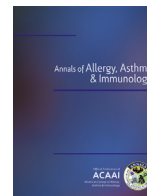




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Efficacy and safety of budesonide administered by pressurized metered-dose inhaler in children with asthma

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ABSTRACT

Background: Budesonide is approved for delivery using a nebulized solution and dry-powder inhaler, but its use through a pressurized metered-dose inhaler (pMDI) in pediatric patients with asthma has not been determined.

Objective: To examine the efficacy and safety of 160 μ g twice daily of budesonide through a pMDI vs placebo in children 6 to younger than 12 years with asthma and a demonstrated need for inhaled corticosteroids.

Methods: A 6-week, international, multicenter, double-blinded, parallel-group, phase 2 study randomized 304 pediatric patients (mean age, 9 years; 21.7% <8 years) 1:1 to 160 μ g (80 μ g $\times$ 2 inhalations) twice daily of budesonide through a pMDI or placebo after a 7- to 21-day run-in period. The primary efficacy end point was change from baseline in morning peak expiratory flow (PEF); safety end points included adverse events, vital signs, and discontinuations.

Results: Budesonide treatment significantly improved morning PEF vs placebo; mean treatment effect (budesonide vs placebo) was 13.6 L/min ($P < .0001$). Budesonide also showed significant improvements vs placebo for forced expiratory volume in 1 second, evening PEF, forced expiratory flow at 25% to 75% of pulmonary volume, reliever medication use, nighttime awakenings, awakenings with reliever use, and percentage of patients with at least 15- and at least 30-L/min increase in morning PEF from baseline. The numbers of patients experiencing adverse events and discontinuations were smaller in the budesonide than in the placebo group. No serious adverse events were reported.

Conclusion: Budesonide at 160 μ g twice daily through a pMDI was generally well tolerated and significantly improved lung function, symptoms, rescue medication use, and nighttime awakenings vs placebo in children 6 to younger than 12 years with asthma and a demonstrated need for inhaled corticosteroids.

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Introduction

Inhaled corticosteroids (ICSs) are the most consistently effective long-term asthma-control medication and are recommended as first-line treatment for pediatric patients with asthma.^{1,2} The National Asthma Education and Prevention Program Expert Panel Report 3 recommends ICSs as the preferred therapy to initiate long-term asthma-control treatment for children of all ages.¹ The

National Asthma Education and Prevention Program Expert Panel Report 3 also asserts that the effectiveness of ICSs as the initial therapy for children with persistent asthma is demonstrated by high-quality evidence.¹ Similarly, the Global Initiative for Asthma guidelines designate ICSs as the most effective asthma-control therapy and recommended ICS treatment for children with asthma of all ages.²

Previous studies have demonstrated the efficacy of the ICS, budesonide, in children with asthma 12 months to 8 years old (delivered in a nebulized solution)³ and 6 to 17 years old (delivered in dry-powder inhaler).⁴ However, there are no published data comparing budesonide with placebo when delivered through a pressurized metered-dose inhaler (pMDI) in children with asthma.

This study was designed to evaluate the efficacy and safety of 160 μ g of budesonide twice daily (bid) through a pMDI vs placebo

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in children 6 to younger than 12 years with asthma requiring controller therapy with ICSs.

Methods

Patients

Patients 6 to younger than 12 years with a documented diagnosis of asthma, as defined by the American Thoracic Society, for at least 6 months were eligible. Inclusion and exclusion criteria were designed to select patients with relatively stable asthma but with a demonstrated need for ICS controller therapy. Patients must have required and received treatment with a consistent daily dose of ICS (low-dose range) or leukotriene receptor antagonist for at least 30 days before enrollment. The need for controller therapy was assessed by a decrease in mean forced expiratory volume in 1 second (FEV₁) when stepped down to placebo during the run-in period and a combined (nighttime and following daytime) asthma symptom score of at least 1 (rated on a 4-point scale, where 0 = no symptoms and 3 = severe symptoms) on any 3 of 7 consecutive days before randomization.

Patients were required to have a morning pre-bronchodilator FEV₁ of at least 70% and no greater than 95% of predicted normal according to the method of Polgar and Promadhat⁵ measured at least 6 hours after the last dose of an inhaled short-acting β -agonist. Patients also were required to have a demonstrated reversibility of FEV₁ of at least 12% of the pre-albuterol level within 15 to 30 minutes after administration of standard-dose albuterol (albuterol pMDI; 90 μ g per inhalation [4 actuations with or without a spacer] or nebulized albuterol ≤ 2.5 mg) or a documented reversibility of FEV₁ of at least 12% of the pre-albuterol level within 12 months before enrollment.

Exclusion criteria included at least 1 hospitalization or at least 1 need for emergency treatment (emergency department or urgent-care visit) for an asthma-related condition during the 6 months before enrollment. Patients also were excluded if they had required treatment with systemic corticosteroids within 60 days before enrollment, had participated in another investigational drug study within 30 days of enrollment or a prior budesonide or formoterol clinical trial within the previous 12 months, were currently being treated with a β -blocker (including eye drops), had used any monoclonal or polyclonal antibody therapy (such as intravenous immunoglobulin) within the previous 6 months, or had used an ICS in combination with other nonsteroidal asthma-control medications (eg, leukotriene modifiers, mast cell stabilizers, 5-lipoxygenase inhibitors, or methylxanthines) or with a long-acting β_2 agonist within 30 days before enrollment.

The final study protocol and consent form were approved by an independent institutional review board. Patients and the parent or legal guardian provided written informed assents and consent as appropriate before study procedures began. The study was performed in accordance with ethical principles based on the Declaration of Helsinki and consistent with the International Conference on Harmonization and Good Clinical Practice and applicable regulatory requirements.

Study Design and Treatment

This 6-week, multicenter, phase 2, double-blinded, parallel-group, randomized, placebo-controlled study was conducted in the United States, Bulgaria, Hungary, Latvia, Poland, Slovakia, and South Africa (www.clinicaltrials.gov, NCT01136382). The study was designed to compare 160 μ g bid of inhaled budesonide through a pMDI (80 μ g $\times$ 2 actuations) with placebo bid through a pMDI.

The study consisted of a screening visit (visit 1), an enrollment visit (visit 2), a run-in period, a randomization visit (visit 3), and 6 subsequent treatment visits separated by approximately 7 ± 3 days

(Fig 1A). All clinical visits occurred in the morning. A telephone follow-up interview was conducted approximately 2 weeks after the final study visit to check for possible delayed adverse events (AEs).

Patients who met screening and enrollment criteria underwent a 7- to 21-day run-in period beginning at visit 2, during which they received single-blinded placebo pMDI and albuterol pMDI (90 μ g per actuation) to be taken as needed (1–2 inhalations). The duration of the run-in period was dependent on when a patient met the prespecified asthma symptom criterion (combined asthma symptom score ≥ 1 on any 3 of 7 consecutive days before randomization). At randomization, patients' morning clinic predose FEV₁ was measured at least 6 hours after the last dose of an inhaled short-acting β -agonist to confirm that they met the FEV₁ randomization inclusion criterion: FEV₁ from at least 70% to no greater than 90% of predicted normal or within 5% of the FEV₁ (absolute value in liters) of the FEV₁ measured at enrollment. Predicted normal values for FEV₁ according to Polgar and Promadhat⁵ were used.

At randomization, patients received the double-blinded study drug and were instructed not to use albuterol reliever medication within 6 hours of their weekly morning clinic visit and before completing the morning efficacy assessments unless absolutely necessary. They also were informed that use of a spacer was not permitted throughout the study for administration of study medication or reliever albuterol medication. Patients were instructed to withhold the morning dose of their study medication on the day of clinic visits and to bring their study medication with them.

Concomitant Medications

Medications that could be used from screening and throughout the study included as-needed albuterol reliever, nasal steroids (if the patient was taking a consistent dose for 2 weeks before screening and continued at the same dose and frequency throughout the trial), and nasal cromolyn sodium. Non-asthma medications (such as decongestants, antihistamines, mucolytics, expectorants, antibiotics, analgesics, topical $\leq 1\%$ hydrocortisone, and vitamins) administered at the investigator's discretion were permitted if they were not excluded (see below) and were deemed necessary for the patient's safety and well-being. Allergen immunotherapy could be continued throughout the study if the regimen had been stable for at least 6 weeks before visit 2, but dose escalations were not allowed.

Efficacy and Safety Evaluations

The primary study objective was to determine the efficacy of 160 μ g bid of budesonide through a pMDI on change in morning peak expiratory flow (PEF) from baseline to the treatment period average in children with asthma 6 to younger than 12 years. PEF measurements were collected in a daily electronic patient-reported outcome (ePRO) diary.

A key secondary variable was an evaluation of the change from baseline to the treatment period average in morning FEV₁ measured by in-clinic spirometry. Other secondary efficacy end points included in-clinic spirometric measurements for forced vital capacity (FVC); forced midexpiratory flow between 25% and 75% of the FVC (FEF_{25–75}); variables from patient ePRO diaries, including evening PEF, nighttime and daytime asthma symptom scores, nighttime awakenings owing to asthma symptoms, and nighttime and daytime reliever medication use; and the numbers of predefined asthma events and study withdrawals owing to predefined asthma events.

The criteria for worsening asthma requiring study withdrawal included a decrease of at least 20% in morning predose FEV₁ from the morning predose randomization value or a decrease to lower

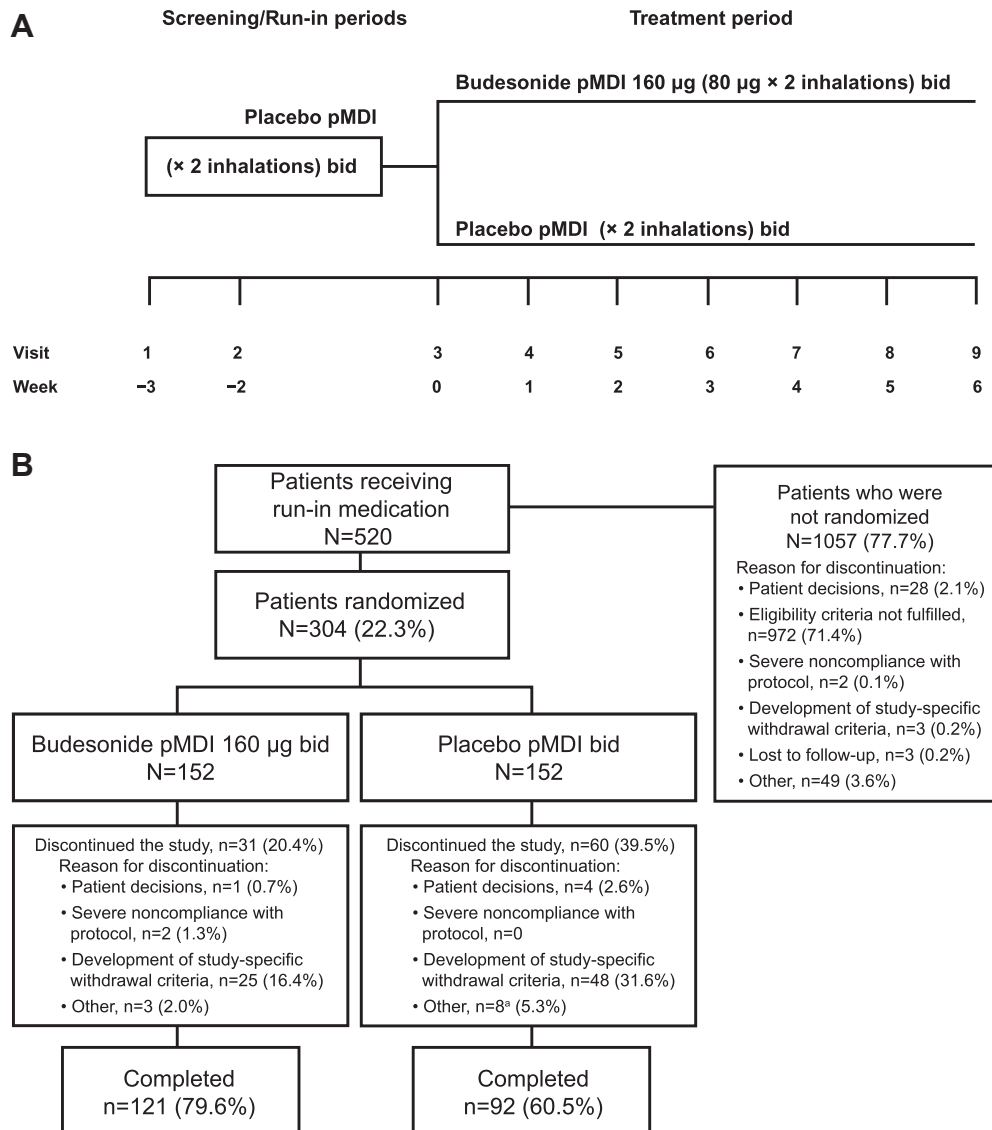


Figure 1. (A) Study design and (B) patient disposition. *Two patients in the placebo group had predefined asthma events, but their primary reason for withdrawal was given as "other." bid, twice daily; pMDI, pressurized metered-dose inhaler.

than 65% of predicted normal; the use of at least 8 actuations of albuterol per day on at least 3 days within any 7 consecutive days after randomization; a decrease of at least 20% from baseline in morning PEF (mean of all values from the 7-day period immediately before randomization) on at least 3 days within any 7 consecutive days after randomization; at least 2 nights with an awakening owing to asthma that required the use of reliever medication within any 7 consecutive days after randomization; or a clinical exacerbation requiring emergency treatment, hospitalization, or use of an asthma medication disallowed by the study protocol.

Exploratory end points also were evaluated for morning and evening FEV₁ values from patient ePRO diaries. At each treatment visit, AEs and vital signs were recorded, and a brief physical examination was performed.

Statistical Analyses

The treatment period was defined as any day from the date of the first dose of randomized treatment (including postdose measurements at randomization only) to the date of study completion or discontinuation inclusively. The primary efficacy variable was measured as the change in predose morning PEF from baseline

(mean of the last 7 days of the run-in period) to the treatment average (average of all data in the treatment period) using analysis of covariance with terms for treatment, age group (<8 and ≥8 years), and country, with baseline morning PEF as a covariate. Recorded values from all specified treatment period days were used with no replacement or imputation for missing data for the predose morning PEF. A last observation carried forward sensitivity analysis was performed for patients who terminated prematurely from the study, with the mean of the last 3 observations carried forward.

An analysis of covariance was used for changes in baseline (latest available predose value) for all in-clinic spirometric measurements (FEV₁, FVC, FEV_{25–75}) to the treatment period average (average of all data in the treatment period) and end of treatment value, with terms for treatment, age group (<8 and ≥8 years), and country, with baseline value as a covariate.

For secondary variables, recorded values from all specified treatment period days were used with no replacement or imputation for missing data. A last observation carried forward sensitivity analysis was performed for patients who terminated prematurely, with the value of the patient's last visit carried forward.

A post hoc responder analysis was conducted, in which the mean change in predose morning PEF from baseline (mean of the last 7 days of the run-in period) was calculated for each patient at each time point (treatment visit) including last observation carried forward values. Patients were classified as a responder (morning predose PEF ≥ 15 or ≥ 30 L/min) or nonresponder (morning predose PEF < 15 or < 30 L/min). A Mantel-Haenszel χ^2 test was used to assess for statistical significance between treatment groups.

Efficacy analyses included data from all patients who were randomized and received at least 1 dose of study medication and contributed sufficient data for at least 1 efficacy end point. A stepdown procedure was used to address multiplicity. For the efficacy analysis set, if the treatment difference for the primary variable, change in morning PEF, was statistically significant ($P < .05$), then the key secondary variable, change in morning FEV₁, was tested at the $P < .05$ level of significance. For all other variables, nominal P values were reported. The safety analysis set included all randomized patients who received at least 1 dose of study medication. All hypothesis testing was conducted using 2-sided tests. All P values reported for secondary variables were uncorrected for multiplicity.

Results

Patients

A total of 1,361 patients were screened during the study. Owing to an initially high screening failure rate (84% [578 of 688 patients initially screened]) and initial study completion of only 37 patients, the protocol was amended to broaden the target population and allow eligibility for rescreening to increase the probability of successful patient screening and randomization in the following ways: (1) initially, reversibility of FEV₁ of at least 12% from the pre-albuterol level within 15 to 30 minutes of administration had to be demonstrated at visit 2, but this was updated to include patients with a documented history of FEV₁ reversibility of at least 12% within 12 months of visit 2; (2) patients were allowed to satisfy inclusion criteria at visit 2, instead of only at visit 1; (3) daily therapy with a leukotriene inhibitor for at least 30 days before enrollment was accepted, in addition to ICS therapy, which was the only initial treatment considered; (4) pre-bronchodilator morning clinic FEV₁ range was widened from 75% to 95% of predicted normal to 70% to 95% of predicted normal; and (5) asthma symptom scores during the run-in period were decreased from a combined asthma symptom score of 3 on any 4 of 7 consecutive days before randomization to a combined asthma symptom score of 1 on any 3 of 7 consecutive days before randomization.

Expansion of the target population through these protocol changes was critical to the conduct of the study; before implementing the protocol amendment that broadened the target population, 785 of 933 patients had a failed screening (84%). After implementing the amendment that expanded the target population, the screening failure rate decreased to 44% (187 of 428 patients with a failed screening), resulting in a final screening failure rate of 71%. Overall, implementing these protocol amendments did not affect the interpretation of the study results.

Of 520 patients who received run-in medication (placebo pMDI and as-needed albuterol reliever therapy), 304 were randomized from 72 centers (budesonide, $n = 152$; placebo, $n = 152$), and 213 completed the study. Patient disposition is shown in Figure 1B. Of note, despite the expansion of the pre-bronchodilator FEV₁ eligibility criterion to 70% to 95% of predicted normal, only 7% ($n = 10$) of budesonide-treated patients and 12% ($n = 18$) of placebo-treated patients discontinued treatment owing to a decrease in predose FEV₁ to lower than 65% of predicted normal or a decrease in clinic morning predose FEV₁ of at least 20% from the randomization visit. Patient demographic characteristics are presented in Table 1.

Table 1

Demographics of all randomized patients

Demographic characteristics	Budesonide pMDI 160 μ g bid ($n = 152$)	Placebo pMDI bid ($n = 152$)
Age (y), mean (SD)	9 (1.6)	9 (1.6)
Age group, n (%)		
<8 y	33 (21.7)	33 (21.7)
≥ 8 y	119 (78.3)	119 (78.3)
Sex, n (%)		
Boys	98 (64.5)	94 (61.8)
Girls	54 (35.5)	58 (38.2)
Race, n (%)		
White	132 (86.8)	138 (90.8)
Black or African American	13 (8.6)	7 (4.6)
Asian	1 (0.7)	0
Other	6 (3.9)	7 (4.6)

Abbreviations: bid, twice daily; pMDI, pressurized metered-dose inhaler.

Baseline demographic characteristics were similar between treatment groups. No asthma medications other than short-acting β -agonists were taken by any patient during the run-in period. More budesonide-treated ($n = 121$; 79.6%) than placebo-treated ($n = 92$; 60.5%) patients completed the study (Fig 1B).

Efficacy

Primary variable

Greater improvement in morning predose PEF was observed for budesonide-treated vs placebo-treated patients (least-squares [LS] mean change from baseline to treatment period average of 17.8 vs 4.1 L/min, respectively), with an average treatment effect (budesonide vs placebo) of 13.6 L/min ($P < .0001$) during the study period. Improvements began at week 1, continued through week 3, and were maintained thereafter for the duration of the 6-week treatment period (Fig 2). Sensitivity analysis of the improvement in morning predose PEF showed no qualitative difference by country, region, or age group.

Post hoc PEF responder analysis

The percentage of patients who met the response criterion of an improvement of at least 15 L/min in predose morning PEF was significantly larger in the budesonide group than in the placebo group beginning at week 1 (38.7% vs 20.5%; $P < .001$) and continuing through the 6-week treatment period (week 2 [50.3% vs

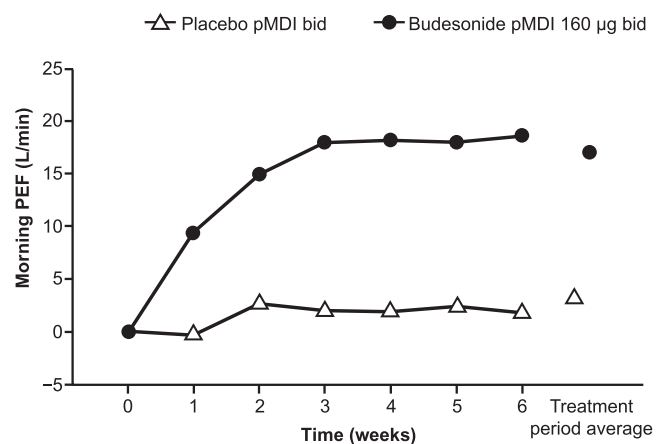


Figure 2. Mean change from baseline in morning PEF. Data points are means of patients' weekly mean change from baseline (including last observation carried forward). Baseline is the mean of the last 7 available days of the run-in period. Treatment period averages (excluding last observation carried forward values) are plotted at the end for each treatment group. bid, twice daily; PEF, peak expiratory flow; pMDI, pressurized metered-dose inhaler.

29.1%; $P < .001$], week 3 [53.6% vs 31.1%; $P < .0001$], week 4 [55.0% vs 34.4%; $P < .001$], week 5 [51.0% vs 33.8%; $P = .0025$], and week 6 [52.9% vs 36.4%; $P = .0039$]; Fig 3A).

When the morning predose PEF response criterion was increased to at least 30-L/min improvement, the percentage of patients who met the responder criteria was significantly larger in the budesonide group than in the placebo group at week 2 (31.8% vs 11.3%; $P < .0001$), week 3 (29.8% vs 17.2%; $P = .01$), week 4 (33.1% vs 20.5%; $P = .014$), week 5 (32.5% vs 19.9%; $P = .013$), and week 6 (34.4% vs 21.9%; $P = .015$) but not at week 1 (16.7% vs 10.0%; $P = .086$; Fig 3B).

Secondary variables

Treatment with budesonide resulted in significantly greater improvements from baseline in morning predose FEV₁ vs those with placebo (LS mean change from baseline to treatment period average of 0.00 vs 0.06 L, respectively), with a treatment effect of 0.06 L in favor of budesonide ($P = .0047$). The improvement in morning predose FEV₁ began in the first week of treatment and was maintained throughout the rest of the treatment period (Fig 4). In contrast, placebo-treated patients showed a decrease in morning predose FEV₁ after week 1, which continued to decrease throughout the rest of the treatment period (Fig 4).

Budesonide-treated patients had a LS mean improvement of 0.04 L over placebo for mean FVC, but this difference was not statistically significant (Table 2). Mean baseline FEF_{25–75} was significantly improved with budesonide treatment from baseline to treatment period average vs placebo (Table 2). Statistically significant improvement in evening PEF mean change from baseline to

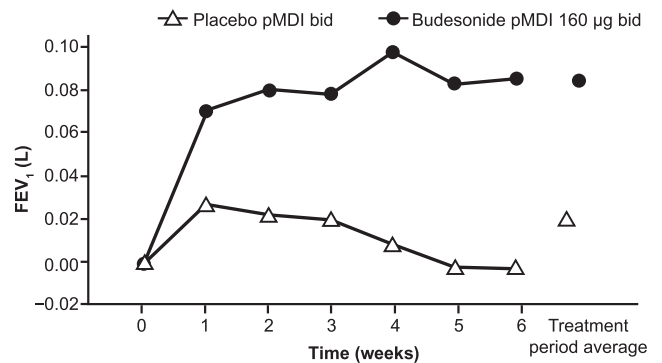


Figure 4. Mean change from baseline for in-clinic morning predose FEV₁. Data points are means of the individual patient FEV₁ change from baseline (including last observation carried forward values) at that visit. Baseline is defined as the latest non-missing assessment before the first dose (typically, visit 3 [randomization]). Treatment period averages (excluding last observation carried forward values) also are plotted at the end for each treatment group. bid, twice daily; FEV₁, forced expiratory volume in 1 second; pMDI, pressurized metered-dose inhaler.

treatment period average also was observed with budesonide vs placebo (Table 2).

Daytime and nighttime asthma symptom scores were significantly lower with budesonide vs placebo (Table 2). The LS mean percentages of nighttime awakenings owing to asthma symptoms and nighttime awakenings with reliever medication use also were significantly decreased with budesonide vs placebo (Table 2).

Mean total rescue medication use was significantly decreased from baseline (defined as the mean of the last 7 available days of the run-in period) with budesonide vs placebo (Table 2). Treatment with budesonide also significantly decreased daytime and nighttime rescue medication use vs placebo (Table 2).

Thirty-three patients (21.7%) in the budesonide group and 61 patients (40.1%) in the placebo group had at least 1 predefined asthma event, and the time to first predefined asthma event was significantly longer for budesonide-treated vs placebo-treated patients ($P = .0002$). Significantly fewer patients in the budesonide vs placebo group withdrew from the study because of a predefined asthma event (25 [16.4%] vs 50 [32.9%], respectively; $P = .0004$). Time to study withdrawal owing to a predefined asthma event favored budesonide ($P = .0004$). The difference in withdrawal rate for the budesonide group compared with placebo was evident after week 1 and increased during the treatment period (Fig 5).

For the exploratory end points of morning and evening FEV₁ recorded in patients' ePRO diaries, budesonide resulted in significant improvements vs placebo, with treatment effects of 0.068 L ($P = .0004$) and 0.082 L ($P = .0014$), respectively.

Safety

The incidence of AEs reported in all treatment arms raised no new safety concerns for budesonide, and no serious AEs were reported. Fewer budesonide-than placebo-treated patients had at least 1 AE (28.9% vs 40.8%, respectively; Table 3). The most common AEs (those reported in $\geq 2\%$ of patients in any treatment group) were related to respiratory infections, which were similar in frequency between the 2 groups. There were no clinically important treatment group differences in AEs except for asthma (7.2% in placebo group vs 0.7% in budesonide group). Fewer budesonide-than placebo-treated patients discontinued because of an AE (2% vs 8.6%, respectively).

Discussion

The primary study objective of demonstrating an improvement in morning predose PEF with 160 µg bid of budesonide through a

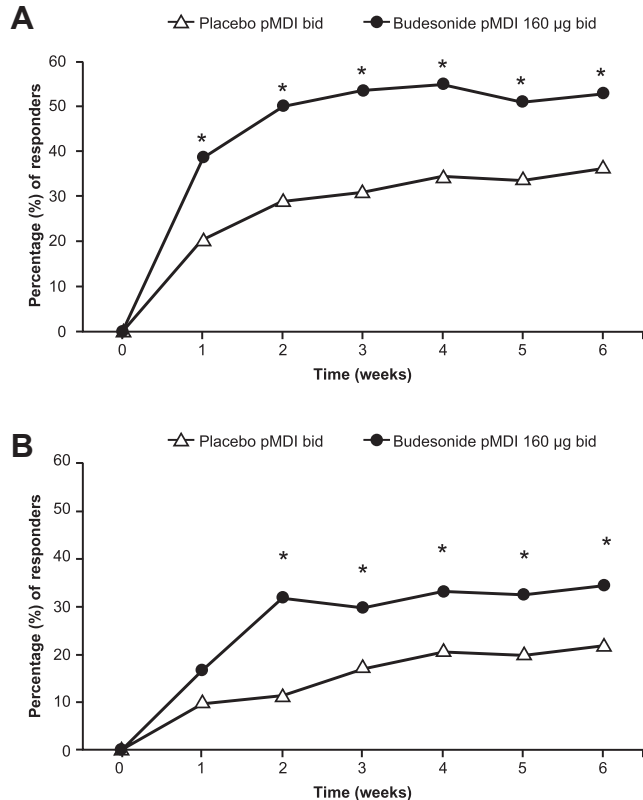


Figure 3. Percentage of patients with improvements of (A) at least 15 L/min and (B) at least 30 L/min in morning peak expiratory flow. Data points are percentages of patients with mean change from baseline (including last observation carried forward) of at least 15 and at least 30 L/min. Baseline is the mean of the last 7 available days of the run-in period. * $P < .05$ for budesonide vs placebo. bid, twice daily; pMDI, pressurized metered-dose inhaler.

Table 2

Treatment effect for other secondary outcomes

Change from baseline to treatment period average ^a	Baseline budesonide pMDI 160 µg bid	Baseline placebo pMDI bid	Treatment effect ^b (budesonide vs placebo)	P value ^c
FVC (L) ^d	2.18	2.18	0.04	.0673
FEF _{25–75} (L/s) ^d	1.55	1.59	0.10	.0216
Evening PEF (L/min) ^e	217.2	221.0	10.8	.0004
Daytime asthma symptom score ^e	1.3	1.3	–0.2	.0004
Nighttime asthma symptom score ^e	1.1	1.2	–0.1	.0079
Nighttime awakenings due to asthma symptoms (%) ^e	23.3	20.7	–4.7	.0095
Nighttime awakenings with reliever medication use (%) ^e	12.4	14.0	–3.9	.0007
Total rescue medication use (inh/d) ^d	1.3	1.4	–0.5	<.0001
Daytime rescue medication use (inh/d) ^d	0.8	0.8	–0.3	.0001
Nighttime rescue medication use (inh/d) ^d	0.6	0.6	–0.2	<.0001

Abbreviations: bid, twice daily; FEF_{25–75}, forced midexpiratory flow between 25% and 75% of forced vital capacity; FVC, forced vital capacity; inh/d, inhalations per day; PEF, peak expiratory flow; pMDI, pressurized metered-dose inhaler.

^aTreatment period average is defined as the mean value across all available on-treatment visits. Change from baseline to the end point was analyzed using an analysis of covariance model with terms for treatment, age group (<8 and ≥8 years of age), and country, with baseline as a covariate.

^bLeast-squares mean treatment difference (budesonide vs placebo).

^cBaseline is defined as the latest non-missing assessment before the first dose (typically visit 3, randomization).

^dBaseline is defined as the mean of the last 7 available days of the run-in period.

^eBaseline is defined as the percentage of days on which a patient experienced nighttime awakenings out of the available days on which data were collected during the last 7 days of the run-in period.

pMDI compared with placebo in children with asthma 6 to younger than 12 years was achieved. The improvement was evident in the first week of treatment, continued through week 3, and was maintained throughout the duration of the 6-week treatment period. The continued improvement with budesonide for some weeks in this study has been observed in other studies with budesonide and with other ICSs.^{4,6,7} Also in support of these findings, a meta-analysis of 8 fluticasone propionate trials observed significant benefits in PEF, symptoms, and rescue medication within 1 day of treatment and significant benefits in FEV₁ after week 1; however, the greatest magnitude of effects occurred within 3 weeks for FEV₁ (+0.52 L) and PEF (+36 L/min) and 2 weeks for rescue medication use and symptom scores.⁸ Improvements in other lung function end points (predose FEV₁, FEF_{25–75}, evening PEF) and patient-reported outcomes (daytime, nighttime, and total daily asthma scores), nighttime awakenings owing to asthma symptoms, nighttime awakenings for which reliever medication

was used, reliever medication use (daytime, nighttime, and total), and study withdrawals owing to predefined asthma events also supported the efficacy of budesonide over placebo. Although some have argued that PEF response is an effort-dependent measurement that yields less reliable and clean data than spirometry,⁹ the results of this study found consistent results between the types of measurements with the exception of mean FVC, which was numerically, but not statistically, improved ($P = .0673$).

Currently, there are no established criteria of what is a clinically meaningful change from baseline in PEF response to ICS treatment in a pediatric asthma population. However, the 2 response criteria chosen (mean change from baseline) in predose morning PEF of at least 15 L/min and at least 30 L/min have been used previously to demonstrate therapeutic equivalency¹⁰ and statistical power¹¹ for similar studies in this patient population. The 30-L/min improvement in PEF is commonly used as a criterion to indicate a clinically meaningful change in adult studies. Children have smaller lung volumes; therefore, the authors initially hypothesized that the 15-L/min criterion would be more appropriate in this study population.

The 15- and 30-L/min cutoffs appeared to be appropriate response criteria for the pediatric patients in this study. The percentage of children who met the 2 response criteria was significantly larger for the budesonide group than for the placebo group as soon as weeks 1 to 2 of treatment (~40% of budesonide-treated

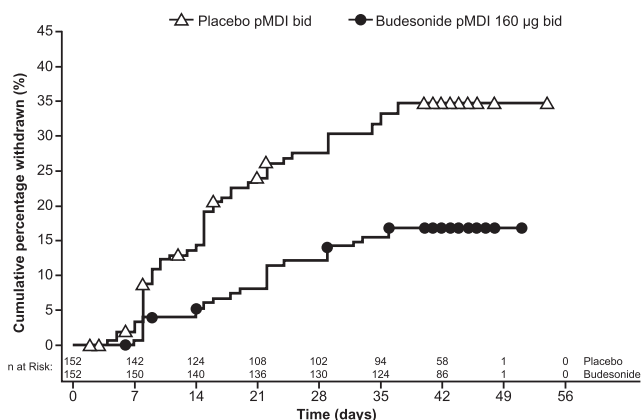


Figure 5. Time to withdrawal owing to an asthma-related event. Time to withdrawal from the study was defined as the time (days) from the date of the first dose at randomization to the date of withdrawal. For patients who completed the study, time to withdrawal was censored at the day of study completion. The symbols on each line indicate those censored patients. A fraction of patients from each treatment group continued beyond the nominal end of the study (42 days), without withdrawing because of a predefined asthma event. Each symbol beyond 42 days notes the day that a patient stopped treatment. Only 1 patient in each treatment group remained in the study beyond 49 days and 0 beyond 56 days. bid, twice daily; pMDI, pressurized metered-dose inhaler.

Table 3Most common adverse events^a (frequency ≥2%)

Adverse event	Budesonide pMDI 160 µg bid (n = 152)	Placebo pMDI bid (n = 152)
Patients with any adverse event, n (%)	44 (28.9)	62 (40.8)
Nasopharyngitis	12 (7.9)	9 (5.9)
Pharyngitis	5 (3.3)	8 (5.3)
Asthma	1 (0.7)	11 (7.2)
Viral upper respiratory tract infection	3 (2.0)	8 (5.3)
Influenza	4 (2.6)	4 (2.6)
Oropharyngeal pain	3 (2.0)	4 (2.6)
Epistaxis	1 (0.7)	3 (2.0)
Sinusitis	1 (0.7)	3 (2.0)
Cough	0	3 (2.0)

Abbreviations: bid, twice daily; pMDI, pressurized metered-dose inhaler.

^aAdverse events include those with an onset on or after the date of the first randomized dose and up to and including 24 hours after the date of the last dose of the randomized study medication.

patients at week 1 and >50% throughout the study for the 15-L/min criterion) and sustained throughout the treatment period, further supporting the efficacy benefits of budesonide over placebo. However, it is important to note that this study was designed for patients who required a low-dose ICS with a relatively mild impact of asthma; therefore, the 15-L/min criterion is appropriate for this population with mild asthma; future studies are required to evaluate appropriate response criteria in pediatric patients with more severe asthma.

As a group, the change in PEF and other secondary outcome measurements occurred rapidly in response to budesonide treatment (by weeks 1–3) and were maintained throughout the rest of the treatment period. However, in the placebo group, morning PEF remained flat and morning predose FEV₁ decreased after week 1 of treatment. These data in the placebo group confirm that this patient population did require ICS therapy, because they began to experience a more significant impact of asthma on lung function when left untreated. Future studies of longer duration including pediatric patients with asthma of different severities are needed to evaluate whether this rapid response to budesonide treatment has predictability for a patient's long-term response to treatment and whether it is consistent across different patients.

Results of safety analyses did not show any concerns for the doses tested, and no serious AEs were reported. Importantly, the safety profile was similar to the known safety profile of budesonide in other formulations and devices when studied in children 6 to younger than 12 years.^{3,4,12} As in the present study, common AEs reported in studies with budesonide administered by dry-powder inhaler and nebulizer were respiratory infections (eg, sinusitis, rhinitis, pharyngitis).^{4,12} Although 5 serious AEs were reported across all groups in a study by Shapiro et al,⁴ including 2 asthma exacerbations, none were judged to be causally related to the study drug. In the findings of all studies, the incidence of AEs for budesonide was similar to that for placebo.^{3,4,12} Together, the efficacy and safety data support the administration of a suspension formulation of 160 µg bid of budesonide administered through a pMDI in children with asthma 6 to younger than 12 years.

Currently, budesonide is approved in the United States for use as maintenance treatment for asthma once or twice daily as a suspension from a nebulizer in children 12 months to 8 years old¹³ and twice daily as an inhalation powder through a dry-powder inhaler in children 6 to 17 years old.¹⁴ Budesonide delivered through a pMDI would allow the introduction of another device option for this age group, because differences in attributes, such as metering, means of dispersion, type of formulation, and design, can make one device more preferred by or suitable for some patients than others.^{15,16}

Ultimately, the health care professional will select the device that best meets the individual patient's needs and with which the patient is satisfied and comfortable.¹⁵ For these reasons, it is beneficial to show the efficacy and safety of asthma medications

across a range of delivery devices. Overall, the efficacy and safety data from this study support the administration of a suspension formulation of 160 µg bid of budesonide administered through a pMDI in children with asthma 6 to younger than 12 years.

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