VI.D.2. EXCLUSION CRITERIA

1. significant medical condition or laboratory profile that might compromise patient safety, compliance, interfere with evaluation or preclude completion
2. history of malignancy or treatment for malignancy within 5 years
3. reactions to test medication or components
4. QTc ≥ 0.46 seconds
5. respiratory tract infection, excluding sinusitis, within one month of visit 1
6. hospitalization or ER visit for acute asthma exacerbation within one month of visit 1
7. potentially unreliable patients or patients with a history of noncompliance to medical therapy
8. treatment with investigational drugs within one month
9. parenteral or oral steroids within one month of visit 1 or required these medications during the placebo run-in period
10. any change in dose, schedule, formulation or product of inhaled or nasal steroids within one month of visit 1 or taking a dose that exceeds that recommended in the package insert
11. short-acting beta-2 agonists within 6 hours of reversibility testing at visit 1
12. long-acting beta-2 agonists within 48 hours of visit 1
13. theophylline within 24 hours of visit 1
14. anti-histamines within 96 hours or astemizole within three months of visit 1
15. parenteral, oral or nebulized beta-2 agonists within one month of visit 1
16. oral or inhaled anti-cholinergics within 48 hours of visit 1
17. any change in dose, schedule, formulation or product of disodium cromoglycate, cromolyn sodium, nedocromil, ketotifen, or theophylline within one month of visit 1
18. desensitization therapy within three months of visit 1
19. treatment with non-potassium sparing diuretics, beta-blocking drugs, quinidine, quinidine-like anti-arrhythmics, tricyclic anti-depressants, fluoxetine or MAO inhibitors
20. vaccination with live-attenuated virus within one month of visit 1; oral polio vaccine (Sabin) was allowed

VI.E. TREATMENT

Capsules containing formoterol 12 mcg (formulation #835; batches 905/17, 905/18 and E18/96) or placebo (formulation #846; batches 906/13, 906/14 and E19/96) were stored in blister packs and patients inhaled two capsules twice daily according to the following scheme.

NDA #20-831 TRIAL #049 - BLISTER PACK DOSING COMPONENTS [13:22]		
Twice Daily Dose	Components Of Twice Daily Dose	
	Capsule 1	Capsule 2
24 mcg	12 mcg	12 mcg

NDA #20-831 TRIAL #049 - BLISTER PACK DOSING COMPONENTS [13:22]		
Twice Daily Dose	Components Of Twice Daily Dose	
	Capsule 1	Capsule 2
12 mcg	12 mcg	placebo
placebo	placebo	placebo

Trial treatment was administered 6:00-9:00 am (morning dose) and 6:00-9:00 pm (evening dose). Trial procedures at visits 2, 5 and 14 were scheduled to begin between 6:00-9:00 am and the morning dose of medication was withheld until all baseline studies had been done. If rescue salbutamol was taken within 6 hours before baseline spirometry at visits 1, 2, 5 or 14, the visit was rescheduled [13:21-2].

VI.E.1. CONCOMITANT MEDICATIONS

Patients had to have been treated concomitantly with one or more of the following medications to be eligible for study entry: disodium cromoglycate, cromolyn sodium, nedocromil, and/or inhaled corticosteroids. Patients were also allowed to receive nasal corticosteroids and theophylline. Patients receiving these medications had to have been taking the same product at the same dose for at least one month prior to visit 1 and throughout the trial, except for changes allowed to treat exacerbations. Maximum permitted doses were those indicated in the package insert. Patients on theophylline had to stop taking it 24 hours before visits 2, 5 and 14 (months 0, 3 and 12). Patients were allowed to take short-acting antihistamines such as hydroxyzine, loratadine or terfenadine during the trial but had to discontinue them four days (96 hours) before visits 1, 2, 5 and 14 (week -2, months 0, 3 and 12) or the visit had to be rescheduled. Patients receiving desensitization 3 months before the start of the trial could maintain this therapy unchanged throughout the trial, but could not initiate it [13:24-5].

VI.E.2. RESCUE MEDICATION

The rescue medication, salbutamol, was locally purchased, but the formulation (pMDI or powder and manufacturer) was consistent for each patient throughout the trial. Salbutamol had to have been discontinued 6 hours prior to study visits 1, 2, 5 and 14 (week -2, months 0, 3 and 12), or the visit had to be rescheduled. The number of doses was recorded in the patient diary and over each 24-hour period could not exceed 4 doses (800 mcg) for more than 3 consecutive days. Patients who were symptomatic despite maximal rescue were to contact the clinical investigator and, in most cases, then underwent pre-specified asthma exacerbation therapy [13:25].

VI.E.3. EXACERBATION THERAPY

Patients requiring institution of any concomitant regular asthma therapy were discontinued from the trial except in the case of asthma exacerbations. These were treated with oral or parenteral corticosteroids and/or beta-2 agonist nebulization, but the course could not exceed ten days. A course lasting more than ten days, more than six

ten-day courses over the 12-month trial, a second course within two weeks of a preceding course or a dose of corticosteroid greater than the equivalent of 20 mg of prednisone, or 1 mg/kg/day, was considered as a treatment failure and the patient was discontinued [13:24-6].

VI.F. PARAMETERS

VI.F.1. EFFICACY

The primary efficacy variable was the $FEV_{1.0}$ AUC at the 3rd double-blind month (visit 5) after a six-hour wash-out of salbutamol rescue medication. Missing values in the 12 hours of serial spirograms were estimated by linear interpolation. If rescue medication was used during these 12 hours, all further testing was stopped for that visit. To incorporate truncated tests supplied by patients requiring rescue medication, the $FEV_{1.0}$ AUC was "standardized" by the number of hours over which it was recorded. The $FEV_{1.0}$ AUC is usually presented in units of Liter-hours. In the current study, Liter-hours was divided by the number of hours before study termination, thus converting the units to Liters and producing $FEV_{1.0}$ AUC's of approximately the same magnitude as the individually measured $FEV_{1.0}$'s [3/16/2000 Teleconference]. This introduced a source of bias. The earliest and most favorable part of the descending $FEV_{1.0}$ time-curve represented the entire curve in patients who required rescue. This overestimated the standardized $FEV_{1.0}$ AUC, where the entire descending curve would otherwise have contributed to a lower standardized value. Because rescue treatment and this truncated test would be more likely in groups receiving less effective treatment, their $FEV_{1.0}$ AUC would be over estimated. That is, this strategy likely overestimated the true Type I Error of LS mean differences between groups. The consequence of this would be to make efficacy more difficult to demonstrate by statistical significance of each of the three cascading planned $FEV_{1.0}$ AUC comparisons which are presented below.

Stepwise comparisons were made in the following order, with progression contingent upon statistical significance of the preceding comparison.

1. Formoterol 24 mcg compared with Placebo
2. Formoterol 12 mcg compared with Placebo
3. Formoterol 24 mcg with Formoterol 12 mcg

These sequential comparisons obviated the need to correct for multiple endpoints because each was "protected" by the statistical significance of the preceding one.

Other secondary variables derived from the spirograms at week -2 and months 0, 3 and 12 (visits 1, 2, 5 and 14) were also available to support efficacy. Asthma exacerbations were recorded as an endpoint at all visits (visits 2-5 were pre-specified, but results are available from all). Several endpoints derived from the patient diary were also secondary. Twice daily domiciliary pretreatment PEFR's were recorded. The number of inhalations of rescue medication was also placed in the patient diary as were reflective nighttime and daytime symptom scores [13:28-30, 33, 37-40, 212].

NDA #20-831 TRIAL #049 - NIGHTTIME ASTHMA SYMPTOM SCORE [13:29]	
Score	**Description**
0	I did not wake up because of breathing problems.
1	I woke up at least once because of my breathing problems, but did not use my rescue medication.
2	I woke up once because of my breathing problems, but my rescue medication controlled them.
3	I woke up more than once because of my breathing problems, but my rescue medication controlled them.
4	I had difficulty sleeping because of my breathing problems even though I used my rescue medication.

NDA #20-831 TRIAL #049 - DAYTIME ASTHMA SYMPTOM SCORE [13:29-30]	
Score	**Description**
0	No breathing problems at all; my activity was not restricted.
1	Breathing problems occurred with little or no discomfort, and did not restrict my activity.
2	Breathing problems occurred with some discomfort, and limited strenuous activity.
3	Breathing problems occurred with discomfort, and limited routine activity.
4	Breathing problems occurred at rest with major discomfort, and limited routine activity.

VI.F.2. SAFETY

These measures included vital signs, clinical laboratory tests, ECG's, AE's and PK determinations. Pulse rate and blood pressure were measured at visits 1, 2, 5 and 14. On the days that 12-hour spirograms were performed, visits 2, 5 and 14, these vital signs were also measured pre-dose and at 30 minutes, 60 minutes, 2 hours and at 2-hourly intervals through 12 hours and the completion of the spirograms. In all centers, a fasting venous blood sample was obtained prior to $FEV_{1.0}$ reversibility testing at visit 1. Patients at US centers were to have additional fasting samples drawn at visits 3, 5, 8 and 14. The following testing was performed on these blood samples:

HEMATOLOGY - Hgb, Hct, RBC, WBC, differential WBC counts, platelets

CHEMISTRY - creatinine, BUN, potassium, glucose, LDH, GGTP, AST, ALT, alkaline phosphatase, total bilirubin, triglycerides, cholesterol

Patients with clinically abnormal laboratory tests were followed until the value normalized or until a plausible reason, other than a drug-related AE, was identified. A 12-lead ECG was done at visit 1 at all centers. All US centers obtained ECG's at all visits. AE's were sought by the clinical investigators at each visit by questioning and examining the patients and examining the diaries. PK determinations were made at selected US centers [13:30-1, 33].

VI.G. UNPLANNED DATA ANALYSIS

A second and additional analysis of the primary efficacy variable was carried out because of possible impropriety. Four centers were excluded from the analysis because of suspected problems with the spirometry data. Centers 1 and 2 in Russia showed discrepancies in comparisons between these data in the spirometry print-out and in the CRF, suggesting data "adjustment." Data from centers 9 and 10 in Argentina and Chile were thought to be of questionable quality. These centers had been closed early because of administrative problems [13:36].

VI.H. PATIENT DISPOSITION

Randomization of 324 patients (63%) was made to 25 US centers; 109 patients were randomized to 9 centers in Argentina and Chile; 57 patients were randomized to 2 centers in Russia; and, 28 patients were randomized to 4 centers in Spain. The breakdown of patients screened, enrolled, randomized and completing the trial is shown in the following table, as are the details of patients discontinuing prematurely [13:43-4, 150].

NDA #20-831 TRIAL #049 - PATIENT DISPOSITION, COUNT (% RANDOMIZED) [13:44, 150]				
	Placebo	12 mcg BID	24 mcg BID	Total
Screened				601
Randomized	176	171	171	518
Completed	135 (77)	134 (78)	138 (81)	407 (79)
Discontinued				
total	41 (23)	37 (22)	33 (19)	111 (21)
for AE's	11 (6)	11 (6)	14 (8)	36 (7)
withdrew consent	10 (6)	7 (4)	8 (5)	25 (5)
non-compliance	7 (4)	7 (4)	2 (1)	16 (3)
lost to follow-up	4 (2)	3 (2)	4 (2)	11 (2)
unsatisfactory Rx effect	3 (2)	4 (2)	3 (2)	10 (2)
protocol criteria not met	2 (1)	4 (2)	1 (1)	7 (1)
administrative problems	3 (2)	0 (0)	0 (0)	3 (1)
unknown reason	1 (1)	1 (1)	1 (1)	3 (1)

Patients were evenly distributed among the three treatment groups in terms of randomization, completion, and early discontinuation categories. Some of the early discontinuation categories are hard to interpret like "non-compliance" and "unsatisfactory treatment effect." Compliance was explicitly not measured, at least for medication use, and inefficacious treatment might well be considered as an AE [13:36]. It was confirmed that these ambiguous categories were not further defined and assignment to them was left to the discretion of the clinical investigators [3/21/2000 & 3/24/2000 Teleconferences with Kathleen Creedon].

Dropouts from all causes were reported to have occurred between a month at which data was available and a month at which there was no patient data and are presented in the table below. The percentages use a denominator of the remaining patients at the first "Between Months" entry [13:44]. There was a fairly constant dropout rate over the 12-month duration of the trial, as shown by the entries below. Somewhat surprisingly, the dropout rate for all groups was very similar.

NDA #20-831 TRIAL #049 - PATIENT PREMATURE TERMINATION BETWEEN DOUBLE-BLIND TREATMENT MONTHS, COUNT (% ELIGIBLE) [13:44]				
Between Months	Placebo	Formoterol 12 mcg	Formoterol 24 mcg	Total
0 - 1	3 (1.7)	0 (0.0)	0 (0.0)	3 (0.6)
1 - 3	11 (6.4)	12 (5.9)	5 (2.9)	28 (5.4)

NDA #20-831 TRIAL #049 - PATIENT PREMATURE TERMINATION BETWEEN DOUBLE-BLIND TREATMENT MONTHS, COUNT (% ELIGIBLE) [13:44]				
Between Months	Placebo	Formoterol 12 mcg	Formoterol 24 mcg	Total
3 - 6	11 (6.8)	10 (6.2)	13 (7.8)	34 (7.0)
6 - 9	10 (6.6)	8 (5.4)	7 (4.6)	25 (5.5)
9 - 12	6 (4.3)	7 (5.0)	8 (5.5)	21 (4.9)
Total (0 - 12)	41 (23.3)	37 (21.6)	33 (19.3)	111 (21.4)

VI.I. BASELINE DEMOGRAPHICS

Demographic data and baseline characteristics are summarized for randomized patients in the table below. These data suggest that randomization resulted in a uniform distribution of many characteristics among treatment groups [13:49-50].

NDA #20-831 TRIAL #049 - DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS [13:50, 152]				
Variable Descriptive Statistics	Placebo n = 176	12 mcg BID n = 171	24 mcg BID n = 171	Total n = 518
Age (years)				
mean (SD)	9 (2)	9 (2)	9 (2)	9 (2)
minimum	5	5	5	5
25% quantile	8	8	8	8
median	10	9	10	10
75% quantile	11	10	11	11
maximum	12	12	12	12
Sex, n (%)				
Male	120 (68)	107 (63)	97 (57)	324 (63)
Female	56 (32)	64 (37)	74 (43)	194 (37)
Race, n (%)				
White, Caucasian	156 (89)	153 (89)	143 (84)	452 (87)
Black	11 (6)	9 (5)	16 (9)	36 (7)
Oriental	1 (1)	1 (1)	2 (1)	4 (1)
Other	8 (5)	8 (5)	10 (6)	26 (5)
Asthma Duration (years)				
mean (SD)	5.3 (3.0)	5.3 (2.9)	5.1 (3.2)	5.2 (3.0)
Visit 2 - Pre-dose Baseline $FEV_{1.0}$ (L)				
mean (SD)	1.65 (0.49)	1.63 (0.48)	171 (0.51)	1.66 (0.50)
Vital Signs				
mean SBP/DBP (mm Hg)	102/63	101/61	102/63	102/62
mean pulse rate (bpm)	78	81	79	79
Abnormal ECG, n (%)	30 (17)	20 (12)	17 (10)	67 (13)

The only apparent maldistribution among groups at baseline was the relatively greater frequency of abnormal ECG's in the placebo group. This trial had disproportionately more Caucasians and males than other categories of race and gender. The entire age distribution appeared to under-represent the younger ages. Only 25% of the enrollees were 5-8 years old and 75% were 8-12 years old. A more detailed breakdown of ages was provided by the sponsor.

NDA #20-831 TRIAL #049 - AGE DISTRIBUTION AT ENTRY INTO THE TRIAL, COUNT (%) [FAX 3/21/2000]				
Age (years)	Formoterol 24 mcg	Formoterol 12 mcg	Placebo	Total
5	4 (2.3)	5 (2.9)	3 (1.7)	12 (2.3)
6	13 (7.6)	12 (7.0)	19 (10.8)	44 (8.5)
7	17 (9.9)	16 (9.4)	17 (9.7)	50 (9.7)
8	17 (9.9)	31 (18.1)	21 (11.9)	69 (13.3)
9	27 (15.8)	32 (18.7)	22 (12.5)	81 (15.6)
10	37 (21.6)	35 (20.5)	30 (17.0)	102 (19.7)
11	26 (15.2)	21 (12.3)	32 (18.2)	79 (15.3)
12	30 (17.5)	19 (11.1)	32 (18.2)	81 (15.6)
Total	171 (100.0)	171 (100.0)	176 (100.0)	518 (100.0)

There were eight separate ages at trial entry and had these been equally represented, 12.5% of patients should have been in each. The youngest three ages, 5-7 years, were all under represented, with the lowest frequency of entrants at 5 years of age [3/21/2000 FAX]. If these three youngest ages were to suffer drop-outs during the efficacy portion of the trial, it might be hard to conclude that formoterol was approvable in them. This information was requested, FAXed for inclusion in this review and presented below [4/5/2000 FAX from Pat McGovern].

NDA #20-831 TRIAL #049 - AGE DISTRIBUTION FOR AGES 5-7 YEARS AT EACH 12-HOUR $FEV_{1.0}$ AUC, COUNT [FAX 4/5/2000]					
Month (Visit)	Age (years)	Formoterol 24 mcg	Formoterol 12 mcg	Placebo	Total
Month 0 (Visit 2)	5	4	5	3	12
	6	13	12	19	44
	7	17	16	17	50
Month 3 (Visit 5)	5	3	4	3	10
	6	12	10	17	39
	7	17	15	16	48
Month 12 (Visit 14)	5	4	4	2	10
	6	10	10	16	36
	7	17	11	11	39

The month 0 (visit 2) participation of the three youngest ages was identical to the counts at entry into the trial in the preceding table, possibly because they refer to the same time point. By month 3 (visit 5) when the primary efficacy variable was defined, 9 children who were 5 through 7 years of age had dropped out. However, by protocol the last values were carried forward from month 0 (visit 2), so despite the slightly lower participation, all present at month 0 were represented at the month 3 $FEV_{1.0}$ AUC. By month 12 (visit 14) an additional 12 had been dropped or discontinued. The three youngest age groups, 5 through 7 years of age, lost 21 of the original 106 patients over the 12-month trial duration.

VI.J. EFFICACY

VI.J.1. $FEV_{1.0}$ AUC

The primary efficacy variable was the $FEV_{1.0}$ AUC measured after three months of treatment. It was "standardized" for the number of hours actually recorded to allow for data collection from those who required rescue medication during these 12-hour serial spirograms, therefore prematurely terminating them. This topic as a source of bias was previously addressed in this review (see: PARAMETERS, EFFICACY). The number and group identity of patients who prematurely terminated this 12-hour study period at the third month were requested and provided by the sponsor.

NDA #20-831 TRIAL #049 - NUMBER (%) OF PATIENTS WHO HAD TRUNCATED $FEV_{1.0}$ AUC'S AT MONTH 3 (VISIT 5) [3/21/2000 TELECONFERENCE]			
Formoterol 24 mcg n = 171	Formoterol 12 mcg n = 171	Placebo n = 176	Total n = 518
1 (0.6)	12 (7.0)	24 (13.6)	37 (7.1)

The numbers shown above confirm previous speculation that more patients receiving less efficacious treatments had truncated tests at visit 5. This same pattern was also present at visits 2 and 14 (months 0 and 12) [3/24/2000 FAX].

There were 52 (10%) patients for whom no standardized $FEV_{1.0}$ AUC could be determined at month 3 (visit 5). The last available standardized $FEV_{1.0}$ AUC value for these patients was carried forward (LVCF) from month 0 (visit 2), after the first dose of trial medication. This practice could also have biased the results of this third-month endpoint even if the truncated patients were evenly distributed among treatment groups. Adult studies of this drug showed tachyphylaxis, a diminishing efficacy with continued treatment. If also present in children, incorporating data from initial treatment with data from the third month of treatment probably improved apparent third month efficacy. In fact, least squared (LS) mean differences of both formoterol doses from placebo at month 0 (visit 2) were superior to the same LS mean differences at month 3 (visit 5) and month 3 was superior to month 12 (visit 14) [13:56]. These findings suggest that some degree of tachyphylaxis was present in children.

The standardized LS mean $FEV_{1.0}$ AUC differences in the table below were based on a model of the following covariates: treatment + country + center (country) + sex + baseline. Comparisons of both formoterol doses with placebo achieved statistical significance in the original modified intent to treat analysis and in the analysis excluding centers with questionable data collection. Neither analysis showed a difference between the two formoterol doses, though the standardized LS mean $FEV_{1.0}$ AUC differences from placebo did show dose ordering [13:54].

NDA #20-831 TRIAL #049 - ESTIMATES OF TREATMENT GROUP DIFFERENCES WITH ASSOCIATED 95% CONFIDENCE INTERVALS FOR $FEV_{1.0}$ AUC MEASURED AT VISIT 5 (MONTH 3) [13:54]			
Treatment Group Difference	**Estimate (L)**	**95% CI (L)**	**Type I Error**
Modified Intent To Treat Analysis (n = 518)			
Formoterol 24 mcg - Placebo	0.18	0.12 - 0.24	<0.0001
Formoterol 12 mcg - Placebo	0.15	0.10 - 0.21	<0.0001
Formoterol 24 mcg - Formoterol 12 mcg	0.03	-0.03 - 0.09	0.3445
Analysis Excluding Centers With Possible Data Problems (n = 456)			
Formoterol 24 mcg - Placebo	0.17	0.11 - 0.23	<0.0001
Formoterol 12 mcg - Placebo	0.12	0.06 - 0.18	<0.0001
Formoterol 24 mcg - Formoterol 12 mcg	0.04	-0.01 - 0.10	0.1433
LS Mean AUC = treatment + country + center (country) + sex + baseline			

VI.J.2. SERIAL $FEV_{1.0}$

Analysis of the $FEV_{1.0}$ values at selected time-points for each of the three 12-hour trials at months 0, 3 and 12 (visits 2, 5 and 14) was instructive because it showed the durable duration of action of the formoterol treatment. Times to onset of effect and peak effect were similar to those found in the adult studies. A near-maximal effect onset was seen at 15-30 minutes and a peak effect occurred at 1-4 hours. The rising pre-dose $FEV_{1.0}$ between months 0 and 3 probably represented a trough treatment effect because it was larger in the active treatment groups than in placebo and showed dose-ordering. The further increase at month 12 may have reflected a selection bias brought about by the 21% dropout rate, because the pre-dose differences between months 3 and 12 were approximately the same for all three groups and the dropout rates were similar. Tachyphylaxis was difficult to determine from the three sets of serial spirograms supplied because of this rising $FEV_{1.0}$ in all treatment groups over the year of follow-up [13:185-6, 190-3].

NDA #20-831 TRIAL #049 - MEAN $FEV_{1.0}$ FOR SELECTED TIME POINTS AFTER DRUG AT MONTHS 0, 3 AND 12 IN THE MODIFIED INTENT-TO-TREAT SAMPLE [13:185-6, 190-3]									
Spirogram	**Placebo**			**Formoterol 12 mcg**			**Formoterol 24 mcg**		
Timing	**Mo 0**	**Mo 3**	**Mo12**	**Mo 0**	**Mo 3**	**Mo 12**	**Mo 0**	**Mo 3**	**Mo 12**
Pre-Dose	1.65	1.71	1.89	1.63	1.75	1.92	1.71	1.85	2.00
5 min.	1.67	1.72	1.92	1.80	1.86	2.05	1.90	1.97	2.16
15 min	1.68	1.73	1.94	1.84	1.89	2.08	1.92	1.99	2.19
30 min	1.70	1.74	1.97	1.86	1.90	2.11	1.96	1.99	2.20
1 hour	1.72	1.75	1.98	1.91	1.93	2.14	1.97	2.03	2.23
2 hours	1.72	1.77	1.99	1.92	1.94	2.16	2.00	2.03	2.23
3 hours	1.73	1.78	2.01	1.92	1.93	2.14	1.99	2.03	2.22
4 hours	1.73	1.79	2.01	1.91	1.92	2.13	1.99	2.01	2.21
6 hours	1.71	1.76	1.99	1.90	1.90	2.09	1.99	1.99	2.17
9 hours	1.70	1.75	1.97	1.86	1.86	2.07	1.96	1.95	2.15
12 hours	1.69	1.73	1.97	1.86	1.85	2.02	1.95	1.93	2.12

VI.J.3. PEFR

Pre-treatment morning PEFR's are displayed in the table below as averages of the last seven days of selected months over the year of follow-up. The rising values for all

three groups probably represented selection bias caused by dropouts. The ad hoc statistic "Month Mean - Baseline Mean" serves as a rough and comparative measure of both efficacy and drop-out bias over the year-long double-blind treatment. Recall that dropout rates, and presumably bias, for all three groups were similar so comparing formoterol to placebo by "Month Mean - Baseline Mean" should be mostly a measure of efficacy. This measure showed dose-ordering and a difference from placebo of about 10 L/min for the 12 mcg formoterol dose for most months. The 24 mcg formoterol dose was generally 15-20 L/min greater than placebo at each month and over the entire year [13:194-5].

NDA #20-831 TRIAL #049 - PRE-TREATMENT MEAN AM PEFR (L/min) OVER THE LAST WEEK (7 DAYS) OF SELECTED MONTHS IN THE MODIFIED INTENT-TO-TREAT SAMPLE (MONTH MEAN - BASELINE MEAN) [13:194-5]

	Placebo	Formoterol 12 mcg	Formoterol 24 mcg
Baseline	243	234	246
Month 1	250 (7)	258 (24)	272 (26)
Month 3	256 (13)	260 (26)	279 (33)
Month 6	269 (26)	268 (34)	287 (41)
Month 9	274 (31)	277 (43)	293 (47)
Month 12	283 (40)	276 (42)	300 (54)

The pre-treatment evening PEFR's, in the table below, show results that were virtually identical to those shown by the pre-treatment morning PEFR's. Taken together, the pre-treatment (trough) PEFR data reflected the greater effect of the 24 mcg formoterol dose over the 12 mcg dose and of both doses over placebo [13:196-7].

NDA #20-831 TRIAL #049 - PRE-TREATMENT MEAN PM PEFR (L/min) OVER THE LAST WEEK (7 DAYS) OF SELECTED MONTHS IN THE MODIFIED INTENT-TO-TREAT SAMPLE [13:196-7]

	Placebo	Formoterol 12 mcg	Formoterol 24 mcg
Baseline	253	245	256
Month 1	258 (5)	265 (20)	278 (22)
Month 3	263 (10)	267 (22)	283 (27)
Month 6	277 (24)	274 (29)	291 (35)
Month 9	282 (29)	283 (38)	298 (42)
Month 12	291 (38)	282 (37)	306 (50)

VI.J.4. ASTHMA SYMPTOM SCORE

The mean Daytime Asthma Symptom Scores, displayed in the table below, were averages of the last seven days of selected months over the year of follow-up. The ad hoc statistic "Baseline Mean - Month Mean" serves as a rough and comparative measure of both efficacy and drop-out bias over the year-long double-blind treatment. With almost equal number of dropouts in all groups, comparison of active treatments with placebo should be a measure of efficacy. Parenthetically, I strong placebo effect was seen between baseline and month 1. Further reductions in this symptom score in any group could equally represent placebo effect or bias introduced by early withdrawal of the sickest patients. Comparison of active treatments with placebo showed an effect of both formoterol treatments, but dose-ordering was not supported by this measure [13:198-9]. Recall that smaller scores mean less severe symptoms and that all of these averages were

between '0' ("No breathing problems at all; my activity was not restricted.") and '1' ("Breathing problems occurred with little or no discomfort, and did not restrict my activity.").

NDA #20-831 TRIAL #049 - MEAN REFLECTIVE DAYTIME ASTHMA SYMPTOM SCORE (0-4) OVER THE LAST WEEK (7 DAYS) OF SELECTED MONTHS IN THE MODIFIED INTENT-TO-TREAT SAMPLE (BASELINE MEAN - MONTH MEAN) [13:198-9]			
	Placebo	Formoterol 12 mcg	Formoterol 24 mcg
Baseline	0.70	0.68	0.63
Month 1	0.55 (0.15)	0.48 (0.20)	0.41 (0.22)
Month 3	0.49 (0.21)	0.40 (0.28)	0.37 (0.26)
Month 6	0.46 (0.24)	0.40 (0.28)	0.31 (0.32)
Month 9	0.41 (0.29)	0.27 (0.41)	0.37 (0.26)
Month12	0.35 (0.35)	0.29 (0.39)	0.22 (0.41)

The mean Nighttime Asthma Symptom Score showed results that were similar to those of the mean Daytime Asthma Symptom Score [13:201-2]. Recall that all of these averages were between '0' ("I did not wake up because of breathing problems.") and '1' ("I woke up at least once because of my breathing problems, but did not use my rescue medication.").

NDA #20-831 TRIAL #049 - MEAN NIGHTTIME ASTHMA SYMPTOM SCORE (0-4) OVER THE LAST WEEK (7 DAYS) OF SELECTED MONTHS IN THE MODIFIED INTENT-TO-TREAT SAMPLE (BASELINE MEAN - MONTH MEAN) [13:201-2]			
	Placebo	Formoterol 12 mcg	Formoterol 24 mcg
Baseline	0.46	0.50	0.47
Month 1	0.40 (0.06)	0.32 (0.18)	0.28 (0.19)
Month 3	0.32 (0.14)	0.27 (0.23)	0.32 (0.15)
Month 6	0.35 (0.11)	0.23 (0.27)	0.22 (0.25)
Month 9	0.30 (0.16)	0.15 (0.35)	0.22 (0.25)
Month12	0.26 (0.20)	0.19 (0.31)	0.13 (0.34)

VI.J.5. RESCUE MEDICATION USE

Daytime use of rescue medication by group is displayed in the table below as averages of the last seven days of selected months over the year of follow-up. This endpoint showed a reduction over the 12-month double-blind period in all groups with the greatest reduction in the two formoterol groups and no dose-ordering. "Baseline Mean - Month Mean" is included as a summary measure of efficacy and mirrors the findings previously described [13:204-5]. The treatment effect is quite small. At baseline the mean for all groups was less than one dose of rescue medication every two days, which is a compelling argument for the efficacy of the baseline treatment regimen.

NDA #20-831 TRIAL #049 - MEAN NUMBER OF DOSES OF RESCUE MEDICATION INHALED DURING THE DAY OVER THE LAST WEEK (7 DAYS) OF SELECTED MONTHS IN THE MODIFIED INTENT-TO-TREAT SAMPLE (BASELINE MEAN - MONTH MEAN) [13:204-5]			
	Placebo	Formoterol 12 mcg	Formoterol 24 mcg
Baseline	0.43	0.45	0.45
Month 1	0.34 (0.09)	0.31 (0.14)	0.17 (0.28)

NDA #20-831 TRIAL #049 - MEAN NUMBER OF DOSES OF RESCUE MEDICATION INHALED DURING THE DAY OVER THE LAST WEEK (7 DAYS) OF SELECTED MONTHS IN THE MODIFIED INTENT-TO-TREAT SAMPLE (BASELINE MEAN - MONTH MEAN) [13:204-5]			
	Placebo	Formoterol 12 mcg	Formoterol 24 mcg
Month 3	0.31 (0.12)	0.25 (0.20)	0.23 (0.22)
Month 6	0.30 (0.13)	0.22 (0.23)	0.22 (0.23)
Month 9	0.22 (0.21)	0.15 (0.30)	0.28 (0.17)
Month12	0.21 (0.22)	0.14 (0.31)	0.21 (0.24)

Nighttime use of rescue medication also showed a reduction in all groups over the 12-month double-blind period with marginally greater and equal reductions shown by the two active treatment groups [13:207-8].

NDA #20-831 TRIAL #049 - MEAN NUMBER OF DOSES OF RESCUE MEDICATION INHALED DURING THE NIGHT OVER THE LAST WEEK (7 DAYS) OF SELECTED MONTHS IN THE MODIFIED INTENT-TO-TREAT SAMPLE (BASELINE MEAN - MONTH MEAN) [13:207-8]			
	Placebo	Formoterol 12 mcg	Formoterol 24 mcg
Baseline	0.23	0.26	0.27
Month 1	0.21 (0.02)	0.17 (0.09)	0.12 (0.15)
Month 3	0.19 (0.04)	0.13 (0.13)	0.15 (0.12)
Month 6	0.19 (0.04)	0.10 (0.16)	0.10 (0.17)
Month 9	0.15 (0.08)	0.06 (0.20)	0.13 (0.14)
Month 12	0.13 (0.10)	0.08 (0.18)	0.09 (0.18)

VI.J.6. ASTHMA EXACERBATIONS

At each visit after the start of the trial, the patient was asked how many asthma exacerbations had occurred since the previous visit. The reported exacerbation frequencies for all groups were summarized over the entire double-blind treatment interval [13:212]. About 40% of each group reported ≥ 1 exacerbation during the double-blind period and group separation was inapparent by this measure.

NDA #20-831 TRIAL #049 - FREQUENCY TABLE OF NUMBER OF ASTHMA EXACERBATION RECALLED AT EACH VISIT OVER 12 MONTHS OF TREATMENT [13:212]			
Number Of Asthma Exacerbations	Placebo n (%)	Formoterol 12 mcg n (%)	Formoterol 24 mcg n (%)
0	102 (59.0)	104 (60.8)	103 (60.2)
1	26 (15.0)	27 (15.8)	29 (17.0)
2	24 (13.9)	16 (9.4)	21 (12.3)
3	11 (6.4)	11 (6.4)	5 (2.9)
4	2 (1.2)	6 (3.5)	7 (4.1)
5	4 (2.3)	4 (2.3)	3 (1.8)
6	1 (0.6)	1 (0.6)	2 (1.2)
7	0 (0.0)	1 (0.6)	0 (0.0)
8	2 (1.2)	0 (0.0)	0 (0.0)
9	0 (0.0)	1 (0.6)	0 (0.0)
11	1 (0.6)	0 (0.0)	0 (0.0)
13	0 (0.0)	0 (0.0)	1 (0.6)
Total	173 (100.0)	171 (100.0)	171 (100.0)

VI.K. SAFETY

VI.K.1. ADVERSE EVENTS

The numbers of patients who reported adverse events was comparable in the three treatment groups: 146 patients (85%) on formoterol 24 mcg; 147 patients (86%) on formoterol 12 mcg; and, 151 patients (86%) on placebo. Slightly more AE's were reported in the placebo group (664) than in the formoterol 12 mcg (639) or the formoterol 24 mcg (617) groups. The following table presents the numbers of patients (%) with the most frequent AE's (frequency > 2.5% in ≥ 1 of the treatment groups and ≥ 5 patients in ≥ 1 treatment group) by WHO term [13:67-8].

NDA #20-831 TRIAL #049 - NUMBER OF PATIENTS WITH THE MOST FREQUENT* AE'S SUMMARIZED BY WHO CATEGORIES WHERE PATIENTS IN BOTH FORMOTEROL GROUPS WERE MORE FREQUENT THAN THE PLACEBO GROUP, COUNT (%) [13:68]

WHO Term	Placebo n = 176	Formoterol 12 mcg n = 171	Formoterol 24 mcg n = 171
number of patients with any AE	151 (86)	147 (86)	146 (85)
infection viral	58 (33)	64 (37)	64 (37)
rhinitis	30 (17)	32 (19)	35 (20)
abdominal pain	11 (6)	15 (9)	20 (12)
tonsillitis	5 (3)	13 (8)	8 (5)
gastroenteritis	6 (3)	11 (6)	9 (5)
nausea	6 (3)	8 (5)	9 (5)
dyspepsia	4 (2)	6 (4)	5 (3)
dizziness	2 (1)	5 (3)	6 (4)
allergy aggravated	2 (1)	5 (3)	3 (2)
rash	2 (1)	5 (3)	3 (2)

* Most Frequent = >2.5% of patients in ≥ 1 treatment group AND ≥5 patients in ≥ 1 treatment group

None of these AE's appear to be among the more usual and dose-ordered complaints of adult patients on formoterol; e.g., tremor, muscle cramps, tachycardia and insomnia.

Of the 77 AE's which were assessed by the investigators as at least possibly drug-related; 17 were reported by 12 patients (7%) in the formoterol 24 mcg group; 28 were reported by 18 patients (11%) in the formoterol 12 mcg group; and, 32 were reported by 24 patients (14%) in the placebo group [13:69].

VI.K.2. DEATHS

There were no deaths [13:70].

VI.K.3. SERIOUS ADVERSE EVENTS

Patients who reported SAE's were more frequent in the two active treatment groups than in the placebo group. In the formoterol 24 mcg group, 13 SAE's were reported by 12 patients (7%) and 11 of these were asthma-related. The remaining two

were syncope and pneumonia. In the formoterol 12 mcg group, 11 SAE's were reported by 9 patients (5%) and 8 of these were asthma-related. The other three were pneumonia, pain and stridor. In the placebo group, 3 SAE's were reported by 3 patients (2%), pneumonia by two and injury by one [13:70, 72]. The preponderance of asthma-related SAE's in the active treatment groups is a bit worrisome and may reflect the loss of challenge protection noted in the adult NDA. Almost complete loss of protection against a methacholine challenge was demonstrated in trial DP/SP2 following two weeks of treatment with formoterol 24 mcg BID compared with placebo [6/24/97 87:38, 77]. The adult ISS of SAE's in multiple-dose, controlled trials was incomplete but did show twice the frequency of early withdrawals for asthma in patients regularly treated with formoterol or salbutamol than with placebo [6/24/97 377:122]. The similarity of the methacholine challenge to other episodic and natural bronchoconstrictive stimuli may explain this finding of increased asthma-related SAE's in children.

VI.K.4. ADVERSE EVENTS LEADING TO EARLY WITHDRAWAL

AE's leading to premature termination were more common in the placebo group than in either active treatment. In the formoterol 24 mcg group, 5 AE's led to withdrawal of 4 patients (2%) and 3 of these were asthma-related. The remaining two were abdominal pain and tremor. In the formoterol 12 mcg group, 10 AE's led to withdrawal of 5 patients (3%). The ten included 3 GI disorders, 2 psychiatric disorders, 2 central and peripheral autonomic nervous system disorders and one case each of asthma, fever and eye complaints. In the placebo group, 12 AE's led to the withdrawal of 10 patients (6%). Of the 12, 7 were asthma and one each was pneumonia, retching, hyperkinesia, headache and sinusitis [13:72-3].

VI.K.5. LABORATORIES

VI.K.5.a. HEMATOLOGY

Very few abnormal values in the double-blind period were dispersed fairly evenly over the three treatment groups and consisted of both increased and decreased neutrophils and lymphocytes, decreased hemoglobin, hematocrit and RBC and increased eosinophils. The table below breaks down the total number of abnormal labs and the patients contributing them by treatment group [13:75-6]. No apparent relation to treatment was suggested.

NDA #20-831 TRIAL #049 - ABNORMAL HEMATOLOGY LABS BY TREATMENT GROUP, LABS ABNORMAL / PATIENTS ABNORMAL [1375-6]		
Placebo	Formoterol 12 mcg	Formoterol 24 mcg
5 / 4	11 / 6	4 / 3

VI.K.5.b. CHEMISTRY

Several evanescent changes in hepatic enzymes, and lipids were noted and were scattered over all three treatment groups. Potassium and glucose received special attention because beta adrenergic agents have been associated with both hypokalemia and hyperglycemia. Adult studies of formoterol confirmed the latter but offered no support for the former. In the current pediatric study, 4 patients in the formoterol 24 mcg group, 3 in the formoterol 12 mcg group and 2 in the placebo group had single potassium values < 3.4 mmol/L. Transient fasting hyperglycemia (> 140 mg/dL) was found in 2 patients in the formoterol 24 mcg group, 3 patients in the formoterol 12 mcg group and 1 patient in the placebo group [13:76-7].

VI.K.6. VITAL SIGNS

The mean values of systolic and diastolic blood pressure were similar in all treatment groups. The largest effect was seen in a comparison of pulse rate in the formoterol 24 mcg group and the placebo group, where a mean difference of 2.9 beats/minute was found [13:77-8, 257-65].

VI.K.7. ELECTROCARDIOGRAMS

Shifts from baseline "normal" to "abnormal" ECGs at each study visit, were about equal and similar across treatment groups. Abnormal QTc intervals (> 0.460 sec) were evenly distributed between all three groups, were mostly isolated and occasionally attributed to calculation errors [13:78, 272-3, 392-412].

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20-831	**APPLICATION TYPE:**	NDA
SPONSOR:	Novartis	**PROPRIETARY NAME:**	Foradil
CATEGORY:	beta-2 agonist	**USAN NAME:**	formoterol fumarate
		ROUTE:	inhaled
MEDICAL OFFICER:	R. F. Anthracite	**REVIEW DATE:**	20 May 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
24 June 1997	26 June 1997	NDA	
15 August 1997	18 August 1997	request response	indexing tables
11 August 1997	12 August 1997	request response	indexing tables
24 October 1997	27 October 1997	package inserts	sponsor proposals
27 October 1997	28 October 1997	request response	tables (#40 & #41)

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY:

I recommend approvability of inhaled formoterol dry powder capsules at a starting dose of 12 µg b.i.d. for the [redacted] Because the onset of action is, the first dose may be given for initiation of treatment in acutely ill patients, but absence of safety information for more frequent administration limits repeat dosing to every 12 hours. The same starting dose and retreatment interval should also be approved for the indications, prevention of nocturnal asthma symptoms and exercise induced bronchoconstriction. Cautionary notes about hyperglycemia, hypokalemia, tachycardia and tremor should be included. Though tachyphylaxis has been shown with chronic administration, it is also seen with chronically administered albuterol. The rapid loss of protection against methacholine challenge and similarity of this to other episodic and natural bronchoconstrictive stimuli is both speculative and provocative. Finally, labeling will have to address incomplete capsule emptying and the need for repeated inhalations until the entire dose is delivered.

OUTSTANDING ISSUES:

1. DSI audits and return of data sheets
2. Complete accounting and analysis of all SAE's and early D/C due to AE's
3. CRF reviews of deaths and early D/C due to AE's

RECOMMENDED REGULATORY ACTION

New Clinical Studies: _____ **HOLD** _____ **MAY PROCEED**

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

NDA/Efficacy/Label Supplements: XXX APPROVABLE _____ NOT APPROVABLE

SIGNATURES

Reviewer: /S/ _____ Date: 3 June 1998

Team Leader: /S/ _____ Date: June 5, 1998

See T.L. memo for further comments.

/S/ 6/5/98

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ON ORIGINAL

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ON ORIGINAL

EXECUTIVE SUMMARY OF EFFICACY AND SAFETY

The two almost identical U.S. pivotal trials (#40 and #41) included close to 1100 adult and adolescent patients (ages 12-75 years) with mild to moderate asthma ($FEV_{1.0}$ > 40% predicted off therapy), 15% $FEV_{1.0}$ beta-2 agonist reversibility who required daily short-acting beta-2 agonists for symptom control. Stable treatment regimens of twice-daily oral theophylline, inhaled or nasal corticosteroids, short-acting antihistamines or desensitization allergy therapy were all allowed. Treatments with 12 or 24 μg of dry powder formoterol capsule doses b.i.d. were compared with albuterol MDI, 180 μg q.i.d., and with placebo in a double-dummy design.

Serial morning spirometry was performed at baseline and after the fourth, eighth and twelfth weeks of treatment. The serial time points for each spirogram were baseline, before morning medication had been given, and post-treatment time points of 5, 15, 30, 60 minutes and hourly through the twelfth hour. A second blinded treatment was given at the sixth post-treatment hour to provide for the administration of active drug to the albuterol group. The earliest time points (5, 15 and 30 minutes) for the first treatment at the baseline visit showed that the bronchodilation produced by the higher formoterol dose was as good or better than that of albuterol. The two formoterol doses provided the largest improvement in mean $FEV_{1.0}$'s which were dose proportional, became near-maximal by 30 minutes after dosing and peaked at about the third hour. Both formoterol dose groups were statistically significantly better than placebo at the 12-hour post-treatment time point at the 12-week visit, the primary efficacy variable. These were about 20% and 25% improvement over the pretreatment baseline for the low and high formoterol doses respectively compared with 6-10% for albuterol and 5-8% for placebo. As expected, albuterol produced two $FEV_{1.0}$ peaks one hour after each dose.

After visit 2, the formoterol groups showed higher morning, pre-treatment $FEV_{1.0}$ values, consistent with sustained trough improvement in flows of 10-19% over the week 0 pretreatment baseline compared with 5-7% for placebo and albuterol. The $FEV_{1.0}$ endpoint showed statistically significant superiority of the 24 μg dose over the 12 μg dose for all randomized patients at virtually all post-treatment time points at every visit in protocol #41 but failed to achieve statistical significance in protocol #40 at most time points and visits. The $FEV_{1.0}$ AUC supported the superiority of the larger formoterol dose over the smaller in protocol #41, but did not, after the first treatment visit (visit 2) in protocol #40. No other secondary endpoint reviewed demonstrated a preponderance of statistical separation between the two formoterol doses. Secondary endpoints supported the efficacy of both formoterol doses over placebo and, less frequently, over albuterol; e.g., PEFR's, nocturnal and combined asthma symptom scores and rescue medicine use.

Onset of action was further elucidated by a single-dose, crossover design of 15 asthma patients in protocol DP/DF2. Specific airway resistance (sRaw) was used to track very early differences between single doses of formoterol dry powder (6, 12 and 24 μg), salbutamol dry powder (400 μg) and placebo. The sRaw was measured at baseline, 1, 3, 5, 10, 15 and 30 minutes post-treatment. Single doses of formoterol 12 μg, 24 μg and salbutamol 400 μg produced very similar mean values at all of these early time points.

The 6 μg formoterol dose lagged behind other active treatments at post-treatment time points through 30 minutes.

Efficacy in children with reactive obstructive airways disease (ROAD) was studied in protocol DP/PD2. Over 200 5-13 year old children were enrolled in a 12-week, parallel-group trial of two formoterol dry powder doses (6 and 12 μg b.i.d.) or salbutamol dry powder (400 μg t.i.d.). Improvement in mean morning pretreatment peak expiratory flow rate (PEFR) from the salbutamol run-in period, the primary efficacy variable, showed superiority of the higher formoterol dose over the other two active treatments. No difference between the three treatments was supported by any secondary efficacy variable (evening PEFR, asthma symptoms, sleep disturbance, rescue medicine use or morning pretreatment visit spirograms).

Exercise induced bronchoconstriction (EIB) was the focus of three studies. In DP/PD3, sixteen children ages 10-14 were given single doses of formoterol dry powder (12 μg), salbutamol dry powder (400 μg) or placebo, followed with serial spirograms and challenged with exercise tests at three and twelve hours post-treatment. Both active treatments provided EIB protection through the twelfth hour, a somewhat surprising duration of action for salbutamol. Protocol #45 enrolled 18 patients, 12-50 years of age, in a single dose, four-period crossover design. Treatments were formoterol dry powder (12 and 24 μg), albuterol metered dose inhaler (180 μg) or placebo. Exercise challenge tests were performed 15 minutes, 4, 8 and 12 hours post-treatment and protection was assessed by serial spirograms after each. Both formoterol doses were statistically superior to placebo from 15 minutes through 12 hours after treatment, superior to albuterol from 4 through 12 hours post-treatment and were not statistically separable. Protocol #46 was identical to #45, randomized 20 patients and produced similar results, except that the smaller formoterol dose surprisingly provided somewhat greater protection than the larger at all time points.

Tachyphylaxis to chronic beta agonist use was suggested by declining $FEV_{1.0}$ AUC values over the 12 weeks of protocols #40 and #41 for one or both formoterol doses and for albuterol. Tachyphylaxis was also the focus of FO/UK2, a placebo-controlled crossover trial in which beta agonist washout preceded two treatment periods of 4-6 weeks each. The two treatments were formoterol dry powder (24 μg b.i.d.) or placebo and the outcome was post-formoterol serial spirograms followed for 6 hours at the end of each treatment period. Ipratropium inhaler was used for rescue. A decline in the magnitude and duration of formoterol stimulated bronchodilation following 4-6 weeks of chronic formoterol treatment was shown by serial $FEV_{1.0}$ measurements compared with placebo treatment. Almost complete loss of protection against a methacholine challenge was demonstrated in DP/SP2 following two weeks of treatment with formoterol 24 μg b.i.d. compared with placebo. No rebound methacholine responsiveness was found from 36 hours to two weeks after the two-week formoterol treatment period.

The formoterol dry powder safety data base included 39 trials and 4,244 subjects or patients. Twelve healthy subjects and 2,617 patients with reversible obstructive

airways disease received one or more doses from formoterol capsules and 602 received multiple doses for over 48 weeks. The most common doses studied in multiple-dose trials were 12 and 24 μg b.i.d. The safety data base was largely comprised of white adult patients with a slight male majority and moderate-to-severe flow obstruction by spirogram ($FEV_{1.0}$ > 50% predicted). Children, under the age of 7 years, constituted less than two dozen cases and the elderly, over the age of 64 years, contributed about 300 cases.

Multiple-dose controlled trials of 1,882 patients exposed to formoterol capsules indicated that four AE's occurred more often with formoterol than placebo treatment and showed a dose proportional frequency. These were tremor (3.5%), muscle cramps (1.3%), tachycardia (1.1%) and insomnia (1.1%) and these occurred between 2-times (insomnia) and 6-times (tremor) more frequently with formoterol than placebo. Among these four AE's, longer uncontrolled trials confirmed only tremor as occurring with a frequency of greater than 1%. When tremor occurred, it was usually reported by patients within the first few days after starting treatment with formoterol.

Single-dose trials demonstrated both hyperglycemia and hypokalemia associated with higher formoterol doses. Multiple-dose studies confirmed only fasting glucose elevations, relative to baseline and placebo, with chronic exposure to proposed doses of 12 and 24 μg b.i.d. A categorical analysis of ECG's was unrevealing. Although a dose-related heart rate increase was found in single-dose trials, no consistent effect on vital signs was demonstrated with proposed clinical doses.

This drug clearly works for mild-to-moderate asthma in adults (ages ≥ 12 years) with a 12-hour duration of action that will permit twice daily dosing. Though not studied, one might speculate that a once-daily dosing interval might even be efficacious. The onset of action of the 24 μg dose is at least as rapid as albuterol 180 μg by inhalation. In this age group, it is efficacious for nocturnal asthma and acute use ameliorates exercise-induced bronchoconstriction. Efficacy in patients from 6-12 years of age is less clear. The only pivotal study that addressed it did not resolve dose selection, duration or onset of action. The efficacy demonstration was weak and unsupported by consistent findings in secondary efficacy variables, much of which may be attributable to the lack of a placebo group. Exercise-induced bronchoconstriction was not studied in patients < 10 years of age.

I recommend approvability of inhaled formoterol dry powder capsules at a starting dose of 12 μg b.i.d. for the

Because the onset of action is, the first dose may be given for initiation of treatment in acutely ill patients, but absence of safety information for more frequent administration limits repeat dosing to every 12 hours. The same starting dose and retreatment interval should also be approved for the indications, prevention of nocturnal asthma symptoms and exercise induced bronchoconstriction. Cautionary notes about hyperglycemia, hypokalemia, tachycardia and tremor should be included. Though tachyphylaxis has been shown with chronic administration, it is also seen with chronically

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/S/

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