

# Inhaled fluticasone propionate delivered by means of two different multidose powder inhalers is effective and safe in a large pediatric population with persistent asthma

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**Background:** Inhaled corticosteroids are increasingly being used to treat mild-to-moderate asthma in children. However, data regarding therapy with this class of compounds, especially in children under age 6 years, is limited. Fluticasone propionate is a third generation inhaled corticosteroid with an optimal therapeutic index. Few large prospective clinical trials have been conducted to evaluate the efficacy and safety of fluticasone propionate powder in children.

**Objective:** We sought to determine the efficacy and safety of fluticasone propionate powder administered by means of the Diskus and Diskhaler multidose powder inhalers in pediatric patients with persistent asthma.

**Methods:** Fluticasone propionate powder (50 µg or 100 µg twice daily) or placebo was administered by means of the Diskus or Diskhaler inhalers to 437 children (4 to 11 years old) with persistent asthma for 12 weeks in a randomized, double-blind, parallel-group, multi-center trial. Patients were stratified according to whether they were receiving prior treatment with inhaled corticosteroids or cromolyn or  $\beta_2$ -agonists alone. **Results:** Fluticasone propionate powder administered by means of Diskus or Diskhaler significantly improved FEV<sub>1</sub> (mean increase from baseline of 0.22 to 0.24 L;  $p \leq 0.023$ ), clinic morning peak expiratory flow (mean increase from baseline of 48 to 55 L/min;  $p \leq 0.006$ ), patient-measured morning ( $p \leq 0.001$ ) and evening ( $p \leq 0.003$ ) peak expiratory flow, and asthma symptom scores (in all but the 50 µg Diskus group;  $p \leq 0.036$ ), as well as reduced albuterol use ( $p \leq 0.002$ ) and nighttime awakenings ( $p \leq 0.019$ ) at endpoint. Efficacy parameters were not significantly different between the two doses with either device. More placebo-treated patients discontinued the study because of lack of efficacy than patients in any fluticasone propionate group ( $p < 0.001$ ). Fluticasone propionate did

not suppress morning plasma cortisol concentrations and did not affect 24-hour urinary free-cortisol excretion. Adverse events were primarily pharmacologic effects of inhaled corticosteroids, and those related to the study drug occurred with low frequency. Patient satisfaction with both the Diskus and Diskhaler devices was high, with a majority of patients (> 80%) rating them favorably.

**Conclusion:** This study demonstrated that fluticasone propionate powder, at the conventional recommended doses of up to 200 µg/day administered by means of Diskus or Diskhaler, was well tolerated and improved lung function in children even as young as 4 and 5 years old regardless of whether they were previously treated with inhaled corticosteroids or cromolyn or  $\beta_2$ -agonists alone. (*J Allergy Clin Immunol* 1998;102:32-8.)

**Key words:** Asthma, children, Diskhaler, Diskus, fluticasone propionate

There is considerable evidence to support the strategy of early intervention with inhaled corticosteroids in an attempt to prevent the chronic progression of asthma. Extensive airway inflammation, previously considered a hallmark of fatal asthma,<sup>1</sup> has been observed even in mild and subclinical disease.<sup>2,3</sup> Epidemiologic studies have shown a correlation between early respiratory symptoms and subsequent diagnosis of asthma in children 1 to 4 years of age,<sup>4,5</sup> as well as a decline in lung function by as early as age 6 years.<sup>6</sup> Treatment with inhaled corticosteroids early in the disease process has resulted in a greater magnitude of lung function improvement in adults<sup>7</sup> and children,<sup>8</sup> thus supporting their current favorable position within the various treatment guidelines.<sup>9,10</sup>

Yet many children are not treated with inhaled corticosteroids, primarily because of concerns about potential adverse systemic side effects. Fluticasone propionate, a third generation corticosteroid, has minimal oral bioavailability, resulting from poor oral absorption and rapid inactivation in the liver.<sup>11</sup> Additionally, its high topical antiinflammatory activity combined with an increased affinity for the glucocorticoid receptor<sup>12</sup> aid in achieving clinical effect at low doses. Several prospective clinical trials have demonstrated fluticasone propionate to be safe and effective in controlling asthma in children.<sup>13-15</sup>

In addition to drug potency, the drug delivery system is of prime importance in maintaining effective asthma

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*Abbreviations used*

HPA: Hypothalamic-pituitary-adrenal

PEF: Peak expiratory flow

control in children. Metered-dose inhalers, which require coordination of inhaler actuation with inspiration, have been found to pose significant problems to young children and result in inadequate treatment.<sup>16</sup> Breath-actuated devices, such as the Diskus and Diskhaler, have low airflow resistance, require less coordination and skill, and consequently are easy for children to use. This study was conducted to evaluate the comparative efficacy and safety of fluticasone propionate administered by means of the Diskus or Diskhaler multidose powder inhalers at doses of 50 µg and 100 µg twice a day in a large group of pediatric patients with persistent asthma.

## METHODS

### Patients

In this study we enrolled 437 children between the ages of 4 and 11 years with a diagnosis of a history of chronic asthma made according to the American Thoracic Society criteria<sup>17</sup> and with symptoms requiring maintenance treatment over the 3 months immediately before the study. Criteria for lung function measurements at the onset of the study included a baseline peak expiratory flow (PEF) of 85% or less of Polgar<sup>18</sup> predicted values (age range, 4 to 5 years), an FEV<sub>1</sub> of 50% to 85% of Polgar predicted values (age range, 6 to 11 years), and demonstration of a 15% or greater reversibility in FEV<sub>1</sub> (age range, 6 to 11 years) within 30 minutes after inhalation of two puffs of albuterol (Ventolin, Glaxo Wellcome Inc.) or documentation of this reversibility within 6 months before the study. Reversibility was assessed in 4 to 5 year old patients by measuring PEF before and 30 minutes after administering two puffs of albuterol aerosol.

Patients were excluded if they had life-threatening asthma or other severe concurrent disease; been exposed to or had chicken pox within 3 weeks before the study; had a lower respiratory tract infection within the previous 2 weeks; used oral or parenteral corticosteroids within 1 month before the study, used methotrexate or gold salts, or used any prescription or over-the-counter medication that might have affected the course of asthma or its treatment; or had participated in any previous clinical trial with the Diskus or Diskhaler devices.

### Study design

This was a double-blind, double-dummy, placebo-controlled, randomized study performed at 34 centers in the United States. All centers obtained a consent form from each patient signed by a parent or legal guardian and Institutional Review Board approval before the start of the study.

Patients were divided into two strata based on whether they were being treated with inhaled corticosteroids or cromolyn or  $\beta_2$ -agonists alone before study entry. All patients entered a 2-week, single-blind, placebo run-in period during which they continued their regular inhaled corticosteroid, cromolyn, or theophylline therapy provided the treatment was started at least 3 months before the study with no change in the dose or dosing regimen within the last month. Patients using inhaled or oral bronchodilators discontinued this therapy, and instead all patients received inhaled albuterol (aerosol or powder) as needed. Spacer devices for albuterol use were allowed if patients used them consistently throughout the study. All patients received placebo administered by means of the Diskus and Diskhaler and were instructed in the proper use of these devices.

Patients eligible for randomization had to demonstrate asthma stability on the basis of the following criteria during the last 7 days of the run-in period: no more than 3 days of 12 or more puffs of albuterol aerosol per day or six or more doses of albuterol powder per day, no more than three mornings during which the decrease in PEF was greater than 20% of the previous evening's PEF, and no more than three nighttime awakenings resulting from asthma requiring albuterol. Patient's compliance to study procedures was measured by their ability to withhold antiasthma medications before clinic visits, use 70% or greater of the placebo during the run-in period, and complete diary cards.

### Treatments

During the double-blind period, patients meeting the inclusion criteria discontinued all other inhaled corticosteroid or cromolyn therapy and were randomly assigned by strata (baseline therapy of inhaled corticosteroids or cromolyn or  $\beta_2$ -agonists alone) to receive one of the following five treatments twice daily for 12 weeks: 50 µg fluticasone propionate or 100 µg administered either by means of the Diskus or Diskhaler or placebo. Patients had to withhold theophylline treatment, if any, for 24 to 36 hours before clinic visits and albuterol use for 6 or more hours before clinic visits.

### Assessments

Patients visited the clinic weekly for the first 4 weeks and every other week for the remaining 8 weeks. Efficacy assessments included measurement of FEV<sub>1</sub> and PEF (by means of Mini-Wright peak flowmeter) at each clinic visit, patient-measured morning and evening PEF, patient-rated asthma symptoms, number of nighttime awakenings requiring albuterol, and albuterol use. To determine if fluticasone propionate was effective in 4 and 5 year old patients, a subgroup analysis was performed on PEF data because this was the only lung function test performed consistently in this group of patients. Data for the two devices were combined for this analysis because of the small number of patients in this subgroup. Patient compliance was measured by means of the device dose counters at weeks 4, 8, and 12 or study termination.

At each clinic visit, FEV<sub>1</sub> values had to be greater than the FEV<sub>1</sub> stability limit (a 15% decrease in the best FEV<sub>1</sub> value obtained at baseline for ages 6 to 11 years), and PEF values had to be greater than the PEF stability limit (a 20% decrease in mean morning PEF obtained during the last 7 days of the run-in period for all patients). Additionally, during the 7 days immediately preceding each visit, patients should have had 2 or fewer days of 12 or more puffs of albuterol aerosol per day or six or more doses of albuterol powder per day, two or fewer nighttime awakenings resulting from asthma and requiring albuterol, and 2 or fewer days during which a morning or evening PEF was below the PEF stability limit. Patients who failed to meet these criteria, and those whose asthma required hospitalization or medication excluded by the study protocol, were discontinued from the study for lack of efficacy.

Safety assessments for all patients included adverse event monitoring, routine clinical laboratory tests, physical examinations (including oropharyngeal examination and vital signs), and 12-lead electrocardiograms. Assessment of the integrity of the hypothalamic-pituitary-adrenal (HPA) axis was measured by morning unstimulated plasma cortisol concentrations (all patients) and 24-hour urinary free-cortisol excretion in a subgroup of patients.

At baseline, parents or caregivers were asked to complete a device satisfaction questionnaire rating the importance of five characteristics, including convenience to carry, ease of holding and operating, ease of loading and cleaning (Diskhaler only), and ease of reading number of doses remaining. At week 6 and week 12 or at the endpoint, device performance was rated for each characteristic, and patients also rated their overall level of satisfaction and comfort with the devices.

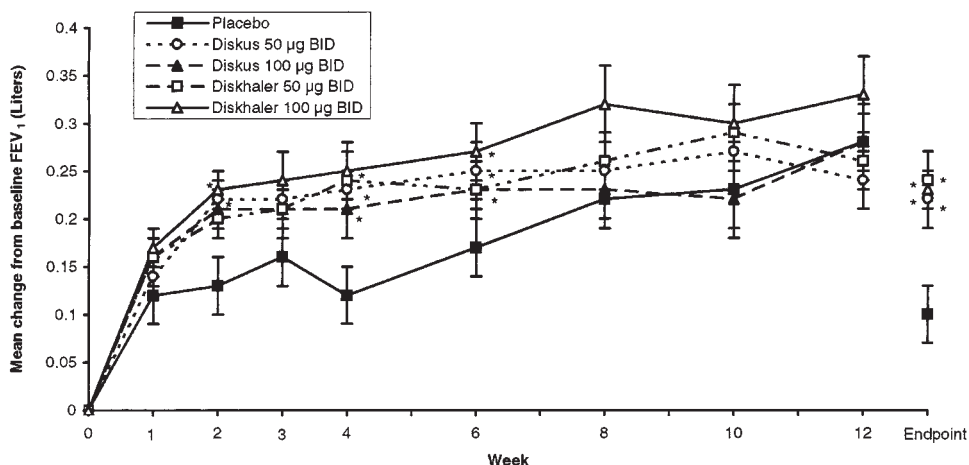


FIG. 1. Mean change from baseline in morning predose FEV<sub>1</sub>. BID, Twice daily; Endpoint, final evaluable measurement regardless of whether patient completed the study. \* $p \leq 0.05$  for each experimental group versus placebo.

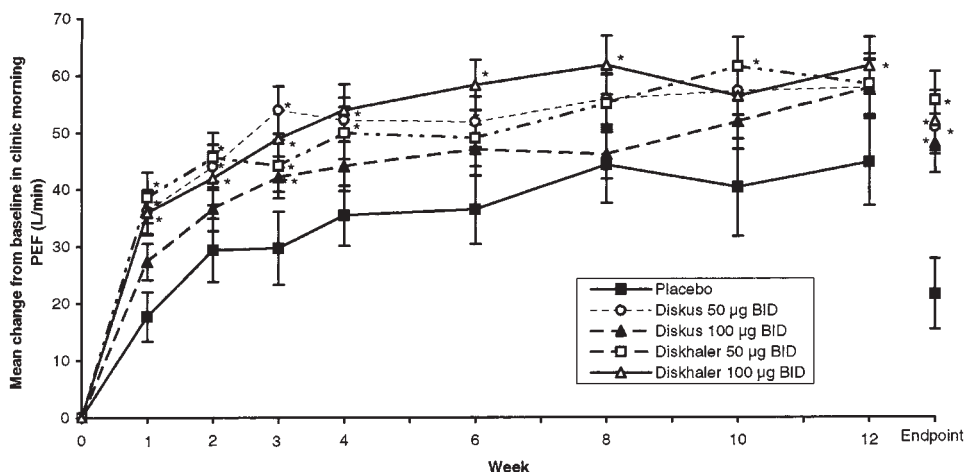


FIG. 2. Mean change from baseline in morning clinic PEF. BID, Twice daily; final evaluable measurement regardless of whether patient completed the study. \* $p \leq 0.05$  for each experimental group versus placebo.

## Statistical analyses

The primary efficacy parameters were spirometric measurement of FEV<sub>1</sub> and clinic visit PEF. The number of evaluable patients required per treatment group to detect a mean difference of 0.25 L in FEV<sub>1</sub> and 16 L/min in morning PEF with a power of 80% was estimated to be 75 and 80, respectively. Two-sided statistical tests with a 0.05 level of significance were used. The intent-to-treat population (all patients exposed to study drug) was used for all safety and efficacy analyses. Endpoint data, defined as the final evaluable measurement regardless of whether the patient completed the study or not, were also analyzed. Testing was performed on combined data from all investigators, controlling for investigator effect.

FEV<sub>1</sub> and PEF values were tested for treatment differences by using an analysis of variance F test. Determination of the probability of remaining in the study over time was made on the basis of Kaplan-Meier estimates of survival. Patient-rated asthma symptom scores (0 = none, 1 = mild, 2 = moderate, and 3 = severe), albuterol use, and nighttime awakenings were averaged over 7 days, and

because these symptom scores are discrete, all testing was based on the nonparametric van Elteren test.

## RESULTS

Demography, asthma history, and baseline pulmonary function of the 437 pediatric patients (age range, 4 to 11 years) who met entry criteria and were enrolled in the study at 34 clinical centers showed no statistically significant differences (Table I). Fifty-seven patients (13%) were 4 or 5 years old. A slightly higher percentage of patients received inhaled corticosteroids (45%) and cromolyn (9%) therapy (a total of 54%) than  $\beta_2$ -agonists alone (46%). Patients withdrew from the study chiefly because of lack of efficacy on the basis of predetermined criteria, with the highest percentage of withdrawal seen in the placebo group. The mean study drug compliance rate in all treatment groups ranged from 89% to 91%.

**TABLE I.** Demographics, asthma characteristics, and disposition of patients at baseline\*

|                                | Placebo     | Diskus      |             | Diskhaler   |             |
|--------------------------------|-------------|-------------|-------------|-------------|-------------|
|                                |             | 50 µg BID   | 100 µg BID  | 50 µg BID   | 100 µg BID  |
| No. of patients enrolled       | 86          | 90          | 87          | 91          | 83          |
| 4 to 5 years old (%)           | 7 (8)       | 11 (12)     | 14 (16)     | 13 (14)     | 12 (14)     |
| 6 to 11 years old (%)          | 79 (92)     | 79 (88)     | 73 (84)     | 78 (86)     | 71 (86)     |
| Sex, M/F (%)                   | 71/29       | 59/41       | 68/32       | 55/45       | 60/40       |
| FEV <sub>1</sub> (L)           | 1.42 ± 0.20 | 1.61 ± 0.22 | 1.96 ± 0.21 | 1.73 ± 0.19 | 1.61 ± 0.23 |
| FEV <sub>1</sub> (% predicted) | 73          | 73          | 74          | 73          | 72          |
| Clinic AM PEF (L/min)          | 226 ± 7     | 217 ± 7     | 216 ± 8     | 222 ± 8     | 205 ± 8     |
| Clinic AM PEF (% predicted)    | 79          | 78          | 80          | 81          | 77          |
| Diary AM PEF (L/min)           | 234 ± 8     | 229 ± 8     | 220 ± 8     | 232 ± 8     | 213 ± 7     |
| Diary PM PEF (L/min)           | 245 ± 8     | 243 ± 8     | 233 ± 8     | 244 ± 8     | 227 ± 8     |
| Asthma symptom scores†         | 0.72 ± 0.07 | 0.81 ± 0.06 | 0.80 ± 0.06 | 0.86 ± 0.06 | 0.76 ± 0.06 |
| Albuterol use (puffs/day)      | 1.42 ± 0.20 | 1.61 ± 0.22 | 1.96 ± 0.21 | 1.73 ± 0.19 | 1.61 ± 0.23 |
| Nighttime awakenings/night     | 0.06 ± 0.02 | 0.05 ± 0.01 | 0.08 ± 0.02 | 0.05 ± 0.01 | 0.09 ± 0.02 |
| No. completed study (%)        | 39 (45)     | 69 (77)     | 71 (82)     | 77 (85)     | 63 (76)     |
| No. withdrawn (%)              | 47 (55)     | 21 (23)     | 16 (18)     | 14 (15)     | 20 (24)     |
| Adverse events (%)             | 2 (2)       | 1 (1)       | 1 (1)       | 2 (2)       | 0           |
| Lack of efficacy (%)           | 40 (47)     | 13 (14)     | 7 (8)       | 5 (5)       | 13 (16)     |
| Other reasons‡ (%)             | 5 (6)       | 7 (8)       | 8 (9)       | 7 (8)       | 7 (8)       |

BID, Twice daily.

\*Unless otherwise expressed, values presented are means ± SEM.

†Asthma symptom scores (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

‡Includes protocol violations and patients who failed to return

**TABLE II.** Mean change ± SEM in efficacy variables from baseline at endpoint

| Efficacy variable                   | Placebo      | Diskus        |               | Diskhaler     |               |
|-------------------------------------|--------------|---------------|---------------|---------------|---------------|
|                                     |              | 50 µg BID     | 100 µg BID    | 50 µg BID     | 100 µg BID    |
| No. of patients enrolled            | 86           | 90            | 87            | 91            | 83            |
| FEV <sub>1</sub> AM before dose (L) | 0.10 ± 0.03  | 0.22 ± 0.03*  | 0.24 ± 0.03*  | 0.24 ± 0.03*  | 0.23 ± 0.04*  |
| FEV <sub>1</sub> (% change)         | 6.96 ± 2.45  | 15.77 ± 1.97* | 17.93 ± 2.44* | 17.89 ± 2.28* | 18.61 ± 3.08* |
| FEV <sub>1</sub> (% predicted)      | 4.72 ± 1.71  | 11.25 ± 1.37* | 12.53 ± 1.68* | 12.26 ± 1.52* | 12.74 ± 1.99* |
| Clinic AM PEF (L/min)               | 22 ± 6       | 51 ± 5*       | 48 ± 5*       | 55 ± 5*       | 52 ± 5*       |
| Clinic AM PEF (% change)            | 14 ± 4       | 26 ± 3*       | 27 ± 3*       | 30 ± 3*       | 33 ± 4*       |
| Clinic AM PEF (% predicted)         | 8 ± 2        | 20 ± 2*       | 20 ± 2*       | 23 ± 2*       | 23 ± 3*       |
| Diary AM PEF (L/min)                | 13 ± 5       | 34 ± 3*†      | 40 ± 5*       | 41 ± 5*       | 42 ± 4*       |
| Diary PM PEF (L/min)                | 12 ± 5       | 26 ± 3*†      | 34 ± 4*       | 36 ± 4*       | 36 ± 4*       |
| Asthma symptom scores‡              | -0.02 ± 0.09 | -0.36 ± 0.07  | -0.41 ± 0.07* | -0.41 ± 0.07* | -0.36 ± 0.07* |
| Albuterol use (puffs/day)           | 0.08 ± 0.23  | -0.75 ± 0.23* | -1.04 ± 0.20* | -1.02 ± 0.18* | -0.90 ± 0.23* |
| Nighttime awakenings/night          | 0.07 ± 0.04  | -0.03 ± 0.01* | -0.06 ± 0.02* | -0.04 ± 0.01* | -0.06 ± 0.02* |

BID, Twice daily.

\*Indicates a significant ( $p \leq 0.05$ ) effect versus placebo.†Indicates a significant ( $p \leq 0.05$ ) effect for Diskus versus Diskhaler.

‡Asthma symptom scores (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

## Efficacy

**Pulmonary function.** At endpoint, each fluticasone propionate group showed a significantly greater improvement ( $p \leq 0.023$ ) in mean change from baseline FEV<sub>1</sub> (Fig. 1) and in percent predicted FEV<sub>1</sub> ( $p \leq 0.013$ ) compared with the placebo group, but no statistically significant differences were observed between the two doses or devices (Table II). Similar treatment differences were observed when FEV<sub>1</sub> data were expressed as mean percentage change from baseline. Analysis by strata revealed that at endpoint, in all fluticasone propionate groups except the Diskhaler 50 µg twice daily

group, patients previously receiving  $\beta_2$ -agonists alone showed somewhat greater improvement in FEV<sub>1</sub> (mean increases of 0.23 to 0.28 L) than those previously receiving inhaled corticosteroid or cromolyn therapy (mean increase of 0.21 L).

At endpoint, significantly greater improvements were noted in mean change from baseline in clinic morning PEF (Fig. 2;  $p \leq 0.006$ ) and percent predicted PEF ( $p \leq 0.002$ ) in all fluticasone propionate groups compared with the placebo group, but no significant differences were observed between the two doses or devices. Similar treatment-related increases were observed at end point in mean change from baseline diary morning ( $p \leq 0.001$ )

**TABLE III.** Mean morning plasma cortisol concentrations (micrograms per deciliter)  $\pm$  SEM

|            | Placebo                 | Diskus                  |                         | Diskhaler               |                         |
|------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|            |                         | 50 $\mu$ g BID          | 100 $\mu$ g BID         | 50 $\mu$ g BID          | 100 $\mu$ g BID         |
| Screening  | 8.4 $\pm$ 0.4 (n = 84)  | 9.0 $\pm$ 0.6 (n = 88)  | 8.5 $\pm$ 0.5 (n = 87)  | 8.2 $\pm$ 0.4 (n = 90)  | 7.7 $\pm$ 0.4 (n = 79)  |
| Last visit | 10.3 $\pm$ 0.5 (n = 73) | 11.0 $\pm$ 0.6 (n = 86) | 10.6 $\pm$ 0.6 (n = 81) | 10.4 $\pm$ 0.5 (n = 88) | 10.8 $\pm$ 0.5 (n = 78) |
| Change     | 1.7 $\pm$ 0.6 (n = 72)  | 2.0 $\pm$ 0.5 (n = 84)  | 2.0 $\pm$ 0.7 (n = 81)  | 2.3 $\pm$ 0.5 (n = 87)  | 3.1 $\pm$ 0.6 (n = 74)  |

BID, Twice-daily.

**TABLE IV.** Mean total urinary free-cortisol excretion (micrograms per 24 hours) at baseline and endpoint

|                       | Placebo     | Diskus         |                 | Diskhaler      |                 |
|-----------------------|-------------|----------------|-----------------|----------------|-----------------|
|                       |             | 50 $\mu$ g BID | 100 $\mu$ g BID | 50 $\mu$ g BID | 100 $\mu$ g BID |
| No. of patients       | 64          | 68             | 66              | 65             | 59              |
| Mean (SD) at baseline | 12.5 (12.6) | 11.8 (10.6)    | 10.2 (6.8)      | 10.3 (8.1)     | 12.8 (12.4)     |
| No. of patients       | 35          | 61             | 57              | 63             | 47              |
| Mean (SD) at endpoint | 9.8 (6.9)   | 11.1 (8.8)     | 11.3 (12.7)     | 10.5 (9.1)     | 11.9 (14.3)     |

BID, Twice daily.

and evening ( $p \leq 0.003$ ) PEF. At endpoint, no statistically significant differences were seen between the two dosing groups; however, the Diskhaler 50  $\mu$ g twice daily group showed significantly improved morning ( $p = 0.030$ ) and evening ( $p = 0.023$ ) PEF when compared with the Diskus 50  $\mu$ g twice daily group (Table II).

Analysis by strata at endpoint indicated that patients in the Diskus and Diskhaler 50  $\mu$ g twice daily groups showed similar improvements in clinic morning PEF in both strata, whereas patients in the 100  $\mu$ g twice daily groups previously treated with  $\beta_2$ -agonists showed somewhat greater improvement (mean increases of 51 and 61 L/min) than those previously treated with inhaled corticosteroids or cromolyn (mean increases of 45 and 44 L/min). Improvements in diary morning PEF in all fluticasone propionate groups was somewhat higher in the  $\beta_2$ -agonist stratum (mean increases of 35 to 46 L/min) than in the inhaled corticosteroids or cromolyn stratum (mean increases of 33 to 40 L/min).

Analysis of data in the subgroup of 4 and 5 year old patients showed that at endpoint, all fluticasone propionate-treated patients had increases in clinic morning PEF (mean increases of 56 to 58 L/min) compared with patients receiving placebo (mean increase of 26 L/min) and in percent predicted PEF (mean increase of 38%) compared with patients receiving placebo (mean increase of 20%).

**Probability of remaining in the study.** Kaplan-Meier survival analysis, or the probability of remaining in the study over time without being withdrawn for lack of efficacy, showed a significant overall treatment effect ( $p < 0.001$ ). At endpoint, 47% of the patients in the placebo group had discontinued from the study because of lack of efficacy compared with 14% and 8% in the Diskus 50 and 100  $\mu$ g twice daily groups, and 5% and 16% in the Diskhaler 50 and 100  $\mu$ g twice daily groups, respectively. Patients in each fluticasone propionate group had a significantly lower probability of discontinuing the study because of lack of efficacy than those in the placebo

group, but there were no significant differences between the two doses or devices.

A similar proportion of patients previously treated with inhaled corticosteroids or cromolyn (19%) discontinued the study because of lack of efficacy as those previously treated with  $\beta_2$ -agonists (16%). However, in both strata, more placebo-treated patients (50% and 42%, respectively) discontinued the study because of lack of efficacy than patients treated with Diskus 50  $\mu$ g twice daily (19% and 10%), Diskus 100  $\mu$ g twice daily (11% and 5%), Diskhaler 50  $\mu$ g twice daily (6% and 5%), or Diskhaler 100  $\mu$ g twice daily (9% and 23%).

**Asthma symptoms, albuterol use, and nighttime awakenings.** Asthma symptoms scores were significantly decreased at endpoint in the Diskus 100  $\mu$ g twice daily and both Diskhaler groups ( $p \leq 0.036$ ) compared with the placebo group. At endpoint, albuterol use in all fluticasone propionate-treated patients declined significantly ( $p \leq 0.002$ ), with reductions of 47% and 53% in the Diskus 50 and 100  $\mu$ g twice daily groups and 59% and 56% in the Diskhaler 50 and 100  $\mu$ g twice daily groups, respectively, compared with a 6% increase in the placebo group. All fluticasone propionate-treated patients had significantly fewer nighttime awakenings at endpoint compared with patients receiving placebo ( $p \leq 0.019$ ). No statistically significant differences were noted at endpoint between the two fluticasone propionate doses or the Diskus and Diskhaler devices in asthma symptom scores, albuterol use, or nighttime awakenings (Table II).

## Safety

**Adverse events.** Fluticasone propionate was well tolerated during the 12-week study, with a low incidence of drug-related adverse events (placebo, 3%; active, 2% to 5%). These included hoarseness or dysphonia, candidiasis of the mouth or throat, throat irritation, oral ulcerations, skin rash, nausea and vomiting, gastrointestinal discomfort and pain, and behavioral disorder, all of which

occurred with a very low frequency (1%). Three patients experienced serious adverse events, none of which were related to the study drug (i.e., asthma exacerbation in a placebo patient and one incidence each of pneumonia and viral gastroenteritis in patients receiving active treatment). Of these, the patients with asthma exacerbation and pneumonia were discontinued from the study. Four other patients were withdrawn from the study because of adverse events (i.e., one placebo patient with hoarseness and sore throat considered probably drug-related, one fluticasone propionate-treated patient with behavior changes considered possibly drug-related, and two patients receiving active treatment who had chicken pox during the study).

**HPA-axis evaluation.** Fluticasone propionate treatment did not suppress morning plasma cortisol concentrations (Table III). At screening, a higher frequency of morning plasma cortisol abnormalities ( $<5 \mu\text{g/dl}$ ) was observed in patients previously treated with inhaled corticosteroids or cromolyn (17%) than those previously treated with  $\beta_2$ -agonists (12%). At the last study visit, this frequency had decreased to 4% in both strata. Compared with placebo, fluticasone propionate treatment did not significantly affect 24-hour urinary cortisol excretion (Table IV).

**Other laboratory and clinical tests.** Laboratory evaluations, vital signs, physical examinations, and electrocardiograms showed no treatment-related trends or clinically significant changes.

### Device satisfaction

Results from the device satisfaction questionnaire indicated that a majority of patients ( $>80\%$ ) rated performance by both the Diskus and Diskhaler favorably on all characteristics designated as important, such as convenience of carrying, ease of holding and operating, ease of loading and cleaning (Diskhaler only), and ease of determining number of doses left in the device.

### DISCUSSION

The therapeutic efficacy of fluticasone propionate was clearly demonstrated in this large pediatric patient population with persistent asthma. Patients treated with 50 or 100  $\mu\text{g}$  fluticasone propionate twice daily had improved lung function and reduced asthma symptoms, nighttime awakenings, and albuterol use. These improvements were observed even in patients as young as 4 and 5 years old and those dependent on inhaled corticosteroids. Fluticasone propionate was well tolerated, with a low incidence of pharmacologically expected adverse events.

Some important features of this study include a large pediatric patient population, the use of a double-dummy technique to maintain blinding of study treatment, use of parental or caregiver assistance in the daily evaluation of symptoms, and the use of objective measurements of lung function. Although  $\text{FEV}_1$  is the single best measure for assessing the severity of airflow obstruction, most children 4 to 5 years of age cannot perform  $\text{FEV}_1$  measurement adequately. Therefore PEF, an additional objective measure of lung function, was determined both in the

clinic and at home. The slightly higher treatment-related improvements in morning PEF measured at the clinic than those measured at home was possibly a consequence of coaching during clinic visits. Significant treatment-related improvements in PEF observed in children 4 and 5 years of age indicated that inhaled fluticasone propionate was able to control asthma effectively in this age group.

Fluticasone propionate improved lung function in children regardless of whether they received prior treatment with inhaled steroids, although the greater magnitude of improvement in patients previously treated with  $\beta_2$ -agonists alone may have been the consequence of less severe asthma in this group of patients and their greater potential for improvement. Efficacy measures showed no dose-related effects, possibly because the degree of asthma severity was not sufficient to observe any differences in efficacy between the two dose levels. These results are consistent with those observed in previous studies with fluticasone propionate<sup>19,20</sup> and other inhaled corticosteroids.<sup>21,22</sup> However, dose-related increases in efficacy have been reported with higher doses in adults with moderate-to-severe asthma.<sup>23-25</sup>

From a safety standpoint, important features included measurement of both morning plasma cortisol concentrations and 24-hour urinary free-cortisol excretion as endpoints of HPA-axis activity. A prior comparative study demonstrated that the 24-hour urinary free-cortisol estimation has comparable sensitivity to a 250  $\mu\text{g}$  bolus dose of adrenocorticotrophic hormone or an insulin stress test, whereas morning plasma cortisol alone is much less sensitive.<sup>26</sup>

No evidence of HPA-axis suppression was observed in this study. In fact, the frequency of abnormal morning plasma cortisol concentrations decreased throughout the study, with greater decreases seen after fluticasone propionate treatment, and no significant changes were observed in urinary cortisol output. These findings are consistent with previous studies in children in which daily treatment with 50 to 400  $\mu\text{g}$  fluticasone propionate powder for up to 3 months showed no effect on mean morning plasma cortisol concentrations,<sup>13-15</sup> whereas repeated twice daily dosing with 200 to 400  $\mu\text{g}$  fluticasone propionate aerosol at steady state did not significantly affect overnight urinary free-cortisol excretion.<sup>27</sup>

The level of patient comfort and satisfaction with a delivery device can significantly influence adherence to treatment. Because adherence encompasses both medication use, as well as good inhalation technique, the choice of an inappropriate device could have a negative impact on treatment outcome. Both the Diskus and Diskhaler multidose powder inhalers used in this study were comparable in efficacy, were rated favorably by a majority of patients, and were able to deliver drug effectively even to children 4 and 5 years of age.

Results of this study demonstrate that both from a therapeutic and adverse effects standpoint, inhaled fluticasone propionate can meet the challenge of treating and controlling persistent asthma in children. Its favorable pharmacologic profile coupled with an effective drug

delivery system should help to effectively control asthma symptoms and improve compliance, thus enhancing the treatment of children with asthma.

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