Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma

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Background: Budesonide inhalation suspension and the leukotriene receptor antagonist montelukast have demonstrated efficacy in children with mild persistent asthma, but comparative long-term studies in young children are needed.
Objective: To compare the long-term efficacy and safety of budesonide inhalation suspension and montelukast.
Methods: After a run-in period, children 2 to 8 years old with mild asthma or recurrent wheezing were randomized to once-daily budesonide inhalation suspension 0.5 mg or once-daily oral montelukast 4 or 5 mg for 52 weeks. Subjects were stepped up to twice-daily budesonide inhalation suspension or oral corticosteroids for mild or severe asthma worsening, respectively. The primary outcome was time to first additional medication for asthma worsening at 52 weeks. Secondary variables included times to the first additional asthma medication measured at 12 and 26 weeks; times to the first asthma exacerbation (mild and severe) measured at 12, 26, and 52 weeks; exacerbation rates (mild and severe) over a period of 52 weeks; diary variables (eg, peak expiratory flow [PEF]); patient-reported outcomes; and Global Physician and Caregiver Assessments.
Results: No significant between-group differences were observed for time to first additional asthma medication at 52 weeks; however, time to first additional asthma medication was longer (unadjusted $P = .050$) at 12 weeks and exacerbation rates were lower over a period of 52 weeks (unadjusted $P = .034$) for budesonide versus montelukast. Time to first severe exacerbation (requiring oral corticosteroids) was similar in both groups, but the percentage of subjects requiring oral corticosteroids over a period of 52 weeks was lower with budesonide (25.5% vs 32.0%). Peak flow and Caregiver and Physician Global Assessments favored budesonide.
Conclusion: Both treatments provided acceptable asthma control; however, overall measures favored budesonide inhalation suspension over montelukast.
Clinical implications: These findings are consistent with studies in older children demonstrating better outcomes with inhaled corticosteroids versus montelukast. (J Allergy Clin Immunol 2007;120:1043-50.)

Key words: *Budesonide inhalation suspension, montelukast, asthma, pediatric, efficacy, safety*

The 2002 National Asthma Education and Prevention Program (NAEPP) guidelines recommend the use of long-term inhaled corticosteroids (ICSs) as the preferred treatment for persistent asthma in children of all ages.[1] Because very young children may lack the coordination or the ability to use dry powder inhalers or metered-dose inhalers correctly,[2] nebulized delivery of ICS may facilitate treatment adherence. Budesonide inhalation suspension (BIS; Pulmicort Respules; AstraZeneca LP, Wilmington, Del) is the first and only nebulized ICS approved in the United States for the management of asthma in children 1 to 8 years of age.[3] The efficacy and safety of BIS were established in 3 randomized, pivotal, placebo-controlled trials in which 1018 children age 6 months to 8 years were treated with 0.25, 0.5, or 1.0 mg nebulized BIS delivered either once or twice daily.[4-6]

The use of leukotriene receptor antagonists (LTRAs) is an alternative to ICS therapy for the treatment of mild and moderate persistent asthma in children.[1] The efficacy and safety of montelukast 4 or 5 mg (Singulair; Merck, Whitehouse Station, NJ) were demonstrated in 2 pivotal randomized, placebo-controlled trials of children 2 to 5 years of age[7] and 6 to 14 years of age,[8] respectively.

Results from 2 short-term and 2 long-term comparative studies of ICS therapy (beclomethasone or fluticasone propionate) and montelukast suggest that ICS therapy is generally more effective than montelukast in children older than 6 years.[9-12] The results of 2 studies that assessed either exercise-induced bronchoconstriction in children and adults[13] or induced allergic response in children suggest that budesonide may provide more protection than montelukast.[14]

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Abbreviations used

AE: Adverse event
BIS: Budesonide inhalation suspension
CHQ-PF50: Child Health Questionnaire Parent Form-50
CSHA: Children's Health Survey for Asthma
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
LTRA: Leukotriene receptor antagonist
NAEPP: National Asthma Education and Prevention Program
PACQLQ: Pediatric Asthma Caregiver's Quality of Life Questionnaire
PEF: Peak expiratory flow
SABA: Short-acting β_2-adrenergic agonist

The current study is the first to compare BIS and montelukast as long-term asthma controller therapies in young children 2 to 8 years of age with mild persistent asthma or recurrent wheezing episodes over a 1-year period.

METHODS

Subjects

Children 2 to 8 years of age were eligible for the study if they had symptoms of mild persistent asthma as determined by 2002 NAEPP guidelines[1] or had, in the year before screening, a history of $\geq$3 wheezing episodes that lasted >1 day and affected sleep. In addition, to be eligible for randomization, subjects were required to have a cumulative asthma symptom score (daytime plus nighttime) of $\geq$2 on $\geq$3 of 7 consecutive days and must have required the use of β_2-adrenergic agonists on $\geq$3 of 7 consecutive days during the run-in period. Exclusion criteria are described in this article's Online Repository at www.jacionline.org.

Study design

This was a 52-week, open-label, randomized, active-controlled, multicenter study (DX-RES-2103). This study consisted of a 3-day to 21-day qualifying run-in period during which subjects could not receive orally administered albuterol, leukotriene modifiers, inhaled long-acting β_2-adrenergic agonists (single agent or in combination products), systemic corticosteroids or ICSs, inhaled anticholinergic medications, or omalizumab, followed by a 52-week treatment period (Fig 1). Subjects who met eligibility criteria were randomized to BIS 0.5 mg or to montelukast 4 mg or 5 mg, both administered once daily in the evening. The lowest indicated dosage for these products was selected in accordance with NAEPP guidelines[1] for the treatment of mild persistent asthma (ie, low-dose ICS or LTRA). BIS was administered via a PARI Pro Neb compressor and PARI LC plus nebulizer (PARI Respiratory Equipment Inc, Midlothian, Va) with a mouthpiece or face mask provided by PARI. No specific discontinuation criteria were predefined; subjects experiencing exacerbations could remain in the study, but study subjects could be discontinued at any time at the discretion of the investigators.

Compliance with BIS or montelukast treatment was assessed by review of diary data, which was to be completed and transmitted daily by caregivers using an electronic diary (LogPad; PHT Corp, Charlestown, Mass). Subjects were counseled if they did not maintain $\geq$80% study treatment compliance and were discontinued from the study at the discretion of the investigator for continued poor compliance.

The study was approved by the investigational review board affiliated with each center and conducted in accordance with Good Clinical Practice Guidelines. All parents or legal guardians provided written informed consent before the conduct of the study and any study-related procedures; subjects 6 years of age and older also provided signed assent. Allowed and disallowed medications are detailed in this article's Online Repository at www.jacionline.org. Rescue medication use (nebulized or inhaled albuterol for all subjects) was recorded in daily diaries.

Medications during asthma exacerbations

A mild asthma exacerbation was defined as the need for $\geq$3 doses of short-acting β_2-adrenergic agonist (SABA) on 4 of 7 consecutive days or as having nighttime awakenings caused by asthma symptoms on $\geq$2 of 7 days during each of 2 consecutive weeks. A severe asthma exacerbation was defined as the need for 6 doses of SABA in a 24-hour period, 10 doses of SABA in a 48-hour period, or hospitalization for worsening of symptoms. The electronic diaries alerted caregivers to call the clinic when subjects met asthma exacerbation criteria requiring step-up therapy.

Subjects in both treatment groups who experienced mild exacerbations received step-up therapy with BIS 0.5 mg every morning for 14 days—that is, subjects in the BIS 0.5-mg once-daily treatment arm increased to BIS 0.5 mg twice daily, whereas subjects on montelukast received BIS 0.5 mg once daily in the morning in addition to the evening montelukast dose. Subjects in both treatment arms who experienced severe exacerbations received a 3-day to 10-day standardized course of oral corticosteroids. Step-up BIS and oral corticosteroid treatments were dispensed to all patients with instructions to be used only if the criteria for a mild exacerbation were met; education was given to caregivers about the criteria for a mild exacerbation and when to take the BIS.

Efficacy assessments

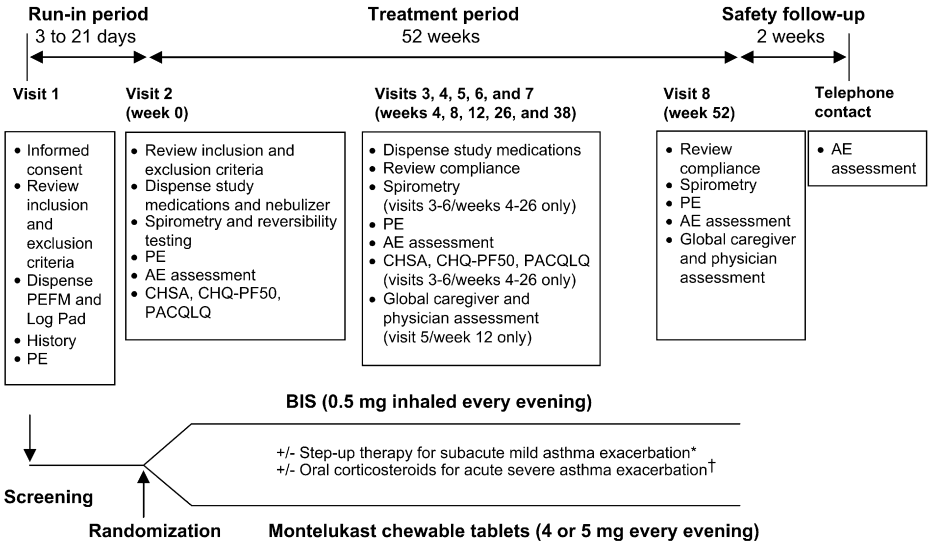
The primary efficacy variable was time to first additional asthma medication for mild or severe asthma exacerbation (either morning step-up therapy with BIS or oral corticosteroids) measured over a period of 52 weeks. Secondary efficacy variables included time to first additional asthma medication measured at 12 and 26 weeks; times to the first mild and severe asthma exacerbation measured at 12, 26, and 52 weeks; and rates of occurrence of mild and severe exacerbations (number/subject/year) over a period of 52 weeks.

Symptom scores (0 = none to 3 = severe), rescue medication use, and peak expiratory flow (PEF) rates (MiniWright peak flow meter, Clement Clarke International Ltd, Harlow, Essex, United Kingdom [UK]) were recorded daily by caregivers in the electronic diary. Diary-related secondary variables analyzed included mean changes from baseline to the average over the period of the first 12 weeks and average over a period of 52 weeks of randomized treatment in daily use of rescue medication, daytime and nighttime symptom scores, and daily morning and evening PEF measurements.

In children able to perform spirometry, pulmonary function was measured during study visits at weeks 0, 4, 8, 12, 26, and 52 by using a calibrated spirometer that met American Thoracic Society standards. Changes from baseline to the average over the period of the first 12 weeks of randomized treatment in FEV_1, forced vital capacity (FVC), and forced expiratory flow (L/s) during the middle 50% of the FVC exhalation were measured.

Patient-reported outcomes and global assessments

Patient-reported outcomes and global assessments were evaluated by using the Child Health Questionnaire Parent Form-50 (CHQ-



*BIS 0.5 mg inhaled every morning for 14 days
†Three- to 10-day course of prednisone, prednisolone, or methylprednisolone.

FIG 1. Study flow chart. *PE,* Physical examination; *PEFM,* PEF meter.

PF50),[15] the Children's Health Survey for Asthma (CSHA),[16] the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ),[17] and the Global Physician and Caregiver Assessments (details provided in this article's Online Repository at www.jacionline.org).

Safety evaluations

Safety was evaluated by recording adverse events (AEs), serious AEs, deaths, and discontinuations caused by AEs. Furthermore, vital sign parameters and physical examination findings were assessed at each visit. Although height was measured, comparison of growth was not an objective of the study, and the study was not conducted according to the Food and Drug Administration guidelines for evaluating the effects of corticosteroids on growth in children.[18]

Statistical analyses

A sample size of 190 subjects per treatment group was estimated to have 80% power ($\alpha = 0.05$) to detect a difference between the treatment groups of $\geq$10% in the time to the first addition of step-up therapy or oral corticosteroids at 52 weeks. The primary and secondary efficacy measures were evaluated by using the intention-to-treat population (ie, all randomized subjects who took $\geq$1 dose of study medication and contributed sufficient data for $\geq$1 efficacy measure). Differences between treatment groups on the secondary efficacy variables were considered nominally statistically significant if the unadjusted *P* value was <.05.

Results from the primary efficacy measure were compared between treatment groups using a log-rank test, with age group used as a stratification variable. Results from secondary time-to-event measures were analyzed using the same methods. Analyses of event rates were performed using a Poisson regression model, with treatment and age group as study factors and time in study as an offset variable. Data from other secondary efficacy measures reported in the first 12 weeks (primary time point for secondary efficacy variables), including daily diary variables, patient-reported outcomes, and spirometric variables, were compared between treatment groups using a 2-way analysis of covariance model, with change from baseline (baseline defined as the mean of values recorded during the run-in period for all diary variables or the value recorded at randomization for patient-reported outcomes and spirometric variables) as the dependent variable; treatment, center, and age group as main effects; and the baseline value as a covariate. The distribution of scores on the Global Physician and Caregiver Assessments was analyzed with a Mantel-Haenszel-Cochran test for ordinal data with modified-ridit scores, using treatment and age group as strata.

RESULTS

Subjects

Of 645 subjects screened, 395 were randomized at 55 centers in the United States between October 16, 2002, and February 2, 2005, to receive BIS (n = 197) or montelukast (n = 198). One hundred fifteen subjects (29.1%) did not complete the study (Fig 2; see this article's Online Repository at www.jacionline.org). Subject demographics were similar in both treatment groups (Table I; see this article's Table E1 in the Online Repository at www.jacionline.org). Subjects in both treatment groups were comparable with respect to baseline asthma characteristics and baseline pulmonary function (in a subset of subjects able to perform these tests), which was nearly normal and indicative of relatively mild asthma. Only a minority of subjects had been on previous ICS therapy (~12%). The mean subject-reported compliance (derived from electronic diaries) was 82.9% for BIS and 82.8% for montelukast, but the percentage of subjects with $\geq$80% compliance over the course of the year-long study was low in both the BIS (68.5% of subjects) and montelukast (67.5% of subjects) groups. Compliance of $\geq$80% was highest during weeks 1 to 13 and decreased over time.

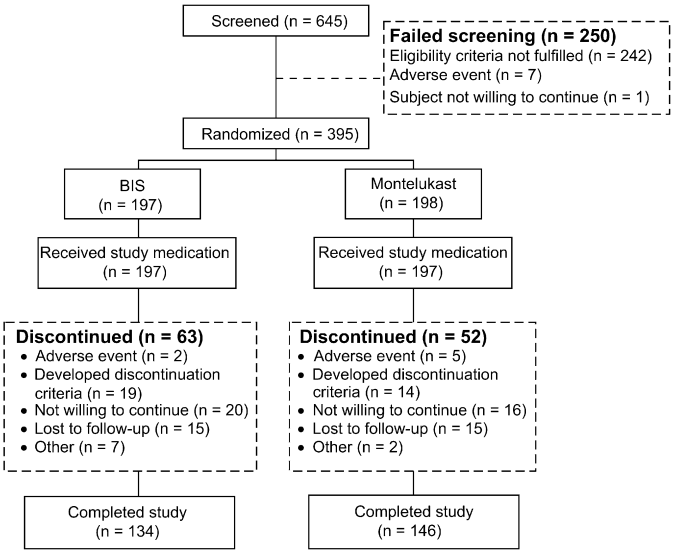


FIG 2. Subject disposition.

TABLE I. Baseline asthma and demographic characteristics of randomized subjects

Characteristic	BIS (n = 197)	Montelukast (n = 197)
Age in years, mean (SD)	4.6 (2.0)	4.7 (1.9)
Age distribution, n (%)		
0-1 y	2 (1.0)	0
2-5 y	129 (65.5)	126 (64.0)
6-8 y	66 (33.5)	71 (36.0)
Male, n (%)	122 (61.9)	118 (59.9)
Race, n (%)		
White	162 (82.2)	164 (83.2)
Black	27 (13.7)	29 (14.7)
Asian	3 (1.5)	3 (1.5)
Other	5 (2.5)	1 (0.5)
Previous* ICS use, n (%)	25 (12.7)	24 (12.2)
Previous LABA use, n (%)	6 (3.0)	4 (2.0)
Diary variables†	n = 197	n = 197
AM asthma symptom score, mean (SD)	1.30 (0.50)	1.30 (0.45)
PM asthma symptom score, mean (SD)	1.24 (0.52)	1.17 (0.54)
24-h rescue medication use (puffs), mean (SD)	1.69 (1.37)	1.75 (1.33)
AM PEF (L/min), mean (SD)	126.53 (50.33)	132.42 (51.42)
PM PEF (L/min), mean (SD)	130.29 (52.97)	138.37 (53.08)
Spirometry at visit 2	n = 100	n = 100
FEV_1 (L), mean (SD)	1.18 (0.36)	1.17 (0.36)‡
% Predicted FEV_1, mean (SD)	89.88 (17.75)	91.67 (18.07)

LABA, Long-acting β_2-adrenergic agonist.
*Subjects were excluded from the study if they received ICS within 1 week before screening.
†Average during the run-in period between visits 1 and 2.
‡n = 102.

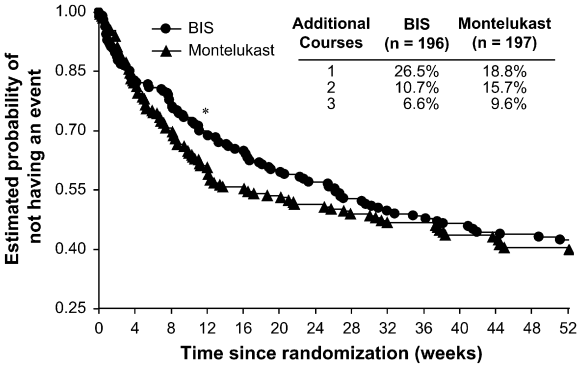


FIG 3. Kaplan-Meier probability curve for the time to first additional asthma medication (step-up BIS or oral corticosteroids) over the 52-week study period. *Unadjusted $P = .05$.

Efficacy

Time to first additional asthma medication (ie, step-up BIS or oral corticosteroids for mild and severe exacerbations, respectively) over a period of 52 weeks was not significantly different ($P = .285$) between the 2 groups (Fig 3). However, separation of treatment groups was evident, beginning at approximately 1 month after randomization, and was most pronounced at 12 weeks (unadjusted $P = .05$); the Kaplan-Meier probability curves for the treatment groups converged at approximately 26 weeks and remained so until 52 weeks after randomization.

The percentages of subjects who received ≥1 course of additional asthma medication (step-up BIS or oral corticosteroids) over the 52-week treatment period in the BIS group versus the montelukast group were as follows: 12 weeks (29.1% vs 38.6%, respectively), 26 weeks (41.3% vs 48.2%, respectively), and 52 weeks (52.0% vs 56.9%, respectively). Subjects treated with BIS experienced a lower rate of exacerbations (number/subject/year) that required step-up BIS therapy or oral corticosteroids

TABLE II. Secondary efficacy variables

Variable	Treatment	n*	Value	*P* value (BIS – montelukast)
Exacerbations				
Mild or severe asthma exacerbations, events/subject/y	BIS	196	1.23	.034
	Montelukast	197	1.63	
Diary-related variables, adjusted mean (SEM) change from baseline†				
AM asthma symptom score	BIS	195	−0.40 (0.04)	.36
	Montelukast	196	−0.35 (0.04)	
PM asthma symptom score	BIS	195	−0.43 (0.04)	.12
	Montelukast	196	−0.35 (0.04)	
24-h rescue medication use	BIS	195	−0.69 (0.11)	.84
	Montelukast	196	−0.72 (0.11)	
Rescue medication–free days, %	BIS	190	38.74 (2.14)	.59
	Montelukast	194	37.24 (2.13)	
Asthma-free days, %	BIS	190	19.91 (1.99)	.19
	Montelukast	194	16.48 (1.97)	
AM PEF	BIS	169	21.07 (2.30)	.007
	Montelukast	161	14.03 (2.28)	
PM PEF	BIS	171	16.83 (2.30)	.005
	Montelukast	163	9.42 (2.27)	
Pulmonary function variables, adjusted mean (SEM) change from baseline†				
FEV_1 (L)	BIS	77	0.09 (0.02)	.19
	Montelukast	82	0.05 (0.02)	
% Predicted FEV_1	BIS	77	7.52 (1.59)	.64
	Montelukast	80	6.55 (1.62)	

*Subjects with baseline and postbaseline values at week 12.
†Change from baseline to the average for weeks 1 through 12 using the last observation carried forward.

compared with subjects treated with montelukast (1.23 vs 1.63, respectively; unadjusted $P = .034$; Table II), a 24.5% reduction in the total number of exacerbations.

Severe asthma exacerbations

The percentages of subjects who received oral corticosteroids for an acute severe exacerbation over the 52-week treatment period in the BIS group versus the montelukast group were as follows: week 12 (10.7% vs 14.7%, respectively), week 26 (17.3% vs 22.3%, respectively), and week 52 (25.5% vs 32.0%, respectively). Likewise, the rate (number/subject/year) of acute severe exacerbations requiring treatment with oral corticosteroids was lower in the BIS group compared with the montelukast group (0.52 vs 0.67, respectively; $P = .149$; Table II), with an estimated reduction in the total number of courses of additional oral corticosteroid therapy of 22.7% in the BIS group compared with the montelukast group.

Secondary diary and spirometry variables

Diary variables: short-term results. The mean changes from baseline to the average over the first 12 weeks in secondary diary variables generally were similar in both treatment groups, with the exception of morning and evening PEF, for which improvements were greater in the BIS group compared with the montelukast group (morning PEF, unadjusted $P = .007$; evening PEF, unadjusted $P = .005$; Table II). The mean daytime and nighttime asthma symptom scores showed greater improvements in the BIS group compared with the montelukast group, although the differences between the groups were not significant (adjusted mean change from baseline, –0.40 vs –0.35 and –0.43 vs –0.35, respectively; Table II). The mean changes from baseline to the average over the first 12 weeks in the daily use of rescue medication were similar in both treatment groups (Table II).

Diary variables: long-term results. Improvements from baseline in all diary variables were greater over a period of 52 weeks compared with 12 weeks in both treatment groups (see this article's Table E3 in the Online Repository at www.jacionline.org). Similar results were observed in the BIS and montelukast groups on all variables over a period of 52 weeks, with the exception of morning and evening PEF, for which the mean changes from baseline were greater with BIS compared with montelukast (morning PEF, 28.39 vs 20.63, respectively; evening PEF, 25.25 vs 16.85, respectively).

Spirometry variables. Spirometry measurements were completed only in subjects who were willing and able to perform them, which included approximately 40% of subjects in each treatment group. Improvements from baseline to the average over the first 12 weeks in spirometry variables (FEV_1, FVC [data not shown], forced expiratory flow during the middle 50% of the FVC exhalation [data not shown], and % predicted FEV_1) were small in both treatment groups, with no significant differences observed

between the groups (Table II). Results were similar at the end of treatment (see this article's Online Repository at www.jacionline.org).

Patient-reported outcomes and global assessments

The results of Physician and Caregiver Global Assessments were significantly better ($P \leq .0164$) for BIS compared with montelukast at week 12 (see this article's Figs E1 and E2, respectively, in the Online Repository at www.jacionline.org). The results of Physician Global Assessments also were significantly better ($P \leq .0171$) for BIS compared with montelukast at the end of treatment (see this article's Online Repository at www.jacionline.org). The results of the CHQ-PF50 questionnaire, the CHSA, and the PACQLQ generally were similar between the groups at the end of week 12 (see this article's Table E2 in the Online Repository at www.jacionline.org) and the end of treatment (see this article's Table E3 in the Online Repository at www.jacionline.org).

Safety

The incidence of AEs generally was similar in both treatment groups; the majority of AEs were of mild to moderate intensity in both treatment groups (see this article's Table E4 in the Online Repository at www.jacionline.org). Among subjects who completed 52 weeks of treatment, similar increases in height from baseline to 52 weeks were observed between the treatment groups (BIS, 110.1 cm to 116.6 cm; montelukast, 110.3 cm to 117.1 cm).

DISCUSSION

The results of this study demonstrated that both BIS and montelukast were efficacious and well tolerated in this group of children with mild asthma or recurrent wheezing, with no new safety findings or concerns identified. No significant differences were observed between the BIS and montelukast groups on the primary efficacy variable, time to first additional asthma medication with either step-up BIS for mild asthma exacerbations or oral corticosteroid for severe exacerbations at 52 weeks. However, several secondary outcomes suggested that BIS was more efficacious than montelukast. Better outcomes were observed for BIS versus montelukast on the rate of asthma exacerbations requiring additional asthma medication over the 52-week study period and the changes from baseline in morning and evening PEF values. Results on all other measures favored BIS over montelukast, though not significantly, with the exception of rescue medication use, spirometry variables, most CHSA domains, and the PACQLQ, on which similar results were observed in both treatment groups. On the Emotional Health domain of the CHSA, results were better for montelukast than for BIS, which were driven by the responses to items that assessed the frustration with the need to rely on asthma treatments. In addition, the results of the Global Caregiver Assessment (week 12) and the Global Physician Assessment indicated that asthma control was greater with BIS compared with montelukast.

The lack of significant differences between the 2 treatments on the primary efficacy measure of time to the first additional asthma medication at 52 weeks was unexpected on the basis of previous literature reporting better outcomes with an ICS compared with montelukast[11,12,19] and may be explained by 3 factors. First, the recruited study population probably had asthma that was milder than intended, as suggested by the low percentage of subjects who used ICSs before screening (12.4% of all subjects) and the low percentage of subjects (28.8%) who required oral corticosteroids over a period of 52 weeks. Disease severity at study entry seems to be overestimated from the asthma symptoms during the run-in period (Table I) because subjects were not allowed to receive controller medications during the week before screening and during the run-in period (3-21 days). It is also possible that the severity of asthma may have improved spontaneously over time in some subjects because of the variability of the disease itself; particularly, subjects included in the study on the basis of repeated episodes of wheezing may have outgrown that phenotype rather than developing persistent asthma. Second, the percentage of subjects with $\geq$80% compliance to study medication was low in both treatment groups and worsened as the study progressed, and this may have reduced the ability to show the expected treatment differences. The treatment compliance rate was lower in the current study than that observed in previous studies comparing ICSs with montelukast (approximately 90%),[9,12] possibly related to the length of the study and inclusion of subjects with intermittent asthma or transient wheezing phenotype. Importantly, diary-reported compliance, with its intrinsic limitations, was similar in both treatment groups. Third, the use of step-up therapy with BIS for mild worsening in the montelukast group was, in retrospect, a suboptimal design for assessing treatment differences, because step-up BIS may have sustained clinical effects, which may have masked the extent of differences between the treatment groups. However, it could not affect the results of the primary efficacy endpoint (time to first additional asthma therapy) because no step-up occurred by definition.

The lack of specific study withdrawal criteria may explain the high rates of study discontinuation in this study compared with those observed in the previous long-term study by Sorkness et al.[12] However, the number of subjects who discontinued was similar in both treatment groups, suggesting that the time to administer a nebulized versus an oral medication was not a factor affecting compliance. Other factors that may have led to a higher than expected discontinuation rate include the length of the trial, and perhaps spontaneous improvement in some children, particularly those with recurrent wheezing rather than persistent asthma.

The results from the present study were generally consistent with those reported by Garcia Garcia et al,[10] in which similar outcomes were observed between fluticasone and montelukast on the primary outcome of the

percentage of asthma rescue medication–free days at 52 weeks in children age 6 to 14 years with mild persistent asthma. However, in the study by Garcia Garcia et al,[10] significantly better results were observed with the ICS compared with montelukast on several secondary measures, including changes in mean percentage predicted FEV_1, β_2-agonist use, systemic corticosteroid use, and asthma control (Pediatric Asthma Therapy Assessment Questionnaire). Although greater differentiation was observed between the ICS and montelukast treatments in the study by Garcia Garcia et al,[10] significant differences also were observed on secondary efficacy measures in the current study, including rate of mild or severe asthma exacerbations and morning and evening PEF. Taken together, the results of the study by Garcia Garcia et al[10] and those of the current study suggest more favorable results with ICS than with montelukast in subjects with mild persistent asthma.

Results from a 12-week study of children 6 to 12 years of age with moderate asthma (on the basis of the requirement for subjects to have a baseline FEV_1 of 60% to 80% of predicted) reported by Ostrom et al[11] showed significantly better results for the ICS fluticasone (50 μg twice daily) than for montelukast (5 mg once daily) on the primary efficacy measure of the percentage change from baseline in morning predose FEV_1, as well as on most secondary efficacy measures. The inconsistencies between the current study and that reported by Ostrom et al[11] may have resulted from the fact that baseline asthma characteristics were more severe in the study by Ostrom et al,[11] as evidenced by greater use of albuterol over a period of 24 hours and a percentage predicted FEV_1 of approximately 76% compared with 91% in this study. However, consistent with the 12-week study by Ostrom et al,[11] the current analysis found better outcomes with BIS compared with montelukast on several measures, including morning and evening PEF, at 12 weeks.

The aforementioned studies of ICS versus LTRA focused on only school-age children, whereas the current study included preschool-age children with either mild persistent asthma or a history of frequent wheezing; the latter group may not have had chronic asthma and may have responded differently to treatment compared with subjects with persistent asthma. It is well known that early intervention with ICSs in childhood asthma enhances disease management by improving asthma control and normalizing lung function,[1] but it does not appear to modify the processes that determine disease progression in children.[20,21]

Taken together, the results of the current study and the other comparative trials of ICS versus LTRA suggest that ICSs such as BIS are the most effective single-agent controller medications for preschool and school-age children with persistent asthma, even of mild persistent severity. However, regular controller therapy use with either an ICS or LTRA in children with episodic wheezing or mild intermittent asthma needs to be examined further. Because BIS is administered via a nebulizer, young children who require ICS therapy but are unable to use inhalers properly are potentially able to benefit from BIS. However, the use of a nebulizer is more time-consuming compared with administration of montelukast, which has the advantage of oral administration. Other differentiating characteristics relate to the mechanism of action of these treatments: ICSs work via multiple targets compared with LTRAs, which are more selective.[9] One study showed that, overall, more children respond to an ICS alone compared with an LTRA alone, although a substantial proportion of children responded to neither medication.[9]

In conclusion, the results of the current study suggest that both BIS and montelukast are effective and well tolerated as long-term controller medications in children 2 to 8 years of age with mild asthma, with potentially greater benefits with regard to efficacy and asthma control for BIS than for montelukast.

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METHODS

Exclusion criteria

Subjects were excluded if they had a history of severe or unstable asthma; had a hypersensitivity to budesonide or montelukast sodium; had a clinically significant disease (past or present) or other medical condition that, in the opinion of the investigator, could interfere with the study or place the subject at risk because of participation in the study; had an acute exacerbation of asthma or a respiratory tract infection within 30 days before screening that, in the opinion of the investigator, could have affected the results of the study; or used montelukast or an inhaled corticosteroid within 1 week of screening, systemic corticosteroids within 2 weeks of screening or during the run-in period, or omalizumab within 6 months of screening.

Allowed and disallowed medications

Rescue medication use was allowed in all subjects throughout the study, with 1 dose defined as either 2 puffs of a SABA from a metered-dose inhaler or 1 treatment with a nebulized SABA. Additional medications that were permitted during the study period included nasal corticosteroids, decongestants, antihistamines (other than astemizole and hydroxyzine), mucolytics, and expectorants not containing bronchodilators, antibiotics, topical hydrocortisone ($\leq$1%), and vitamins.

The same medications that were disallowed during the run-in period (eg, controller therapies) also were disallowed after randomization, with the exception of the per-protocol administration of BIS, montelukast, and oral corticosteroids. In addition, theophylline, chromones, astemizole, and hydroxyzine were disallowed during the treatment period.

Patient-reported outcomes and global assessments

The CHQ-PF50 measured the general child health status from the perspective of the caregiver at weeks 0, 4, 8, 12, and 26 by assessing the Child's Global Health (1 item), the Child's Physical Activities (6 items), and the Child's Health (6 items).[E1] The CSHA, which described the asthma-specific child health status from the perspective of the caregiver, was measured at weeks 0, 4, 8, 12, and 26 and assessed the domains of physical health—child (15 items), activities—child (5 items), activities—family (6 items), emotional health—child (5 items), and emotional health—family (17 items).[E2] The PACQLQ measured caregiver burden at weeks 0, 4, 8, 12, and 26[E3] and evaluated Activity Limitations (4 items) and Emotional Function (9 items). A change of 0.5 units in the PACQLQ score was considered a minimally important difference.[E4] All patient-reported outcomes were rated using Likert scales, with higher scores indicating more positive outcomes.

The Global Caregiver and Physician Assessments were administered at week 12 and at the end of treatment. Caregivers and physicians answered the following questions: (1) ''Since the start of the study, how would you rate your child's health now (caregiver) or how would you evaluate the subject's asthma symptoms (physicians)?'' (2) ''Since the start of the study, how would you evaluate your ability to manage your child's asthma (caregiver) or how would you evaluate your ability to manage the subject's asthma (physician)?'' The Global Caregiver and Physician Assessments were scored on 5-point Likert scales: question 1 (responses: ''a great deal better,'' ''somewhat better,'' ''unchanged,'' ''somewhat worse,'' and ''a great deal worse''), and question 2 (responses: ''a great deal easier,'' ''somewhat easier,'' ''unchanged,'' ''somewhat more difficult,'' and ''a great deal more difficult'').

RESULTS

Subjects

The most common reasons for study discontinuation were lack of willingness by the subject to continue, development of study-defined discontinuation criteria (eg, poor compliance, use of a disallowed medication), and loss to follow-up. Other reasons for study discontinuation included the occurrence of an intolerable AE and subject presentation with a disease or medical condition that was clinically significant and had the potential to interfere with study procedures or put the subject at risk.

Patient-reported outcomes and global assessments

Baseline values for patient-reported outcome measures are provided in Table E1. Physicians reported more favorable scores on the Global Physician Assessment for subjects who received BIS compared with those who received montelukast on both items: asthma symptoms (unadjusted $P = .001$) and the ability to manage the subject's asthma (unadjusted $P = .0164$) at week 12 (Fig E1). At the end of treatment, more favorable scores also were observed in subjects who received BIS compared with montelukast on both items (unadjusted $P \leq .0171$). Caregivers also reported better scores on the item assessing their ability to manage their child's asthma for subjects in the BIS versus montelukast group at week 12 (unadjusted $P = .0139$; Fig E2) and numerically better scores at the end of treatment (unadjusted $P = .067$). Similarly, caregivers reported better scores on the item assessing their child's health for subjects who received BIS compared with those who received montelukast at week 12 (unadjusted $P = .0024$; Fig E2) and numerically better scores at the end of treatment (unadjusted $P = .0524$).

There were no statistically significant differences between the treatment groups on any of the selected domains of the CHQ-PF50 questionnaire at any time point (Tables E2 and E3). Similar results were observed in both treatment groups on all domains of the CHSA, with the exception of the Emotional Health (child) domain, on which greater improvements from baseline were observed in subjects in the montelukast group compared with subjects in the BIS group at week 12 (adjusted mean change from baseline, 16.56 vs 8.69, respectively; unadjusted $P < .001$) and the end of treatment (adjusted mean change from baseline: 17.6 vs 9.0, respectively; unadjusted $P < .001$). This observed difference was largely driven by responses to items that assessed the patient's frustration with having to rely on asthma treatments (individual item data not shown). No significant differences were observed between the groups on either domain of the PACQLQ.

Safety

The incidence of AEs generally was similar in both treatment groups, and the majority of AEs were of mild to moderate intensity in both treatment groups (Table E4). Five reported AEs were judged by the investigator to be

drug-related, including pneumonia (n = 1) and epistaxis (n = 1) in the BIS group and lower respiratory tract infection (n = 1), headache (n = 1), and abnormal behavior (n = 1) in the montelukast group. No subject died during the course of the study. Fifteen serious AEs were reported, including 5 events in the BIS group (in 4 subjects) and 10 events in the montelukast group (in 8 subjects); all serious AEs were resolved. One serious AE (pneumonia) that occurred in the BIS group was judged by the investigator to be related to treatment. Two subjects in the BIS group and 5 subjects in the montelukast group discontinued because of an AE. The most common AEs leading to study discontinuation were asthma and pneumonia. There were no clinically important findings or group differences in vital signs or physical examination results.

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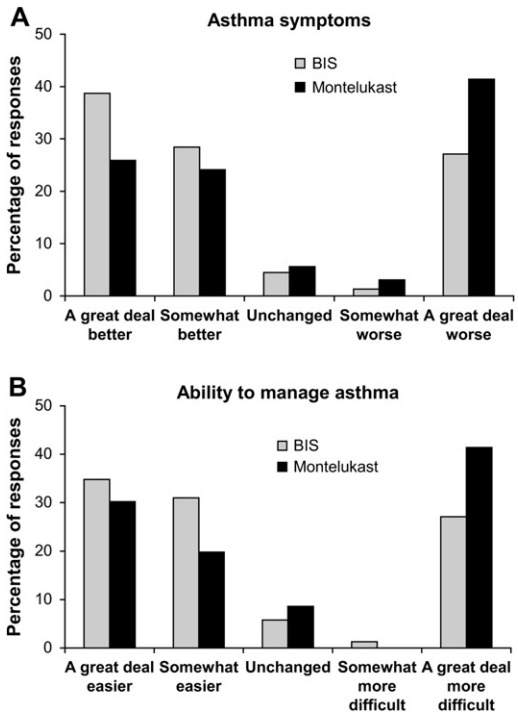


FIG E1. Distribution of responses to items assessing the physician's rating of the patient's asthma symptoms **(A)** and ability to manage the patient's asthma **(B)** on the Global Physician Assessment at week 12. Last observation carried forward methodology used for early withdrawals.

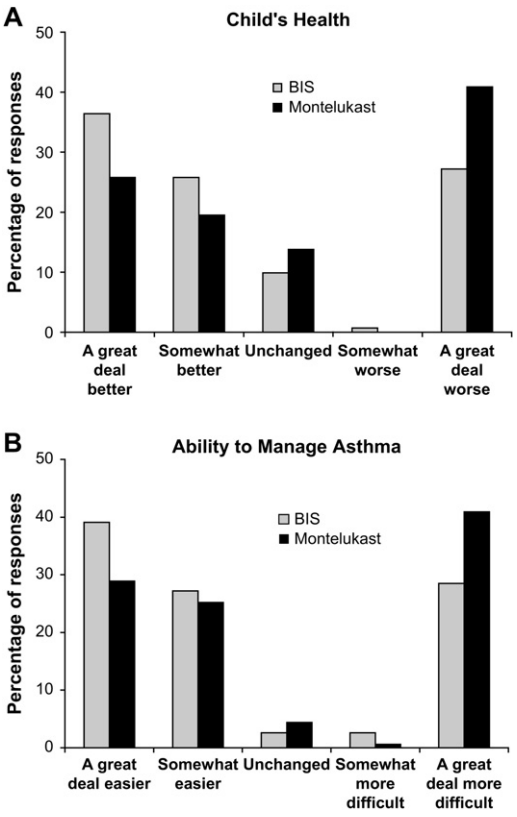


FIG E2. Distribution of responses to items assessing the caregiver's **(A)** rating of his or her child's health and **(B)** ability to manage his or her child's asthma on the Global Caregiver Assessment at week 12. Last observation carried forward methodology used for early withdrawals.

TABLE E1. Baseline values for patient-reported outcomes*

Measurement†	BIS	Montelukast
CHQ-PF50	n = 155	n = 157
General health	48.84 (1.36)‡	54.06 (1.38)
Health vs 1 y ago	55.03 (1.85)‡	52.39 (1.56)
Single-item health	66.71 (1.49)	67.93 (1.52)
Physical activities	80.65 (1.27)	81.63 (1.24)
CHSA	n = 154	n = 155
Physical health	66.78 (1.31)	66.52 (1.18)
Activities, child	72.89 (1.33)	73.19 (1.16)§
Activities, family	72.89 (1.33)	73.19 (1.16)§
Emotional health, child	64.42 (2.06)	68.31 (1.91)
Emotional health, family	64.17 (1.31)‖	66.99 (1.28)¶
PACQLQ	n = 155	n = 156
Overall	5.01 (0.09)	5.16 (0.09)
Activity limitations	4.95 (0.11)	4.98 (0.10)
Emotional function	5.04 (0.09)	5.24 (0.09)

*All values are reported as means (SEs).
†Efficacy analysis set; higher scores indicated more positive outcomes.
‡n = 154.
§n = 153.
‖n = 155.
¶n = 156.

TABLE E2. Changes from baseline to week 12 in patient-reported outcomes

Variable*	Treatment	n†	Adjusted mean (SEM) change from baseline‡	*P* value (BIS – montelukast)
CHQ-PF50				
General health	BIS	125	6.64 (1.12)	.118
	Montelukast	134	4.37 (1.09)	
Health vs 1 y ago	BIS	125	23.07 (1.97)	.101
	Montelukast	134	18.92 (1.90)	
Single-item health	BIS	126	5.08 (1.56)	.191
	Montelukast	134	2.45 (1.52)	
Physical activities	BIS	126	7.90 (1.38)	.431
	Montelukast	134	6.51 (1.34)	
CHSA				
Physical health	BIS	126	16.64 (1.41)	.162
	Montelukast	131	14.08 (1.38)	
Activities, child	BIS	126	13.17 (1.33)	.069
	Montelukast	130	10.02 (1.31)	
Activities, family	BIS	126	13.17 (1.33)	.069
	Montelukast	130	10.02 (1.31)	
Emotional health, child	BIS	125	8.69 (1.73)	<.001
	Montelukast	133	16.56 (1.68)	
Emotional health, family	BIS	126	12.62 (1.17)	.752
	Montelukast	133	13.10 (1.14)	
PACQLQ				
Overall	BIS	126	0.91 (0.08)	.568
	Montelukast	133	0.85 (0.08)	
Activity limitations	BIS	126	1.25 (0.01)	.119
	Montelukast	133	1.06 (0.09)	
Emotional function	BIS	126	0.76 (0.08)	.950
	Montelukast	133	0.75 (0.08)	

*Higher scores indicated more positive outcomes.
†Subjects with baseline and postbaseline values at week 12.
‡Change from baseline to the last mean value at week 12 using last observation carried forward.

TABLE E3. Changes from baseline to the end of treatment in secondary efficacy variables

Variable	Treatment	n*	Value	*P* value (BIS – montelukast)
Diary-related variables, mean (SD) change from baseline*				
AM Asthma symptom score	BIS	196	–0.67 (0.49)	—†
	Montelukast	197	–0.64 (0.53)	
PM asthma symptom score	BIS	196	–0.65 (0.50)	—†
	Montelukast	197	–0.56 (0.57)	
24-h rescue medication use	BIS	196	–1.17 (1.25)	—†
	Montelukast	197	–1.20 (1.20)	
Rescue medication–free days, %	BIS	196	45.77 (31.38)	—†
	Montelukast	197	48.49 (27.49)	
Asthma-free days, %	BIS	196	27.14 (27.68)	—†
	Montelukast	197	25.64 (25.55)	
AM PEF	BIS	170	28.39 (29.63)	—†
	Montelukast	162	20.63 (22.81)	
PM PEF	BIS	172	25.25 (28.87)	—†
	Montelukast	164	16.85 (22.41)	
Pulmonary function variables, mean (SD) change from baseline‡				
FEV_1 (L)	BIS	91	0.10 (0.21)	—†
	Montelukast	94	0.08 (0.16)	
% Predicted FEV_1	BIS	91	7.47 (16.06)	—†
	Montelukast	92	6.93 (13.37)	
Patient-reported outcomes, adjusted mean (SEM) change from baseline§				
CHQ-PF50				
General Health	BIS	154	6.23 (1.12)	.177
	Montelukast	157	4.23 (1.10)	
Health vs 1 y ago	BIS	154	24.99 (1.92)	.157
	Montelukast	157	21.42 (1.88)	
Single-item health	BIS	155	6.05 (1.62)	.236
	Montelukast	157	3.53 (1.59)	
Physical activities	BIS	155	7.27 (1.27)	.885
	Montelukast	157	7.03 (1.24)	
CHSA				
Physical health	BIS	154	14.02 (1.23)	.478
	Montelukast	155	15.17 (1.21)	
Activities, child	BIS	154	10.88 (1.20)	.944
	Montelukast	153	10.99 (1.18)	
Activities, family	BIS	154	10.88 (1.20)	.944
	Montelukast	153	10.99 (1.18)	
Emotional health, child	BIS	154	9.00 (1.53)	<.001
	Montelukast	155	17.55 (1.50)	
Emotional health, family	BIS	155	12.04 (1.10)	.347
	Montelukast	156	13.40 (1.08)	
PACQLQ				
Overall score	BIS	155	0.91 (0.07)	.866
	Montelukast	156	0.92 (0.07)	
Activity limitations	BIS	155	1.22 (0.08)	.651
	Montelukast	156	1.17 (0.08)	
Emotional function	BIS	155	0.77 (0.07)	.677
	Montelukast	156	0.81 (0.07)	

*Subjects with baseline and postbaseline values at week 52 (observed).
†No hypothesis testing performed.
‡Change from baseline to the average for weeks 1 through 52.
§Change from baseline to the end of treatment (week 26 or last observed value) using last observation carried forward; higher scores indicated more positive outcomes.

TABLE E4. Adverse events reported by ≥10% of subjects in either study group

Adverse event	No. of subjects (%)	
	BIS (n = 197)	Montelukast (n = 197)
Upper respiratory tract infection	53 (26.9)	57 (28.9)
Pyrexia	35 (17.8)	46 (23.4)
Otitis media	22 (11.2)	34 (17.3)
Sinusitis	25 (12.7)	27 (13.7)
Nasopharyngitis	23 (11.7)	23 (11.7)
Headache	19 (9.6)	22 (11.2)
Pharyngitis	12 (6.1)	20 (10.2)