

The Safety and Tolerability Characteristics of Mometasone Furoate/Formoterol (MF/F) Combination Therapy in Patients With Persistent Asthma: Findings from the MF/F Phase III Clinical Development Program

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ABSTRACT

Introduction: Mometasone furoate/formoterol (MF/F) is under study for the treatment of persistent asthma. We report findings from a post hoc investigation performed to evaluate the consistency of the MF/F safety and tolerability characteristics across 12-, 26-, and 52-week efficacy and safety trials conducted as part of the MF/F phase III clinical development program.

Methods: Adverse event (AE) data from all randomized trials of ≥12 weeks' duration (two 12-week, two 26-week, and one 52-week in duration) that investigated the efficacy and safety of MF/F administered via a pressurized metered dose inhaler (MDI) were analyzed. Prior to entry, subjects (≥12 y old) had persistent asthma for at least 12 months. Investigated treatment arms in this analysis included twice-daily MF/F (100/10 µg, 200/10 µg, 400/10 µg), twice-daily MF (MF-MDI; 100 µg, 200 µg, 400 µg), twice-daily formoterol (F-MDI; 10 µg), twice-daily fluticasone propionate/salmeterol (FP/S; 250/50 µg and 500/50 µg), and twice-daily placebo.

Results: Data from 3381 subjects randomized to 12-week (MF/F: n=859, MF: n=240, FP/S: n=351), 26-week (MF/F: n=373, MF: n=380, F: n=390, placebo: n=384), or 52-week (MF/F: n=271, FP/S: n=133) treatments were analyzed. The most common treatment-emergent AEs in the 12-, 26-, and 52-week trials are listed in **Table 2**. The incidence of treatment-related AEs was low; the most common were headache, dysphonia, upper respiratory tract infection, and oral candidiasis (**Table 3**). Asthma-related SAEs were uncommon (n=7) and only 1 subject reported an asthma-related SAE considered treatment related (26-week: formoterol-10 [severe asthma exacerbation]; **Table 4**). Discontinuations due to AEs were low (**Table 4**). No unusual or unexpected AEs were reported, and no treatment-related deaths occurred.

Conclusions: Multiple clinical trials representing a combined large population of asthma patients treated with MF/F for 12-, 26-, or 52-weeks, demonstrated that AE profiles associated with three different strengths of MF/F were consistently comparable to those of the monocomponents. No new safety signals were detected.

Clinical Implications: Clinical trials indicate that treatment with MF/F 100/10, 200/10, or 400/10 µg twice daily was found to be safe and well tolerated.

INTRODUCTION

The National Asthma Education and Prevention Program and the Global Initiative for Asthma guidelines recommend using combined inhaled corticosteroid (ICS) and long-acting β₂-agonist (LABA) therapy as a treatment of choice for asthma patients not adequately controlled with ICS monotherapy.^{1,2}

Mometasone furoate (MF) delivered via a dry powder inhaler (DPI) is an ICS currently approved in the United States for the maintenance treatment of asthma in patients ≥4 years of age.³ Formoterol fumarate delivered via DPI is a LABA currently approved in the United States for maintenance treatment of asthma and the prevention of bronchospasm in patients ≥5 years of age.⁴

Mometasone furoate/formoterol (MF/F) administered via a pressurized metered dose inhaler (MDI) with a hydrofluoroalkane propellant is a new combined inhaled corticosteroid (ICS)/long-acting β₂-agonist (LABA) compound currently under investigation as a potential new treatment for persistent asthma.

MF/F has been filed with the US Food and Drug Administration and European regulatory agencies for the treatment of persistent asthma and is under development for the treatment of chronic obstructive pulmonary disorder.

The MF/F clinical development program included 5 phase III clinical trials of at least 12 weeks' duration that investigated MF/F efficacy and safety in patients with moderate or severe asthma previously treated with ICSs with or without a LABA.

We report findings from a post hoc analysis performed to study the safety and tolerability characteristics associated with MF/F across 12-, 26-, and 52-week efficacy and safety trials conducted as part of the MF/F phase III clinical development program; this was accomplished by comparing the AE profile of MF/F with that of its monocomponents and, when available, an active comparator.

OBJECTIVE

To investigate the safety and tolerability characteristics of MF/F compared with its monocomponents and an active comparator across studies with 12-, 26-, and 52-weeks duration conducted as part of the phase III MF/F clinical development program

METHODS

Data for the incidence and severity of adverse events (AEs) from 5 randomized trials originally conducted to investigate the efficacy and safety of MF/F administered via a pressurized MDI were combined according to trial duration and analyzed.

The analyzed trials were (Figure 1)

- 12-week studies**
 - Study 1 (P04431) was a 12-week, non-placebo-controlled, efficacy and safety study in subjects with moderate-to-severe asthma previously treated with high-dose ICS with or without a LABA.
 - Study 2 (P04705) was a 12-week, active comparator-controlled, efficacy and safety study in subjects with moderate asthma previously treated with medium-dose ICS with or without a LABA.
 - AEs for these two 12-week studies were combined and analyzed for incidence and categorized based on severity.

26-week studies

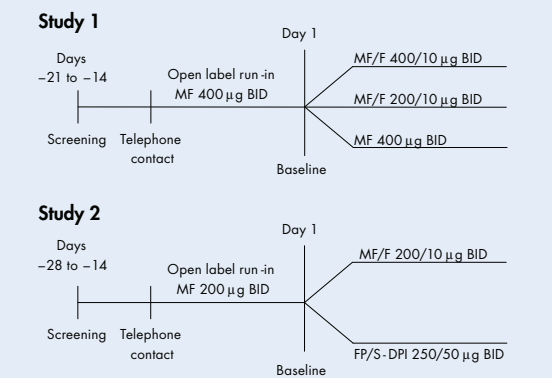
- Study 3 (P04073) was a 26-week, placebo-controlled, efficacy and safety study in subjects with moderate asthma previously treated with low-dose ICS with or without a LABA.
- Study 4 (P04334) was a 26-week, placebo-controlled, efficacy and safety study in subjects with moderate asthma previously treated with medium-dose ICS with or without a LABA.
- AEs for these two 26-week studies were combined and analyzed for incidence and categorized based on severity.

52-week study

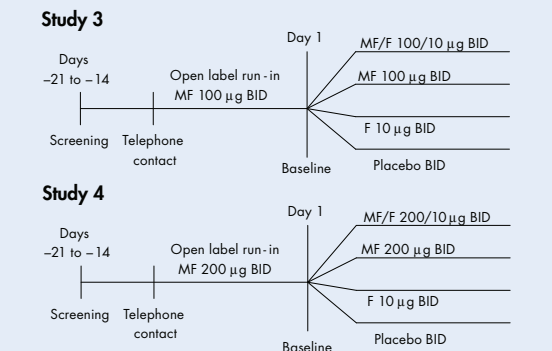
- Study 5 (P04139) was a long-term 52-week active comparator-controlled safety study in subjects with persistent asthma previously treated with either medium- or high-dose ICS.
- Since only one 52-week study was conducted, AE data from this trial were not combined with any other study.

Figure 1. Study Design

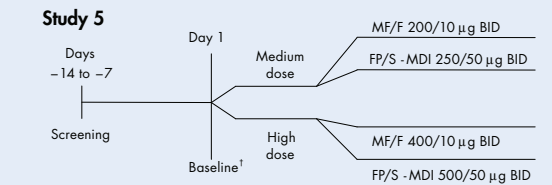
12-Week Studies



26-Week Studies



52-Week Study



*MF/F, MF, and F were all administered via a metered dose inhaler.
[†]Subjects were stratified according to their current ICS dose (medium or high) and then randomized to either medium or high doses of study drug. Randomization was in a 2:1 ratio for MF/F and FP/S.
 BID=twice daily; DPI=dry powder inhaler; F=formoterol; FP/S=fluticasone propionate/salmeterol; ICS=inhaled corticosteroid; MDI=metered-dose inhaler; MF=mometasone furoate; MF/F=mometasone furoate/formoterol.

Adverse Events

- AEs from the two 12-week studies were combined to determine the incidence of each specific AE after 12 weeks of treatment.
- AEs from the two 26-week studies were also combined to obtain a 26-week incidence for each AE.
- AEs with an incidence ≥5% were reported for the 52-week study.

- AEs from the 12-, 26-, and 52-week studies were collected from subject reporting in daily diaries; subjects were questioned for evidence of AEs at each visit.
- Intra-ocular changes were determined in the 52-week study using ophthalmological tests (applanation tonometry and slit lamp examination with full dilatation) conducted at screening, 6 months, and end of treatment to assess the number and percentage of patients who had a change of at ≥1 in the Lens Opacities Classification System, Version III (LOCS III) grade or intraocular pressure ≥22 mm Hg.

RESULTS

Demographics and Baseline Characteristics

- AE data from a total of 3381 subjects receiving either MF/F (12 wk, n=859; 26 wk, n=373; 52 wk, n=271), MF (12 wk, n=240; 26 wk, n=380), F (26 wk, n=390), fluticasone propionate/salmeterol (FP/S; 12 wk, n=351; 52 wk, n=133), or placebo (26 wk, n=384) were analyzed.
- Demographics and baseline characteristics of the combined 12-week studies, the combined 26-week studies, and the 52-week study are shown in **Table 1**.
- The majority of subjects were white females with a mean age of approximately 40 years.
- Baseline disease severity varied among studies according to enrollment criteria.

Treatment-Emergent Adverse Events

- No unusual or unexpected AEs were reported with the MF/F combination therapy or its monocomponents.
- Common treatment-emergent AEs are depicted in **Table 2**.
- The most common treatment-emergent AEs were headache, nasopharyngitis, and upper respiratory tract infection.

12-week studies

- The overall incidence of treatment-emergent AEs across the investigated groups was:
 - MF/F 200/10=36.6%, MF/F 400/10=29.4%, MF 400=27.5%, FP/S 250/50=39.0%

26-week studies

- The overall incidence of treatment-emergent AEs across the investigated groups was:
 - MF/F 100/10=41.2%, MF/F 200/10=50.8%, MF 100=45.7%, MF 200=45.8%, F=42.3%, and placebo=38.5%

52-week study

- The overall incidence of treatment-emergent AEs across the investigated groups was:
 - MF/F 200/10=77.3%, MF/F 400/10=79.2%, FP/S 250/50=82.4%, and FP/S 500/50=76.9%

Treatment-Related Adverse Events

- All treatment-related AEs for MF/F were similar to those typically associated with ICS/LABA combination treatments.
- The most common treatment-related AEs are depicted in **Table 3**.
- The frequency of treatment-related AEs was low for all treatment groups.

12-week studies

- The overall incidence of treatment-related AEs across the investigated groups was:
 - MF/F 200/10=6.3%, MF/F 400/10=5.5%, MF 400=5.0%, FP/S 250/50=7.7%
- Although the incidence for each was very low, the most common treatment-related AEs were dysphonia, headache, and oropharyngeal candidiasis (**Table 3**).

26-week studies

- The overall incidence of treatment-related AEs across the investigated groups was:
 - MF/F 100/10=8.8%, MF/F 200/10=8.9%, MF 100=5.3%, MF 200=5.7%, F=6.7%, and placebo=6.0%
- The most common treatment-related AEs were upper respiratory tract infection, dysphonia, headache, and oral candidiasis, but the incidence of each was low (**Table 3**).

52-week study

- The overall incidence of treatment-related AEs across the investigated groups was:
 - MF/F 200/10=28.4%, MF/F 400/10=23.1%, FP/S 250/50=23.5%, and FP/S 500/50=20.0%
- Headache, dysphonia, tremor, and bronchitis were the most common treatment-related AEs, but the incidence of each was low (**Table 3**).

Ocular Findings

- During the 52-week study, 15 subjects demonstrated ocular changes; MF/F 200/10 (n=5), MF/F 400/10 (n=5), FP/S 250/50 (n=4), FP/S 500/50 (n=1).
- Ocular AEs included lens disorder, ocular hypertension, vision blurred, visual acuity reduced, and visual disturbance.
- Five of the ocular change events were considered serious AEs (MF/F 400/10, n=4 [3.1%]; FP/S 250/50, n=1 [1.5%]) and were possibly treatment related (**Table 4**).
- None of the ocular changes were posterior subcapsular cataracts.

Serious Treatment-Emergent Adverse Events

- The incidence of serious AEs was low (**Table 4**) and ranged from
 - 1.2%–2.3% in the 12-week studies
 - 1.0%–2.7% in the 26-week studies
 - 3.1%–6.2% in the 52-week study
- 7 subjects reported asthma-related serious AEs; only 1 was considered possibly treatment related (26-week: formoterol-10 [severe asthma exacerbation]).
- No treatment-related deaths occurred.

Discontinuations Due to Adverse Events

- The incidence of discontinuations due to AEs (**Table 4**) ranged from 1%–2% in the 12-week studies, 2%–5% in the 26-week studies, and 0%–5% in the 52-week study.
- There appeared to be no difference in discontinuations due to AEs between the MF/F combination therapy, the monocomponents, or placebo.

Table 1. Demographics and Baseline Characteristics

Adverse Event, %	12-Week Studies (Combined)					26-Week Studies (Combined)					52-Week Study				
	MF/F-MDI		MF-MDI	FP/S-DPI	Placebo-MDI	MF/F-MDI		MF-MDI	F-MDI	Placebo-MDI	MF/F-MDI		FP/S-MDI		
	200/10 µg BID n=604	400/10 µg BID n=255	400 µg BID n=240	250/50 µg BID n=351	100/10 µg BID n=182	200/10 µg BID n=191	100 µg BID n=188	200 µg BID n=192	10 µg BID n=390	n=384	200/10 µg BID n=141	400/10 µg BID n=130	250/50 µg BID n=68	500/50 µg BID n=65	
Sex, n (%)															
Female	374 (62)	138 (54)	136 (57)	220 (63)	99 (54)	97 (51)	105 (56)	112 (58)	232 (59)	228 (59)	92 (65)	86 (66)	38 (56)	40 (62)	
Race, n (%)															
White	532 (88)	227 (89)	215 (90)	301 (86)	142 (78)	136 (71)	140 (74)	135 (70)	294 (75)	286 (74)	68 (48)	60 (46)	30 (44)	32 (49)	
Age, y															
Mean (SD)	46 (15)	48 (16)	48 (16)	45 (15)	37 (17)	43 (16)	39 (17)	43 (15)	40 (16)	40 (16)	33 (15)	39 (15)	32 (15)	37 (15)	
Range	12–84	12–77	12–80	12–80	12–79	12–77	12–77	12–73	12–79	12–79	12–75	12–69	12–67	12–65	
Age, n (%)															
12 to <18 y	40 (7)	23 (9)	22 (9)	18 (5)	28 (15)	19 (10)	30 (16)	10 (5)	40 (10)	46 (12)	30 (21)	11 (8)	13 (19)	8 (12)	
19 to <65 y	510 (84)	200 (78)	189 (79)	308 (88)	141 (77)	161 (84)	148 (79)	173 (90)	332 (85)	312 (81)	109 (77)	113 (87)	54 (79)	56 (86)	
≥65 y	54 (9)	32 (13)	29 (12)	25 (7)	13 (7)	11 (6)	10 (5)	9 (5)	18 (5)	26 (7)	2 (1)	6 (5)	1 (1)	1 (2)	
Duration of asthma, y															
Mean (SD)	15 (12)	14 (11)	14 (12)	16 (12)	14 (13)	16 (14)	16 (14)	17 (15)	16 (13)	14 (14)	15 (12)	19 (13)	17 (12)	18 (12)	
Mean percentage predicted FEV ₁ at screening (SD)	71 (10)	67 (11)	66 (12)	75 (9)	77 (10)	72 (9)	76 (10)	72 (11)	75 (10)	74 (10)	79 (17)	71 (14)	79 (17)	73 (16)	
Prior ICS use, n (%)															
Biclonmethasone	154 (25)	77 (30)	63 (26)	92 (26)	17 (9)	33 (17)	18 (10)	31 (16)	44 (11)	50 (13)	40 (28)	28 (22)	14 (21)	15 (23)	
Budesonide	89 (15)	35 (14)	32 (13)	33 (9)	47 (26)	36 (19)	54 (29)	38 (20)	102 (26)	98 (26)	44 (31)	25 (19)	24 (35)	13 (20)	
Ciclesonide	8 (1)	1 (<1)	4 (2)	7 (2)	5 (3)	2 (1)	4 (2)	1 (1)	8 (2)	6 (2)	1 (1)	3 (2)	1 (1)	0 (0)	
Fluticasone	0 (0)	0 (0)	0 (0)	2 (1)	5 (28)	47 (25)	40 (21)	41 (21)	83 (21)	91 (24)	38 (27)	46 (35)	21 (31)	24 (37)	
Mometasone	136 (23)	80 (31)	84 (35)	49 (14)	6 (3)	3 (2)	8 (4)	5 (3)	13 (3)	13 (3)	1 (1)	5 (4)	0 (0)	1 (2)	
Triamcinolone	17 (3)	5 (2)	5 (2)	5 (1)	0 (0)	0 (0)	1 (1)	1 (<1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Prior ICS + LABA use, n (%)															
Budesonide/formoterol	156 (26)	62 (24)	59 (25)	115 (33)	10 (5)	15 (8)	15 (8)	12 (6)	29 (7)	18 (5)	3 (2)	1 (1)	1 (1)	0 (0)	
Fluticasone/salmeterol	77 (13)	12 (5)	15 (6)	59 (17)	50 (27)	60 (31)	49 (26)	68 (35)	114 (29)	115 (30)	21 (15)	31 (24)	11 (16)	16 (25)	

BID=twice daily; DPI=dry powder inhaler; F=formoterol; FEV₁=forced expiratory flow in 1 second; FP/S=fluticasone propionate/salmeterol; ICS=inhaled corticosteroid; LABA=long-acting β₂-agonist; MDI=metered dose inhaler; MF=mometasone furoate; MF/F=mometasone furoate/formoterol.

Table 2. Most Common Treatment-Emergent Adverse Events*

Adverse Event, %	12-Week Studies (Combined)					26-Week Studies (Combined)					52-Week Study				
	MF/F-MDI		MF-MDI	FP/S-DPI	Placebo-MDI	MF/F-MDI		MF-MDI	F-MDI	Placebo-MDI	MF/F-MDI		FP/S-MDI		
	200/10 µg BID n=604	400/10 µg BID n=255	400 µg BID n=240	250/50 µg BID n=351	100/10 µg BID n=182	200/10 µg BID n=191	100 µg BID n=188	200 µg BID n=192	10 µg BID n=390	n=384	200/10 µg BID n=141	400/10 µg BID n=130	250/50 µg BID n=68	500/50 µg BID n=65	
Abdominal pain															
Upper abdominal pain															
Aphthous stomatitis															
Dyspepsia															
Chest pain															
Pyrexia	0.3	0.0	0.0	2.0	0.5	3.1	1.6	2.6	1.5	0.8	5.7	4.6	5.9	1.5	
Bronchitis	1.0	2.7	2.5	1.1	0.5	2.6	2.7	1.6	2.1	2.3	12.1	15.4	20.6	10.8	
Gastroenteritis															
Influenza	1.7	1.2	0.4	2.8	1.6	2.6	2.1	3.6	2.1	2.3	9.9	10.0	13.2	16.9	
Nasopharyngitis	5.1	4.7	5.4	4.0	9.3	6.3	6.9	7.8	5.1	3.1	20.6	16.2	19.1	12.3	
Pharyngitis															
Rhinitis															
Sinusitis	2.0	2.0	1.7	0.9	1.6	2.6	4.3	3.1	3.8	0.8	5.0	3.1	2.9	1.5	
URT [†]	2.6	3.1	1.7	2.8	5.5	5.8	9.0	8.3	8.2	7.6	3.5	3.8	7.4	1.5	
Viral infection															
Viral URTI															
Arthralgia															
Back pain	1.3	0.4	1.7	2.0											
Headache	7.6	2.0	3.3	10.8	6.6	4.7	5.9	5.2	3.8	3.6	23.4	23.8	25.0	20.0	
Muscle spasms															
Cough															
Dysphonia	2.0	0.8	1.3	3.1											
Oropharyngeal pain	1.2	0.0	0.0	2.0	0.0</										