Original Article

Serious Asthma Outcomes and Asthma Exacerbations with Maintenance on Inhaled Corticosteroid (Mometasone Furoate)/Long-Acting Beta Agonist (Formoterol) Combination Compared to Step Down to Mometasone Monotherapy

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What is already known about this topic? Because of historical safety concerns with the use of long-acting β-agonists (LABAs) in asthma, step-down from inhaled corticosteroid (ICS)/LABA combination therapy to ICS monotherapy is recommended once asthma control is achieved. Recently, ICS/LABA therapy has been shown not to pose a significantly greater risk of serious asthma outcomes compared with ICS monotherapy.

What does this article add to our knowledge? The results of the present analysis add to our knowledge about risk/benefit of these therapies by demonstrating that maintenance on ICS/LABA combination therapy with mometasone furoate (MF)/formoterol reduces the risk of asthma exacerbation compared with LABA step-down to MF alone, without altering the safety profile.

How does this study impact current management guidelines? These additional findings may further assist the prescriber when making treatment decisions, particularly in patients who are being considered for step-down from ICS/LABA to ICS.

BACKGROUND: Because of historical safety concerns with the use of long-acting β-agonists (LABA) in asthma, step-down from inhaled corticosteroid (ICS)/LABA combination therapy to ICS monotherapy is recommended once asthma control is achieved.
OBJECTIVE: To evaluate the benefit/risk question about whether patients with asthma who achieve disease control on fixed-dose ICS/LABA combination therapy, such as mometasone furoate/formoterol fumarate (MF/F), should continue with this therapy or be stepped down to ICS monotherapy, such as MF.
METHODS: Using data from 8447 clinically stable patients with persistent asthma in the Safety Pharma Investigation of Respiratory Outcomes trial who had been receiving a stable dose of ICS/LABA for ≥4 weeks, this *post hoc* analysis evaluated the risk of serious asthma outcomes (SAOs) (adjudicated hospitalization, intubation, or death) and asthma exacerbation (AEX) (composite of hospitalizations ≥24 hours, emergency visits <24 hours requiring systemic corticosteroid, or systemic corticosteroid for ≥3 consecutive days) in participants randomized to remain on ICS/LABA (MF/F) or step down to ICS (MF) for 26 weeks.
RESULTS: There was no significant difference in SAO risk among patients maintained on ICS/LABA with MF/F compared with those who stepped down from ICS/LABA to MF (hazard ratio [HR], 1.03 [95% confidence interval (CI):

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Conflicts of interest: C. L. J. Weinstein, N. Ryan, X. Zhang, T. Shekar, and D. Gates are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, and may hold stock or stock options in the company. R. A. Nathan receives grant/research support from AstraZeneca, Dyax, Genentech, GlaxoSmithKline, Lupin, Novartis, Pearl, sanofi-aventis, Shire, Spirosure, Teva, 3M, and Watson; is a consultant/scientific advisor at Boehringer Ingelheim, Optinose, Stallergenes Greer, and CSL Behring; and is in speaker's bureau at Boehringer Ingelheim, Stallergenes Greer, and Merck. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
ACQ- Asthma Control Questionnaire
CI- Confidence interval
FDA- US Food and Drug Administration
HR- Hazard ratio
ICS- Inhaled corticosteroid
IVRS/IWRS- Interactive voice/web response system
LABA- Long-acting β-agonist
MF/F- Mometasone furoate plus formoterol fumarate
SAO- Serious asthma outcome
SPIRO- Safety Pharma Investigation of Respiratory Outcomes

0.61, 1.75], $P = .913$). The risk of AEX was significantly lower in patients maintained on ICS/LABA with MF/F compared with those who stepped down from ICS/LABA to MF (HR, 0.87 [95% CI: 0.78, 0.98], $P = .020$). CONCLUSIONS: In this *post hoc* analysis of a large clinical trial dataset, maintenance on ICS/LABA with MF/F is not associated with an increased risk of SAOs and also significantly reduces the risk of AEX compared with step-down from ICS/LABA to MF. **(J Allergy Clin Immunol Pract 2020;■:■-■)**

Key words: *Long-acting β-agonists; Inhaled corticosteroids; Asthma treatment step-down*

Asthma management requires choosing the appropriate therapy to achieve and maintain asthma control and reduce the risk of asthma exacerbation, while minimizing the risk of adverse effects. Combination therapy with an inhaled corticosteroid and a long-acting β_2-agonist (ICS/LABA) is widely used to achieve and maintain control in moderate-to-severe persistent asthma. A fixed-dose combination of mometasone furoate plus formoterol fumarate (MF/F) is an ICS/LABA that is indicated for the treatment of asthma in patients 12 years and older with asthma who are not adequately controlled on a long-term asthma control medication such as an ICS, or whose disease warrants initiation of treatment with both an ICS and LABA.

Historical safety concerns with the use of LABA monotherapy in asthma led to a regulatory directive by the US Food and Drug Administration (FDA) to include a black box warning about serious asthma outcomes (SAOs), including death, associated with the use of LABA in the labels of all LABA-containing asthma products.[1] This black box warning also advised prescribers to step down treatment from ICS/LABA combination therapy to ICS monotherapy once asthma control was achieved and maintained, to minimize long-term exposure to LABA.[1]

In addition to requiring the inclusion of the black box warning in the US labels of ICS/LABA asthma products, FDA also required the manufacturers of these products (AstraZeneca, GlaxoSmithKline, MSD, and Novartis) to conduct separate, but similarly designed, trials to assess whether the concurrent use of a LABA with an ICS mitigates the safety risks observed with LABA monotherapy.[2] Weinstein et al[3] recently reported results from the Safety Pharma Investigation of Respiratory Outcomes (SPIRO) study, a 26-week, double-blind, randomized-controlled trial of 11,729 persistent asthmatics ≥12 years of age. Consistent with the published findings from the other FDA-mandated ICS/LABA safety outcome trials,[4-6] the SPIRO study demonstrated that the combination of MF/F compared with MF alone did not pose a significantly greater risk of SAOs and also reduced the risk of asthma exacerbation.[3] The results from the 4 individual ICS/LABA safety trials served as the basis for the removal of the black box warning by the US FDA for ICS/LABA asthma medications.[7]

Although the black box warning has been removed, uncertainty remains as to whether patients with asthma who are clinically stable on their current ICS/LABA asthma medication should be stepped down from the LABA. Current asthma treatment guidelines suggest that to avoid potential side effects, patients on ICS/LABA whose asthma has been controlled for at least 3 months may be considered for LABA discontinuation.[8]

Concerns about loss of asthma control with discontinuation of LABA have been raised[9,10]; however, the impact of the step-down from ICS/LABA combination therapy to ICS monotherapy on SAOs and asthma exacerbation has not been evaluated in a single large, randomized controlled long-term study with robust adherence to study medication and follow-up using objective, guideline-based criteria for detection of SAOs and asthma exacerbation. Therefore, the present *post hoc* analysis using data from the SPIRO study was performed to answer the lingering benefit/risk question about whether patients with asthma who achieve disease control on fixed-dose ICS/LABA combination therapy, such as MF/F, should continue with this therapy or be stepped down to ICS monotherapy, such as MF. Specifically, this *post hoc* analysis evaluated SAOs and asthma exacerbation in the subgroup of patients who, on study entry, remained on fixed-dose ICS/LABA combination therapy (MF/F maintenance) compared with those who stepped down from ICS/LABA to ICS monotherapy (step down to MF alone). The primary subgroup analysis was performed on all subjects incoming on ICS/LABA regardless of their baseline asthma control, history of asthma exacerbation, or disease severity (incoming asthma treatment/control). Additional subgroup analyses were performed to further investigate these and other factors that may impact the risk of asthma exacerbation.

METHODS

Patient selection criteria

This *post hoc* analysis is based on data from a global, double-blind, randomized, active-comparator, parallel-group, multicenter trial of persistent asthmatics ≥12 years old (registered as ClinicalTrials.gov number NCT01471340 [Protocol No. 202]). Detailed entry criteria have previously been published.[3] Briefly, the entry criteria were designed to select a patient population whose asthma was clinically stable at the time of study entry, but at risk for asthma exacerbation based on a history of at least 1 asthma exacerbation requiring systemic corticosteroid or hospitalization in the past year. All patients had an asthma diagnosis for at least 1 year and had been on a stable dose of their current asthma medication for at least 4 weeks before randomization. Although the full study population (11,729 participants) included patients on any asthma controller medication who could warrant ICS ± LABA treatment per investigator judgment, the present subgroup analysis includes only the subset of patients who had been receiving ICS/LABA. The 6-question Asthma Control Questionnaire (ACQ-6) was used to assess baseline asthma control, where a total score of <1.5 was considered controlled and a total score of ≥1.5 was considered not well controlled.[11] Patients on low- or medium-dose ICS plus LABA were eligible for inclusion regardless of their level of asthma control, whereas patients on high-dose

ICS plus LABA had to be controlled (refer to study design for ICS dose assignment). Although participants had varying levels of asthma control at baseline, they all had to be sufficiently stable (including no asthma exacerbation within the past month) to discontinue their previously prescribed treatment and to determine the appropriate ICS dose level to be assigned at randomization.[3] To ensure that patients were sufficiently stable for potential LABA step-down, an assessment of asthma symptoms and short-acting β_2 agonists (SABA) use was performed during the 2-week screening period. Patients were not eligible for randomization if they had persistent asthma symptoms on $\geq$2 consecutive days or asthma symptoms severe enough to limit normal daily activities, nighttime awakening due to asthma on $\geq$3 nights per week, required either >8 puffs per day of SABA for $\geq$2 consecutive days, or $\geq$25 puffs of SABA in 1 day. In addition, eligible patients could not require chronic use of systemic corticosteroid or anti-IgE (eg, Xolair), and had no more than 4 asthma exacerbations or more than 2 hospitalizations for asthma in the past year. To avoid confounding, patients were also excluded from the study if they had a history of >10 pack-years of tobacco use, unstable asthma, a history of life-threatening asthma, or any clinically significant, nonasthmatic lung disease or condition.

Study design

The study design for this subgroup analysis mirrors the overall study design for the full population. After an initial screening period of up to 2 weeks on their previously prescribed asthma medication (ICS/LABA), eligible patients received up to 26 weeks of double-blinded treatment with MF/F (200/10 or 400/10 μg) or MF (200 or 400 μg), twice daily (BID). Throughout the study, all participants received open-label albuterol/salbutamol in a metered-dose inhaler with a dose counter to relieve asthma symptoms, as needed. Oral prednisone/prednisolone was also dispensed to patients at the investigator's discretion for treatment of an acute asthma exacerbation.

Within the ICS dose stratum, patients were randomly assigned by an interactive voice/web response system (IVRS/IWRS) in a 1:1 ratio to receive either the combination of MF/F (2 puffs of 100/5 or 200/5 μg) or MF alone (2 puffs of 100 or 200 μg), administered twice daily by a pressurized metered-dose inhaler. The assigned ICS dose (200 or 400 μg, BID) was based on the patient's prior asthma medication and ACQ-6 total score. Consistent with Global Initiative for Asthma guidelines, the ICS dose was stepped up from the prior ICS dose for patients on low-to-medium doses of ICS plus LABA who were not well controlled (ACQ $\geq$1.5) at screening. Patients not well controlled on prior high-dose ICS/LABA were not eligible for randomization.

During the treatment period, patients were contacted at least every 4 weeks by phone for adherence to study medication and safety monitoring with on-site visits at weeks 4, 12, and 26.

The follow-up period consisted of a phone contact scheduled at 7 days after the last dose of study medication or at week 26, whichever occurred later, to collect any serious adverse events and confirm vital status at a minimum.

Study endpoints and assessments

The primary study objective was to evaluate SAOs (a composite endpoint defined as asthma-related: hospitalizations, intubations, and deaths), with the first serious asthma-related event as the primary endpoint, assessed in a time-to-event analysis. Hospitalizations were evaluated by a rotating member of an adjudication committee who confirmed that the stay was $\geq$24 hours and ruled out events clearly not asthma-related. Hospitalizations considered possibly asthma-related were adjudicated by the full adjudication committee. All intubations and deaths were adjudicated by the full adjudication committee. Asthma-relatedness was only determined for intubations that were identified as endotracheal by the adjudication committee.

Additional safety assessments included serious adverse events (including death from any cause), treatment discontinuations due to adverse events, and treatment discontinuations due to asthma exacerbations.

To evaluate the risk/benefit ratio of MF/F compared with MF in the same study population, this study was also designed to compare the risk of asthma exacerbation. Specifically, the prespecified key efficacy endpoint evaluated the time-to-first asthma exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 consecutive days (equivalent to $\geq$1 depot injectable), or an in-patient hospitalization for asthma ($\geq$24-hour stay), or an emergency department visit for asthma (<24 hours) that required systemic corticosteroids.

Statistical analysis

Primary subgroup analyses: ICS/LABA → MF/F versus ICS/LABA → MF. *Post hoc* analyses of the primary safety endpoint and the key efficacy endpoint were performed using those patients in the study population who had been receiving ICS/LABA combination therapy before randomization. Patients who had been receiving anything other than ICS/LABA were not included in these analyses. In the primary subgroup analyses, SAO and asthma exacerbation events for patients who remained on ICS/LABA combination therapy (ie, ICS/LABA → MF/F) were compared with patients who were stepped down to ICS monotherapy (ie, ICS/LABA → MF), regardless of their baseline asthma control or other prognostic factors.

The primary safety and key efficacy endpoints were assessed using Cox proportional hazards regression analysis with covariates of treatment and an ICS dose level. All primary evaluations pooled the 2 ICS dose levels within each treatment group.

The primary safety and efficacy populations were based on the full analysis set, which, for this *post hoc* analysis, consisted of all randomized patients who received at least 1 dose of blinded treatment and who had been receiving ICS/LABA combination therapy before randomization.

A modified intent-to-treat analysis, censoring information collected 7 days after the last dose of blinded treatment, was used for the asthma exacerbation endpoint.

All safety assessments included data collected within 6 months after the first dose of blinded treatment or 7 days after the last dose of blinded treatment, whichever was greater. Patients who received a treatment different from what was assigned by the IVRS/IWRS were included in the analysis using the actual treatment initially received. Other safety endpoint analyses included descriptive summaries of serious adverse events (including death from any cause), study treatment discontinuations due to adverse events, and study treatment discontinuations due to asthma exacerbations.

Additional asthma exacerbation subgroup analyses: asthma control, asthma exacerbation history, and asthma severity (incoming asthma treatment/asthma control). Owing to the small number of SAOs within the primary subgroup analysis, further subanalyses were not performed on this outcome. Additional subgroup analyses were performed to compare

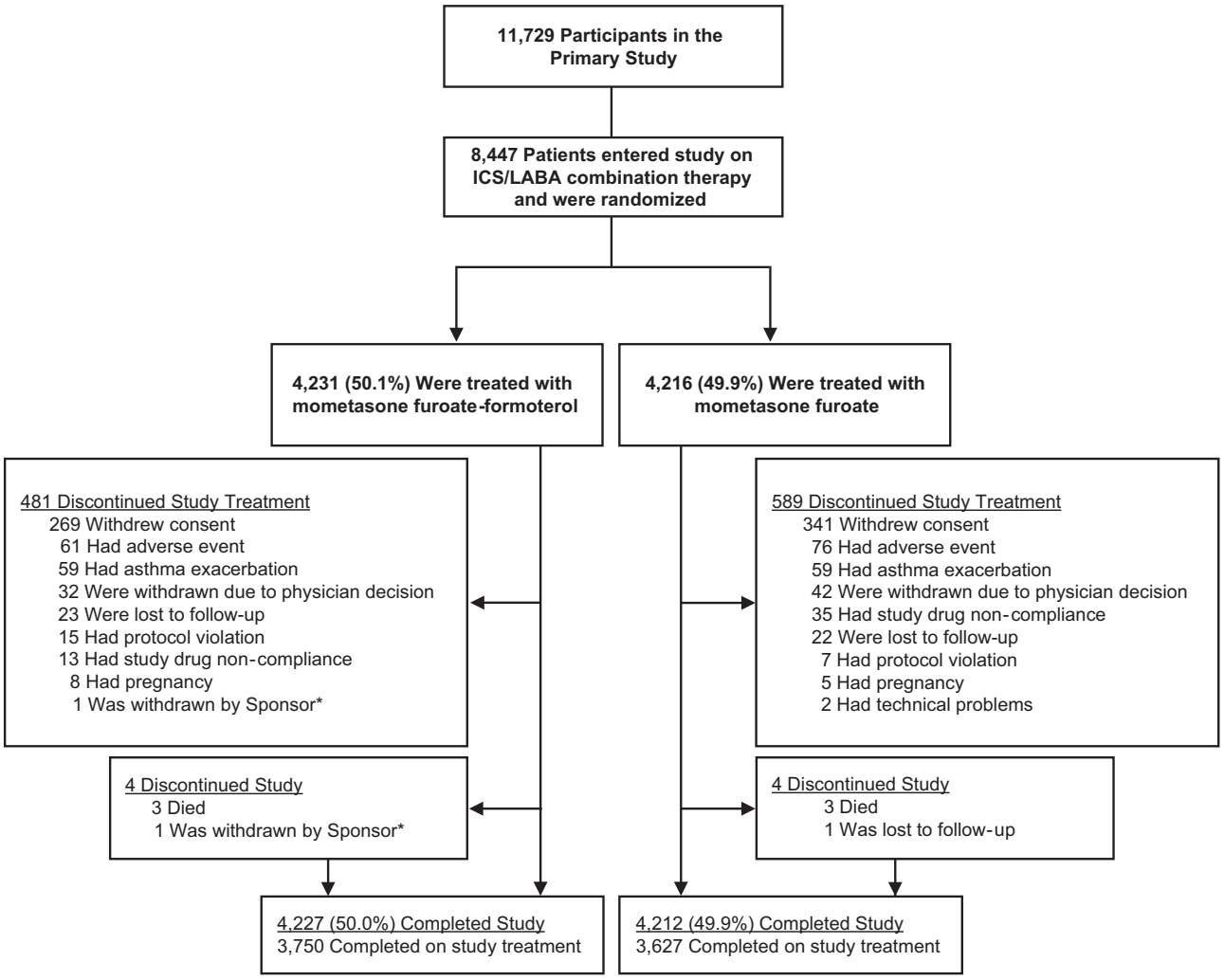


FIGURE 1. Participant flowchart. *ICS*, Inhaled corticosteroid; *LABA*, long-acting β-agonist.

asthma exacerbation events based on prestudy asthma control, asthma exacerbation history, and disease severity based on incoming asthma treatment/asthma control. Within each of these partitioned subgroups, risk differences (in percent of patients) without covariates were used to assess treatment group differences among participants who were maintained on ICS/LABA (MF/F) compared with those who stepped down from LABA to ICS (MF) monotherapy. In addition, to identify any prognostic factors supporting step-down from ICS/LABA, logistic regression was used to examine patient characteristics using criteria outlined in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

Asthma control was dichotomized using the patient's ACQ-6 total score, where controlled and not well controlled are differentiated by a cutoff of 1.5.[11]

Asthma exacerbation history was dichotomized as ≤3 or >3 months based on the duration since the last asthma exacerbation requiring systemic corticosteroids or hospitalization.

Disease severity was based on the participants' previous asthma treatment and prestudy asthma control based on the ACQ-6 total score. Four increasing levels of asthma severity were predefined: group 1—controlled on low-dose ICS/LABA ± other therapies; group 2—not well controlled on daily low-dose ICS/LABA ± other therapies OR controlled on medium-dose ICS/LABA ± other therapies; group 3—not well controlled on medium-dose ICS/LABA ± other therapies; group 4—controlled on high-dose ICS/LABA ± other therapies. Consistent with the guideline-based stepwise approach to therapy, groups 1 and 2 received MF 200 or MF/F 200/10 μg BID and groups 3 and 4 received MF 400 or MF/F 400/10 μg BID.

Additional analyses. Additional analyses were performed for clinically relevant secondary endpoints in the ICS/LABA → MF/F group compared with the ICS/LABA → MF group, including analysis of asthma exacerbation rates, SABA use, and add-on asthma treatment.

TABLE I. Baseline demographic characteristics

Baseline characteristic	ICS/LABA → MF/F (N = 4231)	ICS/LABA → MF (N = 4216)	Total (N = 8447)
Mean (SD) age (y)	47.1 (16.6)	46.8 (16.9)	47.0 (16.8)
Age distribution (y), n (%)			
12-17	258 (6.1)	270 (6.4)	528 (6.3)
18-64	3326 (78.6)	3319 (78.7)	6645 (78.7)
>64	647 (15.3)	627 (14.9)	1274 (15.1)
Females, n (%)	2750 (65.0)	2822 (66.9)	5572 (66.0)
Race subgroup of interest, n (%)			
Black	303 (7.2)	258 (6.1)	561 (6.6)
Non-black	3927 (92.8)	3958 (93.9)	7885 (93.3)
Tobacco use, n (%)			
Nonuser	3363 (79.5)	3368 (79.9)	6731 (79.7)
Ex-user	736 (17.4)	694 (16.5)	1430 (16.9)
Current user	132 (3.1)	154 (3.7)	286 (3.4)
Smoking (pack-years), mean (SD)	4.3 (4.2)	4.2 (3.3)	4.3 (3.8)

F, Formoterol; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *MF*, mometasone furoate; *SD*, standard deviation.

TABLE II. Baseline asthma characteristics

Baseline characteristic	ICS/LABA → MF/F (N = 4231)	ICS/LABA →MF (N = 4216)
Mean (SD) age of first asthma treatment (y)	31.1 (20.0)	30.7 (19.6)
Duration of prior ICS/LABA, n (%)		
≤3 mo	795 (18.8)	837 (19.9)
>3 mo	3341 (80.0)	3255 (77.2)
Unknown	95 (2.2)	124 (2.9)
Median (range) duration of prior ICS/LABA (mo)	13.4 (0.03-399.9)	13.3 (0.03-648.6)
Patients hospitalized for asthma between 4 and 52 wk before the randomization visit, n (%)	567 (13.4)	522 (12.4)
Mean (SD) duration since last asthma exacerbation (wk)	20.6 (13.1)	20.4 (13.0)
ACQ-6 total score, n (%)		
≥1.5 (not well controlled)	1441 (34.1)	1343 (31.9)
<1.5 (controlled)	2790 (65.9)	2873 (68.1)
Asthma exacerbation history,* n (%)		
≤3 mo	1640 (38.8)	1658 (39.3)
>3 mo	2586 (61.1)	2557 (60.7)
Unknown	5 (0.1)	1 (<0.1)
Incoming asthma treatment and level of asthma control,† n (%)		
Group 1: controlled on low-dose ICS/LABA ± other therapies	726 (17.2)	766 (18.2)
Group 2: not well controlled on daily low-dose ICS/LABA ± other therapies OR controlled on medium-dose ICS/LABA ± other therapies	1648 (39.0)	1631 (38.7)
Group 3: not well controlled on medium-dose ICS/LABA ± other therapies	1009 (23.8)	936 (22.2)
Group 4: controlled on high-dose ICS/LABA ± other therapies	848 (20.0)	883 (20.9)

ACQ-6, 6-Question Asthma Control Questionnaire; *F*, formoterol; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *MF*, mometasone furoate; *SD*, standard deviation.
*No participants had an asthma exacerbation within 1 month of randomization.
†Groups 1 and 2 received MF 200 or MF/F 200/10 μg BID and groups 3 and 4 received MF 400 or MF/F 400/10 μg BID.

RESULTS

Trial population

Among the 11,729 participants in the full study population, a total of 8447 (72%) adolescent and adult patients (aged ≥12 years) entered the trial on ICS/LABA combination therapy and were included in this *post hoc* analysis (Figure 1). Of these 8447 patients, 4231 were randomized to remain on ICS/LABA combination therapy, receiving MF/F (ICS/LABA → MF/F group), and 4216 were randomized to be stepped down to ICS monotherapy, receiving MF (ICS/LABA → MF group) (Figure 1). Patient demographics and baseline disease characteristics were well balanced across the 2 treatment subgroups (Tables I and II; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Patients included in this analysis had a mean age of 47 years, were predominantly nonsmokers (80%) and non-black (93%), and about two-thirds were female. The majority (67%) of participants had a controlled disease status (ACQ <1.5), had been receiving a stable dose of

TABLE III. Summary of safety events related to primary safety endpoint

Safety endpoint*	ICS/LABA → MF/F (N = 4231)	ICS/LABA → MF (N = 4216)
Composite safety endpoint	28 (0.7%)	27 (0.6%)
Asthma-related death	0	0
Asthma-related intubation	0	0
Asthma-related hospitalization	28 (0.7%)	27 (0.6%)
Total number of asthma-related events		
Asthma-related hospitalization events	31	30
Total number of events NOT asthma-related		
Deaths	3	3
Invasive (endotracheal) intubations	16	20
Hospitalizations	38	41

F, Formoterol; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *MF*, mometasone furoate.
*Adjudicated by an independent committee.

TABLE IV. Summary of patients with adverse events*

Patients in analysis population with 1 or more	ICS/LABA → MF/F (N = 4231), n (%)	ICS/LABA → MF (N = 4216), n (%)
Any serious adverse event	103 (2.4)	109 (2.6)
Adverse event with outcome of death	3 (0.1)	3 (0.1)
Adverse event leading to treatment discontinuation	61 (1.4)	76 (1.8)
Asthma exacerbation leading to treatment discontinuation†	59 (1.4)	59 (1.4)

F, Formoterol; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *MF*, mometasone furoate.
*Reflects patients in the full analysis set, ie, all randomized patients who received at least 1 dose of blinded study treatment.
†Reflects investigator-assessed asthma exacerbations.

ICS/LABA for at least 3 months (78%), and most (61%) had an asthma exacerbation greater than 3 months before randomization (Table II). Asthma disease severity, based on the patient's prior asthma treatment and baseline level of control, adequately represented the 4 prespecified moderate-to-severe persistent asthmatic groups with contributions ranging from 1492 (18%) participants in the smallest subgroup (ie, group 1, patients controlled on low-dose ICS plus LABA) to 3279 (39%) participants in the largest subgroup (ie, group 2, patients not well controlled on low-dose ICS plus LABA and patients controlled on medium-dose ICS plus LABA).

The majority of patients included in this analysis took their study medication as prescribed for the full trial duration. In total, 8439 (99.9%) patients included in this analysis completed the study through week 26, and among these, a total of 7377 (87.3%) patients completed the study on treatment, 3750 (88.6%) in the ICS/LABA → MF/F group and 3627 (86.0%) in the ICS/LABA → MF group. The reasons for study treatment discontinuation are provided in Figure 1. Overall, 7502 patients (88.8%) in the full analysis set (89.5% of those receiving ICS/LABA → MF/F and 88.2% of those receiving ICS/LABA → MF) used between 80% and 120% of their prescribed dose (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

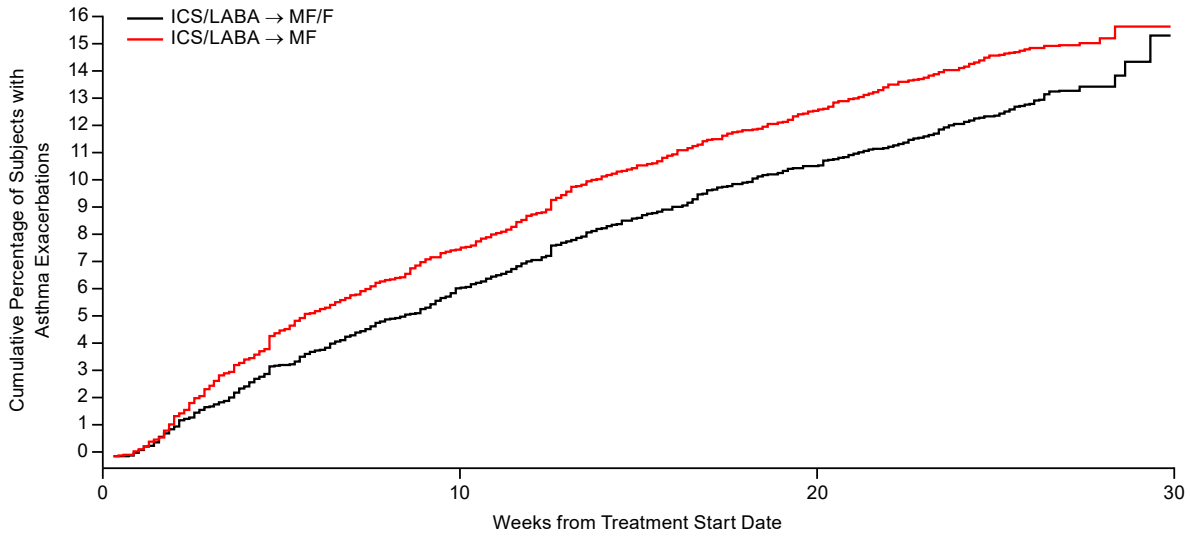
Serious asthma outcomes

In this *post hoc* analysis, a total of 61 SAOs occurred in 55 (0.6%) patients, 31 events in 28 patients in the ICS/LABA → MF/F group and 30 events in 27 patients in the ICS/LABA → MF group (Table III). These events were all asthma-related hospitalizations; no asthma-related intubations or asthma-related deaths were observed (Table III; Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

Analyses showed a similar risk of asthma-related events with maintenance on ICS/LABA (MF/F) combination therapy compared with stepping down to ICS (MF) monotherapy. Specifically, the hazard ratio (HR) for the time to first SAO in the ICS/LABA → MF/F group compared with the ICS/LABA → MF group was 1.03 (95% confidence interval [CI]: 0.61, 1.75) ($P = .913$), indicating noninferiority between the treatment subgroups (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). The 3% increase in the risk of first SAO (asthma-related hospitalization) with maintenance on MF/F compared with step-down to MF estimated by the HR is comparable with a risk difference of 0.02 (or an added percentage of 0.02% with ICS/LABA → MF/F compared with ICS/LABA → MF), with a 95% CI of −0.33 to 0.38 among patients with an overall event rate of 0.6% (Table E6, available in this article's Online Repository at www.jaci-inpractice.org).

Other safety endpoints/assessments

Other serious events of interest (hospitalizations, intubations, and deaths) not adjudicated as asthma-related were balanced between the treatment subgroups (Table III). There were 3 deaths from any cause (ie, not asthma related) reported in both the ICS/LABA → MF/F and ICS/LABA → MF groups (Table IV; Table E7, available in this article's Online Repository at www.jaci-inpractice.org). The overall incidence of serious adverse events was low and balanced between the 2 groups (2.4% in the ICS/LABA → MF/F group and 2.6% in the ICS/LABA → MF group) (Table IV). Similarly, few patients in either treatment group discontinued treatment because of an adverse event or an asthma exacerbation. There were 61 (1.4%) participants in the ICS/LABA → MF/F group and 76 (1.8%) participants in the ICS/LABA → MF group who discontinued study treatment because of an adverse event



Subjects at Risk:

ICS/LABA → MF/F	4231	3749	3471	50
ICS/LABA → MF	4216	3618	3309	54

Population consists of all randomized patients previously on ICS/LABA who received at least one dose of blinded study medication.
Follow-up time is censored at 7 days after last dose of blinded study medication.

FIGURE 2. Kaplan-Meier curves of time-to-first asthma exacerbation with maintenance on ICS/LABA (MF/F) combination versus step-down to ICS (MF) monotherapy. *F*, Formoterol; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *MF*, mometasone furoate.

(Figure 1; Table IV). Similarly, the proportion of patients who discontinued study treatment due to asthma exacerbation was 1.4% in both groups (Figure 1). The 2 treatment groups also had similar profiles for time to study treatment discontinuation (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Key efficacy endpoint

Primary subgroup analysis. A total of 1143 (13.5%) patients previously receiving ICS/LABA experienced at least 1 asthma exacerbation: 543 (12.8%) subjects in the ICS/LABA → MF/F group and 600 (14.2%) in the ICS/LABA → MF group (Table E8, available in this article's Online Repository at www.jaci-inpractice.org). The HR for the time to first asthma exacerbation in the ICS/LABA → MF/F group versus the ICS/LABA → MF group was 0.87 (95% CI: 0.78-0.98, $P = .020$), indicating a 13% lower risk of asthma exacerbation with maintenance on combination ICS/LABA (MF/F) therapy (Figure 2; Table E9, available in this article's Online Repository at www.jaci-inpractice.org).

Asthma exacerbations requiring the use of systemic corticosteroids (for at least 3 consecutive days or ≥1 depot injectable) accounted for 87.7% (1002 of 1143) of the total number of first asthma exacerbation events (Table E8, available in this article's Online Repository at www.jaci-inpractice.org). The ICS/LABA → MF/F group had a 15% reduction in the risk of first asthma exacerbation requiring systemic corticosteroid compared with the ICS/LABA → MF group (0.85 [95% CI: 0.75-0.96, $P = 0.010$]) (Table E10, available in this article's Online Repository at www.jaci-inpractice.org).

The results within the 2 ICS dose groups (200 and 400 μg, BID) were consistent with those seen in the overall step-down analysis population, with a smaller proportion of patients experiencing an asthma exacerbation in the ICS/LABA → MF/F group compared with the ICS/LABA → MF group, although the overall incidence of events was higher in the 400 μg, BID dose group (Table E11, available in this article's Online Repository at www.jaci-inpractice.org).

Primary subgroup analysis by demographic subgroups and asthma baseline characteristics. The proportion of patients with asthma exacerbations by demographic subgroups and other baseline characteristics was generally lower in the ICS/LABA → MF/F group compared with the ICS/LABA → MF group.

Analyzing the effect of baseline asthma control, asthma exacerbation history, and asthma disease severity (incoming asthma treatment/asthma control) all supported a reduction in the risk of asthma exacerbation with maintenance on ICS/LABA combination therapy compared with stepping down to ICS monotherapy (Table V). The observed reduction in the risk of asthma exacerbation with MF/F maintenance compared with step-down to MF alone was more pronounced in patients who were not well controlled at baseline (ACQ-6 ≥1.5) or who had had a recent asthma exacerbation (within ≤3 months) before step-down. Similarly, the overall proportion of patients with asthma exacerbation increased with increasing asthma severity based on the 4 prespecified incoming asthma treatment/control groups (8.8%, 12.7%, 15%, and 17.4% for groups 1, 2, 3, and 4, respectively) (Table E12, available in this article's Online Repository at www.jaci-inpractice.org). However, there was a similar proportion of patients who experienced an asthma exacerbation in the ICS/LABA → MF/F group and the ICS/LABA → MF group within group 1 (ie, controlled on low-dose ICS

TABLE V. First asthma exacerbation with maintenance on ICS/LABA (MF/F) combination vs step-down to ICS (MF) monotherapy by baseline asthma characteristics

Incoming treatment → received treatment	N	Number of subjects with events	Percentage of of subjects with events	ICS/LABA → MF/F vs ICS/LABA → MF Risk difference* (95% CI)
ACQ ≥1.5 (not well controlled)				
ICS/LABA → MF/F	1441	188	13.05	−1.85 (−4.42, 0.73)
ICS/LABA → MF	1343	200	14.89	
ACQ <1.5 (controlled)				
ICS/LABA → MF/F	2790	355	12.72	−1.20 (−2.97, 0.57)
ICS/LABA → MF	2873	400	13.92	
Asthma exacerbation history ≤3 mo†				
ICS/LABA → MF/F	1640	236	14.39	−2.68 (−5.16, −0.20)
ICS/LABA → MF	1658	283	17.07	
Asthma exacerbation history >3 mo				
ICS/LABA → MF/F	2586	307	11.87	−0.53 (−2.31, 1.26)
ICS/LABA → MF	2557	317	12.40	
Baseline asthma severity based on incoming asthma treatment/asthma control				
Group 1				
ICS/LABA → MF/F	726	65	8.95	0.21 (−2.68, 3.09)
ICS/LABA → MF	766	67	8.75	
Group 2				
ICS/LABA → MF/F	1648	190	11.53	−2.39 (−4.67, −0.11)
ICS/LABA → MF	1631	227	13.92	
Group 3				
ICS/LABA → MF/F	1009	143	14.17	−1.75 (−4.93, 1.44)
ICS/LABA → MF	936	149	15.92	
Group 4				
ICS/LABA → MF/F	848	145	17.10	−0.68 (−4.26, 2.89)
ICS/LABA → MF	883	157	17.78	

Group 1: controlled on low-dose ICS/LABA ± other therapies.
Group 2: not well controlled on daily low-dose ICS/LABA ± other therapies OR controlled on medium-dose ICS/LABA ± other therapies.
Group 3: not well controlled on medium-dose ICS/LABA ± other therapies.
Group 4: controlled on high-dose ICS/LABA ± other therapies.
ACQ-6, 6-Question Asthma Control Questionnaire; *CI*, confidence interval; *F*, formoterol; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *MF*, mometasone furoate.
*Risk difference = difference in % of subjects with events ([ICS/LABA → MF/F] − [ICS/LABA → MF]). The risk difference analyses used the Miettinen and Nurminen method to estimate the point estimate and the 95% confidence intervals for the treatment differences (shown in percentages) and their *P* values. This method does not adjust for covariates.
†No participants had an asthma exacerbation within 1 month of randomization.

plus LABA) and group 4 (controlled on high-dose ICS/LABA) (Table V; Table E13, available in this article's Online Repository at www.jaci-inpractice.org).

Consistent with the results in the overall analysis population, the proportion of subjects with asthma exacerbations was higher in the ICS/LABA → MF group compared with the ICS/LABA → MF/F group in each of the 3 prespecified age subgroups (Table E13, available in this article's Online Repository at www.jaci-inpractice.org). The largest treatment difference (4.1%) in favor of the ICS/LABA → MF/F group was observed in the elderly subgroup.

The proportion of patients with asthma exacerbation in the black subgroup was higher than that for the overall analysis population (23.0% vs 12.9%, respectively); however, fewer asthma exacerbations occurred in black patients in the ICS/LABA → MF/F group (21.5%) compared with that in the ICS/LABA → MF group (24.8%) (Table E14, available in this article's Online Repository at www.jaci-inpractice.org).

Further examination of patient characteristics in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) using logistic regression (data not shown) did not identify any prognostic factors that would support step-down from ICS/LABA to MF.

Additional subgroup analyses. The size of the study and the absence of discontinuation criteria requiring patients experiencing an asthma exacerbation to be discontinued from treatment permitted an analysis of asthma exacerbations rates, given that more than 1 event was observed for a substantial number of patients. Analysis of asthma exacerbation rates showed a reduction in the risk of asthma exacerbation with maintenance on ICS/LABA (MF/F) compared with step-down to ICS monotherapy (MF) (rate ratio, 0.88; 95% CI, 0.78-1.00; $P = .044$) (Table E15, available in this article's Online Repository at www.jaci-inpractice.org). Endpoints closely related to asthma exacerbation such as SABA use and additional add-on asthma

treatment further support clinically meaningful improvement in symptoms of asthma exacerbation and overall asthma control in patients who did not step down to ICS monotherapy (Tables E16 and E17, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Current asthma treatment guidelines suggest that patients on ICS/LABA combination therapy whose asthma has been controlled for at least 3 months can have their asthma therapy reduced either to a lower dose of ICS or discontinued from LABA.[8] Potential loss of asthma control resulting in asthma exacerbation and the need for additional medication and hospitalization is a concern with either step-down approach, and has been the subject of many investigations.[10,12-21] Previous randomized controlled studies examining the safety and efficacy of LABA step-down in patients with asthma on ICS/LABA combination therapy have generally been performed in relatively small patient populations and have not used guideline-based composite criteria for the detection of SAOs and asthma exacerbation.[10,12-21] Brozek et al[10] and Ahmad et al[21] each performed comprehensive reviews and meta-analyses to compare outcomes associated with continued use of ICS/LABA versus LABA discontinuation in adult and adolescent patients with stable asthma. In the Brozek analysis, data suggested that LABA discontinuation poses an increased risk of asthma impairment (eg, worse quality of life and disease control [ACQ], fewer symptom free days, and greater risk of study withdrawal due to lack of efficacy or loss of asthma control); however, the risk of SAOs or asthma exacerbation after LABA discontinuation was not evaluable due to the small number of events and short follow-up period.[10] Similarly, Ahmad's analysis suggested that stopping LABA may increase the risk of asthma exacerbation, but the evidence was inconclusive given the small number of events and greater number of study withdrawals among the group who discontinued LABA.[21] As a result, both reports concluded that a longer trial measuring important asthma outcomes be conducted.[10,21]

The present analysis includes data from 8447 patients (72% of the 11729 patients who participated in the SPIRO study[3]) whose asthma was adequately controlled on a stable dose of ICS/LABA therapy for at least 3 months before randomization to MF/F or MF. In addition, over 500 adolescents (aged 12-17 years) and over 1200 elderly (aged ≥65 years) patients were included in this step-down analysis, which is larger than the overall size of most previously published trials. To our knowledge, this analysis represents the largest dataset from a single, multicenter, global asthma outcomes study to assess the safety and efficacy of LABA step-down using guideline-based composite criteria for the detection of SAOs and asthma exacerbation in adult and adolescent patients with persistent asthma.

Our study showed that long-term maintenance on ICS/LABA combination therapy does not increase the risk of SAOs (all asthma-related hospitalizations) or other serious adverse events compared with step-down from LABA. These findings are robust given the strong adherence to study medication and thorough safety follow-up in both treatment groups. In addition, these results are not biased by an imbalance in treatment discontinuation due to adverse events or asthma exacerbation.

Consistent with directional findings from smaller studies reporting decreased lung function, loss of asthma control, and an increase in asthma exacerbation events with LABA step-down to ICS monotherapy,[10,12-21] our study demonstrated that maintenance on ICS/LABA combination therapy with MF/F provided a 13% reduction in the risk of asthma exacerbation over 26 weeks compared with LABA step-down to MF alone. These results were driven by the need for systemic corticosteroid, consistent with the primary study results.[3] The observed reduction in the risk of asthma exacerbation with MF/F maintenance compared with step-down to MF alone was more pronounced in patients who were less well controlled at baseline (ACQ ≥1.5) or who had had a recent asthma exacerbation (≤3 months) before LABA step-down, underscoring the importance of maintaining ICS/LABA therapy long term in individuals at risk for asthma exacerbation.

The SAO and asthma exacerbation results observed for the ICS/LABA → MF/F group compared with the ICS/LABA → MF group in the overall step-down analysis population were generally consistent within the ICS dose subgroups. Furthermore, there were no other patient characteristics (age, race, asthma severity, smoking in pack-years, and history of asthma exacerbation) that would support step-down from ICS/LABA to ICS. However, treatment adherence in this study was measured by dose counter changes and does not account for the exact time of medication usage; therefore, it is possible that the results may be affected by differential use of medication among the subgroups.

The overall higher incidence of asthma exacerbations observed in the black population compared with the non-black population is consistent with published literature and has been attributed to a number of factors, ranging from treatment adherence to genetics. African Americans are more likely to be homozygous for Arg16 (ie, to have the Arg/Arg genotype) of the β_2-adrenergic receptor polymorphism,[22] which has been linked to more frequent exacerbations independent of β-agonist use.[23] Despite the higher incidence of asthma exacerbation in the black subgroup of the present study, prolonged ICS/LABA (MF/F) exposure was associated with a reduction in the incidence of asthma exacerbation compared with LABA step-down to MF alone. Prior studies have suggested that compared with people who are Gly16 homozygous, people who are homozygous for Arg16 have a greater benefit from single doses of β-agonist,[24] but are at higher risk of asthma exacerbation if they use β-agonist on a regular basis;[25] however, concurrent use of ICS had not been evaluated. Although the present study did not analyze patient genotypes, the clinical data do not provide any evidence that would warrant limiting ICS/LABA exposure to African Americans. Similar to race, the present study does not provide evidence that would warrant limiting ICS/LABA exposure to patients of any age; data suggest that maintenance on ICS/LABA may particularly benefit older patients (≥65 years) with respect to risk of asthma exacerbation.

The *post hoc* nature of the present analysis may be considered a limitation. However, the SPIRO study design, guidance-based endpoints, and large size of the step-down analysis population are significant strengths. Real-world evaluations indicate a high prevalence of suboptimally controlled asthma despite treatment with ICS or ICS/LABA, highlighting the importance of understanding risk factors associated with asthma exacerbation.[26] The overall high level of adherence to treatment in this study relative to the real-world setting, where adherence is not always optimal, may limit generalizability. However, it does allow for a robust

risk/benefit assessment of ICS/LABA maintenance (MF/F) compared with step-down to ICS (MF). The patient population in this analysis is geographically diverse and represents a broad range of persistent asthmatics on ICS/LABA with varying levels of disease severity typically encountered in the real-world clinic setting. The 6-month study duration may be viewed as a limitation with regard to detecting long-term effects of LABA exposure that may be observed in a 1-year trial. In addition to strong adherence to study medication, treatment exposure to randomized treatment was high in both treatment groups (mean duration: ICS/LABA → MF/F, 171 days; ICS/LABA → MF, 168 days). Moreover, given that all patients in this subgroup analysis had been receiving a stable dose of ICS/LABA for at least 4 weeks and had been on any ICS/LABA for a median of 13 months before randomization, any long-term effects of LABA exposure would likely have been identified. The absence of any new or unexpected safety findings, including any asthma-related death or intubation in a population of this size, supports this conclusion. The global nature of the trial, involving countries located in both hemispheres, also helps to account for any effects of seasonal variation that might be observed in a 1-year trial.

All patients in this study had a history of at least 1 asthma exacerbation in the past year, suggesting an increased risk for future exacerbation. Therefore, it is noteworthy that the majority of participants in the SPIRO study, with an estimated median compliance rate of 97.3% (MF/F 97.5% and MF 97.1%), did not experience an SAO (99.4%) or asthma exacerbation (87.3%).[3] In the overall study population of 11,729 participants, 81 SAOs occurred in 71 patients.[3] The ICS/LABA subgroup examined in the present analysis accounted for 75% of the SAOs and 77% of the patients with an SAO observed in the SPIRO study. Similarly, the ICS/LABA subgroup accounted for 77% of the 1487 patients in the full study population who had at least 1 asthma exacerbation.[3] Taken together, these findings suggest that the incidence of SAOs and asthma exacerbation events is higher among patients with more severe asthma, who are generally managed with combination therapy. These results are consistent with previous reports suggesting that there is a higher incidence of asthma exacerbation in patients with severe asthma.[27-30]

In conclusion, this *post hoc* analysis of data from the SPIRO study in adolescent and adult patients with persistent asthma demonstrated that maintenance on ICS/LABA combination therapy with MF/F was not associated with an increased risk of SAOs and also significantly reduced the risk of asthma exacerbation compared with LABA step-down to MF alone. The observed reduction in the risk of asthma exacerbation with MF/F maintenance compared with step-down to MF alone was more pronounced in patients who were not well controlled at baseline or who had had a recent asthma exacerbation before step-down, underscoring the importance of maintaining ICS/LABA therapy long term in individuals at risk for asthma exacerbation. Furthermore, no specific patient characteristics were identified that would support step-down from ICS/LABA to ICS.

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Merck Sharp & Dohme Corp.'s (a subsidiary of Merck & Co., Inc., Kenilworth, NJ) data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the study data can be submitted through the EngageZone site or via e-mail to dataaccess@merck.com.

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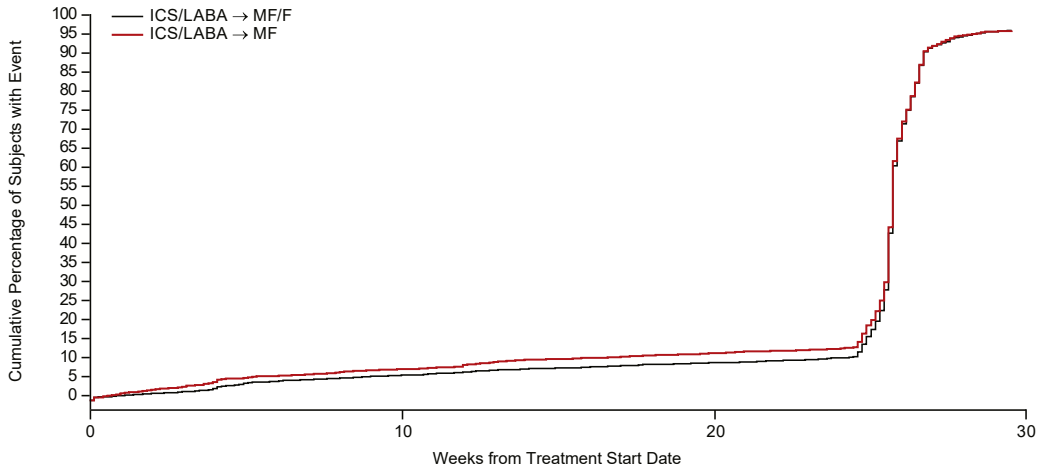

Subjects at Risk:

ICS/LABA → MF/F	4231	3951	3810	28
ICS/LABA → MF	4216	3869	3691	29

Population consists of all randomized patients previously on ICS/LABA who received at least one dose of blinded study medication.

FIGURE E1. Kaplan-Meier curves of time to treatment discontinuation. *F*, Formoterol; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *MF*, mometasone furoate.