Long-Term Safety of 2 Different Doses of Mometasone Furoate/Formoterol Combination in Persistent Asthmatics: Analysis of Adverse Event Incidence, Plasma Cortisol, and Ocular Changes

J. Maspero,[1] H. Nolte,[2] I. Chérrez[3]

[1]Fundacion CIDEA, Allergy/Respiratory Research, Buenos Aires, Argentina; [2]Schering Corp., a Division of Merck & Co., Kenilworth, NJ, USA; [3]RESPIRALAB. Allergy, Respiratory & Sleep Center, Guayaquil, Ecuador

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 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 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.

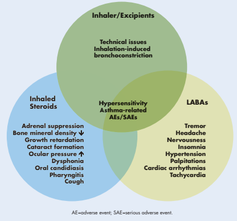
Results: Both MF/F doses were well tolerated and associated with AEs of frequency and nature similar to those observed with F/S. Overall, 99 subjects (24.5%; MF/F 200/10 µg =28.4%; MF/F 400/10 µg =23.1%; F/S 250/50 µg =23.5%; F/S 500/50 µg =20.0%) reported treatment-related AEs. Compared with baseline, both MF/F and F/S caused a similar decrease in plasma cortisol 24-hour AUC. For subjects on lower doses of ICS, decreases were MF/F=6% and F/S=17%; on higher doses of ICS, decreases were MF/F=31% and F/S=34%. 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, the National Asthma Education and Prevention Program guideline recommends the addition of a long-acting β_2-agonist (LABA).[1]
- ICSs and LABAs are generally well tolerated. Common local ICS-related adverse events (AEs) include oral candidiasis, pharyngitis, dysphonia, and cough[2]; common LABA-related AEs include tremor, heart palpitations, and headache (**Figure 1**).[3]
- Suppression of the hypothalamic-pituitary-adrenal axis and ocular changes are additional systemic safety concerns with ICSs.[2]
- Fluticasone/salmeterol (F/S) hydrofluoroalkane delivered via a metered dose inhaler (MDI) is a commonly prescribed ICS/LABA combination.
  - The most common adverse events associated with F/S are headache, upper respiratory tract infection, and throat irritation.[4]
- Mometasone furoate/formoterol (MF/F) administered via a pressurized MDI is a combination ICS/LABA recently developed in 3 dosages (100/10 µg, 200/10 µg, and 400/10 µg twice daily [BID]) to meet the needs of patients with various degrees of asthma severity and control.
  - 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.[5-7]
  - Formoterol (F) is a LABA characterized by a fast onset of action and has been demonstrated to improve lung function and asthma symptoms.[8]
- The individual components of MF/F have well-established long-term safety records in patients with obstructive airway disease,[9-12] and MF/F is expected to have similar safety characteristics.

Figure 1. Known Class Effects of Inhaled Corticosteroids, Long-Acting β_2-Agonists (LABAs), and Inhalers



AE=adverse event; SAE=serious adverse event.

OBJECTIVE

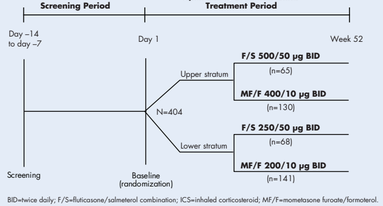
- To evaluate the long-term safety of MF/F 200/10 µg twice daily (BID) and 400/10 µg BID in subjects with persistent asthma previously treated with ICS with or without a LABA

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 flunisolide, >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 flunisolide, >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*



BID=twice daily; F/S=fluticasone/salmeterol combination; ICS=inhaled corticosteroid; MF/F=mometasone furoate/formoterol.

*All treatments were delivered via a pressurized metered dose inhaler using 2 inhalations of the appropriate dose. Subjects previously using ICSs were grouped into upper and lower strata depending on previous ICS dose levels and then were each assigned to study treatments in an MF/F to F/S ratio of 2:1.

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 (FEV_1) ≥50% predicted at screening and baseline

Key Exclusion Criteria

- Change >20% in FEV_1 between screening and baseline
- Required >12 short-acting β_2-agonist inhalations or 2 nebulized treatments on 2 consecutive days between screening and baseline
- Exacerbation 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 each study visit)
- In a subpopulation (n=66 subject samples were collected), 24-hour plasma cortisol area under the curve (AUC; assessed at baseline, week 26, and week 52) calculated from subjects with both 0-hour and 24-hour plasma cortisol evaluations (n=57)
- 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 SAEs were reported (both unrelated to drug)

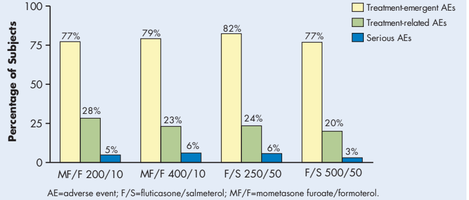
24-Hour Plasma Cortisol AUC

- Of the 66 samples collected in randomized subjects, 57 had complete 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

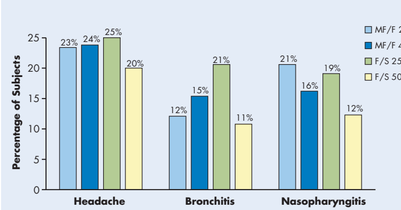
- The total percentage of subjects with a LOCS III grade change ≥1 unit was low for each treatment group (1.5%–5.9%; **Table 3**) and similar between treatment groups.
- No posterior subcapsular cataracts were reported.
- 1 subject had intraocular hypertension that was possibly treatment related (MF/F 400/10 µg BID), and 1 subject (MF/F 400/10 µg BID group) 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.

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



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

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



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

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 Range	32.7 12–75	39.3 12–69	32.4 12–67	37.1 12–65	35.5 12–75
Mean baseline % predicted FEV_1	81	75	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)

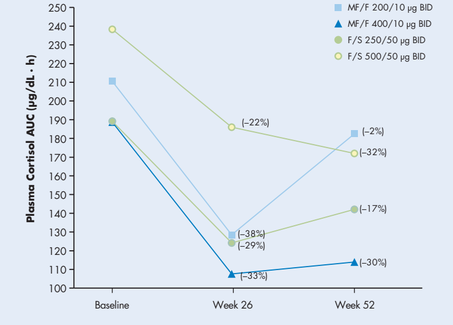
BID=twice daily; FEV_1=forced expiratory volume in 1 s; F/S=fluticasone/salmeterol; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; MF/F=mometasone furoate/formoterol.
*Subjects could have used >1 ICS or ICS/LABA medication during the 3 mo before randomization.

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

	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)	Total (N=404)
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 SAE/AEs were in line with previous observations with the MF and F single ingredients although with a lower frequency of local AEs.**

REFERENCES

1. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Summary Report. Bethesda, MD: National Heart, Lung, and Blood Institute; October, 2007.
2. Irwin RS and Richardson ND. *Chest.* 2006;130(1 suppl):41S-53S.
3. Guhan AR, et al. *Thorax.* 2000;55(8):650-656.
4. Advair® HFA (fluticasone propionate/salmeterol). Full Prescribing Information, GlaxoSmithKline, Research Triangle Park, NC, 2008.
5. Bernstein DI, et al. *Respir Med.* 1999;93(9):603-612.
6. Karpel JP, et al. *Respir Med.* 2007;101:628-637.
7. D'Urzo A, et al. *Curr Med Res Opin.* 2005;21(8):1281-1289.
8. Bensch G, et al. *Ann Allergy Asthma Immunol.* 2001;86(1):19-27.
9. Rossi A, et al. *Chest.* 2002;121(4):1058-1069.
10. Bensch G, et al. *Ann Allergy Asthma Immunol.* 2002;89(2):180-190.
11. Noonan M, et al. *BMC Pediatr.* 2009;9:43.
12. Murray J, et al. *Eur Respir J.* 2000;16:280s-281s.

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