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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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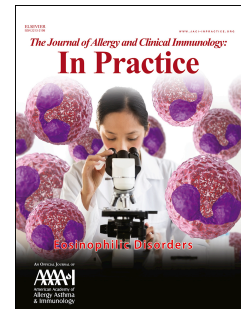
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Cindy Weinstein, Nicholas Ryan, Xiaoli Zhang, Tulin Shekar, and Davis Gates are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may hold stock or stock options in the company.

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ABSTRACT

Background: Due to historical safety concerns with use of long-acting beta agonists in asthma, step-down from inhaled corticosteroid/long-acting beta agonist (ICS/LABA) combination therapy to ICS monotherapy is recommended once asthma control is achieved.

Objective: To evaluate the benefit/risk question about whether asthma patients 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.

Methods: Using data from 8,447 clinically stable patients with persistent asthma in the SPIRO trial who had been receiving a stable dose of ICS/LABA for ≥ 4 weeks, this post-hoc analysis evaluated the risk of SAOs (adjudicated hospitalization, intubation, or death) and AEX (composite of hospitalizations ≥ 24 h, emergency visits < 24 h 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 to those who stepped down from ICS/LABA to MF [HR 1.03 (95% CI 0.61, 1.75), $p = 0.913$]. The risk of AEX was significantly lower in patients maintained on ICS/LABA with MF/F compared to those who stepped down from ICS/LABA to MF [HR 0.87 (95% CI 0.78, 0.98), $p = 0.020$].

Conclusions: In this post-hoc analysis of a large 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. **ClinicalTrials.gov number, NCT01471340.**

Keywords (3 keywords): long acting beta agonists, inhaled corticosteroids, asthma treatment step-down

HIGHLIGHTS

1. What is already known about this topic?

- Due to historical safety concerns with use of long-acting beta 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 to ICS monotherapy.

2. 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/formoterol (MF/F) reduces the risk of asthma exacerbation compared with LABA step-down to MF alone, without altering the safety profile.

3. 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.
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84 **Abbreviations:**

85 ACQ: Asthma Control Questionnaire

86 BID: twice daily

87 FDA: U.S. Food and Drug Administration

88 HR: hazard ratio

89 ICS: Inhaled corticosteroid

90 IVRS/IWRS: Interactive Voice/Web Response System

91 LABA: Long-acting beta agonist

92 MF/F: mometasone furoate plus formoterol fumarate

93 SAO: serious asthma outcomes

INTRODUCTION

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 beta2 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 United States Food and Drug Administration (FDA) to include a black box warning about serious asthma outcomes, 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 in order to assess whether concurrent use of a LABA with an ICS mitigates the safety risks observed with LABA monotherapy.² Weinstein et al., 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.³ 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 mometasone furoate and formoterol (MF/F) compared with

mometasone (MF) alone did not pose a significantly greater risk of serious asthma outcomes (SAO) and also reduced the risk of asthma exacerbation.³ The results from the four 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 asthma patients 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 three months may be considered for LABA discontinuation.⁸

Concerns about loss of asthma control with discontinuation of LABA have been raised; however,^{9,10} the impact of the step-down from ICS/LABA combination therapy to ICS monotherapy on serious asthma outcomes 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 serious asthma outcomes 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 asthma patients 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 serious asthma outcomes and asthma exacerbation in the subgroup of patients who, upon study entry, remained on fixed-dose ICS/LABA combination therapy (MF/F maintenance) compared to 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).

142 Additional subgroup analyses were performed to further investigate these and other factors that
143 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 aged ≥ 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 one 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 prior to randomization. Although the full study population (11,729 participants) included patients on any asthma controller medication who could warrant ICS $\pm$ 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, while 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) in order to discontinue their previously prescribed treatment and to determine the appropriate ICS dose level to be assigned at randomization.³ To ensure patients were sufficiently stable for potential LABA step-down, an assessment of asthma symptoms and 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 ≥ 3 nights per week, required either > 8 puffs per day of SABA for ≥ 2 consecutive days, or ≥ 25 puffs of SABA in one day. Additionally, eligible patients could not require chronic use of systemic corticosteroid or anti-IgE (e.g., Xolair), and had no more than four asthma exacerbations or more than two 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, non-asthmatic 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 μg or 400/10 μg) or MF (200 μg 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 (two puffs of 100 /5 μg or 200/5 μg) or MF alone (two puffs of 100 μg or 200 μg), administered twice daily by a pressurized metered-dose inhaler. The assigned ICS dose (200 μg or 400 μg , BID) was based on the patient's prior asthma medication and ACQ-6 total score. Consistent with GINA 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 four 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 seven 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 serious asthma outcomes (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 the stay was ≥ 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.

In order 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 ≥ 1 depot injectable), or an in-patient hospitalization for asthma (≥ 24 hour stay), or an emergency department visit for asthma (< 24 hours) that required systemic corticosteroids.

Statistical Analysis

Primary Subgroup Analyses: ICS/LABA $\rightarrow$ MF/F vs ICS/LABA $\rightarrow$ 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 prior to randomization. Patients who had been receiving anything other than ICS/LABA were not included in these analyses. In the primary subgroup analyses, serious asthma outcome and asthma exacerbation events for patients who remained on ICS/LABA combination therapy (i.e., ICS/LABA $\rightarrow$ MF/F) were compared with patients who were stepped down to ICS monotherapy (i.e., ICS/LABA $\rightarrow$ 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 ICS dose level. All primary evaluations pooled the two 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 one dose of blinded treatment and who had been receiving ICS/LABA combination therapy prior to randomization.

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

All safety assessments included data collected within six months after the first dose of blinded treatment or seven 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, 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 serious asthma outcomes within the primary subgroup analysis, further sub-analyses were not performed on this outcome. Additional subgroup analyses were performed to compare asthma exacerbation events based on pre-study 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 to those who stepped down from LABA to ICS (MF) monotherapy. In addition, in order 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 in the Online Repository**.

Asthma control was dichotomized using the patient's ACQ-6 total score, where controlled and not well controlled are differentiated by a cut-off of 1.5.¹¹

Asthma exacerbation history was dichotomized as ≤ 3 months 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 pre-study 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 $\pm$ other therapies; Group 2 - not well controlled on daily low-dose ICS/ LABA $\pm$ other therapies OR controlled on medium-dose ICS/ LABA $\pm$ other therapies; Group 3 - not well controlled on medium-dose ICS/ LABA $\pm$ other therapies; Group 4: controlled on high-dose ICS/ LABA $\pm$ other therapies. Consistent with the guideline-based stepwise approach to therapy, Groups 1 and 2 received MF 200 or MF/F 200/10 μ g BID and Groups 3 and 4 received MF 400 or MF/F 400/10 μ g BID.

Additional Analyses

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

RESULTS

Trial Population

Among the 11,729 participants in the full study population, a total of 8,447 (72%) adolescent and adult patients (age ≥ 12 years) entered the trial on ICS/LABA combination therapy and were included in this post-hoc analysis (**Figure 1**). Of these 8,447 patients, 4,231 were randomized to remain on ICS/LABA combination therapy, receiving MF/F (ICS/LABA $\rightarrow$ MF/F group), and 4,216 were randomized to be stepped down to ICS monotherapy, receiving MF (ICS/LABA $\rightarrow$ MF group) (**Figure 1**). Patient demographics and baseline disease characteristics were well balanced across the two treatment subgroups (**Table 1; Table 2; Table E2 in Online Repository**). Patients included in this analysis had a mean age of 47 years, were predominantly non-smokers (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 ICS/LABA for at least 3 months (78%), and most (61%) had an asthma exacerbation greater than 3 months prior to randomization (**Table 2**). Asthma disease severity, based on the patient's prior asthma treatment and baseline level of control, adequately represented the 4 pre-specified moderate-to-severe persistent asthmatic groups with contributions ranging from 1492 (18%) participants in the smallest subgroup (i.e., Group 1, patients controlled on low-dose ICS plus LABA) to 3279 (39%) participants in the largest subgroup (i.e., 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, 8,439 (99.9%) patients included in this analysis completed the study through Week 26, and among these, a total of 7,377 (87.3%) patients completed the study on treatment, 3750 (88.6%) in the ICS/LABA $\rightarrow$ MF/F group and 3627 (86.0%) in the

ICS/LABA→MF group. Reasons for study treatment discontinuation are provided in **Figure 1**. Overall, 7,502 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 in Online Repository**).

Serious Asthma Outcomes

In this post-hoc analysis, a total of 61 serious asthma outcomes 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 3**). These events were all asthma-related hospitalizations; no asthma-related intubations or asthma-related deaths were observed (**Table 3; Table E4 in Online Repository**).

Analyses showed a similar risk of asthma-related events with maintenance on ICS/LABA (MF/F) combination therapy compared to stepping down to ICS (MF) monotherapy. Specifically, the hazard ratio (HR) for the time to first serious asthma outcome in the ICS/LABA→MF/F group compared with the ICS/LABA→MF group was 1.03 (95% CI: 0.61, 1.75) ($p=0.913$), indicating non-inferiority between the treatment subgroups (**Table E5 in Online Repository**). 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 to 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 in Online Repository**).

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 3**). There were 3 deaths from any cause (i.e., not asthma related) reported in both the ICS/LABA→MF/F and ICS/LABA→MF groups (**Table 4; Table E7 in Online Repository**). The overall incidence of serious adverse events was low and balanced between the two groups (2.4% in the ICS/LABA→MF/F group and 2.6% in the ICS/LABA→MF group) (**Table 4**). Similarly, few patients in either treatment group discontinued treatment due to 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 discontinued study treatment due to an adverse event (**Figure 1; Table 4**). Similarly, the proportion of patients who discontinued study treatment due to asthma exacerbation was 1.4% in both groups (**Figure 1**). The two treatment groups also had similar profiles for time to study treatment discontinuation (**Figure E1 in Online Repository**).

Key Efficacy Endpoint

Primary Subgroup Analysis

A total of 1143 (13.5%) patients previously receiving ICS/LABA experienced at least one 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 in Online Repository**). 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 to 0.98, $p = 0.020$), indicating a 13% lower risk of asthma exacerbation with maintenance on combination ICS/LABA (MF/F) therapy (**Figure 2; Table E9 in Online Repository**).

Asthma exacerbations requiring the use of systemic corticosteroids (for at least 3 consecutive days or ≥ 1 depot injectable), accounted for 87.7% (1,002 of 1,143) of the total number of first asthma exacerbation events (**Table E8 in Online Repository**). The ICS/LABA $\rightarrow$ MF/F group had a 15% reduction in the risk of first asthma exacerbation requiring systemic corticosteroid compared to the ICS/LABA $\rightarrow$ MF group [0.85 (95% CI: 0.75 to 0.96, $p = 0.010$)] (**Table E10 in Online Repository**).

The results within the two ICS dose groups (200 μ g and 400 μ g, 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 $\rightarrow$ MF/F group compared to the ICS/LABA $\rightarrow$ MF group, although the overall incidence of events was higher in the 400 μ g, BID dose group (**Table E11 in Online Repository**).

Primary Subgroup Analysis by Demographic Subgroups and Asthma Baseline Characteristics

The proportion of patients with asthma exacerbations by demographic subgroups and other baseline characteristics were generally lower in the ICS/LABA $\rightarrow$ MF/F group compared to the ICS/LABA $\rightarrow$ 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 risk of asthma exacerbation with maintenance on ICS/LABA combination therapy compared to stepping down to ICS monotherapy (**Table 5**). 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 ($ACQ-6 \geq 1.5$) or who had had a recent asthma exacerbation (within ≤ 3 months) prior to step down. Similarly, the overall proportion of patients with asthma

exacerbation increased with increasing asthma severity based on the four prespecified incoming asthma treatment/control groups, (8.8%, 12.7%, 15%, and 17.4% for Groups 1, 2, 3, and 4, respectively) (**Table E12 in Online Repository**). However, there was a similar proportion of patients who experienced an asthma exacerbation in the ICS/LABA → MF/F group and ICS/LABA → MF group within Group 1 (i.e., controlled on low dose ICS plus LABA) and Group 4 (controlled on high-dose ICS/LABA) (**Table 5, Table E13 in Online Repository**).

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 to the ICS/LABA→MF/F group in each of the three prespecified age subgroups (**Table E13 in Online Repository**). 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 to that in the ICS/LABA→MF group (24.8%) (**Table E14 in Online Repository**).

Further examination of patient characteristics in **Table E1 in Online Repository** 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 more than one event was observed for a substantial number of patients. Analysis of asthma exacerbation rates showed a reduction in the risk of asthma

392 exacerbation with maintenance on ICS/LABA (MF/F) compared with step down to ICS
393 monotherapy (MF) (rate ratio, 0.88; 95% CI, 0.78 to 1.00; P = 0.044) (**Table E15 in Online**
394 **Repository**). Endpoints closely related to asthma exacerbation such as SABA use and additional
395 add-on asthma treatment further support clinically meaningful improvement in symptoms of
396 asthma exacerbation and overall asthma control in patients that did not step down to ICS
397 monotherapy (**Table E16 and Table E17 in Online Repository**).

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DISCUSSION

Current asthma treatment guidelines suggest that patients on ICS/LABA combination therapy whose asthma has been controlled for at least three 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.^{11-16,18-21} Previous randomized controlled studies examining the safety and efficacy of LABA step down in asthma patients on ICS/LABA combination therapy have generally been done in relatively small patient populations and have not used guideline-based composite criteria for the detection of serious asthma outcomes and asthma exacerbation.^{11-16,18-21} Brozek et al.¹⁰ and Ahmad et al.¹⁷ have each performed comprehensive reviews and meta analyses in order 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 LABA discontinuation poses an increased risk of asthma impairment (e.g., 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 serious asthma outcomes 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.¹⁷ As a result, both reports concluded that a longer trial measuring important asthma outcomes be conducted.^{10,17}

The present analysis includes data from 8,447 patients (72% of the 11,729 patients who participated in the SPIRO study³) whose asthma was adequately controlled on a stable dose of

ICS/LABA therapy for at least 3 months prior to randomization to MF/F or MF. Additionally, over 500 adolescents (ages 12-17 years) and over 1200 elderly (ages ≥ 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 serious asthma outcomes 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 serious asthma outcomes (all asthma-related hospitalizations) or other serious adverse events compared to 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,^{11-16,18-21} 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 ($ACQ \geq 1.5$) or who had had a recent asthma exacerbation (≤ 3 months) prior to LABA step down, underscoring the importance of maintaining ICS/LABA therapy long-term in individuals at risk for asthma exacerbation.

The serious asthma outcome and asthma exacerbation results observed for the ICS/LABA→MF/F group compared to 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 to 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 (i.e., to have the Arg/Arg genotype) of the beta2-adrenergic receptor polymorphism,²² which has been linked to more frequent exacerbations independent of beta-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 to LABA step-down to MF alone. Prior studies have suggested that compared to people who are Gly16 homozygous, people who are homozygous for Arg16 have a greater benefit from single doses of beta-agonist,²⁴ but are at higher risk of asthma exacerbation if they use beta-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 sub optimally 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 to 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 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 prior to 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 a serious asthma outcome (99.4%) or asthma

exacerbation (87.3%).³ In the overall study population of 11,729 participants, 81 serious asthma outcomes occurred in 71 patients.³ The ICS/LABA subgroup examined in the present analysis accounted for 75% of the serious asthma outcomes and 77% of the patients with a serious asthma outcome 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 one asthma exacerbation.³ Taken together, these findings suggest that the incidence of serious asthma outcomes 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 serious asthma outcomes 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 prior to 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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Data Availability

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA’s 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 email to dataaccess@merck.com.

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Figure Legend

Figure 1. Participant flowchart.

Figure 2. Kaplan-Meier Curves of Time-to-First Asthma Exacerbation with Maintenance on ICS/LABA (MF/F) Combination vs Step Down to ICS (MF) Monotherapy. MF/F= mometasone furoate – formoterol; F= formoterol.

Tables

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Table 1. Baseline Demographic Characteristics

Baseline Characteristic	ICS/LABA → MF/F		ICS/LABA →MF		Total	
	N = 4231		N = 4216		N = 8447	
Mean (SD) age — years	47.1	(16.6)	46.8	(16.9)	47.0	(16.8)
Age Distribution, years — no. (%)						
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 — no. (%)	2750	(65.0)	2822	(66.9)	5572	(66.0)
Race subgroup of interest — no. (%)						
Black	303	(7.2)	258	(6.1)	561	(6.6)
Non-Black	3927	(92.8)	3958	(93.9)	7885	(93.3)
Tobacco Use — no. (%)						
Non-user	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 – mean (SD) pack-years	4.3	(4.2)	4.2	(3.3)	4.3	(3.8)

Table 2. Baseline Asthma Characteristics

Baseline Characteristic	ICS/LABA → MF/F N = 4231		ICS/LABA → MF N = 4216	
Mean (SD) age of first asthma treatment — years	31.1	(20.0)	30.7	(19.6)
Duration of prior ICS/LABA — no. (%)				
≤ 3 months	795	(18.8)	837	(19.9)
> 3 months	3341	(80.0)	3255	(77.2)
Unknown	95	(2.2)	124	(2.9)
Median (range) duration of prior ICS/LABA— months	13.4	(0.03-399.9)	13.3	(0.03-648.6)
Patients hospitalized for asthma between 4 and 52 weeks prior to the randomization visit — no. (%)	567	(13.4)	522	(12.4)
Mean (SD) duration since last asthma exacerbation — weeks	20.6	(13.1)	20.4	(13.0)
ACQ-6 Total Score — no. (%)				
≥ 1.5 (not well controlled)	1441	(34.1)	1343	(31.9)
< 1.5 (controlled)	2790	(65.9)	2873	(68.1)
Asthma exacerbation history* — no. (%)				
≤ 3 months	1640	(38.8)	1658	(39.3)
> 3 months	2586	(61.1)	2557	(60.7)
Unknown	5	(0.1)	1	(<0.1)
Incoming Asthma Treatment and Level of Asthma Control** — no. (%)				
Group 1: <i>Controlled</i> on low-dose ICS/ LABA ± other therapies	726	(17.2)	766	(18.2)
Group 2: <i>Not well controlled</i> 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: <i>Not well controlled</i> on medium-dose ICS/ LABA ± other therapies	1009	(23.8)	936	(22.2)
Group 4: <i>Controlled</i> on high-dose ICS/ LABA ± other therapies	848	(20.0)	883	(20.9)

ACQ-6 = 6-question Asthma Control Questionnaire

*No participants had an asthma exacerbation within one month of randomization.

**Groups 1 & 2 received MF 200 or MF/F 200/10 µg BID and Groups 3 & 4 received MF 400 or MF/F 400/10 µg BID.

Table 3. 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

*Adjudicated by an independent committee
Data presented as n or n (%).

Table 4. Summary of Patients with Adverse Events^a

Patients in analysis population with one or more	ICS/LABA → MF/F	ICS/LABA → MF
	N = 4231 n (%)	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 ^b	59 (1.4)	59 (1.4)

^aReflects patients in the full analysis set; i.e., all randomized patients who received at least one dose of blinded study treatment

^bReflects investigator-assessed asthma exacerbations
Data presented as n (%).

Table 5. 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	% 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 months**				
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 months				
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	

*Risk difference = difference in % of subjects with events ([ICS/LABA → MF/F] – [ICS/LABA → MF]). The risk difference analyses used the Miettinen & 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.

ACQ = 6-item Asthma Control Questionnaire

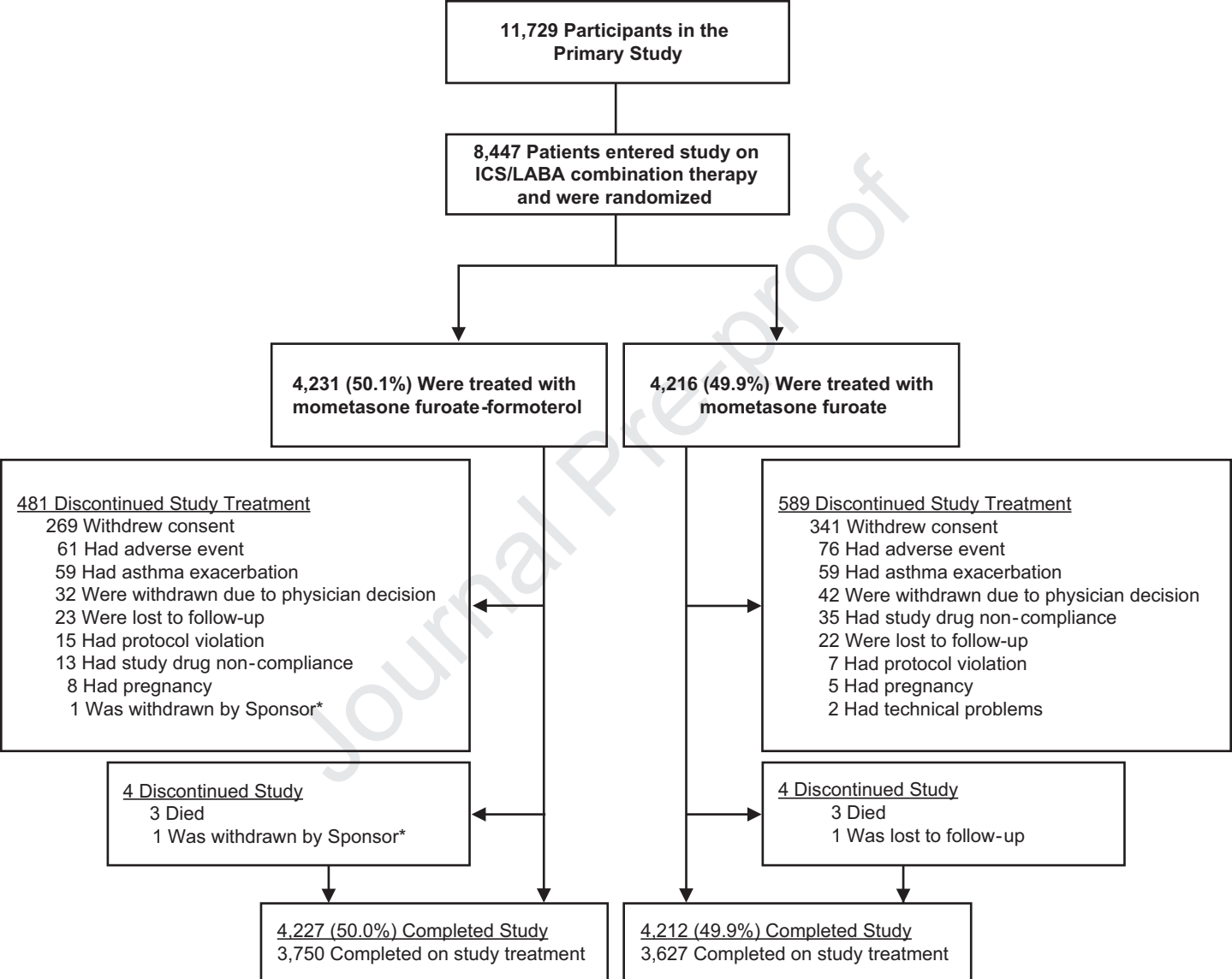
**No participants had an asthma exacerbation within one month of randomization.

Group 1: Controlled on low-dose ICS/ LABA ± other therapies;

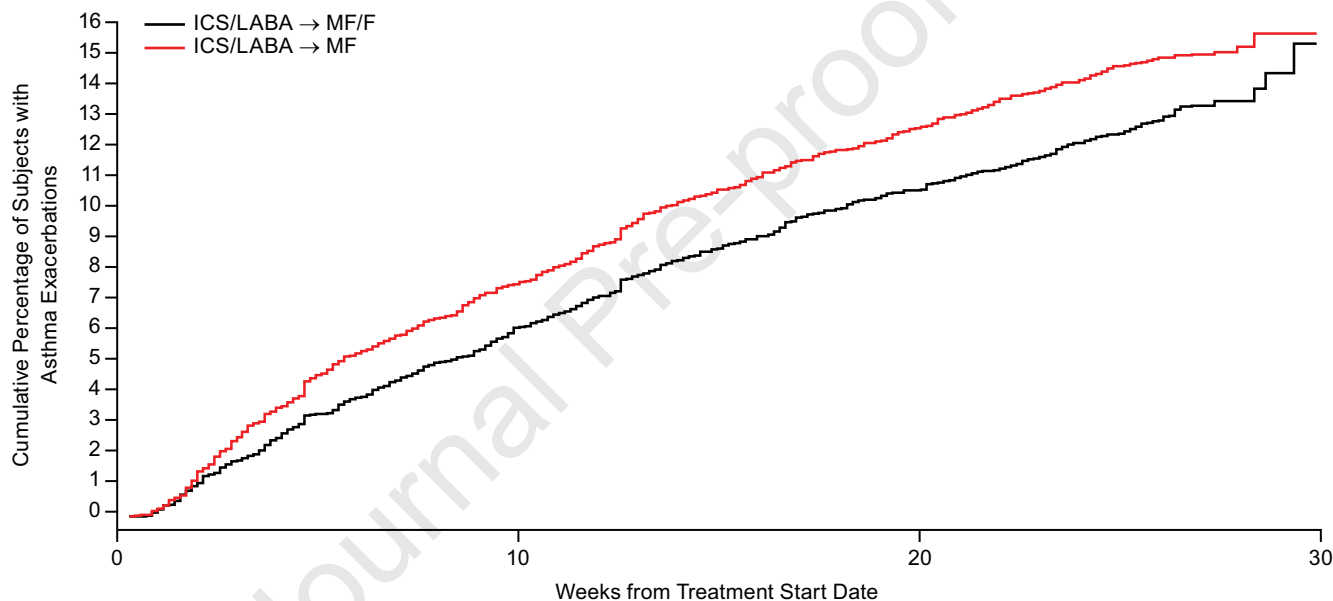
Group 2: Not well controlled on daily low-dose ICS/ LABA ± other therapies OR controlled on medium-dose ICS/ LABA ± other therapies;

Group 3: Not well controlled on medium-dose ICS/ LABA ± other therapies;

Group 4: Controlled on high-dose ICS/ LABA ± other therapies



*Due to invalid ICF and IRB request to not follow patient



Subjects at Risk:

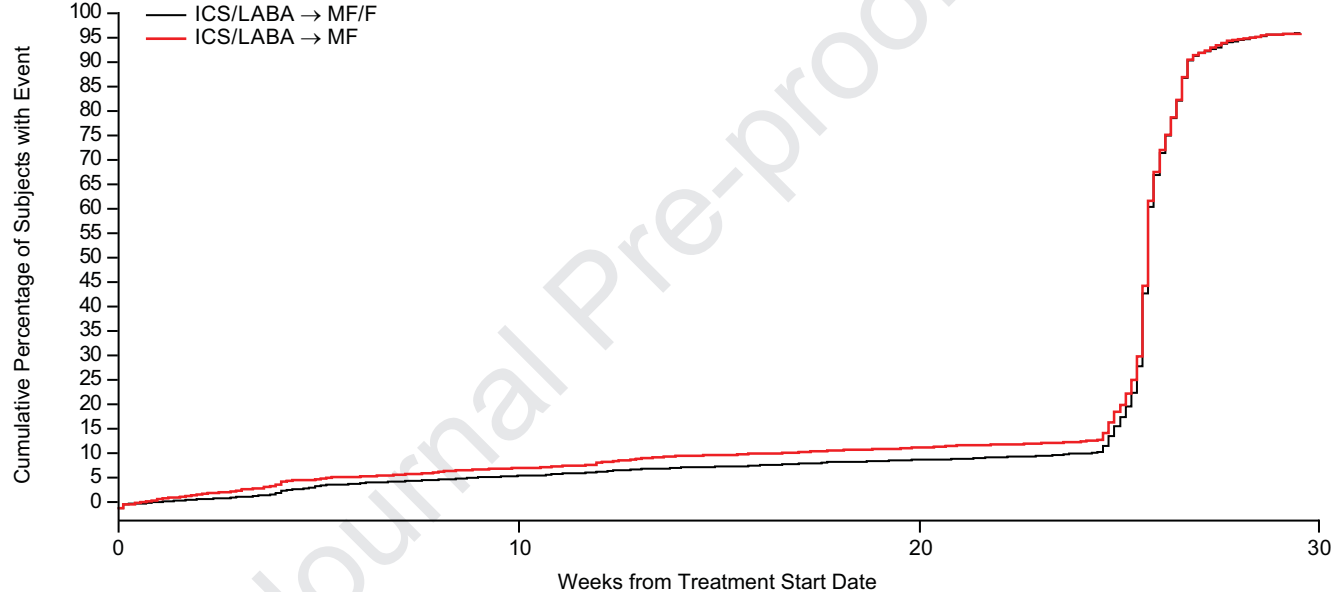
ICS/LABA → MF/F	4231
ICS/LABA → MF	4216

3749
3618

3471
3309

50
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.



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.

Table E1. Asthma Exacerbations by Baseline Characteristics.

Baseline Characteristic	ICS/LABA → MF/F N=4231 n (%) [no. of events]	ICS/LABA → MF N=4216 n (%) [no. of events]
Age Group (years)		
≥12 to ≤17 (adolescent)	36/258 (14.0) [682]	40/270 (14.8) [48]
≥18 to ≤34	86/762 (11.3) [103]	94/757 (12.4) [118]
≥35 to ≤64	345/2564 (13.5) [435]	367/2562 (14.3) [463]
≥65 (elderly)	76/647 (11.7) [101]	99/627 (15.8) [124]
Gender		
Male	173/1481 (11.7) [214]	167/1394 (12.0) [208]
Female	370/2750 (13.5) [468]	433/2822 (15.3) [545]
Race Subgroup of Interest		
Black	65/303 (21.5) [91]	64/258 (24.8) [91]
Non-Black	478/3927 (12.2) [591]	536/3958 (13.5) [662]
Smoking (pack-years)		
0 (non-smokers)	416/3363 (12.4) [520]	459/3368 (13.6) [580]
>0 to <5	73/491 (14.9) [96]	85/473 (18.0) [107]
≥ 5 to <10	47/334 (14.1) [57]	52/346 (15.0) [61]
≥ 10	7/43 (16.3) [9]	3/26 (11.5) [3]
Unknown	0/0 (0.0) [0]	1/3 (33.3) [2]
Asthma Exacerbation History [†]		
≤3 months	236/1640 (14.4) [308]	283/1658 (17.1) [367]
>3 months	307/2586 (11.9) [374]	317/2557 (12.4) [386]
Unknown	0/5 (0.0) [0]	0/1 (0.0) [0]
Incoming Asthma Treatment/Control		
Group 1	65/726 (9.0) [76]	67/766 (8.7) [85]
Group 2	190/1648 (11.5) [233]	227/1631 (13.9) [278]
Group 3	143/1009 (14.2) [184]	149/936 (15.9) [186]
Group 4	145/848 (17.1) [189]	157/883 (17.8) [204]

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

[†]Duration since last exacerbation requiring systemic corticosteroids or hospitalization prior to randomization.

Categorization of 'Black' versus 'Non-Black' was based on clinical database entries for race. Subjects reported as 'Black', where 'Black or African American' was selected, were included in the 'Black' category; all other subjects are reported as 'Non-Black'.

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

Analysis consists of all randomized patients previously on ICS/LABA who received at least one dose of blinded treatment.

Follow-up time is censored at 7 days after last dose of blinded study medication.

Table E10. Analysis of Time to First Asthma Exacerbation Deterioration of Asthma Requiring the Use of Systemic Corticosteroids for ≥ 3 Consecutive Days

Treatment	N	Number of SAEXs ^a	% of Patients with SAEXs	Patient years At- Risk	Event Rate ^b	ICS/LABA→MF/F versus ICS/LABA→MF	
						Hazard Ratio (95% CI) ^c	p-Value ^c
ICS/LABA→MF/F	4231	470	11.11	1946.1	0.24151	0.85 (0.75, 0.96)	0.010
ICS/LABA→MF	4216	532	12.62	1871.5	0.28427		

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

SAEX = protocol-defined asthma exacerbation.

Patient years = Sum of total number of days from treatment start date to time of first SAEX divided by 365.25.

^aFor a given patient, first SAEX denotes first event per patient.

^bEvent Rate = Number of first SAEXs / Patient years At-Risk.

^cBased on Cox proportional-hazard model with covariates of treatment (ICS/LABA→MF/F versus ICS/LABA→MF) and ICS dose level (200 and 400 µg) as treated.

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

Table E11. Summary of Asthma Exacerbation by ICS Dose Level Subgroup

Treatment Group	ICS Dose Level Group			
	200 µg		400 µg	
	N	n (%)	N	n (%)
ICS/LABA → MF/F	2378	255 (10.7)	1853	288 (15.5)
ICS/LABA → MF	2397	299 (12.5)	1819	301 (16.6)

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; ICS=inhaled corticosteroid.

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

For modified ITT analysis, follow-up time is censored at 7 days after last dose of blinded study medication.

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

Table E12. Summary of Asthma Exacerbations by Asthma Severity

Treatment Group	Asthma Severity Group							
	Group 1		Group 2		Group 3		Group 4	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
ICS/LABA → MF/F	726	65 (9.0)	1648	190 (11.5)	1009	143 (14.2)	848	145 (17.1)
ICS/LABA → MF	766	67 (8.7)	1631	227 (13.9)	936	149 (15.9)	883	157 (17.8)
Total	1492	132 (8.8)	3279	417 (12.7)	1945	292 (15.0)	1731	302 (17.4)

MF/F= mometasone furoate – formoterol; MF= mometasone furoate

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

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

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

Table E13. Summary of Asthma Exacerbations by Age Group

Treatment Group	Age Group					
	≥12 to ≤17 (adolescent)		≥18 to ≤64 (adult)		≥65 (elderly)	
	N	Number (%) of Patients with First SAEX	N	Number (%) of Patients with First SAEX	N	Number (%) of Patients with First AEX
ICS/LABA → MF/F	258	36 (14.0)	3326	431 (13.0)	647	76 (11.7)
ICS/LABA → MF	270	40 (14.8)	3319	461 (13.9)	627	99 (15.8)

AEX=asthma exacerbation; MF/F= mometasone furoate – formoterol; MF= mometasone furoate

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

SAEX = protocol-defined asthma exacerbation.

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

There were 3 patients with a calculated age of less than 12 years who were included in adolescent subgroup. One patient (ICS/LABA → MF/F 200/10 µg group) was less than two weeks under the age of 12 at the time of randomization. One other patient (ICS/LABA → MF 400 µg group) programmatically appeared to be under the age of 12, but was at least 12 years of age at the time of randomization.

Table E14. Summary of Asthma Exacerbations by Race Subgroup of Interest Analysis

Treatment Group	Race Group			
	Black ^a		Non-Black ^a	
	N	n (%)	N	n (%)
ICS/LABA → MF/F	303	65 (21.5)	3927	478 (12.2)
ICS/LABA → MF	258	64 (24.8)	3958	536 (13.5)

MF/F= mometasone furoate – formoterol; MF= mometasone furoate

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg. Population consists of all randomized patients previously on ICS/LABA who received at least one dose of blinded treatment. Follow-up time is censored at 7 days after last dose of blinded study medication.

^aFor the race subgroup of interest comparison (Black versus Non-Black), the two subgroups were based on clinical database entries for race. Patients who selected 'Black or African American' were included in the Black subgroup. When a patient selected 'Multi-Racial', they had to further select two race groups from the following list: 'American Indian or Alaska Native', 'Black', 'Native Hawaiian or Other Pacific Island', 'White', 'Asian'; if they selected 'Black' as one of the two race groups, they were included in the Black subgroup. All other patients were categorized as Non-Black.

Table E15. Analysis of Asthma Exacerbation Rates

Treatment Group	N	Number of SAEXs ^a	% of SAEXs	Patient Years ^b At-Risk	Event Rate ^c (95% CI)	ICS/LABA → MF/F vs. ICS/LABA → MF	
						Relative Rate (95% CI) ^c	p-Value ^c
ICS/LABA → MF/F	4231	543	12.8	2060.6	0.3439 (0.3142, 0.3764)	0.88 (0.78, 1.00)	0.044
ICS/LABA → MF/F	4216	600	14.2	2011.4	0.3913 (0.3584, 0.4272)		

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

SAEX = protocol-defined asthma exacerbation.

^aFor a given patient's first exacerbation.

^bPatient years = Sum of total number of days from treatment start date to censor date divided by 365.25.

^cBased on the Negative Binomial regression model accounting for the intercept and treatment effect.

Population is based on all randomized patients 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

Table E16. Daily Study-Provided SABA Use

Treatment Group	N	Mean (SD) Daily SABA Use (inhalations/day) ^a	Daily SABA Use LS Mean (95% CI) ^b	Difference (95% CI) in LS Means ICS/LABA→MF/F vs. ICS/LABA→MF	p-Value
ICS/LABA→MF/F	4129	0.94 (1.40)	0.93 (0.89, 0.98)	-0.16 (-0.23, -0.10)	<0.001
ICS/LABA→MF	4101	1.09 (1.49)	1.10 (1.05, 1.14)		

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

SD = Standard Deviation; LS = Least Squares.

^aReflects Electronic Patient Reported Outcome (ePRO) data collected via IVRS/IWRS while subjects on blinded study medication

^bBased on analysis of variance model with terms for treatment, (Incoming ICS/LABA -> Received MF/F versus Incoming ICS/LABA -> Received MF), and incoming asthma treatment/control as treated.

Daily Study-Provided SABA Use = Total number of puffs reported via the daily IVRS/IWRS during the treatment period / Number of report days

Subjects with no ePRO data collected or all missing responses to ePRO Question 3 have been excluded.

^cBased on analysis of variance model with covariates of treatment (ICS/LABA→MF/F versus ICS/LABA→MF) and incoming asthma treatment/control as treated.

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

Table E17. Subjects who Needed Additional Asthma Treatment, Other than Study-Provided SABA or Any Study-Provided Systemic Corticosteroid Across the Treatment Period

Subjects in population	ICS/LABA→MF/ F N=4231	ICS/LABA→M F N=4216	Difference in % vs ICS/LABA→MF	
			Estimate (95% CI) ^a	p-value ^a
Subjects who needed additional asthma treatment other than study-provided SABA or any study-provided systemic corticosteroid—no. (%)	207 (4.9)	262 (6.2)	-1.3 (-2.3, -0.3)	0.008
Subjects who did not need additional asthma treatment other than study-provided SABA or any study-provided systemic corticosteroid—no. (%)	4024 (95.1)	3954 (93.8)		

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

SABA = Short Acting Beta Agonist = study-provided albuterol/salbutamol.

Study-provided systemic corticosteroid includes oral prednisone and prednisolone.

^aConfidence intervals and p-values calculated using the Miettinen & Nurminen method.

Every subject is counted a single time for each applicable row and column.

Population is based on all randomized subjects 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.

Table E2. Patient Baseline Characteristics.

Baseline Characteristic	ICS/LABA → MF/F (N=4231)	ICS/LABA → MF/ (N=4216)
Asthma exacerbation history between 4 and 52 weeks prior to the randomization visit		
Patients treated with systemic corticosteroids for asthma between 4 and 52 weeks prior to the randomization visit — no. (%)	4153 (98.2)	4149 (98.2)
Number of times patient was treated with a systemic corticosteroid for asthma between 4 and 52 weeks prior to the randomization visit — no. (%)		
0	78 (1.8)	76 (1.8)
1	3569 (84.4)	3557 (84.4)
2	466 (11.0)	440 (10.4)
3	89 (2.1)	109 (2.6)
4	29 (0.7)	33 (0.8)
>4	0	1 (0.0)
Patients hospitalized for asthma between 4 and 52 weeks prior to the randomization visit — no. (%)	567 (13.4)	522 (12.4)
Number of times patient was hospitalized for asthma between 4 and 52 weeks prior to the randomization visit — no. (%)		
0	3664 (86.6)	3694 (87.6)
1	533 (12.6)	487 (11.6)
2	34 (0.8)	35 (0.8)
ACQ-6 Score <1.5 (controlled) — no. (%)		
Overall ACQ-6 Score <1.5	2790 (65.9)	2873 (68.1)
Low-dose ICS/ LABA ± other adjunctive therapies	726 (17.2)	766 (18.2)
Medium-dose ICS/ LABA ± other adjunctive therapies	1216 (28.7)	1224 (29.0)
High-dose ICS/ LABA ± other adjunctive therapies	848 (20.0)	883 (20.9)
ACQ-6 Score ≥1.5 (not well controlled) — no. (%)		
Overall ACQ-6 Score ≥1.5	1441 (34.1)	1343 (31.9)
Low-dose ICS/ LABA ± other adjunctive therapies	432 (10.2)	407 (9.7)
Medium-dose ICS/ LABA ± other adjunctive therapies	1009 (23.8)	936 (22.2)

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; SD= standard deviation.

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

Table E3. Compliance with Study Treatment

Compliance (%)	Number (proportion) of Participants		
	ICS/LABA → MF/F N= 4231	ICS/LABA → MF N= 4216	All Participants N= 8447
< 80%	390 (9.2)	436 (10.3)	826 (9.8%)
≥80% to <120%	3785 (89.5)	3717 (88.2)	7502 (88.8%)
≥120%	26 (0.6)	35 (0.8)	61 (0.7%)

Compliance (%) = $100 \times ((\text{Total Number of Actuations of blinded study medication} / 4) / \text{Number of Days Prescribed blinded study medication})$.

Overall Compliance was based on the number of participants who completed study medication or discontinued.

Compliance Percentages were calculated based on the number of participants in each disposition category.

Participants who had not returned inhalers and had missing or insufficient dose counter records were assumed to have taken 2 puffs of blinded study medication, if the site had confirmed that their first dose was taken under site supervision.

Participants whose first dose date was the same as their last dose date were excluded.

Table E4. Summary of Serious Adverse Events.

Serious Adverse Event	ICS/LABA → MF/F N=4231 n (%) [no. of events]	ICS/LABA → MF/F N=4216 n (%) [no. of events]
Serious Adverse Events	103 (2.4) [120]	109 (2.6) [135]
Serious Adverse Events Sent for Adjudication	98 (2.3) [113]	104 (2.5) [130]
Serious Adverse Events Not Sent for Adjudication	7 (0.2) [7]	5 (0.1) [5]
Potential Study Endpoints		
Hospitalizations	97 (2.3) [108]	103 (2.4) [121]
Screened Not Asthma Related	36 (0.9) [36]	43 (1.0) [47]
Screened Possibly Asthma Related	61 (1.4) [72]	63 (1.5) [74]
Adjudicated Not Hospitalization	3 (0.1) [3]	3 (0.1) [3]
Adjudicated Not Asthma Related	34 (0.8) [38]	35 (0.8) [41]
Adjudicated as Asthma Related	28 (0.7) [31]	27 (0.6) [30]
Intubations [†]	16 (0.4) [17]	18 (0.4) 24
Adjudicated Not Intubation [†]	1 (0.0) [1]	3 (0.1) 4
Adjudicated Not Asthma Related	15 (0.4) [16]	16 (0.4) 20
Adjudicated as Asthma Related	0	0
Deaths	3 (0.1) [3]	3 (0.1) [3]
Adjudicated Not Asthma Related	3 (0.1) [3]	3 (0.1) [3]
Adjudicated as Asthma Related	0	0
Total Serious Asthma Outcomes	28 (0.7) [31]	27 (0.6) [30]

MF/F= mometasone furoate – formoterol; MF= mometasone furoate.

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

Serious Asthma Outcomes=Potential Study Endpoints adjudicated as asthma-related

Table E5. Time to First Serious Asthma Outcome Estimated by Hazard Ratio

Treatment	N	Number of SAOs ^a	% of Patients with SAOs	Patient years At-Risk	Event Rate ^b	ICS/LABA→MF/F versus ICS/LABA→MF	
						Hazard Ratio (95% CI) ^c	p-value ^c
ICS/LABA→MF/F	4231	28	0.66	2195.1	0.01276	1.03 (0.61, 1.75)	0.913
ICS/LABA→MF	4216	27	0.64	2183.3	0.01237		

MF/F= mometasone furoate – formoterol; MF= mometasone furoate

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

ICS=inhaled corticosteroid; LABA=long-acting beta agonist

SAO = Serious Asthma Outcome; all asthma-related hospitalizations (no intubations or deaths were adjudicated as asthma-related)

Patient years = Sum of total number of days from treatment start date to time of first SAO divided by 365.25.

^aFor a given patient, first SAO denotes first event per patient.

^bEvent Rate = Number of first SAOs / Patient years At-Risk.

^cBased on Cox proportional-hazard model with covariates of treatment (ICS/LABA→MF/F versus ICS/LABA→MF) and ICS dose level (200 versus 400 µg) as randomized.

Analysis consists of all patients previously taking ICS/LABA who received at least one dose of blinded treatment.

Table E6. Time to First Serious Asthma Outcome Estimated by Risk Difference

Treatment	N	Number of Patients with SAOs	% of Patients with SAOs	ICS/LABA→MF/F versus ICS/LABA→MF Risk Difference (95% CI)
ICS/LABA→MF/F	4231	28	0.66	0.02 (-0.33, 0.38)
ICS/LABA→MF	4216	27	0.64	

MF/F= mometasone furoate – formoterol; MF= mometasone furoate.

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

ICS=inhaled corticosteroid; LABA=long-acting beta agonist

SAO = Serious Asthma Outcome; all asthma-related hospitalizations (no intubations or deaths were adjudicated as asthma-related)

Patient years = Sum of total number of days from treatment start date to time of first SAO divided by 365.25.

Analysis consists of all patients previously taking ICS/LABA who received at least one dose of blinded treatment.

Details of the six deaths that occurred during the study are shown in **Table E7**. None of the adverse events resulting in death were considered related to the study treatment by the investigator (or the Sponsor) and none were adjudicated as asthma-related.

Table E7. Listing of Patients with AEs Resulting in Death

Treatment	Age / Sex/ Race	Preferred Term (Verbatim Term)	Last Dose Relative to Date of First Dose	Death Relative to Date of First Dose	Compliance (Based on Change in Dose Counter)
ICS/LABA→MF/F 200/10	48 / F / Multiracial	COPD (COPD)* Cardiomegaly (cardiomegaly)	Day 36	Day 36	1%
ICS/LABA→MF/F 200/10	64 / M / White	Completed suicide (complete suicide)	Day 125	Day 126	95%
ICS/LABA→MF/F 400/10	68 / F / White	Ischaemic stroke (ischaemic stroke)	Day 98	Day 104	101%
ICS/LABA→MF 200	75 / M / White	Gastrointestinal necrosis (necrosis of intestinal tract)	Day 130	Day 133	92%
ICS/LABA→MF 200	57 / F / White	Completed suicide (completed suicide)	Day 47	Day 48	99%
ICS/LABA→MF 400	48 / M / White	Pneumonia (bilateral bronchopneumonia)	Day 21	Day 26	2%

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; treatment doses shown in µg.

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

*Post-mortem diagnosis upon autopsy that is not corroborated by patient's medical history per study investigator.

Table E8. Summary of Asthma Exacerbations

	ICS/LABA→MF/F N=4231 n (%)	ICS/LABA→MF N=4216 n (%)	Total N=8447 n (%)
First Asthma Exacerbation	543 (12.83)	600 (14.23)	1143 (13.5)
Used systemic corticosteroids ^a	470 (11.1)	532 (12.6)	1002 (11.9)
ED Visit <24 hrs that required systemic corticosteroids ^b	47 (1.1)	48 (1.1)	95 (1.1)
Hospitalized ≥24 hrs (in any healthcare facility) ^c	26 (0.6)	20 (0.5)	46 (0.5)

MF/F= mometasone furoate – formoterol; MF= mometasone furoate;

MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

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

ED = Emergency Department or any Urgent Care facility where systemic corticosteroids are prescribed for asthma.

^aTablets, suspension or injection for at least 3 consecutive days or received ≥1 depot injectable prescribed for asthma.

^b< 24 hrs that required systemic corticosteroids prescribed for asthma.

^c≥24 hrs (in any healthcare facility) prescribed for asthma.

Table E9. Analysis of Time to First Asthma Exacerbation

Treatment	N	Number of SAEs ^a	% of Patients with SAEs	Patient years At-Risk	Event Rate ^b	ICS/LABA→MF/F versus ICS/LABA→MF	
						Hazard Ratio (95% CI) ^c	p-Value ^c
ICS/LABA→MF/F	4231	543	12.83	1927.5	0.28171	0.87 (0.78, 0.98)	0.020
ICS/LABA→MF	4216	600	14.23	1856.4	0.32320		

MF/F= mometasone furoate – formoterol; MF= mometasone furoate; MF/F MDI BID = 200/10 and 400/10 µg; MF MDI BID = 200 and 400 µg.

SAEX = protocol-defined asthma exacerbation.

Patient years = Sum of total number of days from treatment start date to time of first SAEX divided by 365.25.

^aFor a given patient, first SAEX denotes first event per patient.

^bEvent Rate = Number of first SAEs / Patient years At-Risk.

^cBased on Cox proportional-hazard model with covariates of treatment (ICS/LABA→MF/F versus ICS/LABA→MF) and ICS dose level (200 versus 400 µg) as treated.

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