showed a post-dose increase of ≥ 25% and/or a measured QTc interval of > 0.5 seconds at any time point in the study. These analytic cut points were selected retrospectively and were the only ones reported by the sponsor. Patients exceeding them included four in the formoterol 12 μg group, three in the formoterol 24 μg group, one in the albuterol group and five patients in the placebo group. Only one of these had a category 4 ECG interpretation and this patient had received placebo [91:154-7].

Holter Monitor (24-hour continuous ECG)

This was obtained 2-7 days after visit 1 (during placebo run-in), on the day of visit 3 (after two weeks of treatment) and 2-7 days after visit 5 (after two months of treatment) for all patients enrolled at ten designated centers. The Holter monitor after visit 1 served as the baseline recording for comparison. All groups showed either a decrease and/or little change in 'Mean Total VPB/hour' as the study progressed. Similar trends were seen for the variable 'Most VPB/hour', with all groups having a lower value at visit 5 than at baseline. Episodes of technical ventricular tachycardia, defined as three VPB's with a rate ≥ 100 beats/minute, were rare throughout the trial except in the albuterol group at baseline and this was due to a single patient (M013R/0062/2044). Change in the variable 'Mean VPB's/hour' between baseline and either visit 3 and/or visit 5 for each variable showed that the majority of patients had no evidence of ventricular ectopy at any time. A total of 11 patients had no ectopy at baseline, but did have some on treatment and included 4 in each formoterol group, 2 in the albuterol group and 1 who received placebo. Eighteen patients showed ectopy at visits 3 or 5 as well as at baseline and 6 patients had ectopy at baseline but not during treatment. Inspection of similar variables applied to supraventricular premature beats was more variable across visits and treatments than was true for ventricular ectopy, however no treatment-related trends were evident. Mean, maximum and minimum heart rate information derived from the Holter monitor showed only slightly higher mean values at all visits for the two formoterol groups than for either the albuterol or placebo groups [91:157-61].

Clinical Laboratory

Fasting laboratory specimens were collected at all visits, prior to drug administration. The visit 2 baseline specimen was the last sample taken prior to patient exposure to double-blind treatment and the terminal lab sample was the last specimen obtained while the patients were on treatment. Values identified as 'high' incorporated patients who were within or below the normal range at baseline, who then experienced a shift to above the normal range at the terminal visit. Values identified as 'low' included patients who were within or above the normal range at baseline, who then showed a shift to below that range at the terminal visit. The denominator for the percentage calculation is the total number of patients who fulfilled the baseline criterion.

Mean values of hematology laboratory variables for the four treatment groups at the baseline and terminal visits did not show any large or consistent changes. Categorical shifts, as described in the first paragraph, were also infrequent and inconsistent, as can be seen in the table below. Specifically the white blood cell count (WBC), which might have been expected to increase because of demargination mediated systemic adrenergic

stimulation in formoterol and albuterol groups, did not do so by either measure (means or shift count) when compared with placebo and active control [91:163-5].

PROTOCOL #40 – NUMBER (%) OF PATIENTS WITH FASTING HEMATOLOGY LAB VALUES SHIFTING TO OUTSIDE OF THE NORMAL RANGE BETWEEN THE BASELINE AND TERMINAL VISITS FOR ALL RANDOMIZED PATIENTS [91:165]

	Formoterol 12		Formoterol 24		Albuterol		Placebo	
Lab Test	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)
WBC	0	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
RBC	0	0	0	0	0	0	0	0
Hgb	0	0	0	0	0	0	0	0
Hct	0	0	0	0	0	0	0	0
Neutrophils	0	0	0	0	0	0	5 (3.7)	0
Bands	0	0	0	0	0	0	0	0
Lymphocytes	0	1 (0.7)	0	0	0	0	0	2 (1.5)
Monocytes	0	0	0	0	0	1 (0.7)	0	0
Eosinophils	0	0	0	1 (0.7)	0	1 (0.7)	0	0
Basophils	0	0	0	0	0	0	0	0
Metamyelocytes	0	0	0	0	0	0	0	0
Myelocytes	0	0	0	0	0	0	0	0
Promyelocytes	0	0	0	0	0	0	0	0
Platelets	0	0	0	0	0	0	0	2 (1.5)

Mean values of chemistry laboratory variables by treatment group at baseline and terminal visits also did not show any obvious or consistent changes. Categorical shifts, as described in the first paragraph, were also infrequent and inconsistent, as can be seen in the table below. Absent, was evidence of trends toward hypokalemia or hyperglycemia, by either measure [91:165-9].

PROTOCOL #40 – NUMBER (%) OF PATIENTS WITH FASTING CHEMISTRY LAB VALUES SHIFTING TO OUTSIDE OF THE NORMAL RANGE BETWEEN THE BASELINE AND TERMINAL VISITS FOR ALL RANDOMIZED PATIENTS [91:168]

	Formoterol 12		Formoterol 24		Albuterol		Placebo	
Lab Test	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)
Glucose	0	3 (2.2)	1 (0.7)	0	0	0	0	0
BUN	0	1 (0.7)	0	0	0	0	0	0
Creatinine	0	1 (0.7)	0	0	0	0	0	0
Sodium	0	0	0	0	0	0	0	2 (1.5)
Potassium	0	0	0	0	0	0	0	0
Chloride	0	1 (0.7)	0	0	0	0	0	0

PROTOCOL #40 – NUMBER (%) OF PATIENTS WITH FASTING CHEMISTRY LAB VALUES SHIFTING TO OUTSIDE OF THE NORMAL RANGE BETWEEN THE BASELINE AND TERMINAL VISITS FOR ALL RANDOMIZED PATIENTS [91:168]								
	Formoterol 12		Formoterol 24		Albuterol		Placebo	
Lab Test	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)
Carbon Dioxide	0	0	0	0	0	0	0	1 (0.7)
Alk. Phosphatase	1 (0.7)	0	0	0	0	0	0	0
SGOT	0	0	0	3 (2.2)	0	1 (0.7)	0	1 (0.7)
SGPT	0	4 (2.9)	0	2 (1.5)	0	1 (0.7)	0	3 (2.2)
LDH	0	0	0	1 (0.7)	0	0	0	0
Bilirubin	0	2 (1.5)	0	1 (0.7)	0	1 (0.7)	0	2 (1.5)
Cholesterol	0	0	0	0	0	0	0	0
Trigycerides	0	1 (0.7)	0	2 (1.5)	0	0	0	2 (1.5)

Serum potassium and glucose were further evaluated. On visits 2-6 a second fasting specimen was collected two hours after trial drug administration. On the 12-hour visit days (visits 2, 4, 5 and 6) additional non-fasting specimens were also collected at 4 and 6 hours post-trial drug administration. These non-fasting samples were analyzed only for potassium and glucose because beta agonists are known to decrease the former and increase the latter. The mean and minimum values for serum potassium and the mean and maximum values for serum glucose were drawn pre-treatment and at 2, 4 and 6 hours post-treatment. The potassium variables did not show any consistent difference between the treatment groups. However, mean serum glucose measurements were elevated in the two formoterol groups compared to both the albuterol and placebo groups. This was most evident in the 4-hour post-treatment values [91:169-72].

PROTOCOL #40 – MEAN VALUES FOR SERUM GLUCOSE BY TREATMENT GROUP [91:172]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Visit 2				
0-hour	92.3	91.4	92.0	92.9
2-hour	93.9	94.9	92.3	89.4
4-hour	108.2	110.4	97.7	93.1
6-hour	99.0	98.3	90.4	90.3
Visit 3				
0-hour	92.3	90.8	90.9	92.2
2-hour	94.0	95.0	94.1	92.7
Visit 4				
0-hour	93.5	92.6	91.0	92.2
2-hour	94.2	94.1	93.0	91.6
4-hour	100.7	101.1	96.8	94.9
6-hour	93.7	93.0	94.3	92.1

PROTOCOL #40 – MEAN VALUES FOR SERUM GLUCOSE BY TREATMENT GROUP [91:172]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Visit 5				
0-hour	93.2	91.9	92.4	90.5
2-hour	93.6	94.5	94.8	89.9
4-hour	100.1	100.8	99.8	95.0
6-hour	96.3	95.2	92.4	92.3
Visit 6				
0-hour	92.4	92.1	92.1	91.2
2-hour	94.0	94.8	90.8	89.6
4-hour	100.6	102.8	93.1	94.6
6-hour	93.8	95.3	91.0	88.8

Urinalysis results were said to have revealed no clinically significant trends within treatments when pre-dose visit 2 results were compared with the terminal visit results, or between treatments [91:173].

Inhalations Required To Empty Capsules

A total of 41.8% of the capsules were completely emptied with one inhalation, 49.5% were completely emptied with two inhalations and 8.0% required three inhalations. Only 0.6% of capsules were not completely emptied after three inhalations. With close to 60% of capsules requiring more than one inhalation, checking the capsule for complete emptying and reinhalation will have to be salient labeling instructions [91:175].

041 A TWELVE-WEEK, DOUBLE-BLIND, PARALLEL GROUP TRIAL COMPARING THE SAFETY, TOLERABILITY AND EFFICACY OF FORMOTEROL DRY POWDER CAPSULES FOR INHALATION DELIVERED BY A SINGLE-DOSE INHALER VERSUS ALBUTEROL METERED-DOSE INHALER (MDI) VERSUS PLACEBO IN PATIENTS WITH MILD TO MODERATE ASTHMA

SUMMARY

This was a Phase III, multicenter, randomized, double-blind, double-dummy, parallel-group, 12-week study of two doses (12 or 24 μg) of twice daily inhaled formoterol fumarate dry powder compared with four times daily albuterol metered dose inhaler and matching placeboes. This protocol was virtually identical to protocol #40 except that additional urine collections were performed in this protocol for pharmacokinetic analyses. This study randomized 554 adolescent and adult patients in the same age range (12-75 years) and asthma severity as in protocol #40.

Serial 12-hour spirograms were performed at weeks 0, 4, 8 and 12 and showed post-treatment improvement with all treatments, including placebo. 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. This duplicates findings in protocol #40. 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, 19.4 and 26.1% improvement over the pretreatment baseline for the low and high formoterol doses respectively compared with 5.8% for albuterol and 7.9% for placebo. After visit 2, the formoterol groups showed higher morning-visit, pre-treatment $FEV_{1.0}$ values, consistent with sustained trough improvement in flows over the 12 weeks of 10.3-18.9% over the week 0 pretreatment baseline compared with less than 6.5% for placebo and albuterol. The formoterol 24 μg b.i.d. group was found to be statistically superior to the formoterol 12 μg b.i.d. group at most post-treatment time points during all visits. This is in contrast to protocol #40 in which later visits showed post-treatment mean $FEV_{1.0}$ values between the two formoterol groups that were just slightly beneath the level of statistical significance. Multiple analyses were performed on all primary and secondary variables to compare the two formoterol doses. 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. The $FEV_{1.0}$ AUC also showed superiority of the larger formoterol dose over the smaller at all visits for all randomized patients. No other secondary endpoint reviewed above demonstrated a preponderance of statistically significant differences between the two formoterol doses.

Both formoterol treatments showed lower mean peaks and less sustained flow increases; i.e., earlier declines toward trough values over the 3-month treatment period. These results suggested that tachyphylaxis may have developed with chronic use of this drug. The 12-hour $FEV_{1.0}$ AUC supported these observations for both formoterol doses and for albuterol. This finding supports a similar finding in protocol #40, in which only

the highest formoterol dose and albuterol showed evidence of tachyphylaxis. 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.

Five AE's were more frequent with formoterol treatment than with placebo and were dose proportional; fatigue, muscle cramps, insomnia, nervousness and tremor. The last of these, tremor, was the only AE with a frequency greater than placebo that was dose-proportional in both US pivotal trials, this study and protocol #40. Although the highest formoterol dose was associated with more discontinuations because of asthma, as in protocol #40, placebo treatment was associated with the most asthma SAE's of any treatment. Mean serum glucose values rose by about 10 mg/dL in both formoterol groups at the fourth post-treatment hour. A smaller rise was seen with albuterol. About 50% of formoterol capsules required more than one inhalation to empty, but only 0.2% failed to empty completely after three inhalations.

OBJECTIVES

This was a pivotal multicenter study of two doses of formoterol compared with an active control and with placebo to determine efficacy, tolerability, safety and examine the dose-response relationship [178:1, 14].

PROTOCOL

This Phase III, multicenter, randomized, double-blind, double-dummy, parallel-group study of two doses of formoterol dry powder administered by inhalation twice daily compared with albuterol metered dose inhaler administered four times daily and matching placeboes in adolescent and adult patients with mild to moderate asthma [178:1, 15].

There were two periods in the trial. The first (visits 1-2), consisted of a 2-week, screening, run-in, baseline period. Patients received placebo matched to formoterol and placebo matched to albuterol administered in a single-blind, double-dummy manner, and albuterol as rescue medication. The second (visits 2–6), was a 12-week double-blind treatment period in which patients were randomly assigned to one of three active drugs or placebo. There were 12-hour observation periods at visits 2, 4, 5, and 6. An 8-hour washout period free of rescue medication was required prior to each visit and baseline spirometry. Patients receiving b.i.d. theophylline therapy were not to take their evening theophylline dose prior to the trial visits and their morning theophylline dose on the day of all trial visits, with the exception of visit 3.

For all patients enrolled at 10 designated trial centers, a 2-channel Holter monitor was used for 24-hour continuous electrocardiographic monitoring 2-7 days after visit 1, on the day of visit 3, and 2-7 days after visit 5. The Holter recording obtained after visit 1 was the baseline recording for comparison to the Holter recordings obtained at visits 3 and 5. Holter monitoring was not initiated within eight hours after receiving albuterol rescue [178:15-6].

PROTOCOL #41 – SCHEDULE OF PROCEDURES [178:16, 30]						
Procedure	Visits (Weeks)					
	1 (-2)	2 (0)	3 (2)	4 (4)	5 (8)	6 (12)
Informed Consent	X					
Medical History	X					
Smoking History	X					
Concomitant Medications	X	X	X	X	X	X
Complete Physical Examination	X					X
Interim Physical Examination		X	X	X	X	
Adverse Experience Recording*		X	X	X	X	X
Asthma Exacerbation Recording		X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Electrocardiogram	X	X	X	X	X	X
Laboratory Analysis (blood and urine)**	X	X	X	X	X	X
Serum Theophylline Level**	X	X	X	X	X	X
Serum Pregnancy Test**	X	X	X	X	X	X
Urine Pregnancy Test		X				
Urine Drug Screen**	X					
$FEV_{1.0}$ Reversibility to Beta-2-agonist	X					
Spirometry pre-and post-dose		X	X	X	X	X
Chest Radiograph***	X					
24-hour Holter Monitoring****	X		X		X	

* Case report form and patient diary record
** Central Laboratory
*** Unless chest radiograph with normal findings or findings consistent with asthma has been obtained within the 12 months prior to Visit 1.
**** For designated centers only, 2-7 days after Visits 1 and 5, and on the day of Visit 3

TREATMENT

A double-dummy technique was used with separate placebo MDI's matched to albuterol MDI's and placebo capsules matched to formoterol capsules. Trial medications were to be administered between 6:00–9:00 A.M. (morning dose), 12:00–3:00 P.M. (midday dose), 6:00–9:00 P.M. (early-evening dose) and 10:00 P.M.–1:00 A.M. (bedtime dose) throughout the course of the trial. The morning dose of trial medication on the trial visit day was to be administered 11.5 to 12.5 hours from the time the early-evening dose was taken the evening before the visit. If this schedule was not possible, the visit was to be rescheduled. All trial visits were to be scheduled to begin between 6:00–9:00 A.M. The MDI's were designated as 'A' and '2A,' the active and placebo inhalers. Active and placebo dry powder capsules were distributed in blister packs. Dosing with the trial inhalers was as follows:

Morning (1st) and Early Evening (3rd) Doses

Take two inhalations for inhaler A (or 2A) and inhale the contents of two capsules from the Aeroliser inhaler.

Midday (2nd) and Bedtime (4th) Doses

Take two inhalations from inhaler A (or 2A).

At visits 2, 4, 5, and 6, the midday (second) dose of trial medication was to be administered after spirometry, vital signs, ECG and laboratory samples were collected at six hours. At visits 2, 4, and 5, the early-evening (third) dose of trial medication was to be administered after spirometry and vital signs were performed at 12 hours. At visit 6, the early-evening (third) dose was not to be administered (i.e., the last dose of trial medication was the midday (second) dose on the day of visit 6).

For each inhalation capsule, patients were instructed to inhale once, and then to open the Aeroliser inhaler to check for complete emptying of the capsule. If complete emptying had not been achieved, the patient was instructed to repeat the inhalations up to three times, checking for complete emptying of the capsule after each attempt. If the patient still had problems emptying the capsule, he/she was instructed to report this to the investigator at the next visit, at which time the investigator was to document the problem in the source documents [178:23-5].

The formoterol formulation used in this, and in the other large pivotal trial #40, was #Q874, a blue:clear gelatin capsule imprinted with black ink that contained 12 µg of formoterol fumarate and 25 mg lactose dry powder. An identical placebo capsule contained only lactose dry powder and was designated as formulation #Q966 [7:195, 204, 208-9]. 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 #41 – TREATMENT MATERIALS [178:208]			
Unit Drug	**Dose**	**Batch Number**	**Formulation Number**
12 µg formoterol blister	formoterol 12 µg card	E-15586	H-3891
	formoterol 12 µg capsule	E-15491	H-3831
	placebo capsule	E-15493	H-3833
24 µg formoterol blister	formoterol 24 µg card	E-15585	H-3890
	formoterol 12 µg capsule (2)	E-15491	H-3831
Placebo blister	placebo card	E-15587	H-3892
	placebo capsule	E-15493	H-3833

Patients experiencing symptoms between visits were allowed to take inhaled albuterol rescue medication, not to exceed 180 µg (two inhalations) at any one time and 720 µg (eight inhalations) during any 24-hour period. Continued symptoms despite maximal rescue treatment was an indication for the patient to contact the investigator for

further evaluation. Albuterol rescue treatment within eight hours prior to a trial visit was an indication for the visit to be rescheduled. Patients becoming symptomatic during the observation period at any visit were to be treated with either the MDI or a nebulizer (dose unspecified). More than one dose of nebulized albuterol was considered as an asthma exacerbation.

Allowable concomitant regular asthma therapy included 12-hour sustained release theophylline and inhaled corticosteroids if the dose had been stable prior to enrollment. The same formulation of inhaled corticosteroids had to be maintained throughout the trial and at the pre-trial dose. Theophylline serum level had to have been within the therapeutic range prior to starting the trial and individual dose adjustments were allowed at the discretion of the investigator. Nasal corticosteroids and desensitization therapy were allowed if a stable dose had been maintained for at least one month before enrollment. Short-acting antihistamines were permitted but not during the four days prior to a trial visit. Oral contraceptives were also permitted.

Unacceptable concomitant therapies included: oral, parenteral, nebulized or aerosol β-agonists other than the trial and rescue medication; regular nonsustained release or 24-hour sustained release theophylline; cromolyn sodium; disodium cromoglycate; nedocromil; ketotifen; oral or inhaled anticholinergic therapy; nonpotassium sparing diuretics; β-blocking agents; quinidine/quinidine-like (antiarrhythmic) agents; tricyclic antidepressants; fluoxetine (Prozac); MAO inhibitors vaccinations with live-attenuated vaccines; long-acting antihistamines; and, any investigational drugs. Patients were asked to avoid aspirin, nonsteroidal anti-inflammatory drugs, codeine (and related drugs) and, if taking theophylline, to avoid medications known to alter the theophylline serum concentration [178:22, 27-9].

PATIENTS

There were 707 patients enrolled in the trial, and 554 patients were randomized into the double-blind treatment phase. Of the 153 patients who discontinued from the trial prior to randomization, four were terminated due to AE's, 14 discontinued due to abnormal laboratory values, 93 terminated for not meeting protocol criteria, 19 withdrew consent and 23 quit for 'other' reasons. Of the 554 randomized patients, 484 completed the double-blind phase (visits 2 through 6). Five-hundred and fifty-three randomized patients were included in the primary efficacy analysis of $FEV_{1.0}$ for at least one post-treatment time point: 139 in the formoterol 12 μg b.i.d., 135 in the formoterol 24 μg b.i.d., 138 in the albuterol 180 μg q.i.d., and 141 in the placebo treatment groups, respectively. One patient in the formoterol 24 μg b.i.d. treatment group was missing pre-dose spirometry at visit 2 and was not included in the efficacy analyses for any of the spirormetry variables or for the AUC $FEV_{1.0}$. Thirty-eight patients completed the pharmacokinetic portion of the trial. Of these, 9 received placebo, 10 got albuterol 180 μg q.i.d., 10 received formoterol 12 μg b.i.d., 9 got formoterol 24 μg b.i.d. Sixteen of the formoterol-treated patients completed all urine collections and were evaluated for pharacokinetics, the others having either terminated prematurely or incomplete urine collections [178:60].

PROTOCOL #41 – PATIENT BASELINE DEMOGRAPHIC CHARACTERISTICS OF TREATMENT GROUPS [178:66-7]						
Statistic	Characteristic	Formoterol 12	Formoterol 24	Albuterol	Placebo	Total
Counts (%)	Male	69 (50)	76 (56)	62 (45)	66 (47)	273 (49)
	Female	70 (50)	60 (44)	76 (55)	75 (53)	281 (51)
	Caucasian	113 (81)	116 (85)	123 (89)	121 (86)	473 (85)
	Black	13 (9)	13 (10)	4 (3)	13 (9)	43 (8)
	Other	13 (9)	7 (5)	11 (8)	7 (5)	38 (7)
Means (SD)	Age in years	32.6 (13.9)	32.6 (14.9)	33.8 (14.3)	33.5 (14.9)	33.1 (14.5)
	Height in cm	170.2 (10.4)	171.6 (10.3)	170.4 (9.2)	169.5 (10.6)	170.4 (10.1)
	Asthma Duration in mo	217.4 (148.4)	218.8 (150.2)	220.0 (160.2)	207.3 (160.2)	215.8 (154.5)
TOTAL NUMBERS		139	136	138	141	554

All patient inclusion/exclusion criteria were reviewed at visits 1 and 2 prior to randomization.

Inclusion Criteria

These were identical to those enumerated for protocol #40 [178:20].

Exclusion Criteria

These were also identical to those found in protocol #40 [178:20-3].

PARAMETERS

These are identical to Protocol #40 with one addition. A 12-hour urine collection was carried out for all patients enrolled at three designated centers determined before the start of the trial to measure the presence of unchanged and total formoterol fumarate. A series of samples were collected at Visit 2, 4 and 6.

At Visit 1 or 2, a baseline urine sample was collected prior to the administration of any trial medication. At Visit 2, a 12 hour urine collection was obtained beginning at the time of administration of the first dose of trial medication. At Visit 6, urine was collected during the following time intervals after administration of the morning (first) dose of trial medication.

0-2 hours
2-4 hours
4-6 hours
6-8 hours
8-12 hours

All urine specimens were subject to pharmacokinetic analysis of formoterol [178:32-4, 45-8].

EFFICACY

Primary

Serial 12-hour spirograms were performed at visits 2, 4, 5 and 6 (weeks 0, 4, 8 and 12). The serial time points for each spirogram were baseline, before morning medication had been given, and post-treatment timepoints of 5, 15, 30, 60 minutes and hourly through the twelfth hour. These spirograms showed post-treatment mean $FEV_{1.0}$ improvement with all treatments, including placebo. The two formoterol doses provided the largest improvement which were dose proportional, became near-maximal at 30 minutes after dosing and peaked at about the third hour. These mean values declined very little from their peak during the 12-hour follow-up period at visit 2. After visit 2, the formoterol groups showed higher pre-treatment $FEV_{1.0}$ values, consistent with trough improvement in morning flows. Albuterol produced a peak effect at about one hour, which gradually diminished to a minimum at the sixth hour after which another treatment was administered. The mean $FEV_{1.0}$ 60 minutes after the second albuterol treatment at the seventh post-treatment hour was usually higher than the first peak at the first post-treatment hour, a comparison of hours 1 and 7. The mean albuterol peaks, at 1 and 7 hours post-treatment, were usually between the mean $FEV_{1.0}$ values for the two formoterol doses at the same post-treatment time points. Figures 5-8 at the end of this document illustrate all of these observations. [181:318, 320, 322, 324, 326].

The mean $FEV_{1.0}$ and percent change from baseline are presented in the table below for the second, fourth, fifth and sixth visits (double-blind weeks 0, 4, 8 and 12) for pre-treatment and post-treatment hours 1, 3, 6, 7 and 12 to capture the various peak and trough values for all groups. The number of patients represented by each cell is different for each treatment at each visit but approximations are about 140 patients in each treatment group at visit 2 and about 120 at visits 4, 5 and 6. Percent changes at visits 4, 5 and 6 reference the visit 2 (week 0) pre-treatment baseline and are calculated only for those patients who have not dropped out [178:71-2, 10/27/97 Protocol 41:3-6].

PROTOCOL #41 – $FEV_{1.0}$ MEAN AND PERCENT CHANGE FROM BASELINE AT WEEKS '0' THROUGH '12' FOR ALL TREATMENTS AT SELECTED POST-TREATMENT TIME POINTS [178:68, 73-6, 78-81, 83-6, 10/27/97 Protocol 41:3-6]

	Formoterol 12 L (% Change)	Formoterol 24 L (% Change)	Albuterol L (% Change)	Placebo L (% Change)
Visit 2 (Week 0)				
Pre-Treatment	2.3 (0.0)	2.4 (0.0)	2.3 (0.0)	2.3 (0.0)
1 Hour	2.9 (27.5)*†	3.1 (37.1)*†‡	3.0 (31.5)*	2.4 (5.2)
3 Hours	3.0 (31.6)*†	3.2 (41.6)*†‡	2.8 (23.7)*	2.5 (7.5)
6 Hours	2.9 (28.8)*†	3.1 (37.9)*†‡	2.6 (11.5)*	2.4 (5.0)
7 Hours	2.9 (26.8)*	3.1 (36.5)*‡	3.0 (34.5)*	2.4 (5.4)
12 Hours	2.9 (25.1)*†	3.0 (32.4)*†‡	2.6 (12.5)*	2.4 (3.2)
Visit 4 (Week 4)				
Pre-Treatment	2.6 (11.5)*†	2.7 (16.9)*†	2.3 (0.4)	2.4 (3.9)
1 Hour	3.0 (30.0)*	3.1 (40.4)*†‡	3.0 (31.3)*	2.4 (7.6)
3 Hours	3.0 (31.9)*†	3.2 (41.0)*†‡	2.8 (23.0)*	2.5 (9.8)

PROTOCOL #41 – $FEV_{1.0}$ MEAN AND PERCENT CHANGE FROM BASELINE AT WEEKS '0' THROUGH '12' FOR ALL TREATMENTS AT SELECTED POST-TREATMENT TIME POINTS [178:68, 73-6, 78-81, 83-6, 10/27/97 Protocol 41:3-6]

	Formoterol 12 L (% Change)	Formoterol 24 L (% Change)	Albuterol L (% Change)	Placebo L (% Change)
6 Hours	2.9 (25.4)*†	3.0 (33.4)*†‡	2.6 (10.8)	2.4 (7.2)
7 Hours	2.9 (24.3)*	3.0 (33.3)*‡	3.0 (31.6)*	2.4 (6.9)
12 Hours	2.8 (19.6)*†	2.9 (27.5)*†	2.6 (10.0)	2.4 (5.5)
Visit 5 (Week 8)				
Pre-Treatment	2.6 (10.3)†	2.8 (15.3)*†	2.4 (3.3)	2.4 (6.5)
1 Hour	2.9 (27.2)*	3.1 (37.6)*‡	3.0 (31.9)*	2.5 (10.1)
3 Hours	3.0 (29.9)*	3.2 (39.5)*†‡	2.8 (23.7)*	2.5 (12.6)
6 Hours	2.8 (22.8)*†	3.0 (32.9)*†‡	2.5 (10.3)	2.5 (9.8)
7 Hours	2.8 (21.9)*†	3.0 (32.6)*‡	3.0 (31.7)*	2.5 (10.0)
12 Hours	2.7 (16.2)*	2.9 (26.3)*†‡	2.5 (10.1)	2.4 (7.2)
Visit 6 (Week 12)				
Pre-Treatment	2.6 (11.4)*†	2.7 (17.0)*†	2.3 (1.8)	2.3 (5.0)
1 Hour	3.0 (29.0)*	3.1 (38.1)*†‡	2.9 (28.3)*	2.4 (8.3)
3 Hours	3.0 (30.8)*†	3.2 (39.4)*†‡	2.7 (18.3)*	2.5 (10.7)
6 Hours	2.9 (24.5)*†	3.0 (32.7)*†‡	2.4 (6.0)	2.5 (9.2)
7 Hours	2.8 (21.9)*	3.0 (32.0)*‡	2.9 (29.4)*	2.4 (7.2)
12 Hours	2.8 (19.4)*†	2.9 (26.1)*†‡	2.5 (5.8)	2.4 (7.9)

* Formoterol or Albuterol $FEV_{1.0}$ significantly different from Placebo ($p \leq 0.05$)
† Formoterol $FEV_{1.0}$ significantly different from Albuterol ($p \leq 0.05$)
‡ Formoterol 24 $FEV_{1.0}$ significantly different from Formoterol 12 ($P \leq 0.05$)

The placebo group showed a 3.9-12.6% increase in mean $FEV_{1.0}$ at all time points after the visit 2 pre-treatment baseline in the table above. This was as substantial a placebo effect as was seen in the other pivotal trial. Both formoterol groups were statistically significantly superior to placebo at virtually all of the three visits and five time points shown in the table. This same measure showed statistically significant superiority of the albuterol group over placebo at each post-treatment time point at visit 2, but was consistently superior to placebo over visits 4, 5 and 6 only at hours 1, 3 and 7, two of which are times of albuterol peak effect (hours 1 and 7). Both formoterol doses were statistically superior to albuterol at many time points during most visits, particularly at the pretreatment baseline, at the time of peak formoterol effect (hour 3) and at the times of trough albuterol effect (hours 6 and 12). The formoterol 24 μg b.i.d. group was found to be statistically superior to the formoterol 12 μg b.i.d. group at post-treatment time points during all visits. This is in contrast to the other pivotal trial in which later visits showed post-treatment mean $FEV_{1.0}$ values in the formoterol 24 μg b.i.d. group that were just slightly beneath the level of statistical significance [178:68, 73-6, 78-81, 83-6, 10/27/97 Protocol 41:3-6].

Although not identified as a separate outcome variable, the pre-treatment $FEV_{1.0}$ at each visit provided some insight into the relative 'trough' effect of the four treatments. The shaded cells in the table above represent successively fewer patients at each subsequent visit and the percent change refers to changes from the pre-treatment baseline at visit 2. Both formoterol groups had trough mean $FEV_{1.0}$ values that were 10.3-18.9% over baseline and comparable to one another. Albuterol and placebo groups showed up to 6.5% trough improvements over baseline. A separate analysis of 'acceptable' patients, did not affect the overall interpretation of these data [178:50-1, 65, 72].

The onset of action of action was determined at each visit by serial spirograms performed before and for one hour after the first dose of the blinded treatment drug and is shown in the following table. Percent changes from baseline are all in reference to the visit 2 (Week 0) pretreatment baseline.

PROTOCOL #41 – ONSET OF ACTION AS SHOWN BY $FEV_{1.0}$ MEAN AND PERCENT CHANGE FROM BASELINE AT WEEKS '0' THROUGH '12' FOR ALL TREATMENTS AT SELECTED EARLY POST-TREATMENT TIME POINTS [178:69, 73, 75, 78, 80, 83, 85, 10/27/97 Protocol 41:3, 6]

	Formoterol 12 L (% Change)	Formoterol 24 L (% Change)	Albuterol L (% Change)	Placebo L (% Change)
Visit 2 (Week 0)				
Pre-Treatment	2.3 (0.0)	2.4 (0.0)	2.3 (0.0)	2.3 (0.0)
5 Minutes	2.7 (18.4)*†	2.9 (27.7)*‡	2.9 (24.7)*	2.3 (0.4)
15 Minutes	2.8 (21.9)*	3.0 (31.4)*‡	2.9 (28.0)*	2.3 (1.4)
30 Minutes	2.9 (25.0)*	3.1 (33.0)*‡	3.0 (29.7)*	2.4 (2.7)
60 Minutes	2.9 (27.5)*	3.1 (37.1)*†‡	3.0 (31.5)*	2.4 (5.2)
Visit 4 (Week 4)				
Pre-Treatment	2.6 (11.5)*†	2.7 (15.9)*†	2.3 (0.4)	2.4 (3.9)
5 Minutes	2.8 (21.0)*	2.9 (29.3)*‡	2.8 (24.2)*	2.4 (3.8)
15 Minutes	2.8 (23.9)*	3.0 (34.1)*‡	2.9 (28.3)*	2.4 (3.8)
30 Minutes	2.9 (27.6)*	3.1 (37.2)*‡	2.9 (29.6)*	2.4 (5.7)
60 Minutes	3.0 (30.0)*	3.1 (40.4)*†‡	3.0 (31.3)*	2.4 (7.6)
Visit 5 (Week 8)				
Pre-Treatment	2.6 (10.3)*†	2.6 (15.3)*†	2.4 (3.3)	2.4 (6.5)
5 Minutes	2.7 (20.0)*	2.9 (27.2)*‡	2.8 (25.9)*	2.4 (4.7)
15 Minutes	2.8 (22.4)*	3.0 (30.8)*‡	2.9 (29.5)*	2.4 (6.3)
30 Minutes	2.9 (24.8)*	3.0 (32.6)*‡	3.0 (31.1)*	2.4 (8.2)
60 Minutes	2.9 (27.2)*	3.1 (37.6)*‡	3.0 (31.9)*	2.5 (10.1)

PROTOCOL #41 – ONSET OF ACTION AS SHOWN BY $FEV_{1.0}$ MEAN AND PERCENT CHANGE FROM BASELINE AT WEEKS '0' THROUGH '12' FOR ALL TREATMENTS AT SELECTED EARLY POST-TREATMENT TIME POINTS [178:59, 73, 76, 78, 80, 83, 85, 10/27/97 Protocol 41:3, 5]				
	Formoterol 12 L (% Change)	Formoterol 24 L (% Change)	Albuterol L (% Change)	Placebo L (% Change)
Visit 6 (Week 12)				
Pre-Treatment	2.0 (11.4)*†	2.7 (17.0)*†	2.3 (1.6)	2.3 (5.0)
5 Minutes	2.8 (22.3)*	2.9 (30.6)*‡	2.8 (21.8)*	2.4 (5.8)
15 Minutes	2.9 (25.3)*	3.0 (32.9)*	2.8 (26.0)*	2.4 (5.3)
30 Minutes	2.9 (27.0)*	3.1 (35.7)*	2.9 (25.5)*	2.4 (5.8)
60 Minutes	3.0 (29.0)*	3.1 (38.1)*†‡	2.9 (28.3)*	2.4 (8.3)

* Formoterol or Albuterol $FEV_{1.0}$ significantly different from Placebo ($p \leq 0.05$)
† Formoterol $FEV_{1.0}$ significantly different from Albuterol ($p \leq 0.05$)
‡ Formoterol 24 $FEV_{1.0}$ significantly different from Formoterol 12 ($P \leq 0.05$)

All three active treatments provide greater bronchodilation than placebo at all visits. During visit 2, both the higher formoterol dose and albuterol showed superiority to the smaller formoterol dose at some time points after the first treatment. Unlike the other pivotal study (protocol #40), separation of onset of action efficacy between the two formoterol doses was noted at all visits and most time points.

Secondary

SPIROGRAPHIC

The other visit-obtained, spirographically-derived variables including the $FEV_{1.0}$ AUC showed findings that were qualitatively very similar to the primary efficacy variable. The mean values for each group at each visit/week are displayed as shaded cells in the table below:

PROTOCOL #41 – $FEV_{1.0}$ AUC (Liters x Hours) FOR ALL RANDOMIZED PATIENTS [178:92-5]					
Visit (Week)	Statistic	Formoterol 12	Formoterol 24	Albuterol	Placebo
2 (0)	N	139	135	138	141
	Mean	5.3	7.1	5.5	0.9
	S.D.	4.4	5.0	4.1	4.3
4 (4)	N	127	121	132	129
	Mean	6.4	8.1	5.1	1.2
	S.D.	5.4	6.3	5.0	5.5
5 (8)	N	123	116	128	122
	Mean	5.6	7.9	5.0	1.7
	S.D.	5.7	6.3	5.3	6.4
6 (12)	N	121	114	126	116
	Mean	6.0	7.8	4.2	1.7
	S.D.	6.2	6.2	5.0	6.3

The $FEV_{1.0}$ AUC data support the observation that reduced efficacy with chronic treatment (tachyphylaxis) was apparent in both formoterol groups. By this measure, it also appears as a feature of the albuterol group [178:92-5].

PATIENT DIARY DATA

These were averaged (or calculated as a percentage) over the entire treatment period from visit 2 to the final visit (referred to as 'overall'), and over each period between two consecutive visits from visit 2 to the final visit. The pre-treatment average of the measurements from the seven days prior to randomization (visit 2) was considered the baseline for the diary data [184:5].

Peak Expiratory Flow Rates

Over each treatment period and 'overall,' the AM PEFR showed a statistically significant difference ($p \leq 0.05$) from placebo and from albuterol for the 24 μg formoterol dose. The 12 μg formoterol dose was significantly different from albuterol 'overall' and over each treatment period. It was also significantly different from placebo 'overall' and over the first four weeks (visit 4) of treatment, but not over the 5-8 and 9-12 week treatment periods (visits 5 & 6). Albuterol achieved statistical significance from placebo by this measure only over the first treatment period (weeks 1-4, visit 4). Formoterol 24 never achieved statistical significance over formoterol 12 at any visit. The PM PEFR showed similar results. Both formoterol doses were statistically significantly different from placebo and albuterol, but not from each other, 'overall'. Albuterol never achieved statistical significance over placebo [178:105-9]. As in the other pivotal study, only summary tables of mean differences between groups and the resultant Type I Errors at visits 4, 5, 6 and 'overall' were supplied by the sponsor, but the AM and PM PEFR variables seemed to be less sensitive measures of efficacy than were the $FEV_{1.0}$ end points.

Nocturnal Asthma Symptom Score

Nocturnal asthma symptom scores for all randomized patients were calculated over each treatment interval and 'overall' and are presented in the following table.

PROTOCOL #41 – NOCTURNAL ASTHMA SYMPTOM SCORES FOR ALL RANDOMIZED PATIENTS [178:100]

Visit (Weeks)	Statistic	Formoterol 12	Formoterol 24	Albuterol	Placebo
2*	N	136	135	137	140
(Baseline)	Mean (SD)	0.6 (0.7)	0.7 (0.8)	0.7 (0.8)	0.8 (0.9)
4	N	135	134	136	138
(1-4)	Mean (SD)	0.4 (0.5)	0.4 (0.6)	0.7 (0.7)	0.8 (0.8)
5	N	124	121	130	126
(5-8)	Mean (SD)	0.4 (0.5)	0.3 (0.5)	0.7 (0.7)	0.7 (0.8)
6	N	121	118	128	122
(9-12)	Mean (SD)	0.4 (0.6)	0.4 (0.5)	0.6 (0.7)	0.7 (0.8)
Overall	N	135	134	136	138
(1-12)	Mean (SD)	0.4 (0.5)	0.4 (0.6)	0.6 (0.7)	0.8 (0.8)

PROTOCOL #41 – NOCTURNAL ASTHMA SYMPTOM SCORES FOR ALL RANDOMIZED PATIENTS [178:100]					
Visit (Weeks)	Statistic	Formoterol 12	Formoterol 24	Albuterol	Placebo
* pre-treatment average from the 7 days prior to randomization (Lower mean scores indicate less severe symptoms.)					

Both formoterol treatment groups were statistically significantly different from both placebo and albuterol groups by this measure at each and 'overall' visits with one exception. Formoterol 12 was not significantly different from albuterol over weeks 9-12 (visit 6), but achieved statistical significance over the other two treatment periods and 'overall'. However, the albuterol group was not significantly different from placebo nor were the two formoterol doses significantly different from one another for any treatment period, or 'overall' comparisons [178:101].

Combined Asthma Symptom Score

The combined asthma symptom scores for all randomized patients were calculated over each treatment interval and 'overall' and are presented in the following table.

PROTOCOL #41 – COMBINED ASTHMA SYMPTOM SCORES FOR ALL RANDOMIZED PATIENTS [178:103]					
Visit (Weeks)	Statistic	Formoterol 12	Formoterol 24	Albuterol	Placebo
2*	N	136	135	137	140
(Baseline)	Mean (SD)	1.0 (0.7)	1.0 (0.7)	1.1 (0.7)	1.2 (0.8)
4	N	135	134	136	139
(1-4)	Mean (SD)	0.7 (0.6)	0.7 (0.6)	1.0 (0.6)	1.1 (0.8)
5	N	124	121	129	127
(5-8)	Mean (SD)	0.7 (0.6)	0.6 (0.6)	0.9 (0.6)	1.0 (0.8)
6	N	121	118	128	122
(9-12)	Mean (SD)	0.7 (0.7)	0.6 (0.6)	0.9 (0.6)	1.0 (0.8)
Overall	N	135	134	136	139
(1-12)	Mean (SD)	0.7 (0.6)	0.7 (0.6)	0.9 (0.6)	1.0 (0.7)
* pre-treatment average from the 7 days prior to randomization (Lower mean scores indicate less severe symptoms.)					

Both formoterol treatment groups were statistically significantly different from the albuterol and from placebo groups by this measure for each and 'overall' visits. The albuterol group was not statistically separable from placebo. The two formoterol groups were not different from one another [178:104].

Rescue Medication Use

The median number of puffs of rescue albuterol taken during the AM and during the PM were separately analyzed for all randomized patients and showed similar findings. 'Overall' both formoterol groups and the albuterol group were statistically superior (used fewer puffs post-treatment) to placebo over both time periods (AM and PM). The night time (PM) measure additionally showed 'overall' significance of the formoterol 24 group

compared with the albuterol group. The two formoterol groups were not separable by this measure during either AM or PM [178:112-7].

OTHER SECONDARY EFFICACY ENDPOINTS

These eclectic categorical summary parameters for the double-blind treatment period included percentage of days with symptoms, percentage of nights with awakening, percentage of patients with one or more asthma exacerbations, number of asthma exacerbations and percentage of nights in which patients took rescue albuterol [178:121-3].

PROTOCOL #41 – OTHER SECONDARY EFFICACY ENDPOINTS [178:121-3]				
Parameter	Formoterol 12	Formoterol 24	Albuterol	Placebo
Days With Symptoms (%)	48	46	65	66
Nights Awakened (%)	29	26	42	46
Exacerbations (%)	13	10	12	20
Number Exacerbations	24	16	21	33
Nights Took Rescue (%)	25	24	33	48

The percent of days with symptoms, percent nights with awakening and percent nights in which patients took rescue albuterol all qualitatively favored the superiority of both formoterol doses over placebo and over albuterol. By inspection of the table above, there is only the slightest indication that the larger formoterol dose was superior to the smaller dose.

Dose-Response

This was performed on primary and secondary efficacy variables essentially comparing the two formoterol doses. The $FEV_{1.0}$ endpoint showed statistically significant superiority of the 24 μg dose over the 12 μg dose for all randomized patients at all post-treatment time points at every visit, except for the 12 hour time point at visit 4. The $FEV_{1.0}$ AUC also showed superiority of the larger formoterol dose over the smaller at all visits for all randomized patients. No other secondary endpoint reviewed above demonstrated a preponderance of statistically significant differences between the two formoterol doses [178:124].

SAFETY

Adverse Events

The following table shows the number and percent of patients reporting at least one adverse event during the 12-week double-blind treatment period for all randomized patients. If an AE was reported by $\geq$ 2% of the patients in any one of the treatment groups then the AE was captured for all treatment groups. The table includes only the subset of these AE's in which the percent was greater for the highest formoterol dose than for placebo [178:128-31].

PROTOCOL #41 – NUMBER (%) OF ALL RANDOMIZED PATIENTS REPORTING AE's DURING TREATMENT WHERE AE FREQUENCY ≥ 2% FOR ANY GROUP AND FORMOTEROL 24 > PLACEBO PERCENT [178:129-30]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Total Treated	139 (100)	136 (100)	138 (100)	141 (100)
Total Reporting AE	95 (68.3)	88 (64.7)	96 (69.6)	95 (67.4)
Fatigue	3 (2.2)	4 (2.9)	3 (2.2)	1 (0.7)
Chest Pain	1 (0.7)	2 (1.5)	3 (2.2)	2 (1.4)
Abdominal Pain	2 (1.4)	3 (2.2)	8 (5.8)	2 (1.4)
Tooth Ache	0 (0.0)	3 (2.2)	0 (0.0)	2 (1.4)
Viral Infection	22 (15.8)	14 (10.3)	21 (15.2)	11 (7.8)
Muscle Cramps	3 (2.2)	5 (3.7)	1 (0.7)	1 (0.7)
Anxiety	3 (2.2)	2 (1.5)	1 (0.7)	0 (0.0)
Insomnia	3 (2.2)	4 (2.9)	2 (1.4)	2 (1.4)
Nervousness	1 (0.7)	3 (2.2)	2 (1.4)	0 (0.0)
Tremor	4 (2.9)	10 (7.4)	1 (0.7)	2 (1.4)
Bronchitis	0 (0.0)	3 (2.2)	2 (1.4)	2 (1.4)
Epistaxis	0 (0.0)	3 (2.2)	0 (0.0)	2 (1.4)
Sinus Headache	0 (0.0)	2 (1.5)	4 (2.9)	2 (1.4)
Pharyngitis	13 (9.4)	11 (8.1)	20 (14.5)	7 (5.0)
Rhinitis	5 (3.6)	9 (6.6)	13 (9.4)	8 (5.7)
Rash	1 (0.7)	2 (1.5)	3 (2.2)	1 (0.7)

AE's in this table that were also found in a similarly constructed table for protocol #40 include: muscle cramps, insomnia, nervousness, tremor, viral infection and rhinitis. The first three of these are recognized complications of beta-agonist use. The shaded rows emphasize a subset of AE's that were more frequent for both formoterol doses than for placebo and that showed dose proportionality between the two formoterol doses. Tremor was the only dose-proportional AE that was found in both pivotal trials. Albuterol was associated with more frequent chest pain, abdominal pain, sinus headache, pharyngitis, rhinitis and rash than was either formoterol dose and these findings were not replicates of protocol #40.

Serious Adverse Events

A total of thirteen SAE's were reported during the double-blind treatment period of the trial and are narrated in some detail below, grouped by treatment [178:134, 136-43, 157-8].

1. A 12 year old female was hospitalized for an asthma exacerbation twelve days after beginning formoterol 12
2. A 26 year old male had an episode of urticaria and anaphylaxis two days after beginning formoterol 24 μg b.i.d. requiring Emergency Room treatment. He had experienced hives during the placebo run-in period and on the first day of drug dosing which resolved.

3. A 45 year old female who received formoterol 24 µg b.i.d. was hospitalized with an exacerbation of previously diagnosed sarcoidosis three weeks after starting treatment which required a course of oral steroids.
4. A 19 year old female was hospitalized for an asthma exacerbation ten days after starting treatment with formoterol 24 µg b.i.d.
5. A 66 year old female had a severe asthma exacerbation leading to a respiratory arrest, a cardiac arrest and death. She had been taking formoterol 24 µg b.i.d. for nineteen days at the time of the incident.
6. A 49 year old male had received formoterol 24 µg b.i.d. for twenty-five days when she suffered increasing respiratory symptoms and a respiratory arrest during the bronchodilator wash-out period prior to a visit.
7. A 33 year old female had been receiving formoterol 24 µg b.i.d. for thirteen days when she developed status asthmaticus.
8. A 13 year old female was hospitalized for status asthmaticus two and one half months after starting treatment with formoterol 24 µg b.i.d.
9. A 26 year old female died from an episode of hemorrhagic pancreatitis about two weeks after beginning albuterol 180 µg q.i.d.
10. A 74 year old female was hospitalized for elective urological surgery (bladder neck suspension and rectocoele repair) five weeks after beginning treatment with albuterol 180 µg q.i.d.
11. A 15 year old male was hospitalized for an asthma exacerbation six weeks after starting treatment with placebo.
12. A 12 year old male was hospitalized for an asthma exacerbation two months after starting treatment with placebo.
13. A 35 year old female was hospitalized for an elective hysterectomy two months after receiving placebo.

Four other serious SAE's were reported outside of the double-blind treatment period. A 31 year old male was hospitalized for acute appendicitis and volvulus of the omentum with infaction during the placebo run-in period. A 29 year old male had a motor vehicle accident the day after completing the trial. A 14 year old female suffered gastroenteritis with dehydration three weeks after completing the study. A 47 year old female underwent evaluation for a breast lump noted two months after completing the study as a member of the formoterol 12 µg b.i.d. group. This was diagnosed as breast cancer [178:134, 143-4].

Premature Discontinuations Due to Adverse Events

A total of 30 randomized patients were prematurely discontinued for safety reasons (AE's, abnormal tests or unsatisfactory therapeutic responses), 9 of which were the result of an SAE (numbers 1-3, 5-9 and 11 above) [178:145-57, Telecon 4/3/98 with Dr. Kathleen Creedon]. Patients who terminated early are listed below, grouped by treatment category, and include the SAE patients that were reported in more detail above.

Formoterol 12	7 = total
	4 asthma exacerbations

	1 dizziness
	1 elevated liver function tests
	1 elevated theophylline level
Formoterol 24	10 = total
	5 asthma exacerbations
	1 anaphylaxis/urticaria
	1 tremor
	1 sarcoidosis
	1 abnormal Holter (2.6 second ventricular pause)
Albuterol	4 = total
	1 nausea/headache/dizziness
	1 pancreatitis (death)
	1 positive pregnancy test
	1 abnormal Holter (increased PVC's)
Placebo	9 = total
	6 asthma exacerbations
	1 hypertension
	1 abnormal Holter (increased PVC's)
	1 unsatisfactory therapeutic response

The high frequency of asthma causing premature discontinuations because of SAE's in the higher formoterol dose (protocol #40) is not supported by the above data, where the placebo group shows the highest frequency.

Deaths

A 66 year old female died in an apparent asthma exacerbation 19 days after beginning formoterol 24 µg b.i.d. A 26 year old female died of hemorrhagic pancreatitis about two weeks after beginning albuterol 180 µg q.i.d. [178:157-8]

Vital Signs

These included pulse rate, respiratory rate, systolic and diastolic blood pressures. During the 12-hour visit days vital signs were determined prior to trial drug administration and at 30 minutes, 1 hour and hourly thereafter through 12 hours after the morning dose. There were four patients with maximum pulse rates > 120 beats/minute, one from each treatment group. These maximum pulse rates were 132 (formoterol 12 µg), 128 (formoterol 24 µg), 128 (albuterol) and 132 (placebo). The distribution of the three patients with high maximum systolic blood pressures > 180 mm Hg did not favor any treatment group. These maximum systolic pressures were 192 (formoterol 24 µg), 200 (albuterol) and 182 (placebo). High maximum diastolic pressures > 100 mm Hg occurred in 20 patients, 4 in the formoterol 12 µg group (range ———), 4 in the formoterol 24 µg group (range ———), 6 in the albuterol group (range ——— and 6 in the placebo group (range ———. [178:159-62].

Electrocardiograms

During the visits 2, 4, 5 and 6 standard 12-lead ECG's were obtained pre-dose, 2, 4 and 6 hours after trial drug administration. At visit 3, ECG's were taken pre-dose and 2 hours after trial drug administration. These were interpreted to fall into one of four mutually exclusive categories. Category 1 was normal; category 2 was abnormal but clinically insignificant; category 3 was abnormal and intermediate between categories 2 and 4; and, category 4 was abnormal and clinically significant. Counts and percentages of category 4 interpretations for each time point at each visit are shown in the table below [178:163].

PROTOCOL #41 – COUNTS (%) OF CATEGORY '4' ABNORMAL ELECTROCARDIOGRAM READINGS BY TREATMENT GROUP, VISIT AND OBSERVATION TIMEPOINT [178:164]

Visit # / Timepoint	Formoterol 12		Formoterol 24		Albuterol		Placebo	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Visit 2								
Total Category 4 = 38		19		10		5		4
0-hour (baseline)	139	6 (4.3)	135	4 (3.0)	138	1 (0.7)	140	1 (0.7)
2-hour	138	6 (4.3)	135	3 (2.2)	138	3 (2.2)	135	1 (0.7)
4-hour	139	3 (2.2)	136	2(1.5)	138	0 (0.0)	129	1 (0.8)
6-hour	139	4 (2.9)	135	1 (0.7)	138	1 (0.7)	123	1 (0.8)
Visit 4								
Total Category 4 = 28		8		8		6		6
0-hour	127	2 (1.6)	120	2 (1.7)	133	1 (0.8)	129	0 (0.0)
2-hour	127	3 (2.4)	119	2 (1.7)	132	3 (2.3)	124	2 (1.6)
4-hour	127	2 (1.6)	121	2 (1.7)	131	1 (0.8)	123	1 (0.8)
6-hour	124	1 (0.8)	121	2 (1.7)	127	1 (0.8)	124	3 (2.4)
Visit 5								
Total Category 4 = 21		6		4		5		6
0-hour	123	2 (1.6)	118	1 (0.8)	127	2 (1.6)	122	2 (1.6)
2-hour	123	2 (1.6)	118	2 (1.7)	127	2 (1.6)	121	1 (0.8)
4-hour	123	1 (0.8)	118	1 (0.8)	125	0 (0.0)	116	2 (1.7)
6-hour	122	1 (0.8)	118	0 (0.0)	119	1 (0.8)	114	1 (0.9)
Visit 6								
Total Category 4 = 29		10		0		9		10
0-hour	121	4 (3.3)	115	0 (0.0)	127	3 (2.4)	119	3 (2.5)
2-hour	121	3 (2.5)	115	0 (0.0)	126	3 (2.4)	114	3 (2.6)
4-hour	120	1 (0.8)	114	0 (0.0)	124	1 (0.8)	109	2 (1.8)
6-hour	120	2 (1.7)	114	0 (0.0)	121	2 (1.7)	106	2 (1.9)
All Visits & Timepoints								
Total Category 4		43		22		25		26

Generally, the total number of category 4 ECG's was highest at visit 2 and the number for each treatment declined at later visits for the two formoterol groups and increased at later visits for albuterol and placebo groups. The formoterol 12 μg group showed the most and the formoterol 24 μg group the least number, with albuterol and placebo groups falling somewhere between the two formoterol groups.

Concern that the arrythmogenicity of β-agonists could be related to prolongation of repolarization was addressed by analysis of the QTc interval, using the Bazett formula for rate correction which is division by the square root of the RR interval. Mean values by treatment group, visit and observation timepoint were unrevealing.

Eight patients showed a post-dose increase of ≥ 25% and/or a measured QTc interval of > 0.5 seconds at any time point in the study. These analytic cut points were selected retrospectively and were the only ones reported by the sponsor. Patients exceeding them included four in the formoterol 12 μg group, one in the albuterol group and three patients in the placebo group. None of these patients had a category 4 ECG interpretation [178:165-8].

Holter Monitor (24-hour continuous ECG)

This was obtained 2-7 days after visit 1 (during placebo run-in), on the day of visit 3 (after two weeks of treatment) and 2-7 days after visit 5 (after two months of treatment) for all patients enrolled at ten designated centers. The Holter monitor after visit 1 served as the baseline recording for comparison. Both formoterol groups and the placebo group showed a decrease in the 'Mean Total VPB/hour' from the the first to the third and fifth visits. The albuterol group demonstrated an increase in this measure at each successive visit. Similar findings for all groups were noted for the variable 'Most VPB/hour' with the exception of the formoterol 12 group. It showed a slightly higher value at visit 5 than at visits 1 or 3. Episodes of technical ventricular tachycardia, defined as three VPB's with a rate ≥ 100 beats/minute, were rare throughout the trial, occurring once in each group thoughout the three visits. A comparison of patients showing ventricular ectopy at visit 1 and at subsequent visits showed that the majority of patients had no evidence of ventricular ectopy at any time. A total of nine patients had no ectopy at baseline, but did have some on treatment and included three patients from each of the following groups: formoterol 24, albuterol and placebo. Inspection of similar endpoints applied to supraventricular premature beats was more variable across visits and treatments than was true for ventricular ectopy, however no treatment-related trends were evident. Mean, maximum and minimum heart rate information derived from the Holter monitor showed only similar mean values at all visits for all groups [178:168-72].

Clinical Laboratory

Fasting laboratory specimens were collected at all visits, prior to drug administration. The visit 2 baseline specimen was the last sample taken prior to patient exposure to double-blind treatment and the terminal lab sample was the last specimen obtained while the patients were on treatment. Values identified as 'high' incorporated patients who were within or below the normal range at baseline, who then experienced a

shift to above the normal range at the terminal visit. Values identified as 'low' included patients who were within or above the normal range at baseline, who then showed a shift to below that range at the terminal visit. The denominator for the percentage calculation is the total number of patients who fulfilled the baseline criterion.

Mean values of hematology laboratory variables for the four treatment groups at the baseline and terminal visits did not show any large or consistent changes. Categorical shifts, as described in the first paragraph, were also infrequent and inconsistent, as can be seen in the table below. Specifically the white blood cell count (WBC), which might have been expected to increase because of demargination mediated systemic adrenergic stimulation in formoterol and albuterol groups, did not do so by either measure (means or shift count) [178:173-5]. These findings confirm similar ones in the other pivotal trial.

PROTOCOL #41 – NUMBER (%) OF PATIENTS WITH FASTING HEMATOLOGY LAB VALUES SHIFTING TO OUTSIDE OF THE NORMAL RANGE BETWEEN THE BASELINE AND TERMINAL VISITS FOR ALL RANDOMIZED PATIENTS [178:175, Telecon 4/6/98 Kathleen Creedon]

	Formoterol 12		Formoterol 24		Albuterol		Placebo	
Lab Test	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)
WBC	2 (1.4)	2 (1.4)	0	2 (1.5)	1 (0.7)	1 (0.7)	0	0
RBC	0	0	0	0	0	0	0	0
Hgb	1 (0.7)	0	0	0	0	0	2 (1.4)	0
Hct	1 (0.7)	0	0	0	0	0	1 (0.7)	0
Neutrophils	2 (1.4)	0	3 (2.2)	0	1 (0.7)	0	1 (0.7)	0
Bands	0	1 (0.7)	0	0	0	0	0	0
Lymphocytes	0	0	0	0	1 (0.7)	0	0	0
Monocytes	0	1 (0.7)	0	2 (1.5)	0	0	0	2 (1.4)
Eosinophils	0	0	0	1 (0.7)	0	0	0	0
Basophils	0	0	0	0	0	0	0	0
Metamyelocytes	0	1 (0.7)	0	0	0	0	0	0
Myelocytes	0	0	0	1 (0.7)	0	0	0	0
Promyelocytes	0	0	0	0	0	0	0	0
Platelets	0	0	0	0	0	0	0	0

Mean values of chemistry laboratory variables by treatment group at baseline and terminal visits also did not show any obvious or consisten changes. Categorical shifts, as described in the first paragraph, were also infrequent and inconsistent, as can be seen in the table below. Conspicuously absent was evidence of trends toward hypokalemia or hyperglycemia, by either measure [178:175-7]. This agrees with the findings of the other pivotal study

PROTOCOL #41 – NUMBER (%) OF PATIENTS WITH FASTING CHEMISTRY LAB VALUES SHIFTING TO OUTSIDE OF THE NORMAL RANGE BETWEEN THE BASELINE AND TERMINAL VISITS FOR ALL RANDOMIZED PATIENTS [178:178]								
	Formoterol 12		Formoterol 24		Albuterol		Placebo	
Lab Test	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)	Low N (%)	High N (%)
Glucose	2 (1.4)	1 (0.7)	0	2 (1.5)	0	1 (0.7)	0	1 (0.7)
BUN	0	0	0	0	0		0	0
Creatinine	0	0	0	1 (0.7)	0		0	0
Sodium	1 (0.7)	0	0	0	0		0	0
Potassium	0	0	0	0	0		0	0
Chloride	0	0	0	0	0		0	0
Carbon Dioxide	0	0	0	0	0		0	0
Alk. Phosphatase	0	1 (0.7)	0	0	0		0	0
SGOT	0	1 (0.7)	0	2 (1.5)	0		0	2 (1.4)
SGPT	0	1 (0.7)	0	0	0		0	4 (2.8)
LDH	0	1 (0.7)	0	0	0		0	0
Bilirubin	0	0	0	1 (0.7)	0		0	1 (0.7)
Cholesterol	0	0	0	0	0		0	0
Trigycerides	0	0	0	2 (1.5)	0		0	3 (2.1)

Serum potassium and glucose were further evaluated. On visits 2-6 a second fasting specimen was collected two hours after trial drug administration. On the 12-hour visit days (visits 2, 4, 5 and 6) additional non-fasting specimens were also collected at 4 and 6 hours post-trial drug administration. These non-fasting samples were analyzed only for potassium and glucose because beta agonists are known to decrease the former and increase the latter. The mean and minimum values for serum potassium and the mean and maximum values for serum glucose were drawn pre-treatment and at 2, 4 and 6 hours post-treatment. The potassium variables did not show any consistent difference between the treatment groups. However, mean serum glucose measurements were elevated in the two formoterol groups compared to both the albuterol and placebo groups. This was most evident in the 4-hour post-treatment values [178:180-2].

PROTOCOL #41 – MEAN VALUES FOR SERUM GLUCOSE BY TREATMENT GROUP [178:182]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Visit 2				
0-hour	91.8	91.8	92.1	90.6
2-hour	90.5	93.7	91.9	88.1
4-hour	101.3	115.4	99.8	92.0
6-hour	95.4	101.8	92.2	88.7

PROTOCOL #41 – MEAN VALUES FOR SERUM GLUCOSE BY TREATMENT GROUP [178:182]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Visit 3				
0-hour	90.6	91.7	90.4	90.6
2-hour	91.4	94.1	91.9	87.7
Visit 4				
0-hour	92.4	92.0	91.7	90.2
2-hour	93.3	93.0	90.8	87.3
4-hour	99.0	100.8	98.3	94.2
6-hour	95.3	95.6	91.2	88.3
Visit 5				
0-hour	91.2	90.5	91.3	89.4
2-hour	91.8	92.2	90.8	87.3
4-hour	100.4	103.6	96.3	93.0
6-hour	93.6	98.2	91.1	91.9
Visit 6				
0-hour	92.8	93.3	91.1	91.3
2-hour	91.6	94.8	90.6	90.0
4-hour	103.9	103.2	92.5	95.8
6-hour	94.8	95.0	87.9	93.0

Urinalysis results were said to have revealed no clinically significant trends within treatments when pre-dose visit 2 results were compared with the terminal visit results, or between treatments [178:183].

Inhalations Required To Empty Capsules

A total of 50% of the capsules were completely emptied with one inhalation, 44.4% were completely emptied with two inhalations and 5.4% required three inhalations. Only 0.2% of capsules were not completely emptied after three inhalations. With close to 50% of capsules requiring more than one inhalation, checking the capsule for complete emptying and reinhalation will have to be salient labeling instructions. These data are very similar to the findings of the other pivotal study [178:190].

PHARMACOKINETICS

Sixteen patients comlpleted all urine collections for pharmacokinetics. Seven of these received formoterol 12 µg b.i.d. and nine received 24 µg b.i.d. One patient from the formoterol 12 group and two from the formoterol 24 group demonstrated the presence of formoterol in their baseline urine collections, both in unchanged and conjugated forms. Repeat analysis verified these findings and there was no explanation for them. The pharmacokinetic results obtained for these patients were said to be consistent with those calculated for the other patients participating in the trial. Group results are presented in