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Pediatrics 2010;126:e565-e575; originally published online Aug 16, 2010;
DOI: 10.1542/peds.2009-2970

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American Academy of Pediatrics

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Once- vs Twice-Daily Budesonide/Formoterol in 6- to 15-Year-Old Patients With Stable Asthma

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KEY WORDS

children, adolescents, asthma, combination therapy, once-daily dosing

ABBREVIATIONS

ICS—inhaled corticosteroid
LABA—long-acting β_2 -adrenergic agonist
DPI—dry powder inhaler
pMDI—pressurized metered-dose inhaler
FEV₁—forced expiratory volume in 1 second
PEF—peak expiratory flow
PAQLQ(S)—standardized Pediatric Asthma Quality of Life Questionnaire
PACQLQ—Pediatric Asthma Caregiver's Quality of Life Questionnaire
AE—adverse event
ANCOVA—analysis of covariance
CMH—Cochran-Mantel-Haenszel

Drs Eid, Noonan, and Chipps contributed substantially to data acquisition, data analysis/interpretation, intellectual input, and critical revision during drafting of the article and approval of the final draft before submission; Drs Parasuraman and O'Brien contributed substantially to study conception and design, data interpretation, intellectual input, and critical revision during drafting of the article and approval of the final draft; and Mr Miller contributed substantially to data analysis/interpretation, intellectual input, and critical revision during drafting of the article and approval of the final draft.

Data from this study were presented at the American Academy of Allergy, Asthma & Immunology annual conference, March 14–18, 2008, Philadelphia, PA; and the American Thoracic Society 2008 annual conference, May 16–21, 2008, Toronto, Ontario, Canada.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00646321).

www.pediatrics.org/cgi/doi/10.1542/peds.2009-2970

doi:10.1542/peds.2009-2970

Accepted for publication Jun 1, 2010

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WHAT'S KNOWN ON THIS SUBJECT: Once- and twice-daily budesonide/formoterol have similar effectiveness at the same daily doses in adults with asthma. Once-daily budesonide/formoterol has shown greater efficacy than once-daily budesonide at the same daily budesonide dose in adolescents/adults with asthma previously stabilized with twice-daily budesonide/formoterol.



WHAT THIS STUDY ADDS: Published literature on efficacy of ICS/LABA combination therapy in pediatrics is sparse. Although once-daily budesonide/formoterol maintained pulmonary function, twice-daily budesonide/formoterol resulted in improved pulmonary function, fewer discontinuations for worsening asthma, and less daytime rescue medication.

abstract



OBJECTIVE: To assess efficacy/tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler (pMDI) versus budesonide pMDI (primary) and twice-daily budesonide/formoterol (secondary) in children/adolescents with asthma stabilized with twice-daily budesonide/formoterol.

METHODS: This 12-week multicenter, double-blind randomized controlled study (www.clinicaltrials.gov identifier NCT00646321) included 521 patients aged 6 to 15 years with mild/moderate persistent asthma. Patients stabilized during a 4- to 5-week run-in with twice-daily budesonide/formoterol pMDI 40/4.5 $\mu\text{g} \times 2$ inhalations (160/18 μg daily) received twice-daily budesonide/formoterol pMDI 40/4.5 $\mu\text{g} \times 2$ inhalations (160/18 μg daily), once-daily budesonide/formoterol pMDI 80/4.5 $\mu\text{g} \times 2$ inhalations (160/9 μg daily; evening), or once-daily budesonide pMDI 80 $\mu\text{g} \times 2$ inhalations (160 μg daily; evening).

RESULTS: Once- or twice-daily budesonide/formoterol was more effective than budesonide for evening peak expiratory flow (primary variable) at the end of the 24-hour once-daily dosing interval ($P \leq .027$). Twice-daily budesonide/formoterol demonstrated better efficacy versus once-daily treatments for evening predose forced expiratory volume in 1 second ($P \leq .011$), versus budesonide for daytime/nighttime rescue medication ($P \leq .023$), and versus once-daily budesonide/formoterol for daytime rescue medication (last 12 hours of once-daily dosing) ($P = .032$). There were no significant between-group differences for daytime/nighttime asthma symptoms, nighttime awakenings attributed to asthma, or health-related quality of life. Fewer patients experienced asthma worsening (predefined criteria) with twice-daily budesonide/formoterol (8.2%) versus once-daily budesonide (15.5%) ($P = .036$) or once-daily budesonide/formoterol (19.6%) ($P = .002$). All treatments were well tolerated.

CONCLUSIONS: Once-daily budesonide/formoterol demonstrated significantly better efficacy than once-daily budesonide for most pulmonary-function variables. Twice-daily budesonide/formoterol (160/18 μg daily) maintenance therapy was generally more effective than stepping down to once-daily dosing (160/9 μg daily). Treatments were well tolerated, and there was no evident safety benefit for once- versus twice-daily dosing. *Pediatrics* 2010;126:e565–e575

Current asthma management guidelines recommend the combination of an inhaled corticosteroid (ICS) and a long-acting β_2 -adrenergic agonist (LABA) as a preferred treatment for patients aged 5 years and older with asthma that is not controlled with an ICS alone.¹ Recommendations also include using the least amount of pharmacologic agents necessary to control asthma.¹

Once-daily dosing of budesonide/formoterol dry powder inhaler (DPI) (Symbicort Turbuhaler [AstraZeneca, Lund, Sweden]) has shown significantly better results for asthma-control variables versus a fourfold higher dose of once-daily budesonide alone in 4- to 11-year-old asthmatic children.² Once- and twice-daily budesonide/formoterol DPI administered at the same daily doses of budesonide and formoterol have yielded similar results for asthma-control and pulmonary-function variables in adults with asthma.^{3,4} Once-daily budesonide/formoterol administered via pressurized metered-dose inhaler (pMDI) (Symbicort Inhalation Aerosol [AstraZeneca LP, Wilmington, DE]) has shown better maintenance of asthma control and pulmonary function during 12 weeks versus once-daily budesonide monotherapy at the same daily budesonide dose in patients aged 12 years and older with mild-to-moderate persistent asthma that was previously stabilized with twice-daily budesonide/formoterol pMDI.⁵ Better asthma control, however, was shown with twice-daily budesonide/formoterol dosing versus once-daily budesonide/formoterol at half the daily formoterol dose, and there was no evident safety benefit for once-daily dosing.

The primary objective of this study was to assess the efficacy and tolerability of once-daily budesonide/formoterol via pMDI compared with the same dose of once-daily budesonide via pMDI in

children and adolescents aged 6 to 15 years with asthma that was previously stable with twice-daily budesonide/formoterol pMDI. This comparison permitted assessment of formoterol's contribution to once-daily budesonide/formoterol pMDI therapy. Secondary objectives were to assess the efficacy of remaining on twice-daily budesonide/formoterol pMDI versus stepping down to once-daily budesonide/formoterol pMDI at half the daily formoterol dose or once-daily budesonide via pMDI alone.

METHODS

Patients

At screening, patients aged 6 to 15 years with a documented asthma diagnosis⁶ for ≥ 6 months, stable disease based on consistent previous therapy, a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of 60% to 90% of predicted normal, and bronchodilator reversibility of $\geq 12\%$ and ≥ 0.20 L in FEV_1 ($\geq 12\%$ alone for patients younger than 11 years) were eligible for enrollment. Patients had mild-to-moderate asthma, which was based on ICS use (low-to-medium doses⁷ for ≥ 4 weeks) and pulmonary function at screening.

Exclusion criteria included severe asthma or asthma that required treatment with systemic corticosteroids ≤ 1 month before screening, current smoking, a >10 pack-year smoking history, any significant confounding disease or disorder, or hypersensitivity to β_2 -adrenergic agonists, budesonide, formoterol, or any excipients of the product formulation.

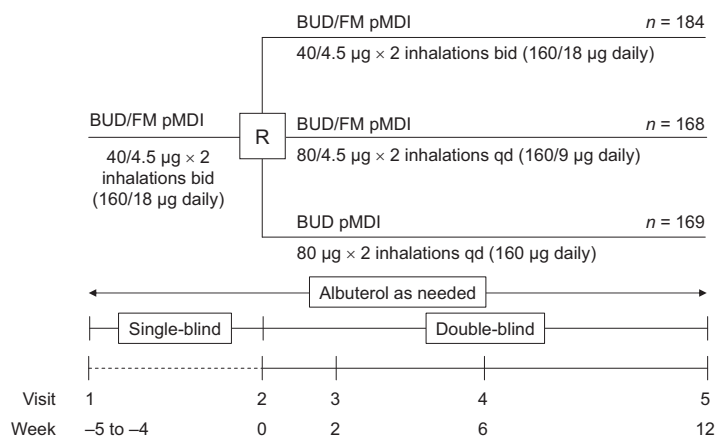
This study was approved by multiple institutional review boards. Written, informed consent from the parent/guardian and assent from the child were obtained before any study procedures were performed.

Study Design and Treatment

In this 12-week, multicenter (95 US centers), double-blind, parallel-group, active-controlled, randomized study (www.clinicaltrials.gov identifier NCT00646321; www.astrazeneca clinicaltrials.com identifiers SD-039-0725 and D5896C00725) conducted from January 29, 2003, to August 12, 2004, patients who met eligibility criteria discontinued current therapy and received budesonide/formoterol pMDI 40/4.5 $\mu\text{g} \times 2$ inhalations twice daily (160/18 μg daily) and as-needed rescue albuterol during a 4- to 5-week run-in period. To be eligible for randomization, patients had to have stable asthma and a predose FEV_1 of $>75\%$ of predicted normal ~ 12 hours after the last dose of run-in treatment. Patients' asthma was considered stable if, during a consecutive 7-day period after 3 weeks of run-in therapy, the following criteria were met: symptom score of ≤ 1 (on a scale of 0 [no symptoms] to 3 [severe symptoms]) for ≥ 5 days, no daytime or nighttime symptom scores of 3, cumulative daytime-plus-nighttime symptom scores of ≤ 12 , and ≤ 2 nighttime asthma awakenings.

After the run-in period, eligible patients were stratified according to age at screening (6–11 or 12–15 years) and randomly assigned to receive 1 of 3 treatments (see Fig 1) 1:1:1 in balanced blocks of size 3 within each stratum at each center via a computer-generated randomization scheme produced centrally in advance. Patients who were assigned to receive once-daily treatments administered placebo pMDI in the morning and active product in the evening with identical delivery devices to maintain study blinding.

Follow-up clinic visits occurred at weeks 2, 6, and 12 after randomization. Patients had to have ≥ 1 evening visit during the study to assess trough FEV_1 levels (after ~ 20 – 24 hours for the

**FIGURE 1**

Study design. Patients who were receiving budesonide/formoterol pMDI twice daily were administered treatment in the morning and evening, whereas patients who were receiving once-daily treatments were administered placebo pMDI in the morning and active product in the evening using identical delivery devices to maintain study blinding. BUD indicates budesonide; FM, formoterol; bid, twice daily; R, randomization; qd, once daily.

once-daily treatments and after ~11–13 hours for twice-daily budesonide/formoterol pMDI). Patients who met any predefined criteria for worsening asthma were required to be withdrawn automatically from the study (Table 1).

Concomitant Medications

Albuterol pMDI was provided as rescue medication. Treatment with systemic corticosteroids, dermatologic corticosteroids at a concentration of >1%, routine nebulized albuterol, hydroxyzine, or β -blockers and initiation

of immunotherapy were not allowed during the study. Continuation of treatment with nasal corticosteroids was permitted if treatment began before screening. The use of a spacer device for the administration of study or rescue medication was not permitted.

Efficacy Evaluations

The primary efficacy variable was evening peak expiratory flow (PEF), which was chosen to assess the efficacy of once-daily budesonide/formoterol via pMDI 20 to 24 hours after taking the previous evening's dose of study medication (trough levels) and ≥ 6 hours after taking rescue medication. Patients (or caregivers) recorded the highest of 3 PEF measurements in an electronic diary (Logpad [PHT Corporation, Charlestown, MA]).

Secondary efficacy variables recorded by patients in the electronic diaries included morning PEF, daytime and nighttime asthma symptom scores (0 [no symptoms] to 3 [severe symptoms]), nighttime awakenings attributable to asthma, and daytime and nighttime rescue-medication use (number of inhalations). Diary data were applied to predefined criteria for wors-

ening asthma (Table 1) on a daily basis by using a 7-day rolling window. Events of worsening asthma were assessed. Morning and evening predose FEV₁ values (recorded at each clinic visit) also were assessed. Because active treatment was administered in the evening for the once-daily treatment arms, morning PEF and FEV₁ represented assessments halfway through the once-daily dosing interval.

Caregiver and Physician Global Assessments

At the end of the study, physicians and caregivers assessed the patients' overall level of asthma control by using a 5-point scale⁸ in response to 2 questions: (1) How would you evaluate your patient's symptoms or child's health now versus at randomization (possible responses included "a great deal better," "somewhat better," "unchanged," "somewhat worse" and "a great deal worse")? and (2) How would you evaluate your ability to manage your patient's/child's asthma (possible responses included "a great deal easier," "somewhat easier," "unchanged," "somewhat more difficult," and a "great deal more difficult").

Health-Related Quality of Life

Health-related quality of life was assessed by using the validated standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ[S]) and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ),^{9,10} which were completed by patients aged 7 years or older or their caregivers at screening and at all subsequent clinic visits. Both questionnaires were scored on a 7-point scale (1 [greatest possible impairment] to 7 [least impairment]). The minimal important difference was prespecified as a change in the overall or domain scores of ≥ 0.5 points on the 7-point scale.¹¹

TABLE 1 Predefined Criteria for Worsening Asthma

Decrease in FEV ₁ to <50% of predicted normal
Decrease in morning PEF of >35% from baseline ^a on ≥ 3 d within a consecutive 7-d period
≥ 10 inhalations per d of albuterol on >2 d within a consecutive 7-d period
≥ 5 nights with an awakening attributable to asthma that required the use of rescue medication within a consecutive 7-d period
Cumulative daytime and nighttime symptom score of >15 summed over any consecutive 3-d period
Clinical exacerbation that required emergency treatment, hospitalization, or treatment with a medication not permitted by the protocol

Patients who experienced any predefined criteria were withdrawn automatically from the study.

^a Defined as the mean of all values during the last 10 days of the run-in.

Safety Evaluations

Safety was evaluated on the basis of adverse events (AEs), laboratory evaluations, 24-hour urinary cortisol level, electrocardiograms, and physical examinations. An asthma-related AE (symptom or sign such as wheeze, cough, chest tightness, dyspnea, breathlessness, and phlegm) was to be recorded as an AE when it was serious, resulted in the patient discontinuing the study, was new to the patient, or was not consistent with the patient's preexisting asthma history. For each AE, the study investigator was to assess whether it was caused by the study medication by responding yes or no to the question, "Do you consider that there is reasonable possibility that the event may have been caused by the drug?" Blood specimens for chemistry and hematology were obtained, and 12-lead electrocardiograms were performed before dosing at screening and at the end of treatment. Twenty-four-hour urine samples for urinary free-cortisol analysis were collected ≤ 1 week after the screening visit and ≤ 1 week before the final clinic visit.

Statistical Analyses

The efficacy-analysis population included all patients in the safety-analysis population (randomly assigned patients who received ≥ 1 dose of study medication) who completed ≥ 1 evening PEF diary entry after random assignment. The study was designed with a sample size of 540 subjects (180 per treatment group) to provide 88% power to test the null hypothesis that the mean difference between treatments in change from baseline in evening PEF was 0 L/minute versus the alternative of 10 L/minute (assuming a population SD of 30.0 L/minute and 5% type I error rate). The primary comparison for all variables was budesonide/formoterol pMDI 160/9 μg

versus budesonide pMDI 160 μg , both administered once daily; the secondary comparison was the once-daily treatments versus budesonide/formoterol via pMDI 160/18 μg (total daily dose) administered twice daily. All statistical comparisons were 2-sided tests, and $P \leq .05$ was considered significant.

Analysis of covariance (ANCOVA) was used to assess treatment differences in numeric variables while adjusting for center, treatment, age strata, and baseline; results are presented as least-squares mean differences with associated 95% confidence intervals and P values. The percentages of patients who had ≥ 1 predefined event of worsening asthma or were withdrawn because of predefined criteria for worsening asthma were compared between treatment groups by using the Cochran-Mantel-Haenszel (CMH) test while adjusting for age strata. Potential differences in treatment effects according to age (6–11 or 12–15 years) were evaluated by adding the age strata-by-treatment interaction term to the ANCOVA models for evening PEF and evening predose FEV_1 . The percentages of physicians and caregivers who reported positive responses (top 2 response categories) on the global assessment questions were compared between groups by using a CMH test while adjusting for age strata. Data on AEs were summarized descriptively. Numerical safety variables were analyzed with ANCOVA models to detect differences in mean effects and with graphical and shift-table methodology to detect outliers.

RESULTS

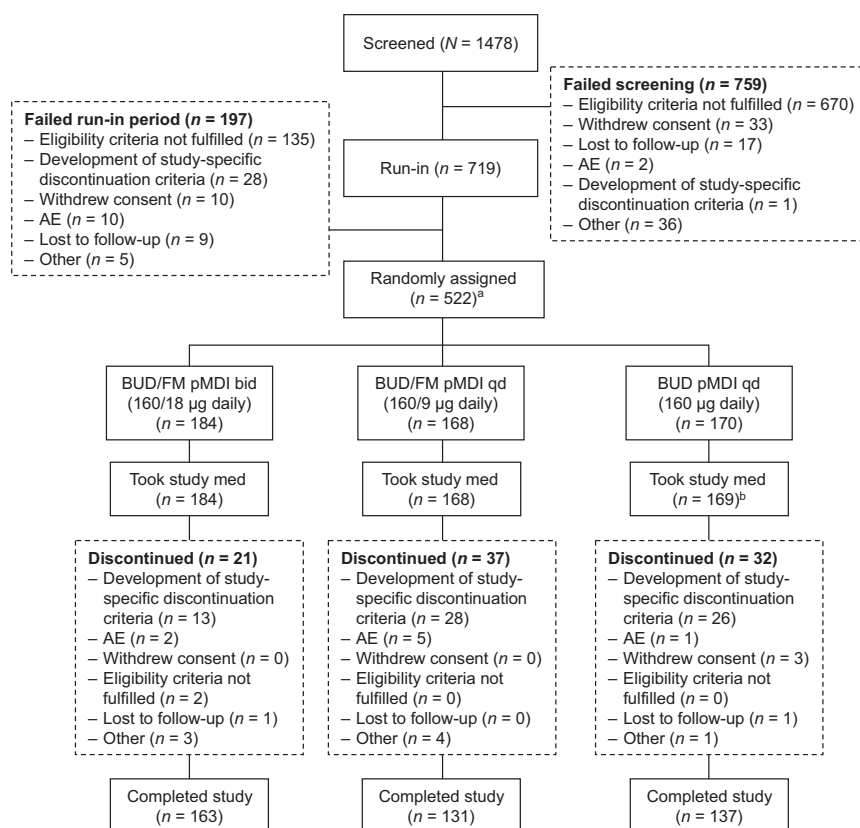
Of the 719 patients who entered the run-in period, 522 were randomly assigned to receive study treatment (Fig 2). The most common reason for withdrawal during the run-in period was failure to meet the entry criteria (135

[68.5%]), which most commonly included asthma symptom-related (44 [32.6%]) or pulmonary-function-related (36 [26.7%]) eligibility criteria at visit 2. Demographic and baseline clinical characteristics were generally similar across the treatment groups, and there were no clinically significant differences observed that would affect our conclusions (Table 2). All randomly assigned patients were receiving ICS alone or in combination at study entry, most commonly fluticasone propionate (181 [34.7%]), fluticasone propionate/salmeterol (146 [28.0%]), or budesonide (141 [27.0%]).

Efficacy

Pulmonary-Function Variables

Both budesonide/formoterol pMDI dosing regimens maintained evening PEF significantly more effectively than once-daily budesonide pMDI dosing ($P \leq .027$ for both) (Table 3). During the 12-week randomized treatment period, mean evening PEF values steadily improved from baseline values with twice-daily budesonide/formoterol pMDI, whereas they were maintained at the baseline level with once-daily budesonide/formoterol pMDI (Fig 3). However, mean changes in evening PEF from baseline to the treatment-period average were not significantly different between the once- and twice-daily budesonide/formoterol pMDI groups (Table 3). Evening predose FEV_1 improved from baseline values with twice-daily budesonide/formoterol pMDI and decreased with once-daily budesonide/formoterol pMDI and budesonide pMDI ($P \leq .011$ for twice-daily budesonide/formoterol pMDI versus both once-daily treatments) (Table 3); differences between the once-daily budesonide/formoterol pMDI and budesonide pMDI treatments were not significant. For both evening PEF and evening predose FEV_1 , there was no evidence of a differ-

**FIGURE 2**

Patient disposition. ^a Because of randomization within each age stratum at each study center using balanced blocks of size 3 (1:1:1), imbalances between treatment groups in the overall number of randomly assigned patients occurred. ^b One patient was randomly assigned but did not receive study medication. BUD indicates budesonide; FM, formoterol; bid, twice daily; qd, once daily.

TABLE 2 Patient Demographics and Baseline Clinical Characteristics

Characteristic	BUD/FM pMDI bid (160/18 µg Daily) (n = 184)	BUD/FM pMDI qd (160/9 µg Daily) (n = 168)	BUD pMDI qd (160 µg Daily) (n = 169)
Gender, n (%)			
Male	130 (70.7)	110 (65.5)	107 (63.3)
Female	54 (29.3)	58 (34.5)	62 (36.7)
Race, n (%)			
White	140 (76.1)	120 (71.4)	128 (75.7)
Black	28 (15.2)	29 (17.3)	23 (13.6)
Other	16 (8.7)	19 (11.3)	18 (10.7)
Mean (SD) age, y	10.5 (2.4)	10.2 (2.5)	10.1 (2.5)
Age distribution, n (%)			
6–11 y	120 (65.2)	117 (69.6)	114 (67.5)
12–15 y	64 (34.8)	51 (30.4)	55 (32.5)
Mean (SD) duration of asthma, y	6.8 (3.4)	6.7 (3.4)	6.8 (3.5)
Mean (SD) ICS dose at entry, µg/d	243.4 (155.1)	241.9 (153.8)	250.8 (175.2)
Prebronchodilator FEV ₁ at screening, mean (SD)			
Liters	1.9 (0.6)	1.9 (0.6)	1.8 (0.5)
% predicted	77.9 (8.2)	79.0 (8.6)	77.9 (8.9)
% reversibility	19.8 (8.3)	18.3 (8.0)	19.1 (7.7)
Predose FEV ₁ at randomization, mean (SD)			
Liters	2.2 (0.6)	2.1 (0.7)	2.0 (0.6)
% predicted	88.9 (10.4)	88.3 (9.2)	88.0 (8.7)

BUD indicates budesonide; FM, formoterol; bid, twice daily; qd, once daily.

ential effect of treatment across age groups ($P = .713$ and $.290$ for interaction test, respectively).

For morning PEF and morning predose FEV₁, both budesonide/formoterol pMDI dosing regimens were significantly more effective than once-daily budesonide pMDI dosing ($P \leq .010$), and there were no significant differences noted between the budesonide/formoterol pMDI groups (Table 3). Morning PEF was well maintained during the randomized treatment period with both budesonide/formoterol pMDI dosing regimens; improvement from baseline values was observed for twice-daily budesonide/formoterol pMDI (Fig 4).

Asthma-Control Variables

For daytime and nighttime asthma symptoms, symptom-free days, awakening-free nights, and asthma-control days, the level of asthma control established during the run-in period was well maintained in all treatment groups, and there were no significant between-group differences observed (Table 4). Compared with once-daily budesonide pMDI, treatment with twice-daily budesonide/formoterol pMDI resulted in significantly less daytime and nighttime rescue-medication use and more rescue-medication-free days ($P \leq .023$). Daytime rescue-medication use increased and rescue-medication-free days decreased with once-daily versus twice-daily budesonide/formoterol pMDI ($P \leq .039$).

The percentages of patients who experienced worsening asthma or were withdrawn from the study because of worsening asthma (on the basis of predefined criteria) were significantly lower with twice-daily budesonide/formoterol pMDI versus once-daily budesonide pMDI and once-daily budesonide/formoterol pMDI ($P \leq .036$) (Table 4). In children aged 6 to 11 years, the percentage of

TABLE 3 Mean Changes From Baseline to the Average During the Randomized Treatment Period in Pulmonary-Function Variables

Variable	BUD/FM pMDI bid (160/18 μg Daily)	BUD/FM pMDI qd (160/9 μg Daily)	BUD pMDI qd (160 μg Daily)	Least-Squares Mean Difference Between Treatment Groups (95% CI)		
				BUD/FM pMDI bid Minus BUD pMDI qd	BUD/FM pMDI bid Minus BUD/FM pMDI qd	BUD/FM pMDI qd Minus BUD pMDI qd
Evening PEF						
No. of patients	183	168	168	—	—	—
Baseline, mean (SD), L/min ^a	299.3 (82.8)	294.6 (98.5)	284.5 (82.0)	—	—	—
Change, mean (SD), L/min	6.7 (35.5)	0.5 (34.9)	−5.8 (29.9)	12.96 (5.69 to 20.23) ^b	4.55 (−2.75 to 11.84)	8.41 (0.94 to 15.89) ^c
Morning PEF						
No. of patients	183	168	168	—	—	—
Baseline, mean (SD), L/min ^a	293.0 (81.0)	289.6 (98.9)	278.5 (78.3)	—	—	—
Change, mean (SD), L/min	7.6 (31.9)	4.3 (35.1)	−4.7 (31.0)	12.47 (5.55 to 19.38) ^b	1.48 (−5.46 to 8.41)	10.99 (3.89 to 18.09) ^d
Evening predose FEV₁						
No. of patients	169	150	157	—	—	—
Baseline, mean (SD), L ^e	2.2 (0.6)	2.2 (0.7)	2.1 (0.6)	—	—	—
Change, mean (SD), L	0.02 (0.2)	−0.04 (0.2)	−0.07 (0.2)	0.09 (0.04 to 0.13) ^b	0.06 (0.01 to 0.10) ^c	0.03 (−0.01 to 0.08)
Morning predose FEV₁						
No. of patients	131	124	120	—	—	—
Baseline, mean (SD), L ^e	2.2 (0.6)	2.2 (0.7)	2.0 (0.6)	—	—	—
Change, mean (SD), L	−0.04 (0.17)	−0.03 (0.16)	−0.11 (0.18)	0.06 (0.01 to 0.10) ^d	−0.02 (−0.07 to 0.02)	0.08 (0.04 to 0.13) ^b

BUD indicates budesonide; FM, formoterol; bid, twice daily; qd, once daily; CI, confidence interval; —, not applicable.

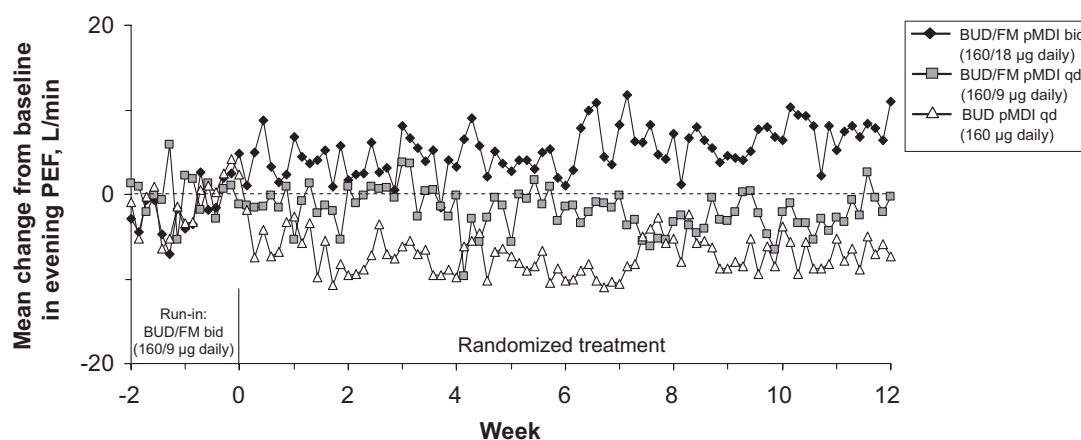
^a Baseline was defined as the mean of values during the last 10 days of the run-in period.

^b $P < .001$.

^c $P < .05$.

^d $P \leq .01$.

^e Baseline was defined as the morning predose FEV₁ value on the day of randomization.

**FIGURE 3**

Mean changes from baseline in evening PEF during the 12-week study, using last-observation-carried-forward methodology for early terminations. BUD indicates budesonide; FM, formoterol; bid, twice daily; qd, once daily.

patients with ≥ 1 predefined event of worsening asthma was lower with twice-daily budesonide/formoterol pMDI (7.5%) than with once-daily budesonide pMDI (18.6%) or once-daily budesonide/formoterol pMDI (24.8%); in patients aged 12 to 15 years, the percentages were similar across treatment groups (9.5%, 9.1%, and 7.8%, respectively).

Global Assessments

The percentage of caregivers whose responses indicated improvements in their child's asthma symptoms or the ease of asthma management since the randomization visit was similar across treatment groups (56.7%–60.4% for both questions). Similar results were observed for comparisons of the percentage of physicians whose responses

indicated improvements in the patient's asthma symptoms (70.0%–77.8%). However, a significantly greater percentage of physicians' responses indicated improvements in the ease of asthma management since the randomization visit for patients who were receiving twice-daily budesonide/formoterol pMDI versus those who were receiving once-daily budesonide pMDI (75.0% vs

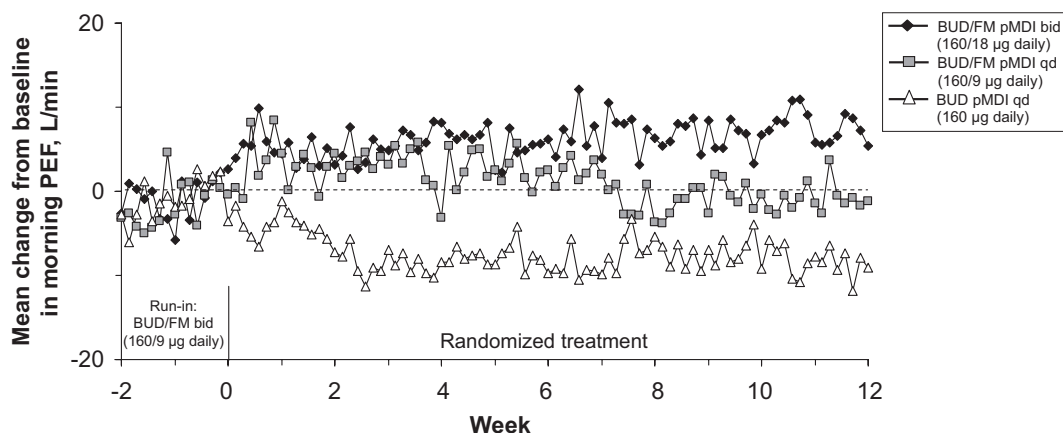


FIGURE 4

Mean changes from baseline in morning PEF during the 12-week study, using last-observation-carried-forward methodology for early terminations. BUD indicates budesonide; FM, formoterol; bid, twice daily; qd, once daily.

64.4%; $P = .035$) but not those receiving once-daily budesonide/formoterol pMDI (70.4%; $P = .362$).

Health-Related Quality of Life

Health-related quality of life and caregiver burden, which were based on the PAQLQ(S) and PACQLQ, respectively, were stable at baseline and well maintained during the randomized study period in all treatment groups (see Supplemental Table 6). Neither the magnitude of mean changes within each treatment group nor the magnitude of mean differences between treatment groups was considered clinically meaningful according to the predefined minimal important difference of 0.5 for any of the PAQLQ(S) or PACQLQ overall or domain scores.

Safety

All treatments were generally well tolerated. Most AEs were of mild (72%) to moderate (25%) intensity. The incidence of overall AEs was similar across the treatment groups (Table 5). The incidence of AEs judged by the investigator to be related to study medication was low and similar across treatment groups; the most common AEs were oral candidiasis (1.3%), headache (0.4%), and pharyngolaryngeal pain (0.4%). Six patients

experienced serious AEs during the randomized treatment period that were not considered related to study medication by the investigators: 2 in the twice-daily budesonide/formoterol pMDI group (abdominal pain and asthma), 3 in the once-daily budesonide/formoterol pMDI group (influenza [$n = 1$] and asthma [$n = 2$]), and 1 in the once-daily budesonide pMDI group (asthma). Eight patients discontinued the study because of an AE: 3 in the twice-daily budesonide/formoterol pMDI group (asthma [$n = 2$] and influenza [$n = 1$]), 4 in the once-daily budesonide/formoterol pMDI group (asthma [$n = 2$], influenza [$n = 1$], and face injury/facial bones fracture [$n = 1$]), and 1 in the budesonide pMDI group (asthma). Only 1 discontinuation attributable to an AE, which occurred in the twice-daily budesonide/formoterol pMDI group (influenza), was considered by the investigator to be related to the study medication.

There were no clinically significant findings for laboratory assessments, electrocardiograms, vital signs, 24-hour urinary cortisol level, or physical examination in any treatment group. Results for serum glucose, serum potassium, electrocardiogram, and 24-hour urinary cortisol measures are

presented in Supplemental Table 7 and Supplemental Table 8. No clear differences between treatment groups with respect to outliers in urinary cortisol level were observed.

DISCUSSION

Better maintenance of pulmonary function occurred during the 12-week treatment period with once-daily budesonide/formoterol pMDI versus once-daily budesonide pMDI for most variables (primary objective), including evening PEF (primary variable), which was timed to coincide with the end of the 24-hour once-daily dosing interval. These experimental results suggest that formoterol may contribute clinically beneficial effects for at least 24 hours after dosing when administered in combination with budesonide. Similarly, findings from previous studies revealed a measurable bronchodilatory effect 24 hours after dosing of budesonide/formoterol via DPI in adults with asthma.^{12,13}

It should be noted that, in contrast to the pulmonary-function results, no significant differences were observed between the once-daily budesonide/formoterol pMDI and once-daily budesonide pMDI groups for measures of asthma symptoms and control. Health-

TABLE 4 Results of Asthma-Control and Rescue-Medication–Use Variables During the 12-Week Study

Variable	BUD/FM pMDI bid (160/18 µg Daily) (n = 183)	BUD/FM pMDI qd (160/9 µg Daily) (n = 168)	BUD pMDI qd (160 µg Daily) (n = 168)	Least-Squares Mean Difference Between Treatment Groups (95% CI)		
				BUD/FM pMDI bid Minus BUD pMDI qd	BUD/FM pMDI bid Minus BUD/FM pMDI qd	BUD/FM pMDI qd Minus BUD pMDI qd
Daytime symptom score, mean (SD) ^{a,b}						
Baseline ^c	0.14 (0.24)	0.20 (0.28)	0.15 (0.24)	—	—	—
Change ^d	0.03 (0.21)	0.03 (0.26)	0.06 (0.28)	−0.03 (−0.08 to 0.02)	−0.01 (−0.06 to 0.05)	−0.02 (−0.08 to 0.03)
Nighttime symptom score, mean (SD) ^b						
Baseline ^c	0.08 (0.15)	0.12 (0.19)	0.12 (0.21)	—	—	—
Change ^d	0.02 (0.18)	0.03 (0.24)	0.05 (0.26)	−0.03 (−0.08 to 0.01)	−0.01 (−0.06 to 0.04)	−0.02 (−0.07 to 0.03)
% symptom-free days, mean (SD) ^e						
Baseline ^c	81.7 (24.3)	75.3 (28.4)	79.1 (27.1)	—	—	—
Change ^d	−0.9 (21.3)	−0.2 (24.6)	−3.7 (27.3)	3.39 (−1.43 to 8.21)	0.49 (−4.38 to 5.35)	2.90 (−2.05 to 7.86)
% awakening-free nights, mean (SD) ^f						
Baseline ^c	95.4 (7.9)	95.9 (7.5)	96.2 (7.3)	—	—	—
Change ^d	−1.8 (9.0)	−2.4 (8.9)	−2.7 (9.0)	0.41 (−1.06 to 1.87)	0.31 (−1.16 to 1.78)	0.10 (−1.41 to 1.60)
Daytime rescue-medication use, mean (SD), inhalations						
Baseline ^c	0.13 (0.36)	0.20 (0.47)	0.10 (0.23)	—	—	—
Change ^d	0.00 (0.33)	0.08 (0.43)	0.10 (0.31)	−0.08 (−0.15 to −0.01) ^g	−0.08 (−0.15 to −0.01) ^g	0.00 (−0.08 to 0.07)
Nighttime rescue medication use, mean (SD), inhalations						
Baseline ^c	0.09 (0.24)	0.14 (0.44)	0.07 (0.19)	—	—	—
Change ^d	−0.01 (0.26)	0.02 (0.30)	0.07 (0.29)	−0.07 (−0.12 to −0.02) ^h	−0.04 (−0.09 to 0.01)	−0.03 (−0.08 to 0.02)
% rescue-medication–free days, mean (SD) ⁱ						
Baseline ^c	90.2 (20.3)	88.2 (23.4)	91.9 (14.6)	—	—	—
Change ^d	1.6 (18.6)	−2.2 (16.7)	−5.4 (17.5)	5.38 (2.16 to 8.61) ^j	3.41 (0.17 to 6.65) ^g	1.97 (−1.34 to 5.28)
% asthma-control days, mean (SD) ^k						
Baseline ^c	75.4 (26.7)	68.7 (30.8)	75.2 (27.6)	—	—	—
Change ^d	−3.5 (23.7)	−3.9 (23.8)	−8.0 (27.6)	4.50 (−0.19 to 9.19)	2.46 (−2.27 to 7.19)	2.04 (−2.79 to 6.87)
Odds Ratio (95% CI)						
Patients with ≥1 predefined event of worsening asthma, n (%)	15 (8.2)	33 (19.6)	26 (15.5)	0.49 (0.25 to 0.96) ^g	0.37 (0.19 to 0.71) ^h	1.32 (0.74 to 2.33)

BUD indicates budesonide; FM, formoterol; bid, twice daily; qd, once daily; CI, confidence interval; —, not applicable.

^a Assessed the 12 hours at the end of the 24-hour once-daily dosing interval.

^b Symptoms rated on a 4-point severity scale: 0, none; 1, mild; 2, moderate; 3, severe.

^c Baseline was defined as the mean of values during the last 10 days of the run-in period.

^d Values are presented as the mean (SD) change from baseline to the average over the randomized treatment period.

^e Days with no daytime or nighttime asthma symptoms and no awakenings attributable to asthma.

^f Nights with no awakenings attributable to asthma.

^g $P < .05$.

^h $P < .01$.

ⁱ Days with no daytime or nighttime rescue-medication use.

^j $P \leq .001$.

^k Symptom-free days with no daytime or nighttime rescue-medication use.

related quality of life, as assessed by the PAQLQ(S) and PACQLQ, also was well maintained in both the twice-daily and once-daily treatment groups during our study, and no clinically mean-

ingful changes or differences between the treatment groups were observed. The asthma-control results contrast with those reported by Bisgaard et al,² in which significantly better asthma

control was observed with once-daily budesonide/formoterol DPI compared with a fourfold higher dose of once-daily budesonide DPI in children with asthma. These contrasting results are

TABLE 5 AEs Reported in $\geq 3\%$ of Patients in Any Treatment Group

AE	No. (%) of Patients		
	BUD/FM pMDI bid (160/18 μg Daily) (<i>n</i> = 184)	BUD/FM pMDI qd (160/9 μg Daily) (<i>n</i> = 168)	BUD pMDI qd (160 μg Daily) (<i>n</i> = 169)
Headache	21 (11.4)	13 (7.7)	17 (10.1)
Pharyngolaryngeal pain	20 (10.9)	14 (8.3)	8 (4.7)
Nasopharyngitis	15 (8.2)	15 (8.9)	10 (5.9)
Upper respiratory tract infection	11 (6.0)	13 (7.7)	16 (9.5)
Viral upper respiratory tract infection	14 (7.6)	15 (8.9)	3 (1.8)
Pyrexia	14 (7.6)	9 (5.4)	7 (4.1)
Sinusitis	4 (2.2)	10 (6.0)	10 (5.9)
Upper abdominal pain	8 (4.3)	7 (4.2)	5 (3.0)
Vomiting	5 (2.7)	4 (2.4)	6 (3.6)
Influenza	5 (2.7)	6 (3.6)	3 (1.8)
Otitis media	7 (3.8)	1 (0.6)	5 (3.0)
Streptococcal pharyngitis	4 (2.2)	3 (1.8)	6 (3.6)
Nausea	6 (3.3)	5 (3.0)	1 (0.6)
Epistaxis	2 (1.1)	3 (1.8)	6 (3.6)
Bacterial respiratory tract infection	2 (1.1)	5 (3.0)	1 (0.6)
Musculoskeletal chest pain	2 (1.1)	5 (3.0)	0 (0.0)

BUD indicates budesonide; FM, formoterol; bid, twice daily; qd, once daily.

potentially explained by differences in the run-in period that resulted in patients with more severe baseline asthma symptoms and greater margins for improvement in the study by Bisgaard et al² versus those in our study.

Twice-daily budesonide/formoterol pMDI produced significantly better results for all pulmonary-function variables versus once-daily budesonide pMDI. These results are consistent with those reported by Tal et al,¹⁴ in which similar asthma control and better pulmonary function were observed with twice-daily budesonide/formoterol versus twice-daily budesonide alone at the same daily budesonide dose in children and adolescents. In our study, the results for asthma worsening (based on predefined criteria) and rescue-medication use significantly favored twice-daily budesonide/formoterol pMDI versus once-daily budesonide pMDI. Similarly, Kerwin et al,⁵ reported significantly better asthma control for twice-daily budesonide/formoterol pMDI (320/18 μg daily) compared with once-daily budesonide pMDI (320 μg daily) in patients with asthma aged ≥ 12 years. In contrast to those from the study by Ker-

win et al, the results of most other asthma-control measures in our study were similar between the twice-daily budesonide/formoterol pMDI and once-daily budesonide pMDI groups. These different results may be related to differences in asthma severity between the patient populations, as evidenced by the deterioration in asthma control observed with once-daily budesonide pMDI in the study by Kerwin et al⁵ versus the maintenance of asthma control in all treatment groups in our study.

To identify the minimum medication necessary to maintain control, current asthma guidelines recommend a step down in pharmacologic therapy once asthma control is achieved.¹ These recommendations stem from potential adverse effects that have been described for both ICS and LABA components.^{1,15} In our study and the study by Kerwin et al,⁵ patients were stabilized on twice-daily budesonide/formoterol via pMDI, which corresponds with step 3 of the current asthma guidelines,¹ before stepping down to once-daily ICS or ICS/LABA treatment. In our study, significantly better results were observed with twice-daily versus once-daily budesonide/formoterol pMDI for

evening predose FEV₁, daytime rescue-medication use, rescue-medication-free days, and worsening asthma. Differences between the 2 budesonide/formoterol pMDI dosing regimens were more apparent for variables assessed at the end of the 24-hour once-daily dosing interval, and no safety benefits were observed with once-daily versus twice-daily dosing regimens. Similar results were seen by Kerwin et al, who reported significantly better outcomes for twice-daily dosing.⁵ Taken together, the results of these studies suggest that in patients appropriate for treatment with combination therapy, stepping down to once-daily ICS/LABA or once-daily ICS alone at the doses studied does not confer additional safety advantages and may lead to decreased asthma control relative to continuation on twice-daily ICS/LABA maintenance therapy.

CONCLUSIONS

Once-daily dosing of budesonide/formoterol pMDI resulted in significantly better efficacy versus once-daily budesonide pMDI for evening PEF (primary variable) and most other pulmonary-function variables in this population of children and adolescents with persistent asthma previously stabilized with budesonide/formoterol via pMDI twice daily. However, continued maintenance with twice-daily budesonide/formoterol (160/18 μg daily) pMDI produced clinical benefits relative to once-daily budesonide/formoterol (160/9 μg daily) pMDI, administered at half the daily formoterol dose, for some pulmonary-function and asthma-control variables measured at the end of the 24-hour once-daily dosing interval. Safety profiles were similar among the treatments. Overall, these results suggest that for children and adolescents determined to be appropriate candidates for ICS/LABA combination therapy,

consistent with step 3 of current asthma guidelines, stepping down to once-daily ICS/LABA at a lower LABA dose or once-daily ICS alone does not confer additional safety advantages and may lead to decreased asthma control relative to continuation on twice-daily ICS/LABA maintenance therapy.

ACKNOWLEDGMENTS

Support for this study was provided by AstraZeneca LP.

We acknowledge Cynthia Gobbel, PhD, and Anny Wu, PharmD, from Scientific Connexions (Newtown, PA) for writing assistance, funded by AstraZeneca LP. We also acknowledge the following investigators for their contributions to the study: John R. Adams, MD (Houston, TX), Richard C. Ahrens, MD (Iowa City, IO), Dean Atkinson, MD (Oklahoma City, OK), Biron D. Baker, MD (Bismarck, ND), Janet D. Barnes, MD (Metairie, LA), Malik N. Baz, MD (Fresno, CA), Scott A. Becker, MD (Pembroke Pines, FL), Marshall J. Benbow, MD (San Antonio, TX), David I. Bernstein, MD (Cincinnati, OH), Eugene Bleecker, MD (Winston-Salem, NC), Michael Blumberg, MD (Richmond, VA), Dawn L. Bruner, MD (Newport Beach, CA), Karen B. Burgess, MD (Tuscaloosa, AL), Robert S. Call, MD (Richmond, VA), Robert J. Carson, MD (Cincinnati, OH), Lazaro (Larry) C. Castillo, MD (Cape Coral, FL), Christopher Chang, MD (Crescent City, CA), Domingo Chardon-Feliciano, MD (Ponce, Puerto Rico), David A. Claassen, MD (Ozark, AL), John J. Condemi, MD (Rochester, NY), Dan A. Dalan, MD (Fargo, ND), Carolyn B. Daul, MD, PhD (Metairie, LA), James N. DeAngelo, DO (Pittsburgh, PA), Bruce DeCotiis, MD (Brick, NJ), David T. Denmead, MD (Walnut Creek, CA), Joseph D. Diaz, MD (San Antonio, TX), Kerry L. Drain, MD (Spokane, WA), Dean Edell, MD (Marrero, LA), David Elkayam, MD (Bellingham, WA), Steven S. Elliott, MD (Evansville, IN), John E. Firestone Jr, MD (New Orleans, LA), Mark B. Fischer, MD (Plymouth Meeting, PA), Ritchard L.

Fishman, MD (Pico Rivera, CA), Denise FitzSimon-Williams, MD (Temple, TX), Arthur F. Fost, MD (Verona, NJ), Stanley P. Galant, MD (Orange, CA), William A. Geffen, MD (Tulsa, OK), John W. Georgitis, MD (Winston-Salem, NC), Patrick J. Gillette, MD (Medford, OR), Mary C. Goessler, MD (Pittsburgh, PA), Pinkus Goldberg, MD (Indianapolis, IN), Brad H. Goodman, MD (Savannah, GA), David L. Gossage, MD (Knoxville, TN), Gregory M. Gottschlich, MD (Cincinnati, OH), Alan B. Halsey, MD (Valrico, FL), Michael Haydel, MD (Marrero, LA), Alan M. Heller, MD (San Jose, CA), Russell J. Hopp, DO (Omaha, NE), Stanley R. Horner, MD (Jefferson City, MO), Judy A. Hunter, MD (Torrance, CA), Anne-Marie Irani, MD (Richmond, VA), Neil L. Kao, MD (Greenville, SC), Roger M. Katz, MD (Santa Monica, CA), David R. Katzen, MD (Warwick, RI), Samir S. Keblawi, MD (Spokane, WA), Cynthia S. Kelly, MD (Norfolk, VA), H. William Kelly, PharmD (Albuquerque, NM), Edward F. Kent Jr, MD (South Burlington, VT), Kenneth T. Kim, MD (Long Beach, CA), Patrice Kirchoff, MD (Morganton, NC), Chandra M. Kumar, MD (Charleston, WV), Lawrence P. Landwehr, MD (Warrensburg, MO), Miguel Lanz, MD (Coral Gables, FL), David B. Laughlin, MD (Tuscumbia, AL), Haesoon Lee, MD (Mineola, NY), Burton L. Lesnick, MD (Atlanta, GA), Arden L. Levy, MD (Spartanburg, SC), Robyn J. Levy, MD (Atlanta, GA), Edward E. Lisberg, MD (River Forest, IL), David E. Mansfield, MD (Beaumont, TX), Isaac Marcadis, MD (West Palm Beach, FL), William A. McCann, MD (Asheville, NC), John A. Meadows, MD (Montgomery, AL), Steven M. Meltzer, MD, MBA (Long Beach, CA), Mark W. Millard, MD (Dallas, TX), Andrew D. Moore, MD (Glen Burnie, MD), Kevin R. Murphy, MD (Omaha, NE), John J. Murray, MD (Nashville, TN), Lawrence J. Newman, MD (Cincinnati, OH), William A. Nish, MD (Gainesville, GA), Gregory J. Omlor, MD (Akron, OH), Anthony J. Palazzo, MD (Covington, LA), Amit I. Patel, MD (Riverside, CA), Pragnesh H. Patel, MD (Altamonte Springs, FL), David B. Peden, MD

(Chapel Hill, NC), Stephen J. Pollard, MD (Louisville, KY), Bruce M. Prenner, MD (San Diego, CA), Paul Y. Qaqundah, MD (Huntington Beach, CA), William C. Rees, MD (Burke, VA), Santiago Reyes, MD (Oklahoma City, OK), Stephen Rodgers, MD (Virginia Beach, VA), Jose Rodriguez-Santana, MD (Hato Rey, Puerto Rico), Jeffrey M. Rosch, MD (Altoona, PA), Michael E. Ruff, MD (Dallas, TX), Ned Rupp, MD (Charleston, SC), Marsha J. Salman, MD (Little Rock, AR), Bruce Schnapf, DO (Tampa, FL), Shailen R. Shah, MD (Collegeville, PA), Paul A. Shapero, MD (Bangor, ME), Wayne D. Sinclair, MD (Missoula, MT), Neil S. Skolnik, MD (Jenkintown, PA), David P. Skoner, MD (Pittsburgh, PA), Theodore R. Smith Jr, MD (Montgomery, AL), William Smits, MD (Ft Wayne, IN), Juan L. Sotomayor, MD (Liverpool, NY), Sheldon L. Spector, MD (Palmdale, CA), Jon E. Stahlman, MD (Lawrenceville, GA), Brett E. Stanaland, MD (Naples, FL), Gary Steven, MD, PhD (Greenfield, WI), Randy S. Stoloff, MD (Plattsburgh, NY), Martha M. Tarpay, MD (Oklahoma City, OK), Timothy A. Tolson, MD (Elizabeth City, NC), James L. Troutman, MD (Bellingham, WA), Richard Vath, MD (Baton Rouge, LA), Jeffrey A. Wald, MD (Overland Park, KS), Russell L. Walker, MD (Chattanooga, TN), Richard L. Wasserman, MD, PhD (Dallas, TX), Ron Weiner, MD (Lawrence, KS), Steven F. Weinstein, MD (Huntington Beach, CA), Michael J. Welch, MD (San Diego, CA), Thomas G. Westbrook, MD (Pensacola, FL), Scott L. Wexelblatt, MD (Lebanon, OH), Hugh H. Windom, MD (Sarasota, FL), Irwin Wolfert, MD (Springhouse, PA), Robert A. Wood, MD (Luther-ville, MD), Richard A. Wyatt, MD (Minneapolis, MN), John A. Yarbrough, MD (Gainesville, GA), and John F. Zwetchkenbaum, MD (Lincoln, RI).

Requirements of the International Committee of Medical Journal Editors (ICMJE) and Joint Position of the international pharmaceutical companies for registering protocols on clinicaltrials.gov

included trials starting enrollment after July 1, 2005, or ongoing at that time. Because this pediatric study was completed on August 12, 2004, results were

posted on the publically accessible AstraZeneca clinical trials Web site (www.astrazenecaclinicaltrials.com) on February 17, 2005, in lieu of registration of the

protocol. The study protocol was subsequently registered on clinicaltrials.gov on March 28, 2008. All authors met ICMJE requirements for authorship.

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(Continued from first page)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: Dr Eid has consulted for and received honoraria from AstraZeneca, Teva Specialty Pharmaceuticals, Schering-Plough Corporation, Novartis, and Genentech and has received grant/research support from Genentech, Inc; Dr Noonan has served on the speakers bureau for and received payment for clinical studies from AstraZeneca; Dr Chipps has received grant/research support from Aventis, Genentech, AstraZeneca, GlaxoSmithKline, Novartis, Schering-Plough Corporation, Sepracor, and Merck, has received educational grants from Alcon, Aventis, Genentech, AstraZeneca, GlaxoSmithKline, and Novartis, has consulted for Alcon, Aventis, Genentech, AstraZeneca, GlaxoSmithKline, MedPoint, Novartis, Schering-Plough Corporation, Sepracor, and Merck, and has served on the speakers bureau for Alcon, Aventis, Genentech, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MedPoint, Novartis, Pfizer, Schering-Plough Corporation, Sepracor, and Merck; and Dr Parasuraman, Mr Miller, and Dr O'Brien are employees of AstraZeneca.

Once- vs Twice-Daily Budesonide/Formoterol in 6- to 15-Year-Old Patients With Stable Asthma

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Pediatrics 2010;126:e565-e575; originally published online Aug 16, 2010;
DOI: 10.1542/peds.2009-2970

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