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ORIGINAL RESEARCH

Onset of Bronchodilation with Fluticasone/Formoterol Combination Versus Fluticasone/Salmeterol in an Open-Label, Randomized Study

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ABSTRACT

Introduction: The inhaled corticosteroid, fluticasone propionate (fluticasone), and the long-acting beta$_2$-agonist, formoterol fumarate (formoterol), have been combined in a single aerosol inhaler (fluticasone/formoterol). In a randomized, open-label study, fluticasone/formoterol showed similar efficacy to fluticasone/salmeterol after 12 weeks of treatment. This post-hoc analysis compared the onset of bronchodilation with the two treatments.

Methods: Adults with mild-to-moderate-severe persistent asthma were randomized to fluticasone/formoterol (100/10 or 250/10 µg twice daily [b.i.d.]) or fluticasone/salmeterol (100/50 or 250/50 µg b.i.d.) for 12 weeks. The onset of bronchodilation (the first post-dose time point at which the forced expiratory volume in 1 second [FEV$_1$] was ≥12% greater than the pre-dose value), responder rates (the proportion of patients achieving bronchodilation), and changes in FEV$_1$ were assessed at days 0 (baseline) and 84.

Results: Fluticasone/formoterol (n = 101) provided more rapid onset of bronchodilation than fluticasone/salmeterol (n = 101) over the first 120 min post-dose on days 0 (hazard ratio [HR] = 1.47 [95% CI 1.05–2.05]) and 84 (HR = 1.77 [95% CI 1.14–2.73]). The odds of a patient achieving bronchodilation within 5 min of dosing were almost four-times higher with fluticasone/formoterol than with fluticasone/salmeterol on day 0 (odds ratio [OR] = 3.97 [95% CI 1.96–8.03]) and almost 10-times higher on day 84 (OR = 9.58 [95% CI 2.14–42.90]);

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the odds of achieving bronchodilation within 120 min post-dose were approximately twofold higher with fluticasone/formoterol on both days. The overall percentage increase in least-squares (LS) mean FEV_1 during the 120-min post-dose period was significantly greater with fluticasone/formoterol than fluticasone/salmeterol on days 0 (LS mean treatment difference: 4.70% [95% CI 1.57–7.83]; $P = 0.003$) and 84 (2.79% [95% CI 0.65–4.93]; $P = 0.011$).

Conclusion: These analyses showed that fluticasone/formoterol provided a faster onset of bronchodilation than fluticasone/salmeterol, which was maintained over 12 weeks of treatment. This benefit may facilitate treatment adherence among patients with asthma.

Keywords: Asthma; Bronchodilation; Combination therapy; Fluticasone; Forced expiratory volume; Formoterol; Inhaled corticosteroid; Long-acting $beta_2$-agonist; Respiratory

INTRODUCTION

Asthma is one of the most common chronic diseases in the world, and is associated with substantial direct and indirect healthcare costs, as well as significant morbidity and mortality [1, 2]. The combination of an inhaled corticosteroid (ICS) and a long-acting $beta_2$-agonist (LABA) is a highly efficacious treatment option for asthma, and is advocated by treatment guidelines for use in patients whose asthma is not controlled with an ICS alone [3]. Indeed, data from randomized clinical trials suggest that asthma control can be achieved with ICS/LABA therapy in the majority of patients [4, 5].

Despite the availability of several ICS/LABA combination therapies, many patients in the real world have suboptimal asthma control [6, 7]. This may reflect the presence of practical and physical barriers to control, such as comorbidities, smoking, under-treatment, and suboptimal inhaler technique. Achieving asthma control is also hindered by perceptual barriers, contributing to reduced patient adherence to treatment regimens [8, 9]. Studies have suggested that therapies with a rapid onset of bronchodilation may encourage adherence and, thus, improve real-world asthma outcomes [10, 11].

An additional ICS/LABA combination has been developed for the treatment of asthma. It combines the potent ICS, fluticasone propionate (fluticasone) [3, 12], with the rapid-acting LABA, formoterol fumarate (formoterol) [13, 14], in a single hydrofluoroalkane aerosol inhaler (fluticasone/formoterol; flutiform®; registered trademark of Jagotec AG, Muttenz, Switzerland, which is used under licence). The inclusion of formoterol in this combination would be expected to produce a rapid-onset bronchodilatory effect [13, 14]. Formoterol has been shown to reverse methacholine-induced severe bronchoconstriction more rapidly than salmeterol xinafoate (salmeterol) and as rapidly as the short-acting $beta_2$-agonist, salbutamol [13, 15].

The authors have previously reported the results of a randomized, open-label study, which showed that fluticasone/formoterol provides comparable improvements in lung function and measures of asthma control to fluticasone/salmeterol over 12 weeks of treatment in patients with mild-to-moderate-severe asthma [16]. Notably, fluticasone/formoterol had a significantly faster onset of bronchodilation (defined as the first post-dose time point at which the forced expiratory volume in 1 second [FEV_1] was at least 12% greater than the pre-dose value) than fluticasone/salmeterol throughout the course of the study (overall hazard ratio [HR] = 1.64 [95% CI 1.28–2.10]; $P < 0.001$).

Here, the authors report the results of a post-hoc analysis of data from this study,

conducted to characterize further the speed of onset of bronchodilation with fluticasone/formoterol compared with fluticasone/salmeterol.

MATERIALS AND METHODS

Full details on the methodology of this study (including further information on inclusion and exclusion criteria, the randomization procedure and dose allocation, study assessments, and statistical analyses) have been published previously [16]. The details relevant to this post-hoc analysis are presented briefly here.

Study Design

This was a 12-week, open-label, randomized, active-controlled, parallel-group, phase 3 study, conducted in 25 European centers in five countries (Germany, Hungary, Poland, Romania, and the UK; ClinicalTrials.gov identifier: NCT00476073). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and approved by independent ethics committees in each of the participating countries. Written informed consent was obtained from all participating patients.

This study consisted of a screening phase of 4–10 days to assess eligibility, after which eligible patients were randomized to treatment and entered the 12-week active treatment phase. The study was designed to demonstrate non-inferiority of fluticasone/formoterol compared with fluticasone/salmeterol in controlling mild-to-moderate-severe persistent asthma in adult patients; the primary efficacy measure was mean pre-dose FEV_1. Onset of bronchodilation (defined as the first post-dose time point at which FEV_1 was at least 12% greater than the pre-dose value) was assessed as a secondary endpoint.

Patients

Men and women (≥18 years old) with a history of mild-to-moderate-severe persistent asthma for at least 6 months before screening were eligible for inclusion in this study. Patients were also required to have an FEV_1 of ≥40–≤85% of predicted normal values following appropriate withholding of asthma medications. In addition, patients had to show reversibility in FEV_1 of ≥15% after salbutamol inhalation (two actuations, 100 μg per actuation) from the pre-salbutamol value. If reversibility was not met, salbutamol administration was repeated and reversibility re-assessed. If the subject still failed to show reversibility, the test could be repeated at a separate, unscheduled visit before the randomization visit. Only patients who could demonstrate correct inhaler technique were eligible for inclusion. Exclusion criteria included life-threatening asthma within the past year, and hospitalization or emergency department visit for asthma in the 4 weeks prior to screening.

Study Treatments

Patients were randomly assigned (1:1) to receive 12 weeks of treatment with fluticasone/formoterol (two actuations of 50/5 μg or 125/5 μg every 12 h [i.e., 100/10 μg or 250/10 μg twice daily]), or fluticasone/salmeterol (two actuations of 50/25 μg or 125/25 μg every 12 h [i.e., 100/50 μg or 250/50 μg twice daily]). The starting dose for either treatment was selected based on each patient's asthma history and pre-study medication. Patients who required an ICS at doses of 100–250 μg/day (fluticasone or equivalent doses of another ICS) received the lower dose of study medication; those who required an ICS at doses of 250–1,000 μg/day (fluticasone or equivalent doses of another ICS) received the higher dose of study medication.

Patients receiving the lower dose were permitted to switch to the higher dose if their asthma was uncontrolled. Both treatments were administered via a hydrofluoroalkane pressurized metered-dose inhaler with an AeroChamber Plus® spacer device (AeroChamber Plus®; registered trademark of Trudell Medical International, Ontario, Canada). The use of salbutamol (two actuations, 100 µg per actuation, up to four times per day) was permitted as rescue medication.

Assessments

Lung function tests were performed in the 30 min prior to the administration of study medication and repeated 5, 10, 30, 60, 90, and 120 min post-dose, on day 0 (baseline) and on days 14, 42, and 84.

Onset of bronchodilation was assessed as part of the original study. Additional analyses were performed post-hoc on data from day 0 and day 84 to characterize further the bronchodilation profile of fluticasone/formoterol compared with that of fluticasone/salmeterol. These included assessments of responder rates (defined as the proportion of patients achieving onset of bronchodilation) within 5 min and within 120 min post-dose for each treatment group, and the percentage changes in FEV_1 and actual changes in least-squares (LS) mean FEV_1 from pre-dose to 5, 10, 30, 60, 90, and 120 min post-dose. The use of LS means allows for adjustments for differences between the groups in other factors that may affect the change in FEV_1 (see Statistical Analyses section for details).

Statistical Analyses

In the original, pre-planned study analysis, the onset of bronchodilation was assessed for the intention-to-treat (ITT) population using a multiple failures time model, and Kaplan-Meier plots were produced, by visit, for each treatment. Patients with no pre-dose measurement were excluded from the analysis for that visit, and those who did not achieve onset of bronchodilation within 120 min post-dose were censored at that point.

In the post-hoc analysis, HRs for the onset of bronchodilation were calculated post-hoc for day 0 and day 84. In addition, odds ratios (ORs) for responder rate in the fluticasone/formoterol group compared with the fluticasone/salmeterol group were determined using logistic regression with treatment and dose group as factors. For the analysis of percentage and actual changes in FEV_1 from pre-dose to each post-dose time point, LS means were calculated from a repeated-measures analysis of covariance model with treatment, dose, pre-dose FEV_1, time point and treatment × time point interaction as factors, and center as a random effect. Differences in LS mean values were determined between the two treatment groups overall and for each post-dose time point, and *P*-values were calculated.

The ITT population comprised all randomized patients who received study treatment and had at least one post-dose primary efficacy (FEV_1) measurement.

RESULTS

Study Population

The ITT population comprised 202 patients. The demographics and asthma characteristics of the two treatment groups were similar at screening (Table 1), including pre-study ICS dose (based on the Global Initiative for Asthma 2011 guideline on equipotency of ICS [3]) and pre-study LABA use. At baseline (day 0), mean pre-dose FEV_1 was 2.22 L in the fluticasone/formoterol group and 2.20 L in the fluticasone/salmeterol group.

Table 1 Demographic characteristics, asthma status, and treatment at screening (intention-to-treat population)

	Fluticasone/formoterol (*N* = **101**)	**Fluticasone/salmeterol** (*N* = **101**)
Age, years	47.6 ± 12.6	46.0 ± 12.9
Gender		
Male, *n* (%)	47 (46.5)	39 (38.6)
Female, *n* (%)	54 (53.5)	62 (61.4)
Race		
Caucasian, *n* (%)	101 (100)	101 (100)
BMI, kg/m^2	27.3 ± 4.8	27.1 ± 5.3
FEV_1 pre-salbutamol, L	2.1 ± 0.56	2.1 ± 0.52
FEV_1 post-salbutamol, L	2.7 ± 0.79	2.6 ± 0.66
Predicted FEV_1, L	3.2 ± 0.73	3.1 ± 0.65
FEV_1 % predicted	66.1 ± 10.1	68.6 ± 9.2
FEV_1 reversibility, %	27.6 ± 12.8	24.9 ± 9.9
Treatment		
ICS dose (μg), median (range)[a]	500 (100–1,000)	400 (100–1,000)
LABA use, *n* (%)	78 (77.2)	78 (77.2)

Data are shown as mean ± SD unless otherwise stated
BMI body mass index, *FEV_1* forced expiratory volume in 1 second, *ICS* inhaled corticosteroid, *LABA* long-acting beta$_2$-agonist
[a] Based on fluticasone equivalent, according to the Global Initiative for Asthma guideline on equipotency of ICS [3]

During the study, eight patients required a change in dose strength from low to high (five in the fluticasone/formoterol group and three in the fluticasone/salmeterol group).

Onset of Bronchodilation

Fluticasone/formoterol treatment provided a faster onset of bronchodilation than fluticasone/salmeterol therapy on day 0, and this effect was maintained at the end of the study. On day 0, fluticasone/formoterol was superior to fluticasone/salmeterol for onset of bronchodilation over the first 120 min post-dose (HR = 1.47; 95% CI 1.05–2.05). Figure 1a shows the Kaplan-Meier plot for the onset of bronchodilation on day 0 (as published previously [16]). Similarly, a significantly more rapid onset of bronchodilation with fluticasone/formoterol was observed on day 84 (HR = 1.77; 95% CI 1.14–2.73; Fig. 1b).

Responder rates were greater with fluticasone/formoterol than with fluticasone/salmeterol within 5 min and within 120 min post-dose on day 0 and day 84 (Table 2). On day 0, the odds of a patient "responding to treatment" (i.e., achieving onset of bronchodilation) were almost four-times higher with fluticasone/formoterol than fluticasone/salmeterol within 5 min post-dose (OR = 3.97; 95% CI 1.96–8.03),

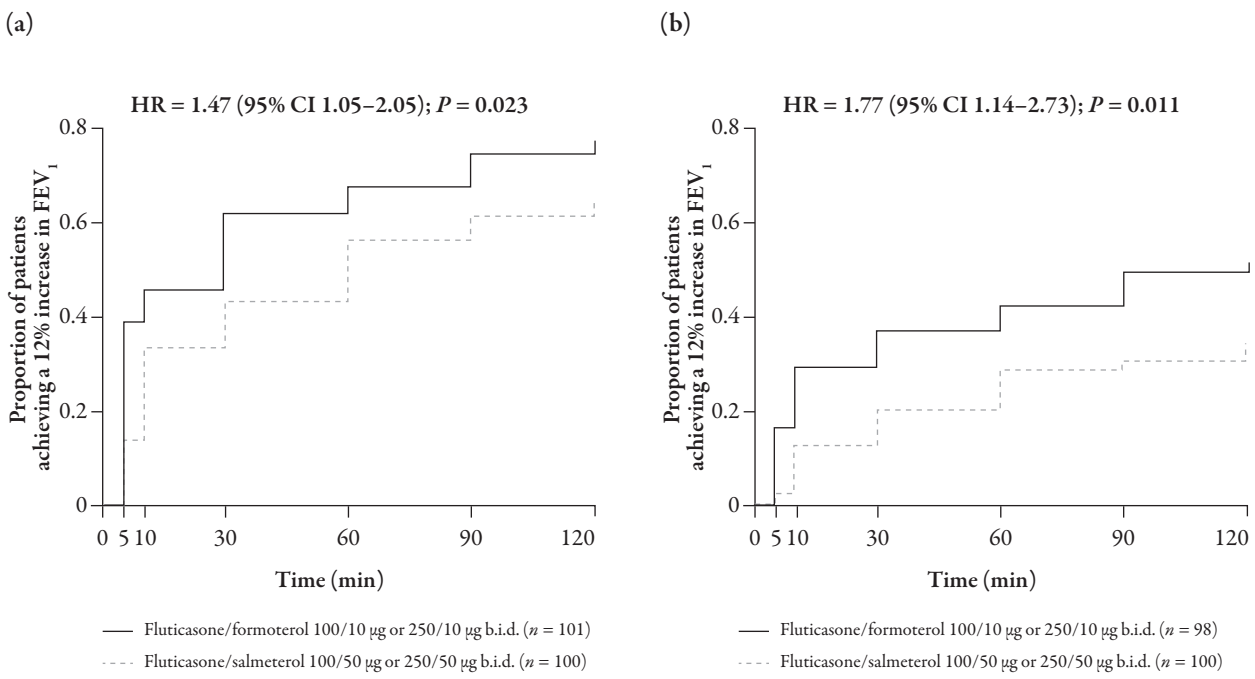

Fig. 1 Kaplan-Meier plots showing the onset of bronchodilation on (**a**) day 0 and (**b**) day 84 (intention-to-treat population). HRs are from post-hoc analyses. Onset of bronchodilation was defined as the first post-dose time point at which FEV_1 was at least 12% greater than the pre-dose value. *This figure is modified from [16] Bodzenta-Lukaszyk A, Dymek A, McAulay K, Mansikka H. Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. BMC Pulm Med. 2011;11:28. b.i.d.* twice daily, *HR* hazard ratio, *FEV_1* forced expiratory volume in 1 second, *CI* confidence interval

and twofold higher within 120 min post-dose (OR = 2.03; 95% CI 1.07–3.89). Moreover, on day 84, the odds of a patient responding within 5 min post-dose were almost 10-fold higher with fluticasone/formoterol than with fluticasone/salmeterol (OR = 9.58; 95% CI 2.14–42.90) and nearly twofold higher within 120 min post-dose (OR = 1.93; 95% CI 1.08–3.43; Table 2).

Changes in FEV_1

Fluticasone/formoterol provided more rapid bronchodilation than fluticasone/salmeterol for change in FEV_1 during the 120-min post-dose period on day 0 (Fig. 2a) and day 84 (Fig. 2b). On day 0, the overall percentage increase in LS mean FEV_1 was significantly greater with fluticasone/formoterol than with fluticasone/salmeterol (17.33% vs. 12.63%; LS mean treatment difference: 4.70% [95% CI 1.57–7.83]; $P = 0.003$). Similarly, on day 84, fluticasone/formoterol provided a significantly greater percentage increase in overall LS mean FEV_1 than fluticasone/salmeterol (8.99% vs. 6.20%; LS mean treatment difference: 2.79% [95% CI 0.65–4.93]; $P = 0.011$).

The between-group difference in overall LS mean change in FEV_1 from pre-dose on day 0 was statistically significantly in favor of fluticasone/formoterol (LS mean treatment difference: 0.112 L [95% CI 0.042–0.181]; $P = 0.002$; Table 3). Similarly, on day 84, the between-group difference from pre-dose FEV_1 in favor of fluticasone/formoterol was statistically

Table 2 Proportion of patients achieving onset of bronchodilation within 5 min and within 120 min post-dose on day 0 and day 84 (intention-to-treat population)

	Fluticasone/ formoterol	Fluticasone/ salmeterol	Percentage difference (95% CI)	Odds ratio[b] (95% CI)
Day 0, within 5 min post-dose				
n	101	100	–	–
Onset of bronchodilation[a], *n* (%)	39 (38.6)	14 (14.0)	24.6 (12.9–36.3)	3.97 (1.96–8.03)
Day 0, within 120 min post-dose				
n	100	100	–	–
Onset of bronchodilation[a], *n* (%)	78 (78.0)	64 (64.0)	14.0 (1.6–26.4)	2.03 (1.07–3.89)
Day 84, within 5 min post-dose				
n	98	100	–	–
Onset of bronchodilation[a], *n* (%)	16 (16.3)	2 (2.0)	14.3 (6.5–22.1)	9.58 (2.14–42.90)
Day 84, within 120 min post-dose				
n	98	97	–	–
Onset of bronchodilation[a], *n* (%)	50 (51.0)	34 (35.1)	16.0 (2.3–29.7)	1.93 (1.08–3.43)

Data are shown as number (%) of patients achieving an onset of bronchodilation
CI confidence interval
[a] Onset of bronchodilation defined as an increase of at least 12% in forced expiratory volume in 1 second from pre-dose value
[b] Odds ratio, relative to fluticasone/salmeterol, of a patient experiencing onset of bronchodilation

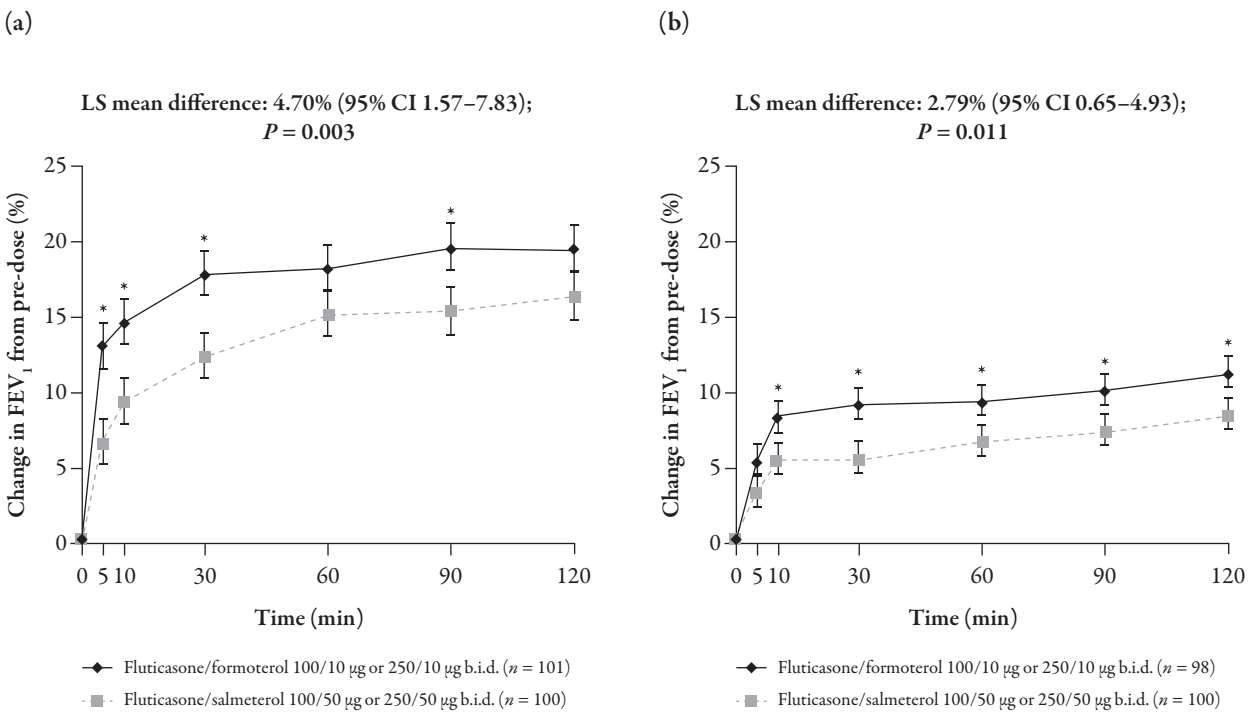

Fig. 2 Percentage change in FEV_1 from pre-dose to each post-dose time point on (**a**) day 0 and (**b**) day 84 (intention-to-treat population). Data are shown as percentage change in LS mean FEV_1 from baseline ± standard error. * $P \leq 0.05$ versus fluticasone/salmeterol. *b.i.d.* twice daily, *FEV_1* forced expiratory volume in 1 second, *LS* least-squares

Table 3 Least-squares mean changes in FEV_1 from pre-dose to 5–120 min post-dose on day 0 and day 84 (intention-to-treat population)

Post-dose time point (min)	Change from baseline in FEV_1, L		Between-treatment difference in FEV_1, L	*P*-value
	Fluticasone/formoterol (*N* = 101)	Fluticasone/salmeterol (*N* = 101)		
Day 0				
5	0.296 (0.228, 0.365)	0.147 (0.078, 0.216)	0.149 (0.072, 0.226)	<0.001
10	0.333 (0.265, 0.401)	0.206 (0.137, 0.275)	0.127 (0.050, 0.204)	0.001
30	0.402 (0.333, 0.470)	0.272 (0.203, 0.341)	0.130 (0.053, 0.207)	0.001
60	0.410 (0.342, 0.479)	0.335 (0.266, 0.404)	0.076 (−0.002, 0.153)	0.055
90	0.443 (0.375, 0.511)	0.336 (0.267, 0.405)	0.107 (0.030, 0.184)	0.007
120	0.441 (0.372, 0.509)	0.359 (0.290, 0.428)	0.081 (0.004, 0.159)	0.039
Overall	0.388 (0.323, 0.452)	0.276 (0.211, 0.341)	0.112 (0.042, 0.181)	0.002
Day 84				
5	0.113 (0.062, 0.164)	0.077 (0.026, 0.128)	0.036 (−0.026, 0.098)	0.257
10	0.187 (0.136, 0.238)	0.123 (0.072, 0.174)	0.064 (0.002, 0.126)	0.043
30	0.208 (0.157, 0.259)	0.121 (0.070, 0.172)	0.087 (0.025, 0.149)	0.006
60	0.214 (0.163, 0.265)	0.154 (0.103, 0.205)	0.060 (−0.002, 0.122)	0.058
90	0.226 (0.175, 0.277)	0.170 (0.119, 0.221)	0.056 (−0.006, 0.118)	0.077
120	0.255 (0.204, 0.305)	0.196 (0.145, 0.247)	0.059 (−0.003, 0.121)	0.064
Overall	0.200 (0.155, 0.246)	0.140 (0.095, 0.186)	0.060 (0.008, 0.113)	0.024

Data are shown as least-squares mean
FEV_1 forced expiratory volume in 1 second

significant (overall LS mean treatment difference: 0.060 L [95% CI 0.008–0.113]; *P* = 0.024; Table 3).

DISCUSSION

The authors have previously reported that fluticasone/formoterol combination therapy provides similar efficacy to fluticasone/salmeterol over 12 weeks of treatment in adults with mild-to-moderate-severe persistent asthma [16]. The results of the post-hoc analyses presented here provide further evidence that fluticasone/formoterol produces significantly faster bronchodilation than fluticasone/salmeterol.

Using a definition for onset of bronchodilation consistent with those used by other investigators [15], the authors showed that fluticasone/formoterol was superior to fluticasone/salmeterol for onset of bronchodilation on the first day of treatment. Importantly, this effect was maintained after 12 weeks of therapy. Moreover, the odds of a patient responding to treatment (assessed by onset of bronchodilation) within 5 min of dosing were almost four-times higher with fluticasone/

formoterol than with fluticasone/salmeterol on the first day of treatment and almost 10-fold higher after 12 weeks of therapy. Similarly, the odds of a patient having a response to treatment within 120 min of dosing were approximately twice as great with fluticasone/formoterol as with fluticasone/salmeterol on both days 0 and 84. Small differences in mean percentage FEV_1 reversibility at baseline were observed between the two treatment groups. However, this is unlikely to have affected the results of the analyses. These findings suggest that consistently more patients achieve bronchodilation with fluticasone/formoterol than with fluticasone/salmeterol.

The present analyses also consistently demonstrated differences in favor of fluticasone/formoterol over fluticasone/salmeterol for changes in FEV_1, a clinically important measure for the practicing physician. The effects of both therapies were larger on day 0 than on day 84, as would be expected given the improvement in FEV_1 during the course of treatment. The lower proportion of patients responding to treatment at day 84 compared with day 0 reflects the fact that lung function had improved from baseline during the course of the study, as indicated by pre-dose FEV_1, and so patients were less likely to achieve the FEV_1 reversibility of ≥12% used to define bronchodilation.

In interpreting the findings reported here, it is important to bear in mind that they are from post-hoc analyses of data from an open-label study. However, onset of bronchodilation was a pre-specified secondary endpoint in the original study, and these post-hoc analyses strengthen the earlier data. Furthermore, the measures evaluated were physical and objective, rather than subjective [17], so it was not deemed likely that the absence of blinding had a detrimental effect on the results.

In this study, the fluticasone/formoterol combination contained 10 µg formoterol and the fluticasone/salmeterol combination contained 50 µg salmeterol. Formoterol is a full agonist, whereas salmeterol is a partial agonist; therefore, a lower dose of formoterol is needed for equipotent effects, and 12 µg formoterol is considered equipotent to 50 µg salmeterol. A clear dose-effect relationship has been demonstrated for formoterol, but not for salmeterol [18]. Higher doses of formoterol provided increased efficacy in protecting against methacholine-induced bronchoconstriction in a study in asthma patients, whereas salmeterol showed a much flatter dose-response curve [19]. As such, 50 µg is the highest available dose of salmeterol, but a higher dose of formoterol is available with the fluticasone/formoterol combination (500/20 µg).

Palmqvist et al. reported faster median onset of bronchodilation with higher doses of formoterol (3.6 min for 24 µg vs. 12.4 min for 12 µg) [15]; therefore, it would be expected that there would be even greater differences in the onset of action between fluticasone/formoterol and fluticasone/salmeterol if the highest available doses were compared. However, it is unlikely that a higher dose of salmeterol would have affected the outcomes in the present study, given the lack of a clear dose-effect relationship for the drug, and the slower onset of action resulting from its mechanism of action [20]. Full and partial agonists differ in their effects on $beta_2$-receptors, which occur in either activated or inactivated conformations and oscillate between the two states. Partial agonists are thought to stabilize the conformations, whereas full agonists move the balance completely towards the activated form [20]. Pharmacological differences between treatments may, therefore, be associated with clinically relevant differences for the management of asthma.

The more rapid onset of bronchodilation with fluticasone/formoterol compared with

fluticasone/salmeterol is consistent with findings of other studies [13–15, 21]. Differences favoring a formoterol-containing therapy (formoterol/budesonide) were found for mean FEV_1 at 3 min post-dose and average FEV_1 from 0–15 min post-dose [14], as well as for recovery from methacholine-induced bronchoconstriction [19]. Interestingly, assessment of patient perception of the onset of bronchodilation showed that the difference between the formoterol- and salmeterol-containing treatments (which was similar to that observed in the present study) was perceptible to patients [19]. Patient assessment of difficulty in breathing showed significantly greater improvement at 1 min after budesonide/formoterol inhalation than after salmeterol/fluticasone inhalation during recovery from methacholine-induced bronchoconstriction. This is important because evidence shows that patients prefer asthma maintenance medication when they are satisfied with how quickly they can feel it beginning to work [10]. Indeed, a group of patients who were nonadherent to their controller medications cited being able to feel a medication working soon after administration as a factor that could improve their adherence [22].

In real-world clinical practice, many patients with asthma remain uncontrolled [23] so may be more appreciative of controller therapy that they can perceive as working quickly. Patient perception has an important influence on medication use, with patients reporting that being able to feel their asthma medication working straight away would help remind them to take their medication in the future [24]. This suggests that initial impressions of the effectiveness of asthma medications may be a key factor in future medication use. A fast onset of bronchodilatory action will provide positive reinforcement for continuing with the medication.

The speed of onset of bronchodilation with an LABA has also been identified as a key attribute of an ICS/LABA combination therapy for asthma by primary and secondary care asthma specialists, and a broader group of physicians with a specialist interest in asthma treatment across Europe [25]. The relevance of this parameter has also been indicated by a consensus panel of practicing physicians, with the suggestion that a rapid onset of LABA action may promote adherence of patients to their combination therapy [26].

Furthermore, natural variations in lung function occur due to diurnal rhythms, with pulmonary function often poorest in the early morning, and this variation often can be exaggerated in patients with uncontrolled and/or severe asthma [27, 28]. Hence, therapies with a rapid onset of action following morning dosing may help patients to perform morning activities sooner than is possible with slower-acting therapies. Indeed, a double-blind, cross-over study of 442 patients with chronic obstructive pulmonary disease showed that budesonide/formoterol therapy provided a more rapid onset of effect than fluticasone/salmeterol therapy and was associated with greater improvements in patients' abilities to perform morning activities [29].

In conclusion, these post-hoc analyses have provided strong additional evidence that fluticasone/formoterol has a more rapid onset of bronchodilation than fluticasone/salmeterol. By assessing both a pre-determined definition of onset of bronchodilation and mean changes in FEV_1 over a 120-min post-dose period, this study has revealed significantly faster onset of bronchodilation with fluticasone/formoterol compared with fluticasone/salmeterol, which was maintained over a 12-week treatment period. This benefit is consistent with the well-documented rapid effects of formoterol, and may facilitate treatment adherence among patients with asthma, and help them to perform morning activities sooner.

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