Table 14: Summary of Mean Changes from Baseline PEF Values (L/min)

Treatment Period	Placebo		Salmeterol 50mcg	
	N	Change	N	Change
Morning PEF				
Baseline (actual value)	105	(235.1)	102	(237.0)
Weeks 1-4	105	7.1	102	21.5*
Weeks 5-8	98	16.9	99	24.4
Weeks 9-12	95	19.7	97	29.6*
Weeks 1-12	105	13.2	102	25.1*
Evening PEF				
Baseline (actual value)	105	(250.0)	102	(252.0)
Weeks 1-4	104	5.7	102	17.6*
Weeks 5-8	98	11.8	99	19.4
Weeks 9-12	95	14.4	97	22.8
Weeks 1-12	104	10.1	102	20.0*

*$p \leq 0.033$ vs. placebo (ANOVA F-test)

Mean **daily use of Ventolin MDI backup** in the seven days prior to Day 1 was 1.6 puffs for the placebo group and 1.7 puffs in the salmeterol group. A continuous decline in Ventolin use was observed in both treatment groups. The overall change for the twelve week trial was -0.3 in the placebo group and -0.8 in the salmeterol group, statistically favoring salmeterol.

In the seven days prior to Day 1, 84.3 percent of placebo patients and 85.8 percent of salmeterol patients experienced **no nighttime awakenings**. Both groups showed a continued increase in the percentage of nights without awakenings. Overall there was an increase of 4.1 percent in the placebo group and 9.1 in the salmeterol group. Although the salmeterol group showed a favorable trend, no statistical differences were observed.

Patients in both the placebo and salmeterol groups reported having generally mild **asthma symptoms**. A maximum asthma score was determined by looking at the maximum value reported for any of the rated symptoms (chest tightness, shortness of breath, wheezing and coughing). The mean maximum score reported during the seven days prior to Day 1, on a 6-point scale, was 1.1 for placebo and 1.2 for salmeterol. Mean maximum scores declined in both groups throughout the study, with an overall change of -0.1 in the placebo group and -0.4 in the salmeterol group. The decline in maximum asthma score was statistically better for the salmeterol group than the placebo group, though numerically small.

Analyses of percent of days with no symptoms shows similar improvement among both groups with consistently greater improvement among the salmeterol patients. Only improvement in wheezing scores was statistically superior among the salmeterol patients relative to placebo.

Physician-rated global scores provided similar findings to the patient-rated asthma symptoms, with a consistently greater proportion of salmeterol patients than placebo patients reported to have no symptoms at Day 1 and Weeks 4, 8 and 12. At Week 12,

61 percent of salmeterol patients were reported to have no symptoms while 49 percent of placebo patients were reported to have no symptoms.

In a "pharmacoeconomic assessment," functional status was assessed with the FSII-R at Screening and Weeks 4, 8 and 12. Possible outcome scores ranged from 0 to 100, with 100 being the best possible functional state. Means were consistently above 90 for both groups. Salmeterol patients showed significantly higher scores at Weeks 8 and 12. Magnitude of improvement from baseline was also generally higher for salmeterol patients (approximately 7 points) than placebo patients (approximately 3 points). The SLP-C was used to assess sleep at the same clinic visits using a scoring system that also ranged from 0 to 100. Mean scores were generally in the range of 80 to 90. Salmeterol means were statistically superior to placebo means at Visits Weeks 4 and 8. Salmeterol patients showed somewhat greater improvement from baseline (approximately 12 points) than did placebo patients (approximately 6 points). Parents were asked to complete the NEMCH which evaluated 14 dimensions of health, including mental health and emotions. These data largely favored placebo at Screening and did not show a pattern of differences between treatment groups at the Week 12. Overall, the pharmacoeconomic assessments can be considered supportive of the efficacy of salmeterol.

The number of out-of-clinic asthma exacerbations in each group are reported for the treatment and post-treatment periods in Table 15. Fewer events were seen for the salmeterol group during treatment, although in the post-treatment period, the salmeterol group was observed to experience a greater number of events, raising the possibility of some rebound worsening with cessation of salmeterol.

Table 15: Frequency of Out-of-Clinic Asthma Exacerbations

	Placebo (N = 105)	Salmeterol 50 mcg (N = 102)
During Treatment		
1	23 (22%)	18 (18%)
2	10 (10%)	6 (6%)
≥ 3	1 (<1%)	1 (<1%)
Post-Treatment		
1	2 (2%)	12 (12%)
2	0	0
≥ 3	0	0

Other **post-treatment analyses** revealed no indication of rebound effects following discontinuation of treatment. Post-treatment AM and PM PEFR means remained above baseline levels for both treatment groups throughout the post-treatment week. AM PEFR showed a gradual declining trend in the salmeterol group. Ventolin use, percent of nights with no nighttime awakenings and maximum asthma scores were lower than baseline in both treatment groups throughout the post-treatment period.

Efficacy Conclusions

Pulmonary function evaluations, including PEFR, FEV_1, $FEF_{25-75\%}$, and FVC, were each consistently supportive of the efficacy of salmeterol relative to placebo. The spirometric endpoints, but not serial PEFR or A.M. or P.M. PEFR scores from the daily diary, showed some decline in effect over 12 weeks of treatment. This was particularly apparent in the serial FEV1 data, longer time to onset, shorter duration of effect and a decline in the proportion of patients who reached critical increases.

The clinical significance of these findings can be evaluated largely by looking at clinical outcomes. Use of Ventolin MDI back-up, asthma symptom scores and physician rated global scores did not reflect a diminution of response to salmeterol. Overall, it appears that the decline in effect was not clinically problematic for the group as a whole, however, further evaluation of this finding will be undertaken in the subsequent study. This trial employed the [redacted] Diskhaler to deliver salmeterol. This formulation is not approved in the United States and its performance characteristics may have contributed to the observed outcomes.

Consistent with the findings in the dose ranging study, patients age 4 to 8 generally showed enhanced PEFR scores relative to the subgroup of patients age 9 to 11. This trend was observed throughout the12 weeks.

Corticosteroid use did not appear to significantly alter treatment effect.

There does not appear to be strong evidence of rebound following discontinuation of treatment with salmeterol based on diary data, however salmeterol patients were noted to experience higher rates of asthma exacerbation than placebo patients during the post-treatment period.

The generalizability of the efficacy data from this trial with the [redacted] Diskhaler to the Diskus device are limited given the lack of a definitive clinical link in this age group. However, Dr. Meyer's September 17, 1998 review of SEI-001, for prevention of pediatric exercise-induced bronchospasm, relates findings from Trial SLGA2003, in which 50 mcg salmeterol doses from the [redacted] Diskhaler and Diskus devices were compared. This trial provided reassurance that the two devices appear to have comparable clinical performance.

Safety Outcomes

No deaths were reported during this study.

Serious adverse events were reported for four salmeterol patients (Pt #s M255, M259, Pe165, W195) and five placebo patients (Pt #s H72, L86, L106, PR21, W282). The four salmeterol patients each experienced an asthma exacerbation. Three patients experienced the events during the double blind treatment period, between Day 45 and Day 77. One of these patients was withdrawn from the study. The fourth patient

experienced the event during the post-treatment period, four days after the last dose of salmeterol.

Two of the five placebo events were asthma exacerbations. One patient was withdrawn and one patient completed the study. There were two patients with appendicitis, one of whom completed the study and one who was withdrawn. The fifth placebo patient experienced symptoms of abdominal pain, diarrhea, vomiting and dehydration, later diagnosed as a "possible kidney obstruction." This patient was lost to follow-up.

One patient (# M251) experienced an asthma exacerbation during the placebo run-in thought to be due to exposure to allergen. This patient was withdrawn as a screening failure.

There were three additional patients withdrawn from the study due to adverse events that were not considered serious. Pt # PR12 experienced a moderate erythema multiforme over his entire body during the placebo run-in period. Pt # K32 was discontinued from salmeterol treatment on Day 42 due to an upper respiratory infection and Pt # W292 was withdrawn from placebo on Day 36 due to severe bronchitis.

A total of three salmeterol and three placebo patients were withdrawn from the study due to adverse events.

Other adverse events are summarized in Table 16. Events are listed in the table if they occurred in three percent or more of the patients in the salmeterol group and in a larger proportion of the salmeterol group than the placebo group.

Table 16: Adverse Events

	Placebo	Salmeterol 50 mcg
Total	79 (75%)	75 (74%)
Pharyngitis	14 (13%)	15 (15%)
Nasopharyngitis	9 (9%)	10 (10%)
Otitis media	8 (8%)	9 (9%)
Otalgia	0 (0%)	3 (3%)
Rash/skin eruption	3 (3%)	6 (6%)
Pain in limb	1 (<1%)	3 (3%)
Cough	4 (4%)	8 (8%)
Abnormal cardiovasc. tests	2 (2%)	4 (4%)
Allergy	1 (<1%)	3 (3%)
Urticaria	0 (0%)	3 (3%)

Clinical laboratory evaluations were conducted at Screening and Week 12. There were four patients (4 percent) in the placebo group and 12 in the salmeterol group (12 percent) who were observed to have one or more laboratory value beyond threshold levels. Most were attributable to concurrent disease, such as URTI, asthma or allergy. Low bicarbonate was reported in two placebo and four salmeterol patients and appears unrelated to concurrent disease. None of these abnormalities were considered related to treatment. Categorical analyses of transitions in clinical laboratory data revealed no trends that appear to be clinically important.

Vital sign data were collected with pulmonary function testing. Change from baseline and categorical analyses of increase and decrease of 15, 20 or 30 bpm from baseline fail to show meaningful differences between placebo and salmeterol with regard to pulse rate throughout the study.

Mean change from baseline of systolic blood pressure was somewhat greater for salmeterol than for placebo, with some statistical differences between groups at Day 1 and Week 12. These statistical findings were associated with mean differences of only approximately 3 mmHg. Categorical analyses did not suggest clinically important differences between the treatments.

Diastolic blood pressure, analyzed as change from baseline or categorically, was not suggestive of meaningful differences between treatments.

Electrocardiograms were abnormal in two salmeterol and three placebo patients. The events in the placebo group were observed at Day 1 and at none of the subsequent visits. They were judged to be unlikely related to study drug. Mean heart rates were generally 2 to 4 bpm higher among salmeterol patients than placebo patients. However, range data show a narrower range of values for salmeterol patients at pre- and post-dose testing on Day 1 and Weeks 4, 8 and 12. QT_c data did not show trends in either the placebo or salmeterol groups and mean values were comparable throughout the study. Instances of QT_c prolongation (values $\geq$441 msec) were considered isolated events with no clinical significance.

Continuous Holter monitoring revealed no treatment related effects on cardiac rate or ventricular ectopic events. Supraventricular ectopic events were statistically more frequent among salmeterol patients than placebo patients at Week 12, but this finding was largely consistent with differences between the groups at baseline, and was not found with the first dose where SVT occurrences were more numerous among placebo patients than salmeterol patients.

Pulmonary auscultation at each clinic visit revealed consistent findings for the two treatment groups.

Physical examination results showed abnormalities in 66 and 67 percent of the placebo and salmeterol groups, respectively, at Screening. These proportions increased by 13 and 8 percent in each group, respectively, by the end of treatment. Individual physical findings were comparable between treatment groups.

Overall, safety data are supportive of the safety of salmeterol 50 mcg in children age 4 to 11. No findings were suggestive of important clinical concerns associated with the use of this drug in pediatric patients for a period of twelve weeks.

Conclusions

The efficacy of salmeterol 50 mcg BID via [redacted] Diskhaler relative to placebo BID was consistently established with PEFR, spirometric data and patient-rated evaluations of symptoms and back-up medication use. Some decline in bronchodilation response is seen between beginning and end of the 12 week treatment. This finding will be further evaluated in the following study which employs the Diskus formulation.

Younger patient appear to have consistently greater bronchodilation responses than older children. Use of concomitant inhaled corticosteroids does not appear to alter response to salmeterol. Post-treatment rebound does not appear to be a significant concern, although salmeterol patients experienced a higher rate of post-treatment asthma exacerbations.

Safety concerns with salmeterol are minimal. The principle finding was a slight increase in systolic blood pressure associated with salmeterol relative to placebo.

Trial SLGA3014

Study Dates

First patient enrolled: December 16, 1995
Last patient completed: October 12, 1996
Three protocol amendments:
Dates of the amendments were July 12, September 29 and November 10, 1995, each prior to initiation of the trial.

Investigators (36 sites)

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Note: Dr. Rob Fiddes has been disqualified by the FDA as a principal investigator. Since only five patients were enrolled at his investigator site, their impact on the trial outcomes is expected to be minimal and a reanalyses to exclude these patients was not requested.

Design

The design of Trial SLGA3014 was similar to that of the previous pivotal trial, SLD-390. The following critical aspects distinguish Trial SLGA3014:

- Four treatment arms including salmeterol 25 and 50 mcg powder BID via Diskus, albuterol Rotacaps 200 mcg QID and placebo (1:1:1:1 randomization).
- Double dummy design such that at each dosing both the Diskus and [redacted] devices were used.
- Screening PEFR (for 4 to 5 year olds) and FEV_1 (for 6 to 11 year olds) required to be between 45 and 75 percent of predicted normal.
- 1:1 stratification for 4 to 8 year old and 9 to 11 year old age groups.
- No placebo used between Screening and Day 1. All patients were converted to Ventolin MDI from other beta agonist therapy. Patients were required to be within 45

and 80 percent of predicted normal on Day 1 to be randomized to double blind treatment.
- Serial pulmonary function assessments on Day 1 and Week 12; pre-dose and 2 hour post-dose assessments at Week 6.

Endpoints

The following endpoints differed in Trial SLGA3014 from those used in Trial SLD-390.
- Serial pulmonary function assessments were collected at 30 minutes and immediately pre-dose, then 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose.
- Weighted averages (WAVE) were used in addition to AUC to summarize serial PEFR and FEV_1 data, as in the dose ranging study, SLGA2016.
- Responders were defined as those who achieved at least a 15 percent increase over baseline post-dose response within 4 hours of dosing.
- No evening PEFR assessment was recorded in diaries.
- Daily assessment of severity of asthma symptoms was made using a 4-point scale:
  1 = No symptoms at all.
  2 = Symptoms occurred with little or no discomfort, unrestricted activity.
  3 = Symptoms occurred; were sometimes annoying or affected routine activity.
  4 = Symptoms occurring even at rest; were annoying or affected routine activity.
- Continuous Holter monitoring was conducted at six investigator sites on Day 1 and Week 12.
- At Day 1 and Week 12, the parent/guardian was asked to complete the Health-Related Quality of Life (HRQOL) and Device Satisfaction Questionnaire. The HRQOL consisted of the FSII-R for functional status assessment, the Sleep Scale-C for sleep assessment and an instrument to measure the quality of life of parents/guardians, QOL-PAC-2. The QOL-PAC-2 assessed three domains (burden, subjective norm and social function) on a 1-5 scale, with lower scores indicating better QOL. Device satisfaction was assessed with regard to durability, ease to load with medicine, ease to hold and operate, ease in telling how many doses are left, ease of use, comfort of use, overall opinion and satisfaction.

Statistical Considerations

A sample size of 100 patients per treatment group was based on providing 80 percent power to detect a difference in percent of predicted PEFR and FEV_1 of 6 percent between any two treatment groups.

Patient Disposition

A total of 449 patients enrolled in the study. There were 307 patients screened but not enrolled. The majority of these patients failed to meet entry criteria, particularly PEFR or FEV_1 requirements. Of the 449 enrolled, 390 completed the study. A summary of the reasons for discontinuation of 59 patients is summarized in Table 17. The greatest proportion of discontinuations occurred in the 50 mcg salmeterol group, largely due to lack of efficacy and protocol violations.

Table 17: Summary of Patient Disposition[a]

Category	Placebo		Albuterol		25mcg Diskus		50mcg Diskus	
	n	(%)	n	(%)	n	(%)	n	(%)
Total Screened/Not Enrolled (N=307)								
Total Treated	110	(100)	115	(100)	115	(100)	109	(100)
Total Completed	95	(86)	105	(91)	103	(90)	87	(80)
Total Discontinued	15	(14)	10	(9)	12	(10)	22	(20)
Lack of efficacy[b]	2	(2)	1	(<1)	2	(2)	6	(6)
Other[c]	10	(9)	8	(7)	4	(3)	11	(10)
Adverse event	2	(2)	1	(<1)	3	(3)	2	(2)
Failure to return	1	(<1)	0	(0)	3	(3)	3	(3)

[a] This table contains counts of patients.
[b] Includes asthma exacerbation (unless classified as an SAE).
[c] Includes protocol variations.

The majority of patients were Caucasian (78 percent) and male (61 percent). Twelve percent of the population were "Black," eight percent were "Hispanic" and the remainder were "Oriental" or "Other." The mean age was 8 years, with a range of 4 to 11. Distribution of patients age 4 to 8 and age 9 to 11 was consistent among treatment groups.

The history of asthma was consistent among groups in terms of duration and hospitalizations or episodes requiring emergency care in the previous year. Approximately two-thirds of each group reported nocturnal symptoms and 80 percent of each group reported that asthma symptoms interfere with regular activities more than one day a week.

Approximately half of each treatment group used inhaled corticosteroids during the trial and 25 percent used either cromolyn or nedocromil sodium. Concomitant non-asthma medication was used by 80 to 90 percent of patients in each treatment group, primarily analgesics and anti-infectives.

Efficacy Outcomes

Serial PEFR as a percent of predicted for Day 1, including the weighted average (WAVE), are presented in Table 18 and graphically represented in Appendix 6. Both the 25 and 50 mcg Diskus strengths were statistically superior to placebo at each timepoint, but there were no statistically significant differences between the 25 and 50 mcg strengths.

Albuterol was statistically superior to placebo at each timepoint except Hours 4 and 6. Albuterol was statistically superior to salmeterol 25 mcg at 0.25 and 0.5 hours, but not statistically different from the 50 mcg strengths at those timepoints. The 25 mcg Diskus treatment was statistically superior to albuterol at Hours 3, 4 and 6 hours, while the 50 mcg Diskus treatment was statistically superior to albuterol at Hours 2, 3, 4, 6, 10 and 12.

Table 18: Percent of Predicted (%) Serial PEFR Values[a] Treatment Day 1

Time (Hours)	Placebo (N=108)	Albuterol (N=114)	25mcg Diskus (N=113)	50mcg Diskus (N=107)
Baseline[b]	80.2	79.4	78.0	81.3
0.25	85.4	92.9	87.3	92.2
0.5	84.9	96.1	90.8	96.4
1.0	87.2	**96.5**	94.1	99.7
2.0	88.6	94.2	97.2	102
3.0	89.3	92.8	97.8	102
4.0	**89.9**	91.5	**98.0**	**103**
6.0	88.2	88.8	95.6	102
8.0	88.2	**96.9**	95.1	98.7
10.0	86.9	92.9	93.4	98.1
12.0	87.8	90.8	93.5	97.7
W. Ave.[c]	88.0	92.7	95.0	99.8

[a] Maximum mean percent of predicted PEFR values in each treatment group are presented in bold-faced type. Because albuterol patients were dosed at 0 and 6 hours, the highest values from 0.25 to 6 hours *and* from 8 to 12 hours post-dose are given for this group.
[b] The baseline mean is the average of the -0.5 hour and 0.0 hour percent of predicted PEFR values on Treatment Day 1.
[c] W. Ave.=weighted average of post-dose percent of predicted PEFR over 12 hours.

Serial PEFR data for Week 12 data appear in Table 19 and Appendix 7. While the number of subjects in each treatment group declined between Day 1 and Week 12, the 50 mcg Diskus treatment was most reduced in number. WAVE values for each treatment group increased between Day 1 and Week 12.

The 25 mcg Diskus treatment was statistically superior to placebo at Hours 1, 2, 3, 4, 6, 8 and 12. Despite the reduced number of patients, the 50 mcg Diskus treatment was shown to be statistically superior to placebo at the same timepoints, plus Hours 0.5 and 10. No statistically significant differences were found between the 25 and 50 mcg salmeterol treatments. Numerical trends favored the 50 mcg strength at both Day 1 and Week 12.

Albuterol was statistically superior to placebo at Hours 0.25, 0.5, 1, 2, 3, 8 and 10. Albuterol was also statistically superior to 25 mcg salmeterol at Hours 0.25 and 0.5 and to 50 mcg at Hour 0.25 consistent with its comparatively faster onset. Both salmeterol strengths were statistically superior to albuterol at Hours 4 and 6.

While means were generally the same between Day 1 and Week 12 for salmeterol 50 mcg, means for each of the other treatment groups, including placebo, increased from the beginning to end of the trial.

Table 19: Percent of Predicted (%) Serial PEFR Values[a] Treatment Week 12

Time (Hours)	Placebo (N=96)	Albuterol (N=104)	25mcg Diskus (N=103)	50mcg Diskus (N=86)
Baseline[b]	80.5	79.2	78.4	80.6
-0.5	89.5	86.3	87.4	88.8
0.0	89.1	87.3	88.9	91.1
0.25	91.7	101	93.9	95.2
0.5	92.7	102	96.0	98.5
1.0	94.0	**103**	97.9	99.6
2.0	**95.1**	100	101	102
3.0	94.4	99.0	**102**	**103**
4.0	94.8	96.9	101	102
6.0	92.6	94.4	99.0	102
8.0	93.4	**101**	97.7	99.3
10.0	92.9	96.8	95.9	98.5
12.0	91.8	94.5	95.9	98.1
W. Ave.[c]	93.2	97.7	98.1	100

[a] Maximum mean percent of predicted PEFR values in each treatment group are presented in bold-faced type. Because albuterol patients were dosed at 0 and 6 hours, the highest values from 0.25 to 6 hours *and* from 8 to 12 hours post-dose are given for this group.
[b] The baseline mean is the average of the -0.5 hour and 0.0 hour percent of predicted PEFR values on Treatment Day 1.
[c] W. Ave.=weighted average of post-dose percent of predicted PEFR over 12 hours.

Analyses of PEFR values as absolute change from baseline show similar statistical outcomes. In particular, there are no statistical differences between the 25 and 50 mcg salmeterol treatments. However, absolute PEFR means, which show consistent numerical superiority for the 50 mcg Diskus treatment on Day 1, are essentially the same for the 25 and 50 mcg strengths at Week 12. Analyzed as change from baseline, absolute PEFR values on Day 12 for the 25 mcg dose are actually larger than for the 50 mcg dose at most timepoints.

Table 20 shows the maximum percentage of patients who achieved a 15 percent increase in PEFR from baseline. These data were derived from the single data point of the 12 hour interval at which the highest percentage of patients had reached this threshold. While it does reflect a small decline during the 12 week trial in the percentage of patients who reached the 15 percent increase among 50 mcg salmeterol patients, the data also reflect a substantial increase between Day 1 and Week 12 in the maximum percentage figures for albuterol and 25 mcg salmeterol. These same trends were found in reviewing data for percentage of responders at each timepoint.

Table 20: Maximum Percentage (%) of Patients Who Achieved a ≥15% Increase From Baseline in PEFR Values[a] at Treatment Day 1 and Week 12

	Placebo		Albuterol		25mcg Diskus		50mcg Diskus	
Treatment Visit	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Treatment Day 1	45/108	(42)	75/114	(66)	72/113	(64)	79/107	(74)
Treatment Week 12	46/96	(48)	76/104	(73)	79/103	(77)	61/86	(71)

Functions of serial PEFR at Day 1 are presented in Table 21. Table 22 contains FEV_1 functions for Week 12. At both Day 1 and Week 12, the proportion of responders in each active treatment group was statistically higher than among placebo patients. On Day 1, the onset of effect was faster for each of the active treatments than for placebo. In addition, albuterol onset was statistically faster than salmeterol 25 mcg, but no statistical difference was seen between albuterol and the 50 mcg treatment. At Week 12, the only statistical differences observed were that albuterol and 25 mcg salmeterol had a shorter time to onset than placebo.

Table 21: Functions of Serial PEFR[a] Treatment Day 1

	Placebo (N=108)	Albuterol (N=114)	25mcg Diskus (N=113)	50mcg Diskus (N=107)
Percentage of responders[b]	50	81	72	81
Median onset of effect (hr)	7.95	0.23	0.48	0.48
Mean max effect (% change)	23.3	33.5	37.4	36.6
Median duration of effect (hr)	0.0	3.6	9.6	10.5
Mean AUC(BL) (L·hr)	228	413	530	581
Percentage of patients with W. Ave. ≥15% of baseline[c]	28	51	57	64

[a] Refer to Section 6.4 for definitions of serial PEFR functions.
[b] Responders were defined as those patients who achieved a ≥15% increase in PEFR over baseline (average of the -0.5 hour and 0.0 hour PEFR values on Treatment Day 1) within 4 hours post-dose.
[c] W. Ave.=weighted average of post-dose PEFR over 12 hours.

Table 22: Functions of Serial PEFR[a]
Treatment Week 12

	Placebo (N=96)	Albuterol (N=104)	25mcg Diskus (N=103)	50mcg Diskus (N=86)
Percentage of responders[b]	61	81	81	79
Median onset of effect (hr)	1.60	0.10	0.14	0.15
Mean max effect (% change)	32.9	42.1	42.1	38.6
Median duration of effect (hr)	1.2	11.2	11.8	11.4
Mean AUC(BL) (L-hr)	373	570	657	623
Percentage of patients with W. Ave. ≥15% of baseline[c]	45	60	70	60

[a] Refer to Section 6.4 for definitions of serial PEFR functions.
[b] Responders were defined as those patients who achieved a ≥15% increase in PEFR over baseline (average of the -0.5 hour and 0.0 hour PEFR values on Treatment Day 1) within 4 hours post-dose.
[c] W. Ave.=weighted average of post-dose PEFR over 12 hours.

On Day 1, maximum effect was statistically greater in each of the active treatment groups than in the placebo group. Maximum effect was increased among all the treatment groups at Week 12, but less so in the 50 mcg salmeterol group than the others. Statistical differences at Week 12 were seen only between the 25 mcg Diskus and placebo groups. Statistical analyses of duration of effect are consistent with those of maximum effect at Day 1 and Week 12.

AUC(BL) was statistically greater for each of the active treatments than for placebo at Day 1 and Week 12 and statistically greater in the 25 and 50 mcg salmeterol groups than in the albuterol group on Day 1.

The percentage of patients with WAVE values at least 15 percent over baseline was statistically higher in the active treatment groups than in the placebo group at Day 1 and Week 12.

WAVE values were also used to compare the responses of patients less than nine years of age to those of patients nine years or older. As seen in Table 23, younger children showed more bronchodilation response to each treatment, based on change from baseline, than the older children at both Day 1 and Week 12. WAVE values were generally higher for the younger children with salmeterol, but not with placebo or albuterol. Responses to each treatment increased between Day 1 and Week 12, particularly for older children in the 25 mcg salmeterol and albuterol groups. WAVE and change from baseline WAVE were also calculated for children age 6 and older and showed that responses to each treatment increased between Day 1 and Week 12, with the least change seen in the 50 mcg salmeterol group.

Table 23: Weighted Average of Post-dose Percent of Predicted (%) PEFR Values by Age Subgroup at Treatment Day 1 and Week 12

Timepoint/ Age Subgroup	Placebo	Albuterol	25mcg Diskus	50mcg Diskus
Treatment Day 1				
<9 years				
N	51	55	54	48
W. Ave.[a]	86.4	91.8	95.4	103
Change[b]	10.7	16.7	21.4	21.0
≥9 years				
N	57	59	59	59
W. Ave.	89.5	93.7	94.6	97.3
Change	5.2	10.3	12.9	16.3
Treatment Week 12				
<9 years				
N	46	50	48	36
W. Ave.	95.3	96.2	96.5	102
Change	18.5	21.2	21.8	21.0
≥9 years				
N	50	54	55	50
W. Ave.	91.4	99.1	99.5	99.0
Change	7.5	16.1	18.0	18.5

[a] W. Ave.=the weighted average of post-dose percent of predicted PEFR over 12 hours.
[b] Change from baseline for the W. Ave.

Serial FEV_1 values, expressed as a percent of predicted, are shown in Table 24 for Day 1 (graphical representation in Appendix 8) and in Table 25 for Week 12 (graphical representation in Appendix 9). On Day 1, both the 25 and 50 mcg salmeterol groups were statistically superior to placebo at all timepoints. At Hour 8, the 50 mcg salmeterol group was statistically superior to the 25 mcg group. Statistically significant differences between the 25 and 50 mcg strengths were not seen at other timepoints, although numerical trends suggest superiority of the 50 mcg treatment. The salmeterol treatments were both statistically superior to albuterol at Hours 2, 3, 4, 6 and 12. In addition, 50 mcg salmeterol was superior to albuterol at Hour 10.

Albuterol was statistically superior to placebo at 0.25, 0.5, 1, 2, 8 and 10 hours after dosing. Albuterol was also statistically superior to both the 25 and 50 mcg salmeterol doses at Hour 0.25 and superior to the 25 mcg salmeterol dose at Hour 0.5.

Table 24: Percent of Predicted (%) Serial FEV_1 Values[a]

Treatment Day 1

Time (Hours)	Placebo (N=98)	Albuterol (N=107)	25mcg Diskus (N=110)	50mcg Diskus (N=99)
Baseline[b]	69.1	69.6	70.0	69.9
0.25	74.8	82.6	78.7	79.9
0.5	76.8	83.7	81.5	83.4
1.0	78.0	**85.2**	83.8	86.0
2.0	77.8	82.4	85.7	86.4
3.0	78.0	80.4	85.7	87.1
4.0	**78.1**	78.4	**86.2**	**88.1**
6.0	76.9	77.5	84.0	85.9
8.0	75.4	**84.2**	82.4	85.4
10.0	75.7	79.8	81.5	83.4
12.0	74.9	77.7	81.9	82.5
W. Ave.[c]	76.4	80.3	83.3	85.0

[a] Maximum mean percent of predicted FEV_1 values in each treatment group are presented in bold-faced type. Because albuterol patients were dosed at 0 and 6 hours, the highest values from 0.25 to 6 hours and from 8 to 12 hours post-dose are given for this group.

[b] The baseline mean is the average of the -0.5 hour and 0.0 hour percent of predicted FEV_1 values on Treatment Day 1.

[c] W. Ave.=weighted average of post-dose percent of predicted FEV_1 over 12 hours.

At Week 12, both the 25 and 50 mcg salmeterol treatments were statistically superior to placebo at Hours 1, 2, 3, 4, 6, and 8. In addition, the 50 mcg treatment was also superior to placebo at Hours 0.25 and 0.5. There were no statistically significant differences between the two salmeterol strengths. It is notable that at Hours 3 and 4, the 25 mcg Diskus mean exceeds that of the 50 mcg Diskus. At Hours 4 and 6, both salmeterol strengths are statistically superior to albuterol.

Albuterol was statistically superior to both salmeterol strengths at 0.25 and 0.5 hours and superior to placebo at all timepoints except Hours 4, 6 and 12.

Table 25: Percent of Predicted (%) Serial FEV_1 Values[a]
Treatment Week 12

Time (Hours)	Placebo (N=88)	Albuterol (N=97)	25mcg Diskus (N=100)	50mcg Diskus (N=79)
Baseline[b]	69.3	69.9	69.9	69.8
-0.5	78.1	74.7	77.7	78.9
0.0	78.6	76.6	78.2	80.2
0.25	79.3	88.3	82.5	83.3
0.5	80.7	88.6	83.4	85.0
1.0	81.3	88.7	86.8	86.2
2.0	81.2	87.1	87.6	87.6
3.0	80.9	84.9	87.7	87.2
4.0	80.6	81.9	87.5	87.0
6.0	79.3	81.1	85.6	85.5
8.0	78.3	87.3	84.1	84.1
10.0	78.1	82.3	82.1	82.3
12.0	78.4	80.2	81.9	80.9
W. Ave.[c]	79.3	83.7	84.6	84.4

[a] Maximum mean percent of predicted FEV_1 values in each treatment group are presented in bold-faced type. Because albuterol patients were dosed at 0 and 6 hours, the highest values from 0.25 to 6 hours and from 8 to 12 hours post-dose are given for this group.
[b] The baseline mean is the average of the -0.5 hour and 0.0 hour percent of predicted FEV_1 values on Treatment Day 1.
[c] W. Ave.=weighted average of post-dose percent of predicted FEV_1 over 12 hours.

Between Day 1 and Week 12, mean values increased for each treatment group except the 50 mcg salmeterol group. The largest increases were seen among the placebo patients, followed by albuterol, 25 mcg salmeterol. The smaller differences between salmeterol groups at Week 12 than on Day 1 appear to be attributable to a substantial increase in response to the 25 mcg strength in addition to a small decline in response to the 50 mcg strength.

Review of absolute FEV_1 means and statistical analyses of change from baseline FEV_1 showed outcomes that were consistent with the percent of predicted analyses.

The maximum percentage of patients who achieved an improvement of at least 15 percent from baseline at any timepoint is shown for Day 1 and Week 12 in Table 26. There was a decline in the proportion of 50 mcg salmeterol patients who achieved this threshold between Day 1 and Week 12 and an increase in the proportion of the other treatment groups. Evaluation of these responders by timepoint showed that the changes in response rates within each group is consistent throughout the 12 hour interval and is not reflected solely in the maximal percentage values.

Table 26: Maximum Percentage (%) of Patients Who Achieved a ≥15% Increase From Baseline in FEV_1 Values[a] at Treatment Day 1 and Week 12

	Placebo		Albuterol		25mcg Diskus		50mcg Diskus	
Treatment Visit	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Treatment Day 1	40/98	(41)	72/107	(67)	77/110	(70)	78/99	(79)
Treatment Week 12	49/88	(56)	70/97	(72)	73/100	(73)	57/79	(72)

The functions of FEV_1 are presented in Table 27 for Day 1 and in Table 28 for Week 12. On Day 1, each active treatment was statistically superior to placebo for each function. There were no statistically significant differences between the 25 and 50 mcg treatments for any function. The 50 mcg Diskus was superior to the albuterol group with respect to proportion of responders, duration of effect, AUC (BL) and percentage of patients with WAVE values at least 15 percent over baseline. The 25 mcg Diskus was superior to the albuterol group with respect to AUC(BL) and WAVE percentages.

Table 27: Functions of Serial FEV_1[a]

Treatment Day 1

	Placebo (N=98)	Albuterol (N=107)	25mcg Diskus (N=110)	50mcg Diskus (N=99)
Percentage of responders[b]	55	78	80	89
Median onset of effect (hr)	2.61	0.23	0.54	0.32
Mean max effect (% change)	21.8	30.4	29.6	33.1
Median duration of effect (hr)	0.6	2.8	9.3	11.2
Mean AUC(BL) (L·hr)	1.8	2.4	3.1	3.6
Percentage of patients with W. Ave. ≥15% of baseline[c]	31	48	62	69

[a] Refer to Section 6.4 for definitions of serial FEV_1 functions.

[b] Responders were defined as those patients who achieved a ≥15% increase in FEV_1 over baseline (average of the -0.5 hour and 0.0 hour FEV_1 values on Treatment Day 1) within 4 hours post-dose.

[c] W. Ave.=weighted average of post-dose FEV_1 over 12 hours.

At Week 12, there were fewer statistically significant differences shown than at Day 1. This may be due in part to the smaller number of subjects and resultant reductions in statistical power, but is also appears to be related to shifts in the data. Percentage of responders, maximum effect and percentage of WAVE responders increased for each treatment group except the 50 mcg Diskus, in which these functions decreased. Time to onset was shorter and duration of effect was longer at Week 12 than Day 1 for each treatment group. No statistically significant differences were seen among the active treatments. The 50 mcg Diskus group was superior to placebo for AUC (BL) and percentage of WAVE responders. The 25 mcg Diskus group was superior to placebo

for responders, maximum effect, AUC (BL) and percentage of WAVE responders. Finally, albuterol was statistically superior to placebo for maximum effect and AUC (BL).

Table 28: Functions of Serial FEV_1[a]

Treatment Week 12

	Placebo (N=88)	Albuterol (N=97)	25mcg Diskus (N=100)	50mcg Diskus (N=79)
Percentage of responders[b]	68	78	84	81
Median onset of effect (hr)	0.26	0.10	0.20	0.16
Mean max effect (% change)	26.9	35.2	33.5	31.9
Median duration of effect (hr)	2.8	9.5	8.3	10.9
Mean AUC(BL) (L·hr)	2.2	3.1	3.4	3.6
Percentage of patients with W. Ave. ≥15% of baseline[c]	45	58	59	62

[a] Refer to Section 6.4 for definitions of serial FEV_1 functions.

[b] Responders were defined as those patients who achieved a ≥15% increase in FEV_1 over baseline (average of the -0.5 hour and 0.0 hour FEV1 values on Treatment Day 1) within 4 hours post-dose.

[c] W. Ave.=weighted average of post-dose FEV_1 over 12 hours.

Subgroup analysis by age, in Table 29, shows WAVE values and bronchodilation responses to be greater among the younger children in all treatment groups except the 50 mcg group. This finding is also seen in the subgroup of children at least six years of age.

Table 29: Weighted Average of Post-dose Percent of Predicted (%) FEV_1 Values by Age Subgroup at Treatment Day 1 and Week 12

Timepoint/ Age Subgroup	Placebo	Albuterol	25mcg Diskus	50mcg Diskus
Treatment Day 1				
<9 years				
N	41	47	50	39
W. Ave.[a]	76.2	80.9	83.9	83.4
Change[b]	7.7	12.8	14.4	14.5
≥9 years				
N	57	60	60	60
W. Ave.	76.5	79.9	82.8	86.0
Change	6.9	9.1	12.3	15.5
Treatment Week 12				
<9 years				
N	39	42	45	27
W. Ave.	82.2	85.0	85.4	83.8
Change	13.0	16.6	15.9	14.8
≥9 years				
N	49	55	55	52
W. Ave.	77.0	82.6	83.9	84.7
Change	7.7	11.7	13.7	14.4

[a] W. Ave.=the weighted average of percent of predicted FEV_1.
[b] Change from baseline for the W. Ave.

Data from the 2-hour post-dose pulmonary function assessments were reviewed to determine whether the trends seen between Day 1 and Week 12 were also seen at Week 6. In fact, PEFR and FEV_1 as a percent of predicted showed increases in the mean values for each treatment group at 2 hours post when comparing Week 6 to Day 1. The directions of change (increase or decrease) between Week 6 and Week 12 were variable and not apparently associated with treatment groups. These data suggest that the 2 hour timepoint may not be a useful metric for predicting overall response to treatment and that differences in parameters such as duration and AUC(BL) may be more sensitive to changes. Alternatively, the decline in response to the 50 mcg dose may not have occurred prior to Week 6.

The sponsor noted that that mean PEFR values, expressed as a percent of predicted, were approximately 10 percent greater than FEV_1 means, expressed as a percent of predicted. This outcome was due to inclusion criteria being based on FEV_1 alone, for all but the 4 and 5 year old patients, and concurrent PEFRs did not necessarily fall within a pre-specified range. In order to consider the outcomes of a population defined by PEFR values, the sponsor chose to repeat many of the efficacy analyses for patients whose baseline PEFRs were between 55 an 90 percent of predicted normal. This group represented approximately two thirds of the entire study population. WAVE analyses for the whole group and analyses by age were consistent with those of the whole group. WAVE analyses by gender showed no consistent differences between males and females and suggested that the changes between Day 1 and Week 12 were comparable for both subgroups. Analyses were also conducted by severity, comparing

patients with baseline PEFRs between 55 and 75 percent of predicted normal to those with baselines of greater than 75 to 90 percent of predicted normal. As expected, WAVE values were higher among the patients with higher baseline values, but patients with lower baseline values exhibited a greater bronhcodilation response.

The rate of out-of-clinic **asthma exacerbations** was fairly comparable among treatment groups during the treatment period. Approximately 20 to 25 percent of each group experienced at least one exacerbation, with the absolute rate lowest among albuterol patients and highest in the 25 mcg Diskus groups. Only 3 to 5 percent of each treatment group experienced an out-of-clinic exacerbation during post-treatment. This compares favorably to the 12 percent of patients who experienced such post-treatment events in Trial SLD-390.

Morning PEFR recorded in daily diaries were averaged by week and were highest among 50 mcg Diskus patients and lowest among albuterol patients throughout the trial. Analyses were conducted to compare the four week means for each treatment group. The 25 mcg Diskus group was statistically superior to placebo at Weeks 1-4, 5-8 and 9-12 and to albuterol at Weeks 1-4 and 5-8. The 50 mcg Diskus group was statistically superior to placebo and albuterol for Weeks 1-4. Morning PEFR means increased for each treatment group between Day 1 and Week 12, with the greatest increase seen in the 25 mcg Diskus group (24 L/min) and the smallest increase seen among placebo patients (14 L/min).

Similar analyses were conducted to compare **back-up Ventolin use** among treatment groups. Each active treatment was statistically superior to placebo at Weeks 1-4 with regard to the percent of days that patients used no Ventolin. There was a decline in use of Ventolin back-up among each of the treatment groups ranging from 1.1 to 1.5 fewer puffs per day.

Overall **daily asthma symptom score** means fell from 1.9 to 1.6 or 1.7 in each of the treatment groups. No statistically significant differences among treatments were seen. Days with no symptoms increased between Day 1 and Week 12 for each treatment group. Maximum improvement was seen in the 25 mcg Diskus group and minimum improvement was seen among placebo patients.

The percentage of nights with no **nighttime awakenings** ranged from 84 to 87 percent among treatment groups in the week prior to Day 1. Increases in each treatment group were seen to a maximum of 93 percent for the 50 mcg Diskus group. No statistically significant differences were seen among the treatment groups.

Health-related "quality of life" evaluation using both FSII-R and the Sleep Scale-C showed no statistically significant differences among treatment groups, although each group improved significantly from baseline with treatment. Statistically significant decreases (improvement) was seen for at least one domain of the parent evaluation, QOL-PAC-2, in each treatment group. No statistically significant differences among treatment groups were observed.

Device satisfaction ratings are summarized in Table 30. Most patients responded favorably to the device and seemed to view the device more favorably with time. However, nearly 30 percent did not report that they were comfortable using the device.

Table 30: Favorable Patient Satisfaction Scores for the Diskus Device[a,b]

	Study Period			
	Baseline		Endpoint	
Assessment	n/N	(%)	n/N	(%)
Overall Opinion: Like Device	349/429	81	403/436	92
Ease of Use	382/429	89	424/436	97
Satisfaction	NA	NA	391/436	90
Comfort Using the Device	302/429	70	312/436	72
Ease to Hold and Operate	376/429	88	430/436	99
Ease in Telling Number of Doses Left	359/429	84	396/435	91

[a] The best two ratings (eg, strongly like or like) were considered to be favorable responses for each item.
[b] Percentages are based on the total number of caregivers who responded to the questionnaire for each item, regardless of treatment group.
NA = not applicable; not measured.

Efficacy Conclusions

Serial PEFR data indicated that both the 25 and 50 mcg doses were statistically superior to placebo on both Day 1 and at Week 12. At both timepoints, albuterol showed a consistently shorter time to onset, but both salmeterol doses demonstrated longer durations of effect. Numerical trends favored the 50 mcg salmeterol dose relative to each of the other treatments on both days, but no statistically significant differences were seen between the treatments.

Increased responses to each treatment were reflected in serial PEFR and in functions of PEFR between Day 1 and Week 12, with the smallest increases seen in the salmeterol 50 mcg group. At Week 12, some parameters, such as maximum effect and percentage of responders was higher for the 25 mcg group than the 50 mcg group, although no statistically significant differences between the 25 and 50 mcg groups were seen.

Serial FEV_1 values confirmed the statistical superiority of both the 25 and 50 mcg salmeterol doses, as well as albuterol, to placebo. Each treatment showed an increased response between Day 1 and Week 12, with the exception of the 50 mcg dose, which showed a small decline in effect. No statistically significant differences were seen between the two groups and the 50 mcg dose retained a longer duration of action than the 25 mcg dose at Week 12.

For both PEFR and FEV_1 analyses by age group showed that children age 9 to 11 years exhibited less bronchodilation response than children less than 9 years of age to each treatment.

The respective effects of the 25 and 50 mcg treatments on PEFR and FEV_1 responses were not reflected in diary data including, morning PEFR, back-up Ventolin MDI use, daily asthma symptom scores, nighttime awakenings, nor in the "quality of life" scores. There were, however, a higher proportion of patients who discontinued from the 50 mcg treatment group than the 25 mcg treatment group due to lack of efficacy.

Overall, it appears that the 50 mcg salmeterol dose is more consistently effective from the initiation of treatment than the 25 mcg dose. Both are significantly superior to placebo. A decline in the effect occurred in some patients over the course of 12 weeks and this finding should be reflected in the labeling.

Safety Outcomes

There were **no deaths** reported during this trial.

Serious adverse events were reported in eight patients, one albuterol patient, three 25 mcg Diskus patients and four 50 mcg Diskus patients. The albuterol patient (Pt # SI22396) and three 50 mcg Diskus (Pts # BA20795, PR20666, SI223860) patients experienced asthma exacerbations. Pt # PR20666 was discontinued due to status asthmaticus for which no trigger was identified. Each of the other events was associated with a concurrent infection. The remaining four patients experienced pneumonia (Pt # LA20542), appendicitis (Pt # PE20631), fractured left tibia (Pt # NA20613) and nausea, vomiting and diarrhea associated with a *Clostridium difficile* infection(Pt # NA20616).

There were a total of eight adverse **events that led to premature discontinuation**, including the single case of status asthmaticus described above. For the placebo group, an abnormal EKG in Pt # BA21084 and headaches in Pt # RU20523 were reported. A chest cold was reported to have caused discontinuation of Pt # MU21195. Among Diskus 25 mcg patients, Pt # BA20796 discontinued due to worsening migraine (considered unrelated by investigator), Pt # LA20925 due to headache (considered possibly related) and Pt # WE20753 due to pneumonitis. Among 50 mcg Diskus patients, Pt # PR20655 discontinued due to uriticaria and angioedema (considered probably related) and Pt # PR20666 due to status asthmaticus.

Other events are summarized in Table 31. Events are listed in the table if they occurred in three percent or more of the patients in one of the salmeterol groups and in a larger proportion of one salmeterol group than the placebo group.

Table 31: Adverse Events

	Placebo	Albuterol	Diskus 25	Diskus 50
Total	54 (49%)	58 (50%)	54 (47%)	57 (52%)
URTI	22 (20%)	21 (18%)	25 (22%)	24 (22%)
Throat Irritation	7 (6%)	13 (11%)	11 (10%)	10 (9%)
Ear Signs & Symptoms	6 (5%)	10 (9%)	5 (4%)	6 (6%)
Pharyngitis/Throat Infection	2 (2%)	3 (3%)	6 (5%)	4 (4%)
Rhinorrhea/Post Nasal Drip	3 (3%)	5 (4%)	2 (2%)	4 (4%)
Rhinitis	2 (2%)	3 (3%)	4 (3%)	3 (3%)
Nausea and vomiting	10 (9%)	13 (11%)	12 (10%)	9 (8%)
Diarrhea	6 (5%)	2 (2%)	4 (3%)	8 (7%)
Dental Discomfort and Pain	1 (<1%)	2 (2%)	1 (<1%)	4 (4%)
Headaches	17 (15%)	25 (22%)	35 (30%)	26 (24%)
Fever	8 (7%)	11 (10%)	13 (11%)	7 (6%)
Pain	0	0	3 (3%)	4 (4%)
Malaise and Fatigue	2 (2%)	0	4 (3%)	1 (<1%)
Asthma	0	1 (<1%)	1 (<1%)	4 (4%)
Lower Resp. Signs and Sx.	1 (<1%)	0	0	3 (3%)
Urticaria	0	2 (2%)	1 (<1%)	4 (4%)
Fractures	0	1 (<1%)	2 (2%)	6 (6%)

Clinical laboratory evaluations were beyond threshold levels in 12 instances:

Placebo	Low glucose	Week 12
Albuterol	High glucose	Week 12
	Low glucose x 2	Week 12
	Low glucose	Discontinuation Visit (chest cold)
25 mcg Diskus	High hematocrit	Week 12
	Low glucose	Discontinuation Visit (pneumonitis)
	Low glucose	Screening, Week 12
50 mcg Diskus	Low hematocrit	Screening, Week 12
	Low WBC	Discontinuation Visit (status asthmaticus)
	Low glucose	Week 12
	Low sodium	Week 12

Categorical analyses of patient shifts from normal to abnormal values showed relatively low rates of such occurrences. Overall, there appear to be no clinically significant trends in the clinical laboratory evaluations.

Vital signs were collected with serial pulmonary function testing. Changes from baseline and categorical analyses of increase or decrease of 15, 20 or 30 bpm from baseline failed to show clinically meaningful differences among treatments throughout the study.

Mean changes from baseline of systolic blood pressure and categorical analyses of shifts in 15, 20 or 30 mmHg also failed to show clinically meaningful trends. There appears to be a slight indication that diastolic blood pressure is reduced more by the 25 and 50 mcg Diskus treatments than by the other treatments, but this numerical trend does not seem to suggest strong clinical importance.

Electrocardiograms were characterized as abnormal during treatment of four patients, including one placebo patient, two albuterol patients and one 50 mcg salmeterol patient.

The latter was a patient who had a normal screening EKG, but experienced frequent PACs post-dose at Week 12. Both albuterol patients had EKGs subsequent to the abnormal findings that did not show the abnormality. The placebo patient was discontinued due to post-dose ST elevations in leads V2 an V3 at Week 6. Mean heart rates were slightly higher in the salmeterol treatment groups than placebo (maximum of 5 bpm greater than placebo) and there was a numerical dose response. The clinical significance of this finding appears to be minimal.

QT_c analyses were largely consistent among treatments at Day 1, Week 6 and Week 12. One possible exception is that the mean QT_c value for salmeterol 25 mcg at post-dose Week 12 was slightly larger (7 msec) than the other values. The clinical significance does not appear to be great, particularly given that only 8 patients in the study experienced a QT_c over 440 mcsec (1 placebo, 2 albuterol, 2 salmeterol 25 mcg and 3 salmeterol 50 mcg patients), and these were sporadic throughout the trial (no temporal or dose-related trends).

Continuous Holter monitoring revealed no apparent treatment related effects on cardiac rates. The number of ventricular ectopic beats was noted to show a rank order of placebo, 25 mcg salmeterol, albuterol and 50 mcg salmeterol at Day 1 and Week 12. The clinical significance of this finding does not appear to be great given the limited number of events (maximum of 23). In looking at the number of supraventricular events, it was noted that one 50 mcg Diskus patient experienced 1248 SVEs at Screening, 193 on Day 1 and 3293 at Week 12. No other patients were reported to have similar findings. This pattern of response, with a "nadir" following the first dose, does not argue for a treatment effect.

Physical examinations showed unfavorable changes between Screening and Week 12 in only eight patients, with no clinically meaningful trends.

Withdrawal effects were examined during the post-treatment period by comparing asthma exacerbation rates, previously noted to be consistent among treatment groups and adverse event rates, that will be discussed further in the Integrated Summary of Safety.

Overall, the safety data are supportive of the safety of each of the active treatments. They do not appear to show clinically meaningful differences among the active treatments, nor suggest a dose response between the 25 and 50 mcg salmeterol groups. It does appear that the 50 mcg treatment in this trial was associated with a slightly higher number of asthma events than the other treatments. Use of salmeterol appears to have been associated with the occurrence of uriticaria and headaches.

Conclusions

Pulmonary function testing consistently supported the effectiveness of the 25 and 50 mcg treatments. There was an indication, particularly among the FEV_1 data that the 25 mcg treatment group showed an enhancement of effects during the trial, while the 50 mcg treatment groups showed a decline, at least in some patients. Overall, there were no statistically significant differences between the 25 and 50 mcg groups and no secondary efficacy endpoints demonstrated a trend similar to that of the pulmonary function testing.

Safety evaluations supported the safety of salmeterol in the 4 to 11 year old age group. The 25 and 50 mcg treatments appear similar, with the exception that the 50 mcg treatment group experienced a slight increase in the number of asthma events relative to the 25 mcg and placebo treatment groups.