A randomized pragmatic trial of changing to and stepping down fluticasone propionate/formoterol in asthma


Publication summary

Introduction

• The Global Initiative for Asthma (GINA) document recommends a step-wise reduction of combination treatment with an inhaled corticosteroid (ICS) and a long-acting β₂-agonist (LABA) once asthma has been well controlled for at least 3 months.

• Although a few randomized trials have investigated step-down of ICS therapy, none of the studies has undertaken simultaneous step-down of both the ICS and LABA, which is highly relevant in daily clinical practice.

• Very few studies have investigated predictors for response to step-down, and there are no conclusive data as to which patients with asthma can be stepped down while maintaining disease control.

• This randomized, controlled trial assessed asthma control following switching from a fluticasone propionate/salmeterol xinafoate (FP/SAL; Seretide® Evohaler®) pressurized metered-dose inhaler (pMDI) to fluticasone propionate/formoterol fumarate (FP/FORM; flutiform®) pMDI, followed by step-down of FP/FORM. Factors predicting a worsening of asthma following step-down were also assessed.

Fast facts

• Guidelines recommend reducing inhaled corticosteroid/long-acting β₂-agonist treatment in patients if their asthma has been well controlled for at least 3 months; however, there is inadequate real-life data to guide physicians on therapy change in daily practice.

• In this 24-week, open-label trial, 225 patients with well-controlled asthma were randomized (1:2) to stay on high-dose fluticasone propionate/salmeterol (FP/SAL; Seretide® Evohaler®) 1000/100 μg or to switch to fluticasone propionate/formoterol (FP/FORM; flutiform®) 1000/40 μg, administered daily by pressurized metered-dose inhaler (pMDI) for 12 weeks (phase 1). At week 12, 116 patients stable on FP/FORM were subsequently randomized (1:1) to stay on this therapy or to step down to FP/FORM 500/20 μg pMDI daily for 12 weeks (phase 2).

• Patients previously stable on FP/SAL1000/100 μg maintained good asthma control after switching to FP/FORM 1000/40 μg, and asthma control was maintained after stepping down to FP/FORM 500/20 μg.

– In phase 1, FP/FORM 1000/40 μg (n = 126) was non-inferior to FP/SAL 1000/100 μg (n = 73) for 7-question Asthma Control Questionnaire (ACQ7) scores at week 12 (difference in means: −0.12; 95% confidence interval [CI]: −0.32, 0.09).

– In phase 1, the odds of being more controlled according to Global Initiative for Asthma (GINA) criteria were significantly higher with FP/FORM 1000/40 μg (n = 151) than with FP/SAL 1000/100 μg (n = 74; odds ratio = 2.00; 95% CI: 1.14, 3.52; p = 0.016).

– In phase 2, FP/FORM 500/20 μg (n = 52) was non-inferior to FP/FORM 1000/40 μg (n = 52) for ACQ7 scores at week 12 (difference in means: 0.01; 95% CI: −0.20, 0.22).

• Experiencing one or two exacerbations in the 12 months before phase 1 was associated with the occurrence of an exacerbation after step-down to FP/FORM 500/20 μg (p = 0.007).

– This suggests that a patient’s exacerbation history can provide a practical and simple predictor that can be easily and readily applied in day-to-day clinical practice to identify patients suitable for step-down.

• Four serious adverse events were reported during the study, two of which (hospitalization due to pneumonia in the FP/SAL 1000/100 μg and FP/FORM 500/20 μg groups) were considered to be possibly related to study drug.
Results

• In phase 1, 225 participants were randomized to FP/FORM [1000] (n = 151) and FP/SAL [1000] (n = 74), and of these, 134 (88.7%) and 73 (98.6%), respectively, completed the 12-week visit. In phase 2, 116 participants who completed FP/FORM [1000] therapy in phase 1 were randomized equally to FP/FORM [1000] and FP/FORM [500], and of these, 54 (93%) and 53 (91%), respectively, completed the 12-week visit.

• In phase 1, asthma was well controlled with FP/FORM [1000] and FP/SAL [1000] at week 12 (Table 1), and FP/FORM [1000] (n = 126) was non-inferior to FP/SAL [1000] (n = 73) for ACQ7 scores (difference in mean scores: −0.12; 95% CI: −0.32, 0.09; Table 1).

• Study participants were recruited from 27 primary care practices across England.

• Patients with asthma were eligible for phase 1 if they were aged 18–75 years, had been prescribed FP/SAL [1000] (as Seretide® 250 Evohaler® pMDI two puffs twice a day) for at least 6 months before enrolment and showed satisfactory inhaler technique at screening.

• Participants randomized to FP/FORM in phase 1 were eligible for phase 2 if they had not had any severe exacerbations during phase 1.

• The primary outcome in both phases was asthma control, measured using the 7-question Asthma Control Questionnaire (ACQ7). The non-inferiority boundary for the difference in adjusted mean ACQ7 score between groups was set at 0.3; non-inferiority was declared if the upper limit of the 95% confidence interval (CI) was 0.3 or lower.

• Secondary outcomes included GINA 2012-defined asthma control (GINA-defined control), rate of severe exacerbations (defined as worsening of asthma requiring treatment with a course of oral corticosteroids, hospitalization, or accident and emergency department attendance), Mini Asthma Quality of Life score (Mini-AQLQ), visual analogue scale test score (to assess patients’ perceptions of asthma symptoms) and lung function.

<table>
<thead>
<tr>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>This 24-week randomized, controlled, pragmatic, open-label trial consisted of a 12-week switch phase (phase 1) followed by a 12-week step-down phase (phase 2).</td>
</tr>
</tbody>
</table>

- In phase 1, eligible patients were randomized (1:2) either to remain on high-dose FP/SAL 1000/100 μg (FP/SAL [1000]) or to switch to FP/FORM 1000/40 μg (FP/FORM [1000]) daily for 12 weeks.

- In phase 2, participants in the FP/FORM arm who had remained stable in phase 1 were randomized (1:1) to either stay on FP/FORM [1000] or to step down to FP/FORM 500/20 μg (FP/FORM [500]) daily for 12 weeks.

• The odds of being more controlled according to GINA criteria were significantly higher with FP/FORM [1000] (n = 151) than with FP/SAL [1000] (n = 74; odds ratio = 2.00; 95% CI: 1.14, 3.52; p = 0.016; Table 2). There was no significant difference between the FP/FORM [1000] and FP/SAL [1000] treatment groups for other secondary outcome measures.

### Table 1. ACQ7 scores with FP/FORM 1000/40 μg and FP/SAL 1000/100 μg (phase 1).

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 12</th>
<th>Estimate of treatment effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td><strong>FP/FORM 1000/40 μg (n = 126)</strong></td>
<td><strong>FP/SAL pMDI 1000/100 μg (n = 73)</strong></td>
<td><strong>FP/FORM 1000/40 μg (n = 125)</strong></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.7 ± 0.6</td>
<td>0.7 ± 0.8</td>
</tr>
<tr>
<td>Min, max</td>
<td>0.0, 3.1</td>
<td>0.0, 2.4</td>
</tr>
</tbody>
</table>

ACQ7, 7-question Asthma Control Questionnaire; CI, confidence interval; FP/FORM, fluticasone propionate/formoterol fumarate; FP/SAL, fluticasone propionate/salmeterol xinafoate; max, maximum; min, minimum; pMDI, pressurized metered-dose inhaler; SD, standard deviation.
The European prescribing information can be found at the end of this document.

• In phase 2, good asthma control was maintained when FP/FORM [1000] was stepped down to FP/FORM [500] at week 12 (Table 3) and FP/FORM [500] (n = 52) was non-inferior to FP/FORM [1000] (n = 52) for ACQ7 at week 12 (difference in means = −0.01; 95% CI: −0.20, 0.22; Table 3).

• There was no significant difference between the FP/FORM [1000] and FP/FORM [500] treatment groups for other secondary outcome measures.

• The severe exacerbation rate did not differ significantly between the groups in phase 1 (p = 0.143) or phase 2 (p = 0.753); however, a history of one or two exacerbations in the 12 months before phase 1 was associated with the occurrence of an exacerbation after step-down (p = 0.007).

• Four serious adverse events were reported during the study, two of which (hospitalization due to pneumonia in the FP/SAL [1000] and FP/FORM [500] groups) were considered to be possibly related to study drug. The other two serious adverse events were death and self-inflicted injury, both considered unrelated to study treatment.

Table 2. GINA 2012-defined asthma control with FP/FORM 1000/40 µg and FP/SAL 1000/100 µg (phase 1).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 12</th>
<th>Estimate of treatment effect (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FP/FORM 1000/40 µg (n = 151)</td>
<td>FP/SAL pMDI 1000/100 µg (n = 74)</td>
<td>FP/FORM 1000/40 µg (n = 134)</td>
<td>FP/SAL pMDI 1000/100 µg (n = 73)</td>
</tr>
<tr>
<td>Controlled</td>
<td>68 (45.0)</td>
<td>32 (43.2)</td>
<td>71 (53.0)</td>
<td>28 (38.4)</td>
</tr>
<tr>
<td>Partially controlled</td>
<td>83 (55.0)</td>
<td>42 (56.8)</td>
<td>53 (39.6)</td>
<td>33 (45.2)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>10 (7.5)</td>
<td>12 (16.4)</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise stated.
CI, confidence interval; FP/FORM, fluticasone propionate/formoterol fumarate; FP/SAL, fluticasone propionate/salmeterol xinafoate; GINA, Global Initiative for Asthma; pMDI, pressurized metered-dose inhaler.

ACQ7, 7-question Asthma Control Questionnaire; CI, confidence interval; FP/FORM, fluticasone propionate/formoterol fumarate; max, maximum; min, minimum; SD, standard deviation.

Table 3. ACQ7 scores with FP/FORM 1000/40 µg and FP/FORM 500/20 µg (phase 2).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 12</th>
<th>Estimate of treatment effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FP/FORM 1000/40 µg (n = 52)</td>
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<td>FP/FORM 1000/40 µg (n = 52)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.6 ± 0.6</td>
<td>0.6 ± 0.8</td>
<td>0.7 ± 0.8</td>
</tr>
<tr>
<td>Min, max</td>
<td>0.0, 2.7</td>
<td>0.0, 5.1</td>
<td>0.0, 3.7</td>
</tr>
</tbody>
</table>
Discussion

- This study showed that patients previously stable on FP/SAL [1000] maintained good asthma control after switching to FP/FORM [1000], and that asthma control was maintained after stepping down to FP/FORM [500].
  - The odds of being more controlled were significantly higher with FP/FORM [1000] than with FP/SAL [1000], when control was defined according to GINA 2012 criteria.

- This is the first study to step down both the ICS and LABA components of a combination treatment simultaneously in patients with well-controlled asthma, and the results are consistent with previous studies suggesting that reducing ICS therapy can maintain asthma control.

- Patients who had an exacerbation following step-down of their ICS/LABA dose had experienced significantly more exacerbations in the 12 months before the study than those who did not.
  - Reviewing the exacerbation history of a patient over a longer time frame may help to identify individuals who would be least suitable for step-down.

- Larger studies with longer follow-up periods and further reductions in therapy will help to investigate further asthma outcomes following step-down, and to confirm whether other factors could be useful for predicting response to step-down.

References


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flutiform® (fluticasone propionate and formoterol fumarate)

pressurised inhalation suspension

European Prescribing Information

Please read the Summary of Product Characteristics before prescribing.

Presentation
Pressurised inhalation suspension, in a pressurised metered dose inhaler (pMDI), containing fluticasone propionate and formoterol fumarate dihydrate at strengths of 50 µg/5 µg, 125 µg/5 µg or 250 µg/10 µg per actuation.

Indications
Regular treatment of asthma where the use of a combination product (inhaled corticosteroid and long-acting β₂-agonist) is appropriate.

For patients not adequately controlled with inhaled corticosteroids and ‘as required’ doses of a β₂-agonist (SABA), or for patients already adequately controlled on an inhaled corticosteroid and a long-acting β₂-agonist (LABA).

Flutiform 50 µg/5 µg and 125 µg/5 µg per actuation are indicated for use in adults and adolescents 12 years and above. Flutiform 250 µg/10 µg per actuation is only indicated for use in adults.

Dosage and administration
For inhalation use. The patient should be shown how to use the inhaler correctly by a physician or other healthcare professional.

Patients should be given the strength of flutiform containing the appropriate fluticasone propionate dose for their disease severity (note that flutiform 50 µg/5 µg per actuation is not appropriate in patients with severe asthma). The appropriate strength should be taken as two inhalations, twice daily (normally in the morning and evening) and used every day, even when asymptomatic. Flutiform should not be used in children under 12 years. Prescribers should be aware that in asthmatics, fluticasone propionate is as effective as some other inhaled steroids when administered at approximately half the total daily microgram dose.

Total daily dose can be increased if asthma remains poorly controlled by administering a higher strength inhaler. Appropriate doses of the β₂-agonist and inhaled corticosteroid (ICS) in separate inhalers, or the ICS alone, should be prescribed if a patient requires doses outside the recommended dose regimens.

Patients should be assessed regularly and once asthma is controlled, treatment should be reviewed and stepped down to the lowest effective dose, or an ICS alone. It is extremely important to regularly review patients as their treatment is stepped down. ICSs alone are first line treatment for most patients. Flutiform is not intended for initial treatment of mild asthma. For patients with severe asthma the ICS therapy should be established before prescribing a fixed-dose combination product.

Patients on flutiform must not use an additional LABA. An inhaled SABA should be taken for immediate relief of asthma symptoms arising between doses.

The AeroChamber Plus® spacer device is recommended in patients who find it difficult to use inhalers; re-titraton should always follow the introduction of a spacer device.

Patients should be advised to contact their prescriber when the flutiform dose counter is getting near zero.

Contraindications
Hypersensitivity to the active substances or to any of the excipients.

Precautions and warnings
Flutiform should not be used for the first treatment of asthma, to treat acute asthma symptoms or for prophylaxis of exercise-induced asthma. It should not be initiated during an exacerbation, during significantly worsening or acutely deteriorating asthma, and should not be stopped abruptly. Patients should use their flutiform maintenance treatment as prescribed, even when asymptomatic.

If a patient experiences serious asthma-related adverse events or exacerbations, they should continue treatment but also seek medical advice. Patients should be reviewed as soon as possible if there is any indication of deteriorating asthma control. In the case of sudden and progressive deterioration, which is potentially life-threatening, an urgent medical assessment should be carried out.

Use with caution in patients with: pulmonary tuberculosis; quiescent tuberculosis; uncorrected hypokalaemia; predisposition to low levels of serum potassium; impaired adrenal function (monitor HPA axis function regularly); hypertrophic obstructive cardiomyopathy; idiopathic subvalvular aortic stenosis; severe hypertension; aneurysm or other severe cardiovascular disorders.

There is risk of potentially serious hypokalaemia with high doses of β₂-agonists or concomitant treatment with β₂-agonists and drugs that can induce or potentiate a hypokalaemic effect. Particular caution is recommended in unstable or acute severe asthma and other conditions when the likelihood for hypokalaemia adverse effects is increased. Monitoring of serum potassium levels is recommended during these circumstances. Formoterol may induce prolongation of the QTC interval. Caution must be observed when using flutiform in patients with existing prolongation of QTC interval. Flutiform should be discontinued immediately if there is evidence of paradoxical bronchospasm.

Systemic effects with an ICS may occur, particularly at high doses for prolonged periods or when combined with potent CYP3A4 inhibitors, but are less likely than with oral corticosteroids. Use of a spacer device may also cause an increased systemic exposure. Increased exposure can be expected in patients with severe hepatic impairment.

Prolonged treatment with high doses of corticosteroids may result in adrenal suppression and acute adrenal crisis, particularly in adolescents and children or potentially as a result of trauma, surgery, infection or rapid dose reduction. Patients should be advised that flutiform contains a small amount of ethanol; however, this negligible amount does not pose a risk to patients.

Flutiform is not recommended in children under 12 years of age.

Interactions
Caution is advised in long-term co-administration with strong CYP3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, iracanazole, nelfinavir, saquinavir, ketoconazole and telithromycin); co-administration should be avoided if possible. Ritonavir in particular should be avoided, unless the benefits outweigh the risks of systemic side-effects.

Caution is advised with use of non-potassium sparing diuretics (e.g. loop or thiazide), xanthine derivatives, glucocorticosteroids, L-Dopa, L-thyroxine, oxytocin, alcohol or other adrenergic drugs.

There is an increased risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons. Hypokalaemia may increase the risk of arrhythmias in patients being treated with digitalis glycosides.

Concomitant use of β-adrenergic drugs can have a potentially additive effect. Caution should be taken when using formoterol fumarate with drugs known to prolong the QTc interval, such as tricyclic antidepressants or MAOIs (and for two weeks following their discontinuation), as well as antipsychotics (including phenothiazines), quinidine, disopyramide, procainamide and antihistamines.

Concomitant use of an MAOI or a similar agent, such as furazolidone or procarbazine, may precipitate hypertensive reactions. β-blockers and formoterol fumarate may inhibit the effect of each other. β-blockers may produce severe bronchospasm in asthma patients, and they should not normally be treated with β-blockers including those that are used as eye drops to treat glaucoma. Under certain circumstances, e.g. as prophylaxis after myocardial infarction, cardioselective β-blockers could be considered with caution.

Pregnancy and lactation
Flutiform is not recommended during pregnancy. It should only be considered if benefits to the mother outweigh risks to the foetus.

It is not known whether fluticasone propionate or formoterol are excreted in breast milk; a risk to the breast feeding infant cannot be excluded. A decision should be made on whether to discontinue breastfeeding or discontinue/abstain from flutiform.

Side-effects
Potentially serious side-effects: hyperglycaemia; depression; aggression; behavioural changes (predominantly in children); paradoxical bronchospasm; agitation; vertigo; palpitations; ventricular extrasystoles; angina pectoris; tachycardia; hypertension; dyspnoea; peripheral oedema; Cushings syndrome; adrenal suppression; growth retardation; cataract and glaucoma; hypersensitivity reactions and QTc interval prolongation.

Please consult the SPC for details of non-serious side-effects and those reported for the individual molecules.

Legal category
POM

Package quantities
One inhaler containing 120 actuations
Multipack of 3 x 1 inhaler (120 actuations)
Not all pack sizes may be marketed

Shelf life
2 years
In-use shelf life: 3 months after opening the foil pouch

Date of preparation
July 2015

Date effective
August 2015

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Adverse events should be reported. Reporting to the applicable regulatory authorities should be in accordance with National requirements and to the applicable holder of the marketing authorization for flutiform, details of which can be found on the product packaging and/or inserts.

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