relvar Ellipta 92/22 mcg is a low to medium strength ICS/LABA and can therefore be used as initial add-on therapy for the treatment of asthma in adults. Relvar Ellipta 184/22 mcg is a high dose ICS/LABA. The positioning of both Relvar Ellipta doses in relation to the British Guideline on the management of asthma are shown below.
Clinical Information

- Relvar Ellipta is a once-daily ICS/LABA licensed for the treatment of asthma delivering 24 hours of continuous efficacy from just one dose.\(^1,2,14-17\)
- In SLS Asthma, initiating Relvar had twice the odds of achieving an improvement in asthma control, as measured by the Asthma Control Test (ACT), compared to patients continuing on usual care (71% vs 56%; OR 2.0, CI 1.70, 2.34; \(p<0.0001\)).\(^19\)
- In SLS Asthma, initiating Relvar resulted in a 27% greater improvement in the proportion of Asthma Quality of Life Questionnaire (AQLQ) responders compared to continuing on ICS/LABA usual care (Relvar: 56% vs Usual Care: 44%).\(^19\)
- In an exacerbation study, Relvar reduced the annual rate of severe exacerbations by 25% vs FF (Relvar: 0.14 vs FF: 0.19; \(p=0.014\)).\(^18\)
- Relvar is generally well tolerated in asthma\(^1,2\)

The Efficacy studies include:
- O’Byrne et al., 2014
- Bleecker et al., 2014
- Bernstein et al., 2015
- Woodcock et al., 2013
- Bateman et al., 2014
- Woodcock et al., 2017
- Bernstein et al., 2017

The Dose-ranging information describes:
- The clinical development programme for Relvar Ellipta that resulted in two marketed doses for the treatment of asthma: 92/22 mcg and 184/22 mcg

The Safety studies include:
- Busse et al., 2016
- Busse et al., 2013
- Allen et al., 2013

Please note that fluticasone furoate (FF) is not licensed as a monotherapy for the treatment of asthma in the UK

Date of preparation: February 2019
Efficacy study summaries

Dosing information

Please note that the licensed doses of FF/VI are 92/22 mcg and 184/22 mcg. Each single inhalation of Relvar Ellipta provides a delivered dose (the dose leaving the mouthpiece) of 184 mcg or 92 mcg of fluticasone furoate and 22 mcg of vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 200 mcg or 100 mcg of fluticasone furoate and 25 mcg of vilanterol (as trifenatate).\(^1\)\(^2\)

Licensing information

FF is not licensed as a monotherapy for the treatment of asthma in the UK.

Interpreting clinical trial results – statistical hierarchy

When reviewing the outcomes of clinical trials it is important to understand the relevance of statistical hierarchy and how that impacts upon the conclusions that can be derived from a study. This concept is explained below.

Statistical hierarchy sequentially tests the significance of a number of endpoints in a study programme in a predetermined order. For each endpoint, a determination of significance can only be made if all prior endpoints were also significant. Treatment comparisons for the primary endpoints are required to be statistically significant in order to infer significance for the secondary endpoints. Therefore, if the trial does not meet its primary endpoint, the secondary endpoints cannot be statistically analysed; those results are described as ‘descriptive only’.

```
Primary endpoint:  
If statistically significant, move to secondary endpoint 1

Secondary endpoint 1:  
If statistically significant, move to secondary endpoint 2

Secondary endpoint 2:  
If statistically significant, move to next secondary endpoint
```
O’Byrne et al., 2014

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or click here to download the publication via PubMe online.

<table>
<thead>
<tr>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Byrne et al., Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J 2014;43:773–82</td>
</tr>
</tbody>
</table>

| Study objective | To compare the efficacy and safety of once-daily fluticasone furoate/vilanterol (FF/VI) with fluticasone furoate (FF) alone and twice-daily fluticasone propionate (FP) in patients aged ≥12 years with moderate-to-severe persistent asthma |

| Patient population | Inclusion criteria:  
- ≥12 years with a diagnosis of asthma  
- Documented use of ICS, with or without LABA, for ≥12 weeks with stable ICS dose (FP 500 mcg BD [or equivalent]) or mid-dose ICS/LABA (FP/SAL 250/50 mcg BD or equivalent) for ≥4 weeks  
- Able to demonstrate an evening pre-bronchodilator FEV1 of 40–90% of predicted normal  
- FEV1 reversibility of ≥12% and ≥200 mL on inhalation of albuterol/salbutamol |

| Design | Phase III, multicentre, randomised, double-blind, double-dummy, parallel-group study |

| Treatments |  
| 4-week run-in period; 24-week treatment period:  
- FF/VI 184/22 mcg OD (n=197)  
- FF 200 mcg OD (n=194)  
- FP 500 mcg BD (n=195) |

| Baseline characteristics |  
| Mean age, years | FF/VI 184/22 mcg OD | FF 200 mcg OD | FP 500 mcg BD |
|---------------------|---------------------|
|                     | 46.6                | 44.6          | 47.3          |
| Female sex, n (%)   | 116 (59)            | 113 (58)      | 116 (59)      |
| Duration of asthma, years | 17.0               | 14.7          | 14.9          |
| Mean FEV1, % predicted normal | 66.6               | 66.7          | 67.6          |

| Primary endpoint results |  
| LS mean difference in clinic visit trough FEV1 at Week 24  
- FF/VI 184/22 mcg OD vs FF 200 mcg OD: 193 mL; p<0.001  
- FF/VI 184/22 mcg OD vs FP 500 mcg BD: 210 mL; p<0.001  
- FF 200 mcg OD vs FP 500 mcg BD: 18 mL (95% CI −66, 102); non inferior  
  
LS mean difference in wm 0–24h serial FEV1 at Week 24  
- FF/VI 184/22 mcg OD vs FF 200 mcg OD: 136 mL; p=0.048  
- FF/VI 184/22 mcg OD vs FP 500 mcg BD: 206 mL; p=0.003 |

| Secondary and other efficacy endpoint results |  
| LS mean difference in change from baseline in percentage of rescue-free 24h periods  
- FF/VI 184/22 mcg OD vs FF 200 mcg OD: 11.7; p<0.001  
- FF/VI 184/22 mcg OD vs FP 500 mcg BD: 6.3; p=0.067  
  
LS mean difference in change from baseline in percentage of symptom-free 24h periods  
- FF/VI 184/22 mcg OD vs FF 200 mcg OD: 8.4; p=0.01  
- FF/VI 184/22 mcg OD vs FP 500 mcg BD: 4.9; p=0.137  
  
LS mean differences to Week 24 in daily trough AM and PM PEF |

Please note that fluticasone furoate (FF) is not licensed as a monotherapy for the treatment of asthma in the UK.

Date of preparation: February 2019
• Difference FF/VI 184/22 mcg OD vs FF 200 mcg OD alone: AM PEF = 33.5 L/min; PM PEF = 30.7 L/min; p<0.001 for both
• Difference FF/VI 184/22 mcg OD vs FP 500 mcg BD: AM PEF = 32.9 L/min; PM PEF = 26.2 L/min; p<0.001 for both

Patient-reported outcomes

LS mean difference in baseline AQLQ +12 scores
• FF/VI 184/22 mcg OD vs FF 200 mcg OD: 0.05; p=0.587
• FF/VI 184/22 mcg OD vs FP 500 mcg BD: 0.03; p=0.786

LS mean change from baseline in ACT score at Week 24
• FF/VI 184/22 mcg OD vs FF 200 mcg OD: 5.5 vs 5.2; difference = 0.3 (95% CI −0.5, 1.1)
• FF/VI 184/22 mcg OD vs FP 500 mcg BD: 5.5 vs 4.7; difference = 0.7 (95% CI −0.1, 1.5)

More information about patient factors associated with Relvar Ellipta, including the results of patient-reported outcome studies, is provided in the Patient Factors & Ellipta Device section

Safety

Any AEs on-treatment, % / Treatment-related AEs, %
• FF/VI 184/22 mcg OD: 47% / 9%
• FF 200 mcg OD: 46% / 4%
• FP 500 mcg BD: 50% / 8%

Frequency of on-treatment AEs >5%
• FF/VI 184/22 mcg OD: nasopharyngitis (13%), headache (6%)
• FF 200 mcg OD: nasopharyngitis (14%), headache (7%)
• FP 500 mcg BD: nasopharyngitis (20%), headache (8%), cough (7%)

Other clinically relevant safety findings
• No clinically relevant effects on haematology, clinical chemistry, liver function, vital signs, 24h urinary cortisol excretion, or ECG parameters were observed

Number of asthma exacerbations
• 8 (6 with FF 200 mcg OD; 2 with FP 500 mcg BD)
• 1 subject (FF 200 mcg OD) was hospitalised

More information about the safety of Relvar Ellipta from studies with primary endpoints as safety outcomes is provided in the summary of Safety studies

ACT = asthma control test; AE = adverse event; AQLQ+12 = Asthma Quality of Life Questionnaire; BD = twice daily; CI = confidence interval; ECG = electrocardiogram; FEV1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate; FP/SAL = fluticasone propionate/salmeterol; ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; LS = least squares; OD = once daily; PEF = peak expiratory flow; VI = vilanterol; wm = weighted mean

Bleecker et al., 2014
For more detailed information about this study, please see the Relvar Asthma Evidence Dossier. You can also request further information by contacting ukmedinfo@gsk.com.

Citation
Bleecker et al., Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014;2: 553–61

Study objective
To compare the efficacy and safety of fluticasone furoate/vilanterol (FF/VI) and fluticasone furoate (FF) in patients (≥12 years old) with persistent asthma

Please note that fluticasone furoate (FF) is not licensed as a monotherapy for the treatment of asthma in the UK.
## Inclusion criteria:  
- ≥12 years with a diagnosis of asthma  
- Reversibility after 2 to 4 inhalations of salbutamol of ≥12% and ≥200 mL  
- Prebronchodilator FEV₁ of 40–90% of the predicted normal value at screening  
- Receiving a stable dose of a low-to-medium-dose ICS (FP 100–250 mcg BD, or the equivalent), or a low-dose ICS/LABA (FP/SAL 100/50 mcg BD, or the equivalent) for 4 weeks before screening

### Design
Phase III, multicentre, randomised, double blind placebo-controlled, parallel-group study

### Treatments
4-week run-in period; 12-week treatment period; 2-week follow-up period:
- Placebo OD (n=203)
- FF 100 mcg OD (n=205)
- FF/VI 92/22 mcg OD (n=201)

### Baseline characteristics

<table>
<thead>
<tr>
<th>Placebo OD</th>
<th>FF 100 mcg OD</th>
<th>FF/VI 92/22 mcg OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>38.1</td>
<td>40.4</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>111 (55)</td>
<td>126 (61)</td>
</tr>
<tr>
<td>Mean FEV₁, % predicted normal</td>
<td>70.2</td>
<td>70.5</td>
</tr>
</tbody>
</table>

### Co-primary endpoint results
Change from baseline in trough FEV₁ at Week 12:
- FF/VI 92/22 mcg OD vs placebo: 172 mL; p<0.001
- FF 100 mcg OD vs placebo: 136 mL; p=0.002
- FF/VI 92/22 OD mcg vs FF 100 mcg OD: 36 mL; p=0.405

Change from baseline in wFEV₁ (0–24h) at Week 12:
- FF/VI 92/22 mcg OD vs placebo: 302 mL; p<0.001
- FF 100 mcg OD vs placebo: 186 mL; p=0.003
- FF/VI 92/22 mcg OD vs FF 100 mcg OD: 116 mL; p=0.060

### Secondary and other efficacy endpoint results
All secondary endpoints are descriptive as the primary superiority endpoint was not met

Change from baseline in the percentage of rescue-free 24h periods:
- FF/VI 92/22 mcg OD vs placebo: 19.3 (95% CI 13.0, 25.6)
- FF 100 mcg OD vs placebo: 8.7 (95% CI 2.4, 15.0)
- FF/VI 92/22 mcg OD vs FF 100 mcg OD: 10.6 (95% CI 4.3, 16.8)

Change from baseline in the percentage of symptom-free 24h periods:
- FF/VI 92/22 mcg OD vs placebo: 18.0 (95% CI 12.0, 23.9)
- FF 100 mcg OD vs placebo: 5.8 (95% CI –0.1, 11.8)
- FF/VI 92/22 mcg OD vs FF 100 mcg OD: 12.1 (95% CI 6.2, 18.1)

Withdrawals due to lack of efficacy:
- FF/VI 92/22 mcg OD vs placebo: 7 vs 32
- FF 100 mcg OD vs placebo: 6 vs 32
- FF/VI 92/22 mcg OD vs FF 100 mcg OD: 7 vs 6

LS mean change from baseline to Week 12 in daily trough AM and PM PEF:
- Difference FF/VI 92/22 mcg OD vs placebo: AM PEF = 33.3 L/min (95% CI 26.5, 40); PM PEF = 28.2 L/min (95% CI 21.7, 34.8)
- Difference FF/VI 92/22 mcg OD vs FF 100 mcg OD: AM PEF = 14.6 L/min (95% CI 7.9, 21.3); PM PEF = 12.3 L/min (95% CI 5.8, 18.8)

Please note that fluticasone furoate (FF) is not licensed as a monotherapy for the treatment of asthma in the UK.

Date of preparation: February 2019
### Patient-reported outcomes

Change from baseline in total AQLQ+12\(^{15}\)
- FF/VI 92/22 mcg OD vs placebo: 0.30 (95% CI 0.13, 0.46)
- FF 100 mcg OD vs placebo: 0.15 (95% CI –0.01, 0.31)
- FF/VI 92/22 mcg OD vs FF 100 mcg OD: 0.15 (95% CI –0.01, 0.30)

LS mean change from baseline to Week 12 in ACT Score\(^{15}\)
- FF/VI 92/22 mcg OD vs placebo: 4.4 vs 2.5; difference = 1.9 (95% CI 1.2, 2.6)
- FF/VI 92/22 mcg OD and FF 100 mcg OD: 4.4 vs 3.8; difference = 0.6 (95% CI 0.0, 1.3)

More information about patient factors associated with Relvar Ellipta, including the results of patient-reported outcome studies, is provided in the Patient Factors & Ellipta Device section

### Safety

Any AEs on-treatment, % / Treatment-related AEs, %\(^{15}\)
- Placebo: 21% / 1%
- FF 100 mcg OD: 25% / 5%
- FF/VI 92/22 mcg OD: 29% / 7%
- SAEs occurred in <1% of subjects (none treatment-related)

Frequency of on-treatment AEs ≥3%\(^{15}\)
- AEs occurring in ≥3% in any group included nasopharyngitis (7–10%) and headache (4–5%)

Other clinically relevant safety findings\(^{15}\)
- No clinically significant differences among groups were observed in vital signs or ECG, or from clinical chemistry or haematologic assessments

Oral candidiasis\(^{15}\)
- 9 patients (FF 100 mcg OD: 4[2%]; FF/VI 92/22 mcg OD: 5[2%]; placebo: 0)

Number of severe asthma exacerbations\(^{15}\)
- 14 (placebo: 9[4%]; FF 100 mcg OD: 4[2%]; FF/VI 92/22 mcg OD: 1[<1%])
- No hospitalisations due to asthma exacerbations

More information about the safety of Relvar Ellipta from studies with primary endpoints as safety outcomes is provided in the summary of Safety Studies section

ACT = asthma control test; AE = adverse event; AQLQ+12 = Asthma Quality of Life Questionnaire; BD = twice daily; CI = confidence interval; ECG = electrocardiogram; FEV\(_1\) = forced expiratory volume in 1 second; FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate; FP/SAL = fluticasone propionate/salmeterol; ICS = inhaled corticosteroid; LABA = long-acting β\(_2\) agonist; LS = least squares; OD = once daily; PEF = peak expiratory flow; SAE = serious adverse event; VI = vilanterol; wm = weighted mean

### Bernstein et al., 2015

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier. You can also request further information by contacting ukmedinfo@gsk.com.

### Citation

Bernstein et al., Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. J Asthma. 2015;52:1073–83\(^{16}\)

### Study objective

To examine the efficacy and safety of once-daily fluticasone furoate/vilanterol (FF/VI) 92/22 mcg OD versus fluticasone furoate (FF) 100 mcg OD, over 12 weeks, in patients ≥12 years of age with moderate-to-severe persistent asthma\(^{16}\)
### Patient population

Inclusion criteria:
- ≥12 years with moderate-to-severe asthma
- Treated with an ICS±LABA for ≥12 weeks; a dose that was equivalent to twice-daily fluticasone propionate (FP) >250 mcg or FP/SAL 250/50 mcg BD that was stable for ≥4 weeks
- Pre-bronchodilator FEV₁: 40–80% of predicted normal
- FEV₁ reversibility of ≥12% and ≥200 mL following salbutamol at randomisation

### Design

Phase III, multicentre, randomised, double-blind, parallel-group study

### Treatments

4-week run-in period; 12-week treatment period:
- FF/VI 92/22 mcg OD (n=346)
- FF 100 mcg OD (n=347)
- FF/VI 184/22 mcg OD (n=346)

### Baseline characteristics

<table>
<thead>
<tr>
<th>FF/VI 92/22 mcg OD</th>
<th>FF/VI 184/22 mcg OD</th>
<th>FF 100 mcg OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>45.9</td>
<td>46.6</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>205 (59)</td>
<td>224 (65)</td>
</tr>
<tr>
<td>Mean FEV₁, % predicted normal</td>
<td>62.6</td>
<td>62.1</td>
</tr>
</tbody>
</table>

### Primary endpoint results†

LS mean difference in wmo–24h serial FEV₁ at Week 12:
- FF/VI 92/22 mcg OD vs FF 100 mcg OD: 108 mL; p<0.001
- FF/VI 92/22 mcg OD vs FF/VI 184/22 mcg OD: 24 mL (95% CI –0.037, 0.086)

### Secondary and other efficacy endpoint results†

#### LS mean change from baseline to Week 12 in daily AM and PM PEF:
- FF/VI 92/22 mcg OD vs FF 100 mcg OD: AM PEF = 25.2 L/min; PM PEF = 24.2 L/min; p<0.001 for both comparisons
- FF/VI 92/22 mcg OD vs FF/VI 184/22 mcg OD: AM PEF = 3.4 L/min (95% CI –2.8, 9.7); PM PEF = 2.0 (95% CI –4.2, 8.2)
### Patient-reported outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>FF/VI 92/22 mcg OD vs FF 100 mcg OD</th>
<th>FF/VI 92/22 mcg OD vs FF/VI 184/22 mcg OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS mean change from baseline to Week 12 in 12h post-bronchodilator FEV₁&lt;sub&gt;16&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of withdrawals due to lack of efficacy during the 12-week period, n (%)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

More information about patient factors associated with Relvar Ellipta, including the results of patient-reported outcome studies, is provided in the Patient Factors & Ellipta Device section.

### Safety

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>FF 100 mcg OD</th>
<th>FF/VI 92/22 mcg OD</th>
<th>FF/VI 184/22 mcg OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs on-treatment, % / Treatment-related, %&lt;sup&gt;16&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Most frequent AEs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Number of patients experiencing severe asthma exacerbations&lt;sup&gt;16&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Number of patients with treatment-related oropharyngeal candidiasis&lt;sup&gt;16&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Other clinically relevant safety findings<sup>16</sup>:
- No clinically relevant effects on clinical chemistry, haematology or vital signs

More information about the safety of Relvar Ellipta from studies with primary endpoints as safety outcomes is provided in the summary of Safety studies.  

† The study was not powered to compare FF/VI 92/22 mcg OD with FF/VI 184/22 mcg OD

ACT = asthma control test; AE = adverse event; AQLQ+12 = Asthma Quality of Life Questionnaire; BD = twice daily; FEV₁ = forced expiratory volume in 1 second; FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate; FP/SAL = fluticasone propionate/salmeterol; ICS = inhaled corticosteroid; LABA = long-acting β₂ agonist; LS = least squares; NA = not available; OD = once daily; PEF = peak expiratory flow; wm = weighted mean

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16 UK/FFT/0030/17(7)

Date of preparation: February 2019
Woodcock et al., 2013

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or [click here](#) to download the publication via PubMed online.

| Citation | Woodcock et al., Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest* 2013;144:1222–1229
 |
| Study objective | To compare the efficacy of fluticasone furoate/vilanterol (FF/VI) 92/22 mcg OD with fluticasone propionate/salmeterol (FP/SAL) 250/50 mcg BD over a 24-week treatment period in patients aged ≥12 years with persistent asthma uncontrolled on medium-dose of ICS
 |
| Patient population | Inclusion criteria:
  - ≥12 years of age with asthma
  - Prior to screening taking an ICS for ≥12 weeks with a stable medium dose of FP 250 mcg BD or equivalent for ≥4 weeks
  - ≥12% and ≥200 mL reversibility of FEV₁ following salbutamol inhalation at screening
  - Best evening FEV₁ 40–85% of predicted normal value at screening and at randomisation
 |
| Design | Phase III, multicentre, randomised, double-blind, double-dummy, parallel-group study
 |
| Treatments | 4-week run-in period; 24-week treatment period:
  - FF/VI 92/22 mcg OD (n=403)
  - FP/SAL 250/50 mcg BD (n=403)
 |
| Baseline characteristics | FF/VI 92/22 mcg OD<sup>14</sup> | FP/SAL 250/50 mcg BD<sup>14</sup>
---|---|---
Mean age, years | 43.8 | 41.9
Female sex, n (%) | 244 (61) | 245 (61)
Mean FEV₁ % predicted normal | 68.0 | 68.8

| Primary endpoint results | LS mean difference in wm24h serial FEV₁ at Week 24<sup>14</sup>
---|---
- FF/VI 92/22 mcg OD vs FP/SAL 250/50 mcg BD: −0.037L; p=0.162 (superiority not met)

All secondary endpoints are descriptive as the primary superiority endpoint was not met

Sustained 24h duration of action for both FF/VI 92/22 mcg OD and FP/SAL 250/50 mcg BD at all time points<sup>14</sup>

Difference in median time to onset of bronchodilator effect<sup>14</sup>
- FF/VI 92/22 mcg OD vs FP/SAL 250/50 mcg BD: HR 0.948 (95% CI 0.797, 1.128)

LS mean difference in wm0–4h serial FEV₁ at Week 24<sup>14</sup>
- FF/VI 92/22 mcg OD vs FP/SAL 250/50 mcg BD: 34 mL (95% CI −86, 17)

Percentage of subjects obtaining ≥12% and ≥200 mL increases from baseline in FEV₁ 12 and 24h postdose at Week 24<sup>14</sup>
- FF/VI 92/22 mcg OD vs FP/SAL 250/50 mcg BD: OR 1.31 (95% CI 0.96, 1.78) at 12h postdose; OR 1.09 (95% CI 0.80, 1.48) at 24h postdose

LS mean difference in clinic visit trough FEV₁ at Week 24<sup>14</sup>
### Patient-reported outcomes

- **LS mean difference from baseline in AQLQ+12 at Week 24**
  - FF/VI 92/22 mcg OD vs FP/SAL 250/50 mcg BD: difference = 0.09 (95% CI –0.03, 0.21)

- **LS mean difference from baseline in ACT at Week 24**
  - FF/VI 92/22 mcg OD vs FP/SAL 250/50 mcg BD: difference = 0.2 (95% CI –0.2, 0.7)

- **LS mean difference from baseline in EQ-5D VAS score at Week 24**
  - FF/VI 92/22 mcg OD vs FP/SAL 250/50 mcg BD: difference = 1.4 (95% CI –0.3, 3.0)

**More information about patient factors associated with Relvar Ellipta, including the results of patient-reported outcome studies, is provided in the Patient Factors & Ellipta Device section**

### Safety

- **Any AEs on-treatment, % / treatment-related AEs, %**
  - FF/VI 92/22 mcg OD: 53% / 5%
  - FP/SAL 250/50 mcg BD: 49% / 4%
  - AEs >5% with FF/VI 92/22 mcg OD: nasopharyngitis (11%), headache (8%), URTI (6%)
  - AEs >5% with FP/SAL 250/50 mcg BD: nasopharyngitis (11%), headache (10%), URTI (4%)

- **Other clinically relevant safety findings**
  - No clinically relevant findings on haematology, clinical chemistry, vital signs, 24h urinary cortisol excretion, or ECG were observed

- **Subjects reporting asthma exacerbations**
  - FF/VI 92/22 mcg OD: 3%; FP/SAL 250/50 mcg BD: 2%
  - 3 subjects (FF/VI 92/22 mcg OD: 1; FP/SAL 250/50 mcg BD: 2) were hospitalised due to exacerbation but none were considered related to treatment

**More information about the safety of Relvar Ellipta from studies with primary endpoints as safety outcomes is provided in the summary of Safety studies**

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**Bateman et al., 2014**

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or click here to download the publication via PubMed online.

**Citation**


**Study objective**

To evaluate the effect of the addition of vilanterol (VI) to fluticasone furoate (FF) OD on the risk of severe asthma exacerbations in patients with uncontrolled asthma.

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Please note that fluticasone furoate (FF) is not licensed as a monotherapy for the treatment of asthma in the UK.
### Patient population
Inclusion criteria: 18
- ≥12 years with a history of asthma for ≥1 year
- Pre-bronchodilator FEV₁ 50–90% predicted normal
- FEV₁ reversibility of ≥12% and ≥200 mL following salbutamol at randomisation
- FF ≥200 mcg/day (or equivalent) or FP/SAL 200/100–500/100 mcg (or equivalent) for ≥12 weeks prior to screening
- ≥1 asthma exacerbation requiring systemic corticosteroids and/or hospital or emergency room visit in the previous year

### Design
Phase III, multicentre, randomised, double-blind, parallel-group 18

### Treatments
2-week run-in period; ≥24-78 week treatment period: 18
- FF 100 mcg OD (n=1,010)
- FF/VI 92/22 mcg OD (n=1,009)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>FF 100 mcg OD 18</th>
<th>FF/VI 92/22 mcg OD 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>42.3</td>
<td>41.1</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>689 (68)</td>
<td>661 (66)</td>
</tr>
<tr>
<td>Mean FEV₁ % predicted normal</td>
<td>69.0</td>
<td>68.8</td>
</tr>
<tr>
<td>Number of exacerbations in last 12 months, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>599 (59)</td>
<td>553 (55)</td>
</tr>
<tr>
<td>2</td>
<td>229 (23)</td>
<td>252 (25)</td>
</tr>
<tr>
<td>3</td>
<td>100 (10)</td>
<td>101 (10)</td>
</tr>
<tr>
<td>4</td>
<td>37 (4)</td>
<td>57 (6)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>44 (4)</td>
<td>46 (5)</td>
</tr>
</tbody>
</table>

### Primary endpoint results
Time to first severe asthma exacerbation* (ITT Population) 18
- Probability of ≥1 severe asthma exacerbations by 52 weeks
  - FF 100 mcg OD: 15.9% (95% CI 13.5, 18.2)
  - FF/VI 92/22 mcg OD: 12.8% (95% CI 107, 14.9)
  - FF/VI 92/22 mcg OD vs FF 100 mcg OD hazard ratio: 0.795 (95% CI 0.642, 0.985); p=0.036

### Secondary and other efficacy endpoint results
Rate of severe asthma exacerbations per subject per year (ITT Population) 18
- FF 100 mcg OD: 0.19/year
- FF/VI 92/22 mcg OD: 0.14/year
- 25% (95% CI 5, 40) reduction for FF/VI 92/22 mcg OD vs FF 100 mcg OD; p=0.014

Number of patients experiencing ≥1 on-treatment severe exacerbation 18
- FF 100 mcg OD: 186 (18%)
- FF/VI 92/22 mcg OD: 154 (15%)

Significantly greater improvements in trough FEV₁ (89–95 mL; p<0.001) were observed with FF/VI 92/22 mcg OD than with FF 100 mcg OD at weeks 12, 36, 52 and at endpoint 18

### Patient-reported outcomes
Significantly greater improvements in the ACQ7 score were observed in patients receiving FF/VI 92/22 mcg OD compared with FF 100 mcg OD at all time points (p<0.001; Week 12, Week 36 and endpoint) 18

* A severe asthma exacerbation was defined using the ERS/ATS Task Force recommendation as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days, or inpatient hospitalisation, or emergency department visit due to asthma requiring systemic corticosteroids

**UK/FFT/0030/17(7)**

Date of preparation: February 2019
ORs for well controlled asthma (ACQ7 ≥0.75) for FF/VI versus FF
• Week 12: 1.49; 95% CI 1.20, 1.84 (p<0.001)
• Week 36: 1.49; 95% CI 1.21, 1.83 (p<0.001)
• Endpoint: 1.50; 95% CI 1.23, 1.82 (p<0.001)

At endpoint, more patients in the FF/VI 92/22 mcg group than the FF 100 mcg OD group were well controlled (44% vs 36%)18

More information about patient factors associated with Relvar Ellipta, including the results of patient-reported outcome studies, is provided in the Patient Factors & Ellipta Device section

Safety

Any AEs on-treatment, % / treatment-related AEs, % 18
• FF 100 mcg OD: 65% / 7%
• FF/VI 92/22 mcg OD: 63% / 7%

Most frequent AEs18
• Headache (FF 100 mcg OD 18%; FF/VI 92/22 mcg OD 19%)
• Nasopharyngitis (FF 100 mcg OD 13%; FF/VI 92/22 mcg OD 15%)

Number of subjects with hospitalisations/Emergency department or urgent care clinic visits / unscheduled healthcare provider visits18
• FF 100 mcg OD: 9 / 26 / 142 subjects
• FF/VI 92/22 mcg OD: 8 / 22 / 119 subjects
• No subjects were intubated

Other clinically relevant safety findings18
• No clinically relevant effects noted on vital signs or liver function parameters

More information about the safety of Relvar Ellipta from studies with primary endpoints as safety outcomes is provided in the summary of Safety studies

Woodcock et al., 2017

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or click here to download the publication via pubmed online

Citation

Woodcock et al., Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial (Salford Lung Study in Asthma). Lancet. 2017 Nov 18;390(10109):2247-2255 19

Study objective

The objective of this study was to compare the effectiveness and safety profile of initiating treatment with FF/VI with usual asthma maintenance therapy over a 52 week period19

Patient population

• Patients recruited were 18 years or older and had a documented diagnosis of symptomatic asthma made by a general practitioner19
• Patients had to be taking regular maintenance inhaler therapy with inhaled corticosteroids (ICS) alone or in combination with a long-acting β-agonist (LABA)19
• Exclusion criteria were minimal, such as a recent history of life-threatening asthma, a history of COPD, or concomitant life-threatening disease19

Design

• This study was a prospective, 12-month, open-label, parallel group, randomised trial done at 74 general practice clinics in Salford and South Manchester, UK19

ACQ = asthma control questionnaire; AE = adverse event; CI = confidence interval; ED = emergency department; FEV1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; FP/SAL = fluticasone propionate/salmeterol; ITT = intention to treat; OD = once daily
A total of 4,233 patients were recruited and randomised to receive either:
- FF/VI 92/22 mcg or FF/VI 184/22 mcg
- Or usual care (ICS or ICS/LABA combinations)

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Usual Care (n=2219)</th>
<th>FF/VI (n=2114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 (17)</td>
<td>50 (16)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1241 (59%)</td>
<td>1257 (59%)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>429 (20%)</td>
<td>420 (20%)</td>
</tr>
<tr>
<td>Asthma control test score at baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>605 (29%)</td>
<td>601 (28%)</td>
</tr>
<tr>
<td>16-19</td>
<td>653 (31%)</td>
<td>655 (31%)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>861 (41%)</td>
<td>857 (41%)</td>
</tr>
<tr>
<td>Duration of asthma ≥5 years</td>
<td>1844 (87%)</td>
<td>1819 (86%)</td>
</tr>
<tr>
<td>Daytime symptoms &gt; 2 per week</td>
<td>1926 (91%)</td>
<td>1904 (90%)</td>
</tr>
<tr>
<td>Nocturnal symptoms in last week</td>
<td>1053 (50%)</td>
<td>1064 (50%)</td>
</tr>
<tr>
<td>Number of exacerbations 12 months prior to randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1314 (62%)</td>
<td>1378 (65%)</td>
</tr>
<tr>
<td>1</td>
<td>501 (24%)</td>
<td>472 (22%)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>304 (14%)</td>
<td>264 (12%)</td>
</tr>
<tr>
<td>Co-morbidities (any)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>812 (38%)</td>
<td>813 (38%)</td>
</tr>
<tr>
<td>Vascular diabetes</td>
<td>164 (8%)</td>
<td>182 (9%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>559 (26%)</td>
<td>540 (26%)</td>
</tr>
<tr>
<td></td>
<td>201 (9%)</td>
<td>205 (10%)</td>
</tr>
</tbody>
</table>

### Primary endpoint results

- Percentage of patients at week 24 with either an ACT score of ≥20 or an increase in the ACT score from baseline of ≥3.
  - In the PEA population, a significantly higher percentage of patients with uncontrolled asthma and initiated on treatment with FF/VI achieved better control of their asthma (71%) compared with patients continuing usual care treatment (56%) (odds ratio 2.0, CI 1.70, 2.34; p<0.0001)

- Percentage of patients at week 24 with either an ACT score of ≥20 or an increase in the ACT score from baseline of ≥3 in the ICS/LABA subgroup (pre-specified subanalysis)
  - In patients for whom the general practitioner had found an ICS/LABA combination to be indicated for usual therapy, the odds of being a responder were also higher for those in the fluticasone furoate and vilanterol group than for those in the usual care group at week 24 (637 [70%] responders and 271 [30%] non-responders vs 511 [56%] responders and 405 [44%] non-responders; OR 1.95 [95% CI 1.60–2.38])

* The primary effectiveness analysis population is defined as all ITT subjects who have an ACT total score of < 20 at baseline (Randomisation Visit)

### Secondary and other efficacy endpoints results

- Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) total score at Week 52
  - The proportion of patients who were responders based on AQLQ total score was significantly higher in the fluticasone furoate and vilanterol group than in the

Please note that fluticasone furoate (FF) is not licensed as a monotherapy for the treatment of asthma in the UK.
usual care group at week 52 (increase from baseline of ≥0.5; OR 1.79 [95% CI 1.55–2.06], p<0.0001)\textsuperscript{19}

Work Productivity and Activity Impairment Questionnaire at week 52
- Patients initiated with fluticasone furoate and vilanterol reported a greater decrease in work impairment due to asthma on WPAI than did those continuing with usual care (−6.7% vs −4.0%; difference −2.8% [95% CI −4.4 to −1.1], p<0.0001) and a greater decrease in activity impairment due to asthma (−10.4% vs −5.9%; difference −4.5% [−5.9 to −3.2], p<0.0001)\textsuperscript{19}

All asthma-related primary and secondary care contacts
- There was no difference in the annual rate of asthma-related contacts with primary care in the total population. The annual rate of all primary care contacts in the group initiating fluticasone furoate and vilanterol versus the usual care group increased (9.7% increase [95% CI 4.6–15.0%]); there was no difference in the annual rate of all secondary health-care contacts between the two groups (1.0% decrease [−8.2 to 9.5])\textsuperscript{19}

Number of salbutamol inhalers dispensed
- The number of salbutamol inhalers prescribed was lower in the group initiated with fluticasone furoate and vilanterol than in the usual care group (7.2 vs 8.0; difference −0.8 [95% CI −1.1 to −0.5], p<0.0001)\textsuperscript{19}

Safety
- No difference was seen in the incidence of SAE’s in the ITT population between the two treatment arms (FF/VI & usual care)\textsuperscript{19}
- The incidence of pneumonia in the ITT population was low in both study arms (FF/VI 1%, usual care, <1%), however non-inferiority of FF/VI to usual care was not confirmed (23 vs 16; incidence ratio 1.4; 95% CI 0.8–2.7)\textsuperscript{19}
- In addition a second on treatment pre-specified assessment was performed, which was based upon the treatment patients were exposed to at the time of the event. This was because the study design allowed patient treatment to be modified throughout the study\textsuperscript{19}
- When the 42 events were summarised according to actual treatment patients were on at the time of the event, 21 events were recorded for FF/VI and 21 events for usual care\textsuperscript{19}

Bernstein et al., 2017
For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or click here to download the publication via pubmed online.

Citation

Study objective
The overall aim of this study was to demonstrate non-inferiority of FF/VI 100/25 mcg OD to FP/SAL 250/50 mcg BD with regards to lung function in subjects with persistent bronchial asthma adequately controlled on twice daily ICS/LABA.

Patient population
- Male and female subjects ≥12 years
- Clinical history of asthma for at least 12 weeks prior to entry into study.
- FEV\textsubscript{1} ≥80% of the predicted normal value.
- Receiving mid-dose ICS/LABA (equivalent to FP/SAL 250/50 mcg BD)
- Asthma well controlled determined by physician
- No recent severe exacerbations requiring OCS within ≥12 weeks or hospitalisation within ≥6 months
### Design

This was a 24-week, multicenter, randomized, Phase IIIa, double-blind, double-dummy, parallel-group study.\(^{38}\)

### Treatments

Subjects with well-controlled asthma* at the end of the 4-week run-in period were randomised to the following treatments for 24 weeks:

- **FF/VI 100/25 mcg OD** (n= 504)
- **FP/SAL 250/50 mcg BD** (n= 501)
- **FP 250 mcg BD** (n= 499)

*Well-controlled asthma was defined as reversibility of ≥150 mL increase in FEV1 (following a LABA washout period); daytime asthma symptoms and rescue use on ≤2 days each week and no night-time awakenings due to asthma during the last 14 consecutive days of the run-in period.

### Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FF/VI 92/22 OD (n=504)</th>
<th>FP/SAL 250/50 BD (n=501)</th>
<th>FP 250 BD (n=499)</th>
<th>Total (n=1504)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>44.4 (16.30)</td>
<td>43.0 (15.20)</td>
<td>43.0 (16.58)</td>
<td>43.5 (16.04)</td>
</tr>
<tr>
<td>Range</td>
<td>11-78</td>
<td>11-80</td>
<td>12-79</td>
<td>11-80</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>190 (38)</td>
<td>165 (33)</td>
<td>185 (77)</td>
<td>540 (36)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>416 (83)</td>
<td>408 (81)</td>
<td>412 (83)</td>
<td>1236 (82)</td>
</tr>
<tr>
<td>Black or African Asian</td>
<td>12 (2)</td>
<td>14 (3)</td>
<td>17 (3)</td>
<td>43 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>66 (13)</td>
<td>68 (14)</td>
<td>65 (13)</td>
<td>199 (13)</td>
</tr>
<tr>
<td><strong>Duration of asthma Years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.9 (12.61)</td>
<td>14.6 (12.16)</td>
<td>15.06 (12.13)</td>
<td>14.88 (12.30)</td>
</tr>
<tr>
<td>Range</td>
<td>0.3-65.0</td>
<td>0.3-66.0</td>
<td>0.4-65.0</td>
<td>0.3-66.0</td>
</tr>
<tr>
<td><strong>Pre-dose FEV(_1) L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.808 (0.7591)</td>
<td>2.806 (0.7522)</td>
<td>2.867 (0.8096)</td>
<td>2.827 (0.7738)</td>
</tr>
<tr>
<td>Range</td>
<td>0.97-5.24</td>
<td>1.07-5.16</td>
<td>1.17-5.73</td>
<td>0.97-5.73</td>
</tr>
<tr>
<td><strong>Percent predicted FEV(_1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>90.26 (12.544)</td>
<td>89.99 (12.620)</td>
<td>90.47 (12.509)</td>
<td>90.24 (12.551)</td>
</tr>
<tr>
<td>Range</td>
<td>40.9-138.7</td>
<td>56.9-129.4</td>
<td>52.4-132.0</td>
<td>40.9-138.7</td>
</tr>
</tbody>
</table>

### Primary endpoint results

- The study met its primary endpoint, demonstrating non-inferiority of FF/VI to FP/SAL for evening trough FEV\(_1\) at Week 24 (treatment differences of 19 mL [95% CI - 11 to 49] in the ITT population and 6 mL [95% CI -27 to 40] in the PP population, with the lower bounds of the 95% CI surpassing the pre-defined non-inferiority margin of -100 mL)
- In the ITT population, the least squares (LS) mean improvement in evening trough FEV\(_1\) at Week 24 was significantly greater for FF/VI than with FP (123 mL, p< 0.001) and for FP/SAL than with FP (104 mL, p < 0.001)\(^{38}\). Assay sensitivity was therefore demonstrated.

### Safety

- Rates of on-treatment AEs were comparable across treatment arms the most common on-treatment AEs were nasopharyngitis (12% in the FF/VI 100/25 mcg
group, 13% in the FP/SAL 250/50 mcg group, and 11% in the FP 250 mcg group) and headache (8% in the FF/VI 100/25 mcg and FP 250 mcg groups and 7% in the FP/SAL 250/50 mcg group).

- Rates of drug related AEs were 3% for FF/VI, 3% for FP/SAL and 2% for FP.

Dose-ranging information

The clinical development programme for Relvar Ellipta resulted in two marketed doses for the treatment of asthma: 92/22 mcg and 184/22 mcg. The FF doses contained with the two licensed doses resulted from Phase II dose-ranging studies of FF that investigated the efficacy and safety/tolerability of a range of FF doses (Table 1). Please note that FF is not licensed as a monotherapy for the treatment of asthma in the UK.

Table 1: Dose-ranging studies

<table>
<thead>
<tr>
<th>Study publication</th>
<th>Study objective and primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman et al., Dose effect of once-daily fluticasone</td>
<td>• This 8-week dose ranging study compared 4 exploratory \n</td>
</tr>
<tr>
<td></td>
<td>• The primary endpoint was mean change from baseline in pre- \n</td>
</tr>
<tr>
<td>Bleecker et al., Once-daily fluticasone furoate is</td>
<td>• This 8-week dose ranging study compared 4 exploratory \n</td>
</tr>
<tr>
<td></td>
<td>• The primary endpoint was mean change from baseline in pre- \n</td>
</tr>
<tr>
<td>Busse et al., Fluticasone furoate demonstrates efficacy</td>
<td>• This 8-week dose ranging study compared 4 exploratory \n</td>
</tr>
<tr>
<td></td>
<td>• The primary endpoint was mean change from baseline in \n</td>
</tr>
</tbody>
</table>

Please see the Relvar Asthma Evidence Dossier for more detailed information about the study design and outcomes of each of the three studies listed here.

BD = twice daily; FEV1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhaled corticosteroid; OD = once daily

As part of the Relvar Ellipta clinical development programme, one aim was to identify doses of FF that would achieve an acceptable level of clinical efficacy, for both lung function and symptomatic parameters, without compromising the safety profile. These doses were identified in three dose-ranging studies in subjects with persistent asthma (including subjects symptomatic on SABA and low to medium doses of ICS) and tested a range of doses of FF (from 25 mcg OD to 800 mcg OD, dosed in the evening) over an 8-week treatment period. The FF doses selected for progression into Phase III studies had to demonstrate a pre-defined 200 mL difference from placebo. This programme resulted in two doses (rather than the traditional three doses of ICS/LABAs) of Relvar Ellipta being approved for the treatment of asthma: FF/VI 92/22 mcg and FF/VI 184/22 mcg, one inhalation once daily. These two dosing regimens were deemed to be the most efficacious in terms of lung function improvement.

Please note that fluticasone furoate (FF) is not licensed as a monotherapy for the treatment of asthma in the UK.
Safety study summaries

Please consult the full Summary of Product Characteristics (SPC) for Relvar before prescribing.

Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with FF/VI. In the asthma clinical development programme, a total of 7,034 patients were included in an integrated assessment of adverse reactions. In the COPD clinical development programme, a total of 6,237 subjects were included in an integrated assessment of adverse reactions.\(^1,2\)

The most commonly reported adverse reactions with FF and VI were headache and nasopharyngitis. With the exception of pneumonia and fractures (asthma-specific information given in Table 2), the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently commonly observed in patients with COPD.\(^1,2\)

Table 2: Summary of adverse reactions\(^1,2\)

<table>
<thead>
<tr>
<th>Frequency of adverse event</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common adverse reactions (≥1/10)</strong></td>
<td>Headache, nasopharyngitis</td>
</tr>
<tr>
<td><strong>Common adverse reactions (≥1/100 to &lt;1/10)</strong></td>
<td>Pneumonia, upper respiratory tract infection, bronchitis, influenza, candidiasis of mouth and throat, oropharyngeal pain, sinusitis, pharyngitis, rhinitis, cough, dysphonia, abdominal pain, arthralgia, back pain, fractures, muscle spasms, pyrexia</td>
</tr>
<tr>
<td><strong>Other important adverse reactions include</strong></td>
<td>Vision blurred, hyperglycaemia</td>
</tr>
<tr>
<td>Frequency: <strong>Uncommon</strong> (≥1/1,000 to &lt;1/100)</td>
<td>Paradoxical bronchospasm, hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria</td>
</tr>
<tr>
<td>Frequency: <strong>Rare</strong> (≥1/10,000 to &lt;1/1,000)</td>
<td>Please consult the full Summary of Product Characteristics for further information and guidance on discontinuation of treatment and/or appropriate patient referral in the event of disease deterioration, paradoxical bronchospasm, cardiovascular effects, hyperglycaemia, systemic steroid effects, visual disturbance, psychological effects, pneumonia and use in hepatic impairment.</td>
</tr>
</tbody>
</table>

**Considerations**

Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. There is no additional benefit compared with 92/22 mcg and there is a potential increased risk of adverse reactions.
**Busse et al., 2016**

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or [click here](#) to download the publication via the journal website online.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Busse et al., An integrated analysis of fluticasone furoate/vilanterol (FF/VI) versus FF safety data across Phase II and Phase III asthma studies. <em>Pulm Ther</em> 2016;2:91–114</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study objective</strong></td>
<td>To assess the safety risk associated with fluticasone furoate/vilanterol (FF/VI) compared with fluticasone furoate (FF) or placebo <strong>12</strong></td>
</tr>
</tbody>
</table>
| **Patient population**    | Inclusion criteria:**12**  
  - ≥12 years of age with a diagnosis of persistent asthma  
  - Pre-bronchodilator FEV₁ 40–90% of predicted normal  
  - FEV₁ reversibility of ≥12% and ≥200 mL, within 10–40 min, following inhalation of albuterol/salbutamol  |
| **Design**                | Integrated analysis of safety data from 18 randomised, parallel-group, Phase IIb and Phase III studies from the FF/VI GSK asthma clinical study programme **12**                                              |
| **Treatments**            | Across the 18 studies, patients (N=7,229) were randomised to one of six key treatment groups:**12**  
  - FF/VI 184/22 mcg OD (n=956)  
  - FF/VI 92/22 mcg OD (n=2,369)  
  - FF 200 mcg OD (n=608)  
  - FF 100 mcg OD (n=2,010)  
  - VI 25 mcg OD (n=216)  
  - Placebo (n=1,070)                                                                |
| **Baseline characteristics** | Placebo | FF/VI 184/22 mcg OD | FF/VI 92/22 mcg OD | FF 200 mcg OD | FF 100 mcg OD | VI 25 mcg OD |
| Mean age, years (SD)      | 40.1 (16.4) | 44.2 (15.2) | 42.3 (16.6) | 43.3 (15.4) | 42.1 (16.6) | 41.5 (16.2) |
| Female sex, n (%)         | 635 (59) | 583 (61) | 1470 (62) | 378 (62) | 1290 (64) | 129 (60) |
| Duration of asthma, years (SD) | 15.0 (12.6) | 16.8 (13.7) | 16.1 (13.7) | 17.0 (13.3) | 16.2 (13.3) | 18.0 (13.3) |
| **Primary endpoints/results** | AEs | Most frequently experienced AEs were headache, nasopharyngitis, upper respiratory tract infection  
  AEs of special interest:**12**  
  - A greater incidence of local steroid effects was reported with FF-containing treatment groups versus placebo  
  24h urinary cortisol:**12**  
  - At the end of treatment, the 24h urinary cortisol excretion geometric means were numerically similar to baseline between each of the FF groups and placebo and between each of the FF/VI groups and placebo  
  Asthma composite endpoints defined as asthma-related hospitalisations, intubations or death:**12**  
  - No statistically significant difference was observed for all FF/VI doses versus all ICS doses  |
| **Secondary**             | A statistically significant difference between FF/VI and FF treatment groups was reported                                                                                                                 |
**Busse et al., 2013**

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or click here to download the publication via PubMed online.

### Citation

Busse et al., Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β2 agonist vilanterol administered once daily for 52 weeks in patients ≥12 years old with asthma: a randomised trial. Thorax 2013;68(6):513–520

### Study objective

To assess the safety and tolerability of fluticasone furoate/vilanterol (FF/VI) over 52 weeks in patients with asthma

### Patient population

Inclusion criteria:

- ≥12 years of age with a diagnosis of asthma and using ICS
- FEV\(_1\) of ≥50% of predicted normal
- FEV\(_1\) reversibility of ≥12% and ≥200 mL following inhalation of albuterol/salbutamol

### Design

Phase III, randomised, multicentre, double-blind, double-dummy, active comparator, parallel group, 52-week study

### Treatments

2-week run-in period; 52-week treatment period; 1-week follow-up period:

- FF/VI 184/22 mcg OD in the evening (n=202)
- FF/VI 92/22 mcg OD in the evening (n=201)
- FP 500 mcg BD (n=100)

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>FF/VI 184/22 mcg OD(^{13})</th>
<th>FF/VI 92/22 mcg OD(^{13})</th>
<th>FP 500 mcg BD(^{13})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>38.5 (15.6)</td>
<td>39.7 (15.9)</td>
<td>38.6 (16.0)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>124 (61)</td>
<td>130 (65)</td>
<td>62 (62)</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV(_1), mean (SD)</td>
<td>2.3 (0.7)</td>
<td>2.3 (0.7)</td>
<td>2.4 (0.7)</td>
</tr>
<tr>
<td>% predicted FEV(_1), mean (SD)</td>
<td>74.1 (14.1)</td>
<td>74.2 (13.5)</td>
<td>75.2 (12.5)</td>
</tr>
<tr>
<td>Number of exacerbations in previous 12 months, n (%)</td>
<td>140 (69)</td>
<td>139 (69)</td>
<td>74 (74)</td>
</tr>
<tr>
<td>0</td>
<td>41 (20)</td>
<td>43 (21)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>1</td>
<td>21 (10)</td>
<td>19 (9)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>≥2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Primary endpoints/results

- AEs\(^{13}\)
  - On-treatment and treatment-related AEs were similar across groups
- Safety evaluations\(^{13}\)
  - Statistically significant (ps0.006) cortisol suppression was seen with FP compared with FF/VI at Weeks 12 and 28 but not at Week 52
  - No clinically significant differences between groups in laboratory or ophtalmic assessments were reported
  - Pulse rate was significantly increased (ps0.001) in FF/VI groups versus FP group
- Mean heart rate at post-baseline visits were similar to screening (no increase reported). All groups had a slight decrease from screening values at weeks 28 and 52.
- Three patients (1%) on FF/VI 92/22 mcg OD, six (3%) on FF/VI 184/22 mcg OD and three (3%) on FP 500 mcg BD experienced a severe exacerbation during the treatment period. Three patients (one on FF/VI 92/22 mcg OD and two on FP 500 mcg BD) were hospitalised as a result.

**AE = adverse event; BD = twice daily; FEV\textsubscript{1} = forced expiratory volume in 1 second; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate; ICS = inhaled corticosteroid; OD = once daily; SD = standard deviation**

**Allen et al., 2013**

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or [click here](#) to download the publication via PubMed online.

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study objective</td>
<td>To assess the effect of fluticasone furoate/vilanterol (FF/VI) compared with placebo on the HPA axis by evaluating 24-h weighted mean serum cortisol levels in adolescent and adult patients with persistent asthma.¹¹</td>
</tr>
</tbody>
</table>
| Patient population | Inclusion criteria:¹¹  
- 12–65 years of age  
- >12 weeks of history of asthma  
- Best FEV\textsubscript{1} of ≥50% predicted normal value  
- FEV\textsubscript{1} reversibility >12% and 200 mL with inhaled salbutamol  
- No ICS use within 4 weeks of screening |
| Design | Phase III, randomised, multicentre, double-blind, parallel-group, double-dummy, placebo-controlled, 42-day study.¹¹ |
| Treatments | 1–2-week run-in period; 6-week treatment period; 5–7-day follow-up period.¹¹  
- FF/VI 184/22 mcg OD + placebo capsules (n=56)  
- FF/VI 92/22 mcg OD + placebo capsules (n=56)  
- Placebo inhalation + placebo capsules (n=58)  
- Placebo inhalation + prednisolone 10 mg capsules (n=15) |
| Baseline characteristics | | | | |
| | FF/VI 184/22 mcg OD + placebo capsules¹¹ | FF/VI 92/22 mcg OD + placebo capsules¹¹ | Placebo inhalation + placebo capsules¹¹ | Placebo inhalation + prednisolone¹¹ |
| Mean age, years (SD) | 34.0 (13.7) | 34.4 (15.6) | 36.1 (15.4) | 37.5 (14.2) |
| Female sex, n (%) | 23 (41) | 31 (55) | 27 (47) | 6 (40) |
| Pre-bronchodilator FEV\textsubscript{1} (L) mean (SD) | 2.9 (0.8) | 2.9 (0.8) | 2.8 (0.7) | 3.0 (1.0) |
| Pre-bronchodilator % predicted FEV\textsubscript{1}, mean (SD) | 77.5 (13.2) | 79.9 (12.6) | 77.0 (11.9) | 78.6 (13.2) |
| Primary endpoints/results | 0–24 hour weighted mean serum cortisol\(^{11}\)
| --- | --- |
|  | FF/VI 92/22 mcg OD and 184/22 mcg OD showed non-inferiority in effect on serum cortisol concentration compared with placebo after 6 weeks of treatment (0.99, 95% CI 0.87, 1.12; 0.97, 95% CI 0.86, 1.10, respectively)
| Other | FF/VI was well-tolerated, and no safety concerns were identified: no SAE was reported in any period, AEs were reported during treatment period even if none of these was considered treatment-related\(^ {11}\)

AE = adverse event; CI = confidence interval; FEV\(_1\) = forced expiratory volume in 1 second; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate; ICS = inhaled corticosteroid; HPA = hypothalamic-pituitary-adrenal; OD = once daily; SD = standard deviation
Patient Factors & Ellipta Device

- However efficacious an inhaled medication is, if it not delivered optimally, it will not work as effectively.\textsuperscript{23} Improper asthma inhaler device use is associated with poor asthma control, and inhaler handling errors impact the effectiveness of drug delivery.\textsuperscript{24}
- When patients are prescribed an inhaler, the choice should in part be based on how easy an inhaler is to use, and training to minimise errors in the use of the device is essential to achieve the desired drug effect.\textsuperscript{25}
- An assessment of inhaler technique to ensure effectiveness should be routinely undertaken and formally documented at annual review, and also checked by the pharmacist when a new device is dispensed.\textsuperscript{26}

The Ellipta device

The Ellipta device is a multi-dose dry powder inhaler (DPI). The inhaler consists of a light grey body, a yellow mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant packet. The tray is sealed with a peelable foil lid.\textsuperscript{1,2}

The Ellipta inhaler is easy-to-use and fewer patients make critical errors\textsuperscript{‡} after reading the patient information leaflet compared to other commonly used inhalers (the difference was only statistically significant vs Turbohaler \textit{[p<0.001]}).\textsuperscript{27,28}

A total of 95\% of patients used the inhaler correctly after the initial demonstration.\textsuperscript{127}

\textsuperscript{†} A critical error is an error that is most likely to result in no, or minimal, medication being inhaled.\textsuperscript{26}
\textsuperscript{‡} Pooled data from three randomised, double-blind studies in which Relvar Ellipta 92/22 mcg OD or fluticasone furoate 92 mcg OD was delivered via the Ellipta dry powder inhaler (N=989).\textsuperscript{26}
Device study summaries

Van der Palen et al., 2016

For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or click here to download the publication via PubMed online.

Citation
Van der Palen et al., A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of Ellipta with other inhaler devices. NPJ Prim Care Respir Med. 2016;26:16079

Study objective
To compare the Ellipta inhaler with other devices

Patient population
Inclusion criteria:
- Aged ≥18 years with a physician diagnosis of asthma and currently receiving treatment for asthma
- Naïve to Ellipta inhaler use

Design
Multicentre, single-visit, randomised, open-label, cross-over study

Treatments
Patients with asthma (n=162) were assigned to one of three groups:
- Ellipta vs Accuhaler (n=70)
- Ellipta vs MDI (n=32)
- Ellipta vs Turbohaler (n=60)

Baseline characteristics
<table>
<thead>
<tr>
<th></th>
<th>Total (N=162)</th>
<th>Ellipta vs Accuhaler (N=70)</th>
<th>Ellipta vs MDI (N=32)</th>
<th>Ellipta vs Turbohaler (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>46.3 (17.9)</td>
<td>48.6 (17.8)</td>
<td>41.6 (16.4)</td>
<td>46.1 (18.5)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>94 (58)</td>
<td>37 (53)</td>
<td>17 (53)</td>
<td>40 (67)</td>
</tr>
<tr>
<td>Asthma history, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>3 (1)</td>
<td>0</td>
<td>2 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>≥1 to &lt;5 years</td>
<td>32 (20)</td>
<td>11 (16)</td>
<td>6 (19)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>≥5 to &lt;15 years</td>
<td>48 (30)</td>
<td>19 (27)</td>
<td>14 (44)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>≥15 years</td>
<td>79 (49)</td>
<td>40 (57)</td>
<td>10 (32)</td>
<td>29 (48)</td>
</tr>
</tbody>
</table>

Primary endpoints/results
Critical errors using the inhaler, n (%):
- Ellipta vs Accuhaler: 3 (4) vs 9 (13); p=0.221
- Ellipta vs MDI: 2 (6) vs 8 (25); p=0.074
- Ellipta vs Turbohaler: 3 (5) vs 20 (33); p<0.001
Overall errors using the inhaler, n (%):<sup>28</sup>
- Ellipta vs Accuhaler: 15 (21) vs 22 (31); p=0.186
- Ellipta vs MDI: 9 (28) vs 13 (41); p=0.217
- Ellipta vs Turbhaler: 15 (25) vs 28 (47); p=0.022

Percentage of patients requiring instruction from trained respiratory nurse after reading the Patient Information Leaflet (PIL):<sup>28</sup>
- Ellipta vs Accuhaler: 21% vs 31% (p=0.174)
- Ellipta vs MDI: 28% vs 41% (p=0.273)
- Ellipta vs Turbhaler: 25% vs 47% (p=0.004)

Percentage of patients who rated the ease of use of the device as very easy or easy:<sup>28</sup>
- Ellipta vs Accuhaler: 92% vs 71% (p<0.001)
- Ellipta vs MDI: 88% vs 50% (p<0.001)
- Ellipta vs Turbhaler: 97% vs 61% (p<0.001)

Patient preference - the majority of patients preferred Ellipta overall compared with:<sup>28</sup>
- Accuhaler: p<0.001
- MDI: p=0.002
- Turbhaler: p<0.001

Safety
No adverse events were reported throughout the study<sup>28</sup>

COPD = chronic obstructive pulmonary disease; MDI = metered-dose inhaler; SD = standard deviation

Svedsater et al., 2014
For more detailed information about this study, please see the Relvar Asthma Evidence Dossier, or [click here](#) to download the publication via PubMed online.
<table>
<thead>
<tr>
<th>Data were analysed and interpreted descriptively; no statistical inference was planned.</th>
</tr>
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<tbody>
<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td>94% of respondents reported the Ellipta inhaler was very easy or easy to use.</td>
</tr>
<tr>
<td>96% of respondents reported that it was very easy or easy to tell how many does of medication were left in the Ellipta inhaler.</td>
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<tr>
<td>95% of patients used the inhaler correctly after the initial demonstration of correct usage, and did not require additional instruction.</td>
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<tr>
<td>The most common error made at randomisation (before any additional instruction) was to open the cover incorrectly (20 [1.9%] of all patients).</td>
</tr>
<tr>
<td>At Week 2 and Week 4, &gt;99% of patients used the inhaler correctly.</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
</tr>
<tr>
<td>No adverse events were reported throughout the study.</td>
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</tbody>
</table>

DPI = dry powder inhaler; FF/VI = fluticasone furoate/vilanterol; MDI = metered-dose inhaler; SD = standard deviation
Financial & Environmental Implications

Financial Impact

Relvar Ellipta is the only once-daily ICS/LABA licensed for the treatment of asthma delivering 24 hours of continuous efficacy from just one dose, taken once a day, delivered in the Ellipta inhaler. Relvar Ellipta is available in two strengths at a 30-day cost of:29

- £22.00 for Relvar Ellipta 92/22 mcg
- £29.50 for Relvar Ellipta 184/22 mcg

At the most commonly prescribed dose of ICS/LABA (medium dose), the 30-day cost of Relvar is over £7 cheaper than Fostair 100/6 mcg (two doses twice a day) as of 3rd May 2018. This is equivalent to an annual saving of £84 for each clinically appropriate patient, assuming complete adherence over the 12 months.

To access the most current cost comparison chart of all ICS/LABA’s licensed for asthma use the following link for the GSK HCP website (GSKPro.com): Cost of Asthma

The Cost of Asthma chart compares the current 30-day list price of all ICS/LABA inhalers indicated for the treatment of asthma. The graph shows the 30-day acquisition cost of the treatment combinations of ICS/LABA asthma therapies. The therapies are first categorised by ICS strength (low, low/medium, medium and high dose therapies), according to the BTS/SIGN guideline, and then ranked by cost within each strength of dose (from lowest to highest cost). Relvar Ellipta is highlighted in orange.

A GSK Health Outcomes Consultant can demonstrate the affordability and potential cost savings that Relvar can offer your local health economy or health care system. To arrange an appointment with a Health Outcomes Consultant to discuss, please email uk.hoc-on-demand@gsk.com.

An appointment may be arranged to suit your preference - either in person, telephone or digitally on-line.
Environmental Impact

When considering respiratory medicine optimisation, in addition to the clinical, patient and financial impact, it is also important to consider the environmental sustainability of inhalers. GSK and the NHS are bound by the targets set out in the Climate Change Act (2008). A key milestone within the 2008 act is for companies bound by this act, such as GSK and the NHS, to achieve a 25% reduction in their entire CO₂ footprint by 2020.³⁰

Healthcare procurement, which accounts for 61% of the NHS' total carbon footprint, offers several significant opportunities for carbon footprint reduction.³¹ Within healthcare procurement, 35% of emissions are attributed to pharmaceuticals, from which carbon footprint is calculated from aspects such as manufacturing, distribution and use phase.³¹

Each year around 73 million inhalers are prescribed for asthma and COPD in the UK.³² Approximately 70% of these inhalers are pMDIs (pressurised Metered Dose Inhalers) containing greenhouse gases, such as HFA (hydrofluoroalkane) propellants, that are either discharged into the local environment during use by patients or put into household waste.³³ UK emissions of HFA from inhalers are equivalent to 8% of the NHS's entire carbon footprint.³³ Dry Powder Inhalers (DPIs) that do not contain greenhouse gases are available as an alternative to pMDIs and may be equally appropriate.³³⁻³⁵ For example, the Ellipta inhaler (DPI), has a carbon footprint 24 times smaller than Evohaler.³⁶ The British Thoracic Society (BTS) are now advocating change:³⁷

‘Complete elimination of pMDIs may not be possible due to patient preference and the need to generate sufficient inspiratory flow to activate the DPIs. However, BTS encourages all prescribers and patients to consider switching pMDIs to DPIs whenever they are likely to be equally effective.’²⁷

Figure 1: Carbon footprint associated with Evohaler MDI and Ellipta DPI³⁶

GSK have an inhaler recycling and recovery scheme for all respiratory inhalers. By working together with patients, pharmacies and healthcare professionals, we aim to reduce waste and greenhouse gas emissions, moving towards a more environmentally sustainable treatment of respiratory disease.

To find out more about information about how decreasing your reliance on MDIs may help your local health economy to meet their carbon emission reduction target by 2020 contact uk.hoc-on-demand@gsk.com.
References


How to request additional information from GSK

Should you require any further information, please contact the GSK customer contact centre:

- By phone on 0800 221 441. Lines are open from Monday to Friday 8.30am to 5.30pm. Outside these hours and on bank holidays, an answer phone service is available.
- By email at [customercontactuk@gsk.com](mailto:customercontactuk@gsk.com)
Relvar Ellipta (fluticasone furoate/vilanterol) 
Prescribing Information

Please consult the full Summary of Product Characteristics (SmPC) before prescribing.

Relvar Ellipta (fluticasone furoate/vilanterol [as trifenatate]) inhalation powder. Each single inhalation of fluticasone furoate (FF) 100 micrograms (mcg) and vilanterol (VI) 25 mcg provides a delivered dose of 92 mcg FF and 22 mcg VI. Each single inhalation of FF 200 mcg and VI 25 mcg provides a delivered dose of 184 mcg of FF and 22 mcg of VI. Indications: Asthma: Regular treatment of asthma in patients ≥12 years where a long-acting β2-agonist (LABA) and inhaled corticosteroid (ICS) combination is appropriate; i.e. patients not adequately controlled on ICS and “as needed” short-acting inhaled β2-agonists or patients already adequately controlled on both ICS and LABA. COPD: Symptomatic treatment of adults with COPD with a FEV1<70% predicted normal (post-bronchodilator) and an exacerbation history despite regular bronchodilator therapy.

Dosage and administration: Inhalation only. Asthma: Adults and adolescents ≥12 years: one inhalation once daily of Relvar 92/22 mcg for patients who require a low to mid dose of ICS in combination with a LABA. If patients are inadequately controlled then the dose can be increased to one inhalation once daily Relvar 184/22 mcg. Relvar 184/22 mcg can also be considered for patients who require a higher dose of ICS in combination with a LABA. Regularly review patients and reduce dose to lowest that maintains effective symptom control. COPD: one inhalation once daily of Relvar 92/22 mcg. Relvar 184/22 mcg is not indicated for patients with COPD. Contraindications: Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate & magnesium stearate). Precautions: Pulmonary tuberculosis, severe cardiovascular disorders or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia, patients predisposed to low levels of serum potassium, chronic or untreated infections, diabetes mellitus, paradoxical bronchospasms. In patients with moderate to severe hepatic impairment 92/22 mcg dose should be used. Acute symptoms: Not for acute symptoms, use short-acting inhaled bronchodilator. Warn patients to seek medical advice if short-acting inhaled bronchodilator use increases. Therapy should not be abruptly stopped without physician supervision due to risk of symptom recurrence. Asthma-related adverse events and exacerbations may occur during treatment. Patients should continue treatment but seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of Relvar. Systemic effects: Systemic effects of ICSs may occur, particularly at high doses for long periods, but much less likely than with oral corticosteroids. Possible Systemic effects include: Cushing’s syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents. Eye symptoms such as blurred vision may be due to underlying serious conditions such as cataract, glaucoma or central serous choroidopathy (CSCR); consider referral to ophthalmologist. More rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Increased incidence of pneumonia has been observed in patients with COPD receiving inhaled corticosteroids. Risk factors for pneumonia include: current smokers, old age, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m² and patients with a FEV1<50% predicted. If pneumonia occurs with Relvar treatment should be re-evaluated. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Relvar.

Interactions with other medicinal products: Interaction studies have only been performed in adults. Avoid β-blockers. Caution is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, cobicistat-containing products). Concomitant administration of other sympathomimetic medicinal products may potentiate the adverse reactions of FF/VI. Relvar should not be used in conjunction with other long-acting β2-adrenergic agonists or medicinal products containing long-acting β2-adrenergic agonists. Pregnancy and breast-feeding: Experience limited. Balance risks against benefits. Side effects: Very Common (≥1/10): headache, nasopharyngitis. Common (≥1/100 to <1/10): candidiasis of the mouth and throat, dysphonia, pneumonia, bronchitis, upper respiratory tract infection, influenza, oropharyngeal pain, sinusitis, pharyngitis, rhinitis, cough, abdominal pain, arthralgia, back pain, fractures, pyrexia, muscle spasm.

Other important side effects include: Uncommon (≥1/1,000 to <1/100); blurred vision, hyperglycaemia. Rare (≥1/10,000 to <1/1,000) paradoxical bronchospasms and hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria. See SmPC for other adverse reactions. Legal category: POM. Presentation and Basic NHS cost: Relvar Ellipta. 1 inhaler x 30 doses. Relvar Ellipta 92/22 - £22.00. Relvar Ellipta 184/22 - £29.50. Marketing authorisation (MA) nos. 92/22 mcg 1x30 doses [EU/1/13/886/002]; 184/22 mcg 1x30 doses [EU/1/13/886/005]. MA holder: Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS, UK. Last date of revision: September 2018. UK/FFT/0227/15(6). Trademarks are owned by or licensed to the GSK group of companies. © 2018 GSK group of companies or its licensor. Relvar Ellipta was developed in collaboration with Innoviva Inc.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.
Seretide Accuhaler and Evohaler (salmeterol xinafoate and fluticasone propionate) Prescribing Information

Please refer to the full Summary of Product Characteristics (SmPC) before prescribing.

Seretide Accuhaler and Evohaler (salmeterol xinafoate and fluticasone propionate) Uses: Asthma: Regular treatment of asthma, where use of a combination product (LABA and ICS) is appropriate, i.e. patients not adequately controlled on ICS and ‘as needed’ short-acting inhaled bronchodilator or patients controlled on ICS and LABA. Note: Seretide 50 Evohaler and Seretide 100 Accuhaler are not appropriate in severe asthma. COPD: Symptomatic treatment of patients with COPD with a FEV1 <60% predicted normal (prebronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. Dosage and administration: See SPC for more detail on dosing Inhalation only. Asthma: Adults and adolescents ≥12 years: Seretide Accuhaler - one inhalation b.d. of Seretide 100, 250 or 500 Accuhaler or Seretide Evohaler – two inhalations b.d. of Seretide 50, 125 or 250 Evohaler Children 4-11 years: Seretide 50 Evohaler two inhalations b.d. Volumatic or AeroChamber Plus spacer device use recommended. Seretide 100 Accuhaler one inhalation b.d. Maximum licensed dose of fluticasone propionate delivered by Seretide inhaler in children is 100 microgram twice daily. Regularly review patients and reduce dose to lowest that maintains effective symptom control. Where the control of symptoms is maintained with the lowest strength of the combination, patients may be prescribed an inhaled corticosteroid alone stepped down. COPD: one inhalation b.d. of Seretide 500 Accuhaler. Contraindications: Hypersensitivity to active substances or excipient; Accuhaler inhalation b.d. of Seretide 100, 250 or 500 Accuhaler or Seretide Evohaler are not appropriate in severe asthma. COPD: Symptomatic treatment of patients with COPD with a FEV1 <60% predicted normal (prebronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. Dosage and administration: See SPC for more detail on dosing Inhalation only. Asthma: Adults and adolescents ≥12 years: Seretide Accuhaler - one inhalation b.d. of Seretide 100, 250 or 500 Accuhaler or Seretide Evohaler – two inhalations b.d. of Seretide 50, 125 or 250 Evohaler Children 4-11 years: Seretide 50 Evohaler two inhalations b.d. Volumatic or AeroChamber Plus spacer device use recommended. Seretide 100 Accuhaler one inhalation b.d. Maximum licensed dose of fluticasone propionate delivered by Seretide inhaler in children is 100 microgram twice daily. Regularly review patients and reduce dose to lowest that maintains effective symptom control. Where the control of symptoms is maintained with the lowest strength of the combination, patients may be prescribed an inhaled corticosteroid alone stepped down. COPD: one inhalation b.d. of Seretide 500 Accuhaler. Contraindications: Hypersensitivity to active substances or excipient; Accuhaler contains lactose monohydrate. Special warnings and Precautions: Not for acute treatment of asthma attack, nor initiation in significantly or acutely deteriorating asthma. Advise patients to seek medical attention if symptoms deteriorate. Caution in patients with: Pulmonary infections e.g. TB, fungal, viral; severe cardiovascular disorders, heart rhythm abnormalities, diabetes mellitus, thyrotoxicosis and hypokalaemia. May cause cardiac arrhythmias, paradoxical bronchospasm post-dose, hyperglycaemia, β2 agonist effects and pneumonia. Risk factors for pneumonia include current smoking, older age, low BMI and severe COPD. Systemic effects of inhaled corticosteroids may occur, particularly at high doses for prolonged periods, but much less likely than with oral steroids. Eye symptoms may be due to underlying serious conditions - consider referral to ophthalmologist. Cessation of and dose changes to steroids, transfer from oral steroids and stressful situations require caution. Regularly monitor height of children receiving prolonged treatment with ICS. The dose of ICS should be reduced to the lowest dose at which effective control of asthma is maintained. Drug interactions: Avoid betablockers in asthma. Potentially serious hypokalaemia may result from β2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics. Avoid concomitant administration with potent and moderate CYP3A4 inhibitors unless benefits outweigh potential risk. Pregnancy and lactation: Experience limited. Balance risks against benefits. Side effects: Very Common: headache, nasopharyngitis. Common: oropharyngeal candidiasis, pneumonia (in COPD), bronchitis, hypokalaemia, throat irritation, hoarseness/dysphonia, sinusitis, contusions, muscle cramps, traumatic fractures, arthralgia, myalgia. Serious other - uncommon: hyperglycaemia, cataract cardiac arrhythmias, angina pectoris. Rare: oesophageal candidiasis, angioedema, respiratory symptoms (bronchospasm), anaphylaxis, Cushing’s syndrome, cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, behavioural changes (predominantly in children), glaucoma, cardiac arrhythmias and paradoxical bronchospasm. Not known: depression or aggression (predominantly in children). Paradoxical bronchospasm: substitute alternative therapy. Legal category: POM. Presentation and Basic NHS cost: Accuhaler 60 inhalations. Seretide 100 - £18.00. Seretide 250 - £35.00. Seretide 500 - £32.74. Evohaler 120 inhalations. Seretide 50 - £18.00. Seretide 125 - £23.45. Seretide 250 - £39.85. Product Licence (PL) nos: 10949/0314-0316, 10949/0337-0339. PL holder: Glaxo Wellcome UK Limited, trading as GlaxoSmithKline UK, Stockley Park West, Uxbridge, UB11 1BT. Last revision: August 2018. Zinc code: UK/RESP/0333/14(4). Seretide, Accuhaler and Evohaler are registered trademarks of the GlaxoSmithKline Group of Companies. For the UK, further information is available from Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; customercontactuk@gsk.com; Freephone: 0800 221 441.