Fixed combinations of corticosteroids and long-acting beta-2-receptor agonists for inhaled use in patients with asthma - supplementary commission

Executive Summary

1 Translation of the executive summary of the final report “Fixe Kombinationen aus Kortikosteroiden und lang wirksamen Beta-2-Rezeptoragonisten zur inhalativen Anwendung bei Patienten mit Asthma bronchiale - Ergänzungsauftrag” (Version 1.0; Status: 05.09.2008). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.
Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Fixed combinations of corticosteroids and long-acting beta-2-receptor agonists for inhaled use in patients with asthma – supplementary commission to project A05-13 (on the same topic) due to the new approval of combination drugs, as well as the extension of approval of known combinations

Contracting agency:
Federal Joint Committee

Commission awarded on:
06.03.2007

Internal Commission No.:
A07-01

Address of publisher:
Institute for Quality and Efficiency in Health Care
Dillenburger Str. 27
51105 Cologne
Germany

Tel: +49 (0) 221/35685-0
Fax: +49 (0) 221/35685-1
E-mail: berichte@iqwig.de
Website: www.iqwig.de
Fixed combinations of corticosteroids and long-acting beta-2-receptor agonists for inhaled use in patients with asthma – supplementary commission

Executive summary

Background

In a letter of 06.03.2007, the Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) with the supplementary assessment of fixed combinations of inhaled corticosteroids (ICS) and inhaled long-acting beta-2-receptor agonists (LABA) in patients with asthma. This commission was a supplementation to commission A05-13 and referred to the new approval and extension of approval for these drug classes that took place during the production of report A05-13.

Research questions

The aims of the planned research result from the wording of the commission of the Federal Joint Committee, as well as from the new approval and extension of approval in Germany for fixed combinations of ICS and LABA in the treatment of patients with asthma.

In the following text, the term “fixed combination” refers to a combination of 2 drugs administered by a fixed combination inhaler. The term “individual drugs” refers to the individual drugs of the combination therapy administered by separate inhalers.

The aims of this research were:

**Fixed combination of beclomethasone and formoterol**

- The comparative benefit assessment between the fixed combination of beclomethasone/formoterol and the 2 individual drugs.

- The comparative benefit assessment between the fixed combination of beclomethasone/formoterol and other approved ICS/LABA fixed combinations.

**Budesonide/formoterol SMART<sup>2</sup>**

- The comparative benefit assessment between the fixed combination of budesonide/formoterol for maintenance and reliever therapy and the 2 individual drugs.

- The comparative benefit assessment between the fixed combination of budesonide/formoterol for maintenance and reliever therapy and other approved ICS/LABA fixed combinations (The relevant comparator interventions are described in Section 3.2 of the final report.)

---

<sup>2</sup> Symbicort® Maintenance and Reliever Therapy
The main focus of the comparisons was on patient-relevant therapy goals.

In addition, within the framework of this benefit assessment, an update was performed of the assessment of the fixed combinations of fluticasone/salmeterol and budesonide/formoterol (application outside the SMART regimen).

Methods

A systematic literature search was performed in the databases MEDLINE, EMBASE, and CENTRAL (unlimited search period; in each case, last search in November 2007). In addition, reference lists were screened of relevant secondary publications (systematic reviews, HTA reports), trial registries, and publicly accessible drug approval documents. Moreover, the manufacturers of the drugs approved in Germany were asked to provide information on published and unpublished trials. Finally, in June/July 2008, information on further trials relevant to the topic under investigation was requested within the framework of the commenting procedure on the preliminary version of the report (preliminary report).

Randomized controlled trials (RCTs) in patients with asthma were included that compared the fixed combinations of budesonide/formoterol (Bud/Form or Bud/Form-SMART), fluticasone/salmeterol (Flu/Salm), or beclomethasone dipropionate/formoterol (BDP/Form) with the 2 individual drugs of the combination therapies (Bud+Form, Flu+Salm, BDP+Form). The minimum study duration was 12 weeks. RCTs investigating these fixed combinations in a direct comparison were also included.

The literature screening was performed by 2 reviewers independently of one another. After an assessment of study quality, the results of the individual trials were collated according to therapy goals and outcomes. If possible and meaningful, meta-analyses were conducted. IQWiG’s preliminary benefit assessment, the preliminary report, was published on the Internet (www.iqwig.de) and interested parties were invited to submit comments.

Results

The literature search identified 16 trials for the assessment of the fixed combinations of ICS/LABA (including 2 paediatric trials). Five trials compared Bud/Form versus Bud+Form (including 1 paediatric trial), and 4 trials compared Flu/Salm versus Flu+Salm (including 1 paediatric trial). Relevant trials on BDP/Form versus BDP+Form were not identified. Seven trials investigating direct comparisons of fixed combinations were identified. Of the trials included, 9 showed no deficiencies, 2 showed minor deficiencies, and 5 showed major deficiencies regarding study and publication quality.

In all trials comparing ICS/LABA versus ICS+LABA, the drugs were administered via identical inhaling systems in each treatment group (Bud/Form: Turbohaler®, Flu/Salm: Diskus®). No trials were identified that applied different inhaling systems within the comparator groups. In the trials comparing fixed combinations with each other, Bud/Form was administered by Turbohaler® and Flu/Salm was administered by Diskus® (with 2 exceptions, in which Flu/Salm was administered by metered-dose inhaler [MDI]). BDP/Form
was administered by MDI. The following table provides an overview of the patient-relevant outcomes investigated in the trials included.

Table 1: Overview of the patient-relevant outcomes in the trials included

<table>
<thead>
<tr>
<th></th>
<th>Asthma symptoms</th>
<th>Asthma exacerbations</th>
<th>Hospital admissions/outpatient visits</th>
<th>Adverse events</th>
<th>Health-related quality of life/activities of daily living</th>
<th>Treatment satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bud/Form versus Bud+Form</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jenkins 2006</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pohunek 2006</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zetterström 2001</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenhall 2002</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenhall 2003a+b</td>
<td>(●)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bud/Form-SMART versus Bud+Form-AMD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flu/Salm versus Flu+Salm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aubier 1999</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bateman 1998</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapman 1999</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van den Berg 2000</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BDP/Form versus BDP+Form</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bud/Form versus Flu/Salm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aalbers 2004</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAM40040</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004/Dahl 2006</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAM40048 2003</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuna 2007</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bud/Form-SMART versus Flu/Salm-AMD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vogelmeier 2005</td>
<td>(●)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td>(●)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Bud/Form-SMART versus BDP/Form-AMD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No trial available</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BDP/Form versus Bud/Form</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papi 2007a</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BDP/Form versus Flu/Salm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papi 2007b</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: No direct assessment of asthma symptoms, but assessment of the use of reliever medication or of the ACQ (Asthma Control Questionnaire); these data were only presented as supplementary information.

b: The publications Rosenhall 2003a+b refer to a 6-month continuation performed by the Swedish study centres participating in the trial by Rosenhall 2002.

c: Data on patient satisfaction were collected, but not reported.

AMD: Adjustable Maintenance Dosing; SMART: Symbicort® Maintenance and Reliever Therapy

Data that allow an evaluation of the therapy goal “maintenance and improvement of physical capacity” were not collected in the trials. In respect of their design and duration, none of the trials included was designed to investigate the effect of the drugs investigated on asthma-related mortality or overall mortality. No evidence of a benefit of ICS/LABA fixed combinations is therefore available for these outcomes.
Budesonide/formoterol versus budesonide+formoterol

Asthma symptoms

In the comparison of Bud/Form versus Bud+Form, a direct recording of asthma symptoms was performed in the trials in adolescents and adults by Jenkins 2006 and Zetterström 2001, as well as in the paediatric trial by Pohunek 2006. In these trials, asthma symptoms improved in both treatment groups. In Jenkins 2006, the proportion of symptom-free days during treatment with Bud/Form and Bud+Form compared with prior medication increased by 31% and 32% respectively. In Zetterström 2001, the proportion of symptom-free days with Bud/Form and Bud+Form increased by 25% and 22% respectively; the proportion of asthma-related nocturnal awakenings decreased by 8% (Bud/Form) and by 6% (Bud+Form), compared in each case with previous medication.

In Pohunek 2006, both groups of children investigated showed an improvement in asthma symptom scores. The changes in both daytime and nighttime symptom scores were comparable between treatment groups. With treatment, both groups showed fewer nocturnal awakenings compared with baseline (7% vs. 18% for Bud/Form and 7% vs. 17% for Bud+Form), and a higher proportion of symptom-free days (53% vs. 20% for Bud/Form and 51% vs. 18% for Bud+Form).

Therefore, regarding asthma symptoms, no advantage for either treatment option was shown. With respect to the outcome “asthma symptoms”, no additional benefit of Bud/Form compared with Bud+Form was demonstrated; in fact, for this outcome, the trials showed similar results for both types of administration.

Asthma exacerbations

In Jenkins 2006, more patients in the Bud+Form group reported a mild exacerbation than those in the Bud/Form group (51% vs. 45%). This difference was not statistically significant. In Zetterström 2001, the proportion of patients with mild exacerbations was the same in both groups (about 40%).

In Zetterström 2001, the proportion of patients with severe exacerbations was slightly higher with Bud+Form (9.6%) than with Bud/Form (6.5%); the difference was not statistically significant. In Rosenhall 2002, the proportion of patients with severe exacerbations was comparable between treatment groups (Bud/Form: 15%; Bud+Form: 14%).

Therefore, the trials do not provide evidence of different exacerbation rates for either type of administration.

Hospital admissions and outpatient visits

In Rosenhall 2003a+b, the Bud+Form group showed higher mean values for visits to an emergency department (ED) (0.34 visits/patient/12 months) and outpatient visits (0.42 visits/patient/12 months) than the Bud/Form group (0.10 and 0.27 visits/patient/12 months).
However, these rates, expressed as the mean number of visits per person per 12 months, were very low in both groups (<1 visit per person per 12 months). Statistical significance tests were not conducted. The relevance of the observed differences is unclear. The results cannot be assessed as evidence of a difference between either type of administration.

**Adverse drug effects**

In the 5 trials assessed, no differences in adverse events (AEs) were shown between either type of administration (Bud/Form and Bud+Form). There was hence no indication of differences in the harm potential of these treatment options.

**Health-related quality of life**

Overall, health-related quality of life was assessed in 3 trials (Pohunek 2006, Rosenhall 2002, and Rosenhall 2003a+b). A change in health-related quality of life during the course of the trial was only reported in Pohunek 2006 and Rosenhall 2002. In both trials, an increase in health-related quality of life (total score) by about 0.5 points was determined in both treatment groups. The improvements in the scores of the individual domains of the questionnaire by Rosenhall 2002 were also comparable between both groups. Rosenhall 2003a+b merely reported that regarding health-related quality of life, there were no differences between treatment groups. A difference in the quality of life and therefore an additional benefit in patients treated with Bud/Form or Bud+Form cannot be inferred from these trials.

**Fluticasone/salmeterol versus fluticasone+salmeterol**

**Asthma symptoms**

In the comparison Flu/Salm versus Flu+Salm, the proportion of patients who experienced symptom-free days or nights increased in all trials in both treatment groups (patients with 100% symptom-free days: baseline 0% to 5%, end of study 10% to 20%; patients with 100% symptom-free nights: baseline 10% to 15%, end of study 25% to 35%). In general, the results of both types of administration were comparable. A numerical (statistically non-significant) advantage of Flu/Salm versus Flu+Salm in respect of symptom-free nights (33% vs. 26% of patients), as seen in Chapman 1999, was not shown in the other trials. The results of the Flu/Salm and Flu+Salm groups were also comparable in the paediatric trial (van den Berg 2000).

In summary, with respect to the reduction in asthma symptoms, the trials do not provide evidence of an advantage for either type of administration. Hence, they do not provide evidence of an additional benefit of Flu/Salm compared with Flu+Salm. In fact, they indicate that asthma symptoms are reduced to a similar extent with both types of administration.

**Hospital admissions and outpatient visits**

In Aubier 1999, most patients did not need asthma-related medical care outside the study visits (Flu/Salm: 66% of patients; Flu+Salm: 68%). The proportion of patients who received
additional medical care was comparable between both groups. The number of outpatient visits and the number of patients admitted to hospital were also comparable between groups (hospital admissions for Flu/Salm vs. Flu+Salm: 4 vs. 6 patients).

For the outcome “hospital admissions and outpatient visits”, the data do not provide evidence of an additional benefit of either type of administration.

Adverse drug effects

No trials showed clinically relevant or statistically significant differences regarding the frequency and type of AEs. There are hence no indications of differences in the harm potential of either type of administration.

Activities of daily living

In Aubier 1999, about 25% of patients in each treatment group had to interrupt work or other activities because of asthma symptoms. For most affected patients, this interruption of daily activities lasted less than an hour. More than half of the patients had to work or perform other major activities under the effect of asthma symptoms; this impairment lasted 4 hours or longer in about 20% of patients.

The asthma-related restriction in activities of daily living was comparable between Flu/Salm and Flu+Salm; i.e. there was no advantage for either type of administration. There is hence no evidence of an additional benefit of either treatment option.

Treatment satisfaction

In Aubier 1999, before the start of the study, most patients were satisfied or very satisfied with their prior medication (74% and 64% of patients who were later randomized to the Flu/Salm and Flu+Salm groups). At the end of study, the proportion of patients who were satisfied or very satisfied with the medication had increased to 81% (Flu/Salm) and 79% (Flu+Salm). Treatment satisfaction at the end of study was therefore comparable between groups.

In this double-blind, double-dummy trial, a possible advantage of the use of a single inhaler in the Flu/Salm group compared with the use of 2 separate inhalers in the Flu+Salm group could not be perceived by patients. Patient satisfaction therefore referred to the treatment effect and not to how the drugs were administered. The impact of the differences in the type of administration could not be investigated in this trial.

In summary, the data do not provide evidence of an additional benefit of either type of administration (Flu/Salm or Flu+Salm).
Budesonide/formoterol versus fluticasone/salmeterol

Asthma symptoms

In the comparison Bud/Form versus Flu/Salm, asthma symptoms decreased in all trials in both treatment groups. The asthma symptom scores at the end of study were comparable between groups. In SAM40040 2004 (Dahl 2006), the proportion of patients with > 75% symptom-free days throughout the whole course of the trial was 40% in each group. Moreover, in each group, 58% of patients were symptom-free in > 75% of nights throughout the trial. In SAM40048 2003, the proportion of symptom-free days increased to a similar extent in both treatment groups (Bud/Form 22%; Flu/Salm 27%). In Kuna 2007, both groups also achieved a comparable increase in symptom-free days (from 9% in each group before the start of the study to 45% [Bud/Form] and 46% [Flu/Salm] during the study). In Kuna 2007, nocturnal awakenings were reduced from 33% of nights to 15% with Bud/Form and from 32% to 14% with Flu/Salm.

Regarding the effect on asthma symptoms, the trials therefore did not show a clinically relevant and statistically significant difference between the fixed combinations of Bud/Form and Flu/Salm. There is hence no evidence of an additional benefit of either treatment option.

Asthma exacerbations

In Aalbers 2004, the mean exacerbation rate was comparable between treatment groups (Bud/Form: 0.036/month; Flu/Salm: 0.041/month).

Likewise, in SAM40040 2004 (Dahl 2006), no statistically significant difference between both fixed combinations was shown with regard to the mean exacerbation rate (Bud/Form: 2.79/24 weeks; Flu/Salm: 2.69/24 weeks), the number of exacerbations per patient, the severity of exacerbations, and time to the first exacerbation. However, in the calculation of the adjusted annual exacerbation rate for moderate and severe exacerbations, at the end of study, statistically significant differences in favour of the Flu/Salm combination were reported.

In Kuna 2007, the number of patients with at least one severe exacerbation was comparable between both treatment groups (11% for Bud/Form versus 12% for Flu/Salm). The proportion of patients with mild exacerbations and of those with at least one hospital admission/ED visit was also comparable (mild exacerbations: 63% for Bud/Form vs. 59% for Flu/Salm; ≥ 1 hospital admissions/ED visit: 5% for Bud/Form vs. 6% for Flu/Salm). A statistically significant difference between groups in favour of Bud/Form was shown for the rate of hospital admissions/ED visits per 100 patients per 6 months. The rate in the Flu/Salm group was statistically significantly higher than in the Bud/Form group (8 vs. 5).

In the meta-analysis of SAM40040 (Dahl 2006) and Kuna 2007, no statistically significant difference between both fixed combinations was shown for the number of patients with at least one severe exacerbation (OR 1.03; 95% CI [0.79; 1.35]; medium heterogeneity). This lack of a difference also applied to the rate of severe exacerbations per period of time (no summary [effect] estimate provided due to high heterogeneity). For both of the above
outcomes, the results of the individual trials were inconsistent. Furthermore, in the meta-analysis of these 2 studies, no significant difference between groups was shown for exacerbations leading to an ED visit or hospital admission (OR 0.87; 95% CI [0.47; 1.60]).

In summary, a single statistically significant positive effect was shown for the fixed combinations of Bud/Form versus Flu/Salm with regard to the rate of hospital admissions/ED visits per patient per period. An opposite trend in favour of the Flu/Salm fixed combination was observed in SAM 40040 (Dahl 2006) with respect to the overall rate of severe exacerbations. Meta-analyses did not show statistically significant differences between the fixed combinations. Overall therefore, no evidence of an advantage for either fixed combination can be inferred from the results. Likewise, there is no evidence of an additional benefit of either fixed combination with regard to less severe exacerbations.

Hospital admissions and outpatient visits

Data on the use of outpatient and inpatient services were only collected in SAM40040 2004 (Dahl 2006) and Kuna 2007. Regarding outpatient visits (including ED visits), the number of affected patients, the absolute number of visits, and the rates (mean value/patient/6 months) were comparable between both fixed combinations. In respect of the use of inpatient services, the absolute risks with the fixed combination of Flu/Salm were numerically higher than with the fixed combination of Bud/Form (hospital admissions: 0.1% vs. 0.7%; stays in an intensive care unit: 0% vs. 0.3%; stays in a general ward: 0.1% vs. 0.6%). However, the overall number of observed cases was very small and the differences between groups were not statistically significant. Likewise, the data from Kuna 2007 did not show differences between treatment groups with regard to the follow items: transportation in an ambulance (0.007 Bud/Form versus 0.011 Flu/Salm); hospital days (0.101 Bud/Form versus 0.154 Flu/Salm); ED visits (0.061 Bud/Form versus 0.089 Flu/Salm); visits to doctors (specialists: 0.195 Bud/Form versus 0.135 Flu/Salm); general practitioners: 0.178 Bud/Form versus 0.135 Flu/Salm); house calls (0.013 Bud/Form versus 0.008 Flu/Salm); and days on oral steroids (1.06 Bud/Form versus 1.12 Flu/Salm).

In summary, no differences between either fixed combination with regard to hospital admissions and outpatient visits could be shown in these trials. An additional benefit of either therapy option has therefore not been demonstrated.

Adverse effects

No marked differences between both fixed combinations were shown with respect to the overall AE rate and the rate of study discontinuations due to AEs. In Aalbers 2004, the rate of patients with SAEs was higher in the Bud/Form group than in the Flu/Salm group (5% vs. 2%; 11 vs. 5 patients). In SAM40040 2004 (Dahl 2006), the absolute number of SAEs was higher with Flu/Salm than with Bud/Form (29 events in 20 [3%] patients vs. 13 events in 12 [2%] patients).
In Kuna 2007, the rates for overall AEs, SAEs, and study discontinuations due to AEs were slightly higher in the Bud/Form group than in the Flu/Salm group (Bud/Form vs. Flu/Salm: 40% vs. 38%; 4% vs. 3%; 1.2% vs. 0.9%). The differences were not statistically significant. In summary, no indications of differences can be inferred concerning the harm potential of the fixed combinations assessed (Bud/Form and Flu/Salm).

**Health-related quality of life**

In the comparison Bud/Form versus Flu/Salm, only Kuna 2007 collected data on health-related quality of life. The score of the AQLQ quality of life questionnaire increased on average by about 0.8 points in both groups. Regarding health-related quality of life, the trial did not show an advantage for either fixed combination investigated.

**Budesonide/formoterol SMART versus fluticasone/salmeterol-AMD**

**Asthma symptoms**

In the trial included in the comparison between Bud/Form-SMART and Flu/Salm-AMD (Vogelmeier 2005), asthma symptoms were only recorded indirectly. Regarding this outcome, there is hence no evidence available of an additional benefit of either fixed combination.

**Asthma exacerbations**

In the assessment of severe exacerbations (with hospital admissions/ED visits and/or oral steroid therapy > 3 days), patients treated with the combination of Bud/Form-SMART showed statistically significantly less severe exacerbations than those treated with Flu/Salm-AMD (0.19 vs. 0.23 events per patient and year; patients with exacerbations: 12% vs. 16%). The rate of severe exacerbations leading to hospital admission or an ED visit was similar in both treatment groups (Bud/Form-SMART vs. Flu/Salm-AMD: 0.04 vs. 0.05 [hospital admissions/ED visits per patient and year]; 3% vs. 4% [patients with exacerbations leading to a hospital admission or an ED visit]).

In summary, with regard to the occurrence of severe exacerbations (with hospital admissions/ED visits and/or oral steroid therapy > 3 days) Vogelmeier 2005 showed a positive effect of Bud/Form-SMART compared with Flu/Salm-AMD. This result indicates an additional benefit of Bud/Form-SMART; however, this is to be viewed with reservation, as it is unclear whether all studies conducted were available for the benefit assessment, and unpublished data could potentially call the result of the assessment into question (see Sections 5.1.4 and 6.2).

**Hospital admissions and outpatient visits**

The patients in the Bud/Form-SMART group used fewer non-physician health services (Bud/Form-SMART vs. Flu/Salm-AMD: 0.05 vs. 0.10) and needed fewer house calls by non-
physician health service providers (Bud/Form-SMART vs. Flu/Salm-AMD: 0.00 vs. 0.01) than those in the Flu/Salm-AMD group. The data refer to the number per patient per year. Other data on unplanned visits to physicians, ED visits, hospital days, or days on oral steroids were comparable. As the statistical methods applied in the group comparison were not clearly described in the study publication, it remained unclear whether the group differences were statistically significant. Therefore no indication of an additional benefit of either therapy option assessed can be inferred from the available data.

**Adverse drug effects**

In Vogelmeier 2005, the overall rate of SAEs was comparable between both groups (8% in each treatment group). A total of 1% (Bud/Form-SMART) and 2% (Flu/Salm-AMD) of patients discontinued the trial due to AEs. Therefore no indications result from these data of differences in the harm potential of Bud/Form-SMART and Flu/Salm-AMD.

**Health-related quality of life**

In Vogelmeier 2005, health-related quality of life (measured with the AQLQ) improved in both treatment groups (mean changes from baseline: 0.60 for Bud/Form-SMART vs. 0.57 for Flu/Salm-AMD). There were no statistically significant differences between groups. As far as health-related quality of life is concerned, on the basis of this study there is hence no evidence of an additional benefit of either therapy option investigated.

**Patient satisfaction with asthma medication**

Vogelmeier 2005 collected data on patient satisfaction with asthma medication, but did not report the results. The trial registry report contained only a general statement on the difference between groups; data on the questionnaire referring to the group comparison were not available. According to the registry report on Bud/Form-SMART versus Flu/Salm-AMD, “similar improvements were seen for both groups, and no differences were detected between the treatment groups”. There is hence no evidence of an additional benefit of either combination therapy that is explained by increased patient satisfaction.

**Beclomethasone/formoterol versus budesonide/formoterol**

**Asthma symptoms**

In the comparison between BDP/Form versus Bud/Form, Papi 2007a investigated the daytime and nighttime symptom scores separately and also investigated symptom-free days. Asthma symptoms decreased to a similar extent with both fixed combinations. With BDP/Form, the number of symptom-free days increased from 3% before the start of the study to 42% at the end of study (Bud/Form: from 4% to 38%). No advantage for either combination was observed. Therefore an additional benefit of BDP/Form or Bud/Form has not been demonstrated.
Asthma exacerbations

In Papi 2007a, no severe exacerbations leading to hospital admission were reported. The number of patients with moderate exacerbations was the same (2 per group with BDP/Form and Bud/Form). Papi 2007a did not show an advantage for either fixed combination assessed. Therefore this trial did not demonstrate an additional benefit of BDP/Form or Bud/Form.

Adverse drug effects

The overall AE rate was 37% in the BDP/Form group and 39% in the Bud/Form group. No SAEs were reported. With Bud/Form, one study discontinuation due to AEs was reported. Therefore Papi 2007a showed no difference in the harm potential of BDP/Form and Bud/Form.

Beclomethasone/formoterol versus fluticasone/salmeterol

Asthma symptoms

In the comparison BDP/Form versus Flu/Salm, Papi 2007b also investigated the daytime and nighttime asthma symptom scores separately. Data on symptom-free days were also reported. The results for the BDP/Form group and the Flu/Salm group were similar for the outcomes investigated; at the end of study, 56% symptom-free days were reported in the BDP/Form group and 54% in the Flu/Salm group. With regard to (a reduction in) asthma symptoms, no superiority of either combination was shown; concerning this outcome, Papi 2007b did not therefore provide evidence of an additional benefit of either fixed combination.

Asthma exacerbations

In Papi 2007b, a total of 8 patients (2 in the BDP/Form group versus 6 in the Flu/Salm group) experienced moderate exacerbations. Severe exacerbations leading to hospital admission were not reported. Statistically significant differences between groups were not shown. Regarding the occurrence of asthma exacerbations, Papi 2007b did not therefore provide evidence of an additional benefit of BDP/Form or Flu/Salm.

Adverse drug effects

The overall AE rate was 18% in the BDP/Form group and 14% in the Flu/Salm group. No SAEs and study discontinuations due to AEs occurred. Therefore Papi 2007b did not provide indications of a difference in the harm potential of BDP/Form and Flu/Salm.

Conclusion

Adolescents and/or adults

In respect of patient-relevant therapy goals, there is no evidence in adolescents and adults of an additional benefit of the fixed combinations (administered by a fixed combination inhaler) of budesonide/formoterol, fluticasone/salmeterol, or beclomethasone/formoterol compared
with the individual drugs (administered by separate inhalers). Vice versa, there is no additional benefit of the administration of the individual drugs. In fact, when the same inhaling system is applied in each treatment group (Bud/Form: Turbohaler®, Flu/Salm: Diskus®), overall the trials on budesonide/formoterol and fluticasone/salmeterol provide similar results for the use of both types of administration. No relevant studies were found comparing the fixed combination of beclomethasone/formoterol versus the individual drugs.

In adolescents and adults, there is no evidence of a difference in benefit or harm between the fixed combination of budesonide/formoterol (fixed dose via Turbohaler®) and the fixed combination of fluticasone/salmeterol (fixed dose via Diskus® or Evohaler®).

In adults there is an indication of an additional benefit of the fixed combination of budesonide/formoterol for maintenance and reliever therapy (Bud/Form-SMART via Turbohaler®) compared with the fixed combination of fluticasone/salmeterol (Flu-Salm-AMD via Diskus®) with regard to severe exacerbations. However, this is to be viewed with reservation, as it is unclear whether all studies conducted were available for the benefit assessment, and unpublished data could potentially call the result of the assessment into question (see Section 6.2 of the final report). Regarding further patient-relevant outcomes (asthma symptoms, hospital admissions, AEs, health-related quality of life), treatment with these types of fixed combinations did not show different effects.

In adults, there is no evidence of a difference in the benefit of the fixed combination of beclomethasone/formoterol (via MDI) and the fixed combination of budesonide/formoterol (via dry powder inhaler, DPI).

The same applies to the comparison between the fixed combination of beclomethasone/formoterol (via MDI) and the fixed combination of fluticasone/salmeterol (via MDI).

**Children**

Data in children were available for the fixed combinations of fluticasone/salmeterol and budesonide/formoterol compared with the individual drugs of the combination therapies. For both comparisons, these trials did not provide evidence of a difference between either type of administration. In fact, when the same inhaling system is applied in each treatment group (fluticasone/salmeterol: Diskus®; budesonide/formoterol: Turbohaler®), overall the trials provide similar results for the fixed combinations and the individual drugs.

**Key words:** asthma, long-acting beta-2-receptor agonists, glucocorticosteroids, combination drugs, fixed combinations, systematic review