

# **Efficacy and safety of formoterol Turbuhaler<sup>®</sup> when added to inhaled corticosteroid treatment in children with asthma**

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## ABSTRACT

This double-blind, placebo-controlled, randomized, parallel-group, multicenter study was conducted in 302 children aged 6–11 years with asthma not optimally treated with inhaled corticosteroids alone. Patients continued with their existing dose of inhaled corticosteroids and in addition received placebo, formoterol 4.5 µg or formoterol 9 µg bid for 12 weeks (all delivered via Turbuhaler®). Terbutaline was available as reliever medication. The primary efficacy variable was change from baseline in morning peak expiratory flow (PEF); secondary efficacy variables included forced expiratory volume in 1 s (FEV<sub>1</sub>), serial PEF measured over 12 h, evening PEF, asthma symptom score, and quality of life. Compared with placebo, formoterol 4.5 µg and 9 µg improved morning PEF by 8 L/min ( $P = 0.035$ ) and 11 L/min ( $P = 0.0045$ ), respectively. Evening PEF and FEV<sub>1</sub> were also significantly increased compared with placebo, with no statistically significant difference between the formoterol doses. Lung-function improvements compared with placebo were greater in the middle of the day. Twelve-h average serial PEF after 3 months increased by 24 L/min (95% CI 9, 39 L/min) in the formoterol 9 µg group and by 14 L/min (95% CI 0, 29 L/min) in the formoterol 4.5 µg group. The incidence of severe exacerbations in both formoterol groups was numerically lower than in the placebo group, indicating that formoterol may have the potential to improve exacerbation control in children. Both formoterol doses were well tolerated, and tolerance to the drug's bronchodilator effect was not observed. Formoterol provided sustained improvements in lung function and was well tolerated in children with asthma suboptimally treated with inhaled corticosteroids alone.

**Word count:** 257    **Key words:** Asthma, children, formoterol, efficacy, safety

## INTRODUCTION

International guidelines for the treatment of asthma currently recommend rapid-acting  $\beta_2$ -agonists for immediate symptom relief and long-acting  $\beta_2$ -agonists in conjunction with inhaled corticosteroids for maintenance therapy in patients with persistent asthma.<sup>1</sup>

Two long-acting  $\beta_2$ -agonists are currently available, formoterol and salmeterol. Both have a duration of action in excess of 12 h, but formoterol has a significantly faster onset of effect (within 3 min in adults) than salmeterol.<sup>2,3</sup>

In adults with mild and moderate persistent asthma treated with inhaled corticosteroids, the addition of formoterol 4.5  $\mu\text{g}$  or 9  $\mu\text{g}$  as regular maintenance treatment has been shown to reduce the frequency of asthma exacerbations, improve lung function and asthma symptoms and reduce the need for reliever medication.<sup>4,5</sup> The effect of formoterol in adults is dose-dependent, both in single-dose studies<sup>3</sup> and as maintenance treatment.<sup>6</sup> In single dose studies in younger children, dose-dependent efficacy has also been observed with formoterol.<sup>7,8</sup>

Children with asthma have specific treatment needs, distinct from those of adults, which should be taken into account when selecting a treatment regimen. Many children have difficulty using asthma medication and may require help from a carer to take their medication effectively. This may present a considerable problem for children attending school, who may be away from their regular carer for 7 or 8 h a day. Furthermore, exercise-induced bronchoconstriction (EIB) is common in children, who are likely to be active at frequent intervals throughout the day.<sup>9</sup> A long-acting  $\beta_2$ -agonist such as formoterol could help to overcome these problems, and

may be a valuable treatment option in children with suboptimal treatment on inhaled corticosteroids alone.

Acute studies have demonstrated the rapid onset and long duration of bronchodilation produced by formoterol in children with asthma,<sup>10,11</sup> with the added benefit of protection against EIB for up to 12 h after a single dose.<sup>7</sup> Formoterol 9 µg is also well tolerated and has been reported to provide greater efficacy than salmeterol 50 µg in children with moderate persistent asthma.<sup>8,12</sup>

The present study was conducted to examine the efficacy and safety of adding regular formoterol at 2 different doses to maintenance treatment with inhaled corticosteroids in children with asthma that was not optimally treated by inhaled corticosteroids alone.

## PATIENTS AND METHODS

The trial was a double-blind, placebo-controlled, randomized, parallel-group study conducted at 27 centers in Canada. All patients gave verbal informed consent and their parents or legal guardians gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by local ethics committees.

Children aged 6–11 years who had a clinical diagnosis of asthma according to the American Thoracic Society criteria<sup>13</sup> for at least 6 months were eligible for the study if they had: forced expiratory volume in 1 s (FEV<sub>1</sub>) of 50–90% of predicted normal; documented post-bronchodilator reversibility of at least 15%, or at least 9% of predicted normal; and treatment with regular inhaled corticosteroids for at least 3 months before trial entry. Patients also had to have asthma symptoms sufficient to suggest that additional therapy might be needed. Patients also had to be able to use a peak flow meter and Turbuhaler<sup>®</sup> correctly and to answer questions from the Pediatric Asthma Quality of Life Questionnaire (PAQLQ), and the parent/guardian had to be able to complete a daily diary card.

Patients were excluded from the study if they had: known or suspected hypersensitivity to formoterol or inhaled lactose; deteriorating asthma or a respiratory infection; clinically significant concurrent disease; significant seasonal allergy; or if they smoked. Patients were also excluded if they had taken disallowed asthma medications before trial entry: oral corticosteroids or anti-leukotrienes within 30 days; astemizole within 60 days; sodium cromoglycate or ketotifen within 7 days; salmeterol or formoterol within 72 h; or xanthines or antihistamines within 48 h.

Nasal corticosteroids and immunotherapy were permitted provided the dose had been constant for at least 30 days and 90 days, respectively, prior to trial entry.

After a 2-week run-in period, when patients continued with their usual dose of inhaled corticosteroids, patients meeting the eligibility criteria were randomized to receive either placebo, inhaled formoterol 4.5 µg (Oxis<sup>®</sup> Turbuhaler) bid, or inhaled formoterol 9 µg (Oxis Turbuhaler) twice daily for 12 weeks, in addition to continuing with their inhaled corticosteroids. All study drugs were delivered via Turbuhaler and the dose refers to delivered dose. Terbutaline (Bricanyl<sup>®</sup> Turbuhaler) was provided as rescue medication. The run-in eligibility criteria included: post-bronchodilator reversibility of at least 12% of the pre-bronchodilator value, or at least 9% of predicted normal, or diurnal variability of at least 15% on any 5 of the last 10 days of the run-in; 75–125% compliance with the prescribed dose of inhaled corticosteroids during the run-in as assessed by diary card data; and symptoms during the last 10 days of the run-in (defined as having one or more of the following: 4 or more inhalations of rescue medication; daytime symptoms on 4 or more days; or night-time awakening on 1 or more nights).

Clinic assessments were carried out at trial entry, at randomization, and after 4, 8 and 12 weeks of randomized treatment. FEV<sub>1</sub> was measured at each visit and patients completed the PAQLQ<sup>14</sup> at randomization and at the end of treatment. Parents recorded morning and evening peak expiratory flow (PEF), use of rescue and study medication, and asthma symptoms in a daily diary. Serial measurements of PEF were also taken after 1 and 3 months of treatment in a subset of patients in each of the three treatment groups who were willing to carry out the measurements. PEF was measured by the patient at home on a weekend day before and at 30 min,

1, 2, 4, 6, 8, 10 and 12 h after the morning inhalation of study drug and recorded on a diary card. Patients were not allowed to exercise on this day, and any use of rescue medication was recorded in the diary. As the measurements were performed on a weekend day, the children would not have been attending school, and their activities are likely to have been curtailed by the need to measure PEF every hour and the prohibition of exercise.

A severe asthma exacerbation was defined as asthma symptoms requiring oral corticosteroids or an increase in the dose of inhaled corticosteroids as judged by the investigator.

The primary efficacy variable was the change in morning PEF, calculated as the difference between the mean value recorded over the last 10 days of the run-in and the mean value over the complete 12-week treatment period. Secondary efficacy variables included FEV<sub>1</sub>, serial PEF, evening PEF, time to first exacerbation, and use of rescue medication.

Adverse events (AEs), pulse and blood pressure were recorded at each visit. Deterioration of asthma was not recorded as an AE unless the deterioration was serious or led to the patient withdrawing from the study.

PEF, FEV<sub>1</sub>, and diary card variables were compared between treatment groups by an analysis of variance. The time to first exacerbation was compared between treatment groups by Kaplan–Meier survival analysis and a Cox proportional hazards model.

## RESULTS

### Demographics and patient flow

A total of 447 children were enrolled, 302 were randomized to treatment and 267 completed the study. Demographic data and baseline characteristics of the randomized patients are shown in Table 1. The groups were generally well matched in most baseline characteristics, with the exception of as-needed terbutaline use, which was twice as high in the placebo group as in the higher dose formoterol group.

Compared with placebo, significantly fewer patients in the formoterol 4.5 µg group withdrew from treatment ( $P = 0.02$ ). The total number of patients withdrawn was 7 in the formoterol 4.5 µg group, 11 in the formoterol 9 µg group and 16 in the placebo group. The reasons for discontinuing from the study were: no change or deterioration in asthma (0, 1 and 2 patients in the formoterol 4.5 µg, formoterol 9 µg and placebo groups, respectively); AEs (2, 1 and 0 patients, respectively); lost to follow-up (1, 2 and 5 patients, respectively); eligibility criteria not fulfilled (1, 3 and 5 patients, respectively); and other reasons (3, 4 and 4 patients, respectively).

### Efficacy

Figure 1 shows the daily mean value of morning PEF for all three treatment groups. Both doses of formoterol improved morning PEF from the beginning of treatment, and the improvement was maintained throughout the study period. Figure 2 shows the change from baseline in FEV<sub>1</sub>; all three treatment groups showed an improvement in FEV<sub>1</sub>.

Table 2 shows the mean values of morning PEF, evening PEF and FEV<sub>1</sub> (% predicted normal) at baseline and during treatment. Both doses of formoterol

improved % predicted normal FEV<sub>1</sub>, morning PEF and evening PEF statistically significantly more than placebo. There was no significant difference between the 2 doses of formoterol, although there was a numerical trend in favor of the higher dose in the morning PEF measurement.

Serial PEF measurements were performed at 2-h intervals by 50 children in the placebo group, 66 children in the formoterol 4.5 µg group, and 61 children in the formoterol 9 µg group on study days following maintenance treatment for 1 and 3 months. PEF values after 3 months of treatment showed a more marked improvement than morning and evening PEF with both doses of formoterol, with an apparent dose–response relationship (Fig. 3). The formoterol 9 µg group experienced greater improvements in PEF throughout the day than either the formoterol 4.5 µg group or the placebo group. After 3 months, the differences appeared to be larger during the middle of the day than at the beginning or end of the day (Fig. 3). The average 12-h PEF was statistically significantly higher in the formoterol 9 µg group than in the placebo group at both 1 and 3 months, with increases of 17 L/min (95% CI 3, 31 L/min) and 24 L/min (95% CI 9, 39 L/min), respectively. In the formoterol 4.5 µg group, the corresponding increase was not statistically significant at 1 month (9 L/min [95% CI –5, 22 L/min]) but approached statistical significance at 3 months (14 L/min [95% CI 0, 29 L/min]).

Table 3 shows the change from baseline in symptom score, use of rescue medication and PAQLQ score. It has been shown previously that a change in the PAQLQ score of 0.5 represents a clinically relevant improvement.<sup>14</sup> All three treatment groups showed an improvement in symptom score, a decrease in the use

of rescue medication, and an improvement in PAQLQ score. There were no statistically significant differences between treatments.

## **Safety**

A total of 19 exacerbations were recorded during the study. There was a trend towards a lower risk of exacerbations in the formoterol groups than in the placebo group (hazard ratio compared with placebo, 0.529 [95% CI 0.173, 1.618] in the formoterol 4.5 µg group and 0.747 [95% CI 0.259, 2.156] in the formoterol 9 µg group). The differences were not statistically significant.

All three treatments were well tolerated. The most frequently reported AEs are shown in Table 4. The number and type of AEs were similar between the three treatment groups. Respiratory infection was the most frequently reported AE, and the incidence of  $\beta_2$ -agonist class effects was low in all groups: 2 cases of tremor (1 placebo, 1 formoterol 4.5 µg); 2 cases of muscle cramps (1 placebo, 1 formoterol 9 µg) and 1 case of palpitations (1 formoterol 4.5 µg). No clinically significant differences in pulse rate or blood pressure were reported.

## Discussion

In children suboptimally treated with inhaled corticosteroids alone, the addition of formoterol 4.5 µg or 9 µg bid to the treatment regimen improved lung function, as measured by PEF or FEV<sub>1</sub>. Both doses were statistically significantly superior to placebo. The improvements in lung function were apparent at the first measurement after beginning treatment, and were maintained throughout the 12-week treatment period. This finding is consistent with previous studies, which have shown improvements in lung function with formoterol in single-dose studies<sup>8,11,15</sup> and in maintenance studies lasting up to 6 weeks in length.<sup>15,16</sup> Evidence from this 12-week study also indicates that tolerance to the effect of formoterol did not develop during treatment.

In the present study, formoterol 9 µg bid produced an improvement in 12-h average PEF at 1 month of 17 L/min and at 3 months of 24 L/min vs. placebo, which was greater than the improvement in morning PEF of 11 L/min compared with placebo after 3 months of treatment ( $P < 0.05$  vs. placebo for both parameters). The average serial PEF results, in contrast with the morning and evening PEF values, showed a greater dose-related effect, and only the formoterol 9 µg dose was statistically significantly superior to placebo. This apparent discrepancy may be because the serial PEF measurements reflect lung function over the whole of a 12-h period, including the maximal bronchodilator effect between 2 h and 8 h after dosing, whereas morning and evening PEF measurements taken at the end of the dosing intervals do not assess the maximal effect of formoterol (Fig. 3). After 3 months of treatment, serial PEF was higher in both formoterol groups than in the placebo group, with the greatest differences seen during the middle of the day when the child

would normally be at school or engaged in leisure activity. This is a potentially interesting finding, and would be missed by conventional measurement of PEF at morning and evening only. Future dose-ranging trials performed in children may need to take this into account by devising a protocol for assessing lung function throughout the school day, and possibly investigating whether the potential for increased lung function is associated with increased activity levels.

A limitation of this study was the low level of symptoms and as-needed reliever use in the study population at baseline. Patients were selected primarily for suboptimal lung function and high reversibility. The mean symptom score at baseline was only 1.5 (on a scale of 0–6), and during the run-in period almost 90% of patients had a symptom score of 1 or less. Moreover, the formoterol 9 µg group had a particularly low level of symptoms, a higher PAQLQ score (indicating less impairment than the placebo group) and reliever medication use ~~was~~ only half that in the placebo group at baseline, and consequently there was little room for improvement. Nevertheless, the higher dose formoterol (9 µg bid) group had the lowest symptom score and highest quality of life on completion of the study, although the differences between groups were not statistically significant.

The higher dose of formoterol (9 µg bid) used here has also been compared to salmeterol 50 µg in an open-label study performed in 156 children (aged 6–17 years) with moderate persistent asthma <sup>17</sup> and in this study, formoterol (9 µg bid) increased the percentage of days when patients were symptom and reliever free to a greater extent than salmeterol.

A substantial placebo response on symptom measures in our milder study population may have limited the ability to determine differences in the subjective

efficacy measures. The quality of life improvement in the placebo group in the current study was clinically relevant ( $>0.5$  units) and similar to that in the active treatment groups. These substantial placebo effects appear to be common in asthma trials in children.<sup>18–20</sup> To investigate this effect, an exploratory analysis was performed dividing patients by steroid dose at entry as a marker of severity, this revealed an increasing trend for symptom improvements in both formoterol groups compared with placebo in children using higher concomitant doses of inhaled steroids (data not shown). Further studies in more symptomatic children are warranted to reduce the influence of any placebo response and to assess the dose response to formoterol on these more important measures of asthma control.

A dose response to formoterol has been reported in moderately severe adult asthmatics.<sup>6</sup> Furthermore, a recent placebo-controlled study in children (aged 6–17 years) with EIB showed that 4.5 and 9  $\mu$ g of formoterol provided 12-h protection against EIB, although in younger children (aged 6–12 years) the 9  $\mu$ g dose of formoterol showed a trend for greater levels of protection from EIB than the 4.5  $\mu$ g dose.<sup>7</sup>

Both doses of formoterol were well tolerated. The number and type of AEs were similar to placebo. The risk of an exacerbation was reduced by 25–47% in the formoterol groups compared with the placebo group. This was not statistically significant, probably because of the small number of exacerbations recorded during the study (19 in total), but does indicate that regular formoterol treatment was associated with a trend for improved asthma control. This potential treatment benefit needs to be confirmed in a similarly sized study of longer duration. In a 1-year study

of comparable size, formoterol 4.5 µg bid has been shown to significantly decrease the risk of exacerbations in adults using low dose corticosteroids.<sup>5</sup>

In conclusion, this study demonstrates that formoterol 4.5 µg bid or 9 µg bid provides sustained improvement in lung function and is well tolerated when added to existing corticosteroid treatment in children with asthma not optimally treated by inhaled corticosteroids alone. As the children in the study had few symptoms at entry, further studies in a more symptomatic population are required to assess the full potential benefits of formoterol on asthma control when used in combination with inhaled corticosteroids.

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## **TABLE AND FIGURE LEGENDS**

TABLE 1. Patient demographics and baseline characteristics. All values are quoted as mean (range)

TABLE 2. Pulmonary function at baseline and during treatment

TABLE 3. Changes from baseline for symptom scores, use of rescue medication and PAQLQ scores

TABLE 4. Summary of most frequently reported adverse events. All values expressed as number (%) of patients

FIG. 1. Daily mean values of morning peak expiratory flow

FIG. 2. Percentage change from baseline (randomization visit) to the visits at 4, 8 and 12 weeks of treatment in forced expiratory volume in 1 s

FIG. 3. Serial peak expiratory flow measurements after 1 and 3 months of treatment

TABLE 1. Patient demographics and baseline characteristics. All values are quoted as mean (range)

	<b>Formoterol 9 µg (N = 95)</b>	<b>Formoterol 4.5 µg (N = 106)</b>	<b>Placebo (N = 101)</b>
No. of boys/girls	58/37	65/41	65/36
Age (y)	9 (6–11)	8 (6–11)	9 (6–11)
Body mass index (kg/m <sup>2</sup> )	18.3 (13.2–29.8)	18.6 (13.0–35.7)	17.7 (12.4–28.2)
Diagnosis (y)	5.6 (0.7–11.0)	5.4 (0.5–11.3)	5.8 (0.2–10.9)
Dose (µg) of ICS at entry	422 (100–1200)	450 (100–1500)	464 (150–1200)
FEV <sub>1</sub> (L)	1.50 (0.56–2.81)	1.53 (0.64–2.54)	1.49 (0.56–2.41)
FEV <sub>1</sub> (% normal)	77.5 (47.0–110.0)	78.3 (40.0–126.0)	77.2 (45.0–107.0)
Reversibility (% normal)	14.5 (6.0–36.0)	15.0 (3.0–43.0)	16.4 (8.0–43.0)
Morning PEF (L/min) <sup>a</sup>	204.5 (107–374)	207.9 (84–390)	204.8 (80–345)
Evening PEF (L/min) <sup>a</sup>	210.8 (113–378)	213.5 (80–478)	210.2 (91–342)
Mean number terbutaline inhalations (per 24 h)	0.74 (0.0–5.6)	1.04 (0.0–5.4)	1.36 (0.0–9.2)
Mean symptom score	1.3 (0.0–4.0)	1.6 (0.1–4.2)	1.5 (0.0–4.0)

ICS: inhaled corticosteroids; FEV<sub>1</sub>: forced expiratory volume in 1 s; PEF: peak expiratory flow

<sup>a</sup> N= 94 for formoterol 9 µg, 105 for formoterol 4.5 µg and 97 for placebo

TABLE 2. Pulmonary function at baseline and during treatment

	<i>N</i>	Baseline mean (range)	Treatment mean (range)	Treatment difference vs. placebo (95% CI)	<i>P</i> -value
<b>Morning PEF, L/min</b>					
Placebo	97	204.8 (80–345)	210.7 (73–354)		
Formoterol 4.5 µg	105	207.9 (84–390)	221.4 (88–391)	7.8 (0.6–15.0)	0.035
Formoterol 9 µg	94	204.5 (107–374)	221.7 (127–415)	10.8 (3.4–18.2)	0.0045
<b>Evening PEF, L/min</b>					
Placebo	97	210.2 (91–342)	213.5 (77–356)		
Formoterol 4.5 µg	105	213.5 (80–478)	225.5 (93–384)	9.2 (2.1–16.4)	0.011
Formoterol 9 µg	94	210.8 (113–378)	223.4 (128–416)	9.2 (1.9–16.6)	0.014
<b>FEV<sub>1</sub>, % predicted normal</b>					
Placebo	97	77.13 (45.0–107.0)	84.56 (50.5–123.3)		
Formoterol 4.5 µg	105	78.31 (40.0–126.0)	88.41 (45.2–142.1)	4.01 (1.22–6.81)	0.0051
Formoterol 9 µg	88	77.55 (47.0–110.0)	88.17 (57.6–123.9)	3.63 (0.72–6.55)	0.015

FEV<sub>1</sub>: forced expiratory volume in 1 s; PEF: peak expiratory flow

TABLE 3. Changes from baseline for symptom scores, use of rescue medication and PAQLQ scores

	<b>Formoterol 9 µg</b>	<b>Formoterol 4.5 µg</b>	<b>Placebo</b>
<b>Total symptom score</b>			
<i>N</i>	94	105	98
Baseline mean (range)	1.32 (0.0–4.0)	1.58 (0.1–4.2)	1.50 (0.0–4.0)
Treatment mean (range)	1.02 (0.0–3.3)	1.28 (0.0–4.2)	1.23 (0.0–4.4)
Adjusted mean change	–0.37	–0.28	–0.27
<b>Mean number of terbutaline rescue medication inhalations per day</b>			
<i>N</i>	94	105	98
Baseline mean (range)	0.74 (0.0–5.6)	1.04 (0.0–5.4)	1.36 (0.0–9.2)
Treatment mean (range)	0.72 (0.0–5.2)	0.73 (0.0–8.4)	0.95 (0.0–7.7)
Adjusted mean change	–0.13	–0.27	–0.21
<b>PAQLQ total score</b>			
<i>N</i>	83	99	85
Baseline mean (range)	5.33 (2.4–6.9)	5.13 (2.5–7.0)	5.09 (1.6–6.9)
Treatment mean (range)	5.80 (3.4–7.0)	5.72 (2.7–7.0)	5.76 (2.2–7.0)
Adjusted mean change	0.49	0.52	0.57

PAQLQ: Pediatric Asthma Quality of Life Questionnaire

TABLE 4. Summary of most frequently reported adverse events. All values expressed as number (%) of patients

<b>Disorder</b>	<b>Formoterol 9 µg (N = 95)</b>	<b>Formoterol 4.5 µg (N = 105)</b>	<b>Placebo (N = 101)</b>
Respiratory infection	31 (33)	45 (43)	36 (36)
Headache	10 (11)	13 (12)	14 (14)
Pharyngitis	6 (6)	11 (10)	11 (11)
Asthma aggravated	6 (6)	5 (5)	11 (11)
Rhinitis	8 (8)	4 (4)	10 (10)
Fever	3 (3)	7 (7)	7 (7)
Infection, viral	7 (7)	4 (4)	5 (5)
Abdominal pain	1 (1)	6 (6)	5 (5)
Sinusitis	4 (4)	5 (5)	2 (2)
Conjunctivitis	3 (3)	4 (4)	4 (4)

FIG. 1. Daily mean values of morning peak expiratory flow (PEF)

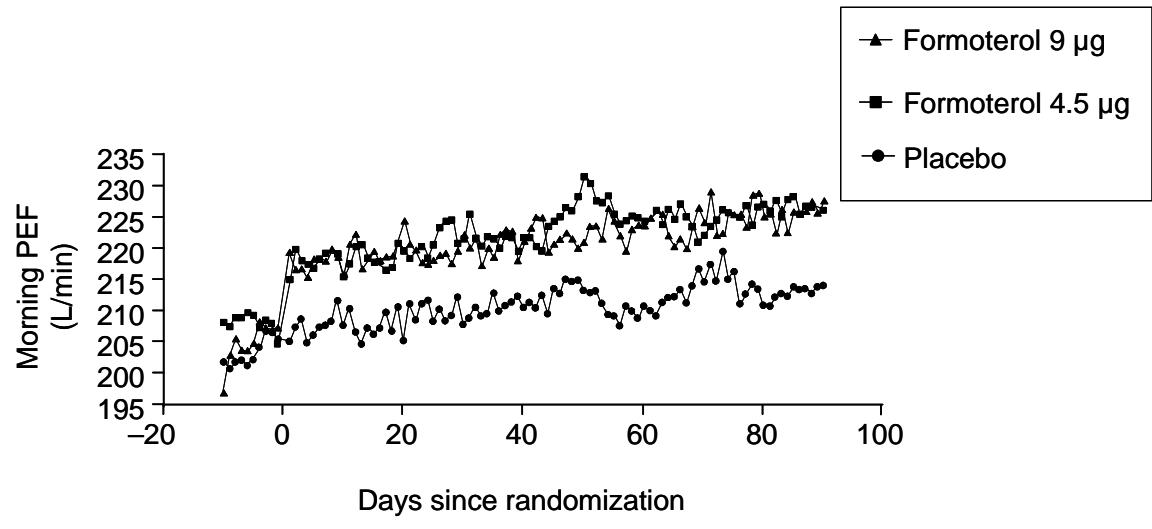


FIG. 2. Percentage change from baseline (randomization visit) to the visits at 4, 8 and 12 weeks of treatment in forced expiratory volume in 1 s (FEV<sub>1</sub>)

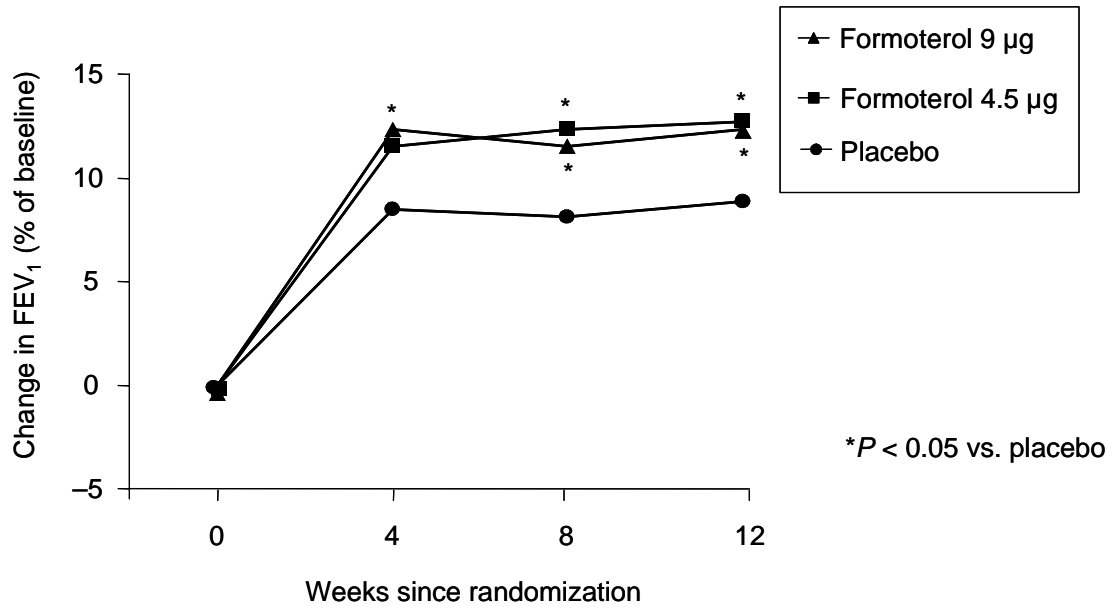


FIG. 3. Serial peak expiratory flow (PEF) measurements after 1 and 3 months of treatment

