

Bronchodilator effect of single-dose formoterol administered by pressurized metered-dose inhaler in children with asthma aged 6 to <12 years receiving budesonide

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ABSTRACT

Dose–response of formoterol via pressurized metered-dose inhaler (pMDI) has not been determined in asthmatic pediatric patients aged 6 to <12 years. This study was designed to assess the bronchodilating dose–response of three formoterol pMDI doses in children with stable asthma aged 6 to <12 years receiving twice-daily (b.i.d.) budesonide 160 micrograms. A U.S., multicenter, five-way crossover study compared single doses of formoterol, a long-acting beta-agonist, via pMDI (2.25, 4.5, and 9 micrograms) or dry powder inhaler (12 micrograms; active comparator) and placebo, with a 3- to 14-day washout period between doses. Budesonide pMDI 160 micrograms, an inhaled corticosteroid, was given b.i.d. throughout the study. Fifty-four pediatric patients (mean age, 9.2 years; mean asthma history, 6.1 years) were randomized. All formoterol doses showed significantly higher average 12-hour forced expiratory volume in 1 second (FEV₁; area under the curve) versus placebo (primary efficacy). Formoterol pMDI 4.5 and 9 micrograms showed significantly greater average 12-hour FEV₁ than formoterol 2.25 micrograms ($p = 0.0007$ and $p = 0.0001$, respectively). Formoterol also resulted in significant improvement in maximum FEV₁ during the 12-hour treatment period (secondary efficacy) with formoterol 4.5-, 9-, and 12-microgram doses versus placebo and the formoterol 2.25-microgram dose. Bronchodilation was not maintained during the 12-hour dosing interval with formoterol 2.25 micrograms. No serious adverse events were reported. Formoterol pMDI showed generally dose-proportional pharmacokinetics to 9 micrograms, as determined by urinary excretion. Single doses of formoterol pMDI showed a dose–response, with formoterol 9 micrograms exhibiting a maximum response, in pediatric patients aged 6 to <12 years with persistent stable asthma maintained on b.i.d. budesonide pMDI 160 micrograms.

Clinical trial NCT01136655, www.clinicaltrials.gov.

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Inhaled corticosteroids (ICSs) are the most consistently effective long-term asthma control medications and are recommended as first-line treatment for patients with persistent asthma.^{1,2} For most patients with asthma not well controlled on ICS alone, the addition of a long-acting inhaled β_2 -agonist (LABA) is an effective and safe treatment to improve lung function and provide symptomatic relief.^{1,2}

Recommendations for asthma in children aged 5 to <12 years mirror those for adults, with guidelines suggesting that the addition of an LABA to a low-dose ICS is an appropriate option for patients whose asthma is not adequately controlled on low-dose ICSs.^{1,2} In line with these recommendations, the combination of budesonide, an ICS, and formoterol, a LABA, in a

pressurized metered-dose inhaler (pMDI) has shown greater efficacy and similar tolerability compared with budesonide alone in asthmatic patients aged ≥ 12 years^{3–5} and children aged 6 to <12 years with persistent asthma.^{6,7}

Currently, budesonide/formoterol pMDI is not indicated in the United States for use in asthma for children <12 years of age. This study evaluated the bronchodilating effects of three doses of formoterol administered via pMDI in a population of asthmatic children aged 6 to <12 years with stable disease maintained on a medium-dose ICS. The safety and systemic exposure to formoterol when used in combination with budesonide in asthmatic children was also assessed.

METHODS

Patients

Patients between the ages of 6 and <12 years with a documented diagnosis of asthma, as defined by the American Thoracic Society, for at least 6 months before the first study visit were eligible. Inclusion and exclusion criteria were designed to select patients who were

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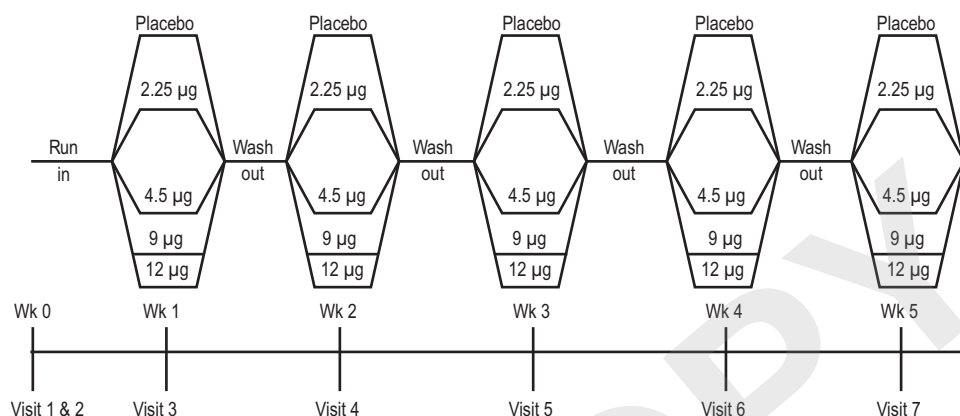
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Figure 1. Study design. At each visit, patients received one of the double-blind formoterol (or single blind in the case of formoterol DPI 12 μ g) treatments. During the run-in/qualification and washout periods, patients received open-label budesonide pMDI 160 μ g b.i.d. to maintain stable asthma. pMDI, pressurized metered-dose inhaler; b.i.d., twice daily; DPI, dry-powder inhaler.



stable and asymptomatic on medium-dose ICSs. If a patient was taking a fixed combination of ICS and LABA, the patient was placed on a comparable dose of ICS without LABA at least 48 hours before spirometry.

Patients were required to have forced expiratory volume in 1 second (FEV₁) of ≥ 60 and $\leq 85\%$ of predicted normal measured ≥ 6 hours after the last dose of inhaled short-acting β -agonist (SABA) and ≥ 48 hours after the last dose of inhaled LABA.

Reversibility was required by FEV₁ measurement of $\geq 15\%$ of prealbuterol level within 15–30 minutes after administration of standard-dose albuterol (MDI, 90 μ g/inhalation, 2–4 actuations, or ≤ 2.5 mg of nebulized albuterol).

Exclusion criteria included hospitalization for >24 hours at least once or emergency treatment more than once for acute deterioration of asthma during the 6 months before enrollment. Patients were also excluded if they had required treatment with systemic corticosteroids for any reason within the 12 weeks before enrollment, had participated in another investigational drug study within 4 weeks or a prior Symbicort clinical study within the previous 12 months, were currently being treated with a β -blocker (including eye drops), or had used any monoclonal or polyclonal antibody therapy for any reason within the 6 months before the study run-in period.

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. The final study protocol was approved by institutional review boards at each center. Each investigator ensured that the patient provided written informed assent and the parent or legal guardian provided written informed consent, as appropriate, before study procedures were begun.

Study Design and Treatment

This was a phase 2, single-dose, randomized, double-blind, five-way crossover, active- and placebo-con-

trolled study conducted at 19 centers in the United States (NCT01136655; Fig. 1).

All randomized patients received budesonide 160 μ g twice daily (b.i.d.) *via* pMDI throughout the study period. In this study, single delivered doses of formoterol 2.25, 4.5, and 9 μ g administered *via* pMDI and metered-dose formoterol 12 μ g delivered *via* dry powder inhaler (DPI) were compared with placebo. The doses administered per device at each treatment visit are summarized in Table 1. Each single-dose treatment day was followed by a washout period of between 3 and 14 days. The washout for formoterol was a minimum of 5 half-lives (3 days). The minimum washout for formoterol of 3 days was based on five times the half-life of formoterol in plasma to ensure nearly complete elimination of formoterol from systemic circulation. The maximum of 14 days was to allow patient flexibility in attending visits. There would be no difference expected in results for 3 days versus 14 days between doses because all were considered to be single doses with no residual formoterol.

After initial screening (visit 1) and enrollment (visit 2) visits, eligible patients underwent a 1- to 2-week run-in period during which they received open-label budesonide pMDI 80 μ g $\times$ 2 inhalations (160 μ g) b.i.d. and albuterol pMDI 90 μ g/actuation to be taken as needed (1–2 inhalations).

Randomization was at visit 3, by which time patients had discontinued all asthma medications other than those provided at visit 2, and was also when patients received one of the five treatments. Asthma stability criteria were confirmed *via* a predose FEV₁ measured ≥ 6 hours after the last dose of inhaled SABA, which had to show $\leq 12\%$ variation from the predose baseline FEV₁ measurement obtained at the visit where the patient established FEV₁ reversibility of $\geq 15\%$. This visit was followed by four subsequent treatment visits to administer single-dose formoterol or placebo, separated by a minimum of 3 days and maximum of 14 days. Open-label budesonide and SABA were withheld on the morning of visits 3–7.

Table 1 Single-dose regimens for each of the four blinded and one partially blinded treatment groups

Total Delivered Dose	No. of Inhalations per Each pMDI or DPI					Placebo pMDI
	BUD pMDI 40 µg	BUD pMDI 80 µg	BUD/FM pMDI 80/2.25 µg	BUD/FM pMDI 80/4.5 µg	FM DPI 12 µg	
BUD/FM 160/2.25 µg	2		1			
BUD/FM 160/4.5 µg			2			1
BUD/FM 160/9 µg				2		1
BUD/FM 160/12 µg (partially blinded)		2			1	
BUD 160 µg		2				1

BUD = budesonide; DPI = dry powder inhaler; FM = formoterol; pMDI = pressurized metered dose inhaler.

At each of five treatment visits, patients were randomized to receive a blinded (or in the case of formoterol DPI 12 µg, partially blinded) single dose of budesonide in combination with placebo or formoterol as indicated in Table 1.

Concomitant Medications

Other nonsteroidal asthma medications (*e.g.*, leukotriene modifiers and mast cell stabilizers) were not allowed. Allergen immunotherapy could be continued throughout the study as long as the regimen had been stable for ≥6 weeks.

Efficacy and Safety Evaluations

The primary outcome variable was the average 12-hour FEV₁ calculated by area under the curve divided by time for a final value expressed in liters. Secondary outcome variables were FEV₁ at 12 hours after dosing and maximum FEV₁ during the 12-hour treatment period. Adverse events (AEs), physical examination, and vital signs were recorded at each visit.

Systemic Exposure

Systemic exposure to formoterol was measured by urinary excretion of unchanged formoterol over the 12-hour postdose period (Ae[0–12]). The fraction of the nominal delivered dose of formoterol excreted unchanged in the urine 0–12 hours after dosing (fe[0–12]) was also calculated. Analysis of formoterol in urine was performed by PRA–Early Development Services, Bioanalytical Laboratory (Groningen, The Netherlands). The formoterol assay was based on a combined method of liquid chromatography and mass spectrometry and was validated across the concentration range of 40.0–50,000 pmol/L using a 1.0-mL sample volume.

Statistical Analyses

The safety analysis set included all randomized patients who took ≥1 dose of study medication, and the efficacy analyses included data from all patients who

were randomized and received ≥1 dose of study medication and contributed sufficient data for one or more efficacy end point.

An adequate number of patients were to be randomized to obtain 50 completed patients. The efficacy end point of average 12-hour FEV₁ used the last observation carried forward method of extrapolation and had an additive analysis of covariance model appropriate for a crossover design, adjusting for the fixed factors of patient, period, and treatment and for the covariate of predose FEV₁ from each visit. A sensitivity analysis was performed on the primary efficacy end point using mixed-effects analysis of covariance. Baseline was defined as the latest nonmissing value collected before or on the same day of randomization, and change from baseline was calculated as the assessment value minus the baseline value.

All statistical comparisons were based on a two-sided *t*-test using an α -level of significance of 5%. Secondary analyses reported nominal 5% levels of significance.

RESULTS

Patients

A total of 169 patients were screened with 54 patients randomized from 14 of the 19 participating sites in the United States. The mean age of the randomized patients was 9.2 years (range, 6 to <12 years), with 11 patients (20.4%) between the ages of 6 to <8 years. These patients had a mean time of 6.1 years since asthma diagnosis. The study population was composed of 57% white, 41% black/African American, and 2% other. Patient disposition is shown in Fig. 2, and demographics and time since asthma diagnosis are shown in Table 2.

Efficacy

A dose–response was established for formoterol comprising the three pMDI doses (2.25, 4.5, and 9 µg)

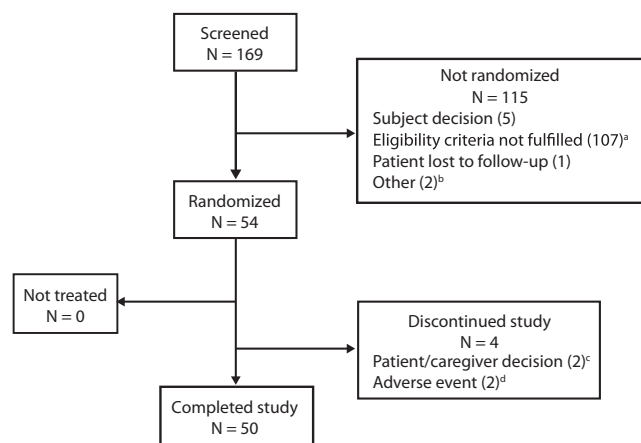


Figure 2. Patient disposition. ^aThe inclusion criteria that most frequently led to exclusion were the requirements for a FEV₁. A total of 62.6% of patients (67 patients) had an FEV₁ measured at least 6 hours after the last dose of inhaled SABA, and at least 48 hours after the last dose of inhaled LABA of ≥ 60 and $\leq 85\%$ of predicted normal. A total of 34.6% of patients (37 patients) showed reversibility of FEV₁ of $\geq 15\%$ from prealbuterol level within 15–30 minutes after administration of a standard dose of albuterol at visit 2. ^bThe two patients who were not randomized due to “other” had initially qualified for enrollment, but on further review it was determined that these patients did not meet all eligibility criteria. ^cThe two patients who discontinued due to patient/caregiver decision were 10 and 11 years old. ^dThe two patients who discontinued due to adverse event were 8 and 10 years old. FEV₁, forced expiratory volume in 1 second; LABA, long-acting β_2 -agonist; SABA, short-acting β_2 -agonist.

Table 2 Demographics and time since asthma diagnosis

Characteristic	All Randomized (n = 54)
Sex, n (%)	
Boys	31 (57.4)
Girls	23 (42.6)
Age, yr	9.2 (1.79)
Age group in yr, n (%)	
6 to <8	11 (20.4)
≥ 8 to <12	43 (79.6)
Race, n (%)	
White	31 (57.4)
Black/African American	22 (40.7)
Other	1 (1.9)
Months since asthma diagnosis	73.2 (39.16)
Range	10–142

Values shown are mean (SD) unless otherwise indicated.

Table 3 Efficacy outcomes by FM treatment

FM Treatment*	Average 12-hr FEV ₁ (L)	FEV ₁ at 12 hr (L)	Maximum FEV ₁ during 12-h (L)
pMDI 2.25 μ g	1.546#	1.681	1.844§
pMDI 4.5 μ g	1.594#	1.705§	1.885#
pMDI 9 μ g	1.603#	1.714#	1.866#
DPI 12 μ g	1.603#	1.715§	1.880#
Placebo	1.489	1.648	1.767

*All patients received budesonide 160 μ g pMDI b.i.d.

$p \leq 0.0001$ vs placebo.

§ $p < 0.01$ vs placebo.

b.i.d. = twice daily; DPI = dry powder inhaler; FEV₁ = forced expiratory volume in 1 s; FM, formoterol; pMDI = pressurized metered-dose inhaler.

and formoterol DPI 12 μ g. All three formoterol pMDI doses (2.25, 4.5, and 9 μ g) and the formoterol DPI 12- μ g dose had significantly higher average 12-hour FEV₁ versus placebo ($p \leq 0.0001$), and both formoterol pMDI doses of 4.5 and 9 μ g were statistically superior to the 2.25- μ g dose ($p = 0.0007$ and $p = 0.0001$ respectively; Tables 3 and 4). There were numerical differences between average 12-hour FEV₁ for formoterol pMDI 4.5 and 9 μ g versus formoterol DPI 12 μ g, but these were not significantly different. The curve for average change in FEV₁ for formoterol pMDI doses of 4.5 and 9 μ g were consistent with those for formoterol DPI 12 μ g (Fig. 3).

For secondary outcomes, the formoterol pMDI 4.5- and 9- μ g doses resulted in significant improvements in FEV₁ at 12 hours after inhalation of study medication versus placebo ($p = 0.009$ and $p < 0.0001$, respectively; Table 3) and were also significantly superior to the 2.25- μ g dose ($p = 0.040$ and $p = 0.0004$, respectively; Table 4). There was no significant difference between formoterol pMDI at the 4.5- and 9- μ g doses (Table 4). Between-treatment comparisons showed no statistically significant differences in FEV₁ at 12 hours between formoterol pMDI 4.5 and 9 μ g compared with formoterol DPI 12 μ g (Table 4). Formoterol DPI 12 μ g showed significant improvements in FEV₁ at 12 hours versus formoterol 2.25 μ g and placebo ($p = 0.008$ and $p = 0.001$, respectively; Table 4). The bronchodilating effect of the formoterol pMDI 2.25- μ g dose was not maintained during the 12-hour dosing interval (Fig. 3).

All three formoterol pMDI doses resulted in significantly greater maximum FEV₁ during the 12-hour study period compared with placebo ($p = 0.001$, $p < 0.0001$, and $p < 0.0001$ for 2.25, 4.5, and 9 μ g, respectively; Table 3). Both formoterol pMDI 4.5 and 9 μ g showed greater maximum FEV₁ than formoterol 2.25

Table 4 Between-group comparisons of efficacy parameters

FM Comparisons	Average 12-hr FEV ₁ (L)	FEV ₁ at 12 hr (L)	Maximum FEV ₁ during 12 hr (L)
Comparisons of FM vs PBO			
FM pMDI 2.25 µg vs PBO	0.058* (0.030, 0.085)	0.015 (−0.0350, 0.065)	0.057# (0.023, 0.090)
FM pMDI 4.5 µg vs PBO	0.105* (0.078, 0.133)	0.066# (0.017, 0.116)	0.112* (0.078, 0.146)
FM pMDI 9 µg vs PBO	0.114* (0.087, 0.142)	0.105* (0.056, 0.155)	0.107* (0.073, 0.140)
PBO vs FM DPI 12 µg	−0.114* (−0.142, −0.086)	−0.083# (−0.133, −0.034)	−0.115* (−0.149, −0.081)
Comparisons between FM pMDI groups			
FM 2.25 µg vs 4.5 µg	−0.048# (−0.075, −0.020)	−0.051# (−0.100, −0.002)	−0.055# (−0.089, −0.022)
FM 2.25 µg vs 9 µg	−0.057* (−0.084, −0.029)	−0.090# (−0.140, −0.041)	−0.050# (−0.084, −0.017)
FM 4.5 µg vs 9 µg	−0.009 (−0.036, 0.018)	−0.039 (−0.088, 0.010)	0.005 (−0.028, 0.039)
Comparisons of FM pMDI vs DPI 12 µg			
FM pMDI 2.25 µg vs FM DPI 12 µg	−0.056* (−0.084, −0.028)	−0.068# (−0.118, −0.018)	−0.058# (−0.092, −0.024)
FM pMDI 4.5 µg vs FM DPI 12 µg	−0.009 (−0.036, 0.019)	−0.017 (−0.067, 0.033)	−0.003 (−0.037, 0.031)
FM pMDI 9 µg vs FM DPI 12 µg	0.000 (−0.027, 0.028)	0.022 (−0.027, 0.071)	−0.008 (−0.042, 0.025)

All treatments were administered on a background of budesonide pMDI 160 µg b.i.d. Values shown are ANCOVA least-squares means (95% CI).

* $p \leq 0.0001$.

$p < 0.05$.

ANCOVA = analysis of covariance; b.i.d. = twice daily; CI = confidence interval; DPI = dry powder inhaler; FEV₁ = forced expiratory volume in 1 s; FM = formoterol; PBO = placebo; pMDI = pressurized metered-dose inhaler.

µg ($p = 0.001$ and $p = 0.004$, respectively; Table 4). Between-treatment comparisons of formoterol pMDI 4.5 and 9 µg (Table 4) versus formoterol DPI 12 µg were not statistically significant (Table 4). Formoterol DPI 12 µg showed significantly greater maximum FEV₁ during the 12-hour study period compared with formoterol pMDI 2.25 µg ($p = 0.0008$; Table 4).

Safety

All treatments were generally well tolerated with similar AE profiles. The incidence of AEs in all treatment arms was low, and no serious AEs were reported.

The incidences of AEs for formoterol pMDI 2.25 and 4.5 µg (7.4 and 7.5%, respectively) were similar to that in the prerandomization period (7.4%) and lower than that reported for placebo (9.8%). The formoterol pMDI 9-µg dose had a slightly higher AE incidence (13.2%), and the formoterol DPI 12-µg dose had a slightly lower incidence (6.0%). Two AEs led to discontinuation, one each for formoterol pMDI 2.25 µg (mild acute sinusitis and mod-

erate asthma exacerbation) and formoterol pMDI 9 µg (mild headache); AEs resolved in both cases after 6 days.

Most AEs (20 of 23) were reported as a single occurrence in one treatment. The only AE reported by more than one patient in a single treatment was mild headache, which was reported by five patients in the formoterol pMDI 9 µg group and two patients in the placebo group.

Vital sign and physical examination findings did not raise any safety concerns.

Systemic Exposure

As shown in Table 5, the mean amount of formoterol excreted in the urine increased with increasing formoterol pMDI dose for 2.25, 4.5, and 9 µg, whereas the fraction of the dose that was excreted in the urine differed by just 4% across the three doses, suggesting generally dose-proportional pharmacokinetics to 9 µg *via* pMDI.

The mean amount of formoterol and the fraction of the dose excreted in the urine for the formoterol DPI

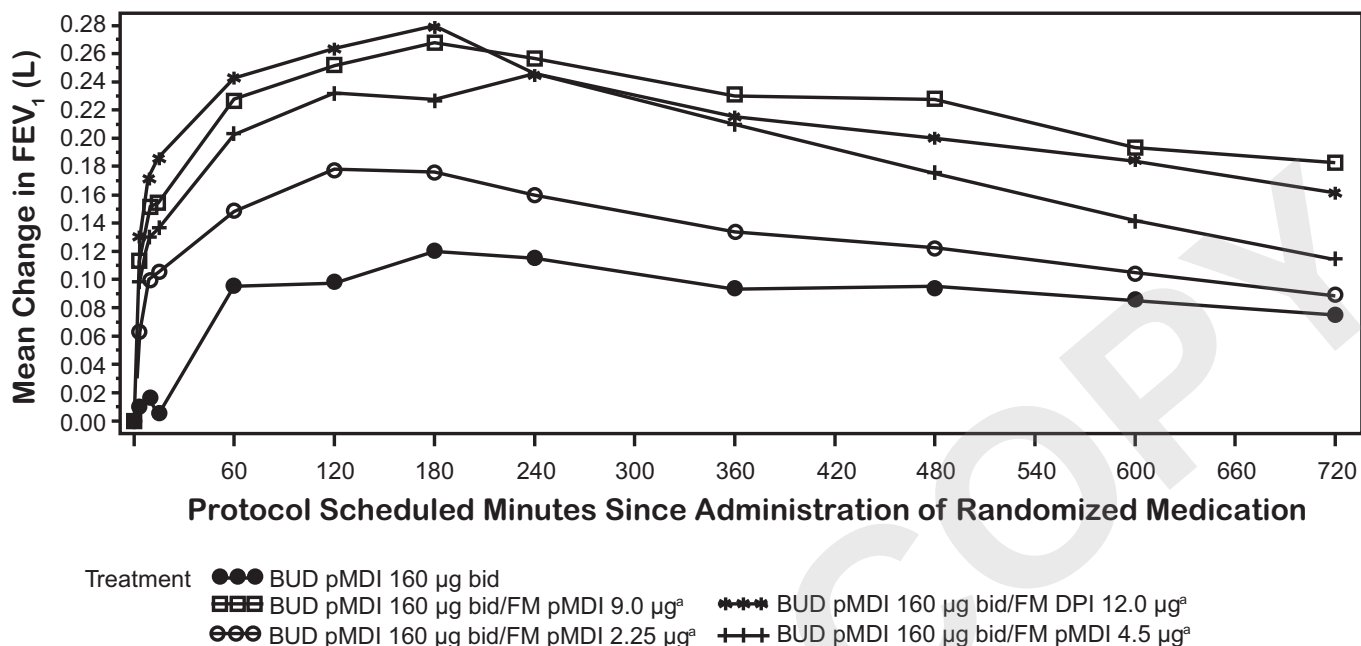


Figure 3. Mean change from baseline in FEV₁ over 12 hours. Change in FEV₁ was derived at 3, 9, 15, 60, 120, 180, 240, 360, 480, 600, and 720 minutes after administration of randomized study medication (^a*p* ≤ 0.0001 versus BUD pMDI 160 µg b.i.d.). bid = twice daily; BUD = budesonide; DPI = dry powder inhaler; FEV₁ = forced expiratory volume in 1 second; FM = formoterol; pMDI = pressurized metered dose inhaler.

Table 5 FM excretion in urine by treatment group

FM Treatment	n	Amount of FM Excreted (pmol)	Fraction of FM Excreted (%)
pMDI 2.25 µg	51	278.39 (204.52)	5.20 (3.82)
pMDI 4.5 µg	52	532.65 (416.76)	4.98 (3.90)
pMDI 9 µg	51	1090.88 (681.94)	5.10 (3.19)
DPI 12 µg	49*	860.42 (806.56)	3.64 (3.42)

All patients also received budesonide pMDI 160 µg b.i.d. Values shown are mean (SD).

*All available data.

b.i.d. = twice daily; DPI = dry powder inhaler; FM = formoterol; pMDI = pressurized metered dose inhaler.

12-µg dose were lower than those for formoterol pMDI 9-µg dose. However, six patients were found to have undetectable formoterol in the urine on the formoterol DPI 12 µg treatment day. When these six patients were excluded from analysis, the mean amount and fraction of the formoterol DPI 12-µg dose excreted (980.47 ± 789.3 pmol and $4.14 \pm 3.3\%$, respectively) were generally similar to those of the formoterol pMDI 9-µg dose (1090.88 ± 681.9 pmol and $5.10 \pm 3.2\%$, respectively).

DISCUSSION

The results of a 26-week randomized study of 187 children with asthma have previously shown the safety and clinical benefit of a pMDI-delivered combi-

nation of budesonide/formoterol (160/4.5 µg × 2 inhalations b.i.d.) versus DPI-delivered budesonide alone (200 µg × 2 inhalations b.i.d.) for improving lung function.⁷ However, studies have not assessed the dose-dependent bronchodilating effects of single doses of formoterol in a pediatric population aged <12 years with asthma maintained on budesonide pMDI b.i.d. One of this study's strengths is the enrollment of an ethnically diverse pediatric population, which included 41% black/African Americans.

In this study of children with stable asthma maintained on budesonide pMDI 160 µg b.i.d., there was a trend for a dose-response for the three formoterol doses administered *via* pMDI (2.25, 4.5, and 9 µg), with formoterol 9 µg exhibiting a maximum response. Although improvements in lung function were statistically significant with all three formoterol pMDI doses versus placebo, as assessed by the average 12-hour FEV₁ and the maximum FEV₁ during the 12-hour study period, bronchodilation was not maintained during the 12-hour dosing interval with the formoterol pMDI 2.25-µg dose.

These dose-finding results in children are in line with those of a similar study that compared budesonide/formoterol administration by pMDI versus budesonide pMDI plus formoterol DPI in 201 adults with stable asthma.⁸ This multicenter, crossover study compared single doses of formoterol 4.5, 9, and 18 µg administered by DPI or pMDI on a background of budesonide administered by pMDI (320 µg). Dose-ordered responses for average 12-hour FEV₁ were reported with

formoterol delivered by either device. As in this present study, the FEV₁ at 12 hours for pMDI-delivered 4.5- and 9- μ g formoterol doses were numerically but not statistically significantly different.

The present study included formoterol 12 μ g *via* DPI as a Food and Drug Administration–approved treatment benchmark. However, formoterol was not detected in urine samples from 6 of 49 patients after administration of formoterol *via* DPI. Inspection of inhalers found empty capsules and powder residue in all but one, and reanalysis of urine samples confirmed formoterol concentrations below the lower limit of quantification, suggesting that the study drug was not successfully administered on the study day. Possible explanations for the lack of systemic formoterol exposure in these cases include poor inhalation technique or inadequate inspiratory flow. Covar and Gelfand reported other potential errors related to failure to receive a dose of formoterol *via* DPI: failure of capsule to rotate in inhalation chamber, sticking of piercing needle or capsule, or inadequate piercing or crushing of the capsule.⁹ To ensure that these apparent administration failures did not affect the results, a reanalysis of efficacy outcomes with exclusion of data from these six patients was performed (data not shown), and this did not result in any changes in conclusions with regard to treatment comparisons.

When the six patients with undetectable formoterol in the urine were excluded, the mean amount and fraction of the dose excreted for the formoterol DPI 12- μ g dose were similar to those of the formoterol pMDI 9- μ g dose. Of the 12 μ g of formoterol in the individual gelatin capsules manufactured for DPI, ~10 μ g of formoterol is delivered from the mouthpiece; however, the actual amount received is dependent on inhalation technique.¹⁰ The amount of formoterol excreted in the urine increased with dose across the range of 2.25, 4.5, and 9 μ g, with the fraction of the dose that was excreted in the urine differing by just 4% across the three doses, suggesting generally dose-proportional pharmacokinetics to 9 μ g with pMDI.

The urinary excretion results in this present study are in line with data reported by Tronde *et al.*,¹¹ who assessed the urinary excretion of single-dose formoterol (18 μ g) administered *via* pMDI and by DPI in a randomized study involving 24 children with chronic asthma. In the Tronde *et al.* study,¹¹ the fraction of the formoterol dose excreted in the urine (during 24 hours) was ~3.5% for pMDI and 3.1% for DPI.

Results of safety analyses did not reveal safety concerns for the doses tested. There were no serious AEs reported, and the two discontinuations due to AEs were mild to moderate in severity and resolved. The AE profile did not differ between doses of formoterol or between doses of formoterol and placebo. Mild

headache was the only AE with multiple reports across treatment groups with a higher number of patients reporting mild headache in the formoterol pMDI 9 μ g treatment group. Although headache is included in the budesonide/formoterol U.S. product labeling, headache was not reported in a 26-week open-label study of budesonide/formoterol 320/9 μ g b.i.d. versus budesonide 400 μ g b.i.d. in 187 children aged 6 to <12 years.⁷

Formoterol *via* pMDI showed a dose–response in all doses examined when administered in combination with budesonide pMDI 160 μ g b.i.d. The low rate of AEs and absence of serious AEs indicates that all treatments were well tolerated in children aged 6 to <12 years with persistent asthma.

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