Comparison of the Efficacy, Tolerability, and Safety of Formoterol Dry Powder and Oral, Slow-Release Theophylline in the Treatment of COPD*

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Study objective: **To compare the efficacy, tolerability, and safety of therapy with formoterol and oral slow-release theophylline (THEO) in patients with COPD.**
Design: **A randomized, parallel-group study, with double-blind arms for formoterol and placebo (PL) and an open arm for oral slow-release THEO administered in individual doses on the basis of plasma concentrations.**
Setting: **Eighty-one centers worldwide.**
Patients: **Eight hundred fifty-four patients with symptomatic COPD.**
Intervention: **Comparison of twice-daily inhaled formoterol dry powder (12 or 24 μg), PL, and THEO (individualized doses) over 12 months.**
Measurements and results: **Compared to PL, doses of formoterol and THEO both significantly improved the area under the curve for FEV_1 measured over a period of 12 h following the morning dose of study medication at 3 and 12 months ($p < 0.001$ for all comparisons). Therapy with formoterol, 12 μg, was significantly more effective than that with THEO ($p \leq 0.026$). Formoterol significantly reduced the percentage of "bad days" (*ie*, days with at least two individual symptom scores ≥ 2 and/or a reduction in peak expiratory flow from a baseline of > 20%; $p \leq 0.035$ vs PL and THEO), and the use of salbutamol rescue medication ($p \leq 0.003$ vs PL) over the whole treatment period, while the effect of THEO was similar to that of PL. Therapy with formoterol and THEO was more effective than PL at improving quality of life for > 12 months ($p \leq 0.030$). Treatment-related adverse events and discontinuations were more frequent among patients receiving THEO than among those receiving formoterol.**
Conclusions: **Long-term treatment with inhaled formoterol dry powder is more effective and better tolerated than treatment with therapeutically appropriate doses of oral slow-release THEO in symptomatic patients with COPD.** ***(CHEST 2002; 121:1058–1069)***

Key words: β_2-agonists; COPD; formoterol; inhaled lung function; theophylline

Abbreviations: AE = adverse event; ANCOVA = analysis of covariance; AUC = area under the curve; F12 = formoterol 12 μg; F24 = formoterol 24 μg; PEF = peak expiratory flow; PL = placebo; QOL = quality of life; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire; THEO = theophylline

Inhaled short-acting β_2-agonists, anticholinergics, and oral theophylline (THEO) are the most broadly used medications for the symptomatic treatment of patients with COPD.[1–3]

The β_2-adrenoceptor agonists formoterol fumarate and salmeterol xinafoate have a longer duration

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of action than previously available inhaled β_2-adrenoceptor agonist agents and can be administered twice daily.[4] There is increasing evidence that they represent a therapeutic advance in the management of all forms of COPD, when used as monotherapy[5] or in combination therapy with other bronchodilators in patients requiring multidrug therapies.[6]

In the most recent guidelines for the management of COPD,[7] the administration of formoterol and salmeterol is recommended as an alternative to or in combination with anticholinergic agents or slow-release THEO preparations in patients with moderate and severe disease who require treatment with bronchodilators on a regular basis. However, there are no clinical data on the therapeutic value of formoterol administered as an alternative to THEO. In this study, we therefore compared the effects of a 12-month treatment with formoterol, oral slow-release THEO, and placebo (PL) in terms of airflow obstruction, symptoms, quality of life (QOL), safety, and tolerability in patients with COPD.

Materials and Methods

Patients

Patients were male or female outpatients aged ≥ 40 years, who were either current smokers or ex-smokers of > 10 pack-years had received a diagnosis of COPD, made according to the American Thoracic Society guidelines.[1,8] All patients gave written informed consent.

Inclusion criteria required that the patients' FEV_1 was < 70% of the predicted value and ≥ 0.75 L, with an FEV_1/vital capacity ratio of < 88% of that predicted in men and < 89% of that predicted in women.[1,2,8] Daytime and/or nighttime symptoms were to be present on at least 4 of the last 7 days of the run-in period. The specific exclusion criteria were those reported elsewhere.[6,9] Following reversibility testing with 200 μg salbutamol at screening, patients were classified as irreversible/poorly reversible when their FEV_1 increased < 15% from the baseline value, and for these patients a separate analysis of the primary variable was performed. These patients also presented with a mean absolute change in FEV_1 of < 200 mL, which is in line with the rationale as to what constitutes a nonsignificant bronchodilatory response, according to COPD guidelines.[3] Patients were recruited after the approval of the local ethics committees.

Study Design

This was a multicenter, randomized, parallel-group, PL-controlled study. After screening at visit 1, patients entered the run-in period of 10 to 21 days, during which they became accustomed to the trial procedures, inhalation practices, and dosing regimens. During this period, they received inhaled salbutamol (100 μg per puff), or equivalent doses of albuterol in the US centers, as needed.

Eligible patients then were randomized to receive, for 12 months, 12 μg inhaled formoterol (F12) or 24 μg inhaled formoterol (F24) twice daily via a single-dose, breath-activated inhaler (Foradil Aerolizer dry powder capsules for inhalation; Novartis; Basel, Switzerland),[10] or PL matching formoterol twice daily, or oral slow-release THEO (Theo-Dur, 200-mg or 300-mg tablets; AstraZeneca; London, UK) twice daily. F12, F24, and PL were administered in a double-blind manner, but the required dose titration of oral slow-release THEO made blinding impossible, and it was therefore administered at individualized doses on the basis of plasma concentrations in an open-label fashion. The titration of the oral slow-release THEO dose was performed by targeting plasma levels between 8 and 20 mg/L[11,12] at 3 to 4 h after the morning dose. Patients not achieving the desired plasma levels following two titrations were discontinued from the study. Subsequent measurements of oral slow-release THEO plasma concentrations were performed at 3, 6, 9, and 12 months, and dose adjustments were performed if required.

Stable patients receiving inhaled corticosteroid treatment were instructed to remain on that treatment throughout the study. Inhaled salbutamol (up to 8 puffs per day) was allowed as the rescue medication. Short courses of antibiotics, oral corticosteroids, and/or oxygen were permitted in case of exacerbations or respiratory infection up to two times during the study.

The primary efficacy variable was the standardized area under the curve (AUC) for FEV_1 measured over a period of 12 h following the morning dose of study medication after 3 and 12 months of treatment. FEV_1 was determined predose and at 5, 15, 30 min, 1 h, and hourly up to 12 h postdose. The standardized AUC-FEV_1 (*ie*, the AUC divided by the time period that the patient was observed) was calculated using absolute FEV_1 values through the 12-h interval.[9] The patients were requested to abstain from taking rescue medication within 6 h prior to and during serial spirometry.

Other efficacy variables were the standardized AUC for FVC, the absolute FEV_1 values at all the individual time points during each 12-h spirometry period, the predose FEV_1 at all 3-monthly visits, the daily morning premedication peak expiratory flow (PEF), the daily total symptom score, the daily number of puffs of rescue salbutamol, the frequency of COPD exacerbations, and QOL.

The following six symptoms were recorded daily by patients: the ability to perform the usual daily activities; breathlessness over the previous 24 h; waking at night due to respiratory symptoms; breathlessness on rising; cough; and sputum production. The scoring system for each symptom allowed values in the range from 0 (no symptoms) to 3 (worst), and the six questions allowed for up to a maximum total score of 18 per day.

Three levels of COPD exacerbation were identified as follows: first level (mild), "bad days," defined as days with at least two individual symptom scores of ≥ 2 and/or a reduction in PEF from baseline (*ie*, the average value over the last 7 days of the run-in period) of > 20%; second level (moderate), undergo a course of additional therapy (*ie*, corticosteroids, antibiotics, or oxygen); and third level (severe), COPD-related hospitalizations.

QOL was measured before the first dose of study medication and after 12 months of treatment by the validated St. George's Respiratory Questionnaire (SGRQ).[13,14]

Vital signs were obtained during the screening visit. At subsequent visits, vital signs were obtained before the morning dose and at 1, 2, 4, and 12 h postdose. ECGs also were performed at visits predose and up to 2 h postdose (the latter in selected centers). A clinical laboratory evaluation was performed at the screening visit, at randomization, and after 6 and 12 months of treatment. Patients recorded adverse events (AEs) in the patient diary throughout the study.

Statistical Analysis

The sample size estimate was based on the primary efficacy variable, the standardized AUC-FEV_1. The between-patient SD was assumed to be 400 mL. To allow for an expected dropout rate

of 15%, a minimum sample size of 206 patients per treatment group was required to demonstrate a clinically relevant difference of 120 mL between treatment groups with a power of 80% and a significance level of 5% (two-sided).

The statistical analysis was carried out according to the intent-to-treat principle. Analysis of covariance (ANCOVA) was used to estimate all treatment differences for standardized AUC-FEV_1. The ANCOVA model allowed for the effects of country, center within country, gender, reversibility, and smoking status at entry into the study. The baseline FEV_1 value (*ie*, the last FEV_1 measured before randomization) was used as a covariate. All the other variables were analyzed by ANCOVA or the van Elteren test, as appropriate. No adjustment of the significance level was used for multiple comparisons of the primary variable as an ordered hierarchical procedure was defined. As a large number of secondary variables were tested in an exploratory sense, no adjustment was made for repeated measures testing of the data recorded at a series of time points.

Results

Patients

One thousand one hundred twenty-seven patients were screened, and 854 were randomized into this study (F12, 211 patients; F24, 214 patients; PL, 220 patients; and THEO, 209 patients) [Table 1]. A total of 232 patients were discontinued from the study prematurely, and 622 completed the 12-month treatment period. The lowest discontinuation rates were seen in the F12 and F24 groups, and the highest was seen in the THEO group (Table 1). The proportion of patients discontinuing the study in the first 3 months of treatment was about threefold higher with the patients receiving THEO (27%) than among those receiving F12 (10%) and F24 (8%) [Table 1]. The main reason given for premature discontinuation was AEs that were not related to COPD (Table 1).

The demographic and baseline characteristics of the intent-to-treat population are summarized in Table 2. The patients categorized as irreversible/poorly reversible represented 56%, 45%, 53%, and 50%, respectively, of the total number of patients randomized to F12, F24, PL, and THEO. Even among the reversible patients (*ie*, those patients whose FEV_1 values increased $\geq 15\%$ after receiving salbutamol), the mean postbronchodilator FEV_1 ranged from 43% of predicted (THEO group) to 48% of predicted (PL group), and the mean FEV_1/vital capacity ratio was $< 50\%$ in all the treatment groups. In addition, the population satisfied the other inclusion criteria reported above, and their smoking histories and symptoms were compatible with the diagnosis of symptomatic COPD, as indicated by international guidelines.[1–3,7,12]

The only concomitant medications that were allowed were inhaled corticosteroids, which were received by 47% of the patients in each formoterol group, 49% of the patients in the PL group, and 46% of the patients in the THEO group. The most frequently used inhaled corticosteroids were beclomethasone dipropionate and budesonide, at mean daily doses that were within the recommended range. The percentages of patients who required oral corticosteroid therapy over the whole treatment period were 13% in the F12 group, 10% in the F24 group, 17% in the PL group, and 8% in the THEO group.

The majority of patients who were treated with THEO received doses that maintained plasma levels that were well within the acceptable range of 8 to 20 mg/L. A plasma level of > 20 mg/L was recorded on only 11 separate occasions after the start of treatment. Only three of the patients who discontin-

Table 1—*Patient Disposition for Each Treatment Group

Variables	F12	F24	PL	THEO	Total
Total of patients studied					
Screened					1,127
Randomized	211	214	220	209	854
Completed study	159 (75)	174 (81)	161 (73)	128 (61)	622 (73)
Discontinued in first 3 mo	21 (10)	18 (8)	34 (15)	56 (27)	129 (15)
Discontinuations, total	52 (25)	40 (19)	59 (27)	81 (39)	232 (27)
Deaths	3 (1)	1 (1)	0	0	4 (1)
COPD-related AEs	2 (1)	2 (1)	7 (3)	5 (2)	16 (2)
Non-COPD-related AEs	10 (5)	9 (4)	16 (7)	43 (21)	78 (9)
Unsatisfactory therapeutic effect	5 (2)	4 (2)	6 (3)	2 (1)	17 (2)
Abnormal laboratory values	1 (1)	0	0	2 (1)	3 (< 1)
Protocol criteria not met	3 (1)	5 (2)	3 (1)	6 (3)	17 (2)
Noncompliance	10 (5)	5 (2)	7 (3)	11 (5)	33 (4)
Withdrawal of consent	11 (5)	5 (2)	15 (7)	9 (4)	40 (5)
Lost to follow-up	6 (3)	8 (4)	5 (2)	3 (1)	22 (3)
Administrative problems	1 (1)	1 (1)	0	0	2 (< 1)

*Values given as No. (%).

Table 2—*Summary of Demographic and Baseline Data (Intent-to-Treat Population)

Variables	F12 (n = 211)	F24 (n = 214)	PL (n = 220)	THEO (n = 209)	Total (n = 854)
Age, yr					
Mean	63	62	63	64	63
Range	37–80	40–82	44–84	34–88	34–88
Gender, No. (%)					
Male	184 (87)	178 (83)	175 (80)	172 (82)	709 (83)
Female	27 (13)	36 (17)	45 (21)	37 (18)	145 (17)
Duration of COPD, yr					
Mean	9.6	7.9	7.7	8.5	8.4
Range	0–50	0–41	0–47	0–50	0–50
FEV_1, L†					
Mean	1.36	1.39	1.40	1.33	1.37
Range	0.5–3.2	0.5–3.9	0.5–3.1	0.6–3.0	0.5–3.9
FEV_1, % predicted‡					
Mean	47	47	49	46	47
Range	23–75	19–71	19–70	21–72	19–75
FEV_1/VC, %‡					
Mean	49	49	50	49	49
Range	16–75	25–96	24–77	25–80	16–96
Morning premedication PEF, L/min§					
Mean	259	251	252	247	253
Range	109–515	78–520	88–511	90–494	78–520

*VC = vital capacity.
†Recorded at randomization visit.
‡Recorded at screening visit.
§Averaged over the last 7 days of the run-in period.

ued treatment prematurely because of an AE had plasma levels of > 20 mg/L, and all stopped taking THEO shortly after randomization. Only seven other patients with plasma levels of > 15 mg/L but < 20 mg/L withdrew from treatment because of AEs. All other patients who discontinued treatment early because of an AE were receiving doses of THEO that had been stabilized to give a plasma level of < 15 mg/L, as recommended by most experts.[2,12]

Spirometric Measures

The analysis of the standardized AUC-FEV_1 at 3 months of treatment in the entire population showed that both F12 and F24 were more effective than PL, with differences that were statistically significant and exceeded the 120-mL threshold for clinical relevance (Table 3). Both F12 and F24 were also statistically significantly superior to THEO (Table 3). The comparison between THEO and PL produced a statistically significant result (Table 3), which confirmed the sensitivity of the study. Baseline FEV_1, country, center within country, and reversibility were shown to be significantly related to the primary outcome ($p < 0.001$, $p = 0.025$, $p = 0.005$, and $p = 0.004$, respectively), whereas gender and baseline smoking status were not.

The ANCOVA of the standardized AUC-FEV_1 at 12 months of treatment also showed that both F12 and F24 were superior to PL, with estimated differences that were again statistically significant and clinically relevant (Table 3). F12 was significantly more effective than THEO (Table 3). THEO was significantly more effective than PL (Table 3).

An analysis of the primary variable in the subpopulation of patients who were defined as irreversible/poorly reversible showed that F12 and F24 produced significant bronchodilation vs PL also in this group of patients (Table 3). This effect was evident both at 3 and 12 months into the treatment period. In this group of irreversible/poorly reversible patients, therapy with THEO did not cause any significant improvement in AUC-FEV_1 vs PL at any time point (Table 3).

An additional analysis of the primary variable indicated that both F12 and F24 were superior to PL whether or not the patients were receiving concomitant therapy with corticosteroids throughout the trial.

The 12-h profile plots of mean FEV_1 values after 3 and 12 months of treatment in the entire population are reported in Figure 1. Compared to PL, therapy with both F12 and F24 improved postmedication FEV_1 at every time point and for each visit. Treatment differences were highly statistically significant (all $p < 0.001$), and all exceeded the 120 mL that had been stated to be clinically relevant in the

Table 3—*Treatment Group Contrasts of Standardized AUC-FEV_1 Over 12 h Following the Morning Dose of Study Medication After 3 and 12 Months (Intent-to-Treat Population)***

Contrast	3 mo Estimated Difference, L	3 mo p Value	12 mo Estimated Difference, L	12 mo p Value
Total				
F12-PL	0.200	< 0.001	0.207	< 0.001
F24-PL	0.208	< 0.001	0.170	< 0.001
F12-THEO	0.085	0.005	0.077	0.026
F24-THEO	0.092	0.002	0.041	0.233
F24-F12	0.008	0.787	− 0.037	0.246
THEO-PL	0.116	< 0.001	0.130	< 0.001
Irreversible/poorly reversible				
F12-PL	0.109	0.007	0.145	0.002
F24-PL	0.166	< 0.001	0.141	0.003
F12-THEO	0.067	0.114	0.057	0.240
F24-THEO	0.125	0.006	0.053	0.293
F24-F12	0.058	0.158	− 0.004	0.932
THEO-PL	0.042	0.339	0.088	0.073
Reversible				
F12-PL	0.331	< 0.001	0.343	< 0.001
F24-PL	0.271	< 0.001	0.238	< 0.001
F12-THEO	0.109	0.020	0.123	0.025
F24-THEO	0.049	0.259	0.018	0.716
F24-F12	− 0.060	0.156	− 0.105	0.030
THEO-PL	0.222	< 0.001	0.220	< 0.001

*Estimated differences are based on the following model: AUC-FEV_1 = (pre-medication FEV_1 at randomization) + country + (center within country) + gender + reversibility + (smoking status at randomization) + treatment; irreversible/poorly reversible = patients whose FEV_1 increased < 15% after receiving salbutamol; reversible = patients whose FEV_1 increased ≥ 15% after receiving salbutamol.

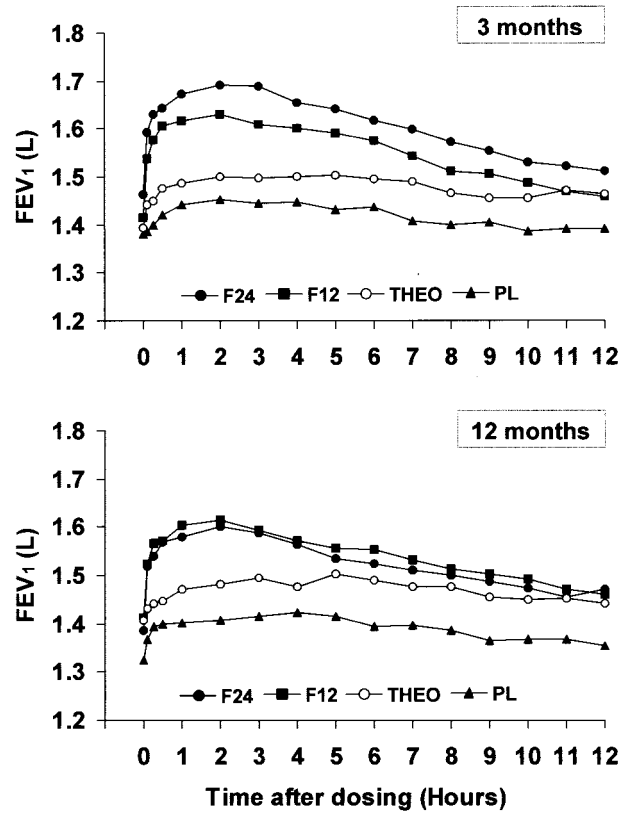

FIGURE 1. Mean FEV_1 values measured predose (time point 0) and over 12 h following the morning dose of study medications at 3 months (*top*) and 12 months (*bottom*) of the treatment period (Intent-to-treat population). At each time point postdose, a difference in mean FEV_1 of 120 mL between treatment groups was considered to be clinically relevant.

protocol. For both doses, the effect of formoterol was similar throughout the study. THEO was also significantly more effective than PL at every time point and for each visit (all $p < 0.05$), and the difference was clinically relevant at 5, 7, 8, 10, 11, and 12 h.

Concerning the effect of treatments on morning premedication FEV_1 values, F12 and F24 were significantly more effective than PL at every time point of the treatment period ($p \leq 0.026$), with the exception of F24 at 9 months. THEO also significantly improved morning premedication FEV_1 over PL during the entire treatment period ($p \leq 0.013$).

The ANCOVA of the standardized AUC-FVC over 12 h at 3 and 12 months of treatment also showed that both F12 and F24 were significantly more effective than PL (all $p < 0.001$). THEO was significantly more effective than PL (all $p \leq 0.007$). Both F12 and F24 were superior to THEO, with statistically significant differences at 3 months ($p \leq 0.016$).

Morning Premedication PEF

The mean values of the morning premedication PEF over the 3 months preceding each visit are reported in Figure 2, together with the mean values over the last 7 days of the run-in period (*ie*, baseline values). The ANCOVA of the data averaged over the 3 months between visits showed that F12 and F24 were significantly more effective than PL at every time point. F24 was invariably more effective than THEO, with statistically significant differences at every time point. F12 was significantly more effective than THEO during the first 3 months. Afterward, treatment differences did not reach statistical significance, although mean morning premedication PEF was still higher when patients received F12 than when they received THEO (Fig 2).

ANCOVA of PEF values averaged over the whole treatment period showed that both F12 and F24 were significantly superior to PL (all $p < 0.001$) and significantly more effective than THEO (all $p \leq 0.020$). THEO was also significantly more effective than PL ($p = 0.007$).

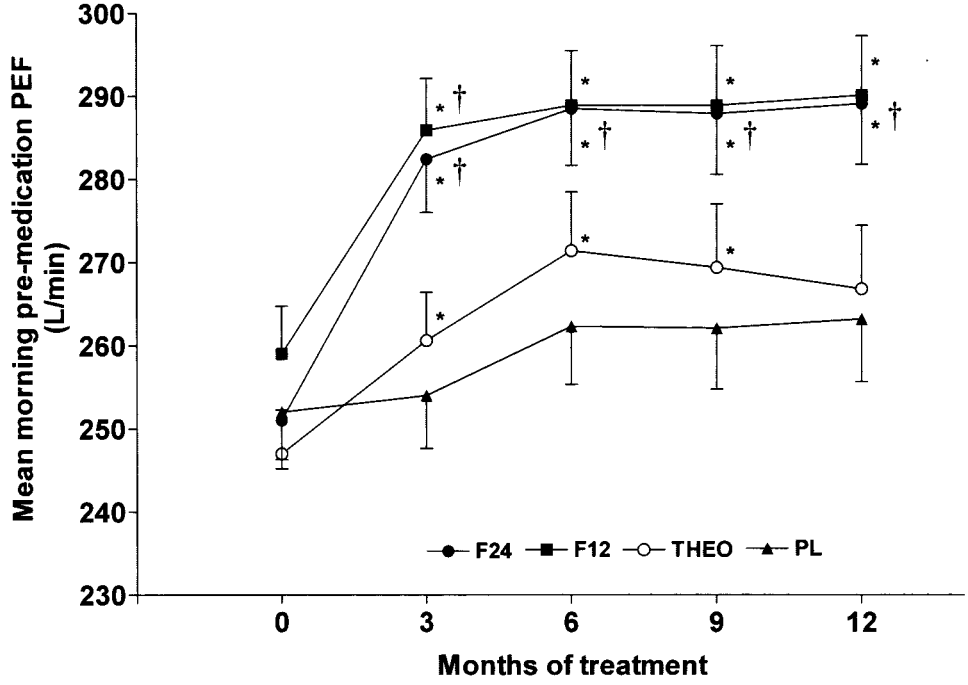

FIGURE 2. Mean morning premedication PEF values averaged over the last 7 days of the run-in period (time point 0) and over the 3 months preceding each visit at 3, 6, 9, and 12 months of the treatment period. Error bars indicate SEMs. Intent-to-treat population. * = $p \leq 0.022$ vs PL; † = $p \leq 0.010$ vs THEO (determined by ANCOVA based on the following model: mean PEF = [mean PEF during the last 7 days of the run-in period] + country + [center within country] + gender + reversibility + [smoking status at randomization] + treatment).

Total Diary Symptom Score and Use of Rescue Medication

For every 3-month time interval, the average symptom scores tended to be slightly lower with patients receiving F12 and F24 than when they received PL and THEO. The median symptom scores averaged over the entire treatment period were 4.7 while receiving F12, 4.8 while receiving F24, 5.5 while receiving PL, and 5.4 while receiving THEO. There was no statistical significance among the treatment groups.

The median numbers of puffs of rescue medication inhaled per day over the 3 months preceding each visit are shown in Figure 3, together with the median number of puffs of rescue medication inhaled per day over the last 7 days of the run-in period (*ie*, the baseline value). Considering the results over the whole treatment period, the median numbers of puffs of rescue medication inhaled by patients were 1.1 while receiving F12, 0.7 while receiving F24, 1.8 while receiving PL, and 1.6 while receiving THEO. Both F12 and F24 produced reductions in the use of rescue medication over the whole treatment period that was significant compared to PL (all $p \leq 0.003$). The median percentage of days with no use of rescue medication over the entire treatment period was higher while patients were receiving F12 (44%) and F24 (62%) than when they were receiving PL (13%) and THEO (22%).

COPD Exacerbations

Figure 4 shows the mean percentages of bad days (first level, mild COPD exacerbations) averaged over the 3 months preceding each visit at 3, 6, 9, and 12 months. Both F12 and F24 were significantly superior to PL ($p \leq 0.008$) and to THEO ($p \leq 0.035$), while there was no significant difference between THEO and PL ($p = 0.617$).

The mean percentage of days of additional therapy for COPD (second level, moderate COPD exacerbations) was lower while patients were receiving F24 (4%) and THEO (5%) than when they were receiving PL (8%) or F12 (7%). The differences reached statistical significance for F24 and THEO compared with PL ($p = 0.043$ and $p = 0.019$, respectively) but not for F12 compared to PL. Similar results were observed with the percentage of patients receiving additional therapy for COPD exacerbations (patients receiving F12, 32%; patients receiving F24, 23%; patients receiving PL, 34%; and patients receiving THEO, 20%). The number of COPD-related hospi-

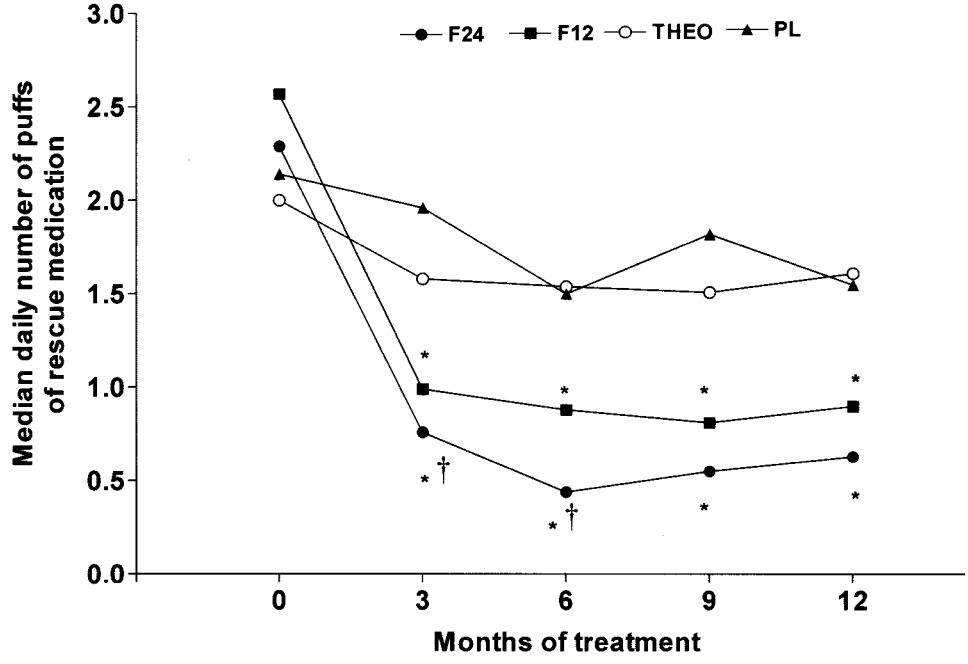

FIGURE 3. Median daily numbers of puffs of rescue medication averaged over the last 7 days of the run-in period (time point 0) and over the 3 months preceding each visit at 3, 6, 9, and 12 months of the treatment period in the intent-to-treat population. * = $p \leq 0.040$ vs PL; † = $p \leq 0.026$ vs THEO (determined by the van Elteren test).

talizations (third level, severe COPD exacerbations) was four times higher in the PL group (20) than in the F24 group (5). Marked differences also were seen in the comparisons between the PL group and the F12 groups (10) and the THEO group (6).

QOL

QOL was assessed before administration of the first dose of study medication and after 12 months of treatment, and the absolute scores are reported in Table 4. Compared to patients receiving PL, those receiving both F12 and F24 showed statistically significant improvement in the total SGRQ score at the end of the treatment period ($p = 0.030$ and $p = 0.009$, respectively). THEO was also statistically significantly more effective than PL ($p = 0.013$).

Considering the three domains of the total SGRQ scores, F12 produced a statistically significant improvement in the symptoms subscore in comparison with PL ($p = 0.009$). F24 caused a statistically significant improvement over PL for the impacts subscore ($p = 0.016$). THEO produced a statistically significant reduction in the activity subscore vs PL ($p = 0.003$).

AEs and Safety Variables

Of the 854 patients randomized into the study, 565 (66%) reported AEs. The most frequently occurring AEs are reported by treatment in Table 5. There were higher numbers of GI AEs in the THEO group compared to the other treatment groups.

Forty-nine percent of all AEs were considered to be mild in severity, and 12% were severe. The number of patients reporting severe AEs was 36 in F12 group, 39 in the F24 group, 59 in the PL group, and 56 in the THEO group. A total of 211 AEs reported by 119 patients were considered by the investigators to be drug-related. Of these, 20 were reported by 18 patients (9%) receiving F12, 28 were reported by 18 patients (8%) receiving F24, 27 were reported by 17 patients (8%) receiving PL, and 136 were reported by 66 patients (32%) receiving THEO.

A total of 115 patients discontinued the study prematurely because of AEs, unsatisfactory therapeutic effect, or death (Table 1). In the THEO group, the total number of withdrawals due to AEs (COPD-related and not COPD-related) was threefold higher than that in the F12 and F24 groups and was twofold higher than that in the PL group (Table 1). The mean time to discontinuation was 115 days in the F12 group, 135 days in the F24 group, 116 days in the PL group, and 65 days in the THEO group. Patients receiving THEO were four times more likely to discontinue treatment because of AEs or unsatisfactory therapeutic effect than were patients receiving F24 and were three times more

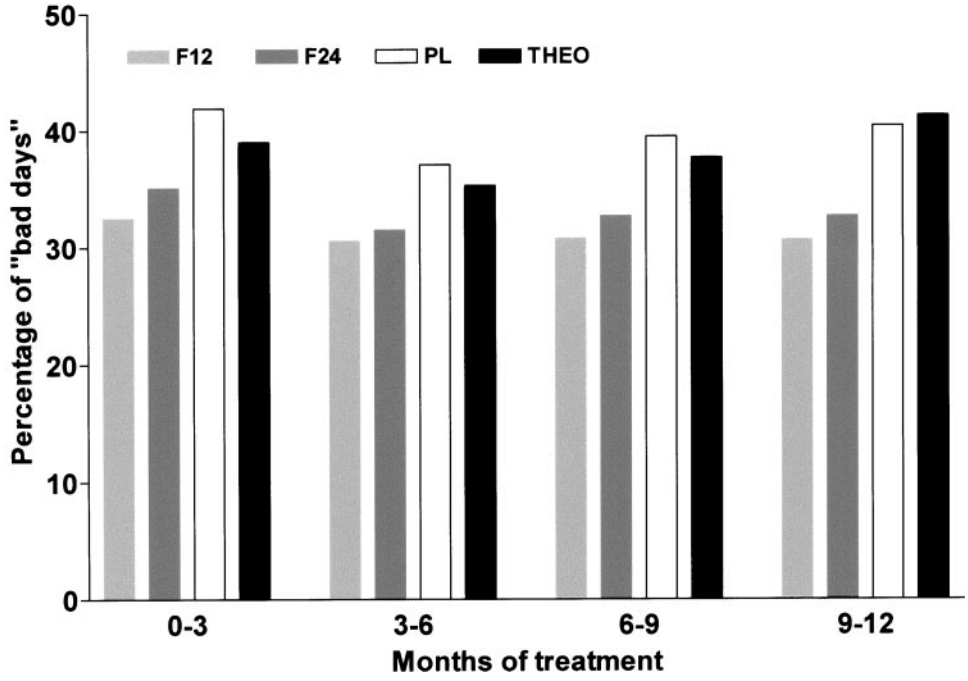

FIGURE 4. Mean percentage of bad days averaged over the 3 months preceding each visit at 3, 6, 9, and 12 months of the treatment period in the intent-to-treat population. Over the whole treatment period, F12 and F24 were significantly superior to PL ($p \leq 0.008$) and to THEO ($p \leq 0.035$), while there was no significant difference between THEO and PL ($p = 0.617$) as determined by an ANCOVA model that used the mean total diary score during the last 7 days of the run-in period as a covariate.

likely to discontinue treatment than those receiving F12 (F24/THEO hazard ratio, 0.27; and F12/THEO hazard ratio, 0.34; both $p < 0.001$). Patients receiving THEO were twice as likely as patients receiving PL to discontinue for the same reasons (THEO/PL hazard ratio, 2.05; $p = 0.002$).

There were four deaths during treatment in this study (Table 6). Three occurred in the F12 group and one occurred in the F24 group. Three deaths were considered not related to study medication (suicide, one patient; post-traumatic death, one patient; possible myocardial infarction, one patient).

Table 4—*Absolute QOL Scores (Intent-to-Treat Population)*

	Baseline*		After 12 mo	
SGRQ Scores	No.	Mean (SD)	No.	Mean (SD)
Total				
F12	211	46.2 (17.4)	159	40.9 (17.8)
F24	210	48.4 (16.8)	171	42.3 (19.0)
PL	218	47.2 (16.8)	160	45.3 (18.7)
THEO	206	47.7 (16.9)	127	41.5 (19.6)
Symptoms				
F12	211	58.9 (18.4)	159	46.7 (20.1)
F24	210	58.1 (19.0)	169	48.1 (21.6)
PL	218	58.4 (19.7)	158	51.3 (21.2)
THEO	206	58.2 (19.7)	127	47.4 (22.1)
Activity				
F12	210	58.8 (20.0)	157	55.9 (19.5)
F24	208	62.5 (19.9)	171	57.0 (21.3)
PL	218	62.2 (19.2)	160	60.7 (20.5)
THEO	206	61.3 (18.5)	127	54.7 (21.3)
Impacts				
F12	211	35.2 (20.5)	159	30.9 (21.4)
F24	210	37.4 (19.2)	171	32.1 (21.2)
PL	218	35.3 (19.5)	160	34.5 (21.0)
THEO	206	36.8 (20.0)	127	32.1 (21.6)

*Recorded at the randomization visit.

Table 5—*Patients With AEs and Most Frequent AEs (> 5% in Any Group)**

Characteristics	F12	F24	PL	THEO
Patients randomized	211	214	220	209
Patients with an AE	139 (66)	136 (64)	148 (67)	142 (68)
Most frequent AEs				
Viral infection	34 (16)	31 (15)	39 (18)	25 (12)
COPD exacerbated	34 (16)	26 (12)	33 (15)	23 (11)
Bronchitis	21 (10)	21 (10)	20 (9)	12 (6)
Upper respiratory tract infection	20 (10)	14 (7)	16 (7)	12 (6)
Dyspnea	12 (6)	13 (6)	11 (5)	9 (4)
Headache	13 (6)	8 (4)	20 (9)	22 (11)
Insomnia	3 (1)	1 (1)	5 (2)	11 (5)
Dyspepsia	2 (1)	3 (1)	3 (1)	19 (9)
Abdominal pain	1 (1)	8 (4)	9 (4)	14 (7)
Tremor	1 (1)	4 (2)	2 (1)	12 (6)
Nausea	1 (1)	1 (1)	4 (2)	32 (15)
Vomiting	1 (1)	1 (1)	0	14 (7)

*Values given as No. (%).

Table 6—*Patients With SAEs, Significant AEs, or Other Premature Discontinuations

Characteristics	F12	F24	PL	THEO
Patients randomized	211	214	220	209
Total patients with SAEs or significant AE and/or premature discontinuations	65 (31)	48 (22)	73 (33)	92 (44)
Deaths	3 (1)	1 (1)	0	0
Other SAEs	23 (11)	15 (7)	33 (15)	21 (10)
Leading to premature discontinuation	8 (4)	4 (2)	10 (5)	10 (5)
Not leading to premature discontinuation	15 (7)	11 (5)	23 (11)	11 (5)
Other significant AEs†	4 (2)	7 (3)	12 (5)	38 (18)
Other premature discontinuations‡	35 (17)	25 (12)	28 (13)	33 (17)

*Values given as No. (%).
†Nonserious AEs leading to permanent withdrawal from the study.
‡Premature discontinuations for the following reasons: withdrawal of consent, noncompliance, lost to follow-up, unsatisfactory therapeutic effect, administrative problems, protocol criteria not met, abnormal laboratory value, or unknown reason.

One death was due to myocardial infarction with a rupture of the interventricular cardiac septum and was considered by the investigator to be possibly related to receiving the study drug.

The numbers of other serious AEs (SAEs) and significant AEs are reported by treatment in Table 6. Cardiac SAEs were reported by five patients receiving F12, by no patients receiving F24, by two patients receiving PL, and by five patients receiving THEO. Heart/rhythm disorders occurred in four patients (2%) receiving F12, in six patients (3%) receiving F24, by five patients (2%) receiving PL, and by nine patients (4%) receiving THEO. There was no difference between treatment groups in the incidence of ECG abnormalities, clinically relevant abnormal serum potassium values, and fasting glucose plasma levels. The incidence of the prolongation of the QTc beyond 0.46 s during the treatment period was 16% for both the F12 and F24 groups, 14% for the PL group, and 22% for the THEO group. In the US centers, ECGs were recorded up to 2 h postdose at randomization, and at each 3-month visit abnormal and clinically significant ECG findings were detected in one patient receiving F12, in two patients receiving F24, in two patients receiving PL, and in no patients receiving THEO.

The number of serious and non-SAEs tended to be lower among patients receiving F24 than among those receiving F12, indicating no dose-related effect.

Discussion

The current first-line therapies for COPD patients are inhaled short-acting β_2-adrenoceptor agonists and ipratropium bromide, with THEO being the recommended add-on treatment for patients not adequately controlled by therapy with inhaled bronchodilators.[1–3,7] Slow-release preparations of THEO have a prolonged action and can be administered orally twice daily. For this reason, they are considered to be particularly indicated for those COPD patients who have nocturnal or early morning symptoms or who are incapable of inhaling drugs.[1–3] In addition, THEO augments central respiratory drive, may have an effect on respiratory muscles, and reduces pulmonary vascular resistance, effects that may be desirable in clinically important obstructive disease.[15,16] However, careful dosing is needed, and the necessity of monitoring plasma levels to adjust the dosage is cumbersome.

The β_2-adrenoceptor agonist formoterol fumarate combines the rapid onset of action of previously available β_2-adrenoceptor agonists with a prolonged duration of the bronchodilator effect and can be administered twice daily.[4]

A recent study[9] has indicated that formoterol is more effective than ipratropium bromide at improving pulmonary function, symptoms, use of rescue medication, and QOL among patients with COPD. The results of the present study suggest that formoterol dry powder delivered via the breath-activated inhaler (Aerolizer) is not only superior to PL with on-demand salbutamol/albuterol but also is superior to oral slow-release THEO in terms of the magnitude of the bronchodilator effect (AUC-FEV_1, over 12 h) and may have a role in the prevention of mild COPD exacerbations.

An analysis of the standardized AUC-FEV_1 following the morning dose of study medication in the entire intent-to-treat population revealed that the bronchodilator effect of both F12 and F24 was statistically and clinically significant compared to that of PL at 3 and 12 months of the treatment period. THEO was also significantly more effective than PL after 3 and 12 months of treatment. The lower dose of formoterol produced a significant improvement of the AUC-FEV_1 over THEO at both time points of the treatment period, and F24 was significantly more effective than THEO at 3 months. Both F12 and F24 were also significantly more effective than PL in the subpopulation of patients who are considered to have relatively fixed airflow obstruction according to current guidelines,[3,7] while THEO had an effect similar to PL in these irreversible/poorly reversible individuals.

The analysis of the absolute FEV_1 values at individual time points following the morning dose of

study medication at 3 and 12 months of treatment showed that a statistically significant and clinically relevant superior bronchodilator effect over PL was detectable with both F12 and F24 as early as 5 min after dosing and that it persisted for at least 12 h. A statistically significant and prolonged superior bronchodilator effect over PL also was detected with THEO, but it did not reach the predefined threshold for clinical relevance (*ie*, 120 mL) at all time points. The bronchodilator effect of THEO was significantly smaller in magnitude compared to the effect of both F12 and F24, especially for the first 4 h following the morning dose of study medications (Fig 1).

Compared to the PL group, there was an improvement in the morning premedication FEV_1 in both the F12 and F24 groups and in the THEO group, with differences that were statistically significant at every 3-month visit, with the sole exception of the F24 group at 9 months. This indicates that treatment with formoterol allows the control of nocturnal symptoms in a way that is similar to treatment with THEO and is therefore indicated for patients who have nocturnal or early morning symptoms.

The persistent increase in morning premedication PEF by formoterol over the entire 12 months of treatment confirmed that there was no diminution of the bronchodilating effect of this agent.

The improvement in pulmonary function by formoterol was associated with a significant reduction in the use of rescue medication in the absence of a concomitant increase in symptoms and with a significant decrease in the frequency of mild exacerbations (ie, the number of bad days as defined in the "Study Design" section), while THEO had no significant effect on these parameters.

The reduction in the number of bad days by formoterol would suggest that this drug might alter the course of acute exacerbations of COPD. This may be the result of the inhibitory effect of β_2-adrenoceptor agonists on plasma exudation and neutrophil migration[17,18] or may reflect an additional reduction in the expression of adhesion molecules and in the activation of inflammatory cells in the airways of those patients receiving inhaled corticosteroid therapy as concomitant medication (*ie*, $> 40\%$ in each treatment group).[19] However, it should be noted that the definition of *bad days* included changes in PEF values. Thus, the beneficial effect of formoterol in comparison to THEO for this outcome may merely reflect a more potent bronchodilator activity at the time of the exacerbation. Interestingly, the number of severe COPD exacerbations/COPD-related hospitalizations was low among the formoterol-treated patients, indicating that the more potent bronchodilatory activity of formoterol was not associated with mere masking of mild exacerbations and that the observed decrease in the number of bad days may after all reflect a true effect of formoterol. In this context, the findings in this study of a possible beneficial effect of formoterol on mild COPD exacerbations (according to the definition of bad days in the study protocol) warrants further investigation before any conclusion can be drawn.

The patients receiving formoterol perceived the beneficial impact on the quality of their daily life as indicated by the statistically significant improvement in the total score of the SGRQ after 12 months of treatment with formoterol in comparison with treatment with PL. THEO was also more effective than PL. The result of the latter comparison should be interpreted with caution due to the disproportionate number of premature discontinuations in the THEO arm of the study that might have resulted in the under-representation of poorly controlled patients in this group. It is important to consider, however, that the unblinded nature of the THEO arm might have contributed to the very high dropout rate associated with this treatment and that there was no difference among the treatment groups in the number of patients who discontinued treatment because of a lack of efficacy. Most withdrawals were due to GI side effects, not to the improper control of symptoms.

In the present study, there was no clear indication of a dose response to formoterol in the tested population. Although F24 improved some parameters more than F12, such as the morning PEF, the use of rescue medication, and the total score of the QOL questionnaire, the differences were not statistically significant and were not in the same direction for other parameters.

One study[20] has demonstrated an additive effect of salmeterol and fluticasone in patients with COPD who were treated for 3 months. Differing from that investigation, our trial was not designed to examine a relationship between corticosteroid use and specific outcomes. Although a *post hoc* analysis of the primary variable indicated that both F12 and F24 were superior to PL, whether or not the patients were receiving concomitant inhaled corticosteroid therapy, we did not compare the magnitude of the improvement in the two subgroups, and further investigation is warranted.

Compared to therapeutically effective doses of oral, slow-release THEO that was administered twice daily, F12 and F24 administration twice daily caused fewer AEs and fewer premature discontinuations. Most of the patients who discontinued THEO treatment prematurely were receiving doses resulting in plasma levels considered to be relatively well-tolerated (*ie*, < 15 mg/L).[2,11,12] However, it

should be noted that the plasma concentrations of THEO were measured 3 to 4 h after dosing. Although plasma sampling at 4 h postdose is within the recommended time range,[3,21,22] higher plasma concentrations of THEO may have been reached at ≥ 6 h.[3,11] In addition, in senile patients the AEs caused by therapy with THEO may occur even at plasma concentrations < 15 mg/L, and the currently recommended plasma levels for patients with concomitant diseases such as right heart failure, cor pulmonale, and hepatic insufficiency are lower than those used in our study (*ie*, between 5 and 12 mg/L).[1]

There were four deaths in this study. One death that occurred in the F12 group was considered possibly to be related to treatment by the investigator, but there were no deaths due to serious cardiac AEs in the group receiving F24. This suggests that there was no dose relationship to formoterol. Also, heart rate/rhythm abnormalities and QTc changes occurred with the same frequency in both the formoterol and PL groups.

Overall, both F12 and F24 showed a safety and tolerability profile that was similar to that of PL.

In conclusion, the results of this study support the use of inhaled formoterol dry powder in the long-term treatment of COPD patients and indicate that this agent is more effective and better tolerated than oral, slow-release THEO in symptomatic patients with COPD. The results also indicate that formoterol is effective in improving lung function in patients with varying degrees of reversibility of the airflow obstruction, while the bronchodilating effectiveness of oral, slow-release THEO is limited to the group of patients who display a more variable airflow obstruction.

Our findings are in agreement with the statement that a policy of minimal therapeutic intervention in COPD is no longer justified.[2] In comparison with no or minimal treatment (*ie*, PL or PL and salbutamol/albuterol on demand), regular treatment with formoterol was well-tolerated and improved airflow obstruction even in the apparently less reversible patients. More importantly, use of formoterol improved QOL and decreased the use of supplemental salbutamol/albuterol for symptom relief.

Appendix

The following investigators, listed by country, also contributed randomized data to the Formoterol in Chronic Obstructive Pulmonary Disease (FICOPD) II Study.

Austria: K. Aigner, W. Domej, K. Puganigg, and K. Sertl.

Belgium: R. Deman.

Czech Republic: V. Vondra, J. Erban, O. Ostadal, Z. Merta, and J. Skrickova.

France: J.-L. Racineaux, J. Rochemaure, C. Wallaert, M. Aubier, J.F. Muir, X. Lebas, Piquet, Zuck, and J.-M. Vergnon.

Germany: H. Matthys, S. Scmidtmann, D. H. Worth, Wagner, and A. Forster.

Greece: S. Constantopoulos, L. Sichletidis, N. Georgatou-Papageorgiou, N. Bahlitzanakis, and D. Bouros.

Hungary: P. Magyar, Gyorgy, B. Nagy, K. Fonay, and G. Berta.

Italy: D. Olivieri, P.L. Paggiaro, C. Sanguinetti, A. Potena, L. Gandola, G. D'Amato, C. Franco, N. Ambrosino, M. Neri, I. Cerveri, A. Rossi, M. Dottorini, E. Pozzi, R. Balduin, and V. Brusasco.

Slovakia: D. Magula and J. Zucha.

South Africa: C. Smith, A.P. Foden, A. Brunig, M. van der Linden, I. Rossouw, and M. Laher.

Spain: F.J. Gispert, J. Martinez, J. Morera, P. de Lucas, J.L. Izquierdo, and J.E. Boada.

United States: T.R. Amgott, R. Benkert, J.A. Bernstein, E. Bleeker, S.C. Campbell, D. Collins, A.C. DeGraff, E.C. Federman, M. Friedman, S. Kreitzer, E. Lisberg, W. Lumry, SD. Miller, J.J. Murray, R.M. Ovetsky, E.J. Schelbar, S.J. Simon, H. Smith, and R. Wolfe.

Also, Mr. Aidan Byrne, from the United Kingdom, significantly participated in the implementation of the study and contributed to the preparation of this manuscript.

References

1 American Thoracic Society. ATS statement: standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152(suppl): S77–S120

2 Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). Eur Respir J 1995; 8:1398–1420

3 British Thoracic Society. BTS guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997; 52(suppl):S1–S28

4 Moore RH, Khan A, Dickey BF. Long-acting inhaled β_2-agonists in asthma therapy. Chest 1998; 113:1095–1108

5 Cazzola M, Donner CF. Long-acting β_2-agonists in the management of stable chronic obstructive pulmonary disease. Drugs 2000; 60:307–320

6 D'Urzo AD, De Salvo MC, Ramirez-Rivera A, et al. In patients with COPD, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium: a 3-week, randomized, double-blind, within-patient, multicenter study. Chest 2001; 119: 1347–1356

7 Pauwels RA, Buist AS, Calverley PMA, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care Med 2001; 163:1256–1276

8 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225–244

9 Dahl R, Greefhorst LAPM, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 164:778–784

10 Eliraz A, Ramirez-Rivera A, Ferranti P, et al. Similar efficacy following four weeks treatment of asthmatics with formoterol 12 μg b.d. delivered by two different dry powder inhalers:

differences in inhaler handling. Int J Clin Pract 2001; 55:164–170
11 McFadden ER. Asthma. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. Harrison's principles of internal medicine. 14th ed. New York, NY: McGraw-Hill, 1998; 1419–1426
12 Boushey HA. Bronchodilators, other agents used in asthma. In: Katzung BG, ed. Basic and clinical pharmacology. 7th ed. New York, NY: Lange Medical Books/Mc Graw-Hill, 1998; 325–342
13 Jones PW, Quirk FH, Baveystock CM. The St. George's Respiratory Questionnaire. Respir Med 1991; 85(suppl):25–31
14 Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145:1321–1327
15 McKay SE, Howie CA, Thomson AH, et al. Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. Thorax 1993; 48:227–232
16 Ziment I. Pharmacological therapy of obstructive airway disease. Clin Chest Med 1990; 11:461–486
17 Whelan CJ, Johnson M, Vardey CJ. Comparison of the anti-inflammatory properties of formoterol, salbutamol and salmeterol in guinea-pig skin and lung. Br J Pharmacol 1993; 110:613–618
18 Barnes PJ. Effect of beta-agonists on inflammatory cells. J Allergy Clin Immunol 1999; 104(suppl):S10–S17
19 Walters EH, Bjermer L, Faurschou P, et al. The anti-inflammatory profile of inhaled corticosteroids combined with salmeterol in asthmatic patients. Respir Med 2000; 94(suppl):S26–S31
20 Cazzola M, Di Lorenzo G, Di Perna F, et al. Additive effects of salmeterol and fluticasone or theophylline in COPD. Chest 2000; 118:1576–1581
21 Weinberger M, Hendeles L. Slow-release theophylline: rationale and basis for product selection. N Engl J Med 1983; 308:760–764
22 Hendeles M, Massanari M, Weiberger M. Update on the pharmacodynamics and pharmacokinetics of theophylline. Chest 1985(suppl):103S–111S