CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-692 S001/002

MEDICAL REVIEW(S)

Medical Officer Review

Division of Pulmonary Drug Products (HFD-570)

Application #:	NDA 20-692	**Category of Drug:**	Long Acting Beta-Agonist
Sponsor:	GlaxoWellcome	**Route of Administration:**	Oral Inhalation
Proprietary Name:	Serevent Diskus	**Medical Reviewer:**	Susan Johnson, Pharm.D.
USAN/Established Name:	Salmeterol Inhalation	**Review Date:**	September 22, 1998

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
September 24, 1997	September 26, 1997	Efficacy Supplement	Pediatric Asthma
January 15, 1998	January 20, 1998	120 Day Safety Update	
August 12, 1998	August 13, 1998	Pre-app. Safety Update	
September 1, 1998	September 2, 1998	Correspondence	Data Files

Related Applications (if applicable)

Overview of Application and Review:

This is a pediatric efficacy supplement to support use of Serevent Diskus 50 mcg BID in children ages 4 to 11 for maintenance treatment of asthma and the prevention of bronchospasm. Pivotal studies include dose ranging Trial SLGA2016 and 12-week safety and efficacy Trials SLD-309 and SLGA3014. Doses of 25, 50 and 100 mcg of salmeterol were consistently statistically superior to placebo. In dose ranging comparisons, the 50 mcg dose performed consistently better than 25 mcg, although statistical differences were minimal. Some evidence of decline of effect during the two 12 week trials was shown for the 50 mcg salmeterol dose, suggesting the potential for tolerance in some patients. Some evidence of adverse withdrawal effects was observed. No significant safety concerns were associated with the pediatric population.

Outstanding Issues:

Agreement with the sponsor must be reached regarding final labeling content.

Recommended Regulatory Action

New Clinical Studies: _____ Clinical Hold
_____ May Proceed

NDA/Supplements: __X__ Approval
_____ Approvable

Signature: /S/ **Medical Reviewer** **Date:** 9-24-98

Concurrence: /S/ **Team Leader** **Date:** 9/24/98

cc: **Div File**
NDA 20-692
HFD-570: Jani, Johnson

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I. Background

Serevent Diskus was approved on September 19, 1997 for use ~~in~~ maintenance treatment of asthma and prevention of bronchospasm in adults and children age 12 years and older. The NDA approval was based on two 12 week pivotal studies comparing the Diskhaler formulation with albuterol and placebo controls, as well as appropriate information bridging the safety and efficacy of the Diskhaler and Diskus formulations. In addition, two 12 week placebo controlled trials were submitted in which the Diskus and Serevent Inhalation Aerosol (MDI) formulations were compared in adult and adolescent patients. As the currently approved labeling states, the Diskus and MDI formulations can be considered clinically comparable, however an equivalent response cannot necessarily be expected in each patient. The trials suggested that some patients respond better to the approved 42 mcg BID dose from the MDI formulation than to the 50 mcg BID Diskus formulation.

Serevent MDI was approved in February, 1994 for asthma and the prevention of exercise induced bronchospasm (EIB) in adults and adolescents. A pediatric MDI supplement was subsequently submitted proposing an indication in pediatric asthma and pediatric exercise induced bronchospasm (EIB), but was reviewed and not approved in April, 1995. As summarized in the November 10, 1997 filing review for the current Diskus supplement, the primary reason for not approving the pediatric asthma indication was a failure to show efficacy with respect to the active albuterol control. No placebo was included in the pivotal efficacy trials. In addition, the 21 mcg dose appeared to be somewhat more effective than the 42 mcg dose. The EIB trials, although suggestive of efficacy, were considered to be inadequately designed to support approval of the indication. The overall safety profile of the MDI in the pediatric population appeared similar to that of the adult population and failure to approve the MDI pediatric supplement does not preclude approval of the current submission.

S-002 for the Diskus proposes to extend the current indication in maintenance treatment of asthma and prevention of bronchospasm from the current lower limit of 12 years of age to pediatric asthma for patients as young as 4 years of age. The application is supported by dose ranging and pivotal safety and efficacy trials, as well as supplementary studies. Trial SLGA2016 was a placebo controlled dose ranging study comparing doses of 25 and 50 mcg of salmeterol via Diskus. This was followed by pivotal trials SLGA3014, which compared 25, 50 and 100 mcg of salmeterol BID via Diskus with albuterol 200 mcg QID via Rotacaps and placebo, and SLD-390, which compared 50 mcg doses of salmeterol BID via Diskhaler with placebo. Both of these latter trials were 12 weeks in duration. The combined N for these trials is 546 patients, including 211 who received the proposed salmeterol 50 mcg BID. The sponsor claims that, unlike the MDI outcomes, the 50 mcg salmeterol dose is more consistently efficacious than the 25 mcg dose.

There are nine supportive non-U.S. studies including three dose selection trials (SLPT02, SLPT08 and SLPT14), two 12 month trials (SLPT09 with placebo control and SLPT02 with active control), two six month placebo controlled trials (SLPX01 and

SLPX07), an active controlled trial (SLPT03) and an investigation of the interaction of salmeterol and terfenadine (SLPT07). The sponsor was told that long term U.S. data from the adult and adolescent population, as reviewed for the approval of the Diskus product, would be adequate to meet the requirements for long term data relevant to the pediatric population. This was based on the availability of foreign long term data in pediatrics (submitted as supporting data) and the presumption that shorter term trials do not indicate a unique safety concern in the pediatric (4 to 11 year old) population.

At a pre-sNDA teleconference with the sponsor on November 4, 1996, it was agreed the peak expiratory flow rates (PEFR) and forced expiratory flow rates (FEV_1) would serve as the primary endpoints. Emphasis was placed on the PEFR data because the general inability to conduct spirometry to measure FEV_1 in the youngest patients enrolled in the pivotal trials, i.e., four and five year old children, prevented the FEV_1 assessments from representing the entire study population. The FEV_1 data presented are important confirmatory data of the PEFR findings.

II. Chemistry, Manufacturing and Controls

This supplement proposes modifications in indications for the currently marketed Serevent (salmeterol xinafoate) Diskus Inhalation Powder for the pediatric population. The formulation contains 50 mcg salmeterol in lactose to 12.5 mg weight. Modification was made to this formulation to create a 25 mcg dose for investigational use and a placebo (lactose only). Some of the clinical trials discussed in this review employed the Serevent [redacted] for the Diskhaler device, not currently approved in the United States.

III. Preclinical Pharmacology / Toxicology

Given that the proposed formulation is a currently approved product and there are no specific preclinical pharmacologic concerns for the proposed 4 to 11 year old age group, there are expected to be no additional preclinical issues.

IV. Clinical Pharmacology and Biopharmaceutics

As noted in Dr. Bradley Gillespie's review, a limited pharmacokinetic sampling was undertaken in a non-U.S. trial, SLPT02. Sampling was inadequate to determine total salmeterol exposure or peak plasma concentrations, thus no meaningful comparison to adult pharmacokinetic data can be undertaken. These data are not required for approval of this supplement, given the extent of the clinical data available.

Dr. Gillespie commented in his review dated August 18, 1998 that it was necessary for the sponsor to submit results of Trial [redacted] prior to approval of this supplement. Per Ms. Jani's conversations with the sponsor, the study report for this trial has not been completed as of the data of this review. The sponsor intends to submit the results of this study as soon as they become available and to submit a labeling

supplement to modify labeling, if necessary. Dr. Gillespie concurs that this response is acceptable.

V. Conduct of Review

Dr. Nicklas' and Dr Himmel's medical reviews dated March 14 and March 15, 1995, respectively, were consulted to establish the historical background regarding the previous submission of pediatric salmeterol data in association with Serevent MDI. In addition, Dr. Johnson's review of the original NDA 20-692 for adult indications, dated June 16, 1997, was reviewed, as was the filing review for this supplemental application, dated November 10, 1997.

Complete reviews for the U.S. Trials SLGA2016 (dose ranging), SLD-390 (12 week pivotal safety and efficacy with [redacted] Diskhaler formulation) and SLGA3014 (12 week pivotal safety and efficacy with Diskus formulation) were conducted and appear in this review. Seven additional non-U.S. trials were briefly examined, primarily for safety outcomes, including:

Dose ranging trials - SLPT08 and SLPT14
12 month placebo controlled trial - SLPT09
12 month active controlled trial - SLPT02 (dose ranging design)
6 month placebo controlled trials - SLPX01 and SLPT07
Active controlled trial - SLPT03

The non-U.S. trials were conducted using the salmeterol Rotadisk/Diskhaler and doses of 25, 50 or 100 mcg. Given the differences in formulation, particularly uncharacterized differences in dose delivery, conclusions from non-U.S. dose ranging trials are not considered to have contributed substantially to dose selection for the Diskus formulation.

In addition, Dr. Meyer's review, dated September 17, 1998, regarding the supplement for indications in exercise induced bronchospasm in adults, adolescents and pediatric patients (SEI-001) was consulted, particularly for safety data and labeling recommendations.

VI. Auditing & Checking Functions

Given the recent approval of the Serevent Diskus product in adults, no requests were made of the Division of Scientific Investigations to conduct clinical trial audits of any investigational sites associated with the trials in this application.

Submission documents were reviewed including study reports, supplementary figures, tables and appendices, where necessary to confirm or modify primary analyses. Case report forms were reviewed for each patient discontinued from trials SLGA2016, SLD-390 or SLGA3014 due to serious adverse events.

VII. Dose Ranging Trial

Trial SLGA2016

Study Dates

First patient enrolled: January 3, 1996
Last patient completed: September 13, 1996
Single Protocol amendment: February 20, 1996. Minor protocol modifications that are not expected to have introduced bias into the trial.

Investigators

Kathryn Blake, Pharm.D., Jacksonville FL
S. Allan Bock, M.D., Boulder CO
James Kemp, M.D., San Diego CA
William Lumry, M.D., Dallas TX
Robert Nathan, M.D., Colorado Springs CO

Design

This was a randomized, double blind, double dummy, five-way crossover comparison of single doses of 25, 50 and 100 mcg via the Diskus, albuterol Rotacaps 200 mcg via Rotahaler and placebo in pediatric patients. Male and pre-menarchal females between the ages of 4 and 11 inclusive were eligible to enroll if they had been diagnosed with asthma at least 6 months prior to screening, demonstrated a baseline FEV_1 between 45 and 75 percent of predicted normal after withholding beta agonists and/or theophylline.

Each investigator was asked to enroll at least one 4 and one 5 year old patient. Enrollment of these patients could be based on baseline PEFR if it was concluded that spirometry assessments were too variable (> 10%). PEFR was required to be 45 to 75 percent of predicted normal if used as the primary eligibility criteria. Patients also needed to demonstrate 20 percent reversibility, on the appropriate assessment, 30 minutes following two puffs of Ventolin MDI.

Patients were required to be tolerant of withholding beta-agonists, theophylline, corticosteroids, ipratropium, atropine, and antihistamines for the specified number of hours prior to the screening visit and until completion of the post-treatment visit. In addition, influenza vaccination, macrolide antibiotics, tricyclic antidepressants, monoamine oxidase inhibitors, beta-receptor blocking agents, calcium channel blockers and NSAIDs were not to be used during the study. Fixed doses of immunotherapy, inhaled or intranasal corticosteroids or cromolyn or inhaled nedocromil were allowed, as were short-acting antihistamines and decongestants, if appropriately withheld prior to treatment visits.

Patients who had been diagnosed with a viral or bacterial infection of the upper or lower respiratory tract or sinuses in the six weeks prior to screening, or between screening

and treatment, were not eligible for study enrollment. Patients with a middle ear infection, without sinus or respiratory complications, were eligible to enroll. Patients with significant concomitant disease, abnormal 12-lead ECG or clinical laboratory findings or exposure to tobacco smoke for four or more hours per day were ineligible.

Procedures

Eligibility criteria were evaluated during the Screening Visit. The subsequent five treatment visits were separated by 3 to 14 days. Post-treatment evaluations were made at the fifth visit, following the last treatment. Treatment visits were conducted if baseline FEV_1 or PEFR was < 45 percent of predicted and within ±12 percent of the screening value. Data collected at each visit included a 12-lead EKG and 15 second rhythm strip (predose and 1.5 hours post-dose), serial vital signs and PEFR or FEV_1 (predose, 15 and 30 minutes postdose, and 1, 2, 3, 4, 6, 8, 10 and 12 hours postdose) and adverse event assessments. Physical examinations were conducted at screening and post-treatment. Patients age 6 to 11 had both FEV_1 and PEFR assessed, but patients age 4 or 5 who could not perform spirometry had only PEFR assessments.

For each treatment, patients were administered medication from three devices, two Diskus devices (containing placebo, 25 or 50 mcg of salmeterol per blister) and a [redacted] (either placebo or 200 mcg albuterol dose).

Endpoints

The primary measures of efficacy were spirometric measures of FEV_1 and PEFR, specifically, serial FEV_1 as AUC over baseline, as absolute values and as percent of predicted, to compensate for patient size variability. The following terms were applied to the analyses:

Baseline	- the average of –0.5 and 0 hour predose FEV_1 on a given study day.
Effect	- increase of at least 15 percent over baseline.
Onset	- interpolated timepoint within 4 hours of dose when effect is first observed.
Offset	- interpolated time at which response fell below 15 percent prior to the first of two consecutive timepoints showing lack of effect.
Duration	- time of offset minus onset.
Peak Effect	- maximum change in FEV_1 (percent above baseline).
AUC	- area above baseline minus area below baseline, if any.

Three summary statistics were calculated to provide a characterization of the entire dosing interval. The weighted average (WAVE) could be characterized as average designed to summarize the response as a single point, while the AUC (BL) is a representation of the entire response profile.

WAVE =	{0.25*(FEV3+FEV4) + 0.5*FEV5 + FEV6 + FEV7 + FEV8 + 2*(FEV9 + FEV10 + FEV11 + FEV12) / 12
%PAVE =	Same as above, using percent of predicted.
AUC(BL) =	0.125*FEV2 + 0.25*FEV3 + 0.375*FEV4 + 0.75*FEV5 + FEV6 + FEV7 + 1.5*FEV8 + 2(FEV9 + FEV10 + FEV11) + FEV12 – FEVBL*12

where FEV2 to FEV12 are measurements at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hr.

Safety endpoints included physical examinations, clinical laboratory tests, vital signs, 12-lead EKGs and clinical adverse events.

Statistical Considerations

Enrollment was planned for a total of 60 patients, 12 per each of five centers. The sample size calculation was based on having 80 percent power to detect a difference of 0.10L in FEV_1, using an alpha of 0.05 and assuming a standard deviation of 0.18L.

All efficacy analyses were conducted with the intent to treat population. PEFR and FEV_1 were designated as primary endpoints. While not specifically stated in the protocol, it was presumed that the sponsor was required to demonstrate efficacy on both endpoint. Emphasis was placed on the PEFR data due to its inclusion of the entire study population.

Analysis of variance F-tests were the primary statistical comparison for AUC(BL) and peak effect, Friedman's Chi-Square was used for onset and duration, Wilcoxon rank test was used for pairwise comparisons and McNemar's test was used to compare responders.

Patient Disposition

Sixty four patients were enrolled in the study and 60 completed the study. Two were discontinued due to AEs and two were discontinued due to a protocol violation.

The majority of patients were Caucasian and male (72 percent each). Mean age was 8.2 years, ranging from 4 to 11 years. Twelve patients were 4 or 5 years old, 17 patients were between 6 and 8 years of age and 35 were between 9 and 11. Thirty four percent were using a stable dose of inhaled corticosteroids, 30 percent used "anti-allergic" compounds and 28 percent used beta agonists. Most had a history of asthma between 1 and 10 years in duration.

Efficacy Outcomes

Serial PEFR values expressed as a percent of predicted, including baseline values, are presented in Table 1 on the following page.

Repeated measures ANOVA of change from baseline in PEFR, expressed as percent of predicted, indicate that each active treatment was superior to placebo. In addition, 25, 50 and 100 mcg salmeterol treatments was superior to albuterol. No statistically significant differences were seen among the Diskus treatments.

An analysis of individual timepoints for PEFR as a percent of predicted was undertaken using baseline as a covariate. Each Diskus treatment was statistically superior to placebo at each timepoint. Albuterol was statistically superior to placebo at Hour 0.25

through Hour 4, but no differences were seen between Hours 6 through 12. Albuterol was statistically superior to both 25 and 50 mcg Diskus at 0.25 hours and statistically superior to 25 mcg Diskus at 0.5 hours. From Hour 2 to Hour 12, 50 and 100 mcg Diskus treatments were statistically superior to albuterol. Diskus 25 mcg was superior to albuterol from Hour 3 through Hour 12. Among the Diskus treatments, the 100 mcg treatment was statistically superior to the 25 mcg treatment at Hour 0.25 and the 50 mcg treatment was statistically superior to the 25 mcg treatment at Hour 1. The dose response profiles of PEFR as a percent of predicted are illustrated in Appendix 1.

In addition to PEFR as a percent of predicted, absolute serial PEFR were analyzed as change from baseline. Repeated measures analyses showed the same overall statistical outcomes, and covariate analyses at each timepoint showed the same statistical outcomes, as percent of predicted analyses.

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

Time (Hrs)	Placebo (N=63)	200mcg Albuterol (N=64)	25mcg Diskus Salmeterol (N=61)	50mcg Diskus Salmeterol (N=60)	100mcg Diskus Salmeterol (N=61)
Baseline[b]	72.7	74.4	73.7	75.5	74.9
0.25	78.9	91.2	85.1	86.6	89.9
0.5	80.9	95.3	89.8	91.6	92.0
1.0	83.1	**95.9**	93.1	96.8	96.1
2.0	83.7	94.4	96.4	98.1	98.8
3.0	**84.3**	91.0	**96.7**	**99.3**	**100.0**
4.0	81.6	88.0	95.8	**99.3**	99.4
6.0	82.1	84.0	95.1	97.7	98.5
8.0	82.1	84.0	95.6	96.1	97.0
10.0	83.5	84.3	94.5	95.2	96.7
12.0	82.9	82.7	91.8	94.9	96.8
WAVE[c]	82.7	86.5	94.4	96.5	97.5
CWAVE[d]	10.0	12.1	20.7	21.0	22.6

[a] Maximum percent of predicted PEFR values in each treatment are presented in bold-faced type.
[b] The baseline mean (PEFRBL) is the average of the –0.5 hour and 0.0 hour PEFR values. The baseline for percent of predicted PEFR is (PEFRBL/predicted PEFR)%.
[c] WAVE is the weighted average of post-dose percent of predicted PEFR over 12 hours.
[d] CWAVE is the change from baseline in the WAVE (ie, WAVE minus Baseline).

Table 2 reports functions of serial PEFR. Each active treatment was statistically superior to placebo in that they showed a higher number of responders, a shorter time to onset, a higher peak effect and a longer duration of effect. Each Diskus treatment was statistically superior to placebo and to albuterol with respect to AUC(BL). In addition, each Diskus strength was superior to albuterol with respect to duration of effect. The onset of 25 mcg salmeterol was statistically longer than for albuterol, although no differences were seen between albuterol and either the 50 and 100 mcg Diskus treatments. The 50 mcg Diskus treatment showed a statistically higher number

of responders than the 25 mcg Diskus treatment, although there was no statistically significant difference in responder rate between 50 and 100 mcg Diskus.

Table 2: Functions of Serial PEFR
Definition of Response: Effect Achieved Within 4 Hours

Function	Placebo (N=63)	200mcg Albuterol (N=64)	25mcg Diskus Salmeterol (N=61)	50mcg Diskus Salmeterol (N=60)	100mcg Diskus Salmeterol (N=61)
% of responders[a]	63	84	85	93	85
Median onset of effect (h)	1.3	0.2	0.4	0.4	0.2
Mean max. effect (% change)	32.4	39.2	47.2	42.3	45.7
Median duration of effect (h)	1.3	5.5	11.6	11.5	11.8
Mean AUC(BL) (L/h)	896	986	1289	1302	1341

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

Serial FEV_1 means are shown in Table 3, and graphically Appendix 2, as a percent of predicted. Repeated measures analyses indicate that, overall, albuterol was statistically superior to placebo and the 25, 50 and 100 mcg salmeterol doses were statistically superior to placebo and albuterol. In addition, the 100 mcg dose was statistically superior to both the 25 and 50 mcg strengths.

Table 3: Percent of Predicted (%) Serial FEV_1 Values[a]

Time (Hrs)	Placebo (N=57)	200mcg Albuterol (N=58)	25mcg Diskus Salmeterol (N=55)	50mcg Diskus Salmeterol (N=54)	100mcg Diskus Salmeterol (N=55)
Baseline[b]	67.0	67.8	68.5	68.3	66.7
0.25	72.3	84.4	79.5	78.8	81.1
0.5	73.1	85.0	82.3	81.8	84.3
1.0	75.6	**86.2**	85.2	85.5	87.3
2.0	**77.0**	83.9	86.3	85.6	87.9
3.0	73.6	80.9	**88.4**	86.9	**89.5**
4.0	75.2	78.6	87.1	**87.3**	88.0
6.0	73.4	77.9	86.7	84.0	86.2
8.0	72.7	74.9	84.6	84.1	85.9
10.0	75.0	75.7	84.6	82.8	85.4
12.0	74.0	75.4	83.6	82.5	85.1
WAVE[c]	74.2	78.0	85.3	84.1	86.3
CWAVE[d]	7.2	10.2	16.8	15.8	19.6

[a] Maximum percent of predicted FEV_1 values in each treatment are presented in bold-faced type.

[b] The baseline mean (FEVBL) is the average of the –0.5 hour and 0.0 hour FEV_1 values. The baseline for percent of predicted FEV_1 is (FEVBL/predicted FEV_1)%.

[c] WAVE. is the weighted average of post-dose percent of predicted FEV_1 over 12 hours.

[d] CWAVE is the change from baseline in the WAVE (ie, WAVE minus Baseline).

Analyses at individual timepoints indicate that albuterol was superior to placebo, except at Hours 4, 8, 10 and 12. Each Diskus strength was superior to placebo at all timepoints. For 25 and 50 mcg Diskus, albuterol was superior at Hour 0.25, but the Diskus treatments were superior to albuterol from Hour 3 to Hour 12. The 100 mcg Diskus was superior to albuterol from Hour 1 to Hour 12. There were no statistically significant differences between the 25 and 50 mcg salmeterol strengths. The 100 mcg strength was statistically superior to the 25 mcg strength at Hours 0.25 through Hour 2 and at Hour 8. The 100 mcg strength was statistically superior to the 50 mcg strength at all timepoints except Hour 6.

Analyses of change from baseline yielded similar statistical outcomes. Functions of serial FEV_1 are shown in Table 4. Each active treatment was statistically superior to placebo for each function. No statistically significant differences were seen among active treatments with regard to number of responders. The onset of effect was statistically longer for the 25 mcg Diskus treatment than for albuterol and shorter for the 100 mcg Diskus treatment than either the 25 or 50 mcg treatments.

Peak effect was statistically greater for the 100 mcg Diskus than for any of the other active treatments. Duration of effect was statistically longer for the 25, 50 and 100 mcg Diskus treatments than for albuterol and statistically longer for the 100 mcg than for either the 25 or 50 mcg treatments. AUC(BL) was statistically greater for each of the salmeterol treatments than for albuterol and statistically greater for the 100 mcg Diskus than for either the 50 or 25 mcg treatments.

Table 4: Functions of Serial FEV_1

Definition of Response: Effect Achieved Within 4 Hours

Function	Placebo (N=57)	200mcg Albuterol (N=58)	25mcg Diskus Salmeterol (N=55)	50mcg Diskus Salmeterol (N=54)	100mcg Diskus Salmeterol (N=55)
% of responders*	61	86	89	81	91
Median onset of effect (h)	1.4	0.1	0.2	0.2	0.2
Mean max. effect (% change)	23.8	34.7	36.3	35.5	42.2
Median duration of effect (h)	0.3	3.2	11.5	11.5	11.8
Mean AUC(BL) (L/h)	5.4	6.3	7.9	7.7	8.4

* Responders were defined as those patients who achieved a ≥15% increase in FEV_1 over baseline (average of the –0.5 hour and 0.0 hour FEV_1 values) within 4 hours post-dose.

Comparison by age groups was undertaken using the weighted average (WAVE) as defined in the efficacy endpoints section. The difference between the WAVE value and the more traditional AUC(BL) is that in the WAVE calculation, assessments beginning at 0.25 hours are included in the calculation and each assessment is weighted by the amount of time between it and the preceding timepoint. The total area is then divided by the 12 hour interval to create an average. In AUC(BL), the zero timepoint is used and each assessment is weighted by half of the time interval preceding it plus half of the time interval following it. The baseline is multiplied by 12 and subtracted from the total area. The overall WAVE PEFR and FEV_1 values are presented in Table 5 with values by age subgroup (children less than nine years old versus age nine or older).

Table 5: WAVE Values by Age

Age	Placebo	200 mcg Albuterol	25 mcg Diskus Salmeterol	50 mcg Diskus Salmeterol	100 mcg Diskus Salmeterol
WAVE PEFR					
Overall	82.7	86.5	94.4	96.5	97.5
< 9 years	81.1 (N = 28)	89.3 (N = 29)	93.8 (N = 27)	96.1 (N = 26)	99.4 (N = 26)
≥9 years	84.0 (N = 35)	84.2 (N = 35)	94.9 (N = 34)	96.7 (N = 34)	96.0 (N = 35)
WAVE FEV_1					
Overall	74.2	78.0	85.3	84.1	86.3
< 9 years	78.7 (N = 22)	84.1 (N = 23)	89.3 (N = 21)	87.2 (N = 20)	92.4 (N = 20)
≥9 years	71.3 (N = 35)	74.1 (N = 35)	82.9 (N = 34)	82.3 (N = 34)	82.8 (N = 35)

PEFR WAVE means reflect that the patients less than nine on albuterol and 100 mcg Diskus treatments showed a greater response than the older patients. For FEV_1 WAVE values, the younger patients showed a consistently greater response. The difference in PEFR and FEV_1 trends responses may be due in part to the smaller number of patients less than nine who were able to perform the spirometric maneuvers. Because the WAVE is a weighted average of the entire 12 hour assessment interval, the differences among groups can not be attributed specifically to onset, duration or peak responses. The Diskus treatments performed better than the albuterol and placebo treatments for both older and younger patients. A dose response trend was suggested among the Diskus treatments for PEFR values, but not for FEV_1 values. Differences between the Diskus treatments do not appear to be substantial enough to merit further exploration of age-related responses.

Efficacy Conclusions

PEFR data indicate that 25, 50 and 100 mcg of salmeterol administered via the Diskus are superior to placebo. Each Diskus strength shows differences as compared to albuterol, particularly in that the salmeterol treatments had both a slower onset of action and longer duration of effect. There is a minor dose response trend among the three doses that is statistically evident between the 25 and 50 mcg doses at Hour 1 and in the greater number of responders associated with the 50 mcg treatment. Comparable statistical differences were not seen between the 50 and 100 mcg treatments.

FEV_1 outcomes are consistent with PEFR in that all Diskus treatments were shown to be superior to placebo. Duration of the salmeterol treatments was again shown to be superior to albuterol. The dose response among the Diskus treatments was not as strongly supported by this measure, although the 100 mcg dose consistently performed better than the other two dosage strengths. Despite minor numerical trends, there was no statistical evidence that the 25 mcg dose was superior to the 50 mcg dose.

It is notable that the nominal 25 mcg dose was delivered via a formulation that was developed for the purpose of evaluating dose response. Its in vitro dose delivery characteristics have not been extensively evaluated and were not controlled to the same extent as the marketed 50 mcg per puff device. The resultant variability of data, or relative dose delivered, can not be characterized.

Safety Outcomes

No deaths were reported during the study.

Patient #10184 was the only individual to experience a **serious adverse event**. Two days following treatment with 100 mcg Diskus, the patient developed moderate sinusitis and severe bronchitis leading to a severe asthma exacerbation that required hospitalization. The event was not thought to be related to treatment. This patient was discontinued from the study due to a protocol violation (use of excluded concomitant medication).

Adverse events causing discontinuation included a URTI with pharyngitis in Pt. # 10174 following placebo treatment and a URTI in Pt. # 10178 following albuterol treatment.

Asthma exacerbations were experienced by 18 patients in 26 separate events. Twelve of the events were attributed to withholding medication, six were attributed to serial PFT's and the remainder to various URIs. One patient, #10184, was discontinued due to a protocol violation that led to hospitalization.

Other adverse events were generally infrequent. Those that occurred in at least three percent (more than one individual) of any of the Diskus treatment groups, and more frequently in one of the Diskus groups than in the placebo group, are summarized with the overall number of events in Table 6. The only event that occurred in at least three percent of the albuterol group was upper respiratory inflammation (2 patients, 3 percent). There were no reports of this event among any of the other groups. There appeared to be a dose response relationship in the frequency of events among the Diskus treatments, although the rate of events for all Diskus groups remained lower than that of the placebo group.

Table 6: Rate of Adverse Events

	Placebo (N = 63)	Albuterol 200mcg (N = 64)	25 mcg Diskus (N = 62)	50 mcg Diskus (N = 60)	100 mcg Diskus (N = 61)
All Events	9 (14%)	7 (11%)	0	5 (8%)	7 (11%)
Sinusitis	1 (2%)	0	0	2 (3%)	2 (3%)
Nausea and vomiting	1 (2%)	0	0	3 (5%)	0
Headache	0	1 (2%)	0	0	2 (3%)

Clinical laboratory evaluations revealed only one patient with post-treatment laboratory values outside sponsor-defined threshold values. Patient #10185 had a glucose value of 113 mg/dL at screening and 184 mg/dL at post-treatment.

Interpretability of this information is limited because samples were collected under non-fasted conditions.

Vital sign data include pulse and systolic and diastolic blood pressure.

Pulse rate was increased from baseline for each treatment, with the greatest mean changes observed in the albuterol and 100 mcg Diskus treatments. Maximum mean change in the 100 mcg Diskus group was 9.4 bpm at Hour 6 and 8.8 bpm at Hour 10 for albuterol. Looking at the proportion of patients who increased or decreased by 15, 20 or 30 bpm from baseline in each group, a slight dose response among the 25, 50 and 100 mcg Diskus treatments can be observed. Overall, none of the Diskus treatments were markedly different than placebo. Maximal increases were seen following albuterol treatment, with 20 percent of patients showing an increase of ≥ 30 bpm, and maximal decreases were seen following the 50 mcg Diskus treatment, with five percent of patients showing a decrease of ≥ 30 bpm.

Mean increases in **systolic blood pressure** ranged from 1.4 to 2.2 mmHg among the treatment groups and were highest in the Diskus 25 and 100 mcg groups. Mean decreases ranged from 1.0 to 1.5 mmHg and the largest decline was seen in the albuterol group. Categorical analyses of increases and decreases did not suggest clinically meaningful differences among the treatments, including placebo. **Diastolic blood pressure** data also showed minimal mean changes (maximum increase of 1.0 mmHg in the albuterol group and decrease of 3.1 mmHg in the 50 mcg Diskus group). Categorical analyses did not reflect clinically meaningful differences among the treatment groups.

EKGs were analyzed for rhythm abnormalities, QT_c and heart rate. EKGs were conducted at pre-dose and 90 minutes post-dose. They were considered significantly abnormal at post-dose for two patients with tachycardia. Pt. #10104 had been treated with albuterol and Pt. #10166 had been treated with 50 mcg Diskus.

Mean **QT_c** intervals were shortened between pre-dose and post-dose for placebo and albuterol, lengthened for the 50 and 100 mcg Diskus treatments and unchanged for the 25 mcg Diskus. The maximum change was an increase of 7 msec in the 100 mcg Diskus group. Four patients were reported to have QT_c intervals > 440 msec. Those patients for whom events were reported in association with albuterol dosing included Pt. # 10106 whose pre-dose value was 459 msec, but otherwise < 440 msec and Pt. #10130 whose pre-dose and post-dose values were 447 and 443 msec, respectively. Pt. #10144 showed a placebo post-dose value of 444 msec after a pre-dose value of 412 msec and Pt. #10169 had a post-dose value of 444 msec after a pre-dose value of 413 msec and treatment with 50 mcg Diskus.

Each treatment was associated with an increase in **heart rate** between pre-dose and post-dose ranging from 4 to 10 bpm. There was a minimal dose response seen among the Diskus treatments. The 25 and 50 mcg treatments were similar to both placebo and albuterol (mean of 82, 84, 83 and 83 bpm, respectively), while the 100 mcg treatment

appeared to lead to slightly higher (88 bpm) heart rates and showed the greatest net increase.

Ranges for the data for each of the vital sign and EKG parameters fail to suggest outliers that merit particular concern.

Physical examinations revealed abnormalities at the screening, particularly in the ear, nose and throat system (52 percent of patients). Detrimental changes occurred in one patient's eyes, six patients' ENT systems and 4 patients' respiratory systems. Comments from the investigators detailing the observations were reviewed and none of the changes can be considered serious. In addition, they can not be associated with a single treatment, given that physical examinations were conducted only at screening the post-treatment visit (following the final treatment).

Given the minor safety concerns presented by these data, further evaluation by age group is considered unnecessary.

Overall, safety data, particularly vital sign and EKG data, suggest that there is a dose response among the Diskus treatments, which most clearly separates the 25 mcg dose from the 50 and 100 mcg doses. None of the Diskus treatments appeared to pose significantly greater clinical safety concern than the albuterol treatment when assessed in this single dose study.

Conclusions

Efficacy data suggest that there is a dose response among the treatments, however there appears to be relatively small gains between levels. PEFR data provide more substantial support of the superiority of both the 50 and 100 mcg doses relative to the 25 mcg dose, while FEV_1 data primarily support the superiority of the 100 mcg dose relative to the other two doses. Age differences do not appear to significantly affect efficacy outcomes.

Safety data support the safety of each Diskus dose level, but are also suggestive of a dose response.

Based in part on these data, the sponsor chose to pursue development of the 50 mcg dose (the approved dose for patients age 12 years and older). This appears to adequately optimize the relative benefit and risk information derived from this trial. Long term studies described in the subsequent sections will provide additional information regarding the safety and efficacy of the selected dose.

VIII. Pivotal Safety and Efficacy

SLD-390

Study Dates

First patient enrolled: January 10, 1994
Last patient completed: November 11, 1994
Single protocol amendment:
January 18, 1994. Added Holter monitoring prior to dosing on Day 1 in addition to treatment Week 12. Other changes were minor and not expected to have had significant impact on trial outcomes.

Investigators

Edwin Bronsky, M.D., Salt Lake City UT
Paul Chervinsky, M.D., North Dartmouth MA
William Howland, M.D., Austin TX
James Kemp, M.D., San Diego CA
Craig LaForce, M.D., Raleigh NC
Federico, Montealegre, D.V.M., Ph.D., Ponce PR
David Pearlman, M.D., Aurora CO
Stephen Pollard, M.D., Louisville KY
Bruce Prenner, M.D., San Diego CA
Steven F. Weinstein, M.D., Huntington Beach CA
James Wolfe, M.D., San Jose CA

Design

This trial was a randomized, double-blind, parallel group comparison of salmeterol powder via [redacted] Diskhaler 50 mcg BID versus inhaled placebo BID in pediatric patients. Male and premenarchal females were eligible to enter the study if they were between the ages of 4 and 11 years of age, inclusive, at Screening, had been diagnosed with asthma at least 6 months prior to Screening and had baseline PEFR and/or FEV_1 values between 50 and 80 percent of predicated normal. Children age four or five were required to meet PEFR criteria, while children age six to eleven were required to meet both PEFR and FEV_1 requirements.

Demonstration of reversible airway disease was required in children age 6 and older (15 percent improvement in FEV_1 following two puffs of Ventolin). Each of the investigators was asked to enroll a sufficient number of four and five year olds to comprise at least one-third of their study population. Eligibility criteria regarding concomitant disease and medication use was similar to that of the dose ranging trial, SLGA2016, described in the previous section. Concurrent use of fixed regimens of immunotherapy, inhaled or intranasal corticosteroids, cromolyn or nedocromil sodium, and intermittent use of selected antihistamines, was allowed during the study. Ventolin MDI was used as needed for symptomatic treatment.

Procedures

A flowchart of procedures appears in Appendix 3. Patients who met criteria at Screening were enrolled in a 7 to 14 day lead-in period during which each patient received placebo BID with Ventolin MDI back-up. At the end of the lead-in period, patients' diaries were assessed. Patients were enrolled into the double blind portion of the trial if they had not experienced an asthma exacerbation or lower respiratory tract infection, compliance was between 75 and 125 percent and there were no protocol violations.

During the 12 week, double-blind period, patients were assigned to receive salmeterol 50 mcg or placebo via [redacted] BID. Clinic visits were conducted every 2 weeks. For the purposes of this review, Day 1 is the initiation of double blind treatment and Weeks 1 to 12 correspond to the weeks of the double blind treatment. At Day 1 and Week 12 visits, serial PFTs (FEV_1, FVC and $FEF_{25-75\%}$) and PEFR evaluations were conducted at 30 minutes and immediately pre-dose and at 15 and 30 minutes and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours post-dose. Children age 4 or 5 who could not perform the spirometric maneuvers provided PEFR measurements only. At Weeks 4 and 8, PEFR and FEV_1 data were collected pre-dose and 2 hours post-dose.

Between clinic visits in the double-blind period, patients recorded the following in a diary format: daily morning and evening PEFR (both prior to dosing), frequency of self-medication with back-up Ventolin MDI, frequency of nighttime awakenings, asthma symptom scores and frequency of asthma exacerbations. Physician global assessments were recorded at clinic visits at Screening and Weeks 4, 8 and 12. The Functional Status II-R (FSII-R) and the Sleep Scale – Children (SLP-C) were used to assess quality of life at Screening and clinic visits at Weeks 6, 10 and post-treatment. Experience of the parent/guardian in relationship to patient's asthma was recorded as a pilot using the New England Medical Center Child Health Survey-Long (NEMCH) at Screening and Week 12.

A post-treatment period of 7 to 14 days followed the Week 12 visit. Patients continued to complete their diaries during this period and were evaluated at a post-treatment visit at the end of this period.

Endpoints

Primary efficacy endpoints related to FEV_1 and PEFR are similar to those described for Trial SLGA2016. Primary analyses were conducted using Day 1 and Week 12 data. Number of responders and onset of effect were assessed differently than in SLGA2016. Both were calculated twice, looking for 15 percent improvement over baseline at 30 minutes and 4 hours after dosing. Baseline, which was measured on each treatment day in the previous study, was the mean of the Hour -0.5 and 0 timepoints on Day 1 for the current study.

Other efficacy endpoints included the spirometric assessments at Weeks 4 and 8 and the daily diary data. Patient-rated asthma symptom scores for chest tightness,

shortness of breath, wheezing and coughing, and the physician global assessment, were made using the following 6-point scale:

0 = No symptoms
1 = Some symptoms PRESENT that caused little or no discomfort
2 = MILD symptoms that were ANNOYING to the patient, but caused little or no discomfort
3 = MODERATE symptoms that caused DISCOMFORT, but did not affect normal daily activities
4 = SEVERE symptoms which INTERFERED at least once today with normal at least once today with normal activities
5 = Symptoms SO SEVERE that the patient COULD NOT go to school/do other normal activities.

Safety endpoints included clinical adverse events (evaluated at each clinic visit), clinical laboratory evaluations (evaluated at Screening and Week 12), 12 lead EKGs and 15 second rhythm strips (evaluated at Screening and pre-dose and 1.5 hours post-dose at Day 1 and Weeks 4, 8 and 12), continuous Holter monitoring (evaluated at a subset of five study centers for 12 hours on Day 1 and Week 12), vital signs (recorded with serial pulmonary function measurements), pulmonary auscultation (performed at each clinic visit), and physical examinations (conducted at Screening and Week 12).

Statistical Considerations

A sample size of 80 completed patients per treatment, with approximately 65 patients between 6 and 11 years of age, was calculated to provide at least 80 percent power of detecting a difference of 0.15 L in FEV_1 between two treatment groups with a significance level of 0.05. All analyses were conducted with the intent to treat population.

Patient Disposition

A total of 207 patients completed the single-blind placebo lead-in phase. Thirty three additional patients were screened and not enrolled in the double blind phase due to failure to meet entry criteria (n = 23), adverse events (n = 6) or asthma exacerbation (n = 4). Of the 207 who entered the double blind phase, 187 completed the trial and 20 were withdrawn. A summary of the disposition of patients appears in Table 7. Salmeterol and placebo treatments appear comparable with respect to patient disposition.

Table 7: Patient Disposition Summary

	Number of Patients		
	Placebo	Salmeterol	Total
Enrolled	105	102	207
Completed	95	92	187
Withdrawn:	10	10	20
Adverse event	3	3	6
Asthma instability/exacerbation	3	2	5
Lack of efficacy	2	2	4
Protocol violation	1	2	3
Lost to follow-up	1	1	2

The majority of patients were male (69 percent) and "Caucasian" (75 percent). Eleven percent of patients were "Black", 12 percent were "Hispanic" and the remainder were "Oriental" or "Other." Treatment groups were comparable with respect to these parameters.

Age ranged from 4 to 11 years in both treatment groups, with means of 8.3 years and 8.5 years in the placebo and salmeterol treatment groups, respectively. There was some difference between the treatment groups with respect to distribution of ages as seen in Table 8.

Table 8: Age Distribution

	Placebo (N = 105)	Salmeterol 50 mcg (N = 102)
4-5 years	21 (20%)	11 (11%)
6-8 years	27 (26%)	33 (32%)
9-11 years	57 (54%)	58 (57%)

The history of asthma was consistent between groups in terms of duration and number of hospitalizations or episodes of acute care in the previous year (a total of 11 percent of patients had been hospitalized and 56 percent had received acute care). Nocturnal symptoms were reported by 63 percent of each treatment group. Approximately 85 percent of each group reported that they suffered from an allergic disorder in addition to asthma.

Regular use of concomitant asthma medication during treatment was reported by 85 percent of the population, with 57 percent reporting use of corticosteroids, 32 percent using "other anti-inflammatories" and 39 percent using bronchodilators. A somewhat greater proportion of placebo patients than salmeterol patients reported use of albuterol for asthma exacerbation (47 versus 29 percent).

Efficacy Outcomes

Serial PEFR values, expressed as a percent of predicted, including baseline values, are presented in Table 9 for Day 1 and Week 12. Appendix 4 contains a graphic representation of these data. On both treatment days, pairwise comparisons showed that mean values for salmeterol were statistically higher than for placebo at each timepoint. Mean values for both groups were consistently higher at Week 12 than on Day 1. Absolute PEFR data were analyzed as change from baseline and comparable findings were observed.

Table 9: Percents of Predicted (%) Serial PEF Values

Time (hr)	Treatment Day 1		Treatment Week 12	
	Placebo (n=105)	Salmeterol 50mcg (n=101)	Placebo (n=93)	Salmeterol 50mcg (n=91)
Baseline	85.0	85.2	85.5	86.6
-0.5	NA	NA	92.6	99.0**
0.0	NA	NA	93.9	98.9**
0.25	88.5	96.7*	95.7	102.9**
0.5	89.9	99.8*	97.2	105.3**
1	92.1	102*	99.2	106.9**
2	93.0	105*	***101.7***	107.3**
3	93.0	***106****	101.4	***109.7****
4	93.5	105*	100.8	109.6**
5	***94.0***	105*	99.4	107.9**
6	92.0	104*	100.2	107.6**
7	91.6	104*	98.6	107.0**
8	91.5	103*	98.6	106.5**
9	92.4	104*	98.4	105.3**
10	90.6	102*	98.2	104.7**
11	91.0	102*	97.4	104.4**
12	90.5	101*	97.7	104.2**

*p<0.001 vs. placebo - Day 1; ** p≤0.038 vs. placebo - Week 12 (ANOVA F-test)
Note: maximum percent of predicted values bolded

Comparison of percent predicted PEFR between the subgroups of children age 4 to 8 and those age 9 to 11 are presented below in Table 10. These findings are consistent with the dose ranging study, SLGA2016, in that younger children had a consistently greater change than older children for both placebo and salmeterol. This appears to be due in part to their higher baselines, but also appears attributable to a greater bronchodilation response.

Table 10: Comparison of Percent Predicted 12-hour Serial Mean PEF by Age Group on Day 1 and at Week 12

Time	Ages 4-8 Years				Ages 9-11 Years			
	Day 1		Week 12		Day 1		Week 12	
	Placebo (n=48)	Salmet (n=43)	Placebo (n=43)	Salmet (n=40)	Placebo (n=57)	Salmet (n=58)	Placebo (n=50)	Salmet (n=51)
Baseline	86.4	87.0	86.9	88.2	83.8	83.8	84.2	85.3
0.25 hr	89.5	99.5	98.7	107.6	87.7	94.6	93.0	99.2
Peak	98.1	111.4	105.6	116.7	90.5	102.8	98.7	104.5
12 hr	93.0	102.9	101.0	110.4	88.3	99.5	94.9	99.3
Timepoints at <100% of predicted	All	0.25 hr	-0.5 to 0.5 hr	None	All	0.25, 0.5 11,12 hr	All	-0.5 to 0.5 hr and 9-12 hr
Timepoints at ≥100% of predicted	None	0.5-12 hr	1-12 hr	All	None	1-10 hr	None	1-8 hr

Percent predicted PEFR were assessed by corticosteroid use. On Day 1, both treatments had slightly higher means among corticosteroid users. However, at the

Week 12 visit, this finding was reversed among placebo patients. The salmeterol patients at Week 12 did not show a consistent difference between users and non-users. The salmeterol treatment effect was evident among both users and non-users at Day 1 and Day 12.

Functions of serial PEFR, such as number of responders, onset, etc., were not analyzed, although functions of serial FEV_1 will be discussed in a subsequent section.

Table 11 depicts mean **serial FEV_1** data as a percent of predicted and a graphic of these data is contained in Appendix 5. As with PEFR data, the salmeterol means were statistically greater than placebo at each timepoint. Although mean values for the placebo group were somewhat higher at Week 12 than on Day 1, the converse is true for the salmeterol group. The absolute differences between salmeterol means at Day 1 and Week 12 are small. Further evaluation of changes among individuals were undertaken to determine the clinical relevance of this finding and will be described later in this review.

Percents of Predicted (%) Serial FEV_1 Values

	Treatment Day 1		Treatment Week 12	
Time (hr)	Placebo (n=84)	Salmeterol 50mcg (n=91)	Placebo (n=75)	Salmeterol 50mcg (n=81)
Baseline	75.1	78.1	75.3	78.9
-0.5	NA	NA	78.0	83.3**
0.0	NA	NA	79.1	83.9**
0.25	77.0	86.0*	80.2	87.1**
0.5	77.7	88.0*	80.7	89.2**
1	***78.6***	90.7*	82.4	90.2**
2	78.3	***92.3****	82.5	91.0**
3	78.5	92.1*	***82.9***	***91.9****
4	77.6	91.1*	82.4	90.7**
5	76.9	91.0*	82.0	89.9**
6	77.2	90.9*	81.5	89.5**
7	75.5	89.5*	80.8	88.7**
8	75.1	90.0*	80.0	88.2**
9	75.6	89.2*	79.6	88.2**
10	75.3	89.0*	80.8	86.8**
11	75.8	87.1*	80.4	87.4**
12	75.0	86.6*	79.8	86.7**

*$p<0.001$ vs. placebo - Day 1; **$p\leq0.005$ vs. placebo - Week 12 (ANOVA F-test)
Note: maximum mean percent of predicted values bolded

Mean change from baseline analyses reflect the same statistical superiority of salmeterol means, as well as the same trends in each treatment group between Day 1 and Week 12. Again, mean differences within the salmeterol group at the two timepoints are relatively small.

FEV_1 outcomes were not analyzed by age group, given that the 4 to 8 year subgroup would be substantially limited due to the inability of 4 to 5 year olds to complete spirometric assessments.

Serial FEV_1 as a percent of predicted was analyzed by inhaled corticosteroid use. On Day 1 and at Week 12, corticosteroid users had slightly higher means for both the salmeterol and placebo groups. This finding differs from the Week 12 trends of the parallel analysis of PEFR data in which the small advantage shown by corticosteroid users at Day 1 was no longer evident at Week 12. The superiority of salmeterol relative to placebo was evident in both user and non-users at each timepoint.

Functions of serial FEV_1 are shown in Table 12, looking at effect achieved within four hours of dosing. Proportion of responders, median time to onset of effect, mean maximum effect, median duration of effect and AUCs (calculated as both the area of the FEV_1 response-time profile above baseline and above a 15 percent improvement over baseline) were each statistically superior in the salmeterol group relative to placebo on Day 1. The same statistical findings were not observed at Week 12, apparently due largely to the improvements in spirometry in placebo patients. However, there were declines within the salmeterol group in each parameter, most notably the decrease in median duration of effect from 4.7 on Day 1 to 1.9 hours at Week 12.

Table 12: Functions of Serial FEV_1
Definition of Response: Effect Achieved within 4 Hours

Function	Treatment Day 1		Treatment Week 12	
	Placebo	Salmeterol 50mcg	Placebo	Salmeterol 50mcg
% Pts achieving ≥15% increase over baseline	27%	64%#	51%	63%
Median onset of effect (hr)	12.00	0.89*	2.58	1.08
Mean max effect (max % change from baseline)	13.6	27.4*	19.4	25.8
Median duration of effect (hr)	0.0	4.7*	0.0	1.9
Mean AUC(15%) (L-h)	0.0	1.2*	0.6	1.1
Mean AUC(BL) (L-h)	0.4	2.9*	1.5	2.6

#p<0.001 vs. placebo (Fisher's Exact test); *p<0.001 vs. placebo (van Elteren)

Given that the mean onset observed in the previous analysis was consistently close to one hour for salmeterol, and longer for placebo, the functions of serial FEV_1 analyses using a definition of 30 minute onset did not provide additional insight into the outcomes of the trial.

To further explore individual outcomes of the trial, the percentage of patients whose FEV_1 reached at least 15 percent above baseline during serial assessment are presented in Table 13. Among placebo patients, a clear increase in the proportion of patients who did demonstrate an "effect" is observed between Day 1 and Week 12. Conversely, a decline in the number of patients who reached this threshold is seen between Day 1 and Week 12 among salmeterol patients. Between 34 and 56 percent of salmeterol patients were observed to have improved at least 15 percent above baseline at each Day 1 post-dose assessment, while only 30 to 54 percent of salmeterol

patients were similarly improved at Week 12. The same trend was observed when the serial FEV_1 data were examined to look for improvement of at least 12 percent over baseline.

Table 13: Percentage of Patients with ≥15% Increase in FEV_1 Over Time*

	Percentage of Patients			
	Treatment Day 1		Treatment Week 12	
Time (hr)	Placebo (n=84)	Salmeterol 50mcg (n=91)	Placebo (n=75)	Salmeterol 50mcg (n=81)
-0.5	NA	NA	26	21
0.0	NA	NA	25	25
0.25	10	34	28	31
0.5	6	37	33	42
1	12	45	33	44
2	11	54	36	49
3	***13***	***56***	***40***	***54***
4	11	54	33	49
5	***13***	54	37	47
6	***13***	***56***	33	42
7	6	52	36	41
8	7	47	35	40
9	11	43	27	35
10	11	49	32	35
11	11	42	27	37
12	6	42	28	30

*All values are relative to the average of the -0.5 hr and 0 hr measurements on Day 1
Note: maximum percentage of patients is bolded

Mean FEV_1 as a percent of predicted, recorded at a single timepoint at two hours post-dose on Day 1 and Weeks 4, 8 and 12, was 92.3, 89.8, 89.6 and 91.0 percent, respectively. These data do not appear adequate to establish whether the decline in mean FEV_1 within the salmeterol group was a gradual trend throughout the 12 week trial or had a relatively abrupt onset. The placebo group, with means of 78.3, 80.9, 82.1 and 82.9, respectively, seems to show a progressive increase.

Serial $FEF_{25-75\%}$ and FVC data are consistent with FEV_1 data in that they show significant effects of the salmeterol group relative to placebo at each timepoint. They also reflect increases in mean placebo group responses and decreases in mean salmeterol responses between Day 1 and Week 12.

Diary data provided secondary efficacy endpoints and a mechanism to assess the clinical relevance of the observed trends in pulmonary function data. **Morning and evening PEFR** means for each four week period are summarized in Table 14 as changes from baseline. For both measurements, a continued improvement from baseline is observed in the salmeterol and placebo patients. This finding is in contrast to the FEV_1 outcomes that declined during the course of the trial. The daily PEFR assessments provide some reassurance that the clinical outcomes of treatment were not substantially reduced. Statistically greater improvement was seen for both parameters in the salmeterol group relative to the placebo group.