



Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function

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ABSTRACT: This study evaluated the effect of mometasone furoate (MF)/formoterol (F) versus its monocomponents, each administered *via* metered-dose inhaler, on asthma deteriorations and lung function.

This 26-week, multicentre, double-blind, placebo-controlled study included subjects aged ≥ 12 yrs with not well-controlled asthma on low-dose inhaled corticosteroids. After a 2–3-week open-label run-in (MF 100 μg *b.i.d.*), 746 subjects were randomised to receive placebo, F 10 μg , MF 100 μg or MF/F 100/10 μg *b.i.d.* Co-primary end-points were time to first asthma deterioration (MF/F versus F to assess effect of MF) and change in forced expiratory volume in 1 s (FEV₁) area under the curve of serial spirometry measurements over the 12-h period following the morning dose (AUC_{0–12h}) (baseline to week 12; MF/F versus MF to assess effect of F).

The therapeutic effect of MF in the combination was demonstrated by a reduction in asthma deterioration incidence with MF/F versus F and a delayed time to first asthma deterioration ($p < 0.001$). Asthma deterioration incidence was also reduced with MF/F versus MF ($p = 0.006$). The therapeutic effect of F in the combination was demonstrated by MF/F versus MF in FEV₁ AUC_{0–12h} change (4.00 versus 2.53 L·h, respectively; $p = 0.001$). MF/F treatment also resulted in a marked improvement in health-related quality of life.

MF/F 100/10 μg *b.i.d.* treatment showed greater clinical efficacy than its individual components or placebo; both components contributed to the efficacy of MF/F.

KEYWORDS: Asthma control, asthma deterioration, asthma exacerbation, efficacy, mometasone furoate/formoterol combination therapy, randomised clinical trial

Asthma guidelines recommend treatments that can control asthma and prevent exacerbations (*i.e.* asthma deterioration) [1, 2]. However, despite the availability of effective medications, the incidence of asthma deteriorations has not improved, and rates of asthma-related resource utilisation in 2009 (hospitalisation (7%), emergency room visits (16%) and unscheduled doctor visits (26%)) remained comparable to 1998 levels [3]. Such data support a rationale for new and improved therapeutic options.

Inhaled corticosteroids (ICS) are anti-inflammatory drugs and recommended as preventative maintenance therapy for all patients with persistent disease [1, 2, 4]. Inhaled long-acting β_2 -agonists (LABA) are bronchodilator drugs with an extended duration of action. Clinical trials confirm improved control of asthma when a LABA is added to ICS therapy (*i.e.* fewer asthma symptoms, less requirement for

rescue bronchodilator medication, better lung function, lower risk of acute worsening of asthma and improved quality of life (QoL)) [5–9].

Mometasone furoate (MF), a potent ICS with high affinity for the glucocorticoid receptor and low bioavailability, improves lung function, decreases asthma symptoms and reduces the frequency and severity of asthma deteriorations at daily doses of 100–800 μg [10–12]. Formoterol (F), a LABA, rapidly increases lung function and maintains control over 24 h when administered twice daily (*b.i.d.*) [13].

This study assessed the effects of a novel combination of MF and F (MF/F 100/10 μg administered *b.i.d.* *via* metered-dose inhaler (MDI)) on asthma deteriorations, lung function and asthma control versus its monocomponents and placebo in subjects with persistent asthma not well controlled with low-dose ICS therapy.

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Received:

Feb 05 2010

Accepted after revision:

July 15 2011

First published online:

Aug 04 2011

European Respiratory Journal

Print ISSN 0903-1936

Online ISSN 1399-3003

METHODS

Study design

This 26-week, randomised, multicentre, double-blind, double-dummy, placebo-controlled, parallel-group, MF/F registration study was conducted in 172 sites worldwide (in North America, Latin America, Europe and Asia) in compliance with Good Clinical Practice guidelines. The protocol was approved by institutional review boards for each centre. All subjects gave written informed consent before any study activity.

Screening was followed by a 2–3-week, open-label run-in with MDI-administered MF monotherapy 100 µg *b.i.d.* Eligible patients were randomised in a 1:1:1:1 ratio to one of four 26-week, MDI-administered, *b.i.d.* treatment groups: placebo, F 10 µg, MF 100 µg and MF/F 100/10 µg. Targeted delivery per inhalation (ex-actuator) was MF 50 µg and/or F 5 µg administered with two inhalations per dose. Although recent regulatory guidelines in the USA caution against the use of LABA monotherapy for the treatment of asthma [14], this study included an F treatment arm to comply with US [15] and European [16] regulatory requirements on the clinical development of a combination drug product.

Throughout the study, subjects were monitored for asthma deteriorations by electronic diary (Cardinal Health Inc., Dublin, OH, USA) alerts based on twice-daily recordings of peak expiratory flow (PEF), asthma symptoms and short-acting β₂-agonist (SABA) and systemic steroid usage. Additionally, subjects were provided with an asthma action plan, emergency rescue oral corticosteroids and SABA and had scheduled clinic visits and 24-h access to a physician consultation.

Subjects were eligible for enrolment if they were aged ≥12 yrs with asthma of ≥12 months' duration, were on a stable asthma regimen (daily dose unchanged) for ≥2 weeks prior to screening and had a history of low-dose ICS use (*e.g.* 100–250 µg beclomethasone hydrofluoroalkane) for ≥12 weeks with or without additional LABA. For inclusion, subjects had to fulfil one of the following criteria at screening or at any time before baseline: an increase in forced expiratory volume in 1 s (FEV₁) of ≥12% and a volume increase of ≥200 mL ~15–20 min after administration of albuterol/salbutamol or of a nebulised SABA; PEF variability of ≥20%; diurnal PEF variation of ≥20%. Key exclusion criteria were asthma that was not well controlled between screening and baseline and requiring emergency treatment, hospitalisation or treatment with systemic corticosteroids. Other exclusion criteria were use of concomitant asthma medication, current or prior history of smoking (>10 pack-yrs), clinically significant abnormal vital signs or visible evidence of oropharyngeal candidiasis at baseline or earlier. At baseline, FEV₁ had to be 60–85% of predicted after all restricted medications had been withheld for the appropriate interval.

Clinic visits were scheduled at screening, pre-baseline, baseline (day 1) and weeks 1, 4, 8, 12, 16, 20 and 26. Efficacy was evaluated by pulmonary function tests at all visits prior to the morning dose of study medication, and serial spirometry was performed at baseline, weeks 1 and 12 and at the final visit. Subjects also recorded daily SABA usage, number of nocturnal awakenings due to asthma requiring SABA use, twice-daily reflective asthma symptom scores and twice-daily PEF measurements in e-diaries. In addition, the Asthma Quality of Life Questionnaire with Standardised Activities (AQLQ(S)) [17] and Asthma Control

Questionnaire (ACQ) [18] were completed at baseline and at weeks 4, 12 and 26.

Study end-points

The contribution of MF to MF/F was assessed by quantifying the time to first asthma deterioration (*i.e.* severe asthma exacerbation) over the 26-week treatment period, based on comparison of the MF/F *versus* F groups. An asthma deterioration was defined as a clinically judged deterioration (*i.e.* asthma attack resulting in emergency treatment, hospitalisation or treatment with additional, excluded asthma medication (*i.e.* systemic corticosteroids)) or a meaningful reduction in lung function (*i.e.* a decrease in FEV₁ of >20% from baseline at any study visit or a decrease in PEF of >30% from baseline for ≥2 days consecutively at any time during the treatment period). The contribution of F to MF/F was assessed by measuring the mean change in FEV₁ area under the curve of serial spirometry measurements over the 12-h period following the morning dose (FEV₁ AUC_{0–12h}) from baseline to week 12, based on comparison of MF/F *versus* MF. Serial spirometry testing was conducted using validated equipment and procedures [19].

Key secondary end-points (MF/F *versus* placebo) were: 1) change from baseline in morning FEV₁ pre-dose assessment (trough FEV₁) at each visit and end-point; 2) change from baseline in AQLQ(S) total score; 3) change from baseline in ACQ total score; 4) change from baseline (across the treatment period) in proportion of nights with nocturnal awakenings due to asthma requiring SABA use, where baseline was the proportion of nights with nocturnal awakenings prior to the first dose of double-blind treatment (days -7 to 1).

Additional secondary end-points included the following. 1) Time to first moderate asthma exacerbation defined as any one of the following criteria: two consecutive nights with at least one nocturnal awakening due to asthma symptoms requiring SABA use; a decrease in 24-h PEF of ≥25% on two consecutive days of treatment; a clinically significant increase in short-acting bronchodilator use (two consecutive days of ≥8 units of SABA). 2) Changes from baseline to week 26 in morning PEF and 24-h symptom scores. 3) 24-hr SABA usage.

Safety and tolerability

Reports of adverse events (AEs) and serious AEs, physical examinations, clinical laboratory tests, vital signs and ECGs were monitored throughout the study to assess safety and tolerability of study drugs.

Statistical analysis

Assuming 5% and 18% event rates (time to first asthma deterioration) for MF/F and F treatments, respectively, and a 90% power to detect treatment-related differences, a sample size of 169 subjects per treatment group was chosen (target total: 676 subjects; ~135 subjects per group expected to remain at week 26). This sample size was required to detect a difference of 3.1 L·h in change from baseline FEV₁ AUC_{0–12h} (an average and clinically meaningful difference of 0.26 L in FEV₁ across the 12-h period) between MF/F and MF with 96% power at a 5% significance level. The target sample size of 676 allowed for a 20% dropout before completion of treatment.

A log-rank test comparing the equality of survival curves was used to analyse time to first asthma deterioration and moderate

asthma exacerbation. ANCOVA with treatment and study site as effects and baseline as a continuous covariate was used to analyse mean FEV₁ AUC_{0-12h} change from baseline at week 12. Changes from baseline to week 26 and/or end of treatment (EOT) in AQLQ(S) score, ACQ score, proportion of nights with nocturnal awakenings due to asthma requiring SABA use and 24-h SABA use were assessed using pairwise comparisons of least square means (from the described ANCOVA model) between treatment groups. Trough FEV₁ was analysed by the longitudinal average method due to higher than expected differential dropouts in the F and placebo treatment arms.

Efficacy analyses included all randomised subjects with non-missing baseline and at least some post-baseline data; safety analyses included all randomised subjects. Incomplete FEV₁ AUC_{0-12h} data were imputed prior to analysis, provided data were available at the 0- and 2-h time-points. FEV₁ AUC_{0-12h} data from subjects who were terminated or used SABA prior to the final 12-h time-point were imputed using the last observation carried forward (LOCF; ≥ 2 h post-dosing) so that a full set of serial FEV₁ measurements were available for an AUC calculation at a given visit. An end-point visit was computed by using LOCF for all visit-based data. For asthma deterioration analyses, censoring occurred at the last day of treatment for subjects who completed the study without an asthma deterioration or dropped out for reasons other than asthma deterioration.

RESULTS

Subject disposition

A total of 882 subjects were enrolled, and 746 were randomised to placebo or active therapy (fig. 1). Of these 746 subjects, 536 (72%)

completed the double-blind treatment period, and 210 (28%) discontinued early. Higher discontinuation rates were observed for placebo and F than for MF and MF/F (fig. 1). The most common reason for discontinuation was treatment failure (placebo: n=42 (22%); F: n=29 (15%); MF: n=13 (7%); MF/F: n=4 (2%)). Only 28 (3.8%) subjects discontinued due to AEs, with no difference in rates across treatment arms.

Baseline demographic characteristics were comparable across the four groups (table 1). Subjects in all groups had impaired lung function with a mean FEV₁ % pred of 75% and mean FEV₁/forced vital capacity ratio of 0.75. Asthma was inadequately controlled (mean ACQ total score 1.31) and QoL was impaired (mean AQLQ(S) total score 5.69). Before screening, 69% of subjects received low-dose ICS monotherapy without LABA.

Asthma deteriorations: measuring the contribution of MF

Overall, 253 subjects experienced an asthma deterioration (*i.e.* severe asthma exacerbation, defined as lung function reduction or clinically judged deterioration) at some point during the study (table 2). MF significantly contributed to the efficacy of the MF/F combination, as shown by the delay in time to first asthma deterioration (fig. 2) and the lower percentage of subjects experiencing an asthma deterioration (fig. 3a) during treatment with MF/F *versus* F alone ($p < 0.001$). Subjects treated with MF/F were also less likely to experience an asthma deterioration than those receiving placebo or MF alone ($p \leq 0.006$) (figs 2 and 3a). The effect of MF was further demonstrated by the significantly lower percentage of subjects experiencing asthma deterioration during treatment with MF alone *versus* F alone or placebo ($p \leq 0.002$).

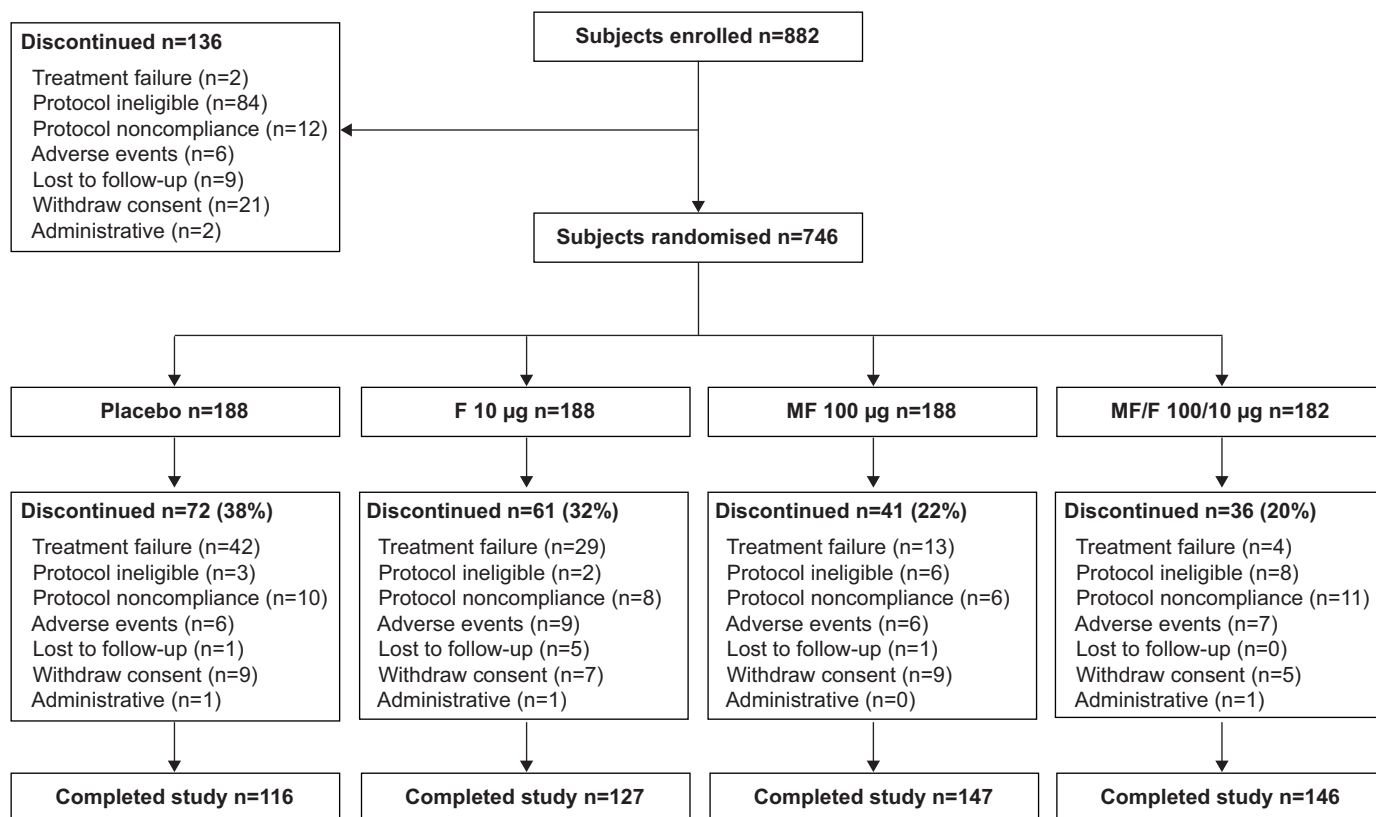


FIGURE 1. Subject disposition. F: formoterol; MF: mometasone furoate.

TABLE 1 Baseline demographic and asthma-related characteristics of all treated subjects

	Placebo	F 10 µg	MF 100 µg	MF/F 100/10 µg	Total
Subjects n	188	188	188	182	746
General demographics					
Female sex	106 (56)	103 (55)	105 (56)	99 (54)	413 (55)
White race	143 (76)	148 (79)	140 (74)	142 (78)	573 (77)
Age yrs	38.1±17.4	38.5±15.6	39.4±16.7	37.1±16.9	38.3±16.6
Asthma-related characteristics					
Duration of asthma yrs	13.5±13.7	15.4±13.8	15.9±14.4	14.3±12.5	14.8±13.6
FEV ₁ at screening					
L	2.5±0.7	2.6±0.7	2.5±0.6	2.6±0.8	2.5±0.7
% pred	76.0±9.2	76.3±9.8	75.8±9.9	76.9±10.2	76.2±9.7
% reversibility	19.1±11.4	19.8±9.9	17.3±8.9	18.6±8.8	18.7±9.8
FEV ₁ at baseline					
L	2.5±0.7	2.5±0.7	2.5±0.7	2.6±0.7	2.5±0.7
% pred	75.4±8.2	74.9±8.2	74.5±8.9	75.6±7.7	75.1±8.3
FEV ₁ /FVC	0.74±0.10	0.75±0.10	0.74±0.10	0.75±0.09	0.75±0.10
ACQ total score at baseline	1.2±0.7	1.4±0.8	1.3±0.7	1.3±0.7	1.3±0.7
AQLQ(S) total score at baseline	5.8±1.0	5.7±0.9	5.7±1.0	5.7±0.9	5.7±1.0
Prior ICS use [#]					
Without a LABA	136 (72)	126 (67)	125 (66)	126 (69)	513 (69)
With a LABA	56 (30)	65 (35)	64 (34)	60 (33)	245 (33)

Data are presented as n (%) or mean±SD, unless otherwise stated. F: formoterol; MF: mometasone furoate; FEV₁: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; AQLQ(S): Asthma Quality of Life Questionnaire with Standardised Activities; ICS: inhaled corticosteroid; LABA: long-acting β₂-agonist. [#]: subjects could have used more than one ICS without LABA and/or ICS with LABA during the 3-month period before screening.

Although 27 subjects experienced a clinically judged deterioration as the criterion for their first asthma deterioration and were discontinued, an additional 25 subjects experienced a clinically judged deterioration at or beyond the day of their first asthma deterioration (due to a decrease in FEV₁ or PEF values), giving a total of 52 subjects experiencing a clinically judged deterioration at some time during the study (table 2 and fig. 3b). As observed for asthma deteriorations, subjects in the MF/F group had significantly fewer clinically judged deteriorations than subjects in the F monotherapy and placebo groups ($p \leq 0.001$). Subjects receiving MF alone also had significantly fewer clinically judged deteriorations than those receiving F alone or placebo ($p \leq 0.008$).

Similar to asthma deteriorations, significantly fewer subjects receiving MF/F experienced a moderate exacerbation than with F, placebo or MF ($p \leq 0.002$) (table 2 and fig. 3c). Compared with placebo, significantly fewer subjects receiving MF or F experienced moderate exacerbations ($p \leq 0.013$).

Lung function: measuring the contribution of F

Improvements from baseline in lung function for both MF/F and F groups were apparent as early as 5 min post-dose, peaked at ~2 h and were sustained throughout the 12-h evaluation. These improvements were seen as early as day 1 (fig. 4a) and through to week 12 (fig. 4b). F significantly contributed to the effectiveness of the MF/F combination as shown by the greater mean FEV₁ AUC_{0-12h} improvement from baseline at week 12 with MF/F *versus* MF alone (4.00 *versus* 2.53 L·h, respectively; $p = 0.001$). The effect of F was also demonstrated by a significantly greater mean improvement in FEV₁ AUC_{0-12h} (3.83 L·h) *versus* MF and placebo (2.53

and 1.11 L·h, respectively; $p \leq 0.004$). Both the MF/F *versus* MF and F *versus* placebo comparisons remained statistically significant until week 26. Treatment with MF/F and MF also resulted in a significantly greater mean improvement in FEV₁ AUC_{0-12h} at week 12 compared with placebo ($p \leq 0.002$). Mean FEV₁ AUC_{0-12h} improvements at week 12 in placebo, F, MF and MF/F treatment groups corresponded to mean increases in FEV₁ of 0.09 L (4.1%), 0.32 L (12.3%), 0.21 L (9.0%) and 0.33 L (13.8%), respectively.

For other lung function evaluations, longitudinal analysis of trough FEV₁ showed that MF/F improved morning pre-dose lung function more than F alone during treatment ($p = 0.029$) (fig. 4c). Also, mean percentage changes from baseline to EOT in morning PEF values (LOCF using the final 7 days of available diary data) were -5.3%, 1.4%, 1.6% and 5.2% for placebo, F, MF and MF/F groups, respectively (fig. 4d). At EOT, the change from baseline in morning PEF was significantly greater for MF/F than for the other treatment groups ($p \leq 0.007$). For MF/F *versus* placebo, the magnitude of change was 41.6 L·min⁻¹, attaining a clinically relevant difference of >15 L·min⁻¹ [20].

Nocturnal awakenings and daily SABA use

At EOT, treatment with MF/F, MF or F reduced the proportion of nights over the treatment period during which subjects experienced nocturnal awakenings due to asthma requiring SABA use compared with placebo ($p \leq 0.015$) (fig. 5a). Treatment with MF/F ($p = 0.035$), but not MF ($p = 0.742$), reduced nocturnal awakenings more than F alone. At EOT, 24-h SABA use was significantly reduced from baseline in both MF/F (-53.4%, -0.16 puffs·day⁻¹) and MF (-47.5%, -0.37 puffs·day⁻¹) groups *versus* placebo (+47.5%,

TABLE 2 Incidence of asthma deteriorations, clinically judged deteriorations and moderate asthma exacerbations

	Placebo	F 10 µg	MF 100 µg	MF/F 100/10 µg
Subjects n	188	188	188	182
Asthma deterioration (i.e. severe asthma exacerbation)				
First asthma deterioration	86 (46)	84 (45)	53 (28)	30 (17)
FEV ₁ decrease [#]	29 (15)	25 (13)	14 (7)	5 (3)
PEF decrease [†]	42 (22)	44 (23)	35 (19)	23 (13)
Clinically judged deterioration [‡]	13 (7)	10 (5)	3 (2)	1 (<1)
PEF decrease [†] and deterioration [‡]	1 (<1)	2 (1)	1 (<1)	0
FEV ₁ decrease [#] and deterioration [‡]	1 (<1)	3 (2)	0	1 (<1)
Clinically judged deterioration (i.e. asthma attack)				
Any clinically judged deterioration [§]	27 (14)	17 (9)	5 (3)	3 (2)
Hospitalisation	0	0	0	0
Emergency treatment	1 (<1)	2 (1)	0	0
Systemic glucocorticoids	19 (10)	15 (8)	4 (2)	3 (2)
Other additional medications [¶]	8 (4)	2 (1)	1 (<1)	0
Moderate exacerbation				
Any moderate asthma exacerbation	123 (65)	104 (55)	91 (48)	61 (34)
Nocturnal awakening ^{##}	69 (37)	54 (29)	49 (26)	33 (18)
PEF decrease ^{††}	47 (25)	44 (23)	36 (19)	24 (13)
SABA rescue medication ⁺⁺	2 (1)	3 (2)	3 (2)	4 (2)
Nocturnal awakening ^{##} and SABA rescue medication ⁺⁺	3 (2)	3 (2)	1 (<1)	0
PEF decrease ^{††} and SABA rescue medication ⁺⁺	0	0	1 (<1)	0

Data are presented as n (%), unless otherwise stated. F: formoterol; MF: mometasone furoate; FEV₁: forced expiratory volume in 1 s; PEF: peak expiratory flow; SABA: short-acting β₂-agonist. [#]: decrease in FEV₁ below 80% of baseline; [†]: decrease in PEF below 70% of baseline on two consecutive days; [‡]: requiring a course of action, as judged by the clinical investigator; [§]: patients can have more than one course of action for a clinically judged deterioration; [¶]: includes only subjects with no record of systemic corticosteroid use; ^{##}: one or more nocturnal awakenings on two consecutive nights (requiring SABA); ^{††}: decrease in PEF below 75% of baseline on two consecutive days (no more than one day of decrease); ⁺⁺: more than eight combined units of SABA rescue medication use on two consecutive days.

+0.82 puffs·day⁻¹; p ≤ 0.004). Additionally, MF was significantly better than F (+82.6%, +0.31 puffs·day⁻¹; p = 0.049).

Asthma control and QoL

At baseline, subjects were considered to have asthma that was not well controlled, as indicated by mean scores >1.0 across groups

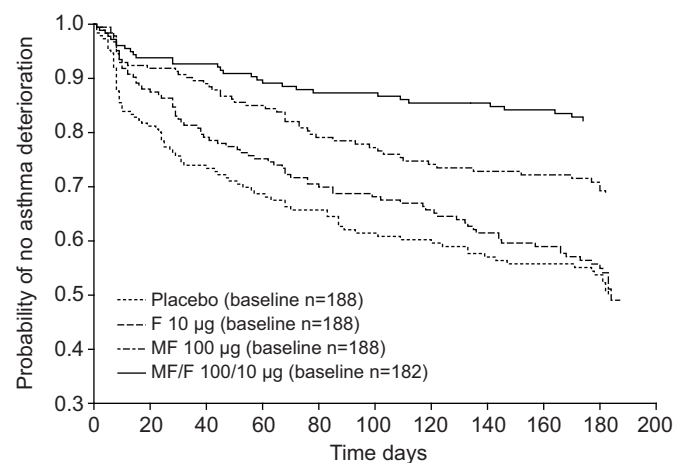


FIGURE 2. Time to first asthma deterioration (i.e. severe asthma exacerbation) up to week 26. F: formoterol; MF: mometasone furoate. p ≤ 0.006 for MF/F versus placebo, F and MF.

(“well controlled” score threshold ≤ 1.0 [21]). Treatment with MF/F resulted in a significantly greater mean improvement in ACQ total score at week 26 (-0.40) versus F (-0.12) and placebo (-0.11; p ≤ 0.001) (fig. 5b) but not MF (-0.32). At EOT, there was a statistically significant and clinically important improvement (minimal important difference of ≥ 0.5 [22]) in mean baseline-adjusted ACQ total score for subjects treated with MF/F (-0.36) versus placebo (0.24; p < 0.001) and a statistically significant improvement with MF/F versus F (0.07; p < 0.001) (fig. 5b) but not versus MF (-0.26). At week 26 and EOT, mean changes in ACQ total score with MF were also significantly better than mean change with F or placebo (p ≤ 0.019). Treatment with F was not significantly different from placebo at either time-point. Only the MF/F group achieved a “well controlled” degree of asthma control at EOT.

Similarly, treatment with MF/F resulted in significantly greater changes from baseline (i.e. mean improvement) in total AQLQ(S) total score at week 26 (0.44) versus F (0.15) and placebo (0.06; p ≤ 0.003) (fig. 5c) but not MF (0.39). At EOT, there was a significant and clinically important (minimal important difference ≥ 0.5 [23]) mean improvement from baseline in AQLQ(S) score for MF/F (0.41) versus placebo (-0.21; p < 0.001); a significant difference was also observed for MF/F versus F (0.41 versus 0.00; p < 0.001) (fig. 5c) but not MF (0.32). Similar significant results were observed at week 26 and EOT for MF versus F and placebo (p ≤ 0.013). Treatment with F also resulted in significantly greater improvement in AQLQ(S) total score versus placebo at EOT (p = 0.027).

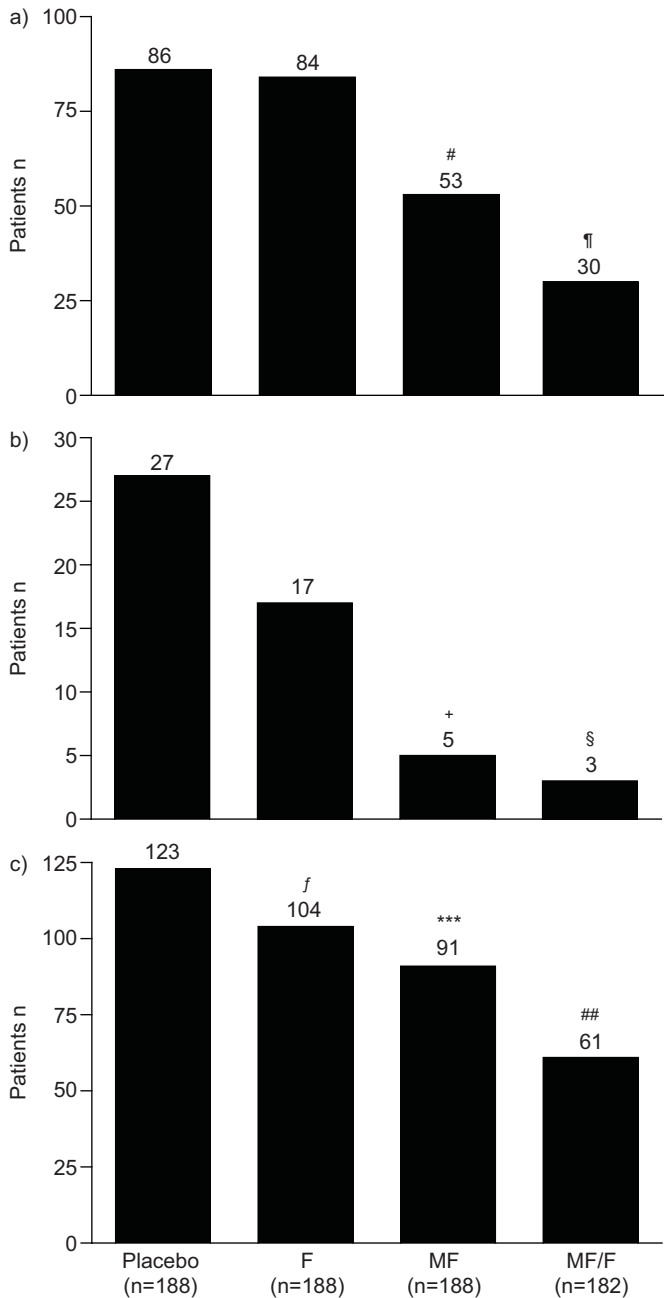


FIGURE 3. Number of subjects with a) at least one asthma deterioration (*i.e.* severe asthma exacerbation), b) at least one clinically judged deterioration (*i.e.* asthma attack) and c) at least one moderate exacerbation. F: formoterol; MF: mometasone furoate. ***: $p < 0.001$ versus placebo; #: $p \leq 0.002$ versus placebo and F; ¶: $p \leq 0.006$ versus placebo, F and MF; +: $p \leq 0.008$ versus placebo and F; §: $p \leq 0.001$ versus placebo and F; ^f: $p = 0.013$ versus placebo; ##: $p \leq 0.002$ versus placebo, F and MF.

Mean AQLQ(S) total scores at EOT suggested that asthma no longer impaired QoL (*i.e.* score ≥ 6.0) in the MF/F treatment group (6.01) but not the MF (5.97), F (5.60) or placebo (5.55) groups.

Safety

The most frequent treatment-emergent AEs in the overall population (table 3) were upper respiratory tract infections (7.9%), nasopharyngitis (5.6%) and headache (5.2%). Dysphonia

was reported by four (0.5%) subjects, one in each group. Oral candidiasis was reported by two subjects (0.3%), one in the MF/F group and one in the MF group. Oropharyngeal candidiasis was reported by one subject in the MF/F group.

The majority of subjects experiencing AEs were considered by investigators as having mild or moderate AEs (90.4%; $n = 273$) and AEs unrelated to treatment (83.8%; $n = 253$). The most frequent treatment-related AEs in the overall population were pharyngolaryngeal pain (0.8%), upper respiratory tract infection (0.7%) and headache (0.7%). Serious AEs were reported for 11 subjects during the double-blind treatment period; all were considered unlikely to be related to study medication. There were no treatment-related severe AEs, deaths or life-threatening events. No clinically relevant changes in mean vital signs or ECG measurements were observed. Clinically meaningful abnormal laboratory values, such as elevated levels of phosphate and liver enzymes, were reported for 11 subjects (four in the MF group, three in the F group and two each in the MF/F and placebo groups).

DISCUSSION

Treatment with MF/F 100/10 μg *b.i.d.* MDI showed greater overall efficacy than either MF 100 μg *b.i.d.* MDI or F 10 μg *b.i.d.* MDI alone, with both components contributing to the efficacy of the combination. It is a regulatory requirement in both the USA and Europe for fixed-dose combination drugs to show the effect of individual components, preferably by parallel group comparisons. Inclusion of a placebo group is recommended whenever feasible. Accordingly, treatment comparators and co-primary end-points in the current MF/F trial were selected to facilitate evaluation of the individual contributions of MF and F. The corticosteroid component of an ICS/LABA combination product provides a long-term anti-inflammatory effect on lung function, which should be documented by composite assessment of asthma deteriorations. As such, the contribution of MF to the MF/F combination was assessed in this study *via* the co-primary end-point of time to first asthma deterioration over the 26-week treatment period for MF/F *versus* F. Since the LABA component of an ICS/LABA combination product provides an extended bronchodilator effect, we also assessed the contribution of F to the MF/F combination *via* the co-primary end-point of mean change in FEV₁ AUC_{0-12h} from baseline to week 12 for MF/F *versus* MF.

Prevention of asthma deterioration is a critical component of disease control for improving patient health and QoL [1, 2]. However, the exact definition of this parameter varies from trial to trial, making comparisons between trials problematic. In this trial, the effect of MF/F was assessed prospectively using a definition that included clinically judged deteriorations and diminished lung function; this definition is similar to the 2009 American Thoracic Society/European Respiratory Society joint statement definition for severe asthma exacerbation [4]. The effect of MF/F treatment on asthma deteriorations (and contribution of MF to MF/F) was pronounced, as shown by a delay in time to first asthma deterioration and a reduced frequency of first asthma deterioration (nearly three-fold) and clinically judged deteriorations (six- to nine-fold) compared with F monotherapy and placebo in subjects with asthma who were previously not well controlled on low-dose ICS therapy. MF/F treatment also resulted in a significantly lower incidence of both asthma deteriorations and moderate exacerbations compared with MF

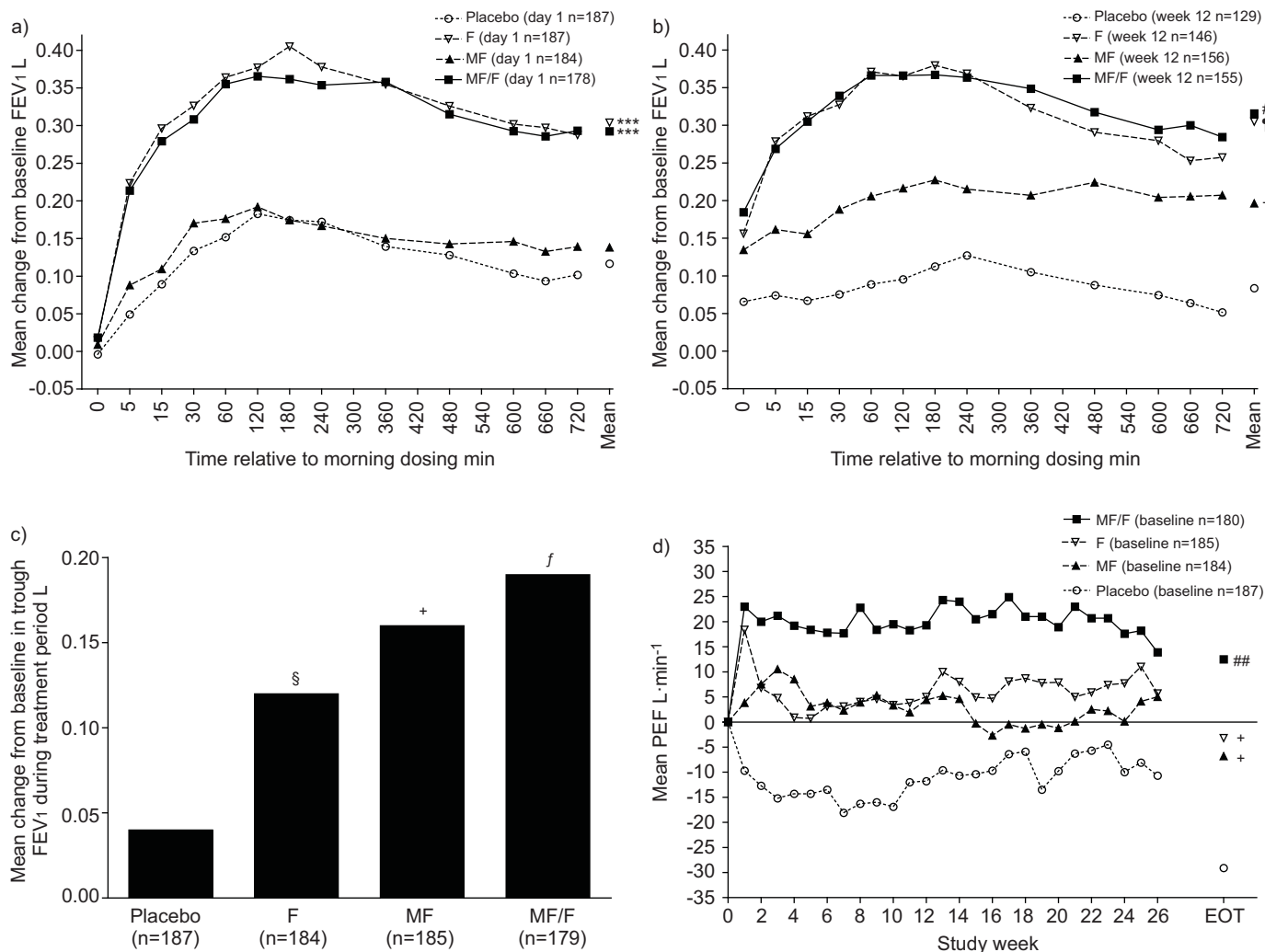


FIGURE 4. Serial evaluations (0–12 h) of forced expiratory volume in 1 s (FEV₁) at a) day 1 and b) week 12. Please note nonlinear scale up to 60 min. c) Mean change from baseline in trough (morning pre-dose) FEV₁ by longitudinal analysis. d) Weekly mean morning peak expiratory flow (PEF). F: formoterol; MF: mometasone furoate; EOT: end of treatment. ***: $p < 0.001$ versus placebo and MF; #: $p \leq 0.001$ versus placebo and MF; †: $p < 0.004$ versus placebo and MF; ‡: $p < 0.001$ versus placebo; §: $p = 0.019$ versus placebo; ††: $p \leq 0.029$ versus placebo and F; †††: $p \leq 0.007$ versus placebo, F and MF.

monotherapy, which suggests a possible additive effect between MF and F in the combined formulation. A numerical but not statistically significant reduction in the incidence of clinically judged deteriorations was also observed with MF/F compared with MF monotherapy (1.6% versus 2.7%, respectively), although this study was not powered to measure this comparison. Clinically judged deteriorations are relatively rare events that are perhaps the most clinically relevant subgroup of asthma deteriorations, as they have the potential to be life threatening. Given the general rarity of such events, it is perhaps not surprising that incidence rates in this study were not significantly different between the MF/F and MF treatment groups, and that longer and/or larger trials may be needed to demonstrate a significant treatment effect. Overall, these data show that MF/F is capable of reducing the incidence of asthma deteriorations to a significantly greater extent than MF monotherapy, suggesting that MF/F 100/10 µg *b.i.d.* is a viable treatment option for patients with persistent asthma who are not well controlled with low-dose ICS therapy.

The FEV₁ AUC_{0–12h} results confirmed the significant contribution of F to MF/F. Improvements in lung function were observed as early as day 1 and sustained throughout treatment. Serial spirometry demonstrated that bronchodilation occurred rapidly (within 5 min of drug administration) and was sustained throughout the 12-h evaluation. Whereas inclusion of an active run-in may have contributed to a higher baseline and lower bronchodilator effect, the data reported here may reflect a more clinically relevant assessment of the efficacy of an ICS/LABA combination than in trials without an ICS treatment run-in. There was no evidence of the development of tolerance to MF/F during treatment. Improvements in PEF observed at week 1 with F monotherapy may have been due to a carry-over effect from the MF monotherapy run-in period.

The impact of asthma on patient QoL is substantial, and patients may be unable to perform normal daily activities [24, 25]. Therefore, it is important to continuously assess asthma control, as it can fluctuate over time and patients with asthma

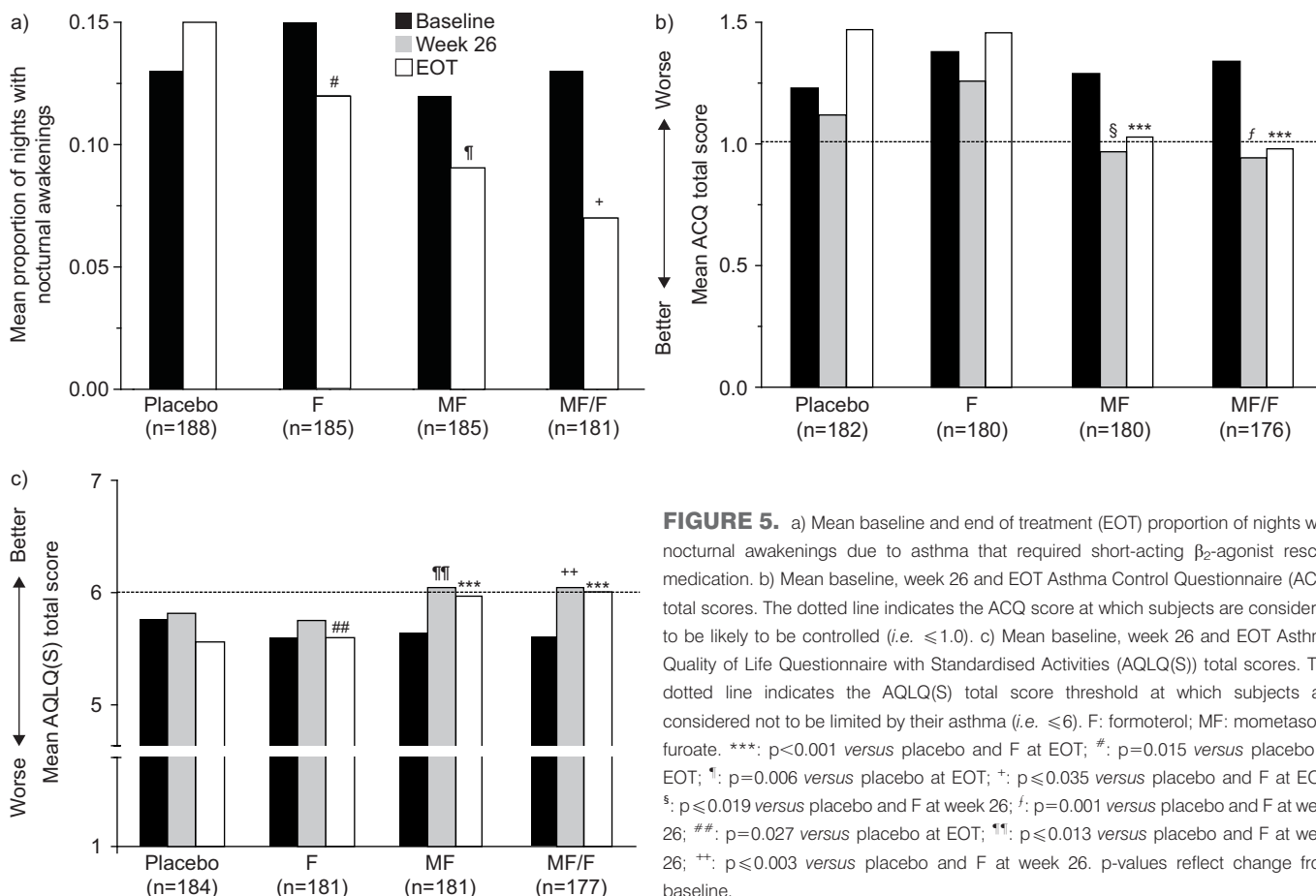


TABLE 3 Treatment-emergent adverse events reported in $\geq 2\%$ of all treated subjects during the double-blind period

	Placebo	F 10 μ g	MF 100 μ g	MF/F 100/10 μ g	Total
Subjects n	188	188	188	182	746
Any treatment-emergent adverse events	66 (35.1)	75 (39.9)	86 (45.7)	75 (41.2)	302 (40.5)
Upper respiratory tract infection	12 (6.4)	20 (10.6)	17 (9.0)	10 (5.5)	59 (7.9)
Nasopharyngitis	5 (2.7)	7 (3.7)	13 (6.9)	17 (9.3)	42 (5.6)
Headache	7 (3.7)	9 (4.8)	11 (5.9)	12 (6.6)	39 (5.2)
Sinusitis	1 (0.5)	8 (4.3)	8 (4.3)	3 (1.6)	20 (2.7)
Pharyngolaryngeal pain	4 (2.1)	5 (2.7)	4 (2.1)	7 (3.8)	20 (2.7)
Pharyngitis	6 (3.2)	3 (1.6)	2 (1.1)	5 (2.7)	16 (2.1)
Cough	5 (2.7)	4 (2.1)	5 (2.7)	2 (1.1)	16 (2.1)
Pyrexia	2 (1.1)	4 (2.1)	3 (1.6)	1 (0.5)	10 (1.3)
Bronchitis	5 (2.7)	3 (1.6)	5 (2.7)	1 (0.5)	14 (1.9)
Influenza	4 (2.1)	3 (1.6)	4 (2.1)	3 (1.6)	14 (1.9)
Viral infection	4 (2.1)	1 (0.5)	5 (2.7)	3 (1.6)	13 (1.7)
Dyspepsia	0	0	4 (2.1)	1 (0.5)	5 (0.7)
Chest pain	0	1 (0.5)	4 (2.1)	0	5 (0.7)
Subjects reporting treatment-related adverse events	8 (4.3)	15 (8.0)	10 (5.3)	16 (8.8)	49 (6.6)
Subjects reporting severe adverse events	5 (2.7)	7 (3.7)	8 (4.3)	9 (4.9)	29 (3.9)

Data are presented as n (%), unless otherwise stated. F: formoterol; MF: mometasone furoate.

that is not well controlled are at risk for deterioration [3]. Patients requiring rescue medication for nocturnal awakenings are also at increased risk of asthma deterioration. In this study, subjects receiving MF/F reported significant and clinically meaningful improvement in asthma control, QoL and need for rescue medication.

Optimal control of persistent asthma requires the use of varying strengths of medication depending on disease severity. A low-dose ICS/LABA combination using the lowest effective dose is an important therapeutic option to reduce the potential for AEs. Only three asthma attacks were observed in the MF/F group in this 26-week study, suggesting that 100 µg of MF *b.i.d.*, combined with a LABA, was sufficient for disease control.

This trial was designed to prevent the ethical and safety concerns associated with placebo and LABA monotherapy in patients with persistent asthma by constant monitoring of patient e-diary data, thereby ensuring that any deterioration was quickly detected. The safety data indicate that all three treatments were well tolerated at the doses studied. The number and type of AEs in the MF/F group were similar to those with the individual components [26, 27] and similar to those reported for other ICS/LABA combination drugs. Most AEs were mild to moderate in severity and considered unrelated to treatment. No treatment-related severe AEs, deaths or life-threatening events were reported. In this trial, we detected very low rates of dysphonia and oral candidiasis, two AEs that are typically associated with ICS therapy.

Conclusions

This study demonstrates that MDI-administered MF/F 100/10 µg *b.i.d.* was well tolerated and a more efficacious overall asthma treatment than either of its components in subjects not well controlled on low-dose ICS monotherapy, with both MF and F contributing to the therapeutic efficacy of the combination product. Importantly, the MF/F 100/10 µg *b.i.d.* combination was superior to MF 100 µg *b.i.d.* monotherapy in exacerbation incidence and change from baseline to week 12 in FEV₁ AUC_{0-12h}. Such results support the use of MF/F combination therapy for the management of asthma not well controlled by low-dose ICS therapy.

STATEMENT OF INTEREST

Statements of interest for all authors and the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

ACKNOWLEDGEMENTS

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The authors would like to acknowledge D. Gates of Merck Sharp & Dohme Corp. (Whitehouse Station, NJ, USA) for his assistance with statistical design and analyses. Original editorial support was provided by R. Beck Jr, P. Lane and M. Nori, all of UBC Scientific Solutions (Southport, CT, USA); additional editorial support was provided by B.D. Mahon and T. Wetter of Complete Publication Solutions, LLC (Horsham, PA, USA), and J. Moreno-Cantu, Office of the Chief Medical Officer, Merck Sharp & Dohme Corp. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station.

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