

PHARMACOTHERAPEUTICS

Effects of Inhaled Mometasone Furoate on Growth Velocity and Adrenal Function: A Placebo-Controlled Trial in Children 4–9 Years Old with Mild Persistent Asthma

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Objective. To assess the effects of long-term mometasone furoate delivered via a dry powder inhaler (MF-DPI) on growth velocity and hypothalamic–pituitary–adrenal axis function in children with asthma. **Study design.** Children aged 4–9 years with asthma ($n = 187$) were randomized to MF-DPI 100 μg (delivered dose; actuated dose is 110 μg) once daily in the morning (QD AM), 100 μg twice daily (BID), 200 μg QD AM, or placebo for 52 weeks followed by a 3-month follow-up period. The primary outcome was growth velocity calculated from stadiometric heights recorded at each visit. Secondary outcomes included serum and 12-h urinary cortisol, serum osteocalcin, and urinary N-telopeptide. **Results.** MF-DPI 100 μg QD AM treatment did not significantly affect growth velocity compared with placebo (-0.10 ± 0.31 cm/y, $p = 0.76$). When the effect of a total daily dose of 200 μg MF-DPI on growth velocity was examined, no significant effect was demonstrated for MF-DPI 100 μg BID compared with placebo (-0.64 ± 0.39 cm/y, $p = 0.10$), although the change in mean growth velocity with MF-DPI 200 μg QD AM reached statistical significance (-0.70 ± 0.29 cm/y, $p = 0.02$). The effects of all examined doses of MF-DPI on mean plasma cortisol levels were similar to cortisol changes seen in the placebo group, suggesting an absence of drug-related effects. No differences in 12-h urinary cortisol or other outcomes were observed between groups. **Conclusions.** One year of treatment with a total daily dose of 100 μg of MF-DPI in the morning resulted in no significant difference, whereas a total daily dose of 200 μg of MF-DPI was associated with some changes in growth velocity when compared with placebo. The differences in growth velocity, and the absence of drug-related cortisol effects, support the use of a total daily dose of 100 μg of MF-DPI in children aged 4–9 years with mild persistent asthma.

Keywords height, hypothalamic–pituitary–adrenal axis, inhaled corticosteroid, mometasone furoate, pediatric

INTRODUCTION

Asthma is a common childhood illness that affects more than 6 million children in the United States (1). Although the number of deaths due to asthma has decreased in the past two decades, the prevalence of asthma is increasing. Children under the age of 15 years have the highest hospitalization rates for asthma of any age group (2).

Although some patients may require additional asthma medications to achieve optimal control, inhaled corticosteroid (ICS) therapy is the current standard of initial care for the treatment of persistent asthma in children of all ages (3, 4). However, depending on the dosage required to control asthma, ICSs can have systemic effects that interfere with the growth and the activity of the hypothalamic–pituitary–adrenal (HPA) axis. As a result, suppression of serum and urinary cortisol (5) and a reduction of growth velocity in children (6–8) can occur. The available clinical evidence suggests that ICS-induced changes in growth velocity may be transient

(9–11) and that treated children will attain normal adult height (12). However, in a post-trial follow-up, 4.8 years after discontinuing approximately 4 years of twice daily (BID) budesonide treatment, a significant decrease in height compared with placebo was still evident, particularly in girls (13). Thus, concerns remain about the long-term effects of ICS therapy, particularly in young children.

Mometasone furoate (MF) delivered via a dry powder inhaler (MF-DPI) is an ICS that in the United States is indicated for the maintenance treatment of asthma in adults and children as young as 4 years of age (14–18). The current approved pediatric dose is 110 μg (actuated dose; 100 μg is the delivered dose) taken once daily in the evening. When compared with placebo, once-daily MF-DPI 100 μg has been shown to significantly improve lung function, physician-evaluated response to therapy scores, and quality of life scores, as well as significantly reduce short-acting β_2 -agonist (SABA) use in children with mild asthma (16, 17).

This safety study was designed to assess the effects of long-term treatment with MF-DPI at the approved total daily delivered pediatric dosage on growth velocity and HPA axis function in children with mild persistent

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asthma. The effects of twice the recommended delivered dosage were also evaluated.

METHODS

This was a phase III, multicenter, randomized, placebo-controlled, parallel-group, double-blind, long-term safety study of children aged 4–9 years with persistent asthma who were previously maintained on β_2 -agonists. An Institutional Review Board for each study center approved the study protocol and any protocol amendments. The study was conducted in accordance with Good Clinical Practice along with the 1996 World Medical Association Declaration of Helsinki concerning informed consent and the protection of rights of human subjects. Parents or guardians were required to provide written informed consent before enrollment.

Study Design and Treatments

After a run-in period of 1–2 weeks between screening and baseline visits, subjects were randomized in a 1:1:1:1 ratio to receive one of four regimens for a period of 52 weeks: delivered doses of MF-DPI 100 μ g once-daily in the morning (QD AM), MF-DPI 100 μ g BID, MF-DPI 200 μ g QD AM, or placebo (Figure 1). Subjects receiving MF-DPI QD AM also received a placebo inhalation in the evening to maintain blinding. Subjects also participated in the follow-up evaluations for 3 months after the 52-week treatment period. Study visits occurred at 1, 2, 4, 8, 12, 16, 26, 38, and 52 weeks. Follow-up visits occurred at 56, 60, and 64 weeks. At each study visit, investigators performed physical examinations, including recordings of height, weight, blood pressure, temperature, pulse, and respiratory rate, as well as oropharyngeal examination and ophthalmic examination (slit lamp examination and intraocular pressure measurements). Treatment non-adherence was judged by querying subjects and parents/guardians along with reviewing patient diaries and was defined as the use of <75% or >125% of protocol-specified doses.

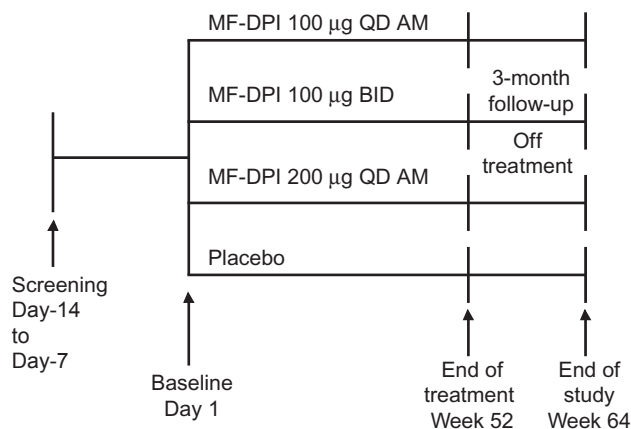


FIGURE 1.—Study design.

Note: BID, twice daily; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning.

An albuterol inhaler was provided at the screening visit. Subjects were instructed not to use albuterol or any other SABA regularly or in anticipation of asthma symptoms unless before exercise or exposure to an animal likely to cause an asthmatic response. Nebulized β_2 -agonists were permitted, and one nebulized treatment was equivalent to four inhalations of albuterol for the purposes of the study. As long as dosing remained constant, subjects requiring theophylline as part of their current therapeutic regimen were permitted to continue this therapy throughout the run-in and randomized phases of the study.

Subjects were discontinued from the study if they experienced a clinically significant worsening of asthma, defined as requiring oral, intravenous, or intramuscular corticosteroid treatment for more than 15 days; hospitalization for asthma on more than two occasions during the course of the study; ventilator support for asthma; or chronic treatment with an additional ICS. The use of any corticosteroids during the 3-month follow-up period was also a cause for discontinuation.

Key Inclusion Criteria

Children aged 4–9 years with a history of asthma ≥ 6 months were eligible. Subjects were required to exhibit a forced expiratory volume in 1 second (FEV₁) of at least 75% of predicted normal at both the screening visit and the baseline visit, when all restricted medications had been withheld. An increase in absolute FEV₁ of at least 12% after reversibility testing at the screening visit or historically within the past 12 months was demonstrated. Since children aged 4–5 years often have difficulty producing consistent spirometry results, slightly different requirements were allowed for this age group. Children 4–5 years old who could demonstrate $\geq 75\%$ predicted FEV₁ for any one measurement, or a morning average peak expiratory flow (PEF) of $\geq 75\%$ predicted normal at screening or baseline were eligible. In addition, if these subjects could not demonstrate reversibility, the subjects qualified for enrollment if the investigator determined that the patient met the National Heart, Lung and Blood Institute criteria for the diagnosis of asthma in this age group.

Additional inclusion criteria for all subjects included normal height (5th–95th percentile on standard growth charts) upon measurement with a stadiometer; at least one stadiometer measurement taken between 3 and 24 months before screening; skeletal age within 2 years of chronological age (as determined by left hand-wrist radiograph) (19); morning (8 am $\pm$ 1 h) plasma cortisol levels ≥ 5 μ g/dL; and no greater than stage 1 in the Tanner Classification of Sex Maturity, as measured by preadolescent penis and testes in boys, and preadolescent pubic hair and breasts in girls (20). Female subjects were premenarchal.

Key Exclusion Criteria

Any subject with the following was excluded from the study: increase or decrease in FEV₁ of $\geq 20\%$ between

screening and baseline visits; ≥ 12 puffs per day of albuterol on any 2 consecutive days between screening and baseline visits; inpatient hospitalization for asthma control within the previous 3 months; ventilator support for respiratory failure secondary to asthma within the previous 5 years; hospital admission for the management of airway obstruction on two or more occasions over the past 6 months; asthma requiring the daily use of nebulized SABA or any use of long-acting β_2 -agonists; asthma requiring the chronic use of inhaled or systemic corticosteroids; inability to use a DPI device or a peak flow meter; history or evidence of abnormal growth; presence of any disease or condition with the potential to substantially affect growth or that required concomitant corticosteroid therapy; evidence of gross malnutrition; or history of any disease that could have interfered with the study evaluations. Individuals experiencing an upper or lower respiratory tract infection within 2 weeks of screening and baseline visits were also excluded.

Washout times required for corticosteroids before screening were as follows: inhaled (3 months); nasal or ocular (2 weeks); oral, intravenous, or short-acting intramuscular (1 month, and not more than 15 days in the previous 6 months); intra-articular or intramuscular depot (3 months); and mid-strength, potent, or superpotent dermatological (1 month).

Study Evaluations

Safety. The primary endpoint analyzed in this study was growth velocity, determined from heights measured by a Harpenden Stadiometer, during the 52-week treatment period. Height measurements were taken in bare feet, and a mean of three values was recorded. When possible, the same study personnel performed the height measurements for a given subject throughout the study, at approximately the same time of day for each visit. Secondary endpoints included growth velocity during the 3-month follow-up period, HPA axis effects of MF-DPI, changes in bone markers, occurrences of clinical asthma exacerbations (CAEs), occurrences of adverse events (AEs), along with changes from baseline in vital signs, and physical examination.

The effect of MF-DPI on the HPA axis was evaluated by comparing differences from baseline in 8 am (± 1 h) plasma cortisol values and 12-h urinary cortisol concentrations. Urinary creatinine concentrations were used to normalize urinary cortisol concentrations. Changes from baseline in markers of bone formation and resorption (serum osteocalcin and N-telopeptide, respectively) were also evaluated. Blood samples and 12-h urinary collections were obtained for analysis at screening, week 26, and the final treatment visit (week 52). Twelve-hour urine samples were collected between 8 pm and 8 am beginning the evening before each of the three visits; one 13 mL aliquot from well-mixed samples over each 12-h collection period was used for laboratory testing. All laboratory tests were performed at

one central laboratory (Covance, Indianapolis, IN, USA) to ensure consistency in measurements.

Investigators recorded each occurrence of a CAE, which was defined as a deterioration of asthma that resulted in hospitalization, asthma symptoms requiring the addition of medication (other than SABA therapy), exacerbations requiring oral corticosteroid bursts, or exacerbations requiring a significant increase in medication dosages. All AEs were also recorded, whether or not the investigator suspected that events were related to the study medication.

Efficacy. This study was not designed to evaluate efficacy measures. The efficacy measurements collected were only used to demonstrate that long-term treatment with MF-DPI did not result in asthma deterioration. Spirometry was used to measure forced vital capacity, FEV₁, and forced expiratory flow (L/sec) between 25% and 75% of vital capacity (FEF_{25%–75%}) at each study visit. PEF was measured twice daily by subjects and recorded in daily dairies. In addition to spirometry, SABA use and CAE were used to monitor asthma worsening.

Statistical Analysis

A sample size of 44 subjects per group was anticipated to detect a mean treatment difference in growth velocity of 1.8 cm/y with at least 90% power, assuming a pooled standard deviation of 2.6 cm/y. Growth velocities were analyzed in two ways, using a longitudinal random slope (LRS) model and an individual regression (IR) model. Both data outputs are provided for completeness. The LRS was the prespecified method of analysis that factored in the unexpectedly large number of subjects who dropped out early in the treatment phase. The IR analysis was requested by the Food and Drug Administration (FDA) when it was considering the approval of MF-DPI in children. However, when the IR analysis was performed, the small number of available height measurements for the early dropouts resulted in poor estimates of growth rates, suggesting a more robust output from the LRS analysis.

As indicated above, disparate factors contribute to the data output generated from the LRS and IR analyses. For the LRS model, treatment, age, gender, and time were fixed effects and the subject was random. The covariance structure was unstructured. The IR approach to analysis required that per-subject estimates of velocity be determined first using IR of height over time using all available height data (21). The resulting growth velocities were then analyzed using an analysis of variance (ANOVA) extracting sources of variation due to treatment, age, and gender. Treatment comparisons for both methods were based on least squares means from the analysis model. A post hoc analysis of historical height data was used to calculate pre-study growth velocities for each group using the LRS model. Continuous secondary variables were analyzed using two-way ANOVA with treatment and center effects, and a Fisher's exact test was used to evaluate a binary response to therapy.

Kaplan–Meier estimates were calculated to determine the time to first asthma worsening.

RESULTS

Patient Population and Baseline Characteristics

A total of 187 subjects were randomized and received at least one dose of study medication. Of these, 135 completed the treatment period, 122 continued into the 3-month follow-up period, and a total of 108 subjects (89%) completed the follow-up period (Figure 2). Many of the dropouts occurred early in the treatment period with only one or two height measurements collected. However, 70% of subjects received treatment for at least 50 weeks. Baseline demographics were similar between treatment groups, except that there were almost twice as many boys in the study as girls and the placebo group was slightly taller (Table 1). Treatment adherence was generally satisfactory; the percentage of subjects with $\geq 90\%$ adherence for the MF-DPI 100 μg QD AM, MF-DPI 100 μg BID, MF-DPI 200 μg QD AM, and placebo groups were 83%, 75%, 78%, and 89%, respectively. Only 11 subjects (5.8%) were considered non-adherent, 9 due to reporting $<75\%$ of scheduled doses and 2 because of missing data.

Effects on Growth Velocity and Stadiometer Height During Treatment

Pre-study growth velocities were calculated for each group in addition to comparison of mean heights at baseline to ensure that no differences in growth velocity were present across groups prior to randomization. The pre-study and treatment period mean growth velocities calculated using the LRS model are presented in Table 2. There was no statistically significant difference in growth velocity for the MF-DPI 100 μg QD AM group compared with placebo (Figure 3). Growth velocity differences were similar by the LRS model but not by the IR model when the total daily dose equaled 200 μg of MF-DPI. There was no significant difference in growth velocity when comparing MF-DPI 100 μg BID with placebo, whereas the MF-DPI 200 μg QD AM group exhibited a significantly lower growth velocity compared with placebo and the MF-DPI 100 μg QD AM group (Figure 3). When growth velocities were calculated using the LRS model, least squares mean growth velocities for MF-DPI 100 μg QD AM, MF-DPI 100 μg BID, MF-DPI 200 μg QD AM, and placebo were 6.42, 5.88, 5.82, and 6.52 cm/y, respectively. When growth velocities were calculated using the IR model, least squares mean growth velocities for MF-DPI 100 μg QD AM, MF-DPI 100 μg BID, MF-DPI 200 μg QD AM, and placebo were 6.15, 5.34, 5.93, and 6.44 cm/y, respectively (Table 2). Using this method, none of the differences among the MF-DPI groups and placebo were statistically significant (Figure 3).

On average, all groups increased in stadiometer height from baseline to endpoint. The average height for the MF-DPI 100 μg BID group was numerically lower than

all the other groups at every timepoint, including baseline (Figure 4). However, all the subjects were within normal height limits at the end of treatment based on standard growth charts (Table 3). No subjects in any group were measured in the extreme ends of the height spectrum for their age ($<3\text{rd}$ percentile or $>97\text{th}$ percentile, Table 3).

Effect on Growth Velocity During 3-Month Follow-Up

During the 3-month off-treatment follow-up, there were no statistically significant differences in growth velocity between the MF-DPI 100 μg QD AM and placebo groups. Again, the growth velocity effects were more variable with a total daily dose of 200 μg MF-DPI. There were no significant differences between the MF-DPI 100 μg BID and placebo groups; statistically significant differences in growth velocity in the MF-DPI 200 μg QD AM treatment group (twice the approved total delivered pediatric dosage) were shown when compared with placebo (Table 2). Overall treatment effect on growth velocity was borderline significant for MF-DPI-treated subjects ($p = 0.09$) compared with placebo.

Effect on HPA Axis

Baseline 8 am (± 1 h) plasma cortisol levels were similar across all treatment groups. At the end of the study, mean plasma cortisol values increased from baseline and were within normal ranges. The mean percentage changes from baseline were 13.2% in the MF-DPI 100 μg QD AM group, 13.5% in the 100 μg BID group, 6.4% in the 200 μg QD AM group, and 10.4% in the placebo group (Figure 5). A total of nine subjects (three in the 100 μg QD AM group, two in the 100 μg BID group, three in the 200 μg QD AM group, and one in the placebo group) demonstrated plasma cortisol levels below 5 $\mu\text{g}/\text{dL}$ (the normal lower limit) (22) after 1 year of treatment. There were no clinically meaningful differences in change from baseline between the groups.

At the end of the study, mean 12-h urinary cortisol levels adjusted to creatinine concentrations (urinary cortisol corrected for creatinine concentration (UCCR); $n = 158$) were decreased from baseline by 30.8% in the MF-DPI 100 μg QD AM group, 30.0% in the 200 μg QD AM group, and 36.3% in the placebo group. In contrast, by the end of the study the mean UCCR for the 100 μg BID group increased 2.3% from baseline (Figure 5). No clinically meaningful between-group differences in mean 12-h UCCR changes from baseline were observed.

Effect on Markers of Bone Formation and Resorption

Compared with baseline, mean serum osteocalcin values increased by 4.9% in the MF-DPI 100 μg QD AM group, 7.3% in the 100 μg BID group, 0.9% in the 200 μg QD AM group, and 7.3% in the placebo group (Figure 5). There were no statistically significant between-group differences in changes in serum osteocalcin from baseline.

Mean urinary N-telopeptide values were higher in the MF-DPI 100 μg BID group at baseline, with a mean level of 521 bone collagen equivalents (BCE)/L, whereas the means of the other groups ranged from 425 to 457 BCE/L.

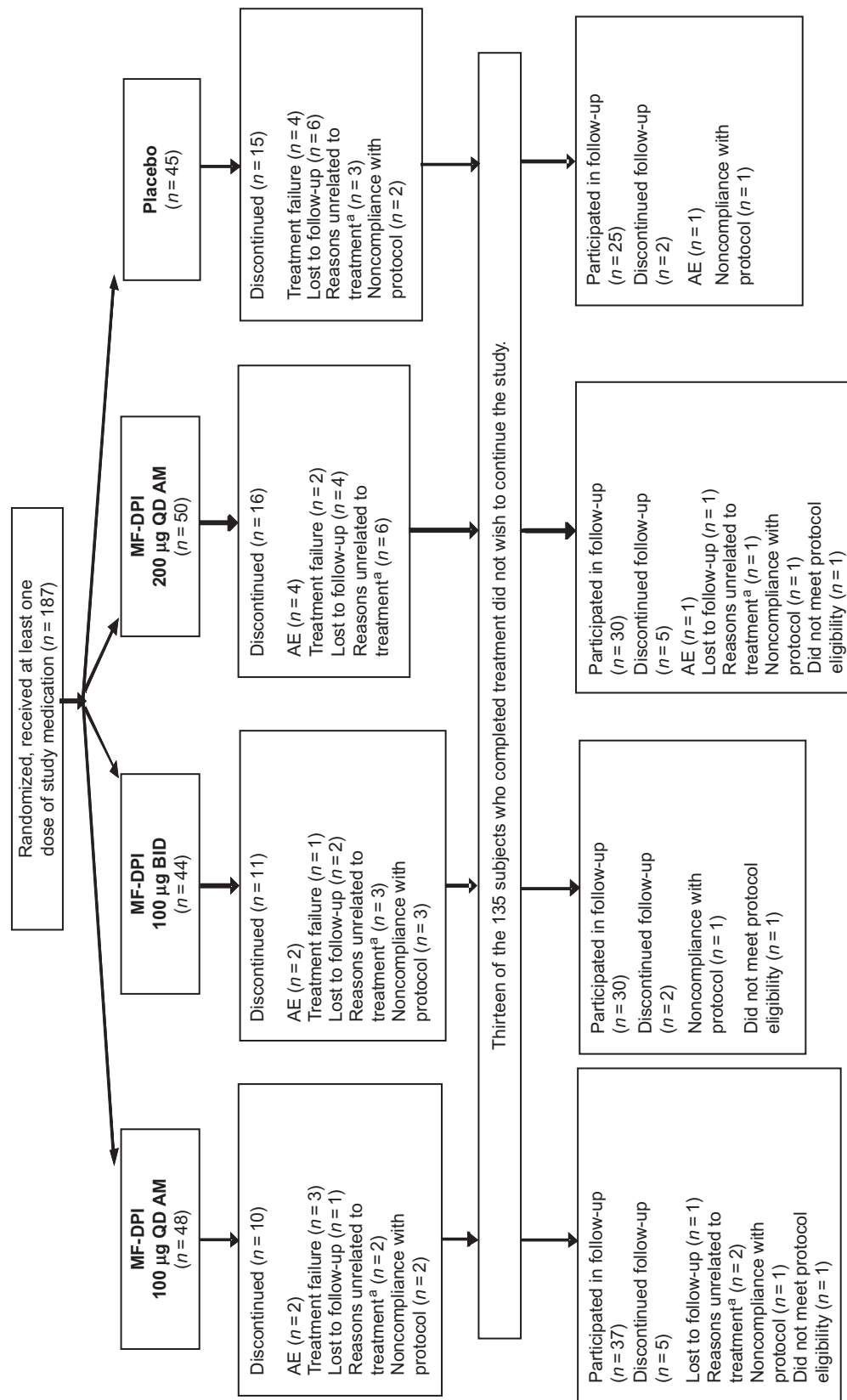


FIGURE 2.—Subject disposition.
Notes: AE, adverse event; MF-DPI, mometasone furoate delivered via a dry powder inhaler.
^aReasons unrelated to treatment included moving from vicinity of study site and withdrawal of consent.

TABLE 1.—Baseline subject demographics and clinical characteristics.

	MF-DPI 100 µg QD AM (n = 48)	MF-DPI 100 µg BID (n = 44)	MF-DPI 200 µg QD AM (n = 50)	Placebo (n = 45)
Age, mean (years)	6.4	6.3	6.6	6.6
4–5	14	15	13	11
6–9	34	29	37	34
Sex				
Girls	14	16	17	9
Boys	34	28	33	36
Race				
White	40	33	37	40
Other	8	11	13	5
Weight, mean (kg)	25.3	25.4	26.5	27.6
Min.–max.	12–43	15–43	17–49	15–67
Height, mean (cm)	120.6	120.3	122.1	123.3
Min.–max.	95.6–143.4	99.6–139.3	102.7–138.5	96.1–141.9
Asthma duration, mean (years)	3.8	4.0	3.6	4.5
Min.–max.	0.67–8.0	0.83–9.0	0.42–8.0	0.5–8.0
Theophylline used	0	1	0	0
Baseline percent predicted FEV ₁ , mean	87.2	89.3	89.5	85.4
Min.–max.	61.0–115.3	74.9–111.3	47.5–112.1	61.4–115.3

Note: BID, twice daily; FEV₁, forced expiratory volume in 1 second; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning.

TABLE 2.—Growth velocities before, during, and after the treatment period.

Growth velocity	MF-DPI 100 µg QD AM	MF-DPI 100 µg BID	MF-DPI 200 µg QD AM	Placebo
Pretreatment period, <i>n</i>	48	41	49	45
Mean growth velocity (cm/y)	5.59	6.14	6.21	5.85
LRS model				
Treatment period, <i>n</i>	48	42	49	45
Mean growth velocity (cm/y)	6.42	5.88	5.82	6.52
Δ from placebo (±SE)	−0.10 (0.31)	−0.64 (0.39)	−0.70 (0.29)	
<i>P</i> -value	0.76	0.10	0.02	
IR model				
Treatment period, <i>n</i>	48	44	50	45
Mean growth velocity (cm/y)	6.15	5.34	5.93	6.44
Δ from placebo (95% CI)	−0.30 (−1.48, 0.89)	−1.11 (−2.34, 0.12)	−0.51 (−1.69, 0.67)	
<i>P</i> -value	0.62	0.08	0.40	
Post-treatment period				
Mean growth velocity (cm/y)	7.66	5.96	4.50	6.91
Δ from placebo (±SE)	0.75 (1.76)	−0.95 (1.51)	−2.42 (1.18)	
<i>P</i> -value	0.67	0.53	0.05	

Note: BID, twice daily; CI, confidence interval; Δ, difference; IR, individual regression; LRS, longitudinal random slope; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning; SE, standard error.

At the end of the study, urinary N-telopeptide increased 11.9% in the MF-DPI 100 µg QD AM group, 41.6% in the 200 µg QD AM group, and 77.0% in the placebo group, while decreasing 63.5% in the 100 µg BID group (Figure 5). The change from baseline was significantly different for the 100 µg BID group compared with the 200 µg QD AM and placebo groups ($p = 0.05$ and $p = 0.01$, respectively).

Monitoring of Long-Term Lung Function

Monitoring of spirometry tests, CAE, and SABA use confirmed that MF-DPI did not result in asthma worsening. The median time to first asthma worsening

was 120 days for the placebo group compared with ≥ 274 days in the MF-DPI groups (Figure 6; $p = 0.03$). The median time to worsening for the MF-DPI 100 µg BID group could not be calculated because less than 50% of subjects in this group experienced worsening. As indicated previously, this study was not powered to evaluate efficacy parameters.

Adverse Events

Most AEs reported during the study were considered unrelated to treatment and are common ailments in the age group studied. AEs reported in $\geq 15\%$ of subjects by treatment group are shown in Table 4. Headache

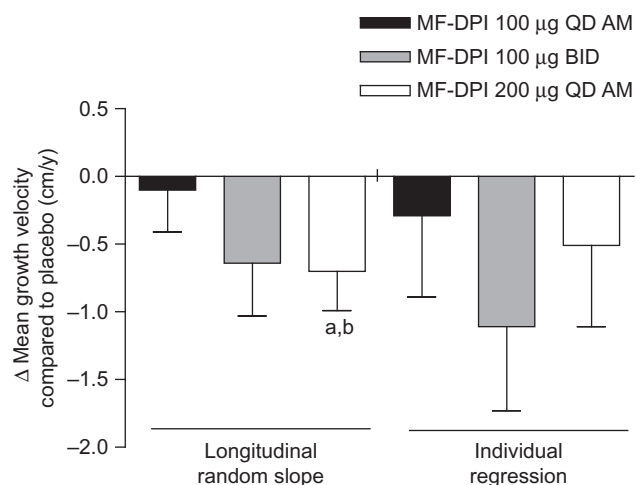


FIGURE 3.—Mean growth velocity changes compared with placebo during 1-year treatment. Error bars represent the standard error.

Notes: BID, twice daily; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning. ^aMean $p = 0.02$ compared with placebo mean. ^bMean $p = 0.04$ compared with 100 μg QD AM mean.

was the most commonly reported adverse effect. Serious AEs were reported in five subjects, although none of these were categorized as treatment related. The serious AEs included asthma aggravated (four subjects), syncope (one patient), and pneumonia (one patient, who also had asthma aggravated). There were no reported life-threatening AEs or deaths during the treatment or follow-up periods of the study. There were four reports of oral candidiasis during the study (MF-DPI 100 μg BID, $n = 3$; MF-DPI 100 μg QD AM, $n = 1$), two of which were considered treatment related (both in the MF-DPI 100 μg BID group). Ophthalmologic examinations and vital signs revealed no treatment effects.

DISCUSSION

ICSs are considered to be the most effective controller therapy option recommended for the treatment of mild to

TABLE 3.—Distribution of subjects' endpoint height by percentile after 1 year of treatment.^a

Treatment	Number (%) of subjects				
	<3%	$\geq 3\%$ to <25%	$\geq 25\%$ to $\leq 75\%$	$> 75\%$ to $\leq 97\%$	$> 97\%$
MF-DPI 100 μg QD AM	0 (0)	6 (16)	21 (55)	11 (29)	0 (0)
MF-DPI 100 μg BID	0 (0)	8 (24)	17 (52)	8 (24)	0 (0)
MF-DPI 200 μg QD AM	0 (0)	6 (18)	21 (62)	7 (21)	0 (0)
Placebo	0 (0)	6 (20)	10 (33)	14 (47)	0 (0)

Note: BID, twice daily; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning.

^a(National Center for Health Statistics percentiles in normal, healthy kids).

moderate persistent asthma in children ≤ 12 years of age (3, 4). The clinical efficacy of MF-DPI has been studied in children and adults with mild, moderate, and severe asthma (14–17, 23–31). Given the possible adverse effects of ICS agents on growth velocity and adult height (32), it is important to evaluate each ICS at its therapeutic dose plus at higher doses to understand their effects on children. Long-term safety of ICSs is critical in light of the renewed emphasis on ICS as first-line treatment and as a step-down treatment from combination ICS/long-acting β_2 -agonists. The growth velocity effects observed with MF-DPI 100 μg QD AM in these studies were small and not statistically significant. However, 200 μg of total daily doses of MF-DPI demonstrated numerical decreases in growth velocity that were significant in the 200 μg QD AM treatment arm. Previous studies have shown that total daily doses of 100 and 200 μg MF-DPI have similar effects on efficacy (16, 17). The time to asthma worsening reported in this study provides evidence for the first time that patients in the same study population can experience a clinical benefit from an ICS dose (100 $\mu\text{g}/\text{day}$) that has no effect on growth compared with placebo. This is the goal of asthma treatment, to provide clinical benefit with optimal safety.

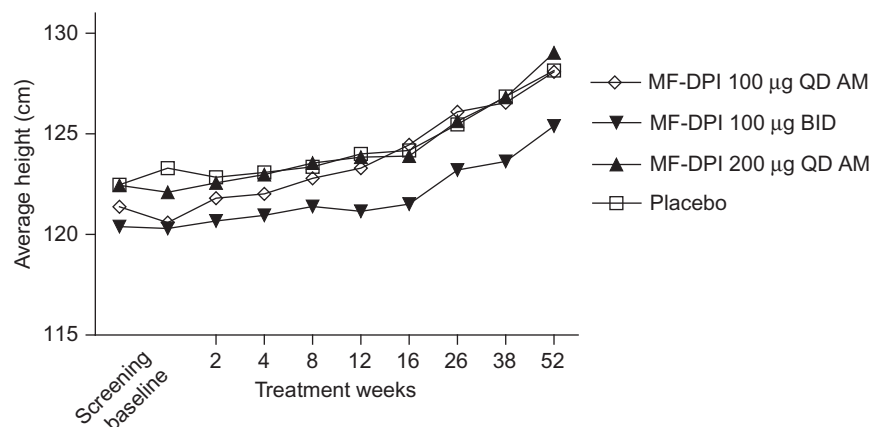


FIGURE 4.—Average height for each treatment group over time.

Note: BID, twice daily; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning.

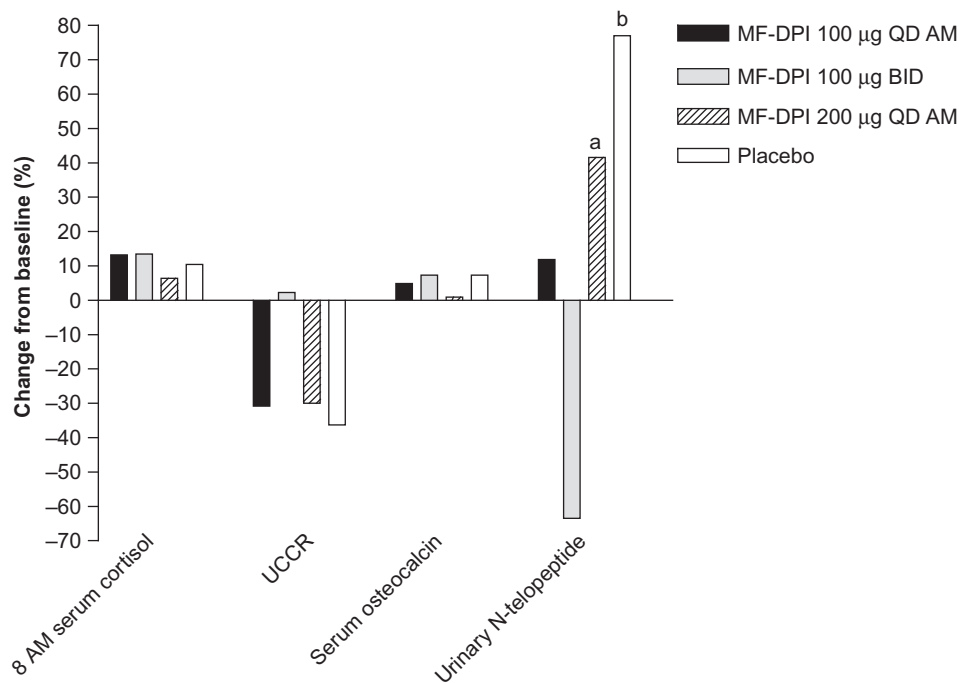


FIGURE 5.—Percent change from baseline in markers of hypothalamic–pituitary–adrenal (HPA) axis and bone formation/resorption.

Notes: BID, twice daily; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning; UCCR, urinary cortisol corrected for creatinine concentration.

^a $p = 0.05$. ^b $p = 0.01$ compared with 100 µg BID.

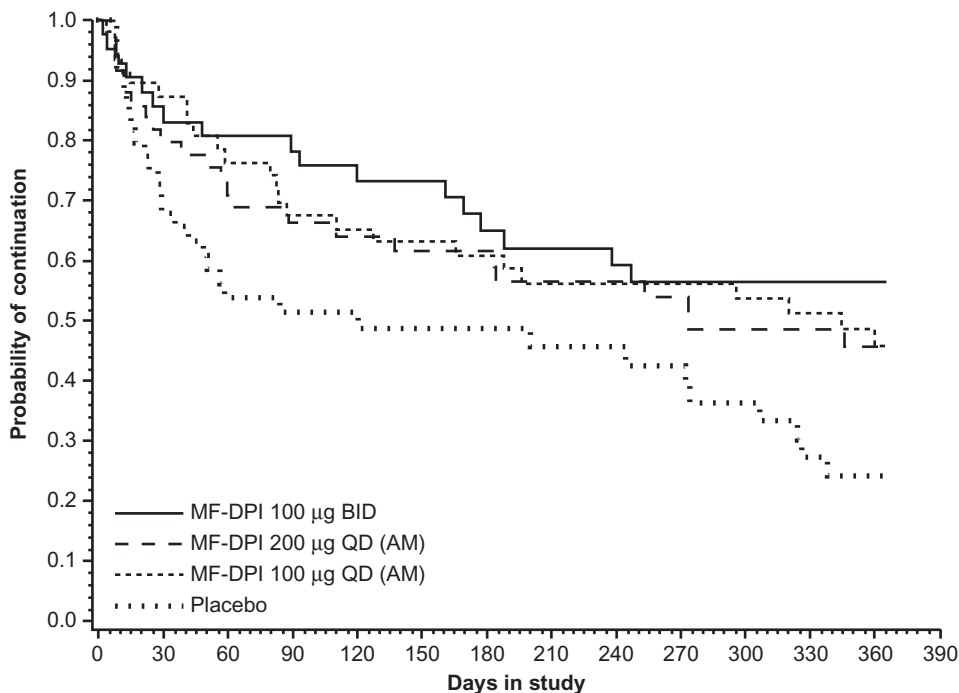


FIGURE 6.—Time to asthma worsening.

Note: BID, twice daily; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning.

The lack of additional efficacy advantages with 200 µg daily MF-DPI (over the 100 µg dose) and the possible effect on long-term growth velocity at the threshold of detection support the selection of the 100 µg daily dose of MF-DPI. A large trial in children aged 4–11 years found no significant effects on growth velocity when MF was

delivered via a metered dose inhaler (MDI) in QD PM or BID dosing regimens of 100 µg, thus confirming the results of this study and providing additional evidence for the systemic safety of MF administered once daily (33).

The effect of an ICS on growth velocity most likely depends on systemic bioavailability, which in turn is

TABLE 4.—Adverse events (AEs) reported in $\geq 15\%$ of subjects by treatment group.

Adverse events, <i>n</i> (%)	MF-DPI 100 μ g QD AM (<i>n</i> = 48)	MF-DPI 100 μ g BID (<i>n</i> = 44)	MF-DPI 200 μ g QD AM (<i>n</i> = 50)	Placebo (<i>n</i> = 45)
Upper respiratory tract infection	19 (40)	26 (45)	26 (52)	25 (56)
Headache	16 (33)	17 (39)	12 (24)	14 (31)
Viral infection	20 (42)	16 (36)	19 (38)	11 (24)
Fever	14 (29)	16 (36)	15 (30)	10 (22)
Pharyngitis	15 (31)	12 (27)	15 (30)	14 (31)
Rhinitis	12 (25)	10 (23)	8 (16)	8 (16)
Otitis media	16 (33)	9 (20)	8 (16)	6 (13)
Aggravated rhinitis	5 (10)	5 (11)	7 (14)	8 (18)
Bronchitis	6 (13)	8 (18)	4 (8)	5 (11)
Cough	8 (17)	8 (18)	11 (22)	4 (9)
Nasal congestion	5 (10)	8 (18)	12 (24)	11 (24)
Allergy	5 (10)	6 (14)	5 (10)	10 (22)
Aggravated allergy	9 (19)	9 (20)	9 (18)	4 (9)
Sinusitis	7 (15)	7 (16)	7 (14)	9 (20)
Dyspepsia	5 (10)	7 (16)	7 (14)	9 (20)

Note: BID, twice daily; MF-DPI, mometasone furoate delivered via a dry powder inhaler; QD AM, once daily in the morning.

dependent on many factors, including ICS formulation, delivery device, potency, and dose (34). For example, budesonide delivered via the Turbuhaler DPI has a reported mean systemic bioavailability of 38% at a daily dose of 1000 μ g (35). Growth velocity of budesonide via Turbuhaler (200 μ g BID) was investigated in a long-term (4 years) study by the Childhood Asthma Management Program. Children aged 5–12 years with mild-to-moderate asthma were randomized to either budesonide, nedocromil, or placebo. Those children treated with budesonide showed a 1.1 cm decrease in growth velocity when compared with children who received placebo ($p = 0.005$). This decline in growth velocity was mostly limited to the first year of treatment (36). Although the growth velocities among groups were similar at the end of the 4-year trial (36), 4.8 years after the treatment was discontinued, children who had received budesonide were still 0.9 cm shorter than children who received placebo ($p = 0.01$) (13). For beclomethasone dipropionate delivered via an MDI at a daily dose of 1000 μ g, the active metabolite beclomethasone 17-monopropionate has a reported mean systemic bioavailability of 62% (37). In a 44-week study of beclomethasone dipropionate hydrofluoroalkane 40 μ g BID, growth was 1.1 cm less ($p < 0.0001$) compared with placebo (38). In contrast, fluticasone delivered via the Diskhaler DPI at a daily dose of 1000 μ g has a systemic bioavailability of 16% (39). Accordingly, a 1-year study of fluticasone delivered via the Diskhaler DPI (50 and 100 μ g BID) in children aged 4–11 years with asthma found no significant difference in growth velocity between fluticasone and placebo groups (40). Differences in growth velocity from placebo were -0.2 and -0.4 cm/y in the 50 and 100 μ g BID doses, respectively. MF-DPI has a systemic bioavailability of $<1\%$ (41), and the differences in growth velocity were -0.10 cm/y for the 100 μ g daily dose and -0.64 to -0.70 cm/y for the 200 μ g daily dose, respectively.

The growth velocities in this study were calculated by two different statistical methods, a LRS model and an IR model. The latter was used by the FDA during consideration of MF-DPI for approval in children, and the numbers derived from the IR model are included in the FDA-approved prescribing information. However, in this trial, the LRS model is likely to provide a more robust assessment because of a large number of dropouts early in the treatment phase. Growth velocities for early dropouts were based on only a few height measurements, leading to poor estimates of average growth rates when the IR model was used. The longitudinal model borrows information from completed subjects in the same treatment group to impute missing data for dropouts. The resulting mean estimates for each treatment group are less variable and appear inherently discriminating. However, it should be noted that only 14 of the 37 discontinuations from the MF-DPI groups were due to AEs or treatment failure and the number of discontinuations was similar for MF-DPI-treated subjects and placebo.

At the end of the treatment period, there were no subjects outside the range of normal height percentiles ($<3\%$ or $>97\%$); however, 47% of placebo-treated subjects were in the $>75\%$ to $\leq 97\%$ percentiles after 1 year of treatment, indicating the placebo patients were taller than normal population averages, although this study could not differentiate whether or not the trend was random. In contrast, 21–29% of MF-DPI-treated subjects were in the $>75\%$ to $\leq 97\%$ percentiles and 52–62% were in the $\geq 25\%$ to $\leq 75\%$ percentiles. These data provide reassurance that MF-DPI-treated subjects were well within normal height ranges at the end of treatment.

An analysis of data from the 3-month, post-treatment follow-up period also revealed no significant differences in growth velocity in the 100 μ g QD group. There was no significant difference in growth velocity for the 100 μ g BID group compared with placebo, whereas a trend of decreased growth velocity was observed in the 200

μg QD AM treatment group compared with placebo. It is interesting to note the seemingly random differences in the 100 μg BID and 200 μg QD AM treatment groups during the post-treatment period, even though the overall daily dosages were both 200 μg . It is unknown if these results are evidence of a residual treatment effect, or if the group receiving 200 μg QD AM was simply a slow-growing group. No significant overall treatment effect in terms of growth velocity was observed during the follow-up period.

Based on plasma/urinary cortisol levels measured during and after therapy, MF-DPI did not appear to have a significant effect on HPA axis function at the doses studied, and it was also not associated with any significant effect on other markers of growth or bone metabolism, although these latter assessments were highly variable. Studies in adults ≥ 18 years of age receiving MF-DPI indicate that at the 1600 $\mu\text{g}/\text{d}$ dosage (twice the highest approved dose of 800 $\mu\text{g}/\text{d}$), suppressive effects on the HPA axis may exist (42, 43). It is noteworthy that although no statistically significant effect on the HPA axis was observed after MF-DPI treatment, there was a significant effect on growth velocity with 200 μg QD AM, twice the recommended delivered dosage in children. This observation confirms the opinion recently published by the FDA that growth assessments are a more sensitive marker of systemic corticosteroid effects than HPA axis measurements (44). The small suppression of growth velocity observed for the 200 μg QD AM dosage provides assurance that the study was suitably robust to ensure that the once-daily 100 μg dose indeed has a minimal effect.

In general, MF-DPI did not have an effect on markers of bone formation and resorption, except for a difference between the mean N-telopeptide values in the MF-DPI 100 μg BID group and both the MF-DPI 200 μg QD AM and placebo groups. An increase in mean N-telopeptide levels in the placebo group was unexpected and suggested that a higher degree of bone resorption occurred in this group. Based on the differences in mean N-telopeptide values at baseline, these changes over the course of the study may reflect a normalization in values between treatment groups rather than a treatment effect. Because these data were not normally distributed, results were confirmed by a nonparametric analysis.

Adherence rates were generally satisfactory and similar between treatment groups and were therefore unlikely to contribute to the observed outcomes. It is also important to note that uniform dosing of MF-DPI is achieved by inspiratory flow rates as low as 28 L/min (45), and an evaluation of inhaler technique in children aged 5–12 years found that the lowest recorded inspiratory flow rate was 46 L/min (46). Therefore, young children can generate adequate flow rates to ensure proper MF-DPI dosage administration.

Important study limitations should be considered in the interpretation of these findings. The normal or near-normal lung function in this population of children with mild asthma may have increased intrapulmonary deposition, thereby absorbing more drug and enhancing

the effects of the higher 200 μg MF-DPI doses on growth velocity (7). Furthermore, this study was performed prior to the 2007 recommendations by the FDA for the design of growth studies with the administration of ICS therapy (44). These recommendations are reflected in a growth velocity study of ciclesonide that included a 6-month pretreatment baseline growth velocity estimate and a sample size powered to detect a non-inferiority δ of 0.5 cm/y (47). This study was designed to detect a mean treatment difference of 1.8 cm/y. A post hoc analysis of historical data was performed to evaluate pre-study growth velocity data. Since these values were generated from historical data, it should be noted that height data may not have been collected at the same level of rigor as the on-study heights. In addition, although the follow-up period of 3 months fits within the recommended 8-week follow-up period, 3 months may still be too short to infer definite conclusions, since variations in height over this relatively short period may adversely affect the estimation of growth velocity (48).

CONCLUSIONS

In conclusion, the study found that 1 year of treatment with a total daily dose of MF-DPI 100 μg administered QD AM resulted in no significant difference in growth velocity compared with placebo. Daily doses of 200 μg of MF-DPI (twice the total approved delivered pediatric dosage) were associated with numerical decreases in growth velocity that reached statistical significance with the 200 μg QD AM dose. Although previous studies of total daily doses of 100 and 200 μg MF-DPI showed similar trends in terms of clinical efficacy and systemic safety in children aged 4–9 years with mild persistent asthma, the current findings denote a difference in their long-term growth velocity effects, thus supporting the recommended use of a total daily dose of 100 μg MF-DPI. The lack of significant growth or systemic effects in children receiving MF-DPI at its approved total delivered dose (i.e., 100 μg) for mild persistent asthma may also encourage greater adherence to therapy by alleviating safety concerns.

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The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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