DP/SP2 RANDOMISED, DOUBLE-BLIND, CROSSOVER COMPARISON BETWEEN FORMOTEROL 24 µG TWICE DAILY AND PLACEBO TO ASSESS EFFECT ON BRONCHIAL HYPER-RESPONSIVENESS (BHR) DURING AND AFTER TREATMENT IN MILD ASTHMATIC SUBJECTS

SUMMARY

This was a two-period, crossover study of 19 adult patients with mild asthma to test the effect of two weeks of formoterol 24 µg b.i.d., or placebo, on the response to a methacholine challenge. The protective effect of formoterol on a methacholine challenge, twelve hours after dosing, was almost entirely lost after two weeks of twice daily formoterol treatment. There was no rebound BHR, as measured by a methacholine challenge, from 36 hours through two weeks after the two-week repeated dose treatment interval with formoterol by this same measure. The similarity of a methacholine challenge to other episodic and natural bronchoconstrictive stimuli is both speculative and provocative.

OBJECTIVES

Determination of whether withdrawal of continuous formoterol treatment after two weeks results in rebound bronchial hyper-responsiveness, as measured by the methacholine PC20, and whether the effect of formoterol on methacholine PC20 is maintained during treatment [87:1, 9].

PROTOCOL

This crossover trial compared two weeks of formoterol treatment (24 µg b.i.d.) followed by two weeks of washout and two weeks of placebo treatment followed by two weeks of a second washout. Rebound BHR was determined by methacholine challenges, and derived PC20's, done 36, 60, 108 hours and 2 weeks after stopping treatment. Methacholine challenges were also performed within 12 hours after the first and last doses of the treatment drugs to investigate the development of BHR during treatment. This latter effect has been referred to as 'tolerance' or 'tachyphylaxis' to the bronchoprotective effect of formoterol against methacholine [87:10, 12-3, 40].

PROTOCOL DP/SP2 – TRIAL DESIGN [87:10]					
Period	Run-In	DB Treatment 1	Washout 1	DB Treatment 2	Washout 2
Visit	1	2 - 4	4 - 8	8 - 10	10 - 14
Days		1 - 15	15 - 29	29 - 43	43 - 57
Treatment	Rescue Atrovent	Formoterol or Placebo	Rescue Atrovent	Formoterol or Placebo	Rescue Atrovent

The methacholine challenges used sequentially doubling concentrations sufficient to reduce the $FEV_{1.0}$ by 20% from the pre-challenge baseline, thus the name PC20 (Provocative Concentration 20). The results were reported as natural, or Napierian, logarithms of the concentration. Because doubling or halving a concentration is

equivalent to adding or subtracting the natural log of '2,' a change in the natural log concentration of 0.693147 (the natural log of '2') represents such a doubling, or halving. Interpolations between log concentrations above and below the target 20% $FEV_{1.0}$ reduction were made by the method of Cockcroft [87:125-6].

TREATMENT

Formoterol dry powder 24 µg capsules were used from batch #904/8 and formulation #Q833. A placebo to match the 24 µg capsules was also supplied and both were manufactured by Ciba Pharmaceuticals at Horsham, UK. Inhaled ipratropium was available throughout the trial as a rescue medication. No other concomitant bronchodilators, anti-inflammatory medications, diuretics or aspirin were allowed [87:1, 13-4, 7:199].

PATIENTS

Adults of any race and either gender between the ages of 18 and 55 years were recruited from outpatient clinics. Mild asthmatics were the target population and defined as:

- controlled by intermittent beta-2 agonist use
- no beta-2 inhaler use for three weeks before the trial
- current non-smokers with at least 6 months of abstention
- $FEV_{1.0} \geq 75\%$ predicted
- methacholine PC20 $\leq$ 8 mg/mL

Exclusionary criteria included inhaled anti-inflammatory medication for asthma for the previous 6 months, oral beta-2 agonists during the previous 3 months, oral corticosteroids at any time as well as the usual exclusions. Nineteen patients were recruited, 10 were randomized to formoterol and the remaining 9 randomized to placebo. Two patients discontinued prematurely leaving 17 for the efficacy analysis. The ages of the randomized patients were 20 through 45 years; 11 were male and all were non-smokers including one who was an ex-smoker who had abstained for 6 months [87:13-4, 24, 31]

PARAMETERS

This was an exploratory pharmacologic study without formal criteria defined prospectively, but it was considered to be important to find a two-fold difference in PC20 between formoterol and placebo treatment periods during the crossover [87:19, 21]. PC20 values obtained within 12 hours of rescue medication use would be treated as missing [87:22]. Adverse events were determined by questioning and/or examining patients at treatment visits. No clinical laboratory data or other tolerability evaluations were recorded [87:23].

EFFICACY

Rebound BHR, as measured by a doubling sensitivity to methacholine after two weeks of treatment, was not found at any post-treatment time point from 36 hours to 2 weeks. The following table does not show any time period with a PC20 in the formoterol group that was 0.69 natural logarithm units less (greater value that is negative = more

negative) than placebo, the requirement for a halving of the methacholine concentration necessary to produce a 20% fall in the $FEV_{1.0}$. The finding at 108 hours post-treatment for the two groups, 'Without Regard To Order,' showed a reversal of this expectation. The mean PC20 for the formoterol group was slightly greater than for the placebo group. The formoterol group findings are shaded to facilitate comparisons.

PROTOCOL DP/SP2 – LOG METHACHOLINE PC20 (Ln mg/mL) AT SPECIFIED TIMES AFTER EACH TREATMENT PERIOD, FOR PATIENTS WHO COMPLETED THE STUDY [87:70, 72, 74, 76]

Sequence	Treatment	Mean (S.D.)			
		36 Hours	60 Hours	108 Hours	2 Weeks
Formoterol Then Placebo	Formoterol	- 0.652 (1.034)	- 0.864 (1.108)	- 0.705 (1.010)	- 1.066 (1.118)
	Placebo	- 0.970 (1.125)	- 0.882 (1.062)	- 1.070 (1.222)	- 0.846 (0.982)
Placebo Then Formoterol	Placebo	- 0.051 (1.254)	- 0.082 (1.260)	- 0.303 (1.130)	- 0.328 (1.277)
	Formoterol	- 0.636 (1.500)	- 0.256 (1.175)	- 0.327 (1.065)	- 0.721 (1.116)
Without Regard To Order	Formoterol	- 0.579 (1.280)	- 0.578 (1.147)	- 0.527 (1.022)	- 0.928 (1.092)
	Placebo	- 0.511 (1.245)	- 0.506 (1.195)	- 0.709 (1.209)	- 0.619 (1.112)

BHR during treatment was measured by a change in methacholine challenge PC20's 12 hours after the first and last dose of the treatment drug over the two-week double-blind period. A change of 0.69 natural logarithm units, where formoterol < placebo, would imply the development of BHR during treatment in the formoterol group. Results for the formoterol group are, again, shaded.

PROTOCOL DP/SP2 – CHANGE IN LOG METHACHOLINE PC20 (Ln mg/mL) OVER THE TWO-WEEK DOUBLE-BLIND PERIODS FROM 12 HOURS AFTER THE FIRST TREATMENT TO 12 HOURS AFTER THE LAST TREATMENT, FOR PATIENTS WHO COMPLETED THE STUDY [87:77]

Sequence	Treatment	Mean Change in PC20 (S.D.)
Formoterol Then Placebo	Formoterol	- 1.218 (1.165)
	Placebo	- 0.265 (0.644)
Placebo Then Formoterol	Placebo	+ 0.031 (0.609)
	Formoterol	- 0.637 (1.451)
Without Regard To Order	Formoterol	- 0.964 (1.291)
	Placebo	- 0.125 (0.626)

The change in PC20 over the two-week treatment period favored greater than doubling of methacholine sensitivity (halving of the concentration) in the formoterol group for the 'Formoterol Then Placebo' sequence and 'Without Regard To Order,' and was very close to a doubling of sensitivity (0.637) in the 'Placebo Then Formoterol' sequence. This reduction in protection against a methacholine challenge declined statistically significantly between 12 hours after the first and last doses, respectively, compared to the change during placebo treatment 'Without Regard To Order' [87:38]. A table showing the mean values contributing to this change in both treatment groups was not provided, but a figure

with the comparable information was. See Figure 10 at the end of this review. It showed that the log PC20 was about +0.7 (about 2 mg/mL) twelve hours after the first dose of formoterol and -0.2 (about 0.8 mg/mL) twelve hours after the last dose, the latter similar to placebo (about 0.5 mg/mL) [87:89]. The protective effect against methacholine was largely lost by the end of the 12-hour treatment interval after two weeks.

SAFETY

There were no deaths and no serious adverse experiences. Two patients discontinued from the study prematurely, one because of hayfever and worsening asthma and the other because of compliance problems and work schedule difficulties. The first of these patients represented discontinuation because of adverse experiences [87:25, 35].

INTEGRATED SAFETY SUMMARY

SUMMARY

The formoterol inhalation capsule data base includes 39 clinical trials and 4,244 healthy subjects and patients. Twelve healthy subjects and 2,617 patients with reversible obstructive airways disease received one or more doses from formoterol capsules and 602 received multiple doses for over 48 weeks. The most common doses studied in multiple-dose trials were 12 and 24 μg b.i.d. The safety data base is largely comprised of white adult patients with a slight male majority and moderate-to-severe flow obstruction by spirogram ($FEV_{1.0}$ > 50% predicted). Children, under the age of 7 years, constituted less than two dozen cases and the elderly, over the age of 64 years, contributed about 300 cases.

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

Of the 4,224 patients studied, 222 patients were discontinued from the trials early because of AE's or laboratory abnormalities, 185 (9.8%) of these were from 1,882 formoterol-exposed patients in multiple-dose controlled trials and 29 (4.4%) from the 666 formoterol-exposed patients in multiple-dose uncontrolled trials. Serious AE's were fairly evenly distributed between treatment groups in multiple-dose controlled clinical studies: formoterol = 2.4%, salbutamol = 2.2%, placebo = 1.9% and formoterol comparator = 2.7%. There were 10 deaths in this data base, 6 who had received formoterol, 2 who had been treated with salbutamol and 2 who had been given placebo. These fatalities afflicted mostly the elderly. The larger data base of over 7000 patients who had been exposed to different formoterol formulations showed only 20 fatalities, 16 of which were temporally related to formoterol exposure. These too showed a predominance of cardiac deaths in elderly male patients.

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

OVERVIEW

Formulations

Though this drug has been studied with different formulations and inhalation devices, the focus of this submission is formoterol (Foradil™) formulated as dry powder capsules for inhalation and delivered by means of a single-dose capsule inhaler called an Aerosoliser™, or ISF device. Three other inhaled formulations have been developed and tested in clinical trials: 1)solution aerosol metered dose inhaler (MDI); suspension aerosol MDI; and, ——————————— the —— device. The solution aerosol MDI and inhalation capsules are marketed in countries outside of the US.

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Subject Accounting

If any subject received one dose of an intended treatment, whether or not this was an active drug, that subject was considered to have been 'exposed' and is included in the safety data set. Subjects taking part in the run-in period before randomization, who did not subsequently receive any intended treatment, were not part of this safety data set. In the overall count (grand total), each subject was counted only once regardless of how many treatments or dose levels received. In the count by total daily dose, each subject was counted only once regardless of how many times that the dose was taken. These rules were relevant primarily in crossover and uncontrolled safety follow-up trials. In crossover trials, subjects received more than one treatment and/or more than one dose of the same treatment. Subjects in uncontrolled safety follow-up trials were generally a subset of participants in preceding core trials. These procedures explain why the grand total of all subjects may be less than the sum of treatment totals and why the treatment total may be less than the sum of the daily dose totals [377:13-4].

Protocol Data Sets

The 39 formoterol inhalation capsule trials included 4,244 healthy subjects and patients of all treatment groups, including active control and placebo. The table below shows all studies divided into different study types. The category, 'Multiple-Dose Placebo Controlled' is a subset of the category, 'Multiple-Dose Placebo and/or Active Controlled' [377:17-8]. Those trials that are both bolded and underlined have been formally reviewed in this document.

ISS – PROTOCOLS IN THE FORMOTEROL INHALATION CAPSULE TRIAL DATA BASE [377:18, 20]				
Data Set	**Protocol Designations**	**Number of Trials**	**Number Of Formoterol Subjects**	**Number Of Total Subjects**
Single-Dose	DPCU1, DPDA2, DPDF1, **DPDF2**, DPDF3, DPDF4, DPEX1, DPFL2, DPME1, DPME2, DPON1, DPON2, DPPD1, **DPPD3**, DPPD6, DPPK1, DPSP4, FOIT2, —O2, **PROT45**, **PROT46**	21	499	504
Multiple-Dose, Placebo	**PROT40**, **PROT41**, DPRD1, — O3,	14	1882	3740

ISS – PROTOCOLS IN THE FORMOTEROL INHALATION CAPSULE TRIAL DATA BASE [377:18, 20]				
Data Set	Protocol Designations	Number of Trials	Number Of Formoterol Subjects	Number Of Total Subjects
and/or Active Controlled	DPNA2, **DPSP2**, **FOUK2**, FOS02, FOOD1, DPRD2, DPRD3, **DPPD2**, DPPD5, DPNA1			
Multiple-Dose Placebo Controlled	**PROT40**, **PROT41**, DPRD1 — O3, DPNA2, **DPSP2**, **FOUK2**, FOS02, FOOD1	(9)*	(1252)*	(2822)*
Multiple-Dose Uncontrolled	DPRD1F, DPRD2F, DPRD3F, DPPD2F	4	666	666
GRAND TOTAL (all trials)		39	2629	4244
* these are a subset of the row above **bolded and underlined** studies have been formally reviewed in this document.				

EXPOSURE

A total of 12 healthy subjects and 2,617 patients with reversible obstructive airways disease (ROAD) received one or more doses of the formoterol capsules. Of these 2,629 total participants, 105 were exposed to formoterol capsules for 24-48 weeks, 602 were exposed for > 48 weeks and 1922 were exposed for ≤ 24 weeks. The extent of exposure by daily dose is presented in the table below [377:19].

ISS – FORMOTEROL INHALATION CAPSULE EXPOSURE IN ALL TRIALS BY TOTAL DAILY DOSE [377:19]			
	24 µg/day	48 µg/day	Total (all doses)
All Subjects/Patients	1760	869	2629
Exposure ≤ 24 Weeks	1183	720	1922
24 Weeks < Exposure ≤ 48 Weeks	139	84	105
48 Weeks < Exposure	438	65	602

The 24 and 48 µg/day doses, the most frequently studied, do not sum to the value in the last column, which includes daily doses both less and greater than these. A total of 1,882 patients were exposed to formoterol inhalation capsules in multiple-dose placebo and/or active controlled trials. The cross tabulation of these patients by duration of exposure and total daily dose is shown in the table below [377:20, 24].

ISS – DURATION OF EXPOSURE TO FORMOTEROL INHALATION CAPSULES BY TOTAL DAILY DOSE IN MULTIPLE-DOSE, PLACEBO AND/OR ACTIVE CONTROLLED TRIALS [377:24]					
Exposure	Daily Dose n(%)				
	12 µg	24 µg	48 µg	> 48 µg	All Doses
1 Day	0	21 (2.1)	8 (1.2)	1 (5.9)	13 (0.7)
2 - 7 Days	17 (7.2)	13 (1.3)	3 (0.4)	16 (94.1)	33 (1.8)
>1 - 4 Weeks	6 (2.5)	108 (10.9)	45 (6.7)	0	156 (8.3)
>4 - 12 Weeks	53 (22.4)	201 (20.3)	156 (23.2)	0	413 (21.9)
>12 - 24 Weeks	161 (67.9)	576 (58.3)	461 (68.5)	0	1198 (63.7)

ISS – DURATION OF EXPOSURE TO FORMOTEROL INHALATION CAPSULES BY TOTAL DAILY DOSE IN MULTIPLE-DOSE, PLACEBO AND/OR ACTIVE CONTROLLED TRIALS [377:24]					
	Daily Dose n(%)				
Exposure	12 µg	24 µg	48 µg	> 48 µg	All Doses
>24 - 36 Weeks	0	69 (7.0)	0	0	69 (3.7)
>36 - 48 Weeks	0	0	0	0	0
>48 Weeks	0	0	0	0	0
Total	237 (100)	988 (100)	673 (100)	17 (100)	1882 (100)

The individual dose-columns (2-5) do not sum to the value in the 'All Doses' column (6). This is because of the definitions of each dose and of 'All Doses' [5/13/98 FAX from Kathy Creedon].

1. The duration of exposure was calculated for each daily dose of formoterol; e.g. 12 µg, 24 µg or 48 µg, for each patient.
2. Additionally, the duration of exposure to ANY dose of formoterol was calculated for each patient.
3. The number of patients in each interval of exposure, e.g. 2-7 days, was counted for each daily dose separately and this forms the main body of the table.
4. The final column ('All Doses') on the extreme right of the table contains the number of patients in each interval for the duration of exposure to ANY dose of formoterol.

The sum of the row values in each column is correctly represented by the last row, the column 'Total.' The majority of entries in this table, 1252 (67%) of the patients, are from placebo-controlled trials which drive the data distribution in it [377:25].

Four clinical trials were conducted as uncontrolled safety extensions of core double-blind studies. Patients who had completed the core trials without serious adverse events and were willing to continue were eligible. These screening criteria introduced a selection bias by which patients who were more likely to experience safety problems and unsatisfactory therapeutic responses could be excluded from the uncontrolled trials. In these uncontrolled trials, all patients were to receive formoterol and were to start treatment on a 12 µg b.i.d. regimen. At subsequent visits the dose could be titrated up as far as 24 µg b.i.d., or back down to the original starting dose, depending upon clinical control and rescue medication use [377:15, 27]. The following table lists a cross-tabulation of duration of exposure to formoterol inhalation capsules by total daily dose.

ISS – DURATION OF EXPOSURE TO FORMOTEROL INHALATION CAPSULES BY TOTAL DAILY DOSE IN MULTIPLE-DOSE, UNCONTROLLED TRIALS [377:28]				
	Daily Dose n(%)			
Exposure	12 µg	24 µg	48 µg	All Doses
1 Day	0	1 (0.2)	0	0
2 - 7 Days	0	5 (0.8)	3 (1.6)	3 (0.5)

ISS – DURATION OF EXPOSURE TO FORMOTEROL INHALATION CAPSULES BY TOTAL DAILY DOSE IN MULTIPLE-DOSE, UNCONTROLLED TRIALS [377:28]				
Exposure	Daily Dose n(%)			
	12 µg	24 µg	48 µg	All Doses
>1 - 4 Weeks	0	49 (7.5)	6 (3.2)	8 (1.2)
>4 - 12 Weeks	2 (66.7)	57 (8.8)	13 (6.8)	15 (2.3)
>12 - 24 Weeks	0	47 (7.2)	23 (12.1)	13 (2.0)
>24 - 36 Weeks	0	28 (4.3)	30 (15.8)	13 (2.0)
>36 - 48 Weeks	0	46 (7.1)	68 (35.8)	31 (4.7)
>48 Weeks	1 (33.3)	418 (64.2)	47 (24.7)	583 (87.5)
Total	3 (100)	651 (100)	190 (100)	666 (100)

The failure of the individual dose-columns to sum to 'All Doses' has the same explanation as for the last table.

DEMOGRAPHICS

Baseline characteristics of gender, age and percent predicted $FEV_{1.0}$ are presented for the various study types in the table below. As before, the sum of any row over estimates the number of people in that row because of individuals who participated in more than one study. The prototype for this over estimation is the uncontrolled trial which represents a safety extension of controlled a core clinical trial and includes the many of the same participants. Most of the single-dose trials were carried out in Europe and the majority of the participants (89.5%) were white. The multiple dose active and/or placebo controlled trials were also carried out mostly in Europe and had the same racial bias, 86.5% white. This is also true for a subset of this group, the multiple dose placebo controlled trials, and the multiple dose uncontrolled trials that followed them [377:31, 33, 34, 36].

ISS – SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF PATIENTS WHO RECEIVED FORMOTEROL INHALATION CAPSULES [377:34, 38, 43]			
Baseline Characteristics	Single-Dose n(%)	Multi-Dose Controlled n(%)	Uncontrolled n(%)
Total Patients	499	1882	666
Sex:			
Male	317 (63.5)	1017 (54.0)	387 (58.1)
Female	182 (36.5)	865 (46.0)	279 (41.9)
Age Range:			
< 7	6 (1.2)	13 (0.7)	8 (1.2)
7 - 11	23 (4.6)	126 (6.7)	59 (8.9)
12 - 18	47 (9.4)	129 (6.9)	16 (2.4)
19 - 64	397 (79.6)	1336 (71.0)	351 (52.7)
> 64	26 (5.2)	278 (14.8)	232 (34.8)

ISS – SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF PATIENTS WHO RECEIVED FORMOTEROL INHALATION CAPSULES [377:34, 38, 43]			
Baseline Characteristics	**Single-Dose n(%)**	**Multi-Dose Controlled n(%)**	**Uncontrolled n(%)**
% Predicted FEV1.0 At Baseline:			
≤ 50	103 (21.1)	358 (19.2)	145 (24.9)
> 50	384 (78.9)	1507 (80.8)	437 (75.1)
Not Stated	12	17	84

The safety data base is largely comprised of white patients, who were predominantly adults, over the age of 18 years, with a slight male majority.

ADVERSE EVENTS (AE'S)

AE's were broken down by trial type, single-dose, multiple-dose controlled and multiple-dose uncontrolled. For the 504 patients in single-dose trials, 18.8% of those who received formoterol inhalation capsules reported ≥ 1 AE's, compared to 10.5% who received salbutamol, 11.0% of patients who received placebo and 14.6% who received a formoterol comparator. The most frequent of these, in patients exposed to formoterol, were headache (5.0%), tremor (2.6%), asthma (1.8%) and dyspnea (1.8%) [377:46-7].

Of the 3,740 patients in multiple-dose controlled trials, 1,882 were treated with formoterol inhalation capsules. Of those receiving formoterol, 55.2% reported ≥ 1 AE's, compared to 61.6% who received salbutamol, 59.5% who received placebo and 41.9% who were treated with a formoterol comparator. The following table shows AE's in which the frequency was greater in the formoterol than in the placebo group. Shaded cells represent those AE's that also showed dose proportionality among the three daily doses of 12, 24 and 48 μg [377:54-5, 58].

ISS – NUMBER AND FREQUENCY OF AE's ≥ 1% IN THE FORMOTEROL GROUP IN MULTIPLE-DOSE, CONTROLLED TRIALS, WITHOUT REGARD TO TREATMENT RELATIONSHIP, WHERE FREQUENCY IN FORMOTEROL GROUP WAS GREATER THAN IN PLACEBO GROUP [377:55, 58]		
Adverse Event	**Formoterol Capsule n(%)**	**Placebo n(%)**
Total Patients	1882 (100)	692 (100)
Total Patients With AE's	1038 (55.2)	412 (59.5)
Pharyngitis	96 (5.1)	31 (4.5)
Tremor	66 (3.5)	4 (0.6)
Bronchitis	59 (3.1)	14 (2.0)
Chest Infection	56 (3.0)	4 (0.6)
Dyspnea	50 (2.7)	9 (1.3)
Abdominal Pain	27 (1.4)	8 (1.2)
Muscle Cramps	25 (1.3)	2 (0.3)
Tachycardia	21 (1.1)	2 (0.3)
Insomnia	20 (1.1)	4 (0.6)

ISS – NUMBER AND FREQUENCY OF AE's ≥ 1% IN THE FORMOTEROL GROUP IN MULTIPLE-DOSE, CONTROLLED TRIALS, WITHOUT REGARD TO TREATMENT RELATIONSHIP, WHERE FREQUENCY IN FORMOTEROL GROUP WAS GREATER THAN IN PLACEBO GROUP [377:55, 58]		
Adverse Event	**Formoterol Capsule n(%)**	**Placebo n(%)**
shaded rows show dose-proportionality among formoterol capsule daily doses of 12, 24 and 48 µg (higher doses have a greater frequency of the specific AE)		

All 666 patients in the uncontrolled trials received formoterol inhalation capsules and 68.2% of these reported one or more AE's. The frequencies of the most reported AE's are listed in the table below [377:87-8].

ISS – NUMBER AND FREQUENCY OF AE's ≥ 1% IN THE FORMOTEROL GROUP IN MULTIPLE-DOSE, UNCONTROLLED TRIALS, WITHOUT REGARD TO TREATMENT RELATIONSHIP [377:88]			
Adverse Event	**n (%)**	**Adverse Event**	**n (%)**
Total Patients	666 (100)	Total Patients with AE's	454 (68.2)
ADVERSE EVENTS:			
Chest Infection	94 (14.1)	Arthralgia	11 (1.7)
Asthma	91 (13.7)	Dizziness	10 (1.5)
Viral Infection	90 (13.5)	Diarrhea	9 (1.4)
Rhinitis	63 (9.5)	Tremor	9 (1.4)
Bronchitis	61 (9.2)	Bronchospasm	9 (1.4)
Dyspnea	58 (8.7)	Palpitation	8 (1.2)
Coughing	34 (5.1)	Moniliasis	8 (1.2)
Pharyngitis	29 (4.4)	URI	8 (1.2)
Headache	23 (3.5)	Nausea	7 (1.1)
Abdominal Pain	22 (3.3)	Vomiting	7 (1.1)
Back Pain	18 (2.7)	Leg Pain	7 (1.1)
Chest Pain	15 (2.3)	Laryngitis	7 (1.1)
Dyspepsia	15 (2.3)	Conjunctivitis	7 (1.1)
Sinusitis	13 (2.0)		

Note that the selection process for patients enrolled in the uncontrolled trials introduced a possible bias against reporting new AE's. Eligible patients had not experienced a serious AE in the preceding core trials and were willing to continue, suggesting some expectation of a salutary risk/benefit ratio associated with continued treatment [377:91].

ADVERSE EVENT SUBGROUP ANALYSES

Subgroup analyses of AE's were carried out by duration of exposure to onset, age group, sex, race, use of concomitant theophylline and inhaled corticosteroids and by baseline disease severity. The multiple-dose controlled trial data set was used for all analyses except race and concomitant medication use, for which the combined data set of protocols 40 and 41 was used. When tremor occurred, it was usually reported by patients

within the first few days after the start of treatment with formoterol. None of the other AE's showed any particular pattern with respect to time of first occurrence. Children, age 11 and under, treated with formoterol or salbutamol reported less tremor and more 'Total' and 'Asthma' AE's compared with older age groups. The sponsor speculates that this may reflect a lower formoterol dose in younger age groups, but this does not explain comparable findings in children receiving salbutamol. No children < 12 years of age received placebo during comparable multiple-dose controlled trials. In all active and placebo treatment groups, female patients reported AE's slightly more frequently than males. Because of the few non-white patients, no meaningful conclusions could be drawn from subgroup analysis by race. In all treatment groups, patients receiving concomitant treatment with theophylline or inhaled corticosteroids reported 'Asthma' AE's more frequently than patients not receiving these concomitant medications. This pattern may have reflected a confounding effect by disease severity. The overall frequency of AE's was higher in patients receiving concomitant inhaled corticosteroids in the formoterol and salbutamol groups compared with those not receiving corticosteroids. Patients on concomitant inhaled corticosteroids had a higher frequency of viral infections, upper respiratory infections, asthma, pharyngitis and bronchitis. This pattern was less apparent, though still present, in the placebo group. Chest infection and dyspnea were the only AE's reported more frequently by patients with more severe disease at baseline, as defined by $FEV_{1.0} \leq 50\%$ predicted [377:100-5, 110, 112].

PREMATURE DISCONTINUATIONS DUE TO ADVERSE EVENTS

Of the 4,244 patients studied, a total of 222 patients in the clinical trial program were discontinued from a trial due to AE's or laboratory abnormalities. This included 8 patients in the single-dose trials, 185 patients in the multiple-dose controlled studies and 29 patients in the multiple-dose uncontrolled trials. The number and percent of early terminating patients for the various multiple-dose controlled trial groups is shown in the table below which includes only those AE's leading to premature discontinuation for which the frequency of that AE was ≥ 2% in the formoterol group [377:113, 115].

ISS – FREQUENCY OF EARLY DISCONTINUATIONS DUE TO AE's OR LABORATORY ABNORMALITIES WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN MULTIPLE-DOSE CONTROLLED TRIALS [377:115]

Adverse Events	Formoterol n (%)	Salbutamol n (%)	Placebo n (%)
Total Patients	1882	821	692
Patients Stopping Early	79 (4.2)	35 (4.3)	32 (4.6)
Early Terminators Displayed	36	26	20
Viral Infection	0	2 (0.2)	0
Headache	5 (0.3)	6 (0.7)	0
Asthma	16 (0.9)	12 (1.5)	11 (1.6)
Pharyngitis	0	1 (0.1)	1 (0.1)
Rhinitis	1 (0.1)	0	0
URI	2 (0.1)	0	2 (0.3)

ISS – FREQUENCY OF EARLY DISCONTINUATIONS DUE TO AE's OR LABORATORY ABNORMALITIES WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN MULTIPLE-DOSE CONTROLLED TRIALS [377:115]			
Adverse Events	Formoterol n (%)	Salbutamol n (%)	Placebo n (%)
Coughing	0	0	2 (0.3)
Tremor	7 (0.4)	4 (0.5)	0
Bronchitis	2 (0.1)	0	0
Chest Infection	1 (0.1)	1 (0.1)	0
Dyspnea	4 (0.2)	0	4 (0.6)
all percentages (%) are calculated in terms of 'Total Patients'			

By this method of reckoning, the only category of AE in which early terminations in the formoterol group exceeded both of the other two groups is 'Bronchitis.' This presentation of the data includes only 146 of the 185 patients terminating early from these trials because 'Budesonide' and 'Formoterol Comparator' groups are not shown. The early terminators also are not shown in this table unless the underlying AE frequency ≥ 2%, which unfortunately excludes over half of the early terminators in the formoterol group. The total number of patients who discontinued early specifically shown and attributable to an AE in the table is in the row entitled, 'Early Terminators Displayed.' The shaded cells allow a comparison of the total number of patients who discontinued early because of an AE or laboratory abnormality and those accounted for in the table of attributable AE's.

A comparable method of displaying the patients who discontinued early because of an AE or laboratory abnormality in the multiple-dose uncontrolled trials is shown below and the shaded cells emphasize the same comparison as in the table above [377:117-8].

ISS – FREQUENCY OF EARLY DISCONTINUATIONS DUE TO AE's OR LABORATORY ABNORMALITIES WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN MULTIPLE-DOSE UNCONTROLLED TRIALS [377:118]	
Adverse Event	n (%)
Total Patients	666
Patients Stopping Early	29 (4.4)
Early Terminators Displayed	13
Chest Infection	1 (0.2)
Asthma	3 (0.5)
Viral Infection	1 (0.2)
Bronchitis	1 (0.2)
Coughing	1 (0.2)
Headache	4 (0.6)
Chest Pain	2 (0.3)
all percentages (%) are calculated in terms of 'Total Patients'	

As before, the actual number of patients whose early termination was attributable to an AE category in the table is shown in the row called, 'Early Terminators Displayed.' Those that were not displayed presumably had corresponding specific AE-reported frequencies of < 2%. More extensive information was requested about patients who discontinued early in all trials and reference was made to sixteen pages of tables showing these data listed by body system of the AE associated with early termination [5/12/98 Telecon with Kathy Creedon, 378:147-63]. Nothing of particular relevance is apparent in this data display.

SERIOUS ADVERSE EVENTS (SAE'S)

A total of 158 (3.7%) of 4,244 patients in the 39 clinical trials had SAE's. When all formoterol inhalation capsule trials were pooled excluding uncontrolled trials, the frequency of patients reporting SAE's was only slightly higher in the formoterol group (2.4%) than in the salbutamol (2.2%) or placebo (1.9%) groups, but lower than the formoterol comparator group (2.7%). The majority of SAE's were reported in the multiple-dose uncontrolled trials with formoterol inhalation capsules which may be related to the longer observation period of up to one year [377:120-1]. The patients in single-dose, multiple-dose controlled and multiple-dose uncontrolled trials may contain duplicate counts so that 'All Trials' may be less than a sum of these. The 'Formoterol Comp.' group represents other formoterol formulations [377:17].

ISS – NUMBER OF PATIENTS REPORTING SAE's IN ENTIRE DATA BASE OF 39 TRIALS [377:120]				
Patients with SAE's	Formoterol	Salbutamol	Placebo	Formoterol Comp.
All Trials	113	18	14	13
Single-Dose Trials	1	0	1	1
Multi-Dose Controlled	45	18	13	12
Multi-Dose Uncontrolled	68	n/a	n/a	n/a

A display of SAE's for multiple-dose controlled and uncontrolled trials follow the same format as reports of early discontinuations due to AE's. That is, the following two tables display the number and frequency of SAE's that correspond to those AE's with a reported frequency of ≥ 2% among patients treated with formoterol inhalation capsules [377:122, 124].

ISS – FREQUENCY OF SAE's WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN MULTIPLE-DOSE CONTROLLED TRIALS [377:122]			
Serious Adverse Event	Formoterol n (%)	Salbutamol n (%)	Placebo n (%)
Total Patients	1882	821	692
Patients Stopping Early	45 (2.4)	18 (2.2)	13 (1.9)
Early Terminators Displayed	29	12	4
Asthma	22 (1.2)	10 (1.2)	4 (0.6)
URI	1 (0.1)	0	0

ISS – FREQUENCY OF SAE's WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN MULTIPLE-DOSE CONTROLLED TRIALS [377:122]			
Serious Adverse Event	**Formoterol n (%)**	**Salbutamol n (%)**	**Placebo n (%)**
Sinusitis	1 (0.1)	0	0
Chest Infection	3 (0.2)	1 (0.1)	0
Dyspnea	2 (0.1)	1 (0.1)	0
all percentages (%) are calculated in terms of 'Total Patients'			

ISS – FREQUENCY OF SAE's WHERE THE FREQUENCY OF SPECIFIC AE's ≥ 2% OF FORMOTEROL PATIENTS IN MULTIPLE-DOSE UNCONTROLLED TRIALS [377:124]	
Serious Adverse Event	**n (%)**
Total Patients	666
Patients Stopping Early	68 (10.2)
Early Terminations Displayed	34
Chest Infection	8 (1.2)
Asthma	12 (1.8)
Viral Infection	1 (0.2)
Rhinitis	1 (0.2)
Bronchitis	6 (0.9)
Dyspnea	1 (0.2)
Coughing	1 (0.2)
Abdominal Pain	1 (0.2)
Chest Pain	3 (0.5)
all percentages (%) are calculated in terms of 'Total Patients'	

As before, this method of accounting fails to provide a useful comparative profile of many patients who suffered SAE's. More information was also requested about these patients who suffered SAE's and reference was made to 193 pages of tables showing these data listed by body system of the SAE and narrative summaries [5/12/98 Telecon with Kathy Creedon, 379:2-195]. Nothing of relevance was gleaned from these data.

DEATHS

Ten deaths were recorded during the 39 trials including 6 patients who had received formoterol inhalation capsules, 2 who had received salbutamol and 2 who had gotten placebo. Short narratives of these deaths follow [377:125-32].

Case T92HQ20641, Great Britain 21/242 (Protocol DP/RD3F) Formoterol
A 77 year old male who had received formoterol inhalation capsules 24 μg/day collapsed an died of a myocardial infarction 199 days after beginning treatment.

Case T92HQ22601, Great Britain 41/116 (Protocol DP/RD3F) Formoterol
A 73 year old male who had also been treated with formoterol inhalation capsules 24 µg/day experienced abdominal pain, later diagnosed as a myocardial infarction, after 125 days on this drug and died 21 days later of ischemic heart disease.

Case T93HQ44661, Netherlands 4/3062/358 (Protocol ——.02) Placebo
A 60 year old male was found dead 3 days after taking the third trial medication (placebo) of a presumed myocardial infarction.

Case T96USA00061, USA M0161Y/4625/6410 (Protocol 41) Formoterol
A 66 year old female treated with formoterol inhalation capsules 48 µg/day for 19 days was found unresponsive after calling for help because of a severe exacerbation of asthma.

T93HQ34801, Great Britain 37/354 (Protocol DP/RD3F) Formoterol
A 69 year old female was treated with 48 µg/day of formoterol in the double-blind phase and 24 µg/day in the follow up period for a total of 313 days. She contracted bronchopneumonia from which she died three days later.

T92HQ23011, Great Britain 14/161 (Protocol DP/RD3) Salbutamol
A 69 year old male was hospitalized with a chest infection after 79 days of treatment with salbutamol 1600 µg/day. The trial treatment was stopped and the patient died after the trial of a bronchogenic carcinoma.

T92HQ00921, Denmark Unk/425 (Protocol DP/RD1) Placebo
A 47 year old female had taken placebo as the last trial medication 4 weeks prior to her death from a respiratory arrest at her home.

T94HQ00077, Great Britain 5/58 (Protocol DP/RD3F) Formoterol
A 78 year old male received a total of 14 months of treatment, first with formoterol 48 µg/day in the double-blind period, then 24 µg/day in the follow up period. He died of metastatic cancer, primary unknown.

T95USA00332, USA M0171B/4313/6208 (Protocol 41) Salbutamol
A 26 year old female treated with salbutamol 720 µg/day for 12 days experienced chest pain 3 days prior to her death. Symptoms of nausea and vomiting developed and she died of autopsy-proven hemorrhagic pancreatitis, peritonitis and hypovolemic shock from a gastrointestinal hemorrhage.

T94HQ00311, Norway 2/2016 (Protocol ——03) Formoterol
A 56 year old male had received formoterol inhalation capsules 24 µg/day for 84 days when he completed the trial. Ten days after completion of the study he was hospitalized for hemiparesis the etiology of which was squamous cell carcinoma of the lung metastatic to the brain and adrenal glands.

These fatalities afflicted mostly elderly patients and are too small in number to suggest any meaningful trend.

A slightly larger data base 7243 patients exposed to any formoterol formulation in 160 trials were further analyzed. In 90 of these, no age or sex was recorded leaving 7153 patients in the data base. All but one death occurred in the open label follow up where there was no comparator treatment group. The formoterol doses studied were mainly 12 or 24 μg, usually single doses in the crossover trials and twice daily doses in others. This population had a mean age of 42 years (range: 3-87), a mean $FEV_{1.0}$ percent predicted of 66 (range: 5-142) and a mean treatment duration of 109 days (range: 1-699). Twelve percent were older than 65 years of age. This group produced 16 counted fatalities that are displayed in the following table [379:222-9].

ISS – COUNTED FATALITIES FROM ALL PATIENTS EXPOSED TO A FORMOTEROL FORMULATION [379:228]

Trial	Patient #	Age (death)	Sex	FEV1.0 % Pred.	Cause
DPRD3F	242	77	m	47	MI
DPRD3F	116	73	m	53	MI
DPRD3F	354	69	f	40	pneumonia
DPRD3F	58	78	m	56	CA
DFORC8	94	51	f	30	asthma
DFORC8	304	57	m	53	MI
DFORC8	409	58	m		MI
DFORC8	331	61	m	70	pneumonia
DFORC8	403	67	m	30	bladder CA
GGB7	23	75	m	48	MI
GGB7	37	77	m	25	cardiac failure
GGB7	55	74	m	16	MI
GGB7	87	74	m	40	prostate CA
NLBA1F	152	68	m		LV failure
NLBA1F	803	65	m		PE
PROT 41	4625	66	m	62	cardio-respiratory arrest

MI = myocardial infarction
CA = cancer
LV = left ventricular
PE = pulmonary embolism

Nine of the 16 'counted' fatalities were probably cardiac deaths, 14 were male and 11 were over ≥ 66 years of age. Four 'uncounted' deaths also were found in this data base and are summarized below [379:229].

A 59 year old male died one month after the end of the trial from a myocardial infarction.

A 74 year old female died of COPD having taken fenoterol as her last treatment exposure.

A 60 year old male died of a probably myocardial infarction having taken placebo as his last treatment medication.

A 26 year old female having last received albuterol died of hemorrhagic pancreatitis.

The sponsor also used historic controls from the three countries involved, the USA, Germany and the Netherlands to determine that all-cause, circulatory and myocardial causes of death. Point estimates were comparable in this data base of asthmatics treated with formoterol and in the general populations of these three countries and the 95% confidence intervals were wide. The sponsor hypothesizes that this was a conservative analysis because the risk of dying in the asthmatic population is higher than in the general population [379:232-3].

Post-Marketing Death Reports

During the period October 1990 to 31 May 1996, ———— formoterol solution aerosol canisters (100 puffs/canister) and ———— formoterol single-dose inhalation capsules were sold worldwide. A total of 99 AE's from 91 case reports were received in this period. Fifty-nine AE's were considered to be non-serious and 40 AE's were considered to be serious. Seventeen of the latter were fatalities. Broadly categorized, these can be divided into deaths from myocardial infarction (2), sudden deaths (5), slowly progressive deaths from respiratory insufficiency (4), status asthmaticus fatalities (3) and the ubiquitous 'other.' Brief descriptions of these 17 fatalities are presented below [377:328-37].

95CH10059 An 82 year old male received formoterol for his COPD for 8 months. He experienced acute precordial chest pain radiating to his left arm and neck and died 15 minutes later.

S9412971 A 61 year old male with a history of past MI, and RBBB by ECG took formoterol for three months and the suspected cause of death was MI.

95E10066 A 67 year old female with cor pulmonale and hypertension died suddenly.

S9029881 A 33 year old female with a several year asthma history on oral steroids was found dead on the same day that formoterol was prescribed, though it is not known if she received the drug.

S9200661 A 75 year old female with a history of MI, diabetes, asthma and hypertension was found dead in her home 16 days after beginning formoterol 24 μg daily.

S96F10361 A 47 year old male with asthma and one exacerbation per month reported feeling improved 10 days after receiving formoterol. Two days later, on a hiking trip, he collapsed and could not be resuscitated.

S96F10362 A 72 year old male with angina pectoris and asthma died suddenly two weeks after starting formoterol, though he had symptomatically improved.

95CH10058 A 69 year old female with a history of emphysema, cor pulmonale and cachexia died of respiratory insufficiency.

95CH10060 An 82 year old female with long-standing COPD developed cor pulmonale and succumbed to respiratory insufficiency 4 years thereafter.

95CH10062 A 76 year old male with COPD requiring steroid treatment gradually developed cor pulmonale and died of respiratory insufficiency.

95CH10064 An 83 year old male with COPD and frequent hospitalizations for his lung disease deteriorated requiring steroids and diuretics and succumbed to cor pulmonale and respiratory insufficiency.

S9222981 A 60 year old female with asthma suffered an attack, called for help and was found dead when medical help arrived.

96GB-10104 A 47 year old female died in a episode of status asthmaticus.

95CH10061 A 58 year old male who smoked developed a bronchial carcinoma from which died.

95CH10063 A 65 year old male who smoked was found to have a pancoast tumor which was fatal.

96NZ10002 A 79 year old female patient died of septicemia.

96CH10025 A female patient receiving formoterol treatment had a stillbirth and the fetal death was reported.

The preponderance of these fatalities were in elderly patients with severe disease and do not contribute to an increased level of concern about the safety of the drug.

CLINICAL LABORATORY

These included the usual blood chemistries, hematology and urinalysis variables. The data from multiple-dose controlled trials, excluding crossover studies, were displayed as shift tables showing baseline to final visit values categorized as 'low,' 'normal' or 'high.' Data were extracted for inclusion in this report if the counts shifting from higher categories to lower was disproportionate to the counts showing shifts from lower

categories to higher among the treatment groups. The underlying concept is that random shifts should be about equal in both directions and unequal directional shifts might be an indication of a signal especially if they were inconsistent between treatment groups. Seven laboratory values demonstrated unbalanced shifts from baseline to final visit that differed among treatments. The shaded cells emphasize the different directional shifts and are included to facilitate comparisons.

ISS – FASTING BLOOD GLUCOSE PATIENT COUNT SHIFT TABLES FROM BASELINE TO FINAL VISIT FOR MULTIPLE-DOSE CONTROLLED PARALLEL-GROUP TRIALS [377:136]

Treatment	Baseline	Final		
		Low	Normal	High
Formoterol Capsules	Low	1	5	0
	Normal	2	478	18
	High	0	13	6
Salbutamol	Low	0	2	0
	Normal	2	240	5
	High	0	9	3
Placebo	Low	0	1	0
	Normal	0	245	6
	High	0	10	2

The fasting blood glucose showed a disproportionate shift to higher values in the formoterol group compared with salbutamol and placebo groups. This observation is entirely consistent with the adrenergic effect of formoterol, though why it wasn't also seen with salbutamol is not known. The relation between treatment and serum values of glucose and potassium were thoroughly investigated in Protocols #40 and #41 where elevations in glucose were also see with formoterol.

ISS – HEMOGLOBIN PATIENT COUNT SHIFT TABLES FROM BASELINE TO FINAL VISIT FOR MULTIPLE-DOSE CONTROLLED PARALLEL-GROUP TRIALS [377:137]

Treatment	Baseline	Final		
		Low	Normal	High
Formoterol Capsules	Low	48	21	0
	Normal	27	1276	8
	High	0	26	9
Salbutamol	Low	25	17	0
	Normal	15	526	8
	High	0	14	3
Placebo	Low	5	2	0
	Normal	3	424	9
	High	0	9	7

Both formoterol and salbutamol showed shifts to lower values which were not reflected by the placebo group. This trend was not mirrored in similar shift tables of hematocrit where all three groups shifted to lower categories over the course of the trial [377:136]. This is probably a false signal.

ISS – PLATELET COUNT PATIENT COUNT SHIFT TABLES FROM BASELINE TO FINAL VISIT FOR MULTIPLE-DOSE CONTROLLED PARALLEL-GROUP TRIALS [377:138]

Treatment	Baseline	Final		
		Low	Normal	High
Formoterol Capsules	Low	5	15	0
	Normal	11	1304	23
	High	0	16	31
Salbutamol	Low	6	5	0
	Normal	4	560	9
	High	0	5	9
Placebo	Low	1	5	0
	Normal	1	426	5
	High	0	9	9

This table shows a shift to higher platelet counts over the course of the studies for formoterol but not for salbutamol or placebo and is not readily explainable.

ISS – SERUM POTASSIUM PATIENT COUNT SHIFT TABLES FROM BASELINE TO FINAL VISIT FOR MULTIPLE-DOSE CONTROLLED PARALLEL-GROUP TRIALS [377:138]

Treatment	Baseline	Final		
		Low	Normal	High
Formoterol Capsules	Low	5	16	1
	Normal	12	1456	36
	High	0	34	10
Salbutamol	Low	1	12	0
	Normal	9	623	16
	High	0	7	4
Placebo	Low	2	7	0
	Normal	2	538	4
	High	0	8	2

The finding of shifts to higher serum potassium values for the formoterol and salbutamol groups, compared with no shift seen in the placebo group, was not expected. The prototypical adrenergic effect is to produce hypokalemia. The effect on serum potassium of typical formoterol doses (12 & 24 µg b.i.d.) has been more thoroughly studied in

protocols 40 and 41 where no effect was found. A single-dose crossover trial (DP/SP4) in 19 patients did demonstrate dose-related hypokalemia with doses of 24, 48 and 96 µg [377:147].

ISS – SERUM AST (SGOT) PATIENT COUNT SHIFT TABLES FROM BASELINE TO FINAL VISIT FOR MULTIPLE-DOSE CONTROLLED PARALLEL-GROUP TRIALS [377:140]

Treatment	Baseline	Final		
		Low	Normal	High
Formoterol Capsules	Low	2	4	0
	Normal	2	1336	37
	High	0	22	17
Salbutamol	Low	0	3	0
	Normal	2	523	7
	High	0	12	7
Placebo	Low	1	2	0
	Normal	2	419	3
	High	0	5	5

ISS – SERUM ALT (SGPT) PATIENT COUNT SHIFT TABLES FROM BASELINE TO FINAL VISIT FOR MULTIPLE-DOSE CONTROLLED PARALLEL-GROUP TRIALS [377:140]

Treatment	Baseline	Final		
		Low	Normal	High
Formoterol Capsules	Low	5	17	0
	Normal	10	1243	44
	High	1	32	28
Salbutamol	Low	1	7	0
	Normal	4	481	11
	High	0	14	10
Placebo	Low	2	8	9
	Normal	3	370	12
	High	0	8	9

These two are presented together because they may reflect information about the same target organs. The AST and ALT show disproportionate shifts to higher values in the formoterol group. Neither salbutamol nor placebo show comparable shifts for AST, but placebo does show a shift to higher values for ALT. The greater size of the formoterol group suggests that if these shifts were expressed as percentages of the treatment group, they would excite less interest. The following table extracts the patient counts from the two tables above and calculates the percentage of patients shifting, derived from the numbers in the shaded cells.

ISS – SERUM AST (SGOT) AND ALT (SGPT) PATIENT COUNTS AND PERCENT SHIFTS FROM BASELINE TO FINAL VISIT FOR MULTIPLE-DOSE CONTROLLED PARALLEL-GROUP TRIALS [377:140]		
Treatment (N)	Shift To Lower n (%)	Shift To Higher n (%)
AST (SGOT)		
Formoterol Capsules (1420)	24 (1.69)	41 (2.89)
Salbutamol (554)	14 (2.53)	10 (1.81)
Placebo (436)	7 (1.61)	5 (1.15)
ALT (SGPT)		
Formoterol Capsules (1380)	43 (3.12)	61 (4.42)
Salbutamol (528)	18 (3.41)	18 (3.41)
Placebo (412)	11 (2.67)	20 (4.85)

Shifts to both higher and lower categories seem to occur in up to about 5% of patients in treatment groups. The largest such shift was noted to higher ALT categories in the placebo group. This diminishes the probable importance of shifts to higher transaminase values in the formoterol treatment group.

ISS – TOTAL WHITE BLOOD CELL COUNT (WBC) PATIENT COUNT SHIFT TABLES FROM BASELINE TO FINAL VISIT FOR MULTIPLE-DOSE CONTROLLED PARALLEL-GROUP TRIALS [377:141]				
		Final		
Treatment	Baseline	Low	Normal	High
Formoterol Capsules	Low	9	12	0
	Normal	25	1244	43
	High	1	42	38
Salbutamol	Low	5	9	0
	Normal	5	537	18
	High	0	20	12
Placebo	Low	3	8	0
	Normal	9	403	11
	High	0	13	9

The WBC shows shifts to lower values by the end of the study in the formoterol group which is not reflected in either salbutamol or placebo groups.

ELECTROCARDIOGRAMS

In most trials which contributed ECG data, these were dichotomized as 'normal' or 'abnormal.' A tabulation of these categorizations for multiple-dose parallel group controlled clinical trials showed more normal ECG's in the placebo treatment group became abnormal after treatment than in either formoterol or salbutamol groups. Within the formoterol group there was a dose-proportional relation with the frequency of normal ECG's which became abnormal after treatment. These findings are demonstrated in the

table below [377:151-4]. Cells representing shifts from normal baseline ECG's to abnormal after treatment are shaded to facilitate comparisons.

ISS – SUMMARY OF ECG CHANGES OVER THE TREATMENT PERIOD IN MULTIPLE-DOSE, PARALLEL GROUP, CONTROLLED TRIALS [377:163-4]

Treatment	Dose	Baseline ECG	Final ECG	
			Normal n (%)	Abnormal n (%)
Formoterol Capsules	All Doses	Normal	1158 (93.6)	67 (5.4)
		Abnormal	79 (27.8)	202 (71.1)
	12 µg/day	Normal	125 (96.9)	4 (3.1)
		Abnormal	3 (17.6)	14 (82.4)
	24 µg/day	Normal	593 (93.5)	35 (5.5)
		Abnormal	41 (29.3)	97 (69.3)
	48 µg/day	Normal	440 (92.8)	26 (5.9)
		Abnormal	35 (27.6)	91 (71.7)
Salbutamol		Normal	482 (93.1)	32 (6.2)
		Abnormal	23 (22.5)	78 (76.5)
Placebo		Normal	469 (93.6)	32 (6.4)
		Abnormal	28 (29.2)	68 (70.8)

percentages are in terms of the total number of the baseline ECG category

ECG's were more intensively studied in protocols 40 and 41. An ECG abnormality four-category scale did not show any safety concerns attributable to formoterol, nor was any unique treatment group effect on the QTc reported [377:156-8].

VITAL SIGNS

These included pulse rate, respiratory rate, systolic and diastolic blood pressure and were extensively reviewed in protocols 40 and 41. Essentially, no consistent effect on any of these variables was ascribed to any treatment group. Doses as high as 96 µg did produce increased heart rates in a single-dose crossover trial (DP/SP4) in 19 patients [377:161-6].

120-DAY SAFETY UPDATE (6/1/96 TO 7/31/97)

SUMMARY

This safety update of 1,636 patients exposed to formoterol included total of 774 patients who had been exposed for a duration exceeding 24 weeks. Half of the patients from this data set belonged to each gender and most, about 80%, were between the ages of 19 and 64 years, inclusive. Asthma, headache and tremor led the frequency counts for both SAE's and early discontinuations because of AE's. No deaths were reported.

PROTOCOL DATA SETS

During the period covered by this Safety Update, the data from the following three clinical trials with formoterol dry powder capsules were represented.

- Single-dose protocol #54, a pharmacokinetic study in 12 healthy subjects all treated with formoterol 120 µg administered as ten 12 µg capsules taken in rapid sequence.
- Multiple-dose active controlled trial protocol #27 (also called FO/SA1), an open-label, parallel-group, randomized trial in 480 patients with two treatment groups, formoterol 12 µg b.i.d. and salmeterol 50 µg b.i.d.
- Multiple-dose uncontrolled trial protocol FFOR14/F, an open-label study with flexible formoterol dosing between 12 and 24 µg b.i.d. in 1383 core patients (FFOR14) with 891 continuing into the follow-up (FFOR14F) [SU1:11, 16-7, 23, 377:301-2].

EXPOSURE

The three trials in this Safety Update include data on 1,875 healthy subjects and patients. A total of 1,636 healthy subjects or patients with reversible obstructive airways disease received one or more doses of formoterol dry powder inhalation capsules and 239 patients were exposed to salmeterol. A cross tabulation of these patients by duration of exposure, study and treatment is shown in the table below [SU1:12-3, 14].

SU1 – DURATION OF EXPOSURE BY STUDY AND TREATMENT [SU1:14]

Duration Of Exposure	Treatment				
	Protocol #54	Protocol #27		FFOR14/F	Total
	Formoterol n(%)	Formoterol n(%)	Salmeterol n(%)	Formoterol n(%)	Formoterol n(%)
TOTAL	12 (100)	241 (100)	239 (100)	1383 (100)	1636 (100)
= 1 day	12	0	0	3 (0.2)	15 (0.9)
2-7 days	0	2 (0.8)	2 (0.8)	20 (1.4)	22 (1.3)
> 1-4 weeks	0	6 (2.5)	4 (1.7)	70 (5.1)	76 (4.6)
> 4-12 weeks	0	10 (4.1)	11 (4.6)	392 (28.3)	402 (24.6)
> 12-24 weeks	0	53 (22.0)	66 (27.6)	294 (21.3)	347 (21.2)
> 24-36 weeks	0	170 (70.5)	156 (65.3)	462 (33.4)	632 (38.6)
> 36-48 weeks	0	0	0	141 (10.2)	141 (8.6)
> 48 weeks	0	0	0	1 (0.1)	1 (< 0.1)