

# Clinical utility and development of the fluticasone/formoterol combination formulation (Flutiform<sup>®</sup>) for the treatment of asthma

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**Abstract:** Pharmacologic treatment of asthma should be done with a stepwise approach recommended in treatment guidelines. If inhaled corticosteroids (ICSs) alone are not adequate, ICSs in combination with long-acting  $\beta$ -agonists (LABAs) are now established and widely used as the next step in effective controller therapy. Fixed-dose ICS/LABA combinations in a single device are the preferred form of delivery and improve compliance by enabling patients to get symptom relief from the LABA while receiving the anti-inflammatory benefits of ICSs. Fluticasone propionate/formoterol fumarate is one of the newest fixed-dose combinations. It has been in use in Europe in 2012, but is still under regulatory review in the US. Fluticasone is a synthetic ICS with potent anti-inflammatory effects, while formoterol is a selective  $\beta_2$ -adrenergic receptor agonist with a rapid onset of bronchodilation within 5–10 minutes and a 12-hour duration of action. Fluticasone/formoterol has shown superior efficacy when compared to fluticasone or formoterol alone in multiple well-designed studies. The combination has shown comparable or “noninferior” benefits in lung function, clinical symptoms, and asthma control when compared with fluticasone and formoterol administered concurrently in separate inhalers. Fluticasone/formoterol provides similar efficacy with fluticasone/salmeterol, but with more rapid symptom relief. It has been compared directly with budesonide/formoterol with comparable results. Fluticasone/formoterol is well tolerated, with no unusual or increased safety concerns versus each individual component or other available ICS/LABA combinations. Fluticasone/formoterol is the latest entry into a relatively crowded market of branded fixed-dose preparations. Upcoming generic fixed-dose combinations and once-daily agents pose significant market challenges. In clinical practice, most practitioners consider all the currently available fixed-dose preparations to be of comparable efficacy and safety.

**Keywords:** fixed-dose combination, fluticasone/formoterol, inhaled corticosteroid, long-acting  $\beta$ -agonist

## Introduction

Asthma is a global public health problem that affects up to 300 million persons worldwide. Despite advances in pharmacologic treatment, there is still widespread undertreatment of asthma, particularly in developed regions, such as the US and Europe, specifically in the underutilization of controller or maintenance therapy for targeting the underlying airway inflammation. Chronic asthma treatment should be a stepwise approach based on asthma severity or level of control. International guidelines, including the Global Initiative for Asthma<sup>1</sup> and the US National Asthma Education and Prevention Program,<sup>2</sup> provide criteria for assessing severity or control based on daytime symptoms, nighttime awakenings, use of short-acting  $\beta$ -agonists (SABAs), forced expiratory volume in 1 second (FEV<sub>1</sub>) or peak expiratory flow rate,

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and interference with normal activity. The goals of asthma treatment are to reduce impairment and risk.<sup>2</sup> Impairment from asthma includes uncontrolled symptoms, frequent use of reliever medications, decreased pulmonary function, limitation of activity, and decreased quality of life. Risks from uncontrolled asthma include recurrent exacerbations leading to emergency room visits or hospitalizations, loss of lung function, and adverse medication side effects.

For patients with mild persistent asthma, low-dose inhaled corticosteroids (ICSs) are the preferred choice for starting daily controller therapy. If ICSs alone are not adequate, ICSs in combination with LABAs are now established and widely used as the next step in effective controller therapy. The effectiveness of LABAs as add-on therapy to ICSs compared to higher dose ICSs alone has been demonstrated.<sup>3,4</sup>

In the US, due to ongoing concern about the cardiovascular safety of LABAs, the Food and Drug Administration (FDA) adds a black-box warning to all LABA-containing products stating that an ICS/LABA combination should be used only if the patient is not controlled on low- or medium-dose ICSs or if the severity of the asthma warrants immediate initiation of a combination ICS/LABA agent. The FDA also recommends that once asthma control is achieved and maintained, the physician should assess the patient at regular intervals and step down therapy if possible without loss of asthma control, and maintain the patient on a long-term controller medication, such as an ICS alone.<sup>5</sup>

Over the last decade, fixed-dose ICS/LABA combinations in a single device have become the preferred form of delivery for these drugs.<sup>6</sup> Patient compliance is often cited as the most important benefit of these combination inhalers, as many patients may not use the ICS as prescribed if separate from the LABA, which provides symptom relief that motivates regular use. In addition to making it easier for patients to receive the anti-inflammatory benefits of the ICS while getting symptom relief from the LABA, both components appear to have benefits that enhance each other's effects. While ICSs may have effects on airway inflammation within 24–48 hours that contribute to early symptom relief,<sup>7</sup> LABAs may have mild effects on inflammatory events due to the inhibition of mast cells, as well as some other less prominent effects.<sup>7</sup> In a study of attitudes and perceptions of specialists in Europe toward combined ICS/LABA agents, the potency of the ICS and the speed of onset of the LABA were considered among the most important attributes.<sup>8</sup>

The first combined ICS/LABA product introduced was fluticasone/salmeterol.<sup>9</sup> Subsequently, budesonide/formoterol and mometasone/formoterol combinations were introduced

and are now widely used internationally.<sup>10–12</sup> Beclomethasone/formoterol is available in Europe, but not in the US.<sup>13</sup>

Fluticasone is an established ICS that has been in use for decades, while formoterol is a LABA with a rapid onset of action. Both agents are available individually and strongly supported by large amounts of efficacy and safety data collected over the past 2 decades.<sup>14–17</sup> The fluticasone/formoterol fixed-dose combination was approved in the European Union in 2012 and is currently available in Europe as Flutiform<sup>®</sup> (Mundipharma International, Cambridge, UK) delivered in a dry-powder device in strengths of 50/5 µg, 125/5 µg, and 250/10 µg. It is indicated for the maintenance treatment of asthma in patients 12 years and older. It is currently under FDA review and not yet approved for use in the US. The aim of this article is to review the pharmacology and summarize clinical safety and efficacy studies done with the fluticasone/formoterol combination.

## Pharmacology

Formoterol fumarate (henceforth called formoterol) is a selective  $\beta_2$ -adrenergic receptor agonist with a 12-hour duration of action and a rapid onset of action that occurs within 5–10 minutes, with maximum effect in 2 hours.<sup>18</sup> Inhaled formoterol has a 200-fold greater agonist activity on  $\beta_2$ -compared to  $\beta_1$ -adrenergic receptors. Beta-2 adrenergic agents stimulate intracellular adenylyl cyclase, which catalyzes the conversion of adenosine triphosphate to cyclic 3',5' adenosine monophosphate, which results in bronchial smooth-muscle relaxation. Formoterol is rapidly absorbed into plasma following inhalation, with a half-life of 10 hours. Approximately 61%–64% of the drug is bound to serum proteins, with serum drug concentrations of 0.1–100 ng/mL. It is metabolized primarily by direct conjugation at the phenolic hydroxyl group. A second pathway is by *O*-demethylation by cytochrome P450 isozymes followed by conjugation at the 2'-hydroxyl group. About 10% of inhaled formoterol is excreted unchanged in the urine, while 15%–18% is excreted as direct conjugates.<sup>18</sup>

Fluticasone is a synthetic, trifluorinated glucocorticoid that binds to the glucocorticoid receptor in mast cells, eosinophils, and other inflammatory cells, causing a variety of anti-inflammatory effects, including decreased leukocyte adhesion, decreased capillary permeability, inhibition of histamine release, and downregulation of proinflammatory mediators, such as IL-1, IL-3, and IL-5.<sup>19</sup> Clinically, it blocks the late-phase allergen in the response in the lung<sup>20</sup> and decreases airway hyperresponsiveness.<sup>21</sup> It is rapidly absorbed from the lungs into the systemic circulation, with a half-life of 7.8 hours. Systemic bioavailability is approximately 17%.<sup>22,23</sup>

It is highly protein-bound (91%), and is metabolized extensively in the liver by the cytochrome P450 3A4 subfamily pathway, with only one resulting metabolite: 17 $\beta$ -carboxylic acid. It is eliminated mainly through the fecal route, with less than 0.02% cleared through the kidneys.<sup>19,22</sup>

The pharmacokinetics and pharmacodynamics of the fluticasone/formoterol combination in a single inhaler appear to correspond to its individual components. After two actuations of fluticasone/formoterol 250/10  $\mu$ g, the terminal elimination half-life of fluticasone and formoterol were 14.2 hours and 6.5 hours, respectively. Flutiform® 50/5  $\mu$ g is equivalent to a delivered dose (ex-actuator) of approximately 46  $\mu$ g of fluticasone propionate/4.5  $\mu$ g of formoterol fumarate dehydrate. The 125/5  $\mu$ g strength has a delivered dose of 115/4.5  $\mu$ g while the 250/10  $\mu$ g strength has a delivered dose of 230/9.0  $\mu$ g.<sup>24</sup>

## Efficacy studies

### Fluticasone/formoterol versus fluticasone alone

The fluticasone/formoterol combination has been demonstrated to be clinically superior to fluticasone alone, as would be expected from the addition of a LABA to an ICS. In one study, fluticasone propionate/formoterol fumarate 250/10  $\mu$ g twice daily (bid [bis in die]) was compared to two formulations of the corresponding dose of fluticasone propionate alone from two manufacturers (SkyePharma, London, UK; GlaxoSmithKline, London, UK) in patients 12 years and older with moderate-to-severe asthma for 12 weeks. Fluticasone/formoterol showed superior efficacy compared to both fluticasone formulations based on the primary efficacy variable of the change in FEV<sub>1</sub> from morning predose at baseline to 2 hours postdose at week 12, as well as secondary end points for symptoms, asthma exacerbations, use of rescue medications, and pulmonary function. Fluticasone/formoterol was superior to the SkyePharma fluticasone with the least squares mean difference in FEV<sub>1</sub> from baseline predose to 2 hours postdose at week 12 at 0.161 L (95% confidence interval [CI] 0.078–0.245,  $P < 0.001$ ). It was also superior to the GlaxoSmithKline fluticasone, with a least squares mean difference at 0.185 L (95% CI 0.102–0.268,  $P < 0.001$ ). This study confirmed the greater benefit on clinical symptoms and lung function with a combined ICS/LABA preparation over ICS alone with no increased safety concerns.<sup>25</sup>

### Fluticasone/formoterol versus fluticasone or formoterol alone

In a recent large trial with 395 moderate-to-severe asthmatics aged 12 years and older, subjects were randomized to receive

either fluticasone/formoterol 250/10  $\mu$ g bid, fluticasone/formoterol 100/10  $\mu$ g bid, fluticasone 250  $\mu$ g bid alone, formoterol 10  $\mu$ g bid alone, or placebo for 12 weeks.<sup>22</sup> Three primary end points were utilized to compare fluticasone/formoterol specifically to either fluticasone, formoterol, or placebo, including mean change in FEV<sub>1</sub> from morning predose at baseline to predose at week 12 (compared to formoterol), mean change in FEV<sub>1</sub> from morning predose at baseline to 2 hours postdose at week 12 (compared to fluticasone), and number of patients who discontinued due to lack of efficacy (compared to placebo). Symptoms, lung function, and asthma control were followed as secondary end points. Results showed that fluticasone/formoterol was superior to fluticasone alone, formoterol alone, and placebo for the three primary end points. When compared to formoterol, fluticasone/formoterol showed greater improvement in mean change in FEV<sub>1</sub> from morning predose at baseline to predose at week 12 (least squares mean difference 0.189 L,  $P < 0.001$ ). It also showed superior benefit compared to fluticasone in mean change in FEV<sub>1</sub> from morning predose at baseline to 2 hours postdose at week 12 (least squares mean difference 0.146 L,  $P = 0.006$ ). Fluticasone/formoterol was superior to placebo in terms of subjects discontinuing due to worsening asthma (10.2% versus 39.0%). The secondary end points also showed greater improvement with fluticasone/formoterol. This study demonstrated that fluticasone/formoterol has superior benefits compared to the individual components and placebo, with a good safety and tolerability profile.<sup>26</sup>

At least two similarly designed studies have been reported in patients with mild-to-moderate asthma. Nathan et al evaluated fluticasone/formoterol in comparison with each component administered alone as monotherapy.<sup>27</sup> A total of 475 subjects were randomized to fluticasone/formoterol 100/10  $\mu$ g bid, fluticasone 100  $\mu$ g bid, formoterol 10  $\mu$ g bid, or placebo for 12 weeks. Fluticasone/formoterol produced significantly greater improvements in the three primary end points: change in FEV<sub>1</sub> from morning predose at baseline to predose at week 12 compared with formoterol (least squares mean difference 0.101 L, 95% CI 0.002–0.199;  $P = 0.045$ ) and fluticasone (least squares mean treatment difference 0.200 L, 95% CI 0.109–0.292;  $P < 0.001$ ), and time to discontinuation due to lack of efficacy from baseline to week 12 compared to placebo ( $P = 0.015$ ). Secondary end points also showed consistently superior efficacy with fluticasone/formoterol.<sup>27</sup> Pearlman et al reported another recent study in mild-to-moderate asthmatics comparing fluticasone/formoterol 100/10  $\mu$ g bid, fluticasone 100  $\mu$ g bid alone, formoterol 10  $\mu$ g bid alone, or placebo. The two primary

end points showed superior improvement with fluticasone/formoterol, including change in FEV<sub>1</sub> from morning predose at baseline to predose at week 12 compared to formoterol (least squares mean treatment difference 0.118 L, 95% CI 0.034–0.201;  $P=0.006$ ) and change in FEV<sub>1</sub> from morning predose at baseline to 2 hours postdose at week 12 compared to fluticasone (least squares mean treatment difference 0.122 L, 95% CI 0.040–0.204;  $P=0.004$ ). Of the secondary end points studied, only mean change from baseline of the morning peak expiratory flow rate between fluticasone/formoterol and formoterol was statistically significant. The authors added that the other secondary endpoints (symptoms, pulmonary function, rescue medication use, and overall asthma control) were “supportive” of the greater efficacy of the combination product. The study also demonstrated statistically significant superior efficacy with fluticasone/formoterol combination over each component alone and placebo.<sup>28</sup> The results of these two studies extend the potential benefits of fluticasone/formoterol to mild-to-moderate asthmatics.

### Fluticasone/formoterol versus fluticasone plus formoterol given concurrently in separate inhalers

Fixed-dose ICS/LABA combinations are often required by regulatory authorities to show that they are comparable to the individual components administered separately at the same time. In 2011, the first large multicenter, randomized, double-blind trial of fluticasone/formoterol was performed in 620 severe asthmatics aged 18 years and older. Subjects received either a single inhaler with fluticasone/formoterol (500/20 or 100/10 µg bid), fluticasone 500 µg and formoterol 24 µg bid taken concurrently in separate inhalers, or fluticasone 500 µg bid alone for 8 weeks. The high-dose combination showed similar efficacy to the two components taken separately in terms of the primary outcome measure of mean change in pre-morning dose from baseline to week 8 (least squares mean treatment difference 0.060 L, 95% CI –0.059 to 0.180;  $P<0.001$ ) and the coprimary end point of mean change in baseline pre-morning dose to 2 hours post-morning dose at week 8 (least squares mean treatment difference 0.018 L, 95% CI –0.098 to 0.135;  $P<0.001$ ). Secondary measures of symptoms, lung function, and asthma control were also comparable in the two groups. This study supported the comparable efficacy and safety of the fluticasone/formoterol single inhaler to concurrently administered fluticasone plus formoterol in the severe asthmatic population.<sup>29</sup>

In a more recent trial reported in 2013 that included mild, moderate, and severe patients, Bodzenta-Lukaszyk et al

performed an open-label, parallel-group study in subjects aged 12 years or older. A total of 210 subjects were randomized to 12 weeks of treatment with either fluticasone/formoterol (100/10 or 250/10 µg bid) or fluticasone plus formoterol administered concurrently (100 µg + 12 µg bid or 250 µg + 12 µg bid). The primary outcome measure (mean FEV<sub>1</sub> 30–60 minutes postdose on day 84) was calculated to be approximately 2.6 L in both the fluticasone/formoterol combination and the fluticasone + formoterol treatment groups (treatment difference least squares mean –0.03 L, 95% CI –0.148 to 0.081). Based on these results, the two fluticasone/formoterol doses were both shown to be “noninferior” to the individual components administered concurrently.<sup>30</sup>

### Comparison studies Fluticasone/formoterol versus fluticasone/salmeterol

Fluticasone/formoterol and fluticasone/salmeterol have been compared in an open-label, randomized, parallel-group, active-controlled study.<sup>27</sup> A total of 202 patients with mild, moderate, or severe asthma aged 18 years and older were randomized to receive either fluticasone/formoterol (100/10 or 250/10 µg bid) or fluticasone/salmeterol (100/50 or 250/50 µg bid) for 12 weeks. Dosing was stratified based on asthma severity, and the primary end point was predose FEV<sub>1</sub> at week 12. Results showed that all doses of fluticasone/formoterol and fluticasone/salmeterol were comparable in efficacy at corresponding doses for both primary and secondary end points. In addition, safety and tolerability were similar for both preparations. The authors concluded that the “noninferiority” of fluticasone/formoterol to the active control had been demonstrated.<sup>31</sup>

A post hoc analysis of the same data focusing on the onset of bronchodilation was reported in a separate publication. The onset of bronchodilation was defined as the first time point where FEV<sub>1</sub> was  $\geq 12\%$  greater than predose FEV<sub>1</sub>. The results demonstrated that subjects were four times more likely to have bronchodilation within 5 minutes with fluticasone/formoterol than with fluticasone/salmeterol at baseline (odds ratio 3.97, 95% CI 1.96–8.03) and on day 84 (odds ratio 9.58, 95% CI 2.14–42.90). The overall percentage increase in mean FEV<sub>1</sub> 120 minutes postdose was also significantly greater with fluticasone/formoterol than fluticasone/salmeterol at baseline (least squares mean treatment difference 4.70%, 95% CI 1.57–7.83;  $P=0.003$ ) and day 84 (2.79%, 95% CI 0.65–4.93;  $P=0.011$ ). These findings illustrated that rapid bronchodilation with fluticasone/formoterol is retained and does not diminish over 12 weeks



of treatment, and that formoterol is slightly more efficacious 2 hours after dosing.<sup>32</sup>

## Fluticasone/formoterol versus budesonide/formoterol

At least two studies have compared fluticasone/formoterol to budesonide/formoterol. In an open label, active-controlled, parallel-group study, 196 subjects with uncontrolled asthma were randomized to receive either fluticasone/formoterol 250/12 µg bid in a dry-powder inhaler or budesonide/formoterol 400/12 µg bid for 12 weeks. Fluticasone/formoterol appeared to have a statistically significant greater improvement than budesonide/formoterol with regard to both lung function (FEV<sub>1</sub>,  $P=0.01$ ) and asthma control ( $P=0.02$ ) while both were comparable in terms of asthma exacerbations. Safety and tolerability were also comparable between the two groups.<sup>33</sup> In a second trial, 279 patients with moderate-to-severe asthma were randomized to receive either fluticasone/formoterol 250/10 µg bid or budesonide/formoterol 400/12 µg bid for 12 weeks. In this study, fluticasone/formoterol and budesonide/formoterol showed comparable efficacy in the primary outcome, which was change in predose FEV<sub>1</sub> from baseline to week 12.<sup>34</sup> Results from both these studies showed that fluticasone/formoterol was “noninferior” to budesonide/formoterol based on primary and secondary outcome measures of lung function, symptoms, and asthma control, and no significant differences were found for safety or tolerability.

## Safety

Fluticasone/formoterol has been found to be safe and well tolerated at the recommended doses in all the major clinical trials conducted to date.<sup>26,27,29,30</sup> As would be expected from studies of fluticasone and formoterol, adverse events are universally mild. In an open-label study of the long-term safety of fluticasone/formoterol, 472 mild-to-moderate asthmatics were treated with fluticasone/formoterol 100/10 µg or 250/10 µg bid for up to 12 months. The most common adverse events reported in >2% of the study population included nasopharyngitis, dyspnea, pharyngitis, and headache. No significant laboratory abnormalities were reported in this study.<sup>35</sup>

Local side effects from the fluticasone component can include hoarseness and oral thrush, both of which can be minimized by proper inhaler technique and by mouth rinsing after inhalation. At the recommended doses, the risk for osteoporosis, growth retardation, cataracts, or hypothalamic-pituitary axis suppression is minimal.<sup>36</sup>

The long-term safety of LABAs continues to be an issue of controversy in the US. The FDA cites concern about increased risk of serious asthma exacerbations and asthma-related death with LABAs based on data published several years ago in the Salmeterol Multicenter Asthma Research Trial (SMART).<sup>37</sup> However, most asthma experts believe that although monotherapy with LABAs may lead to increased asthma morbidity (possibly by masking worsening airway inflammation), the concomitant use of an ICS and LABA is safe.<sup>38</sup> More studies are needed to definitively show that concurrent use of an ICS decreases the risk of asthma-related deaths with LABAs. There is currently a large cooperative study of ICS/LABA safety being conducted by all three manufacturers of currently available agents.<sup>39</sup>

Precautions and warnings from the manufacturers of fluticasone/formoterol highlight the potential effects of β<sub>2</sub>-agonists (tachycardia, hypokalemia, hyperglycemia, corrected QT [QTc] prolongation) and ICSs (Cushing's syndrome, depression, anxiety, osteoporosis) that could be seen with high-dose prolonged treatment. The prescription of β<sub>2</sub>-agonists in patients with underlying cardiac conditions should be done cautiously.<sup>40</sup> Caution is also advised in patients with compromised immunity (eg, pulmonary tuberculosis, fungal or other airway infections), metabolic disorders (diabetes mellitus), cardiovascular disease (eg, severe hypertension, cardiomyopathy, idiopathic subvalvular aortic stenosis), conditions with tachycardia (eg, thyrotoxicosis, pheochromocytoma), and impaired adrenal function. One should also look out for potentially dangerous interactions that can aggravate ICS and LABA effects, including use of non-potassium-sparing diuretics, drugs that prolong the QTc interval (eg, tricyclic antidepressants, monoamine oxidase inhibitors, disopyramide, phenothiazines, quinidine), and anesthesia with hydrogenated hydrocarbons.<sup>41</sup>

The manufacturers do not recommend the use of Flutiform® in pregnancy. There are limited data in pregnant women, but a reproductive study in animals with Flutiform® showed toxicity (pregnancy category C).<sup>41</sup>

## Discussion

Fluticasone propionate/formoterol fumarate is the newest fixed-dose combination introduced for use as controller therapy in asthma. It was approved for use in Europe in 2012, but is still under regulatory review in the US. Fluticasone is a potent synthetic inhaled corticosteroid, while formoterol is a rapid-acting LABA. Both agents are already marketed in combination with other ICSs and LABAs, so commercially fluticasone/formoterol is the latest entry into a relatively crowded market.

Fluticasone/formoterol has shown superior efficacy when compared to fluticasone or formoterol alone in multiple well-designed studies using the same primary end points, namely mean change in FEV<sub>1</sub> from morning predose at baseline to predose at the end of the study (compared to formoterol), mean change in FEV<sub>1</sub> from morning predose at baseline to 2 hours postdose at end of the study (compared to fluticasone). The combination has shown comparable or “noninferior” benefits in lung function, clinical symptoms, and asthma control when compared with fluticasone and formoterol administered concurrently in separate inhalers. Fluticasone/formoterol provides similar efficacy to fluticasone/salmeterol, but with more rapid symptom relief. It has been compared directly with budesonide/formoterol with comparable results. Fluticasone/formoterol has a good tolerability profile with no unusual or increased safety concerns versus each individual component or other available ICS/LABA combinations.<sup>24,42</sup>

The combination of fluticasone/formoterol includes a high-potency ICS agent with very low oral bioavailability and a rapidly acting and highly effective LABA. Despite its excellent characteristics, fluticasone/formoterol is part of a crowded and competitive marketplace in the US and EU for branded fixed-dose combinations. In clinical practice, both the dry-powder and pressurized metered-dose inhalers have their advocates among physicians and patients. Patients’ choices are often based on personal preference and familiarity rather than on true efficacy or device efficiency.

Several developments will potentially affect the clinical use of fluticasone/formoterol. The anticipated FDA approval of a generic fixed-dose combination in the US in the near future will pose a challenge to all the currently available brands. A once-daily combination, fluticasone/vilanterol, is available for the treatment of chronic obstructive pulmonary disease and asthma in the EU, and is awaiting approval for use in asthma in the US.<sup>43</sup> The once-daily dosing may offer an advantage in patient compliance in some patients compared to twice-daily combinations; however, most studies have not demonstrated significant differences in adherence between once- and twice-daily dosing.<sup>44</sup> The use of fixed ICS/LABA combinations as reliever (as-needed) therapy has been gaining momentum, especially in the EU.<sup>45</sup> Only budesonide/formoterol currently has both the maintenance and reliever indications in the EU, while none of the combinations have the reliever indication in the US.<sup>46</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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