

Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma

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This article reviews the short-term and long-term safety profile of budesonide inhalation suspension (BIS) for nebulization in infants and young children with persistent asthma. Short-term safety (12 weeks) was assessed by pooling the results from the 3 randomized, double-blind, placebo-controlled, multicenter studies (studies A, B, and C) on the efficacy and safety of once- and twice-daily BIS. Long-term safety of BIS and conventional asthma therapy (CAT) was assessed in 52-week extension studies of the 12-week double-blind trials. CAT consisted of any available therapy for asthma; in 2 studies, CAT could have included treatment with inhaled glucocorticosteroids. Safety was assessed by monitoring adverse events (AEs), physical examinations, and basal and ACTH-stimulated plasma cortisol levels (in a subset of subjects). In the 52-week open-label extensions, the effects of BIS on growth velocity and skeletal age also were determined. In the 12-week studies, a total of 1017 subjects was evaluated for safety; totals of 231, 185, 229, 327, and 45 subjects were randomized to receive placebo or BIS at total daily doses of 0.25 mg, 0.5 mg, 1.0 mg, and 2.0 mg, respectively. Subject demographics and baseline asthma characteristics were similar across treatment groups, except that age, weight, height, and duration of asthma appeared higher in the 2.0-mg daily dose group. For BIS groups, mean age was 58.9 months; mean weight was 20.3 kg; mean height was 108.9 cm, and mean duration of asthma was 3.2 years. There were no differences in the incidence, severity, or types of AEs reported among the BIS and placebo groups. There were no significant differences between placebo and BIS treatment groups in basal or ACTH-stimulated cortisol levels, physical examinations, clinical laboratory values, or fungal cultures. A total of 670 subjects completed the 52-week extension studies; 223 subjects received CAT and 447 received BIS. Median total daily doses of BIS ranged from 0.50 mg to 1.0 mg in the 3 studies, and the mean duration of treatment exposure was 304 ± 119 days and 342 ± 83 days in CAT and BIS groups, respectively. During the 52-week treatment period, the incidences of reported AEs were comparable between treatment groups and were mild-to-moderate in intensity; no new AEs occurred during the 52-week studies compared with 12-week studies. No significant differences were observed between BIS and CAT in basal or ACTH-stimulated cortisol levels, physical examinations, clinical laboratory values, or fungal cultures. There was a small but statistically significant reduction in growth velocity (a difference of 0.8 cm) in the BIS-treated

group compared with the CAT group in study A. In studies B and C, growth velocity was not different between BIS and CAT groups. In pooled analyses, no statistically significant differences in growth velocity, standard median heights, or skeletal age were observed between BIS and CAT groups. Short-term and long-term treatment with BIS, over a wide range of doses, was well tolerated for the treatment of persistent asthma in infants and young children. (*J Allergy Clin Immunol* 1999;104:S200-9)

Key words: Budesonide, budesonide inhalation suspension, asthma, inhaled corticosteroid, pediatric, safety, growth

Inhaled glucocorticosteroids are recognized in the 1997 National Asthma Education and Prevention Program Guidelines as the most effective and potent anti-inflammatory medications for the long-term management of persistent asthma.¹ Despite overwhelming evidence of the efficacy and safety of inhaled glucocorticosteroids, many physicians and parents remain reluctant to use these agents in children because of concerns about long-term safety risks and their potential effects on growth. Although inhaled glucocorticosteroids have a lower potential to produce systemic effects than oral glucocorticosteroids, the possibility remains that systemic complications could occur.² The results of studies on the effects of inhaled glucocorticosteroids on growth have been mixed. Evidence of growth suppression in children has been observed with beclomethasone dipropionate (BDP; doses ≥ 400 μ g daily)³⁻⁵ and in some,⁶ but not all,⁷ studies with fluticasone propionate. Such evidence of growth suppression has been more difficult to document in children treated with budesonide.⁸⁻¹² The interpretation of growth studies is further complicated by the presence of confounding variables in several studies, including the lack of evaluation and inadequate evaluation of subject pubertal status, lack of adequate control groups, lack of titration according to asthma severity, and baseline differences in age, height, and previous oral glucocorticosteroid therapy between treatment and control groups.

Budesonide is an inhaled glucocorticosteroid with a favorable ratio between topical anti-inflammatory activity and systemic activity, probably because of a combination of high local anti-inflammatory activity, extensive first-pass hepatic metabolism of orally absorbed drug (85%-95%), and low potency metabolites that have minimal systemic effects.¹³ Budesonide inhalation suspension (BIS; Pulmicort Respules™; AstraZeneca, Wayne, Pa) has been formulated to meet the needs of infants and young children with persistent asthma who do not have

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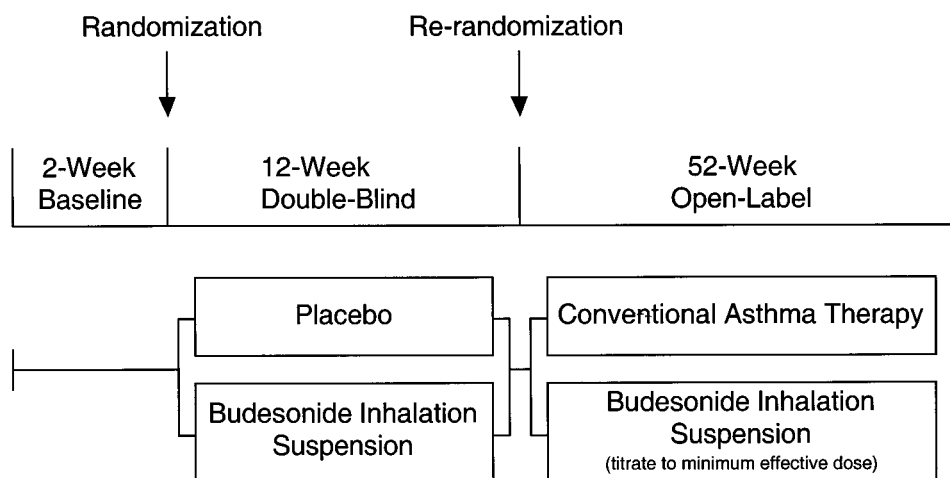


FIG 1. Study designs of the 12-week double-blind and 52-week open-label trials.

Abbreviations used

AE:	Adverse event
BDP:	Beclomethasone dipropionate
BIS:	Budesonide inhalation suspension
CAT:	Conventional asthma therapy
HPA:	Hypothalamic-pituitary-adrenal
PEF:	Peak expiratory flow
SDS:	Standard deviation score

the understanding or coordination to effectively use other formulations such as pressurized metered-dose inhalers or inhalation-driven dry powder inhalers. BIS has been shown to be effective and well tolerated in 3 US randomized, placebo-controlled, double-blind studies¹⁴⁻¹⁶ involving more than 1000 pediatric subjects (6 months to 8 years of age) with persistent asthma of varying disease severity. ("Efficacy of Budesonide Inhalation Suspension in Infants and Young Children with Persistent Asthma" in this issue.)

The purpose of this article is to summarize the short-term (12-week) and long-term (52-week) safety of BIS. Short-term (12-week) safety data are presented from pooled results of the 3 randomized, double-blind, placebo-controlled clinical studies¹⁴⁻¹⁶ of BIS previously described. Long-term effects of BIS on safety and growth were obtained from 52-week open-label extensions after each of the 12-week double-blind studies. The main objective of the extension studies was to compare the long-term safety of the lowest maintenance dose of BIS with that of conventional asthma therapy (CAT) in children with persistent asthma.

METHODS

Short-term (12-week) treatment

A detailed description of the methods for the double-blind studies is provided by Kemp ("Study Designs and Challenges in Clinical Studies Conducted in Infants and Children with Asthma") in this issue. Briefly, 3 multicenter, randomized, double-blind, placebo-controlled

studies (involving a total of 1018 pediatric subjects with asthma) were conducted at 26 centers in the United States. In study A, children ages 6 months to 8 years with mild persistent asthma who received bronchodilator therapy or noncorticosteroid anti-inflammatory agents before the study were treated with 0.25 mg, 0.5 mg, or 1.0 mg BIS or placebo once daily.¹⁵ In study B, children between 4 and 8 years of age with moderate-to-severe persistent asthma who received inhaled corticosteroids before the study were treated with BIS 0.25 mg, 0.5 mg, or 1.0 mg or placebo twice daily.¹⁶ Study C evaluated BIS 0.25 mg once daily, 0.25 mg twice daily, 0.5 mg twice daily, and 1.0 mg once daily in children (6 months to 8 years of age) with moderate persistent asthma that was treated with either bronchodilators or inhaled corticosteroids.¹⁴

Long-term (52-week) treatment

Subjects who successfully completed the 12-week, double-blind treatment phase of each study or whose treatment was discontinued because of worsening of asthma symptoms were eligible to enter an optional 52-week extension study (Fig 1). Overall, the extension studies were multicenter, randomized, open-label, active-controlled, and parallel-group studies, in which a total of 670 subjects was randomized at 26 centers located throughout the United States. There was no washout period between the 12-week double-blind treatment phases and the open-label studies. Subjects in each study were rerandomized in a 2:1 ratio to receive either BIS or CAT for 52 weeks. BIS was initially administered at a dose of 0.5 mg once or twice daily; attempts made at each clinical visit to gradually reduce the dose to the minimally effective dose (as judged by the investigator), which included dose reductions to 0.25 mg once daily, 0.25 mg every other day, and eventually no BIS treatment. Asthma under poor control was treated by an increase of the dose of breakthrough medications and/or an increase of the dose of BIS. CAT included any available therapy, such as β_2 -agonists (short-acting oral and

TABLE I. Subject demographics from short-term (12-week) studies

	Placebo (n=231)	BIS total daily dose (mg)				Total BIS (n=786)
		0.25 (n=185)	0.5 (n=229)	1.0 (n=327)	2.0 (n=45)	
Gender (%)						
Male	139 (60.2)	122 (65.9)	151 (65.9)	215 (65.7)	29 (64.4)	517 (65.8)
Female	92 (39.8)	63 (34.1)	78 (34.1)	112 (34.3)	16 (35.6)	269 (34.2)
Race (%)						
Caucasian	189 (81.8)	138 (74.6)	171 (74.7)	259 (79.2)	40 (88.9)	608 (77.4)
Black	25 (10.8)	33 (17.8)	41 (17.9)	39 (11.9)	2 (4.4)	115 (14.6)
Hispanic	14 (6.1)	10 (5.4)	12 (5.2)	17 (5.2)	3 (6.7)	42 (5.3)
Asian	1 (0.4)	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.3)
Other	2 (0.9)	3 (1.6)	5 (2.2)	11 (3.4)	0 (0.0)	19 (2.4)
Age (mo)						
Mean $\pm$ SD	63.0 $\pm$ 26.4	54.9 $\pm$ 25.3	58.5 $\pm$ 27.1	58.4 $\pm$ 27.3	81.4 $\pm$ 15.1	58.9 $\pm$ 26.8
Range	5-108	7-107	7-107	6-108	49-107	6-108
Weight (kg)						
N	230	184	229	327	45	785
Mean $\pm$ SD	20.9 $\pm$ 6.7	19.8 $\pm$ 8.2	19.8 $\pm$ 6.9	20.4 $\pm$ 7.7	25.2 $\pm$ 6.4	20.3 $\pm$ 7.6
Range	8.2-44.4	8.6-72.9	8.2-52.1	6.8-56.2	14.9-49.8	6.8-72.9
Height (cm)						
N	221	174	219	315	45	753
Mean $\pm$ SD	111.4 $\pm$ 15.6	107.0 $\pm$ 16.5	107.7 $\pm$ 17.2	109.1 $\pm$ 16.8	121.6 $\pm$ 10.3	108.9 $\pm$ 16.8
Range	68.1-139.3	69.8-152.5	66.7-142.3	64.1-147.0	101.0-140.0	64.1-152.5

inhaled), methylxanthines, or cromolyn sodium in study A; in studies B and C, CAT also could have included treatment with inhaled glucocorticosteroids. Asthma exacerbations were treated with combinations of these therapeutic agents followed by intermittent courses of oral prednisone on an as-needed basis.

Safety

Safety was assessed in both 12-week and 52-week studies by an evaluation of the incidence and severity of adverse events (AEs) recorded on diary cards, by active questioning, and by an assessment of changes from baseline in basal and ACTH (Cortrosyn; Organon, West Orange, NJ)-stimulated plasma cortisol at the end of the 12-week and 52-week study periods in a subset of subjects from approximately one half of the study sites. AEs were classified by the legal guardian as mild (easily tolerated symptoms), moderate (enough discomfort to cause interference with daily life/usual activities), or severe (incapacitating, such as the inability to attend day care/school or take part in normal activities). Secondary safety variables included changes from baseline in basal cortisol levels, clinical laboratory values, oropharyngeal and/or nasal fungal cultures, and physical examination.

Blood samples for the evaluation of basal cortisol levels were obtained in a subset of subjects in each study between 6 and 8:30 AM. ACTH 0.25 mg was administered intravenously in children older than 2 years, and 0.125 mg ACTH was administered intramuscularly in children 2 years old and younger. Sixty minutes after ACTH administration, another blood sample was obtained to assess ACTH-stimulated cortisol levels. All plasma samples were analyzed with HPLC by BCO Medical Services B.V. (The Netherlands). Normal adren-

al function was defined as basal plasma cortisol of more than 150 nmol/L and either ACTH-stimulated plasma cortisol increased by 200 nmol/L above basal cortisol level or by more than 400 nmol/L after 60 minutes.

Growth

The effects of BIS on growth were assessed in the 52-week open-label studies. Three aspects of growth were examined: height, growth velocity, and skeletal age. Height was measured by stadiometry every 4 weeks. Growth was normalized by comparing the differences between the observed height (centimeters) and the standard median heights (observed 50th percentile height) for specific age and sex, based on information from the National Center for Health and Statistics.¹⁷ Growth velocity is expressed in terms of centimeters per year. In 2 of the studies (studies B and C), changes in skeletal age were assessed. For skeletal age, left hand-wrist radiographs were obtained at weeks 0 and 52, and skeletal age was determined by a computation of differences between skeletal maturity indicators (external and internal [medullary cavity] diameters and cortical thickness of the midshaft of the second metacarpal from hand-wrist radiographs) and chronologic age (years).¹⁸

Statistical analysis

Data from the 12-week double-blind and 52-week open-label trials were analyzed separately and consisted of individual study and pooled analyses. Analysis of variance was used to compare each active budesonide treatment group with placebo for all safety variables. Growth data were analyzed only for subjects who completed the study. Growth standard deviation scores (SDSs) were calculated with the following formula: SDS = (observed

TABLE II. Subject baseline asthma characteristics from short-term (12-week) studies

	Placebo (n=231)	BIS total daily dose (mg)				Total BIS (n=786)
		0.25 (n=185)	0.5 (n=229)	1.0 (n=327)	2.0 (n=45)	
Duration of asthma (mo)						
N	231	185	229	327	45	786
Mean $\pm$ SD	38.9 $\pm$ 23.8	34.8 $\pm$ 22.6	37.9 $\pm$ 24.4	36.7 $\pm$ 23.9	53.1 $\pm$ 19.2	37.5 $\pm$ 23.8
Range	5-102	2-97	4-107	5-107	11-100	2-107
FEV ₁ % predicted						
N	113	62	109	140	45	356
Mean $\pm$ SD	80.0 $\pm$ 14.9	81.1 $\pm$ 18.5	81.7 $\pm$ 17.0	78.8 $\pm$ 16.5	80.2 $\pm$ 15.0	80.2 $\pm$ 16.8
% Reversibility						
N*	115	62	110	141	45	358
Mean $\pm$ SD	28.9 $\pm$ 15.6	27.6 $\pm$ 15.2	33.1 $\pm$ 16.7	30.3 $\pm$ 16.1	32.3 $\pm$ 18.8	30.9 $\pm$ 16.5
Morning PEF (L/min)						
N	114	61	109	138	45	353
Mean $\pm$ SD	159.2 $\pm$ 41.1	158.9 $\pm$ 45.7	154.8 $\pm$ 40.5	158.3 $\pm$ 45.8	167.6 $\pm$ 67.6	158.5 $\pm$ 47.6
Range	60.7-250.0	87.9-324.3	72.1-274.0	65.0-341.7	58.6-465.7	58.6-465.7

*Numbers of subjects with % reversibility values may be higher than the numbers of subjects with FEV₁ values because of unavailable FEV₁ data from case report forms.

height – 50th percentile)/gender-specific SD for the age. Growth velocity was determined with least-square estimates of linear regression line slopes. Summary statistics were calculated for observed heights and differences between observed and standard median heights for the BIS and CAT groups at each visit. Changes from baseline SDSs for height were analyzed with general linear growth models with the change in SDSs as the dependent variable; and terms for treatment, center, treatment-by-center interaction, and the baseline SDSs were used as exploratory variables. In addition, the numbers of subjects above or below the standard 50th percentile height were compared within treatment groups across visits with shift tables, which indicated shifts in observed height relative to the 50th percentile height from baseline to the open-label extension treatment phase visits. Skeletal age over the 52-week study period was assessed by a computation of the differences between skeletal maturity indicators and chronologic age (years). Summary statistics were calculated for observed mean skeletal ages and differences between observed and chronologic mean years for the BIS and CAT groups at week 52.

RESULTS

Subjects

Short-term (12-week) treatment. A total of 1017 subjects were evaluated for safety; of these, 231 subjects received placebo and 786 subjects received BIS. A total of 185, 229, 327, and 45 subjects were randomized to receive BIS at total daily doses of 0.25 mg, 0.5 mg, 1.0 mg, and 2.0 mg, respectively (Table I). Subject demographics and baseline asthma characteristics are shown for the pooled population in Tables I and II, respectively (subject demographics and baseline asthma characteristics are described in detail for each of the 3 studies by Kemp [“Study Designs and Challenges in Clinical Studies Conducted in Infants and Children with Asthma”) in this issue. No differences were apparent among treatment

TABLE III. Subject demographics and baseline asthma characteristics from pooled analysis of long-term (52-week) studies

	CAT (n=223)	BIS (n=447)
Gender (%)		
Male	142 (63.7)	291 (65.1)
Female	81 (36.3)	156 (34.9)
Race		
Caucasian	165 (74.0)	357 (79.9)
Black	35 (15.7)	60 (13.4)
Hispanic	17 (7.6)	21 (4.7)
Asian	0 (0)	2 (0.4)
Other	6 (2.7)	7 (1.6)
Age (mo)		
Mean $\pm$ SD	63.0 $\pm$ 27.8	60.9 $\pm$ 25.9
Range	11-112	8-113
Weight (kg)		
N	223	446
Mean $\pm$ SD	21.3 $\pm$ 8.4	20.7 $\pm$ 7.7
Range	8.6-58.9	7.7-76.6
Height (cm)		
N	222	443
Mean $\pm$ SD	110.4 $\pm$ 17.8	109.1 $\pm$ 16.5
Range	72.0-150.1	68.6-155.3
FEV ₁ % predicted		
N	96	184
Mean $\pm$ SD	83.42 $\pm$ 17.3	84.2 $\pm$ 18.2
Morning PEF (L/min)		
N	107	213
Mean $\pm$ SD	166.9 $\pm$ 45.7	169.4 $\pm$ 56.9

groups with regard to gender and race. Age, weight, height, and duration of asthma were higher in the highest BIS-dose group, probably because study B was the only study to include children with a higher minimum age (4 years); for BIS groups, mean age was 58.9 months; mean weight was 20.3 kg; mean height was 108.9 cm, and mean duration of asthma was 3.2 years. Approximately

TABLE IV. Number of subjects evaluable for safety, total daily BIS dose, and mean duration of exposure by treatment group in 52-week open-label studies

	Study A	Study B	Study C	Pooled
CAT n	90	30	103	223
Asthma medications (% subjects)				
Cromolyn sodium	79	23	58	62
Albuterol	52	30	39	44
Nedocromil	8	—	—	3
Theophylline	6	3	5	5
Inhaled glucocorticosteroid				
Beclomethasone	3	43	25	20
Triamcinolone	—	23	13	10
Fluticasone	—	7	—	<1
Flunisolide	—	3	8	4
Mean duration of exposure				
Days $\pm$ SD	293 $\pm$ 122	322 $\pm$ 125	308 $\pm$ 116	304 $\pm$ 119
Prednisone use				
No. of subjects (%)	48 (53)	19 (63)	56 (54)	123 (55)
Mean daily dose $\pm$ SD (mg)	0.53 $\pm$ 0.70	1.40 $\pm$ 2.71	0.63 $\pm$ 0.97	0.69 $\pm$ 1.29
BIS n	182	61	204	447
Median total BIS daily dose (mg)	0.50	0.80-1.0	0.50	0.50-1.0
Mean duration of BIS exposure (d $\pm$ SD)	338 $\pm$ 87	347 $\pm$ 70	343 $\pm$ 83	342 $\pm$ 83
Prednisone use				
No. of subjects (%)	84 (46)	34 (56)	105 (51)	223 (50)
Mean daily dose (mg $\pm$ SD)	0.47 $\pm$ 0.96	0.65 $\pm$ 0.93	0.58 $\pm$ 1.38	0.54 $\pm$ 1.17

TABLE V. AEs with 10% or more incidence reported by subjects during short-term studies*

	Placebo (n)	BIS total daily dose (mg)			
		0.25 (n)	0.5 (n)	1.0 (n)	2.0 (n)
Respiratory infection (%)	84 (36)	63 (34)	82 (36)	124 (38)	17 (38)
Fever (%)	53 (23)	35 (19)	43 (19)	60 (18)	4 (9)
Sinusitis (%)	40 (17)	22 (12)	27 (12)	48 (15)	7 (16)
Otitis media (%)	28 (12)	23 (12)	26 (11)	29 (9)	3 (7)
Rhinitis (%)	22 (10)	14 (8)	24 (10)	39 (12)	5 (11)

*Where incidence was greater in any budesonide group than in the placebo group.

46% of randomized subjects were able to consistently perform peak expiratory flow (PEF) evaluations and spirometry. As shown in Table II, pulmonary function tests at baseline were similar among treatment groups, as were mean morning PEF levels; mean baseline FEV₁ level was 80.1% of predicted, with 29.9% reversibility.

Long-term (52-week) treatment. A total of 670 subjects were evaluated for safety in the 52-week extension studies; of these, 223 subjects received CAT and 447 subjects received BIS (Table III). Subject demographics and baseline asthma characteristics for the pooled, long-term data are shown in Table III. Gender and race distributions were comparable between the BIS and CAT groups; mean age was 62.0 months; mean weight was 21 kg, and mean height was 110 cm. Approximately 42% of randomized subjects were able to consistently perform PEF and spirometry. Pulmonary function tests at baseline were similar among treatment groups (Table III).

The mean durations and doses of treatment for BIS and CAT groups in each study are shown in Table IV. The total mean duration of treatment exposure was 304 $\pm$ 119 days in the CAT group and 342 $\pm$ 83 in the BIS treatment group. Median total daily doses of BIS were 0.50 mg, 0.8 to 1.0 mg, and 0.50 mg in studies A, B, and C, respectively. In study A, 3% of patients in the CAT group were treated with inhaled glucocorticosteroids (BDP). In study B, more than 43% of patients in the CAT group were treated with inhaled glucocorticosteroids (43% BDP, 23% triamcinolone, 7% fluticasone propionate, and 3% flunisolide). In study C, more than 25% of patients in the CAT group were treated with inhaled glucocorticosteroids (25% BDP, 13% triamcinolone, and 8% flunisolide; Table IV).

AEs

Short-term (12-week) treatment. The overall incidence, type, and severity of nonasthma-related AEs were similar between the placebo and the BIS treatment groups, with no apparent dose-related effects among the BIS groups. The incidences of commonly reported AEs (reported for $\geq 10\%$ of subjects in at least 1 treatment group) for the pooled analysis of the 3 double-blind studies are shown in Table V. In general, the most frequently reported AEs were respiratory infection (36%), fever (18%), sinusitis (13%), rhinitis (10%), and otitis media (10%). Subgroup analyses showed no apparent gender-related, age-related, or race-related (Caucasian vs black) effects on AEs; nor was there a dose-dependent increase in incidence of reported AEs. The incidence of serious AEs (2% in active treatment versus 3% in placebo) and the proportion of subjects for whom treatment was discontinued

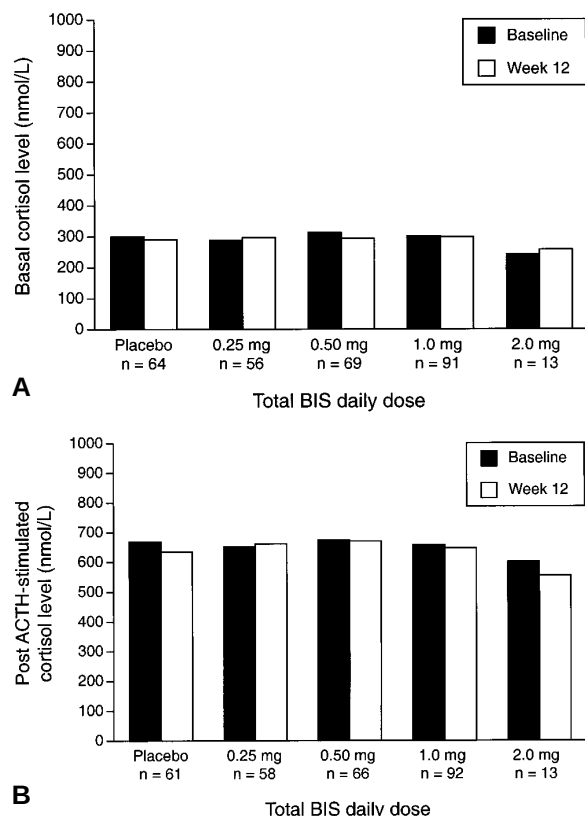


FIG 2. Mean basal (A) and ACTH-stimulated (B) cortisol levels at baseline and after the 12-week double-blind treatment period in short-term studies.

because of AEs (1% in active treatment vs 2% in placebo) were similar between BIS and placebo groups.

There were no clinically significant differences between the BIS and placebo groups in changes in vital signs, physical examination findings, or laboratory tests (including nasal or oral fungal cultures) during the course of the study, nor were there serious AEs attributed to BIS during the 12-week study period. In addition, although these were only short-term studies, the measured heights and weights observed over 12 weeks of treatment were similar in each of the BIS and placebo groups (data not shown).

Long-term (52-week) treatment. The incidences of commonly reported AEs (reported for 10% or more of subjects in at least 1 treatment group) for the pooled analysis of the 52-week extension studies are shown in Table VI. The most frequently reported AEs were similar to those reported during the 12-week double-blind treatment phase. In general, the incidence of AEs was slightly higher in the BIS group compared with the CAT group, probably because of the increased duration of drug exposure in the BIS group (342 vs 304 days). After adjusting for the length of time in the study, the incidence of reported AEs was comparable between the BIS and CAT groups (data not shown). The most commonly reported AEs were respiratory infection (58%), sinusitis (33%), fever (28%), otitis media (22%), and pharyngitis

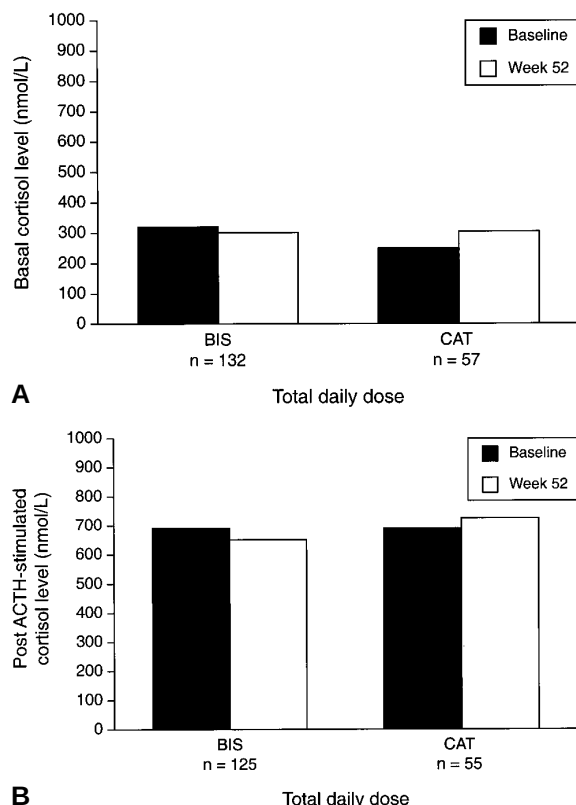


FIG 3. Mean basal (A) and ACTH-stimulated (B) cortisol levels at baseline and after the 52-week open-label treatment period in long-term studies.

TABLE VI. AEs with $\geq 10\%$ incidence reported by subjects during long-term studies

	CAT (n)	BIS (n)
Respiratory infection (%)	109 (49)	259 (58)
Sinusitis (%)	60 (27)	147 (33)
Fever (%)	45 (20)	124 (28)
Otitis media (%)	42 (19)	97 (22)
Pharyngitis (%)	38 (17)	87 (19)
Accident and/or injury (%)	28 (13)	72 (16)
Rhinitis (%)	24 (11)	76 (17)
Ear infection (%)	24 (11)	58 (13)
Headache (%)	23 (10)	51 (11)
Viral infection (%)	27 (12)	41 (9)
Bronchitis (%)	17 (8)	50 (11)
Gastroenteritis (%)	16 (7)	44 (10)

(19%). The proportions of subjects who experienced serious AEs (8.3% vs 8.1%) or whose treatment was discontinued because of an AE (0.7% vs 0.4%) were comparable between BIS and CAT groups; all serious AEs were judged unlikely to be caused by the study medications. There were no apparent gender-related, age-related, or race-related (caucasian vs black) treatment effects on the incidence or severity of AEs. No clinically significant differences between the BIS and CAT groups were

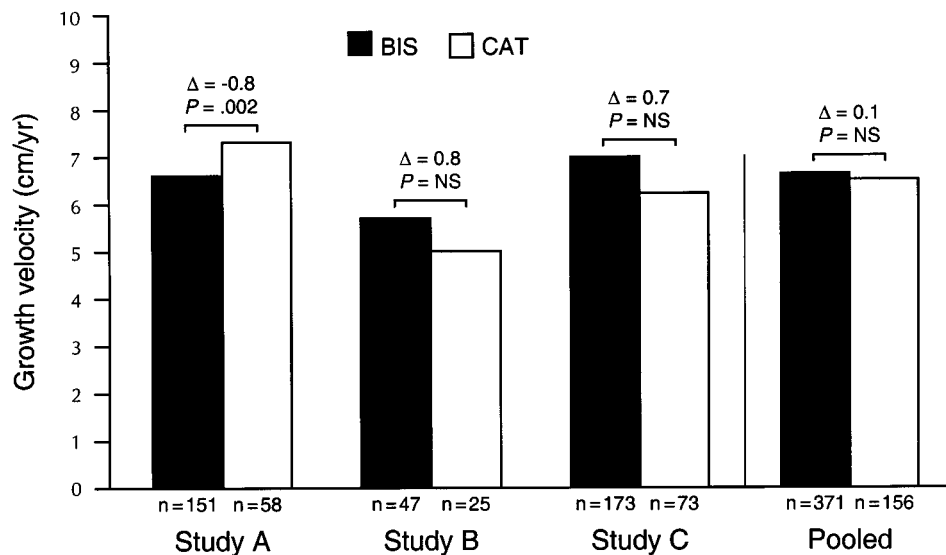


FIG 4. Mean growth velocity (centimeters per year) for BIS and CAT groups in studies A, B, C, and pooled data. NS, Not significant.

observed in changes in vital signs, physical examination findings, or laboratory tests (including nasal or oral fungal cultures) during the course of the study.

HPA-axis function

Short-term (12-week) treatment. There were no significant differences between placebo and any of the BIS groups in basal and ACTH-stimulated cortisol levels over the 12-week treatment period. Fig 2 shows basal and ACTH-stimulated cortisol levels for each treatment group at baseline and after the double-blind period. The adjusted mean changes from baseline to week 12 in ACTH-stimulated cortisol levels were -27.9 , 22.5 , -2.8 , -2.3 , and -35.1 nmol/L for subjects in the placebo and BIS 0.25 mg, 0.5 mg, 1.0 mg, and 2.0 mg groups, respectively. In addition, there were no differences among the groups in the number of subjects showing a shift from normal to abnormal response from baseline to week 12; 15%, 12%, 13%, 10%, and 9% of subjects showed a shift from a normal to an abnormal response to ACTH stimulation in the placebo, 0.25-mg, 0.50-mg, 1.0-mg, and 2.0-mg BIS treatment groups, respectively.

Long-term (52-week) studies. The long-term effects of BIS on HPA-axis function were studied in a subpopulation ($n = 189$ for basal cortisol test and $n = 180$ for the ACTH-stimulated cortisol test) of the 670 subjects in the 52-week open-label studies. Similar to double-blind study results, there were no significant differences between BIS and CAT in changes from baseline to week 52 in basal and ACTH-stimulated cortisol levels (Fig 3). The proportion of subjects with shifts in response from normal at baseline to abnormal at week 52 in ACTH-stimulated cortisol levels was not different between the BIS and the CAT groups (24% in the BIS group compared with 21% in the CAT group).

Growth

Long-term (52-week) studies. Of the 670 children who were randomized into the 52-week open-label extension studies, a total of 371 subjects in the BIS group and 156 subjects in the CAT group completed the 3 studies and were included in the analysis of growth. Fig 4 shows mean growth velocity (centimeters/year) for the BIS and CAT groups in each study and for BIS and CAT groups pooled across studies. In study A, a small but statistically significant difference in growth velocity was observed between BIS and CAT groups ($P = .002$); the growth velocity in BIS-treated children was 6.55 ± 2.08 cm/yr compared with 7.39 ± 2.52 cm/yr in CAT-treated children. In studies B and C, no differences in growth velocity were observed between BIS and CAT groups. In study B, growth velocity for BIS-treated children was 5.68 ± 1.71 cm/yr and 4.97 ± 2.0 cm/yr for children treated with CAT. In study C, growth velocity for children treated with BIS was 6.96 ± 2.34 cm/yr and for CAT was 6.21 ± 2.43 cm/yr. The pooled analysis showed that overall mean growth velocity was 6.64 ± 2.28 cm/yr for the BIS group and 6.45 ± 2.52 cm/yr for the CAT group. The pooled analysis of the 3 open-label studies showed no significant difference in growth velocity between BIS and CAT groups over 52 weeks in all subjects or when stratified by gender or by age (data not shown).

Fig 5 shows the distribution of changes in growth SDSs for the BIS and CAT groups for each of the 3 open-label studies and for the pooled analysis. As the figure shows, in studies B and C and in the pooled analysis, BIS did not have an effect on growth compared with CAT. However, a small but significant difference in change in growth SDS was observed between BIS and CAT groups in study A ($P = .003$). The significant difference in

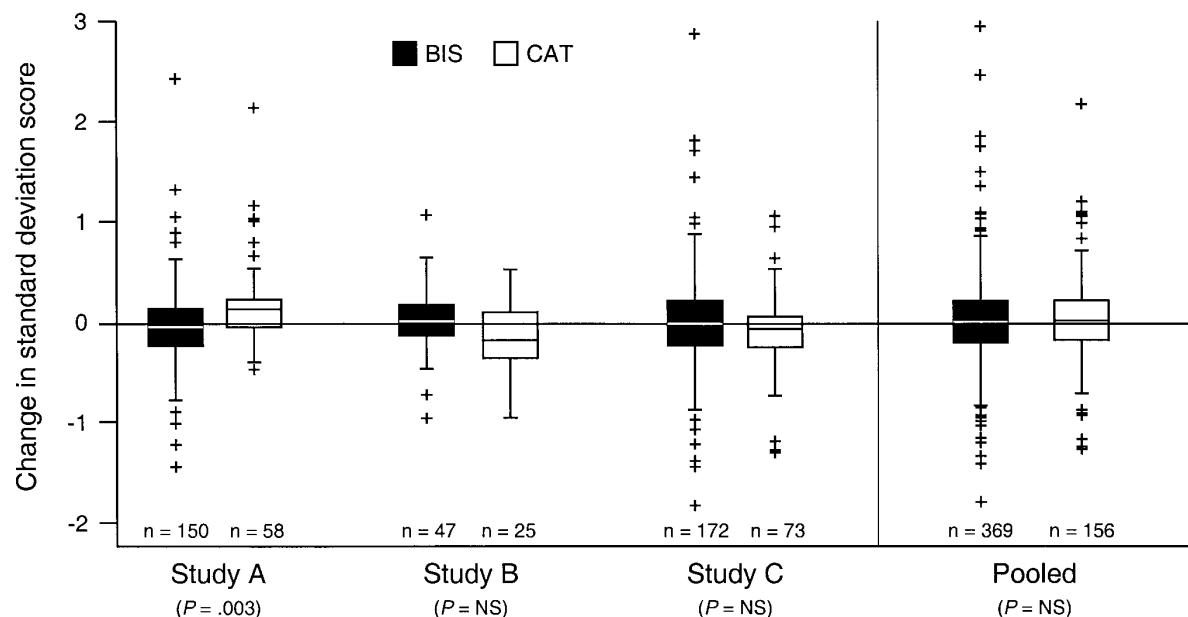


FIG 5. Mean change in SDSs from baseline to week 52 for BIS and CAT groups in studies A, B, C, and pooled data. The boxes span the 25th and 75th percentiles of the data, with the median noted by the inside bar. The length of the whiskers is based on 1.5 times the interquartile range, with outlying data points plotted individually. NS, Not significant.

change in SDS between BIS and CAT groups in study A may be explained by the fact that the CAT group appeared to have a preponderance of outliers who were growing at a faster rate than that normally observed for children of this age. There was a higher number of patient discontinuations because of worsening asthma in the CAT group compared with the BIS group in study A, and it is possible that the CAT-treated children who were discontinued from the study may have had more severe disease and less growth compared with patients who remained in the study. Alternatively, the difference observed in study A could be because (unlike CAT-treated subjects in studies B and C) CAT-treated subjects in study A did not receive inhaled glucocorticosteroids. The overall difference between BIS and CAT in growth SDS was 0 for all children, 0.01 for boys, and -0.01 for girls.

In the 2 studies that assessed skeletal age (studies B and C), the mean differences between skeletal and chronologic ages for all children and those children stratified by gender were similar between the BIS and CAT groups (data not shown). The mean differences between skeletal age and chronologic age at week 52 were 0.13 ± 1.14 for BIS and -0.09 ± 0.97 for CAT in study B, and 0.23 ± 0.87 for BIS and 0.09 ± 0.91 for CAT in study C.

DISCUSSION

Budesonide inhalation suspension was well tolerated for the treatment of persistent asthma in infants and young children for up to 15 months of treatment (double-blind plus open-label treatment). There were no differences in the incidence, severity, and types of AEs report-

ed among the BIS and placebo groups during short-term (12-week) treatment; reported AEs in both groups were mild to moderate in intensity. During long-term (52-week) treatment with BIS, after an adjustment for the length of treatment time, the incidences of reported AEs were comparable between the BIS and CAT treatment groups and were mild to moderate in intensity. No new AEs occurred during the long-term open-label studies compared with the 12-week double-blind studies. Results from both the 12-week double-blind and the 52-week open-label trials showed no differences between BIS and placebo and BIS and CAT, respectively, in basal or ACTH-stimulated cortisol levels, physical examinations, clinical laboratory results, or fungal cultures.

There were no short-term or long-term effects of BIS on HPA-axis function. Children (≤ 8 years old) treated for up to 52 weeks in the 3 open-label trials did not exhibit significant effects on either basal or stimulated plasma cortisol levels with BIS. Pooled data from the 3 open-label trials also demonstrated that the percentage of subjects with shifts in ACTH-stimulated cortisol levels from normal at baseline to abnormal at week 52 was similar between the 2 treatment groups; 24% of subjects who received BIS and 21% of subjects who received CAT. These studies indicate that treatment with BIS for over 1 year has a low risk for HPA-axis effects in infants and young children.

The effect of BIS on growth was assessed in each of the 52-week open-label extension studies. There was a small but statistically significant lower growth velocity (a difference of 0.8 cm) in the BIS-treated group compared

with the CAT group in study A. However, in studies B and C, growth velocity was not different between the BIS and CAT treatment groups. The pooled analysis showed no statistically significant difference in growth velocity or standard median heights between BIS and CAT groups. One possible explanation for the significant difference in growth velocity in study A was that subjects receiving CAT in this study were not treated with inhaled glucocorticosteroids, whereas over 25% and 43% of subjects receiving CAT in studies B and C, respectively, were being treated with inhaled glucocorticosteroids. Inhaled glucocorticosteroid exposure in subjects receiving CAT in studies B and C could have resulted in lower growth in these subjects compared with subjects receiving CAT in study A; therefore the differences between CAT and BIS groups would not be as large in studies B and C compared with study A. The effect of BIS on skeletal age was investigated in studies B and C; similar to the results for growth velocity, no significant differences between BIS and CAT were observed with regard to mean differences between skeletal age and chronological age over 1 year.

There has been particular concern about growth because systemic glucocorticosteroids are associated with growth suppression in children. However, the effects of inhaled glucocorticosteroids on growth remain uncertain. Interpretation of growth data is complicated, and several factors must be considered when the results of clinical trials are interpreted. Short-term growth studies (≤ 6 -9 months) have little to no value, and intermediate studies (> 6 -9 months) have low predictive value (26%) of final attained height.¹⁹ In fact, the only reliable measure of the effects of inhaled glucocorticosteroids on final attained adult height is by direct observation of the final height in relation to predicted final height.¹⁹ However, a marked effect on growth velocity in an intermediate study (changes in height SDS greater than 0.5 SDS in 1 year) can be an indication of systemic effects. Furthermore, decreased growth velocity may indicate an adverse effect of illness (eg, poor asthma control), poor nutrition, or medication effects, and may not accurately predict changes in final height (the most meaningful end point for an individual's growth). In addition, asthma is associated with delayed maturation in children and a longer period of reduced growth before puberty.²⁰⁻²² Children with asthma, regardless of treatment with or without a corticosteroid, have exhibited decreased growth velocity in late childhood and early adolescence; however, these delays do not appear to compromise the attainment of final predicted adult height.^{21,23}

The results of studies on the effects of inhaled glucocorticosteroids on growth are mixed. In a 1-year controlled study by Tinkelman et al,⁴ children with mild-to-moderate asthma were randomized to treatment with either inhaled BDP (400 μ g daily) or oral theophylline. Subjects who received BDP showed significant suppression of growth velocity ($P < .05$) compared with the theophylline group. Verberne et al⁵ found a 1.4-cm reduction in height in children treated with BDP (400 μ g daily) for

1 year compared with children treated with salmeterol for 1 year. Two other studies showed growth impairment in children treated with high-dose fluticasone propionate (≥ 1000 μ g daily)⁶ or BDP (400 μ g daily).³ However, both studies have potential confounding factors, which include previous treatment with oral glucocorticosteroids⁶ and the inclusion of older children in the inhaled glucocorticosteroid treatment group.³

Consistent with the results of the long-term studies reported here, an almost equal number of studies have shown no evidence of growth suppression in children treated with budesonide or low-dose fluticasone propionate.^{7,8,10,12} For example, Reid et al¹⁰ found no effect of BIS (≥ 1 mg daily) on linear growth after more than 6 months of continuous therapy. In a study by Agertoft and Pedersen,⁸ 3 to 6 years of treatment with budesonide in children significantly increased pulmonary function ($P < .01$) but had no effect on growth velocity at daily doses up to 400 μ g daily; growth velocity was 5.6 cm/yr in the placebo group and 5.5 cm/yr in the budesonide group.⁸

An important consideration with respect to the issue of growth suppression is whether inhaled glucocorticosteroids reduce final attained height. Although the effects of long-term treatment of children with inhaled corticosteroids, including BIS, on final height are not fully known, the findings from several studies are reassuring.^{21,23-25} For example, in a study by Silverstein et al,²⁵ the adult height of children with asthma who were treated with glucocorticosteroids (oral and/or inhaled) was not significantly different than the adult height of children with asthma who were not treated with glucocorticosteroids. A meta-analysis of 21 studies by Allen et al,²⁶ which included 810 children with asthma, found that although oral glucocorticosteroids such as prednisone were significantly associated with diminished final height ($P = .01$) there was a tendency for inhaled glucocorticosteroids to be associated with the attainment of normal stature. In addition, the preliminary results of an ongoing study by Agertoft and Pedersen,²⁴ reported at the 1998 American Thoracic Society annual meeting, suggest that long-term treatment with budesonide does not affect attained final height. In their study, the first 31 children to attain final height were treated with budesonide 222 to 750 μ g (mean, 445 μ g) delivered with a pressurized metered-dose inhaler and/or dry-powder inhaler (Turbuhaler) for at least 7 years and up to 11 years; growth was measured by stadiometry. No significant effect of budesonide was observed on subjects' ability to achieve their predicted final height, nor was there a relationship between final height and the average dose administered or the duration of treatment. Furthermore, conflicting findings in the literature on growth may be explained if inhaled glucocorticosteroid-related growth suppression is a transient phenomenon and has no effect on final attained height. A study by Doull et al²⁷ suggests that this may be the case. In this study, an initial suppression of growth velocity with BDP was observed that returned to pretreatment levels after 6 to 18 weeks of continued BDP treatment.

Because not all inhaled glucocorticosteroids are alike and all carry the potential for systemic effects, their use (especially in young children) should be closely monitored. It is recommended that when available, BIS be dosed individually according to disease severity and that the subject should be maintained on the lowest dose of inhaled glucocorticosteroid that effectively controls the asthma. In addition, physicians should closely monitor the growth of children and adolescents who are taking corticosteroids by any route and weigh the benefit of inhaled glucocorticosteroid therapy and subsequent asthma control against the possibility of growth suppression, if growth appears slowed. The present results demonstrate that BIS was safe and well tolerated for more than 1 year of treatment. Both short-term and long-term studies showed no differences between BIS and placebo and CAT, respectively, in the incidence and severity of AEs, changes in HPA-axis function, and skeletal age. Although there was a statistically significant difference in growth velocity between BIS-treated and CAT-treated groups in study A, the reduction in growth velocity over 52 weeks was small (-0.8 cm). Studies B and C and the pooled analysis showed no differences between BIS and CAT with regard to growth. The potential effects of nebulized budesonide on growth in children over the long term (>1 year) and on final attained adult height remain to be characterized.

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