

Budesonide Inhalation Suspension Versus Montelukast in Children Aged 2 to 4 Years with Mild Persistent Asthma

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What is already known about this topic? Current guidelines recommend inhaled corticosteroids as the preferred treatment of childhood persistent asthma with leukotriene receptor antagonist therapy proposed as an alternative. A previous study has found that the inhaled corticosteroid budesonide, administered as an inhalation suspension (BIS), and the leukotriene receptor antagonist montelukast provided acceptable asthma control in children with mild persistent asthma aged 2 to 8 years over a 1-year period with overall measures that favored BIS.

What does this article add to our knowledge? The results of this analysis found that both BIS and montelukast provided acceptable asthma control in children aged 2 to 4 years with mild persistent asthma with no significant difference in between treatments in the primary end point; however, several secondary outcomes found statistically significant differences in favor of BIS over montelukast. Furthermore, no new safety findings or concerns were identified in this young patient population.

How does this study impact current management guidelines? The results of this analysis support the current treatment guidelines and support the use of both BIS and montelukast, but particularly BIS, in children with asthma age 2 to 4 years.

BACKGROUND: Budesonide inhalation suspension (BIS) and montelukast provide acceptable asthma control, whereas overall measures favored BIS in children aged 2 to 8 years with mild persistent asthma.

OBJECTIVE: We compared BIS and montelukast over a 1-year period in children aged 2 to 4 years with asthma.

METHODS: Data were derived from a 52-week, open-label, randomized, active-controlled, multicenter study (NCT00641472). Children with mild asthma received either BIS 0.5 mg or montelukast 4 to 5 mg once daily. Patients were stepped up to twice-daily BIS or oral corticosteroids for mild or severe asthma worsening, respectively. Primary efficacy

assessment was time to first additional asthma medication for exacerbation over 52 weeks.

RESULTS: Two hundred two patients, age 2 to 4 years, received BIS (n = 105) or montelukast (n = 97). No difference was observed between the BIS and montelukast groups in median time to first additional asthma medication over 52 weeks (183 vs 86 days). Statistically significant differences were observed in favor of BIS over montelukast in the percentage of patients requiring oral steroids at 52 weeks (21.9% vs 37.1%; $P = .022$), the rate (number/patient/year) of additional courses of medication (1.35 vs 2.30; $P = .003$), the rate of additional oral steroid therapy (0.44 vs 0.88; $P = .008$), and caregivers' ability to manage the patient's symptoms ($P = .026$). Both treatments were well tolerated.

CONCLUSION: BIS and montelukast provided acceptable asthma control in children aged 2 to 4 years with mild persistent asthma with no significant difference between treatments in the primary end point; however, several secondary outcomes showed statistically significant differences (and many had numerical differences) in favor of BIS over montelukast. © 2012 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:58-64)

Key words: Budesonide inhalation suspension; Montelukast; Asthma; Pediatric; Efficacy; Tolerability

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The management of persistent asthma in young children can be challenging because children may lack the required coordination for successful operation of dry-powder or metered-dose inhalers. Nebulizers offer an alternative delivery route for respiratory medications in this patient group.

Current guidelines recommend inhaled corticosteroids (ICS) as the preferred treatment of childhood persistent asthma¹⁻³ with leukotriene receptor antagonist (LTRA) therapy proposed as an alternative. The ICS budesonide as an inhalation suspension has established efficacy in children up to 8 years with asthma,⁴⁻⁶ and

Abbreviations used

AE- Adverse event
BIS- Budesonide inhalation suspension
CHQ-PF50- Child Health Questionnaire Parent Form-50
CSHA- Children's Health Survey for Asthma
ICS- Inhaled corticosteroid
LTRA- Leukotriene receptor antagonist
SABA- Short-acting β_2 -agonist

the LTRA montelukast has efficacy data in children up to 14 years.^{7,8} A previous study has found that both budesonide inhalation suspension (BIS) and montelukast provided acceptable asthma control, whereas overall measures favored BIS in children with mild persistent asthma aged 2 to 8 years over a 1-year period.⁹ These findings are consistent with studies in older children that showed better outcomes with ICS than with montelukast.

Here, we perform a *post hoc* subanalysis of the study by Szeffler et al⁹ to determine whether the differences in asthma outcomes observed over a 1-year period between BIS and montelukast in children aged 2 to 8 years still remain in the younger ones with asthma, namely children aged 2 to 4 years, over the same 1-year period.

METHODS

Patients

The main inclusion and exclusion criteria have been described in the original publication,⁹ but, in brief, children 2 to 8 years of age were eligible if they had symptoms of mild persistent asthma as determined by the guidelines from the National Asthma Education and Prevention Program¹⁰ or had, in the year before screening, a history of ≥ 3 wheezing episodes that lasted >1 day and affected sleep. In addition, patients were required to have a cumulative asthma symptom score (daytime plus nighttime) of ≥ 2 on ≥ 3 of 7 consecutive days and must have required the use of β_2 -agonists on ≥ 3 of 7 consecutive days during the run-in period.

Study design

This was a 52-week, open-label, randomized, active-controlled, multicenter study (Study No. DX-RES-2103; ClinicalTrials.gov identifier NCT00641472). This study comprised a 3- to 21-day run-in period during which patients could not receive orally administered salbutamol, leukotriene modifiers, inhaled long-acting β_2 -agonists (single agent or in combination), systemic corticosteroids or ICSs, inhaled anticholinergics, or omalizumab, followed by a 52-week treatment period. Eligible children with asthma were randomized to receive BIS 0.5 mg or montelukast 4 mg, both once daily in the evening. The lowest indicated dosage for these products was selected in accordance with guidelines for the treatment of mild persistent asthma by the National Asthma Education and Prevention Program.¹⁰ 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; children experiencing exacerbations could remain in the study, but they could also be discontinued at any time at the discretion of the investigators.

The study was approved by the investigational review board affiliated with each center and conducted in accordance with

Good Clinical Practice Guidelines. All parents/legal guardians provided written informed consent before the study.

This subanalysis compared the efficacy and safety of BIS and montelukast over a 1-year period in children aged 2 to 4 years with mild persistent asthma.

Asthma exacerbations

A mild asthma exacerbation was defined as the need for ≥ 3 doses of short-acting β_2 -agonist (SABA) on 4 of 7 consecutive days or as having nighttime awakenings caused by asthma symptoms on ≥ 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. Electronic diaries alerted caregivers to call the clinic when patients met asthma exacerbation criteria that required step-up therapy.

Patients in both treatment groups who experienced mild exacerbations received step-up therapy with BIS 0.5 mg every morning for 14 days in addition to the randomized treatment. Patients in both treatment arms who experienced severe exacerbations received a 3- to 10-day standardized course of oral corticosteroids (prednisone, prednisolone, or methylprednisone); the initial allowed starting dose was 1 to 2 mg/kg and was not to exceed 60 mg/d, with tapering permitted as applicable.

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 exacerbations measured at 12, 26, and 52 weeks; and rates of occurrence of mild and severe exacerbations (number/patient/year) over a period of 52 weeks. In addition, because the investigator was not required to prescribe additional asthma medication after determination that a patient had had an exacerbation (based on investigator judgment, diary data, hospitalization data, and actual additional asthma medication intake), the time to meeting criteria for the use of additional asthma medication was also measured at 12, 26, and 52 weeks.

Symptom scores (0 = none to 3 = severe), rescue medication use, and peak expiratory flow rates were recorded daily by caregivers in the electronic diary. Diary-related secondary variables were analyzed as mean changes from baseline to the average over the period of the first 12 weeks and average over the 52-week treatment period.

Patient-reported outcomes and global assessments were evaluated with the Child Health Questionnaire Parent Form-50 (CHQ-PF50),¹¹ the Children's Health Survey for Asthma,¹² the Pediatric Asthma Caregiver's Quality of Life Questionnaire,¹³ and the Global Physician and Caregiver Assessments.

Safety was evaluated by recording adverse events (AEs), serious AEs, deaths, and discontinuations caused by AEs. 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.¹⁴

TABLE I. Summary of patient disposition

	No. of patients (%)			
	Not randomized (n = 125)	BIS (n = 105)	Montelukast (n = 98)	Total randomized (n = 203)
Screened	125 (100.0)	105 (100.0)	98 (100.0)	203 (100.0)
Eligibility criteria not fulfilled	121 (96.8)	0	0	0
Adverse event	4 (3.2)	0	0	0
Randomized	0	105 (100.0)	98 (100.0)	203 (100.0)
Completed	0	74 (70.5)	72 (73.5)	146 (71.9)
Discontinued	125 (100.0)	31 (29.5)	26 (26.5)	57 (28.1)
Reason for discontinuation				
Adverse event	—	0 (0.0)	4 (4.1)	4 (2.0)
Development of study-specific discontinuation criteria	—	12 (11.4)	6 (6.1)	18 (8.9)
Other	—	4 (3.8)	2 (2.0)	6 (3.0)
Patient lost to follow-up	—	7 (6.7)	8 (8.2)	15 (7.4)
Patient not willing to continue	—	8 (7.6)	6 (6.1)	14 (6.9)

Statistical analyses

All performed analyses reported here were *post hoc*, and the study was powered for the original study analysis rather than these *post hoc* ones. Results from the primary efficacy measure and secondary time-to-event measures (intention-to-treat population) were compared between treatment groups with the use of a log-rank test. Analyses of event rates were performed with a Poisson regression model, with treatment as the study factor and time in study as an offset variable. Data from other secondary efficacy measures reported in the first 12 weeks were compared between treatment groups with the use of 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 and center 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 as the stratum.

Differences between treatment groups were considered statistically significant if $P < .05$.

RESULTS

Of 328 patients ages 2 to 4 years that were screened, 203 were randomized to receive BIS (n = 105) or montelukast (n = 98), and 202 received treatment (BIS, n = 105; montelukast, n = 97); patient disposition is shown in Table I. This represented 51% of the original study population.⁹ Patients' baseline asthma characteristics and pulmonary function were well balanced between the treatment groups (Table II).

Efficacy

Overall, 61 patients (58.1%) who received BIS used an additional asthma medication during the 52-week treatment period compared with 64 patients (66.1%) receiving montelukast. The median time to the first use of additional asthma medication was 183 days in the BIS group and 86 days in the montelukast group ($P = .128$) (Figure 1A). A separation of the curves was observed at approximately 1 month, and this remained for the rest of the study period (unlike that seen in

TABLE II. Baseline demographics and disease characteristics

Demographic characteristic	BIS (n = 105)	Montelukast (n = 97)
Sex, no. (%)		
Female	34 (32.4)	37 (38.1)
Male	71 (67.6)	60 (61.9)
Race, no. (%)		
White	86 (81.9)	82 (84.5)
Black	15 (14.3)	14 (14.4)
Asian	2 (1.9)	1 (1.0)
Other	2 (1.9)	0 (0.0)
Age (y), mean $\pm$ SD	3.04 $\pm$ 0.87	3.03 $\pm$ 0.85
Morning asthma score, mean $\pm$ SD	1.31 $\pm$ 0.52	1.29 $\pm$ 0.46
Evening asthma score, mean $\pm$ SD	1.22 $\pm$ 0.53	1.17 $\pm$ 0.54
Morning PEF (L/min), mean $\pm$ SD	89.8 $\pm$ 30.4	91.9 $\pm$ 32.3
Evening PEF (L/min), mean $\pm$ SD	91.9 $\pm$ 31.9	97.7 $\pm$ 34.7
Use of 24-h rescue medication (inhalations), mean $\pm$ SD	1.61 $\pm$ 1.23	1.63 $\pm$ 1.13
FEV ₁ , (L), mean $\pm$ SD	0.85 $\pm$ 0.16	0.71 $\pm$ 0.26
No.	21	21
Mean FVC, L (SD)	0.91 $\pm$ 0.14	0.75 $\pm$ 0.26
No.	21	22
Previous ICS use, no. (%)	8 (7.6)	7 (7.2)
Previous LTRA use, no. (%)	1 (1.0)	0

FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

patients aged 2 to 8 years whereby the curves converged at 26 weeks). The percentages of patients who used an additional asthma medication in the BIS versus montelukast groups during the first 12 and 26 weeks were 34.3% versus 48.5% ($P = .052$) and 46.7% versus 56.7% ($P = .133$), respectively.

The percentages of patients who required oral steroid therapy at 12, 26, and 52 weeks in the BIS versus montelukast group were 8.6% versus 18.6% ($P = .044$), 14.3% versus 27.8% ($P = .029$), and 21.9% versus 37.1% ($P = .022$), respectively (Figure 1B). The percentages of patients who meet criteria for additional asthma medication in the BIS versus montelukast group at 12, 26, and 52 weeks were 46.7% versus 59.8%

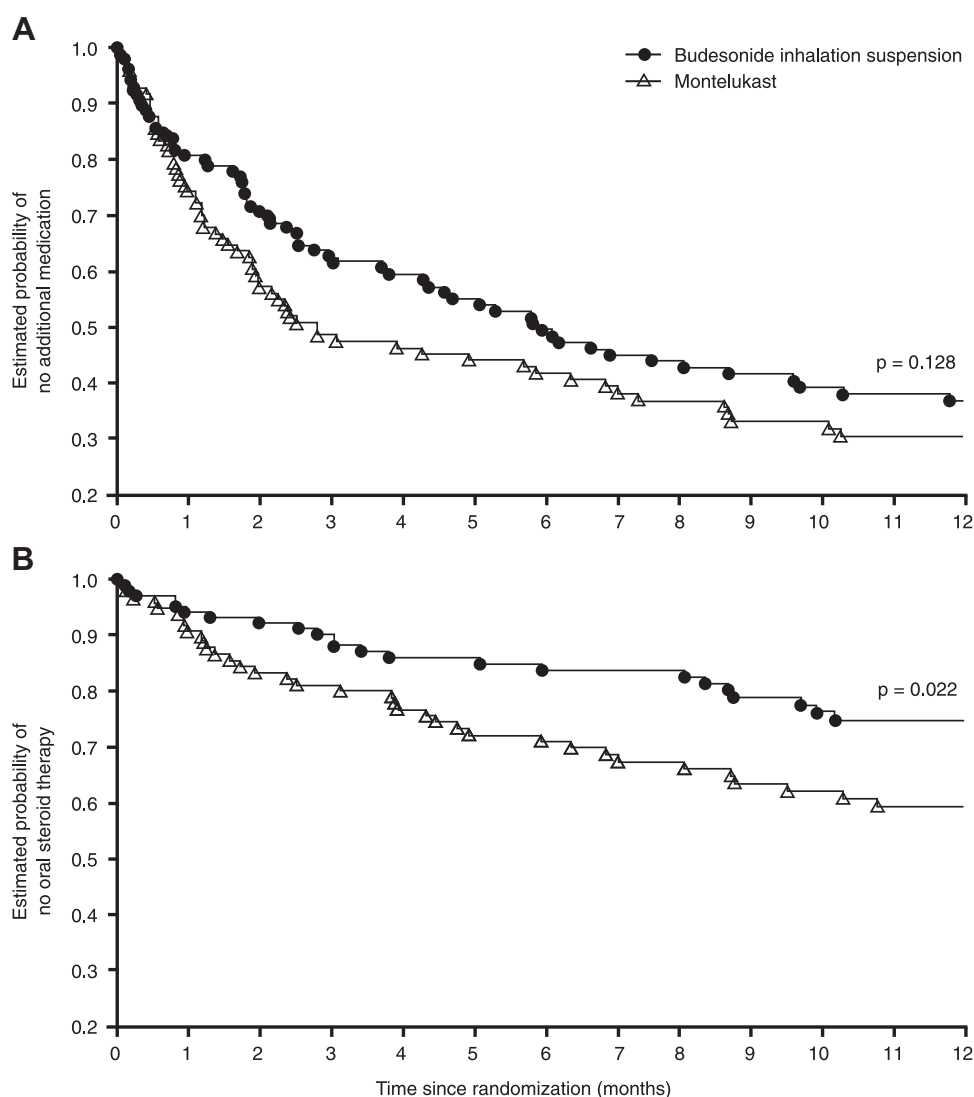


FIGURE 1. Kaplan-Meier plot of time to first additional asthma medication (A) and first severe asthma exacerbation (B) requiring oral steroid therapy over the 52-week study period.

($P = .103$), 61.9% versus 66.0% ($P = .319$), and 70.5% versus 75.3% ($P = .287$), respectively. The values were numerically lower for the BIS group than for the montelukast groups at all 3 time points, but there were no statistically significant differences between the treatments.

The rate (number/patient/year) of additional courses of medication was significantly lower (an estimated reduction of 41%) in the BIS versus montelukast group (1.35 vs 2.30; $P = .003$) (Table III). Furthermore, the rate of additional oral steroid therapy was also statistically significantly lower for the BIS versus montelukast group (0.44 vs 0.88; $P = .008$), which translates to an estimated reduction of 50%. The rate was higher in the montelukast group reported here versus that reported in the original study in children age 2 to 8 years (2.30 vs 1.63), whereas little change was observed in the BIS group (2-4 years, 1.35 vs 2-8 years, 1.23).⁹

The mean changes from baseline to the average over the first 12 weeks in secondary diary and spirometry variables were similar in both treatment groups (Table III).

Global assessments

Physicians reported a statistically significantly greater improvement in asthma symptoms (compared with study start) in patients who received BIS than patients who received montelukast at week 12 ($P = .021$), and the difference between treatments numerically favored BIS at the end of treatment ($P = .059$) (Table IV). Furthermore, physicians reported a trend toward a greater improvement in patients' ability to manage their asthma (compared with baseline) in patients who receive BIS than in patients who received montelukast at week 12 ($P = .091$), and this reached statistical significance at the end of treatment ($P = .034$) (Table IV).

Similarly, caregivers reported a statistically significantly greater improvement in their ability to manage the patient's asthma symptoms and their child's health compared with baseline in those patients who received BIS versus patients who received montelukast at week 12 ($P = .021$ and $P = .022$) and at the end of treatment ($P = .026$ and $P = .048$) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

TABLE III. Secondary efficacy variables

Variable	Treatment	No.	Value	P value
Mild or severe exacerbations, events/patient/year	BIS	105	1.35	
	Montelukast	97	2.30	.003
Diary-related variables, adjusted mean (SEM) change from baseline*				
Morning asthma symptom score	BIS	104	−0.40 (0.06)	
	Montelukast	97	−0.31 (0.06)	.28
Evening asthma symptom score	BIS	104	−0.43 (0.04)	
	Montelukast	97	−0.35 (0.04)	.32
Morning PEF	BIS	79	21.1 (2.3)	
	Montelukast	67	14.0 (2.3)	.14
Evening PEF	BIS	81	16.8 (2.3)	
	Montelukast	68	9.4 (2.3)	.22
Use of 24-h rescue medication	BIS	104	−0.69 (0.11)	
	Montelukast	97	−0.72 (0.11)	.86

PEF, Peak expiratory flow.

*Change from baseline to the average for weeks 1 to 12 using the last observation carried forward.

Patient-reported outcomes and CHSA

The change from baseline in the CHQ-PF50 score was similar in the BIS and montelukast groups for all selected domains (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). No notable differences were observed between the 2 treatment groups for the change from baseline in the Children's Health Survey for Asthma (CHSA) domains at week 12 and at the end of treatment with the exception of the patient's emotional health versus baseline, which was statistically significantly greater for the montelukast group than for the BIS group at both time points (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Safety analyses

The incidence of most commonly reported adverse events was similar in both treatment groups and predominately mild in intensity (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). Serious adverse events were reported for 2 patients in the BIS group (croup and vascular anomaly) and for 6 patients in the montelukast group (asthma [$n = 3$], gastroenteritis, viral meningitis, and respiratory distress). No discontinuations due to adverse events were reported with BIS, whereas 4 discontinuations (asthma [$n = 2$], pneumonia, and upper respiratory tract infection) were reported with montelukast. No deaths occurred during this study.

DISCUSSION

The results of this *post hoc* analysis indicated that both BIS and montelukast provided acceptable asthma control and were well tolerated in this group of children aged 2 to 4 years with mild persistent asthma. Furthermore, no new safety findings or concerns were identified in this young patient population. Evaluation of the primary efficacy variable, time to first additional asthma medication with either step-up BIS or oral corticosteroid over 52 weeks, found no significant difference between the BIS and montelukast treatment groups, although there was a separation of the Kaplan-Meier curves in favor of BIS at approximately 1 month, and this was present for the remainder of the study. This separation of the BIS and montelukast curves was more marked than that seen when the entire population of

patients aged 2 to 8 years was analyzed.⁹ Change in height was not part of this *post hoc* analysis because comparison of growth (which was not conducted according to the Food and Drug Administration guidelines¹⁴) was not an objective of the original study.

Evaluation of the secondary efficacy variables found that many of these suggested a significantly greater benefit in children who received BIS than in children who received montelukast. Better outcomes were observed for BIS than for montelukast for the percentage of patients receiving ≥ 1 course of additional asthma medication during the first 12 and 26 weeks; the percentage of patients requiring oral steroid therapy at 12, 26, and 52 weeks; significantly lower rate of acute severe exacerbations requiring treatment with oral corticosteroids in the BIS group than in the montelukast group; physician-reported improvement in asthma symptoms at 12 weeks; physician-reported improvement in asthma management at the end of treatment; and caregiver-reported improvement in their ability to manage the patient's asthma symptoms compared with baseline and in their child's health at all time points versus baseline. For many of the secondary efficacy variables, the changes reported in this analysis were similar to those in the original study.⁹ However, note that the rate of additional courses of medication reported here was higher than that presented in the original study in children aged 2 to 8 years (2.30 vs 1.63 events/patient/year), whereas there was little change in the BIS group (1.35 vs 1.23 events/patient/year),⁹ possibly suggesting that montelukast is less effective at controlling asthma in the younger subpopulation of patients.

An exception to the results favoring BIS over montelukast were the CHSA results for emotional health domain, which were better for montelukast than for BIS.

The changes from baseline in CHQ-PF50 score and the CHSA domains were similar in the BIS and montelukast groups for all selected domains at week 12 and at the end of treatment with the following 2 exceptions: health compared with 1 year ago significantly favored BIS over montelukast at week 12, and the CHSA domain of the patient's emotional health compared with baseline, which significantly favored montelukast over BIS at week 12 and the end of treatment. The latter finding mirrors that seen in the analysis of the full patient population and is not

TABLE IV. Physician's Global Assessment at week 12 and end of treatment

		No. of patients (%)			
Question	Response	BIS	Montelukast	Total	P value*
Asthma symptoms vs study start					
Week 12 [†]	Total	81 (100.0)	81 (100.0)	162 (100.0)	
	A great deal better	28 (34.6)	19 (23.5)	47 (29.0)	
	Somewhat better	22 (27.2)	15 (18.5)	37 (22.8)	
	Unchanged	3 (3.7)	5 (6.2)	8 (4.9)	
	Somewhat worse	1 (1.2)	1 (1.2)	2 (1.2)	
	A great deal worse	27 (33.3)	41 (50.6)	68 (42.0)	.021
End of treatment [‡]	Total	94 (100.0)	90 (100.0)	184 (100.0)	
	A great deal better	38 (40.4)	29 (32.2)	67 (36.4)	
	Somewhat better	17 (18.1)	12 (13.3)	29 (15.8)	
	Unchanged	4 (4.3)	2 (2.2)	6 (3.3)	
	Somewhat worse	2 (2.1)	0 (0.0)	2 (1.1)	
	A great deal worse	33 (35.1)	47 (52.2)	80 (43.5)	.059
Ability to manage asthma vs study start					
Week 12 [†]	Total	81 (100.0)	81 (100.0)	162 (100.0)	
	A great deal better	25 (30.9)	23 (28.4)	48 (29.6)	
	Somewhat better	24 (29.6)	12 (14.8)	36 (22.2)	
	Unchanged	5 (6.2)	5 (6.2)	10 (6.2)	
	Somewhat worse	0 (0.0)	0 (0.0)	1 (0.3)	
	A great deal worse	27 (33.3)	41 (50.6)	68 (42.0)	.091
End of treatment [‡]	Total	94 (100.0)	90 (100.0)	184 (100.0)	
	A great deal better	39 (41.5)	27 (30.0)	66 (35.9)	
	Somewhat better	15 (16.0)	13 (14.4)	28 (15.2)	
	Unchanged	5 (5.3)	3 (3.3)	8 (4.4)	
	Somewhat worse	2 (2.1)	0 (0.0)	2 (1.1)	
	A great deal worse	33 (35.1)	47 (52.2)	80 (43.5)	.034

*Difference in change from baseline for BIS and montelukast treatment arms.

[†]Week 12 refers to assessments done at 12 weeks after randomization (± 1 week).

[‡]End of treatment refers to the last value observed whether at week 52 for completers or earlier for those who withdrew from the study.

unsurprising because these results were driven by the patient's frustration with having to rely on asthma treatments.

The lack of significant difference between the 2 treatments on the primary efficacy measure in the original study was explained by the asthma population recruited being milder than intended, compliance being relatively low in both treatment groups, and use of step-up therapy with BIS for mild worsening was a suboptimal design.⁶ The time to first severe worsening/exacerbation requiring oral steroids might also have been a better primary outcome measure because some children in this age group would be expected to receive an increase in medication for any upper respiratory tract infection even if their asthma was under good control. These reasons also apply to the current analysis, the results of which are similar to those observed in the main study population,⁹ but for some of the end points the differences between treatments observed here in the younger population were numerically greater than those observed in the whole population. However, unfortunately, the lower patient numbers in this analysis have reduced its statistical power; hence, the differences between the 2 treatment arms for the various outcome measures predominantly remain only as numerical differences. That said, an analysis based on roughly one-half of the original sample size would not be expected to detect the originally targeted difference (10%) as statistically significant. However, if the difference in the original (full) group was 10%

and the difference in this subgroup was 10%, it is perhaps reasonable evidence that results within the subgroup are at least consistent with the original results. Indeed, the numerical differences in favor of BIS over montelukast appear to be larger in the children aged 2 to 4 years than in children aged 2 to 8 years, suggesting that BIS provides improved asthma symptom control in the younger patient population.

Other studies that evaluated use of ICS and montelukast in school-age children with asthma have reported findings consistent with those found here, namely an advantage is often observed with ICS therapy over montelukast but not necessarily achieving statistical significance on the primary end point.^{15,16} ICSs work via multiple targets, whereas LTRAs are more selective, which may go some way to explain the results reported here and elsewhere.¹⁵⁻¹⁷ Szeffler et al¹⁷ noted that more children with asthma responded to an ICS alone than a LTRA alone (although a number of children did not respond to either therapy in this study). A cost-effectiveness analysis of the ICS fluticasone versus montelukast in children with mild-to-moderate asthma found the ICS to have a lower cost and higher effectiveness than montelukast, especially in those children with more airway inflammation (as indicated by increased levels of exhaled nitric oxide and increased responsiveness to methacholine).¹⁸

The high rates of study discontinuation observed in the original study⁹ are mirrored in this *post hoc* subanalysis with the most likely

explanation being the lack of specific study withdrawal criteria. The number of patients discontinuing was similar in both treatment groups, suggesting that the time to administer a nebulized versus an oral medication did not noticeably affect compliance.

In conclusion, the results of the current analysis reinforce those of the initial analysis and suggest that both BIS and montelukast are effective and well-tolerated asthma medications in children 2 to 4 years of age with mild asthma, with potentially greater benefits in terms of efficacy and asthma control for BIS than for montelukast.

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