Therapeutic equivalence of budesonide/formoterol delivered via breath-actuated inhaler vs pMDI

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Summary
Rationale: To assess equivalence of twice daily (bid) budesonide/formoterol (BUD/FM) 160/4.5 \( \mu \)g via breath-actuated metered-dose inhaler (BAI) versus pressurized metered-dose inhaler (pMDI).
Methods: This 12-week, double-blind, multicenter, parallel-group study, randomized adolescents and adults (aged \( \geq 12 \) years) with asthma (and \( \geq 3 \) months daily use of inhaled corticosteroids) to BUD/FM BAI 2 \( \times \) 160/4.5 \( \mu \)g bid, BUD/FM pMDI 2 \( \times \) 160/4.5 \( \mu \)g bid, or BUD pMDI 2 \( \times \) 160 \( \mu \)g bid. Inclusion required prebronchodilator forced expiratory volume in one second (FEV1) \( \geq 45 \) to \( \leq 85 \)% predicted, and reversibility of \( \geq 12 \% \) in FEV1 (ages 12 to <18 years) or \( \geq 12 \% \) and 200 mL (ages \( \geq 18 \) years). Confirmation that 60-min postdose FEV1 response to BUD/FM pMDI was superior to BUD pMDI was required before equivalence testing. Therapeutic equivalence was shown by treatment effect ratio of BUD/FM BAI vs BUD/FM pMDI on 60-min postdose FEV1 and predose FEV1 within confidence intervals (CIs) of 80–125%.
Results: Mean age of 214 randomized patients was 42.7 years. BUD/FM pMDI was superior to BUD pMDI (60-min postdose FEV1 treatment effect ratio, 1.10; 95% CI, 1.06–1.14; \( p < 0.001 \)). Treatment effect ratios for BUD/FM BAI versus pMDI for 60-min postdose FEV1 (1.01; 95% CI, 0.97–1.05) and predose FEV1 (1.03; 95% CI, 0.99–1.08) were within predetermined CIs for therapeutic equivalence. Adverse event profiles, tolerability, and patient-reported ease of use were similar.

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Introduction

Inhaled corticosteroids (ICs) are recommended as first-line treatment for patients with persistent asthma, and the addition of an inhaled long-acting β₂-agonist (LABA) can be considered to improve lung function and symptoms in patients whose asthma is not well controlled on ICS alone [1,2]. Combination ICS/LABAs are available as breath-actuated dry powder inhalers (DPI) and manually-actuated pressurized metered-dose inhalers (pMDIs). However, to date, a breath-actuated option in a pMDI device has not been available for the delivery of a combination of ICS/LABA. For some patients, poor coordination between actuation and inhalation with use of a pMDI can lead to dosing errors [3]. A breath-actuated pMDI inhaler (BAI) could provide an alternative option for those patients unable to overcome poor hand-lung coordination [4]. This study was designed to compare the therapeutic efficacy and safety of combined budesonide/formoterol delivered by a BAI currently in clinical development with those of combined budesonide/formoterol delivered by a pMDI in patients with moderate-to-severe, symptomatic asthma.

Methods

Patients

Inclusion and exclusion criteria were designed to select asthmatic patients aged ≥12 years who required medium- to high-dose ICSs and demonstrated reversibility of airflow obstruction with an inhaled bronchodilator after a run-in period. Patients must have used ICSs daily for ≥3 months before study entry and required consistent use of stable daily doses of medium- to high-dose ICSs in the 30 days before study entry. Minimum daily doses permitted were: beclomethasone dipropionate 504 μg/d (chlorofluorocarbon pMDI) or 160 μg/d (actuation counter pMDI), budesonide 400 μg/d, flunisolide 1000 μg/d, fluticasone 264 μg/d (chlorofluorocarbon pMDI) or 300 μg/d (Diskus), triamcinolone acetonide 800 μg/d, mometasone 400 μg/d, or ciclesonide 160 μg/d.

Patients had to have asthma symptom scores (nighttime or daytime) of ≥0 on ≥3 of the last 7 days of the run-in period and prebronchodilator FEV₁ ≥45% and ≤85% of predicted normal at baseline. Asthma symptom score is defined as: 0, no asthma symptoms; 1, you are aware of your asthma symptoms but you can easily tolerate the symptoms; 2, your asthma is causing you enough discomfort to cause problems with normal activities (or with sleep); or 3, you are unable to do your normal activities (or to sleep) because of your asthma.

To ensure reversibility with β₂ agonists, patients had to meet baseline postbronchodilator criteria (4–6 actuations of albuterol pMDI [90 μg/inhalation] or salbutamol pMDI [100 μg/inhalation] or after inhalation of 2.5 mg nebulized albuterol) of a change of ≥12% in FEV₁ from baseline for patients aged ≥12 and <18 years or a change of ≥12% and 200 mL in FEV₁ from baseline for patients aged ≥18 years. In addition, patients must have demonstrated the ability to use the BAI, pMDI, and a peak flow meter correctly.

Exclusion criteria included a history of life-threatening asthma during the past 2 years; hospitalization for asthma-related condition in the previous 6 months; intake of oral, rectal, or parenteral glucocorticosteroids within 30 days before study entry; use of any β-blocking agent, including eye drops; required treatment with systemic steroids during the study run-in period; or a ≥10 pack-year history of smoking. Patients were also excluded if they had any significant disease or disorder which, in the opinion of the investigator, may increase risk to the patient or influence the results.

The final study protocol was approved by institutional review boards at each center. Patients provided written informed consent and written assent as appropriate, before study procedures were begun. The study was performed in accordance with ethical principles based on the Declaration of Helsinki and consistent with the International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements.

Study design and treatment

This double-blind, randomized, active-controlled, multicenter, parallel-group, 12-week study was conducted in the United States, Bulgaria, and Hungary (NCT01360021). A flow chart of the study design is shown in Fig. 1. The study consisted of an enrollment visit (visit 1) and a 2-week run-in period beginning at visit 2, during which LABAs were discontinued, and patients were treated with BUD actuation counter pMDI 160 μg, 2 inhalations twice daily (bid).

Reversibility testing was performed at visit 2 (at the start of the run-in period) and visit 3 (approximately 1–3 days before randomization), and to be eligible for the study, patients had to be reversible on both of these occasions. If a patient did not fulfill the eligibility criteria for reversibility, one retest was allowed at either visit 2 or visit 3 (ie, only one retest total for the duration of the study).
The reversibility requirement was designed to ensure patients are capable of responding to beta agonists and therefore have a potential to show a difference in the primary objective.

Patients were randomized at visit 4 and attended the clinic on 3 further occasions (week 3, 7, and 12), followed by a telephone call follow-up 2 weeks later. Lung function testing, eDiary collection, and adverse event (AE) check occurred at each visit, and device functionality questioning occurred at weeks 3, 7, and 12. AEs were the only data collected on the telephone call. At visit 4, patients were randomized to receive 1 of the 3 following double-blind treatments shown in Fig. 1: BUD/FM BAI 160/4.5 mg (Fig. 2), 2 inhalations bid plus placebo pMDI, 2 inhalations bid; BUD/FM pMDI 160/4.5 mg, 2 inhalations bid plus placebo BAI, 2 inhalations bid; or BUD pMDI 160 mg, 2 inhalations bid plus placebo BAI, 2 inhalations bid. At visit 2 and visit 4, patients were instructed on proper inhaler use, and devices were available at each study center for training purposes and for patients to practice. Instruction and practice also occurred prior to dispensing blinded study drug at visit 4. Confirmation of proper device use was accomplished via patient response in their eDiary to device functionality questions. Additionally, for further confirmation at return visits, the investigator or staff asked the patient if device instructions were being followed and provided additional training if required.

Concomitant medications

Patients were allowed the use of a short-acting β2-agonist (SABA) as rescue medication throughout the study including enrollment, run-in, and treatment periods; albuterol pMDI (90 μg/inhalation)/salbutamol pMDI (100 μg/inhalation) were provided by the study site as rescue medication. Medications not allowed during the study included parenteral, oral, or rectal glucocorticosteroids; leukotriene antagonists; inhaled disodium cromoglycate; inhaled nedocromil sodium or 5-lipoxygenase inhibitors; methylxanthines; inhaled anticholinergics; any monoclonal or polyclonal antibody therapy taken for any reason; or CYP3A4 inhibitors (eg, ketoconazole).

Use of the following medications was allowed during the study: mucolytics and expectorants not containing bronchodilators; antihistamines (other than terfenadine, astemizole, mizolastine); allergen-specific immunotherapy if the patient had been on a maintenance regimen for ≥3 months before visit 1 and remained on a maintenance regimen during the study; topical, nasal, and/or ocular formulations of glucocorticosteroids; topical, nasal and/or ocular disodium cromoglycate and/or nedocromil sodium. Other medication, which was considered necessary for the patient’s safety and well-being, could be administered at the discretion of the investigator(s).

Figure 1  Flow chart of study design. BAI, breath-actuated metered-dose inhaler; bid, twice daily; BUD, budesonide; FM, formoterol; pMDI, pressurized metered-dose inhaler; TC, telephone conversation.

Figure 2  Schematic representation of the breath-actuated inhaler device. Trigger flow rate is less than 28 L/min. Data on file [9].
Study objectives and evaluations

The primary objective of this study was to evaluate therapeutic equivalence of BUD/FM delivered by BAI with BUD/FM delivered by pMDI. The primary efficacy end points for assessing therapeutic equivalence were comparison of the effects of BUD/FM BAI with BUD/FM pMDI on FEV₁ at 60 min postdose and FEV₁ predose. To ensure that any potential differences in efficacy could be detected, it was prespecified that BUD/FM pMDI was superior to BUD pMDI on 60-min postdose FEV₁. Subsequent assessment of therapeutic equivalence would be established if the 95% confidence interval (CI) limits for the ratio of treatment effects of BUD/FM delivered by BAI versus pMDI was contained within the equivalence limits of 80–125% [5].

Secondary efficacy end points collected by means of an electronic diary (eDiary) included mean change from baseline for the overall treatment period for morning and evening peak expiratory flow (PEF), daytime and nighttime total asthma symptom scores, awakening-free nights (nights without awakening due to asthma symptoms), daytime and nighttime rescue medication use, and symptom-free days.

A secondary objective was to assess patient-reported functionality of the 2 devices. Patients used the eDiary to complete an end-of-study questionnaire through which the patient-reported ease of use of each device was evaluated. This questionnaire contained 2 questions ("How easy was it to use the inhaler?" and "How easy is it to determine when you will run out of medicine [from the inhaler]?"). Each question was scored on a 7-point scale, with options ranging from 'Extremely easy' to 'Extremely difficult': (0, extremely easy; 1, very easy; 2, somewhat easy; 3, neither easy nor difficult; 4, somewhat difficult; 5, very difficult; 6, extremely difficult).

Safety evaluations

The safety profile of BUD/FM delivered by pMDI or BAI was assessed by comparing the nature, intensity, and severity of AEs occurring in each treatment group.

Statistical analyses

To assess the therapeutic equivalence of newly developed BUD/FM BAI device with the marketed BUD/FM pMDI device, a step-down procedure was used to address multiplicity. First, superiority needed to be demonstrated for BUD/FM pMDI versus BUD pMDI for the difference in postdose FEV₁ with a statistical significance level of 5%. If this requirement was met, then the 95% CI for the ratio of treatment effects was to be used to assess therapeutic equivalence of BUD/FM pMDI versus BUD/FM BAI. The primary variable for this comparison was the mean of the postdose FEV₁ measurements obtained during treatment period (visits 4–7) expressed as ratio of the predose FEV₁, at randomization (visit 4) to create the treatment:baseline ratio. The logarithm of this value was used for analysis using the analysis of covariance (ANCOVA) model with the fixed factors treatment and country, and the logarithm of the predose FEV₁ at randomization as a covariate.

If the superiority condition was met in comparison to BUD pMDI, a 95% CI for the ratio of treatment effects contained within equivalence limits of 80–125% [5] for FEV₁ 60 min postdose and FEV₁ predose would establish therapeutic equivalence of BUD/FM BAI and BUD/FM pMDI. The model used to estimate the ratio of treatment effects was the same for predose FEV₁ as for postdose FEV₁ described above (ie, a multiplicative ANCOVA with the treatment and country as factors and baseline predose FEV₁ as a covariate).

For all variables other than these, pair-wise comparisons were made and nominal (unadjusted for multiplicity) p values are reported. All hypothesis testing was conducted using 2-sided tests. The p values were rounded to 3 decimal places, and all p values ≤0.05 after rounding were considered statistically significant.

Results

Patients

Patient disposition is shown in Fig. 3, and the key demographics of the randomized population are shown in

![Figure 3](image_url)
Table 1. In total, 214 patients with a mean age of 42.7 years and a mean time from asthma diagnosis of 24/C6 years were randomized, of whom 213 received/C21 dose of study drug. One patient was randomized in error in the randomization system while the investigator intended to mark the patient as a screen failure. The subject was immediately discontinued from the study before receiving study treatment and was therefore excluded from efficacy and safety analyses. This cohort of 213 patients formed the full analysis set for efficacy parameters and the safety analysis set.

Before study entry, 152 of 213 patients (71.4%) were using combination therapy of β2-agonists plus other drugs, with fluticasone plus salmeterol being the most common (n = 86; 40.4%). Inhaled glucocorticoids were used by 211 patients (99.1%) before run-in, with fluticasone being the most common (n = 105; 49.3%). Two patients receiving ICS/LABA combination therapy before study entry were not switched to monocomponent ICS before run-in but were subsequently included in the study. Selective SABAs were used by 210 patients (98.6%), with inhaled albuterol or salbutamol being the most common (n = 190; 89.2%). Other prestudy drugs for asthma included leukotriene receptor antagonists (n = 18; 8.5%), xanthines (n = 5; 2.3%), anticholinergics (n = 1; 0.5%), and allergen extracts (n = 1; 0.5%).

Study medication adherence, which was defined as the percentage of the expected number of medication intakes recorded in the eDiary, as self-reported on a daily basis, was generally good and similar across groups (87.9%, 87.1%, and 85.4% for BUD/FM BAI, BUD/FM pMDI, and BUD pMDI, respectively).

### Efficacy

The geometric ratio of the mean change from baseline in postdose FEV1 over time for the 3 treatment groups is shown in Fig. 4. Table 2 shows the postdose FEV1 treatment comparisons, for which there was a statistically significant difference between BUD/FM pMDI and BUD pMDI (p < 0.001). Therefore, the required superiority of BUD/FM pMDI versus BUD pMDI was demonstrated. For postdose FEV1, the ratio of the treatment effects for the BUD/FM BAI and the pMDI was estimated to be 1.01, with a CI of 0.97–1.05, within the predetermined limits, indicating therapeutic equivalence (Table 2).

The mean change in predose FEV1 over time for the 3 treatment groups is shown in Fig. 5, and Table 2 shows the treatment comparisons for predose FEV1. The predose FEV1 ratio of the treatment effects for BUD/FM BAI and BUD/FM
pMDI was estimated to be 1.03, with a CI of 0.99–1.08, confirming therapeutic equivalence.

Secondary outcomes

The mean change from baseline over time in morning and evening PEF for the 3 treatment groups is shown in Fig. 6.

The degree of improvement in morning and evening PEF was similar for BUD/FM delivered by either BAI or pMDI (nominal \( p = 0.825 \) and 0.810 for morning and evening PEF, respectively). In contrast, BUD/FM delivered by both devices resulted in improved morning and evening PEF versus BUD pMDI (Table 3); Table 3 also shows the other secondary efficacy end points unadjusted for multiplicity. The only nominal \( p \) value favoring BUD/FM pMDI over BAI was for awakening-free nights with the difference \( p < 0.05 \) (unadjusted \( p = 0.025 \)). All secondary end points demonstrated numerical superiority for both BUD/FM BAI and pMDI versus BUD pMDI. Nominal \( p \) values \( < 0.05 \) were observed for all BUD/FM BAI versus BUD pMDI comparisons except awakening-free nights, rescue medication use, and symptom-free days (Table 3).

Based on eDiary answers twice daily to the yes/no question “Did the inhaler deliver a puff every time you inhaled today?”, patients indicated delivery of the dose on 99.2% and 99.4% of occasions for BUD/FM BAI and pMDI, respectively. For both BUD/FM BAI and BUD/FM pMDI, a large majority of patients (86.3% and 88.2%, respectively) reported the ease of use to be ‘extremely easy’ or ‘very easy’. The percentage of patients reporting the ease of determining when the medication will run out as ‘extremely easy’ or ‘very easy’ was numerically greater for BUD/FM BAI than the pMDI device (87.7% and 73.9%, respectively).

Safety

Overall, AEs were experienced by 21 (29.6%), 24 (33.8%), and 19 (26.8%) of patients in the BUD/FM BAI, BUD/FM pMDI, and BUD pMDI groups, respectively. However, only 1 serious AE occurred, a case of appendicitis in the BUD/FM pMDI group, and this was not considered related to treatment.
The most frequently reported AEs were viral upper respiratory tract infections, asthma, bronchitis, bacterial upper respiratory tract infection, nasopharyngitis, oral candidiasis, and enteritis. Viral upper respiratory tract infections occurred in 2 (2.8%), 5 (7.0%), and 3 (4.2%) of patients in the BUD/FM BAI, BUD/FM pMDI, and BUD pMDI groups, respectively. Asthma was listed as an AE in 1 (1.4%), 2 (2.8%), and 3 (4.2%) of the patients in the BUD/FM BAI, BUD/FM pMDI, and BUD pMDI groups, respectively. The corresponding rates for bronchitis were 1 (1.4%), 3 (4.2%), and 0 (0.0%). Other AEs occurred in ≤2 patients in any group.

Eight patients discontinued treatment because of AEs, of whom 5 discontinued because of asthma exacerbations (1, 1, and 3 patients in the BUD/FM BAI, BUD/FM pMDI, and BUD pMDI groups, respectively). Other causes of discontinuation were gout (BUD/FM BAI), eczema and gingival pain (BUD/FM pMDI), and bacterial upper respiratory tract infection (BUD pMDI).

**Discussion**

The aim of this study was to evaluate the therapeutic equivalence of a BAI and conventional pMDI device delivering the BUD/FM combination. For both postdose and predose FEV₁, the CIs for the ratio of the treatment effects for BUD/FM BAI and pMDI were within the 95% CI equivalence limits of 80–125%, demonstrating therapeutic equivalence. All secondary end points provide

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![Figure 5](image_url)

Figure 5 Ratio of geometric mean of treatment to baseline: predose FEV₁ (L) over 12 weeks and treatment average. The ratio is calculated as geometric mean of treatment average divided by geometric mean at baseline. Treatment average is defined as the mean of all available variables after randomization. Baseline is defined as the last predose value before first dose of randomized therapy at visit 4 (week 0). BAI, breath-actuated metered-dose inhaler; BUD, budesonide; FEV₁, forced expiratory volume in 1 s; FM, formoterol; pMDI, pressurized metered-dose inhaler; Trt. Avg., treatment average.

![Figure 6](image_url)

Figure 6 Self-reported morning (A) and evening (B) PEF. Baseline is the mean of run-in period values. BAI, breath-actuated metered-dose inhaler; BUD, budesonide; FEV₁, forced expiratory volume in 1 s; FM, formoterol; PEF, peak expiratory flow; pMDI, pressurized metered-dose inhaler.
supporting evidence for the equivalent efficacy of BUD/FM administered by BAI or pMDI except for awakening-free nights. However, the baseline level of awakening-free nights was relatively high for all groups (79–82%) with accordingly small percent changes at study end (2.5–8.6%) observed across all groups, and there was no statistically significant difference in either night time symptoms or night time rescue inhaler use between BUD/FM BAI and pMDI.

Both primary (postdose FEV$_1$) and secondary (morning and evening PEF) pulmonary function end points are consistent with the superior efficacy of BUD/FM versus BUD alone. Figs. 4–6 show that the improvements in most pulmonary function variables were sustained across the study period. These results are in line with findings of 2 previous 12-week trials in which postdose FEV$_1$ and morning and evening PEF were significantly improved with BUD/FM pMDI versus BUD alone [6,7]. Similarly, the effects of BUD/FM delivered by either device were numerically superior to BUD alone for all patient-reported outcomes. As with pulmonary function improvements, these results are consistent with those of previous studies of BUD/FM and BUD alone [6–8].

Statistical significance of BUD/FM versus BUD alone was observed for postdose FEV$_1$, demonstrating the ability to discriminate differences in efficacy. Improvement in pre-dose FEV$_1$ in response to BUD/FM pMDI versus BUD alone was numerically better, but not statistically significant in our study (Table 2). The magnitude of the response in predose FEV$_1$ observed in the present study was similar to that noted in previously published studies [6–8]. The lack of statistical significance for the average change in predose FEV$_1$ during the treatment period between BUD/FM pMDI and BUD pMDI in the present study could be explained by differences in the dose of medication employed [7,8] and differences in the population studied [7]. Moreover, unlike the previous studies [6–8], our study was not statistically powered to assess differences in average predose FEV$_1$ between BUD/FM pMDI and BUD pMDI as a primary outcome variable.

### Table 3 Treatment group differences for secondary end points.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ANCOVA summary treatment comparisons</th>
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<tbody>
<tr>
<td></td>
<td>LS mean (SE)</td>
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<tr>
<td><strong>Morning PEF (L/min)</strong></td>
<td></td>
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<tr>
<td>BUD/FM BAI minus BUD pMDI</td>
<td>35.01 (6.72)</td>
</tr>
<tr>
<td>BUD/FM pMDI minus BUD pMDI</td>
<td>33.52 (6.80)</td>
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<tr>
<td>BUD/FM BAI minus BUD/FM pMDI</td>
<td>1.49 (6.75)</td>
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<tr>
<td><strong>Evening PEF (L/min)</strong></td>
<td></td>
</tr>
<tr>
<td>BUD/FM BAI minus BUD pMDI</td>
<td>33.73 (6.14)</td>
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<tr>
<td>BUD/FM pMDI minus BUD pMDI</td>
<td>32.25 (6.21)</td>
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<tr>
<td>BUD/FM BAI minus BUD/FM pMDI</td>
<td>1.48 (6.15)</td>
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<tr>
<td><strong>Asthma total symptom score</strong></td>
<td></td>
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<tr>
<td>BUD/FM BAI minus BUD pMDI</td>
<td>–0.27 (0.11)</td>
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<tr>
<td>BUD/FM pMDI minus BUD pMDI</td>
<td>–0.40 (0.12)</td>
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<tr>
<td>BUD/FM BAI minus BUD/FM pMDI</td>
<td>0.13 (0.11)</td>
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<tr>
<td><strong>Awakening-free nights (%)</strong></td>
<td></td>
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<tr>
<td>BUD/FM BAI minus BUD pMDI</td>
<td>1.18 (2.70)</td>
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<tr>
<td>BUD/FM pMDI minus BUD pMDI</td>
<td>7.28 (2.7)</td>
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<tr>
<td>BUD/FM BAI minus BUD/FM pMDI</td>
<td>–6.10 (2.69)</td>
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<tr>
<td><strong>Daily rescue medication use (inhalations/24 h)</strong></td>
<td></td>
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<tr>
<td>BUD/FM BAI vs BUD pMDI</td>
<td>–0.44 (0.23)</td>
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<tr>
<td>BUD/FM pMDI vs BUD pMDI</td>
<td>–0.70 (0.23)</td>
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<tr>
<td>BUD/FM BAI vs BUD/FM pMDI</td>
<td>0.26 (0.23)</td>
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<tr>
<td><strong>Symptom-free days (%)</strong></td>
<td></td>
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<tr>
<td>BUD/FM BAI vs BUD pMDI</td>
<td>5.63 (4.29)</td>
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<tr>
<td>BUD/FM pMDI vs BUD pMDI</td>
<td>11.70 (4.28)</td>
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<tr>
<td>BUD/FM BAI vs BUD/FM pMDI</td>
<td>–6.07 (4.25)</td>
</tr>
<tr>
<td><strong>Rescue-free days (%)</strong></td>
<td></td>
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<tr>
<td>BUD/FM BAI vs BUD pMDI</td>
<td>11.20 (4.66)</td>
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<tr>
<td>BUD/FM pMDI vs BUD pMDI</td>
<td>19.02 (4.66)</td>
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<tr>
<td>BUD/FM BAI vs BUD/FM pMDI</td>
<td>–7.82 (4.65)</td>
</tr>
</tbody>
</table>

ANCOVA includes treatment and country as a factor and baseline value as covariate.
ANCOVA, analysis of covariance; BAI, breath-actuated metered-dose inhaler; BUD, budesonide; CI, confidence interval; FM, formoterol; LS, least squares; PEF, peak expiratory flow; pMDI, pressurized metered-dose inhaler; SE, standard error.

*Nominal p values reported, unadjusted for multiplicity.
The BAI device is similar to the pMDI device in many ways including identical drug formulations, canister, valve type, and stem orifice, as well as very similar mouthpieces. The basic mode of operation is also the same between the pMDI and BAI devices: a force is applied to the canister base, which depresses the metering valve and releases a dose. For a pMDI inhaler, the force is created when the patient presses down on the top of the inhaler while inhaling. For the BAI device, a patient’s inhalation triggers a spring, which applies the force for release of the medication (therefore eliminating the need to coordinate inhalation with manual actuation). The trigger inspiratory flow rate is less than 28 L/min [9] which almost all patients can achieve [10]. The BAI was a new device to all patients in the study, and results from the patient functionality study indicated that the ease of use was similar to the pMDI device.

Patients in both the pMDI and BAI groups reported that their device delivered a dose on greater than 99% of occasions. However, there were differences in the ease of identifying when medication was running out. More patients using the BAI device (55%) than the pMDI device (41%) found it ‘extremely easy,’ which may be because of the different dose counters used on each device. The pMDI device has a fuel-gauge-style dose counter, with an arrow pointing to a circular gauge ranging from 120 to 0, with demarcations every 5 actuations and numerals every 10 actuations. The BAI device has a mechanical digital counter that displays the exact number of actuations remaining, starting at 120 and counting down in increments of 1 after each actuation.

The safety profile of both devices was consistent with that of previously published results [6,7]. Noonan et al. [6] compared BUD/FM pMDI with BUD pMDI, FM DPI, BUD plus FM in separate inhalers (BUD pMDI + FM DPI), and placebo in moderate to severe asthma patients. As with the present study, all treatments were well tolerated, and most AEs were mild to moderate [6]. In the Noonan study, the incidence of oral candidiasis in the BUD/FM pMDI group was higher than that in other groups [6]. However, in the present study, oral candidiasis was experienced by only 1 patient in each patient group.

Corren et al. [7] also reported safety results from a 12-week trial of BUD/FM pMDI versus BUD pMDI and FM DPI in patients with mild to moderate asthma. As with the present study, the treatments were well tolerated, and most AEs were of mild or moderate intensity [7]. In the Corren study [7], the most common AE possibly related to BUD/FM pMDI treatment was cough (2 patients; 1.6%), with single (0.8%) additional cases of headache, pharyngolaryngeal pain, tremor, and jitteriness. In the present study, headache occurred in just 1 patient (1.4%) in the BUD/FM BAI group and in none of the patients receiving BUD/FM pMDI. The only case of cough was reported in the BUD/FM BAI group, and 1 patient in each of the BUD/FM groups experienced tremor.

Conclusion

BUD/FM 160/4.5 μg × 2 inhalations bid administered by a BAI device is therapeutically equivalent to BUD/FM 160/4.5 μg × 2 inhalations bid delivered by a conventional pMDI based on both predose and postdose FEV₁. Furthermore, no difference in safety profiles was identified. The introduction of BUD/FM BAI would represent an expansion of options to help tailor effective ICS/LABA combination therapy for patients with moderate-to-severe asthma.

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Author declaration of financial interest


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