

# The long-term safety and tolerability of two doses of mometasone furoate/formoterol (MF/F) combination, administered via a metered-dose inhaler, for the treatment of moderate-to-severe persistent asthma

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## ABSTRACT

**Rationale:** The combination of mometasone furoate and formoterol (MF/F) administered via a single metered-dose inhaler (MDI) is in development for the treatment of asthma. We report findings from a randomized, parallel-group, multicenter, open-label, evaluator-blinded study assessing the long-term safety of medium- and high-dose MF/F compared with fluticasone-propionate/salmeterol MDI combination (F/S).

**Methods:** Subjects (≥12 years) with moderate-to-severe persistent asthma previously treated with medium- to high-dose inhaled corticosteroids were randomized to twice-daily doses of either medium-dose MF/F (200/10µg), medium-dose F/S (250/50µg), high-dose MF/F (400/10µg), or high-dose F/S (500/50µg) for 1 year. The primary endpoint was the number and percent of subjects reporting adverse events (AEs).

**Results:** 404 subjects were randomized (medium-dose MF/F, n=141; high-dose MF/F, n=130; medium-dose F/S, n=68; high-dose F/S, n=65). Medium and high MF/F doses were well tolerated and were associated with AEs of frequency and nature similar to AEs observed with F/S. In this study, the most common treatment-related AEs in the MF/F group were dysphonia (medium-dose MF/F, 5.0%; high-dose MF/F, 3.1%) and headache (medium-dose MF/F, 4.3%; high-dose MF/F, 3.1%); in the F/S group, headache (medium-dose F/S, 5.9% and high-dose F/S, 1.5%) and arthralgia (medium-dose F/S, 4.4%; high-dose F/S, 1.5%). Oral candidiasis was uncommon (MF/F overall, 1.1%; F/S overall, 2.2%). Six subjects experienced serious AEs that were possibly drug-related; ocular changes (high-dose MF/F, n=4 [3.1%]; medium-dose F/S, n=1 [1.5%]); and pneumonia (medium-dose MF/F n=1 [0.7%]).

**Conclusion:** MF/F was well tolerated over 1 year at medium and high doses, with a safety profile similar to F/S and no unusual/unexpected AEs. Oral candidiasis was uncommon in this study.

## INTRODUCTION

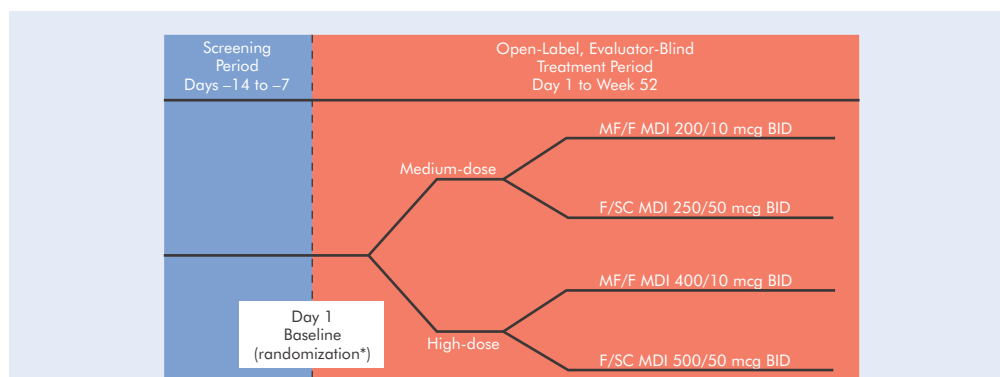
- The concomitant administration of an inhaled corticosteroid (ICS) and a long-acting 2-agonist (LABA) is a well established and effective approach to the treatment of moderate to severe asthma<sup>1</sup>.
- Both classes of drugs are recommended by asthma-treatment guidelines, such as those of the National Heart Lung and Blood Institute (NHLBI)<sup>1</sup> or the Global Initiative for Asthma (GINA)<sup>2</sup>.
- The fixed-dose combination of mometasone furoate and formoterol (MF/F), in a twice-daily (BID) dosing regimen, delivered via a metered-dose inhaler (MDI) formulation, is being developed for the treatment of asthma.
- We report findings from a randomized, parallel-group, multicenter, open-label, evaluator-blinded study designed to assess the long-term safety of medium- and high-dose MF/F compared to that of fluticasone-propionate/salmeterol MDI combination (F/S).

## OBJECTIVE

- To assess the long-term safety of medium- and high-dose MF/F compared with medium- and high-dose F/S as an active comparator in subjects with moderate to severe persistent asthma.

## METHODS

- This was a randomized, parallel-group, multicenter, open-label, evaluator-blind, third-party dispenser, long-term safety study of MF/F in subjects previously treated with medium to high doses of inhaled corticosteroid.
- Adult and adolescent subjects (≥12 years of age) of either sex and any race, with a diagnosis of asthma of at least 12 months duration, were eligible for inclusion.
- Following initial screening, subjects were stratified to the medium- or high-dose group based on their current ICS dose and then randomized to receive MF/F or F/S at the appropriate dose. Subjects were randomized to receive either MF/F or F/S in a 2:1 ratio.
- Figure 1** provides a schematic representation of the study design.
- A total of 11 visits were scheduled over the study period during which a variety of clinical and laboratory evaluations were undertaken.
- The primary endpoint for this study was the number and percent of all randomized subjects reporting adverse events (AEs).



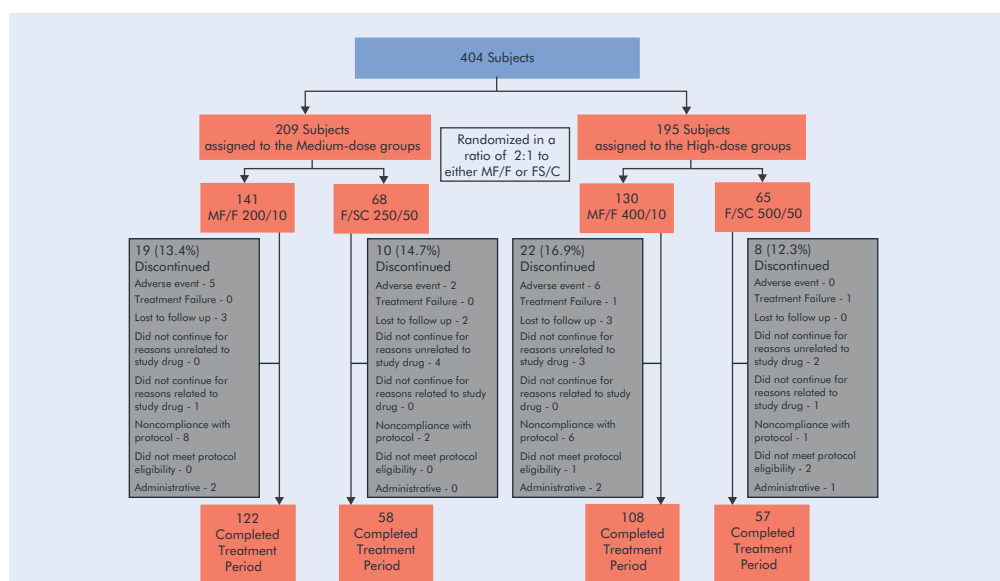
\*Each subject who qualified was stratified at baseline according to their current ICS dose (medium or high) and was then randomized to MF/F or F/S at either the medium or high dose.

**Figure 1.** Schematic representation of the study design

## RESULTS

### Subject Population

- In total, 404 subjects were randomized to receive either MF/F or F/S in a 2:1 ratio (medium-dose MF/F, n=141; high-dose MF/F, n=130; medium-dose F/S, n=68; high-dose F/S, n=65). A representation of subject flow and randomization is shown in **Figure 2**.
- The four-treatment groups were well-balanced with regard to baseline demographics and asthma characteristics (**Table 1**). The mean age, height, and weight of the subjects participating in this trial were: 35.5±15.2 years, 161.1±9.0 cm, and 67.0±14.4 kg, respectively. The majority of subjects were female (63%). Mean BMI was 25.8±5.0 kg/m<sup>2</sup> and ranged from 24.9 to 26.6 kg/m<sup>2</sup> between treatment groups.



**Figure 2.** Subject assignment, randomization, and discontinuation

**Table 1.** Demographic characteristics of the study population

	Medium-dose groups		High-dose groups		Total
	MF/F 200/10 mcg	F/S 250/50 mcg	MF/F 400/10 mcg	F/S 500/50 mcg	
Subjects, n	141	68	130	65	404
Gender, n, %					
Female	92 (65)	38 (56)	86 (66)	40 (62)	256 (63)
Male	49 (35)	30 (44)	44 (34)	25 (38)	148 (37)
Race, n (%)					
White	68 (48)	30 (44)	60 (46)	32 (49)	190 (47)
Non-white	73 (52)	38 (56)	70 (54)	33 (51)	214 (53)
Age, yrs					
Mean (SD)	32.7 (15.2)	32.4 (14.9)	39.3 (14.5)	37.1 (15.0)	35.5 (15.2)
Median	31.0	29.0	41.0	36.0	36.0
Range	12-75	12-67	12-69	12-65	12-75
Age group, n (%)					
12-<18 yrs	30 (21)	13 (19)	11 (8)	8 (12)	62 (15)
18-<65 yrs	109 (77)	54 (79)	113 (87)	56 (86)	332 (82)
≥65 years	2 (1)	1 (1)	6 (5)	1 (2)	10 (2)
BMI (Kg/m <sup>2</sup> )					
Mean (SD)	24.9 (4.9)	25.6 (5.5)	26.5 (4.3)	26.6 (5.5)	25.8 (5.0)
Median	24.2	24.3	26.2	26.0	25.3
Range	15.5-48.3	17.3-42.2	18.4-38.6	16.6-44.2	15.5-48.3
BMI category, n (%)					
<25.0 kg/m <sup>2</sup>	80 (57)	37 (54)	48 (37)	24 (37)	189 (47)
25.0-29.9 kg/m <sup>2</sup>	43 (30)	20 (29)	57 (44)	27 (42)	147 (36)
≥30.0 kg/m <sup>2</sup>	18 (13)	11 (16)	25 (19)	14 (22)	68 (17)
Asthma duration, yrs					
Mean (SD)	15.3 (11.9)	16.5 (12.1)	19.4 (13.2)	18.1 (12.3)	17.3 (12.5)
Median	12.0	14.0	16.0	15.0	14.0
Range	1.0-52.0	1.4-60.0	1.0-49.0	2.0-60.0	1.0-60.0
Baseline FEV1 (liters)					
Mean (SD)	2.6 (0.8)	2.5 (0.8)	2.3 (0.7)	2.3 (0.7)	2.4 (0.8)
Median	2.4	2.4	2.2	2.2	2.4
Range	0.7-4.7	0.9-4.7	1.2-4.4	1.1-4.9	0.7-4.9
Subjects missing data, n	2	2	1	0	5
Historical FEV1 percentage reversibility					
Mean (SD)	21.3 (9.5)	23.7 (11.7)	24.1 (11.7)	24.8 (13.9)	23.1 (11.3)
Median	17.8	18.8	20.7	19.0	19.1
Range	11.6-59.9	12.2-60.0	11.8-62.5	11.9-65.7	11.6-65.7
Subjects missing data, n	39	35	67	39	210

- Subjects in the high-dose treatment groups tended to have a slightly longer duration of asthma, with the mean duration for the overall population being 17.3±12.5 years.
- Pulmonary function values tended to be lower in the subjects on the high-dose ICS therapy compared with those on medium dose ICS. All subjects demonstrated a good degree of β<sub>2</sub>-agonist reversibility (mean for all groups = 23.1±11.3%).

### Safety

- The medium and high MF/F doses investigated in this study were well tolerated and were associated with AEs of frequency and nature similar to AEs observed with F/S (**Table 2**).
- Overall, the occurrence of all treatment-emergent AEs was similar among the four treatment groups. Most of those AEs (95%) were mild to moderate in severity and were judged by the investigators to be unlikely related to treatment.
- No unusual or unexpected AEs were reported.
- The occurrence of discontinuations was similar across all treatment groups (**Figure 2**).
- The most common treatment-related AEs reported by subjects on MF/F were dysphonia (medium-dose MF/F, 5.0%; high-dose MF/F, 3.1%) and headache (medium-dose MF/F, 4.3%; high-dose MF/F, 3.1%) while the most common treatment-related AEs reported by subjects on F/S were headache (medium-dose F/S, 5.9% and high-dose F/S, 1.5%) and arthralgia (medium-dose F/S, 4.4%; high-dose F/S, 1.5%).

**Table 2.** Treatment-related adverse events reported by ≥2% of subjects in any treatment group

	Medium-dose groups		High-dose groups		Total
	MF/F 200/10 mcg	F/S 250/50 mcg	MF/F 400/10 mcg	F/S 500/50 mcg	
Subjects, n	141	68	130	65	404
Any AEs, n (%)	109 (77.3)	56 (82.4)	103 (79.2)	50 (76.9)	318 (78.7)
Treatment-related AEs, n (%)	40 (28.4)	16 (23.5)	30 (23.1)	13 (20.0)	99 (24.5)
Treatment-related adverse events reported by ≥2% of subjects in any treatment group, n (%)					
Headache	6 (4.3)	4 (5.9)	4 (3.1)	1 (1.5)	15 (3.7)
Dysphonia	7 (5.0)	0 (0.0)	4 (3.1)	0 (0.0)	11 (2.7)
Bronchitis	2 (1.4)	2 (2.9)	3 (2.3)	1 (1.5)	8 (2.0)
Tremor	4 (2.8)	0 (0.0)	2 (1.5)	2 (3.1)	8 (2.0)
Arthralgia	2 (1.4)	3 (4.4)	1 (0.8)	1 (1.5)	7 (1.7)
Oral candidiasis	2 (1.4)	1 (1.5)	1 (0.8)	2 (3.1)	6 (1.5)
Muscle spasms	1 (0.7)	1 (1.5)	2 (1.5)	2 (3.1)	6 (1.5)
Pharyngitis	2 (1.4)	2 (2.9)	0 (0.0)	1 (1.5)	5 (1.2)
Lens disorder	0 (0.0)	1 (1.5)	3 (2.3)	0 (0.0)	4 (1.0)
Aphthous stomatitis	3 (2.1)	0 (0.0)	1 (0.8)	0 (0.0)	4 (1.0)
Dysphagia	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	2 (0.5)

- Treatment-related AEs reported by at least 2% of subjects in any of the four treatment groups were:
  - Dysphonia: 7/141 (5.0%) medium-dose MF/F; 4/130 (3.1%) high-dose MF/F
  - Headache: 6/141 (4.3%) medium-dose MF/F; 4/130 (3.1%) high-dose MF/F, 4/68 (5.9%) medium-dose F/S
  - Tremor: 4/141 (2.8%) medium-dose MF/F; 2/65 (3.1%) high-dose F/S
  - Aphthous stomatitis: 3/141 (2.1%) medium-dose MF/F
  - Bronchitis: 3/130 (2.3%) high-dose MF/F, 2/68 (2.9%) medium-dose F/S
  - Lens disorder: 3/130 (2.3%) high-dose MF/F
  - Arthralgia: 3/68 (4.4%) medium-dose F/S
  - Pharyngitis: 2/68 (2.9%) medium-dose F/S
  - Dysphagia: 2/68 (2.9%) medium-dose F/S
  - Oral candidiasis: 2/65 (3.1%) high-dose F/S
  - Muscle spasms: 2/65 (3.1%) high-dose F/S
- Oral candidiasis was uncommon (MF/F overall, 1.1%; F/S overall, 2.2%).
- Severe treatment-emergent AEs were reported by 5.7% and 3.8% of subjects in the medium- and high-dose MF/F groups compared to 5.9% and 6.2% of subjects in the medium- and high-dose F/S groups respectively. Of these events, one in the medium-dose MF/F group was considered to be possibly related to treatment (pneumonia, depressed consciousness) while one in the high-dose F/S group was considered to be probably related to treatment (severe anxiety).
- Of a total of 21 subjects reporting serious AEs, only 6 serious AEs were considered possibly drug-related; pneumonia (medium-dose MF/F, n=1) and ocular changes (high-dose MF/F, n=4; medium-dose F/S, n=1). The clinical significance of the ocular changes is uncertain due to the lack of a placebo control.
- Two subjects died during the study, although these were not related to study treatment (electrocution n=1; gastric cancer n=1).

## CONCLUSION

- MF/F was well tolerated over 1 year at medium and high doses, with a safety profile similar to F/S and no unusual or unexpected AEs. Oral candidiasis was uncommon in this study.

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