Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler®


Comparison of the Efficacy and Safety of Mometasone Furoate Dry Powder Inhaler to Budesonide (BUD) Turbuhaler® in the treatment of moderate persistent asthma.

The patients were randomized to one of four treatment groups: MF DPI (100, 200, 400 μg b.i.d) or BUD Turbuhaler®. 400 μg b.i.d in a 12-week, active-controlled, evaluator-blind, multicentre international trial. The primary efficacy variable was the mean change from baseline to endpoint (last treatment visit) in forced expiratory volume in one second (FEV1).

Changes in FEV1 showed a statistically significant superiority (p<0.05) of MF DPI 200 and 400 μg b.i.d compared with the BUD Turbuhaler® 400 μg b.i.d treatment. Significant superiority (p<0.05) was also seen in scores for several secondary efficacy variables when MF DPI was compared with BUD Turbuhaler® treatment. MF DPI 200 μg b.i.d was comparable to MF DPI 400 μg b.i.d in therapeutic benefit. The incidence of oral candidiasis was no more than 3% in any group. All treatments were well tolerated.

A total daily dose of 400 μg of mometasone furoate administered by dry powder inhaler provides a well-tolerated treatment for patients with moderate persistent asthma and results in a significantly greater improvement, when compared to a daily dose of 800 μg BUD Turbuhaler® in the parameters measured in this study.

with moderate persistent asthma. This randomized, evaluator-blind, active-controlled study compared the efficacy and safety of MF DPI in doses of 100, 200, and 400 μg b.i.d to a single dose of BUD (400 μg by Turbuhaler®) in patients who were previously maintained on daily inhaled corticosteroids for treatment of their moderate persistent asthma. These doses of MF were chosen based on the results from a previous study [12] that indicated efficacy and safety of MF across this dose range in a population of adult and adolescent patients with moderate persistent asthma. The 400 μg b.i.d dose of BUD Turbuhaler® was chosen for comparison since it is a dose commonly used worldwide to treat patients with moderate persistent asthma.

**Methods**

**Patients**

Adults or adolescents (≥12 yrs of age) of either sex, who had a history of asthma for at least six months and who had been using an inhaled glucocorticoid daily for at least 30 days, were eligible to participate in the study. Prior to screening and through to baseline, patients must have been maintained on a stable regimen of inhaled corticosteroid, including flunisolide, triamcinolone acetonide, beclometasone dipropionate, BUD or fluticasone propionate. Patients had to demonstrate a baseline forced expiratory volume in one second (FEV1) 60%-90% of predicted normal value after all restricted medications had been withheld for specified intervals. In addition, they had to demonstrate reversibility of airway disease by an increase in FEV1 of ≥12.0% over the pre-bronchodilator value, with an absolute volume increase of at least 200 mL, within 30 min after two inhalations of salbutamol (Ventolin®). All patients were nonsmokers or had stopped smoking more than six months prior to screening. Clinical laboratory values, 12-lead electrocardiograms (ECGs) and vital signs were all to be clinically acceptable. All patients were free of any clinically significant disease other than asthma.

Patients were excluded for any of the following reasons: premenarche, pregnancy, lactation, requiring allergen-specific immunotherapy, unless on a stable maintenance schedule, treatment with oral corticosteroids for >14 days in the six months prior to screening, treatment with methotrexate, cyclosporine or gold within three months, or systemic steroids or another investigational drug in the month prior to screening, daily use of more than 1 mg of beclometasone dipropionate (MDI) or inhaled powder, depending on the preference of the study site, use of any long-acting β2-adrenergic agonist less than 2 weeks prior to screening, the need for ventilator support in the past five yrs, hospitalization for asthma in the last three months, use of >12 puffs/day³ of salbutamol on any two consecutive days between screening and baseline visits, treatment for asthma in an emergency room or admission to a hospital for management of airway obstruction, on two or more occasions in the past six months, clinical evidence of significant pulmonary disease other than asthma, a history of glaucoma and/or posterior subcapsular cataracts, increase or decrease in FEV1 of ≥20% between screening and baseline visits, any clinically relevant abnormal baseline vital sign, any clinically significant abnormal ECG or chest radiograph at screening or within the previous month, any respiratory tract infection during the two weeks prior to screening, evidence of clinically significant oropharyngeal candidiasis. An acceptable method of birth control was required for all women of childbearing potential.

**Study design**

This randomized, evaluator-blind, active-controlled study compared the efficacy and safety of MF DPI (100, 200, and 400 μg b.i.d) and BUD powder administered as Pulmicort® Turbuhaler® (400 μg b.i.d). The study was double-blind with respect to MF treatment groups, as to whether a patient received MF DPI or BUD Turbuhaler®. In all cases, either a separate pharmacy or drug distribution centre or an individual not otherwise associated with the conduct of the study was identified for the patient and was used to distribute study medication to the patient. Patients were specifically instructed not to discuss any aspect of their study medication with anyone else associated with the study; all questions regarding use or malfunction of study medications were restricted to those individuals dispensing medications, because of the evaluator-blind nature of the study.

The study was conducted at 57 study centres in 17 countries. Randomization was generated in a 1:1:1:1:1:1 ratio with a block size of 4. A random code was generated for each country, and patients were assigned sequentially as they entered each study centre within the country. The study did not contain a placebo treatment group since placebo treatment of patients with moderate persistent asthma is considered unethical in most of the countries in which this study was conducted. An Ethics Committee reviewed the protocol for each centre and each patient, and a parent or guardian for patients <18 yrs of age also provided written informed consent.

Medications prohibited after the screening visit included those linked with clinically significant hepatotoxicity or induction of liver enzymes, beta blockers, nasal, oral, and inhaled corticosteroids (except for inhaled glucocorticoid therapy during the run-in period), dermatologic corticoids other than mild category, oral decongestants, oral or inhaled bronchodilators (other than salbutamol), nedocromil or cromolyn sodium, astemizole and leukotriene modifiers. The last doses of oral beta-adrenergic bronchodilators were withheld for 24 h (syrups and tablets) or 48 h (sustained-release tablets), and long-acting beta-adrenergic bronchodilators (e.g. salmeterol) were withheld for 2 weeks prior to pulmonary function tests at screening and prohibited thereafter. Short-acting inhaled or nebulized β2-adrenergic agonists were withheld six h before any study visit. Overuse of rescue medication
could result in discontinuation from the study. Theophylline was permitted throughout the study if a stable dose was an established part of the patient’s therapeutic regime prior to the screening visit.

During the run-in period, patients received treatment with their normally prescribed inhaled corticosteroid. At the baseline visit, patients eligible for participation in the study discontinued use of their previous inhaled corticosteroid and were randomly assigned to one of the following treatments: MF DPI 100, 200, or 400 μg b.i.d.; or BUD Turbuhaler® 400 μg b.i.d. All treatments were taken twice a day, in the morning and again in the evening, approximately 12 h apart. Patients were instructed to rinse their mouths with water or mouthwash following drug administration.

All patients completed daily diary cards to document morning (a.m.) and evening (p.m.) peak expiratory flow rate (PEFR), recording the highest of triplicate efforts for each. They also recorded salbutamol use, asthma symptoms, number of night-time awakenings requiring salbutamol use, adverse events, and use of study drug and concomitant medications. Daily scores or values were averaged over weekly intervals. Treatment visits occurred after 1, 2, 4, 8, and 12 weeks of treatment. At all treatment visits, pulmonary function, including FEV1 and forced vital capacity (FVC), was measured by spirometry; and investigators performed an oropharyngeal exam for the presence of candidiasis, reviewed diary cards, and assessed response to therapy. Treatment compliance was evaluated at each visit by someone other than the blinded evaluator by direct inquiry of the patient and review of the diary data. Use of <75% or >125% of the protocol-specified doses constituted a protocol deviation. Ten patients (5 in the MF DPI 100 μg b.i.d, 2 in the 200 μg b.i.d, 2 in the 400 μg b.i.d and 1 in the BUD 400 mg b.i.d groups) were excluded from the efficacy evaluation subset for poor compliance (all took <75% of specified doses). Compliance in the use of rescue medication was also evaluated at each visit by someone other than the blinded evaluator. This included an objective assessment of doses used, as well as a review of the patient’s diary data reports.

Efficacy assessments

The primary efficacy variable was the change from baseline to endpoint (the last evaluated treatment visit) in FEV1. Secondary efficacy variables included changes from baseline in the FVC, PEFR, symptom scores, nocturnal awakenings requiring salbutamol use as rescue medication, daily salbutamol use, and physician evaluation of response to therapy. Asthma symptom severity was rated on a 4-point scale (0 = none; 1 = noticeable; 2 = annoying, some interference with daily activities; 3 = very uncomfortable, interference with daily activities). Physicians rated response to therapy comparing current symptom level to level at baseline on a 5-point scale (1 = much improved; 2 = improved; 3 = no change; 4 = worse; 5 = much worse).

Safety assessments

All patients were monitored for adverse events as well as for changes in vital signs and haematologic, urinalysis and blood chemistry profiles during the 12-week treatment period. Plasma samples obtained at 08:00 h ±1 h were analyzed for cortisol levels by radioimmunoassay at screening and week 12. Clinically significant asthma worsening required discontinuation from the study. This included a ≥20% decrease in FEV1 from the baseline value or an asthma exacerbation that resulted in emergency treatment, hospitalization, or treatment with asthma medication in addition to those allowed on study. A clinically significant increase in bronchodilator use was defined as more than 1.6 mg use on 2 consecutive days, or the lower total daily dose restricted by local labelling. A decrease of ≥25% in a.m. or p.m. PEF from baseline a.m. value on two consecutive days, or a clinically significant increase in bronchodilator use, were also considered to be an indicator of significant asthma worsening and led to discontinuation from the study. Investigators graded adverse events with regard to severity and investigators and patients assessed the relationship of any adverse event to the use of a study drug.

Statistical analysis

The study was designed to enroll at least 600 patients, or 150 patients per treatment group. This sample size was chosen to allow detection of a clinically meaningful difference in FEV1 of approximately 6% of the baseline value between any two treatment groups, with 80% power and 5% significance level, assuming a pooled standard deviation (SD) of 0.45 units for FEV1 change from baseline, based on earlier studies. The analyses of efficacy and safety were based on all the randomized patients who received at least one dose of study medication and who had post-baseline data (Intent-to-Treat principle). Endpoint was defined as the last observation obtained for an individual during the treatment period, to account for possible discontinuation of patients during the course of the study. Predicted FEV1 was calculated, as appropriate, according to Crapo formulas [18] (for patients ≥18 yrs of age), European Community Steel and Coal formulas (Nordic countries only, patients 18–70 yrs of age) or the Polgar formula [19] (patients 12–17 yrs of age). Adjustments for patients of African descent were made by programming the spirometer or by hand calculation.

Changes from baseline FEV1, as well as the secondary efficacy variables, were analyzed using a two-way analysis of variance (ANOVA) that extracted sources of variation due to treatment and centre and treatment-by-centre interaction. Since all pairwise comparisons were of independent interest, each ANOVA was followed by Duncan’s multiple range test to compare all treatment groups. The results of these tests are considered significant at the 0.05 level. The assessment of response to therapy as percentage of patients showing improvement or much improvement from baseline was analyzed by Fisher’s Exact Test.

Results

Patient population

A total of 730 patients from 57 study centres in 17 countries were randomized after screening into treatment groups in this study. The description of the groups of all patients who received at least one dose of study medication is described in tables 1 and 2 (Intent-to-Treat groups).
Treatment groups were comparable with respect to demographics (table 1) and asthma-related characteristics (table 2). These measures were assessed using descriptive statistics or the two-way ANOVA previously described, as appropriate. Statistics on treatment safety and efficacy were derived from this group on the “Intent-to-Treat” principle.

Patients enrolled in this study were maintained on prescribed inhaled corticosteroids prior to the initiation of the study. Both the number of patients using a particular prescribed glucocorticoid at baseline and the average dosage of that drug were similar among active treatment groups (table 2). The inhaled corticosteroids used included beclomethasone dipropionate (overall mean 699 mg-day⁻¹), budesonide (662 mg-day⁻¹), flunisolide (659 mg-day⁻¹), fluticasone propionate (438 mg-day⁻¹), or triamcinolone acetonide (416 mg-day⁻¹). The number of patients using theophylline at baseline and throughout the study was low and similar among treatment groups.

Overall, 14% of patients were (n=101/730) discontinued from the study prior to completion and they were similarly distributed across treatment groups; 15%, 10%, and 18% for the MF DPI 100, 200 and 400 mg b.i.d groups, respectively and 14% for the budesonide Turbuhaler group. Treatment failure accounted for 5% overall (n=33/730). Discontinuations resulting from treatment failure were similar in the MF DPI (5%, 3%, and 6% for the 100, 200 and 400 mg b.i.d groups, respectively) or budesonide Turbuhaler (3%) groups.

Adverse events were responsible for discontinuations in 2% of patients overall and these are described later (Evaluation of safety section). Other reasons for discontinuance were: noncompliance with protocol (1%), lost to follow-up (2%), did not meet entry criteria (2%), or other reasons unrelated to treatment (2%).

The requirement of both a baseline measurement and at least one post-baseline measurement was met by 720 patients, and efficacy analyses were based on this set. Some patients entered the study with FEV1 values or variability outside of the selection criteria (table 2). The number of such patients ranged from 2±7% for each group.
group (3 patients in the MF 100 \( \mu g \) b.i.d, 13 in the MF 200 \( \mu g \) b.i.d, 13 in the MF 400 \( \mu g \) b.i.d and 12 in the 400 \( \mu g \) BUD groups), for an overall total of 5.7%. Only 2 patients failed the reversibility test (both in the MF 100 \( \mu g \) b.i.d group). The other principal reasons for protocol deviations were poor compliance (<75% of specified doses taken, n=10 patients) and overuse of rescue medication (n=8 patients). Thus the majority of all protocol deviations were FEV1 deviations. Exclusion of FEV1 and other protocol deviations from the "Intent-to-Treat" set resulted in an efficacy evaluated subset of 654 patients.

**Evaluation of efficacy: forced expiratory volume in one second**

Baseline values were similar across groups for FEV1 (table 2). For analysis of treatment-by-centre interaction, centres with <10 patients were combined, within the same country when possible. The treatment-by-centre interaction term was not significant (p=0.14), while there was a significant treatment effect (p=0.03). For all treatment groups, substitution of study drug for the previously used inhaled corticosteroid was associated with improvement in lung function, as shown by the changes in FEV1 values over time (fig. 1). Both the MF DPI 200 and 400 \( \mu g \) b.i.d groups showed significantly greater improvement compared with the BUD Turbuhaler® 400 \( \mu g \) b.i.d by two weeks and both doses generally maintained this difference throughout the study (fig. 1). Overall, increases in FEV1 values over time with BUD 400 \( \mu g \) b.i.d were of smaller magnitude and, at week 8, were actually significantly less than all three MF DPI b.i.d treatments.

The change in FEV1 from baseline to endpoint is indicated in table 3. This change was significantly greater for MF DPI 200 and 400 \( \mu g \) b.i.d than for BUD 400 \( \mu g \) b.i.d by 0.10 L. Likewise, the change in FEV1 from baseline for MF DPI 400 \( \mu g \) b.i.d was significantly greater than that for MFD DPI 100 \( \mu g \) b.i.d by 0.06 L.

**Table 3** shows that FEV1, reported as percent of predicted (% pred), increased from baseline to endpoint for all treatment groups. In addition, endpoint FEV1 % pred values of the groups treated with MF DPI 200 \( \mu g \) b.i.d and MF DPI 400 \( \mu g \) b.i.d were significantly greater than that of BUD 400 \( \mu g \) b.i.d. Treatment with MF DPI 400 \( \mu g \) b.i.d also produced a significantly higher endpoint FEV1 % pred value than treatment with MF DPI 100 \( \mu g \) b.i.d. These data confirmed the inferences derived from comparison of changes from baseline in absolute FEV1 values.

**Evaluation of efficacy: other pulmonary function measures**

Additional measures of pulmonary function are summarized in table 2, and responses to the study drugs are summarized in table 3. Participants in the study measured a.m. and p.m. PEF each day prior to any study medication and recorded the number of puffs of salbutamol taken daily. Baseline values for a.m. PEF were similar among the treatment groups (table 2). The a.m. PEF was improved over time for all treatment groups (fig. 2 and table 3). The mean increase in a.m. PEF at the endpoint was significantly greater for patients treated with MF DPI 200 \( \mu g \) b.i.d than with MF DPI 100 \( \mu g \) b.i.d by 19.64 L·min\(^{-1}\). The increase for patients treated with MF DPI 400 \( \mu g \) b.i.d was also significantly greater than with MF DPI 100 \( \mu g \) b.i.d by 19.11 L·min\(^{-1}\) (table 3). For p.m. PEF (data not shown) the mean increase at the endpoint was improved for MF DPI 400 \( \mu g \) b.i.d when compared with MF DPI 100 \( \mu g \) b.i.d treatment. There was no significant difference between the MF DPI 200 and 400 \( \mu g \) b.i.d groups.

**Evaluation of asthma symptoms**

Patients rated asthma symptoms (wheezing, difficulty breathing and cough) each morning (a.m.) and evening (p.m.); scores were generally low at baseline in all treatment groups (table 2). Improvement in a.m. wheezing scores at the endpoint was significantly greater for patients in the MF DPI 400 \( \mu g \) b.i.d treatment group than for those in either BUD Turbuhaler® 400 \( \mu g \) b.i.d or MF DPI 100 \( \mu g \) b.i.d groups. Improvement in a.m. difficulty breathing at the endpoint was significantly greater for the MF DPI 400 \( \mu g \) b.i.d group compared with the MF DPI 100 \( \mu g \) b.i.d group. No significant differences were observed between treatment groups for a.m. coughing scores at the endpoint. The results for the p.m. asthma symptoms (data not shown) were generally similar to the a.m. results.

**Daily use of salbutamol and nocturnal awakenings requiring use of salbutamol**

Patients recorded use of salbutamol on their daily diary cards. Since allowed salbutamol preparations varied among different countries and among different sites within countries (i.e. metered dose inhaler versus powder inhaler), salbutamol use is expressed as \( \mu g \) salbutamol-day\(^{-1}\). Mean
significant differences between groups (table 3). Observed for all treatment groups by the endpoint, with no decreases in the number of nocturnal awakenings were patients in all treatment groups at baseline (table 2). Mean rescue medication were very low, and comparable, among Turbuhaler less salbutamol than did patients treated with BUD.

Turbuhaler

Mean total daily salbutamol use at the endpoint, patients treated with MF DPI 200 mg b.i.d required significantly less salbutamol than did patients treated with BUD Turbuhaler® 400 µg b.i.d. (table 3).

Nocturnal awakenings requiring the use of salbutamol rescue medication were very low, and comparable, among patients in all treatment groups at baseline (table 2). Mean decreases in the number of nocturnal awakenings were observed for all treatment groups by the endpoint, with no significant differences between groups (table 3).

Table 3. – Effects of mometasone furoate administered by dry powder inhaler and budesonide Turbuhaler® on pulmonary function, asthma symptoms and physician-evaluated response to therapy

<table>
<thead>
<tr>
<th>Subjects n</th>
<th>185</th>
<th>176</th>
<th>188</th>
<th>181</th>
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<tbody>
<tr>
<td>Pulmonary Function</td>
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<td></td>
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<tr>
<td>FEV1 L</td>
<td>0.10±0.03</td>
<td>0.16±0.03*</td>
<td>0.16±0.03*</td>
<td>0.06±0.03</td>
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<td>FEV1 % pred</td>
<td>79.6±1.1</td>
<td>81.6±1.2*</td>
<td>83.0±1.2*</td>
<td>77.9±1.1</td>
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<tr>
<td>FVC L</td>
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<td>0.16±0.04</td>
<td>0.15±0.04</td>
<td>0.06±0.04</td>
</tr>
<tr>
<td>PEFa.m. L·min⁻¹</td>
<td>18.20±5.3</td>
<td>37.84±5.4*</td>
<td>37.31±5.2*</td>
<td>24.75±5.3</td>
</tr>
<tr>
<td>Patient Self Report-mean score</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing a.m.</td>
<td>-0.07</td>
<td>-0.17</td>
<td>-0.27*</td>
<td>-0.10</td>
</tr>
<tr>
<td>Difficulty breathing a.m.</td>
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<td>-0.20</td>
<td>-0.24*</td>
<td>-0.14</td>
</tr>
<tr>
<td>Nocturnal awakenings</td>
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<td>-0.09</td>
<td>-0.16</td>
<td>-0.07</td>
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<td>Salbutamol use in µg·day⁻¹</td>
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<td>-90.66*</td>
<td>-72.13</td>
<td>-33.90</td>
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<tr>
<td>Physician evaluated response to therapy</td>
<td>2.43</td>
<td>2.33*</td>
<td>2.25*</td>
<td>2.53</td>
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</table>

Values are presented as change from baseline to endpoint (last treatment visit) ±SEM, with the exception of the endpoint FEV1 % pred. FEV1: forced expiratory volume in one second; % pred: per cent predicted; FVC: forced vital capacity; PEFa.m.: peak expiratory flow in the morning; MF DPI: mometasone furoate administered by dry powder inhaler; BUD: budesonide. *: p<0.05 compared with BUD Turbuhaler® 400 µg b.i.d.; †: p<0.05 compared with MF DPI 100 µg b.i.d.

salbutamol use at baseline was very similar among the treatment groups (table 2). Based upon the reduction in mean total daily salbutamol use at the endpoint, patients treated with MF DPI 200 µg b.i.d required significantly less salbutamol than did patients treated with BUD Turbuhaler® 400 µg b.i.d (table 3).

Nocturnal awakenings requiring the use of salbutamol rescue medication were very low, and comparable, among patients in all treatment groups at baseline (table 2). Mean decreases in the number of nocturnal awakenings were observed for all treatment groups by the endpoint, with no significant differences between groups (table 3).

Physician evaluation of response to therapy

The physicians evaluated the response to therapy for every patient at each treatment visit, by comparing symptom levels to those at baseline. At the endpoint, the percentage of patients considered to be much improved or improved was comparable in the MF DPI 100 mg b.i.d (60%), MF DPI 200 µg b.i.d (63%), and MF DPI 400 µg b.i.d (65%) treatment groups, and lower in the BUD Turbuhaler® 400 µg b.i.d (50%) group. The differences, expressed as mean scores, are significant for both the MF DPI 400 µg b.i.d and MF DPI 200 µg b.i.d treatment groups compared with the BUD Turbuhaler® 400 µg b.i.d group (table 3).

Evaluation of safety

All treatments were well tolerated, and no unusual or unexpected adverse events were reported. Most events were mild to moderate in severity and none were life threatening. The most common adverse events, reported by ≥10% of patients in any treatment group, included headache, pharyngitis, viral infection, and rhinitis.

The incidence of adverse events judged by investigators to be related to treatment was similar for all treatment groups (17–20%). The most common treatment-related adverse events were headache (4–8%), pharyngitis (4–5%), and dysphonia (2–5%). Dysphonia was distributed among the groups as n=8, 5, 9, and 4 in the MF DPI 100, 200, 400, µg b.i.d and BUD Turbuhaler® 400 µg b.i.d groups, respectively. Oral candidiasis was uncommon in this study, reported by only 16 patients overall, and had a similar incidence among the treatment groups (n=4, 6, 4, and 3 in the MF DPI 100, 200, 400, µg b.i.d and BUD Turbuhaler® 400 µg b.i.d groups, respectively). Oral candidiasis was predominantly mild to moderate in severity.

Serious adverse events were noted for 11 patients (one in the screening period, two in the MF DPI 100 µg b.i.d...
treatment group, three in the MF DPI 200 μg b.i.d group, two in the MF DPI 400 μg b.i.d group, and three in the BUD Turbuhaler® 400 μg b.i.d group). None of these events was considered to be related to the treatment.

Overall, 17 patients (2%) did not complete the treatment because of adverse events. These included six (3%) in the MF DPI 100 μg b.i.d group, one (<1%) in the MF DPI 200 μg b.i.d group, three (2%) in the MF DPI 400 μg b.i.d group, and seven (4%) in the BUD Turbuhaler® 400 μg b.i.d group. Treatment was interrupted in some patients because of an adverse event (n=16). In the majority of cases, the events causing interruption were thought to be unrelated to treatment. No clinically relevant changes in vital signs or physical exams were observed from baseline to endpoint for any treatment group. The few clinically significant changes in laboratory values were thought to be unrelated to study medication. No ECG abnormalities were reported that indicated any clinically significant effect of investigational treatment.

Compared with screening values, when patients were maintained on their previous inhaled corticosteroid, all four treatment groups demonstrated a slight increase in 08:00 h plasma cortisol levels at week 12. At screening, median plasma cortisol levels were 13.3 μg·dL⁻¹, 13.4 μg·dL⁻¹, 12.8 μg·dL⁻¹, and 13.6 μg·dL⁻¹ for the MF DPI 100, 200, and 400 μg b.i.d groups and the BUD 400 μg b.i.d group, respectively. At week 12, median plasma cortisol levels (percent change) were 13.7 μg·dL⁻¹ (+3%), 13.7 μg·dL⁻¹ (+5%), 12.9 μg·dL⁻¹ (+12%), and 14.2 μg·dL⁻¹ (+9%) for the MF DPI 100, 200, and 400 μg b.i.d groups and the BUD 400 μg b.i.d group, respectively. There were no significant differences in cortisol values among treatment groups when compared at screening or week 12.

**Discussion**

In the first such comparison of its kind, doses of MF 200 μg b.i.d and 400 μg b.i.d administered by a novel breath-actuated DPI were both significantly more effective than a 400 μg b.i.d dose of BUD Turbuhaler® in patients with moderate persistent asthma who required daily use of inhaled corticosteroids to control their asthma. The 400 μg b.i.d dose of BUD administered by Turbuhaler® was comparable in effectiveness to a 100 μg b.i.d dose of MF DPI for most of the parameters examined. This 12-week multicentre study extends the finding of previous studies [12, 13] which demonstrated MF DPI to be effective and well tolerated. In the present study, MF DPI was directly compared to a clinically effective and widely used inhaled glucocorticoid, BUD Turbuhaler®. Treatment with MF DPI, at both the 200 μg and 400 μg b.i.d doses, significantly improved measures of pulmonary function, and to a greater extent than treatment with BUD Turbuhaler® (400 μg b.i.d), within the first two weeks of the study. Since all patients in the study were using recommended (with label) doses of prescribed inhaled corticosteroids to control their asthma prior to beginning this trial, the additional improvement obtained with MF DPI treatment over the previous therapeutic regimen is considered to be clinically meaningful. Some of this improvement may have resulted from the increased compliance that occurs when patients enter a clinical study.

BUD Turbuhaler®, the active control comparator used in this study, has been extensively investigated and has been shown to be effective in controlling asthma in adults [20–22]. In the current study, BUD was delivered via a Turbuhaler® at a dose of 400 μg b.i.d, which is a commonly prescribed dose for patients with moderate persistent asthma. The effectiveness of this dose was assessed against the identical dose of MF DPI, as well as two lower doses of MF DPI. At half of the total daily dose of BUD Turbuhaler®, MF DPI 200 μg b.i.d provided significant improvement compared with BUD in several asthma-related measures, including changes in FEV₁, % pred FEV₁, the amount of rescue medication (salbutamol) required, and physicians' evaluation of response to therapy. Based on the outcomes measured in this study, the results obtained with BUD Turbuhaler®, which is in agreement with in vitro findings [4, 5, 7]. However, only one dose of BUD was used in this study, and it is possible that higher doses of BUD would show an efficacy comparable to that of MF.

Clinical responses to inhaled corticosteroids generally fail to show significant differences over dose ranges of ≥four-fold [14]. In the present study, some endpoint measures did detect differences with dosages of MF that were only two-fold to four-fold higher than the lowest dose.

A significantly greater improvement in the a.m. PEF scores were detected for treatment with MF DPI 200 μg and 400 μg b.i.d compared with the MF DPI 100 μg b.i.d. The improvement in the mean p.m. PEF score of the MF DPI 400 μg b.i.d group was also significantly different from that of the MF DPI 100 μg b.i.d group. Significant differences were noted in several other measures when the MF DPI 100 μg b.i.d group was compared with the MF DPI 400 μg b.i.d group. This suggests that, for some measurements, the study was able to detect differences between the lowest and highest MF DPI dosages. Furthermore, it appears that for the patients in this study with moderate persistent asthma, MF DPI 100 μg b.i.d may represent the lower end of the therapeutically beneficial dose range.

In this study the MF 200 and 400 μg b.i.d doses appeared comparable: MF DPI 200 μg b.i.d provided a benefit equal to MF DPI 400 μg b.i.d in the primary efficacy variable, FEV₁, as well as for most other measures of pulmonary function assessed. This finding is consistent with the results of a previous dose-ranging study of MF [12]. There are reports that higher doses of an inhaled glucocorticoid may lead to a significant improvement in patients with moderate or severe asthma or those with stable disease [22, 23]. In the present study, however, doubling the dose of MF DPI from 200 to 400 μg b.i.d provided no additional benefit, and suggests that the upper threshold of therapeutic benefit may have been attained for this population of patients.

All doses of MF DPI were well tolerated in this study. Oral candidiasis was uncommon in this study and demonstrated a similar incidence among treatment groups. Most adverse events were mild to moderate in severity and were unrelated to the study drug. There were no differences among treatment groups in the overall incidence of adverse events.
The very low bioavailability of MF taken by DPI, and low potential for hypothalamic-pituitary-adrenal (HPA) axis suppression have recently been shown using sensitive measures, such as 24-h area under the curve cortisol concentrations and adrenal response to stimulation [24]. A study using the same dosing range of MF as in the present report found plasma levels of MP to be less than 50 pg·dL⁻¹ and found no evidence of suppression of cortisol response to cosyntropin stimulation [12]. It was not feasible to conduct similar HPA function measurements in this large international study. However, using the change in 08:00 h plasma cortisol concentrations from screening to week 12, there were no clinically relevant differences among treatment groups. In addition, there was no evidence of HPA axis suppression in any group compared with the screening value, obtained while patients were maintained on their previous inhaled corticosteroid. Due to the lower sensitivity of the 08:00 h cortisol measurements, these results should be interpreted with caution. However, the results of this study suggest that, in this patient population, there is little potential for HPA axis suppression by MF or BUD at the doses tested.

To conclude, this 12-week study showed that inhaled mometasone furoate, administered by a novel breath-actuated DPI, was effective and well tolerated by adults and adolescents who were previously maintained on daily inhaled corticosteroids for treatment of moderate persistent asthma. Lower doses of mometasone furoate administered by dry powder inhaler appears to be a more effective treatment for asthma than a clinically recommended daily dose of BUD Turbuhaler® while providing a comparable degree of safety.

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