the table below and show that the fraction of total and unchanged formoterol excreted in the urine is very similar, comparing the two doses [178:184-5].

PROTOCOL #41 – MEAND ± SD PHARMACOKINETIC PARAMETERS FOR UNCHANGED AND TOTAL FORMOTEROL AFTER MULTIPLE INHALED DOSES OF 12 µg (n = 7) AND 24 µg (n = 9) [178:185]

Formoterol Compound	PK Paramter	12 µg	24 µg
Unchanged	ER max (nmol/h)	0.48 ± 0.17	1.04 ± 0.34
	t max (h)	1.00*	1.00*
	t 1/2 (h)	5.60 ± 2.00	2.60**
	Ae(0-12) (% of dose) Wk 0	5.73 ± 0.96	6.39 ± 1.89
	Wk 4	11.92 ± 4.02	10.70 ± 3.15
	Wk 12	9.87 ± 3.65	10.39 ± 2.48
Total	Ae(0-12) (% of dose) Wk 0	18.51 ± 5.26	18.19 ± 7.76
	Wk 4	32.39 ± 6.32	25.52 ± 9.99
	Wk 12	27.44 ± 4.68	25.74 ± 9.91

* median

** one patient

DP/DF2 DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-FINDING, SINGLE-CENTRE, WITHIN-PATIENT TRIAL OF DIFFERENT DOSES OF INHALED FORMOTEROL DRY POWDER (6, 12, 24 µG) AND 400 µG INHALED SALBUTAMOL DRY POWDER IN PATIENTS WITH REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE.

SUMMARY

Fifteen adult asthma patients were studied in a crossover design with single doses of formoterol dry powder at three dose levels (6, 12 and 24 µg), salbutamol dry powder 400 µg or placebo for onset and duration of action. Onset, as determined by improvement in specific airway resistance over the first 30 minutes after treatment, was comparable among the two largest formoterol doses and salbutamol. Duration of action was assessed by the $FEV_{1.0}$ and was comparable through the 12 hours post-treatment for the two largest formoterol doses.

OBJECTIVES

Determine the onset, duration and magnitude of bronchodilatory effect of three different single doses of formoterol dry powder (6, 12, 24 µg) compared with a single dose of salbutamol dry powder (400 µg) and placebo [268:1, 7].

PROTOCOL

The first visit was for screening and consisted of history, physical examination, lung function test, blood tests and ECG. After it, three patients each were allocated to one of five orthogonal block treatment sequences. Each treatment visit lasted one day with 12 hours of formal observation after administration of the drug and each visit was separated from contiguous visits by at least one day. Lung function tests (plethysmography and spirography), blood pressure and pulse rate were sequentially determined throughout the treatment visit. If the $FEV_{1.0}$ baseline on treatment days varied by more than $\pm$ 15%, or if an inhaled bronchodilator was taken within 8 hours of the trial treatment, the examination was postponed for 24 hours. Any patient requiring rescue medication during the visit had the last value, before taking it, carried forward [268:8, 10-12].

TREATMENT

The three formoterol doses came from the following batch numbers: 6 µg/dose from Batch #913/1; 12 µg/dose from Batch #905/1 (Formula #Q835); and, 24 µg/dose from Batch #904/1. The 12 There were two matching placeboes in this double-dummy trial. Salbutamol dry powder capsules containing 400 µg/dose was the comparator and the rescue treatment [268:1, 8, 7:196, 201].

PATIENTS

Patients were to be 18-70 years of age. Their baseline $FEV_{1.0}$ was to have been greater than 40% of predicted and they were to have shown 15% $FEV_{1.0}$ reversibility after bronchodilator administration. The baseline $FEV_{1.0}$ at treatment visits was not to have

varied from this baseline measure by more than ± 15%. The following washout times for bronchodilating medication were required:

- inhaled beta-2 agonists – 8 hours
- caffeinated drinks – 8 hours
- anticholinergics – 8 hours
- oral beta-2 agonists – 24 hours
- oral methylxanthines – 36 hours

The use of all other anti-asthma medication such as oral or inhaled corticosteroids and disodium cromoglycate was acceptable if at a stable dose during at least one month before the trial. Fifteen patients with the diagnosis of bronchial asthma and normal ECG's entered the study. There were 8 males and 7 females and their ages ranged from 39 to 70 years [268:10, 19-20].

PARAMETERS

The primary efficacy variables were $FEV_{1.0}$ assessed 12 hours after treatment and specific airways resistance (sRaw) and conductance (sGaw) for the first 15 minutes after treatment. The $FEV_{1.0}$ was measured pretreatment, 30 minutes, 60 minutes and every hour post-treatment through the twelfth hour. Plethysmography was determined pretreatment and at 1, 3, 5, 10, 15 and 30 minutes post-treatment. Secondary efficacy variables consisted of these same measures at all other time points. An additional analysis of $FEV_{1.0}$ area under the curve was exploratory. Missing values and discontinued patients were handled by last value 'carried forward' analysis.

Safety monitoring consisted of blood pressure and pulse rate determinations made at each treatment visit before dosing, 30 minutes, 60 minutes and every hour post-dosing. Subjective evaluations of tremor, palpitations and bronchodilating effect were recorded as a 'yes'/'no' reply at each visit. Routine CBC and blood chemistries were collected at baseline and at the end of the last visit. Adverse events spontaneously reported or determined by indirect questioning at each visit were used to assess tolerability [268:11-3, 17].

EFFICACY

Onset of action was evaluated by the specific airway resistance (sRaw) or its reciprocal, the specific airway conductance (sGaw). Because these contain the same information, only the first was chosen as representative. The following table displays the data without missing values carried forward. The mean values are shaded to facilitate comparisons among them.

PROTOCOL DP/DF2 – ONSET OF ACTION REFLECTED BY SPECIFIC AIRWAY RESISTANCE (sRaw) PRETREATMENT AND AT TIMEPOINTS AFTER TREATMENT [268:86]

Treatment	Statistic	PreTreat.	1 Min	3 Min	5 Min	10 Min	15 Min	30 Min
Formoterol 6 µg	n	15	15	11	13	15	15	15
	Mean	2.16	2.27	1.75	1.81	1.42	1.60	1.18
	S.D.	0.87	0.83	0.43	0.63	0.53	0.51	0.37

PROTOCOL DP/DF2 – ONSET OF ACTION REFLECTED BY SPECIFIC AIRWAY RESISTANCE (sRaw) PRETREATMENT AND AT TIMEPOINTS AFTER TREATMENT [268:86]								
Treatment	Statistic	PreTreat.	1 Min	3 Min	5 Min	10 Min	15 Min	30 Min
Formoterol 12 µg	n	15	14	12	15	14	14	15
	Mean	2.11	1.94	1.84	1.83	1.15	1.13	1.08
	S.D.	0.73	0.59	0.32	0.31	0.31	0.27	0.30
Formoterol 24 µg	n	15	15	13	15	15	15	15
	Mean	2.30	1.96	1.90	1.86	1.19	1.12	1.06
	S.D.	0.84	0.49	0.36	0.39	0.25	0.38	0.32
Salbutamol 400 µg	n	15	15	13	14	15	15	15
	Mean	2.13	1.77	1.51	1.32	1.24	1.13	1.06
	S.D.	0.73	0.49	0.34	0.35	0.35	0.24	0.29
Placebo	n	15	15	13	15	15	15	15
	Mean	2.07	2.68	2.65	2.26	2.48	2.18	2.03
	S.D.	0.72	0.89	0.98	0.75	0.81	0.71	0.68

Single doses of formoterol 12 µg, 24 µg and salbutamol 400 µg produced very similar mean values over the time period spanning pretreatment to 30 minutes post-treatment. The formoterol 6 µg treatment lagged behind them at all time points, though all active treatments were superior to placebo by inspection. Formal 'carried forward' statistical analysis was done with formoterol 12 µg against placebo and was found to be significant at all post-treatment time points [268:22, 37, 86].

Duration of action was assessed by the $FEV_{1.0}$, which was determined before and at various time points after treatment. The following table displays some of these representative time points without missing values carried forward. The mean values are shaded to facilitate comparisons among them.

PROTOCOL DP/DF2 – DURATION OF ACTION REFLECTED BY $FEV_{1.0}$ PRETREATMENT AND AT SOME REPRESENTATIVE TIMEPOINTS AFTER TREATMENT [268:90-2]								
Treatment	Statistic	PreTreat.	30 Min	4 Hours	6 Hours	8 Hours	10 Hours	12 Hours
Formoterol 6 µg	n	15	14	15	15	14	14	11
	Mean	1.81	2.07	2.00	1.94	1.91	1.76	1.74
	S.D.	0.48	0.52	0.45	0.50	0.46	0.48	0.55
Formoterol 12 µg	n	15	14	15	15	14	14	13
	Mean	1.82	2.17	2.12	2.05	2.02	1.87	1.84
	S.D.	0.43	0.46	0.47	0.52	0.47	0.50	0.41
Formoterol 24 µg	n	15	15	15	15	15	14	13
	Mean	1.77	2.14	2.12	2.10	2.00	1.92	1.95
	S.D.	0.42	0.45	0.46	0.48	0.49	0.42	0.49

PROTOCOL DP/DF2 – DURATION OF ACTION REFLECTED BY $FEV_{1.0}$ PRETREATMENT AND AT SOME REPRESENTATIVE TIMEPOINTS AFTER TREATMENT [268:90-2]								
Treatment	Statistic	PreTreat.	30 Min	4 Hours	6 Hours	8 Hours	10 Hours	12 Hours
Salbutamol 400 µg	n	15	15	15	14	13	13	12
	Mean	1.75	2.13	1.88	1.76	1.68	1.62	1.65
	S.D.	0.40	0.43	0.47	0.43	0.44	0.46	0.47
Placebo	n	15	14	13	13	13	13	13
	Mean	1.80	1.75	1.77	1.68	1.71	1.62	1.80
	S.D.	0.40	0.35	0.48	0.44	0.46	0.41	0.48

These data show that formoterol 12 and 24 µg doses produced very similar increased in $FEV_{1.0}$ through the tenth post-treatment hour, after which the 24 µg dose appeared slightly superior. The formoterol 6 µg dose produced less improvement in $FEV_{1.0}$ than either of the two larger doses at all post-treatment time points. Salbutamol produced improvements in $FEV_{1.0}$ that were comparable to the two largest formoterol doses through the first hour of treatment (data not completely shown). The $FEV_{1.0}$ declined below the lowest formoterol dose at the third post-treatment hour and returned to the pretreatment baseline by the fifth hour (data not completely shown) [268:36, 90-2]. Formal statistical analysis with last value 'carried forward' at the twelfth post-treatment hour showed that both formoterol 12 and 24 µg doses were superior to placebo and to salbutamol. Exploratory analysis of area under the $FEV_{1.0}$ curve showed no statistical difference between formoterol 12 and 24 µg doses [268:21, 24].

SAFETY

One patient reported palpitations while receiving formoterol 12 µg and one reported both tremor and palpitations while receiving formoterol 24 µg, and both recovered during the observation period. One patient had abnormal chemistries (AST and ALT) at the final visit which normalized four weeks later [268:25-6]. There were no deaths and none of the adverse events was identified in the report as 'serious.'

DP/PD2 DOUBLE-BLIND, 12-WEEK, PARALLEL-GROUP, MULTI-CENTRE TRIAL TO ASSESS FORMOTEROL DRY POWDER 12 µG AND 24 µG DAILY VS. SALBUTAMOL DRY POWDER 1200 µG DAILY IN CHILDREN WITH REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASES (ROAD)

SUMMARY

Five to thirteen year old children with reversible obstructive airways disease were treated for 12 weeks in a double-dummy, parallel-group trial with either formoterol (two doses) or salbutamol, both supplied as dry powder formulations. Improvement in the mean morning peak expiratory flow rate (PEFR) from the salbutamol-treatment run-in period to the average over the double-blind period was the primary efficacy variable. It showed the superiority of formoterol 12 µg b.i.d. over both formoterol 6 µg b.i.d. and salbutamol 400 µg t.i.d. No definitive difference between the three treatments was reflected by the average evening PEFR, asthma symptom scores, sleep disturbance score, rescue medicine use or morning treatment visit spirograms.

OBJECTIVES

Comparison of 6 µg and 12 µg of formoterol dry powder inhalation b.i.d. with 400 µg salbutamol dry powder inhalation t.i.d. administered for 12 weeks in a double-dummy trial to children with reversible obstructive airways disease. This trial was intended to show the superior efficacy of formoterol to salbutamol in improving the premedication morning PEFR [322:1, 15].

PROTOCOL

This was a two-phase outpatient study, the first of which was a one-week, open-label baseline run-in during which all patients received salbutamol dry powder capsules 400 µg t.i.d. (1200 µg/day). The second phase was a double-blind, 12-week active treatment period in which patients were randomized to one of three groups: formoterol dry powder 6 µg b.i.d. (12 µg/day); formoterol dry powder 12 µg b.i.d. (24 µg/day); or, salbutamol dry powder 400 µg t.i.d. (1200 µg/day) [322:15].

At the first visit (day -7), history and physical examination, $FEV_{1.0}$, and vital signs were done before and 0.5-1.0 hours after inhaling the first salbutamol 400 µg capsule. Before the second visit, routine laboratory tests had to have been done. During the one-week run-in period, patients recorded in their diaries rescue medication use, asthma symptom score, sleep disturbances, exacerbations requiring physician care and PEFR values before and after inhalation of trial medication in the morning and evening [322:19-21].

At visit 2 (day 1), patients meeting the inclusion criteria were randomized, received the first dose of the treatment drug. Lung function tests and vital signs were done immediately after the first dose and 0.5-1.0 hour after it. A 12-lead ECG was done before and one hour after the first dose of the trial medication. After 1 (visit 3), 4 (visit 4), 8

(visit 5) and 12 weeks (visit 6), these variables were measured before and after the last dose of the trial medication. During the double-blind period, twice daily diary entries, as described above, were recorded [322:20-1].

TREATMENT

Two dose forms of formoterol dry powder capsules were employed in this trial and were designated as:

1. 6 µg/cap CGP 25 827 A Batch #: 913/5, 913/6, 913/8
2. 12 µg/cap CGP 25 827 A Batch #: 905/10, 905/11 Formula Q835

Both of the above, as well as the placeboes matching formoterol and salbutamol dry powder capsules were manufactured by Ciba-Geigy Limited Pharmaceuticals, Horsham, UK. A Salbutamol metered dose inhaler was also used for rescue [322:8, 7:201].

PATIENTS

Male and female outpatients aged 6-12 years with ROAD who had been clinically stable for ≥ 1 month before the trial and who had received daily treatment with inhaled beta-2 agonists were eligible. Reversible obstruction (the 'RO' in ROAD) was defined as: 1)an increase ≥ 15% in $FEV_{1.0}$ 15-30 minutes after inhalation of a beta-2 agonist dose equivalent to 400 µg of salbutamol dry powder or metered dose aerosol inhaler (MDI) within one month of trial entry, or during the run-in period; or, 2)an increase of ≥ 15% in peak expiratory flow (PEFR) after inhalation of salbutamol dry powder capsule at 3 out of 7 days during the run-in period. At visit 2, just before entering the double-blind period, the $FEV_{1.0}$ was to be ≥ 50% or predicted for each patient before inhalation of the beta-2 agonist. The usual exclusion criteria also applied [322:16-7].

A total of 236 patients were screened and 219 were randomized, 74 to formoterol 12 µg/day, 77 to formoterol 24 µg/day, and 68 to salbutamol 1200 µg/day. The trial was conducted in three countries (Sweden, Finland and France), with close to half of the patients (112) from Sweden. The actual patient ages ranged from 5-13 years and 67% were male. Their mean percent predicted $FEV_{1.0}$'s ranged from 44-157% with group means from 74-79% [322:30, 34].

PARAMETERS

The primary efficacy variable was the morning PEFR before inhalation of the trial medication. This maneuver was performed three times and the highest value was recorded in the patient diary. The average over the double-blind period, adjusted by the average over the run-in period, was subject to analysis. This was done by using the trimmed means for each trial week up to week 12 of the double-blind period, analyzed by ANCOVA, including the trimmed mean for the one-week run-in as a covariate. Missing data points were handled by carrying forward the last week of the double-blind period. All patients randomized who were present for at least one double-blind visit were included in the efficacy analysis.

Secondary variables included the evening daily PEFR and spirographic variables from each visit day done before and after inhalation of the trial medication. Twice daily asthma symptom scores consisted of rating the single asthma symptom causing the most discomfort over the preceding evaluation period from among four; shortness of breath (breathlessness), chest discomfort (tightness), wheezing and cough; on a 0-3 scale. Each morning, an asthma-specific sleep disturbance score was evaluated on a 0-3 scale. Asthma visits requiring a doctor's visit and number of puffs of rescue medication taken were also secondary efficacy variables.

Safety variables included adverse events, vital signs, ECG's and clinical laboratory tests. Adverse events were collected at each study period by recollection in response to nonspecific questioning of the investigator or by observation during physical examination. Clinical laboratory examinations involving a complete blood count and the usual chemistry battery was done at the screening and final visits, but was optional at all others [322:20, 22-8].

EFFICACY

The mean improvement over the baseline run-in period of the morning premedication PEFR in the double-blind period (shaded row in the table below) showed that formoterol 24 µg was statistically superior to salbutamol and to formoterol 12 µg. No difference was found between formoterol 12 µg and salbutamol [322:36-7].

PROTOCOL DP/PD2 – SUMMARY OF IMPROVEMENTS IN MEAN MORNING PEFR [322:37]			
	Absolute (L/min) And Relative (%) Increase From Baseline		
	Formoterol 12	Formoterol 24	Salbutamol 1200
Double-Blind Week 1	20.8 (8)	30.8 (12)	8.1 (3)
Double-Blind Week 12	17.4 (7)	30.7 (12)	17.3 (7)
Maximum Improvement Week	22.6 (9)	35.5 (14)	23.5 (9)
All Double-Blind Weeks	18.6 (7)	30.8 (12)	15.0 (6)

The evening PEFR showed no difference between either dose of formoterol and salbutamol. The pre- and post-dose spirograms done at each visit did not show a consistent difference between treatments. There was also no consistent difference between any two treatments in terms of the amount of rescue medication taken, morning or evening symptom score or sleep disturbance score [322:40-3].

PROTOCOL DP/PD2 – SUMMARY OF RESULTS OF SECONDARY EFFICACY VARIABLES [322:41-2]					
			Formoterol 12	Formoterol 24	Salbutamol 1200
Mean Asthma Symptom Score	Night-Time	Mn Baseline Score	0.34	0.27	0.26
		Mn DB score	0.15	0.11	0.17
	Day-Time	Mn Baseline Score	0.38	0.36	0.27
		Mn DB score	0.25	0.19	0.22

PROTOCOL DP/PD2 – SUMMARY OF RESULTS OF SECONDARY EFFICACY VARIABLES [322:41-2]					
			Formoterol 12	Formoterol 24	Salbutamol 1200
Mean Sleep Disturbance Score		Mn Baseline Score	0.22	0.19	0.22
		Mn DB score	0.13	0.07	0.11
Mean Number Of Rescue Puffs	Night-Time	Mn Baseline Score	0.21	0.19	0.14
		Mn DB score	0.15	0.09	0.12
	Day-Time	Mn Baseline Score	0.52	0.48	0.26
		Mn DB score	0.42	0.29	0.21
Number (%) Taking No Rescue Med.	Night-Time	Baseline Days	46 (62)	57 (75)	49 (72)
		DB Days	23 (31)	36 (47)	24 (35)
	Day-Time	Baseline Days	34 (47)	35 (46)	43 (63)
		DB Days	14 (19)	20 (26)	18 (26)

SAFETY

There were no deaths. In total, 17 patients had serious AE's and/or AE's leading to discontinuation from the study. Six patients were taking formoterol 12 µg/day, six were on formoterol 24 µg/day and five took salbutamol 1200 µg/day.—All of these patients, except two, reported worsening of their respiratory symptoms. The other two patients reported serious AE's consisting of angioedema and appendectomy [322:44, 46].

DP/PD3 PLACEBO-CONTROLLED, COMPARATIVE, SINGLE-CENTER, DOUBLE-BLIND, WITHIN-PATIENT TRIAL TO COMPARE THE MAGNITUDE AND DURATION OF PROTECTION AGAINST EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB) OF INHALED FORMOTEROL DRY POWDER CAPSULES 12 µG WITH THAT OF INHALED SALBUTAMOL DRY POWDER 400 µG IN CHILDREN WITH REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE AND PROVEN EIB

SUMMARY

Sixteen patients 10-14 years of age with reversible airways disease and EIB were given single doses of formoterol 12 µg, salbutamol 400 µg or placebo dry powder capsules in a double-dummy crossover design. The two active treatments showed comparable hourly $FEV_{1.0}$ values for the first two hours. Formoterol produced higher values than salbutamol at each time interval for the rest of the 12 hours post-treatment. The maximum mean $FEV_{1.0}$ improvement occurred at three hours and was 13.6% over the pretreatment baseline in the formoterol group. In the salbutamol group, the largest maximum mean $FEV_{1.0}$ increase was one hour post-treatment and was 12.6%. Both formoterol and salbutamol provided better protection against EIB than placebo, as manifest by $FEV_{1.0}$ declines following six-minute exercise challenge tests (ECT) both three and twelve hours after treatment. The protection from EIB afforded by salbutamol twelve hours after treatment was somewhat surprising.

OBJECTIVES

Compare the magnitude and duration of protection against EIB of single doses of inhaled formoterol 12 µg, salbutamol 400 µg and placebo dry powder capsules in 8-15 year old children with reversible obstructive airways disease and EIB [321:1, 11].

PROTOCOL

This was a double-dummy, 4-period, 3-way crossover design with one screening day followed by three treatment day, the latter of which were separated by 2-8 days. At the screening visit, an examination, vital signs, pulmonary function testing and a six-minute ECT were performed. On the three treatment visit days, vital signs and a spirogram were performed at arrival to the clinic, a treatment was administered. Vital signs and pulmonary functions were both frequently monitored and ECT's were performed at 3 and 12 hours after treatment [321:11, 15-6, 18].

TREATMENT

The dry powder formoterol formulation contained 12 µg/cap, was designated CGP 25 827 A, from batch #905/10 and formula Q835. This, the salbutamol single dose dry powder capsules and the placeboes, matching formoterol and salbutamol dry powder capsules, were manufactured by Ciba-Geigy Limited Pharmaceuticals, Horsham, UK [281-7, 7:202].

PATIENTS

Patients were to be from 10-14 years of age and have a baseline $FEV_{1.0} \geq 70\%$ predicted. In addition, they should have had a 15% reduction in $FEV_{1.0}$ 10-15 minutes after a treadmill exercise challenge and, separately, should have shown $FEV_{1.0}$ reversibility of 15% over baseline 15 minutes after inhalation of salbutamol 400 µg dry powder. The baseline $FEV_{1.0}$ values on the crossover treatment examination days should should have been within $\pm$ 15% from the baseline measured at visit 1 before the exercise test. Patients should have been clinically stable for one month before beginning the trial with a stable medication regimen. Oral and inhaled steroids or sodium cromoglycate were permitted if the dose was stable for the month prior to entry. Sixteen patients entered the trial. Their actual ages ranged from 10 to 14 years, inclusive, 13 were male and 10 were using inhaled corticosteroids. All 16 screened patients were randomized, completed the trial and were evaluated for both efficacy and for safety [321:14-5, 22-3, 27-8].

PARAMETERS

The seated $FEV_{1.0}$ was measured before treatment and at 60, 120, 180, 187, 189, 191, 196, 201, 240, 360, 480, 600, 720, 727, 729, 731, 736 and 741 minutes after treatment. This was at 1, 2, 3, 4, 6, 8, 10 and 12 hours after treatment with more frequent sampling (underlined minutes) done after the ECT's, 3 and 12 hours after treatment. The $FEV_{1.0}$ and peak flow (PEFR)at all measured times were evaluated for efficacy. A four-point score (1-4) was completed by both patient and investigator at the end of each treatment day to evaluate 'effectiveness of treatment' from 'poor' to 'very good.' Safety monitoring of vital signs (pulse rate, blood pressure) and adverse events were also recorded [321:18, 20].

EFFICACY

Patients requiring rescue medication during the scheduled visits had the last available post-treatment pulmonary function measure carried forward for the rest of the observation period. This avoided inflating the values because of the recent bronchodilator intervention but did allow for some inflation by using earlier time points following treatment to represent later ones. Missing values were handled by interpolation unless rescue medication had been taken [321:25, 30].

The 6-minute ECT was carried out 3 hours post-treatment and results are shown in the table below.

PROTOCOL DP/PD3 – FIRST (3-HOUR POST-TREATMENT) EXERCISE TEST MEAN FEV1.0 (S.D.) VALUES ADJUSTED FOR RESCUE MEDICATION AND MISSING VALUES [321:142]			
Post-Exercise Time	**Formoterol 12**	**Salbutamol 400**	**Placebo**
3 Hours Post-treatment (Baseline)	2.68 (0.52)	2.58 (0.59)	2.35 (0.64)
1 Minute	2.30 (0.84)	2.10 (0.75)	1.57 (0.68)
3 Minutes	2.30 (0.83)	2.06 (0.75)	1.47 (0.66)
5 Minutes	2.30 (0.76)	2.04 (0.75)	1.46 (0.66)
10 Minutes	2.30 (0.76)	2.10 (0.70)	1.57 (0.70)
15 Minutes	2.33 (0.71)	2.16 (0.77)	1.62 (0.72)
4 Hours Post-Treatment	2.35 (0.54)	2.31 (0.70)	1.87 (0.89)

The greatest post-ECT drop in mean $FEV_{1.0}$ was seen with placebo (37.9%), the second greatest fall was noted in the salbutamol group (20.9%) and the least, in the formoterol group (14.2%). The decline in $FEV_{1.0}$ was relatively constant over the 15-minute period following the ECT and salbutamol and placebo showed some recovery by about 1-hour after the ECT [321:142]. The $FEV_{1.0}$ was also evaluated after the first exercise challenge, 3 hours post-treatment, by capturing the lowest $FEV_{1.0}$'s following the ECT, taking the mean for each group and forming a ratio of these values for each two-group comparison [321:31].

PROTOCOL DP/PD3 – SUMMARY OF LOWEST FEV1.0 RATIOS AFTER THE FIRST (3-HOUR POST-TREATMENT) EXERCISE TEST [321:32]			
Comparison	**Ratio**	**95% C.I.**	**Type I Error**
Formoterol/Placebo	1.66	1.45 - 1.92	0.0001
Formoterol/Salbutamol	1.15	1.00 - 1.32	0.0551
Salbutamol/Placebo	1.44	1.26 - 1.67	0.0001

Formoterol prevented much of the $FEV_{1.0}$ decline following exercise that was experienced by patients treated with placebo. The salbutamol/placebo ratio was also significant, indicating the protective effect of salbutamol on the smallest $FEV_{1.0}$ after the 3-hour ECT. By this measure and at this post-treatment time interval, formoterol was not different from salbutamol.

The 6-minute ECT was carried out a second time 12 hours post-treatment and results are shown below.

PROTOCOL DP/PD3 – SECOND (12-HOUR POST-TREATMENT) EXERCISE TEST MEAN FEV1.0 (S.D.) VALUES ADJUSTED FOR RESCUE MEDICATION AND MISSING VALUES [321:143]			
Post-Exercise Time	**Formoterol 12**	**Salbutamol 400**	**Placebo**
12 Hours Post-treatment (Baseline)	2.48 (0.55)	2.28 (0.68)	1.90 (0.89)
1 Minute	2.15 (0.76)	1.77 (0.62)	1.43 (0.67
3 Minutes	2.18 (0.73)	1.68 (0.60)	1.40 (0.63)

PROTOCOL DP/PD3 – SECOND (12-HOUR POST-TREATMENT) EXERCISE TEST MEAN FEV1.0 (S.D.) VALUES ADJUSTED FOR RESCUE MEDICATION AND MISSING VALUES [321:143]			
Post-Exercise Time	Formoterol 12	Salbutamol 400	Placebo
5 Minutes	2.16 (0.72)	1.72 (0.61)	1.47 (0.65)
10 Minutes	2.19 (0.70)	1.82 (0.67)	1.53 (0.68)
15 Minutes	2.25 (0.69)	1.91 (0.67)	1.62 (0.75)

These results were similar to those seen in the earlier ECT showing the effect of exercise in decreasing the mean $FEV_{1.0}$ in all three treatment groups. The effect was least in the formoterol group (13.3% maximum mean $FEV_{1.0}$ decrease) and equally pronounced in the salbutamol (26.3%) and placebo groups (26.3%). Evaluation of this test by lowest post-exercise $FEV_{1.0}$'s for the second ECT at 12 hours post-treatment is found in the next table.

PROTOCOL DP/PD3 – SUMMARY OF LOWEST FEV1.0 RATIOS AFTER THE SECOND (12-HOUR POST-TREATMENT) EXERCISE TEST [321:31]			
Comparison	Ratio	95% C.I.	Type I Error
Formoterol/Placebo	1.61	1.39 - 1.86	0.0001
Formoterol/Salbutamol	1.31	1.13 - 1.51	0.0011
Salbutamol/Placebo	1.23	1.06 - 1.42	0.0089

The inferential analyses indicated that each pair-wise comparison was statistically significant. The formoterol/placebo ratio was similar to that seen at the 3-hour ECT, but the salbutamol/placebo ratio was smaller, consistent with more of a diminishing effect of salbutamol at this later time since treatment.

The regular post-treatment $FEV_{1.0}$'s, exclusive of those performed following the two exercise challenges, are presented below [321:142-3].

PROTOCOL DP/PD3 – FEV1.0 VALUES ADJUSTED FOR RESCUE MEDICATION AND MISSING VALUES [321:142-3]			
Post-Treatment Time	Formoterol 12	Salbutamol 400	Placebo
Baseline	2.36 (0.51)	2.38 (0.62)	2.32 (0.54)
1 Hour	2.63 (0.59)	2.68 (0.61)	2.37 (0.60)
2 Hours	2.66 (0.54)	2.63 (0.61)	2.35 (0.60)
3 Hours	2.68 (0.52)	2.58 (0.59)	2.35 (0.64)
FIRST EXERCISE CHALLENGE TEST PERFORMED			
4 Hours	2.35 (0.54)	2.31 (0.70)	1.87 (0.89)
6 Hours	2.58 (0.57)	2.38 (0.71)	1.94 (0.91)
8 Hours	2.53 (0.58)	2.33 (0.71)	1.91 (0.88)
10 Hours	2.48 (0.59)	2.35 (0.70)	1.85 (0.88)
12 Hours	2.48 (0.55)	2.28 (0.68)	1.90 (0.89)

PROTOCOL DP/PD3 – FEV1.0 VALUES ADJUSTED FOR RESCUE MEDICATION AND MISSING VALUES [321:142-3]			
Post-Treatment Time	Formoterol 12	Salbutamol 400	Placebo
SECOND EXERCISE CHALLENGE TEST PERFORMED			

In all three groups, the mean $FEV_{1.0}$ declined to below baseline values at 4 hours post-treatment, probably reflecting the ECT done about one hour earlier. It then increased most in the formoterol group at the 6th post-treatment hour only to again decline slowly throughout the 12-hour follow-up period, always remaining greater than baseline. This was probably indicative of a greater continuing drug effect in the formoterol group and was not seen as dramatically with either salbutamol or placebo. The largest improvement in mean $FEV_{1.0}$ was seen at 3 hours in the formoterol group and was 13.6% over baseline. The largest improvement in the same measure in the salbutamol group was at 1 hour and was 12.6%.

On a four-point scale of effectiveness with the categories 'poor,' 'fair,' 'good' and 'very good,' 75% of patients rated formoterol in one of the top two categories, compared with 50% for salbutamol and 26% for placebo. Comparable ratings made by investigators were 88% rated either 'good' or 'very good' in the formoterol group, 76% in the salbutamol group and 19% in the placebo group [321:152].

SAFETY

All 16 patients constituted the safety data set. There were no deaths or serious adverse events. There were only two AE's, headache and coughing. Both were rated as 'moderate' in intensity and resolved spontaneously [321:35-6, 119]. There were no large differences in pulse rate between treatment groups during the non-exercise post-treatment periods. In fact the ratio of pulse rate for both active drugs to placebo was < 1.0 suggesting a higher mean pulse rate in the placebo group at each time point [321:57, 59].

045 A SINGLE DOSE, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, 4-WAY CROSSOVER TRIAL COMPARING 12 µG AND 24 µG OF FORMOTEROL DRY POWDER CAPSULES, 180 µG ALBUTEROL METERED DOSE INHALER (MDI) VERSUS PLACEBO IN THE PREVENTION OF EXERCISE-INDUCED BRONCHO-CONSTRICTION (EIB) IN PATIENTS AGE 12-50 YEARS

SUMMARY

Both formoterol single doses were statistically superior to placebo at the four-hour post-treatment exercise challenge time point that was the primary efficacy variable. Superiority over placebo was apparent at all time points, from 15 minutes to 12 hours post-treatment. The larger formoterol dose produced somewhat greater protection against EIB than the smaller, from 4- through 12-hour post-treatment exercise challenge tests (ECT's), but not at the 15-minute ECT.

OBJECTIVES

Comparison of the protective effect of a single dose of 12 or 24 µg formoterol dry powder capsules with a single dose of 180 µg albuterol MDI and placebo in adolescent and adult patients with EIB and determination of onset and duration of this protection [317:1, 9].

PROTOCOL

This was a two-phase process where Phase I was between visits 1 and 2 and was for patient screening of enrollment eligibility; e.g., response to exercise challenge. Phase II was the double-blind treatment between visits 2 and 5, four visit days for each patient separated by a five-day washout intervals. The treatment sequences was according to the following crossover design [317:10].

PROTOCOL #45 – CROSSOVER SINGLE-DOSE TREATMENT ASSIGNMENT [317:10]				
Treatment Sequence	Visit			
	2	3	4	5
1	Formoterol 12	Formoterol 24	Albuterol MDI	Placebo
2	Formoterol 24	Placebo	Formoterol 12	Albuterol MDI
3	Albuterol MDI	Formoterol 12	Placebo	Formoterol 24
4	Placebo	Albuterol MDI	Formoterol 24	Formoterol 12

After obtaining pre-exercise baseline PFT measurements and vital signs, the 6-minute steady-state ECT was performed on a treadmill. The intensity goal was achieving a target heart rate of 90% of 210 beats/minute minus the patient's age during the second half of the test. During visit 1 (screening), if the baseline $FEV_{1.0}$ was > 70% of predicted, an ECT was performed. If the patient demonstrated ≥ 20% decrease of $FEV_{1.0}$ within 30 minutes, a second ECT was conducted four hours after the first [317:23-4].

The procedure at visits 2-5 depended upon the patient's baseline $FEV_{1.0}$ at that visit being 80-120% of the visit 1 baseline value. If so, a 6-minute steady-state ECT was performed. Spirometry was performed 2, 5, 10, 15, 20, 30, 45 and 60 minutes after the end of each ECT. Post-exercise vital signs were recorded periodically. The ECT was conducted 15 minutes, 4, 8 and 12 hours after administration of the trial medication [317:24].

TREATMENT

Two capsules were included in each of three types of blister pack: 1)two placebo capsules; 2)one placebo and one containing 12 µg of formoterol; and, 3)two capsules each containing 12 µg of formoterol. Each unit dose blister pack was given different batch and formulation numbers according to the table that follows:

PROTOCOL #45 – TREATMENT MATERIALS [317:64]			
Unit Drug	Dose	Batch Number	Formulation Number
12 µg formoterol blister	formoterol 12 µg card	E-15722	H-3949
24 µg formoterol blister	formoterol 24 µg card	E-15721	H-3948
Placebo blister	placebo card	E-15723	H-3950

Ninety µg Ventolin single-dose MDI treatments, rescue MDI's and matching placeboes were also used during the course of this study [317:54].

Several concomitant medications were allowed during the course of this trial. Inhaled and/or nasal corticosteroids in recommended and constant dose and dose regimens were allowed if treatment had been stabilized for ≥ 1 month before visit 2. Desensitization therapy was permitted if treatment had been stable for 3 months before visit 2. Intermittent, on-demand (PRN) use of short-acting inhaled MDI beta-2 agonists was allowed. Patients requiring rescue during visit days received albuterol MDI treatments [317:18-9].

PATIENTS

Subjects were male and female EIB patients 13 through 36 years of age with an $FEV_{1.0} \geq 70\%$ of predicted at screening (visit 1) who had treatment visit baseline $FEV_{1.0} \pm 20\%$ of the visit 1 value. Seventy-eight percent of the patients were male, 89% were white and 28% took inhaled or nasal corticosteroids sometime during the double-blind period [317:34-5]. Among the usual exclusion criteria were the following, exclusionary timing is relative to visit 2:

beta agonists within 2 weeks
parenteral or oral corticosteroids within 1 month
change in dose of inhaled or nasal corticosteroids within 1 month, or whose dose exceeded the maximum recommended
theophylline within 1 month
cromones within 1 month

desensitization therapy initiated within 3 months
short-acting antihistamines within 4 days
astemizole within 3 months

Sixteen patients were required for this trial. A completed patient was one who successfully completed all five visits. Patients who took two different types of study drug and performed at least one post-dose exercise challenge test at the same scheduled ECT and did not take any unacceptable concomitant medications or therapies were included in the efficacy analysis [317:12-5, 26-7]. Twenty-six patients were enrolled into the trial. Among them, 18 were randomized and 17 completed all four treatment sequences. Therefore 17 randomized patients were analyzed for efficacy and 18 for safety [317:31, 34].

PARAMETERS

The primary efficacy variable was the maximum percentage fall in $FEV_{1.0}$ from the pre-exercise value after each ECT. The criteria for efficacy was a statistically significant difference between formoterol and placebo at the 4-hour time point. Secondary efficacy variables were: 1)the maximum percentage fall in PEFR from the pre-exercise value after each ECT; 2)the maximum percentage fall in $FEV_{1.0}$ from the pre-treatment value after each ECT; and, 3)numbers of patients with < 20% decrease in $FEV_{1.0}$ from pre-exercise after each ECT [317:27].

Safety variables include sequential vital signs at each visit, fasting hematology, chemistry and urine laboratory tests, 12-lead electrocardiograms before and 2 hours after dosing at each visit. Screening physical examinations and chest radiographs were also performed [317:21-2].

EFFICACY

The maximum percentage fall in the $FEV_{1.0}$ from the pre-exercise level was assessed for each of the exercise challenge tests at 15 minutes, 4 hours, 8 hours and 12 hours post-dose. Values taken within 6 hours after rescue medication use were considered to be missing values. The sponsor provided a primary analysis wherein values within 6 hours after rescue medication use were carried over from the previous ECT time point, but this was considered to be less informative than the data presentation below [317:35-9, 105-12].

PROTOCOL #45 – MAXIMUM PERCENT FALL IN $FEV_{1.0}$ FROM PRE-EXERCISE VALUES (ALL RANDOMIZED PATIENTS WHO COMPLETED > 1TREATMENT PERIODS; VALUES WITHIN 6 HOURS OF RESCUE MEDICATION USE WERE CONSIDERED TO BE MISSING) [317:105-12, 38]

Maximum % Fall in FEV1.0		Formoterol 12	Formoterol 24	Albuterol 180	Placebo
15 min ECT	N	17	16	17	17
	Mean	5.9*	6.2*	8.6*	37.1
	S.D.	8.7	8.6	10.1	16.4

PROTOCOL #45 – MAXIMUM PERCENT FALL IN $FEV_{1.0}$ FROM PRE-EXERCISE VALUES (ALL RANDOMIZED PATIENTS WHO COMPLETED > 1TREATMENT PERIODS; VALUES WITHIN 6 HOURS OF RESCUE MEDICATION USE WERE CONSIDERED TO BE MISSING) [317:105-12, 38]

Maximum % Fall in FEV1.0		Formoterol 12	Formoterol 24	Albuterol 180	Placebo
	N	17	17	15	7
4 hour ECT	Mean	9.2*†	8.0*†	23.2	30.6
	S.D.	15.5	9.7	13.0	16.2
	N	17	17	14	12
8 hour ECT	Mean	14.9*†	11.1*†	29.5	25.0
	S.D.	17.7	12.6	13.0	19.8
	N	15	15	11	11
12 hour ECT	Mean	13.9*†	11.5*†	23.2	19.6
	S.D.	9.8	10.4	11.9	9.1

* statistically significantly different from placebo

† statistically significantly different from albuterol

shading = mean values for timed ECT by treatment group

reverse shading = patient counts showing missing values

Comparisons between the two doses of formoterol with placebo or albuterol were corrected only for two comparisons at the particular post-treatment ECT test to maintain a Type I Error ≤ 0.05. Comparisons of albuterol versus placebo were unadjusted as were Type I Errors for comparisons of all post-treatment ECT tests, combined [317:36-7].

Missing values were more prevalent in placebo and albuterol groups at, or after, the 4-hour post-treatment ECT and were seen in all groups at the 12-hour post-treatment ECT. This probably signaled flagging efficacy represented by reduced patient numbers because of dropouts or recent rescue medication use. Albuterol only achieved statistical significance from placebo at the 15 minute post-treatment ECT. Both formoterol doses were statistically different from placebo from 15 minutes to 12 hours after treatment and were significantly different from albuterol from 4 through 12 hours post-treatment. The two formoterol doses were not statistically separable. The larger formoterol dose was associated with a slightly smaller maximum mean $FEV_{1.0}$ decline after exercise than the smaller dose, at all ECT's > 15 minutes post-treatment.

A secondary efficacy variable, the number and percent of patients showing < 20% decrease in $FEV_{1.0}$, was only presented with missing values brought forward from the last ECT. This was not considered to be a helpful analysis because it inflated this estimate of efficacy by substituting observations from the previous ECT time point for drop-outs and recent medication users [317:117].

SAFETY

There were no deaths or serious adverse events. One patient discontinued prematurely from the study because of an adverse event, a severe upper respiratory

infection that developed 6 days after visit 2 and spontaneously resolved after another 6 days [317:45].

046 A SINGLE DOSE, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, 4-WAY CROSSOVER TRIAL COMPARING 12 µG AND 24 µG OF FORMOTEROL DRY POWDER CAPSULES, 180 µG OF ALBUTEROL METERED-DOSE INHALER (MDI) VERSUS PLACEBO IN THE PREVENTION OF EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB) IN PATIENTS AGE 12-50 YEARS

SUMMARY

Both formoterol single doses were statistically superior to placebo at the four-hour post-treatment exercise challenge time point that was the primary efficacy variable. Superiority over placebo was apparent at all time points, from 15 minutes to 12 hours post-treatment. The smaller formoterol dose produced somewhat greater protection than the larger, at all time points.

OBJECTIVES

The objectives are the same as in study #45 [319:1, 9].

PROTOCOL

This protocol is identical to study #45 [319:10, 23-4].

TREATMENT

Treatment doses, formulation numbers, batch numbers and allowable concomitant medications were identical to those found in protocol #45 [319:18-9, 54].

PATIENTS

Subjects ranged in age from 13 through 41 years; 90% were Caucasian and 45% were male. Thirty-five patients were screened (enrolled), 20 underwent randomization and 17 completed all four treatment periods. Nineteen met the criteria for the efficacy analysis and all 20 randomized patients were included in the safety analysis. Forty-five percent of those randomized used nasal or inhaled corticosteroids during the trial. All patient inclusion and exclusion criteria were the same as in study #45 [319:12-5, 26-7, 31, 34-5].

PARAMETERS

Primary and secondary efficacy variables and all safety variables were identical to those specified in study #45 [319:21-2, 27]

EFFICACY

Each formoterol dose produced statistical significance from placebo at all post-treatment ECT's, and significance from placebo at post-treatment ECT's from 4 through 12 hours. The same statistical correction for multiple comparisons was made only within each ECT and only for the two formoterol doses, as was done in study #45. Missing values were most common in the placebo group and represented dropouts or recent rescue medication use. The two formoterol doses were not statistically different at any post-

treatment time point and, by inspection, the smaller dose resulted in less of a maximum mean fall in $FEV_{1.0}$ [319:36-8].

PROTOCOL #46 – MAXIMUM PERCENT FALL IN $FEV_{1.0}$ FROM PRE-EXERCISE VALUES (ALL RANDOMIZED WHO COMPLETED > 1 TREATMENT PERIODS; VALUES WITHIN 6 HOURS OF RESCUE MEDICATION USE WERE CONSIDERED TO BE MISSING) [319:38, 106-13]

Maximum % Fall in FEV1.0		Formoterol 12	Formoterol 24	Albuterol 180	Placebo
15 min ECT	N	19	17	19	17
	Mean	4.0*	6.0*	10.0*	31.1
	S.D.	8.8	12.1	18.6	18.7
4 hour ECT	N	19	17	18	16
	Mean	9.5*†	8.9*†	23.1	30.4
	S.D.	12.4	14.5	14.8	14.3
8 hour ECT	N	19	17	17	16
	Mean	11.3*†	13.5*†	29.3	30.7
	S.D.	11.5	17.7	10.7	14.5
12 hour ECT	N	19	17	16	16
	Mean	12.4*†	17.5*†	31.9	30.1
	S.D.	14.6	17.5	15.1	15.4

* statistically significantly different from placebo

† statistically significantly different from albuterol

shading = mean values for timed ECT by treatment group

reverse shading = patient counts showing missing values

A secondary efficacy variable, the number and percent of patients showing < 20% decrease in $FEV_{1.0}$, was only presented with missing values brought forward from the last ECT which inflated this estimate of efficacy by substituting observations from the previous ECT time point for drop-outs and recent medication users [319:116].

SAFETY

There were no deaths or serious adverse events. One patient discontinued from the study early because of pneumonia complicated by an asthma exacerbation that occurred two days after the third visit and resolved after nine days [319:44].

FO/UK2 THE EFFECT OF CONTINUOUS THERAPY WITH INHALED FORMOTEROL ON AIRWAY AND SYSTEMIC β2-RECEPTOR RESPONSIVENESS IN PATIENTS WITH ASTHMA: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED WITHIN-PATIENT CLINICAL TRIAL

SUMMARY

Sixteen adult patients with mild-to-moderate asthma were withdrawn from beta-2 agonists then entered into a two-period orthogonal crossover trial. Each period lasted 4-6 weeks and regular treatment was with formoterol 24 µg twice daily or a matching placebo. The anticholinergic inhaled drug, Atrovent, was supplied for rescue. At the end of each different treatment, a cumulative dose-response curve in response to formoterol was performed with spirographic endpoints. The baseline $FEV_{1.0}$ was higher, the change to maximum $FEV_{1.0}$ lower and the fall from maximum to the end of the dose-response test was greater after formoterol treatment than after placebo. Lymphocyte beta-receptor density and affinity and cAMP accumulation were less after formoterol treatment than after placebo. All of these findings suggest that some degree of tachyphylaxis to formoterol had occurred, but its clinical relevance is unknown.

OBJECTIVES

To assess whether continuous treatment with inhaled formoterol 24 µg twice daily, compared with placebo, is associated with a decrease of airway and/or systemic β2-receptor responsiveness (tachyphylaxis) in adult patients with asthma [88:1, 14].

PROTOCOL

An initial run-in period of 2-4 weeks was used to withdraw then current beta-2 agonist medication and allow down-regulation of beta-2 receptors to be abolished. Concurrent anti-inflammatory medication was continued unchanged through this period and the remainder of the study. Throughout the study, rescue bronchodilation was available through the use of an ipratropium inhaler. At the end of the run-in, suitable patients were randomized to receive 4-6 weeks of treatment with either formoterol or placebo. At the end of the first treatment period, the first dose-response curve was performed. The patient then received the alternate medication for another 4-6 weeks followed by another dose-response curve. The patient was to refrain from rescue medication use for 12 hours and theophylline use for 24 hours before a treatment visit and was not to have taken the inhaled morning treatment drug. The dose-response curve was constructed by giving formoterol 6, 24, 24 and 48 µg (cumulative dose 102 µg) at 45-55 minute intervals. Spirographic measurements were made at 30 minutes before the first dose, 30 minutes after each subsequent dose and 1, 2, 4 and 6 hours after the last dose [88:14, 18-9].

TREATMENT

Formoterol 12 µg dry powder capsules were used for the blinded treatment at a dose of 24 µg b.i.d. and these came from batches #905/12 and #905/13. The dose-

response curve used a 6 µg/capsule formulation from batch #913/8 and 24 µg/capsule formulation from batch #904/8. A placebo to match the 12 µg capsules was also supplied and all were manufactured by Ciba Pharmaceuticals at Horsham, UK. A commercial Atrovent inhaler, made by Boehringer Ingelheim, was the rescue medication [88:1, 10].

PATIENTS

Adult outpatients ages 18-60 year of either gender and any race with the diagnosis of asthma were eligible. The screening $FEV_{1.0}$ should have been 40-80% of predicted and the patient had to have shown $FEV_{1.0}$ reversibility of 15% or 200 mL from a pretreatment value after inhalation of a beta-2 agonist. Recent smoking, exacerbations and respiratory infections were exclusionary. Oral corticosteroids and oral beta-2 agonists during the month before the screening visit were also exclusionary. A single, short course (< 7 days) of oral corticosteroid treatment and antibiotics was permitted in case of a respiratory tract infection during the trial, but the patient must have restarted the trial from the beginning of the same treatment phase. Prophylactic therapy with inhaled/nasal steroids, inhaled nedocromil, inhaled/nasal cromoglycate, theophylline or antihistamine was allowed if the dose was kept constant during the study [88:15. 18].

Eighteen patients were recruited into the study. Two patients discontinued the trial prematurely, one because of an adverse event and a second was lost to follow up. Therefore, 16 patients were included in the comparative dose-response analysis for efficacy. All 18 were included in the analysis of adverse events [88:28-9]. The age range of randomized patients was 18-53 years and 12 (67%) were male. Sixteen patients had never smoked and two were previous smokers. Twelve patients used inhaled corticosteroids at the start of the study and continued their use throughout the trial. One patient received a short course of oral corticosteroids for a chest infection during the run-in phase [88:31-2, 57].

PARAMETERS

The primary efficacy outcome was the absolute maximum value of the $FEV_{1.0}$ during the dose-response test. Secondary variables were various manipulations of the $FEV_{1.0}$ and FEF_{25-75} derived from the dose-response test, rescue medicine use and mean morning/evening PEFR's during the last week of treatment. Diary cards were used for the daily recording of rescue medication puffs used, scheduled medication dosing and twice daily, best of three PEFR's. Safety measures included serum potassium, ECG and QTc, finger tremor, pulse, and blood pressure. Routine adverse events were recalled only at trial visits. Lymphocyte beta-2 receptor density and affinity were assessed by in vitro binding studies. Lymphocyte cAMP accumulation after in vitro stimulation was also measured [88:18, 21, 23-4]. Efficacy analyses were based on a modified intent-to-treat paradigm. Only patients with the appropriate variables recorded for both phases were analyzed, but no patients were dropped because of protocol violations [88:26-7].

EFFICACY

The nine-hour dose-response comparison between placebo and formoterol-treated patients who completed the study was presented only as a figure. See Figure 9 at the end of this revieew. It showed a very slightly higher mean baseline $FEV_{1.0}$ in the formoterol group with a smaller maximum mean increase and more rapid decline during the dose-response curve [88:103]. The primary efficacy variable, the absolute mean maximum $FEV_{1.0}$ during the dose-response curve for patients who completed the study, is shown below. The formoterol group findings are shaded to facilitate comparisons.

PROTOCOL FO/UK2 – ABSOLUTE MAXIMUM FEV1.0 DURING THE DOSE-RESPONSE CURVE FOR PATIENTS WHO COMPLETED THE STUDY [88:60]

Sequence	Treatment	N	Mean (S.D.)
Formoterol then Placebo	Formoterol	9	3.318 (0.72)
	Placebo	9	3.457 (0.60)
Placebo then Formoterol	Placebo	7	3.326 (1.16)
	Formoterol	7	3.248 (1.18)
Without Regard To Order	Formoterol	16	3.286 (0.91)
	Placebo	16	3.399 (0.86)

By this measure, the placebo group had the higher value in both sequences and overall, without regard to order. The inferential analysis of this relied on finding no statistical significance, which reflected only an under powered trial but which was the observed outcome [88:32-3, 60]. The interpretation of both the figure and the table are that there was a smaller $FEV_{1.0}$ increase after a beta-2 agonist challenge in patients who had received prior chronic treatment with a beta-2 agonist than patients who had received an equal duration of treatment with an anticholinergic bronchodilator.

Secondary $FEV_{1.0}$ endpoints were supportive of this interpretation and added more information. The $FEV_{1.0}$ at the start of the dose-response curve was slightly higher after chronic formoterol treatment. The change in $FEV_{1.0}$ from the start to the maximum value during the dose-response test was less after formoterol than after placebo treatment. The decline in $FEV_{1.0}$ from the maximum value to the end of the dose-response test was greater after formoterol treatment than after placebo [88:33]. These all indicated a lesser magnitude and shorter duration of response to beta-agonist after chronic formoterol treatment, perhaps indicating beta-receptor down-regulation. These findings seem to fulfill the definition of tachyphylaxis, the clinical relevance of which is not known.

The beta-2 receptor density was only available for 7 of the 16 patients who completed the trial. It showed statistically significantly lower beta-2 receptor density after formoterol treatment than after placebo. Beta-2 receptor affinity was also only available for 7 of the 16 patients and it too showed significantly less affinity after formoterol treatment. Maximum cAMP response to adrenergic stimulation was recorded for all 16 patients and was less after formoterol treatment than after placebo [88:39].

SAFETY

There were no deaths and one serious adverse event during this study. One patient suffered appendicitis during the second double-blind treatment period (formoterol) 29 days after beginning that period, was hospitalized and had to be withdrawn [88:38].

Analysis of serum potassium during the dose-response curves provided an unexpected result. The potassium rose during the first two hours after the test began, in both groups, to decline late in both, with the largest decline in the placebo group [88:120]. The mean increase in systolic blood pressure and mean decrease in diastolic blood pressure was less in after formoterol than after placebo treatment. Also, the mean increase in heart rate from pretreatment to maximum was less after formoterol than after placebo treatment. From the ECG, the reduction in T-wave amplitude and increase in QTc from pretreatment to min. and max. values respectively, was less after formoterol than after placebo treatment. Surprisingly, the change in finger tremor from pretreatment to maximum was also less after formoterol than placebo treatment [88:36-7].