

Long-Term Safety of Mometasone Furoate/Formoterol 200/10 µg BID and 400/10 µg BID in Persistent Asthmatics: Analysis of Adverse Event Incidence, Plasma Cortisol, and Ocular Changes

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ABSTRACT

Rationale: The safety of long-term use of mometasone furoate/formoterol (MF/F) combination administered via metered dose inhaler (MDI) for treatment of asthma has not been elucidated. We report the results of a 1-year study undertaken to assess the effect of 2 different dosing levels of MF/F on incidence of adverse events (AEs), plasma cortisol level, and ocular changes.

Methods: Subjects (≥12 years) with persistent asthma treated with an inhaled corticosteroid (ICS) were stratified by previous ICS dose and randomized to MF/F or fluticasone/salmeterol combination (F/S) in a 2:1 ratio including twice daily (BID) doses of either MF/F 200/10 µg (n=141), F/S 250/50 µg (n=68), MF/F 400/10 µg (n=130), or F/S 500/50 µg (n=65). The number of subjects reporting AEs, plasma cortisol 24-hour area under the curve (AUC), and ≥1 grade change in Lens Opacities Classification System III and intraocular pressure were determined.

Results: Both MF/F doses were well tolerated and associated with AEs of frequency and nature similar to those observed with F/S. Overall, 99 subjects (25%; MF/F 200/10 µg =28%; MF/F 400/10 µg =23%; F/S 250/50 µg =24%; F/S 500/50 µg =20%) reported treatment-related AEs. Compared with baseline, both MF/F and F/S caused a similar decrease in week 52 plasma cortisol 24-hour AUC. For subjects on lower doses of ICS, decreases were MF/F=2% and F/S=17%; on higher doses of ICS, decreases were MF/F=30% and F/S=32%. Overall, the percentage of ocular events was low (1.5%–5.9%) and similar between MF/F and F/S. The clinical relevance of cortisol and ocular changes could not be elucidated since there was no placebo or active comparator (eg, oral corticosteroid).

Conclusion: In subjects with persistent asthma, treatment with MF/F 200/10 and 400/10 µg BID was associated with a safety and tolerability profile similar to F/S 250/50 and 500/50 µg BID.

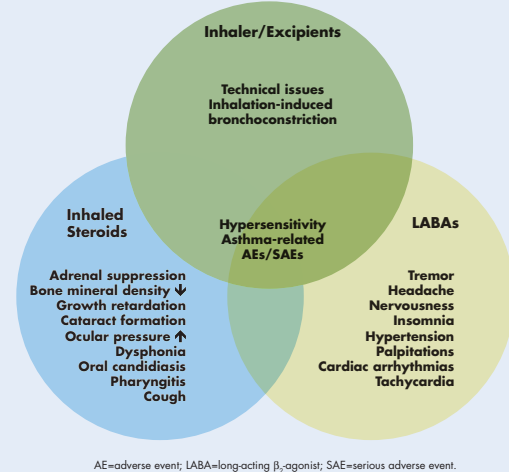
INTRODUCTION

- When inhaled corticosteroid (ICS) treatment alone is not sufficient to establish and maintain asthma control, international asthma management guidelines recommend the addition of a long-acting β₂-agonist (LABA).^{1,2}
- ICSs and LABAs are generally well tolerated. Common local ICS-related adverse events (AEs) include oral candidiasis, pharyngitis, dysphonia, and cough;³ common LABA-related AEs include tremor, heart palpitations, and headache (Figure 1).⁴
- Suppression of the hypothalamic-pituitary-adrenal axis and ocular changes are additional systemic safety concerns with ICSs.⁵
- Fluticasone/salmeterol (F/S) hydrofluoroalkane delivered via a metered-dose inhaler (MDI) is a commonly prescribed ICS/LABA combination.
 - The most common AEs associated with F/S are headache, upper respiratory tract infection, and throat irritation.⁵
- Mometasone furoate/formoterol (MF/F) administered via a pressurized MDI is a combination ICS/LABA recently approved and available in the US as 2 dosages (200/10 µg^a and 400/10 µg^b twice daily [BID]) for patients with persistent asthma aged 12 years and older; MF/F MDI is currently under review for approval by European regulatory authorities.
 - Mometasone furoate (MF) is a safe and well-tolerated ICS that has been demonstrated to improve lung function, asthma symptoms, and quality of life at doses ranging from 100 to 800 µg per day.^{6,10}
 - Formoterol (F) is a LABA characterized by a fast onset of action and has been demonstrated to improve lung function and asthma symptoms.¹¹
- The individual components of MF/F have well-established long-term safety records in patients with obstructive airway disease,^{12,15} and MF/F is expected to have similar safety characteristics.

OBJECTIVE

- To evaluate the long-term safety of MF/F 200/10 µg BID and 400/10 µg BID in subjects with persistent asthma previously treated with an ICS with or without a LABA

Figure 1. Known Class Effects of Inhaled Corticosteroids, Long-Acting β₂-Agonists, and Inhalers



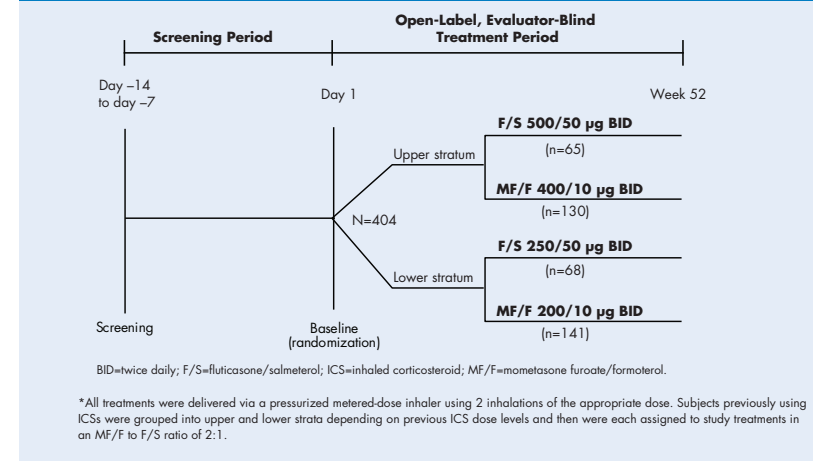
AE=adverse event; LABA=long-acting β₂-agonist; SAE=serious adverse event.

METHODS

Study Design

- 52-week, randomized, parallel-group, multicenter, evaluator-blind, open-label study conducted at 27 sites in Central and South America
- Subjects were stratified based on previous ICS dose and randomized in a 2:1 ratio (MF/F vs F/S combination) to 1 of 4 groups (Figure 2).
 - Lower-dose stratum (subjects previously using >500 to 1000 µg beclomethasone-chlorofluorocarbon [CFC], >250 to 500 µg beclomethasone-hydrofluoroalkane [HFA], >600 to 1000 µg budesonide via dry powder inhaler [DPI], >1000 to 2000 µg fluticasone, >250 to 500 µg fluticasone, 400 µg MF-DPI, or >1000 to 2000 µg triamcinolone acetonide)
 - MF/F-MDI 200/10 µg BID (delivered as 2 inhalations of 100/5 µg)
 - F/S-MDI (250/50 µg BID delivered as 2 inhalations of 125/25 µg)
 - Upper-dose stratum (subjects previously using >1000 µg beclomethasone-CFC, >500 µg beclomethasone-HFA, >1000 µg budesonide-DPI, >2000 µg fluticasone, >500 µg fluticasone, >400 µg MF-DPI, or >2000 µg triamcinolone acetonide)
 - MF/F-MDI 400/10 µg BID (delivered as 2 inhalations of 200/5 µg)
 - F/S-MDI 500/50 µg BID (delivered as 2 inhalations of 250/25 µg)
- Study protocol was institutional review board–approved, and all subjects (or subject's legal guardian for minors) provided written informed consent.

Figure 2. Study Design*



Key Inclusion Criteria

- ≥12 years of age with diagnosis of asthma ≥12 months
- Use of ICS with or without a LABA for ≥12 weeks before screening
- Forced expiratory volume in 1 second (FEV₁) ≥50% predicted at screening and baseline

Key Exclusion Criteria

- Change >20% in FEV₁ between screening and baseline
- Required >12 short-acting β₂-agonist inhalations or 2 nebulized treatments on 2 consecutive days between screening and baseline
- Asthma deterioration requiring emergency treatment, hospitalization, or additional medication between screening and baseline
- Intraocular pressure ≥22 mm Hg in either eye
- Glaucoma or evidence of cataracts at screening
- Current smoker, smoked within year before the study, or >10 pack-year smoking history
- Respiratory infection ≤2 weeks before screening or baseline
- Emergency treatment for asthma-related airway obstruction in the 3 months before screening

Assessments

- Number of subjects reporting AEs (assessed at each study visit)
- In a subpopulation, 24-hour plasma cortisol area under the curve (AUC; assessed at baseline, week 26, and week 52) were calculated from subjects with both 0-hour and 24-hour plasma cortisol evaluations
- Ocular events (≥1 grade change in Lens Opacities Classification System [LOCS] III and intraocular pressure assessed at screening, week 26, and week 52)
- Electrocardiogram (ECG; performed at screening and week 52)

Statistical Analyses

- The study was powered to detect an underlying incidence event rate of 2% in ≥1 of 100 subjects with a probability of 0.87.
- 24-hour plasma cortisol AUC was analyzed by analysis of covariance (ANCOVA) with treatment and baseline AUC as covariates.

RESULTS

Demographics and Baseline Characteristics

- 404 subjects were randomized and 345 subjects completed the study.
 - 13 subjects discontinued because of AEs; only 3 were treatment-related.
- Demographics were well balanced among the treatment groups.
- The majority of subjects were nonwhite (53%) and female (63%); the mean age overall was 35.5 years (Table 1).
- Only 21% of subjects were using ICS with a LABA before the study (Table 1).

Treatment-Emergent Adverse Events

- The incidence of overall treatment-emergent AEs was similar among the four treatment groups and ranged from 77%–82% (Figure 3).
- Most (95%) of the AEs were judged as mild to moderate in severity.
- The most common treatment-emergent AEs were headache, nasopharyngitis, and bronchitis; the incidences of these AEs were similar among the treatment groups (Figure 4).

Treatment-Related Adverse Events

- The incidence of overall treatment-related AEs was similar among the 4 treatment groups and ranged from 20%–28% (Figure 3).
- Overall, the most common treatment-related AE was headache (Table 2).
- The most common treatment-related AE in the MF/F group was dysphonia (Table 2).
- The total frequency of oral candidiasis was low (1.5%), with a higher incidence in the F/S 500/50 µg group (3.1%; Table 2).

Serious Adverse Events

- The incidence of serious AEs was similar among the 4 treatment groups and ranged from 3%–6% (Figure 3).
- Of the 21 serious AEs, 1.5% were considered possibly treatment related.
 - 5 subjects with eye disorders (MF/F 400/10 µg BID, 3.1%; F/S 250/50 µg BID, 1.5%)
 - 1 subject with pneumonia and depressed level of consciousness (MF/F 200/10 µg BID, 0.7%)
- There were 2 deaths, both unrelated to treatment (accidental electrocution and gastric cancer).
- Two cases (MF/F 200/10 µg BID, F/S 250/50 µg BID) of asthma-related serious AEs were reported (both unrelated to drug)

24-Hour Plasma Cortisol AUC

- 66 samples were collected in randomized subjects, of which 57 had completed plasma cortisol evaluations and were included in the analysis.
- The MF/F 200/10-µg BID and F/S 500/50-µg BID groups had higher baseline values (Figure 5), likely because of 2 outliers and 1 outlier in these respective groups.
- Compared with baseline, decreases in plasma cortisol AUC were 2% and 30% in the MF/F 200/10-µg BID and MF/F 400/10-µg BID groups, respectively, compared with 17% and 32% in the F/S 250/50-µg BID and F/S 500/50-µg BID groups, respectively, at week 52 (Figure 5).
- Clinical relevance is undetermined owing to a lack of placebo control or systemic corticosteroid control.

Ocular Events and ECGs

- The total percentage of subjects with a LOCS III grade change ≥1 unit was low for each treatment group (1.5%–5.9%; Table 3) and similar between treatment groups.
- No posterior subcapsular cataracts were reported.
- 1 subject had intraocular hypertension that was possibly treatment related (MF/F 400/10 µg BID), and 1 subject (MF/F 400/10 µg BID) had borderline ocular pressure, with an increase from 14 mm Hg at baseline to 22 mm Hg at week 52.
 - lens disorder (MF/F 400/10 µg BID, 2.3%), reduced visual acuity (F/S 250/50 µg BID, 1.5%), and borderline ocular hypertension (MF/F 400/10 µg BID, 0.8%) were considered treatment-related serious AEs. The clinical relevance of these findings is undetermined owing to a lack of placebo control or systemic corticosteroid control.
- No clinically significant changes from baseline in ECG parameters were observed.

Table 1. Demographic and Baseline Characteristics

	MF/F 200/10 µg BID (n=141)	MF/F 400/10 µg BID (n=130)	F/S 250/50 µg BID (n=68)	F/S 500/50 µg BID (n=65)	Total (N=404)
Sex, female, n (%)	92 (65)	86 (66)	38 (56)	40 (62)	256 (63)
Race, nonwhite, n (%)	73 (52)	70 (54)	38 (56)	33 (51)	214 (53)
Mean age, y	32.7	39.3	32.4	37.1	35.5
Range	12–75	12–69	12–67	12–65	12–75
Mean baseline % predicted FEV ₁	80	74	78	72	77
Prior ICS use, n (%)*					
Beclomethasone	40 (28)	28 (22)	14 (21)	15 (23)	97 (24)
Budesonide	44 (31)	25 (19)	24 (35)	13 (20)	106 (26)
Ciclesonide	1 (1)	3 (2)	1 (1)	0	5 (1)
Fluticasone	38 (27)	46 (35)	21 (31)	24 (37)	129 (32)
Mometasone	1 (1)	5 (4)	0	1 (2)	7 (2)
Prior ICS/LABA use, n (%)*					
Budesonide/formoterol	3 (2)	1 (1)	1 (1)	0	5 (1)
Fluticasone/salmeterol	21 (15)	31 (24)	11 (16)	16 (25)	79 (20)

BID=twice daily; FEV₁=forced expiratory volume in 1 s; F/S=fluticasone/salmeterol; ICS=inhaled corticosteroid; LABA=long-acting β₂-agonist; MF/F=mometasone furoate/formoterol. *Subjects could have used >1 ICS or ICS/LABA medication during the 3 mo before randomization.

Figure 3. Overall Incidences of Treatment-Emergent, Treatment-Related, and Serious AEs

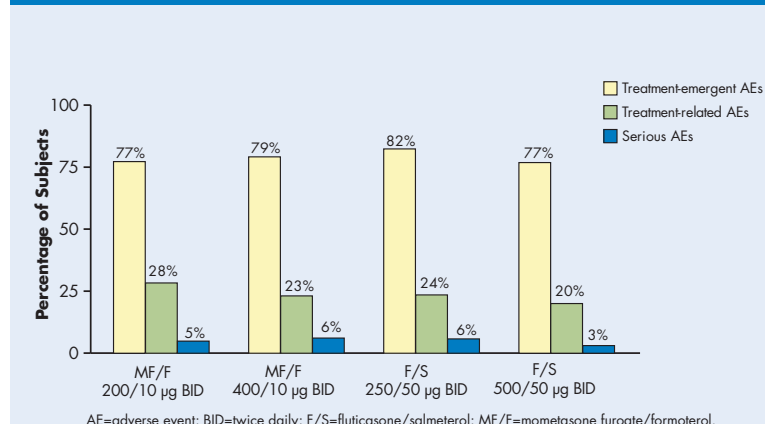


Figure 4. Incidences of the Most Common Treatment-Emergent AEs

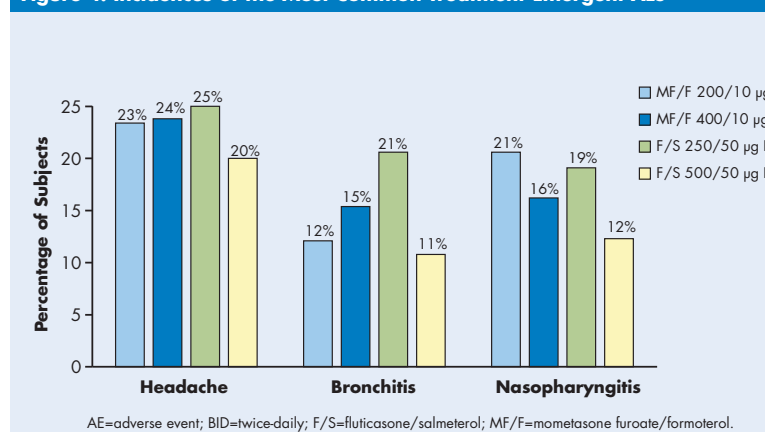
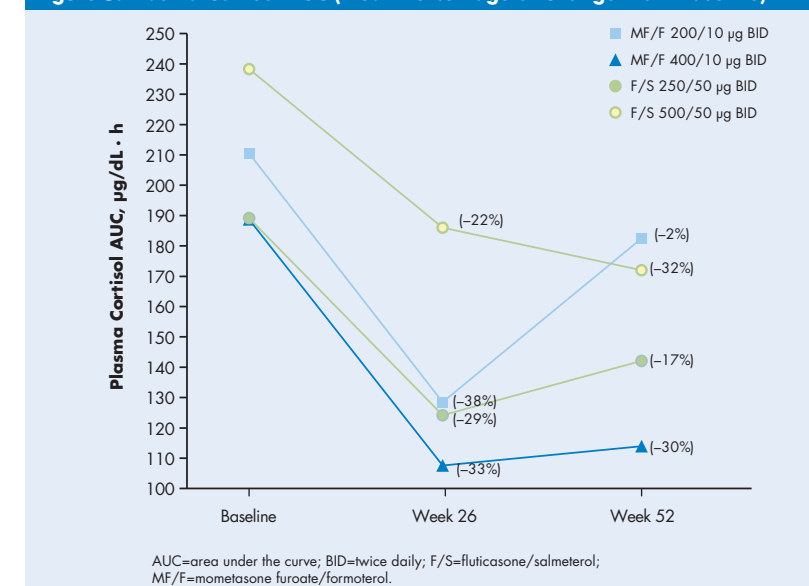


Table 2. Incidences of the Most Common Treatment-Related AEs (≥1% Total)

	Percentage of Subjects				Total (N=404)
	MF/F 200/10 µg BID (n=141)	MF/F 400/10 µg BID (n=130)	F/S 250/50 µg BID (n=68)	F/S 500/50 µg BID (n=65)	
Aphthous stomatitis	2.1	0.8	0	0	1.0
Arthralgia	1.4	0.8	4.4	1.5	1.7
Bronchitis	1.4	2.3	2.9	1.5	2.0
Dysphonia	5.0	3.1	0	0	2.7
Headache	4.3	3.1	5.9	1.5	3.7
Lens disorder	0	2.3	1.5	0	1.0
Muscle spasms	0.7	1.5	1.5	3.1	1.5
Oral candidiasis	1.4	0.8	1.5	3.1	1.5
Pharyngitis	1.4	0	2.9	1.5	1.2
Pharyngolaryngeal pain	1.4	0.8	1.5	0	1.0
Tremor	2.8	1.5	0	3.1	2.0

AE=adverse event; BID=twice daily; F/S=fluticasone/salmeterol; MF/F=mometasone furoate/formoterol.

Figure 5. Plasma Cortisol AUC (Mean Percentage of Change From Baseline)



AUC=area under the curve; BID=twice daily; F/S=fluticasone/salmeterol; MF/F=mometasone furoate/formoterol.

Table 3. Percentage of Subjects With LOCS III Grade Change ≥1 Unit

	Percentage of Subjects			
	MF/F 200/10 µg BID (n=141)	MF/F 400/10 µg BID (n=130)	F/S 250/50 µg BID (n=68)	F/S 500/50 µg BID (n=65)
Week 26	1.4	2.3	5.9	0
Week 52	2.8	2.3	1.5	1.5
Total*	3.5	3.8	5.9	1.5

BID=twice daily; F/S=fluticasone/salmeterol; LOCS=Lens Opacities Classification System; MF/F=mometasone furoate/formoterol. *Subjects could have had an increase at both visits.

CONCLUSIONS

- In subjects with persistent asthma, long-term treatment with MF/F 200/10 µg BID or 400/10 µg BID therapy was associated with a safety and tolerability profile similar to that seen with comparable doses of F/S.
- The overall nature and incidence of AEs and serious AEs were in line with previous observations with the MF and F single ingredients although with a lower frequency of local AEs.

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