CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-692 S001/002

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical

JUL 20 1998

NDA #:	20-692/S-001
Applicant:	Glaxo Wellcome
Name of Drug:	Serevent (salmeterol) Diskus
Indication:	Exercise Induced Bronchospasm in children (age≥4 years) and adults
Documents Reviewed:	Volumes 1.1-1.15 and a volume of data diskettes dated September 24, 1997; a corrected Volume 1 dated October 21, 1997; and an unnumbered volume dated December 18, 1997.

This review pertains to two studies in adults (Studies SLGA2013 and SLGA2017) and two studies in children aged ≥ 4 years (SLGA2003 and SLGA2014) for protection against exercise induced bronchospasm.

The medical officer for this submission was Dr. Susan Johnson, Pharm. D. (HFD-570), with whom this review was discussed.

This reviewer found that the table of FEV_1 values for Study SLGA2003 did not contain the values for the 11.5 hour exercise challenges. The sponsor supplied these values in their December 18, 1997 submission.

I. Adult Studies

A. Study SLGA2013

1. Study Design and Method of Analysis

This was an double-blind, double-dummy, randomized, placebo-controlled, four-way crossover trial comparing salmeterol 50mcg administered via MDI, 50mcg and 100mcg salmeterol administered via Diskus, and placebo in asthmatic patients (12-40 years of age) with exercise-induced bronchospasm (EIB). To enter the trial, patients had to have an FEV_1 of ≥ 70% of predicted and exhibit a decrease of ≥20% in any post-exercise challenge FEV_1 compared to the pre-exercise challenge FEV_1. There was a 3- to 14-day washout period between visits.

Exercise challenges were conducted at 0.5 and 8.5 hours post-dose. Spirometry and vital sign data were collected immediately prior to exercise and at 5, 10, 15, 30, and 60 minutes post-exercise. On visit 1, patients received single-blind placebo. On treatment visits 2-5 they received double-blind medication. The patient's 30 minute pre-dose FEV_1 on a test day had to be within ± 12% of their screening FEV_1; if not, a visit was rescheduled within 10 days. A patient could be rescheduled only once per treatment visit; otherwise they were discontinued from the study. (The study report did not mention how many patients, if any, had their visits rescheduled.)

Enrollment was 24 evaluable patients at two centers. This proposed sample size was designed to provide greater than 80% power of detecting a 12% difference in FEV_1 between any two treatments with a 0.05 significance level.

Blinding was obtained by using 2 Diskus devices and 1 MDI device at each treatment administration. The two Diskus devices were needed to give the 100mcg dose because there was no 100mcg Diskus device.

FEV_1 was taken as the highest of three determinations at each spirometric assessment time.

The primary efficacy measure was the percent fall in FEV_1 following exercise. All of the efficacy assessments were based on the lowest FEV_1 value collected during the first hour after exercise. Baseline FEV_1 was defined as the FEV_1 value collected immediately prior to each exercise. Overall and pairwise

tests were based on a crossover analysis of variance with terms for patient, treatment, period, and carryover (previous treatment). The sponsor made no corrections for multiple comparisons. Pairwise p-values were calculated among treatment means. (This reviewer will comment on multiple comparisons in the Reviewer Comments section.)

The sponsor also analyzed the fall in FEV_1 data using two categories : success (< 20% fall in FEV_1) and failure ($\geq$ 20% fall in FEV_1). This data was analyzed by McNemar's test. This pre-specified analysis addresses whether treatments affect the criterion used to enter patients (a $\geq$ 20% fall in FEV_1 on exercising). Results of this analysis will only be provided for the comparison of placebo with the 50mcg Diskus because that is the recommended dose in the label. (Analyses where the sponsor formed three categories on the percent fall data will not be discussed in this review. The sponsor's analysis of that data was not appropriate because it did not take the crossover nature of the study into consideration as the McNemar's test does.)

If a patient was not able to perform an exercise challenge because the patient had already experienced a fall greater than 20% at a previous exercise challenge on that treatment or because the pre-exercise challenge FEV_1 was too low, creating a potential safety problem, the exercise challenge was considered a failure.

2. Results

There were 24 patients with EIB randomized into the trial. None of the patients discontinued prematurely.

Two patients did not complete the 8.5 Hour exercise challenge while on placebo, because one subject's pre-exercise challenge FEV_1 was too low (Subject 9116) and the maximum fall in FEV_1 during one subject's 0.5 Hour exercise challenge was too low (Subject 9117).

The table below presents the results describing mean percent drops in FEV_1 and p-values compared to double-blind placebo at the two exercise challenges. The Visit 1 evaluation is a single blind placebo evaluation. The effects due to periods and carry-over were not significant at either challenge.

	Visit 1	Placebo	50mcg MDI	50mcg Diskus	100mcg Diskus
0.5 Hour Challenge					
N	24	24	24	24	24
Mean Percent Fall	29	32	9	13	11
Standard Error	2.44	3.39	2.59	3.54	2.69
P-value VS Placebo			<0.001	<0.001	<0.001
8.5 Hour Challenge					
N	24	22	24	24	24
Mean Percent Fall	29	29	13	17	16
Standard Error	1.68	3.01	2.67	3.21	2.94
P-value VS Placebo			<0.001	<0.001	<0.001

All salmeterol treatments were significantly better than placebo. Salmeterol MDI was significantly better than the 50mcg Diskus at the 0.5 Hour exercise challenge (p=0.037) and nearly better at the 8.5 Hour exercise challenge (p=0.055). No other comparisons among salmeterol treatments were significant.

The table below provides the cross-tabulations and p-values comparing the 50mcg Diskus with placebo on whether patients were protected against a 20% fall in FEV_1 or not. If a patient was not permitted to perform an exercise challenge for safety reasons the patient is considered a failure for that treatment.

0.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	5	0	5
	Failure	12	7	19
	Total	17	7	24

$p<0.001$, McNemar's Test

8.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	5	0	5
	Failure	12	7	19
	Total	17	7	24

$p<0.001$, McNemar's Test

The 50mcg diskus in the comparisons with placebo gave a significantly higher proportion of patients protected against a 20% fall in FEV_1. Although the tables are identical, the patients included in the categories of the cross-tabulations are not always identical. At both evaluations the percent protected was 71%. This analysis is not powerful enough to detect differences among active treatments.

3. Reviewer's comments

These analyses show that the 50mcg salmeterol diskus is better than placebo for protecting against exercise induced bronchospasm. As indicated by the analysis on percent fall in FEV_1, the 50mcg diskus was not as effective numerically as the 50mcg MDI. No advantage of the 100mcg diskus over the 50mcg diskus was seen in the analysis of percent fall in FEV_1. These results indicate that, though decreasing, protection was out to 9 hours at least.

The sponsor did not adjust the p-values of diskus comparisons against placebo for multiple comparisons (i.e., two dose levels). However, these comparisons would be significant ($p<0.05$) using any of the commonly applied multiple comparison procedures. In the reviewer's opinion it is not appropriate to adjust the comparison of the 50 mcg Diskus and 50mcg MDI for multiple comparisons, since this is a comparison of special interest.

B. Study SLGA2017

1. Study Design and Method of Analysis

This study was similar to Study SLGA2013, except that 29 patients were entered.

2. Results

There were 29 patients entered into the study. Twenty-eight patients completed the study. One patient (subject 12581) only completed the single blind placebo visit and the 100 mcg diskus visit. This patient showed a greater than 20% fall in FEV_1 on single blind placebo, but was protected against a 20% fall by the 100mcg diskus.

The table below provides the mean percent falls in FEV_1 and p-values compared to double-blind placebo at the two exercise challenges. The Visit 1 evaluation is a single blind placebo evaluation. The effects due to periods and carry-over were not significant at either challenge.

	Visit 1	Placebo	50mcg MDI	50mcg Diskus	100mcg Diskus
0.5 Hour Challenge					
N	29	28	28	28	28
Mean Percent Fall	21	19	4	8	7
Standard Error	2.34	2.54	1.53	1.61	1.72
P-value VS Placebo			<0.001	<0.001	<0.001
8.5 Hour Challenge					
N	29	28	28	28	29
Mean Percent Fall	25	20	9	14	12
Standard Error	2.20	3.08	2.12	2.57	2.15
P-value VS Placebo			<0.001	0.047	0.006

All salmeterol treatments were significantly better than placebo. Salmeterol MDI was significantly better than the 50mcg Diskus at the 8.5 Hour exercise challenge (p=0.020) and nearly better at the 0.5 Hour exercise challenge (p=0.077). No other comparisons among salmeterol treatments were significant.

The table below provides the cross-tabulations and p-values comparing the 50mcg Diskus and placebo, testing whether patients were protected against a 20% fall in FEV_1 or not.

0.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	13	0	13
	Failure	13	2	15
	Total	26	2	28

p=0.002, McNemar's Test

8.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	14	1	15
	Failure	8	5	13
	Total	22	6	28

p=0.039, McNemar's Test

The 50mcg diskus gave a significantly higher proportion of patients protected against a 20% fall in FEV_1 than placebo. At both evaluations the percent protected was > 84%. This analysis is not powerful enough to detect differences among active treatments.

3. Reviewer's comments

These analyses show that the 50mcg salmeterol diskus is better than placebo for protecting against exercise induced bronchospasm. The 50mcg diskus was not as effective numerically as the 50mcg MDI as indicated by the analysis on percent fall in FEV_1. The 100mcg diskus was numerically more effective than the 50mcg diskus in this study.

Although the sponsor did not adjust the p-values of diskus comparisons against placebo for the two diskus dose levels, these comparisons would be significant ($p<0.05$) using any of the commonly used multiple comparison procedures at the 0.5 Hour exercise challenge, but significant only for the 100mcg diskus if,

for example, either the Bonferroni or Dunnett's adjustments are used for the 8.5 Hour challenge. Because of the multiple testing for two exercise challenges, the need for Bonferroni or Dunnett's adjustment is somewhat problematic. [The 50mcg diskus showed significance (uncorrected for multiple comparisons) at the 0.05 level for both the 0.5Hour and 8.5Hour challenges.] In the reviewer's opinion it is not appropriate to adjust the comparison of the 50 mcg Diskus and 50mcg MDI for multiple comparisons since this is *a priori* a comparison of special interest.

II. Pediatric Studies

A. Study SLGA2003

1. Study Design and Method of Analysis

This was similar to Study SLGA2013 with the following exceptions: It was in pediatric patients, there was no single blind placebo period, the exercise challenges were at 0.5 hours, 5.5 hours, and 11.5 hours, and the treatments compared were placebo, 50mcg salmeterol diskus and 50mcg salmeterol rotodisk. Due to an oversight no pre-challenge FEV_1 assessment was done at the initial 0.5 Hour exercise challenge. The pre-dose FEV_1 was used as baseline for these comparisons.

The analyses of variance additionally included treatment by investigator effect in the model. The analyses were done on patients who had exercise challenges on all three treatments.

2. Results

Twenty-four patients were entered into this study. Patients 10102, 10106, and 10108 were not included in both the 5.5 Hour and 11.5 Hour challenges. Patient 50088 was not included in the 11.5 Hour challenge.

The table below provides the mean percent falls in FEV_1 and p-values compared to double-blind placebo at the three exercise challenges.

	Placebo	50mcg Diskus	50mcg Rotodisk
0.5 Hour Challenge			
N	24	24	24
Mean Percent Fall	13	2	1
Standard Error	3	3	3
P-value VS Placebo		0.002	<0.001
5.5 Hour Challenge			
N	21	21	21
Mean Percent Fall	13	6	6
Standard Error	2	1	1
P-value VS Placebo		0.017	0.036
11.5 Hour Challenge			
N	20	20	20
Mean Percent Fall	14	6	5
Standard Error	4	2	2
P-value VS Placebo		0.023	0.016

Both salmeterol treatments were significantly more effective than placebo at all exercise challenges. The sponsor calculated mean percent falls for children aged 4-8 years and 9-11 years and both salmeterol treatments were numerically more effective than placebo in each age categorization.

The table below provides the cross-tabulations and p-values comparing the 50mcg Diskus with placebo whether patients were protected against a 20% fall in FEV_1 or not.

0.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	19	1	20
	Failure	3	1	4
	Total	22	2	24

p=0.625, McNemar's Test

5.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	16	0	16
	Failure	5	3	8
	Total	21	3	24

p=0.063, McNemar's Test

11.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	14	2	16
	Failure	4	4	8
	Total	18	6	24

p=0.687, McNemar's Test

No significant difference from placebo was detected. Most patients did not experience a 20% fall on either drug. The results at the 0.5 Hour exercise challenge are affected by the failure to do a pre-exercise PFT.

3. Reviewer's Comments

The 50mcg salmeterol Diskus showed more efficacy than placebo for fall in FEV_1 at all three exercise challenges.

This reviewer does not know why the sponsor included a treatment by investigator term in the model in this study because in a crossover study, each patient should receive all treatments. Although the sponsor analyzed this study by including only patients who had exercise challenge values for all three treatments, this reviewer got similar results when he reanalyzed the study including all patients.

B. Study SLGA2014

1. Study Design and Method of Analysis

This study was similar to study SLGA2003, except that there were 4 treatments: 180mcg Albuterol, 25mcg salmeterol Diskus, 50mcg salmeterol Diskus and placebo and a pre-exercise PFT was taken before the 0.5 Hour exercise challenge.

2. Results

Twenty-six patients were enrolled into the study. One patient (9811) received only the 25mcg salmeterol diskus treatment. One patient (9804) received all treatments but withdrew before challenges while on placebo. Two patients did not perform the 5.5 Hour exercise challenge (patient 9804 on salmeterol 50mcg and patient 9806 on placebo) and three patients had no 11.5 Hour exercise challenge (9804 on albuterol,

9806 on placebo, and 9810 on salmeterol 25mcg) because their pre-exercise PFTs were too low. Another patient (9865) was excluded because there was no assessment of pre-exercise PFT at the 11.5 Hour exercise challenge while on albuterol, and, hence, the percent fall could not be accurately assessed.

The table below provides the mean percent falls in FEV_1 and p-values compared to double-blind placebo at the three exercise challenges.

	Placebo	180mcg Albuterol	25mcg Diskus	50mcg Diskus
0.5 Hour Challenge				
N	24	25	26	25
Mean Percent Fall	13	4	5	6
Standard Error	2.55	1.46	2.10	2.34
P-value VS Placebo		<0.001	0.003	0.002
5.5 Hour Challenge				
N	23	25	26	24
Mean Percent Fall	12	16	8	7
Standard Error	2.59	2.58	2.02	2.12
P-value VS Placebo		0.751	0.048	0.064
	Placebo	180mcg Albuterol	25mcg Diskus	50mcg Diskus
11.5 Hour Challenge				
N	23	23	25	25
Mean Percent Fall	14	15	7	7
Standard Error	2.35	3.08	1.67	3.06
P-value VS Placebo		0.622	0.003	0.002

Both salmeterol treatments showed significantly more efficacy than placebo at the 0.5Hour and 11.5 Hour exercise challenge. At the 5.5 Hour exercise challenge the 25mcg Diskus was more effective than placebo and the 50mcg Diskus was nearly effective. Both salmeterol doses were significantly more effective than albuterol at the 5.5 and 11.5 Hour exercise challenges. The 25mcg salmeterol diskus and the 50mcg salmeterol Diskus were comparable in efficacy. The sponsor calculated mean percent falls for children aged 4-8 years and 9-11 years, and both salmeterol treatments were numerically more effective than placebo in each age categorization. The 50mcg dose was numerically more effective than the 25mcg dose in the younger children, but the reverse was true for the older children. (A reason for this would be hard to explain other than the variability of PFT testing.)

The table below provides the cross-tabulations and p-values comparing the 50mcg Diskus with placebo whether patients were protected against a 20% fall in FEV_1 or not.

0.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	17	2	19
	Failure	5	0	5
	Total	22	2	24

p=0.453, McNemar's Test

5.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	17	1	18
	Failure	6	0	6
	Total	23	1	24

p=0.125, McNemar's Test

11.5 Hour Exercise Challenge

		Diskus		
		Success	Failure	Total
Placebo	Success	17	1	18
	Failure	6	0	6
	Total	23	1	24

p=0.125, McNemar's Test

No significant difference from placebo was detected. Most patients did not experience a 20% fall on either drug.

3. Reviewer's Comments

Although the 50mcg Diskus was only nearly significant (p=0.064) at the 5.5 Hour exercise challenge, it was significant at the 11.5 Hour exercise challenge. Both salmeterol diskus doses were significantly better than albuterol at the 5.5 Hour and 11.5 Hour exercise challenges. This study showed no advantage of 50mcg over 25mcg salmeterol.

III. Overall Conclusions

The 50mcg Diskus had a significantly lower percent fall in FEV_1 than placebo at the 0.5 Hour and 8.5 Hour exercise challenges in adult patients in Studies SLGA2013 and SLGA2017. The 50mcg salmeterol MDI was significantly better than the Diskus in these studies. The 50mcg Diskus had a significantly lower percent fall in FEV_1 in children ≥ 4 years of age in Studies SLGA2003 and SLGA 2017 than placebo. No advantage over a 25mcg dose was seen in study SLGA2014.

The sponsor has demonstrated adequate evidence of efficacy to include the prevention of exercise induced bronchospasm claim for adults and pediatric patients for Serevent 50mcg Diskus.

/S/

James R. Gebert, Ph. D.
Mathematical Statistician HFD-715

Concur: Dr. Wilson /S/ 7/20/98

Dr. Nevius /S/ 7/20/98

This review contains 8 pages of text.

cc:
Orig NDA 20-692/S-001
HFD-570
HFD-570/Dr. Meyer
HFD-570/Dr. Johnson
HFD570/Ms Jani
HFD-715/Div. File /Chron
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

APPEARS THIS WAY ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION
CLINICAL

NDA #: 20-692/S-002

AUG 3 1998

APPLICANT: Glaxo Wellcome Inc.

NAME OF DRUG: Serevent (salmeterol xinafoate) Diskus Inhalation Powder

INDICATION: Bronchodilator

DOCUMENTS REVIEWED: Volumes 17.1, 17.8-17.35, SAS datafiles dated September 24, 1997 and an unnumbered volume dated November 4, 1997.

This review pertains to two 12-week studies in children aged 4 years or greater with asthma. Study SLD-390 used the [redacted] device to give salmeterol powder rather than the diskus. The Agency agreed that this study could be used to evaluate the efficacy of salmeterol powder, even though the device was different.

The medical officer for this submission is S. Johnson Pharm. D., HFD-570, with whom this review was discussed.

I. Background

Serevent Diskus was approved for the treatment of Asthma in adults and adolescents age≥12 years on September 19, 1997. This submission extends the labeling to children aged 4 or greater.

In evaluating SAS datafiles supplied by the sponsor with the submission, it was discovered that the sponsor did not provide data for percent-predicted PEFR and FEV_1. The sponsor provided these variables in a November 4, 1997 submission.

II. Study SLD-390

A. Study Description and Method of Analyses

This was a double-blind, parallel group, multicenter study comparing salmeterol powder [redacted] 50mcg BID with placebo powder given by [redacted] BID in children 4-11 years of age. There was a 7-14 day run-in period followed by a 12-week treatment period. At screening the children (ages 6-11 years) had to have a PEFR and FEV_1 of 50-80% of predicted value. Children 6 to 11 years had to show an increase of at least 15% in FEV_1 over baseline values within 30 minutes following the inhalation of 2 puffs (180mcg) of Ventolin MDI during the screening period.

Patients were instructed to take their medication at 6-9AM and 6-9PM. Patients were allowed to remain on inhaled corticosteroids or Intal, but had to discontinue theophylline products. Patients were reminded

not to take the morning dose of study medication at home on the morning of their Day 1, and Treatment Weeks 4, 8, and 12 visits. Serial pulmonary assessments were only done at Day 1 and Week 12.

Patients were given a supply of Ventolin MDI for use as "back-up" medication. When need arose, they were directed to inhale 1-2 puffs of Ventolin MDI and record this use on the diary card. Patients were not to exceed 2 puffs every 4-6 hours per day.

Duplicate baseline values were obtained at 30 minutes pre-dose and immediately pre-dose (time 0). Following administration of the initial dose of study medication, serial measurements were conducted at the following times post dose: 15 and 30 minutes, and 1, 2,...,12 hours. For patients 4 and 5 years of age, only PEFRs using ( ) assessments were done. The higher of the duplicate assessments was used. For patients 6 to 11 years of age, both duplicate PEFRs using a ( ) and duplicate spirometry measurements were taken. The higher of the two PEFRs and the higher of the two spirometry assessments was used.

The sponsor carried forward the last pre-intervention assessment value if the patient did not complete the 12-hour serial PFTs due to symptoms or functional deterioration.

The sponsor's sample size discussion stated that a sample size of 80 completed patients per treatment (approximately 65 patients aged 6-11 years) was calculated to provide >80% power of detecting a difference in FEV_1 of 0.15 liters between treatment groups (significance level of 0.05 and standard deviation of 0.30.)

At a pre-NDA meeting on August 27, 1996, it was agreed that percent-predicted FEV_1 and PEFR serial values were appropriate primary efficacy variables to compensate for size differences in the pediatric population. Since all pediatric patients are included in the analysis, this review will mainly discuss percent-predicted PEFR using the ( )

The sponsor analyzed percent-predicted PEFR at the individual assessment times by an analysis of variance with factors for treatment, investigators and treatment-by-investigator interaction. The sponsor also submitted a repeated measures analysis which will not be discussed here. The sponsor did not specify a primary analysis in the protocol.

B. Results

There were 207 pediatric patients (105 on placebo and 102 on salmeterol) entered into the double-blind phase of this study. Twenty of these patients (10 per treatment group) withdrew without completing the trial. Reasons for withdrawal were similar between the two groups. The treatment groups were comparable in demographic variables and baseline pulmonary function.

Table 1 contains the treatment means and p-values comparing treatments for percent-predicted PEFR at the assessment times at Day 1 and Week 12. Two patients, subjects 106 and 257, in the salmeterol group did not have serial PEFRs at Week 12 but did have -0.5 hour and 0 assessments. No carry forward values were used for these patients. The data from Table 1, also, excludes salmeterol subject 229 who did not have a baseline percent-predicted PEFR. All on-treatment assessments showed a significant

difference favoring Salmeterol. Table 1 also shows that there was a large placebo response seen at Week 12. The same factors causing the placebo response might, also, be present in the salmeterol group.

Although other variables tended to be significant at week 12, even in the presence of this placebo effect, there were some analyses that did not show significance at the end of the dosing interval. In particular, the analyses of mean changes in PEFR and FEV_1 were not significant at hours 10, 11 and 12, but the corresponding analyses in percent-predicted FEV_1 and PEFR were significant at these assessment times. Since percent-predicted PEFR is the preferred analysis, end-of-dosing interval efficacy has been established for salmeterol powder.

The sponsor provided means for percent-predicted PEFR for patients aged 4-8 years and for patients aged 9-11 years. Efficacy was apparent in both subgroups.

C. Reviewer's Comments

This study showed efficacy of salmeterol powder in pediatric patients. The analyses of percent-predicted FEV_1 and PEFR showed efficacy at the end of the dosing interval, indicating that salmeterol is a BID drug in pediatric patients. Inclusion of the one subject, subject 229, who did not have a baseline percent-predicted PEFR but had values at other assessment times had negligible effect on the p-values in Table 1 in this reviewer's analyses.

III. Study SLGA3014

A. Study Description and Method of Analyses

This study was similar to Study SLD-390 with the following important exceptions:
Patients had to have both PEFR and FEV_1 within 45-75% of predicted normal. Some 4 and 5 year olds were qualified for FEV_1 testing. On day 1 and week 12, no pulmonary function tests were done at hours 5, 7, 9 and 11. An analysis of covariance with baseline as covariate was used to analysis the response variables. The main difference was in treatments tested. The four treatment groups were 50mcg salmeterol diskus BID and placebo rotacaps given by [redacted] QID, 25 mcg salmeterol diskus BID and placebo rotacaps given by [redacted] QID, placebo diskus BID and albuterol rotacaps given by [redacted] QID, and placebo diskus BID and placebo rotacaps given by [redacted] QID.

B. Results

A total of 449 patients (110 placebo, 115 albuterol, 115 salmeterol 25mcg, 109 salmeterol 50mcg) were enrolled into this study. Fifty-nine patients (15 placebo, 10 albuterol, 12 salmeterol 25mcg, and 22 salmeterol 50mcg) withdrew without completing the study.

The treatment groups were comparable at baseline in demographic and baseline PFT assessments.

Seven patients were not included in the Day 1 ITT analysis. Four of these were because they had no baseline to permit the covariate analysis. The other three were not included because they did not have a 15-minute assessment, which did not allow a LOCF value to be calculated.

Tables 2 and 3 contain the least squares means of percent-predicted PEFR at the various assessment times at day 1 and week 12, respectively. Again a placebo effect may to be present for all treatments at week 12. Both salmeterol doses were significantly better than placebo at all serial assessments on Day 1 and most serial assessments at Week 12. The predose assessments at Week 12 were not significantly different from placebo.

The sponsor provided graphs of the mean changes from baseline in percent-predicted for patients 4-8 and patients 9-12 and these graphs indicted that both salmeterol treatments were effective in both age subgroups.

C. Reviewer's Comments

This study showed efficacy of salmeterol powder in pediatric patients. The analyses of percent-predicted PEFR, which is the primary efficacy variable, showed efficacy at the end of the dosing interval (12 hours) indicating that salmeterol is a BID drug in pediatric patients. No effectiveness was seen at the predose assessments at Week 12. This failure to show efficacy at predose at Week 12 is unusual in adequately sized salmeterol trials.

The sponsor did not adjust for multiple comparisons (i.e., two doses of salmeterol) in this study. Adequate evidence of efficacy would be demonstrated with any commonly used multiple comparison procedure.

IV. Overall Comments

Salmeterol 50mcg powder given by diskus or diskhaler showed efficacy for percent-predicted PEFR in Studies SLD-390 and SLGA3014 at all assessment times except at 0.25 hours at Week 12 in Study SLGA3014, indicating that salmeterol powder is effective in BID dosing in pediatric patients.

The label includes a statement with respect to these studies that says the weighted average of postdose percent-predicted peak expiratory flow rate over twelve hours improved 19.3% (51 L/min), and the weighted average of postdose FEV_1 over 12 hours improved 12.2% (0.25L) in pediatric asthma patients treated with salmeterol powder for 12 weeks. Since the weights are not the more common AUC weighting, the reader of the label would not know what the weighting was and, as such, wouldn't understand what a weighted average was referring to. This reviewer recommends that a more familiar AUC should be used instead, with some averaging to a per hour basis if the medical division feels that such information is important to provide in the label.

/S/

James R. Gebert, Ph.D.
Mathematical Statistician

Concur: Dr. Wilson /S/ 7/22/98

Dr. Nevius /S/ 8/31/98

Table 1
Mean Percent-Predicted Serial PEFR means (LOCF)
Study SLD-390

	Day 1			Week 12		
Time (hrs)	Placebo (N=105)	Serevent (N=101)[a]	p-value	Placebo (N=95)[b]	Serevent (N=91)[c]	p-value
Baseline	85.0	85.2	0.803	85.5	86.6	0.364
-0.5				92.6	99.0	0.015
0				93.9	98.9	0.031
0.25	88.5	96.7	<0.001	95.7	102.9	0.009
0.5	89.9	99.8	<0.001	97.2	105.3	0.005
1	92.1	102	<0.001	99.2	106.9	0.005
2	93.0	105	<0.001	101.7	107.3	0.038
3	93.0	106	<0.001	101.4	109.7	0.007
4	93.5	105	<0.001	100.8	109.6	0.004
5	94.0	105	<0.001	99.4	107.9	0.005
6	92.0	104	<0.001	100.2	107.6	0.026
7	91.6	104	<0.001	98.6	107.0	0.005
8	91.5	103	<0.001	98.6	106.5	0.006
9	92.4	104	<0.001	98.4	105.3	0.012
10	90.6	102	<0.001	98.2	104.7	0.035
11	91.0	102	<0.001	97.4	104.4	0.018
12	90.5	101	<0.001	97.7	104.2	0.034

P- values are from an Anova with factors treatments, investigators and their interaction.
[a] N=100 for 0.25Hrs.
[b] N=93 for 0.25Hrs to 12 hrs.
[c] N=90 for -0.5hrs and 0.0 hrs.
Patient 229 not included in this table because there was no baseline PEFR data.

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ON ORIGINAL

Table 2
Mean Percent-Predicted Serial PEFR means (LOCF)
Study SLGA3014
Day 1

Time (hrs)	Placebo (N=108)	25mcg Diskus (N=107)	50mcg Diskus (N=113)	Albuterol (N=114)
Baseline	80.2	78.0	81.3	79.4
0.25	85.4	87.3*	92.2***	92.9***
0.5	84.9	90.8***	96.4***	96.1***
1	87.2	94.1***	99.7***	96.5***
2	88.6	97.2***	102***	94.2**
3	89.3	97.8***	102***	92.8*
4	89.9	98.0***	103***	91.5
6	88.2	95.6***	102***	88.8
8	88.2	95.1***	98.7***	96.9***
10	86.9	93.4***	98.1***	92.9***
12	87.8	93.5***	97.7***	90.8

Table 3
Mean Percent-Predicted Serial PEFR means(LOCF)
Study SLGA3014
Week 12

Time (hrs)	Placebo (N=96)	25mcg Diskus (N=103)	50mcg Diskus (N=86)	Albuterol (N=104)
Baseline	80.5	78.4	80.6	79.2
-0.5	89.5	87.4	88.8	86.3
0	89.1	88.9	91.1	87.3
0.25	91.7	93.9	95.2	101***
0.5	92.7	96.0	98.5*	102***
1	94.0	97.9*	99.6*	103***
2	95.1	101 **	102**	100**
3	94.4	102***	103 ***	99.0*
4	94.8	101***	102**	96.9
6	92.6	99.0***	102***	94.4
8	93.4	97.7*	99.3*	101***
10	92.9	95.9	98.5*	96.8
12	91.8	95.9*	98.1*	94.5

* P<0.05 compared to placebo.
** P<0.01 compared to placebo.
*** P<0.001 compared to placebo.