ERJ Express. **Published on August 4, 2011 as doi: 10.1183/09031936.00020310**

Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function

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Word count: 3880

Tables/Figures: 3/5; total 8

ABSTRACT

This study evaluated the effect of mometasone furoate/formoterol (MF/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 years with asthma not well controlled on low-dose inhaled corticosteroids. After a 2–3-week open-label run-in (MF 100 µg twice-daily [*b.i.d.*]), 746 subjects were randomised to receive MF/F 100/10 µg, MF 100 µg, F 10 µg, or placebo *b.i.d.* Coprimary endpoints were time-to-first asthma deterioration (MF/F *versus* F to assess MF's effect) and change in FEV_1 $AUC_{0–12h}$ (baseline−week 12; MF/F *versus* MF to assess F's effect).

The therapeutic effect of MF in the combination was demonstrated by a reduction in asthma deterioration incidence with MF/F *versu*s F and a delayed time-to-first asthma deterioration ($p<0.001$). Asthma deterioration incidence was also reduced with MF/F *versu*s MF ($p=0.006$). The therapeutic effect of F in the combination was demonstrated by MF/F *versus* MF in FEV_1 $AUC_{0–12h}$ change (4.00 vs 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.

Word count: 200

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

INTRODUCTION

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%], 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 hours 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.

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 (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- to 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/dose. Although recent US regulatory guidelines 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, Ohio) alerts based on twice-daily recordings of peak expiratory flow (PEF), asthma symptoms, and short-acting β_2-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-hour access to a physician consultation.

Subjects were eligible for enrolment if they were aged ≥12 years with asthma ≥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 one second (FEV_1) of ≥12% and a volume increase of ≥200 mL ~15–20 minutes after administration of albuterol/salbutamol or of a nebulised SABA; PEF variability of ≥20%; or 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-years), clinically significant abnormal vital signs, or visible evidence of oropharyngeal candidiasis at baseline or earlier. At baseline, FEV_1 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 (AM) 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 endpoints

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 FEV_1 of >20% from baseline at any study visit or a decrease in PEF of >30% from baseline for ≥2 consecutive days at any time during the treatment period). The contribution of F to MF/F was assessed by measuring the mean change in FEV_1 area-under-the-curve of serial spirometry measurements over the 12-hour period following the AM dose (FEV_1 $AUC_{0–12h}$) 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 endpoints (MF/F *versus* placebo) were (1) change from baseline in AM FEV_1 pre-dose assessment or trough FEV_1, at each visit and endpoint; (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 endpoints included (1) time-to-first moderate asthma exacerbation defined as any one of the following criteria: 2 consecutive nights with ≥1 nocturnal awakening due to asthma symptoms requiring SABA use; a decrease in 24-hour PEF of ≥25% on 2 consecutive days of treatment; a clinically significant increase in short-acting bronchodilator use (2 consecutive days of ≥8 units of SABA); (2) changes from baseline to week 26 in AM PEF and 24-hour symptom scores; and (3) 24-hour SABA usage.

Safety and tolerability

Reports of adverse events (AEs) and serious AEs (SAEs), physical examinations, clinical laboratory tests, vital signs, and electrocardiograms (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/group expected to remain at week 26). This sample size was required to detect a difference of 3.1 L x hour in change from baseline FEV_1 AUC_{0-12h} (an average and clinically meaningful difference of 0.26 L in FEV_1 across the 12-hour 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. Analysis of

covariance (ANCOVA) with treatment and study site as effects and baseline as a continuous covariate was used to analyse mean FEV_1 $AUC_{0–12h}$ 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-hour SABA use were assessed using pairwise comparisons of least square means (from the described ANCOVA model) between treatment groups. Trough FEV_1 was analysed by the longitudinal average method due to a 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 FEV_1 $AUC_{0–12h}$ data were imputed prior to analysis, provided data were available at the 0- and 2-hour time points. FEV_1 $AUC_{0–12h}$ data from subjects who were terminated or used SABA prior to the final 12-hour time point were imputed using the last observation carried forward (LOCF; ≥2 hours post-dosing) so that a full set of serial FEV_1 measurements were available for an AUC calculation at a given visit. An endpoint 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 536 subjects (72%) who completed the double-blind treatment

period, 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 subjects (3.8%) 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 percent predicted FEV_1 of 75% and mean FEV_1/forced vital capacity (FVC) 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; 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 ($p\leq0.006$; Fig 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 ($p\leq0.002$).

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 FEV_1 or PEF values), for a total of 52 subjects experiencing a clinically judged deterioration at some time during the study (Table 2, 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 ($p \leq 0.001$) groups. 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, Fig. 3c). Compared with placebo, significantly fewer subjects receiving MF or F ($p \leq 0.013$) experienced moderate exacerbations.

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 minutes postdose, peaked at ~2 hours, and were sustained throughout the 12-hour 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 FEV_1 AUC_{0-12h} improvement from baseline at week 12 with MF/F *versus* MF alone (4.00 vs 2.53 L x hour, respectively; $p=0.001$). The effect of F was also demonstrated by a significantly greater mean improvement in FEV_1 AUC_{0-12h} (3.83 L x hour) *versus* MF and placebo (2.53 and 1.11 L x hour, respectively; $p \leq 0.004$). Both the MF/F *versus* MF and F *versus* placebo comparisons

remained statistically significant through week 26. Treatment with MF/F and MF also resulted in a significantly greater mean improvement in FEV_1 $AUC_{0–12h}$ at week 12 compared with placebo (p≤0.002). Mean FEV_1 $AUC_{0–12h}$ improvements at week 12 in placebo, F, MF, and MF/F treatment groups corresponded to mean increases of 0.09 L (4.1%), 0.32 L (12.3%), 0.21 L (9.0%), and 0.33 L (13.8%) in FEV_1, respectively.

For other lung function evaluations, longitudinal analysis of trough FEV_1 showed that MF/F improved AM predose lung function more than F alone (p=0.029) during treatment (Fig. 4c). Also, mean percent changes from baseline to EOT in AM 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 AM PEF was significantly greater for MF/F than for the other treatment groups (p≤0.007). For MF/F *versus* placebo the magnitude of change was 41.6 L/min, attaining a clinically relevant difference of >15 L/min [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≤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-hour SABA use was significantly reduced from baseline in both MF/F (–53.4%, –0.16 puffs/day) and MF (–47.5%, –0.37 puffs/day) groups *versus* placebo (+47.5%, +0.82 puffs/day; p≤0.004). Additionally, MF was significantly better than F (+82.6%, +0.31 puffs/day; 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 ("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 [MID] 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 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 (MID ≥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). Mean AQLQ[S] total scores at EOT suggested that asthma no longer impaired QoL (ie, 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 subjects (0.5%), 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 (4 in the MF group, 3 in the F group, and 2 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 United States 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 coprimary endpoints 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 coprimary endpoint 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 coprimary endpoint of mean change in FEV_1 $AUC_{0–12h}$ 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 (ATS/ERS) 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 to 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 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 FEV_1 $AUC_{0–12h}$ 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 minutes of drug administration) and was sustained throughout the 12-hour 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 carryover 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]. It is therefore important to continuously assess asthma control, as it can fluctuate over time, and patients with asthma 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 FEV_1 $AUC_{0–12h}$. Such results support the use of MF/F combination therapy for the management of asthma not well controlled by low-dose ICS therapy.

Acknowledgements

This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ. The authors would like to acknowledge Davis Gates of Merck Research Laboratories for his assistance with statistical design and analyses. Original editorial support was provided by Ray Beck, Jr, PhD, Paul Lane, PhD, and Mukund Nori, PhD, MBA, of UBC Scientific Solutions; additional editorial support was provided by Brett D. Mahon, PhD, and Tracy Wetter, PhD, of Complete Publication Solutions, LLC; Jorge Moreno-Cantu, PhD, Office of the Chief Medical Officer, Merck & Co., Rahway, NJ. Editorial support was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ.

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Figure Legends

FIGURE 1. Subject disposition. F=formoterol; MF=mometasone furoate; MF/F=mometasone furoate/formoterol.

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

FIGURE 3. a) Number of subjects with ≥1 asthma deterioration (ie, severe asthma exacerbation). *p≤0.002 *versus* placebo and F. †p≤0.006 *versus* placebo, F, and MF. **b)** Number of subjects with ≥1 clinically judged deterioration (*i.e.*, asthma attack) *p≤0.008 *versus* placebo and F. †p≤0.001 *versus* placebo and F. **c)** Number of subjects with ≥1 moderate exacerbation. *p=0.013 *versus* placebo. †p<0.001 *versus* placebo. ‡p≤0.002 *versus* placebo, F, and MF. F=formoterol; MF=mometasone furoate; MF/F=mometasone furoate/formoterol.

FIGURE 4. a) Serial evaluations (0-12 hours) of FEV_1 at day 1. *p<0.001 versus placebo and MF. †p<0.001 *versus* placebo and MF. **b)** Serial evaluations (0-12 hours) of FEV_1 at week 12. *p≤0.001 *versus* placebo and MF. †p≤0.004 *versus* placebo and MF. ‡p<0.001 *versus* placebo. **c)** Mean change from baseline in trough (AM predose) FEV_1. *p=0.019 *versus* placebo. †p<0.001 *versus* placebo. ‡p≤0.029 *versus* placebo and F. **d)** Weekly mean AM PEF. *p≤0.007 *versus* placebo, F, and MF. †p<0.001 *versus* placebo. ‡p<0.001 *versus* placebo. AM=morning; EOT=end of treatment; F=formoterol; FEV_1=forced expiratory volume in 1 second; MF=mometasone furoate; MF/F=mometasone furoate/formoterol; PEF=peak expiratory flow.

FIGURE 5. a) Mean baseline and EOT proportion of nights with nocturnal awakenings due to asthma that required SABA rescue medication. P-values reflect change from baseline. *p=0.015 *versus* placebo at EOT. †p=0.006 *versus* placebo at EOT. ‡p≤0.035 *versus* placebo and F at EOT. **b)** Mean baseline, week 26, and EOT ACQ total scores. The dotted line indicates the ACQ score at which subjects are considered to be "likely to be controlled" (*i.e.*, ≤1.0). P-values reflect change from baseline. *p≤0.019 *versus* placebo and F at W26. †p<0.001 *versus* placebo and F at EOT. ‡p=0.001 *versus* placebo and F at W26. §p<0.001 *versus* placebo and F at EOT. **c)** Mean baseline, week 26, and EOT AQLQ[S] total scores. The dotted line indicates the AQLQ[S] total score threshold at which subjects are considered not to be limited by their asthma (*i.e.*, ≤6). P-values reflect change from baseline. *p=0.027 *versus* placebo at EOT. †p≤0.013 *versus* placebo and F at W26. ‡p<0.001 *versus* placebo and F at EOT. §p≤0.003 *versus* placebo and F at W26. ‖p<0.001 *versus* placebo and F at EOT. ACQ=Asthma Control Questionnaire; AQLQ[S]=Asthma Quality of Life Questionnaire with Standardised Activities; B=baseline; EOT=end of treatment; F=formoterol; MF=mometasone furoate; MF/F=mometasone furoate/formoterol; QoL=quality of life; SABA=short-acting β_2-agonist; W26=week 26.

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

	Placebo (n=188)	**F 10 µg (n=188)**	**MF 100 µg (n=188)**	**MF/F 100/10 µg (n=182)**	**Total (N=746)**
General demographics					
Gender, female, n (%)	106 (56)	103 (55)	105 (56)	99 (54)	413 (55)
Race, white, n (%)	143 (76)	148 (79)	140 (74)	142 (78)	573 (77)
Age, years, mean (SD)	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, years, mean (SD)	13.5 (13.7)	15.4 (13.8)	15.9 (14.4)	14.3 (12.5)	14.8 (13.6)
Mean (SD) FEV_1 at screening					
Litres	2.5 (0.7)	2.6 (0.7)	2.5 (0.6)	2.6 (0.8)	2.5 (0.7)
Percent predicted	76.0 (9.2)	76.3 (9.8)	75.8 (9.9)	76.9 (10.2)	76.2 (9.7)
Percent reversibility	19.1 (11.4)	19.8 (9.9)	17.3 (8.9)	18.6 (8.8)	18.7 (9.8)
Mean (SD) FEV_1 at baseline					
Litres	2.5 (0.7)	2.5 (0.7)	2.5 (0.7)	2.6 (0.7)	2.5 (0.7)
Percent predicted	75.4 (8.2)	74.9 (8.2)	74.5 (8.9)	75.6 (7.7)	75.1 (8.3)
Mean (SD) FEV_1/FVC	0.74 (0.10)	0.75 (0.10)	0.74 (0.10)	0.75 (0.09)	0.75 (0.10)
Mean ACQ total score at baseline (SD)	1.2 (0.7)	1.4 (0.8)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
Mean AQLQ[S] total score at baseline (SD)	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,[a] n (%)	136 (72)	126 (67)	125 (66)	126 (69)	513 (69)
Prior ICS use with a LABA,[a] n (%)	56 (30)	65 (35)	64 (34)	60 (33)	245 (33)

ACQ=Asthma Control Questionnaire; AQLQ[S]=Asthma Quality of Life Questionnaire with Standardised Activities; F=formoterol; FEV_1=forced expiratory volume in 1 second;

FVC=forced vital capacity; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; MF=mometasone furoate; MF/F=mometasone furoate/formoterol; SD=standard deviation.

[a]Subjects could have used more than one ICS without LABA and/or ICS with LABA during the 3-month period before screening.

TABLE 2. Incidence (n [%]) of asthma deteriorations, clinically judged deteriorations, and moderate asthma exacerbations

	Placebo (n=188)	**F 10 µg (n=188)**	**MF 100 µg (n=188)**	**MF/F 100/10 µg (n=182)**
*Asthma deterioration (*i.e.*, severe asthma exacerbation)*				
First asthma deterioration	86 (46)	84 (45)	53 (28)	30 (17)
FEV_1[a]	29 (15)	25 (13)	14 (7)	5 (3)
PEF[b]	42 (22)	44 (23)	35 (19)	23 (13)
Clinically judged deterioration[c]	13 (7)	10 (5)	3 (2)	1 (<1)
PEF and deterioration	1 (<1)	2 (1)	1 (<1)	0
FEV_1 and deterioration	1 (<1)	3 (2)	0	1 (<1)
*Clinically judged deterioration (*i.e.*, asthma attack)*				
Any clinically judged deterioration[d]	27 (14)	17 (9)	5 (3)	3 (2)
Hospitalisation	0 (0)	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[e]	8 (4)	2 (1)	1 (<1)	0
Moderate exacerbation				
Any moderate asthma exacerbation	123 (65)	104 (55)	91 (48)	61 (34)
Nocturnal awakening[f]	69 (37)	54 (29)	49 (26)	33 (18)
PEF[g]	47 (25)	44 (23)	36 (19)	24 (13)

SABA rescue medication[h]	2 (1)	3 (2)	3 (2)	4 (2)
Nocturnal awakening and SABA rescue medication	3 (2)	3 (2)	1 (<1)	0
PEF and SABA rescue medication	0	0	1 (<1)	0

F=formoterol; FEV_1=forced expiratory volume in 1 s; MF=mometasone furoate; MF/F=mometasone furoate/formoterol; PEF=peak expiratory flow; SABA=short-acting β_2-agonist.

[a]Decrease in FEV_1 <80% of baseline.

[b]Decrease in PEF <70% of baseline on 2 consecutive days.

[c]Requiring a course of action, as judged by the clinical investigator.

[d]Patients can have more than one course of action for a clinically judged deterioration.

[e]Includes only subjects with no record of systemic corticosteroid use.

[f]One or more nocturnal awakenings on 2 consecutive nights (requiring SABA).

[g]Decrease in PEF below 75% of baseline on 2 consecutive days (no more than 1 day of decrease).

[h]More than eight combined units of SABA rescue medication use on 2 consecutive days.

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

	Subjects reporting, n (%)				
	Placebo (n=188)	**F 10 µg** (n=188)	**MF 100 µg** (n=188)	**MF/F 100/10 µg** (n=182)	**Total** (N=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	8 (4.3)	15 (8.0)	10 (5.3)	16 (8.8)	49 (6.6)

adverse events					
Subjects reporting severe adverse events	5 (2.7)	7 (3.7)	8 (4.3)	9 (4.9)	29 (3.9)

F=formoterol; MF=mometasone furoate; MF/F=mometasone furoate/formoterol.

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FIGURE 1. Subject disposition.

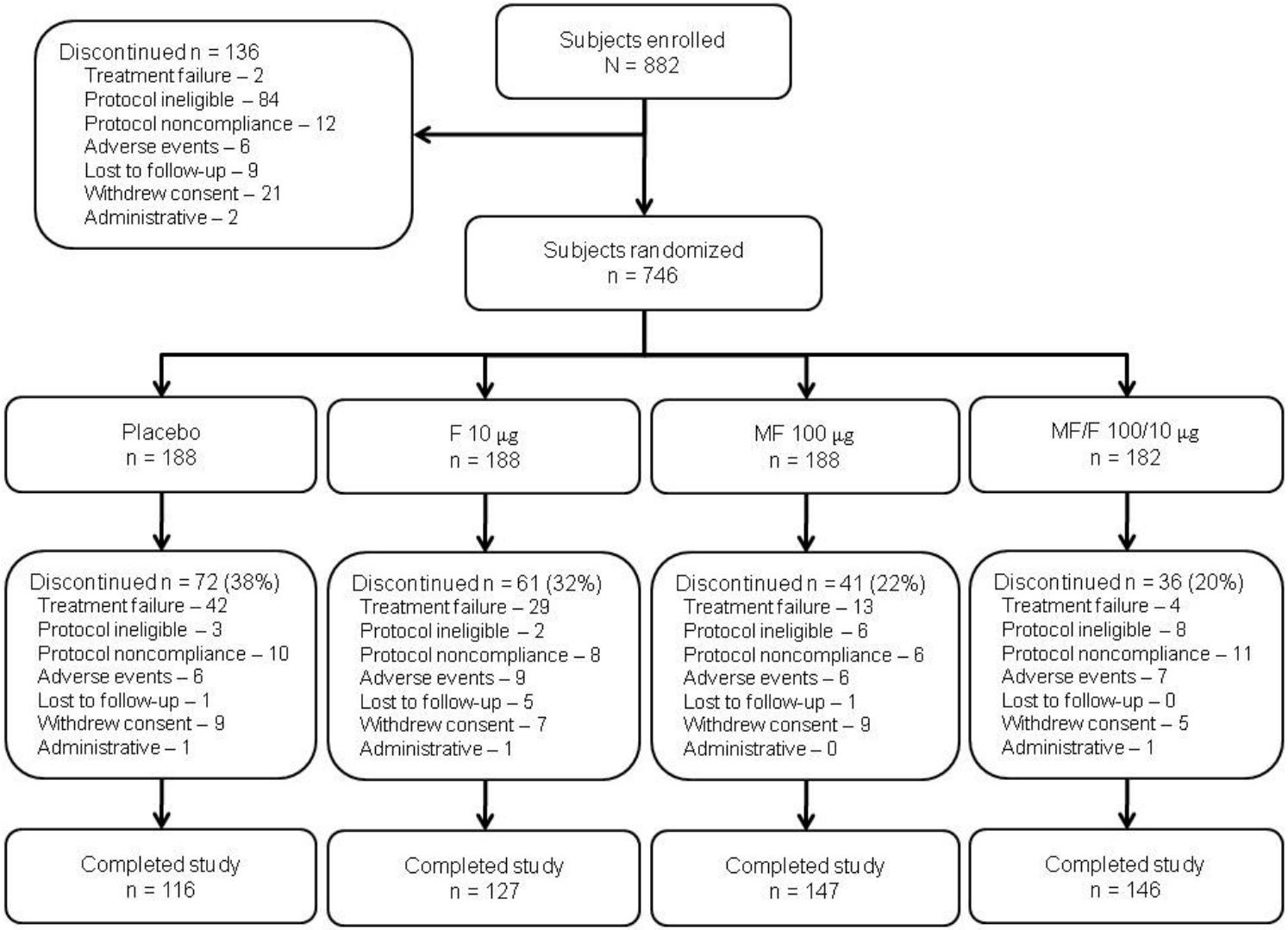

FIGURE 2. Time-to-first asthma deterioration up to week 26 by treatment arm.

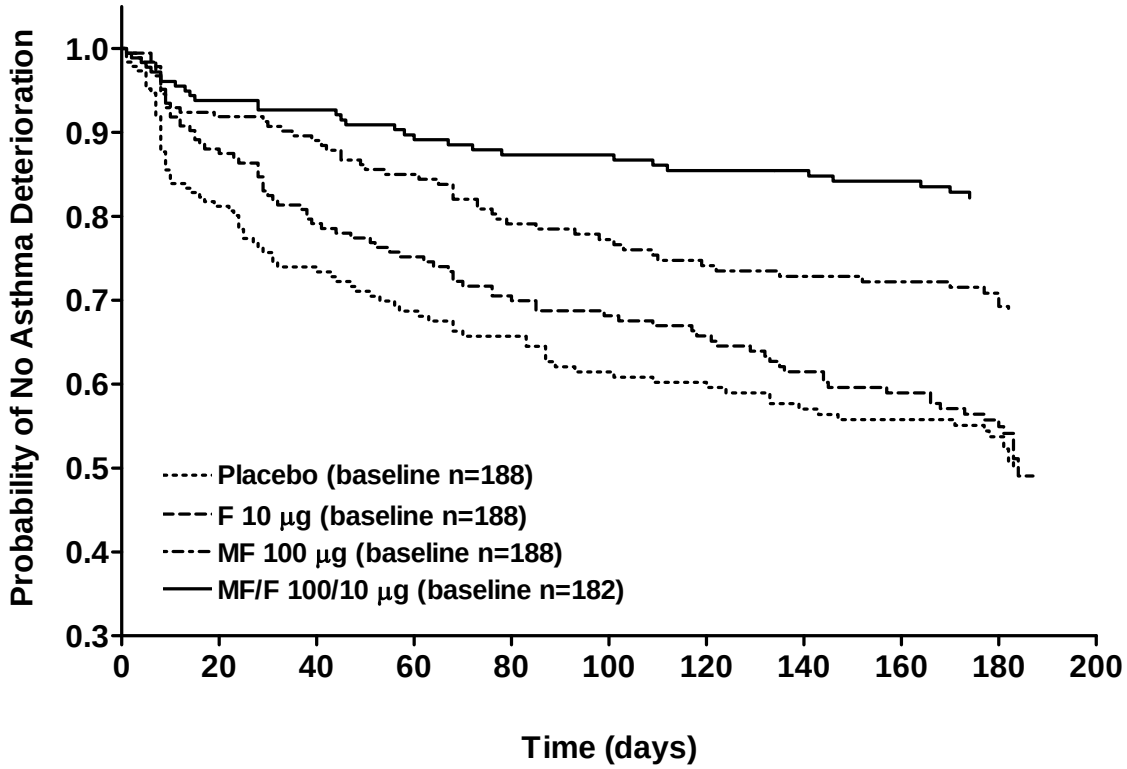

FIGURE 3A. Number of subjects with ≥1 asthma deterioration.

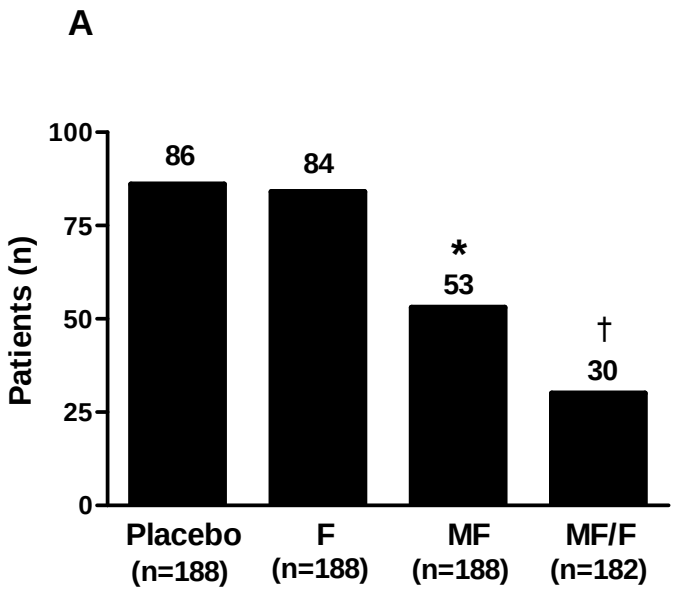

FIGURE 3B. Number of subjects with ≥1 clinically judged deterioration.

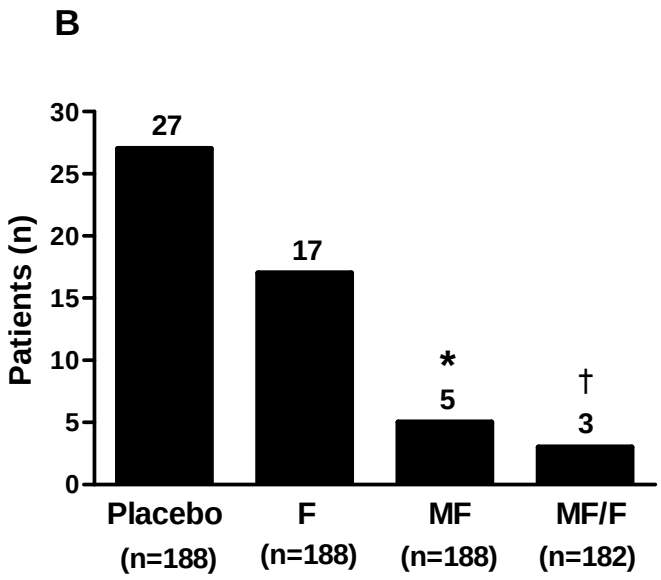

FIGURE 3C. Number of subjects with ≥1 moderate exacerbation.

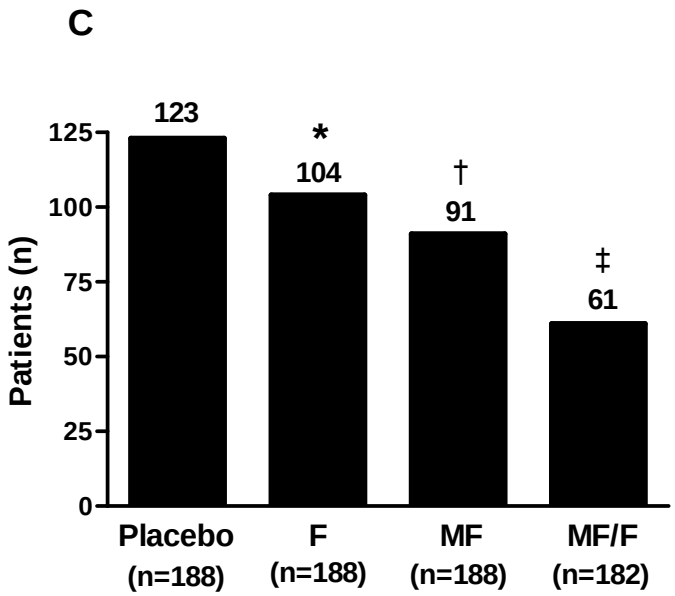

FIGURE 4A. Serial evaluations (0-12 hours) of FEV_1 at day 1.

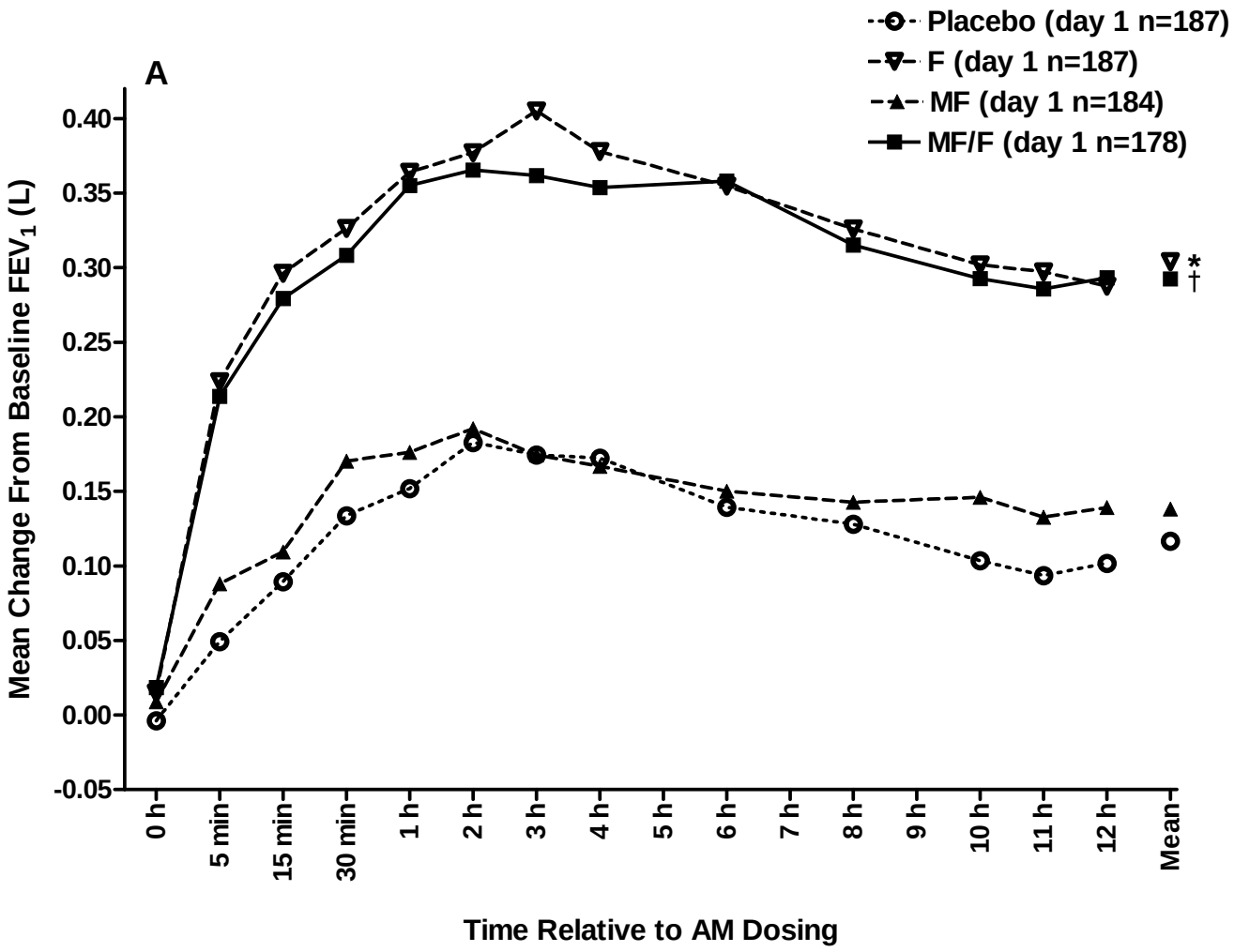

FIGURE 4B. Serial evaluations (0-12 hours) of FEV_1 at week 12.

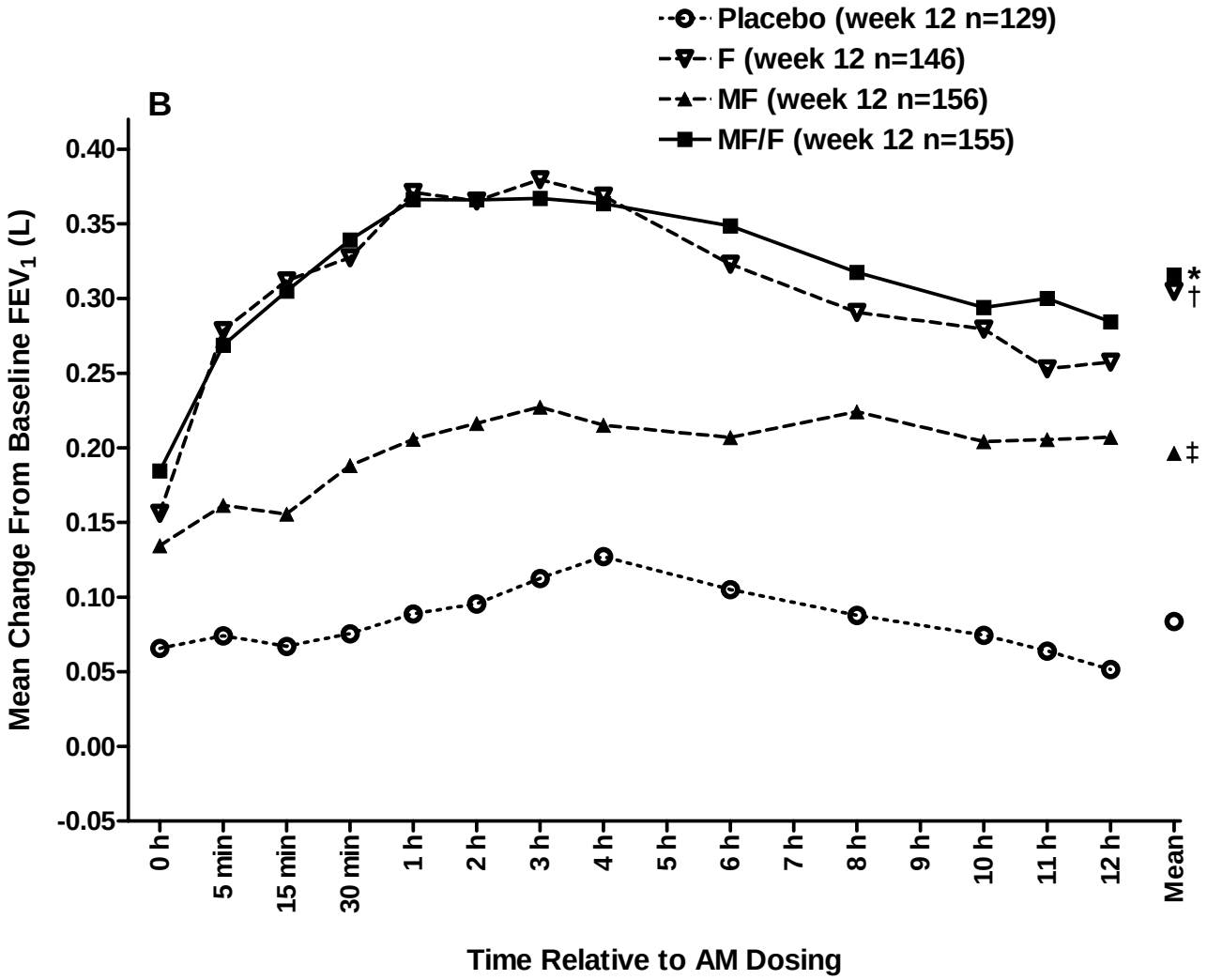

FIGURE 4C. Mean change from baseline in trough (AM predose) FEV_1.

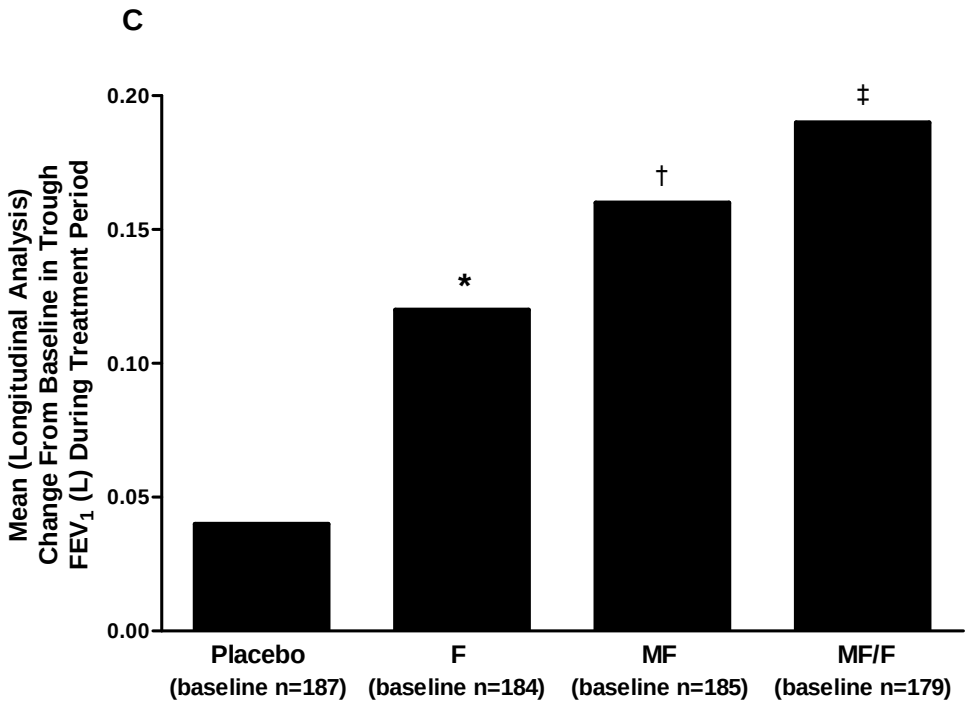

FIGURE 4D. Weekly mean AM PEF.

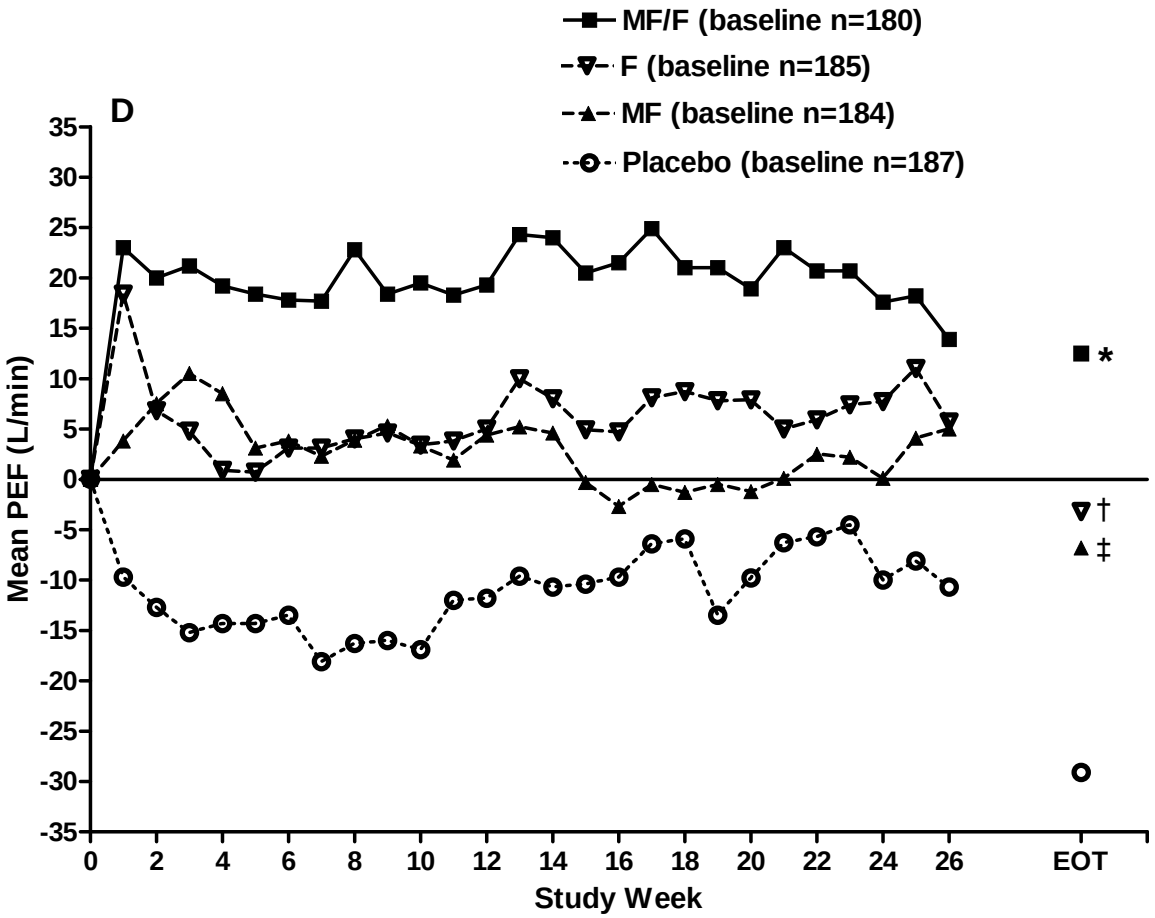

FIGURE 5A. Mean baseline and EOT proportion of nights with nocturnal awakenings due to asthma that required SABA rescue medication.

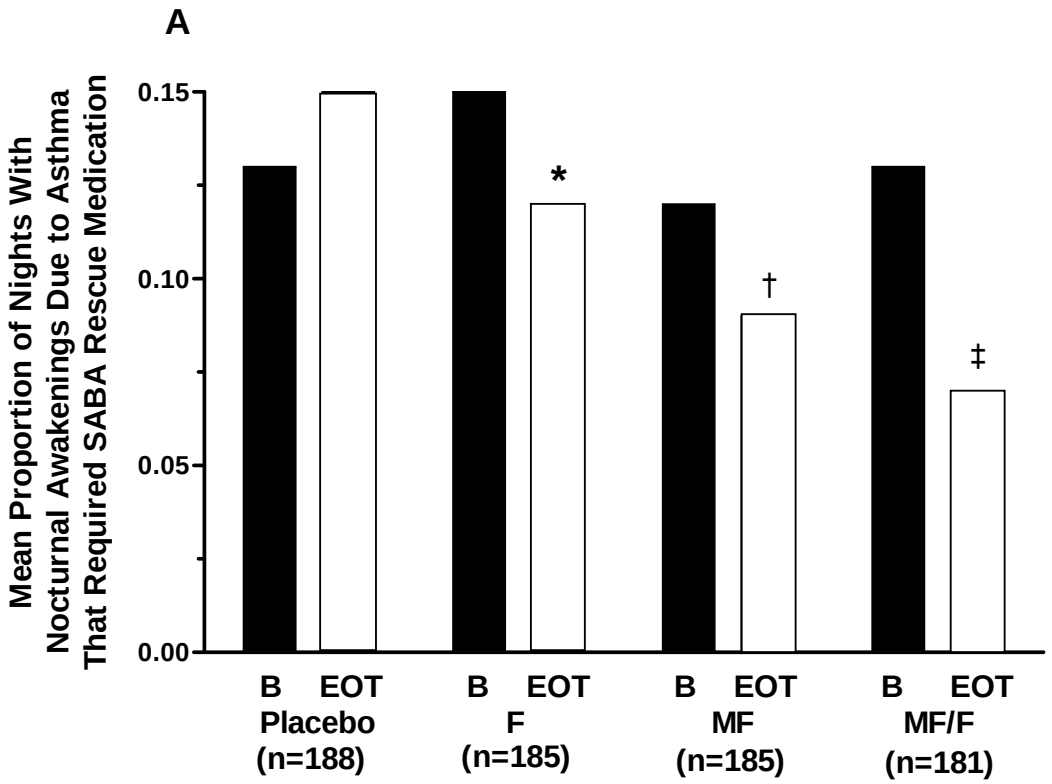

FIGURE 5B. Mean baseline, week 26, and EOT ACQ total scores.

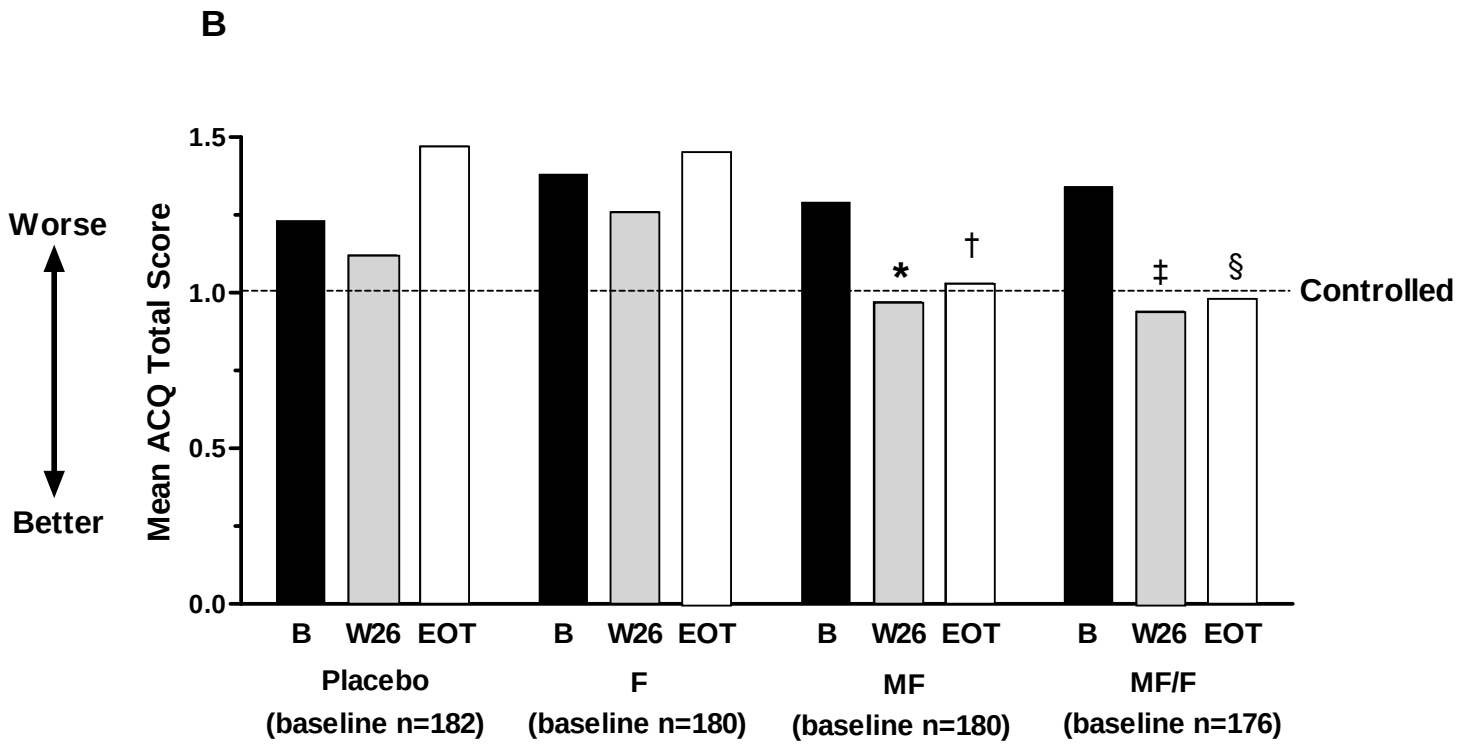

FIGURE 5C. Mean baseline, week 26, and EOT AQLQ[S] total scores.