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APPLICATION NUMBER: NDA 20692

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20-692	APPLICATION TYPE:	Original Submission
SPONSOR:	Glaxo Wellcome	PRODUCT/PROPRIETARY NAME:	Serevent Diskus Inhalation Powder
		USAN / Established Name:	Salmeterol Xinafoate
CATEGORY OF DRUG:	Long-Acting Beta Agonist	ROUTE OF ADMINISTRATION:	Oral Inhalation
MEDICAL REVIEWER:	Susan Johnson, Pharm.D.	REVIEW DATE:	June 16, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
June 19, 1996	June 20, 1996	Original Submission	
September 23, 1996	September 24,1996	Electronic Lung Data	Re: Low Flow Rates
October 16, 1996	October 17, 1996	Safety Update	
November 20, 1996	November 21, 1996	By-Patient Line Listings	For Archival Purposes
April 21, 1997	April 23, 1997	Response to Clinical Fax	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
NDA 20-236	NDA for Oral Inhaler Formulation	
IND		

Overview of Application/Review:

:

Outstanding Issues:

Recommended Regulatory Action APPROVABLE

N drive location: N:\NDA\20692\CLIN\97-04-21.rev

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: _____ Approvable _____ Not Approvable

Signed: **Medical Reviewer:** _____ **Date:** June 16, 1997

Medical Team Leader: _____ **Date:** 6/16/97

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2.0 EXECUTIVE SUMMARY

NDA 20-692 for Serevent Multiple Dose Dry Powder Inhaler (MDPI) is clinically approvable based primarily on three clinical trials, SLD-311, SLD-312 and SLGA2004. SLD-311 and SLD-312 served as pivotal safety and efficacy trials for this application. Each was a randomized, double blind, double dummy, 12-week comparison of salmeterol dry powder, in twice daily doses of 50 mcg, to albuterol metered dose inhaler (MDI), administered as doses of 180 mcg four times daily, and placebo. The salmeterol dry powder administration in these trials was via a Rotadisk/Diskhaler device formulation (DH). On primary spirometric efficacy endpoints, serial FEV_1 data collected every four weeks, the DH showed clinically and statistically favorable outcomes relative to placebo. In general, clinically comparable outcomes were seen relative to albuterol, although comparative conclusions are limited regarding these two treatments, based on the disparity in duration of action of the two drug substances. Secondary efficacy endpoints related to general asthma stabilization, i.e., symptom severity and nocturnal awakenings, supported salmeterol as being a somewhat more effective agent. Safety data from these trials revealed adverse events associated with the pharmacologic class at expected frequencies.

Trial SLGA2004 served as a bridging trial to compare the safety and efficacy of the MDPI to the DH used in the pivotal trials. SLGA2004 was a randomized, placebo controlled, double blind, double dummy design of four weeks in duration, in order to accommodate the life of the MDPI. Spirometric assessments following the initial dose of the individual treatments suggested a marginally faster onset and longer duration for the DH, however, following four weeks of treatment, the MDPI appeared to produce a slightly greater response in serial FEV_1 assessments. Secondary efficacy comparisons of the MDPI and DH, including two single dose crossover trials, were not fully supportive of the comparability of the MDPI and DH, seemingly favoring the DH formulation. The safety profile of the MDPI and DH did not appear different, aside from a slightly lower serum potassium level associated with the DH formulation during a cumulative dose safety trial. This finding is consistent with the relative bioavailability of the two formulations. Overall, each of the differences noted in the bridging trials were considered clinically insignificant, particularly for a chronically administered agent which is not used for treatment of acute symptoms. These trials are sufficiently supportive of the comparability between MDPI and DH formulations that the pivotal trial data are applicable.

Safety data from one year trials conducted with the DH formulation do not reveal unanticipated safety outcomes. Simulation of inhalation profiles from patients with severe obstructive disease suggested that inhalation through the device by such patients should result in delivery of a sufficient proportion of the labeled dose. Device handling and patient satisfaction data derived from the primary trials indicate that the overwhelming majority of patients can successfully use the MDPI device.

3.0 MATERIAL REVIEWED

The original submission of NDA 20-692 was submitted on June 19, 1996. There were 150 clinical volumes (plus case report forms) contained in the submission. The 120-day safety update was submitted on October 16, 1996 and contained 48 clinical volumes. Supplementary submissions include "electronic lung" studies, submitted as a single volume on September 23, 1996, by-patient line listings, submitted November 20, 1996 and a response to a clinical request for reanalyses, submitted April 21, 1997. The principal volume associated with each clinical study is listed in the text. Supplementary volumes were reviewed as necessary for supportive data tables, patient line-listings, case report forms, etc.

4.0 CHEMISTRY, MANUFACTURING, AND CONTROLS

Serevent Diskus is a formulation of salmeterol base, the racemic form of the 1-hydroxy-2-naphthoic acid salt (M.W. 603.8). The powder for oral inhalation is contained in a double-foil blister strip, with 50 mcg salmeterol xinafoate and 12.5 mg lactose per blister. The strip is designed to be enclosed in a plastic device which opens each blister and dispenses medication into the air stream created when a patient inspires through the device mouthpiece.

Comment: As of the finalization of this review, the chemistry portion of the NDA is not yet finalized for approval. Ongoing efforts between the division and the sponsor are attempting to generate sufficient data on a variety of issues, most importantly the particle size distribution of the formulation.

5.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The pharmacology portion of this application was based largely on previous submissions to NDA 20-236 for Serevent Inhalation Aerosol. New pre-clinical data which were generated for this NDA include a single dose inhalation and oral dose toxicity study in rats with the principal impurity of the formulation, GR97980X, a condensation product of salmeterol and hydroxnaphthoic acid, a 13 week inhalation toxicity study in rats with artificially degraded salmeterol xinafoate powder blends, a microbial mutagenicity study with aged salmeterol xinafoate powder blend, and a 13 week repeat dose toxicology study in dogs to compare respiratory tract tolerance to salmeterol xinafoate powders with and without GR97980X.

Comment: The pharmacology reviews completed by Dr. Sancilio find that this NDA is approvable.

6.0 CLINICAL BACKGROUND

Serevent Inhalation Aerosol, a metered dose inhaler formulation (MDI) has been approved in the United States since 1994. Due primarily to the phase out of the use of chlorofluorcarbon propellants, Glaxo Wellcome has undertaken the reformulation of salmeterol xinafoate in a dry powder delivery device. The evolution of the formulation will be described in detail, but it is important to note that the original formulation of this product was a Rotadisk formulation to be delivered via a Diskhaler (DH). Subsequent to the conduct of the pivotal safety and efficacy trials with the DH, the sponsor determined that an alternate device, the Diskus would be marketed. The Diskus device, a multiple dose dry powder inhaler (MDPI) is currently approved in 25 countries, including Canada.

In concert with division input, a program designed to link the DH and MDPI formulations was initiated. The primary trial was a "life of device" study in which safety and efficacy parameters were to be assessed for the two formulations and placebo control.

As part of the bridging program between devices, clinical pharmacokinetics were compared in Trial SLGB1004 for the MDI, DH and MDPI formulations. Per Dr. Uppoor's review, "both Cmax and AUC were significantly lower when salmeterol was given via dry powder formulations as compared to MDI. Cmax and AUC were also significantly lower after administration of salmeterol from MDPI than from the DH. Tmax however is comparable across all three dosage forms." The impact of these findings on efficacy and systemic safety parameters were determined in clinical trials comparing the various formulations.

Pharmacoeconomic and quality of life data were collected in several of the primary trials. Subsequent to submission, the sponsor determined that these data were not supportive of labeling indications or claims. They informed the division that they no longer wished to pursue such claims.

7.0 CONDUCT OF REVIEW

The presentation of the review begins with the pivotal safety and efficacy comparisons of the DH formulation to placebo and an active albuterol control. Two 12-week trials, SLD-311 and SLD-312 were conducted with identical designs. The primary bridging study between the DH formulation and the to be marketed MDPI follows, Trial SLGA2004. Subsequent to this, supportive trials related to the formulation evolution are presented. The most relevant of these trials are SLGA2001 and SLGA2006. Studies of involving patients with low inspiratory flow rates are reviewed next, followed by trials of twelve month duration, primarily SLD-320. An overview of efficacy is next, followed by an overview of safety data and recommended regulatory actions.

Trials in exercise induced bronchospasm, chronic obstructive pulmonary disease and pediatric patients under the age of 12 were not included in the review of this application, with the exception of safety data for the latter two types of trials.

8.0 CLINICAL STUDIES

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8.1 Trial SLD-311: A Randomized, Double-Blind, Comparative Clinical Trial of Twelve-Week Courses of Salmeterol Xinafoate Rotadisk versus Albuterol versus Placebo in Adolescent and Adult Patients with Chronic Reversible Obstructive Airways Disease.

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Initiation Date: 13 May 1992 (first screen data collected)
Completion Date: 25 May 1993 (last posttreatment data collected)

8.1.1 Objective

"To compare the efficacy and safety of salmeterol Rotadisk (powder) 50 mcg BID, albuterol MDI 180 mcg QID and placebo QID when administered in a fixed dosage regimen for 12 weeks to adolescent and adult patients with reversible obstructive airways disease."

8.1.2 Design and Procedures

This trial was a randomized, double-blind, double-dummy, parallel group comparison of salmeterol Rotadisk 50mcg BID (via Diskhaler), albuterol 180mcg QID (via aerosol MDI), or placebo QID (via Diskhaler and aerosol MDI). Patients underwent screening procedures to evaluate eligibility criteria within 7 to 14 days of the initiation of treatment. At the screening visit, each patient's therapy was converted from any currently used oral or inhaled beta-agonists to Ventolin MDI.

Following the screening period, there was a twelve week treatment period during which clinic visits were conducted biweekly. Twelve hour serial pulmonary function tests (PFTs) were conducted on treatment Day 1 and at Weeks 4, 8 and 12. A post-treatment visit was conducted approximately seven days after the visit at Week 12.

On treatment days, the first and fourth dose of each day consisted of an inhalation of the contents of a single blister from the assigned Rotadisk (either salmeterol or placebo) and two puffs from the assigned MDI (either placebo or albuterol). The second and third dose on each treatment day consisted of two puffs from the assigned

MDI (either placebo or albuterol). Patients were instructed to use their medication in the morning after awakening (6 AM) and at 11 AM, 4 PM and 9 PM.

Comment: As specified in the protocol, patients were to use their assigned medication every 5 hours while awake. For Serevent, this corresponds to a 15 hour dosing interval between morning and evening and a nine hour dosing interval between evening and morning. In-clinic evaluations were scheduled to be conducted between 6 and 9 AM, "approximately" 12 hours after the prior evening dose, no sooner than 10 hours and no later than 14 hours after the preceding evening dose. Since the duration of action of salmeterol is known to be somewhat longer than 12 hours in many patients, the patients in this trial who were compliant with their assigned daily regimen prior to clinic visits were likely to have had some residual effect of Serevent remaining at the start of clinic visits. In contrast, the nine hour overnight interval is likely to have completely washed out the bronchodilatory effects of scheduled evening doses of albuterol in all patients.

Peak expiratory flow rate (PEFR) was measured by patients twice daily, prior to the morning dose and prior to the evening dose. The highest of each of these triplicate assessments were recorded in patient diaries. PEFRs was recorded each day between the screening and the post treatment visit. In addition, for each wakeful period between the screening visit and the post treatment visit, patients were asked to rate the severity of their asthma symptoms. The four symptoms rated were chest tightness, shortness of breath, wheezing and cough using the following scale:

0 = NONE
1 = symptom PRESENT, but caused little or no discomfort
2 = mild symptom that became ANNOYING, but caused little or no discomfort
3 = moderate symptom that caused DISCOMFORT, but did not affect your normal daily activities
4 = severe symptom that INTERFERED at least once today with normal daily activities
5 = symptom so severe that you COULD NOT GO TO work/school/other NORMAL DAILY ACTIVITIES.

Comment: The baseline data collection period for PEFR and patient-rated symptom severity varied among patients from 7 to 14 days, the period between screening and Day 1. This may have been a significant source of variability in these endpoints.

On each clinic visit day, vital signs were recorded, diary cards were reviewed and exchanged and pulmonary auscultation and an assessment of clinical adverse events were conducted. On Day 1, and at Weeks 4, 8 and 12, the following additional procedures were conducted:

- 12-lead ECG (pre-dose and 1.5 hours post-dose),
- clinical laboratory tests (1.5 hours post-dose, Weeks 4 and 12),
- serum pregnancy test (if applicable),
- 12-hour serial PFTs (0.5 hours and immediately predose, then 0.25, 0.5 hours post-dose and hourly thereafter),
- physician-rated global assessment.

Assigned medication was dosed every 6 hours during clinic visits.

The physician-rated global assessment was used to describe the patient's status on the day of the evaluation and used the following scale:

0 = NO symptoms
1 = some symptoms PRESENT that caused little or no discomfort
2 = mild symptoms that were ANNOYING to the patient, but cause little or no discomfort
3 = moderate symptoms that caused DISCOMFORT, but did not affect normal daily activities.
4 = severe symptoms that INTERFERED at least once today with normal daily activities.
5 = symptoms so severe that the patient COULD NOT GO TO work/school/other NORMAL DAILY ACTIVITIES.

Between clinic visits, patients were instructed to measure PEFR relative to their "alert values", as defined at the screening visit, and were instructed to contact investigators if values fell to below alert levels on four of the seven most recent days. Ventolin MDI was provided as a rescue medication for use outside of the clinic. Those patients who experienced a post dose decrease in FEV_1 or clinical symptoms during clinic visits that necessitated discontinuation from serial PFTs were to initially receive therapy with Ventolin Solution 2.5 mg via nebulization.

A single protocol amendment was made following initiation of the trial. The minor modification does appear to have the potential to bias the outcomes of the trial.

8.1.3 Population

Inclusion

Males or females who were over 12 years of age were enrolled if they had a diagnosis of asthma in accordance with the American Thoracic Society definition and a medical history of mild-to-moderate asthma of more than 6 months duration which had required a regimen of daily maintenance pharmacotherapy over the 6 months preceding the screening visit. Patients were required to demonstrate an FEV_1 value (medication-free) of 50-80% of their predicted value during the screening visit and an increase in FEV_1 of more than 15% over baseline within 30 minutes after inhalation of 2 puffs (180mcg) of Ventolin•Inhalation Aerosol.

Current non-smokers who had not used tobacco products within the past one year and had less than 10 pack-years of historical use were eligible. Females were eligible only if they were surgically sterilized (bilateral tubal ligation or hysterectomy), at least 1 year post-menopausal or using acceptable methods of contraception (oral contraceptives, Depo-Provera®, or Norplant®) with a negative pretreatment pregnancy test.

Exclusion

Patients were excluded from the study if they: had a culture-documented or suspected viral or bacterial infection of the upper or lower respiratory tract, sinus, or middle ear within 4 weeks of the screening visit; had concomitant cardiovascular disease (including cardiac arrhythmias, coronary artery disease, or uncontrolled hypertension), malignancy, hepatic disease, renal disease, neurological disease, hyperthyroidism, or insulin-dependent diabetes mellitus; exhibited an abnormal 12-lead ECG during the screening visit; began immunotherapy on or after the screening visit or if their immunotherapy regimen was changed during the trial; had an abnormal clinical laboratory test at the screening visit which was still abnormal on repeat analysis and not consistent with the diseases present; or, had an abnormal chest X-ray inconsistent with the presence of asthma alone.

Concomitant Medication

The following washout periods were required prior to screening:

- inhaled beta-agonist — 8 hours
- short-acting forms of any oral beta-agonist: — 12 hours
- twice-a-day forms of beta-agonist: — 24 hours
- short-acting forms of theophylline or other bronchodilators: — 12 hours
- twice-a-day controlled-release forms of theophylline: — 24 hours
- once-a-day controlled-release forms of theophylline: — 36 hours
  (Serum concentration of theophylline was assessed at the screening visit and on Day 1 and was required to be ≤ 5 mcg/ml)
- orally-administered corticosteroid — 4 weeks
- inhaled ipratropium bromide — 2 weeks
- terfenadine — 2 weeks
- astemizole — 12 weeks
- any systemic antibacterial therapy for an upper or lower respiratory tract infection — 2 weeks
- any other investigational drug — 30 days

Patients who routinely required orally administered corticosteroids or inhaled ipratropium were not enrolled into the trial and these agents were prohibited during the trial for routine use. Patients who were receiving a fixed dosage regimen of an inhaled corticosteroid, an intranasal corticosteroid, inhaled cromolyn, intranasal cromolyn, or an antihistamine were eligible to participate if the regimen remained fixed from the time of the screening visit through the post-treatment period.

Asthma exacerbations were defined as asthma requiring treatment in addition to blinded study drug and back-up Ventolin MDI. Administration of parenteral corticosteroids or initiation of an inhaled corticosteroid necessitated discontinuation of patients from the study. Treatment with additional inhaled beta agonists, theophylline or prednisone (≤ 40 mg per day) for five days or less, did not necessitate discontinuation. Serial PFTs were not conducted on patients who required additional

medication within five days of a clinic visit (only pre-dose PFTs were conducted).

8.1.4 Endpoints

Efficacy Endpoints

The primary efficacy assessment is the spirometric measure of FEV_1. Secondary efficacy measures include FVC, $FEF_{25-75\%}$, PEFR, the physician-rated global assessment and the patient self-ratings of asthma symptoms.

Analysis of 12-hour serial PFTs was based on the following definitions:

- Baseline: the average of the 30 minutes predose and the 0 hour FEV_1 measurements on Treatment Day 1.
- Responder: a patient who achieved an increase in FEV_1 >15% from baseline within 1 hour of dosing.
- Onset: time point within 1-hour post-dose at which response was first observed; calculated by linear interpolation.
- Offset: time post-dose at which the patient's FEV_1 curve dropped below the 15% improvement limit for two consecutive time points; calculated by linear interpolation.
- Duration: time of offset minus time of onset of effect.
- Peak effect: maximum observed value of FEV_1 above the predose value on a given study day.
- AUC: area under the FEV_1 versus time curve for the 0 to 12-hour period.

Triplicate measurements were made for spirometric endpoints. Although the procedure was not described in the protocol or in the study report, the set of measurements used in the analysis was the one which produced the highest sum of FEV_1 and FVC.

For patients unable to complete the 12-hour serial PFTs due to deterioration in pulmonary function which necessitated the use of a rescue bronchodilator, the last observed set of PFTs was carried forward as values for each post-intervention observation time. Other missing values were replaced with the value which immediately preceded them.

Safety Endpoints

Safety assessments in this trial included clinical adverse events (collected at each clinic visit), 12-lead electrocardiograms (collected at screening and predose and 1.5 hours post dose at each clinic visit), clinical laboratory tests (assessed at screening, Week 4 and Week 12), vital signs (assessed at each clinic visit immediately prior to each set of PFTs), and physical examination findings assessed at screening and Week 12).

8.1.5 Statistical Considerations

Enrollment was planned for 240 patients across eight investigational centers with a 1:1:1 randomization scheme to yield results from 80 completed patients for each of the three treatments. This proposed sample size provided for >80 percent power of detecting a difference in FEV_1 of 0.25 liters between any two treatment groups, using a two-sample t-test with a significance level of 0.05, assuming a standard deviation of 0.55 liters for FEV_1. It also provided for >80 percent power of detecting a 17 percent difference (e.g., 10 percent vs. 27 percent) between any two treatment groups in the proportion of patients reporting an adverse event.

The protocol stated that for spirometric endpoints, repeated measures analysis and the individual timepoint analysis would be based on change from the pretreatment baseline on Day 1. Pairwise p-values would be interpreted only when the overall test was significant ($p \leq 0.05$). The inferential comparisons to be made between baseline (screening period) and treatment PEFR values and symptom severity ratings were not specified in the protocol. It was specified that symptom scores would be analyzed for Weeks 1-4, Weeks 5-8, Weeks 9-12 and for the entire 12 week period. Global assessments by physicians, frequency of patient withdrawal and asthma exacerbations were to be compared among the treatment groups.

The frequency of adverse events were compared among treatments. Laboratory test outcomes were compared among groups using shift tables, change from pretreatment and frequency of abnormal values.

8.1.6 Patient Disposition

There were 239 patients randomized to treatment (80 salmeterol; 80 albuterol; 79 placebo). Forty six additional patients were screened, but were not enrolled primarily due to having PFT values outside of the required range. Of the 239 patients enrolled, 220 completed the trial and 19 were discontinued. The reasons for discontinuation are provided below.

	Salmeterol	Albuterol	Placebo
Adverse Events	6	1	2
Asthma Exacerbation	1	0	1
Lack of Efficacy	0	1	1
Protocol Violation	2	2	1
Other	1	0	0
Total	10	4	5

Three salmeterol patients and one placebo patient were discontinued due to asthma exacerbations which required hospitalizations. Each of these was counted as an adverse event rather than an asthma exacerbation. Discontinuations due to adverse events were the most numerous and were most frequent in the salmeterol group.

Protocol variations that, in the determination of the sponsor, had the potential to affect efficacy data were recorded for 23 patients (5 salmeterol; 9 albuterol; 9 placebo). Four patients were completely excluded from the efficacy analysis for reasons including violation of prestudy spirometry criteria (two patients), incorrect use of the Diskhaler (one patient), and violation of patient selection criteria (atelectasis noted on screening chest x-ray, one patient). Affected efficacy data was excluded for one or more clinic visits for 19 patients based on the following reasons: taking disallowed concomitant medication, use of prohibited medication within washout windows or noncompliance.

Demographic data and asthma history data were comparable among the three treatment groups. The randomized population was predominantly male (63 percent) and Caucasian (92 percent). Three percent of the population was Black, four percent was Hispanic and one percent was Oriental. Ages ranged from twelve years to 75 years of age with a mean of 30 years. Seventy one percent had been diagnosed with asthma more than 10 years prior to the study and, although 17 percent had received acute care for asthma in the year preceding the study, only three percent had been hospitalized for asthma during the same period. At the screening visit, the following proportion of patients reported nocturnal symptoms that interfered with sleep and/or daytime symptoms that interfered with regular activities:

	Nocturnal Symptoms	Daytime Symptoms
None	25%	15%
< 1 day per week	21%	15%
1 - 3 days per week	36%	36%
4 or > days per week	18%	33%

Use of concomitant corticosteroids differed among the treatment groups. While 44 percent of the albuterol group and 47 percent of the placebo group used inhaled corticosteroids prior to the trial, and remained on them concomitantly during the trial, only 26 percent of the salmeterol group did so. Use of theophylline (a single patient in the albuterol group) and sodium cromoglycate (between five and nine percent of each treatment group) was comparable among the treatment groups.

8.1.7 Efficacy Endpoint Outcomes

The intent to treat population was comprised of all patients for whom measurements were conducted. Exclusion of patients with protocol violations that were determined by the sponsor to affect efficacy data created the "efficacy" population. If patients were

unable to complete the serial PFT assessments at a given clinic visit, the last observation was carried forward for the balance of the assessment period. This was true for both the efficacy and the intent to treat analyses. No values were carried forward from one clinic visit to subsequent visits in either the efficacy or the intent to treat analyses. The sponsor elected to use the efficacy population for their efficacy analyses, although parallel analyses were provided for the intent to treat population. The intent to treat population was analyzed for all safety outcomes.

Comment: There are several concerns regarding the identification of the efficacy population. First, the creation of the efficacy population analyses was not described a priori in the protocol for this trial. In addition, the selection of the patients to be excluded from the efficacy population was based on the detection of violations which may have affected clinic visit data. It is likely that there were additional violations which were not detected, which has the potential to introduce a bias into the exclusion process. Although 23 patients were identified as having protocol violations which may have affected efficacy outcomes, there were a total of 80 patients who were identified as having had protocol violations in general. Some of the additional violations were related to inclusion/exclusion criteria, such as use of cigarettes within the five years prior to the trial, however, many of the violations were related to use of assigned treatment or concomitant medications. The latter violations were not deemed relevant because the infractions were not coincidental with clinic visits, but had the potential to affect the secondary efficacy endpoints, such as PEFR and diary symptoms evaluations. Also, this 12 week trial was, to some extent, designed to determine the effects of regular clinical use of the dry powder formulation of salmeterol, and, to that end, all protocol violations might be considered to have a relevant impact on the efficacy outcomes. The analyses of the intent to treat population are based on this assumption and no changes in the analyses are based on protocol violations.

Like the sponsor's study report, this review will focus primarily on the efficacy population in looking at primary efficacy outcomes. The reason for this decision is that salmeterol is a marketed product and is known to have demonstrated efficacy relative to placebo in previous clinical trials. The inclusion of placebo in this trial serves as confirmation that salmeterol delivered via a dry powder formulation can also demonstrate efficacy, but it is the comparison with the active control which will be of the most utility in characterizing the performance of the dry powder formulation. Since deviations from the protocol tend to diminish the ability to discriminate between two treatments from a statistical perspective, the efficacy group, which includes fewer known deviations, will be considered as the primary analysis group. An evaluation of the intent to treat analyses will also be presented, particularly for instances in which the outcomes of the two analyses differ.

The results of pulmonary function tests at screening are presented in Table 8.1A. There were no statistically significant differences among the three treatment groups at screening.

Table 8.1A Pulmonary Function Outcomes at Screening

	Salmeterol (N = 80)	Albuterol (N = 80)	Placebo (N = 79)
FEV1			
Before Bronchodilation	2.40 (0.59)	2.45 (0.58)	2.39 (0.57)
Percent of Predicted	64.8 (8.6)	65.6 (8.6)	64.6 (8.7)
Percent Reversibility	31.1 (14.6)	31.5 (13.2)	33.9 (17.2)
$FEF_{25-75\%}$			
Before Bronchodilation	1.96 (0.80)	1.92 (0.70)	1.99 (0.89)
Percent of Predicted	49.3 (18.5)	48.2 (16.6)	49.9 (21.8)
FVC			
Before Bronchodilation	3.33 (0.93)	3.41 (0.85)	3.36 (0.87)
Percent of Predicted	77.4 (13.8)	77.4 (10.5)	77.5 (11.8)

8.1.7.1 Serial FEV_1

Baseline

There were no statistically significant differences among the salmeterol, albuterol and placebo treatment group FEV_1 means within the efficacy population at baseline. "Baseline" for spirometric endpoints was defined as the average of the assessment one-half hour prior to dosing and immediately preceding the dose, i.e., the -0.5 hour and 0 hour assessments. Daily baselines were not defined for Weeks 4, 8 and 12.

Mean FEV_1 values at baseline, calculated for the portion of the efficacy population which participated on Day 1 and at Weeks 4, 8 and 12, are shown in Table 8.1B (in bold), along with values for mean FEV_1 at Hour 0 for the efficacy population at Weeks 4. 8 and 12.

Table 8.1B Baseline and Daily Pre-Dose FEV_1

	Salmeterol	Albuterol	Placebo
Baseline, Day 1	**2.43 (N = 79)**	**2.51 (N = 79)**	**46 (N = 77)**
Baseline, Week 4	**2.42 (N = 72)**	**2.47 (N = 73)**	**2.52 (N = 71)**
Hour 0, Week 4	2.76*	2.41	2.62
Baseline Week 8	**2.42 (N = 72)**	**2.52 (N = 71)**	**2.54 (N = 68)**
Hour 0, Week 8	2.73*	2.48	2.65
Baseline, Week 12	**2.44 (N = 70)**	**2.51 (N = 72)**	**2.56 (N = 67)**
Hour 0, Week 12	2.74*	2.50	2.61

* Statistically different than baseline of same week ($p < 0.05$).

The Hour 0 values did not fall to baseline levels at Weeks 4, 8 or 12 for the salmeterol or the placebo group. Hour 0 values were statistically significantly higher than at baseline in the salmeterol group at Weeks 4, 8 and 12.

Comment: Although Hour 0 values were higher for Week 4, 8 and 12 than for Day 1, there is no apparent trend in the Hour 0 values across treatment Weeks 4, 8 and 12 for either the salmeterol or the placebo group. Within the salmeterol group, the Hour 0 assessments were made between 10 and 14 hours after the previous evening's dose and appear to have reflected carryover effects from salmeterol. The overnight washout period was not sufficiently long to eliminate such effects at Weeks 4, 8 and 12 (See Section 8.1.2). The placebo group would not be expected to have residual medication effects at Hour 0 of clinic visits, however, Hour 0 means at Weeks 4, 8 and 12 were increased over the Day 1 value. It is possible that the attrition of patients with low FEV_1 values from the placebo group served to enhance the group mean, but only one patient discontinued from this group due to lack of efficacy.

Whatever the reason for the increase in Hour 0 FEV_1 after Day 1, it can be said that the spirometric endpoints which include baseline in their analyses are expected to differ between Day 1 and Weeks 4, 8 and 12. However, because there is no trend in Hour 0 means between Week 4 and Week 12, it was expected and observed that the outcomes of Weeks 4, 8 and 12 were similar. The ensuing discussion of the sponsor's presentation of spirometric endpoints will contrast Day 1 to Weeks 4, 8 and 12. In addition, reanalyses of Week 4 data using a daily baseline will be presented.

Percent Change from Baseline

Appendix 1 contains the profile of percent change from baseline FEV_1 versus time for Day 1. Profiles for Weeks 4, 8 and 12 are found in Appendices 2 through 4, respectively. The plots are consistent for all four clinic visits in their ability to show two distinct peaks associated with the two doses of albuterol administered during the 12 hour monitoring period and one peak associated with the single salmeterol dose. In addition, a minimal response to placebo administration is observed at each week. It can be seen that the outcomes of Weeks 8 and 12 closely resemble the profiles from Week 4. This is true of the majority of endpoints, thus data from Weeks 8 and 12 will not be presented for other spirometric endpoints.

Maximum percent change from baseline (see Table 8.1C) is similar for salmeterol and albuterol on Day 1 (30.6 and 33.6 percent, respectively), but is higher for salmeterol at Week 4 (38.6 and 30.7 percent, respectively). The difference at Week 4 did not reach statistical significance. Maximum percent change from baseline is statistically greater for both salmeterol and albuterol than for placebo.

Comment: The difference in maximum change from baseline between salmeterol and albuterol at Week 4 appears to be due primarily to the cumulative effect of salmeterol.

Percent of Predicted

Mean profiles of FEV_1 as a percent of predicted normal values across the 12 hour dosing interval for Day 1 and Week 4 are presented in Appendix 5 and 6, respectively. As with the profiles of FEV_1 expressed as a percentage of baseline, it is noted that the maximal effect of salmeterol on Day 1 is less than for albuterol. However, at Week 4, the salmeterol curve is shifted upward, reflecting the carryover effect of salmeterol. No statistical analyses were conducted on the percent of predicted endpoint.

Comment: The ability of this population to respond at a maximum of nearly 85 percent of predicted is largely a function of the mild to moderate severity of asthma in these patients. The population of patients enrolled had a mean FEV_1 at screening of approximately 65 percent of predicted normal.

Table 8.1C FEV$_1$ Outcomes for the Efficacy Population

	Salmeterol	Albuterol	Placebo	P-Values
Day 1	**N = 79**	**N = 79**	**N = 77**	
Max. % Change from Baseline (SD)	30.6 (19.4)	33.6 (21.8)	12.7 (3.4)	S v. P <0.001* A v. P <0.001* S v. A 0.592
# (%) of Responders	52 (66)	63 (80)	11 (14)	S v. P <0.001* A v. P <0.001* S v. A 0.073
Median Time of Onset in Hours	0.47	0.19	12.0	S v. P <0.001* A v. P <0.001* S v. A <0.001 *
Duration of Effect in Hours (SD)	5.7 (5.0)	4.5 (4.3)	0.7 (2.1)	S v. P <0.001* A v. P <0.001* S v. A 0.834
AUC-BL (SD)	5.4 (4.4)	4.6 (3.7)	0.0 (4.3)	S v. P <0.001* A v. P <0.001* S v. A 0.322
Week 4	**N = 72**	**N = 73**	**N = 71**	
Max. % Change from Baseline (SD)	38.6 (31.9)	30.7 (27.3)	17.1 (24.5)	S v. P <0.001* A v. P 0.003* S v. A 0.113
# (%) of Responders	50 (69)	41 (56)	23 (32)	S v. P <0.001* A v. P 0.005* S v. A 0.122
Median Time of Onset in Hours	0.12	0.29	12.0	S v. P <0.001* A v. P 0.050* S v. A 0.012*
Duration of Effect in Hours (SD)	6.4 (5.2)	3.2 (4.3)	2.2 (4.3)	S v. P <0.001* A v. P 0.018* S v. A 0.001*
AUC-BL (SD)	6.8 (6.1)	3.2 (5.5)	1.2 (5.3)	S v. P <0.001* A v. P 0.070 S v. A <0.001*

* Indicates statistical significance at $p < 0.05$.

Onset

The onset of effect, defined as the time required to reach a 15 percent improvement over Day 1 baseline within one hour of dosing, was set to 12 hours for patients in the

efficacy population did not reach 15 percent improvement. Onset was significantly longer for salmeterol than for either albuterol or placebo on Day 1. At Week 4, however, the median time to onset for both albuterol and placebo was significantly longer than for salmeterol. The observed onset for salmeterol on Day 1 was approximately 28 minutes and was 7.2 minutes at Week 4. Median time to onset among the responder population subset (the efficacy population minus patients who did reach a 15 percent improvement from baseline within one hour of dosing) was slightly shorter than in the efficacy population analysis at 22, 13 and 35 minutes for salmeterol, albuterol and placebo, respectively, on Day 1 and 7, 8 and 10 minutes, respectively, at Week 4.

Comment: The Day 1 onset for the diskhaler formulation was slightly longer than the 10 to 20 minute onset specified in the labeling for a single 42 mcg. dose of Serevent Inhalation Aerosol. The Week 4 onset does not provide an appropriate comparison because of the carryover effect of salmeterol. The onset of effect observed in this trial should be compared with other trials of the diskhaler and diskus formulations to determine whether there is a true difference from the Serevent Inhalation Aerosol formulation. The clinical significance of this finding is likely to be minimal as salmeterol is not intended to be used in the treatment of acute exacerbations.

Duration

Duration of effect was defined as time of offset minus time of onset and was set to zero for patients in the efficacy population who did not achieve a 15 percent improvement over baseline. The range of duration of effect on Day 1 and at all subsequent clinical visits was between 0 and approximately 11 hours for all three treatments. In the efficacy population, both salmeterol and albuterol demonstrated statistically longer durations of effect than placebo. The duration of effect of salmeterol was not significantly longer than that of albuterol on Day 1, but was at Week 4, Week 8 and Week 12. Mean duration of effect among the responder population subset was longer than in the efficacy population analysis at 8.6, 5.6 and 4.8 hours for salmeterol, albuterol and placebo, respectively, on Day 1 and 9.2, 5.7 and 6.9, respectively at Week 4.

Comment: No salmeterol patients were observed to have had a duration of effect as long as 12 hours, the labeled duration of action for the Serevent Inhalation Aerosol. This is particularly a concern at Weeks 4, 8 and 12, when it could be anticipated that the carryover effects from cumulative doses would have enhanced the likelihood of observing sustained effect. The baseline shift at Weeks 4, 8 and 12 does, however, indicate the sustained action of salmeterol. Duration of effect will be further assessed in the additional clinical trials.

AUC

AUC was analyzed as two different parameters by the sponsor. AUC(15%) was defined as the area under the FEV_1 curve and above the 15 percent improvement from Day 1 baseline threshold. AUC (BL) was defined as the total area under the FEV_1 curve for the full 12 hours. Area below baseline was subtracted from area above baseline for this analysis. The statistical outcomes of the analyses for each clinic visit were essentially the same for both AUC (15%) and AUC (BL). Although both AUC analyses were affected by the carryover effects and changes in baseline, AUC (BL) was not affected by individual responder status and was, therefore, chosen for discussion in this review. At each clinic visit AUC (BL) was statistically greater for both salmeterol and albuterol than for placebo, with the exception of Week 4 when the albuterol mean was not statistically greater than the placebo mean. The mean AUC(BL) of the salmeterol group was statistically greater than the albuterol mean at Weeks 4, 8 and 12, but not at Week 1.

Comment: Among the FEV_1 outcomes, AUC(BL) is likely to be the most profoundly affected by the carryover effects of salmeterol. As the entire FEV_1 profile is shifted upward after Day 1 for salmeterol only, the AUC calculated using baseline on Day 1 appears larger relative to the AUC of albuterol. This can not be interpreted as an indication that salmeterol produces a substantially greater effect than albuterol.

Change from Daily Baseline

The sponsor was asked to reanalyze FEV_1 data at Week 4 to examine change from daily baseline (the mean of -0.5 hour and 0 hour assessments at Week 4). A plot of these data appears in Appendix 7. The purpose of the reanalysis was to characterize the actual fluctuation of FEV_1 on a treatment day subsequent to Day 1. As the plot indicates, FEV_1 response to the daily salmeterol dose is considerably smaller than for albuterol. This is anticipated based on the sustained action of salmeterol relative to albuterol. Statistical analyses indicate that the response to albuterol is significantly greater at most timepoints, with the exception of the end of the albuterol dosing intervals. It is important to note that this analysis does not take into account the baseline shift from Day 1 for the salmeterol group. Therefore, the analysis is not reflective of overall patient response to treatment. Time to peak response on Day 1 was 4.49, 1.34 and 4.61 hours for salmeterol, albuterol and placebo, while at Week 4 it was 4.51, 1.10 and 3.81 hours, respectively.

Comment: Change from daily baseline analyses indicate that the daily fluctuation in FEV_1 is greatly reduced with salmeterol relative to albuterol, as expected.

8.1.7.2 FVC

Baseline FVC values from Day 1 for the three treatment groups (efficacy population), expressed in liters and as a percent of predicted, are shown in Table 8.1D below. As with FEV_1 data, baseline was considered to be the mean of the Hour -0.5 and Hour 0 values on Day 1. Baselines were comparable among the three treatment groups.

Table 8.1D Baseline FVC

	Salmeterol (N = 79)	Albuterol (N = 79)	Placebo (N = 77)
Baseline FVC in Liters (S.D.)	3.37 (0.94)	3.51 (0.89)	3.40 (1.04)
Baseline FVC as % of Predicted (S.D.)	77.9	79.8	78.5

Response profiles for Day 1 and Week 4 are shown Appendix 8 and 9, respectively. Maximum FVC response was in the range of 87 - 90 percent for albuterol and salmeterol. As with FEV_1 data, the contrast between response on Day 1 and Week 4 appears to reflect the shift in the salmeterol response due to carryover effects.

8.1.7.3 $FEF_{25-75\%}$

Baseline $FEF_{25-75\%}$ values from Day 1 for the three treatment groups (efficacy population), expressed in liters per second and as a percent of predicted, are shown in Table 8.1E. As with FEV_1 data, baseline was considered to be the mean of the Hour -0.5 and Hour 0 values on Day 1. Baselines were comparable among the three treatment groups.

Table 8.1E Baseline $FEF_{25-75\%}$

	Salmeterol (N = 75)	Albuterol (N = 74)	Placebo (N = 68)
Baseline $FEF_{25-75\%}$ in Liters per Second (S.D.)	1.98 (0.92)	1.92 (0.85)	2.03 (1.00)
Baseline $FEF_{25-75\%}$ as % of Predicted (S.D.)	49.6	48.4	50.7

Response profiles for Day 1 and Week 4 are shown Appendix 10 and 11, respectively. Maximum $FEF_{25-75\%}$ response was in the range of 67 - 73 percent for albuterol and salmeterol. As with FEV_1 data, the contrast between response on Day 1 and Week 4 appears to reflect the shift in the salmeterol response due to carryover effects.

8.1.7.4 PEFR

Patients were instructed to measure peak expiratory flow rate in the morning after getting out of bed, but before the first dose of study drug. Evening evaluations were undertaken before the last study dose of the day. Table 8.1F shows the comparison among treatments at baseline (mean of the daily PEFR recordings from the 7 to 14 days between the Screening Visit and Day 1) and for the three subsequent four-week periods.

Comment: The protocol and diary card formats did not provide for instructions to patients regarding the preferred sequence of evaluation of symptom scores followed by PEFR assessment. Collection of the objective PEFR may have the potential to bias symptom assessment. This possibility would have be of more significant concern if the outcomes of the PEFR and symptom scores were supportive of conflicting conclusions and it became necessary to determine which outcome was more reflective of the true clinical state of the patient.

At baseline, both the morning and evening PEFR means failed to show statistically significant differences among the treatment groups and the morning/evening differential ranged from 31 to 35 L/min. After initiation of treatment, morning/evening differentials remained fairly consistent for albuterol (31 to 35 L/min) and placebo (23 to 29 L/min), however, the salmeterol differentials fell (15 to 18 L/min). Both the morning and evening PEFR means increased after initiation of salmeterol, but the change from baseline was greater for the morning PEFR mean.

Comment: As with clinic visit assessments, the increase in morning and evening PEFR means appear to reflect the carryover effect of salmeterol administered at the previous dose. The failure of the evening PEFR means to increase as much as the morning PEFR means is likely to be due to the plateauing of PEFR values as patients reached their personal maximum possible values.

After initiation of the treatment portion of the trial, the morning, evening and the morning/evening differentials stabilized for the salmeterol group and remained essentially constant within all three treatment groups throughout Weeks 1 to 12.

At all analysis timepoints during treatment, the morning and evening PEFR means for the salmeterol group were statistically significantly higher than for either placebo or albuterol.

Comment: This appears to be further evidence that the albuterol group reached trough concentrations via washout of the drug prior to PEFR readings, however, the salmeterol group did not.

The analyses described above were repeated for a "reduced" efficacy population. In these analyses, individual PEFR values were excluded when rescue albuterol had been administered within four hours of the PEFR reading. The outcome of the analyses of the reduced efficacy population revealed a slight reduction in PEFR all means and a diminished morning/evening differential for all three groups. The morning/evening differential during treatment remained lowest for the salmeterol group.

Table 8.1F Mean Morning and Evening PEFR from Diary (S.D.) for Efficacy Population

	Salmeterol	Albuterol	Placebo	P-Values
Morning Baseline	**397 (86)**	**402 (82)**	**397 (97)**	**S v. P 0.963 A v. P 0.665 S v. A 0.671**
Evening Baseline	427 (83)	436 (84)	426 (90)	S v. P 0.969 A v. P 0.469 S v. A 0.465
Morning Weeks 1 - 4	**428 (86)**	**398 (79)**	**397 (98)**	**S v. P <0.001* A v. P 0.320 S v. A <0.001***
Evening Weeks 1 - 4	446 (85)	434 (83)	425 (96)	S v. P <0.001* A v. P 0.997 S v. A <0.001*
Morning Weeks 5 - 8	**432 (87)**	**400 (80)**	**406 (100)**	**S v. P <0.001* A v. P 0.057 S v. A <0.001***
Evening Weeks 5 - 8	447 (85)	433 (80)	428 (95)	S v. P 0.001* A v. P 0.722 S v. A <0.001*
Morning Weeks 9 -12	**431 (86)**	**402 (79)**	**399 (100)**	**S v. P <0.001* A v. P 0.342 S v. A <0.001***
Evening Weeks 9 -12	446 (85)	433 (79)	427 (97)	S v. P 0.012* A v. P 0.368 S v. A <0.001*

* Indicates statistical significance at p< 0.05.

8.1.7.5 Nighttime Awakenings

Patients reported in their daily diaries the number of times per night that they were awakened due to asthma symptoms. Although there were no statistically significant differences among the treatment groups regarding the percent of nights with no nighttime awakenings during the baseline period, the placebo group had a higher percentage of such nights (64, 63 and 71 percent for the salmeterol, albuterol and placebo groups, respectively). The percentage of nights with no nighttime awakenings

increased after initiation of treatment (indicating improvement) by a minor amount for the albuterol group (to approximately 69 percent) and by a greater amount for the salmeterol group (to approximately 88 percent). Statistically significant differences between salmeterol and placebo and between salmeterol and albuterol were observed for Weeks 1-4, Weeks 5-8 and Weeks 9-12.

Comment: The higher proportion of nights with no nighttime symptoms among placebo patients at baseline suggests that it may have been more difficult to show treatment effect relative to this group than it would have been to show treatment effect relative to the placebo group. This factor, as well as albuterol's shorter duration of action, are likely to account for the inability of albuterol group to demonstrate statistically significant improvement relative to the placebo group.

8.1.7.6 Symptom Scores

Symptom were scored in patient diaries on a 0 to 5 severity scale for each daytime wakeful period. The mean scores for each symptom are reported in Table 8.1G for the efficacy population in the baseline period and for the entire 12 week period. Mean symptom scores dropped slightly after initiation of treatment, but remained essentially constant throughout the treatment period, based on the four week interval analyses. No statistically significant differences were seen among the three treatment groups at baseline. Statistically significant differences between placebo and salmeterol were observed for chest tightness, shortness of breath and wheezing in the comparison of mean scores for most of the four week segment comparisons and for the treatment period overall. The albuterol group showed significantly lower (improved) symptom scores at Weeks 9-12 for shortness of breath compared to placebo. The salmeterol group showed significantly lower mean shortness of breath scores compared to albuterol for Weeks 1-4 and for Weeks 1-12. The albuterol wheezing mean was significantly lower at Weeks 9-12 than for salmeterol. No statistically significant differences were seen among treatment groups at any timepoint for coughing.

Comment: The reporting of minimal symptoms during this trial reflects the mild to moderate severity of asthmatics in this population and did not provide a highly discriminatory endpoint. In addition, statistically significant differences were achieved with negligible differences between the treatment groups and it appears inappropriate to conclude that the three treatment groups differed in a clinically significant manner from the others.

Table 8.1G Mean (S.D.) of Symptom Scores at Baseline and Weeks 1-12

	Salmeterol	Albuterol	Placebo
Baseline			
Chest Tightness	1.3 (1.0)	1.1 (0.9)	1.1 (1.0)
Shortness of Breath	1.3 (1.0)	1.1 (0.9)	1.1 (1.0)
Wheezing	1.2 (0.9)	1.0 (0.8)	1.0 (0.9)
Coughing	0.9 (1.0)	0.6 (0.7)	0.8 (0.9)
Weeks 1-12			
Chest Tightness	1.0 (0.8)	0.9 (0.8)	1.1 (0.9)
Shortness of Breath	0.9 (0.8)	1.0 (0.7)	1.1 (0.9)
Wheezing	0.9 (0.8)	0.8 (0.6)	0.9 (0.8)
Coughing	0.6 (0.7)	0.5 (0.5)	0.6 (0.7)

The sponsor also compared the percent of days without individual or any symptoms using descriptive statistics. Overall for Weeks 1 through 12, the percent of days with no symptoms was 30, 18 and 19 percent for the salmeterol, albuterol and placebo groups, respectively.

Comment: This finding suggests more strongly than the individual symptoms that the salmeterol patients experienced a benefit which was clinically superior to that experienced by the patients in the other treatment groups.

8.1.7.7 Physician-Rated Global Assessment

The distribution of symptom scores at screening and on Day 1 were similar for all three treatment groups. For salmeterol at screening, 26 percent of patients were given a 0 rating, 23 percent of patients were rated 1, 29 percent were rated 2, 21 percent were rated 3, 1 percent were rated 4 and no patients were rated 5. With treatment, scores shifted toward the lower end of the scale (improvement) for the salmeterol group more so than in the albuterol or placebo groups such that at Weeks 4, 8 and 12, 15 to 20 percent more patients were rated 0 or 1 in the salmeterol group than in the placebo group. No inferential statistical analyses were conducted for this endpoint.

Comment: Because this endpoint shows symptom improvement for salmeterol and not for albuterol or placebo, it does not appear to correlate well with the patient-rated symptom scores. While the reasons for this discrepancy are unclear and could potentially be related to the degree to which investigators were blinded to PFT

outcomes, it appears that the investigators' rating of patient status only on clinic days may not provide a meaningful assessment of the overall effect of treatment.

8.1.7.8 Use of Rescue Albuterol

Use of rescue during the baseline period between the Screening Visit and Day 1 was similar among the three treatment groups: 3.7, 4.4. and 4.2 puffs per day for the salmeterol, albuterol and placebo groups, respectively. After initiation of treatment, use of rescue fell in all three groups and was fairly consistent across the twelve treatment weeks at approximately 1.5, 2.2 and 3.5 puffs per day, respectively, for the three treatment groups. Use of rescue was statistically significantly lower among the salmeterol and albuterol groups than in the placebo group for the comparison of groups at Weeks 1-4, 5-8 and 9-12. However, there was no statistical difference between salmeterol and albuterol at any timepoint.

Comment: Although it was not statistically significant, it is notable that the use of rescue within the salmeterol group remained lower than that of the albuterol group throughout the treatment period.

8.1.7.9 Use of Concomitant Asthma Therapy

The use of concomitant asthma medications is summarized in Table 8.1H.

Table 8.1H Percentage of Patients Using Concomitant Asthma Medication

	Salmeterol	Albuterol	Placebo
Any Asthma Medication	31	49	48
Theophylline	0	1	0
Sodium Cromoglycate	6	9	5
Beclomethasone Dipropionate	15	21	27
Flunisolide	1	4	3
Triamcinolone	10	19	18
Any Inhaled Corticosteroid	26	44	47

Comment: The use of inhaled corticosteroids was considerably higher among the albuterol and placebo groups than in the salmeterol group. This suggests that the underlying severity of disease among the salmeterol patients may have been somewhat different than among the other treatment groups, despite the similarity of spirometric endpoint outcomes at screening and baseline. If this were true, salmeterol patients

might be expected to show a different predisposition for improvement on active treatment relative to the other groups. Other trials should be examined to determine whether they provide information regarding the comparison of salmeterol to placebo or active control in the setting of comparable corticosteroid use.

The mean FEV_1 of the patients in each of the treatment groups who did not use inhaled corticosteroids was consistently higher than the mean of patients in the same treatment group who used inhaled corticosteroids. Repeated measures analyses, summarizing the change from baseline for the entire 12 hour interval for the entire efficacy population, revealed that both salmeterol and albuterol treatment groups were statistically superior to placebo and that salmeterol was statistically superior to albuterol. In subgroup analyses, both the user and non-user salmeterol subgroups were statistically superior to placebo at each week. Salmeterol patients who used corticosteroids were also statistically superior to albuterol at each week, but albuterol users did not show statistically superiority to placebo at Weeks 4, 8 and 12. Among the non-users, salmeterol was statistically superior to albuterol only at Week 4 and albuterol was statistically superior to placebo only at Week 12.

Comment: The baseline FEV_1 values of non-corticosteroid users was 2.70 L for placebo and 2.56 and 2.61 L for salmeterol and albuterol, respectively, suggesting that the disease severity between the salmeterol and albuterol groups was comparable. Among corticosteroid users, the salmeterol and albuterol groups appeared less comparable, with baseline FEV_1 values of 2.07 and 2.38 L , respectively (placebo baseline was 2.20 L). The ability of the salmeterol group to show improvement relative to the albuterol group may have been enhanced among the user subgroups and may account for the consistent statistical superiority of salmeterol relative to albuterol. In addition, the outcomes of these analyses were likely to have been affected by the disproportionate number of users vs. non-users among the three treatment groups.

Effects of corticosteroid use on AM and PM PEFR scores was not statistically significant.

8.1.7.10 Asthma Exacerbation

The number (and percentage) of patients who experienced asthma exacerbations during treatment is listed in Table 8.1l. Placebo patients had the highest incidence of asthma exacerbations. While the incidence of asthma exacerbations was similar between the salmeterol and albuterol groups, the salmeterol group did experience fewer exacerbations. No inferential statistical comparisons were conducted. The majority of asthma exacerbations were attributed to the withholding of medications within the placebo group. Among the salmeterol and albuterol groups, infection and exposure to allergens were suspected causes of a comparable proportion of asthma exacerbations.

Table 8.1l Number (Percentage) of Patients Experiencing Asthma Exacerbations During Treatment

	Salmeterol N = 80	Albuterol N = 80	Placebo N = 79
No Exacerbations	65 (81)	58 (73)	43 (54)
One Exacerbation	12 (15)	14 (18)	9 (11)
Two Exacerbations	2 (3)	5 (6)	9 (11)
Three or More Exacerbations	1 (1)	3 (4)	18 (23)

8.1.7.11 Quality of Life Measures

Quality of life data were collected on Day 1 and at Weeks 4, 8 and 12 by administration of the Acute Short Form-36 (SF-36), the Greg Sleep Measure Scale and the Living With Asthma (LWA-20A) questionnaires. Measures of patient satisfaction and device handling were also assessed. The outcome of these measures are discussed in the Overview of Efficacy, Section 9.0.

8.1.7.12 Intent to Treat Population

The outcome of the intent to treat population analyses were submitted for most efficacy endpoints. The intent to treat population included 19 patients which were not part of the efficacy population. The intent to treat outcomes were consistent with those of the efficacy population in that salmeterol was shown to be consistently superior to placebo and maintained a longer duration of action than albuterol. No clinically significant differences between the efficacy population and intent to treat populations were identified for FEV_1, FVC, $FEF_{25-75\%}$, morning or evening PEFR, use of rescue medication or symptom scores.

Comment: As mentioned in Section 8.1.7, the efficacy population differed from the intent to treat population in that it excluded patients who were known to have had protocol violations which may have affected their clinic visit outcomes. The differences between the outcomes of the two population which were measured outside of the clinic, e.g. PEFR, rescue medication and symptom scores would not be expected to show a consistent difference between the populations. In fact, neither in-clinic nor diary data showed a consistent difference between the two populations with the exception of AM/PM PEFR scores which were higher among the intent to treat population. The reason is unknown, the difference was clinically insignificant and did not alter the statistical outcomes seen among the efficacy endpoints.

8.1.7.13 Efficacy Conclusion

Trial SLD-311 demonstrated that salmeterol via Rotadisk/Diskhaler maintained consistently superior effects on spirometric endpoints relative to placebo throughout a 12 hour dosing interval. Salmeterol's performance on spirometric endpoints relative to albuterol MDI differed primarily in an expected manner, based on the difference in the duration of action of the drug substances. Carryover effects of salmeterol were noted in the failure of spirometric endpoints and PEFR to return to Day 1 baseline levels on clinic throughout the trial. Change from daily baseline analyses reflect significantly less daily variation in FEV_1 with salmeterol use than with albuterol use.

Onset of effect was somewhat longer than the 10 to 20 minutes specified in the labeling for salmeterol MDI at Day 1, but shorter than the specified interval thereafter. Duration of action, defined as a 15 percent increase over baseline, was not observed to be 12 hours, however effects of salmeterol treatment (i.e., any increase over baseline) were observed throughout a 12 hour dosing interval. Both of these findings should be confirmed in subsequent trials.

Individual symptom scores did not suggest a clinically significant difference among the three treatments included in the trial, however symptom severity may have been insufficiently severe to serve as an adequate discriminator. Salmeterol did demonstrate a minimal advantage in analyses of symptom-free days relative to albuterol and placebo and there were statistically fewer nighttime awakenings among the salmeterol group. Use of rescue albuterol and number of asthma exacerbations was lowest among salmeterol patients, although statistical differences were not demonstrated. The interaction of treatment effects with the use of concomitant asthma medications was confounded by a disparity of corticosteroid users among the treatment groups. This parameter should be evaluated further in subsequent trials.

Overall, salmeterol maintained a consistent improvement throughout the 12 week treatment period on all efficacy endpoints and clearly demonstrated statistical and clinical efficacy.

Comment: No discussion of the diary data which were collected between the Week 12 visit and the end of the study was included in the study report. The sponsor should be asked to do so in order to assess the potential for rebound effects following salmeterol treatment.

8.1.8 Safety Endpoint Outcomes

Each of the safety endpoint analyses was conducted with the intent to treat population.

Table 8.1J Number (Percentage) of Patients Experiencing Adverse Events*

	Salmeterol N = 80	Albuterol N = 80	Placebo N = 79
Any Cardiovascular Event	1 (1)	4 (5)	1 (1)
Precordial Pain	1 (1)	2 (3)	0 (0)
Tachycardia	0 (0)	2 (3)	0 (0)
Any Ear, Nose, Throat Event	**42 (53)**	**29 (36)**	**40 (50)**
Sinusitis	5 (6)	10 (13)	6 (8)
Disease nasal cavity/sinus	5 (6)	6 (8)	4 (5)
Allergic Rhinitis	**5 (6)**	**2 (3)**	**4 (5)**
Nasopharyngitis	1 (1)	3 (4)	0 (0)
Otitis externa	1 (1)	2 (3)	0 (0)
Any Eye Event	2 (3)	4 (5)	1 (1)
Disorders of the Eye	0 (0)	2 (3)	0 (0)
Any Gastrointestinal Event	6 (8)	9 (11)	7 (9)
Stomach Ache	1 (1)	3 (4)	1 (1)
Abdominal Pain	0 (0)	2 (3)	0 (0)
Localized Aches/Pain	3 (4)	3 (4)	0 (0)
Any Mouth Event	2 (3)	3 (4)	3 (4)
Conditions of the Tongue (Separate from Candidiasis)	0 (0)	2 (3)	0 (0)
Any Neurological Event	**15 (19)**	**8 (10)**	**12 (15)**
Headache	**10 (13)**	**5 (6)**	**6 (8)**
Paresthesia	2 (3)	0 (0)	0 (0)
Any Respiratory Event	**17 (21)**	**8 (10)**	**12 (15)**
Tracheitis/Bronchitis	**6 (8)**	**2 (3)**	**5 (6)**
Influenza	5 (6)	5 (6)	1 (1)
Asthma	**4 (5)**	**0 (0)**	**2 (3)**
Cough	**4 (5)**	**1 (1)**	**1 (1)**
L.R.I.	**2 (3)**	**0 (0)**	**1 (1)**
Any Skin Event	**5 (6)**	**4 (5)**	**4 (5)**
Contact Dermatitis/Eczema	**2 (3)**	**1 (1)**	**1 (1)**

* Only adverse events experienced by 3 percent or more of any treatment group, and by a higher proportion of patients in either active treatment group than in the placebo group, are listed. Events with a higher incidence among salmeterol users than albuterol users are shown in bold.

Salmeterol
Chervinsky 81, a 29-year-old Caucasian female salmeterol recipient was admitted to the hospital with status asthmaticus on Day 66. During her 4-day hospitalization, she was initially treated with Solu-Medrol® and aminophylline IV and subsequently orally administered Theo-Dur®, Prednisone®, and amoxicillin. Her condition completely resolved within 10 days.

Lumry 214, a 34-year-old Caucasian male treated with salmeterol was hospitalized on Day 50 due to an asthma exacerbation. The patient was treated with Solu-Medrol®, nebulized terbutaline, beclomethasone, Prednisone®, and Ventolin. His condition resolved within two days and he was discharged.

Seltzer 133, a 40-year-old Caucasian female was hospitalized with status asthmaticus 65 days after starting salmeterol treatment. While hospitalized, she was treated with Solu-Medrol®, nebulized albuterol, Septra®, Atrovent®, and Prednisone®. Her condition improved and she was discharged the next day. The exacerbation completely resolved within 5 days.

Seltzer 139, a 24-year-old Caucasian male salmeterol recipient was hospitalized for an exacerbation of asthma on Day 67. He was diagnosed with pneumonia and treated with Solu-Medrol® IV, Ancef® IV, ampicillin, Ventolin nebules, theophylline, Robitussin®, and Prednisone®. The patient improved and was discharged 3 days later.

Lumry 206, a 39-year-old Caucasian male reported severe nasal obstruction on Day 43 which the investigator determined was due to nasal polyps. No treatment was given, however, the patient was referred for an ENT evaluation. The patient was withdrawn from the study on Day 60 and had the polyps surgically removed 16 days later.

Pearlman 117, a 16-year-old Caucasian male developed severe tremors, became agitated and was unable to concentrate after receiving the first dose of salmeterol on Treatment Day 1. No treatment was given and the events resolved. He was subsequently withdrawn from the study on Day 4.

Albuterol
Pearlman 111, a 29-year-old Caucasian female treated with albuterol was hospitalized on Day 60 after developing severe abdominal pain. While hospitalized, she was treated with triamcinolone acetonide, Zantac®, and Maalox®. The etiology of the abdominal pain was unclear; a series of tests ruled out appendicitis and ureteral obstruction. The patient recovered and was discharged two days later. Study drug was continued during the event and the patient completed the study.

LaForce 178, a 28-year-old Black male treated with albuterol developed severe chest pain and tachycardia on Day 17. Prednisone® and amoxicillin were administered for the chest pain. An ECG, chest x-ray, and stress test were performed; all test results were normal. The event resolved and the patient was withdrawn from the study on Day 23.

Placebo
LaForce 174, a 29-year-old Black female was hospitalized with respiratory acidosis 14 days after starting treatment with placebo. She was diagnosed with status asthmaticus and treated with Solu-Medrol®, aminophylline, and albuterol. The patient's condition resolved and she was discharged two days later.

Wolfe 242, a 44-year-old Caucasian male placebo recipient reported a severe back injury on Day 31. He was treated with a Prednisone burst (7 days) and a single corticosteroid injection. The patient was no longer eligible for study participation because of the medications administered for this event. His condition was unresolved at study withdrawal on Day 59.

8.1.8.3 Cardiac Effects

Mean change in pulse rate and in systolic or diastolic blood pressure over the four 12-hour in-clinic visits did not show a trend within any treatment group across the 12 week trial. No statistically or clinically significant differences in mean change from baseline were observed among the three treatment groups. There was a smaller proportion of patients in the salmeterol group who experienced increases in pulse rate of 15 beats per minute or more during the 12 hour observation periods than in either the albuterol or placebo groups (49 vs. 63 vs. 62 percent). The proportion of patients who experienced decreases of 15 beats per minute was comparable among the groups. There was a higher proportion of patients in the salmeterol and albuterol group who experienced a decrease of 15 mmHg or more in systolic blood pressure (51 vs. 53 vs. 43 percent), but the proportion of patients who experienced an increase of this magnitude was comparable among the groups. Increases and decreases of 15 mmHg or more in diastolic blood pressure were experienced by a comparable number of patients among the three groups.

Twelve lead electrocardiograms were obtained at screening and each clinic visit (predose and 1.5 hours post dose). Minor EKG abnormalities were detected at screening, including two patients in the albuterol group with Wolfe-Parkinson-White Syndrome. No clinically significant changes in EKG were observed in any patients.

QT_c remained consistent across treatment groups before and after treatment. A 51 year old Black female on salmeterol treatment (Lumry 208) was observed to have had intervals of over 500 msec with first degree heart block post-treatment, but this was consistent with findings at screening. No differences were detected in effects on the QT_c between corticosteroid users and non-corticosteroid users.

8.1.8.4 Clinical Laboratory Tests

Most laboratory evaluations were within normal ranges and no treatment-related trends were apparent. Normal to low bicarbonate values were observed for 14 placebo recipients (21.2%), five salmeterol recipients (8.3%), and 11 albuterol recipients (17.2%). This transition was unlikely related to beta-agonist treatment since it was predominate in the placebo group. More patients in the salmeterol group (seven patients, 10.4%) showed normal to low transitions in white blood count than in the placebo (two patients, 2.8%) or albuterol (four patients, 5.6%) groups. None of these transitions fell below the sponsor-defined lower limit for white blood count. Normal to high eosinophil values were observed for five placebo-treated patients (8.2%), eight albuterol-treated patients (12.7%), and ten salmeterol-treated patients (17.5%). This transition was not unexpected since elevated eosinophils are consistent with the asthmatic or allergic disease state.

Three patients experienced clinically significant changes in hepatic function. Two placebo patients experienced transient increases in SGPT or SGOT which resolved within the treatment period. In addition, a single salmeterol patient experienced liver enzyme elevations.

Wolfe 233, a 36-year-old Caucasian male treated with salmeterol had an abnormally high SGPT [125U/L (normal range 6-43U/L)] and an elevated SGOT [44U/L (normal range 11-36U/L)] at Treatment Week 12. At screening, his SGPT was on the high-side of the normal range (43U/L) and his SGOT was normal (26U/L). Throughout the study (Week 4- Week 10), the patient's SGPT was elevated (60-90U/L), however, SGOT, bilirubin, and alkaline phosphatase remained within normal range. Posttreatment tests revealed SGPT values of 86U/L and 97U/L, and SGOT values of 29U/L and 30U/L. The investigator did not comment on the follow-up results, however, it was noted that the patient was negative for hepatitis B, A, and C antibodies.

8.1.8.5 Physical Examinations

Pulmonary auscultation was conducted at clinic visits every two weeks and scored on a scale of 1 = no wheezing to 6 = dyspnea plus audible wheezing without stethoscope. The proportion of patients with scores of 1 varied between 46 and 91 percent, but showed no apparent trend throughout the 12 week trial and no fixed relationship among the treatment groups.

Physical examinations conducted at screening and week 12 revealed clinically significant findings, but none appeared to be consistent such that they could be associated with treatment effects.

8.1.8.6 Use of Non-Asthma Concomitant Medication

Non-asthma medication was reportedly used in 78 percent of salmeterol patients, 83 percent of albuterol patients and 85 percent of placebo patients. Table 8.1K contains a list of medications which were used by 5 percent or more of the patients in any treatment group. The use of topical corticosteroids was somewhat higher among the albuterol group than the other two treatment groups, however, it appears that overall there were no important differences among the treatment groups with respect to use of non-asthma medications.

Table 8.1K Percentage of Patients Using Concomitant Non-Asthma Medication*

	Salmeterol	Albuterol	Placebo
Any Non-Asthma Medication	80	80	79
Acetaminophen	10	9	19
Antitussives	6	4	6
Ibuprofen	13	9	13
Antihistamines	4	3	5
Vasoconstrictors (oral, nasal or ocular)	16	29	28
Topical Corticosteroids	21	31	22
Estrogen/Progesterone	14	26	27
Calcium/Potassium	3	1	5
Antibiotics	20	33	24
Immunotherapy	21	24	18

* Therapeutic classes are listed unless a single agent in the class comprised the majority of use. Only agents which were used by at least five percent of one treatment group were listed.

8.1.8.7 Safety Conclusion

Safety data from this trial appear to be primarily consistent with the known pharmacologic activity of the treatments, but there were several findings of particular note. Headache, respiratory events and ENT events were more frequent among salmeterol users than among the other treatment groups. Discontinuations due to asthma destabilization were more numerous in the salmeterol group than in the albuterol or placebo groups. A single patient (Pearlman 11) experienced a severe episode of tremor and agitation associated with the first dose of salmeterol. Another patient (Wolfe 233) experienced a clinically significant elevation in SGPT during salmeterol treatment. These findings should be compared to those of subsequent clinical trials.

8.1.9 Study Conduct

Patient Compliance

Dosing compliance was generated via the patient diary record of the prescribed doses actually used by the patient. Patient compliance with medication was reported to be approximately 99 percent for all three patients groups for aerosol canisters A and B and for the diskhaler. Values ranged between approximately 90 and 100 percent for

canister A and the diskhaler (administered morning and evening) while the range for the interim doses ranged from 70 to 110 percent.

Comment: While it is likely that compliance data based on patient records may overestimate the degree of compliance, the data do reflect that the doses which were prescribed for mid-day and supper time were adhered to less well than morning and evening doses. This seems to be a predictable pattern and to some extent supports the validity of these data.

Investigator Compliance

The complete list of protocol variations (Appendix 7.54 of the original submission) contains items which may be considered failure of the investigators to comply with protocol specifications. None of the investigators appeared to have had numerous protocol deviations which indicate a systematic misinterpretation of the protocol.

Device Performance

As will be discussed further in the Overview of Efficacy, specific information was provided regarding the device performance in the assessment of quality of life. The reliability of the DH formulation is not of primary interest as it is not the to be marketed formulation.

8.1.10 Conclusion

Overall, this study has demonstrated the clinical efficacy of salmeterol 50 mcg BID via the Rotadisk/Diskhaler device relative to placebo. Efficacy comparisons to albuterol show limited clinical comparability, primarily due to differences in the duration of action of the two drug substances. Safety data appear largely consistent with the pharmacologic profile of the active treatments.

8.2 Trial SLD-312: A Randomized, Double-Blind, Comparative Clinical Trial of Twelve-Week Courses of Salmeterol Xinafoate Rotadisk versus Albuterol versus Placebo in Adolescent and Adult Patients with Chronic Reversible Obstructive Airways Disease.

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Initiation Date: 13 July 1992 (first screen data collected)
Completion Date: 10 June 1993 (last posttreatment data collected)

8.2.1 - 8.2.5 The protocol used in Trial SLD-312 was identical to the protocol used in Trial SLD-311. See Sections 8.1.1-8.1.5.

8.2.6 Patient Disposition

There were 212 patients randomized to treatment (69 salmeterol; 70 albuterol; 73 placebo). There were 57 additional patients screened, but not enrolled, primarily due to abnormal liver enzyme values and PFTs out of range specified by eligibility criteria. Of the randomized patients, 190 completed the trial and 22 were discontinued. The reasons for discontinuation are provided below.

	Salmeterol	Albuterol	Placebo
Adverse Events	2	1	0
Asthma Exacerbation	0	1	2
Lack of Efficacy	0	0	3
Protocol Violation	3	3	4
Failed to Return	0	0	1
Other	1	1	0
Total	6	6	10

One salmeterol and one albuterol patient were discontinued due to asthma exacerbations which required hospitalizations. Each of these was counted as an adverse event rather than an asthma exacerbation.

Protocol variations that, in the determination of the sponsor, had the potential to affect

efficacy data were recorded for 25 patients (11 salmeterol; 7 albuterol; 7 placebo). Five patients were completely excluded from the efficacy analysis for reasons including violation of prestudy spirometry criteria (three patients) or inappropriate use of nebulization therapy (two patients). Affected efficacy data was excluded for one or more clinic visits for 20 patients based on the following reasons: taking disallowed concomitant medication, use of prohibited medication within washout windows, cessation of allowed concomitant medication, incorrect use of Diskhaler or mistiming of PFTs.

Demographic data and asthma history data were comparable among the three treatment groups. The randomized population was predominantly male (52 percent) and Caucasian (92 percent). Five percent of the population was Black, two percent was Hispanic and one percent was categorized as "other". Ages ranged from twelve years to 69 years of age with a mean of 32 years. Sixty six percent had been diagnosed with asthma more than 10 years prior to the study and, although 35 percent had received acute care for asthma in the year preceding the study, only four percent had been hospitalized for asthma during the same period. At the screening visit, the following proportion of patients reported nocturnal symptoms that interfered with sleep and/or daytime symptoms that interfered with regular activities:

	Nocturnal Symptoms	Daytime Symptoms
None	32%	11%
< 1 day per week	17%	8%
1 - 3 days per week	32%	44%
4 or > days per week	19%	37%

Unlike Trial SLD-311, the use of concomitant corticosteroids was not substantially different among the treatment groups. Forty nine percent of the salmeterol patients, 49 percent of the albuterol patients and 45 percent of the placebo patients used concomitant corticosteroids. No patients used theophylline concomitantly during the treatment period of the trial, however six, seven and four percent of the salmeterol, albuterol and placebo patients, respectively, used sodium cromoglycate.

8.2.7 Efficacy Endpoint Outcomes

See Section 8.1.7 for Trial SLD-311 in which the intent to treat and efficacy populations were described. The results of pulmonary function tests at screening are presented in Table 8.2A. There were no statistically significant differences among the three treatment groups at screening.

Comment: The screening means show that, for these parameters, the population of Trial SLD-312 was similar to that of Trial SLD-311.

Table 8.2A Pulmonary Function Outcomes at Screening

	Salmeterol (N = 67)	Albuterol (N = 73)	Placebo (N = 72)
FEV1			
Before Bronchodilation	2.39 (0.57)	2.34 (0.46)	2.32 (0.65)
Percent of Predicted	65.4 (9.5)	65.9 (8.4)	65.8 (9.7)
Percent Reversibility	30.7 (12.2)	28.7 (11.6)	29.1 (13.1)
$FEF_{25-75\%}$			
Before Bronchodilation	1.73 (0.69)	1.76 (0.56)	1.74 (0.87)
Percent of Predicted	43.8 (16.2)	46.0 (16.1)	45.8 (19.8)
FVC			
Before Bronchodilation	3.54 (1.08)	3.37 (0.82)	3.37 (1.00)
Percent of Predicted	80.5 (12.5)	80.0 (10.4)	81.0 (11.1)

8.2.7.1 Serial FEV_1

Baseline

There were no statistically significant differences among the salmeterol, albuterol and placebo treatment group FEV_1 means within the efficacy population at baseline. As in Trial SLD-311 (Section 8.1.7.1), the mean FEV_1 values for Hour 0 in the salmeterol group were statistically higher than the Day 1 baseline values at Weeks 4, 8 and 12. However, placebo and albuterol mean Hour 0 values were at or below baseline levels during these weeks.

Percent Change from Baseline

Appendix 12 and 13 contain the profile of percent change from baseline FEV_1 versus time for Day 1 and Week 4, respectively. As in Trial SLD-311, the profiles of Weeks 8 and 12 are very similar to those of Week 4. Again, the maximum percent change from baseline (see Table 8.2B) is similar for salmeterol and albuterol on Day 1 (31.1 and 31.3 percent, respectively), but is higher for salmeterol at Week 4 (35.6 and 27.9 percent, respectively). The difference at Week 4 did not reach statistical significance. Maximum percent change from baseline is statistically greater for both salmeterol and albuterol than for placebo at both Day 1 and Week 4.

Reanalyses of percent change from daily baseline at Week 4 were comparable to those conducted for Trial SLD-311.

Table 8.2B FEV_1 Outcomes for the Efficacy Population

	Salmeterol	Albuterol	Placebo	P-Values
Day 1	**N = 66**	**N = 70**	**N = 69**	
Max. % Change from Baseline (SD)	31.1 (21.6)	31.3 (19.5)	17.2 (14.6)	S v. P <0.001* A v. P <0.001* S v. A 0.635
# (%) of Responders	40 (61)	50 (72)	11 (16)	S v. P <0.001* A v. P <0.001* S v. A 0.150
Median Time of Onset in Hours	0.68	0.22	12.0	S v. P <0.001* A v. P <0.001* S v. A 0.014 *
Duration of Effect in Hours (SD)	5.2 (5.2)	4.7 (4.7)	0.9 (2.9)	S v. P <0.001* A v. P <0.001* S v. A 0.498
AUC-BL (SD)	5.6 (4.6)	4.5 (4.5)	1.5 (3.7)	S v. P <0.001* A v. P <0.001* S v. A 0.315
Week 4	**N = 62**	**N = 62**	**N = 65**	
Max. % Change from Baseline (SD)	35.6 (30.0)	27.9 (23.2)	14.5 (20.0)	S v. P <0.001* A v. P 0.004* S v. A 0.222
# (%) of Responders	39 (63)	34 (55)	16 (25)	S v. P <0.001* A v. P <0.001* S v. A 0.466
Median Time of Onset in Hours	0.46	0.24	12.0	S v. P <0.001* A v. P 0.002* S v. A 0.056
Duration of Effect in Hours (SD)	5.9 (5.2)	3.9 (4.8)	1.4 (3.3)	S v. P <0.001* A v. P <0.001* S v. A 0.019*
AUC-BL (SD)	6.6 (5.7)	3.5 (5.4)	0.5 (5.3)	S v. P <0.001* A v. P 0.019 S v. A 0.003*

* Indicates statistical significance at $p < 0.05$.

Percent of Predicted

Mean profiles of FEV_1 as a percent of predicted normal values across the 12 hour dosing interval for Day 1 and Week 4 show the same relationship among the treatments as the percent of baseline profiles. The magnitude of the mean values

approximates those shown in Appendix 5 and 6, respectively, for Trial SLD-311.

Onset

The median onset of effect was longer for salmeterol than for albuterol on Day 1 and at Week 4.

Comment: This is inconsistent with the findings from Trial SLD-311 in which the onset of the salmeterol group was shorter than that of the albuterol group after Week 1. The mean percent change from baseline profiles for Week 4 show that the group mean was well above a 15 percent improvement over baseline by 0.25 hours after dosing, however the sponsor responded that the median does not reflect the same information. Apparently, Trial SLD-312 differs from Trial SLD-311 in that this parameter was disproportionately affected by large values. The median value for onset is longer than 0.25 hours for salmeterol.

Comment: As in Trial SLD-311, the Day 1 onset for the diskhaler formulation was longer than the 10 to 20 minute onset specified in the labeling for a single 42 mcg. dose of Serevent Inhalation Aerosol.

Duration

The duration of effect, defined as a 15 percent improvement over baseline, was approximately 6 hours for salmeterol, similar to the duration found in Trial SLD-311. The mean profiles clearly show pharmacologic activity which extends through the anticipated 12 hour dosing interval.

AUC

AUC -BL for salmeterol and albuterol were nearly identical to those observed in Trial SLD-311.

8.2.7.2 FVC

The mean data for serial FVC are similar to the profiles provided in Appendix 8 and 9 for Trial-311, with the exception that in Trial-312 the mean profiles for each treatment are shifted upward by less than five percent. This does not alter the relationship among treatment groups or the clinical interpretation of the findings.

8.2.7.3 $FEF_{25-75\%}$

The mean data for serial $FEF_{25-75\%}$ are similar to the profiles provided in Appendix 10 for Trial SLD-311 at Week 1. At Week 4, results from Trial-312 show that the placebo

and salmeterol curves are shifted upward approximately five percent relative to the albuterol curve from those presented of Week 4 in Trial-311 (Appendix 11). These differences do not change the clinical interpretation of these results.

8.2.7.4 PEFR

Morning peak flow data exhibited the same statistical relationships among the three treatment groups which was described in Table 8.1F for Trial SLD-311 in that the salmeterol groups showed consistently higher means that either the albuterol or placebo groups with no difference between the albuterol and placebo means. Unlike Trial SLD-311, however, the evening PEFR scores failed to statistically distinguish among the three groups. Analyses of AM/PM differentials and of PEFR scores among the reduced efficacy population do not alter the interpretation of the mean findings.

8.2.7.5 Nighttime Awakenings

The percent of nights with no nighttime awakenings during the baseline period, was lowest among the salmeterol group during baseline (62, 73 and 69 percent for the salmeterol, albuterol and placebo groups, respectively). After initiation of treatment, the percentage of nights with no nighttime awakenings did not increase notably for the albuterol group, but did increase (indicating improvement) in the salmeterol group to approximately 83 percent. Statistically significant differences between salmeterol and placebo and between salmeterol and albuterol were observed for Weeks 1-4, Weeks 5-8 and Weeks 9-12. No statistically significant differences between placebo and albuterol were observed.

8.2.7.6 Symptom Scores

Symptoms scores for chest tightness, shortness of breath, wheezing and coughing showed a slightly greater reduction in mean scores associated with treatment with salmeterol than with albuterol or placebo. Fairly consistent demonstration of salmeterol's statistical superiority was seen for chest tightness and wheezing. As in Trial SLD-311 (Section 8.1.7.6), it is difficult to conclude that the differences among these mean scores were clinically significant, but the trend may be important. This trend was also observed when the percent of days with no symptoms was tabulated. Overall, the salmeterol group experienced no symptoms on 37 percent of treatment days, while the albuterol and placebo groups both experienced no symptoms on 27 percent of treatment days.

8.2.7.7 Physician-Rated Global Assessment

The distribution of symptom scores at screening and on Day 1 were similar for all three treatment groups. On treatment, scores shifted toward the less severe end of the scale

(scores of 0 or 1) for the salmeterol and albuterol groups, such that the two groups were nearly identical at Week 12. The placebo group scores did not show similar improvement.

8.2.7.8 Use of Rescue Albuterol

Use of rescue during the baseline period between the Screening Visit and Day 1 was similar among the three treatment groups: 5.0, 4.1 and 4.2 puffs per day for the salmeterol, albuterol and placebo groups, respectively. After initiation of treatment, use of rescue fell in all three groups and was fairly consistent across the twelve treatment weeks at approximately 1.7, 2.2 and 3.1 puffs per day, respectively, for the three treatment groups. Statistically significant differences were consistently seen for salmeterol versus placebo, albuterol versus placebo and salmeterol versus albuterol.

8.2.7.9 Treatment Effects by Use of Concomitant Asthma Therapy

Unlike Trial SLD-311, the use of concomitant corticosteroids was not substantially different among the treatment groups. Forty nine percent of the salmeterol patients, 49 percent of the albuterol patients and 45 percent of the placebo patients used concomitant corticosteroids. As in Trial SLD-311, the mean FEV_1 of the patients in each of the treatment groups who did not use inhaled corticosteroids was consistently higher than the mean of patients in the same treatment group who used inhaled corticosteroids. Repeated measures analyses, summarizing the change from baseline for the entire 12 hour interval for the entire efficacy population, revealed that both salmeterol and albuterol treatment groups were statistically superior to placebo and that salmeterol was statistically superior to albuterol except on Day 1.

In subgroup analyses, both the user and non-user salmeterol subgroups were statistically superior to placebo at each week. Salmeterol patients who used corticosteroids were also statistically superior to albuterol at each week except on Day 1, but albuterol group corticosteroid users did not show statistically superiority to placebo at Weeks 4, 8 and 12. Among the non-users, salmeterol was statistically superior to albuterol at each week, but albuterol was statistically superior to placebo only at Week 4. Overall, use of corticosteroids does not appear to have factored into the outcomes of the salmeterol group in a clinically significant way.

Regarding AM and PM PEFR scores, use of corticosteroids did not significantly factor into the outcome of the salmeterol group, but AM PEFR scores may have been positively affected by the use of concomitant corticosteroids in the albuterol group.

8.2.7.10 Asthma Exacerbation

The number (and percentage) of patients who experienced asthma exacerbations

during treatment is listed in Table 8.2C. Placebo patients had the highest incidence of asthma exacerbations. While the incidence of asthma exacerbations was similar between the salmeterol and albuterol groups, the salmeterol group did experience fewer exacerbations. No inferential statistical comparisons were conducted.

Table 8.2C Number (Percentage) of Patients Experiencing Asthma Exacerbations During Treatment

	Salmeterol N = 69	Albuterol N = 70	Placebo N = 73
No Exacerbations	53 (77)	51 (73)	47 (64)
One Exacerbation	7 (10)	10 (14)	12 (16)
Two Exacerbations	7 (10)	6 (9)	5 (7)
Three or More Exacerbations	2 (3)	3 (4)	9 (12)

8.2.7.11 Intent to Treat Population

The outcomes of the intent to treat population analyses were not substantially different from the outcomes of analyses of the efficacy population.

8.2.7.12 Efficacy Conclusion

Overall, efficacy outcomes from SLD-312 were similar to those observed in Trial SLD-311 in that consistent superiority to placebo was demonstrated on the majority of primary endpoints and limited clinical comparability, based primarily on duration of action, was shown relative to albuterol. Onset of action of salmeterol was again demonstrated to be longer than the 10 to 20 minutes defined by the MDI labeling. Duration of action was again considerably shorter than 12 hours.

Comment: The onset of effect and duration of action issues have arisen based on the use of the sponsor's definition of 15 percent improvement over baseline. Clearly, effect of the salmeterol can be observed at levels lower than this threshold during the dosing interval. This issue of whether the powder formulation differs significantly from the MDI should be settled based on direct comparison of the MDI and powder formulation. Trials designed for such comparison have been completed and will be evaluated in an addendum to this review.

Consistent with SLD-311, the number of nighttime awakenings and days without asthma symptoms was highest in the salmeterol group, with a potential clinical significance in the difference between salmeterol and albuterol. The number of asthma exacerbations was lowest among salmeterol patients. The use of concomitant inhaled corticosteroids was more comparable among treatment groups in this trial than in SLD-

311. Use of concomitant corticosteroids did not appear to have a clinically significant effect on the performance of salmeterol relative to the other treatment groups. The effects of salmeterol treatment were consistent across the 12 week treatment period.

8.2.8 Safety Endpoint Outcomes

Each of the safety endpoint analyses was conducted with the intent to treat population.

8.2.8.1 Adverse Events

All Adverse Events

Overall, 74 percent of the salmeterol patients, 79 percent of the albuterol patients and 63 percent of the placebo patients experienced adverse events. Adverse events which were experienced by at least three percent of any treatment group, and by a larger proportion of either of the active treatment groups than the placebo group, are listed on the following page in Table 8.2D.

The overall incidence of adverse events among albuterol patients was statistically significantly higher than among placebo patients. However, there were no statistically significant differences among the treatment groups for any of the individual events. Headache appears to the be only event which may be related to salmeterol therapy.

There were minimal differences between the incidence of adverse events among patients who were and who were not using inhaled steroids. Differences which appear to have potential clinical relevance were observed within the albuterol treatment group. Thirty two percent (11 patients) of the corticosteroid users experienced a U.R.T.I., while only eight percent (3 patients) of non-users reported the same event. Headache was reported by only three percent of inhaled corticosteroid users (1 patient) while 33 percent (12 patients) of non-users reported the same event.

Table 8.2D Number (Percentage) of Patients Experiencing Adverse Events*

	Salmeterol N=[illegible]	Albuterol N=[illegible]	Placebo N=[illegible]
Any Ear, Nose, Throat Event	**34 (49)**	**33 (47)**	**28 (38)**
U.R.T.I.	11 (16)	14 (20)	8 (11)
Pharyngitis	**8 (12)**	**7 (10)**	**5 (7)**
Disease nasal cavity/sinus	**9 (13)**	**6 (9)**	**5 (7)**
Rhinitis	**7 (10)**	**5 (7)**	**5 (7)**
Nasopharyngitis	4 (6)	5 (7)	4 (5)
Sinusitis	4 (6)	4 (6)	4 (5)
Ear Ache	2 (3)	2 (3)	1 (1)
Otitis Media	0 (0)	2 (3)	1 (1)
Disorders of the Ear	1 (1)	2 (3)	0 (0)
Any Gastrointestinal Event	**9 (13)**	**7 (10)**	**7 (10)**
Nausea	**4 (6)**	**3 (4)**	**2 (3)**
Diarrhea	3 (4)	4 (6)	1 (1)
Nausea & Vomiting	**3 (4)**	**2 (3)**	**2 (3)**
Allergy	**2 (3)**	**0 (0)**	**0 (0)**
Pyrexia of Unknown Origin	**4 (6)**	**1 (1)**	**1 (1)**
Any Mouth Event	**6 (9)**	**4 (6)**	**3 (4)**
Oral Mucosal Abnormality	3 (4)	3 (4)	0 (0)
Conditions of the Tongue	**2 (3)**	**0 (0)**	**0 (0)**
Any Musculoskeletal Event	8 (12)	10 (14)	6 (8)
Pain in Joint	**3 (4)**	**0 (0)**	**1 (1)**
Back Pain	0 (0)	2 (3)	1 (1)
Myalgia/Myositis	1 (1)	2 (3)	0 (0)
Any Neurological Event	13 (19)	16 (23)	9 (12)
Headache	10 (14)	13 (19)	7 (10)
Malaise/Fatigue	**3 (4)**	**1 (1)**	**2 (3)**
Dizziness/Giddiness	1 (1)	2 (3)	1 (1)
Any Respiratory Event	12 (17)	12 (17)	12 (16)
Tracheitis/Bronchitis	**4 (6)**	**3 (4)**	**1 (1)**
Influenza	2 (3)	3 (4)	2 (3)
Any Skin Event	**4 (6)**	**6 (9)**	**4 (5)**
Rash/Skin Eruption	1 (1)	2 (3)	1 (1)
Contusion	**2 (3)**	**1 (1)**	**0 (0)**
Pruritus	0 (0)	2 (3)	0 (0)

* Only adverse events experienced by 3 percent or more of any treatment group, and by a higher proportion of patients in either active treatment group than in the placebo group, are listed. Events with a higher incidence among salmeterol users than albuterol users are shown in bold.

8.2.8.2 Deaths, Discontinuations and Serious Events

There were no deaths reported during this trial. Three patients experienced serious events including two salmeterol patients and one albuterol patient. Descriptions of each case are provided. These were the only patients discontinued due to adverse events.

Salmeterol
Dockhorn #10, a 37-year-old Caucasian female salmeterol recipient was hospitalized on Day 29 due to an acute asthma exacerbation. She was initially treated with Solu-Medrol® and Ventolin, and subsequently administered cefuroxime IV, prednisolone IV, and albuterol. Her condition resolved and she was discharged four days later. Causality was judged by the investigator as possibly due to lack of efficacy of the study drug.

Morris #108, a 43-year-old Caucasian male salmeterol recipient, with a history of non-specific T-wave abnormalities, developed an abnormal ECG (anterolateral ST-T wave change indicative of ischemia) before receiving study drug on Treatment Day 1. The patient received one dose of study medication since the ECG was not reviewed prior to dosing. He was subsequently discontinued from the study and referred to a cardiologist. Follow-up testing (echocardiogram, stress test with imaging, and angiography) was consistent with an episode of coronary spasm involving the right coronary artery silently resulting in subendocardial infarction. The investigator considered the event unrelated to study drug.

Albuterol
Ellis 186, a 35-year-old Caucasian female treated with albuterol was hospitalized on Day 22 with an exacerbation of asthma. The patient was treated with IV and oral corticosteroids, theophylline, and IV antibiotics. Her condition resolved and she was discharged three days later. The patient attributed the event to a respiratory infection. The investigator considered the event unrelated to study drug.

8.2.8.3 Cardiac Effects

Mean change in pulse rate and in systolic or diastolic blood pressure over the four 12-hour in-clinic visits did not show a trend within any treatment group across the 12 week trial. No clinically significant differences in mean change from baseline were observed among the three treatment groups. Approximately half of the patients in each treatment group experienced an increase in pulse rate of 15 beats per minute or more during the 12 hour observation periods and approximately 55 percent of each treatment group experienced decreases of 15 beats per minute. There was a higher proportion of patients in the albuterol group (87 percent) than in the salmeterol group (55 percent) or the placebo group (67 percent) who experienced an increase of 15 mmHg or more in systolic blood pressure, but the proportion of patients who experienced an decrease of this magnitude was comparable among the groups (64 to 72 percent). Increases of 15 mmHg or more in diastolic blood pressure were experienced by a comparable number of patients among the three groups (approximately 40 percent). The incidence of decreases of this magnitude range from 42 to 56 percent and were slightly higher in the active treatment groups.

Most patients (77 to 90 percent) had normal ECGs at screening, but non-significant

ECG abnormalities (e.g., sinus bradycardia, incomplete RBBB, high QRS voltage, possible atrial enlargement, sinus arrhythmia, non-specific T-wave abnormality, ST elevation) were noted at screening in 23, 9, 21 percent of the patients assigned to receive salmeterol, albuterol, and placebo respectively. One patient randomized to albuterol treatment (Ellis 189, a 34- year-old Caucasian female with a history of mitral valve prolapse) had an ECG tracing which appeared clinically abnormal (anterior myocardial infarction) at screening. Echocardiogram showed the entire anterior wall and septum were normal, with no evidence of an anterior wall myocardial infarction. The patient was therefore permitted to participate in the study since the consulting cardiologist considered this ECG finding of no clinical significance.

Unfavorable post dose ECG changes were noted for one placebo recipient and one albuterol recipient.

Ellis 207, a 63-year-old Caucasian female placebo recipient exhibited premature atrial contractions post dose on Treatment Day 1; the investigator judged this event probably related to study treatment. This patient was subsequently discontinued prematurely due to resuming use of a steroid inhaler; the ECG performed at this time was within normal limits.

Morris 118, a 69-year-old Caucasian male albuterol recipient showed altered atrial rhythm post dose at Treatment Weeks 4 and 8. This finding was also noted on the Treatment Day 1 predose ECG. The investigator considered this event possibly related to study drug when it was reported as an adverse event at Treatment Week 4 (Table 53), but also stated he was uncertain of the drug relationship at the Post-Treatment Visit.

One patient each in the placebo and salmeterol treatment groups exhibited predose clinically significant ECGs.

Dockhorn 30, a 41-year-old Caucasian female placebo recipient developed non-specific anterior T-wave abnormalities at Treatment Week 12. The patient also reported flu symptoms (nausea, vomiting, fatigue, headache, and fever) concurrently. The investigator considered this finding related to the patient's condition and unrelated to study drug.

Salmeterol patient, Morris 108, was previous described.

QTc intervals remained consistent across the treatment groups at each of the assessment periods with at least 91% of the patients recording intervals of <440msec. Grossman 51, a 17-year-old Caucasian male in the salmeterol group recorded post dose QTc intervals of 471 msec at Treatment Week 4 and 582 msec at Treatment Week 12. This patient also recorded a predose interval of 582 msec at Week 12. Two albuterol recipients also had prolonged (>470msec) post dose QTc intervals. Grady 70, a 40-year-old Caucasian female recorded pre-and post dose intervals of 480msec at Treatment Week 4. Goldstein 126, a 45 year old Caucasian female had a post dose interval of 480 msec at Week 12. No clinically significant trends were associated with treatment.

8.2.8.4 Clinical Laboratory Tests

Most laboratory evaluations were normal with a few isolated abnormalities noted, however, no treatment-related trends were evident. The incidence of clinically significant abnormalities was similar across the treatment groups:, six salmeterol recipients (9%), five albuterol recipients (7%) and seven placebo recipients (10%). Most of the patients (78%) had abnormalities that were either present prior to treatment, due to the asthmatic/allergic disease state, or considered by the investigator as clinically insignificant deviations from normal values. The most common deviation was in eosinophil counts.

Four patients, discussed below, exhibited sponsor-defined clinically significant laboratory abnormalities during treatment which were considered by the investigator as possibly related to study drug (i.e., not pre-existing and not attributable to concurrent illness or disease process).

Hepatic Function
Grady 76, a 21-year-old Caucasian male salmeterol recipient had an abnormally high SGOT [156U/L (normal range 11-36U/L)] and slightly elevated SGPT [63U/L (normal range 6-43U/L)] at Treatment Week 4. His screening SGOT was slightly elevated (60U/L), however repeat testing disclosed a value of 20U/L. At Treatment Week 12, both SGOT and SGPT values were normal (25U/L and 35U/L, respectively). The investigator also felt the patient's alcohol and dietary habits were possible influencing factors on these elevations.

Renal Function
Grady 88, a 43-year-old Caucasian female treated with albuterol exhibited an abnormally high urea nitrogen value [30mg/dL (normal range 4-24mg/dL)] at Treatment Week 4. Her screening value was normal (21mg/dL) as was the value recorded at Treatment Week 12 (24mg/dL). Serum creatinine and uric acid values were normal throughout the study.

Clinical Chemistry
Ellis 194, a 60-year-old Caucasian female salmeterol recipient had a abnormally high glucose value at Treatment Week 12 [249mg/dL (normal range 70-120)]. Her Screening and Treatment Week 4 lab results revealed mild hyperglycemia (161mg/dL and 122mg/dL, respectively).

Kemp 152, a 13-year-old Hispanic male treated with albuterol showed an abnormally high potassium level at Treatment Week 4 [6.3mEq/L (normal range 3.4-5.4mEq/L)] which remained elevated through the remainder of the study 5.5-5.9mEq/L. His screening value was normal (5.2mEq/dL).

8.2.8.5 Physical Examinations

Pulmonary auscultation was conducted at clinic visits every two weeks and scored on a scale of 1 = no wheezing to 6 = dyspnea plus audible wheezing without stethoscope. The proportion of patients with scores of 1 varied between 51 and 82 percent, but showed no apparent trend throughout the 12 week trial. In general, the salmeterol group had a greater proportion of patients who were reported to have no wheezing,

beginning at Week 2, however, the difference among groups was not marked.

Physical examinations conducted at screening and week 12 revealed clinically significant findings, but none appeared to be consistent such that they could be associated with treatment effects.

8.2.8.6 Use of Non-Asthma Concomitant Medication

Overall, 81, 77 and 84 percent of the salmeterol, albuterol and placebo patients, respectively, used concomitant non-asthma medications. The most frequently used medications were similar to those listed for Trial SLD-311 in Section 8.1.8.6. Overall, it appears that there were no important differences among the treatment groups with respect to use of these medications, including topical corticosteroids.

8.2.8.7 Safety Conclusion

As in Trial SLD-311, the safety profile from this trial appears consistent with the pharmacologic activity of salmeterol. In this trial, ENT, respiratory events and headache were not notably more frequent among the salmeterol patients than among either placebo or albuterol patients.

As in Trial SLD-311, a single salmeterol patient (Grossman 51) experienced prolonged QTc (≥ 440 msec) during treatment. Unlike the previous case, however, this patient's experience was not consistent with screening. An single albuterol patient was also found to have QTc prolongation. In addition, a single patient (Grady 76) experienced elevated SGOT and SGPT during salmeterol treatment while a second patient (Ellis 194) experienced abnormally high glucose values. These findings will have to be compared to the overall safety database for the powder formulation.

8.2.9 Study Conduct

Patient Compliance

Patient compliance with treatment medication was reported in daily diaries to be approximately 99 percent for all three patients groups for aerosol canister A and the diskhaler and approximately 98 percent for aerosol canister B. In the salmeterol and albuterol treatment groups, values ranged between approximately 90 and 100 percent for canister A and the diskhaler (administered morning and evening) while the range for the interim doses ranged from 70 to 110 percent. Two patients in the placebo group and one in the albuterol group had compliance rates of less than 80 percent.

Investigator Compliance

The complete list of protocol variations contains items which may be considered failure of the investigators to comply with protocol specifications. None of the investigators appeared to have had numerous protocol deviations which indicate a systematic misinterpretation of the protocol.

8.2.10 Conclusion

Safety and efficacy outcomes from this trial are largely consistent with those observed in Trial SLD-311. Of remaining concern are the relative onset and duration of effect of the powder formulation and the potential for causal relationships with various adverse events. The former will be examined in clinical comparisons to the MDI in a subsequent review, while the latter will be taken up in the assessment of the integrated safety database.

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8.3 Trial SLGA2004: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Comparative Clinical Trial of Salmeterol Xinafoate via Multi-Dose Powder Inhaler Versus Salmeterol Xinafoate via Diskhaler for Four Weeks in Adolescent and Adult Subjects with Mild to Moderate Asthma. (Vol 1.65)

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Initiation Date: 9 March 1994 (first patient was enrolled)
Completion Date: 8 August 1994 (date of last observation)

8.3.1 Study Description

Objective:
The primary objective of this study was to "demonstrate the safety and efficacy of salmeterol 50 mcg BID via multiple dose dry powder inhaler (MDPI) compared with placebo and salmeterol 50 mcg BID via Diskhaler (DH) compared with placebo over a 4 week treatment period in asthmatic patients ≥ 12 years of age." This trial serves a bridging study to link the DH, which was compared to placebo in Trials SLD-311 and 312, with the MDPI, which the company intends to market. Evaluation of pharmacoeconomic factors, including ease of device use, was a secondary outcome.

There were two protocol amendments made, one prior to initiation of the study and one after initiation of the study. Each amendment consisted of multiple modifications to the protocol. The modifications appear to be appropriate clarifications which should not have biased the trial outcome.

Population:
Males and females, age 12 years and over, with mild to moderate asthma were enrolled if they demonstrated an FEV_1 of 50 to 85 percent of predicted normal during screening and were otherwise healthy. Patients on fixed doses of inhaled or intranasal corticosteroids, inhaled or intranasal cromolyn or inhaled nedocromil were permitted in the study and other concomitant medications were to be appropriately withheld.

Design and Procedures:
This study was a randomized, double blind, double dummy, placebo controlled, four week comparison of salmeterol 50 mcg BID (via MDPI), salmeterol 50 mcg BID (via DH) and placebo (via MDPI). At the Screening Visit, patients were converted from their

current beta agonist to Ventolin MDI on an as needed basis for one to two weeks. The first dose of study drug was administered at Visit 1 (Day 1), followed by a 12 hour evaluation which included spirometric assessments and ambulatory Holter monitoring. Visits 2 and 3 took place at two week intervals. On a daily basis between visits, patients recorded their pre-dose morning and evening PEFR, as well as the incidence of awakenings due to nocturnal asthma (0 to 2 scale) and severity of asthma symptoms (overall severity only, 0 to 5 scale). Ventolin MDI was used as a rescue medication; its use was recorded in patient diaries. Patient compliance with study medication was to be assessed by counting the emptied DH blisters and observing the dose counter on the MDPI.

Endpoints:

Efficacy Endpoints
The primary efficacy assessment is the 12 hour spirometric measure of FEV_1 on Treatment Day 1 (Visit 1) and Day 29 (Visit 3). Spirometry was conducted on Day 14 (Visit 2) only at 0.5 hrs predose and 1 hour post dose. Secondary efficacy measures include FVC, $FEF_{25-75\%}$, PEFR (as recorded in patient diaries), backup use of Ventolin, nighttime awakenings and patient self-ratings of asthma symptoms.

Safety Endpoints
Safety assessments in this trial included clinical adverse events (collected at each clinic visit), 12-lead electrocardiograms (collected at screening and predose and 1.5 hours post dose at each clinic visit), clinical laboratory tests (assessed at screening and Visit 3 or the final visit), vital signs (assessed at each clinic visit immediately prior to each set of PFTs), and physical examination findings (assessed at screening and Visit 3).

Statistical Considerations:

Enrollment was planned for 180 patients across 12 investigational centers with a 1:1:1 randomization scheme to yield results from 60 completed patients for each of the three treatments. This proposed sample size provided for > 80 percent power of detecting a difference in FEV_1 of 0.29 liters between any two treatment groups, using a two-sample t-test with a significance level of 0.05, assuming a standard deviation of 0.55 liters for FEV_1. The protocol stated that for spirometric endpoints, repeated measures analysis and the individual timepoint analysis would be based on change from the pretreatment baseline (average of 0.5 and 0 hour predose FEV_1 measurements on Treatment Day 1).

8.3.2 Patient Disposition

There were 210 patients randomized to treatment (71 salmeterol MDPI; 70 salmeterol DH; 69 placebo) and 59 screened but not enrolled. Of those enrolled, 195 completed

the trial and 15 were discontinued. The reasons for discontinuation are provided below.

	MDPI	DH	Placebo
Adverse Events	2	0	1
Asthma Exacerbation	2	1	2
Lack of Efficacy	0	0	0
Protocol Violation	1	0	1
Other (Logistics)	2	1	2
Total	7	2	6

Comment: Although the discontinuation rate was three-fold lower in the DH treatment group (3 percent) versus the MDPI (10 percent) and placebo (9 percent) groups, the attribution of reasons for discontinuation does not strongly suggest a treatment-related reason for the differences between active treatments.

Demographic data and asthma history data were comparable among the three treatment groups. The randomized population was predominantly male (64 percent) and Caucasian (91 percent). Three percent of the population was Black, four percent was Hispanic, three percent was Oriental and one percent was "other". Ages ranged from twelve years to 75 years of age with a mean of 33 years. Seventy one percent had been diagnosed with asthma more than 10 years prior to the study; 27 percent had received acute care for asthma in the year prior to the study. Nocturnal asthma was reported to occur at least once a week in 42 percent of the patients. Corticosteroids were used by approximately 55 to 60 percent of the patients in each treatment group, while another eight percent received used cromolyn or nedocromil.

The intent to treat population (N = 210) was comprised of all patients for whom measurements were conducted. Exclusion of patients who were discontinued from the trial, plus one patient in the MDPI group who had "unevaluable" spirometric data, determined the "efficacy" population (N = 194). The efficacy population was used for the primary efficacy analysis, although parallel analyses for the intent to treat population have been provided. The intent to treat population was used for safety analyses.

Although the protocol states that patient compliance was to have been assessed by counting used/returned blisters of the DH and with dosing counter readings on the MDPI, the 75 percent compliance figure reported by the sponsor was based on patient recordings of doses taken in their daily diaries. The sponsor clarified that the protocol was followed accurately and that the original submission was in error.

8.3.3 Efficacy Endpoint Outcomes

The results of pulmonary function tests at screening are presented in Table 8.3A for the efficacy population. There was a statistically significant difference among the treatment groups in percent of predicted FVC which was associated with the investigator effect; the clinical significance of this finding appears to be minimal. No other statistically significant differences were found.

Table 8.3A Pulmonary Function Outcomes at Screening - Mean (SD)

	MDPI (N = 63)	DH (N = 66)	PLACEBO (N = 63)
FEV1			
Before Bronchodilation	2.67 (0.65)	2.46 (0.62)	2.51 (0.61)
Percent of Predicted	69.3 (9.9)	67.0 (10.2)	67.4 (9.6)
Percent Reversibility	30.6 (13.0)	28.1 (12.7)	30.1 (17.3)
FEF			
Before Bronchodilation	2.05 (0.85)	1.93 (0.80)	1.90 (0.78)
Percent of Predicted	49.9 (18.1)	50.4 (20.4)	48.3 (20.0)
FVC			
Before Bronchodilation	3.79 (0.98)	3.41 (0.92)	3.63 (0.95)
Percent of Predicted	83.2 (13.5)	77.5 (11.9)	82.2 (13.5)

8.3.3.1 Serial FEV_1

There were no statistically significant differences among the MDPI, DH and placebo treatment group FEV_1 means within the efficacy population at screening. "Baseline" for spirometric endpoints was defined as the average of the assessment one-half hour prior to dosing and immediately preceding the dose, i.e., the -0.5 hour and 0 hour assessments on Day 1 (Visit 1). Daily baselines were not defined for Visit 2 or Visit 3. The Hour 0 values did not fall to baseline levels at Visit 3 for any of the treatment groups, but the statistical significance of the difference between overall and daily baselines was not tested.

Comment: As observed in previous trials, this shift in Hour 0 values over the study is likely to be due to the long duration of action of salmeterol and would serve to dampen the ability to show treatment effects. The appearance of this shift consistently among the various trials suggests that it is a function of the pharmacologic action of the drug rather than a function of the patient population.

Table 8.3B summarizes the baseline data and outcomes for post-dosing spirometric endpoints at the Day 1 and Day 29 visits. At baseline, the mean FEV_1 for the MDPI group was statistically significantly higher than for the DH group. Both the MDPI and DH were statistically superior to placebo on Day 1 and Day 29 for maximum percentage change from baseline, number of patients who experienced a 15 percent increase in FEV_1 within 4 hours after dosing, median time to onset of effect, duration of effect and area under the response curve relative to baseline. No statistical differences between MDPI and DH were noted for these endpoints on either Day 1 or Day 29.

Appendix 14 and 15 contain the profile of percent change from baseline FEV_1 versus time for Day 1 and Day 29, respectively. On Day 1, the mean effect for the MDPI was slightly reduced relative to the DH, particularly after Hour 6. This relationship is reversed on Day 29, when the percent change from baseline for the MDPI exceeded that of the DH throughout the 12 hour dosing interval. Comparison of actual mean change from baseline FEV_1 showed that the response of the MDPI treatment group was statistically higher than the DPI treatment group at Hours 0.5, 1, 2 and 4. Post dose differences between the treatments on Day 29 do not appear to be attributable to baseline differences between treatments. The numerical superiority of the MDPI continues to be evident when the percent change from baseline data are adjusted using baseline as a covariate.

Comment: The difference between MDPI and DH outcomes does not appear to be of sufficient magnitude to have clinical significance. As the difference favors the MDPI device, efficacy data derived from other trials which employed the DH should be applicable to the MDPI. Further evaluation of the safety data will be necessary to determine whether there is an important difference between MDPI and DH.

On Day 1, the median time of onset was approximately 47 minutes for the MDPI and 37 minutes for the DH. This difference was not evidenced at Day 29. Reanalyses of FEV_1 data looking at the efficacy population, and defining responders as those patients who achieved a 15 percent improvement over baseline within 30 minutes of dosing, showed a 35 percent response rate for the MDPI, a 48 percent response rate for the DH and an eight percent response rate for the placebo.

Comment: Day 1 data seem to indicate that the onset of action of the DH product is slightly faster than the MDPI. These differences are not apparent on Day 29, probably due to carryover effects of the long acting drug substance at Hour 0. This finding has little clinical relevance for a product which is not used in the treatment of acute asthma symptoms.

Table 8.3B FEV_1 Outcomes for the Efficacy Population (Responders within 4 Hours of Dosing)

MDPI	MDPI	DH	Placebo	P-Values
Day 1	**N = 63**	**N = 68**	**N = 63**	
Baseline	2.83	2.57	2.69	MDPI v. P 0.449 DH v. P 0.199 MDPI v. DH 0.047*
Max. % Change from Baseline (SD)	27.8 (18.0)	27.1 (14.8)	14.8 (11.9)	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 0.887
# (%) of Responders w/in 4 Hours of Dose	47 (75)	49 (73)	18 (29)	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 1.000
Median Time of Onset in Hours	0.79	0.62	12.0	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 0.477
Duration of Effect in Hours (SD)	6.2 (4.8)	7.0 (5.2)	1.9 (3.8)	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 0.162
AUC-BL (SD)	6.1 (5.1)	5.9 (4.0)	1.8 (4.4)	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 0.923
Day 29	**N = 63**	**N = 67**	**N = 63**	
Max. % Change from Baseline (SD)	32.4 (22.6)	28.9 (20.7)	15.9 (18.6)	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 0.256
# (%) of Responders	43 (68)	46 (69)	24 (38)	MDPI v. P 0.001* DH v. P <0.001* MDPI v. DH 1.000
Median Time of Onset in Hours	0.43	0.44	12.0	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 0.774
Duration of Effect in Hours (SD)	6.5 (5.6)	6.4 (5.5)	3.4 (5.0)	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 0.920
AUC-BL (SD)	7.5 (6.9)	6.2 (5.3)	2.6 (6.0)	MDPI v. P <0.001* DH v. P <0.001* MDPI v. DH 0.146

* Indicates statistical significance at $p < 0.05$.

Effects of each of the active treatments on percent change from baseline exceeded those of the placebo at all timepoints. The shift in baseline within the active treatment groups, which has been discussed in reference to Trials SLGA 311 and 312, is evident at Day 29.

The outcome of the intent to treat population analyses were submitted for selected FEV_1 efficacy endpoints. The intent to treat population included 16 patients who were not part of the efficacy population. The intent to treat outcomes were similar to those of the efficacy population in that the MDPI and DPI were shown to be consistently superior to placebo. Mean percent change from baseline data suggest that there is a shorter time to onset for the DH product on Day 1. As in the efficacy population analyses, the MDPI produced a slightly greater, and statistically higher, effect relative to the DH on Day 29 based on a comparison of mean change from baseline.

Reanalyses of change from daily baseline FEV_1 for Day 29 revealed the same separation of treatment effects as seen in Appendix 15. Maximum mean change was less than 15 percent, as anticipated from similar reanalyses of SLD-311 and SLD-312.

8.3.3.2 FVC

No statistically significant differences were found at baseline among the three treatment groups. Comparisons of change from baseline showed that DH was statistically superior to placebo at all post-dose timepoints on Day 1 and Day 29. In contrast, the MDPI failed to show statistical superiority to placebo at 0.5 hours and 10 hours after dosing on Day 1, although it was statistically superior to placebo at each post dose timepoint on Day 29. No statistically significant differences between MDPI and DH were demonstrated at any timepoint.

Comment: The FVC outcomes on Day 1 appear similar to the FEV_1 outcomes in that they suggest that the MDPI has a slower onset of action than the DH. This difference does not appear to be clinically meaningful on Day 1 and is not evident on Day 29.

Mean maximum percent change was not calculated for this parameter, but it appears that mean percent change from baseline indicates that a somewhat greater maximal effect in the MDPI group (15.9 percent on Day 29) than the DH group (12.9 percent on Day 29). Consistent with the FEV_1 data, this difference is more evident on Day 29 than on Day 1.

8.3.3.3 $FEF_{25-75\%}$

No statistically significant differences were found among the three treatment groups at baseline. At all post-dose timepoints on Day 1 and Day 29, for both the MDPI and DH treatments, change from baseline means were statistically significantly greater than

placebo means. Mean change from baseline for the MDPI group was statistically significantly greater than mean change from baseline for the DH group at 1 hour post-dose on Day 1 and 0.25, 1, and 4 hours post-dose on Day 29. The $FEF_{25-75\%}$ endpoint does not appear to reflect a slower onset on Day 1 for the MDPI relative to the DH. Mean maximum percent change was not calculated for this parameter, but it appears that mean percent change from baseline indicates that a somewhat greater maximal effect in the MDPI group (56.1 percent on Day 29) than the DH group (50.6 percent on Day 29). Consistent with the FEV_1 and FVC data, this difference is more evident on Day 29 than on Day 1.

8.3.3.4 PEFR

Patients were instructed to measure peak expiratory flow rate in the morning after getting out of bed, but before the first dose of study drug. Evening evaluations were undertaken before the last study dose of the day. Table 8.3C shows the comparison among treatments at baseline (mean of the daily PEFR recordings from the 7 days prior to Day 1) and the mean for the daily scores during the first and fourth weeks of the treatment period. The reported p-values correspond to comparisons of mean change from baseline within each treatment group (and on actual values at baseline).

Table 8.3C Mean Morning and Evening PEFR from Diary (S.E.) for Efficacy Population

	MDPI	DH	PLACEBO	P-Values
Morning Baseline	**427 (12)**	**403 (10)**	**416 (12)**	**MDPI v. P 0.305 DH v. P 0.418 MDPI v. DH 0.052**
Evening Baseline	456 (11)	430 (11)	436 (12)	MDPI v. P 0.120 DH v. P 0.720 MDPI v. DH 0.040*
Morning Days 1 - 7	**457 (12)**	**433 (11)**	**425 (11)**	**MDPI v. P 0.003* DH v. P <0.001* MDPI v. DH 0.863**
Evening Days 1 - 7	482 (12)	457 (10)	444 (12)	MDPI v. P 0.004* DH v. P <0.001* MDPI v. DH 0.624
Morning Days 22 - 28	**478 (13)**	**437 (11)**	**433 (12)**	**MDPI v. P < 0.001* DH v. P 0.012* MDPI v. DH 0.116**
Evening Days 22 - 28	490 (13)	460 (10)	452 (12)	MDPI v. P 0.038* DH v. P 0.034* MDPI v. DH 0.901

* Indicates statistical significance at $p < 0.05$.

At baseline, mean morning and evening PEFR values for the MDPI treatment group were numerically higher than for the DH treatment group and the difference was statistically significant for the evening means. The MDPI group persisted in having higher means throughout the trial, however, comparisons of change from baseline for Week 1 and Week 4 of the trial, do not show statistically significant differences from the DH group. The MDPI and DH groups were comparable to the placebo group at baseline, but showed statistical superiority to placebo during the remainder of the trial.

The differential between morning and evening PEFR was statistically comparable among the three treatment groups at baseline. During treatment, the differential was consistently smallest for the MDPI treatment group (11 - 16 L/min) and largest for the DH treatment group (20 - 21 L/min). Analysis of the change from baseline differential showed the MDPI treatment to be statistically superior to placebo at Weeks 2, 3 and 4 and to DH treatment at Week 3. At no time was the DH treatment statistically superior to placebo.

Comment: Due to the baseline differential between MDPI and DH, comparisons of the actual mean PEFR data may not clarify potential differences between the treatments. The AM/PM differential could be considered a better reflection of treatment effect and is suggestive that the MDPI treatment consistently provided the greatest stabilization effect. The clinical significance of this difference is likely to be minimal.

8.3.3.5 Use of Rescue Albuterol

Use of back-up Ventolin MDI was comparable among the three treatment groups at baseline (the seven days prior to Day 1) at 4.2, 4.1 and 3.8 puffs per day for the MDPI, DH and placebo groups, respectively. In the MDPI group, use of rescue albuterol fell to a mean of 1.0 to 1.4 puffs per day and a mean of 1.3 to 1.6 puffs per day in the DH group, with no statistically significant difference between the MDPI and DH. Among the placebo patients, rescue use fell to approximately 2.6 puffs per day during the treatment period. Use in both the MDPI and DH treatment groups was statistically significantly lower than the placebo group. Outcomes related to morning ("AM") and evening ("PM") use of back-up medication were similar.

Comment: The need for rescue medication may provide a threshold for the clinical significance of any potential difference between the MDPI and DH treatments. Although there is a slight trend toward greater rescue use in the DH group, it appears that, at least among these mild to moderate asthmatics, the observed differences between treatments in spirometric endpoints do not translate to a clinically meaningful change in asthma severity or control.

8.3.3.6 Nighttime Awakenings

Patients reported in their daily diaries the number of times per night that they were awakened due to asthma symptoms as "0" (no awakenings), "1" (woke up once) or "2" (woke up more than once). Although there were no statistically significant differences among the treatment groups regarding the percent of nights with no nighttime awakenings during the baseline period, the DH group had a lower percentage of such nights (78, 71 and 76 percent for the MDPI, DH and placebo groups, respectively). The percentage of nights with no nighttime awakenings increased after initiation of treatment (indicating improvement) for each group, to approximately 92 percent for the MDPI group and 85 percent for the DH and placebo groups). Change from baseline was not statistically significantly different for the MDPI and DH groups.

Comment: This endpoint does not appear to suggest a trend favoring either of the active treatment groups.

8.3.3.7 Symptom Scores

Symptoms were scored in patient diaries on a 1 to 5 severity scale for both morning ("AM") and evening ("PM") periods. The percentage of days per week in which patients experienced no symptoms was 15.6, 12.9 and 18.4 percent for the MDPI, DH and placebo at baseline. During treatment weeks, this figure rose to approximately 45 percent for the MDPI, 40 percent for the DH and 32 percent for the placebo groups. No statistical testing was conducted on the percent of days without symptoms. Mean morning symptom severity was numerically comparable for all treatment groups at baseline and during treatment (approximately 2.1 for all groups at baseline and approximately 1.6 to 1.8 on treatment), although the MDPI and DH showed intermittent statistical superiority to placebo. Values for mean evening symptom severity outcomes were virtually identical to morning scores.

Comment: This endpoint fails to discriminate active treatments from placebo and, as such, can not be considered a sensitive endpoint with which a comparison of the two treatments can be made. It can be emphasized, however, that the clinical significance of the differences among treatments in this population appears to be minimal.

8.3.3.8 Asthma Exacerbations

As seen in Table 8.3D, the proportion of MDPI and DH patients who experienced asthma exacerbations was similar and smaller than the proportion of placebo patients who experienced exacerbations. The majority of placebo events and all DH events occurred in the physician's office and were thought to be due to the withholding of anti-asthma medications. One of the MDPI events was thought to be due to the same cause, while the remaining two events required emergency room treatment and were

thought to be due to weather change and an unknown cause, respectively.

Of these patients, two in the MDPI group (Pts # 246 and 230), one in the DH group (Pt # 197), and two in the placebo group (Pts # 198 and 213) discontinued the study due to asthma exacerbation.

Table 8.3D Number (Percentage) of Patients Experiencing Asthma Exacerbations During Treatment

	MDPI N = 71	DH N = 70	Placebo N = 69
No Exacerbations	68 (96)	67 (96)	57 (83)
One Exacerbation	3 (4)	1 (1)	4 (6)
Two Exacerbations	0 (0)	2 (3)	7 (10)
Three or More Exacerbations	0 (0)	0 (0)	1 (1)

Comment: These data support the efficacy of both the MDPI and DH in controlling asthma, but do not suggest a difference in effect between the two active treatments.

8.3.3.9 Use of Concomitant Asthma Therapy

The use of concomitant asthma medications is summarized in Table 8.3E. Distribution of the use of these medications was slightly higher among placebo patients, but their use was comparable in the two active treatment groups.

Table 8.3E Percentage of Patients Using Concomitant Asthma Medication

	MDPI	DH	Placebo
Any Asthma Medication	59	60	68
Corticosteroids	55	54	61
"Anti-allergic" (cromolyn, nedocromil)	7	7	9
Bronchodilators (metaproterenol, isoetharine, theophylline and epinephrine)	4	0	0

Comment: Efficacy data were not reanalyzed by corticosteroid use as in Trials SLD-311 and 312. Since there is little suggestion of a clinically significant difference between the MDPI and DH, there appears to be no substantial rationale for conducting such a reanalysis for data from this trial.

8.3.3.10 Efficacy Conclusion

Trial SLGA2004 trial serves as the pivotal comparison of the DH formulation, which was used in the pivotal safety and efficacy trials of this development program, and the MDPI formulation which is to be marketed. As such, comparisons of each treatment to placebo, which were expected to and did show clinical and statistical superiority of both active formulations, are less meaningful than comparisons between the two active treatments.

Comparisons of spirometric assessments revealed that on Day 1 of the trial, the MDPI and DH responses are nearly identical with a slightly greater effect of the DH late in the dosing interval (longer duration of action). Onset was observed to be somewhat longer for the MDPI than the DH on Day 1. On Day 29, however, mean onset and duration were essentially the same. In addition, the effect of the MDPI was superior to the DH formulation, particularly reflected in the AUC-BL. In some instances, differences between the MDPI was statistically superior to the DH formulation. Overall, none of the differences identified on Day 1 or on Day 29 appear to have clinical significance, particularly because the indication for salmeterol is as a chronic therapy.

This conclusion is supported by lack of evidence of substantial differences between the formulations with regard to use of rescue albuterol, nighttime awakenings or asthma exacerbation rate. PEFR and symptom assessments outcomes were not considered reliable sources of comparative data in this trial.

8.3.4 Safety Endpoint Outcomes

Each of the safety endpoint analyses was conducted with the intent to treat population.

8.3.4.1 Adverse Events

There were no deaths or serious events reported during this trial. Overall, 25 percent of the MDPI patients, 29 percent of the DH patients and 28 percent of the placebo patients experienced adverse events. Adverse events which were experienced by at least three percent of any treatment group, and by a larger proportion of either of the active treatment groups than the placebo group, are listed in Table 8.3F.

Table 8.3F Number (Percentage) of Patients Experiencing Adverse Events*

	MDPI N = 71	DH N = 70	Placebo N = 69
Ear, Nose and Throat Events	6 (8)	10 (14)	7 (10)
Pharyngitis	1 (1)	2 (3)	0 (0)
Neurological	5 (7)	5 (7)	3 (4)
Headache	**4 (6)**	**2 (3)**	**3 (4)**
Musculoskeletal Events	4 (6)	5 (7)	0 (0)
Respiratory Events	2 (3)	2 (3)	0 (0)
Cough	0 (0)	2 (3)	0 (0)
Cardiovascular Events	**2 (3)**	**1 (1)**	**1 (1)**

* Only adverse events experienced by 3 percent or more of any treatment group, and by a higher proportion of patients in either active treatment group than in the placebo group, are listed. Events with a higher incidence among the MDPI users than the DH users are shown in bold.

There were no statistically significant differences among treatment groups in the incidence of any adverse events. Headache and cardiovascular events, in general, were slightly more prevalent among the MDPI users than the DH users. The cardiovascular events included one MDPI patient who experienced cardiac dysrhythmia (Pt # 309 described in Section 8.3.4.2), one MDPI patient who experienced tachycardia, one DH patient who experienced precordial pain and one placebo patient who experienced palpitations.

Comment: This table suggests that there are no clinically significant differences in the adverse event rates between the MDPI and DH treatments. This finding helps to reassure that the apparent enhanced effect for the MDPI which was seen in the spirometric outcomes, does not translate to a safety concern.

Patients who discontinued from the trial due to adverse events included two patients in the MDPI group and one patient in the placebo group. Each patient experienced asthma symptoms, although Pts #174 and #194 were classified as having discontinued due to other causes. The total number of patients discontinued after having asthma symptoms were four MDPI patients, three placebo patients and one DH patient.

MDPI

Pt #174 - A 23 year old female presented to an emergency room with an asthma exacerbation with angioedema and urticaria thought to be related to a food allergy. This patient was technically classified as having discontinued the study due to angioedema and urticaria.

Pt #202 - Described as a case of exacerbation of allergic rhinitis and chest tightness.

Placebo
Pt #194 - This patient experienced an asthma exacerbation associated with an upper respiratory infection and was discontinued seven days later "due to the infection."

8.3.4.2 Cardiac Effects

Mean change in pulse rate and in systolic or diastolic blood pressure over the 12-hour in-clinic visits did not show a trend within any treatment group between Day 1 and Day 29. During the 12 hour dosing interval, maximum change from baseline occurred approximately four to five hours after dosing for the active treatment groups. Increases of 15 or more bpm over baseline occurred in a total of 62 percent of MDPI patients, 74 percent of DH patients and 70 percent of placebo patients. Decreases of 15 or more bpm below baseline occurred in a total of 25 percent of MDPI patients, 21 percent of DH patients and 23 percent of placebo patients.

Minimal changes in mean systolic and diastolic blood pressure were noted on Day 1 and Day 29. Increases (decreases) in systolic blood pressure of 15 mmHg or more were noted in 75 (31) percent of MDPI patients, 67 (54) percent of DH patients and 77 (38) percent of placebo patients. There were no statistically significant differences among treatment groups. There was a statistically significant difference between MDPI and DH mean diastolic blood pressure at baseline (72 MDPI vs. 75 DH). Increases (decreases) in diastolic blood pressure of 15 mmHg or more were noted in 28 (25) percent of MDPI patients, 20 (44) percent of DH patients, and 12 (30) percent of placebo patients. Mean change from baseline was statistically significantly different between MDPI and DH at Hours 1, 8 and 10 on Day 29. The sponsor clarified the original submission of these data in which the hours of assessment were inaccurately reported.

EKGs taken at screening and predose and 1.5 hours post dose on Days 1 and 29. The rate of occurrence of abnormalities which were not considered to be clinically significant was similar among the three treatment groups at screening, predose on Day 1 and predose on Day 29. Post dose data indicated that there were no patients who experienced unfavorable changes after dosing on Day 1 and one MDPI patient who experienced an unfavorable change after dosing on Day 29. Pt # 309 had mild premature supraventricular complexes after doing on Day 29 (QTc interval was 427 msec). The EKG was normal 5 hours later with no therapeutic intervention.

Comparison of mean QTc data pre- and post dose did not reveal statistically significant changes, nor were there statistically significant differences among the treatment groups (means ranged from 403 to 410 msec). The proportion of patients in each treatment group with QTc intervals $\leq$ 440 msec ranged from 90 to 97 percent throughout the trial. There was a very slight increase in the proportion of patients in each treatment group whose QTC was above 440 msec at Day 29 compared to screening and Day 1, but

there appeared to be no clinically important differences among the treatment groups at screening, Day 1 or Day 29.

Holter monitoring was conducted with approximately 30 patients per treatment group at a selected subset of centers. Comparison of mean cardiac rates on Day 29 show a statistically significant difference between the MDPI and placebo and between the DH and placebo (with higher rates associated with the active treatments), but no difference was detected between the active treatments on Day 29 or among any of the treatments on Day 1. Rates of ventricular and supraventricular ectopic beats did not show a treatment related trend.

8.3.4.3 Clinical Laboratory Tests

A total of five MDPI patients (seven percent), 2 DH patients (three percent) and 3 placebo patients (four percent) were reported to have clinically significant abnormalities (as defined by the protocol). Of this minimal number of events, most were reported at screening or Day 1, with some degree of resolution during the course of the trial, and none appeared to be definitively related to treatment.

8.3.4.4 Physical Examinations

Physical examinations were conducted at screening and the Day 29 or discontinuation visit. It does not appear that clinically significant differences among the treatment groups were noted at either timepoint.

8.3.4.5 Use of Non-Asthma Concomitant Medication

Non-asthma medication was reportedly used by 65 percent of MDPI patients, 64 percent of DH patients and 74 percent of placebo patients. There were no apparent differences among the treatment groups with respect to the proportion of patients using various types of medication (predominantly analgesics, hormonal agents, immunotherapy and vasoconstrictors/decongestants).

8.3.4.6 Safety Conclusion

There were no apparent differences in the safety profile of the Serevent MDPI and DH formulations. The adverse events which appear to be potentially related to the drug substance are consistent with the previously identified effects. A single patient (# 309) experienced mild premature supraventricular complexes post MDPI dosing on Day 29. No important difference among treatment groups was observed with regard to QTc prolongation.

8.3.5 Study Conduct

Investigator Compliance

Unlike Trials SLD-311 and 312, no tabulation of investigator protocol violations was provided. The primary medical reviewer, Dr. Susan Johnson, accompanied the field inspector from the Philadelphia district office on an audit of Dr. Rooklin's investigation site. Several minimal protocol violations were noted, but were not thought to have potential ramifications for the protocol outcome.

Device Performance

Information regarding patient satisfaction with the device performance was collected as part of the pharmacoeconomic endpoint evaluations. These data will be considered in the ISE.

8.3.6 Conclusion

Overall, this trial supports the clinical comparability of the MDPI and DH formulations throughout the four week life of the MDPI device. It suggests slightly enhanced performance by the MDPI on efficacy outcomes, but does not appear to suggest a clinically significant difference. Safety data indicate clinical comparability between the active formulations and adverse events expected based on known pharmacologic actions.

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8.4 Dose Selection Trials and Formulation Development

Studies designed to determine the correct salmeterol dose for the powder formulation were conducted outside of the U.S. Dose response trials were initially conducted using the standard formulation of the diskhaler / rotadisk (50mcg salmeterol with sufficient lactose to create a 25 mg dose per blister). The original formulations contained eight blisters per rotadisk (8-place). Following this phase of development, the sponsor modified the formulation, first to a 4-place standard fill rotadisk, then to a 4-place reduced fill rotadisk (50 mcg salmeterol with sufficient lactose to create a 12.5 mg dose per blister). Bridging studies were conducted to link the various formulation changes and some formulations were linked to the MDI. The MDPI was formulated after the dose ranging phase of development and was linked to the 4-place reduced fill formulation in Trials SLGA2001, SLGA2004 and SLGA2006, which are reviewed in other sections. Most studies included an evaluation of efficacy parameters PEFR and FEV_1. Although a primary endpoint was not designated in most protocols, FEV_1 is discussed in the study reports as the primary endpoint. Use of this parameter lends itself to comparison of outcomes with the pivotal trials in this application.

Two dose response trials, **SLGH05** and **SLGH07**, were conducted using the 8-place standard fill powder formulation. In both trials, single doses of 12.5, 25, 50 and 100 mcg salmeterol per blister were compared with 200 mcg albuterol in a five way crossover design (no placebo treatment was included). Spirometric endpoints, tremor, pulse rate, blood pressure and use of rescue albuterol were measured over a 12 hour period.

SLGH05 was conducted at a single site in Sweden and involved ten asthma patients, seven male and three female, each with a screening FEV_1 of 50 to 75 percent. All patients completed the trial during the latter half of a six week hospitalization undertaken due to previously uncontrolled reversible airway disease. A four day washout was allowed between treatment arms. FEV_1 responses were compared using a weighted mean, defined as the area under the response-time profile divided by the total monitored time. The weighted means for the 12.5, 25, 50, 100 mcg salmeterol and 200 mcg albuterol doses, respectively, were 2.39, 2.55, 2.53, 2.63 and 2.51. With the exception of the 25 mcg dose, a dose response trend is noted, although no statistical evidence of a linear dose response relationship was found. The 25 mcg dose was the only dose statistically significantly different than the 200 mcg albuterol dose (largely due to variability in the data). No statistically significant differences were seen among the groups for peak response or time to peak response, although a dose response trend similar to that seen with the weighted mean was observed. Onset of action was statistically longer for each salmeterol dose than for albuterol, with the exception of the 100 mcg dose. Time to offset (end of 15 percent response) was statistically longer for each dose of salmeterol than for albuterol and was over 12 hours for doses of 25 mcg and higher. Adverse events were minimal. Safety data in general did not serve to

discriminate among the dosage levels either statistically or qualitatively, although a dose response trend was observed in blood pressure peak response data (both systolic and diastolic).

Trial SLGH07 (N = 14) was conducted in Scotland and the design was similar to that of SLGH05. The outcomes of this study parallel those of the first dose response trial in that there was a dose response trend noted, with a reversal of progression between the 25 and 50 mcg doses. Weighted mean response for FEV_1 was 2.23, 2.08, 2.37, 2.43 and 2.23 for the 12.5, 25, 50 and 100 mcg salmeterol doses and the 200 mcg albuterol dose, respectively. A significant linear relationship between log dose of salmeterol and duration of response were noted. Adverse events were minimal overall, however, one patient discontinued the trial due to an adverse event considered probably related to study medication. A 31 year old female received 12.5 mcg of salmeterol on the first study day and developed bronchospasm immediately after inhalation. She recovered rapidly after administration of nebulized albuterol. The sponsor speculates that this was a non-specific bronchoconstrictor response due to inhaled particles rather than an effect related to the study drug, due to the patient's "prior history," presumably use of other inhaled beta agonists.

Comment: These two dose ranging trials were of limited sample size, were designed without placebo control and, due to their being conducted outside of the U.S. with a different formulation (8-place standard fill), can not be considered definitive dose response trials for the MDPI. However, they do help to confirm that at these doses a powder formulation of salmeterol has a slower onset, a longer duration of action and produces bronchodilatory effects similar to that of albuterol. The observation of a dose response trend suggests that the lower doses studied are not on the plateau of the dose response curve.

Additional dose response trials were conducted to compare the standard fill formulation to various dosage delivered via the MDI dosage form. Trials **SLGH08**, **SLGH11** and **SLGH12** were single dose comparisons of the 8-place standard fill formulation to the MDI, while Trial **SLGH03** was a cumulative dose comparison of the same formulations. The 8-place and 4-place standard formulations were compared in **Trial SLGH18** cumulative dose study, while the standard and reduced fill formulations (4-place) were compared as single doses in **Trials SLGH28** and **SLGH29**. Table 8.4 summarizes the design and treatments involved in each trial. Because each of these studies was small, thus allowing for minimal power to detect statistical differences among the treatment groups, the table reflects judgement regarding the clinical comparability of mean outcomes. Statistically significant findings of note are described in the respective narratives.

Table 8.4 Summary of Dose Response/Formulation Development Trials

	SLGH08 (UK)	SLGH11 (UK)	SLGH12 (UK)	SLGH03 (Sweden)	SLGH18 (UK)	SLGH28 (UK)	SLGH29 (UK)
Design	Single dose crossover	Single dose crossover	Single dose crossover	Cumulative dose crossover	Cumulative dose crossover	Single dose crossover	Single dose crossover
Treatments[1]	DPI (S8) 50 MDI 50	DPI (S8) 50 MDI 50 ALB 200 PL	DPI (S8) 50 MDI 50 ALB 200 PL	DPI (S8) & MDI - 12.5, 25, 50, 100	DPI (S8) & DPI (S4) - 25, 50, 50, 50	DPI (S4) 25 DPI (R4) 25 PL	DPI (S4) 50 DPI (R4) 50 PL
N	14	13	12	8	22	24	25
FEV1				MDI ≈ DPI See Appendix ****	DPI (S8) ≈ DPI (S4)		
Onset	MDI ≈ DPI	PL >>MDI ≈ DPI >ALB [2]				PL>>DPI(S4) ≈ DPI(R4)	PL>>DPI (S4) ≈ DPI (R4)
Duration	MDI ≈ DPI	MDI ≈ DPI > ALB > PL				DPI (S4) > DPI (R4) > PL	DPI (S4) ≈ DPI (R4)> PL
Pk Effect	MDI ≈ DPI	MDI ≈ DPI ≈ ALB > PL	MDI ≈ DPI ≈ ALB > PL			DPI (S4) ≈ DPI (R4)> PL	DPI (S4) ≈ DPI (R4)> PL
Time to Pk	MDI (210 MIN) DPI (120 MIN)	MDI ≈ DPI ≈ PL > ALB	MDI (180 MIN) ØPI (300 MIN) ALB (75 MIN) PL (240 MIN)			DPI (S4) ≈ DPI (R4)> PL	DPI (S4) ≈ DPI (R4) ≈ PL
PC20							
Pk Effect			MDI (2.98 mmol) DPI (1.34 mmol) ALB (0.60 mmol) PL (0.28 mmol)				
Duration			MDI ≈ DPI > ALB > PL				

[1] DPI 50- Dry Powder Inhaler, 50 mcg dose
S8 - Standard fill, 8 place
S4 - Standard fill, 4 place

[2] ≈ indicates clinically equivalent outcomes
>indicates potential clinical inequivalence
R4 - Reduced fill, 4 place

MDI 50 - Metered Dose Inhaler, 50 mcg dose
ALB 200 - Albuterol MDI, 200 mcg dose
PL - Placebo MDI

In Trial **SLGH08**, doses of 50 mcg from both MDI and DPI formulations were compared. The serial post-dose FEV_1 assessments indicated that onset, duration, and peak response were clinically comparable for these formulations. Although mean time to peak response was longer for the MDI (210 minutes) than for the DPI (120 minutes), this difference was not statistically significant. Adverse event data and other safety parameters did not suggest a difference between formulations.

In Trial **SLGH11**, doses of 50 mcg salmeterol from MDI and DPI to 200 mcg doses of albuterol and placebo. Post-dose FEV_1 data showed comparability between the MDI and DPI salmeterol formulations and statistical superiority of both salmeterol formulations to placebo (albuterol and placebo were not compared). There were statistically significant differences between both salmeterol formulations and albuterol, with a longer onset, duration and time to peak for salmeterol. However, peak response to both drug substances were comparable. Adverse event and other safety data did not clearly discriminate among treatments, including the placebo.

Trial **SLGH12** involved the same treatments as Trial SLGH11, but was designed as a histamine challenge study, with PC_{20} at one, four, eight and 12 hours after each treatment as the primary efficacy endpoint. Outcomes were comparable to those seen in SLGH11 in that each active treatment was statistically superior to placebo. The duration of bronchoprotective effect tended to be longer for both salmeterol formulations than for albuterol. A statistically significant difference in duration was seen between the MDI (mean duration 711 minutes, as defined by PC_{20} greater than twice baseline) and albuterol (mean duration 201 minutes), but not between the DPI (mean duration 630 minutes) and albuterol. The median observed peak response was not statistically different among the active treatments, however, rank order showed that the MDI showed greater protective effect the DPI. Corresponding FEV_1 data failed to show a statistically significant difference between the salmeterol formulations.

The cumulative dose comparison of the DPI(S8) and MDI, **Trial SLGH03**, is the only multiple dose comparison of any dry powder formulation with the MDI submitted to the original NDA. As seen in Appendix 16, the mean percentage change from baseline in FEV_1 in response to cumulative doses which totaled 187.5 mcg. over a four hour period was comparable for the two formulations. Differentiation between the profiles at the initiation and end of the interval appear to offset one another.

A cumulative dose design was also used to compare the 4- and 8- place standard fill DPI formulations in **Trial SLGH18**. A total of 150 mcg. was administered over a 4.5 hour period. Mean FEV_1 responses (rather than a preferred endpoint such as percentage change from baseline) were described and failed to show statistically significant differences between the treatments.

Trials SLGH28 and **SLGH29** were single dose comparisons of the 4-place standard and regular fill DPI formulations, with the latter formulation being the to be marketed version of the product. A placebo treatment arm was included in the design and revealed that the active treatments were generally statistically superior.
In Trial SLGH28, the 25 mg standard formulation had a statistically higher peak effect and longer duration, although the time to onset and time to peak were not statistically better than with the reduced fill formulation. Trial SLGH29 showed no statistically significant differences between the active treatments. Neither trial revealed differences between the active treatments that appeared to be clinically meaningful.

Safety parameters, including pulse, systolic and diastolic blood pressure and tremor were assessed in the majority of formulation comparisons. These data did not consistently demonstrate clinically meaningful differences among the various dosage forms.

Conclusion: The development program for Serevent MDPI did not employ the to be marketed formulation in dose ranging trials. The 50 mcg dose of the 8-place standard fill DPI which was used in dose ranging trials performed comparably to a 200 mcg dose of albuterol, although it could not definitively be identified as the optimal dose for the powder formulation. In subsequent trials, the 50 mcg dose of the 8-place standard fill DPI was compared to a 50 mcg MDI dose, a 50 mcg 4-place standard fill DPI dose and a 50 mcg 4-place reduced fill DPI dose. Each of these comparisons failed to reveal evidence of a lack of clinical comparability. Pivotal trials SLD-311 and SLD-312 were conducted with the 4-place reduced fill DPI which was later compared to the MDPI in bridging studies, Trials SLGA2004, 2001 and 2006. Given the limitations of this serial change and comparison of formulations, it appears that the dose selection and formulation development summarized in this section yielded a dose and dosage form which is relatively comparable to the 50 mcg MDI dose, i.e. the 50 mcg 4-place reduced fill DPI which was used during the pivotal safety and efficacy trials. The sponsor has submitted study reports describing trials which directly compare the MDPI and MDI formulations. These will be evaluated in an addendum to this review.

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8.5 Trial SLGA-2001: A Randomized, Double-Blind, Double-Dummy, Five-Way Crossover Comparative Clinical Trial of Salmeterol Xinafoate via Multi-Dose Powder Inhaler Versus Salmeterol Xinafoate via Diskhaler Versus Placebo in Adolescent and Adult Subjects with Chronic Moderate Asthma. (Vol 1.20)

Investigators:
James Grady, M.D., Boulder CO

Initiation Date: 7 December 1993 (first patient was enrolled)
Completion Date: 22 August 1994 (date of last observation)

8.5.1 Study Description

Objective:
The primary objective of this study was to demonstrate the clinical comparability of the effects on pulmonary function and duration of action of single fixed doses of salmeterol 50 mcg and 100 mcg via MDPI and DH, and placebo, when administered to patients 12 years of age and older with asthma. This trial serves a bridging study to link the DH, which was compared to placebo in Trials SLD-311 and 312, with the MDPI, which the company intends to market, and as supplementary information for Trial SLGA2004, a four week comparison of the 50 mcg dose of MDPI and DH. Each formulation was administered in 50 mcg puffs such that administration of the 100 mcg dose required two puffs.

There were two protocol amendments made, one prior to initiation of the study and one after initiation of the study. Each amendment consisted of multiple modifications to the protocol. The modifications appear to be appropriate clarifications which should not have biased the trial outcome.

Population:
Males and females, age 12 years and over, moderate asthma were enrolled if they demonstrated an FEV_1 of 40 to 65% predicted normal during screening and were otherwise healthy. Patients on fixed doses of inhaled or intranasal corticosteroids were permitted in the study and other concomitant medications were to be appropriately withheld.

Design and Procedures:
This study was a randomized, double blind, double dummy, placebo controlled, five way crossover of single fixed doses of salmeterol 50 and 100 mcg BID (via MDPI), salmeterol 50 and 100 mcg BID (via DH) and placebo (via MDPI). At the Screening Visit, patients were converted from their current beta agonist to Ventolin MDI on an as needed basis for one to two weeks. The first dose of study drug was administered at

Visit 1 (Day 1), followed by a 12 hour evaluation which included spirometric assessments. Visits 2 through 5 took place between 2 and 14 days after the previous visit and data were collected as on Day 1. Between visits, patients were instructed to use Ventolin MDI to relieve acute asthma symptoms.

Endpoints:

Efficacy Endpoints
The primary efficacy assessment is the 12 hour spirometric measure of FEV_1 on each treatment day. Secondary efficacy measures include FVC, and $FEF_{25-75\%}$.

Safety Endpoints
Safety assessments in this trial included clinical adverse events (collected at each clinic visit), 12-lead electrocardiograms (collected at screening and predose and 1.5 hours postdose at each clinic visit), clinical laboratory tests (assessed postdose at screening and Visits 1 through 5), vital signs (assessed at each clinic visit immediately prior to each set of PFTs), and physical examination findings (assessed at screening and Visit 5).

Statistical Considerations:

Enrollment was planned for 20 patients, calculated to provide for >80% power of detecting a difference in FEV_1 of 0.27 liters between any two treatment groups, using an ANOVA F-test with a significance level of 0.05, assuming a standard deviation of 0.3 liters for FEV_1.

8.5.2 Patient Disposition

All 20 patients enrolled completed the trial. The majority of patients were Caucasian (95%) and female (65%). Ages ranged from 20 to 57 years with a mean of 39 years. Eighty percent had been diagnosed with asthma more than 10 years prior to the study; 20 percent had received acute care for asthma in the year prior to the study. Nocturnal asthma was reported to occur at least once a week in 40 percent of the patients. Corticosteroids were used by 50 percent of the patients. At screening, mean FEV_1, FEV_1 as a percent of predicted normal, $FEF_{25-75\%}$, and FVC were 2.00 L, 58.1 percent, 1.33L/second and 3.05L, respectively.

Comment: Enrollment criteria for this trial specified that patients with FEV_1 values between 40 and 65 percent of predicted normal could enter the trial, whereas Trials SLD-311, SLD-312 and SLGA-2004 included patients in the 50 to 85 percent range. The resultant population has a mean FEV_1 as a percent of predicted normal of 58 percent compared to the other trials in which this figure ranged between 65 and 70 percent. The population of this trial may enable the trial to have more power to

determine differences among the active treatments was present in previous trials.

8.5.3 Efficacy Endpoint Outcomes

Functions of serial FEV_1 are described in Table 8.5. No statistical discrimination among the active treatments was observed, however each active treatment was statistically different than placebo for each of the parameters shown, with the exception of baseline. Graphical representations of the percentage change from baseline profiles are shown in Appendix 17.

Comment: No statistical difference was observed between the 50 and 100 mcg doses of either formulation, despite the study having been powered to detect a minor difference between treatments. This may be indicative of the insensitivity of the assay procedure and/or of the fact that both doses maximize patient response, i.e., "put patients on the flat part of the dose response curve." It is notable that this failure to show a separation occurred within the study population of moderate asthmatics.

Comment: In light of the dose response for this application having been conducted with a formulation other than the to be marketed MDPI, this trial helps to confirm that the 50 mcg dose is not inappropriate for the MDPI formulation as it does not offer substantially less benefit than higher doses.

Comment: Although these data do not indicate a statistical difference among active treatments, the trend in the data favors the 50 mcg DH rather than the 50 mcg MDPI. This is similar to the outcome of the comparisons made on Day 1 of Trial 2004, although the trend was not seen on Day 29 of the same study. On Day 29 of Trial 2004, the percentage change from baseline profile favored the MDPI (Appendix 15). It appears that duration of treatment may impact the relative effects for these two dosage forms. AUC-BL, which integrates the serial FEV_1 data, also supports the trend favoring the DH product for the 50 mcg doses. However, the overall difference between the treatments is small. Since this product is not used for acute treatment, small differences evident in single dose comparisons may not predict lack of clinical comparability.

FVC and $FEF_{25-75\%}$ outcomes confirmed the FEV_1 findings, showing a negligible dose response between the 50 and 100 mcg doses, no statistically significant differences among the active treatments and statical superiority of each active treatment to placebo.

Efficacy Conclusion: Trends within the efficacy outcomes suggested that among 50 and 100 mcg doses of MDPI and DH, the 50 mcg MDPI dose performed least well. However, none of the endpoints could distinguish between the 50 and 100 mcg doses, and were therefore too insensitive to detect statistical differences between the same

dose of different formulations. The differences which were observed between treatments, i.e., onset was longer and duration was shorter for the 50 mcg MDPI relative to the 50 mcg DH dose, were also observed in Trial SLGA2004. These differences were not observed after four weeks of therapy in that trial, an observation that can not be replicated in this single dose trial. Overall, there appear to be no clinically significant differences among the four treatments included in this trial, and in particular, no clinically significant differences between the MDPI and DH formulations.

Table 8.5 FEV_1 Outcomes for Responders (within 4 Hours of Dosing)

	MDPI 50 mcg	DH 50 mcg	MDPI 100 mcg	DH 100 mcg	Placebo
Baseline FEV_1 (L)[1]	2.00	2.03	1.98	2.06	1.99
Max. % Change from Baseline (SD)	37.8 (12.8)	39.7 (18.1)	39.2 (16.1)	39.0 (13.2)	22.5 (16.4)
# (%) of Responders w/in 4 Hours of Dose	19 (95)	19 (95)	20 (100)	19 (95)	11 (55)
Median Time of Onset in Hours	0.32	0.23	0.19	0.20	1.27
Duration of Effect in Hours (SD)	8.1	8.4	8.3	9.4	4.3
AUC-BL (SD)	6.5 (4.0)	6.8 (4.6)	7.1 (5.0)	7.2 (3.6)	2.9 (4.7)

[1]Baseline is the average of the -0.5 and 0 hour FEV_1 measurement on each treatment day.

8.5.4 Safety Endpoint Outcomes

Adverse Events

There were no deaths, serious adverse events or dropouts due to adverse events during this trial. A single adverse event was reported during exposure to each treatment, with two adverse events reported among 50 mcg MDPI users. Headache was reported in three patients after dosing with 50 mcg DH, 100 mcg MDPI and placebo. Other adverse events did not appear to be potentially associated with treatment.

A total of 10 asthma exacerbations were reported in eight patients, each occurred in the physician's office and was attributed to withholding medication. Eight events were during placebo treatment and two during 50 mcg DH treatment.

Comment: The is no suggestion from adverse events observed that the 50 mcg MDPI treatment is not clinically comparable to the other formulations.

Clinical Laboratory Tests

Five patients were reported to have significant abnormalities in laboratory values. Temporal relationships eliminate all but one abnormality from being associated to drug treatment. The final event was not considered clinically significant. No statistically significant differences were seen among any of the treatments for pre- and postdose comparisons of potassium or glucose.

Cardiovascular Effects

Mean pulse was statistically analyzed showing no statistical differences among treatments, including placebo. However, pulse, systolic and diastolic blood pressure each, exhibited a slight trend indicating that the 100 mcg DH dose was distinguishable from the other treatments. Pre- and postdose QTc evaluations showed virtually no effect after dosing of any treatment. None of the cardiovascular parameters served to distinguish clinically meaningful differences among treatments.

Physical Examinations

Physical examinations conducted at end of treatment revealed no abnormalities.

Safety Conclusion

There were no apparent differences in the safety profile of the Serevent MDPI and DH formulations, nor between the 50 and 100 mcg dosages.

8.5.5 Conclusion

The MDPI and DH formulations appear to be clinically comparable. Therefore, this trial appears to be generally supportive of the link between the two formulations and use of the pivotal trial data in support of the MDPI. There remains, however, some speculation as to the cause of the trend which favors the DH formulation.

8.6 Trial SLGA2006: A Randomized, Double-Blind, Double-Dummy, Five-Way Crossover Comparative Clinical Trial of Salmeterol Xinafoate via Multi-Dose Powder Inhaler Versus Salmeterol Xinafoate via Diskhaler Versus Placebo in Adolescent and Adult Subjects with Chronic Moderate Asthma. (Vol 1.23)

Investigators:
Andre vanAs, M.D. and Robert Dockhorn, Prairie Village KS

Initiation Date: 17 October 1994 (first patient was enrolled)
Completion Date: 6 June 1995 (date of last observation)

8.6.1 Study Description

Objective:
The primary objective of this study was to demonstrate the clinical comparability of the effects on pulmonary function and duration of action of single fixed doses of salmeterol 50 mcg and 100 mcg via MDPI and DH, and placebo, when administered to patients 12 years of age and older with asthma. Together with Trial SLGA2001, this trial serves a bridging study to link the DH, which was compared to placebo in Trials SLD-311 and 312, with the MDPI, which the company intends to market. This study differs from Trial SLGA2001 in that the primary endpoint in this study was based on a methacholine challenge rather than bronchodilator response. Each dose was administered in 50 mcg puffs such that administration of the 100 mcg dose required two puffs.

There were four protocol amendments made, two prior to initiation of the study and two after initiation of the study. Each amendment consisted of multiple modifications to the protocol. The modifications appear to be appropriate clarifications which should not have biased the trial outcome.

Population:
Males and females, age 12 years and over, were eligible for the trial if they exhibited an FEV_1 of ≥80 percent predicted normal, as well a response to a provocation dose PD_{20} FEV_1 value of ≤5.50 cumulative dosage units of methacholine (based on five inhalations at each concentration). The asthmatic patients were required to be otherwise healthy. Patients on fixed doses of intranasal corticosteroids or cromolyn were permitted in the study and other concomitant medications, including inhaled corticosteroids, were to be appropriately withheld.

Design and Procedures:
This study was a randomized, double blind, double dummy, placebo controlled, five way crossover of single fixed doses of salmeterol 50 and 100 mcg BID (via MDPI), salmeterol 50 and 100 mcg BID (via DH) and placebo (via MDPI). At the Screening

Visit, patients were converted from their current beta agonist to Ventolin MDI on an as needed basis for one to two weeks and a screening methacholine challenge was conducted. At Visit 1, patients underwent a methacholine challenge two hours prior to dosing, followed by additional challenges at 1, 4 and 8 hours postdose. Visits 2 through 5 took place between 3 and 14 days after the previous visit and data were collected as on Day 1. Between visits, patients were instructed to use Ventolin MDI to relieve acute asthma symptoms.

Comment: This protocol utilized a minimal washout of three hours between methacholine challenges. The primary concern in timing challenges so closely is that patients would have insufficient time to recover from the initial challenge prior to a subsequent challenge. However, a review of the line listings indicates that relatively few challenges were missed, having little potential for impacting the outcome of the trial.

Methacholine challenge procedures consisted of establishing a baseline FEV_1, followed by inhalation of five breaths of saline from a nebulizer (saline challenge), followed by inhalation of five breaths each of increasing concentrations of methacholine until a fall in FEV_1 of ≥20 percent from baseline is achieved for three consecutive FEV_1 efforts. The protocol allowed investigators to reduce the number of inhalations from the standard five per concentration, if it was believed that sufficient fall in FEV_1 could be achieved with a lower cumulative dose. Isuprel (isoproterenol) was used to relieve bronchoconstriction effects during methacholine inhalation.

Baseline FEV_1 prior to the first methacholine challenge at each clinic visit must have been within 70 percent of predicted normal and patients were not continued on a given treatment day if saline challenge provoked a decline of 15 percent or more.

Endpoints:

Efficacy Endpoints
The primary efficacy assessment was $PD_{20}FEV_1$, the provocation dose expressed in cumulative breath units of methacholine that produces a 20 percent decrease from baseline FEV_1.

Safety Endpoints
Safety assessments in this trial included clinical adverse events (collected at each clinic visit), 12-lead electrocardiograms (collected at screening and the final visit), clinical laboratory tests (assessed postdose at screening and the final visit), vital signs (assessed at each clinic visit predose and at 1, 4, and 8 hours postdose), and physical examination findings (assessed at screening and the final visit).

Statistical Considerations:

Enrollment was planned for 20 patients, calculated to provide for >80 percent power of detecting a difference in $\log_2(PD_{20})$ of 1.00 doubling dose between any two treatment groups, using an ANOVA F-test with a significance level of 0.05, assuming a standard deviation of 1.5 in $\log_2(PD_{20})$.

The individual $\log_2(PD_{20})$ values and the average across all post dose $\log_2(PD_{20})$ values were analyzed using an analysis of covariance with predose $\log_2(PD_{20})$ serving as the covariate. In addition, repeated measures analysis of variance was used to analyze PD_{20} over the 8 hours of each treatment arm, with change from predose as the response variable. In addition to assessments of the $\log_2$ transformed data, these analyses were also undertaken on raw PD_{20} data.

8.6.2 Patient Disposition

Twenty patients enrolled in the trial of which 19 completed all five treatments. The majority of patients were Caucasian (95%) and male (55%). Ages ranged from 12 to 43 years with a mean of 25 years. Sixty five percent had been diagnosed with asthma more than 10 years prior to the study; 30 percent had received acute care for asthma in the year prior to the study. Nocturnal asthma was reported to occur at least once a week in 60 percent of the patients. At screening, mean FEV_1, FEV_1 as a percent of predicted normal, $FEF_{25-75\%}$, and FVC were 3.2 L, 81.5 percent, 2.4L/second and 4.5L, respectively.

8.6.3 Efficacy Endpoint Outcomes

The covariance analysis of ($PD_{20}FEV_1$), expressed as cumulative breath units is summarized in Table 8.6.

Table 8.6 Covariance Analysis - Efficacy Population

Time (Hrs)	Placebo	50 mcg MDPI	50 mg DH	100 mcg MDPI	100 mcg DH
Predose	2.79	2.40	2.73	2.63	2.61
1 Hr	2.57	4.06^	5.24^#	5.97^#+	5.20^#
4 Hr	1.80	4.09^	4.98^	5.67^#	4.82^
8 Hr	1.70	3.71^	4.23^	4.99^#*	4.80^#
Weighted Avg (over 8 hr)	2.00	4.00^	4.68^#	5.35^#*	4.70^#
Change	-0.63	1.37	2.05	2.72	2.07
Ratio (Avg to predose)	0.65	2.58	4.14	6.59	4.20

Pairwise Treatment Comparisons:
^ $p<0.001$ compared with placebo
# $p \leq 0.0050$ compared with 50 mcg MDPI
* $p \leq 0.0048$ compared with 50 mcg DH
+ $p=0.049$ compared with 100 mcg DH

All active treatments achieved statistically significant enhanced protection compared to placebo at each timepoint, with the exception of predose. The 50 mcg MDPI dose was statistically inferior to both 100 mcg formulations at most timepoints and to the 50 mcg DH at Hour 1 and for the eight hour average. Relationships among the treatments were primarily consistent across the eight hour treatment, although some decline in the protective effect of each treatment can be detected between Hour 1 and Hour 4 and between Hour 4 and Hour 8.

Comment: The numerical trends within this data set appear to suggest that the 50 mcg MDPI dose offers the least protective effect among the active doses, although the 100 mcg MDPI appears to offer the greatest protective effect. This relationship makes it unclear that it is the dosage form that can be designated as the factor which is responsible for these trends in differences among active treatments.

Covariance analysis were repeated with actual PD_{20} (in milligrams) data rather than log transformed data. The numerical trends were similar, with the 50 mcg MDPI showing the least protective effect and the 100 mcg MDPI showing the greatest protective effect. However, the statistical significance of the differences between the 50 mcg MDPI and other treatments was somewhat diminished as compared to the previous analysis.

The repeated measures analysis of variance, using change from predose, showed statistically significant differences in the dose of methacholine required to produce a 20 percent drop in FEV_1 between each active treatment and placebo and between 50 mcg MDPI and 100 mcg MDPI doses. In analysis of actual PD_{20} (in milligrams), the

statistical relationships with between the 50 mcg MDPI and other treatments remained the same.

Although the protocol did not specify, clinical significance is defined in the study report as a difference of one doubling dose. All active treatments were considered clinically superior to placebo. Among the active treatment comparisons, only the comparison of the 100 mcg MDPI to the 50 mcg MDPI was considered clinically significant.

The number of patients (percent) who required treatment with isoproterenol to reverse decline in pulmonary function caused by methacholine challenge were as follows:

MDPI 50 mcg	7 (37)
DH 50 mcg	8 (42)
MDPI 100 mcg	4 (21)
DH 100 mcg	6 (32)
Placebo	13 (65)

It appears as though there was a dose response trend in this parameter.

Efficacy Conclusion

The primary comparison of primary interest in this study, from the standpoint of the drug development program, was that of the 50 mcg MDPI dose and the 50 mcg DH dose. Statistically significant differences were detected, favoring the 50 mcg DH dose, however, the sponsor's definition of clinical significance did not discriminate between the two doses. Overall, the study is not fully supportive of the link between the DH and MDPI, although it does not provide substantial evidence of the lack of effectiveness of the 50 mcg MDPI dose. Since the 100 mcg (2 inhalation) data show the MDPI to be apparently more efficacious than the DH, the results with the 50 mcg dose must be viewed with some caution.

8.6.4 Safety Endpoint Outcomes

There were no deaths, serious adverse events or dropouts due to adverse events during this trial. A single patient (#7872) dropped out at the sponsor's request after receiving only the placebo treatment. In this patient, the PD_{20} at 2-hour predose challenge repeatedly exhibited a significant increase from screening challenge.

Adverse events were reported by 10 of the 20 patients enrolled. Headache was the most frequent event, reported by three placebo patients (15 percent), two 50 mcg DH patients (11 percent) and three 100 mcg DH patients (16 percent). Asthma exacerbations were reported with the efficacy endpoint outcomes which required isoproterenol treatment. Other adverse events appeared to be unrelated to treatment.

Comment: Since headache is an expected adverse event associated with the use of salmeterol and other beta agonists, it is of some concern that the event was reported by

DH users and not by MDPI users. However, the frequency of reporting among DH users did not exceed that of the placebo group and cannot be positively attributed to active drug in this trial.

Clinically significant laboratory abnormalities were reported in two patients, but did not appear to be associated with drug treatment due to lack of an appropriate temporal relationship. Vital signs, EKGs and physical examinations revealed no apparent drug related findings.

Safety Conclusion

With the exception of the asthma exacerbation data, safety endpoints did not discriminate between doses and devices. As stated earlier, the exacerbation data appeared to show a dose response trend, unrelated to device.

8.6.5 Conclusion

Although PD_{20} for FEV_1 using methacholine did discriminate somewhat between the MDPI and DH devices, the results for the two dose levels were disparate and there is no evidence from this trial that these drugs will not perform comparably in the clinical setting. While this trial does not strongly affirm the equivalence of these two devices, it does provide some assurance of clinical comparability.

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8.7 Supplemental Trials Bridging the Multiple Dose Dry Powder Inhaler and the Reduced Fill Diskhaler

Trial C94-041 (Volume 1.25) and Trial C92-043 (Volume 1.26) were conducted in the U.K. to examine the comparability of the two formulations in a cumulative dose trial with pharmacodynamic endpoints and a histamine challenge model, respectively.

Trial C94-041 was a randomized, double blind, double dummy, two-period crossover, cumulative dose comparison of the MDPI and DH formulations conducted in the U.K. and designed to compare the systemic pharmacodynamic effects of the formulations. Eighteen healthy volunteers (nine male and nine female, aged 21 to 47 years) were given between 50 and 400 mcg from respective devices in doubling doses (50, 50, 100 and 200 mcg) at 60 minutes intervals on two treatment days. Measurements of pulse rate, blood pressure, and plasma potassium and glucose were conducted at 30 and 55 minutes after each dose.

No statistically or clinically significant differences were seen between the MDPI and DH devices for pulse rate (maximum mean difference 3 bpm), plasma glucose (maximum mean difference 0.23 mmol/L), systolic blood pressure (maximum mean difference 3 mmHg) or diastolic blood pressure (maximum mean difference 2 mmHg). However, administration of the DH resulted in a statistically lower plasma potassium compared to the MDPI. The mean difference was 0.11 mmol/L which did not exceed the sponsor's pre-defined definition of a clinically significant difference (0.25 mmol/L) and was less than any change observed with a 100 mcg increase in dose.

Adverse events were comparable between formulations, seen predominantly after the highest dose and were largely consistent with those previously identified in association with salmeterol use (headache, tremor and palpitations). One patient was withdrawn after the first treatment due to discomfort from moderate headache, nausea and sweating.

Comment: The review of pharmacokinetic studies submitted in the NDA, which was conducted by Dr. Uppoor of the Division of Pharmaceutical Evaluation-I, concluded that the "systemic availability of salmeterol following administration via Serevent Diskus is lower than that of the MDI or Diskhaler." This conclusion was based on single dose comparisons of the three formulations and it predicts the observed outcome, i.e., that the MDPI would be expected to exhibit slightly less systemic activity than the DH.

Conclusion: The slightly enhanced pharmacodynamic effect of the DH formulation relative to the MDPI suggests that the DH may deliver more drug substance for systemic bioavailability. Due to particularly to the study in a healthy patient population, it is not possible to directly translate these findings to the asthmatic population of Serevent users. The lack of clinically significant differences between the devices is

supportive of the applicability of pivotal trial data to the MDPI.

Trial 92-043 was a randomized, double blind, double dummy, two-period crossover trial designed to examine the protective effects of the MDPI and DH formulations against histamine-induced bronchoconstriction in 12 healthy subjects (8 males and 4 females, aged 23 to 53 years). Subjects were required to exhibit a 15 percent decline in FEV_1 following histamine challenge, but were not required to have been diagnosed with asthma or to exhibit reversibility in FEV_1 in response to bronchodilators. Histamine challenges were administered predose and 1 hour and 12 hours post dose.

Significant protection, defined as more than a doubling dose of histamine greater than the pre-dosing median PD_{15}, was observed for both formulations at Hour 1 and Hour 12. There was no statisically significant difference between treatment groups at Hour 1, however, one did exist at Hour 12. The sponsor's criterion for a clinically significant difference, that the 90 percent confidence interval for median dose include a doubling dose, was not met at Hour 12. Individual patient data also appear to suggest that the formulations were comparable at Hour 1, but that the DH offered a greater protective effect at Hour 12.

Conclusion: As in Trial C94-041, Trial 92-043 suggests that the DH formulation delivers more medication than the MDPI device, as indicated by the longer duration of action. However, the population employed in the trial is substantially different than the population who receives Serevent in the clinical setting and the primary endpoint (PD_{15}) is non-standard. These factors prevent definitive conclusions regarding the generalization of these date to the application. It is noted that gross clinically important differences between devices were not implied by these data.

8.8 Flow Rate Through the Diskus Device

Two trials, Trial FMDT07 and Trial RESB4002 were conducted in the U.K. to determine the inhalation profile through a range of age and lung function impairment levels in order to characterize the ability of patients to generate flow rates through the device. **Trial FMDT07** (Volume 1.29) was conducted in 55 patients (26 males and 29 females) ranging in age from 5 to 50 years who had a history of obstructed airways disease. No screening FEV_1 was specified. **Trial RESB4002** (September 23, 1996 submission) was conducted in the U.K. based on an agreement between the division and the sponsor at the pre-NDA meeting for this application that the sponsor would investigate the ability of patients who generate low flow rates to benefit from the Diskus device. Seventeen patients (12 males and 5 females) between the ages of 45 and 73 with severe obstruction lung disease were included in the trial.

Both trials were single center, randomized, double blind, crossover studies (looking at the Diskus and Turbuhaler devices) designed to record the inhalation profiles of pressure drop versus time in patients as they inhaled with maximal inspiratory effort through the MDPI. The individual MDPI devices used in these trials had been previously validated to ensure that they were representative of the device and that the inclusion of a pressure probe and enclosure of the devices in the inhalation profile recorder (IPR), a PC based recorder of pressure transducer data, did not change their flow properties.

In Trial RESB4002, these profiles were then entered into an inhalation simulator, the so-called "electronic lung," in order to determine *in-vitro* the total emitted dose and the fine particle mass generated by these inhalation profiles. The electronic lung consists of a PC-driven piston which closely simulates the flow associated with the patient-generated flow-volume curves, then delivers the resultant emitted dose into an Andersen cascade impactor. Patients, who were allowed to remain on all normally prescribed medication, performed three technically acceptable flow-volume maneuvers to determine whether their baseline FEV_1 at Visit 1 was $\leq$ 30 percent of predicted normal after regardless of whether bronchodilator had been used in the previous 30 minutes. After a 30 minute washout of any prior bronchodilator dose, patients were asked to inhale as hard and fast they could through the IPR containing the test device. After a rest of unspecified length, patients completed the second flow-volume measurement and inhalation profile (device order, i.e., turbuhaler versus MDPI, was randomized). The inhalation profile data of pressure drop versus time from the patient recordings in the IPR were then downloaded to the electronic lung in order that it reconstruct the associated flows through the device for in-vitro testing of the emitted dose via the cascade impactor.

Trial FMDT07 was designed to look at primarily at peak pressure drop (kPa) and peak inspiratory flow rate (PIFR). Peak expiratory flow rate (PEFR) was correlated to the

peak inspiratory flow rate. Primary endpoint for Trial RESB4002 was total emitted dose and secondary endpoints included fine particle mass, kPa and PIFR and the comparison of FEV_1 with kPa and PIFR. The results of each trial are summarized in Table 8.8.

Table 8.8 Summary of Inhalation Profile Trials

	kPa Mean, S.D. (Range)	PIFR in L/min Mean, S.D. (Range)	Total Emitted Dose % Label
Trial FMDT07			
MDPI	6.19, 1.99 (1.47 - 10.18)	117	Not Measured
DH	6.27, 2.20 (0.94 - 13.34)	118	Not Measured
Trial RESB4002			
MDPI	3.48, 1.26 (1.08 - 6.28)	82.35, 16.54 (46.11 - 110.85)	92.04 (85.60 - 101.14)

Trial FMDT07 also revealed that the 8-11 year subgroup, the 12-17 year subgroup and the 18-60 year subgroup generated similar kPa values. The 4-7 year age group was somewhat lower with a mean of 4.01 for the MDPI and 3.95 for the DH. The correlation coefficient for PIFR and PEFR was positive at 0.674, but was not considered to be strong. The correlation between PEFR and kPa was equivocal and dependent on the subset analyzed.

In Trial RESB4002, outcomes for kPa and PIFR were lower than for the previous trial, however, the total emitted dose remained above 80 percent for each individual. All replicated patient flow efforts led to a fine particle mass between 15 and 25 percent of label claimed emitted dose. Neither kPa or PIFR were well correlated with FEV_1.

Comment: FEV_1 was not generated for Trial RESB4002, preventing a direct comparison of disease severity based on that parameter.

Comment: Data on low flow rates were not submitted for the DH formulation in the severely obstructed patients, so no comparison is possible. This does not pose an obstacle to the approval of the MDPI, as it is primarily the performance of the to be marketed product which is of interest. Comparisons on this parameter would not be well suited to determining the applicability of the pivotal DH data to the MDPI.

Conclusion: Trial RESB4002 appears to establish that while the severely obstructed population generates lower flow rates through the MDPI device than the general asthmatic population, the flow rates observed in the severely obstructed population were sufficient to use the device and to receive a sufficient proportion of the labeled dose. In addition, the data from the 4 to 7 year old patients in Trial FMDT07 suggest that the MDPI device offers equal or less resistance than the DH.