Comment: *The data on the intent-to-treat for efficacy population was imputed. The difference between change in FEV-1 in the formoterol group and the placebo group was also seen when a repeated measures analysis was done with both a fixed effects model and a random effects model. There was a statistically significantly greater improvement in FEV-1 on day 1 and after one month of treatment as well when the data was not imputed (see tables below). There did not appear to be any evidence of tolerance developing to the effect of formoterol based on the 12 hour AUC FEV-1 which was similar on day 1 and after 3 months of treatment.*

12 hour FEV-1 AUC on first day of treatment and after one month of treatment based on the ITTE population (v18, p249) and mean change from baseline

Treatment/time-point	N	Mean FEV-1	Mean change	P value *
on first day of treatment				
Formoterol MDDPI 10 mcg bid	86	5.08 L/hr	2.77 L/hr	< 0.0001
Albuterol MDI 180 mcg qid	88	4.14 L/hr	1.77 L/hr	< 0.0001
Placebo	90	1.34 L/hr	- 1.01 L/hr	-----
After 1 month of treatment				
Formoterol MDDPI 10 mcg bid	80	4.60 L/hr	2.29 L/hr	< 0.0001
Albuterol MDI 180 mcg qid	84	3.38 L/hr	1.01 L/hr	0.001
Placebo	86	1.26 L/hr	1.09 L/hr	-----

e) secondary outcome variables

1] Quality of Life (v18, p44-45. t9-2))

COMMENT: *QOL was evaluated using the validated mini Asthma QOL questionnaire developed by Juniper et al (Juniper EF et al. Development and validation of the mini Asthma QOL questionnaire, Eur Resp J 1999; 14:32-38)(v18, p115), which uses a 7 point scale with higher scores reflecting improvement in the 4 domains in the instrument (the 15 item mini AQLQ is self-administered with patients asked to recall their experiences during the previous two weeks and respond to each question on a 7 point scale ranging from 1 or "all of the time" to 7 or "none of the time"). In the study referenced above, each of the four domains (symptoms, environment, emotions and activity) in addition to the entire instrument were validated (v18, p119). Small, moderate and large effects when comparing two treatments have been defined by the sponsor as a shift of 0.2, 0.5 and 0.8, although it is not specified whether this was applied to all domains. The two pre-specified*

domains were the "total instrument" (average over all 15 items) and "symptoms" (average over items 1,4,6,8 and 10) (v18, p31). Patients under 18 years of age (n=44), as pre-specified, were excluded from the analysis since the MiniAQLQ has only been validated for patients 18 years of age and older. A statistically significant difference between formoterol and placebo was not seen for the entire questionnaire or any specific domain. The changes seen were, by the sponsor's criteria, small at best. Analysis of the data excluding patients less than 18 years of age did not give any significantly different results.

Mean change after 3 months of treatment in the MiniAQLQ for each treatment group based on ITT population (v18, p45, t9-2) can be seen in the table below.

Treatment	Domains	N	Mean at 3 months	Mean difference from placebo*	P value**
Formot-erol	Total instrument	71	5.36	0.20	0.14
	Symptoms	71	5.20	0.26	0.08
	Activity limitation	71	6.02	0.21	0.13
	Emotional function	71	5.20	0.06	0.77
	Environ-mental	71	4.90	0.20	0.32
Albuterol	Total instrument	74	5.38	0.21	0.89
	Symptoms	74	5.27	0.34	0.59
	Activity limitation	74	6.00	0.19	0.88
	Emotional function	73	5.35	0.21	0.42
	Environ-mental	74	4.77	0.07	0.49
Placebo	Total instrument	67	5.16	-	-
	Symptoms	67	4.94	-	-
	Activity limitation	67	5.81	-	-
	Emotional function	67	5.14	-	-
	Environ-mental	67	4.70	-	-

* mean difference between formoterol and placebo effect
** comparison with placebo

2] Serial FEV-1 (v18, pgs 47-53, f9-1, t9-3)

COMMENT: *FEV-1 was measured at pre-specified times over a 12 hour period on day 1 and after 1 and 3 months of treatment. The results after 3 months of treatment can be seen in the table below. Formoterol had an onset of action of 5 minutes and a duration of effect for at least 12 hours. The mean % change in FEV-*

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1 from baseline was 16% one hour after drug administration with the greatest improvement in FEV-1 (27%) coming 3 hours after drug administration. A statistically significant improvement in FEV-1 throughout the 12 hour evaluation period compared with placebo was seen after formoterol administration. As expected, there was statistically significant improvement compared with albuterol 3-6 and 10-12 hours after administration. Throughout the 12 hours of FEV-1 monitoring, formoterol maintained a 0.3-0.4 liter advantage over placebo when evaluated after 3 months of treatment (v18, p50, f9-2).

Serial FEV-1 measurements throughout the 12 hour period after drug administration (ITTE patient population) after 3 months of treatment (v18, p283- p287)

Time point	Albuterol mean % change from baseline	Formoterol mean % change from baseline	formoterol % patients with ≥ 15% increase FEV-1	Formoterol minus placebo (mean)(L) (v18, p283)	Formoterol vs placebo	Formoterol minus albuterol (mean)(L) (v18, p283)	Formoterol vs albuterol
				Mean	P value *	Mean	P value **
Predose	1%	11%	33%	0.17	0.001	0.18	0.0007
5 min	16%	18%	48%	0.31	< 0.0001	- 0.03	0.65
15 min	19%	21%	55%	0.38	< 0.0001	- 0.02	0.76
30 min	20%	23%	59%	0.40	< 0.0001	- 0.01	0.85
1 hour	21%	26%	59%	0.41	< 0.0001	0.02	0.68
2 hour	20%	26%	59%	0.39	< 0.0001	0.07	0.26
3 hour	16%	27%	62%	0.35	< 0.0001	0.16	0.01 •
4 hour	13%	25%	56%	0.31	< 0.0001	0.19	0.001 •
6 hour	11%	22%	48%	0.30	< 0.0001	0.17	0.004 •
8 hour	15%	21%	50%	0.29	< 0.0001	0.06	0.36
10 hour	10%	20%	44%	0.27	< 0.0001	0.14	0.01 •
11 hour	9%	20%	45%	0.25	< 0.0001	0.16	0.01 •
12 hour	8%	19%	47%	0.24	< 0.0001	0.16	0.01 •

* formoterol vs. placebo
** formoterol vs. albuterol

Serial FEV-1 measurements throughout the 12 hour period after drug administration (ITTE patient population) after <u>1 month</u> of treatment (v18, p294-299)

Time point	albuterol mean % change from baseline	Formoterol mean % change from baseline	formoterol% patients with ≥ 15% increase FEV-1	Formoterol minus placebo (mean)(L)	Formoterol vs. placebo	Albuterol minus placebo (mean)(L)	Albuterol vs. placebo
				Mean	P value	Mean	P value
Predose	2%	11%	28%	0.20	< 0.0001	0.03	0.52
5 min	18%	18%	46%	0.32	< 0.0001	0.38	< 0.0001
15 min	20%	20%	49%	0.35	< 0.0001	0.41	< 0.0001
30 min	21%	21%	50%	0.33	< 0.0001	0.39	< 0.0001
1 hour	22%	23%	53%	0.30	<0.0001	0.35	< 0.0001
2 hour	20%	24%	56%	0.30	< 0.0001	0.28	< 0.0001
3 hour	15%	24%	56%	0.31	< 0.0001	0.19	0.001
4 hour	11%	23%	54%	0.29	< 0.0001	0.09	0.09
6 hour	10%	21%	49%	0.28	< 0.0001	0.10	0.07
8 hour	14%	20%	43%	0.27	< 0.0001	0.20	0.001
10 hour	10%	18%	41%	0.25	< 0.0001	0.15	0.01
11 hour	9%	18%	40%	0.24	< 0.0001	0.10	0.07
12 hour	8%	18%	41%	0.23	< 0.0001	0.09	0.10

Serial FEV-1 measurements throughout the 12 hour period after drug administration (ITTE) on <u>day 1</u> of treatment (v18, p300-305)

Time point	albuterol mean % change from baseline	formoterol mean % change from baseline	formoterol% patients with ≥ 15% increase FEV-1	formoterol minus placebo (mean)(L)	formoterol vs. placebo	albuterol minus placebo (mean)(L)	albuterol vs. placebo
				Mean	P value	Mean	P value
Predose							
5 min	18%	14%	28%	0.28	< 0.0001	0.40	< 0.0001
15 min	20%	17%	41%	0.33	< 0.0001	0.44	< 0.0001
30 min	22%	19%	47%	0.35	< 0.0001	0.44	< 0.0001
1 hour	23%	22%	58%	0.34	< 0.0001	0.40	< 0.0001
2 hour	22%	23%	58%	0.35	< 0.0001	0.35	< 0.0001
3 hour	18%	24%	63%	0.33	< 0.0001	0.24	< 0.0001
4 hour	14%	24%	62%	0.33	< 0.0001	0.16	0.0003
6 hour	12%	22%	57%	0.32	< 0.0001	0.14	0.004
8 hour	16%	21%	50%	0.32	< 0.0001	0.26	< 0.0001
10 hour	13%	18%	45%	0.27	< 0.0001	0.20	< 0.0001
11 hour	11%	18%	47%	0.26	< 0.0001	0.15	0.004
12 hour	12%	20%	51%	0.31	< 0.0001	0.19	0.0002

3] <u>serial FVC</u> (v18, p53)

COMMENT: *The data on this parameter does not add anything substantive to the effectiveness of formoterol in terms of objective criteria. There was a statistically significantly greater amount of improvement at all times points in the group that received formoterol compared to the group that received placebo. Formoterol also produced a statistically significantly greater improvement in FVC at most time points than albuterol beyond 2 hours.*

4] PEF (v18, p54, t9-4)

COMMENT: *There was a statistically significantly greater improvement in PEF averaged over all treatment days in the formoterol group than was seen in the albuterol or placebo groups (see table below). This data supports the data generated in terms of FEV-1 and demonstrates the effectiveness of formoterol Certihaler. The PEF data reflects the daily improvement in pulmonary function in the group that received formoterol. The pre-specified analyses were the 1-4 week period of treatment, the 5-8 week period of treatment, the 9-12 week period of treatment and the overall treatment period (1-12 weeks)(v19, p592).*

Estimates of mean treatment effects and treatment contrasts for morning and evening PEF (L/min) averaged over all treatment days (ITTE population) (v18, p54, t9-4)

AM PEF	Treatment	N	Mean PEF	Change over placebo	P value (vs. placebo)
	Formoterol	83	373	19.7	< 0.0001
	Albuterol	86	359	6.0	0.19
	Placebo	89	353	-	-
PM PEF	Treatment	N	Mean PEF	Change over placebo	P value (vs. placebo)
	Formoterol	83	387	25.3	< 0.0001
	Albuterol	86	377	14.9	0.0008
	Placebo	89	362	-	-

5] asthma symptom scores (v18, pgs54-57,339-355) (v19, pgs356-371)

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P values comparing formoterol and albuterol to placebo at each time-point throughout the study in terms of symptoms and rescue medication use (v18, p54, v19, p356) (p values 0.05 or less are underlined)

Parameter	formoterol vs. placebo	albuterol vs. placebo	formoterol vs. placebo	albuterol vs. placebo	formoterol vs. placebo	albuterol vs. placebo	formoterol vs. placebo	albuterol vs. placebo
	days 1-28	days 1-28	Days 57-84	days 57-84	days 57-84	days 57-84	days 1-110	days 1-110
nocturnal symptom score	0.04 ■■■■■	0.16	0.09	0.75	0.27	0.99	0.17	0.36
Morning symptom score	0.02 ■■■■■	0.21	0.54	0.24	0.30	0.68	0.14	0.34
Evening symptom score	0.05 ■■■■■	0.03 ■■■■■	0.36	0.25	0.64	0.99	0.15	0.11
AM shortness of breath	0.01 ■■■■■	0.09	0.04 ■■■■■	0.18	0.23	0.95	0.04	0.21
PM shortness of breath	0.01 ■■■■■	0.04 ■■■■■	0.01 ■■■■■	0.14	0.27	0.89	0.02 ■■■■■	0.06 ■■■■■
AM chest discomfort	0.10	0.68	0.58	0.58	0.65	0.39	0.61	0.78
PM chest discomfort	0.18	0.53	0.63	0.95	0.80	0.41	0.84	0.80
AM wheezing	0.30	0.17	0.89	0.27	0.87	0.73	0.71	0.27
PM wheezing	0.02 ■■■■■	0.05 ■■■■■	0.15	0.12	0.30	0.72	0.09	0.07 ■■■■■
AM cough	0.51	0.08 ■■■■■	0.83	0.10	0.71	0.39	0.99	0.10
PM cough	0.11	0.03 ■■■■■	0.61	0.03 ■■■■■	0.90	0.55	0.44	0.03 ■■■■■
24 hour rescue medication	0.0003 ■■■■■	0.004 ■■■■■	0.06 ■■■■■	0.18	0.19	0.42	0.008 ■■■■■	0.09 ■■■■■
AM 12 hour rescue medication	0.0003 ■■■■■	0.002 ■■■■■	0.10	0.06 ■■■■■	0.11	0.19	0.006 ■■■■■	0.02 ■■■■■
PM 12 hour rescue medication	0.001 ■■■■■	0.02 ■■■■■	0.08 ■■■■■	0.45	0.37	0.69	0.03 ■■■■■	0.23

Individual asthma symptom evaluation was performed by each patient and recorded in the diary card twice daily, in the morning and early evening before taking the study medication (v19, p575). The patient was

asked to consider his/her symptoms over the preceding 12 hours. An asthma symptom score was determined for shortness of breath, cough, chest discomfort (tightness) and wheezing using a four point categorical scale with 0 = no symptoms and 3 = severe symptoms. In addition, each AM the patient recorded a response to the question, "How did you sleep last night?" using a 5 point categorical scale where 0 = not awakening because of breathing problems and 4 = difficulty sleeping because of breathing problems despite using relief medication. A total asthma score for each day was not determined but was recorded for each 12 hour period in a day.

COMMENT: *There was no statistically significant difference between either active treatment and placebo (p value for formoterol vs. placebo was 0.14 based on ITTE population) in terms of nocturnal asthma symptom score (magnitude of change was – 0.08 in the formoterol group and – 0.02 in the placebo group [v18, p336]), possibly because the baseline nocturnal symptom score was very low (MDDPI = 0.43, placebo = 0.46). Nor was there any statistically significant difference between the formoterol group and the placebo group in terms of morning (p = 0.15) or evening (p = 0.15) total asthma symptom score based on assessment of the previous 12 hours in the ITTE population. In regard to individual asthma symptoms (wheeze, cough, dyspnea and chest discomfort), there was a statistically significant decrease in the group that received formoterol compared with placebo only in terms of morning and evening dyspnea averaged over the whole treatment period and on evening wheezing for the first month. This data can not be used to support a claim for the effectiveness of formoterol Certihaler in the treatment of asthma.*

6] <u>rescue medication</u> (v18, p57-58, t9-7) (see table above)

COMMENT: *As noted in the table below, the amount of rescue medication used was statistically significantly less in the group that received formoterol than in the group that received placebo. Clinically, a mean difference of 0.57 puffs for 24 hour use is of questionable significance. As the sponsor notes, asthma in the patient population was probably too mild to be able to pick up a difference. The sponsor analyzed the data by both a two-sided p value using an ANCOVA where the number of puffs = treatment plus center plus baseline plus error*

where baseline was defined as patient baseline minus overall baseline and the van Elteren test stratified by baseline quartiles whereby patient baseline was defined as the mean value of the last 7 available days of the run-in period. This data might weakly support the efficacy of formoterol compared to placebo, if the sponsor had pre-specified criteria for definition of an asthma exacerbation. In the protocol for this study, the sponsor states that an asthma exacerbation will be defined as an occurrence of asthma symptoms that do not resolve with the use of study medication which is a different definition than was used in the analysis.

Number of puffs of inhaled rescue medication based on ITTE population (v18, p58, t9-7)

Daily interval	Time point	Criteria	Formoterol	Albuterol	Placebo
24 hour use	Baseline	N	82	86	89
		Mean (SD)	2.02 (2.41)	1.88 (2.38)	2.03 (2.42)
	Overall **	Mean (SD)	1.29 (1.60)	1.41 (1.75)	1.86 (2.27)
		P value vs. placebo	0.008/0.12*	0.08/0.19	-
Nighttime use	Baseline	N	82	86	89
		Mean (SD)	0.74 (0.96)	0.74 (1.08)	0.70 (1.06)
	Overall **	Mean (SD)	0.50 (0.67)	0.55 (0.74)	0.73 (1.06)
		P value vs. placebo	0.006/0.03	0.02/0.19	-
Daytime use	Baseline	N	82	86	89
		Mean (SD)	1.28 (1.54)	1.13 (1.41)	1.34 (1.54)
	Overall **	Mean (SD)	0.79 (1.02)	0.86 (1.09)	1.14 (1.36)
		P value vs. placebo	0.03/0.03	0.23/0.21	-

* ANCOVA/van Elteren stratified by baseline
** all treatment days up to a maximum of 110 days

7] <u>asthma exacerbation</u>: (v18, p59, t9-8)

<u>COMMENT</u>: *The sponsor used two definitions of an asthma exacerbation. One of these used the MedDRA preferred terms of "asthma aggravated" and "status asthmaticus" and the other used all MedDRA preferred terms for asthma-related adverse events. There were few asthma exacerbations in the study. Using the first definition, there were 2 formoterol and 3 placebo patients who had exacerbations and using the second definition, there were 2 formoterol patients and 4 placebo patients who had asthma exacerbations. There were no albuterol*

patients, using either criterion who had an asthma exacerbation. It seems unusual that there were so few exacerbations of asthma in a study of this length and is consistent with the fact that the patient population generally had mild asthma. This data does not provide any helpful information on the effectiveness or safety of formoterol.

2) <u>SAFETY</u>:

a) <u>adverse events</u>: (v18, pgs 60-65, t10-2, 10-3)

There were 4 serious adverse events, 3 in the albuterol group and 1 in the formoterol group. The serious adverse events in the albuterol group were ventricular tachycardia, arterial occlusion, and spontaneous abortion while the serious adverse event in the formoterol group was small cell lung cancer. Adverse events listed as clinically significant were pregnancy, asthma exacerbation (2), rash, vomiting and anaphylactic reaction in the formoterol group and asthma exacerbation and anaphylactic reaction in the albuterol group. The anaphylactic event in the formoterol group was considered drug-related, as was one of the cases of asthma exacerbation while the anaphylactic event and asthma exacerbation in the albuterol were not considered drug-related. Rash, vomiting and pregnancy in the formoterol group were not considered to be drug-related. In regard to one of the patients in the formoterol group who developed an asthma exacerbation on 2 occasions (a 16 year old white male) it was felt that the study drug could be the cause of the exacerbation (v18, p208). There were no serious or other clinically significant adverse events in the placebo group. There was one reported device failure with the formoterol Certihaler (68 year old white female) (#503) (v18, p207). No further information was provided on this event in this patient.

Frequency, severity and causality of adverse events based on ITTS population (v18, p60-65) can be seen in the table below. The <u>ITTS population</u> was defined as randomized patients who took at least one dose of double-blind treatment (v18, p28).

	formoterol (n = 86)	albuterol (n = 88)	placebo (n = 91)
Number(%) of patients with at least one adverse event	52 (61%)	49 (56%)	49 (54%)
Number (%) of patients with at least one drug-related AE	7 (8%)	3 (3%)	4 (4%)
Number (%) of patients with moderate adverse events	36 (42%)	31 (35%)	31 (34%)
Number of moderate adverse events	70	57	59
Number (%) of patients with severe adverse events	7(8%)	7 (8%)	8 (9%)
Number of severe adverse events	8	8	8
Number of adverse events considered drug-related	9	3	6
Number of patients with significant adverse events **	7 (8%)	4 (5%)	None
Specific adverse events ***			
Asthma-related adverse events +	14 (16%)	12 (14%)	13 (14%)
Asthma aggravated	9 (11%)	10 (11%)	10 (11%)
Nasopharyngitis	8 (9%)	6 (7%)	3 (3%)
Pyrexia *	5 (6%)	1 (1%)	None
Tremor	4 (5%)	1 (1%)	None
Rash	3 (4%)	None	None

* The incidence of bronchitis and influenza were also higher in the formoterol group compared to the other two groups, 3.5% compared to 2.3% and 1.2% in the albuterol group and none and 2.2% in the placebo group.

** Significant adverse events were defined as serious adverse events, adverse events leading to premature discontinuation of study treatment or "other significant adverse events"

+ consisted of reports of aggravated asthma, cough, dyspnea and wheezing

*** specific adverse events = those adverse events that occurred with a 3% or greater incidence in the formoterol group than in the placebo group; asthma-related and asthma aggravated adverse events are included because of their importance for this drug product

COMMENT: *The incidence of adverse events and adverse events considered to be drug-related were higher in the formoterol group than in the albuterol or placebo groups, largely driven by adverse events that suggested various types of infection, i.e. nasopharyngitis, pyrexia, influenza, bronchitis. The clinical significance of this finding, if any, is unclear. Formoterol is not known to have the potential to produce suppression of protective mechanisms against infection and therefore it is unlikely that the greater incidence of such adverse events has any clinical significance. There was also a higher incidence of moderate adverse events (although the incidence of severe adverse events was essentially the same in the three treatment groups) and serious adverse events leading to premature discontinuation of study treatment or other significant adverse events in the formoterol group. Formoterol at a higher dose has been reported to produce deterioration of asthma (Mann M et al. Serious asthma exacerbations in asthmatics treated with high dose formoterol. Chest 2003; 124:70), however there was no increased incidence of exacerbation of asthma in patients who received formoterol in this study. There was one report of anaphylaxis in the group that received formoterol, that was considered to be drug-related.*

b) laboratory tests: (v18, pgs65-68, t10-7a)(v19, pgs424-492)

The number (%) of patients with newly occurring (i.e. not present at screening but present at the end of the randomized treatment period) laboratory abnormalities (ITTS population) (v18, t10-7, v19, p490, t10.3-8) can be seen in the table below.

Parameter	Formoterol	Albuterol	Placebo
RBC decrease	None	None	1 (1.2%)
Platelet count increase	None	1 (1.2%)	2 (2.4%)
WBC total decrease	1 (1.3%)	None	1 (1.2%)
Eosinophils increase	4 (5.6%)	3 (4.2%)	2 (2.5%)
Neutrophils % decrease	2 (2.5%	2 (2.5%)	1 (1.2%)
Lymphocytes %increase	1 (1.3%)	2 (2.5%)	1 (1.2%)
SGOT increase	5 (6.8%)	2 (2.6%)	3 (3.6%)
SGPT increase	4 (5.5%)	3 (4%)	1 (1.2%)
Alk phos increase	1 (1.3%)	None	None
LDH increase	None	1 (1.3%)	None
BUN increase	1 (1.2%)	None	None
Triglyceride increase	3 (4.2%)	3 (3.8%)	5 (6.2%)
Glucose increase	9 (11.1%)	3 (3.6%)	2 (2.3%)

Mean serum glucose and potassium levels (v19, p441-444)

Timing of test	glucose			potassium		
	Formoterol MDDPI	Albuterol MDI	Placebo	Formoterol MDDPI	Albuterol MDI	placebo
Baseline	5.2 mmol/L	5.1 mmol/L	5.2 mmol/L	4.4 mmol/L	4.3 mmol/L	4.4 mmol/L
Day 1 prior to drug administration	5.2 mmol.L	5.1 mmol/L	5.2 mmol/L	4.4 mmol/L	4.3mmol/L	4.4 mmol/L
Day 1, 90 minutes post-drug	5.4 mmol/L	5.4 mmo/L	5.3 mmol/L	4.3 mmol/L	4.3 mmol/L	4.5 mmol/L
After 3 months treatment pre-drug	5.1 mmol/L	5.2 mmol/L	5.3 mmol/L	4.3 mmol/L	4.3mmol/L	4.4 mmol/L
After 3 months, 90 minutes post-drug	5.7 mmol/L	5.4 mmol/L	5.2 mmol/L	4.3 mmol/L	4.4mmol/L	4.6 mmol/L

COMMENT: *The mean SGPT after treatment with formoterol was 23.5 U/L compared and 20.9 U/L after placebo. The maximum value for SGPT was 114 U/L at baseline and 79 U/L after treatment in the formoterol group, compared to a maximum of 115 U/L after treatment after albuterol and 86 U/L after treatment with placebo (v19, p436). There was a mean decrease in the formoterol group in terms of SGOT from 24.2 U/L at baseline to 23.8 U/L after treatment. There was no indication that formoterol had a significant effect on liver function in this study. There were no patients who received formoterol who had an elevation in bilirubin after treatment who had a normal value at baseline (v19, p457).*

Based on BUN and creatinine values, there was no evidence from the data in this study, that formoterol had any adverse effect on renal function (v19, p440, p462). Glucose and potassium levels were measured prior to drug administration on day 1 and at the end of the study (chronic), as well as 90 minutes after drug administration on day 1 and at the end of the study (acute). There was no indication of a significant effect on blood glucose or serum potassium, based on mean changes from baseline to the end of the study. Nor was there any indication of a significant acute effect 90 minutes after drug administration in either the formoterol or the albuterol group based on mean changes (see table above) (v19, p441, 443). There were 12 patients in the formoterol group (15%) who had a normal glucose value at baseline who had an elevation in serum glucose after treatment compared

with 8% in the albuterol group and 3% in the placebo group. Elevation in blood glucose and decrease in serum potassium are recognized potential effects of beta adrenergic agonist drugs. Nevertheless, there are individual patients in whom a significant increase in blood glucose occurred in this study.

There were 3 patients (3.8%) who had a normal hemoglobin at baseline who developed a low hemoglobin after treatment with formoterol compared to no patients in the albuterol group and 1 patient (1.2%) in the placebo group (v19, p447).

c) vital signs (v18, p69)(v19, pgs387-398, 493-510, pgs 534-547):

Laboratory tests were done at visit 1 (screening), visit 2 (day 1) and visit 5 (end of study). Fasting blood samples were obtained prior to drug administration on these days. In addition, on visits 2 and 5, a second fasting blood sample was obtained 90 minutes after drug administration for measurement of serum glucose and potassium (v19, p631). Vital signs were measured at visit 1 (screening). They were also measured at baseline and 30 minutes, 60 minutes and 2 hours after drug administration at visits 2, 3 and 5. At visit 4, they were measured prior to drug administration and 30 minutes after drug administration,

COMMENT: *No significant mean changes from baseline in vital signs were noted after treatment with formoterol, nor was the mean response to formoterol significantly different than the response to albuterol or placebo for systolic or diastolic blood pressure, pulse rate or respiratory rate on day 1, after one month of treatment or at the end of the study. There were infrequent patients who had an increase in systolic blood pressure that was considered "notably abnormal", and the incidence of this occurrence was comparable between the three treatment groups.*

d) ECGs (v18, p69, t10-8, 10-9; v19, p518, t10.5-1); ECGs were obtained at visit 1 (screening), as well as prior to drug administration and 90 minutes after drug administration on visits 2 and 5 (v19, p579). They were conducted by a centralized vendor with review by a central

cardiologist who evaluated each ECG as normal or abnormal but did not evaluate the clinical significance of the abnormal ECGs.

COMMENT: *The percentage of patients in the formoterol group (27.8%) who had ECG findings assessed as more abnormal than at baseline when ECGs were done prior to drug administration at the final visit (after 3 months of treatment) was greater than was seen in the placebo or the albuterol group (19.8%)(v18, p70, t10-9). Acutely, 19.3% of the formoterol group had an such an ECG change 90 minutes after the first dose compared with 26.2% in the albuterol group and 18.2% in the placebo group and 21.3% of the formoterol group, 20.8% of the albuterol group and 20.2% of the placebo group had such an ECG change 90 minutes after drug administration when patients had received study drug for 3 months.*

Mean changes in QTc interval was not significantly greater after formoterol administration than after administration of placebo (see tables below). Note that the data are slightly different in table 10-8 in volume 18 and in table 10.5-1 on page 518 in volume 19 (see sponsor's explanation in submission of 3 September 2003 that the differences are because the data in table 10-8 represents least squares mean and table 10.5-1 represents raw mean data) The data from table 10.5-1 in volume 19 was used for the table below.

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QTc interval (Bazett's correction)(ITTS population)(v19, p518, t10.5-1)

Treatment arm	N	Mean	Mean change from baseline	P value vs. placebo	Maximum
Day 1, 90 minutes after drug administration					
Formoterol	83	418 msec	-2 msec	0.95	460
Albuterol	84	423 msec	3 msec	0.08	450
Placebo	88	420 msec	- 3 msec	-	450
Final visit, before drug administration					
Formoterol	79	424 msec	4 msec	0.83	470
Albuterol	81	419 msec	- 1 msec	0.07*	450
Placebo	81	425 msec	3 msec	-	470
Final visit, 90 minutes post drug administration					
Formoterol	75	423 msec	4 msec	0.67	470
Albuterol	77	420 msec	- 0.4 msec	0.16*	460
Placebo 1	84	423 msec	1 msec	-	460

* based on unexpected decrease in QTc interval after albuterol administration

An outlier analysis for patients with QTs above 440 msec was requested and supplied by the sponsor in the submission of 3 September 2003. Significant prolongation of the QTc interval in individual patients in the formoterol group included the following: 1) patient 24 center 507; a 23 year old white male. baseline 410 msec, 450 after drug administration on day 1, 470 prior to drug administration at study end and 440 after drug administration at study end; and 2) patient 5, center 511: a 54 year old white female, baseline 430 msec, 460 msec after drug administration on day 1. Similar prolongation of the QTc interval was seen in patients who received albuterol and patients who received placebo.

ECG findings assessed as more abnormal
after treatment than at baseline (ITTS
population) (v19, p522)

Treatment arm	N	n	%
Day 1, 90 min after drug administration			
Formoterol	83	16	19.3
Albuterol	84	22	26.2
Placebo	88	16	18.2
Final day, prior to drug administration			
Formoterol	79	22	27.8
Albuterol	81	16	19.8
Placebo	81	16	19.8
Final day, 90 min after drug administration			
Formoterol	75	16	21.3
Albuterol	77	16	20.8
Placebo	84	17	20.2

CONCLUSIONS ON STUDY 2302: *There were no major baseline discrepancies between the three treatment groups that might have biased the study results. The data on the intent-to-treat efficacy population was imputed. After discussion with the Biostatistics reviewer, it is confirmed that this is an acceptable technique. The efficacy of formoterol (p = < 0.0001) and albuterol (p = 0.0005) was clearly demonstrated compared to placebo for the primary outcome variable, change from baseline in mean 12 hour AUC FEV-1 after 3 months of treatment. The quality of life instrument used in this study (Juniper's Mini asthma QOL questionnaire) has been validated. Therefore, the results, despite the fact that it is a secondary outcome variable, are interesting. There was no indication of any effect of formoterol on quality of life of patients with asthma in this study (p value for the all domains = 0.14). Perhaps the best picture of the effect of formoterol on airway obstruction can be seen from the serial FEV-1 measurements made on day 1 and after 1 and 3 months of treatment. An improvement in FEV-1 of 14-24%, 18-24%, and 18-27% was seen over the 12 hours following administration of formoterol on day 1, after 1 month of treatment and after 3 months of treatment, respectively. The change in PEF seen after formoterol administration, as a daily assessment of pulmonary function, supports the efficacy of formoterol demonstrated in regard to the primary outcome variable, although a mean increase of 20-25 L/min*

compared to placebo is not a dramatic clinical improvement. In terms of asthma symptom scores, a statistically significant difference from placebo was seen only for PM shortness of breath. There was significantly less rescue medication used by the group that received formoterol but the results are difficult to interpret because of the mildness of asthma in the patient population studied. For the same reason, asthma exacerbations during the study are not helpful in defining the efficacy of formoterol.

The incidence of adverse events, drug-related adverse events, moderate adverse events and "significant" adverse event, as well as pyrexia, bronchitis, influenza, tremor and rash was highest in the formoterol group. The clinical significance of these findings, if any, is unclear. There was not, on the other hand, any increased incidence of severe or serious adverse events, asthma exacerbations or asthma-related adverse events in the formoterol group. The incidence of increases in SGPT, SGOT, and serum glucose was greater in the formoterol group than in the other two treatment groups. There were no significant changes in vital signs after formoterol administration. There were no significant differences between the treatment groups in regard to change in QTc interval. Overall, the efficacy of formoterol has been demonstrated in this study based on the finding of a significantly greater improvement in the primary outcome variable than placebo. There is no significant safety concern based on the data from this study that would prevent approval or require labeling changes.

2. <u>Study 2303 entitled, "A 12 week randomized, multicenter, double-blind, double-dummy, placebo and active controlled, parallel group study evaluating the safety, efficacy, and pharmacokinetics of Foradil (formoterol fumarate)(10 mcg bid) delivered by the multi-dose dry powder inhaler (MDDPI) versus placebo versus albuterol pMDI qid in patients with persistent asthma."</u> (This study was identical in design to study 2302)

   a. <u>study characteristics</u>: the study was performed at 20 centers in the United States.

1) number of patients: 239 patients randomized; formoterol 80; albuterol 79; placebo 80; 92 (39%) male, 147 (61%) female; 206 (86%) White, 23 (10%) Black, 1 (0.4%) Oriental, and 9 (4%) other (v33, p42)

2) age range: 13-85 years; 9 (4%) 13-17 years, 221 (92%) 18-64 years; 9 (4%) > 64 years (v33, p42)

3) patient population: persistent asthma; duration of asthma 0.3-64.1 years; use of inhaled bronchodilator; FEV-1 40% of predicted or greater; patients could be receiving inhaled corticosteroids;

4) study design: randomized, multicenter, double-blind, double-dummy, active treatment and placebo-controlled, parallel group study

5) drug administration: formoterol 10 mcg bid (1 inhalation bid; 6-9 AM and 6-9 PM) by multi-dose dry power inhaler; albuterol MDI 180 mcg qid (6-9 AM, 12-3 PM, 6-9 PM and 10 PM-1AM); albuterol MDI to be used PRN during the run-in period and during randomized treatment

6) periods of study: 2 week single-blind placebo run-in period; 12 weeks of randomized treatment; visit 1 was 2 weeks before start of the randomized treatment period; visit 2 was on day 1 of treatment; visit 3 was after 4 weeks of treatment, visit 4 was after 8 weeks of treatment and visit 5 was after 12 weeks of treatment

7) parameters evaluated: the *primary efficacy variable* was 12 hour AUC FEV-1 after 3 months of treatment relative to baseline, (i.e. the pre-dose FEV-1 at visit 2 prior to the first dose of study drug); the baseline value was subtracted from each of the serial FEV-1 values taken during the 12 hour evaluation period; if patients prematurely terminated the 12 hour spirometry or used rescue medication during this period, the last FEV-1 value before the premature termination or before the use of rescue medication was carried forward through the 12 hour period of evaluation; if the 3 month spirometry evaluation was missing or AUC was not calculated at this time, the last available spirometry prior to the third month was used to impute the 3 month AUC; imputing data was used in place of missing data or when rescue medication was used within a visit; there were five end points analyzed in regard to the primary efficacy variable: 1) the 3 month (imputed if necessary) value for the ITTE population; 2) the 3 month value for the PP population after at least 75 days of treatment; 3) the 3 month value for the ITTE population after at least 75 days of treatment; 4) the one month value for the ITTE population; and 5) the one day value for the ITTE population (v25, p30).

Secondary variables (v25, p32):

a) *serial FEV-1 and serial FVC* for 12 hours on day 1 and after 1 and 3 months of treatment;

b) *AM/PM PEF,* measured daily by a mini-Wright peak flow meter before administration of the study medication (v26, p564) averaged for weeks 1-4, 5-8, and 9-12 and the total double-blind treatment period;

c) *rescue medication use* (number of puffs of inhaled albuterol) during a 24 hour period and over 12 hours during the day and during the night averaged for weeks 1-4, 5-8, and 9-12 and total double-blind treatment period;

d) *number of asthma exacerbations* (based on adverse events reporting); two definitions of asthma exacerbations were used, "asthma aggravated" and "status asthmaticus"; only one asthma exacerbation was recorded on any one day; a new exacerbation was acceptable only if there was at least one day free of exacerbation after the last previous asthma exacerbation day

e) *asthma symptom scores,* individual (wheezing, cough, chest discomfort, shortness of breath) and combined total symptom score, defined as the sum of these symptoms; symptoms were recorded in the morning and evening for the previous 12 hours and averaged for weeks 1-4, 5-8, and 9-12 and the total period of randomized double-blind treatment;

f) A patient-reported *QOL assessment* after 3 months of treatment was considered by the sponsor to be the "main secondary efficacy variable", was imputed if necessary and only evaluated ITTE patients 18 years of age and older, because the miniAQLQ instrument that used a 7 point scale has not been validated in patients < 18 years of age. An effect size of 0.2 (3.4%), 0.5 (8,4%) and 0.8 (13.4%) was used to indicate a mild, moderate and severe effect compared to placebo. The domains "total instrument" and "symptoms" were the two pre-specified domains for possible labeling indication; this data was only formally analyzed if the primary efficacy variable was statistically significant ("Gatekeeper procedure"); the method of Hochberg was then used to adjust for the comparisons in these

two domains; the domain scores were calculated as the average of the answered items (v25, p31).

Safety was assessed with adverse events, ECGs, laboratory tests, physical examination and vital signs; PK assessment included total urinary excretion over 12 hours after drug administration; plasma AUC over 12 hours after drug administration and renal clearance; AUC FEV-1 was calculated relative to baseline

8) study objectives: to determine if formoterol is significantly better than placebo in regard to 12 hour AUC FEV-1. symptom control, and quality of life and to compare the safety of formoterol to albuterol. The primary objective of the study was to demonstrate the superior efficacy of formoterol Certihaler compared to placebo. The primary efficacy variable was the 12 hour AUC for FEV-1 after 3 months of treatment. The sample size calculation was based on results of previous studies with formoterol delivered by Aerolizer where AUC was calculated relative to baseline FEV-1. Using a two-sided significance level of 0.05 with 95% power, 70 patients per group were required to show a difference in the mean change from baseline in mean AUC between formoterol and placebo after 3 months of treatment.

9) statistical methods: data for the primary outcome variable was imputed if necessary; the primary efficacy variable (the 12 hour AUC FEV-1 relative to baseline. i.e. the pre-dose value prior to the first administration of study drug on day 1) which was then subtracted from each of the serial FEV-1 values taken over the 12 hour evaluation period at the 3 month spirometry evaluation using the ITTE population and compared to placebo;(v26, p564) the primary efficacy variable was imputed, if necessary and analyzed by ANCOVA using a model of treatment + center + baseline + error where baseline was defined as the patient baseline minus an overall baseline average with the overall baseline average being determined for each respective analysis population ignoring the treatment group; serial FEV-1, serial FVC, AM/PM PEF, and use of rescue medication were assessed using ANCOVA; nocturnal asthma symptom score, asthma symptom scores and number of asthma exacerbations were analyzed by the van Elteren test (the generalized Cochran-Mantel-Hanszel test) stratified by

baseline quartiles and/or center; descriptive statistics were used for all
safety variables; QTc data was analyzed by ANCOVA;

Patient populations analyzed included: *intent-to-treat for safety (ITTS)*
patients were those patients who took at least one dose of double-
blind treatment; *intent-to-treat for efficacy (ITTE)* were those patients
who took study drug and had at least one 12 hour spirometry
evaluation during the double-blind treatment period; *per protocol
patients (PP)* were those who completed 12 weeks of double-blind
treatment, had the 12 week spirometry evaluation with a calculable
AUC and did not have any major deviations from the specified
protocol.

b. *study results*:

1) EFFICACY:

a) *patient disposition and discontinuations* (v25, p36): There
were 80 formoterol, 79 albuterol and 80 placebo patients
randomized. There were 70 formoterol, 72 albuterol and 67
placebo patients who completed the study. There were 5
formoterol patients (6.3%), 3 albuterol patients (3.8%) and 4
placebo patients (5%) who were discontinued because of an
adverse event (v25, p203)(see discussion below under Safety:
adverse events).

b) *Baseline demographics* (v25, p39): There were more patients in
the albuterol group (15 [19%]) than in the formoterol group (11
[13.8%]) or the placebo group (9[11.3%]) who used excluded
anti-asthma or anti-allergy medications prior to the study.
There were also more albuterol patients (25 [31.6%]) than
formoterol patients (19 [23.8%]) who used > 8 puffs of rescue
medication over a 24 hour period prior to the study.

The *age range* for the formoterol group was 13-79 years of age,
for the albuterol group 13-71 years of age and for the placebo
group 17-85 years of age. Seven of the albuterol patients were
13-17 years of age compared to one patient in the formoterol
group and one patient in the placebo group. There were 3, 4

and 2 patients 65 years or older in the formoterol, albuterol, and placebo groups, respectively.

Gender: 40% of the formoterol group, 38% of the albuterol group and 37.5% of the placebo group were male. *Race*: 86% of all three groups were Caucasian and 9-10% were African-American. *Mean duration of asthma* was 23 years in the formoterol group, 26 years in the albuterol group and 22 years in the placebo group. The *mean % predicted FEV-1* was 63% in the formoterol group, 65% in the albuterol group and 66% in the placebo group. *Abnormal ECGs* were observed at baseline in 27% of the albuterol group, compared to 24% in the formoterol group and 14% in the placebo group.

Variable	Formoterol	Albuterol	placebo
AGE ••••••••	N = 80	N = 79	N = 80
Range (years)	13-79	13-71	17-85
13-17 years	1	7	1
65 years and older	3	4	2
GENDER ••••••			
Male (%)	40%	38%	38%
Female (%)	60%	62%	62%
RACE •••••••			
Caucasian	86%	86%	86%
African-American	10%	10%	9%
Other	4%	4%	5%
Mean duration of asthma (years)	23	26	22
Mean % predicted FEV-1	63%	65%	66%
Concomitant medication use	84%	90%	90%

c) *Concomitant medication use during the study* (v25, p42): There were more placebo and albuterol patients (90%) than formoterol patients (84%) who took concomitant anti-asthma and/or anti-allergic medications during the study. Fluticasone was taken by 65% of patients in the formoterol group, compared to 68% in the albuterol group and 63% in the placebo group. Only one patient in each group started inhaled corticosteroids for the first time during the study. There were 14% of the formoterol group, 11% of the albuterol group and 6% of the placebo group that

took triamcinolone during the study (v25, p214). There was no significant imbalance between treatment groups in regard to use of inhaled corticosteroids, antihistamines or any other therapy that might have influenced the study results.

d) *Primary efficacy variable (12 hour AUC FEV-1 after 3 months of treatment* (v25, p44): ITTE population is the intent-to-treat for efficacy population and PP is the per protocol population (see definition of these populations above)

Mean 12 hour AUC for FEV-1 after 3 months of treatment relative to baseline (prior to the first dose of study drug on day 1) based on the ITTE population

Patient population	Treatment	Mean FEV-1 AUC (L/hr)	p value vs. placebo
ITTE population month 3 imputed*			
	Formoterol	4.45	0.0002 **
	Albuterol	2.80	0.15
	Placebo	1.79	------
PP population			
	Formoterol	4.44	0.003
	Albuterol	3.01	0.26
	Placebo	2.15	------

* The ITTE population included all randomized patients who took the study drug and had at least one 12 hour spirometry evaluation during the double-blind treatment period.

** pre-specified primary analysis

COMMENT: *There was a statistically significant difference between formoterol and placebo in terms of change in AUC FEV-1 on day 1 and after one month of treatment (see table below) and after three months (see table above) of treatment when the data was imputed. There was no development of tolerance with continued treatment over the 3 month period, based on similar improvement over a 12 hour evaluation period in FEV-1 when formoterol was administered after 3 months of treatment compared to improvement in FEV-1 after the first dose of formoterol (see tables below evaluating serial measurement of FEV-1 after drug administration on day 1 and after 1 and 3 months of treatment).*

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Change from baseline in 12 hour AUC for FEV-1 on day 1 and after one month of treatment based on ITTE population (v25, p242)

Time point	treatment	N	Mean (L/hour)	P value *
After one month of treatment		76		
	Formoterol	72	5.08	0.0001
	Albuterol	72	2.83	0.35
	placebo		2.11	-----
After first dose				
	formoterol	80	4.80	< 0.0001
	Albuterol	79	3.53	< 0.0001
	placebo	80	1.39	-----

> COMMENT: *This data supports the efficacy of formoterol at a dose of 10 mcg bid when administered by MDDPI. However, unlike study 2302, the efficacy of albuterol was not demonstrated in this study, based on mean 12 hour AUC for FEV-1, except after the first dose of study drug on study day 1. Although there was a greater amount of improvement in mean 12 hour AUC FEV-1 in the albuterol group than in the placebo group, there was no statistically significant difference between the two treatment groups based on 12 hour AUC FEV-1. The reason that efficacy was not demonstrated for albuterol in this study is unclear. Despite this unexpected finding, this study supports the efficacy of formoterol based on statistical comparison with placebo.*

e) QOL (v25, p45-47, t9-2): The data was imputed and included patients 18 years of age and older. QOL was evaluated using the validated mini Asthma QOL questionnaire developed by Juniper et al (Juniper EF et al. Development and validation of the mini Asthma QOL questionnaire, Eur Resp J 1999; 14:32-38)(v25, p113) which uses a 7 point scale with higher scores reflecting improvement in the 4 domains in the instrument (the 15 item mini AQLQ is self-administered with patients asked to recall their experiences during the previous two weeks and respond to each question on a 7 point scale ranging from 1 or "all the time" to 7 or "none of the time"). In the study mentioned above, each of the four domains in the instrument (symptoms, activity, environment and emotions) in addition to the entire instrument were validated (v25, p115). Small,

moderate and large effects when comparing two treatments
have been defined by the sponsor as a shift of 0.2, 0.5 and 0.8,
respectively, although it is not specified whether this was
applied to all domains. The two pre-specified domains for a
possible labeling indication were the "total instrument"(average
of all 15 items) and "symptoms" (average over items 1, 4, 6, 8
and 10). Patients under 18 years of age, as pre-specified, were
excluded from the primary analysis, since the MiniAQLQ has
only been validated for patients 18 years of age and older.

miniAQLQ domain scores after 3 months of treatment based on ITTE population

Domain	Treatment	N	Mean at 3 months	Mean difference from placebo	p-value vs. placebo
Total instrument					
	Formoterol	74	5.27	0.33	0.01
	Albuterol	69	5.02	0.08	0.57
	Placebo	75	4.94	-----	-----
Symptoms					
	Formoterol	74	5.16	0.34	0.03
	Albuterol	69	4.76	- 0.06	0.69
	Placebo	75	4.83	-----	-----
Activity limitations					
	Formoterol	74	5.92	0.33	0.02
	Albuterol	69	5.67	0.08	0.59
	Placebo	75	5.59	-----	-----
Emotional function					
	Formoterol	74	5.18	0.38	0.04
	Albuterol	69	4.98	0.17	0.36
	Placebo	75	4.80	-----	-----
Environmental stimuli					
	Formoterol	74	4.66	0.27	0.15
	Albuterol	69	4.62	0.23	0.23
	Placebo	75	4.39	-----	-----

COMMENT: *There was a statistically significantly greater
improvement in mean QOL in the formoterol group than in the
placebo group. There was no statistically significant difference
between the albuterol group and the placebo groups. The difference
between the formoterol and the placebo groups was 0.27-0.38. Small,
moderate and large effects when comparing two treatments have been
defined as a shift of 0.2, 0.5 and 0.8, respectively. By these criteria,
the effect seen in the formoterol group was small.*

f) _serial FEV-1 measurements_ (v25, p48, f9-1, t9-3): FEV-1 was measured over a 12 hour period of time after drug administration at pre-specified times.

serial FEV-1 measurements throughout the 12 hour period after drug administration (ITTE patient population) after 3 months of treatment (v25, pgs276. 278, 280)

Time-point	Albuterol mean % change from baseline	Formoterol mean % change from baseline	Formoterol % patients with ≥ 15% increase FEV-1	Formoterol minus placebo (mean)(L/hr) (N = 80)	Formoterol vs. placebo	Formoterol minus albuterol (mean)(L/hr) (N = 79)	Albuterol vs. Placebo
				Mean	p-value *	Mean	p-value **
Predose	2%	10%	28%	0.15	0.01	0.22	0.0004 •
5 minutes	18%	18%	45%	0.31	< 0.0001	0.06	0.27
15 minutes	20%	20%	53%	0.34	< 0.0001	0.05	0.35
30 minutes	21%	21%	55%	0.36	< 0.0001	0.06	0.34
1 hours	21%	23%	59%	0.33	< 0.0001	0.07	0.27
2 hours	18%	23%	59%	0.33	< 0.0001	0.13	0.04 •
3 hours	15%	23%	58%	0.30	< 0.0001	0.22	0.0004 •
4 hours	11%	21%	58%	0.26	< 0.0001	0.25	< 0.0001 •
6 hours	12%	18%	44%	0.23	0.0004	0.20	0.002 •
8 hours	15%	15%	43%	0.16	0.01	0.04	0.50
10 hours	10%	14%	39%	0.12	0.04	0.11	0.08
11 hours	10%	13%	35%	0.11	0.06	0.12	0.06
12 hours	10%	14%	35%	0.14	0.03	0.12	0.07

* Formoterol vs. placebo
** albuterol vs. placebo

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Serial FEV-1 measurements throughout the 12 hour period after drug administration (ITTE population) after <u>1 month of treatment</u> (v25, p 287-292)

Time point	Albuterol mean % change from baseline	Formoterol mean % change from baseline	Formoterol % patients with ≥15% increase in FEV-1	Formoterol minus placebo (mean)(L) v25,p288	Formoterol vs. placebo	Albuterol minus placebo (mean)(L) v25, p288	Albuterol vs. Placebo
				Mean	P value	Mean	P value
Predose	3%	11%	26%	0.16	0.01	- 0.08	0.23
5 minutes	19%	19%	47%	0.33	< 0.0001	0.27	< 0.0001
15 minutes	21%	20%	54%	0.34	< 0.0001	0.28	< 0.001
30 minutes	22%	22%	53%	0.35	< 0.0001	0.30	< 0.001
1 hours	22%	25%	59%	0.35	< 0.0001	0.25	0.0002
2 hours	20%	25%	57%	0.31	< 0.0001	0.17	0.01
3 h ours	15%	25%	57%	0.28	< 0.0001	0.03	0.64
4 hours	11%	23%	59%	0.26	0.0002	- 0.07	0.35
6 hours	12%	20%	49%	0.24	0.0006	0.02	0.79
8 hours	15%	17%	45%	0.21	0.0002	0.11	0.09
10 hours	9%	17%	43%	0.18	0.0008	- 0.02	0.82
11 hours	9%	18%	46%	0.21	0.0004	- 0.01	0.86
12 hours	10%	18%	43%	0.20	0.0006	0.01	0.87

Serial FEV-1 measurements throughout the 12 hour period after drug administration (ITTE patient population) <u>on day 1</u> of treatment (v25, p294)

Time point	Albuterol mean % change from baseline	Formoterol mean % change from baseline	Formoterol % patients with ≥ 15% increase FEV-1	Formoterol minus placebo (mean)(L) (v25, p294)	Formoterol vs. placebo	Albuterol minus placebo (mean)(L) (v25, p294)	Albuterol Vs. placebo
Predose					P value		P value
5 min	19%	13%	35%	0.27	< 0.0001	0.36	< 0.0001
15 min	22%	17%	50%	0.31	< 0.0001	0.40	< 0.0001
30 min	24%	19%	63%	0.36	< 0.0001	0.43	< 0.0001
1 hour4	24%	20%	66%	0.31	< 0.0001	0.36	< 0.0001
2 hour	21%	22%	66%	0.34	< 0.0001	0.30	< 0.0001
3 hour	17%	23%	66%	0.32	< 0.0001	0.19	< 0.0001
4 hour	12%	22%	65%	0.32	< 0.0001	0.11	0.02
6 hour	14%	20%	56%	0.30	< 0.0001	0.14	0.005
8 hour	16%	18%	53%	0.27	< 0.0001	0.20	< 0.0001
10 hour	11%	16%	44%	0.22	< 0.0001	0.09	0.07
11 hour	9%	16%	48%	0.22	< 0.0001	0.06	0.23
12 hour	10%	17%	45%	0.25	< 0.0001	0.09	0.09

<u>COMMENT</u>: *Serial measurements of FEV-1 over the 12 hours after drug administration demonstrate the continued efficacy of formoterol delivered by MDDPI over the entire 12 hour dosing interval on day 1 and after 4 and 12 weeks of treatment.*

g) *serial FVC measurements* (v25, p53): Serial FVC measurements were done at the same time as FEV-1 determinations.

COMMENT: *The data for this parameter does not add anything substantive to evaluation of the efficacy of formoterol. The conclusions derived from this parameter are the same as those that can be derived from serial FEV-1 determinations in terms of comparing the effectiveness of formoterol relative to placebo. Therefore, the data are not presented in this review.*

h) *PEF* (v25, p53): The pre-specified analyses were the 1-4 week period of treatment, the 5-8 week period of treatment, the 9-12 week period of treatment and the overall treatment period (1-12 weeks).

mean AM/PM PEF (L/min) averaged over all treatment days (ITTE population)

AM PEF	Treatment	N	Mean PEF	Change over placebo	P value (vs. placebo)
	Formoterol	77	376	28	< 0.0001
	Albuterol	77	346	- 2.2	0.73
	Placebo	78	349	-----	-----
PM PEF					
	Formoterol	77	394	26	< 0.0001
	Albuterol	77	367	- 2.9	0.63
	Placebo	78	369	-----	-----

COMMENT: *Although there was a statistically significant difference between the mean PEF in the formoterol group and the placebo group, the differences are very small. i.e. 28 L/min AM and 26 L/min PM. The clinical significance of this degree of improvement is questionable.*

I) *asthma symptom scores* (v25, p54, pgs 329-365): Individual asthma symptom evaluation was performed by each patient and recorded in the diary card twice daily, in the morning and early evening before taking the study medication (v26, p563-564). The patient was asked to consider his/her symptoms over the preceding 12 hours. An asthma symptom score was determined for shortness of breath, cough, wheezing and chest discomfort (tightness) using a four point categorical scale with 0 = no symptoms and 3 = severe symptoms. In addition, each AM the patient recorded a response to the question, "How did you sleep last night?" using a 5 point categorical scale where 0 = not awakening because of breathing problems and 4 = difficult sleeping because of breathing

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problems despite using rescue medication. A total asthma score for each day was not determined but a total asthma symptom score was recorded for each 12 hour period.

p values for comparison with placebo for asthma symptom scores and rescue medication use (ITTE population) at progressive time points throughout the study (see section below on rescue medication)

Parameter	Formoterol vs. placebo	Albuterol vs. placebo	Formoterol vs. placebo	Albuterol vs. placebo	Formoterol vs. placebo	Albuterol vs. placebo	Formoterol vs. placebo	Albuterol vs. placebo
	Days 1-28	Days 1-28	Days 29-56	Days 29-56	Days 57-84	Days 57-84	Days 1-110	Days 1-110
Nocturnal symptom score	0.01 ••	0.38	0.02 ••	0.28	0.008 ••	0.02 ••	0.003 ••	0.68
AM total symptom score	0.002 ••	0.76	0.02 ••	0.32	0.02 ••	0.28	0.006 ••	0.58
PM total symptom score	0.02 ••	0.28	0.009 ••	1.00	0.03 ••	0.68	0.008 ••	0.47
AM shortness of breath	0.0005 ••	0.41	0.01 ••	0.25	0.03 ••	0.14	0.0006 ••	1.00
PM shortness of breath	0.003 ••	0.17	0.06 ••	0.94	0.01 ••	0.57	0.002 ••	0.43
AM chest discomfort	0.001 ••	0.55	0.03 ••	0.09	0.14	0.08	0.02 ••	0.14
PM chest discomfort	0.005 ••	0.82	0.05 ••	0.58	0.08	0.24	0.04 ••	0.70
AM wheezing	0.001 ••	0.41	0.11	0.52	0.06 ••	1.00	0.01 ••	0.87
PM wheezing	0.06 ••	0.81	0.05 ••	0.77	0.02 ••	0.59	0.02 ••	0.99
AM cough	0.53	0.25	0.21	0.70	0.89	0.71	0.62	0.23
PM cough	0.24	0.17	0.12	0.81	0.65	0.66	0.39	0.49
24 h rescue medication days 1-110	0.0006 ••	0.24	0.01 ••	0.89	0.006 ••	0.83	0.002 ••	0.79
AM 12 h rescue medication	0.006 ••	0.42	0.01 ••	0.68	0.009 ••	0.74	0.005 ••	0.75
PM 12 h rescue medication	0.002 ••	0.25	0.04 ••	0.82	0.03 ••	0.66	0.006 ••	0.52

•• statistically significant difference

COMMENT: *Approximately 2/3 of patients had nocturnal asthma symptoms at baseline. There was a baseline imbalance with the formoterol group having a baseline nocturnal asthma score of 0.75 and the albuterol group having a baseline nocturnal asthma score*

of 0.59 (0.16 difference) which was ½ of the improvement seen after formoterol administration (0.35).

j) rescue medication (v25, pgs365-376)

daytime (assessed in PM), nighttime (assessed in the AM) and 24 hour rescue medication use in mean number of puffs over the entire 110 day evaluation period with comparison to placebo

Daily interval	Time point	Criteria	Formoterol	Albuterol	Placebo
24 hour use	Baseline	N	75	76	78
		Mean (SD) # puffs	2.53 (2.34)	2.72 (2.94)	2.57 (2.45)
	Overall *	Mean (SD) # puffs	1.70 (1.71)	2.44 (2.57)	2.43 (2.21)
		P value vs. placebo	0.002	0.79	------
Nighttime use	Baseline	N	77	77	78
		Mean (SD) # puffs	1.04 (1.17)	1.07 (1.48)	0.87 (0.89)
	Overall	Mean (SD) # puffs	0.67 (0.84)	1.03 (1.24)	0.89 (0.95)
		P value vs. placebo	0.005	0.75	------
Daytime use	Baseline	N	76	76	78
		Mean (SD) # puffs	1.48 (1.49)	1.65 (1.71)	1.70 (1.87)
	Overall	Mean (SD) # puffs	1.04 (1.10)	1.41 (1.46)	1.54 (1.52)
		P value vs. placebo	0.006	0.52	------

* All treatment days up to a maximum of 110 days

> *COMMENT: The mean use of rescue medication over a 24 hour period was 1.70 puffs for the formoterol group and 2.43 puffs for the placebo group. This is unlikely to represent any clinically significant difference.*

j) *asthma exacerbations* (v25, p58):

number of asthma exacerbations using ITTE population

Parameter	Formoterol (N = 80)	Albuterol (N = 79)	Placebo (N = 80)
Number of asthma exacerbations per patient (definition 1)			
None	75	69	70
1	5 (6%)	8 (10%)	8 (10%)
2	0	1	2
> 2	0	1	0
Number of asthma exacerbations per patient (definition 2)			
None	72	65	67
1	8 (10%)	12 (15%)	10 (13%)
2	0	1	3
> 2	0	1	0

COMMENT: *The incidence of asthma exacerbations was small in all treatment groups, without any indication that asthma exacerbations were more likely to occur in patients receiving formoterol and no clear-cut demonstration that asthma exacerbations were less in patients receiving formoterol.*

CONCLUSIONS ON EFFICACY: *The efficacy of formoterol when delivered by MDDPI was demonstrated throughout the dosing interval of 12 hours after drug administration when administered at a dose of 10 mcg bid based on the primary efficacy variable, 12 hour AUC FEV-1 as well as serial measurements of FEV-1, AM/PM PEF, asthma symptom scores and rescue medication use.*

2) SAFETY:

a. *adverse events* (v25, p61, t10-2)(ITTS population):

There were 5 patients in the formoterol group (6.3%), 3 patients in the albuterol group (3.8%) and 4 patients in the placebo group (5%) who were *discontinued prematurely* because of an adverse event. The patients in the formoterol group were: 1) a 56 year old white female who on day 57 of treatment developed bronchitis and required a second course of Prednisone; 2) a 44 year old white female who on day 88 of treatment was hospitalized because of respiratory distress considered life-threatening and requiring re-institution of prohibited medications (see description of event below) (v25, p155); 3) a 21 year old white female who on day 75 of treatment had an asthma exacerbation that required a course of Prednisone; 4) a 13 year old white male who on day 1 was noted to have WPW syndrome on ECG; and 5) a 48 year old white female who on day 63 of treatment had an exacerbation of asthma which required increased beta agonist use. By contrast, there were two patients in the placebo group who were prematurely discontinued because of exacerbation of asthma, a 51 year old white female on day 53 of treatment and a 29 year old white male on day 28 of treatment (v25, p203-207).

There were 2 formoterol patients and 3 albuterol patients who had _serious_ adverse events in the study. No serious adverse events were reported in the placebo group. The 2 serious adverse events in the formoterol group were a patient who developed respiratory distress (2) above) and was discontinued from the study and a patient who developed basal cell carcinoma.

The patient who developed respiratory distress presented to the ER with an exacerbation of asthma. She was given nebulized albuterol and sent home on cough medication. The next day, the patient began to experience increased asthma again, became acutely dyspneic with audible wheezing and enroute to the ER became unresponsive and apneic. Emergency intubation was performed and the patient was hospitalized. She was discharged 3 days later. This event was considered to be an extension of the patient's asthma by the investigator and not related to the study drug (v25, p155).

The patient who developed basal cell carcinoma was a 54 year old Caucasian female who had received treatment with formoterol for 33 days prior to making this diagnosis. The patient had a skin biopsy and excision and subsequently was considered completely related. The investigator did not believe that there was any relationship to the study drug (v25, p155).

Adverse events where there was a 2% or greater incidence in the ITTS formoterol group as compared to both the ITTS albuterol and the placebo group can be seen in the table below.

Adverse event	Formoterol (N=80)	Albuterol (N=79)	Placebo (N=80)
Nasopharyngitis	8 (10%)	4 (5%)	5 (6%)
Back pain	3 (4%)	1 (1%)	1 (1%)
Upper abdominal pain	3 (4%)	None	None
Dyspepsia	3 (4%)	None	None
Influenza	2 (3%)	None	None
Allergic rhinitis	2 (3%)	None	None
Fungal vaginosis	2 (3%)	None	None

Severity of adverse events and link to study medication (ITTS population)

Category	Formoterol (N=80)	Albuterol (N=79)	Placebo (N=80)
Severe adverse events	6	11	10
Drug-related AEs	6	8	5
Significant AEs *	6	5	4
Asthma-related AEs **	8 (10%)	14 (18%)	13 (16%)

* adverse events that were considered serious adverse events or led to premature
discontinuation from the study

** There was one patient in the formoterol group who had a serious adverse event that
was an asthma-related adverse event and led to premature discontinuation from the
study. This adverse event was not considered by the investigator to be related to the
study drug.

COMMENT: *Specific adverse events in the formoterol group that
occurred with an incidence that was 2% or greater than seen in the
albuterol and placebo groups was very low, and the difference
between the treatment groups was not clinically significant. There
were less severe, drug-related and asthma-related adverse events
in the formoterol group than in the albuterol group and except for
drug-related adverse events, less than in the placebo group as
well. One patient in the formoterol group developed ventricular
bigeminy (v26 , p417,p520). This patient was a 13 year old white
male (#0516) who developed this event on the first day of
treatment, an event that was considered possibly related to the
study drug (see listing of patients who were prematurely
discontinued because of adverse events on the previous page)*

b) laboratory tests (v25, p66): obtained at screening, visit 2 and visit 5
prior to administration of the study drug (v26, p567)

Number (%) of patients who had liver enzymes or plasma glucose levels after
treatment that were outside the sponsor's extension of the normal reference
range by 0.85 below the lower limit and 1.15 above the upper limit of the
normal reference range

Parameter	Formoterol(N=74)	Albuterol(N=77)	Placebo (N=72)
Increased SGPT (U/L)	3 (4%)	4 (5%)	4 (6%)
Increased SGOT (U/L)	3 (4%)	2 (3%)	4 (6%)
Increased glucose (mmol/L)	1 (1%)	1 (1%)	1 (2%)

COMMENT: *In study 2302, there was a higher incidence of increased SGPT, SGOT, and glucose in the formoterol group than in the albuterol or placebo groups. This finding was not reproduced in this study. The mean increase in SGPT was 2.3 U/L in the formoterol group, a change that was also seen in the albuterol group (v26, p430). The highest SGPT value seen after treatment with formoterol was 105 U/L, which was the highest value seen after albuterol administration, as well. There was a mean increase in SGOT of 2.6 U/L in the formoterol group and 0.8 U/L in the placebo group (v26, p431). The highest level seen after treatment with formoterol was 63 U/L. Therefore, if, based on study 2302, formoterol appeared to have an effect on these parameters, such an effect is inconsistent from study to study. There was a mean decrease in platelet counts (-3.3) in the formoterol group that was not seen in the other two groups (v26, p421). The lowest value recorded, however, after treatment with formoterol was 158,000 while the lowest value seen in the placebo group was 159,000. There were no patients in the formoterol group who had a normal platelet level at baseline who had a decreased platelet level after treatment (v26, p442). There were 2 patients in the formoterol group and 1 patient in the albuterol group who had a normal potassium level at baseline which decreased below the lower limit of the normal reference range after treatment (v26, p457).*

d) *vital signs* (v25, p67, pgs 379-387) (v26, pgs524-534): Vital signs were measured at visit 1 (screening), visit 2 (baseline), visit 2, and visit 5 (v26, p567). There was no clinically significant difference in mean systolic or diastolic blood pressure or pulse rate between the three treatment groups or in the formoterol group compared to baseline on day 1, after one month of treatment or after 3 months of treatment. There was a 50 year old white female in the formoterol group whose diastolic blood pressure rose from 90 mm Hg at baseline to 101 mm Hg 30 minutes after drug administration on day 1 and whose systolic blood pressure rose from 149 mm Hg at baseline to 163 mm Hg at 10 hours after drug administration on day 1. Similar changes were seen in the albuterol and placebo groups.

e) <u>ECGs</u> (v25, p68): ECGs were obtained at screening (visit 1), as well as prior to drug administration and 90 minutes after drug administration on visits 2 and 5 (v26, p568).

1) <u>*QTc interval*</u>: There was a 79 year old white male (#00026) in the formoterol group who had a QTc interval of 490 msec using Bazett's correction (an increase of 50 msec) (using the Fridericia correction, the QTc interval was 468 msec) after drug administration at visit 2 (day 1). Prior to drug administration on day 1, the patients QTc interval was 440 msec using Bazett's correction and 429 msec using Fridericia's correction. Prior to drug administration at the end of the study the QTc interval was 480 msec and after drug administration at that time it was 470 msec using Bazett's correction. The patient's potassium level was normal and the patient had no adverse event related to this prolongation of the QTc interval. There was also one patient in the albuterol group who had a prolongation of the QTc interval of 470 msec prior to drug administration at visit 5 whose potassium level was normal and who also had no adverse effects.

QTc interval (Bazett's correction) (ITTS population) (v25, p68, t10-8, v26, p510, t10.5-1)

Treatment arm and time of measurement	N	Mean	Mean change from baseline	P value vs. placebo	Maximum
Day 1, 90 minutes after drug administration					
Formoterol	80	425 msec	0.4 msec	0.65	490 msec
Albuterol	79	426 msec	1.9 msec	0.32	460 msec
Placebo	80	422 msec	0.3 msec	-----	460 msec
Final visit before drug administration					
Formoterol	71	423 msec	-1.1 msec	0.92	480 msec
Albuterol	75	424 msec	- 1.2 msec	0.57	470 msec
Placebo	69	421 msec	- 1.2 msec	-----	460 msec
Final visit, 90 minutes after drug administration					
Formoterol	71	426 msec	1.7 msec	0.68	470 msec
Albuterol	71	424 msec	- 1.7 msec	0.52	460 msec
Placebo	68	425 msec	0.4 msec	-----	450 msec

QTc interval (Fridericia's correction) (ITTS population) (v26, p512)

Treatment arm and time of measurement	N	Mean	Mean change from baseline	P value vs. placebo	maximum
Day 1, 90 minutes after drug administration					
Formoterol	80	419 msec	0.1 msec	0.73	474 msec
Albuterol	79	417 msec	0.2 msec	0.95	446 msec
Placebo	80	415 msec	0.6 msec	-----	467 msec
Final visit, before drug administration					
Formoterol	71	415 msec	- 2.4 msec	0.92	467 msec
Albuterol	75	416 msec	- 1.3 msec	0.66	461 msec
Placebo	69	415 mec	- 1.1 msec	-----	455 msec
Final visit, 90 minutes post drug administration					
Formoterol	71	419 msec	0.1 msec	0.94	467 msec
Albuterol	71	415 msec	- 1.8 msec	0.32	447 msec
Placebo	68	418 msec	1.3 msec	-----	459 msec

2) *ECG changes*: The number (%) of patients with had more abnormal ECG changes after drug administration compared to baseline (ITTS population) can be seen in the table below (v25, p69).

Treatment arm	N	n	%
Day 1, 90 minutes after drug administration			
Formoterol	80	16	20%
Albuterol	79	19	24%
Placebo	80	13	16%
Final day prior to drug administration			
Formoterol	71	13	18%
Albuterol	75	14	19%
Placebo	69	11	16%
Final day, 90 min after drug administration			
Formoterol	71	11	16%
Albuterol	71	16	23%
Placebo	68	11	16%

CONCLUSIONS ON SAFETY: *Based on a comparison of adverse events in patients who received formoterol delivered by Certihaler and patients who received albuterol or placebo, the*

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incidence of adverse events of 2% or more and severe and serious adverse events was very low in the formoterol group. In addition, the data from measurement of vital signs, ECGs, and laboratory tests in this study does not raise any concern about the safety of formoterol when delivered by the Certihaler.

<u>OVERALL CONCLUSIONS BASED ON THIS STUDY</u>: *This study supports the efficacy and safety of formoterol delivered by Certihaler at a dose of 10 mcg bid in adults.*

APPEARS THIS WAY
ON ORIGINAL

3. Study 604, entitled "A 12 week randomized, multicenter, double-blind, placebo controlled, parallel group study in children (aged 5-12 inclusive) with persistent asthma evaluating the safety, efficacy, and pharmacokinetics of Foradil (formoterol fumarate) 10 mcg bid delivered by the multi-dose dry powder inhaler (MDDPI) versus placebo"(v12-17):

    a. study characteristics: This study was performed at 22 centers in the United States.

    1) number of patients: 249 randomized (127 formoterol, 122 placebo); 167 males (67%) and 82 females (33 %); 167 (67%) White, 54 (21%) Black, 4 (2%) Oriental and 24 (10%) other (v33, p38)

    2) age range: 5-13 years; at least two patients 5-6 years of age at each center; 26 patients (10%) = 5-6 years; 89 patients (36%) = 7-9 years; 133 patients (53%) = 10-12 years; one patient 13 years of age

    3) patient population: persistent asthma; FEV-1 50% of predicted or greater; duration of asthma 0.1-12.8 years; on treatment with bronchodilator; inhaled corticosteroids and montelukast were allowed but patients were excluded if their dose of inhaled corticosteroids changed in the month prior to the first visit or if the total daily dose exceeded the recommended dose; patients were excluded if they used parenteral or oral corticosteroids in the month prior to the first visit; patients with a QTc interval > 0.46 msec were excluded.

    4) study design: randomized, multicenter (22 centers), double-blind, placebo-controlled, parallel group, safety, efficacy and PK study

    5) drug administration: formoterol 10 mcg bid delivered from a multidose dry powder inhaler administered at 6-9 AM and at 6-9 PM; albuterol MDI PRN as rescue medication during run-in and treatment periods with 6 hour washout period prior to each visit; use of a spacer with the albuterol MDI rescue medication was allowed.

    6) periods of study: 12 weeks of randomized treatment; 2 week single blind, placebo run-in period; visit 1 was at the beginning of the single-blind placebo run-in period; visit 2 was at the time of initiation of the double-blind period of randomized treatment; visit 3 was after 4 weeks of treatment; visit 4 was after 8 weeks of treatment and visit 5 was after 12 weeks of treatment.

7) parameters evaluated: the primary efficacy variable was the 12 hour AUC FEV-1 measured at visits 2-5; secondary efficacy variables were: 1) serial FEV-1 and FVC measured at visits 2-5; 2) number of asthma exacerbations recorded at visits 2-5; 3) AM/PM PEFR averaged for weeks 1-4, 5-8, and 9-12 and the total treatment period; 4) asthma symptom scores and nocturnal asthma symptom scores averages for weeks 1-4, 5-8 and 9-12 and the total treatment period – individual asthma symptom scores were recorded in the morning and evening for the previous 12 hours and analyzed; 5) use of rescue medication (number of puffs) during a 24 hour period and also during the previous 12 hours as recorded in the morning and evening for weeks 1-4, 5-8 and 9-12 and the total treatment period; and 6) number of asthma exacerbations, defined as "asthma aggravated", "status asthmaticus" or any asthma-related adverse event;

safety parameters included: 1) adverse events recorded at visits 2-5; 2) ECGs done at visits 1, 2 and 5; 3) laboratory tests done at visits 1, 2 and 5; 4) vital signs measured at each visit; and 5) physical examination;

PK parameters evaluated at visits 2-5 at 3 designated centers in 12 patients per treatment arm were: 1) total urinary excretion over 12 hours after drug administration in nmoles and % of dose; 2) plasma AUC at steady state; and 3) renal clearance.

8) Primary objective: to determine superiority of formoterol over placebo in regard to lung function tests and symptom control.

Statistical considerations: There was an intent-to-treat for efficacy (ITTE), intent-to-treat for safety (ITTS) and a per protocol (PP) population; (v33, p44). The pre-specified primary efficacy variable is the 12 hour AUC for FEV-1 at the 3 month spirometry evaluation using the ITTE population analyzed by ANCOVA compared to placebo response calculated relative the pre-dose FEV-1 value calculated at visit 2 (day 1 of randomized double-blind treatment)(v12, p28). The primary efficacy variable, serial FEV-1 and FVC, AM/PM PEFR and rescue medication use were assessed using ANCOVA. The patient population pre-specified was the ITTE population. Data was imputed if necessary. If the patient prematurely terminated the 12 hour spirometry evaluation or used

rescue medication during this period, the FEV-1 value before premature termination or before the use of rescue medication was carried forward through the 12 hour period. If the 3 month spirometry evaluation was not available, the last spirometry evaluation prior to month 3 was used to impute the 3 month AUC. Therefore, two types of imputation were used by the sponsor: 1) replacing missing and/or rescue medication influenced serial FEV-1 values within a visit; and 2) replacing the 3 month 12 hour spirometry visit for AUC calculation with an earlier 12 hour spirometry visit if the 3 month 12 hour spirometry visit was missing or contained excessive missing or rescue medication influenced data. All secondary efficacy variables were only analyzed using the ITTE population. The Van Elteren test and the ANCOVA for the 12 hour AUC of FEV-1 at the 3 month (imputed) evaluation stratified for baseline FEV-1 quartiles were added after the study was un-blinded. Asthma symptom scores and number of asthma exacerbations were analyzed by the van Elteren test. Descriptive statistics were used for all safety variables except for QTc which was analyzed by ANCOVA. Randomized patients were defined as all patients who received a randomization number. Intent-to-treat for efficacy (ITTE) patients were defined as randomized patients who took study drug and had at least one 12 hour spirometry evaluation during the double-blind treatment period. Per protocol patients were defined as ITTE patients who completed 12 weeks of double-blind treatment, had a 12 week spirometry evaluation with a calculable AUC and did not have any major deviations from the protocol procedures.

a. <u>study results</u>:

1) <u>EFFICACY</u>:

a) <u>patient disposition and discontinuations</u> (v12, p33, p79):

A total of 344 patients were screened; 127 were randomized to receive formoterol by MDDPI and 122 were randomized to receive placebo. There were 116 patients in the MDDPI group and 111 patients in the placebo group who completed the study. In the MDDPI group and in the placebo group 9% of the

patients discontinued treatment. Included in this group were 3 patients in the MDDPI and 3 patients in the placebo group who discontinued because of adverse events. The three patients in the formoterol group were: 1) an 11 year old Caucasian female who developed a rash and swelling around the mouth on study day 29 that was considered to be related to the study drug; and 2) an 11 year old male of other ethnicity who developed sinus bradycardia and PACs after the first dose of formoterol with a positive rechallenge that include PVCs; and 3) a 5 year old Black male who developed successive ectopic beats and premature atrial systoles after drug administration at visit 2. One patient in the placebo group also developed bradycardia and PACs and was discontinued from the study. There were more major protocol deviations in the placebo group but overall, the incidence of protocol violations was not significantly different in the two treatment groups.

b) Demographics (v12, p36):

Patients in both treatment groups were 5-12 years of age, except for one 13 year old patient in the placebo group (see table below).

Demographics – Study 604

Variable	Formoterol MDDPI 10 mcg bid (N = 127)	Placebo (N = 122)
Age (years) ••••••••••••••••••		
5-6 years	13	13
7-9 years	49	40
10-12 years	65	68
> 12 years	0	1
Gender •••••••••••••••••••••		
Male	95 (75%)	72 (59%)
Female	32 (25%)	50 (41%)
Race •••••••••••••••••••••		
Caucasian	81 (64%)	86 (70%)
African-American	33 (26%)	21 (17%)
Asian-American	1 (1%)	3 (3%)
Other	12 (9%)	12 (10%)

COMMENT: *There were a higher percentage of females and Caucasians in the placebo group than in the formoterol group. There were no major differences in baseline disease characteristics or other baseline imbalance. Furthermore, the sponsor used different ANCOVA models adjusting for these variables without changing the conclusion that formoterol produced a statistically significant improvement compared to placebo (v12, p40).*

c) Disease characteristics of treatment groups at baseline:

Variable	Formoterol MDDPI	Placebo
Mean duration of asthma	6.5 years	6.9 years
Minimum duration of asthma	0.1 years	0.6 years
Maximum duration of asthma	12.8 years	12.4 years
Mean FEV-1 before albuterol	1.62	1.63
Mean % FEV-1 before albuterol	76%	74%
Mean FEV-1 increase after albuterol	21%	24%
Mean AM pre-dose PEF (L/min)	247	237
Mean PM pre-dose PEF (L/min)	255	243
Mean nocturnal symptom score	0.25	0.28
Mean nighttime symptom score	1.18	1.48
Mean daytime symptom score	1.23	1.53
Mean puffs of rescue meds 24 hr	0.89	0.98

d) concomitant medications at baseline and used during the study (v12, p38); A greater proportion of patients in the formoterol group used concomitant medications for asthma and allergies during the study – 95% in the formoterol group and 86% in the placebo group. The difference was driven by a greater use of fluticasone in the formoterol group (58% compared to 48% in the placebo group)(v12, p124). There was greater use of diphenhydramine and psuedoephedrine in the formoterol group (13% and 11%, respectively), than in the placebo group (7% and 9%, respectively). In the formoterol group, 75% of patients were using inhaled corticosteroids at baseline compared with 69% in the placebo group.

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e) primary efficacy variable:

The mean change from baseline (defined as FEV-1 measurement before the first dose of drug on day 1) in 12 hour AUC for FEV-1 after 3 months of treatment based on ITT and PP populations can be seen in the table below(v12, p12).

mean change from baseline in 12 hour AUC FEV-1 after 3 months of treatment based on
ITTE population

Treatment	Patient population	N	Mean FEV-1 AUC (L/hr)	P value *
Formoterol	Intent-to-treat	127	2.45	0.01 **
Formoterol	Per protocol	115	2.63	0.003
Placebo	Intent-to-treat	120	1.50	-----
Placebo	Per protocol	108	1.45	-----

*   treatment comparison to placebo
** pre-specified primary analysis

f) secondary efficacy variables (v12, p42):

1] serial measurement of FEV-1:

Change in FEV-1 (L) imputed after treatment administration at the time of the last spirometry, (v12, p42, t9-2a) (v12, p131, f9.2-1, p134, f9.2-4, p137, f9.2-7p140, f9.2-10) (v12, pgs 149-152, tables 9.2-1, 9.2-2, 9.2-3)

Time-point	Formoterol mean % change in FEV-1 from baseline	Placebo mean % change in FEV-1 from baseline	Formoterol % patients with ≥ 15% increase FEV-1	Formoterol minus placebo in mean FEV-1 (L)	Formoterol vs. placebo p value
				Mean	P value
Pre-dose	7%	5%	16%	0.03	0.27
5 minutes	12%	6%	28%	0.10	0.0006 ••
15 minutes	14%	7%	39%	0.12	< 0.0001 ••
30 minutes	15%	8%	35%	0.12	0.0002 ••
1 hour	17%	9%	36%	0.12	0.0002 ••
2 hours	17%	10%	42%	0.11	0.001 ••
3 hours	17%	10%	36%	0.11	0.001 ••
4 hours	16%	10%	37%	0.09	0.004 ••
6 hours	14%	10%	32%	0.08	0.02 ••
8 hours	12%	9%	28%	0.06	0.09
10 hours	11%	8%	24%	0.06	0.10
11 hours	11%	9%	27%	0.04	0.23
12 hours	11%	9%	26%	0.04	0.24

COMMENT: *Effectiveness for formoterol, based on a statistical comparison with placebo for serial FEV-1 determinations, was demonstrated for only the first 6 hours of the 12 hour treatment period when administered after 3 months of treatment. When patients were evaluated after one month of treatment, effectiveness, based on statistical comparison with placebo in terms of FEV-1, was demonstrated for only 10 hours. On the first day of treatment, there was a statistically significant difference from placebo throughout the 12 hour period after formoterol administration. Although a statistically significant improvement in FEV-1 AUC was demonstrated when formoterol was compared to placebo at each time point, there is a suggestion based on serial FEV-1 determinations that effectiveness of formoterol delivered by MDDPI did not persist throughout the dosing interval with repetitive administration. An onset of action was demonstrated within 5 minutes after administration of 10 mcg of formoterol by MDDPI.*

Change in FEV-1 (L) imputed after treatment for <u>one month</u> (ITTE population) (v12, pgs157-160, tables 9.2-7, 9.2-8 and 9.2-9)

time-point	Formoterol mean % change in FEV-1 from baseline	Placebo mean % change in FEV-1 from baseline	Formoterol % patients with ≥ 15% increase FEV-1	Formoterol minus placebo Mean FEV-1 (L)	Formoterol vs. placebo p value
	N = 121	N =114		Mean	P value
Pre-dose	8%	4%	19%	0.07	0.03
5 minutes	11%	5%	26%	0.11	0.005
15 minutes	12%	5%	29%	0.12	< 0.0001
30 minutes	14%	6%	35%	0.13	0.0001
1 hour	15%	8%	34%	0.11	0.0005
2 hours	15%	8%	39%	0.12	0.0003
3 hours	15%	9%	33%	0.11	0.002
4 hours	14%	9%	31%	0.10	0.004
6 hours	13%	8%	27%	0.09	0.006
8 hours	11%	7%	25%	0.07	0.03
10 hours	10%	6%	22%	0.06	0.04
11 hours	9%	6%	22%	0.05	0.12
12 hours	9%	7%	21%	0.03	0.38

Change in FEV-1 (L) imputed after the first dose of study drug on <u>day 1</u> (ITTE population) (v12, pgs161-164) can be seen in the table below.

Time-point	Formoterol mean % change in FEV-1 from baseline	Placebo mean % change in FEV-1 from baseline	Formoterol % patients with ≥ 15% increase in FEV-1	Formoterol minus placebo Mean FEV-1 (L)	Formoterol vs. placebo p value
				Mean	P value
Pre-dose					
5 minutes	9%	2%	16%	0.12	< 0.0001
15 minutes	11%	3%	25%	0.13	< 0.0001
30 minutes	12%	5%	27%	0.13	< 0.0001
1 hour	13%	5%	36%	0.13	< 0.0001
2 hours	14%	5%	36%	0.15	< 0.0001
3 hours	14%	5%	35%	0.14	< 0.0001
4 hours	13%	5%	33%	0.14	< 0.0001
6 hours	12%	3%	30%	0.15	< 0.0001
8 hours	11%	4%	28%	0.12	< 0.0001
10 hours	10%	3%	28%	0.11	< 0.0001
11 hours	9%	3%	26%	-0.09	0.0002
12 hours	9%	4%	26%	0.09	0.0002

2] <u>serial measurement of FVC (v12, p166, t9.2-14)</u>: There was no statistically significant difference between the group that received formoterol and the group that received placebo in terms of change in FVC at any time point after drug administration after 3 months of treatment (p = 0.40-0.98) or after the first dose (p = 0.12-0.88)(v12, p175, t9.2-20) or after one month of treatment (p =0.26-0.93)(v12, p172, t9.2-18).

<u>COMMENT</u>: *FVC is an effort-dependent spirometery measurement and is very unreliable in children.*

3] <u>PEF</u> (v12, p45, t9-3; v12, p179):

Mean AM/PM PEF (L/min)(ITTE population) pre-specified to be averaged over all treatment days, as well as averaged for weeks 1-4, 5-8 and 9-12 (v12, p30)(v12, p179, t9.2-23) can be seen in the table below.

Time-point	Treatment	N	Overall average (mean % change)	Weeks 1-4	Weeks 5-8	Weeks 9-12	P value *
AM PEF							
	Formoterol MDDPI 10 mcg bid	125	260 (8%)	260 (7%)	261 (9%)	261 (9%)	0.05
	Placebo	120	254 (7%)	250 (4%)	253 (6%)	259 (11%)	-----
PM PEF							
	Formoterol MDDPI 10 mcg bid	124	264	262 (6%)	265 (8%)	263 (8%)	0.06
	Placebo	120	259	255 (3%)	257 (5%)	261 (9%)	-----

* comparison of formoterol and placebo over the entire treatment period

> <u>COMMENT</u>: *As can be seen from the table above, at the most, there was a 10 L/minute difference between the formoterol group and the placebo group for AM PEF and an 8 L/minute difference for PM PEF. This difference is of questionable clinical significance and the data relating to this parameter is of questionable use in the support of the efficacy of formoterol MDDPI in this pediatric population.*

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4] <u>symptom scores</u> (v12, p45):

Mean asthma symptom scores (ITTE population) overall (all treatment days up to a maximum of 110 days (v12, p 46-47, t9-5, pgs183-206, tables9.2-27-9.2-50) can be seen in the table below.

Nocturnal symptoms	Treatment	N	Daily mean	P value *
	Formoterol MDDPI 10 mcg bid	125	0.14	0.02
	Placebo	120	0.24	-----
Morning symptoms				
	Formoterol MDDPI 10 mcg bid	125	0.77	0.10
	Placebo	120	1.13	-----
Evening symptoms				
	Formoterol MDDPI 10 mcg bid	125	0.88	1.24
	Placebo	120	0.02	-----
AM dyspnea	Formoterol MDDPI 10 mcg bid	125	0.14	0.39
	Placebo	120	0.26	-----
PM dyspnea	Formoterol MDDPI 10 mcg bid	125	0.19	0.06
	Placebo	120	0.31	-----
AM chest discomfort	Formoterol MDDPI 10 mcg bid	125	0.10	0.25
	Placebo	120	0.19	-----
PM chest discomfort	Formoterol MDDPI 10 mcg bid	125	0.13	0.20
	Placebo	120	0.20	-----
AM wheezing	Formoterol MDDPI 10 mcg bid	125	0.18	0.35
	Placebo	120	0.26	-----
PM wheezing	Formoterol MDDPI 10 mcg bid	125	0.19	0.43
	Placebo	120	0.29	-----
AM cough	Formoterol MDDPI 10 mcg bid	120	0.35	0.08
	Placebo	125	0.42	-----
PM cough	Formoterol MDDPI	120	0.37	0.16
	Placebo	125	0.44	-----

* comparison of formoterol and placebo

Patients recorded individual symptom scores in a daily diary, specifically recording nocturnal symptom scores upon arising in the

morning, in the morning between 6-9 AM for the previous 12 hours, before taking study medication and in the evening between 5-9 PM for the previous 12 hours, before taking the evening dose of medication (v13, p422). Total asthma symptom scores defined as the sum of the 4 individual symptom scores for wheezing, cough, chest .discomfort and shortness of breath, were calculated in conjunction with individual symptom scores for weeks 1-4, 5-8 and 9-12, as well as the total period of randomized double-blind treatment (v12, p30).

COMMENT: *Using the Van Elteren test for nocturnal asthma symptoms, a statistically significant difference from placebo was seen over the entire treatment period for nocturnal symptoms if patients were stratified by baseline quartiles (p = 0.02). but not if they were stratified by center (p = 0.13) when all patients in the ITTE population were included. If only the patients who had symptoms at baseline were included, a statistically significant difference between the formoterol group and the placebo group was demonstrated, whether stratified by baseline quartiles (p = 0.02) or by center (p = 0.03). In terms of morning and evening symptoms, no statistically significant difference between the formoterol and placebo groups was demonstrated with use of either baseline quartiles or center stratification. As with some of the other parameters evaluated in children, the effectiveness of formoterol MDDPI appears to decrease over time with repetitive administration (v12, p190, t9.2-34). No statistically significant or clinically significant difference between formoterol MDDPI 10 mcg bid and placebo was demonstrated for any of the individual asthma symptoms when measured in the morning or in the evening.*

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5] rescue medication (v12, p207-215, tables 9.2-51-9.2-59):

Mean number of puffs of rescue medication (ITTE population)(v12, p48, t9-6)

24 hour use	Treatment	N	Mean	P value *
	Formoterol MDDPI 10 mcg bid	122	0.65	0.10
	Placebo	125	0.90	-----
Night-time use				
	Formoterol MDDPI 10 mcg bid	124	0.21	0.04
	Placebo	125	0.36	-----
Day-time use				
	Formoterol MDDPI 10 mcg bid	123	0.11	0.17
	Placebo	125	0.19	-----

* comparison of formoterol and placebo

COMMENT: *The difference in the use of rescue medication between the two treatment regimens is of questionable clinical significance. Moreover, statistical significance was not demonstrated for day-time use or 24 hour use.*

6] asthma exacerbations (v12, p49, p216):

COMMENT: *Using the definition of "asthma aggravated" or "Status Asthmaticus", there were 17 formoterol patients (13%) and 16 placebo patients (13%) who had one exacerbation and 1 formoterol patient (0.8%) and 5 placebo patients (4%) who had two exacerbations. Based on all asthma-related adverse events, there were 22 formoterol patients (17%) and 16 placebo patients (13%)who had one exacerbation and 2 formoterol patients (2%) and 8 placebo patients (7%) who had two exacerbations. There was one formoterol patient who had 3 exacerbations. There was no statistically significant difference between the treatment groups (p = 0.46 and 0.97, using the two definitions), although using either definition, there were more placebo patients who had more than one asthma exacerbation. There were 20% of patients in each of the two treatment groups who developed an asthma-related adverse event.*

2) <u>safety</u>:

a) <u>adverse events</u> (v12, p50, t10-1, pgs231-249, tables 10.1-1-10.2-3):

Number (%) of patients with an adverse event more frequent in the formoterol group than in the placebo group and occurring with an incidence ≥ 2% in the MDDPI group based on the ITTS population (v12, p51, t10-2) where the <u>ITTS population</u> was defined as randomized patients who took at least one dose of randomized treatment (v12, p27) can be seen in the table below.

Category	Formoterol MDDPI (N = 127)	Placebo (N = 122)
Number of patients with AE	81 (64%)	66 (54%)
Severe adverse events	8 (6%)	5 (4%)
Drug-related adverse events	5 (4%) *	1 (1%)
URI infection	19 (15%)	13 (11%)
Pyrexia	13 (10%)	7 (6%)
Nasopharyngitis	11 (9%)	7 (6%)
Vomiting	11 (9%)	4 (3%)
Pharyngitis	9 (7%)	6 (5%)
Cough	8 (6%)	4 (3%)
URI viral infection	6 (5%)	2 (2%)
Gastroenteritis	4 (3%)	1 (1%)
Streptococcal pharyngitis	4 (3%)	1 (1%)
Allergic rhinitis	4 (3%)	None
Bronchitis	3 (2%)	None

* the adverse events felt to be related to the study drug were perioral swelling, anxiety, insomnia, dry throat and rash

<u>COMMENT</u>: *There were more adverse events, severe adverse events, and drug-related adverse events in the formoterol group than in the placebo group. There was one serious adverse event in the formoterol group (v12, p348), an 8 year old Caucasian female who developed an asthma exacerbation that required discontinuation from the study. The incidence of infections (URIs, gastroenteritis, bronchitis) or manifestations of infection (pyrexia, cough) were consistently greater in the group that received formoterol than in the group that received placebo. The clinical significance of this finding is unclear. There is no reason to believe that an inhaled beta adrenergic agonist drug would place patients at a greater risk of developing infection or in some way lower immune resistance to infections. Nevertheless, the labeling should indicate that a greater incidence of infections occurred in children who received formoterol by MDDPI.*

"Aggravated asthma" occurred more frequently in the placebo group (17%) than in the formoterol group (14%). Exacerbation of asthma could be anticipated in asthmatic patients who are receiving placebo but the 14% incidence in the formoterol group suggests that there was effectiveness was not achieved in a significant percentage of the patients treated.

a) <u>laboratory values</u> (v12, p56, t10-7, p250-321, tables 10.3-1-6): blood for laboratory tests was drawn at visit 1 (screening), at visit 2 (prior to administration of the first dose of test drug), and at visit 5 (after 12 weeks of treatment) (v13, p426).

The number (%) of patients who had a normal laboratory value at baseline that became abnormal at some point after treatment (ITTS patient population) for laboratory tests selected because their was a greater incidence in the formoterol group than in the placebo group of a change that could be clinically significant or because it was considered an important parameter to provide information on (v12, pgs 274-291, table 10.3-4) can be seen in the table below.

Parameter	Formoterol MDDPI 10 mcg bid (n = 127)	Placebo (n = 122)
Hemoglobin decrease	3 (2.6%)	none
Hematocrit decrease	7 (6%)	1 (0.9%)
RBC decrease	3 (2.6%)	1 (0.9%)
WBC decrease	5 (4.3%)	3 (2.6%)
Neutrophil decrease	28 (24%)	23 (20%)
Bilirubin increase	1 (0.8%)	none
SGPT (U/L) increase	3 (2.5%)	2 (1.7%)
SGOT (U/L) increase	3 (2.6%)	3 (2.6%)
BUN increase	None	None
Creatinine (umol/L) increase	12 (10%)	5 (4.3%)
Glucose (mmol/L) increase	1 (0.8%)	4 (3.5%)
Potassium decrease	2 (1.7%)	None

<u>Mean</u> SGPT and SGOT decreased by 0.4 U/L in the formoterol group and increased by 0.5 U/L in the placebo group.

a) <u>vital signs</u> (v12, p57): Vital signs were measured at visit 1 (screening), and at visits 2 (day 1), 3 (after 4 weeks of treatment) and at visit 5 (after 12 weeks of treatment). On each of those days, vital signs were obtained prior to drug administration and 30 minutes, 60 minutes and 2 hours after drug administration and every 2 hours thereafter through 12 hours after administration of the morning dose

of medication. They were also obtained at visit 4 (after 8 weeks of treatment) prior to drug administration and 30 minutes after drug administration (v12, p426). There were 5 patients in the formoterol group who had an elevation in <u>diastolic blood pressure</u> (all 90-95 mm Hg) and 4 patients in the placebo group who had an elevation in diastolic blood pressure (one 90-95, two 96-100 and one 111 mm Hg). There were 7 patients in the formoterol group who had an elevation in <u>systolic blood pressure</u> (5 patients 136-140 mm Hg, 2 patients 141-150 mm Hg) and 4 patients in the placebo group who had a similar elevation (141-150 mm Hg). The mean systolic blood pressure and mean pulse rate increased slightly more in the formoterol group than in the placebo group, most notably on day 1 (v12, p327-329, pgs 335-337, t10.4-1, t10.4-3). There was no significant change in mean diastolic blood pressure or in respiratory rate in the formoterol group (v12, p331-333, t10.4-3).

<u>COMMENT</u>: *Increases in blood pressure and pulse rate are expected after administration of an inhaled beta adrenergic agonist medication in some patients.*

a) <u>ECGs</u>: ECGs were obtained at visit 1 (screening), and prior to drug administration and 90 minutes after drug administration at visits 2 (day 1) and 5 (at the completion of the study) (v13. p 427).

1] <u>QTc interval</u> (v12, p58, t10-8, pgs343-346): QTc interval was analyzed for all time points using the ANCOVA model where QTc = treatment + center + baseline QTc + error. Data based on both Bazett's and Fridericia's correction was analyzed. ECGs were read by a central laboratory.

Mean QTc interval (Bazett's correction) (ITTS patient population) compared to placebo *

Time-point	Treatment	N	Mean	P value *
Day 1, 90 min after drug admin	Formoterol MDDPI 10 mcg bid	127	405 msec	0.18
	Placebo	122	402 msec	-----
Final day, prior to drug admin	Formoterol MDDPI 10 mcg bid	119	404 msec	0.81
	Placebo	117	403 msec	-----
Final day, 90 min after drug admin	Formoterol MDDPI 10 mcg bid	116	403 msec	0.89
	Placebo	114	403 msec	-----

Clinical Review Section

Using Fridericia's correction, the mean QTc interval in the formoterol group was 385, 387, and 381 msec on day 1, 90 minutes after drug administration, pre-dose on the final treatment day and 90 minutes after drug administration on the final treatment day, respectively. The mean QTc interval in the placebo group using Fridericia's correction for the same time points was 385, 387, and 386 msec. P values comparing formoterol and placebo was 0.79 on day 1, 90 minutes after drug administration, 0.51 prior to drug administration on the final treatment day and 0.01 90 minutes after drug administration on the final treatment day.

2] <u>overall ECG findings</u> (v12, p59, t10-9):

Number (%) of patients with ECG findings assessed as more abnormal than at baseline (ITTS population)(note: the sponsor does not specify what findings were considered more abnormal after treatment or provide the specific ECG data for these patients)(v12, p347)

Time-point	Formoterol MDDPI 10 mcg bid (N = 127)	Placebo (N = 122)
Day 1, 90 minutes after drug administration	29 (23%)	12 (10%)
Final day, before drug administration	26 (22%)	24 (21%)
Final day, 90 min after drug administration	16 (14%)	5 (4%)

**APPEARS THIS WAY
ON ORIGINAL**

4. Study 602 (v8-11) entitled, "A randomized, double-blind, placebo controlled, repetitive dose (1 week) finding, multicenter, crossover study in children aged 5 to 12 with persistent asthma comparing 4 doses (5, 10, 15 and 30 mcg) of formoterol bid administered from the multiple dose dry powder inhaler (MDDPI) to one dose (12 mcg) of formoterol administered from the Aerolizer bid.

    a. study characteristics: This study was performed at 11 centers, 3 in the Czech Republic, 2 in Norway, 2 in the Russian Federation, and 4 in South Africa.

    1) number of patients: 81 patients screened; 77 patients randomized; 76 patients completed; 54 received placebo; 51 received 5 mg formoterol by MDDPI; 49 received 10 mg formoterol by MDDPI; 48 received 12 mg formoterol by Aerolizer; 52 received 15 mg formoterol by MDDPI; 53 received 30 mg formoterol by MDDPI; 44 males, 33 females; 62 (81%) white, 15 (19%) other (v33, p21); 100% were included in the ITTE and the ITTS analyses

    2) age range: 5-12 years; 5-6 years = 6 (8%), 7-9 years = 29 (38%), 10-12 years = 42 (54%)(v33, p21)

    3) patient population: persistent asthma; FEV-1 51-89% predicted; daily treatment with an inhaled bronchodilator either on a regular basis or PRN; daily anti-inflammatory treatment; duration of asthma 0.3-11.4 years (v33, p23)

    4) study design: randomized, double-blind, double-dummy (two MDDPI devices were used containing either 5 mcg or 15 mcg of formoterol), placebo-controlled, crossover, incomplete block, repetitive dose, multicenter (11 centers; 3 in Czech Republic, 2 in Norway, 2 in the Russian Federation and 4 in South Africa), dose-finding study

    5) drug administration: formoterol by MDDPI 5, 10, 15, and 30 mcg bid every12 hours; formoterol by Aerolizer 12 mcg bid every 12 hours; drug administration at 6-9 AM and 6-9PM

6) <u>periods of study</u>: 7 day single-blind run-in period; 7 days of double-blind randomized treatment with each dose; each patient received 4 of the 6 doses; 7 days placebo washout between each treatment

7) <u>parameters evaluated</u>: primary efficacy variable = standardized AUC FEV-1 over 12 hours measured at the end of each week of treatment – AUC was standardized according to the length of time from the first to the last measurement excluding measurements after the intake of rescue medication; secondary efficacy variables = FEV-1 measured at 3-5 minutes, 15 minutes, 30 minutes, 60 minutes and hourly for 3 or 12 hours – 3 hour serial FEV-1 measurements were made at the end of weeks 2, 4, and 6 while 12 hour serial FEV-1 measurements were made at the end of weeks 1, 3, 5 and 7; daily asthma symptom scores on a categorical scale of 0-1 ; use of rescue medication; PK = unchanged and total (unchanged + conjugated formoterol) formoterol over 12 hours in cumulative urine samples obtained at the end of weeks 1, 3, 5 and 7 in selected patients; safety parameters = adverse events (asthma exacerbations were reported as an adverse event), ECGs, vital signs, and laboratory values; vital signs and ECGs were obtained at the end of each treatment week; laboratory tests were done prior to initial treatment and at the end of the last week of treatment

8) <u>study objective</u>: to establish an optimally effective dose of formoterol when delivered by MDDPI, to assess dose proportionality at steady state after inhalation of rising doses of formoterol from a MDDPI, and compare the amount of unchanged and total formoterol excreted in the urine

9) <u>statistical considerations</u>: patient populations to be evaluated include: a) ITT population = all patients randomized with data from at least 2 treatment periods; b) PP population = per protocol population (patients without major protocol deviation defined as failure to demonstrate reversibility at baseline and an FEV-1 outside the 50-90% of predicted range); in order to evaluate any bias resulting from potential device malfunction, an additional

analysis was performed which was called the population of the impact of device malfunction analysis; all randomized patients who received at least one dose of study medication were included in the safety population. The pre-specified primary efficacy variable was the standardized AUC (calculated using the trapezoidal rule) for FEV-1 over 12 hours measured at the end of one week of treatment and analyzed by ANCOVA using the ITT population (v8, p26 of protocol, appendix 1).

10) study results:

a) Patient disposition: one patient was discontinued after completing the third treatment period on placebo.

b)Patient demographics: 57% male, 43% female; 80.5% Caucasian, 19.5% Asian; duration of asthma = 0.3-11.4 years;

c) efficacy:
1] FEV-1:

Increase in mean FEV-1 (L) AUC after one week of treatment based on ITT population (v8, p12, p38)

FEV-1 AUC over 12 hours after treatment for one week based on ITT

Treatment	N	Mean FEV-1 (L)	Difference from placebo	P value *
Formoterol MDDPI 30 mcg bid	53	1.94	0.18	< 0.0001
Formoterol MDDPI 15 mcg bid	52	1.91	0.14	0.0003
Formoterol MDDPI 10 mcg bid	49	1.92	0.16	< 0.0001
Formoterol MDDPI 5 mcg bid	61	1.88	0.12	0.004
Formoterol Aerolizer 12 mcg bid	48	1.88	0.12	0.004
Placebo	54	1.76	-----	-----

* comparison with placebo

COMMENT: *There was no statistically significant difference between any dose of formoterol when delivered by MDDPI and 12 mcg bid of formoterol delivered by Aerolizer based on the ITT population (p = 0.15-0.93) or the PP population (p = 0.16-0.88)). There was no statistically significant difference between any dose of formoterol delivered by MDDPI based on the ITT population (p = 0.12-0.72)(v8, p38) or the PP population (p = 0.21-0.78). The maximum increase over placebo with the 30 mcg bid dose of formoterol was 0.18 L. This amount of improvement is of questionable clinical significance. A slightly greater improvement in FEV-1 was seen after administration of formoterol 10 mcg bid (the proposed dose for the Certihaler) compared to 12 mcg of formoterol delivered from the Aerolizer. No dose response was seen after one week of treatment (v8, f9.2-1). There was no significant difference in the improvement in FEV-1 utilizing the per protocol and impact of device malfunction analyses from the intent-to-treat analysis.*

Mean FEV-1 (L) at all time points <u>after one week</u> of treatment (ITT population) (v8, p 41) (v33, p 285)

Time-point	Placebo	Formoterol MDDPI 5 mcg bid	Formoterol MDDPI 10 mcg bid	Formoterol MDDPI 15 mcg bid	Formoterol MDDPI 30 mcg bid	Formoterol Aerolizer 12 mcg bid
Pre-dose	1.69 (n =54)	1.76 (n = 51) p = 0.09 •	1.81 (n = 49) p = 0.004	1.79 (n = 52) p = 0.02	1.80 (n = 53) p = 0.01	1.80 (n = 48) p = 0.01
Post-dose	N = 54	N = 51	N = 49	N = 52	N = 53	N = 48
5 minutes	1.72	1.86 p = 0. 0008	1.92 p< 0.0001	1.90 p< 0.0001	1.90 p < 0.0001	1.90 p < 0.0001
15 minutes	1.74	1.89 p = 0.0003	1.96 p< 0.0001	1.93 p < 0.0001	1.95 p < 0.0001	1.93 p < 0.0001
30 minutes	1.76	1.92 p < 0.0001	1.98 p < 0.0001	1.92 p < 0.0001	1.98 p < 0.0001	1.93 p < 0.0001
1 hour	1.77	1.93 p=0.0003	1.99 p< 0.0001	1.94 p = 0.0001	1.99 p < 0.0001	1.97p < 0.0001
2 hours	1.78	1.93 p = 0.002	1.98 p < 0.001	1.94 p = 0.0006	1.99 p < 0.0001	1.94 p = 0.001
3 hours	1.79	1.92 p = 0.005	1.96 p = 0.0002	1.95 p = 0.0005	1.97 p < 0.0001	1.93 p = 0.003
4 hours	1.77	1.90 p = 0.003	1.96 p < 0.0001	1.92 p = 0.001	1.98 < 0.0001	1.90 p = 0.008
5 hours	1.76	1.89 p = 0.003	1.93 p < 0.0001	1.92 p = 0.0002	1.96 p < 0.0001	1.92 p = 0.0006
6 hours	1.77	1.90 p = 0.005	1.93 p = 0.0005	1.91 p = 0.002	1.94 p = 0.0002	1.86 p = 0.05
7 hours	1.75	1.86 p = 0.02	1.90 p = 0.002	1.91 p = 0.0006	1.92 p = 0.0003	1.86 p = 0.02
8 hours	1.76	1.86 p = 0.02	1.89 p = 0.004	1.90 p = 0.002	1.93 p < 0.0001	1.84 p = 0.06 •
9 hours	1.77	1.86 p = 0.05	1.89 p = 0.007	1.89 p = 0.01	1.92 p = 0.001	1.84 p = 0.14 •
10 hours	1.73	1.84 p = 0.02	1.87 p = 0.002	1.8 p = 0.001	1.91 p < 0.0001	1.81 p = 0.10 •
11 hours	1.74	1.80 p = 0.14 •	1.84 p = 0.02	1.85 p = 0.01	1.89 p = 0.001	1.80 p = 0.15 •
12 hours	1.71	1.82 p = 0.02	1.86 p = 0.001	1.85 p = 0.003	1.88 p = 0.0002	1.80 p = 0.06 •

<u>COMMENT</u>: *There was no statistically significant difference in improvement in FEV-1 between any dose of formoterol delivered by MDDPI at any time point after one week of treatment. There was no statistically significant difference between any dose of formoterol delivered by MDDPI and formoterol delivered by Aerolizer at any time point, as well, although there was also no statistically significant difference between formoterol delivered by Aerolizer and placebo longer than 7*

hours after drug administration. Based on these data, 10 mcg bid is an appropriate dose to recommend for administration to pediatric patients.

Comparison between formoterol 10 mcg bid delivered by MDDPI and formoterol 12 mcg bid delivered by Aerolizer in terms of FEV-1 improvement (L) over the 12 hours of measurement after <u>one week of treatment</u> (v8, t9.2-1)

Treatment	15m	30m	1h	2h	4h	5h	6h	7h	8h	10h	11h	12h
formoterol MDDPI 10 mcg bid	1.96 *	1.97 *	1.98 *	1.96 *	1.96 *	1.92 *	1.92 *	1.89 *	1.88 *	1.86 *	1.83 *	1.84 *
Formoterol Aerolizer 12 mcg bid	1.92 *	1.91 *	1.95 *	1.93 *	1.89 *	1.91 *	1.86 *	1.86 *	1.84 0.06	1.80 0.09	1.80 0.15	1.79 0.06

* statistically significant at $p = 0.05$ or less compared to placebo

Mean FEV-1 (L) at selected time points <u>after the first dose</u> (ITT population)(v8, p43)(v8, t9,2-4)

Time-point	Placebo	Formoterol MDDPI 5 mcg bid	Formoterol MDDPI 10 mcg bid	Formoterol MDDPI 15 mcg bid	Formoterol MDDPI 30 mcg bid	Formoterol Aerolizer 12 mcg bid
Pre-dose	1.66 (n = 54)	1.75 (n = 51)	1.70 (n = 49)	1.65 (n = 52)	1.79 (n = 53)	1.75 (n = 48)
Post-dose	N = 54	N = 51	N = 49	N = 52	N = 53	N = 48
3 minutes	1.72	1.87 *	1.85 *	1.91 *	1.90 *	1.85 *
3 hours	1.81	2.03 $p < 0.0001$	1.99 $p < 0.0001$	2.05 $p < 0.0001$	2.02 $p < 0.0001$	1.95 $p = 0.0004$

* p value comparison with placebo < 0.0001 (v8, p44, t9-7)

<u>COMMENT</u>: *There was no clinically or statistically significant difference between the response seen after administration of 10 mcg of formoterol delivered by MDDPI and 12 mcg of formoterol delivered by Aerolizer (p = 0.20) after the first dose, but there was a statistically significant difference between 10 mcg of formoterol delivered by MDDPI and placebo (p = 0.001)(v8. p42). There was no evidence of a dose response (p = 0.16-0.76) comparing doses of 5-30 mcg of formoterol delivered by MDDPI after the first dose of formoterol (v8, f9.2-4)*

2] <u>use of rescue medication</u> (v8, p 45, t9.8): There was very little use of rescue medication – mean number of doses during the day was 0.10-0.21 and during the night was 0.04-0.14.

COMMENT: *The patient population evaluated was too mild to allow any conclusions regarding the efficacy of formoterol when delivered from the MDDPI based on use of rescue medication.*

3] symptom scores (v8, p45, t9.9): No inferential statistics were planned or performed (v8, p45)

mean nocturnal and daytime asthma symptom scores

Time	Placebo	Formoterol MDDPI 5 mcg bid	Formoterol MDDPI 10 mcg bid	Formoterol MDDPI 15 mcg bid	Formoterol MDDPI 30 mcg bid	Formoterol Aerolizer 12 mcg bid
Daytime	0.43	0.26	0.25	0.32	0.30	0.26
Nighttime	0.36	0.18	0.15	0.21	0.16	0.16

4] safety:

a] adverse events (v8, pgs46-49, t10-1, t10-2, t10-3, t10-4):

Selective adverse event profile per treatment group with inclusion of specific adverse events that occurred significantly more frequently after administration of formoterol MDDPI than after administration of formoterol Aerolizer (% of asthma-related adverse events was included because of the clinical importance of this type of event in patients receiving this type of drug product can be seen in the table below.

Criteria	Placebo	Formoterol MDDPI 5 mcg bid	Formoterol MDDPI 10 mcg bid	Formoterol MDDPI 15 mcg bid	Formoterol MDDPI 30 mcg bid	Formoterol Aerolizer 12 mcg bid
N	54	51	49	62	63	48
% pts with AE	19%	22%	18%	21%	23%	8%
% pts with GI disorders	None	4%	2%	4%	2%	None
% pts with tremor	2%	2%	2%	8%	11%	None
% patients with tachycardia	2%	None	None	2%	4%	None
% patients with palpitations	None	None	None	2%	None	None
# of severe AEs	None	None	None	5	1	None
# drug-related AE	2	1	1	8	12	None
% patients with asthma-related AE	4%	2%	2%	2%	2% *	4%

* The one patient in this group that had an asthma-related adverse event had a serious adverse event that did not lead to withdrawal from the study and the event was not considered related to the study drug.

COMMENT: *Tremor is a recognized side effect of inhaled beta adrenergic agonist medications. However, the increased incidence of this adverse event in the groups that received the 15 and 30 mcg bid doses of formoterol combined with the lack of any significantly greater efficacy with these higher doses, makes the 10 mcg bid dose of formoterol delivered from the MDDPI the appropriate dose for clinical use. There was also a higher incidence of drug-related adverse events in the groups that received the two highest doses of formoterol from the MDDPI.*

b]ECGs:

COMMENT: *The percentage of patients who had abnormal ECG findings after treatment with placebo decreased from 22% to 19% after the first dose and from 17% to 15% after one week of treatment on ECGs done 2 hours after drug administration. The percentage of patients who had abnormal ECG findings after administration of formoterol by Aerolizer remained about the same after drug administration as prior to drug administration. By contrast, the percentage of patients who had abnormal ECG findings after administration of 10 mcg of formoterol bid by MDDPI increased from 17% to 31% after administration of the first dose and from 8% to 12% 2 hours after drug administration given over a period of one week. On the other hand, none of the abnormal ECGs noted in any treatment group was considered to be clinically significant. There was an increased risk of cardiovascular effect after administration of doses of formoterol > 10 mcg bid, especially with a dose of 30 mcg bid. There were individual patients who had ST-T wave depression (v11, p8), PVCs and bigeminy (v11, p20), ST elevation and poor R progression (v11, p124) after receiving 30 mcg bid of formoterol.*

Mean QTc interval (msec) 2 hours after the <u>first dose of medication</u>
(v8, p52, t10-7)

Treatment	N	Mean QTc interval (msec)	P value vs. placebo
Placebo	53	397	-----
Formoterol MDDPI 5 mcg bid	50	404	0.02
Formoterol MDDPI 10 mcg bid	48	405	0.007
Formoterol MDDPI 15 mcg bid	52	406	0.004
Formoterol MDDPI 30 mcg bid	52	407	0.001
Formoterol Aerolizer 12 mcg bid	47	403	0.07

<u>COMMENT</u>: *There was a statistically significant prolongation of the QTc interval after administration of all doses of formoterol delivered from the MDDPI compared to placebo that was not seen after administration of the first dose of formoterol delivered from the Aerolizer. These increases were small and unlikely to be of clinical significance. This effect was not seen after administration of formoterol for one week (see table below).*

Mean QTc interval (msec) after drug administration <u>on day 1</u> and <u>after treatment for one week</u> (v8, t10.5-1)

Treatment	N	First dose Pre-dose	First dose 2 hours after	1 week Rx Pre-dose	1 week Rx 2 hours after	First dose P value vs. placebo	1 week Rx P value vs. placebo	1 week Rx P value vs. placebo
Placebo	54	403	399	401	403	-----	Pre-dose	2 hours
Formoterol MDDPI 5 mcg bid	50	402	405	402	400	0.02	0.56	0.11
Formoterol MDDPI 10 mcg bid	48	403	406	405	402	0.007	0.42	0.39
Formoterol MDDPI 15 mcg bid	52	399	403	401	404	0.004	0.48	0.61
Formoterol MDDPI 30 mcg bid	62	405	407	404	403	0.001	0.70	0.65
Formoterol Aerolizer 12 mcg bid	47	402	403	402	402	0.07	0.49	0.41

<u>COMMENT</u>: *The statistically significant difference between active treatment and placebo after the first dose was related to the decrease*

in QTc interval found in the placebo group. None of the changes noted in the formoterol groups was clinically significant.

c] <u>Vital signs</u> (v8, f10.4-1,10.4-2,10.4-3):

Mean change in systolic blood pressure (mm Hg) (ITTS population) (v8, t10.4-1)

Treatment	First dose	First dose	1 week Rx	1 week Rx	1 week Rx	1 week Rx
	Pre-dose	2 hours after	Pre-dose	2 hours after	4 hours after	6 hours after
Placebo	103	104	104	103	103	104
Formoterol 10 mcg bid MDDPI	103	104	104	102	104	104
Formoterol 12 mcg bid Aerolizer	105	105	103	104	108	107

Mean change in diastolic blood pressure (mm Hg) (ITTS population) (v8, t10.4-3)

Treatment	First dose	First dose	1 week Rx	1 week Rx	1 week Rx	1 week Rx
	Pre-dose	2 hours after	Pre-dose	2 hours after	4 hours after	6 hours after
Placebo	62	62	62	61	61	62
Formoterol 10 mcg bid MDDPI	62	60	61	61	61	60
Formoterol 12 mcg bid Aerolizer	62	63	61	62	64	62

Mean change in pulse rate (bpm) (ITTS population) (v8, t10.4-5)

Treatment	First dose	First dose	1 week Rx	1 week Rx	1 week Rx	1 week Rx
	Pre-dose	2 hours after	Pre-dose	2 hours after	4 hours after	6 hours after
Placebo	78	79	78	79	82	81
Formoterol 10 mcg bid MDDPI	78	83 $p = 0.05$ *	81	84 $p = 0.003$	86	84
Formoterol 12 mcg bid Aerolizer	78	81 $p = 0.36$	79	83 $p = 0.12$	86	85

* formoterol at doses of 15 and 30mcg bid by MDDPI also showed a statistically significant difference from placebo; formoterol at a dose of 5 mcg bid by MDDPI and formoterol by Aerolizer at a dose of 12 mcg bid did not.

** formoterol at all doses showed a statistically significant difference from placebo; formoterol delivered at a dose of 12 mcg bid by Aerolizer did not.

> COMMENT: *There is no clinically significant difference in mean systolic blood pressure or diastolic blood pressure between any of the treatment groups when evaluated 2 hours after the first dose of drug or when evaluated over 6 hours after administration of drug after one week's treatment. On the other hand, there was a mean 12 bpm increase in pulse rate 2 hours after administration of the first dose of 30 mcg by MDDPI, a 9 bpm increase after drug administration at one week and a mean 7 bpm increase after the first dose of 15 mcg by MDDPI after administration of the first dose, compared with essentially no change after placebo. The mean increase in pulse rate was essentially the same after administration of the first dose and after one week of treatment in the groups that received formoterol by MDDPI and Aerolizer.*

1. laboratory values: There were two patients who had an increase in LFTs at the end of the study whose LFTs were normal at baseline. One patient had an increase in SGOT from 26 to 66 U/L and an increase in SGPT from 15 to 89 U/L. Gamma GT rose from 14 to 26 U/L by the end of the study. The second patient had an increase in SGOT from 21 to 87 U/L and an increase in SGPT from 19 to 70 U/L. This patient's gamma GT decreased slightly. The clinical significance of these findings, if any, is unclear. There were no other significantly changed laboratory values.

4. Study 701 (v52-54)

a. <u>number of patients</u>: 16
b. *age range*: 21-49 years of age
c. <u>patient population</u>: mild persistent asthma, FEV-1 $\geq$ 80% predicted; use of short-acting inhaled beta agonist for at lease one month prior to baseline evaluation; patients were allowed to be included if they were using inhaled or nasal corticosteroids at a constant dose and dosing regime for the 6 weeks prior to visit 1.
d. *study design*: randomized, double-blind, double-dummy, active treatment controlled, 2 way crossover, repetitive dose study; patients were confined to the study center for at least 24 hours prior to administration of the study drug during treatment period 1 and for at least 12 hours before administration of study drug in treatment period 2 and were confined until 14 hours after the last dose during both treatment periods.
e. <u>drug administration</u>: 36 mcg tid of formoterol delivered by Aerolizer (12 mcg per puff); 600 mcg tid of albuterol MDI (100 mcg per puff); doses were administered 5 hours apart; both the capsules and the devices used in the study were identical in appearance; a single actuation from the MDI (albuterol or placebo) immediately preceded and followed each single actuation from the Aerolizer (formoterol or placebo); no medication except study drug was allowed from screening to the end of the study; the sponsor states that treatment times reflect the likely pattern of patient response to "symptom clusters" when experiencing an exacerbation of asthma and because in such situations, patients may take greater doses than those indicated in the labeling. The treatment plan is designed to minimize the possibility that order of dosing could compromise the blinding due to the very rapid onset of action of both drugs, i.e. albuterol to be administered both prior to and after each dose of formoterol or matching placebo.
f. <u>periods of study</u>: 3 days of randomized treatment with a washout of 4-7 days between treatments; 21 day screening period
g. <u>parameters evaluated</u>: <u>FEV-1</u> at screening, baseline, 15 minutes before drug administration and 2 hours after drug administration; <u>laboratory</u> tests at screening, baseline and at the end of the study; <u>serum potassium and blood glucose</u> 15 minutes before drug administration and 1, 2, and 3 hours after drug administration as well as 4 hours after the last dose each

day; vital signs at baseline, screening, 15 minutes before drug administration, and 2 hours after each drug administration, as well as 4 hours after the last dose on each day; ECG at screening, baseline, 15 minutes before drug administration and 1 and 2 hours after each drug administration, as well as 1, 2, and 4 hours after the last dose each day; Holter monitoring for 24 hours at baseline and each treatment day, i.e. continuous monitoring throughout the period of treatment; PK trough plasma concentration days 1 and 3 and 24 hour urine samples on days 1 and 3.

h. study objective: to evaluate the safety of high doses of formoterol compared to high doses of albuterol; the sponsor states that this study is the first stage in a program to extend the labeling to a PRN indication and to provide assurance of safety for subsequent larger clinical studies.

i. statistical considerations: Included in the statistical analysis were potassium AUC and minimum, glucose AUC and maximum, pulse rate AUC and maximum, diastolic blood pressure AUC and minimum, QTc interval AUC and maximum and FEV-1 AUC and maximum. The AUC was calculated for 0-24 hours, 24-48 hours, and 48-72 hours after drug administration. For each variable, the log-transformed data were analyzed using a linear mixed effect model including treatment, period and sequence as fixed factors, patient within sequence as a random factor and log-transformed baseline values as covariates. All patients who received at least one treatment were included in the safety evaluation. With a sample size of 16 being evaluated in a crossover study, adverse events occurring with a frequency of 15% or greater would be detected with a probability of 92.6%.

j. study results:

1) adverse events (v52, p 23, t7.3-1; v53, pgs407-428): Drowsiness, nervousness, nausea headache, internal unrest, back pain, muscle tremor, and asthma were reported adverse events after formoterol administration. All of these adverse events except for internal unrest and asthma were noted in the albuterol group, as well as sore throat and palpitations. There were 23 adverse events after treatment with formoterol and 26 adverse events after treatment with albuterol. All adverse events were mild-moderate in intensity.

2) Laboratory tests (v52, p25; v53, pgs431-626): There was a decrease in plasma potassium in 15/16 patients after formoterol administration and in 8/16 patients after treatment with albuterol. There were 93 plasma potassium values < 3.6 mmol/l during treatment with formoterol compared to 33 such values during treatment with albuterol. The lowest plasma potassium value noted during treatment with formoterol was 3.05 mmol/l compared with 3.26 mmol/l during treatment with albuterol. The mean change in plasma potassium was substantially lower during administration of formoterol than during administration of albuterol (v52, p38, t11.1-1; v53, p27). Individual decreases in plasma potassium were very small, just outside the lower limit of the normal reference range, often preceded by low levels prior to the first dose administration and occurred after administration of both formoterol and albuterol in some patients, but not as frequently as increases in plasma glucose (see discussion below). Mean plasma potassium levels did not change significantly over the three days of treatment with either formoterol or albuterol, although mean plasma potassium values were slightly lower at most time points, 1, 2, and 3 hours after formoterol administration than after albuterol administration with either sequence of administration (v53, pgs537-581).

Both formoterol and albuterol produced a mean increase overall in plasma glucose levels (v52, p30, f7.3-4; v52, p39. t11.1-2). Initially, over the first 4 hours after the first dose of formoterol on day 1, there was a mean decrease in plasma glucose, followed by a mean elevation from 4-6 hours, a decrease from 6-10 hours and a mean increase from 10-12 hours. After 12 hours, the mean plasma glucose level generally was lower than baseline throughout the rest of the 62 hour evaluation period. The number of plasma glucose values above the upper limit of the normal reference range during treatment with formoterol was 273 and during treatment with albuterol 204. Most patients had an increase in plasma glucose on both formoterol and albuterol. These increases were modest and many of these patients had an elevation in plasma glucose above the upper limit of the normal reference range prior to administration of the first dose of drug. There was no pattern in regard to dose or day of administration, e.g. dose 1 on day 1 vs.

dose 2 on day 3 (v53, pgs 456-518). There was no clinically significant change in mean plasma glucose after either administration of formoterol or albuterol over the three days of treatment although increases in mean plasma glucose were greater after administration of formoterol when formoterol was administered before albuterol in sequence (v53, pgs 537-481).

COMMENT: *Plasma potassium and plasma glucose are sensitive markers of beta adrenergic effect. It is not surprising that large doses of formoterol would produce a decrease in plasma potassium or changes in plasma glucose. It should be noted, however, that a greater effect on plasma potassium and plasma glucose was seen during formoterol administration than was seen during albuterol administration.*

3) Vital signs (v52, p30): Elevation in pulse rate only occurred during formoterol administration. All blood pressure measurements were normal except for patient 504, whose systolic blood pressure rose to 168 mm Hg 2 hours after administration of the third dose of formoterol on day 1.

4) FEV-1 (v52, p31): A greater increase in FEV-1 was seen after administration of formoterol than after administration of albuterol which was statistically significantly greater (v52, p41, t11.1-4). It should be noted that a few patients had a decrease in FEV-1 of up to 30% after administration of albuterol (v54, p881, p883, p898) but not after administration of formoterol.

5) ECGs (v52, p32): No clinically significant changes in ECGs were noted after administration of either formoterol or albuterol.

a) QTc interval corrected with Bazett's correction: Normal was considered to be < 450 msec in females and < 430 msec in males. A prolonged QTc interval was considered to be > 470 msec in females and > 450 msec in males with values between these being considered borderline. One male patient had a QTc interval of 452 msec prior to the second dose of formoterol on day 1 of treatment and one hour after the third dose on day 2, with a baseline value of

409 msec (v54, p258). One female patient had QTc intervals of 452-464 during treatment with formoterol at a number of time points after drug administration (v54, p800)(patient 506) and another female patient had two values of 452 msec during treatment with formoterol. There were no prolonged or borderline QTc intervals reported in patients while receiving albuterol, although one patient had a measurement of 450 msec 2 hours after the second dose on day 3 (v54, p799). Both the AUC QTc intervals and mean QTc intervals were significantly greater in patients when they received formoterol than when they received albuterol (v52, p40, t11.1-3). In particular, mean QTc intervals were significantly longer in patients while receiving formoterol during days 2 and 3 (baseline 390 msec, day two 401-417 msec, day three 397-410 msec)(v52, p34, f7.3.7)(v54, pgs816-825).

    b) <u>Holter monitoring</u>: no significant changes were seen on Holter monitoring during treatment with either formoterol or albuterol. Patients that experienced PVCs during treatment with albuterol, experienced PVCs during treatment with formoterol, as well, several patients having 500-800 isolated PVCs (v54, p865-866). These findings were not considered clinically significant by the investigator.

6) <u>PK</u>: systemic exposure to formoterol was generally higher and mean trough concentration was greater on day 3 than on day 1 (v54, p942). The amount of formoterol excreted unchanged in the urine was higher on day 3 than on day 1 (see table below, v52, p35; v54, p948):

Amount of formoterol excreted unchanged in the urine

Parameter	Day 1	Day 3
0-12 hours	7.99 ($\pm$ 2.92)	10.18 ($\pm$ 5.55)
12-24 hours	5.63 ($\pm$ 1.53)	6.74 ($\pm$ 2.30)
Total AEs (mol)	13.61 ($\pm$ 2.93)	16.92 ($\pm$ 6.43)
Total AE (% dose)	5.30 ($\pm$ 1.14)	6.59 ($\pm$ 2.50)

5. <u>Study 601</u> (v4-7) (7 centers, one in Denmark and 6 in the Netherlands

    a. <u>number of patients:</u> 67; 42 received placebo; 44 received 5 mcg bid of formoterol MDDPI; 43 received 10 mcg bid of formoterol MDDPI; 47 received 15 mcg bid of formoterol MDDPI; 41 received 30 mcg bid of formoterol MDDPI; 47 received 12 mcg bid of formoterol Aerolizer (v33, p36) in the ITTE analysis; 41 males (61%), 26 females (39%); 66 Caucasian (99%); 1 Oriental patient; ITTE population = 66

    b. <u>age range:</u> 20-73 years (20-64 years = 57 patients, 65 years and older = 10 patients)

    c. <u>patient population:</u> persistent asthma requiring treatment with inhaled bronchodilators and anti-inflammatory medications; FEV-1 38-89% predicted after withdrawal of bronchodilators; patients with a QTc interval > 460 msec were excluded; duration of asthma = 0.4-63 years.

    d. <u>study design:</u> randomized, double-blind, double-dummy, placebo-controlled, repetitive dose, multicenter, incomplete block, crossover study with PK evaluation.

    e. <u>drug administration:</u> formoterol 5, 10, 15 and 30 mcg bid (every 12 hours) delivered from a MDDPI; formoterol 12 mcg (dry powder capsules) bid delivered by Aerolizer (breath-actuated dry powder inhaler); patients were randomized to receive 4 of 6 possible treatments; formoterol was delivered from the MDDPI with concentrations of 5 and 15 mcg per puff

    f. <u>periods of study:</u> 4 one week randomized treatment periods following a one week single-blind placebo run-in period; there was a one week washout between treatments during which time patients received placebo on a single-blind basis

    g. <u>parameters evaluated:</u> primary efficacy variable = standardized AUC for FEV-1 over 12 hours measured at the end of each week of treatment; FEV-1 was also measured at 3, 5, 15, 30 and 60 minutes and hourly up to 3-12 hours after initiation of each treatment; daily symptom scores; use of rescue medication; safety parameters included adverse events, ECGs and vital signs; PK include measurement of unchanged ant total (unchanged + conjugated) formoterol measured in 12 hour cumulative urine samples in selected patients at the end of

each of the four treatment periods and the total urinary excretion within 12 hours of inhalation.

h. <u>study objective:</u> to evaluate the optimal effective dose of formoterol delivered by MDDPI, to compare dose response with the MDDPI and the Aerolizer, to assess dose proportionality, and compare the amount of unchanged and total formoterol excreted in the 12 hour dosing interval

i. <u>statistical considerations</u>: efficacy data was analyzed for three populations – intent-to-treat (all patients randomized with data from at least 2 treatment periods), per protocol population (patients without any major protocol deviation) and potential device malfunction population.

j. <u>study results</u>:

EFFICACY:

a. <u>standardized AUC for FEV-1 (L)</u>

Mean of standardized AUC for FEV-1 (L) (v4, p12):

Treatment	N	Mean	Difference from placebo	P value vs. placebo
Formoterol MDDPI 30 mcg bid	39	2.62	0.24	< 0.0001
Formoterol MDDPI 15 mcg bid	46	2.61	0.23	< 0.0001
Formoterol MDDPI 10 mcg bid	43	2.60	0.22	< 0.0001
Formoterol MDDPI 5 mcg bid	44	2.54	0.16	< 0.0001
Formoterol Aerolizer 12 mcg bid	47	2.58	0.20	< 0.0001
Placebo	42	2.38	-----	-----

APPEARS THIS WAY
ON ORIGINAL

Clinical Review Section

Serial FEV-1 measurements (L) over 12 hours after drug administration for one week (v33, p 269)

Time-point	Placebo (n = 42)	MDDPI 5 mcg bid (n = 44)	MDDPI 10 mcg bid (n= 43)	MDDPI 15 mcg bid (n = 46)	MDDPI 30 mcg bid (n = 41)	Aerolizer 12 mcg bid (n = 47)
Pre-dose	2.30	2.41 $p = 0.008$	2.42 $p = 0.004$	2.41 $p = 005$	2.43 $p = 0.002$	2.41 $p = 0.005$
5 minutes	2.33	2.55 $p < 0.0001$	2.60 $p < 0.0001$	2.58 $p < 0.0001$	2.62 $p < 0.0001$	2.61 $p < 0.0001$
15 minutes	2.36	2.59 $p < 0.0001$	2.64 $p < 0.0001$	2.63 $p < 0.0001$	2.65 $p < 0.0001$	2.62 $p < 0.0001$
30 minutes	2.39	2.63 $p < 0.0001$	2.67 $p < 0.0001$	2.69 $p < 0.0001$	2.70 $p < 0.0001$	2.67 $p < 0.0001$
1 hour	2.44	2.67 $p < 0.0001$	2.73 $p < 0.0001$	2.72 $p < 0.0001$	2.75 $p < 0.0001$	2.71 $p < 0.0001$
2 hours	2.44	2.63 $p < 0.0001$	2.71 $p < 0.0001$	2.71 $p < 0.0001$	2.74 $p < 0.0001$	2.67 $p < 0.0001$
3 hours	2.43	2.65 $p < 0.0001$	2.69 $p < 0.0001$	2.68 $p < 0.0001$	2.73 $p < 0.0001$	2.67 $p < 0.0001$
4 hours	2.43	2,61 $p < 0.0001$	2.66 $p < 0.0001$	2.66 $p < 0.0001$	2.67 $p < 0.0001$	2.64 $p < 0.0001$
5 hours	2.41	2.57 $p\ 0.0003$	2.63 $p < 0.0001$	2.64 $p < 0.0001$	2.63 $p < 0.0001$	2.61 $p < 0.0001$
6 hours	2.38	2.52 0.0006	2.59 $p < 0.0001$	2.61 $p < 0.0001$	2.60 $p < 0.0001$	2.58 $p < 0.0001$
7 hours	2.37	2.53 $p = 0.0001$	2.57 $p < 0.0001$	2.58 $p < 0.0001$	2.59 $p < 0.0001$	2.56 $p < 0.0001$
8 hours	2.33	2.48 $p = 0.005$	2.54 $p < 0.0001$	2.56 $p < 0.0001$	2.59 $p < 0.0001$	2.53 $p = 0.0002$
9 hours	2.35	2.49 $p = 0.003$	2.55 $p < 0.0001$	2.54 $p < 0.0001$	2.54 $p < 0.0001$	2.52 $p = 0.0002$
10 hours	2.32	2.44 $p = 0.009$	2.49 $p = 0.0002$	2.53 $p < 0.0001$	2.52 $p < 0.0001$	2.47 $p = 0.0008$
11 hours	2.35	2.41 $p = 0.18$ •	2.47 $p = 0.009$	2.50 $p = 0.002$	2.49 $p = 0.006$	2.46 $p = 0.02$
12 hours	2.30	2.37 $p = 0.19$ •	2.48 $p = 0.0008$	2.45 $p = 0.004$	2.52 $p < 0.0001$	2.40 $p = 0.05$

Mean FEV-1 (L) at 3 minutes after the first inhalation
based on ITT population

Time point	Placebo	MDDPI 5 mcg bid	MDDPI 10 mcg bid	MDDPI 15 mcg bid	MDDPI 30 mcg bid	Aerolizer 12 mcg bid
N	42	44	43	46	41	47
Pre-dose	2.32	2.26	2.11	2.25	2.23	2.24
3 min post	2.28	2.47	2.54	2.54	2.58	2.55
3 hrs post	2.41	2.70	2.75	2.75	2.81	2.74
P value *	-----	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

* compared to placebo for 3 minute time point

Mean FEV-1 at 12 hours after drug administration after 1 week of treatment

time point	Placebo	MDDPI 5 mcg bid	MDDPI 10 mcg bid	MDDPI 15 mcg bid	MDDPI 30 mcg bid	Aerolizer 12 mcg bid
Pre-dose	2.30	2.41	2.42	2.41	2.43	2.41
12 hours post-drug	2.30	2.37	2.48	2.45	2.52	2.40
P value *	-----	0.19	0.0008	0.004	< 0.0001	0.05

*compared to placebo at 12 hours after administration of drug after one week of treatment

Number of patients not analyzed because of device malfunction

population	Placebo	MDDPI 5mcg bid	MDDPI 10 mcg bid	MDDPI 15 mcg bid	MDDPI 30 mcg bid	Aerolizer 12 mcg bid
N ITT	42	44	43	46	39	47
N PP	35	37	37	38	35	39
N Device malfunction	42	42	42	43	34	47
Number of malfunctions	-----	2	1	3	5	-----
% malfunctions	-----	5%	2%	7%	13%	-----

Device Malfunction Population

- if excluded a single treatment period because of technical problems with at least one active device
- technical problems with placebo device ignored
- data from at least 2 treatment periods without technical device problems
- same conclusions based on this treatment population
- all doses beat placebo for primary efficacy parameter

COMMENT: *The 5 mcg bid dose of formoterol delivered from the MDDPI did not demonstrate efficacy beyond 10 hours after drug administration whereas the 10 mcg bid dose of formoterol demonstrated efficacy in terms of FEV-1 throughout the 12 hour period after drug administration. There were a number of time points later than one hour after drug administration where there was a statistically significant difference between 5 mcg bid and 30 mcg bid*

of formoterol delivered by MDDPI, but the 10 mcg bid dose was not statistically significantly different at any time points compared to the 30 mcg bid dose. Therefore, improvement in FEV-1 is significantly better after 10 mcg bid compared with 5 mcg bid, especially at the later time points after drug administration but 10 mcg bid is not significantly different than 30 mcg bid. Therefore, the choice of 10 mcg bid as the recommended dose is appropriate.

SAFETY:

1) <u>vital signs</u> (v6, appendix 7.1): There were no clinically significant changes in blood pressure or pulse rate, except for a few patients who had a significant increase in pulse rate 2 hours after administration of 30 mcg of formoterol.

2) <u>ECGs</u> (v7, pgs1-153): There were more readings of possible anteroseptal infarct after administration and non-specific ST-T wave changes after administration of formoterol MDDPI at a dose of 30 mcg bid, but these changes were also seen after 12 mcg bid of formoterol from the Aerolizer, 5 mcg bid of formoterol from the MDDPI, 15 mcg bid of formoterol from the MDDPI, and placebo ; multifocal PVCs were also noted after administration of 12 mcg of formoterol from the Aerolizer. One patient developed an abnormal q wave and ST elevation after 5-30 mcg bid of formoterol MDDPI (v7, p67)(this patient did not receive formoterol by Aerolizer or placebo).

3) <u>Adverse events:</u> Two patients discontinued prematurely because of adverse events

PK:

Formoterol excreted in the urine (ITT)(v7, page 12 Clinical Pharmacology Report)

Unchanged	5 mcg bid MDDPI (n=30)	10 mcg bid MDDPI (n=25)	15 mcg bid MDDPI (n=31)	30 mcg bid MDDPI (n=23)	12 mcg bid Aerolizer (n=27)
Mean unchanged (nmoles)	1.47	2.61	3.85	6.80	2.02
% dose unchanged	12%	11%	11%	10%	7%
total (nmoles)	2.36	3.75	5.90	9.12	3.61
% dose total	20%	16%	17%	13%	13%

6. Study 2301 (v56) entitled, "A randomized, double- blind, placebo-controlled, multiple dose, two-period crossover study to assess the effects of bid administrations of 24 mcg formoterol or placebo on glucose control in type 2 diabetic patients".

a. study characteristics: This was a single center study performed in San Antonio, TX.

1) number of patients: 17 enrolled, 16 completed study, 17 completed placebo treatment
1) age range: 30-75 years
2) patient population: type 2 diabetic patients of at least 6 months duration; average fasting plasma glucose of 7-10 mmol (120-180 mg/dl) and HbA1c ≤ 10%, not treated with insulin for at least 3 months
3) study design: randomized, double-blind, placebo-controlled, repetitive dose, 2 period crossover study
4) drug administration: formoterol 24 mcg (2 inhalations of 12 mcg) bid at 6-9 AM and 6-9 PM, delivered by Aerolizer (capsules for oral inhalation)
5) periods of study: 21 days of randomized treatment; 21 day screening period; 21 day washout period between treatments
6) parameters evaluated: evaluation of glucose control; vital signs, ECGs, laboratory tests, adverse events; plasma glucose; pre-dose, 15 min. 30 min, 45 min and 1, 1.5, 2, 2.5, 3 and 4 hours after drug administration at baseline and on day 21 of each treatment period; plasma glucose, peak concentration, AUC, concentration at 2 hours after drug administration, mean change from baseline; serum fructosamine at baseline and day 21 of each treatment period
7) study objective: to assess the effects of formoterol on prandial plasma glucose excursion (AUC plasma glucose concentration) following standardized AM meal; serum fructosamine concentration; plasma

glucose concentration two hours after ingestion of a standardized AM meal.

8) <u>statistical considerations</u>: the sample size was selected to provide approximately 90% power to detect a 50 mg.hr/dL change in AUE-R (area under the effect-time curve from time 0 to 4 hours by the linear-trapezoidal rule) of plasma glucose. A standard deviation of 66 mg.hr/dL for the within-patient difference in AUE-R was assumed. Only descriptive statistics were provided. No inferential statistical analyses were performed. The analysis in support of the primary objective was the key analysis for this study. Mean prandial AUE for plasma glucose after multiple doses of 24 mcg of formoterol were compares with the pre-treatment prandial AUE for plasma glucose. ANCOVA for log-transformed AUE was performed.

b. <u>study results</u>:

1) <u>Discontinuations</u>: There were no serious adverse events. One patient was discontinued from the study because of nervousness after formoterol Aerolizer administration.

2) <u>Demographics</u>: There were 11 males and 6 females in the study. The mean fasting plasma glucose and fructosamine at baseline were similar between the two sequences studied. The mean age was 51 years.

3) <u>Adverse events</u>: after formoterol Aerolizer administration, ten adverse events were reported including single reports of nausea, diarrhea, abdominal bloating, upset stomach, pruritis, wrist pain, nervousness and back pain.

4) <u>Vital signs</u>: There was a mean increase in systolic blood pressure after formoterol Aerolizer administration on day 1 (126-131 mm Hg) and after 3 weeks of treatment (124-138 mm Hg). The mean increase seen after placebo was 124-130 mm Hg on

day 1 and 115-128 mm Hg after 3 weeks of treatment.

5) ECGs: There were no clinically significant changes in ECGs after treatment with formoterol Aerolizer. One patient had an increase from screening in the QTc interval from 400 to 434 msec after formoterol Aerolizer treatment for 3 weeks. Another patient had an increase from baseline in QTc interval from 437 to 465 msec after treatment with formoterol Aerolizer for 3 weeks. Similar or greater increases in QTc interval were seen after administration of placebo.

6) Plasma glucose: After ingestion of breakfast on day 21, higher levels of glucose 1-4 hours after treatment were seen after administration of formoterol than after administration of placebo. This produced a greater AUC (748 mg.h/dL vs. 683 mg.h/dL), concentration at 2 hours (208 mg/dL vs. 182 mg/dL) and Emax (229 mg/dL vs. 209 mg/dL) after formoterol administration than after placebo administration. The 21 day average prandial glucose levels were 50% higher after administration of formoterol than after administration of placebo. The change in plasma fructosamine from day 1 to day 21 was not statistically different after formoterol and placebo administration. Fasting plasma glucose levels were similar after treatment with formoterol and placebo (p=0.90). After 21 days of treatment, the mean prandial glucose concentration increased from 147 mg/dL prior to treatment to 152 mg/dL 4 hours after treatment with formoterol with a peak level of 215 mg/dL 90 minutes after treatment. By contrast, after placebo administration there was a decrease from 144 mg/dL to 132 mg/dL 4 hours after administration with a peak of 198 mg/dL one hour after administration. There were a few patients who had a significant increase in plasma glucose after administration of Foradil Aerolizer that included the following (v56, p280):

- 176 mg/dL prior to the first dose – 265 mg/dL 90 minutes after drug administration on day 21
- 140 mg/dL prior to the first dose – 248 mg/dL 2 hours after drug administration on day 1 and day 21
- 137 mg/dL prior to the first dose – 197 and 192 mg/dl after drug administration on day 1 and day 21, respectively
- 161 mg/dL prior to the first dose – 286 mg/dL 90 minutes after drug administration on day 21
- 159 mg/dL prior to the first dose – 273 mg/dL 90 minutes after drug administration on day 1
- 139 mg/dL prior to the first dose – 276 mg/dL 1 hour after drug administration on day 21

APPEARS THIS WAY
ON ORIGINAL

7. Study 603, entitled "A 12 month multi-center, randomized, double-blind, double-dummy trial to examine the long-term tolerability of formoterol 10 mcg via the Multiple Dose Dry Powder Inhaler (MDDPI), both as bid maintenance therapy, and as on-demand use on-top-of maintenance, in patients with persistent asthma." There were 48 centers in Europe, Australia, South American, South African and New Zealand.

This was a 12 month, multi-center study with open maintenance administration of formoterol at a dose of 10 mcg bid delivered by MDDPI. Rescue medication was blinded in regard to formoterol or albuterol. Patients were randomized in a parallel design to receive either albuterol 200 mcg or formoterol 10 mcg as rescue medication. There were 411 adult patients (13-75 years of age) with an FEV-1 of 50-79%randomized to either rescue formoterol or rescue albuterol use. The adverse events reported in this study can be seen in the table below based on investigator determination whether the adverse event was related to the rescue medication or to the maintenance dose of formoterol.

Category of AE	MDDPI + F	MDDPI + A	MDDPI
N	208	203	204
# (%) patients with AE	135 (65%)	139 (69%)	51 (25%)
# pts asthma-related AE	56 (27%)	62 (31%)	19 (9%)
# pts serious asthma-related	7 (3%)	4 (2%)	4 (2%)
# pts with significant AE	22 (11%)	22 (11%)	6 (3%)
Deaths *	3 (1.4%)	1 (0.5%)	None
Non-fatal serious AEs	14 (7%)	9 (4%)	5 (3%)
Discontinuation due to AEs	9 (4%)	12 (6%)	2 (1%)

MDDPI = multiple dose dry powder inhaler with formoterol
F = formoterol rescue medication
A = albuterol rescue medication

* The 3 patients who were receiving formoterol rescue medication and died, died from probable cerebral hemorrhage, stroke, and respiratory arrest. The patient who died from respiratory arrest was a 19 year old female attributed by the investigator to emotional factors and poor perception of the severity of her asthma. The patient who was receiving albuterol rescue medication, a 17 year old female who was described as poorly compliant died from an acute asthma attack. None of these deaths was considered by the investigator to be related to the study drug.

COMMENT: *There were more fatal and non-fatal serious adverse events in patients who received formoterol as rescue medication than in patients who received albuterol as rescue medication. Since the labeling will indicate that formoterol should not be used to treat exacerbations of asthma, this possible concern does not apply to the safe use of formoterol 10 mcg bid as maintenance therapy for asthma. It should be noted that the sponsor amended the study (amendment 4) to stop PRN use of formoterol in the open portion of the study "due to data collection problems".*

There was no clinically significant mean change in any laboratory test over the 12 months of drug administration and there was no clinically significant shift for any laboratory test from normal at baseline to significantly abnormal after treatment. There were 5% of patients who received formoterol only on a regular basis who had an increase in SGPT and 2.8% who had an increase in SGOT who had a normal value at baseline. This incidence of such elevations is consistent with the incidence seen in placebo-controlled studies in both the formoterol and placebo arms. The incidence of increased blood glucose and decreased serum potassium levels was also consistent with such changes seen in placebo-controlled studies in patients who received formoterol and patients who received placebo.

Mean changes in vital signs was minimal, i.e. less than 1 mm Hg from baseline to the last visit for systolic blood pressure and pulse rate and less than 2 mm Hg from baseline to the last visit for diastolic blood pressure for all the treatment groups, i.e. regular formoterol, regular formoterol with rescue formoterol and regular formoterol with rescue albuterol. There was only one patient who received regular formoterol alone who had a systolic blood pressure that was outside the range of 90-160 mm Hg and no patients in that group who had a diastolic blood pressure outside the 50-100 mm Hg range or pulse rate outside the 50-12 bpm range.

The mean change from baseline in patients who just received formoterol in QTc interval was 1 msec using Bazett's correction. There were less clinically significant changes on ECGs after 12 months of treatment (none) than there were at baseline in the patients who received regular formoterol.

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/s/
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