SUGGESTED DEFICIENCY COMMENTS

The New Drug Application 20-831 for formoterol, single-dose, dry powder, capsules for inhalation is approvable but has the following clinical deficiencies which must be addressed prior to approval:

1. The four-category electrocardiogram (ECG) ratings in protocols #40 and #41 are unacceptable without a catalogue of the components of those categories. Please describe the ECG interpretations that comprise each category, the consistency of interpreters in assigning categories, the relative frequency of these interpretations within treatment groups and use the interpretations to compare the treatment groups.

2. The categorical presentation of quantitative interval data (PR, QRS, QT/QTc) in the ECG database is inadequate. Please provide summary variables of central tendency and data spread to describe distributions and comparisons between different treatment groups.

3. The safety profiles of formoterol formulations for inhalation have been evaluated by approving authorities in other countries. Please send the English translations of the approved labels.

4. The asthma efficacy claim for children aged 6-12 years based on study DP/PD2 is not persuasive. The primary endpoint, as presented, does not allow comparison of the groups over the treatment period nor is efficacy strongly supported by any secondary endpoint. Future studies to readdress efficacy in this age group should be placebo controlled and should display pulmonary function endpoints over the treatment period to facilitate comparison among treatments.

5. The Integrated Summary of Safety incompletely reports analyses of patients who discontinued early because of adverse events and of patients who suffered serious adverse events. In addition, the NDA case report form index for deaths and early discontinuations because of adverse events has been supplied and limited examination of it has shown some missing death references. These deficiencies have been discussed in several telephone conversations with Ms. Kathleen Creedon beginning 12 May 1998 and she is working to correct them.

6. [ ]

7. [ ]

8. [ ]

GENERAL INFORMATION

NOTE TO READERS

In general, information in the Executive Summary is drawn from the summaries of each section. Sections are capitalized and bolded in the Table Of Contents and also identified on the second line of the header on the top left of each page. More detail about the section summaries can be found in the appropriate subsections which contain even more detailed information as references.

Square brackets are used throughout this review to include references to the original NDA volumes and pages. FAX communications and teleconferences are distinguished by the words, 'FAX' or 'Telecon' preceding a date and optional volume and page reference. A leading date indicates a separate submission and is followed by an optional volume number and a page reference. Several volumes/pages, submissions and events may all be referenced in one set of brackets; e.g., **[VOL:PAGE, PAGE-Page, VOL:PAGE-Page, DATE VOL:PAGE, FAX DATE]**.

DRUG DEVELOPMENT HISTORY

Formoterol was developed by ——— and has been marketed as an oral formulation since 1986 in Japan under the name ATOCK®. The adult oral regimen is 80 µg BID or TID which produces an onset of bronchodilation after 20 minutes and a duration lasting ≥ 8 hours. ——— and dry powder inhalers were next developed and were being pursued in this country under ——IND's,

IND ——

[redacted]

IND ——

[redacted]

under IND ——— for the inhaled, single-dose, dry-powder capsule (ISF) formulation. Virtually all of the preliminary work on this formulation was done in Europe and South America.

FOREIGN MARKETING EXPERIENCE OF FORMOTEROL FORMULATIONS

Formulations available world wide are a solution aerosol MDI and dry powder capsule for inhalation. The earliest approval of the solution aerosol was 1990 and is marketed in Austria, Denmark, Dubai, Greece, Holland, Hong Kong, Israel, Italy, South Africa, Spain, Switzerland and Turkey. The dry powder was first approved in 1994 and is marketed in Austria, Denmark, Egypt, France, Finland, Holland, Ireland, Israel, New

Zealand, Sweden, Switzerland and the United Kingdom. A suspension aerosol was submitted in several countries and approved in a few, but was withdrawn by the sponsor and is now not marketed in any country [1:26-8].

PHARMACOKINETICS

Absorption

It is likely that about 90% of inhaled formoterol is swallowed and then absorbed from the gastrointestinal tract. Therefore, the pharmacokinetic characteristics of formoterol obtained from studies with oral administration also apply to those involving inhalation of the drug. When 80 µg of radiolabeled formoterol fumarate was administered orally to two healthy males, at least 65% of the drug was absorbed. Following inhalation of a single 120 µg dose of formoterol fumarate by 12 healthy subjects formoterol was rapidly absorbed into the plasma and reached a maximum concentration of 92 pg/mL within 5 minutes of dosing. After body weight correction plasma drug levels did not differ significantly between males and females in this study. Plasma levels are low or undetectable after inhalation of recommended therapeutic doses (12 or 24 µg b.i.d.). The rate of urinary excretion of unchanged formoterol parallels plasma formoterol levels and may be used as an indirect measure of systemic exposure. In a study in asthma patients, the urinary excretion of unchanged formoterol increased by 62-74% during inhalation of 12 or 24 µg b.i.d. for 12 weeks, suggesting some accumulation of formoterol in plasma during multiple dosing.

Distribution

The binding of formoterol to proteins in human plasma in vitro was 61-64% at concentrations from 0.1-100.0 ng/mL. Binding to human serum albumin in vitro was 31-38% over a range of 5-500 ng/mL. These concentrations were higher than those achieved in plasma following a single 120 µg dose of formoterol.

Metabolism

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and oxidative O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation. At therapeutically relevant concentrations, formoterol does not inhibit the metabolism of drugs by any of the major cytochrome P450 isozymes.

Excretion

Following oral administration of 80 µg of radiolabeled formoterol to two healthy subjects, 59-62% of the radioactivity was eliminated in the urine and 32-34% in the feces over a period of 104 hours. The plasma clearance of formoterol in these subjects was 150 mL/min. Following inhalation of a 12 or 24 µg dose by 12 asthma patients, about 10% of the dose was excreted in the urine as unchanged formoterol and about 15-18% was excreted as glucuronide conjugates [377:369-70].

The pharmacokinetics of formoterol have not been studied in pediatric or elderly patients with hepatic or renal impairment, so caution is recommended when treating these special populations [10/24/97 1:6].

CONDUCT OF THE REVIEW

The sponsor considered eight trials to be pivotal. Seven of these have been reviewed and two more added. DP/DF2 (vol 268) and ——.O2 (vol 269) evaluated the bronchodilator effects of single doses of formoterol dry powder capsules at three dose levels (6, 12 and 24 μg) over a 12-hour period and documented the dose-response and time course of bronchodilation in patients with ROAD (asthma). Protocol ——.O2 was not reviewed because it focused on the comparability between the capsule formulation and ———————— on which development has ceased. Two trials in adolescent and adult patients, 40 (vol 91) and 41 (vol 178), and one in children, DP/PD2 (vol 322) examined prevention and maintenance treatment in patients 6 years of age and older with asthma including patients with nocturnal asthma and those using concomitant steroids and/or theophylline therapy. Two trials in adolescent and adult patients, 45 (vol 317) and 46 (vol 319), and one in children, DP/PD3 (vol 321) supported prevention of EIB in patients 8 years of age and older [1:454, 470]. Multi-dose tachyphylaxis and bronchial hyper-responsiveness trials, FO/UK2 (vol 88) and DP/SP2 (vol 87) were also chosen for review.

040 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 in 541 randomized adolescent and adult patients (12 to 75 years of age) with mild to moderate asthma ($FEV_{1.0} \geq 40\%$ predicted off therapy). Patients had to have required daily, short-acting β2-agonist for symptom control and demonstrated 15% reversibility of $FEV_{1.0}$ to be included. Stable treatment with 12-hour oral theophylline, inhaled oral or nasal corticosteroids, short-acting antihistamines and desensitization therapy were all allowed.

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. 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, 21.3 and 24.5% improvement over the pretreament baseline for the low and high formoterol doses respectively compared with 10.2% for albuterol and 5.5% 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 11.3-18.5% over the week 0 pretreatment baseline compared with less than 5% for placebo and albuterol. No sustained and consistent statistical difference was seen between the two formoterol doses for the 'all randomized' patients.

The highest formoterol treatment (24 μg b.i.d.) also 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 highest dose. The 12-hour $FEV_{1.0}$ AUC supports this observation for both the 24 μg b.i.d. formoterol dose and for albuterol. 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, rescue medicine use and exacerbations.

Four AE's were more frequent with formoterol treatment than with placebo and were dose proportional; tremor, cough, dyspnea and urticaria. The highest formoterol dose was associated with more frequent asthma exacerbations categorized as both serious AE's and as AE's causing premature discontinuations. 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 60% of formoterol capsules required more than one inhalation to empty, but only 0.6% 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 [91:1, 11-2].

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 [91:1, 12].

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 [91:12-3].

PROTOCOL #40 – SCHEDULE OF PROCEDURES [91:13, 26]

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

PROTOCOL #40 – SCHEDULE OF PROCEDURES [91:13, 26]						
Procedure	Visits (Weeks)					
	1 (-2)	2 (0)	3 (2)	4 (4)	5 (8)	6 (12)
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 [91:20-1].

The formoterol formulation used in this, and in the other large pivotal trial #41, 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 #40 – TREATMENT MATERIALS [91:191]			
Unit Drug	**Dose**	**Batch Number**	**Formulation Number**
12 µg formoterol blister	formoterol 12 µg card	E-15610	H-3891
	formoterol 12 µg capsule	E-15491	H-3831
	placebo capsule	E-15609	H-3833
24 µg formoterol blister	formoterol 24 µg card	E-15585	H-3890
	formoterol 12 µg capsule (12)	E-15491	H-3831
Placebo blister	placebo card	E-15587	H-3892
	placebo capsule	E-15493	H-3833
Placebo blister	placebo card	E-15611	H-3892
	placebo capsule	E-15609	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 [91:18-9, 23-5].

PATIENTS

There were 724 patients enrolled into the trial, and 541 patients were randomized into the double-blind treatment phase. Of the 183 patients discontinued from the trial prior to randomization, 7 terminated due to AE's, 12 discontinued because of abnormal laboratory values, 123 were terminated for not meeting protocol criteria, 22 withdrew consent and 19 discontinued for 'other' reasons. Four patients were re-enrolled into the trial and were counted twice in some tables. Of the 541 randomized patients, 458 patients completed the double-blind phase (visits 2 through 6). Five-hundred and thirty-five randomized patients were included in the primary efficacy analysis of $FEV_{1.0}$ for at least one post-treatment time point: 135 in the formoterol 12 μg b.i.d., 134 in the formoterol 24 μg b.i.d., 132 in the albuterol 180 μg q.i.d., and 134 in the placebo treatment groups, respectively. Six patients were excluded from the efficacy analyses for all of the spirometry variables and AUC of $FEV_{1.0}$. Two of the placebo patients discontinued the trial at visit 2 immediately after receiving the initial dose of the trial medication, and no post-baseline efficacy data was recorded for these patients. The other four patients had spirometry data collected for visits 2 through 6, however, the baseline (visit 2 pre-dose) spirometry was missing for these patients [91:51-2, 57].

PROTOCOL #40 – PATIENT BASELINE DEMOGRAPHIC CHARACTERISTICS OF TREATMENT GROUPS [91:57-8]

Statistic	Characteristic	Formoterol 12	Formoterol 24	Albuterol	Placebo	Total
Counts (%)	Male	58 (43)	59 (44)	53 (40)	54 (40)	224 (41)
	Female	78 (57)	76 (56)	81 (60)	82 (60)	317 (59)
	Caucasian	118 (87)	123 (91)	111 (83)	122 (90)	474 (88)

PROTOCOL #40 – PATIENT BASELINE DEMOGRAPHIC CHARACTERISTICS OF TREATMENT GROUPS [91:57-8]						
Statistic	Characteristic	Formoterol 12	Formoterol 24	Albuterol	Placebo	Total
	Black	8 (6)	5 (4)	9 (7)	8 (6)	30 (6)
	Other	10 (7)	7 (5)	14 (10)	6 (5)	37 (7)
Means (SD)	Age (years)	34.2 (14.7)	35.8 (14.3)	35.7 (14.2)	36.2 (15.2)	35.5 (14.6)
	Height (cm)	169.6 (10.8)	169.9 (9.7)	168.4 (9.4)	168.7 (10.3)	169.2 (10.0)
	Asthma Duration (mo)	225.9 (154.6)	228.7 (159.1)	233.6 (156.4)	221.1 (158.7)	227.3 (156.8)
TOTAL NUMBERS		136	135	134	136	541

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

Inclusion Criteria [91:16-7]

1. Cooperative male and female outpatients aged 12 to 75 years, inclusive.
2. Patients who met the following criteria for the diagnosis of mild to moderate asthma:
   a. Patients receiving treatment with an inhaled β2-selective adrenergic agent on a daily basis for the past two or more months.
   b. Patients whose $FEV_{1.0}$ at visit 1 was between 40% and 80%, inclusive, of the predicted normal value for the patient. This criterion for $FEV_{1.0}$ had to be demonstrated after a washout period during which no β2-agonist had been inhaled for at least eight hours prior to the evaluation.
   c. Patients who demonstrated a ≥ 15% increase in $FEV_{1.0}$ over their baseline value within 30 minutes after inhalation of 180 μg (2 inhalations) of albuterol. The administration of albuterol for the reversibility test had to be within 30 minutes after baseline spirometry. Reversibility had to be demonstrated at visit 1 for all patients.
3. Patients who maintained regular day/night, waking/sleeping cycles (e.g. night shift workers were excluded).
4. Patients who had a chest radiograph with normal findings or findings consistent with asthma within the 12 months prior to visit 1, or during the screening period (Period I).

Exclusion Criteria [91:17-9]

1. Pregnant women, nursing mothers, or females of childbearing potential, regardless of whether or not sexually active, who did not use a reliable contraceptive method (oral, mechanical, subcutaneous or surgical contraception). Any patient who became pregnant during the course of the trial was discontinued.
2. Patients with clinically significant, uncontrolled coronary artery disease, congestive heart failure, myocardial impairment, or cardiac dysrhythmia.
3. Patients who had a prior myocardial infarction unless they had been stable for at least two years and were without significant sequelae.

4. Patients with hypertension not controlled by diet or medication (systolic BP >160 mm Hg, diastolic BP >90 mm Hg for patients age 50 or below; systolic BP >180 mm Hg, diastolic BP >95 mm Hg for patients above age 50).
5. Patients with a history of insulin-dependent diabetes mellitus.
6. Patients with a history of convulsive disorders.
7. Patients with a current diagnosis or history within the past two years of any of the following uncontrolled conditions:
   a. noninsulin-dependent diabetes mellitus,
   b. hypothyroidism,
   c. Addison's Disease,
   d. hepatitis, biliary obstruction, cirrhosis, or hepatic failure,
   e. neurologic, neuromuscular, or movement disorders which might interfere with measurements or observations,
   f. conditions associated with hyperadrenergic states (hyperthyroidism, pheochromocytoma, etc.),
   g. uremia, urinary tract obstruction, chronic glomerulonephritis, nephrosis, chronic renal failure.
8. Patients with a history of untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.
9. Patients with fasting laboratory results deviating significantly from the normal reference ranges of the central laboratory. All clinically significant abnormal laboratory results were to be discussed with the Ciba Clinical Research Physician.
10. Patients who had an upper respiratory tract infection within one month prior to visit 1. Patients who developed an upper respiratory tract infection during the placebo run-in period were discontinued from the trial, but were permitted to re-enroll at a later date (at least one month after the resolution of the upper respiratory tract infection).
11. Patients who had been hospitalized or had emergency room treatment for an acute asthma attack in the one month prior to visit 1, or during the placebo run-in period.
12. Patients who had a history of noncompliance to medical regimens and patients who were considered potentially unreliable, including patients with a history of alcoholism and drug abuse.
13. Patients who, in the judgment of the investigator or Ciba Clinical Research Physician, had a clinically significant condition or significantly abnormal laboratory profile that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the trial.
14. Patients who had treatment with other investigational drugs within the past 30 days.
15. Patients who had taken parenteral, oral, or nebulized short-acting β2-agonists in the two weeks prior to visit 1, or inhaled long-acting β2-agonists in the one month prior to visit 1. The use of these medications was not allowed during the placebo run-in period.
16. Corticosteroids:
   a. Patients who had taken parenteral or oral corticosteroids in the one month prior to visit 1. Patients who required newly instituted therapy with these medications during the placebo run-in period were not to be randomized.

b. Patients on inhaled or nasal corticosteroids who had started this treatment or undergone any change in daily dose, dosing schedule, formulation or product in the one month prior to visit 1. Patients who required newly instituted therapy with these medications during the placebo run-in period were not to be randomized.

c. Patients on inhaled corticosteroids whose total daily dose exceeded the maximum recommended dose as listed elsewhere in this protocol, or patients on nasal corticosteroids whose total daily dose exceeded that recommended in the package insert.

d. Patients who had discontinued inhaled or nasal corticosteroids in the one month prior to visit 1.

17. Theophylline:
    a. Patients who had taken non-sustained-release or 24-hour sustained release theophylline in the one month prior to visit 1.
    b. Patients on 12-hour sustained-release theophylline who had started this treatment or undergone any change in formulation or product in the one month prior to visit 1. Patients who required newly instituted therapy with this medication during the placebo run-in period were not to be randomized. Patients on theophylline had to have a theophylline level within the therapeutic range within the one month period prior to visit 1.
18. Other treatments for asthma and allied conditions:
    a. Patients who had taken disodium cromoglycate (all formulations), cromolyn sodium, nedocromil or ketotifen during the one month prior to visit 1.
    b. Patients who had taken oral or inhaled anticholinergics in the one month prior to visit 1.
    c. Patients who had started desensitization therapy within the three months prior to visit 1.
    d. Patients who had taken astemizole (Hismanal) in the three months prior to visit 1.
    e. Patients who had taken hydroxyzine, loratadine (Claritin), terfenadine (Seldane), or other antihistamines in the 4 days (96 hours) prior to visit 1.
19. Other Treatments:
    a. Patients who were being treated with non-potassium sparing diuretics, beta-blocking agents, quinidine and quinidine-like medications (antiarrhythmics).
    b. Patients who were being treated with tricyclic antidepressants, fluoxetine (Prozac), and monoamine oxidase inhibitors.
20. Patients vaccinated with a live attenuated virus within one month prior to visit 1.
21. Patients whose weight was more than 35% above or 25% below their ideal weight for height.
22. Patients who had been smokers within the past two years prior to visit 1, or who had a smoking history >10 pack-years.
23. Patients who had discontinued prematurely from this trial were not to be reinstated, with one exception as noted above in Item 10.
24. Patients who had a diagnosis of malignancy and had any evidence of/or treatment for the disease within the past five years.

PARAMETERS

The primary efficacy variable was the $FEV_{1.0}$ and the sample size was selected to find a difference between either formoterol dose and placebo at the 12-hour evaluation time points, adjusted for multiple comparisons. Secondary efficacy variables included a host of spirometric measures, including $FEV_{1.0}$ AUC, twice daily PEFR's, nocturnal and asthma symptom scores, rescue albuterol use and asthma exacerbations. An 'acceptable' patient analysis was also performed excluding patients without baseline spirometry reversibility, those who had received too recent rescue albuterol, systemic steroids, antihistamines or had a nearly therapeutic serum theophylline level a given visit [91:40-45].

Safety parameters were derived from periodic ECG's, physical examinations, vital signs and laboratory serum (CBC, WBC & differential, platelets, BUN, creatinine, potassium, sodium, chloride, bicarbonate, glucose, LDH, AST, ALT, total bilirubin, alkaline phosphatase, cholesterol, triglycerides, theophylline) and urine (routine and microscopic) measures. Two hundred four patients participated in centers gathering periodic 24-hour Holter monitor data [91:27-9, 52].

The Patient diary card included space to record a number of efficacy and safety parameters on a once or twice daily basis [91:24, 33-35]:

Nocturnal Asthma Score: a reflective 0-4 (best-to-worst) scale with ratings based on awakenings and rescue medication use recorded each morning.

Asthma Symptom Score: a reflective 0-3 (best-to-worst) scale of 'none' to 'severe' recorded morning and evening.

Combined Asthma Symptom Score: a reflective 0-4 (best-to-worst) scale with ratings based on symptoms (shortness of breath, chest discomfort, wheezing and cough) and activity restriction, recorded once daily in the evening.

PEFR: recorded with ———— peak flow meters upon awakening and in the early evening, always before the dose of trial medication.

Albuterol Rescue Medication: number of inhalations taken and whether it was used within four hours of measuring the PEFR.

Adverse Experiences: reflective recording once daily in the early evening.

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. Figures show that 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. The highest formoterol treatment also showed progressively 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 formoterol 24 µg b.i.d.. 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 $FEV_{1.0}$ 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 were usually at or below the mean $FEV_{1.0}$ at the same post-treatment time points for the lowest formoterol dose. Figures 1-4 at the end of this document illustrate all of these observations
[94:320, 322, 324, 326, 328].

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 135 patients in each treatment group at visit 2 and about 115 at visits 4, 5 and 6. Percent changes at visits 4, 5 and 6 reference the visit 2 (week 0) pre-treatment baseline and were calculated only for those patients who had not dropped out [91:62, 10/27/97 Protocol 40:3-6].

PROTOCOL #40 – $FEV_{1.0}$ MEAN AND PERCENT CHANGE FROM BASELINE AT WEEKS '0' THROUGH '12' FOR ALL TREATMENTS AT SELECTED POST-TREATMENT TIME POINTS [91:59, 64-7, 69-71, 74-7, 10/27/97 Protocol 40:3-6]

	Formoterol 12 L (% Change)	Formoterol 24 L (% Change)	Albuterol L (% Change)	Placebo L (% Change)
Visit 2 (Week 0)				
Pre-Treatment	2.8 (0.0)	2.9 (0.0)	2.2 (0.0)	2.2 (0.0)
1 Hour	2.9 (28.2)*	3.0 (36.3)*‡	2.8 (35.2)*	2.3 (6.1)
3 Hours	2.9 (31.7)*†	3.1 (39.0)*†‡	2.7 (26.8)*	2.5 (11.9)
6 Hours	2.8 (28.1)*†	3.0 (34.1)*†‡	2.5 (14.9)*	2.4 (9.1)
7 Hours	2.8 (27.6)*	3.0 (34.3)*‡	2.9 (36.7)*	2.4 (8.2)
12 Hours	2.7 (22.2)*†	2.9 (30.0)*†‡	2.5 (15.2)*	2.3 (5.1)

APPEARS THIS WAY
ON ORIGINAL

PROTOCOL #40 – $FEV_{1.0}$ MEAN AND PERCENT CHANGE FROM BASELINE AT WEEKS '0' THROUGH '12' FOR ALL TREATMENTS AT SELECTED POST-TREATMENT TIME POINTS [91:59, 64-7, 69-71, 74-7, 10/27/97 Protocol 40:3-6]

	Formoterol 12 L (% Change)	Formoterol 24 L (% Change)	Albuterol L (% Change)	Placebo L (% Change)
Visit 4 (Week 4)				
Pre-Treatment	2.6 (15.6)*†	2.6 (14.2)*†	2.1 (0.1)	2.3 (2.9)
1 Hour	2.9 (30.9)*	3.0 (35.4)*	2.7 (32.1)*	2.3 (6.5)
3 Hours	3.0 (34.0)*†	3.1 (38.7)*†	2.6 (23.7)*	2.4 (9.5)
6 Hours	2.8 (25.1)*†	2.9 (29.3)*†	2.3 (9.3)	2.3 (6.4)
7 Hours	2.8 (25.2)*	2.9 (28.9)*	2.8 (33.2)*	2.3 (5.1)
12 Hours	2.7 (18.4)*	2.8 (23.9)*†	2.4 (12.6)	2.3 (3.3)
Visit 5 (Week 8)				
Pre-Treatment	2.5 (14.1)†	2.6 (16.1)*†	2.1 (0.8)*	2.4 (4.2)
1 Hour	2.9 (33.6)*	3.0 (35.6)*	2.7 (32.3)*	2.4 (7.6)
3 Hours	3.0 (36.2)*†	3.0 (37.4)*†	2.6 (24.7)*	2.5 (9.7)
6 Hours	2.8 (27.9)*†	2.9 (28.3)*†	2.3 (11.5)	2.4 (7.8)
7 Hours	2.8 (28.3)*	2.9 (29.1)*	2.7 (30.9)*	2.4 (7.8)
12 Hours	2.7 (20.3)*†	2.8 (24.0)*†	2.3 (11.2)	2.4 (5.2)
Visit 6 (Week 12)				
Pre-Treatment	2.5 (11.5)†	2.6 (15.5)*†	2.1 (0.3)	2.3 (3.9)
1 Hour	2.9 (32.1)*	3.0 (37.6)*†	2.6 (28.6)*	2.3 (6.4)
3 Hours	3.0 (34.0)*†	3.1 (39.0)*†	2.5 (20.1)	2.4 (10.4)
6 Hours	2.8 (28.5)*†	2.9 (31.5)*†	2.3 (6.9)	2.4 (7.4)
7 Hours	2.8 (27.1)*	2.9 (30.7)*	2.7 (29.3)*	2.3 (6.2)
12 Hours	2.7 (21.3)*†	2.8 (24.5)*†	2.3 (10.2)	2.3 (5.5)

* 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 pre-treatment albuterol $FEV_{1.0}$ at visits 4, 5 and 6 were less than at visit 2, yet were represented as positive percent changes because they represented a change from the baseline of only those reduced numbers of patients who were evaluated at the designated visits and had both pre- and post-treatment values [8/27/97 Telecon with Kathy Creedon].

The placebo group showed a 2.9-11.9% increase in mean $FEV_{1.0}$ at all time points after the visit 2 pre-treatment baseline in the table above. This was a substantial placebo effect. 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 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 only at post-treatment time points during the first visit. Later visits showed post-treatment mean $FEV_{1.0}$ values in the formoterol 24 µg b.i.d. group that were just sufficiently reduced to obviate statistical significance [91:59, 64-7, 69-71, 74-7, 10/27/97 Protocol 40:3-6].

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 11-18% over baseline and comparable to one another. Albuterol and placebo groups showed < 5% trough improvements over baseline. A separate analysis of 'acceptable' patients, did not affect the overall interpretation of these data [91:44-5, 56, 62-3].

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 #40 – 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 [91:59, 64, 66, 69, 71, 74, 76, 10/27/97 Protocol 40:3, 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)	2.3 (0.0)	2.2 (0.0)	2.2 (0.0)
5 Minutes	2.7 (20.1)*	2.8 (25.4)*‡	2.7 (27.7)*	2.3 (1.0)
15 Minutes	2.7 (22.6)*†	2.9 (30.2)*‡	2.8 (31.2)*	2.3 (2.8)
30 Minutes	2.8 (25.6)*†	3.0 (34.1)*‡	2.8 (33.9)*	2.3 (2.8)
60 Minutes	2.9 (28.2)*	3.0 (36.3)*‡	2.8 (35.2)*	2.3 (6.1)
Visit 4 (Week 4)				
Pre-Treatment	2.6 (15.8)*†	2.6 (14.2)*†	2.1 (0.1)	2.3 (2.9)
5 Minutes	2.7 (26.1)*	2.8 (27.1)*	2.6 (26.3)*	2.2 (2.3)
15 Minutes	2.8 (26.3)*	2.9 (30.0)*	2.7 (30.3)*	2.2 (2.6)
30 Minutes	2.9 (29.7)*	2.9 (31.8)*	2.7 (31.1)*	2.3 (3.7)
60 Minutes	2.9 (30.9)*	3.0 (35.4)*	2.7 (32.1)*	2.3 (6.5)
Visit 5 (Week 8)				
Pre-Treatment	2.5 (14.1)†	2.6 (16.1)*†	2.1 (0.8)	2.4 (4.2)
5 Minutes	2.7 (24.9)*	2.9 (26.6)*	2.7 (28.3)*	2.3 (3.4)
15 Minutes	2.8 (27.3)*	2.9 (30.7)*	2.7 (30.4)*	2.3 (4.1)
30 Minutes	2.8 (31.4)*	2.9 (33.4)*	2.7 (32.1)*	2.4 (5.2)
60 Minutes	2.9 (33.6)*	3.0 (35.6)*	2.7 (32.3)*	2.4 (7.6)

PROTOCOL #40 – 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 [91:59, 64, 66, 69, 71, 74, 76, 10/27/97 Protocol 40:3, 5]				
	Formoterol 12 L (% Change)	Formoterol 24 L (% Change)	Albuterol L (% Change)	Placebo L (% Change)
Visit 6 (Week 12)				
Pre-Treatment	2.5 (11.3)†	2.6 (18.5)*†	2.1 (0.3)	2.3 (3.9)
5 Minutes	2.7 (23.1)*	2.9 (28.5)*	2.6 (24.2)*	2.2 (2.9)
15 Minutes	2.8 (26.1)*	2.9 (32.1)*	2.6 (27.0)*	2.3 (2.9)
30 Minutes	2.8 (26.7)*	3.0 (34.9)*	2.6 (27.2)*	2.3 (4.4)
60 Minutes	2.9 (32.1)*	3.0 (37.6)*†	2.6 (28.6)*	2.3 (6.4)
* 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. Separation of onset of action efficacy between the two formoterol doses was noted only during visit 2.

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 #40 – $FEV_{1.0}$ AUC (Liters x Hours) FOR ALL RANDOMIZED PATIENTS [91:84]					
Visit (Week)	Statistic	Formoterol 12	Formoterol 24	Albuterol	Placebo
2 (0)	N	134	134	131	133
	Mean	6.4	8.0	5.8	1.6
	S.D.	4.9	4.9	5.1	3.7
4 (4)	N	118	125	119	128
	Mean	8.1	9.9	4.4	0.9
	S.D.	5.9	5.3	6.8	5.4
5 (8)	N	112	119	111	122
	Mean	8.4	9.7	4.3	1.5
	S.D.	6.1	5.6	6.8	5.6
6 (12)	N	108	115	110	121
	Mean	8.4	9.8	3.7	1.2
	S.D.	6.4	6.3	6.5	5.9

The $FEV_{1.0}$ AUC data support the previous observation that reduced efficacy with chronic treatment (tachyphylaxis) was apparent in the formoterol 24 group. By this measure, it also appears as a feature of the albuterol group [91:83-90].

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 [97:5].

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 each of the formoterol doses. Albuterol never achieved statistical significance from placebo by this measure and formoterol 24 was significantly better than formoterol 12 only over the fourth visit. The PM PEFR showed the same results except that the formoterol 24 treatment narrowly missed significance compared with formoterol 12 over the fourth visit [91:96-9]. 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 #40 – NOCTURNAL ASTHMA SYMPTOM SCORES FOR ALL RANDOMIZED PATIENTS [91:91]

Visit (Weeks)	Statistic	Formoterol 12	Formoterol 24	Albuterol	Placebo
2* (Baseline)	N	134	132	134	135
	Mean (SD)	0.7 (0.8)	0.8 (0.8)	0.7 (0.8)	0.7 (0.8)
4 (1-4)	N	133	134	131	132
	Mean (SD)	0.5 (0.6)	0.4 (0.6)	0.6 (0.7)	0.7 (0.7)
5 (5-8)	N	116	123	119	127
	Mean (SD)	0.4 (0.5)	0.4 (0.6)	0.7 (0.8)	0.7 (0.7)
6 (9-12)	N	112	118	114	120
	Mean (SD)	0.4 (0.6)	0.4 (0.6)	0.7 (0.7)	0.7 (0.7)
Overall (1-12)	N	134	134	131	132
	Mean (SD)	0.4 (0.6)	0.4 (0.6)	0.7 (0.7)	0.8 (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 both placebo and albuterol groups by this measure at each and 'overall' visits. However, the albuterol group was not significantly different from placebo nor were the two formoterol doses significantly different from one another for any, or 'overall' comparisons [91:92].

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 #40 – COMBINED ASTHMA SYMPTOM SCORES FOR ALL RANDOMIZED PATIENTS [91:94]

Visit (Weeks)	Statistic	Formoterol 12	Formoterol 24	Albuterol	Placebo
2* (Baseline)	N	136	133	134	135
	Mean (SD)	1.0 (0.8)	1.1 (0.7)	1.1 (0.8)	1.1 (0.7)
4 (1-4)	N	134	134	130	132
	Mean (SD)	0.7 (0.6)	0.7 (0.6)	0.9 (0.6)	1.0 (0.6)
5 (5-8)	N	118	123	119	127
	Mean (SD)	0.6 (0.7)	0.7 (0.7)	0.9 (0.8)	1.0 (0.7)
6 (9-12)	N	112	118	114	120
	Mean (SD)	0.6 (0.7)	0.7 (0.7)	0.9 (0.8)	0.9 (0.6)
Overall (1-12)	N	134	134	131	132
	Mean (SD)	0.7 (0.6)	0.7 (0.6)	0.9 (0.7)	1.0 (0.6)

* 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 placebo group by this measure for each and 'overall' visits. The albuterol group was significantly different from placebo during visit 4 and 'overall,' but not during visits 5 and 6. 'Overall,' both formoterol groups were statistically superior to the albuterol group but not different from one another [91:95].

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 both formoterol dose groups compared with the albuterol group. The two formoterol groups were not separable by this measure during either AM or PM [91:102-7].

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 [91:111-4].

PROTOCOL #40 – OTHER SECONDARY EFFICACY ENDPOINTS [91:111-14]				
Parameter	Formoterol 12	Formoterol 24	Albuterol	Placebo
Days With Symptoms (%)	46.8	48.0	57.7	67.3
Nights Awakened (%)	27.6	27.2	41.4	47.5
Exacerbations (%)	10.4	12.7	16.5	15.8
Number Exacerbations	16	27	30	30
Nights Took Rescue (%)	27.5	25.9	39.6	49.2

The percent of days with symptoms, percent nights with awakening, percent asthma exacerbations 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 no indication that the larger formoterol dose was superior to the smaller dose. In fact, the larger formoterol dose showed less favorable results than the smaller on three of the five secondary efficacy endpoints.

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 time points except 7 hours post-treatment, but only for the 'acceptable' patient subset. The $FEV_{1.0}$ AUC also showed superiority of the larger formoterol dose over the smaller at visit 2 for all randomized patients, but not at any other visit. No other secondary endpoint reviewed above demonstrated a preponderance of statistically significant differences between the two formoterol doses [91:115-6]. The finding of some efficacy difference between formoterol doses at the first visit that disappeared at later visits supports the previous observation that post-treatment $FEV_{1.0}$ values of the higher formoterol dose declined slightly with continued administration, thus narrowing any difference between treatments.

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 ≥ 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 [91:118-22].

PROTOCOL #40 – NUMBER (%) OF ALL RANDOMIZED PATIENTS REPORTING AE's DURING TREATMENT WHERE AE FREQUENCY ≥ 2% FOR ANY GROUP AND FORMOTEROL 24 > PLACEBO PERCENT [91:120-21]				
	Formoterol 12	Formoterol 24	Albuterol	Placebo
Total Treated	136 (100)	135 (100)	134 (100)	136 (100)
Total Reporting AE	92 (67.6)	103 (76.3)	94 (70.1)	96 (70.6)
Tachycardia	1 (0.7)	3 (2.2)	1 (0.7)	1 (0.7)
Viral Infection	22 (16.2)	24 (17.8)	10 (7.5)	22 (16.2)
Muscle Cramps	1 (0.7)	3 (2.2)	0 (0.0)	1 (0.7)
Musculoskeletal Pain	1 (0.7)	1 (0.7)	3 (2.2)	0 (0.0)
Insomnia	1 (0.7)	4 (3.0)	4 (3.0)	2 (1.5)
Nervousness	0 (0.0)	9 (6.7)	4 (3.0)	2 (1.5)
Tremor	4 (2.9)	14 (10.4)	4 (3.0)	0 (0.0)
Coughing	8 (5.9)	9 (6.7)	11 (8.2)	6 (4.4)
Dyspnea	3 (2.2)	4 (3.0)	2 (1.5)	1 (0.7)
Rhinitis	9 (6.6)	13 (9.6)	10 (7.5)	9 (6.6)
URI	14 (10.3)	19 (14.1)	13 (9.7)	15 (11.0)
Urticaria	2 (1.5)	4 (3.0)	0 (0.0)	1 (0.7)
Ear Ache	6 (4.4)	2 (1.5)	1 (0.7)	1 (0.7)

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 more frequent with the highest formoterol dose than with the lowest dose or albuterol. Both formoterol doses resulted in more frequent dyspnea than either placebo or albuterol. Albuterol was associated with more coughing than either formoterol doses. The finding of more frequent and dose proportional urticaria in formoterol groups is difficult to explain.

Serious Adverse Events

A total of nine SAE's were reported during the double-blind treatment period of the trial and are narrated in some detail below, grouped by treatment [91:125, 127-32].

1. A 68 year old male was treated with 50 days of formoterol 12 μg b.i.d. when it was discontinued and he began chemotherapy for a peritoneal mucinous adenocarcinoma without an identifiable primary tumor location.
2. A 36 year old female had received formoterol 24 μg b.i.d. for one month when she was hospitalized for an asthma exacerbation.
3. A 24 year old female was hospitalized for an exacerbation of asthma associated with sinusitis and pneumonia. She had received formoterol 24 μg b.i.d. for approximately two months at the time of hospitalization.
4. A 23 year old male was hospitalized for status asthmaticus with intubation and artificial ventilation about five weeks after starting treatment with formoterol 24 μg b.i.d.

5. A 36 year old female was hospitalized for an asthma exacerbation after about two months of treatment with formoterol 24 μg b.i.d.
6. A 50 year old male was hospitalized for right leg cellulitis after two months of treatment with formoterol 24 μg b.i.d.
7. An 18 year old female was hospitalized for an asthma exacerbation one month after beginning treatment with albuterol 180 μg q.i.d.
8. A 65 year old male was hospitalized for an asthma exacerbation after five weeks of treatment with albuterol 180 μg q.i.d.
9. A 70 year old male placebo patient was hospitalized with dizziness and ataxia. Dizziness was attributed to Procardia treatment that he had received for hypertension and the ataxia was thought to have represented a transient ischemic attack.

Three other SAE's occurred outside of the treatment period. One patient developed a pneumonia and another was hospitalized for a herniated intervertebral disc during the placebo run in period. A 16 year old female in the formoterol 24 μg b.i.d. group was hospitalized on the day after completing the trial for an asthma exacerbation [91:132-3]. The only finding, in these patients with SAE's, was the larger number of patients with asthma exacerbations in the formoterol 24 μg group.

Premature Discontinuations Due to Adverse Events

A total of 35 randomized patients were prematurely discontinued for safety reasons (AE's, abnormal tests or unsatisfactory therapeutic responses), 6 of which were the result of an SAE (numbers 1-4, 7 and 8 above) [91:126, 133-47]. 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
- 3 asthma exacerbations
- 1 peritoneal adenocarcinoma
- 1 insomnia, shakiness
- 1 positive pregnancy test
- 1 abnormal Holter monitor

Formoterol 24 — 9 = total
- 6 asthma exacerbations
- 1 left hand numbness (carpal tunnel syndrome)
- 1 worsening hypertension
- 1 insomnia, nervousness, muscle tremors

Albuterol — 10 = total
- 5 asthma exacerbations
- 1 tremor
- 2 headaches, one with insomnia and pharyngitis
- 1 abnormal ECG, worsening of ST-T wave changes
- 1 abnormal baseline Holter monitor, reported after treatment begun

Placebo — 9 = total
- 3 asthma exacerbations

1 dyspnea
2 increased symptoms
1 fatigue, anorexia
1 positive pregnancy test
1 abnormal baseline Holter monitor, reported after treatment begun

The only salient finding in these patients who discontinued prematurely was the relatively high percentage (6/9 = 67%) of patients with asthma exacerbations in the formoterol 24 μg group. The association between more frequent asthma exacerbations and the largest formoterol dose was noted earlier in the review of SAE's.

Deaths

There were no deaths [91:147].

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 three patients with high maximum pulse rates (>120 beats/minute) and all three were in the formoterol treatment groups. The maximum pulse rates were 124 (formoterol 12 μg), 134 (formoterol 12 μg) and 160 (formoterol 24 μg) and none of these were sustained. The distribution of patients with high systolic blood pressure readings (> 180 mm Hg) was even across all treatments and consisted of five patients: two in the formoterol 12 μg group (maximum values 188 and 184); one in the formoterol 24 μg group (maximum value 188); one in the albuterol group (maximum value 182); and, one in the placebo group (maximum value 192). High peak diastolic blood pressures (> 110 mm Hg) were also evenly distributed across treatments: two in the formoterol 12 μg group (maximum values 112 and 120); one in the formoterol 24 μg group (maximum value 120); one in the albuterol group (maximum value 120); and, one in the placebo group (maximum value 112) [91:149-51].

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 [91:152-3].

PROTOCOL #40 – COUNTS (%) OF CATEGORY '4' ABNORMAL ELECTROCARDIOGRAM READINGS BY TREATMENT GROUP, VISIT AND OBSERVATION TIMEPOINT [91:163]								
Visit #	Formoterol 12		Formoterol 24		Albuterol		Placebo	
Timepoint	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Visit 2								
Total Category 4 = 51		3		21		15		12
0-hour (baseline)	136	1 (0.7)	135	4 (3.0)	134	3 (2.2)	136	3 (2.2)
2-hour	133	1 (0.8)	135	6 (4.4)	134	4 (3.0)	126	6 (4.8)
4-hour	133	0 (0.0)	134	6 (4.5)	132	3 (2.3)	121	1 (0.8)
6-hour	135	1 (0.7)	135	5 (3.7)	130	5 (3.8)	118	2 (1.7)
Visit 4								
Total Category 4 = 40		2		17		6		15
0-hour	120	0 (0.0)	127	5 (3.9)	122	1 (0.8)	128	4 (3.1)
2-hour	117	2 (1.7)	126	5 (4.0)	121	2 (1.7)	118	4 (3.4)
4-hour	118	0 (0.0)	124	3 (2.4)	118	1 (0.8)	114	3 (2.6)
6-hour	100	0 (0.0)	125	4 (3.2)	115	2 (1.7)	109	4 (3.7)
Visit 5								
Total Category 4 = 30		6		11		6		7
0-hour	113	1 (0.9)	120	4 (3.3)	114	2 (1.6)	123	1 (0.8)
2-hour	112	2 (1.8)	119	4 (3.4)	114	1 (0.9)	114	2 (1.6)
4-hour	110	2 (1.8)	118	1 (0.8)	113	1 (0.9)	110	2 (1.8)
6-hour	110	1 (0.9)	119	2 (1.7)	108	2 (1.9)	108	2 (1.9)
Visit 6								
Total Category 4 = 34		3		16		8		7
0-hour	109	0 (0.0)	115	4 (3.5)	111	3 (2.7)	121	1 (0.8)
2-hour	106	2 (1.9)	115	5 (4.3)	111	3 (2.7)	110	4 (3.6)
4-hour	106	0 (0.0)	114	3 (2.6)	107	1 (0.9)	104	1 (1.0)
6-hour	106	1 (0.8)	113	4 (3.5)	103	1 (1.0)	104	1 (1.0)
All Visits & Timepoints								
Total Category 4		14		65		35		41

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 all treatment groups except the formoterol 12 μg group. The formoterol 24 μg group showed the most and the formoterol 12 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. Thirteen patients