CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20692

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

Date: SEP 5 1997

NDA No.	20-692
Applicant:	Glaxo Wellcome Inc.
Name of Drug:	Serevent® (salmeterol xinafoate) Diskus® Inhalation Powder
Statistical Reviewer:	Moh-Jee Ng (HFD-715)
Chemist:	Dr. Richard T. Lostritto (HFD-570)
Date received by reviewer:	August 26, 1997
Data received by reviewer:	August 26, 1997

I. Introduction

In this amendment, the sponsor submitted the updated stability data and proposed a 24-month expiration date based on data of 24-months for Serevent Diskus 50μg Inhalation Powder stored at 30°C/60% RH.

II. Sponsor's Design and Analyses

The sponsor submitted the results of the stability study for Serevent Diskus 50μg Inhalation Powder up to 24 months stored at 30°C/60%RH. The sponsor performed the statistical analysis on three batches (SP94/035, SP94/056 and SP94/062). Evaluations were performed for Salmeterol content per blister, Salmeterol content of the emitted dose, content of GR87890X by The evaluation of particle size distribution by was performed for each of the following variables: mean sum of throat, preseparator and stage 0; fine particle mass; sum of stages 3 and 4; and sum of stage 6, 7 and filter. The test time points were 0, 6, 10 12 and 24 months.

The data were provided by the sponsor on a 3.5 floppy diskette. The statistical method used by the sponsor is in accordance with the FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs and Biologics" (February 1987). The sponsor used the FDA program to perform the statistical analyses.

II Reviewer's Results and Comments

Table 1 below summarizes the results obtained from the 3 batches stored at 30°C/60%RH. The results are presented for each variable.

Table 1
Summary of Results of the Reviewer's analyses

Attribute	Specification	Batch	Model Selection	Study Fitted Line	Expiry Date
Salmeterol Content per blister		SP94/035	Separate	Y=105.8277-0.3053X	38
		SP94/056	Intercepts	Y=103.1152-0.3053X	31
		SP94/062	Common Slope	Y=105.4277-0.3053X	37
Salmeterol Content of the Emitted dose		SP94/035	Separate	Y=47.4662+0.0271X	84
		SP94/056	Intercepts	Y=46.9302+0.0271X	84
		SP94/062	Common Slope	Y=47.9062+0.0271X	84
Particle size distribution by					
. Mean Sum of Throat, Preseparator and Stage 0 (TPO)		SP94/035	Separate	Y=36.1449-0.0027X	67
		SP94/056	Intercepts	Y=35.3082+0.0134X	54
		SP94/062	Separate Slopes	Y=35.8634-0.1002X	19
. Fine particle mass (Sum of Stages 1 to 5)		SP94/035	Separate	Y=11.3200-0.0371X	29
		SP94/056	Intercepts	Y=10.3431-0.0371X	22
		SP94/062	Common Slope	Y=11.2124-0.0371X	37
. Sum of Stages 3 and 4		SP94/035	Separate	Y=6.1569-0.0408X	37
		SP94/056	Intercepts	Y=5.4799-0.0408X	25
		SP94/062	Common Slope	Y=5.9261-0.0408X	33
. Sum of Stage 6,7 and filter (Mass < 1 μm)		SP94/035	Separate	Y=0.1745+0.0157X	34
		SP94/056	Intercepts	Y=0.4843-0.0048X	84
		SP94/062	Separate Slopes	Y=0.6257-0.0109X	84
Content of GR97980X		All batches	Common Intercept Common Slope	Y=0.0610+0.0284X	27
Total impurity content		SP94/035	Separate	Y=0.1035+0.0341X	28
		SP94/056	Intercepts	Y=0.0171+0.0424X	25
		SP94/062	Separate Slopes	Y=0.0935+0.0349X	26

Salmeterol Content per blister

The p-values of statistical tests for the selection of degradation model are presented in Table 2. Based on these p-values, a model with separate intercepts and a common slope was selected. The reviewer used the 2-sided confidence limits for the mean strength of the batch at each storage time because the sponsor specified both the lower and the upper specification limits of 90 and 110 percent of label claim. The estimated expiration dates are 38, 31 and 37 months rather than 40, 33 ad 39 months obtained by the sponsor using a 1-sided lower specification limit for the three individual batches. (see appendix, Table G5.1)

Based on the stability data of this variable, the reviewer's analysis results support the sponsor's proposed 24-month expiration date.

Salmeterol Content of the Emitted Dose

The p-values of statistical tests for the selection of degradation model are presented in Table 3. Based on these p-values, a model with separate intercepts and a common slope was selected.

Based on the stability data of this variable, the reviewer's analysis results support the sponsor's proposed 24-month expiration date.

Sum Throat, Preseparator and Stage 0 by

The p-values of statistical tests for the selection of degradation model are presented in Table 4. Based on these p-values, a model with separate intercepts and separate slopes was selected. The reviewer used the 2-sided confidence limits for the mean strength of the batch at each storage time because the sponsor specified both the lower and the upper specification limits of 32 and 40 µg/blister. The estimated expiration dates are 67, 54 and 19 months rather than 80, 69 ad 21 months obtained by the sponsor using a 1-sided lower specification limit for the three individual batches. (see appendix, Table G5.1)

The sponsor explained that the initial values of TPO data for Batch SP94/062 were more variable than for the other two batches and were "unduly affecting the slope by pulling the initials higher and increasing the steepness of the slope". The sponsor then reanalysed the data, excluding the initial value for batch SP94/062 and showed "no significant slope conforming to a straight line comparable to the other two batches". The shelf life had been extended to 84 months. Therefore, the sponsor proposed a 24-month expiration date for TPO.

The reviewer's could not agree with the sponsor reanalysis by exclusion the initial values for batch SP94/062. Therefore, the reviewer analysis results of the variable TPO do not support the sponsor's proposed 24- month expiration date. The estimated degradation line along with the lower and the upper 95% confidence bounds are presented in Figures 1, 2 and 3.

Fine Particle Mass (Sum of Stages 1 to 5)

The p-values of statistical tests for the selection of degradation model are presented in Table 5. Based on these p-values a model with separate intercepts and a common slope was selected. The reviewer used the 2-sided confidence limits for the mean strength of the batch at each storage time because the sponsor specified both the lower and the upper specification limits of 9 and 14 µg/blister. The estimated expiration dates are 29, 22 and 37 months rather than 42, 24 ad 40 months obtained by the sponsor using a 1-sided lower specification limit. (see appendix, Table G5.1)

Therefore, the reviewer analysis results of this variable do not support the sponsor's proposed 24-month expiration date. The estimated degradation line along with the lower and the upper 95% confidence bounds are presented in Figures 4, 5 and 6.

Sum of Stages 3 and 4 by

The p-values of statistical tests for the selection of degradation model are presented in Table 6. Based on these p-values, a model with separate intercepts and a common slope was selected.

The reviewer's analysis results of this variable support the sponsor's proposed 24-month expiration date.

Sum of Stages 6, 7 and Filter by

The p-values of statistical tests for the selection of degradation model are presented in Table 7. Based on these p-values, a model with separate intercepts and separate slopes was selected.

The reviewer's analysis results of this variable support the sponsor's proposed 24-month expiration date.

Content of GR97980X

The p-values of statistical tests for the selection of degradation model are presented in Table 8. Based on these p-values, a model with common intercept and a common slope was selected.

The reviewer's analysis results of this variable support the sponsor's proposed 24-month expiration date.

Total Impurity Content

The p-values of statistical tests for the selection of degradation model are presented in Table 9. Based on these p-values, a model with separate intercepts and separate slopes was selected.

The reviewer's analysis results of this variable support the sponsor's proposed 24-month expiration date.

IV Summary

The sponsor requested an expiration date of 24 months for Serevent Diskus 50μg Inhalation Powder stored at 30°C/60%. The stability data were collected up to 24 months. However, the data of sum throat, preseparator and stage 0 and fine particle mass by Casscade Impator supported an estimated expiration dating period of less than 24 months. Therefore, the overall stability study data do not support the sponsor proposed 24-month expiration date.

Also, the sponsor did not follow the FDA recommended test schedule in the stability study. Instead of testing the product every three months during the first year and every six months the second year, the sponsor tested at 0, 6, 10, 12 and 24 months only. With only five data points used in the analysis, the estimated expiration dating period may not be as precise as if there were seven data points.

Moh-Jee Ng

Moh Jee Ng

Operation Research Analyst

Karl K. Lin 9/5/97

Concur: Dr. Lin

cc:
Orig. NDA 20-692
HFD-570/ Division Files
HFD-570/ Dr. Talarico
HFD-570/ Dr. Lostritto
HFD-715/ Division File, Chron
HFD-715/ Dr. Lin, Dr. Wilson, Ms. Ng

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Table 2
Salmeterol Content per Blister

SOURCE	SS	DF	MS	F	P
A	73.58	4	18.40	1.83029	0.14097
B	68.62	2	34.31	3.41337	0.04231
C	4.97	2	2.48	0.24721	0.78210
D	422.14	42	10.05		
E	511460.70	6	85243.45		

Table 3
Salmeterol Content of the Emitted Dose

SOURCE	SS	DF	MS	F	P
A	41.79	4	10.45	1.56747	0.18614
B	23.89	2	11.95	1.79228	0.17028
C	17.90	2	8.95	1.34266	0.26440
D	959.77	144	6.67		
E	340800.62	6	56800.10		

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ON ORIGINAL

Table 4
Sum Throat, Preseparator and Stage 0 by (

SOURCE	SS	DF	MS	F	P
A	14.25	4	3.56	2.08034	0.10577
B	7.60	2	3.80	2.21804	0.12479
C	6.65	2	3.33	1.94264	0.15937
D	56.51	33	1.71		
E	49258.69	6	8209.78		

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ON ORIGINAL

Figure 1

Figure 1

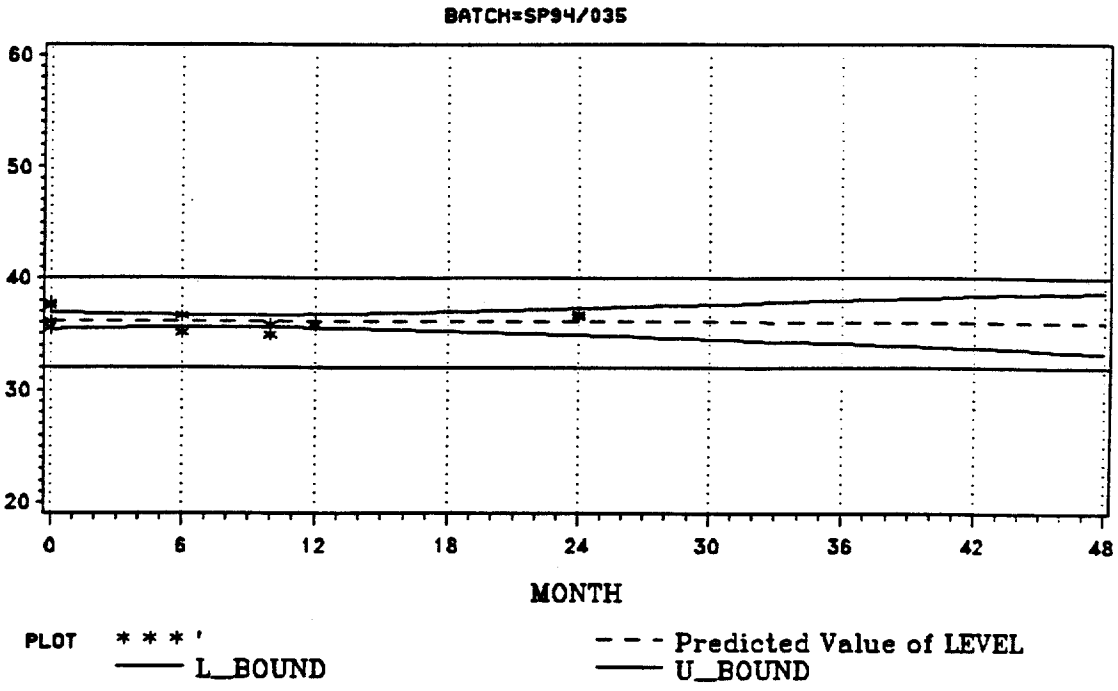

Figure 2

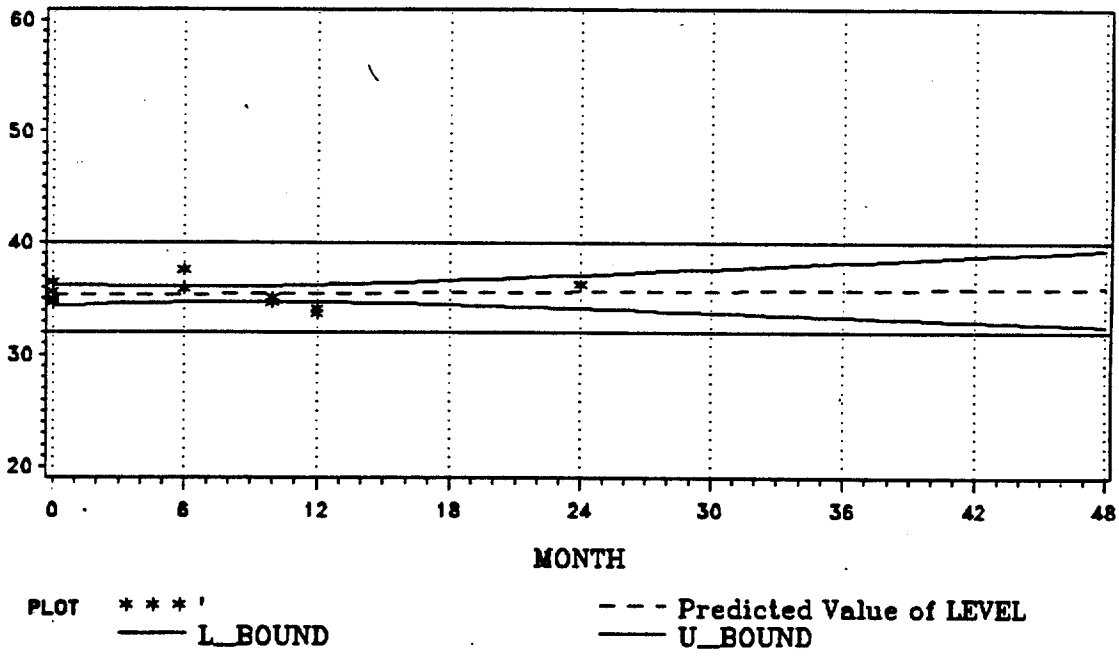

Figure 3

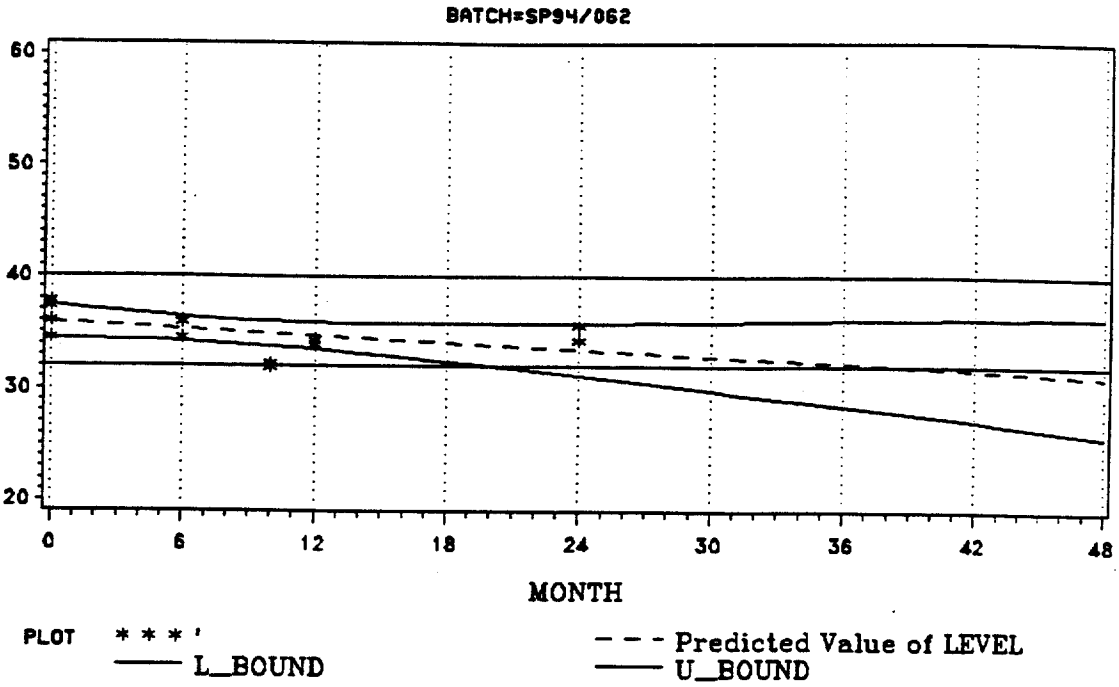

Table 5
Fine particle mass by

SOURCE	SS	DF	MS	F	P
A	7.47	4	1.867	4.56849	0.00478
B	7.46	2	3.730	9.12703	0.00070
C	0.01	2	0.004	0.00994	0.99012
D	13.49	33	0.409		
E	4444.17	6	740.696		

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Figure 4

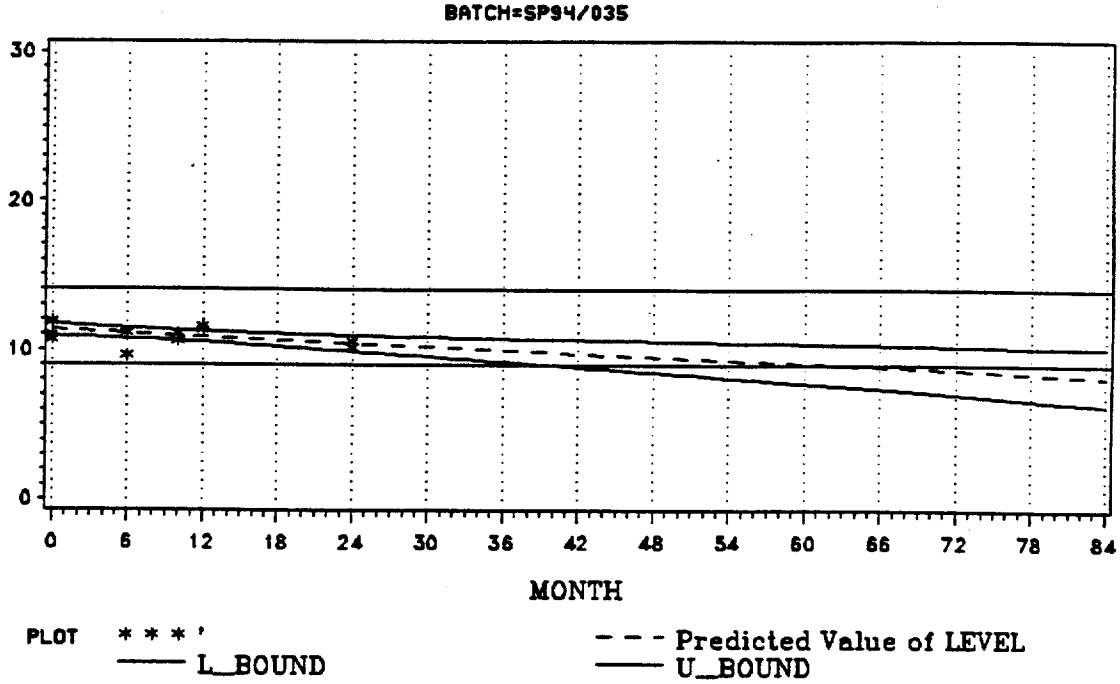

Figure 5

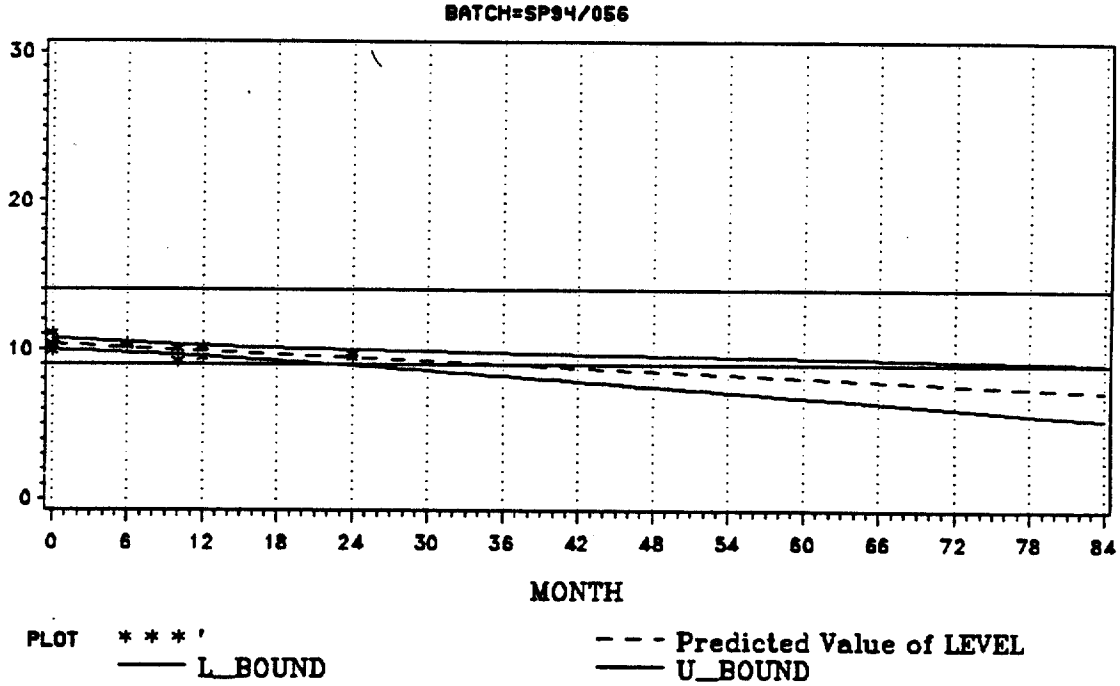

Figure 6

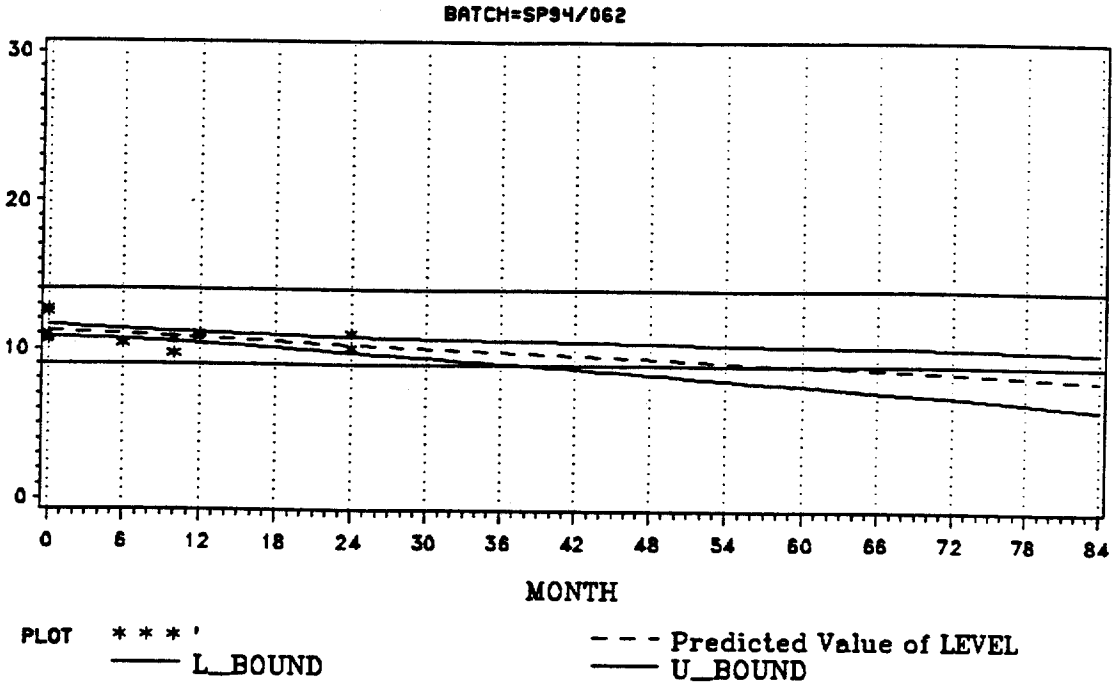

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Table 6
Sum of Stages 3 and 4 by

SOURCE	SS	DF	MS	F	P
A	3.46	4	0.866	2.33994	0.07548
B	3.08	2	1.539	4.16068	0.02447
C	0.38	2	0.192	0.51919	0.59978
D	12.21	33	0.370		
E	1199.73	6	199.955		

Table 7
Sum of Stages 6, 7 and Filter by

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SOURCE	SS	DF	MS	F	P
A	0.71708	4	0.17927	4.47532	0.005335
B	0.37590	2	0.18795	4.69198	0.016094
C	0.34118	2	0.17059	4.25866	0.022631
D	1.32190	33	0.04006		
E	7.86810	6	1.31135		

Table 8
Content of GR97980X

Test of Batch Poolability (p-value cutpoint used: 0.25)
Variable Analyzed: 30/60
14:36 Wednesday, September 3, 1997

SOURCE	SS	DF	MS	F	P
A	0.0004	4	0.0001	0.0355	0.9971
B	0.0002	2	0.0001	0.0283	0.9722
C	0.0002	2	0.0001	0.0428	0.9583
RESIDUAL	0.0254	9	0.0028		

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
B: Ho: com. intercept com. slope, Ha: sep. intercept com. slope
A: Ho: com. intercept com. slope, Ha: sep. intercept sep. slope
Source: C:\data\Poolable.sd2
Analysis of Stability

Table 9
Total Impurity Content

Test of Batch Poolability (p-value cutpoint used: 0.25)
Variable Analyzed: 30/60
14:47 Wednesday, September 3, 1997

SOURCE	SS	DF	MS	F	P
A	0.0133	4	0.0033	0.8458	0.5303
B	0.0000	2	0.0000	0.0017	0.9983
C	0.0133	2	0.0066	1.6898	0.2382
RESIDUAL	0.0354	9	0.0039		

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
B: Ho: com. intercept com. slope, Ha: sep. intercept com. slope
A: Ho: com. intercept com. slope, Ha: sep. intercept sep. slope
Source: C:\data\Poolable.sd2
Analysis of Stability

Table G5.1. Shelf-life Predictions (months) at 30°C/60%RH from the Statistical Evaluation of Analytical Data for Serevent Diskus 50μg

Attribute	Storage	Expiry		
		SP94/035	SP94/056	SP94/062
Content per blister	30°C/60%RH	40	33	39
Emitted dose	30°C/60%RH	84	84	84
Particle size distribution by • (IPO) • Fine particle mass • Stages 3 and 4 • Mass <1μm	30°C/60%RH	 80 42 37 34	 69 24 25 84	 21 40 33 84
GR97980X content	30°C/60%RH	27*	27*	27*
Total impurity content	30°C/60%RH	28	25	26

* Pooled

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ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-692 MAR 28 1997

APPLICANT: Glaxo Wellcome Inc.

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

INDICATION: Bronchodilator

DOCUMENTS REVIEWED: Volumes 1.1, 1.30, 1.45, and 1.65 dated June 18,1996 and volume 9.1 dated November 21, 1996.

This review pertains to two parallel group studies comparing salmeterol Diskhaler, albuterol and placebo in patients with reversible obstructive pulmonary disease (ROPD) and one four week study comparing the serevent given by Diskus with serevent given by Diskhaler and placebo. The last study can be considered a bridging study.

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

I. BACKGROUND

Salmeterol xinafoate (salmeterol) is a long-acting B_2-adrenoceptor agonist bronchodilator. The Metered Dose Inhaler was approved February 4, 1994.

This review will focus on the evaluable patient analyses rather than intent-to-treat analysis because salmeterol is compared with both placebo and an active control. The evaluable patient population is the more meaningful population to compare drugs in active controlled studies because this analysis provides better estimates of treatment effects and treatment differences in the patient population specified by the protocol. The p-values of the intent-to-treat analyses are similar to those of the evaluable patient analyses.

During a quality check of the data files, this reviewer noticed problems with the data files for PFTs with no carry forward data. An inspection of the analysis of PFTS with no carry forward data showed that these analyses were incorrect for Weeks 4, 8 and 12. This reviewer called the sponsor's statistician to report the errors. The sponsor provided new data files and PFT analyses without the carry forward values in their November 21,1996 submission.

II. U.S. DISKHALER STUDIES IN ROPD

A. STUDY DESCRIPTION AND METHOD OF ANALYSES

These were multi-center, double-blind, parallel group 12-week studies comparing salmeterol 50 mcg bid given by diskhaler versus albuterol 180 mcg q.i.d. and placebo q.i.d. in patients with reversible obstructive airways disease. The table below gives the dosing schedule to blind the study:

			Four Doses Per Day (number of puffs per dose)			
Treatment	**Diskhaler**	**Canister**	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**
salmeterol 50 mcg bid	(50 mcg/ puff)		1	0	0	1
		A (Placebo)	2	0	0	2
		B (placebo)	0	2	2	0
albuterol 180 mcg q.i.d.	(Placebo)		1	0	0	1
		A(90 mcg/puff)	2	0	0	2
		B(90 mcg/puff)	0	2	2	0
Placebo q.i.d.	(Placebo)		1	0	0	1
		A (placebo)	2	0	0	2
		B (placebo)	0	2	2	0
Example times of q.i.d. doses:			6 AM	11 AM	4 PM	9 PM

Ventolin (albuterol) metered-dose inhalers were supplied for use as back-up medication to be used on an as needed basis (PRN). [These studies were similar to the phase 3 studies conducted for salmeterol MDI (SLG-311 and SLG-312). The main difference was that in the salmeterol MDI studies, salmeterol was given at dose 3.]

There were nine clinic visits: screening visit, seven treatment period visits (Day 1, Weeks 2, 4, 6, 8, 10 and 12) and one post-study visit (approximately 1 week later).

At Day 1, and Weeks 4, 8, 12 serial spirometric pulmonary function tests were done at 30 minutes predose and time 0 (immediately before the first dose of test drug), and at hours 0.25, 0.5, 1, 2, 3, 4, 5, 6 (prior to the second daily dose of study drug), and hours 7, 8, 9, 10, 11 and 12 (prior to the third daily dose of

study drug). Triplicate maneuvers were done. The maneuver with the highest sum of FEV_1 and FVC was chosen as the recorded PFT values.

Patients had to be ≥ 12 years of age and be current nonsmokers. They had to be have a history of asthma of at least 6-months duration that required daily pharmacotherapy. Their baseline FEV_1 had to be within 50-80% of predicted normal with reversibility in FEV_1 of at least 15% within 30 minutes after 2 puffs of albuterol (180 mcg) [Ventolin Inhalation Aerosol].

Patients received at each clinic visit daily diary cards where they recorded their peak flow readings, Ventolin usage, nighttime awakenings due to asthma and daytime symptom score ratings.

Patients recorded their peak expiratory flow rates (PEFR) in the morning and evening of each day during the study. The morning determination was to be taken before the patient took the first dose of study drug on that day and after getting out of bed. The evening determination was to be taken before taking the last dose of study drug for the day.

Patients recorded daily at bedtime a self-rating for each of the following four symptoms: chest tightness, shortness of breath, wheezing and coughing. The assessment was to be made over the whole course of the day. Patients rated themselves on a 6-point scale with 0 being no symptoms to 5 being so severe that they could not go to work/school/or do other normal daily activities.

The patient recorded daily the number of times that they awoke last night due to asthma symptoms. This number included premature early morning awakening. They also recorded at bedtime the number of puffs of Ventolin used since last night at bedtime. They also recorded whether they took any Ventolin within the last four hours before their AM and PM PEFR measurements.

At the screening visit and at on-treatment visits (Day 1, Weeks 4, 8, and 12) the physician gave a global rating of patient symptoms using nearly the same 6-point scale that the patient used to record his individual daily symptoms. [The scale was modified using the word symptoms rather than reflecting only an individual symptom.]

The sponsor's primary analysis of PFT measurements was a repeated measures analysis of variance which included terms for treatment, investigator and the treatment-by-investigator interaction. The dependent variables included the predose PFT baseline and the 14 postdose changes-from-baseline variables at Day 1, and the 16 changes-from-baseline variables at treatment Weeks 4, 8 and 12. [In each case changes-from-baseline were calculated from Day 1 baseline because the salmeterol FEV_1 values taken 30 minutes before first dose of the day and 0 minute FEV_1 values at later clinic visits were elevated from the Day 1 baseline level.]

At some serial PFT visits, patients were unable to complete the 12-hour evaluations due to increased asthma symptoms that required additional asthma medication. Under these circumstances, the last pre-intervention PFT values were carried-forward for the remainder of the 12-hour schedule before analysis. Occasionally, a set of PFTs were missing for reasons other than increased asthma symptoms. In this case the previous value was carried forward for that PFT. [This latter assignment method was different from the Serevent MDI submission where interpolation was used. Since there were very few such missing PFT values, assignment method would have little impact on the study results.]

The sponsor analyzed both the intent-to-treat population and evaluable population (called by the sponsor "the efficacy population"). The evaluable population included patients from the intent-to-treat population who participated within the constraints of the study protocol.

Morning (AM) PEFR and evening (PM) PEFR were tested using an analysis of Variance F-test on change from the pretreatment period. The pretreatment baseline for each patient was defined as the average of the seven days immediately prior to randomization. Data were summarized and tested for the three 4-week periods (Weeks 1-4, 5-8, and 9-12), and for the entire 12-week treatment period (Weeks 1-12). Only the Weeks 1-12 analysis will be discussed in this review because the other assessment periods lead to similar conclusions.

In addition to the repeated measures analyses of PFT changes from baseline, the sponsor analyzed the serial PFT measures (changes from Day 1 baseline) individually using an analysis of variance with factors treatments, investigator and treatment-by-investigator interaction. PEFR measurements (AM and PM) were analyzed similarly. Patients who had missing data for more than one-half of the period they were treated with study drug were excluded from the efficacy analyses. Although this was not stated in the protocol, it was the method used in the original Serevent MDI submission.

The sponsor analyzed back-up Ventolin usage, percent of nights with no awakenings, patient-rated asthma symptoms using a van Elteren test (Cochran-Mantel-Haenszel test with scores = Modridit in the SAS procedure FREQ) to control for investigators. These analyses were done for averages of Weeks 1-4, Weeks 5-8, Weeks 9-12 and overall Weeks 1-12. [Only the overall Weeks 1-12 analyses will be discussed in this review.]

Pairwise comparisons were calculated using only data from the two treatments tested. These comparisons were not adjusted for multiple comparisons. [This is appropriate as each comparison was, a priori, of interest.]

B. STUDY SLD-311

1. RESULTS

There were 239 patients (79 placebo, 80 salmeterol, 80 albuterol) who entered this 8 center trial. There were 19 patients (5 placebo, 10 salmeterol and 4 albuterol) who withdrew from the study without completing 12 weeks of treatment. There were 9 withdrawals (2 placebo, 6 salmeterol, and 1 albuterol) for an adverse event. However, 4 of these (1 placebo and 3 salmeterol) were for an asthma exacerbation. The evaluable patient analyses included 235 of the 239 patients. Visit data was excluded for an additional 19 patients.

The treatment groups were comparable at baseline in demographic variables, mean symptom scores, mean AM and PM PEFRs, mean daily puffs of back-up Ventolin and percent of nights with no awakenings.

Sponsor's Table 19 (Study SLD-311) presents the results of the p-values comparing treatments for changes from Day 1 baseline for FEV_1 for the evaluable patient population. Significant differences between placebo and salmeterol were seen in the repeated measures analysis at all 4 clinic visits and in all serial time points at these clinic visits.

The repeated measures comparison of salmeterol and albuterol was significant at Weeks 4, 8, and 12 ($P < 0.006$ for all three weeks). Significant differences in changes from Day 1 baseline were observed when the effects of albuterol should be wearing off (at the end of its dosing interval). These significant differences favoring salmeterol over albuterol were at hours 3, 4, 5, 6, 11, 12 on Day 1; at -0.5 hours, 0.0 hours and hours 2, 3, 4, 5, 6, 9, 10, 11, 12 at Week 4; at hours -0.5 hours, 0.0 hours, 2, 3, 4, 5, 6, 10, 11, and 12 at Week 8; and at -0.5 hours, 0.0 hours, and hours 2, 3, 4, 5, 6, 10, 11, and 12 at Week 12.

Significant differences favoring albuterol over salmeterol were seen at 0.25 hours, 0.5 hours and hours 1 and 7 on Day 1 indicative of a shorter onset of effect for albuterol than salmeterol. These assessment times did not show efficacy of albuterol over salmeterol at Weeks 4, 8, and 12 because the effects of the last dose of salmeterol (taken at bedtime) had not worn off at these assessment times.

The -0.5 hour and 0 hour (predose) changes from Day 1 baseline at weeks 4, 8, 12 were between .30 - .36 liters for salmeterol. These differences were significantly different from 0 and significantly different from the -0.06 - .11 liters level observed for placebo and albuterol. This is indicative of salmeterol being long lasting and why the sponsor chose to analyze changes from Day 1 baseline

rather than changes from test day baseline.

The results of the analyses of changes from Day 1 baseline for FEF 25-75% and FVC (not presented here) were essentially similar to those of changes in FEV_1. Similar results to the evaluable patient analyses were also observed in the intent-to-treat population.

Table 1 presents mean values and mean changes from Day 1 baseline over the 12 weeks of treatment for PEFR measurements, daily puffs of back-up Ventolin, percent of nights with no awakenings and asthma symptom scores for the evaluable patient population. Also included are the p-values comparing treatments in changes from baseline from the van Elteren test with investigators as strata. Significant differences favoring salmeterol over placebo were seen in all variables except coughing. Significant differences favoring salmeterol over albuterol were seen in changes in morning PEFR, evening PEFR, percent of nights with no awakenings and shortness of breath.

2. REVIEWER'S COMMENTS

This reviewer does not feel that the repeated measures analyses performed by the sponsor are meaningful. The usual repeat factor is time over the 12 weeks of the trial not the 12.5 hours (including baseline) of serial FEV_1 measurements utilized by the sponsor. It appears that the Day 1 analysis included baseline FEV_1 and 13 on-treatment assessments of changes of FEV_1 from baseline. The analysis on the other evaluation days included 15 changes from baseline, two of which were the before treatment assessments at -0.5 hours and 0 hours (predose). Since the treatment-by-time interaction is highly \significant in the repeated measures analysis, it is the univariate analyses of changes-from-baseline at the serial time points that provide the most information about treatments.

To get a global effect of treatment over the 12 hour dosing interval it is more appropriate to analyze AUC above test day baseline for FEV_1. The sponsor analyzed this variable using a van Elteren test with investigators as strata and found that salmeterol and albuterol were significantly different from placebo for all on-treatment clinic visits. Salmeterol was significantly better than albuterol at Weeks 4, 8, and 12. The mean AUCs above baseline at Week 12 were 0.4, 6.5 and 3.3 liter-hours for placebo, salmeterol and albuterol, respectively.

Overall, this study has demonstrated effectiveness compared to placebo throughout the dosing interval for changes in PFTs. There were also significant differences favoring salmeterol over placebo in PEFRs, daily use of back-up Ventolin, percent of nights with no awakenings, chest tightness, shortness of breath, and all symptoms. Significant differences favoring salmeterol over albuterol were

seen at the end of albuterol's dosing interval 3, 4, 5 , 6, 11 and 12 in PFTs at all clinic visits and some additional hours at some of the clinic visits, in PEFRs, percent of nights with no awakenings and shortness of breath.

This study has shown more significant efficacy assessments of salmeterol diskhaler compared with albuterol for FEV_1 than did the salmeterol MDI studies. This is most probably due to choosing to dose the diskhaler at bedtime rather than at 6 PM as was done in the MDI studies.

C. STUDY SLD-312

1. RESULTS

There were 212 patients (73 placebo, 69 salmeterol, 70 albuterol) who entered this 7 center trial. There were 22 patients (10 placebo, 6 salmeterol and 6 albuterol) who withdrew from the study without completing 12 weeks of treatment. The evaluable patient analyses included 207 of the 212 patients. The main reasons for exclusions were inappropriate usage of nebulization therapy and violation of prestudy spirometry criteria. Efficacy data at some assessment times were excluded for an additional 20 patients.

The treatment groups were comparable at baseline in demographic variables, mean symptom scores, mean AM and PM PEFRs, mean daily puffs of back-up Ventolin and percent of nights with no awakenings.

Sponsor's Table 19 (Study SLD-312) presents the results of the p-values comparing treatments for changes from Day 1 baseline for FEV_1 for the evaluable patient population. Significant differences between placebo and salmeterol were seen in the repeated measures analysis at all 4 clinic visits and in all serial time points.

The repeated measures comparison of salmeterol and albuterol was significant at Weeks 4, 8, and 12 ($P < 0.016$ for all three weeks). Significant differences in changes from Day 1 baseline were observed when the effects of albuterol should be wearing off (at the end of its dosing interval). These significant differences favoring salmeterol over albuterol were at hours 3, 4, 5, 6, 11, 12 on Day 1; at -0.5 hours, 0.0 hours and hours 2, 3, 4, 5, 6, 9, 10, 11, 12 at Week 4; at hours -0.5 hours, 0.0 hours, 2, 3, 4, 5, 6, 10, 11, and 12 at Week 8; and at -0.5 hours, 0.0 hours, and hours 2, 3, 4, 5, 6, 10, 11, and 12 at Week 12. Significant differences favoring albuterol over salmeterol were seen at 0.25 hours, and 0.5 hours on Day 1 indicative of a shorter onset of effect for albuterol than salmeterol. These assessment times did not show efficacy of albuterol over salmeterol at Weeks 4, 8 and 12 because the effects of the last dose of salmeterol had not worn off at these assessment times.

The -0.5 hour and 0 hour (predose) changes from Day 1 baseline at Weeks 4, 8, 12 were between .18 - .36 liters for salmeterol. These differences were significantly different from 0 and significantly different from the -0.11 - .00 liters level observed for placebo and albuterol. This is indicative of salmeterol being long lasting and why the sponsor chose to analyze changes from Day 1 baseline rather than changes from test day baseline.

The results of the analyses of changes from Day 1 baseline for FEF 25-75% and FVC (not presented here) were essentially similar to those of changes in FEV_1. Similar results to the evaluable patient analyses were observed in the intent-to-treat population, also.

Table 2 presents mean values and mean changes from Day 1 baseline over the 12 weeks of treatment for PEFR measurements, daily puffs of back-up Ventolin, percent of nights with no awakenings and asthma symptom scores for the evaluable patient population. Also included are the p-values comparing treatments in changes from baseline from the van Elteren test with investigators as strata. Significant differences favoring salmeterol over placebo were seen in all variables except coughing and shortness of breath. Significant differences favoring salmeterol over albuterol were seen in changes in morning PEFR, percent of nights with no awakenings, Ventolin usage, wheezing and all symptoms.

2. REVIEWER'S COMMENTS

As in Study SLD-311, this reviewer does not feel that the repeated measures analyses performed by the sponsor are meaningful. The usual repeat factor is time over the 12 weeks of the trial not the 12.5 hours (including baseline) of serial FEV_1 measurements utilized by the sponsor. It appears that the Day 1 analysis included baseline FEV_1 and 13 on-treatment assessments of changes of FEV_1 from baseline. The analysis on the other evaluation days included 15 changes from baseline, two of which were the before treatment assessments at -0.5 hours and 0 hours (predose). Since the treatment-by-time interaction is highly significant in the repeated measures analysis, it is the univariate analyses of changes-from-baseline that provide the most information about treatments.

To get a global effect of treatment over the 12 hour dosing interval it is more appropriate to analyze AUC above test day baseline for FEV_1. The sponsor analyzed this variable using a van Elteren test with investigators as strata and found that salmeterol and albuterol were significantly different from placebo for all on treatment clinic visits. Salmeterol was significantly better than albuterol at Weeks 4, 8 and 12. The mean AUCs above baseline at Week 12 were 1.1, 5.7 and 3.5 liter-hours for placebo, salmeterol and albuterol, respectively.

Overall, this study has demonstrated effectiveness compared to placebo throughout the dosing interval for changes in PFTs. There were also significant differences favoring salmeterol over placebo in PEFRs, daily use of back-up Ventolin, percent of nights with no awakenings, chest tightness, wheezing and all symptoms. Significant differences favoring salmeterol over albuterol were seen at the end of albuterol's dosing interval (hours 3, 4, 5 , 6, 11 and 12) in PFTs at all clinic visits and some additional evaluation times at various clinic visits, in morning PEFRs, Ventolin usage, percent of nights with no awakenings, wheezing and all symptoms.

This study has also shown more significant efficacy assessments of salmeterol diskhaler compared with albuterol for FEV_1 than did the salmeterol MDI studies. This is most probably due to choosing to dose the diskhaler at bedtime rather than at 6 PM as was done in the MDI studies.

III. STUDY SLGA2004

A. STUDY DESCRIPTION AND METHOD OF ANALYSES

This study was similar to the other two studies with the following exceptions:

1. It was only a 4 week study.

2. It compared double dummy placebo, salmeterol MDPI Diskus, and Salmeterol Diskhaler b.i.d. (8AM and 8 PM).

3. Each patient recorded on a diary card their AM and PM PEFR, use of backup ventolin, the frequency of nighttime awakenings due to asthma, and a self rating of asthma symptoms in the AM and PM. The assessment was made before taking the next dose. Individual symptoms of asthma were not assessed.

4. PFTs were only taken on Day 1 and Day 29 at 30 minutes predose, immediately predose, and at the following times postdose: 0.25, 0.5, 1, 2, 4, 6, 8, 10 and 12 hours.

B. RESULTS

There were 210 patients (69 placebo, 71 salmeterol MDPI, 70 salmeterol diskhaler) who entered this 12 center trial. There were 15 patients (6 placebo, 7 salmeterol MDPI and 2 salmeterol diskhaler) who withdrew from the study without completing the trial. The evaluable patient analyses included 194 of the 210 patients. The evaluable patient population was the completers with the one exception that patient 330 who completed was not included due to unevaluable spirometric data.

The treatment groups were comparable at baseline in demographic

variables, mean symptom scores, mean AM and PM PEFRs, mean daily puffs of back-up Ventolin and percent of nights with no awakenings.

Sponsor's Tables 18 and 19 (Study SLGA2004) presents the results of the p-values comparing treatments for changes from Day 1 baseline for FEV_1 for the evaluable patient population. Significant differences between placebo and both salmeterol treatments were seen in the repeated measures analysis at both clinic visits and in all serial time points.

The repeated measures comparison of salmeterol MDPI and salmeterol diskhaler was not significant at both clinic visits. No significant difference was seen between the salmeterol treatments in the serial assessments at Day 1. At Day 29, the salmeterol MDPI had a significantly greater change from baseline in FEV_1 than did the diskhaler at hours 0.5, 1, and 4. However, there was a significant difference between the salmeterol groups at baseline. If a baseline covariate is used to adjust for this difference, no significant difference is seen at any of the serial time points. The data numerically favors the diskus.

The -0.5 hour and 0 hour (predose) changes from Day 1 baseline at Day 29 were between .31 - .35 liters for salmeterol MDPI diskus and .25-.27 for salmeterol diskhaler. These differences were significantly different from 0 and significantly different from the 0.12 liters level observed for placebo. This is indicative of salmeterol being long lasting and why the sponsor chose to analyze changes from Day 1 baseline rather than changes from test day baseline.

The results of the analyses of changes from Day 1 baseline for FEF 25-75% and FVC (not presented here) were essentially similar to those of changes in FEV_1. Similar results to the evaluable patient analyses were observed in the intent-to-treat population, also.

Table 3 presents mean values and mean changes from Day 1 baseline over the 4 weeks of treatment for PEFR measurements, daily puffs of back-up Ventolin, percent of nights with no awakenings and asthma symptom scores for the evaluable patient population. Also included are the p-values comparing treatments in changes from baseline from the van Elteren test with investigators as strata. Significant differences favoring both salmeterol treatments over placebo were seen in AM and PM PEFRs, daily use of backup ventolin, and percent of nights with no awakenings. Each salmeterol treatment was significant for one of the two symptom assessments. No significant difference was seen between the two salmeterol treatments.

C. REVIEWER'S COMMENTS

This reviewer does not consider the repeated measures analysis to be that meaningful. To get a global effect of treatment over the 12

hour dosing interval it is more appropriate to analyze AUC above test day baseline for FEV_1. The sponsor analyzed this variable using a van Elteren test with investigators as strata and found that salmeterol and albuterol were significantly different from placebo for all on treatment clinic visits. Both Salmeterol treatments were significantly better than placebo at Day 29. The mean AUCs above baseline at Day 29 were 2.6, 7.5 and 6.2 liter-hours for placebo, salmeterol diskus and salmeterol diskhaler, respectively. A 95% confidence limit on the difference in AUC above baseline for salmeterol diskus - salmeterol diskhaler was -0.8633, 3.3019 liter hours (adjusting for baseline difference). The Salmeterol Diskus could be .86 liter hours worse than the diskhaler or 3.3019 liter hours better.

IV. OVERALL CONCLUSIONS

Studies SLD-311 and SLD-312 showed efficacy of the Salmeterol Diskhaler over placebo in all serial FEV_1 changes from baseline at all clinic visits, and average (over 12 Weeks) changes in Morning and Evening PEFRs , Ventolin Usage, Percent of Nights with no Awakenings, Chest Tightness, Wheezing, All Symptoms and Shortness of Breath (only nearly significant in Study SLD-312).

Study SLGA2004 showed both salmeterol Diskus and salmeterol diskhaler significantly better than placebo at all serial FEV_1 changes from baseline at both Day 1 and Day 29, and average (over 29 days) Morning and Evening PEFRs, Daily Ventolin Usage and either AM or PM Symptom Score. Numerically the Diskus was better than the Diskhaler in all of the measurements. It is therefore reasonable to infer that the diskus would have been significantly different from placebo if it was used rather than the diskhaler in Studies SLD-311 and SLD-312.

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c:
Orig. NDA 20-692
HFD-570
HFD-570/Dr. Johnson
HFD-570/Ms. Jani
HFD-344/Dr. Lisook
HFD-715/Div File
HFD-715/Dr. Wilson
HFD-715/Dr. Gebert
Chron.
This review consists of 11 pages of text and 16 pages of Tables

TABLE 1

MEANS AND MEAN CHANGES FROM DAY 1 BASELINE FOR SECONDARY EFFICACY PARAMETERS (WEEKS 1-12) AND P-VALUES COMPARING TREATMENTS FOR CHANGES FROM BASELINE. STUDY SLD-311 EFFICACY POPULATION.

VARIABLE	PLACEBO (N=79) [2]		SALMETEROL (N=80) [2]		ALBUTEROL (N=79) [2]	
	MEAN (SD)	CHANGE (SD)	MEAN (SD)	CHANGE (SD)	MEAN (SD)	CHANGE (SD)
Morning PEFR (liters/min)	400 (99)	3 (29)	429 (85)	32 (45)	399 (79)	-3 (31)
Evening PEFR (liters/min)	426 (95)	-1 (31)	445 (84)	19 (38)	432 (79)	-4 (35)
Daily use of back-up Ventolin (number of puffs)	3.5 (2.9)	-0.7 (2.0)	1.5 (1.7)	-2.2 (2.2)	2.2 (2.0)	-2.2 (2.2)
Percent of Nights with no awakenings	75 (28)	4 (22)	88 (18)	24 (30)	68 (31)	5 (21)
Asthma Symptoms						
Chest Tightness	1.1 (0.9)	0.0 (0.7)	1.0 (0.8)	-0.3 (0.8)	0.9 (0.8)	-0.1 (0.6)
Shortness of Breath	1.1 (0.9)	-0.0 (0.6)	0.9 (0.8)	-0.4 (0.8)	1.0 (0.7)	-0.1 (0.7)
Wheezing	0.9 (0.8)	-0.1 (0.6)	0.9 (0.8)	-0.3 (0.8)	0.8 (0.6)	-0.1 (0.6)
Coughing	0.6 (0.7)	-0.2 (0.8)	0.6 (0.7)	-0.3 (0.8)	0.5 (0.5)	-0.1 (0.5)
All symptoms	0.9 (0.6)	-0.1 (0.6)	0.8 (0.7)	-0.3 (0.7)	0.8 (0.5)	-0.1 (0.5)

[1] FROM ANALYSIS OF VARIANCE FOR PEFR WITH FACTORS TREATMENT, INVESTIGATOR AND TREATMENT-BY-INVESTIGATOR INTERACTION.
FOR OTHER VARIABLES VAN ELTEREN TEST USED WITH DATA STRATIFIED BY INVESTIGATOR.

[2] PATIENTS ONLY INCLUDED IF THEY HAD OVER 6 WEEKS OF DATA. N=79 FOR SALMETEROL EVENING PEFR, VENTOLIN USAGE AND SYMPTOM ASSESSMENTS.

TABLE 1 (CONT)

MEANS AND MEAN CHANGES FROM DAY 1 BASELINE FOR SECONDARY EFFICACY PARAMETERS (WEEKS 1-12) AND P-VALUES COMPARING TREATMENTS FOR CHANGES FROM BASELINE. STUDY SLD-311 EFFICACY POPULATION.

VARIABLE	TREATMENT PLACEBO VS SALMETEROL	COMPARISON PLACEBO VS ALBUTEROL	P-VALUES [1] SALMETEROL VS ALBUTEROL
Morning PEFR (liters/min)	<0.001	0.194	<0.001
Evening PEFR (liters/min)	< 0.001	0.571	<0.001
Daily use of back-up Ventolin (number of puffs)	< 0.001	<0.001	0.903
Percent of Nights with no awakenings	<0.001	0.718	<0.001
Asthma Symptoms			
Chest Tightness	0.004	0.247	0.098
Shortness of Breath	0.002	0.127	0.044
Wheezing	0.040	0.796	0.216
Coughing	0.255	0.740	0.514
All symptoms	0.002	0.306	0.120

[1] FROM ANALYSIS OF VARIANCE FOR PEFR WITH FACTORS TREATMENT, INVESTIGATOR AND TREATMENT-BY-INVESTIGATOR INTERACTION.
FOR OTHER VARIABLES VAN ELTEREN TEST USED WITH DATA STRATIFIED BY INVESTIGATOR.

[2] PATIENTS ONLY INCLUDED IF THEY HAD OVER 6 WEEKS OF DATA. N=79 FOR SALMETEROL FOR EVENING PEFR, VENTOLIN USAGE AND ALL SYMPTOM ASSESSMENTS.

TABLE 2

MEANS AND MEAN CHANGES FROM DAY 1 BASELINE FOR SECONDARY EFFICACY PARAMETERS (WEEKS 1-12) AND P-VALUES COMPARING TREATMENTS FOR CHANGES FROM BASELINE. STUDY SLD-312 EFFICACY POPULATION.

VARIABLE	PLACEBO (N=72) [2]		SALMETEROL (N=66) [2]		ALBUTEROL (N=69) [2]	
	MEAN (SD)	CHANGE (SD)	MEAN (SD)	CHANGE (SD)	MEAN (SD)	CHANGE (SD)
Morning PEFR (liters/min)	391 (100)	-1 (40)	424 (92)	33 (45)	388 (83)	4 (45)
Evening PEFR (liters/min)	413 (103)	-8 (47)	434 (89)	10 (46)	420 (84)	5 (44)
Daily use of back-up Ventolin (number of puffs)	3.1 (2.6)	-1.2 (2.5)	1.7 (2.4)	-3.2 (2.7)	2.2 (2.1)	-2.0 (1.9)
Percent of Nights with no awakenings	71 (28)	2 (28)	82 (27)	22 (33)	74 (30)	1 (18)
Asthma Symptoms						
Chest Tightness	0.9 (0.8)	-0.1 (0.9)	0.8 (0.9)	-0.4 (0.7)	1.0 (0.8)	-0.1 (0.6)
Shortness of Breath	0.9 (0.8)	-0.2 (0.8)	0.9 (0.9)	-0.5 (0.9)	1.1 (0.8)	-0.2 (0.8)
Wheezing	0.9 (0.8)	-0.1 (0.8)	0.8 (0.8)	-0.5 (0.7)	0.8 (0.8)	-0.2 (0.7)
Coughing	0.6 (0.8)	-0.2 (0.8)	0.6 (0.7)	-0.3 (0.9)	0.6 (0.7)	-0.1 (0.7)
All symptoms	0.8 (0.7)	-0.2 (0.7)	0.8 (0.7)	-0.4 (0.7)	0.9 (0.7)	-0.1 (0.6)

[1] FROM ANALYSIS OF VARIANCE FOR PEFR WITH FACTORS TREATMENT, INVESTIGATOR AND TREATMENT-BY-INVESTIGATOR INTERACTION.
FOR OTHER VARIABLES VAN ELTEREN TEST USED WITH DATA STRATIFIED BY INVESTIGATOR.

[2] PATIENTS ONLY INCLUDED IF THEY HAD OVER 6 WEEKS OF DATA. N FOR SALMETEROL 65 FOR VENTOLIN USAGE, WHEEZING, COUGHING AND ALL SYMPTOMS. N FOR ALBUTEROL IS 70 FOR EVENING PEFR.

TABLE 2 (CONT)

MEANS AND MEAN CHANGES FROM DAY 1 BASELINE FOR SECONDARY EFFICACY PARAMETERS (WEEKS 1-12) AND P-VALUES COMPARING TREATMENTS FOR CHANGES FROM BASELINE. STUDY SLD-312 EFFICACY POPULATION.

VARIABLE	TREATMENT PLACEBO VS SALMETEROL	COMPARISON PLACEBO VS ALBUTEROL	P-VALUES [1] SALMETEROL VS ALBUTEROL
Morning PEFR (liters/min)	<0.001	0.475	<0.001
Evening PEFR (liters/min)	0.031	0.098	0.593
Daily use of back-up Ventolin (number of puffs)	<0.001	0.009	0.008
Percent of Nights with no awakenings	0.003	0.973	0.005
Asthma Symptoms			
Chest Tightness	0.004	0.632	0.060
Shortness of Breath	0.070	0.889	0.059
Wheezing	0.001	0.376	0.027
Coughing	0.424	0.630	0.537
All symptoms	0.005	0.650	0.034

[1] FROM ANALYSIS OF VARIANCE FOR PEFR WITH FACTORS TREATMENT, INVESTIGATOR AND TREATMENT-BY-INVESTIGATOR INTERACTION.
FOR OTHER VARIABLES VAN ELTEREN TEST USED WITH DATA STRATIFIED BY INVESTIGATOR.

[2] PATIENTS ONLY INCLUDED IF THEY HAD OVER 6 WEEKS OF DATA. N FOR SALMETEROL 65 FOR VENTOLIN USAGE, WHEEZING, COUGHING, AND ALL SYMPTOMS. N FOR ALBUTEROL IS 70 FOR EVENING PEFR.

TABLE 3

MEANS AND MEAN CHANGES FROM DAY 1 BASELINE FOR SECONDARY EFFICACY PARAMETERS (DAYS 1-29) AND P-VALUES COMPARING TREATMENTS FOR CHANGES FROM BASELINE. STUDY SLGA2004 EFFICACY POPULATION.

VARIABLE	PLACEBO (N=63) [2]		SALMETEROL MDPI (N=63) [2]		SALMETEROL DH (N=67) [2]	
	MEAN (SE)	CHANGE (SE)	MEAN (SE)	CHANGE (SE)	MEAN (SE)	CHANGE (SE)
Morning PEFR (liters/min)	428 (11)	12 (4)	469 (13)	42 (6)	435 (10)	32 (4)
Evening PEFR (liters/min)	448 (12)	12 (4)	485 (12)	29 (5)	457 (10)	27 (4)
Daily use of back-up Ventolin (number of puffs)	2.7 (0.4)	-1.1 (0.2)	1.2 (0.2)	-3.0 (0.3)	1.5 (0.2)	-2.5 (0.3)
Percent of Nights with no awakenings	85 (3)	9.2 (2.3)	92 (2)	14.4 (2.8)	85 (3)	15.0 (3.2)
Asthma Symptoms						
AM Symptom Score	1.8 (0.1)	-0.2 (0.1)	1.6 (0.1)	-0.5 (0.1)	1.7 (0.1)	-0.4 (0.1)
PM Symptom Score	1.8 (0.1)	-0.2 (0.1)	1.7 (0.1)	-0.5 (0.1)	1.7 (0.1)	-0.4 (0.1)

[1] FROM ANALYSIS OF VARIANCE FOR PEFR WITH FACTORS TREATMENT, INVESTIGATOR AND TREATMENT-BY-INVESTIGATOR INTERACTION.
FOR OTHER VARIABLES VAN ELTEREN TEST USED WITH DATA STRATIFIED BY INVESTIGATOR.

[2] N FOR SALMETEROL DISKHALER IS 66 FOR MORNING AND EVENING PEFR.

TABLE 3 (CONT)

MEANS AND MEAN CHANGES FROM DAY 1 BASELINE FOR SECONDARY EFFICACY PARAMETERS (DAYS 1-29) AND P-VALUES COMPARING TREATMENTS FOR CHANGES FROM BASELINE. STUDY SLGA2004 EFFICACY POPULATION.

	TREATMENT	COMPARISON	P-VALUE [1]
VARIABLE	PLACEBO VS SALMETEROL MDPI	PLACEBO VS SALMETEROL DISKHALER	SALMETEROL MDPI VS SALMETEROL DISKHALER
Morning PEFR (liters/min)	<0.001	<0.001	0.290
Evening PEFR (liters/min)	0.011	0.005	0.996
Daily use of back-up Ventolin (number of puffs)	<0.001	<0.001	0.562
Percent of Nights with no awakenings	0.134	0.087	0.830
Asthma Symptoms			
AM Symptom Score	0.079	0.036	0.743
PM Symptom Score	0.004	0.234	0.731

[1] FROM ANALYSIS OF VARIANCE FOR PEFR WITH FACTORS TREATMENT, INVESTIGATOR AND TREATMENT-BY-INVESTIGATOR INTERACTION.
FOR OTHER VARIABLES VAN ELTEREN TEST USED WITH DATA STRATIFIED BY INVESTIGATOR.

[2] N FOR SALMETEROL IS 66 FOR SALMETEROL DISKHALER FOR MORNING AND EVENING PEFR.

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT DAY 1
Investigator: All

TIME IN HOURS	PLACEBO (N=77)			SALMETEROL (N=79)			ALBUTEROL (N=79)			TREATMENT COMPARISON P-VALUES[2][3]			
	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	OVERALL	PLACEBO vs SALMETEROL	PLACEBO vs ALBUTEROL	SALMETEROL vs ALBUTEROL
BASE[4]	2.46			2.43			2.51			0.799 †	0.780 †	0.721	0.471 ‡
0.25	2.45	-0.01	0.712	2.67	0.24	<.001	2.99	0.49	<.001	<.001	<.001	<.001	<.001
0.5	2.47	0.01	0.773	2.79	0.36	<.001	3.06	0.56	<.001	<.001	<.001	<.001	<.001
1	2.50	0.04	0.191	2.87	0.44	<.001	3.08	0.58	<.001	<.001	<.001	<.001	0.008
2	2.53	0.07	0.081	2.93	0.50	<.001	3.04	0.53	<.001	<.001	<.001	<.001	0.586
3	2.53	0.08	0.091	2.98	0.55	<.001	2.90	0.39	<.001	<.001	<.001	<.001	0.004 †
4	2.50	0.04	0.419	2.96	0.53	<.001	2.83	0.33	<.001	<.001	<.001	<.001	<.001
5	2.49	0.03	0.479	2.97	0.54	<.001	2.73	0.22	<.001	<.001	<.001	0.002	<.001
6	2.42	-0.03	0.460	2.89	0.46	<.001	2.65	0.15	<.001	<.001	<.001	0.003	<.001
7	2.41	-0.04	0.348	2.88	0.45	<.001	3.14	0.64	<.001	<.001	<.001	<.001	0.008
8	2.42	-0.04	0.449	2.87	0.44	<.001	3.04	0.53	<.001	<.001	<.001	<.001	0.167
9	2.42	-0.04	0.402	2.85	0.42	<.001	2.95	0.44	<.001	<.001	<.001	<.001	0.719 †
10	2.43	-0.03	0.540	2.82	0.38	<.001	2.81	0.30	<.001	<.001	<.001	<.001	0.190
11	2.44	-0.02	0.675	2.82	0.39	<.001	2.71	0.20	<.001	<.001	<.001	0.001	0.002
12	2.44	-0.02	0.728	2.79	0.36	<.001	2.67	0.16	<.001	<.001	<.001	0.009	0.002

[1] Within treatment p-values are based on t-tests (a test of whether the change from baseline is significantly different from zero).
[2] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[3] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[4] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect:	<.001	Investigator Effect:	0.214
Time Effect:	<.001	TMT*INV Interaction:	0.604

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs SALMETEROL:	<.001
PLACEBO vs ALBUTEROL:	<.001
SALMETEROL vs ALBUTEROL:	0.514

Supporting data listing in Appendix 7.25
04MAY94/HL/BIO$STAT_SLD:[SLD311.TABLES]PFTTST1.SAS

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT WEEK 4
Investigator: All

TIME IN HOURS	PLACEBO (N=71)			SALMETEROL (N=72)			ALBUTEROL (N=73)			TREATMENT COMPARISON P-VALUES[2][3]			
	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	OVERALL	PLACEBO vs SALMETEROL	PLACEBO vs ALBUTEROL	SALMETEROL vs ALBUTEROL
BASE[4]	2.52			2.42			2.47						
-0.5	2.61	0.09	0.157	2.78	0.36	<.001	2.41	-0.06	0.268	0.755 †	0.465 †	0.798	0.608 †‡
0.0	2.62	0.10	0.097	2.76	0.34	<.001	2.41	-0.06	0.304	<.001	0.002	0.096	<.001
0.25	2.61	0.09	0.143	2.85	0.43	<.001	2.90	0.43	<.001	<.001	0.006	0.077	<.001
0.5	2.62	0.10	0.117	2.92	0.50	<.001	2.96	0.49	<.001	<.001	<.001	<.001	0.940
1	2.64	0.12	0.038	3.01	0.59	<.001	2.94	0.47	<.001	<.001	<.001	<.001	0.994
2	2.64	0.12	0.043	3.07	0.65	<.001	2.86	0.38	<.001	<.001	<.001	<.001	0.207
3	2.71	0.19	0.001	3.08	0.66	<.001	2.75	0.28	<.001	<.001	<.001	0.001	0.003
4	2.68	0.16	0.002	3.07	0.65	<.001	2.62	0.15	0.013	<.001	<.001	0.236	<.001
5	2.67	0.15	0.005	3.03	0.61	<.001	2.56	0.08	0.137	<.001	<.001	0.996	<.001
6	2.64	0.12	0.037	3.01	0.59	<.001	2.53	0.06	0.260	<.001	<.001	0.515	<.001
7	2.60	0.09	0.131	2.97	0.55	<.001	3.00	0.52	<.001	<.001	<.001	0.514	<.001
8	2.58	0.06	0.262	2.97	0.55	<.001	2.90	0.43	<.001	<.001	<.001	<.001	0.843
9	2.57	0.05	0.334	2.98	0.56	<.001	2.79	0.32	<.001	<.001	<.001	<.001	0.204
10	2.57	0.05	0.367	2.93	0.51	<.001	2.62	0.15	0.018	<.001	<.001	<.001	0.014
11	2.54	0.02	0.693	2.89	0.47	<.001	2.58	0.10	0.107	<.001	<.001	0.243	<.001
12	2.55	0.04	0.550	2.89	0.47	<.001	2.56	0.09	0.190	<.001	<.001	0.304	<.001
												0.528	<.001

[1] Within treatment p-values are based on t-tests (a test of whether the change from baseline is significantly different from zero).
[2] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[3] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[4] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect:	<.001	Investigator Effect:	0.773
Time Effect:	<.001	TMT*INV Interaction:	0.841

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs SALMETEROL:	<.001
PLACEBO vs ALBUTEROL:	0.049
SALMETEROL vs ALBUTEROL:	<.001

Supporting data listing in Appendix 7.25
04MAY94/BL/BIO$STAT_SLD:[SLD311.TABLES]PFTTST2.SAS

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT WEEK 8
Investigator: All

TIME IN HOURS	PLACEBO (N=68)			SALMETEROL (N=72)			ALBUTEROL (N=71)			TREATMENT COMPARISON P-VALUES[2][3]			
	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	OVERALL	PLACEBO vs SALMETEROL	PLACEBO vs ALBUTEROL	SALMETEROL vs ALBUTEROL
BASE[4]	2.54			2.42			2.52			0.453 †	0.229 †	0.743	0.346 ††
-0.5	2.66	0.11	0.123	2.75	0.33	<.001	2.47	-0.05	0.404	<.001	0.025	0.112	<.001
0.0	2.65	0.11	0.127	2.73	0.31	<.001	2.48	-0.04	0.510	0.002	0.050	0.146	<.001
0.25	2.62	0.07	0.275	2.81	0.39	<.001	2.98	0.46	<.001	<.001	0.001	<.001	0.384
0.5	2.64	0.10	0.175	2.85	0.44	<.001	3.00	0.48	<.001	<.001	<.001	<.001	0.533
1	2.69	0.14	0.036	2.96	0.54	<.001	2.99	0.47	<.001	<.001	<.001	<.001	0.487
2	2.67	0.13	0.064	3.04	0.62	<.001	2.88	0.36	<.001	<.001	<.001	0.007	0.006
3	2.69	0.15	0.015	3.03	0.62	<.001	2.80	0.28	<.001	<.001	<.001	0.098	<.001
4	2.72	0.17	0.016	3.01	0.59	<.001	2.71	0.19	<.001	<.001	<.001	0.808	<.001
5	2.66	0.11	0.091	3.01	0.59	<.001	2.59	0.07	0.218	<.001	<.001	0.706	<.001
6	2.64	0.09	0.153	2.98	0.56	<.001	2.57	0.05	0.415	<.001	<.001	0.798	<.001
7	2.60	0.05	0.425	2.89	0.48	<.001	3.07	0.55	<.001	<.001	<.001	<.001	0.379
8	2.57	0.02	0.748	2.91	0.49	<.001	2.97	0.45	<.001	<.001	<.001	<.001	0.667
9	2.58	0.04	0.589	2.85	0.43	<.001	2.81	0.29	<.001	<.001	<.001	0.006	0.136
10	2.57	0.02	0.748	2.85	0.43	<.001	2.68	0.16	0.004	<.001	<.001	0.136	0.002
11	2.53	-0.01	0.873	2.85	0.44	<.001	2.61	0.09	0.110	<.001	<.001	0.229	<.001
12	2.54	-0.01	0.917	2.86	0.45	<.001	2.58	0.06	0.321	<.001	<.001	0.410	<.001

[1] Within treatment p-values are based on t-tests (a test of whether the change from baseline is significantly different from zero).
[2] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[3] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[4] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect:	<.001	Investigator Effect:	0.493
Time Effect:	<.001	TMT*INV Interaction:	0.713

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs SALMETEROL:	<.001
PLACEBO vs ALBUTEROL:	0.036
SALMETEROL vs ALBUTEROL:	0.005

Supporting data listing in Appendix 7.25
04MAY94/ML/BIO$STAT_SLD:[SLD311.TABLES]PFTTST2.SAS

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT WEEK 12
Investigator: All

TIME IN HOURS	PLACEBO (N=67)			SALMETEROL (N=70)			ALBUTEROL (N=72)			TREATMENT COMPARISON P-VALUES[2][3]			
	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	OVERALL	PLACEBO vs SALMETEROL	PLACEBO vs ALBUTEROL	SALMETEROL vs ALBUTEROL
BASE[4]	2.56			2.44			2.51						
-0.5	2.64	0.07	0.239	2.73	0.30	<.001	2.47	-0.04	0.568	0.576 †	0.300 †	0.681	0.503 ‡
0.0	2.61	0.05	0.442	2.74	0.30	<.001	2.50	-0.01	0.909	<.001	0.007	0.310	<.001
0.25	2.61	0.05	0.447	2.84	0.40	<.001	2.98	0.48	<.001	0.001	0.004	0.697	0.001
0.5	2.63	0.06	0.326	2.92	0.48	<.001	2.99	0.49	<.001	<.001	<.001	<.001	0.350
1	2.66	0.09	0.144	2.96	0.53	<.001	3.01	0.51	<.001	<.001	<.001	<.001	0.990
2	2.65	0.08	0.177	3.05	0.61	<.001	2.92	0.41	<.001	<.001	<.001	<.001	0.783
3	2.68	0.11	0.095	3.09	0.65	<.001	2.79	0.28	<.001	<.001	<.001	<.001	0.026
4	2.68	0.11	0.060	3.10	0.66	<.001	2.67	0.17	0.003	<.001	<.001	0.016	<.001
5	2.64	0.08	0.188	3.02	0.59	<.001	2.61	0.10	0.045	<.001	<.001	0.307	<.001
6	2.54	-0.03	0.684	3.00	0.56	<.001	2.54	0.04	0.498	<.001	<.001	0.459	<.001 †
7	2.54	-0.02	0.751	2.93	0.49	<.001	3.03	0.52	<.001	<.001	<.001	0.288	<.001
8	2.57	0.01	0.887	2.96	0.52	<.001	2.94	0.43	<.001	<.001	<.001	<.001	0.736
9	2.54	-0.02	0.749	2.93	0.49	<.001	2.83	0.32	<.001	<.001	<.001	<.001	0.312
10	2.56	-0.01	0.940	2.94	0.50	<.001	2.73	0.23	<.001	<.001	<.001	<.001	0.065
11	2.52	-0.05	0.511	2.90	0.46	<.001	2.62	0.12	0.037	<.001	<.001	0.009	0.003
12	2.52	-0.05	0.541	2.89	0.45	<.001	2.57	0.06	0.272	<.001	<.001	0.039	<.001
												0.168	<.001

[1] Within treatment p-values are based on t-tests (a test of whether the change from baseline is significantly different from zero).
[2] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[3] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[4] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect:	<.001	Investigator Effect:	0.246
Time Effect:	<.001	TMT*INV Interaction:	0.668

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs SALMETEROL:	<.001
PLACEBO vs ALBUTEROL:	0.001
SALMETEROL vs ALBUTEROL:	0.003

Supporting data listing in Appendix 7.25
04MAY94/HL/BIO$STAT_SLD:[SLD311.TABLES]PFTTST2.SAS

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT DAY 1
Investigator: All

TIME IN HOURS	PLACEBO (N=68)			SALMETEROL (N=66)			ALBUTEROL (N=69)			TREATMENT COMPARISON P-VALUES[2][3]			
	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	OVERALL	PLACEBO vs SALMETEROL	PLACEBO vs ALBUTEROL	SALMETEROL vs ALBUTEROL
BASE[4]	2.46			2.46			2.48			0.973 †	0.875	0.826	0.956 †
0.25	2.51	0.05	0.101	2.68	0.23	<.001	2.95	0.47	<.001	<.001	<.001	<.001	<.001
0.5	2.53	0.07	0.013	2.79	0.34	<.001	3.01	0.53	<.001	<.001 †	<.001 †	<.001	0.002 †
1	2.57	0.11	<.001	2.87	0.41	<.001	3.01	0.53	<.001	<.001 †	<.001 †	<.001	0.086 †
2	2.60	0.14	<.001	2.96	0.50	<.001	2.93	0.45	<.001	<.001 †	<.001 †	<.001	0.429
3	2.64	0.18	<.001	2.99	0.54	<.001	2.85	0.37	<.001	<.001 †	<.001 †	0.002	0.017 †
4	2.63	0.17	<.001	2.98	0.53	<.001	2.79	0.31	<.001	<.001 †	<.001 †	0.031	0.007 †
5	2.65	0.19	<.001	2.98	0.52	<.001	2.74	0.25	<.001	<.001	<.001 ‡	0.265	<.001
6	2.65	0.19	<.001	2.97	0.52	<.001	2.67	0.19	<.001	<.001	<.001	0.909	<.001
7	2.59	0.13	0.011	2.93	0.48	<.001	3.08	0.60	<.001	<.001 †	<.001	<.001 †	0.116
8	2.58	0.12	0.021	2.92	0.46	<.001	3.06	0.57	<.001	<.001 †	<.001	<.001	0.133
9	2.56	0.10	0.039	2.93	0.47	<.001	2.91	0.42	<.001	<.001	<.001	<.001	0.556
10	2.54	0.08	0.115	2.88	0.43	<.001	2.77	0.29	<.001	<.001	<.001	0.003	0.060
11	2.55	0.09	0.101	2.89	0.43	<.001	2.72	0.24	<.001	<.001 †	<.001	0.028	0.008
12	2.54	0.08	0.112	2.88	0.43	<.001	2.71	0.23	<.001	<.001	<.001	0.024	0.010

[1] Within treatment p-values are based on t-tests (a test of whether the change from baseline is significantly different from zero).
[2] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[3] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[4] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect:	<.001	Investigator Effect:	0.040
Time Effect:	<.001	TMT*INV Interaction:	0.480

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs SALMETEROL:	<.001 †
PLACEBO vs ALBUTEROL:	<.001
SALMETEROL vs ALBUTEROL:	0.357

Supporting data listing in Appendix 7.25
14JUL94/HL/BIO$STAT_SLD:[SLD312.TABLES]PFTTST1.SAS

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT WEEK 4
Investigator: All

TIME IN HOURS	PLACEBO (N=65)			SALMETEROL (N=62)			ALBUTEROL (N=62)			TREATMENT COMPARISON P-VALUES[2][3]			
	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	OVERALL	PLACEBO vs SALMETEROL	PLACEBO vs ALBUTEROL	SALMETEROL vs ALBUTEROL
BASE[4]	2.50			2.44			2.46						
-0.5	2.40	-0.10	0.041	2.78	0.33	<.001	2.36	-0.11	0.052	0.960	0.814	0.817	0.986
0.0	2.42	-0.08	0.104	2.78	0.33	<.001	2.36	-0.10	0.074	<.001	<.001	0.889	<.001
0.25	2.43	-0.07	0.202	2.87	0.42	<.001	2.83	0.37	<.001	<.001	<.001	0.935 †	<.001
0.5	2.44	-0.06	0.282	2.93	0.49	<.001	2.87	0.41	<.001	<.001 †	<.001	<.001 †	0.644
1	2.51	0.00	0.960	3.00	0.56	<.001	2.87	0.41	<.001	<.001 †	<.001	<.001 †	0.497 †
2	2.54	0.04	0.486	3.00	0.56	<.001	2.81	0.35	<.001	<.001 †	<.001 †	<.001 †	0.114
3	2.58	0.08	0.153	3.07	0.63	<.001	2.75	0.29	<.001	<.001 †	<.001 †	<.001 †	0.036 †
4	2.60	0.10	0.102	3.08	0.63	<.001	2.65	0.19	0.002	<.001 †	<.001 †	0.004 †	<.001
5	2.58	0.07	0.213	3.05	0.60	<.001	2.62	0.16	0.011	<.001	<.001 †	0.208	<.001
6	2.55	0.04	0.466	3.01	0.57	<.001	2.63	0.17	0.007	<.001	<.001 †	0.250	<.001
7	2.57	0.07	0.220	2.97	0.53	<.001	2.99	0.53	<.001	<.001	<.001	0.118	<.001
8	2.57	0.07	0.254	2.98	0.53	<.001	2.92	0.46	<.001	<.001	<.001	<.001	0.856
9	2.57	0.07	0.256	2.99	0.55	<.001	2.81	0.34	<.001	<.001	<.001	<.001	0.506
10	2.51	0.01	0.839	2.92	0.47	<.001	2.68	0.22	0.001	<.001	<.001	0.003	0.050
11	2.52	0.02	0.762	2.96	0.52	<.001	2.63	0.17	0.012	<.001 †	<.001 †	0.021	0.011
12	2.56	0.05	0.408	2.95	0.51	<.001	2.57	0.11	0.088	<.001	<.001	0.101	0.001
										<.001	<.001	0.509	<.001

[1] Within treatment p-values are based on t-tests (a test of whether the change from baseline is significantly different from zero).
[2] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[3] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[4] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect:	<.001	Investigator Effect:	0.072
Time Effect:	<.001	TMT*INV Interaction:	0.342

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs SALMETEROL:	<.001
PLACEBO vs ALBUTEROL:	0.002
SALMETEROL vs ALBUTEROL:	0.002

Supporting data listing in Appendix 7.25
14JUL94/HL/BIO$STAT_SLD:[SLD312.TABLES]PFTTST2.SAS

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT WEEK 8
Investigator: All

TIME IN HOURS	PLACEBO (N=59)			SALMETEROL (N=63)			ALBUTEROL (N=63)			TREATMENT COMPARISON P-VALUES[2][3]			
	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	MEAN	CHG	P-VAL[1]	OVERALL	PLACEBO vs SALMETEROL	PLACEBO vs ALBUTEROL	SALMETEROL vs ALBUTEROL
BASE[4]	2.50			2.48			2.48			0.999 †	0.998	0.976	0.969 †
-0.5	2.45	-0.06	0.390	2.83	0.35	<.001	2.43	-0.04	0.499	<.001 †	<.001 †	0.810 †	<.001 ‡
0.0	2.44	-0.06	0.346	2.84	0.36	<.001	2.41	-0.07	0.334	<.001 †	<.001 †	0.957 †	<.001
0.25	2.45	-0.05	0.395	2.96	0.49	<.001	2.88	0.40	<.001	<.001 †	<.001 †	<.001	0.358
0.5	2.49	-0.01	0.869	2.99	0.52	<.001	2.92	0.45	<.001	<.001 †	<.001 †	<.001 †	0.490
1	2.51	0.01	0.846	3.04	0.57	<.001	2.92	0.44	<.001	<.001 †	<.001 †	<.001	0.192
2	2.56	0.06	0.350	3.06	0.58	<.001	2.87	0.39	<.001	<.001 †	<.001 †	<.001	0.042 †
3	2.58	0.08	0.167	3.11	0.63	<.001	2.79	0.32	<.001	<.001 †	<.001 †	0.007	<.001
4	2.56	0.06	0.355	3.10	0.62	<.001	2.72	0.24	<.001	<.001 †	<.001 †	0.050	<.001
5	2.55	0.05	0.444	3.09	0.62	<.001	2.68	0.21	0.001	<.001 †	<.001 †	0.064	<.001
6	2.58	0.08	0.183	3.09	0.62	<.001	2.64	0.16	0.011	<.001	<.001	0.290	<.001
7	2.57	0.07	0.277	3.05	0.58	<.001	3.00	0.53	<.001	<.001	<.001	<.001	0.590
8	2.58	0.08	0.215	3.03	0.55	<.001	2.93	0.46	<.001	<.001	<.001	<.001	0.284
9	2.52	0.02	0.716	3.02	0.54	<.001	2.86	0.39	<.001	<.001	<.001	<.001	0.130
10	2.55	0.04	0.491	3.00	0.52	<.001	2.73	0.25	<.001	<.001	<.001	0.018	0.004
11	2.52	0.02	0.735	2.98	0.51	<.001	2.71	0.24	<.001	<.001	<.001	0.026	0.009
12	2.57	0.07	0.346	2.98	0.51	<.001	2.70	0.22	0.001	<.001	<.001	0.094	0.006

[1] Within treatment p-values are based on t-tests (a test of whether the change from baseline is significantly different from zero).
[2] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[3] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[4] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect:	<.001	Investigator Effect:	0.098
Time Effect:	<.001	TMT*INV Interaction:	0.458

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs SALMETEROL:	<.001
PLACEBO vs ALBUTEROL:	0.002
SALMETEROL vs ALBUTEROL:	0.003

Supporting data listing in Appendix 7.25
14JUL94/HL/BIO$STAT_SLD:[SLD312.TABLES]PFTTST2.SAS

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT WEEK 12
Investigator: All

TIME IN HOURS	PLACEBO (N=58) MEAN	CHG	P-VAL[1]	SALMETEROL (N=54) MEAN	CHG	P-VAL[1]	ALBUTEROL (N=61) MEAN	CHG	P-VAL[1]	TREATMENT COMPARISON P-VALUES[2][3] OVERALL	PLACEBO vs SALMETEROL	PLACEBO vs ALBUTEROL	SALMETEROL vs ALBUTEROL
BASE[4]	2.54			2.53			2.47						
-0.5	2.54	0.00	0.948	2.70	0.18	0.007	2.44	-0.03	0.630	0.901 †	0.882	0.655	0.758
0.0	2.54	0.00	0.928	2.75	0.22	0.001	2.46	-0.01	0.868	0.036 †	0.033 †	0.659	0.022 †
0.25	2.60	0.06	0.232	2.87	0.35	<.001	2.88	0.42	<.001	0.009 †	0.005 †	0.837 †	0.011 †
0.5	2.60	0.06	0.238	2.94	0.41	<.001	2.91	0.45	<.001	<.001 †	<.001 †	<.001	0.601 †
1	2.62	0.08	0.162	3.00	0.47	<.001	2.93	0.46	<.001	<.001 †	<.001 †	<.001	0.876 †
2	2.64	0.11	0.047	3.07	0.55	<.001	2.83	0.36	<.001	<.001 †	<.001 †	<.001 †	0.654 †
3	2.69	0.15	0.016	3.09	0.56	<.001	2.73	0.26	<.001	<.001 †	<.001 †	0.002	0.014 †
4	2.68	0.14	0.029	3.08	0.55	<.001	2.70	0.23	<.001	<.001 †	<.001 †	0.238	<.001 †
5	2.61	0.08	0.184	3.03	0.51	<.001	2.60	0.14	0.026	<.001 †	<.001 †	0.254	<.001 †
6	2.66	0.12	0.073	3.02	0.49	<.001	2.62	0.15	0.005	<.001 †	<.001 †	0.456	<.001 †
7	2.62	0.09	0.136	3.00	0.48	<.001	2.96	0.49	<.001	<.001 †	<.001 †	0.590	<.001 †
8	2.61	0.08	0.217	2.94	0.42	<.001	2.88	0.41	<.001	<.001 †	<.001	<.001	0.941 †
9	2.57	0.04	0.521	2.95	0.43	<.001	2.77	0.30	<.001	<.001 †	<.001 †	<.001	0.768 †
10	2.63	0.09	0.142	2.97	0.44	<.001	2.72	0.26	<.001	<.001 †	<.001 †	0.002	0.083 †
11	2.63	0.09	0.142	2.95	0.43	<.001	2.69	0.22	<.001	<.001 †	<.001	0.045	0.017 †
12	2.64	0.11	0.092	2.96	0.43	<.001	2.65	0.18	<.001	<.001	<.001	0.116	0.012
										<.001	<.001	0.337	0.002

[1] Within treatment p-values are based on t-tests (a test of whether the change from baseline is significantly different from zero).
[2] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[3] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[4] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect:	<.001	Investigator Effect:	0.014
Time Effect:	<.001	TMT*INV Interaction:	0.332

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs SALMETEROL:	<.001 †
PLACEBO vs ALBUTEROL:	0.009
SALMETEROL vs ALBUTEROL:	0.015 †

Supporting data listing in Appendix 7.25
14JUL94/HL/BIO$STAT_SLD:[SLD312.TABLES]PFTTST2.SAS

Table 18
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT DAY 1
Investigator: All

TIME IN HOURS	PLACEBO (N=63) MEAN	PLACEBO (N=63) CHG (SE)	50 MCG MDPI (N=63) MEAN	50 MCG MDPI (N=63) CHG (SE)	50 MCG DISK (N=67) MEAN	50 MCG DISK (N=67) CHG (SE)	TREATMENT COMPARISON P-VALUES[1][2] OVERALL	PLACEBO vs 50 MCG MDPI	PLACEBO vs 50 MCG DISK	50 MCG MDPI vs 50 MCG DISK
BASE[3]	2.69		2.83		2.57		0.121 †	0.449	0.199	0.047
0.25	2.75	0.05 (0.02)	3.09	0.26 (0.04)	2.83	0.26 (0.03)	<.001	<.001	<.001	0.710
0.5	2.79	0.09 (0.02)	3.17	0.34 (0.04)	2.97	0.40 (0.04)	<.001	<.001	<.001	0.577 ‡
1	2.84	0.14 (0.03)	3.32	0.49 (0.04)	3.03	0.46 (0.04)	<.001 ‡	<.001	<.001	0.242 ‡
2	2.88	0.19 (0.04)	3.39	0.57 (0.05)	3.10	0.53 (0.04)	<.001	<.001	<.001	0.310
4	2.88	0.18 (0.05)	3.45	0.63 (0.06)	3.13	0.56 (0.05)	<.001 †	<.001 †	<.001 †	0.313 †
6	2.87	0.17 (0.06)	3.38	0.55 (0.05)	3.11	0.54 (0.05)	<.001 †	<.001 †	<.001 †	0.763
8	2.84	0.14 (0.06)	3.33	0.50 (0.07)	3.05	0.48 (0.04)	<.001 †	<.001 †	<.001 †	0.893
10	2.84	0.15 (0.06)	3.29	0.46 (0.07)	3.05	0.48 (0.05)	<.001 †	<.001 †	<.001 †	0.896
12	2.80	0.10 (0.06)	3.27	0.44 (0.06)	3.02	0.45 (0.05)	<.001 †	<.001 †	<.001 †	0.954 †

[1] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[2] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[3] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect: <.001 Investigator Effect: 0.006
TMT*INV Interaction: 0.245

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs 50 MCG MDPI: <.001 †
PLACEBO vs 50 MCG DISK: <.001 †
50 MCG MDPI vs 50 MCG DISK: 0.700

Supporting data listing in
BIO$STAT_SLD:[000000.SLGA2004.TABLES]PFTTST1.SAS;21 - 03NOV95

Table 19
INFERENTIAL ANALYSES OF SERIAL FEV1 (Liters) ON TREATMENT DAY 29
Investigator: All

TIME IN HOURS	PLACEBO (N=63)		50 MCG DISKUS (N=63)		50 MCG DISK (N=67)		TREATMENT COMPARISON P-VALUES[1][2]			
	MEAN	CHG (SE)	MEAN	CHG (SE)	MEAN	CHG (SE)	OVERALL	PLACEBO vs 50 MCG DISKUS	PLACEBO vs 50 MCG DISK	50 MCG DISKUS vs 50 MCG DISK
BASE[4]	2.69		2.83		2.54		0.066 †	0.449	0.119	0.024
-0.5	2.81	0.12 (0.05)	3.13	0.31 (0.05)	2.79	0.25 (0.04)	0.009	0.006	0.032	0.285
0.0	2.81	0.12 (0.05)	3.18	0.35 (0.06)	2.81	0.27 (0.04)	0.005	0.003	0.040	0.156
0.25	2.84	0.14 (0.05)	3.26	0.43 (0.06)	2.91	0.36 (0.04)	<.001	<.001	0.001	0.207
0.5	2.85	0.16 (0.06)	3.37	0.54 (0.07)	2.95	0.41 (0.04)	<.001 †	<.001 †	<.001	0.040 †‡
1	2.95	0.25 (0.06)	3.48	0.65 (0.08)	3.04	0.50 (0.05)	<.001 †	<.001 †	0.002 †	0.036 †‡
2	2.92	0.22 (0.06)	3.53	0.71 (0.08)	3.10	0.56 (0.06)	<.001 †	<.001 †	<.001 †	0.058
4	2.93	0.24 (0.07)	3.57	0.74 (0.08)	3.11	0.57 (0.06)	<.001 †	<.001 †	<.001 †	0.033 †‡
6	2.91	0.22 (0.07)	3.49	0.67 (0.07)	3.11	0.57 (0.06)	<.001 †	<.001 †	<.001 †	0.181 †
8	2.90	0.20 (0.07)	3.45	0.63 (0.08)	3.05	0.51 (0.06)	<.001 †	<.001 †	<.001 †	0.148 †
10	2.94	0.24 (0.07)	3.37	0.54 (0.07)	3.02	0.48 (0.05)	<.001 †	<.001 †	0.003 †	0.290 †
12	2.90	0.20 (0.07)	3.34	0.52 (0.08)	2.97	0.43 (0.05)	<.001 †	<.001 †	0.003 †	0.227

[1] Treatment comparisons are based on analysis of variance F-tests on change (CHG) from baseline, (on actual values at baseline).
[2] P-value footnotes: † =significant investigator effect (p <=0.05), ‡ =significant treatment-by-investigator interaction (p <=0.05).
[3] Baseline (BASE) is the average of the -0.5 hour and the 0 hour FEV1 measurement on Treatment Day 1.

REPEATED MEASURES ANALYSIS OF VARIANCE ON CHANGE FROM BASELINE

P-VALUES FOR OVERALL TESTS

Treatment Effect: <.001 Investigator Effect: <.001
TMT*INV Interaction: 0.466

P-VALUES FOR PAIRWISE TREATMENT COMPARISONS[3]

PLACEBO vs 50 MCG DISKUS: <.001 †
PLACEBO vs 50 MCG DISK: <.001 †
50 MCG DISKUS vs 50 MCG DISK: 0.092 †

Supporting data listing in
BIO$STAT_SLD:[000000.SLGA2004.TABLES]PFTTST2.SAS;16 - 03NOV95