

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-692

MEDICAL REVIEW(S)

Clinical Team Leader Summary Review Memorandum

Memorandum to: NDA 20-692 file
Product: Serevent Diskus Inhalation Powder
Memo date: 9-15-97
Memo from: Robert J. Meyer, MD Medical Team Leader, DPDP

THIS MEMORANDUM IS TO DOCUMENT THE SECONDARY REVIEW CONCLUSIONS ON THE SEREVENT DISKUS INHALATION POWDER NDA, APPLICATION NUMBER 20-692. THE SECONDARY REVIEW WAS CARRIED OUT CONCURRENTLY WITH DR. JOHNSON'S PRIMARY CLINICAL REVIEW. AS SUCH, MUCH OF THE SECONDARY REVIEW OPINION WAS INCORPORATED, AS APPROPRIATE, INTO THE MEDICAL OFFICER'S REVIEW. HOWEVER, THIS MEMORANDUM WILL HIGHLIGHT SOME OF THE CRUCIAL EFFICACY AND SAFETY REVIEW ISSUES THAT FORM THE BASIS OF THE FINDING OF CLINICAL APPROVABILITY.

OVERVIEW:

SALMETEROL XINAFOATE AS A MOLECULAR ENTITY WAS APPROVED IN 1994 UNDER THE PROPRIETARY NAME SEREVENT INHALATION AEROSOL. THIS APPROVAL WAS FOR THE LONG-TERM, MAINTENANCE TREATMENT OF ASTHMA AND THE PREVENTION OF BRONCHOSPASM (INCLUDING EXERCISE-INDUCED BRONCHOSPASM) IN PATIENTS AGES 12 AND ABOVE WITH REVERSIBLE AIRWAYS OBSTRUCTION. THIS CURRENT NDA IS FOR A MULTIDOSE, DRY POWDER FORMULATION OF SALMETEROL XINAFOATE 50 MCG WITH LACTOSE (TO A TOTAL WEIGHT OF 12.5 MG) AS THE ONLY EXCIPIENT. THE DEVELOPMENT PROGRAM FOR THE DRY POWDER FORMULATION(S) BEGAN AS A 'STAND-ALONE' PROGRAM UTILIZING THE ROTADISK ADMINISTERED BY THE DISKHALER, WITH THE DISKUS PRODUCT BEING A "SWITCH" PROGRAM FROM THE ROTADISK, NOT FROM THE MDI. FOLLOWING THE MERGER OF GLAXO AND BURROUGHS WELLCOME, GLAXO WELLCOME DETERMINED THAT THEY DID NOT WISH TO MARKET THE ROTADISK FORMULATION. IT WAS AGREED TO BY THE SPONSOR AND THE DIVISION THAT IF THE ROTADISK FORMULATION PROGRAM WAS FULLY CLINICALLY APPROVABLE AND A "SWITCH" PROGRAM FOR THE DISKUS FROM THE ROTADISK WAS FULFILLED IN KEEPING WITH THE DIVISION'S "POINTS TO CONSIDER" DOCUMENT OF SEPT. 1994, THIS APPLICATION FOR THE SEREVENT DISKUS COULD BE FILED. THIS PARTICULAR "SWITCH" IS LARGELY BASED ON THE 'SAME FORMULATION, DIFFERENT DEVICE' PORTION OF THIS GUIDANCE, SINCE THE DRUG SUBSTANCE AND LACTOSE FORMULATION ARE IDENTICAL, ALTHOUGH THE DEVICES CLEARLY DIFFER. THERE WAS NO REQUIREMENT FOR THE SPONSOR TO DEMONSTRATE COMPARABILITY OF THIS PRODUCT TO THE MDI PRODUCT, SINCE THE CLINICAL DEVELOPMENT OF THE DRY POWDER FORMULATION WAS DESIGNED BY THE SPONSOR TO BE A STAND-ALONE PROGRAM. NOTABLE FROM THE CLINICAL STANDPOINT IS THAT, AS SUBMITTED, THERE IS NO CURRENT PROPOSED CLAIM FOR EIB FOR THE SEREVENT DISKUS, ALTHOUGH THIS IS AN APPROVED INDICATION FOR THE MDI FORMULATION. ALSO, THE UNDER 12 PEDIATRIC POPULATION IS NOT ADDRESSED IN THIS APPLICATION. THE PEDIATRIC INDICATION FOR THE MDI HAS NOT BEEN APPROVED. IT SHOULD ALSO BE NOTED THAT A PRECLINICAL ISSUE UNIQUE TO THE DRY POWDER FORMULATION OF SALMETEROL AROSE, WITH A NEW DEGRADANT BEING IDENTIFIED FOR WHICH THE DIVISION REQUESTED PRE-CLINICAL QUALIFICATION. THIS ISSUE IS ADDRESSED IN THE PHARM/TOX. REVIEW.

EFFICACY:

THE TWO MAIN TRIALS UPON WHICH JUDGMENT OF EFFICACY (COMPARED TO PLACEBO AND REGULARLY ADMINISTERED ALBUTEROL) IS BASED WERE STUDIES SLD-311 AND 312, BOTH DONE WITH THE ROTADISK FORMULATION. [THESE TRIALS FOLLOWED A SERIES OF DOSE IDENTIFICATION TRIALS WHICH ESTABLISHED THAT 50 MCG FROM A DRY POWDER FORMULATION WAS A REASONABLE DOSE AND THAT THIS DOSE PERFORMED SIMILARLY IN TERMS OF BRONCHODILATION TO A 50 MCG (EX-VALVE) DOSE FROM THE MDI.] THESE STUDIES WERE SIMILAR IN DESIGN TO THE PIVOTAL STUDIES DONE IN SUPPORT OF THE SEREVENT MDI APPLICATION. THEY FOLLOW BOTH FEV₁'S (PRIMARY VARIABLE SERIALLY PERFORMED 12-HOUR FEV₁) DONE AT MULTIPLE TIME POINTS IN THE 12 WEEK TRIALS, AS WELL AS OTHER PHYSIOLOGIC AND CLINICAL MEASURES OF ASTHMA CONTROL. THESE STUDIES SUPPORT THE EFFICACY AND SAFETY OF THE SALMETEROL DRY POWDER FORMULATION IN PROVIDING > 12 HOURS OF BRONCHODILATION (MEDIAN RESPONSE) WITHOUT DEFINABLE TOLERANCE TO THE BRONCHODILATION OCCURRING OVER A 12 WEEK TREATMENT PERIOD. OTHER MEASURES OF ASTHMA CONTROL (PEFR'S, RESCUE BETA-AGONIST USE, SYMPTOMS, NIGHTTIME AWAKENINGS) ALSO SUPPORT EFFICACY OF THIS FORMULATION RELATIVE TO PLACEBO, AND IN SOME CASES, TO REGULARLY ADMINISTERED ALBUTEROL, WITH ACCEPTABLE ADVERSE EVENT PROFILE RELATIVE TO PLACEBO AND ALBUTEROL. THESE STUDIES, THEREFORE, FORM THE BASIS OF A FINDING OF EFFECTIVENESS OF A SALMETEROL DRY POWDER FORMULATION IN THE TREATMENT OF ASTHMATICS (ALBEIT WITH THE DISKHALER DEVICE).

TRIAL SLGA2004 WAS A STUDY COMPARING THE EFFICACY OF THE 50 MCG BID FROM THE DISKUS DEVICE COMPARED TO THE SAME FORMULATION DELIVERED FROM THE ROTADISK PRODUCT/DISKHALER DEVICE VS. PLACEBO. THIS WAS A 'LIFE-OF-DEVICE' STUDY LOOKING AT COMPARATIVE SAFETY AND EFFICACY OVER A FOUR WEEK PERIOD, WHICH WAS SUPPLEMENTED IN TERMS OF THE SWITCH BY TWO SINGLE-DOSE CROSS-OVER STUDIES FOR PD COMPARISONS OVER A DOSE RANGE OF THESE TWO PRODUCTS (SLGA2001 AND 2006). THE CONCLUSION DRAWN FROM THESE DATA IS THAT THESE TWO DEVICES/PRODUCTS, WHEN DELIVERING THIS FORMULATION, PERFORMED COMPARABLY IN THE CLINICAL SETTING BOTH IN TERMS OF PD (WITH THE DISKUS ≥ ROTADISK FOR SPIROMETRIC MEASURES) AND IN TERMS OF CLINICAL USE, INCLUDING SAFETY MEASURES. THERE WERE NO SPECIAL ISSUES WITH THE DISKUS DEVICE EVIDENT IN THE REPORTED DATA FOR THE USE STUDY, WITH NO DEVICE FAILURES OR USAGE PROBLEMS, PARTICULARLY RELATIVE TO THE DISKHALER/ROTADISK DEVICE. TWO COMMENTS WORTH NOTING - PATIENT PREFERENCE FOR USE APPEARED TO FAVOR THE DISKUS IN SOME PATIENT-SCORED RATINGS, COMPARED TO ROTADISK ADMINISTERED VIA DISKHALER. ALSO, THE CROSS-OVER STUDIES (SLGA2001 AND 2006) REVEALED THAT THE DISKUS DEVICE PROVIDED SIMILAR BRONCHODILATORY EFFECTS TO THE ROTADISK/DISKHALER (IN THESE STUDIES, DISKUS ≤ ROTADISK). HOWEVER, THESE STUDIES DID NOT RELIABLY DETECT THE DIFFERENCE BETWEEN 50 AND 100 MCG AND THEREFORE THE SENSITIVITY OF THESE STUDIES IS QUESTIONABLE. HOWEVER, TAKEN ALL TOGETHER, THESE DATA SUPPORT THAT THE SAME NOMINAL DOSE DELIVERED FROM THESE TWO DEVICES PRODUCE COMPARABLE CLINICAL RESULTS BOTH IN SINGLE DOSE AND MULTIDOSE COMPARISONS.

SAFETY:

THE SAFETY DATA IN THIS NDA WERE EXTENSIVE, INCLUDING NOT ONLY NUMEROUS EFFICACY TRIALS OF VARIOUS DRY POWDER FORMULATIONS (E.G., LACTOSE TO 12.5 MG) VS. LACTOSE TO 12.5 MG), BUT ALSO LONG-TERM SAFETY STUDIES (OUT TO 12 MONTH) WITH THE PROPOSED FOR MARKETING FORMULATION. THERE ARE, ADDITIONALLY, POST-MARKETING DATA FROM THE MORE THAN 20 COUNTRIES WHERE THE FORMULATION HAS BEEN APPROVED. AS THESE DATA ARE

SUMMARIZED BY THE MEDICAL REVIEWER, MY ONLY COMMENT ON THESE IS THE ADVERSE EVENT PROFILE IS ACCEPTABLE CONSIDERING THE POPULATION AND INDICATION PROPOSED AND NOT SURPRISING GIVEN WHAT IS KNOWN ABOUT THIS MOLECULE AND THE MODERATE TO SEVERE ASTHMATIC POPULATION. IT IS WORTH STATING THAT ALTHOUGH DEATHS WERE NOTED IN THIS DATABASE, AS WITH THE SEREVENT MDI, THESE APPEAR MORE RELATED TO UNDERLYING DISEASE THAN TO SALMETEROL EXPOSURE. NO CASES CAN BE CONVINCINGLY LINKED TO SALMETEROL AS THE CAUSE OF THE DEATH.

OTHER EFFICACY/SAFETY INFORMATION:

FINALLY, THERE WERE THREE TRIALS DIRECTLY COMPARING THE MDI AND DISKUS PRODUCTS WHICH WERE SUBMITTED LATE IN THE ORIGINAL 12 MONTH REVIEW CYCLE. THESE INCLUDED A SINGLE DOSE, DOSE-RANGING, CROSSOVER STUDY [2015] IN WHICH THE 100 µg DISKUS DOSE APPEARED MOST SIMILAR IN EFFICACY TO THE .50 µg MDI DOSE (THOUGH THE DISKUS GROUP SUFFERED SOMEWHAT MORE ADVERSE EFFECTS). IN TWO PARALLEL GROUP 12-WEEK EFFICACY TRIALS [STUDIES 3010 AND 3011] OF STANDARD 50 µg DOSES FROM THE TWO DEVICES (42 µg EX-ACTUATOR FOR THE MDI), THESE TWO PRODUCTS WERE STATISTICALLY INDISTINGUISHABLE, THOUGH IT APPEARS THAT THE MDI HAD A NUMERICAL ADVANTAGE ON SEVERAL EFFICACY PARAMETERS. HOWEVER, THE DISKUS GROUP STILL HAD CLEAR EFFICACY IN REFERENCE TO PLACEBO.

OVERALL CONCLUSIONS:

I AM IN AGREEMENT WITH DR. JOHNSON'S ASSESSMENT THAT THIS APPLICATION IS APPROVABLE FROM THE CLINICAL STANDPOINT FOR THE PROPOSED AGE RANGE AT THE PROPOSED DOSES. SINCE THE ADEQUATE AND WELL-CONTROLLED DATA WE RECEIVED RELATING THE MDI TO THE DISKUS FORMULATIONS OF SALMETEROL SHOW SOME APPARENT DIFFERENCES IN THE DELIVERY AND EFFICACY OF THE TWO PRODUCTS; THERE NEEDS TO BE SOME SPECIFIC MENTION OF THESE DATA IN THE LABELING SO THAT PATIENTS AND PHYSICIANS KNOW THAT THE CLINICAL RESULTS OF THE TWO PRODUCTS MAY VARY (ALTHOUGH IT IS CLEAR THAT AS A STAND ALONE CONSIDERATION, THE MDPI IS SAFE AND EFFECTIVE AND, OVERALL, IS REASONABLY COMPARABLE TO THE MDI IN SAFETY AND EFFICACY).

RECOMMENDATION:

I RECOMMEND APPROVAL OF THIS PRODUCT, ONCE ALL CMC ISSUES AND LABELING ISSUES ARE RESOLVED TO A SUFFICIENT DEGREE. IT IS STILL AN OPEN ISSUE WITH THE CFC PHASE-OUT IN THE UNITED STATES WHETHER DPIs IN GENERAL WOULD BE CONSIDERED AS VIABLE ALTERNATIVES TO CFC-BASED MDIs FOR PURPOSES OF ESSENTIAL. THE FDA WOULD NEED CONSIDERABLY MORE DATA ON THIS PRODUCT SPECIFICALLY DUE TO SOME OF THE DIFFERENCES APPARENT IN THE MDPI-MDI HEAD-TO-HEAD TRIALS. IF THE SEREVENT DISKUS PRODUCT WERE TO BE CONSIDERED AS A TECHNICALLY FEASIBLE ALTERNATIVE (TEFA) TO THE SEREVENT CFC-BASED MDI, IT WOULD BE VERY USEFUL TO HAVE SOME POST-MARKETING USE TRIAL, PARTICULARLY EXAMINING ISSUES OF TOLERABILITY WHEN CLINICALLY SWITCHING BETWEEN THE MDI AND DPI. SINCE THE RULE MAKING PROCESS ON THE ESSENTIAL USES AND PHASE-OUT OF CFCs IS NOT TO A SUFFICIENT STAGE NOW TO DETERMINE WHETHER AN MDPI WILL BE CONSIDERED AS A TEFA TO AN MDI, WE CERTAINLY CANNOT REQUIRE ANY SUCH STUDY.


ROBERT J. MEYER, MD 9/15/97
MEDICAL TEAM LEADER
DIVISION OF PULMONARY DRUG PRODUCTS

CC: Johnson/Medical Officer/HFD-570
Meyer/Medical Team Leader/HFD-570
Jani/project manager/HFD-570
Division File/HFD-570
NDA #20-692

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 43,097	IND for Multi Dose Dry Powder Formulation	

Overview of Application/Review:

See Executive Summary, Page 3.

Outstanding Issues:

See Recommended Regulatory Actions, Page 127.

Recommended Regulatory Action APPROVABLE

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

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed _____

NDA's:

Efficacy / Label Supp.: _____ Approvable _____ Not Approvable

Signed:

Medical Reviewer:

Date:

Medical Team Leader:

Date:

TABLE 2.2
TABLE OF STUDIES

INDICATION

CONTROLLED CLINICAL STUDIES

Report Number Protocol Number Investigators Publications	Completion Status (Start Date)	Location, Product Code ¹	Full (Summary) Report Vol./Page	Study Design	Treatment Dose (Route)	Number Treated Each Treatment	Age Range (Median) Mean	Sex/Race ² M/F (B/W/O) %	Duration of Drug Treatment
Placebo-Controlled									
RM1996/00095/00 SLGA2013 [See Footnote] N/A	Completed (7/3/95)	United States B, P	6/33	Randomized, Double-Blind, Double-Dummy, Crossover	50mcg MDPI 100mcg MDPI 50mcg MDI Placebo (IH)	24 24 24 24	12-35 (25.0) 23.6	79/21 0/92/8	Single Dose
RM1996/00163/00 SLGA2017 [See Footnote] N/A	Completed (7/17/95)	United States B, P	8/1	Randomized, Double-Blind, Double-Dummy, Crossover	50mcg MDPI 100mcg MDPI 50mcg MDI Placebo (IH)	28 29 28 28	12-38 (24.0) 23.8	41/59 10/90/0	Single Dose
UCR/95/013 SLGA2002 [See Footnote] N/A	Completed (12/9/93)	United States H, P	9/336	Randomized Double-Blind Double-Dummy Crossover	50mcg RD 50mcg MDPI Placebo (IH)	22 22 22	15-36 (21) 22	59/41 0/100/0	Single Dose
UCR/95/014 SLGA2003 [See Footnote] N/A	Completed (1/24/94)	United States H, P	10/1	Randomized Double-Blind Double-Dummy Crossover	50mcg RD 50mcg MDPI Placebo (IH)	24 24 24	4-11 (10) 9	58/42 8/92/0	Single Dose
RM1996/00350/00 SLGA2014 [See Footnote] N/A	Completed (2/4/96)	United States P, Q	12/1	Randomized, Double-Blind, Double-Dummy, Crossover	25mcg MDPI 50mcg MDPI Albuterol 180mcg MDI Placebo (IH)	26 25 25 24	4-11 (8) 7.6	65/35 15/81/4	Single Dose

RD = Rotadisk
IH = Inhaled
PO = Oral

¹ Product Code = See key at end of table.
² Race
= B = Black, W = White, O = Other
= Not available or not applicable

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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 FEV₁ 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 FEV₁ 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 impurity of the formulation,

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

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. Upoor'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.

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

**APPEARS THIS WAY
ON ORIGINAL**

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ON ORIGINAL**

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.

Investigators:

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 were 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 FEV₁ 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 FEV₁ value (medication-free) of 50-80% of their predicted value during the screening visit and an increase in FEV₁ 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 FEV₁. Secondary efficacy measures include FVC, FEF_{25-75%}, PEF, 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 FEV₁ measurements on Treatment Day 1.
- **Responder:** a patient who achieved an increase in FEV₁ >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 FEV₁ 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 FEV₁ above the predose value on a given study day.
- **AUC:** area under the FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁. 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.

	<u>Salmeterol</u>	<u>Albuterol</u>	<u>Placebo</u>
Adverse Events	6	1	2
Asthma Exacerbation	1	0	1
Lack of Efficacy	0	1	1
Protocol Violation	2	2	1
Other	<u>1</u>	<u>0</u>	<u>0</u>
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 PEF 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 FEV₁

Baseline

There were no statistically significant differences among the salmeterol, albuterol and placebo treatment group FEV₁ 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 FEV₁ 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 FEV₁ at Hour 0 for the efficacy population at Weeks 4, 8 and 12.

Table 8.1B Baseline and Daily Pre-Dose FEV₁

	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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ at screening of approximately 65 percent of predicted normal.

Table 8.1C FEV₁ 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 FEV₁ curve and above the 15 percent improvement from Day 1 baseline threshold. AUC (BL) was defined as the total area under the FEV₁ 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 FEV₁ outcomes, AUC(BL) is likely to be the most profoundly affected by the carryover effects of salmeterol. As the entire FEV₁ 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 FEV₁ 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 FEV₁ on a treatment day subsequent to Day 1. As the plot indicates, FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 = 71)	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 FEV₁ 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 been 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

Symptoms 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 FEV₁ 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 statistical 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 FEV₁ 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 FEV₁ 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 8.11. 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 8.11 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 FEV₁, 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 FEV₁ 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

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.

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.

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.

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 nebulers, theophylline, Robitussin®, and Prednisone®. The patient improved and was discharged 3 days later.

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.

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

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 acetate, 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.

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

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.

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 (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.

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 (— 11) experienced a severe episode of tremor and agitation associated with the first dose of salmeterol. Another patient (— 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.

Investigators:

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.

	<u>Salmeterol</u>	<u>Albuterol</u>	<u>Placebo</u>
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	<u>1</u>	<u>1</u>	<u>0</u>
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 = 70)	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 FEV₁

Baseline

There were no statistically significant differences among the salmeterol, albuterol and placebo treatment group FEV₁ means within the efficacy population at baseline. As in Trial SLD-311 (Section 8.1.7.1), the mean FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 than 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 FEV₁ 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 be the 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 = 89	Albuterol N = 70	Placebo N = 73
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

#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.

#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

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.

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.

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.

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.

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. 70, a 40-year-old Caucasian female recorded pre-and post dose intervals of 480msec at Treatment Week 4. 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

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

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

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).

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 (— 151) 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 (— 176) experienced elevated SGOT and SGPT during salmeterol treatment while a second patient (— 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.

APPEARS THIS WAY
ON ORIGINAL

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)

Investigators:

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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁. 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 FEV₁ 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.

	<u>MDPI</u>	<u>DH</u>	<u>Placebo</u>
Adverse Events	2	0	1
Asthma Exacerbation	2	1	2
Lack of Efficacy	0	0	0
Protocol Violation	1	0	1
Other (Logistics)	<u>2</u>	<u>1</u>	<u>2</u>
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 = 63)	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 FEV₁

There were no statistically significant differences among the MDPI, DH and placebo treatment group FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 dosing 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 ≤ 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 12.5 mg dose per blister). The original formulations contained 2 blisters per rotadisk. Following this phase of development, the sponsor modified the formulation, first to a standard fill rotadisk, then to a 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 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 FEV₁. Although a primary endpoint was not designated in most protocols, FEV₁ 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 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 FEV₁ 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. FEV₁ 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 FEV₁ 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 (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 (standard fill) formulation to the MDI, while Trial **SLGH03** was a cumulative dose comparison of the same formulations. The (standard) formulations were compared in Trial **SLGH18** cumulative dose study, while the standard and reduced fill formulations (standard fill) 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 ~ 50 MDI 50	DPI ~ 50 MDI 50 ALB 200 PL	DPI ~ 50 MDI 50 ALB 200 PL	DPI ~ & MDI - 12.5, 25, 50, 100	DPI ~ & DPI ~ - 25, 50, 50, 50	DPI ~ 25 DPI ~ 25 PL	DPI ~ 50 DPI ~ 50 PL
N	14	13	12	8	22	24	25
FEV1				MDI ~ DPI See Appendix ****	DPI ~ & DPI ~		
Onset	MDI ~ DPI	PL > MDI ~ DPI > ALB ²				PL > DPI ~ & DPI ~	PL > DPI ~ & DPI ~
Duration	MDI ~ DPI	MDI ~ DPI > ALB > PL				DPI ~ > DPI ~ > PL	DPI ~ > DPI ~ > PL
Pk Effect	MDI ~ DPI	MDI ~ DPI ~ ALB > PL	MDI ~ DPI ~ ALB > PL			DPI ~ & DPI ~ > PL	DPI ~ & DPI ~ > PL
Time to Pk	MDI (210 MIN) DPI (120 MIN)	MDI ~ DPI ~ PL > ALB	MDI (180 MIN) DPI (300 MIN) ALB (75 MIN) PL (240 MIN)			DPI ~ & DPI ~ > PL	DPI ~ & DPI ~ > 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				

DPI 50- Dry Powder Inhaler, 50 mcg dose

² ~ indicates clinically equivalent outcomes
> indicates potential clinical inequivalence

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 FEV₁ 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 FEV₁ 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 PC₂₀ 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 PC₂₀ 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 than the DPI. Corresponding FEV₁ data failed to show a statistically significant difference between the salmeterol formulations.

The cumulative dose comparison of the DPI —, 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 FEV₁ 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 — standard fill DPI formulations in Trial **SLGH18**. A total of 150 mcg. was administered over a 4.5 hour period. Mean FEV₁ 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 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 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 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 standard fill DPI was compared to a 50 mcg MDI dose, a 50 mcg standard fill DPI dose and a 50 mcg 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 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 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.

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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁.

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 FEV₁, FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ findings, showing a negligible dose response between the 50 and 100 mcg doses, no statistically significant differences among the active treatments and statistical 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 FEV₁ 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)

¹Baseline is the average of the -0.5 and 0 hour FEV₁ 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:

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 FEV₁ of ≥ 80 percent predicted normal, as well a response to a provocation dose PD₂₀ FEV₁ 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 FEV₁, 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 FEV₁ of ≥ 20 percent from baseline is achieved for three consecutive FEV₁ 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 FEV₁ could be achieved with a lower cumulative dose. Isuprel (isoproterenol) was used to relieve bronchoconstriction effects during methacholine inhalation.

Baseline FEV₁ 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 PD₂₀FEV₁, the provocation dose expressed in cumulative breath units of methacholine that produces a 20 percent decrease from baseline FEV₁.

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.

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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≤0.0050 compared with 50 mcg MDPI

^{*} p≤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 PD₂₀ (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 FEV₁ between each active treatment and placebo and between 50 mcg MDPI and 100 mcg MDPI doses. In analysis of actual PD₂₀ (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. Upoor 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 FEV₁ following histamine challenge, but were not required to have been diagnosed with asthma or to exhibit reversibility in FEV₁ 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 PD₁₅, was observed for both formulations at Hour 1 and Hour 12. There was no statistically 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 (PD₁₅) is non-standard. These factors prevent definitive conclusions regarding the generalization of these data to the application. It is noted that gross clinically important differences between devices were not implied by these data.

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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 FEV₁ 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 FEV₁ 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 FEV₁ 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	117	Not Measured
DH	6.27, 2.20	118	Not Measured
Trial RESB4002			
MDPI	3.48, 1.26	82.35, 16.54	92.04

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 FEV₁.

Comment: FEV₁ 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.

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8.9 Twelve Month Trials

Study reports for two trials of one year duration were submitted to the NDA during the initial NDA review cycle. Trial SLGT06 was submitted with the original application on June 19, 1996 and Trial SLD-320 was submitted at the 120 day safety update on October 16, 1996. Trial SLGT06 was conducted with the standard fill DH formulation and Trial SLD-320 was conducted with the reduced fill DH formulation. A third 12 month trial, SLGA 3009, conducted using the to be marketed MDPI, is ongoing, but preliminary safety data have been submitted.

8.9.1 Trial SLD-320: A Randomized, Double-Blind, Parallel Group Clinical Trial of the Effects of 12-Month Courses of Salmeterol Xinafoate Rotadisk (DH) versus Placebo on Methacholine-Induced Bronchial Hyperresponsiveness in Adolescent and Adult Patients With Chronic Mild-To-Moderate Asthma. (Vol 6.1)

Investigators:



Initiation Date: 10 January 1994 (first patient was enrolled)

Completion Date: 8 November 1996 (date of last observation)

8.9.1.1 Study Description

Objective:

The primary objective of this study was to compare the effects of 50 mcg BID DH with placebo on methacholine-induced bronchial hyperresponsiveness and pulmonary function and to determine the safety of the active treatment when administered for 12 months to adolescent and adult patients with reversible obstructive airways disease. This study employed the . — , reduced fill DH formulation which was used in pivotal trials.

The protocol was modified twice, once before and once after initiation. The modifications were a series of minor protocol clarifications, unlikely to have introduced bias into the trial.

Population:

Males and females, age 12 years and over, were enrolled if they demonstrated an FEV₁ of 70 to 90 percent of predicted normal during screening, demonstrated an increase in FEV₁ of 15 percent or more in response of 2 to 4 puffs of Ventolin MDI and were otherwise healthy. Patients were also required to complete two positive methacholine challenges with a PD₂₀ at concentrations of ≤ 7.5 mg/ml of methacholine. PD₂₀ values were required to be within a 3-fold change of each other.

Patients on fixed doses of inhaled or intranasal corticosteroids were permitted in the study and other concomitant medications were to be appropriately withheld.

Comment: Due primarily to the use of methacholine challenge as a primary endpoint in this trial, the population studied is one of relatively mild asthmatics. This population is not representative of the majority of patients who are prescribed Serevent in the clinical setting. The ability to generalize of the safety and efficacy data from this trial to the broader asthma population is limited.

Design and Procedures:

This study was designed with three phases. The first phase was a single blind placebo run-in during which patients used a placebo DH device BID and Ventolin MDI as rescue medication. The double blind randomization phase followed. For a total of 52 weeks (Weeks 1 through 52), patients received monthly supplies of DH devices and returned for monthly clinic visits. There was a single blind placebo run-out phase at the end of the 52 week period.

Methacholine challenges were conducted at screening and 2-3 subsequent times thereafter to determine consistency of response (Visits A, B and C). During the active treatment phase, patients were required to make clinic visits every four weeks and methacholine challenges were conducted at Weeks 1 (Day 1), 4, 12, 24 and 52, as well as Days 1, 2 and 7 of the run-out period. Serial pulmonary function tests were conducted at Weeks 1, 8, 20 and 48. Daily patient data, including symptom assessment and PEFR, were collected in a diary format. A physician global symptom assessment was completed at each clinic visit.

Methacholine challenges were conducted 10 to 14 hours after the previous dose of study medication. After baseline FEV₁, patients were instructed to take five normal breaths from the nebulizer to receive a saline challenge. Barring a decline of 15 percent or more in FEV₁, patients received five breaths each of increasing concentrations of methacholine until the patient had three consecutive FEV₁ values which were 20 percent or more lower than daily baseline. The daily baseline was required to be within 65 percent of predicted normal in order to conduct the methacholine challenge at each visit. Ventolin MDI was used to treat bronchoconstriction effects of methacholine if deemed necessary by the investigator.

Endpoints:

Efficacy Endpoints

The primary efficacy assessment was the PD₂₀ evaluation from the methacholine challenges. Secondary efficacy endpoints included the 12 hour serial spirometry evaluations, daily PEF, daily use of back-up Ventolin MDI, frequency of nighttime awakenings, patient-rated asthma symptoms scores, physician rated global symptoms assessments, and frequency of asthma exacerbations.

Comment: The efficacy of the DH formulation as compared to placebo was assessed and confirmed in pivotal trials SLD-311 and SLD-312. Given this previous verification of the activity of salmeterol in a dry powder formulation, the existence of an approved salmeterol MDI product, and the relatively mild population included in this trial, little utility can be gained from extensive presentation of the efficacy outcomes. Each endpoint was reviewed for major trends, but the only data presented in this review will be the outcome of the primary endpoint, methacholine challenge. This endpoint may help to establish the consistency of the efficacy of salmeterol via DH throughout the one year period. Note, however, that since these patients were never fully washed out of all beta agonists, i.e., Ventolin was used during the run-in phase and throughout the treatment phase, this trial cannot be regarded as a definitive demonstration that there is no tolerance to bronchoprotection with salmeterol.

Safety Endpoints

Safety assessments in this trial included clinical adverse events (recorded at each clinic visit), 12-lead electrocardiograms (collected at screening and predose and 1.5 hours post dose at Weeks 1, 8, 20, 48 and posttreatment Day 7), continuous 24-hour Holter monitoring (at selected centers between Visits A and B and at Weeks 20 and 48), clinical laboratory tests (assessed predose at screening and Weeks 12, 24, 36 and 52), and vital signs (assessed at Weeks 1, 8, 20 and 48 immediately prior to each set of PFTs).

Statistical Considerations:

Enrollment was planned for 150 patients per treatment group, calculated to provide for >80% power of detecting a difference in FEV₁ of 0.18 liters between the 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 FEV₁. The sponsor indicated that a reliable estimate for standard deviation in PD₂₀ is not available, but postulated that if the standard deviation was two doubling doses, then the study would provide >80% power of detecting a difference in PD₂₀ of 0.84 doubling doses.

8.9.1.2 Patient Disposition

A total of 352 patients enrolled in this study, with 176 randomized to each treatment group. Of these, 265 (75 percent) completed the study, including 134 in the placebo group and 131 in the salmeterol group. The reasons for withdrawal of 87 patients are summarized below.

<u>Reason</u>	<u>Placebo</u>	<u>Salmeterol</u>
Noncompliance/Protocol Violation	10	16
Withdrew Consent	8	9
Lack of efficacy	11	3
Failed to Return/Lost to Follow-up	5	5
Adverse Event	3	1
Pregnancy	0	3
Other	5	8
Total	42	45

Protocol variations were primarily related to use of prohibited medications and were comparable between treatment groups, with the exception of slightly greater use among placebo patients of beta agonist prior to a PFT assessment. The term "other" refers primarily to patient relocation.

The two treatment groups were comparable with respect to demographic parameters. Approximately half of the patients were female (49 percent) and most were Caucasian (90 percent). Five percent were categorized as Black. Ages ranged between 12 and 67 with a mean of 30 years. Sixty three percent of patients had been diagnosed with asthma more than ten years prior to the trial. At least one episode of nocturnal asthma was reported per week in 42 percent of the patients.

8.9.1.3 Efficacy Endpoint Outcomes

Baseline FEV₁ was 2.9 L, or 79 percent of predicted normal, for both treatment groups and percent reversibility was 20 to 21 percent. The PD₂₀ (in cumulative breath units) at screening was 2.66 for placebo and 2.63 for salmeterol, with reasonably consistent outcomes at verification Visits A, B and C. Methacholine challenge testing revealed consistently higher mean PD₂₀ values for the salmeterol group (range 3.42 to 3.62 cumulative breath units) than for the placebo group (range 3.07 to 3.47 cumulative breath units) at Weeks 4, 12, 24 and 52. Statistically significant differences were demonstrated at Weeks 4 and 24. Run-out phase PD₂₀ values were higher for the placebo group at Day 1, 2 and 7 than for the salmeterol group. On Day 7 of the run-out, there was a statistical difference between the groups and the salmeterol PD₂₀ value had fallen below baseline levels (2.26 cumulative breath units), although the placebo group reached a minimum above baseline of 2.88.

As noted earlier, the other efficacy endpoints were reviewed for important statistical or clinical trends. Mean post dose FEV₁ values were consistently statistically and clinically superior for the salmeterol group as compared to the placebo group, as were the associated FEV₁ parameters such as onset, duration and AUC. Daily use of Ventolin rescue was in the range of 1.5 to 1.6 puffs per day for salmeterol and 2.5 to 2.8 puffs per day for placebo. Percent of days with no nighttime awakenings was approximately 80 percent for placebo and 90 percent for salmeterol.

8.9.1.4 Efficacy Conclusion

Methacholine challenges appear to confirm that salmeterol exhibited its bronchoprotective effects throughout the 12 month treatment period. Rapid decline in protective effects occurred after treatment cessation, to below baseline levels. The remainder of the efficacy data confirm salmeterol's superiority to placebo, but also emphasize the mild severity of asthma among these patients. Again, it should be noted that these results of this trial may not be generalizable to the entire asthma population.

8.9.1.5 Safety Endpoint Outcomes

Adverse Events

There were no deaths reported during the study. Eleven serious adverse events were reported, including 5 salmeterol and 6 placebo patients. Events for both groups are listed below. An asterisk indicates that the event precipitated discontinuation from the trial. No cases appear to be potentially related to treatment.

<u>Patient No.</u>	<u>Adverse Event</u>
Salmeterol	
429	Bone graft to repair fractured wrist
228	Appendectomy
437	Hospitalization for asthma exacerbation and gastroenteritis
165	Appendectomy
184	Asthma exacerbation
Placebo	
237*	Supraventricular tachycardia
266	TIA
518	Bilateral hernia
36	Status Asthmaticus
169*	Adenocarcinoma
33	Fracture and laceration of arm

Two additional patients were discontinued due to adverse events. 235, a salmeterol patient, was withdrawn on Day 136 due to mild hypertension. No treatment was given and the event resolved. This dechallenge model suggests that the event may be related to study drug, although the investigator considered the relationship unlikely. A placebo patient, 335, was discontinued due to cholelithiasis and

jaundice.

Three patients became pregnant during salmeterol treatment. Two delivered healthy infants and the third had a spontaneous abortion seven days after withdrawal. Pregnancies were discovered during clinic examinations or were reported to investigator, all at four to six months into the treatment. Gestational age was 22.5 weeks when discovered in the first case, pregnancy was thought to have occurred with a "recent" change in birth control pills in the second case, and gestational age was four weeks at the time of the spontaneous abortion.

Adverse events which occurred in at least five percent of the patients and in a greater portion of salmeterol than placebo patients include upper respiratory infection, headache, nasopharyngitis, and viral gastroenteritis. None appear to be clearly related to active treatment.

Clinical Laboratory Tests

Fourteen percent of each treatment group was reported to have had abnormal laboratory values after exposure to the drug. None appeared to be clinically significant or attributable to salmeterol, based on comparison to placebo in shift table analyses.

Cardiovascular Effects

The frequency of increases and decreases in pulse rate and systolic and diastolic blood pressure were mainly comparable between treatment groups, although a slightly greater proportion of salmeterol patients experienced a decrease in systolic blood pressure. EKG data revealed two abnormalities which were thought to be potentially related to salmeterol. A 51 year old female experienced T-wave abnormalities post dose on three occasions and a 57 year old female exhibited nonspecific ST-T abnormalities with a prolonged QTc (475msec). All EKGs for these patients were thought to be within normal limits. The incidence of prolonged QTc was similar for the two treatments. Holter monitoring did not distinguish between treatments.

Physical Examinations

Physical examinations conducted at screening and Week 52 and the low incidence of unfavorable changes between these visits, primarily in respiratory and ENT, was similar between treatment groups. Pulmonary auscultation at each clinic visit showed no clinically significant difference between treatments.

Safety Conclusion

Potentially treatment related adverse events were minimal in this trial, with no gross

differences between active and placebo treatment. Three salmeterol patients became pregnant, with one patient experiencing a spontaneous abortion after drug withdrawal.

8.9.1.6 Conclusion

Methacholine challenge and secondary efficacy endpoints confirm that salmeterol maintained its efficacy as compared to placebo throughout the 12 month investigation period. Some indication of a rebound effect was observed during the run-out, with the bronchial hyperresponsiveness in the salmeterol group being somewhat more than that of pre-baseline levels. Adverse events were not numerous and appeared to have minimal potential to be causally related to treatment. This treatment group is not representative of the population in whom Serevent is routinely prescribed in clinical practice and the ability to generalize the safety or efficacy data to that population is tenuous.

**APPEARS THIS WAY
ON ORIGINAL**

8.9.2 Trial SLGT06: A Double Blind, Parallel Group Study Comparing the Safety Over Nine Months of the Dry Powder Formulations of Inhaled Salmeterol Xinafoate (50 mcg) and Inhaled Salbutamol (400 mcg) Administered Twice a Day. (Volume 1.76)

Trial SLGT06 was conducted with the standard fill DH formulation, which was related by bridging studies to the reduced fill formulation used in the pivotal trials of this applications (See Section 8.4). Although the reduced fill DH formulation was subsequently linked to the to be marketed MDPI formulation, the standard fill DH was not directly linked to the MDPI. Trial SLGT06 was the only twelve month trial completed at the time of the original application and was submitted primarily for that reason. However, the utility of the trial in the determination of approvability of the MDPI product is limited.

Comment: The 120 day safety update to this NDA contained the summary of one year trial SLD-320, which employed the reduced fill DH. Because there is a direct link between the reduced fill DH and the MDPI, SLD-320 is more relevant to the evaluation of the to be marketed product. In addition, SLGT06 was designed using albuterol MDI as an active control at doses of 400 mcg BID. The efficacy and safety of the reduced fill DH formulation, as compared to the albuterol MDI as an active control at customary U.S. doses and to placebo, was undertaken in pivotal trials SLD-311 and SLD-312. Finally, SLGT06 was carried out across 48 centers in 11 European countries and in New Zealand, making it difficult to compare the U.S. experience with that reported for this trial. Therefore, this review focuses on a summary of the adverse event database. The remainder of the study report was reviewed for important statistical and clinical trends.

Trial SLGT06 was designed as nine month follow-up to a three month efficacy and safety trial. It was a randomized, double blind, double dummy, parallel group study comparing 50 mcg salmeterol BID with albuterol at doses of 400 mcg BID (the initial portion of the trial used doses of 400 mcg QID). A total of 449 patients were randomized and of these 342 (51 percent) completed all 12 months. Of the 449 patients who received treatment, 163 (74 percent) salmeterol patients and 188 (82 percent) of the albuterol patients reported adverse events. There was one death reported with albuterol treatment. The case narrative reports a 68 year old female with a history of first degree heart block died in her sleep after 86 days on treatment. She had been well and free of asthma symptoms two days prior and her death was certified as probable myocardial infarction.

There was no apparent difference in the number of patients who withdrew due to adverse events, a total of 21 (10 percent) salmeterol patients and 29 (13 percent) albuterol patients. Serious adverse events were reported by 15 salmeterol patients

(seven of these patients withdrew) and 18 albuterol patients (six of these patients withdrew). Narratives of the cases of serious events were reviewed and those of patients on salmeterol are listed. Those events which caused withdrawal are shown with an asterisk. None appeared to be related to study medication. Serious asthma exacerbations occurred in seven salmeterol patients and 11 albuterol patients.

<u>Subject No.</u>	<u>Adverse Event</u>
D6149*	Asthma exacerbation
D6332*	Hospitalization for depression
D6337*	Asthma exacerbation / Codeine allergy
D6345	Bus accident / whiplash
D6418	TURP
D6436	Erysipelas / Myocarditis
D6466*	Asthma exacerbation
D6484*	? Tumor of the cerebellum
D6485	Bronchitis
D6543	Asthma exacerbation
D6632	Myositis of intercostal muscles
D6647	Asthma exacerbation
D6661*	Asthma exacerbation
D6686	Asthma exacerbation
D6676	Spontaneous pneumothorax

As noted earlier, the study report was reviewed for important statistical and clinical trends. Clinic visit FEV₁ assessments were consistently higher for the salmeterol group than the albuterol group, with statistical significance demonstrated intermittently. Daily use of rescue medication was slightly lower for the salmeterol group. The number of patients who experienced an asthma exacerbation during each three month assessment interval was consistently higher for the albuterol population, with differences between treatment groups of approximately five percent. Laboratory and vital sign data failed to reveal notable differences between treatments.

Conclusion: This trial does not provide information which contradicts efficacy or safety conclusions drawn from the pivotal trials of the reduced fill DH formulation.

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8.9.3 SLGA3009: A 12-Month, Open-Label Trial to Assess the Long-Term Safety of Salmeterol 50 mcg BID via the Diskus in Adolescent and Adult Subjects with Asthma. (Volume 1.96, 6.42)

A study summary of the ongoing trial was submitted with the original application and additional information was contained in the 120-day safety update. In a facsimile communication of January 31, 1997, the sponsor indicated that this trial was ongoing and the final report would be submitted with their application for a pediatric indication.

The primary objective of this trial is to assess the long term safety of 50 mcg salmeterol administered twice daily via the reduced fill DH formulation. No controls were included in the trial design. The trial is being conducted at approximately 25 outpatient centers in the U.S. and Puerto Rico where patients return monthly for assessment of the secondary endpoint, bronchodilator response to nebulized albuterol. Patients were asked to record PEFR and symptom assessments in a daily diary. The projected enrollment is approximately 450 patients and effort has been made to enroll minority populations in this trial.

To date, outcome information has been provided regarding deaths, serious adverse events and withdrawals due to adverse events and deaths. A single patient death has been reported, that of a 41 year old female. Sixty days after starting study drug, she was found dead by relatives. The cause of death was considered to be sudden respiratory failure and is not believed by the investigator to be related to study drug. Additional discussion of patient deaths appears in the Integrated Summary of Safety.

Serious adverse events were reported as follows and those patients who discontinued due the event are indicated with an asterisk. Case narratives were reviewed for each report and case report forms were reviewed for those cases thought which appear to be potentially related to treatment, independent of the investigator assessment, as shown in bold.

<u>Subject No.</u>	<u>Adverse Event</u>
10347*	Elevated blood pressure, possible long term memory loss, dizziness, numbness in arms, visual problems, joint pain
10441*	Mild dyspnea, slight generalized pruritus, erythema of neck and face, wheezing
10621*	Gum edema and tooth pain
10629*	Inpatient hospitalization for moderate chest and stomach pain secondary to suspect GERD
10330	Cholelithiasis /Cholecystectomy
10396	Allergic reaction to ketorolac
10633*	Asthma exacerbation
10469	Cholecystitis / Cholecystectomy
10356*	Upper respiratory infection / Asthma exacerbation
10337	Asthma exacerbation
10487	Lower respiratory infection / Status asthmaticus

10328	Upper respiratory infection / Asthma exacerbation
10486	Status asthmaticus / Asthma exacerbation / GERD / Sinusitis\
10691	Bronchitis / Viral meningitis
10482	Sinusitis / Pneumonia
10372	Abdominal pain / Possible cholecystitis or gastroenteritis
10481	Status Asthmaticus
10450	Hospitalization for depression

Conclusion: With the exception of the death and serious adverse events noted, safety data from this trial have not been submitted. The serious cases which are potentially related to study drug are discussed further in the Integrated Safety Summary.

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9.0 Overview of Efficacy

9.1 Summary of the U.S. Pivotal Clinical Trials

Trials SLD-311 and SLD-312 serve as the pivotal efficacy trials for this application. In these trials, the — reduced fill formulation of the DH was compared to both placebo and albuterol MDI. The purpose of these trials was to demonstrate the effectiveness of the DH formulation relative to placebo in doses of 50 mcg BID and to provide validation of the relative comparability of the effects of salmeterol DH and albuterol MDI. Each was designed as a randomized, double blind, double dummy, parallel group trial with a 12 week duration.

Subsequent to initiation of the pivotal trials, the sponsor determined that the MDPI formulation was to be marketed in lieu of the DH formulation. As discussed in pre-NDA communications with the division, a bridging trial which linked the two formulations over the life of the MDPI device was required. Trial SLGA2004 was a randomized, double blind, double dummy, parallel group four week comparison of the two formulations which included a placebo control arm, based on the "same formulation, different device" part of the division's Points to Consider.

Comment: This development program was intended as a "stand-alone" program, which provided for no pivotal trials in which the comparability of the new dry powder formulation and the approved MDI were to be established. Subsequent to submission of the NDA, the sponsor provided study reports for comparative trials of the MDPI and MDI. These data will be reviewed in an addendum to this document, prior to the final action on the product.

The design of the pivotal trials has been previously described in detail in Section 8.1.2. Efficacy outcomes were described in Section 8.1.7 (SLD-311) and Section 8.2.7 (SLD-312). The design and efficacy outcomes of the bridging trial were described in Section 8.3.3 (SLGA2004). Trials SLD-311 and SLD-312 were of identical design and the efficacy outcomes for these trials were integrated by the sponsor. Due to differences between the designs of these trials and SLGA2004, the latter was not integrated. The efficacy endpoints for each of the trials were spirometric endpoints, with FEV₁ and parameters derived from FEV₁ data serving as primary endpoints. Among the three studies, a total of 661 asthmatic patients were evaluated including 290 who received a dose of 50 mcg salmeterol powder BID.

In SLD-311 and SLD-312, serial hourly PFTs were performed over a 12 hour period following the first dose and after 4, 8 and 12 weeks of treatment. Table 9.1 shows the mean percent change in FEV₁ from the Day 1 baseline for each

treatment at 4, 6 and 12 hours after dosing on Day 1 and Weeks 4, 8 and 12 based on the combination of data from the two trials. Salmeterol was statistically superior to placebo at each post dose timepoint on each clinic day. Albuterol was also statistically superior to placebo at most timepoints, with the exception of those around the end of the six hour dosing intervals. As explained in Section 8.1.7.1, change from Day 1 baseline for salmeterol is generally greater than for albuterol due to the carryover effects of salmeterol doses and upward shift in daily baseline after the Day 1 dose. The comparative data in this table also fail to capture the peak effects of albuterol doses (approximately 30 minutes to one hour after dosing), which were clinically comparable to those of salmeterol. This table does indicate a clinically significant advantage of salmeterol treatment relative to placebo and shows consistency of effect for Week 4 through Week 12. Appendix 18 contains a plot of the percent change from baseline data for Week 4 of the combined analysis. It clearly indicates that the data from the combined analysis are comparable to the outcomes from the individual studies.

Table 9.1 Mean Percent Change in FEV₁ from Treatment Day 1 Baseline in SLD-311 and SLD-312

	N	Baseline ¹ FEV ₁ in L (% of Predicted)	4 Hours Post dose	6 Hours Post dose	12 Hours Post dose
Day 1					
Placebo	145	2.46 (68)	5.0	3.7	1.8
Salmeterol	145	2.44 (67)	23.8	21.4	17.4
Albuterol	148	2.49 (68)	13.9	7.8	8.8
Week 4					
Placebo	137	1.6	6.4	4.6	3.0
Salmeterol	134	16.9	30.2	27.9	23.7
Albuterol	135	-2.5	8.4	5.8	5.1
Week 8					
Placebo	127	2.9	7.1	5.5	3.0
Salmeterol	135	16.6	28.8	27.9	22.2
Albuterol	135	-0.8	10.7	6.7	7.5
Week 12					
Placebo	125	2.7	7.2	4.2	3.3
Salmeterol	125	13.1	28.4	24.9	20.3
Albuterol	133	0.8	9.5	4.9	6.1

¹ Day 1 data are presented as mean FEV₁ value and percent of predicted. Thereafter, data indicate mean percentage change from Treatment Day 1 baseline.

Parameters derived from FEV₁ data were supportive of the clinical effectiveness of both salmeterol and albuterol relative to placebo. As expected, the median time to onset of effect was shorter for albuterol than salmeterol on Day 1 (12.6 minutes versus 30 minutes, $p < 0.001$). The onset of salmeterol was faster than albuterol at subsequent visits due to the shifted daily baseline FEV₁. Onset of both treatments was significantly shorter than for placebo at each clinic visit. Median duration of effect for salmeterol ranged between 8.3 and 10.4 hours, while duration of effect for albuterol ranged between 0.9 and 2.9 hours. Again, this discrepancy is due largely to the inherent duration of action of the drug substances, but is also reflective of the shifted baseline for salmeterol. The percent of patients achieving a 15 percent or greater increase over baseline within 4 hours post dose, AUC and maximum effect were comparable for albuterol and salmeterol on Day 1 and higher for salmeterol thereafter due to the shifted baseline. Both treatments performed consistently better than placebo.

Secondary endpoints in Trials SLD-311 and SLD-312, including peak expiratory flow (recorded by patients both morning and evening), daily patient-rated symptom scores for asthma symptoms, frequency of nocturnal awakenings, frequency of rescue albuterol use, asthma exacerbations and physicians' global assessment of asthma symptoms at clinic visits, were supportive of efficacy. Integration of these data from the two trials does not provide additional information relative to the analyses of the individual trials, but does reiterate the slight advantage provided by salmeterol relative to albuterol.

Serial FEV₁ data following the first dose and after four weeks of treatment in SLGA2004 show that the effect of salmeterol 50 mcg via both DH and MDPI is clinically and statistically superior to placebo. Although neither clinical nor statistical differences between the two active treatments were observed, the MDPI was observed to have a slightly longer onset of action (apparent at Day 1 only), and a slightly greater FEV₁ response in terms of AUC and maximum effect. Peak expiratory flow data corroborated the trend in FEV₁ data which favored the MDPI, but no other secondary endpoints suggested even minor differences between the active formulations.

Overall, the data from each of the three pivotal efficacy trials, as well as the integrated analyses of Trials SLD-311 and SLD-312, indicate statistical and clinical superiority of both the DH and MDPI formulations to placebo. In addition, Trial SLGA2004 provides assurance of the clinical comparability of the DH and MDPI formulations, indicating that the results of SLD-311 and SLD-312 are generally applicable to the MDPI formulation.

9.2 Subgroup Analyses

The pivotal trials, SLD-311 and SLD-312, as well as SLGA2004, were analyzed for important trends among various subgroups. The combined data set for SLD-311 and SLD-312 and for SLGA2004 was analyzed based on serial FEV₁ data for subsets by gender, age and inhaled corticosteroid use. A subset analysis of Caucasian versus non-Caucasian patients was conducted for the SLD-311 and SLD-312 combination data set. Only eight percent (35 of 438) of the population was non-Caucasian, including only three percent of the salmeterol treatment group. No conclusions can be reached due to the small sample sizes of non-Caucasians. Trial SLGA-2004 had only two to nine patients who were non-Caucasian in each treatment group and a subset analysis was not conducted.

Gender

Females represented 41 percent of the total efficacy population for Trials SLD-311 and SLD-312, with similar representation among all treatment groups, and 36 percent of the total efficacy population for Trial SLGA2004, with a slightly greater representation in the DH group. In the combination data set, females had a slightly higher actual (approximately five percent) baseline FEV₁. Post dose on Day 1 and at subsequent visits, males showed a greater mean percent change from baseline. Among the salmeterol treatment group, the difference in response between males and females was approximately five percent, and therefore potentially attributable largely to the baseline difference, except at Week 12. At Week 12, the mean percent change from baseline was up to 10 percent higher among males. The gender discrepancy was also observed, to a lesser degree, among the placebo and albuterol treatment patients.

Statistical analyses of serial FEV₁ data showed that within treatment effects (FEV₁ significantly different than baseline) were evident within the salmeterol group for both genders at all timepoints. Pairwise repeated measures comparisons of treatment effect between salmeterol and placebo was significant for both genders. Among males, salmeterol was favored in pairwise repeated measures comparisons to albuterol, although no difference between the two active treatments was observed for females.

A comparison of the parameters based on FEV₁ in the combination data set indicates that males using salmeterol generally had a faster onset of effect, longer duration of effect, greater maximum effect and higher AUC (BL) than salmeterol-treated females. At Week 12, median onset among males was 0.05 hours, while among females was 1.76 hours. Median duration at Week 12 was 11.4 hours among males and 3.0 hours among females treated with salmeterol. Minimal

discrepancies were noted among the albuterol or placebo groups, but those differences favored males.

No statistical analyses were conducted for SLGA2004, however the serial FEV₁ data for both DH and MDPI formulations, appear to show the same data trend as the combination data set. The same response trend is observed among the placebo patients.

Comment: These data seem to suggest that, particularly in the 12 week trials, a minimal difference in the effect of salmeterol was detected, favoring males. This difference does not appear to have clinical significance, primarily because it is also observed in the placebo and active control treatment arms, albeit to a lesser degree. The factors which may account for this difference are unclear, but it may be attributable a variety of factors such as the generation of variable flow rates through the device or gender differences in study conduct.

Age

The combination data set for SLD-311 and SLD-312, and the data from SLGA2004 were subset into two groups of patients: those under the age of 50 years and those age 50 years and above. The older age group accounted for 12 percent of the population in the combination data set and 16 percent of population in SLGA2004.

Despite the lower predose baseline among the older patients (between two and nine percent lower, depending on treatment group), mean percent change from baseline in serial FEV₁ was relatively comparable among salmeterol patients at each timepoint across all weeks of the trials. Responses to albuterol and placebo were more variable. Albuterol responses tended to favor the younger subgroup, although placebo responses tended to favor the older subgroup. No important statistically significant differences were seen and no consistent trend was observed between the treatment groups for parameters based on FEV₁.

In Trial SLGA2004, the serial FEV₁ data appeared to show no clinically meaningful differences between the responses of the younger and older populations of MDPI users, particularly if the lower baseline for the older population is taken into account. There is a strong trend favoring the younger population among DH users. No statistical analyses were conducted.

Comment: It does not appear that age is a clinically significant determinant of FEV₁ treatment outcomes in these trials.

Inhaled Corticosteroid Use

Baseline values for FEV₁ as a percent of predicted were comparable among the inhaled corticosteroid user and non-user subsets of the three treatment groups. As in the other subgroup analyses, mean percent change from baseline was substantially higher among salmeterol patients than among placebo or albuterol patients, however, no clinically significant difference was seen between the user and non-user subgroups for any treatment. Statistical analyses of these data did not detect meaningful differences between the treatment subgroups. No analysis of the parameters based on FEV₁ was presented.

In Trial SLGA2004, patients using no inhaled corticosteroids had lower baseline FEV₁ as a percent of predicted values (approximately six percent lower) than corticosteroid users among the MDPI treatment group. Post dose values showed comparable differences in mean percent change from baseline values. Differences were not as notable at baseline for the user and non-user populations of the placebo and DH treatment groups and were also not seen in post dose values.

Comment: Use of inhaled corticosteroids does not appear to be a clinically significant determinant of FEV₁ treatment outcomes in these trials.

9.3 Summary of Supportive Trials

As detailed in Section 8.4, dose ranging in this drug development program was not conducted with the to be marketed formulation. Instead, Trials SLGH05 and SLGH07 were conducted using the — standard fill DH formulation to compare doses of 12.5, 25, 50 and 100 mcg. Both trials were inadequately designed to definitively assess the dose response of the MDPI, but both suggested that the 50 mcg dose showed bronchodilatory effects similar to those of albuterol, and exhibited a slower onset and a longer duration of action.

In comparisons of the — standard fill DH to the MDI, Trials SLGH08, SLGH11, and SLGH12, each single dose trials, and SLGH03, a cumulative dose trial, demonstrated the clinical comparability of these devices using FEV₁ and related parameters as primary endpoints. Further, the — standard fill DH was compared to the — standard fill DH in Trial SLGH18. This was in turn compared to the / — reduced fill DH in Trials SLGH28 and SLGH29. Overall, the comparisons of FEV₁ data suggested clinical comparability among the dosage forms. It was the — reduced fill which was then used in pivotal Trials SLD-311 and SLD-312, as well as SLGA2004.

Two crossover comparisons of doses of 50 and 100 mcg of MDPI and reduced fill DH supplement the findings of SLGA2004. While Trials SLGA2001 and SLGA2006 both demonstrated the clinical effectiveness of both dose levels relative to placebo, using FEV₁ bronchodilatory response and PD₂₀ endpoints, respectively, both studies showed data trends which suggested that the least effective dose was the 50 mcg MDPI dose. In some cases, there were statistical differences between the 50 mcg MDPI and other doses. While Trials SLGA2001 and SLGA2006 are less supportive of the comparability of the MDPI and DH than Trial SLGA2004, both failed to show clinically significant differences among the devices and dose levels.

Two additional studies were conducted which link the MDPI and the reduced fill DH formulations. Trial C94-041 suggested that based on pharmacodynamic endpoints, the MDPI has slightly less systemic effect than the DH. This finding is consistent with the outcome of bioavailability comparisons from Trial SLGB1004 which show that the MDPI is less systemically bioavailable. Duration of the bronchoprotective effects of the MDPI were somewhat diminished relative to the DH in Trial 92-043 and are consistent with the existence of minimal, and clinically insignificant, differences between the effectiveness of the formulations.

In Trial FMDT07 and Trial RESB4002, in-vitro simulations of inhalation profiles derived from asthmatic patients were used to demonstrate the ability of low flow rates through the MDPI device to elicit adequate dosing. While severely obstructed patients are likely to generate lower flow rates than patients in the general asthma population, it appears that even severely obstructed patients will be able receive a sufficient proportion of the labeled dose.

Finally, in a completed 12 month trial of the reduced fill DH formulation, Trial SLD-320, methacholine challenges appear to confirm that salmeterol via a dry powder formulation exhibits bronchoprotective effects consistently throughout the duration of the trial.

9.4 Device Performance

The Short Form 36 (SF-36), 3-Item Sleep Scale, the Asthma Quality of Life Questionnaire (AQLQ), as well as patient satisfaction and device handling questionnaires, were used to assess pharmacoeconomic or quality of life effects of salmeterol in a portion of the U.S. trials. In a teleconference on March 11, 1997, the sponsor relayed their conclusion that these data were not supportive of labeling indications or claims, and that they would not be used for advertising purposes. These data have not been reviewed with the exception of the data

related to device handling and patient satisfaction for trials which involved the MDPI device.

In Trial SLGA2004 (Volumes 1.66 and 1.71), device handling was assessed by patients at each clinic visit (Treatment Days 1, 14 and 29). Device handling was assessed by the study coordinator based on the ability to operate the device. Patient satisfaction with the device was rated at the screening and final visits. At screening, patients rated the importance of the following attributes: convenience to carry, durability, ease to load medicine; ease to hold and operate; ease to clean; and ease in telling how many doses are left. At the final visit, patients rated the importance and performance of attributes on a scale of 1 to 5, with the higher score indicating greater importance or better performance. Patients also evaluated the written instructions for each device at screening on a scale of 1 to 6.

Device handling outcomes indicated that not less than 98 percent of patients were able to handle and operate both devices at each clinic visit. Patient satisfaction outcomes at screening related to the importance of the device attributes showed that "convenient to carry", "durability" and "ease to hold and operate" were considered important or very important to 83 percent of the patients. Other attributes appeared to only slightly less important, with the least important feature being "ease of cleaning" (important or very important to 71 percent of patients). Regarding performance of the devices, the percentage of patients with favorable responses, responses of 4 or 5 on the assessment scale correlating to "strongly like" or "like", were tabulated for each device as follows.

<u>Assessment</u>	<u>MDPI</u>	<u>DPI</u>
Like the device	81	52
Comfort of using the device	76	74
Ease of use	92	68
Ease to hold and operate	94	85
Ease in telling number of doses left	96	88
Durability	85	68
Convenient to carry	73	56
Satisfaction	80	57
Ease to load	-	81
Ease to clean	-	76

These data appear to indicate that patients were more satisfied with the MDPI device than the DPI device. Statistical analyses were conducted, with sporadic outcomes favorable to the MDPI. Due to the nature of the data, these analyses do not appear to be helpful in the interpretation of the outcomes. The case report form and patient data listings contain no comment field to accommodate additional data regarding patient experiences with the devices, or to account for the any negative sentiments toward the devices.

Assessment of the written instructions revealed that approximately 45 percent of patients found the instructions for either device to be moderately or very helpful, but approximately 45 to 50 percent of patients did not use the written instructions.

The same patient satisfaction assessment mechanisms were employed in Trials SLGA3010 (Volume 11.7) and SLGA3011 (Volume 11.17) which were 12 week comparisons of the MDI and MDPI formulations. The ratings of importance of the various device attributes were similar to those observed in Trial SLGA2004. Table 9.2 reports the percentage of patients who rated various attributes "like" or "strongly like" for the MDI and MDPI devices at the final assessment in each trial.

Table 9.2 Patient Satisfaction

	Trial 3010		Trial 3011	
	MDPI	MDI	MDPI	MDI
Overall Opinion: Like Device	74	70	73	68
Ease of Use	87	91	91	90
Satisfaction	78	77	74	77
Comfort Using the Device	85	84	83	81
Convenient to Carry	61	72	64	65
Durability	80	77	82	80
Ease to Load	-	86	-	85
Ease to Hold and Operate	89	91	92	93
Ease in Telling Number of Doses Left	91	32	85	48

The MDPI and MDI device appear to perform comparably on most attributes. The MDI appears to be somewhat easier to carry, while patients find it much easier to establish the number of doses remaining with the MDI device.

Assessment of the written instructions in both SLGA3010 and SLGA3011 was similar to that seen with the MDPI and DPI devices in Trial SLGA2004.

Comment: Overall, these data support that patients are able to maintain and operate the MDPI device and that they are satisfied with its performance. These data do not describe individual incidents of product failures and the sponsor should be asked to provide any such available data.

9.5 Efficacy Conclusions

The pivotal trials SLD-311 and SLD-312 adequately establish effectiveness of salmeterol 50 mcg BID via DH formulation relative to placebo and generally support the clinical comparability of this formulation relative to albuterol over a 12 week period. This conclusion is based on spirometric endpoints, as well as supplementary data including PEFR, symptom severity and use of rescue medication. The principal bridging study, SLGA2004, adequately demonstrates comparability of the effectiveness 50 mcg dose of DH and MDPI in a four week comparison. Statistical review by Dr. Gebert was able to establish concurrence with the sponsor's analyses for the primary and some secondary endpoints in these three trials and the statistician agrees with the conclusions presented for these trials.

The supportive dose ranging trials show that development of the DH used in the pivotal trials was based on reasonable comparisons of previous formulations to the DH and to the MDI. Supportive bridging studies SLGA2001 and SLGA2006 were not in complete concordance with SLGA2004, in that they suggested trends favoring the DH formulation. However, these were single dose studies and none of the differences between devices appeared to have clinical significance. Long term trials, with design limitations for the evaluation of efficacy, were supportive of 12 month efficacy.

In subgroup analyses it was shown that age, gender and use of inhaled corticosteroids do not appear to affect clinical efficacy outcomes. In addition, characterization of the device performance in patients with limited ability to generate inspiratory flow was conducted. These trials included actual measurement of flow rates through the device and *in-vitro* simulation of the anticipated particle size distribution using such flow rates. These data appear to suggest that children and severely obstructed patients are able to use the device and receive a sufficient proportion of the labeled dose.

Device handling and patient satisfaction data appear to confirm that both the MDPI and DH devices perform adequately and can be used by the general population. However, the sponsor should provide any available information which describes specific instances of device failure.

Additional consideration will be given to the comparison of the MDI and MDPI devices in an addendum to this review, but the sponsor should be asked to formulate a draft statement regarding the comparison for the labeling.

10.0 Overview of Safety

10.1 Description of Data Sources

Primary Database

In contrast with the sponsor's classification of the safety data, the primary database for safety data for this NDA review is considered to be the U.S. safety data from the chronic dosing studies of adolescents and adults. These studies include Trial SLD-311, SLD-312 and SLGA2004. Each trial was designed with powder formulation and placebo treatment arms. Long term (12 month) safety data from Trial SLD-320, completed in the U.S. and submitted with the 120-day safety update, is considered the primary trial for assessment of extended treatment. The term "primary database" will be used to refer to the combination of Trials SLD-311, SLD-312 and SLGA2004.

Secondary Database

Safety data from acute dosing studies (U.S. and non-U.S.) in adults and adolescents, chronic dosing and long term studies in adults and adolescents (non-U.S.) and pediatric studies (U.S. and non-U.S.) are considered secondary data for adults and adolescents. Several additional trials which were submitted with the 120-day safety update were reviewed. With the exception of Trial SLD-320, considered the primary long-term trial, these studies were limited in size and did not appear to contribute significantly to the safety assessment of salmeterol dry powder. As a result, the sponsor was advised that it was unnecessary to integrate the data into the originally submitted database. Review of the data contained in the 120-day safety update, and the entire secondary database, was conducted primarily to determine whether the types or rates of events were consistent with those seen in the primary database.

The secondary database is comprised of dry powder formulation studies other than those which involved chronic dosing with the lactose blend proposed for marketing in an adult and adolescent population in the U.S. The secondary database includes 17 U.S. and non-U.S. acute dosing trials of adult and adolescent populations (total of 937 patients), 26 non-U.S. trials of adults and adolescents involving chronic dosing (total of 3458 patients), two twelve month trials in adults and adolescents (total of 801 patients) and 16 U.S. and non-U.S. pediatric trials (total of 1509 patients). In addition, a summary of deaths and serious adverse events associated with ongoing studies and studies conducted for local (foreign) marketing purposes has been reviewed.

10.2 Duration of Exposure

Worldwide exposure includes 937 adults and adolescents in acute dosing studies, 4119 adults and adolescents in chronic dosing studies, 752 adults and adolescents in long term studies (exposure of twelve months or more) and 1509 pediatric patients (between the ages of 3 and 11 years). Patients in the long term studies are a subset of those counted in the chronic dosing studies and some patients participated in multiple trials. There were a total of 6453 individuals exposed during these trials; 970 in the U.S. and 5483 outside of the U.S. Of the total exposures, approximately 56 percent (4064 subjects) were to an active salmeterol powder formulation, with a total of 412 patients exposed for at least one year. Eleven percent of the total population (818 subjects) was exposed to the MDPI formulation/device. With the exception of reports of deaths and serious adverse events, no data for patients who have been exposed to the MDPI formulation for one year have yet been submitted to the NDA.

Within the primary database, a total of 661 patients age 12 and older were treated. Of these, there were 71 exposures to MDPI (11 percent), 219 exposures to DH (33 percent), 221 exposures to placebo (33 percent) and 150 exposures to albuterol (23 percent).

10.3 Demographics

The primary database was comprised of 264 females (40 percent) and 397 males (60 percent). Of the females included in these trials, 111 were exposed to an active salmeterol dry powder formulation (42 percent), 24 of whom were exposed to the MDPI (nine percent). Of the males included in these trials, 179 were exposed to an active salmeterol dry powder formulation (45 percent), 47 of whom were exposed to the MDPI (12 percent).

Patients were divided into four age classifications; those between the ages of 12 and 49, those age 50 and older, those age 12 to 64 and those age 65 and over. The number (percentage) of patients in the primary database in each category is listed in Table 10.3 below, followed by the number (percentage of subgroup) of patients who received an dry powder and MDPI formulations.

Table 10.3 Exposure by Age

	Total N (%)	N (%) Dry Powder Users	N (%) MDPI Users
12- 49	569/661 (86)	251/569 (44)	62/569 (11)
≥ 50	92/661 (14)	39/92 (42)	9/92 (10)
12-64	651/661 (98)	285/651 (44)	69/651 (11)
≥ 65	10/661 (2)	5/10 (50)	2/10 (20)

Of the 661 patients in the primary database, 605 (92 percent) were Caucasian, 20 (three percent) were Black and 32 (five percent) were of other ethnic background. This ethnic demographic profile does support vigorous subgroup analyses. The relative ethnic representation in the worldwide database is similar to that of the primary database and fails to provide substantial supportive information.

10.4 Discontinuations

In the primary database, comprised of trials of either 4 or 12 weeks duration, 605 patients (92 percent) completed the trials. Of the 56 discontinued patients, 25 (45 percent) were using a salmeterol dry powder formulation. Seven were using the MDPI. Reasons for discontinuation are provided in the review of the individual trials. Adverse events were the primary reason for discontinuation, but discontinuations due to other reasons (e.g. asthma exacerbation, lack of efficacy, protocol violation, etc) were fairly evenly distributed among the various treatment types. Discontinuations which were attributed to adverse events are discussed in Section 10.6.

Subgroup analyses were not conducted for the primary database. The worldwide database was analyzed for subgroups and does not appear to suggest a correlation between age, gender or ethnic origin and the reason for discontinuation.

10.6 Adverse Events

This section will focus on the adverse events reported for the primary data, but will also selectively address the adverse event rates to be described in the labeling. The primary database consists of data from Trials SLD-311, SLD-312 and SLGA2004. However, due to the differences in design, duration and treatments among these studies, only SLD-311 and SLD-312 will be combined for use in labeling. Because Trial SLGA2004 was the only chronic dosing trial which employed the MDPI formulation, consideration will be given to any inconsistencies in the adverse events data between SLGA2004 and the pivotal trials.

All Adverse Events

In the primary database, 219 patients received 50 mcg doses from the DH formulation BID, 71 patients received 50 mcg doses from the MDPI BID, 150 received 200 mcg albuterol QID and 221 patients received placebo. The overall incidence of adverse events was 58 percent for DH treatment, 25 percent for MDPI treatment, 73 percent for albuterol and 55 percent for placebo. These figures do not represent a true rate, as the exposure of patients in the primary database was variable. In particular, exposure to the MDPI was considerably shorter (approximately four weeks for most patients) than exposure to the DH (approximately 12 weeks for most patients).

Table 10.6A summarizes all adverse events reported in the primary database. Those events with an incidence of less than three percent in either salmeterol treatment group were collapsed into the body system category. Review of the source data revealed that none of the events which are not named specifically in this table appear to add useful information to the evaluation of the adverse event profile.

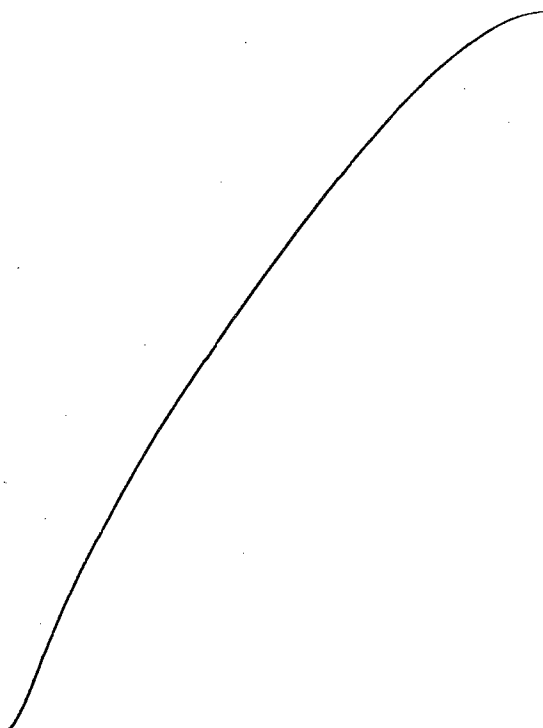
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Table 10.6A Adverse Events from the Primary Database

	Salmeterol MDP	Salmeterol DH	Albuterol	Placebo
Total Patients with ≥ 1 Events (%)	18 (25)	126 (58)	109 (73)	121 (55)
Respiratory (any event)	2 (3)	30 (14)	20 (13)	25 (11)
Bronchitis	0 (0)	9 (4)	5 (3)	7 (3)
Influenza	1 (1)	8 (4)	8 (5)	3 (1)
Cough	0 (0)	7 (3)	5 (3)	6 (3)
Ear, Nose and Throat (any event)	6 (8)	73 (33)	71 (47)	77 (35)
Upper Respiratory Infection	0 (0)	27 (12)	32 (21)	34 (15)
Disease of nasal cavity/sinus	0 (0)	14 (6)	11 (7)	9 (4)
Pharyngitis	1 (1)	12 (5)	10 (7)	12 (5)
Sinusitis	2 (3)	11 (5)	14 (9)	11 (5)
Rhinitis	1 (1)	7 (3)	6 (4)	6 (3)
Nasopharyngitis	1 (1)	6 (3)	8 (5)	4 (2)
Allergic Rhinitis	1 (1)	7 (3)	2 (1)	7 (3)
Neurological (any event)	5 (7)	33 (15)	24 (16)	24 (11)
Headache	4 (6)	22 (10)	18 (12)	16 (7)
Malaise/Fatigue	0 (0)	6 (3)	2 (1)	4 (2)
Cardiovascular (any event)	2 (3)	4 (2)	5 (3)	6 (3)
Gastrointestinal (any event)	1 (1)	17 (8)	16 (11)	20 (9)
Skin (any event)	1 (1)	8 (4)	10 (7)	9 (4)
Musculoskeletal (any event)	4 (6)	19 (9)	14 (9)	10 (5)
Mouth and Teeth (any event)	0 (0)	8 (4)	7 (5)	6 (3)

Table 10.6B summarizes those events which occurred in Trials SLD-311 and SLD-312 with an incidence rate of at least 3.0 percent in the DH treatment group and more frequently in the DH treatment group than in the dry powder placebo group. This data table differs from the sponsor's initial draft labeling in that the sponsor took into account the incidence of adverse events in the albuterol treatment group in compiling their table.

Table 10.6B Adverse Events from Trials SLD-311 and SLD-312 for Labeling



Adverse events reported by less than 3.0 percent of the patients receiving salmeterol DH in the pivotal trials, and by a greater proportion of the salmeterol DH patients than the placebo dry powder patients include the following. The events shown in **bold** have potential to be related to the drug product and should be listed in the labeling:

, sinus headache,
gastritis,

sleep disturbance, paresthesia, ... nt

Comment: The sponsor should be told that this table should be presented in the product labeling without the column related to albuterol treatment. Only percentages, rather than N(%), need to be reported. In addition, the adverse events shown in bold should be reported in the labeling, unless the sponsor can provide reason that they are clearly unrelated to drug use.

The primary long term trial, SLD-320, provided an adverse event profile that was similar to that seen in the pivotal trials, with upper respiratory events and headache as the most prevalent events.

Comment: The adverse events for the primary database and as outlined for the labeling are similar. Given the patient population and drug substance, there appeared to be no unexpected events which were reported at clinically significant rates. Respiratory events showed the highest incidence. Events which occurred with the MDPI did not appear to differ in type or rate from those which were reported in association with DH use and salmeterol did not appear to have a significantly different adverse event profile than albuterol. Finally, the long term trial did not reveal safety concerns which were notably different than in the pivotal trials.

Deaths

Table 10.6C summarizes the total number of deaths which have been reported to date in patients using salmeterol or clinical comparators. The number of cases identified in the original submission is followed, in parentheses, by the number identified in the 120-day safety update.

Table 10.6C Deaths Reported for Salmeterol Formulations, Original Submission (120-Day Update)

	Total	MDPI	MDI	Active Comparator	Unknown
NDA 20-692 (MDPI)					
Clinical Trials					
Foreign	23 (1)	8	11 (1)	3	1
U.S.	0 (1)	1			
Spontaneous		20			
NDA 20-236 (MDI)					
Spontaneous	104 (NR)		104		

In the original NDA submission, there were a total of 23 fatal cases reported in association with the worldwide database of clinical trials involving the powder formulation. These cases include 15 deaths among studies sponsored by local Glaxo Wellcome companies outside the U.S., eight deaths reported from non-U.S. clinical trials sponsored by Glaxo Wellcome in the U.K. and no deaths reported in U.S. trials. Of the 23 deaths reported, eight occurred in patients using a powder formulation of salmeterol, one was using an unknown formulation of salmeterol, 11 deaths were reported in patients using salmeterol MDI as a comparator and three deaths were in patients using other active comparators. The nine deaths which occurred with the powder or unknown formulation were clearly unrelated to salmeterol use in three cases (fatal vertebral injury, cancer of bronchus and metastatic adenocarcinoma). Of the remaining six deaths, four were cardiac in nature (primarily myocardial infarction) and two were cases of acute asthma exacerbation. The 11 cases in patients using salmeterol MDI were similar, with six cardiac deaths, three associated with cancer, one with a road traffic accident, and one case of acute bronchitis.

The 120-day safety update reported two additional deaths which occurred during clinical trials, including one death due to pancreatic cancer in a patient receiving salmeterol MDI and one death in a salmeterol MDPI patient believed to be due to sudden respiratory failure. In the latter case (A0022447), a 41 year old female was receiving 50 mcg BID for the treatment of asthma and was found dead by relatives sixty days after beginning treatment. No additional deaths were reported in the 120 day safety update as part of marketing experience with the salmeterol powder formulation.

Spontaneous reports from the 25 countries in which the MDPI is approved (including Canada) contained 20 additional deaths, submitted with the original NDA. Four cases were considered possibly related to administration of inhaled

salmeterol powder, in nine cases the relationship was thought to be unknown and the remainder of cases were thought to be unrelated. Of the four cases thought to be possibly related to salmeterol treatment, one was a 64 year old male with chronic airways obstruction and ischemic heart disease, one was a 17 year old female with asthma, cor pulmonale and cardiac arrest and the two remaining cases were of respiratory failure/crisis related to asthma in two elderly males, age 65 and 82.

The question of the potential lethality of salmeterol treatment has been evaluated in association with the MDI. A document submitted to the division February 29, 1996 summarized the significant events and was reviewed under the NDA 20-236 for the salmeterol MDI formulation. No update of this submission or report of additional spontaneous reports of deaths associated with the MDI based on marketing experience were reported to NDA 20-692. Overall, no definitive concerns related to the drug substance have been substantiated, due primarily to the limited amount of epidemiologic evidence available with both the MDI and MDPI. Data for the MDPI device do not appear to alter the level of concern which has been raised in association with the approved MDI formulation.

Comment: It appears that the clinical concerns related to the dry powder formulation of salmeterol are consistent with those previously observed with the MDI formulation. While the subject population does experience fatal events in association with their disease state, the potential for salmeterol to increase the rate of lethal events in the asthmatic population remains of concern to the agency. Ongoing surveillance of the serious and fatal events associated with salmeterol will be maintained and will encompass the MDPI formulation data.

Serious Adverse Events

Table 10.6D summarizes the total number of serious events which have been reported to date in patients using a salmeterol powder formulation or relevant clinical comparators. Events which occurred with irrelevant clinical comparators, such as beclomethasone, are not detailed, but are included in the total figures. Figures shown in parentheses are the number of additional events reported in the 120-day safety update.

Table 10.6D Serious Adverse Events

	Total	Salmeterol Powder	Beta Agonist Comparator	Placebo
U.S. Completed Trials (N = 970)	18	10	Albuterol - 2	6
U.S. Ongoing Trials	12 (28)	6 (27)	0	6 (1)
Non-U.S. Completed (N = 5483)	244	145	Albuterol - 50	35
Non-U.S. Ongoing	47 (4)	24 (1)	0	20 (3)
Completed Local Trials	199 (21)	90 (3)	Salmeterol MDI - 66 (16)	42 (1)
PMS Surveillance (Non-U.S., powder)	29 (6)	29 (6)	0	0
PMS Surveillance (U.S., MDI)	149	0	Salmeterol MDI - 149	0
Total	698 (59)	304 (37)	267 (16)	109 (5)

Relative rates of occurrence of adverse events are difficult to compare for the powder formulation versus the MDI and albuterol primarily because of the variation in trial designs and data collection methodologies. Overall, it appears that among the completed U.S. and non U.S. trials, serious adverse events occurred in approximately two to four percent of the population of the completed clinical trials and that salmeterol powder formulations were responsible for approximately 60 percent of the serious adverse events which were reported from those trials. This suggests that salmeterol can not be linked to a high rate of serious event occurrence or to a disproportionate rate of occurrence relative to the other randomized treatments in the completed trials.

The serious events associated with the powder formulation treatment in all of the completed and ongoing U.S. trials, including those reported in the 120-day safety update, totaled 43 cases. Of these, 25 were cases of asthma exacerbation or status asthmaticus, one possible case of subendocardial infarction with EKG T wave inversion, two cases of gastrointestinal/chest pain, one case of depression requiring hospitalization, three cases of cholecystitis and 13 additional cases which appear to be definitely related to other causes.

Review of the serious events from non-U.S. trials and from spontaneous reports from marketing of the powder formulation outside the U.S. (original and 120-day safety update) indicates that the nature of the cases described are not dissimilar to those observed in the U.S. trials. The majority of serious events were related to

asthma exacerbations. Those events which were assessed by the investigator/sponsor to be of almost certain, probable or possible relationship to use of a salmeterol powder formulation included asthma exacerbation (35 events), cardiovascular events (12 events), skin reactions (5), headache (2 events), polyneuropathy (2 events), muscle cramps (1), and grand mal convulsion (1 event).

Discontinuations due to Adverse Events

In the primary database, there were 17 discontinuations due to adverse events, 30 percent of the total number of discontinuations. Of the 17, 10 patients (59 percent) discontinued from salmeterol dry powder therapy and two patients (12 percent) discontinued from MDPI therapy. These events are detailed in the individual study reports. Review of these events in the primary and secondary database revealed that they do not appear to supplement the analysis of the serious adverse event database.

Pregnancies

A total of 35 pregnancies have been reported to the NDA, including 20 among women receiving salmeterol powder formulations, 11 among women receiving salmeterol MDI and 4 receiving other active comparators or placebo. Of 31 women who received salmeterol formulations, 15 used the DH formulation, 12 used the MDI and 4 used the MDPI. Minimally eventful pregnancies and birth of a healthy infant was reported in 22 cases. Outcomes were unknown in two additional cases. Of the remaining seven cases, spontaneous abortion was reported in two cases, and miscarriage, ectopic pregnancy, pre-eclampsia forcing a cesarean section, a missed spontaneous abortion, and death of a fetus in a twin pregnancy were also reported. Incidence appeared to be distributed proportionately with the type of formulation used and the events were considered unlikely to be related to salmeterol treatment.

Demographic Subgroups

Because of the disparity of exposure time and trial design issues, the occurrence of adverse events was summarized by age classification, gender and ethnic origin for the adult and adolescent chronic dosing studies in the worldwide database, a reasonable representation of the entire database. In this database subset, approximately 53 percent of the exposures were in males and 47 percent in females. Patients aged 12 to 49 received 70 percent of the exposures, with the remainder of exposures in patients over 50 years. Approximately 95 percent of this database was Caucasian, with one percent being Black and the remainder

being of other ethnic origin. Table 10.6E summarizes the percentage of each subgroup who experienced common adverse events for the 50 mcg salmeterol MDPI dose. It appears that these demographic parameters have minimal effect on the incidence of these events. Ethnic origin may be associated with differing rates, but given the small number and heterogeneity of the "other" designation, it is not possible to conclude an association.

Table 10.6E Adverse Events by Demographic Factors, 50 mcg MDPI Dose

	All Respiratory	All ENT	Headache
Gender			
Male	15	16	6
Female	20	19	9
Age			
12-49	19	18	9
50 +	16	16	6
Ethnic Origin			
Caucasian	17	17	8
Black	20	20	0
Other	38	29	8

Withdrawal Effects

As stated in Section 8.1.7.13, the sponsor did not provide a description of the PEFR and symptom score outcomes of the one week post treatment period in study reports of Trials SLD-311 and SLD-312, but will be asked to do so. For the purposed of the ISS, the sponsor provided a tabulation of asthma exacerbations and adverse events which occurred during the follow-up period. During treatment, the percentage of patients who had at least one asthma exacerbation was 15, 16 and 14 percent for the salmeterol, albuterol and placebo groups, respectively. In the one week following treatment, 5, 1 and 3 percent of each of the groups experienced at least one asthma exacerbation. These data appear to suggest a relatively greater incidence of asthma exacerbation among the salmeterol patients, particularly relative to the albuterol group. The rate of other adverse events appears comparable among the three treatment groups in the post treatment period.

Comment: It is difficult to discern how reliable this finding may be, particularly without the benefit of a more objective measure of lung function such as PEFR. Additional consideration should be given to the possibility of withdrawal concerns upon receipt of the complete dataset for these trials.

Use of Inhaled Corticosteroids

Adverse events which occurred in Trials SLD-311 and SLD-312 were tabulated based on concomitant use of inhaled corticosteroids. The percentage of patients who experienced the most common events are summarized in Table 10.6F for each treatment. Overall, it does not appear that use of corticosteroids had an significant effect on the occurrence of adverse events, particularly among salmeterol patients. These data may be somewhat influenced by the imbalance in the number of corticosteroid users per treatment group in Trial SLD-311.

Table 10.6F Adverse Events by Use of Inhaled Corticosteroids

	Salmeterol	Albuterol	Placebo
All Respiratory			
Non-User	20	15	16
User	18	12	14
All ENT			
Non-User	41	44	44
User	44	26	23
Headache			
Non-User	13	17	9
User	13	6	9

10.7 Cardiovascular Effects

Electrocardiographic Effects

Among the database for Trials SLD-311 and SLD-312, eight EKG abnormalities were considered clinically significant. Four patients had pre-existing cardiac conditions (Wolfe-Parkinson White Syndrome or mitral valve prolapse) or pre-treatment abnormalities, two patients were on placebo treatment and one patient was using albuterol. The single patients who developed EKG abnormalities during salmeterol treatment was #309, a 50 mcg DH recipient in Trial SLGA2004. This patient was reported to have had premature supraventricular complexes 1.5 hours after dosing at Week 4. A repeat EKG five hours later was normal without therapeutic intervention, however, the event was considered drug-related by the investigator.

QTc

In Trials SLD-311 and SLD-312, seven, three and five percent of patients in the salmeterol, albuterol and placebo groups, respectively, with QTc intervals longer than 440 msec. Postdose on Day 1, these values were five, four and three

percent for the three groups, respectively and at Week 12 the percentages were five, three and one percent. Overall, the proportion of patients with QTc values greater than 440 msec did not appear to reflect a treatment-related change. Mean QTc values also failed to indicate a treatment-related effect.

Data from Trial SLGA2004, however, appeared to suggest that the DH and MDPI formulations were correlated with an increased percentage of patients with QTc values greater than 440 msec over time. At screening, there were three, four and seven percent of patients with high values in the MDPI, DH and placebo groups, respectively, while at Day 29 there were eight, nine and five percent. However, patients with intervals prolonged to longer than 460 msec numbered only one in each group. Overall, there does not appear to be a clinically significant effect of salmeterol on QTc.

Vital Signs

The vital sign data from the primary database and Trial SLGA2004 are remarkable only for their consistency in the demonstration of minimal effects of salmeterol on pulse rate and systolic and diastolic blood pressure. Overall, there was a trend toward minor increases in pulse rate and minor reduction in diastolic blood pressure. These trends did not appear to have clinical significance.

Trial C94-041 was a cumulative dose comparison of up to 400 mcg in 18 healthy volunteers. It showed no difference in effect of the MDPI and DH formulations on vitals signs.

10.8 Clinical Laboratory Findings

The sponsor analyzed a combined data set of Trials SLD-311, SLD-312 and SLGA2004 to evaluate effects on clinical laboratory parameters. Shift analyses of hepatic function, glucose and potassium, and threshold evaluations for clinical chemistry, hepatic function, renal function and hematology parameters revealed no treatment related trends, with one exception. Glucose values appeared to be increased to a greater extent with MDPI treatment than with DH or albuterol. Clinically significant changes in these trials included a single patient in Trial SLD-311 (233) and in Trial SLD-312 (79) who were reported to have elevated liver enzymes during treatment with salmeterol and a single SLD-312 patient (194) was found to have elevated glucose levels.

The results of the long term trial SLD-320 did not appear to have any salmeterol-related effects on clinical laboratory parameters. Finally, Trial C94-041, a cumulative dose comparison of up to 400 mcg in 18 healthy volunteers, showed a statistically lower plasma potassium associated with DH administration than with

MDPI administration and this effect appears to be consistent with the drug class and with relative systemic bioavailability of salmeterol from these formulations.

10.11 Safety Conclusions

The primary safety database, Trials SLD-311, SLD-312 and SLGA2004, with long term trial SLD-320, adequately establish the safety profile of the DH and the MDPI formulations. The worldwide database, which includes numerous clinical trials, as well as marketing data from the 25 countries in which the MDPI is approved, supplemented the primary database. Overall, safety from the exposure of over 4,000 patients to a salmeterol dry powder formulation was described.

The safety data were generally consistent with the known pharmacologic profile of salmeterol. The most frequently reported adverse events are consistent with the disease states of the subject population, most notably respiratory events and ENT events associated with asthma and allergy. Headache and cardiovascular events were also seen at expected rates. A total of 45 deaths were reported worldwide, with only one of these deaths having occurred in the U.S. No deaths definitively linked with the use of a dry powder formulation. Serious adverse events were primarily associated with asthma exacerbations, as expected in the subject population. Other events which may have been associated with dry powder use include various cardiovascular events, allergic-type skin reactions, headache, muscle cramping, polyneuropathy and grand mal convulsion, each consistent with the pharmacologic activity of the drug substance. The overall incidence of these events was very low.

In subgroup analyses, age, gender, ethnic origin and use of inhaled corticosteroids did not appear to be correlated with adverse event frequency. No effect of the test drug on pregnancy outcomes could be described. Rate of asthma exacerbation may have increased upon discontinuation of salmeterol and additional analyses will be requested from the sponsor to complete a final determination.

Salmeterol did not appear to have a clinically significant effect on EKGs, including QTc, vital signs or clinical laboratory data.

11.0 AUDIT FUNCTIONS

This medical reviewer accompanied Mr. Mike Rashti of the Philadelphia FDA field office to conduct the inspection of Trial SLGA2004 conduct at Chester, PA. Dr. Anthony Rooklin was the principal investigator at this site. In addition to assessment of protocol compliance, line listings supplied with the original NDA submission were compared to the investigator records. A three-item FDA-483 was issued to the investigator upon completion of the inspection, citing minor deviations from the protocol and record deficiencies.

The case report forms of patients who died, or were discontinued prematurely due to adverse events, from Trials SLD-311, SLD-312, SLGA2004 and SLD-320 were reviewed and found to be consistent with the sponsor's case narratives and adverse event coding.

12.0 SUMMARY AND CONCLUSIONS

The major objectives of this review were twofold. The first was to determine whether the two pivotal, 12 week clinical trials, SLD-311 and SLD-312, supported the safety and efficacy of the Rotadisk/Diskhaler (DH) formulation of salmeterol in doses of 50 mcg BID. In support of this objective, Trial SLD-320 served as the primary investigation of long term safety of the dry powder formulation. Based on FEV₁ and other spirometric endpoints, the DH formulation was found to be statistically and clinically superior to placebo. In addition, the performance of salmeterol via DH was characterized relative to albuterol MDI and the differences noted were primarily due to the variation in duration of action of the drug substances. The safety profile of the DH formulation was found to be consistent with the known pharmacologic profile of salmeterol and did not provide for unanticipated types or rates of events.

The second objective of this review was to determine from Trial SLGA2004 whether the DH formulation was clinically comparable to the formulation which the sponsor now wishes to market, the multiple dose dry powder inhaler (MDPI). These data revealed that on most efficacy endpoints, both spirometric and general clinical parameters, the MDPI formulation appeared comparable or minimally superior to the DH formulation. The safety profile of the MDPI and DH formulations were comparable.

There were numerous trials submitted which contributed to the overall assessment of the DH and MDPI formulations. Among these were Trials SLGA2001 and SLGA2006. These single dose trials were not supportive of the marginal superiority of the MDPI formulation seen in SLGA2004. They were suggestive

that the onset and duration of the DH formulation was minimally superior at the 50 mcg dose, however, the differences between the treatments were small and not clinically significant. Other supportive trials addressed the dose ranging for the dry powder device, cumulative dose effects, inhalation challenge models and the ability of patients generating low inspiratory effort to use the device. The data were generally favorable for the MDPI. Cumulative dose studies appear to be supportive of the pharmacokinetic finding of increased systemic bioavailability associated with the DH relative to the MDPI.

Submissions of comparative trials of the MDPI and MDI formulations will be reviewed in an addendum to this document in order to construct a statement regarding their comparability for the labeling. The approval of the MDPI product is not dependent on the outcome of these trials, although findings may affect the final labeling of the MDPI product.

13.0 LABELING

The proposed labeling was reviewed for its general consistency with the submitted data, as well as its consistency with the labeling of the approved salmeterol metered dose inhaler (MDI). The labeling is largely adapted from the MDI format and the comments generated at this time are identified in the following section. It is noted that reference to exercise induced bronchospasm (EIB) does not appear in the MDPI labeling, as EIB was not studied during the development program. The onset of action was adjusted based on clinical trial data for the DH formulation. It is noted that the proposed compilation of adverse events contained in the labeling is not based on the same incidence rates as the tables compiled in this review. Rather, the table is compiled based on the scheme used for the MDI labeling. Until the MDPI and MDI comparison trials have been reviewed, the proposed format is acceptable. No claims related to pharmacoeconomics or quality of life data appear in the draft labeling.

14.0 RECOMMENDED REGULATORY ACTION

At this time, the NDA is clinically approvable. The following comments should be forwarded to the sponsor to assist in finalization of the labeling.

1. Please provide an analysis of the PEF and diary data which were collected during the study period post-Week 12 in Trials SLD-311 and SLD-312.
2. We request that you submit the final study report for Trial SLGA3009 to this NDA as soon as it becomes available.

3. Submit any evidence of failure of the Diskus or Diskhaler/Rotadisk devices in clinical trials or general clinical use.
4. Please provide any available information regarding use of the Diskus with a spacer device.
5. Please submit draft statement which describes the clinical comparability of the MDPI and MDI salmeterol formulations.

15.0 APPENDICES

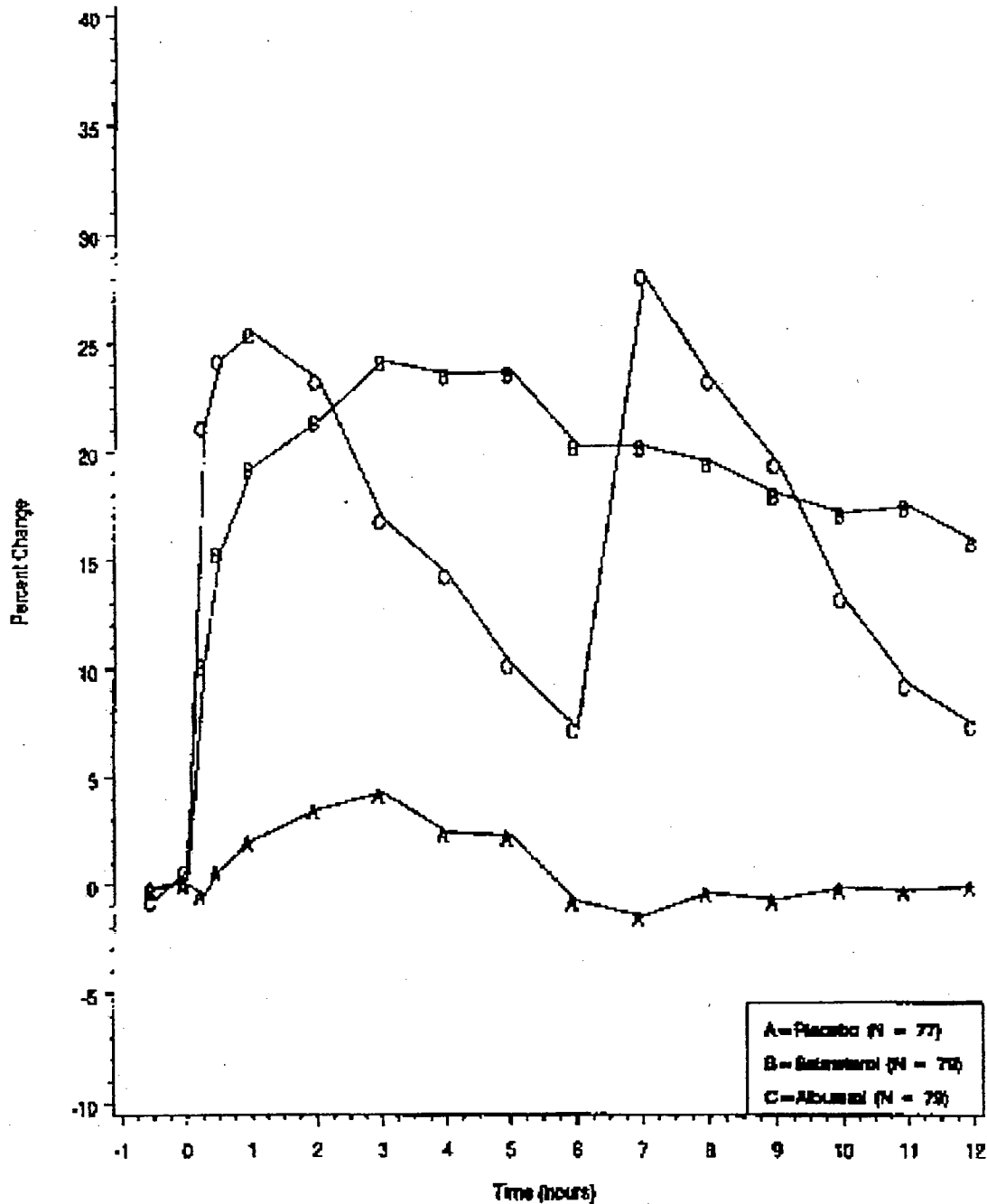
Appendices 1 through 18 appear in numerical order beginning on the following page.

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APPENDIX 1

Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 19
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Day 1

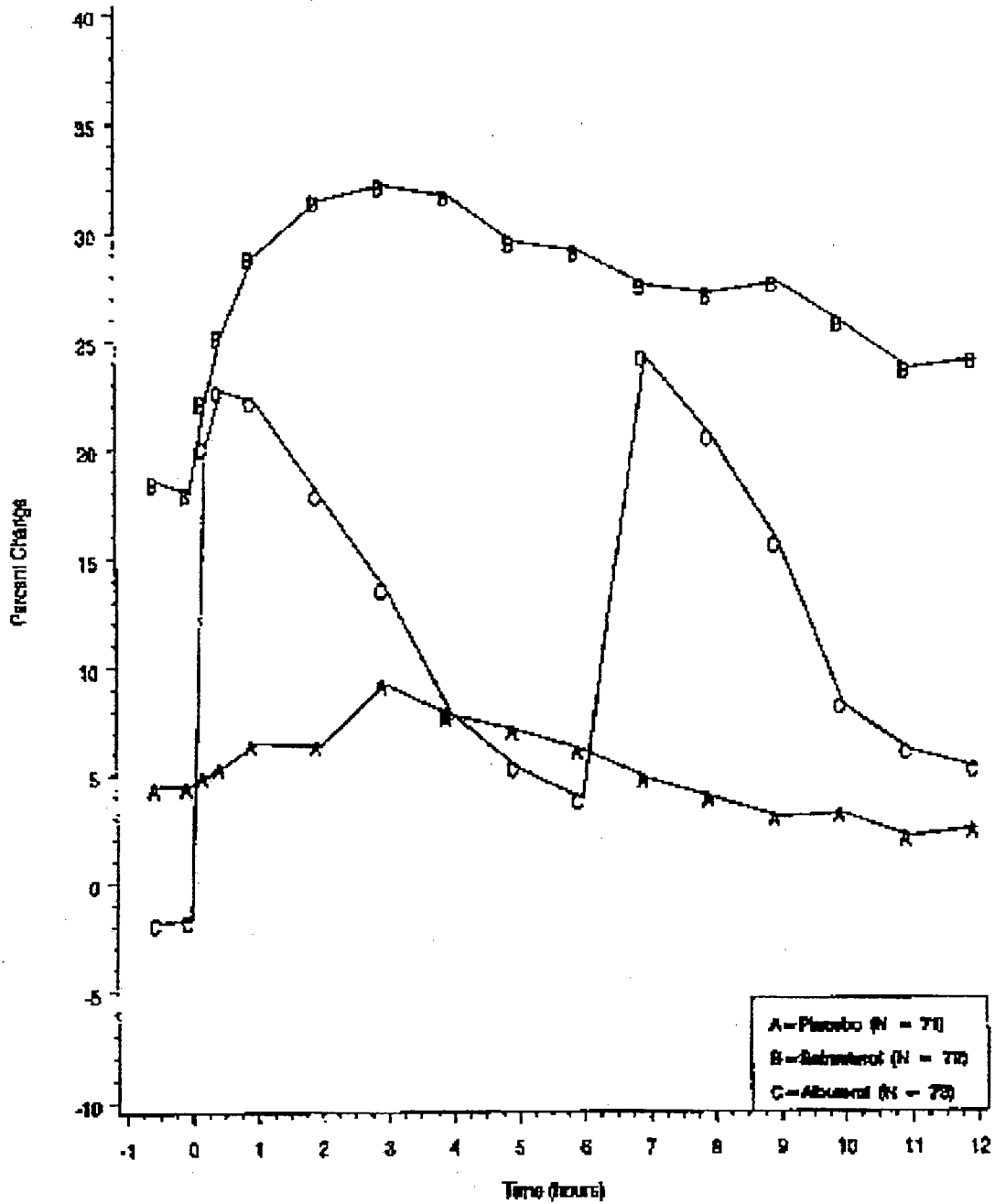


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APPENDIX 2

Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 14
FEV₁: PERCENT CHANGE FROM BASELINE
Treatment Week 4

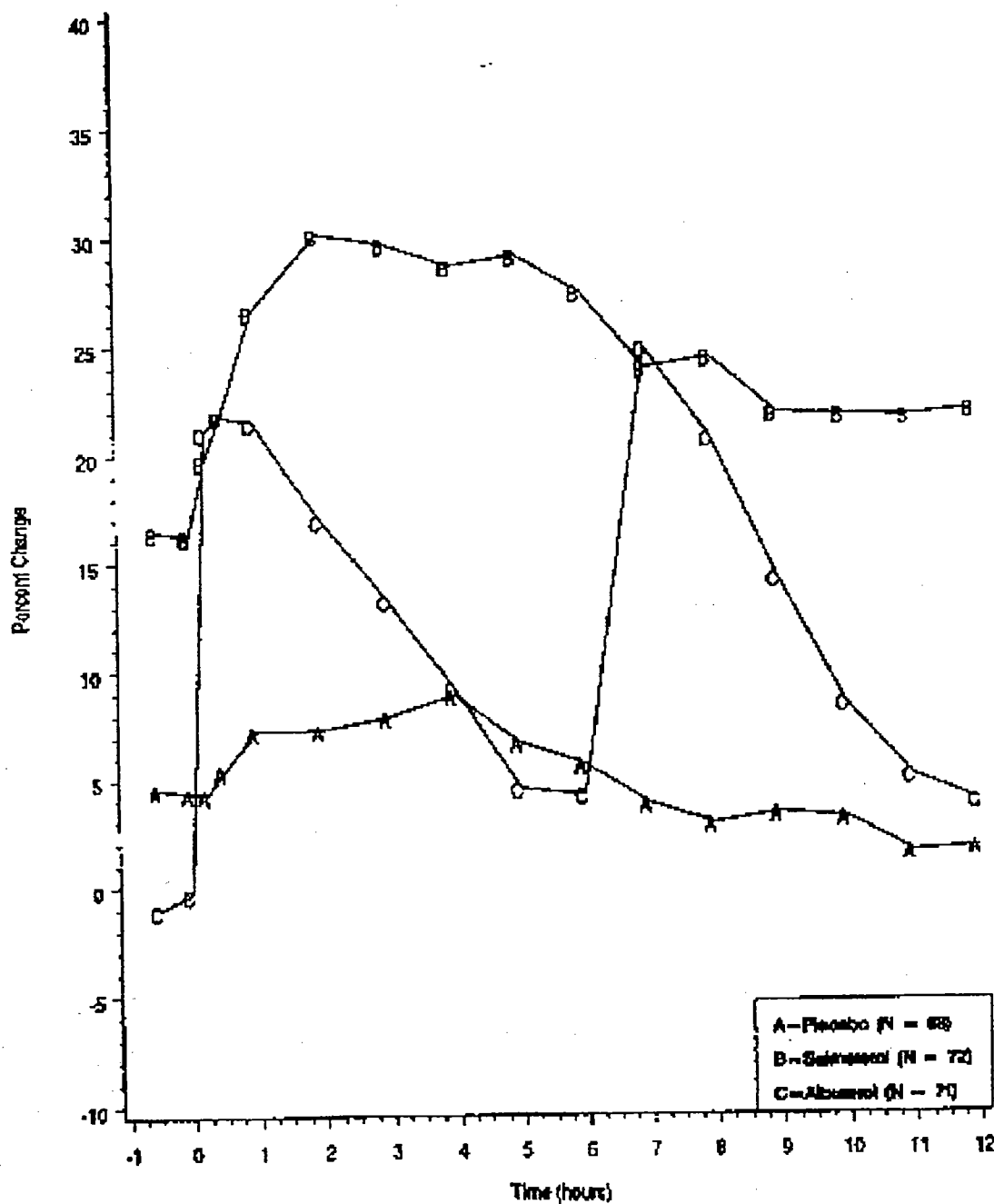


PAGE 10

APPENDIX 3

Salmeterol Xinafoate Powder
Protocol: SLD-316
Population: Efficacy

FIGURE 15
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Week 8

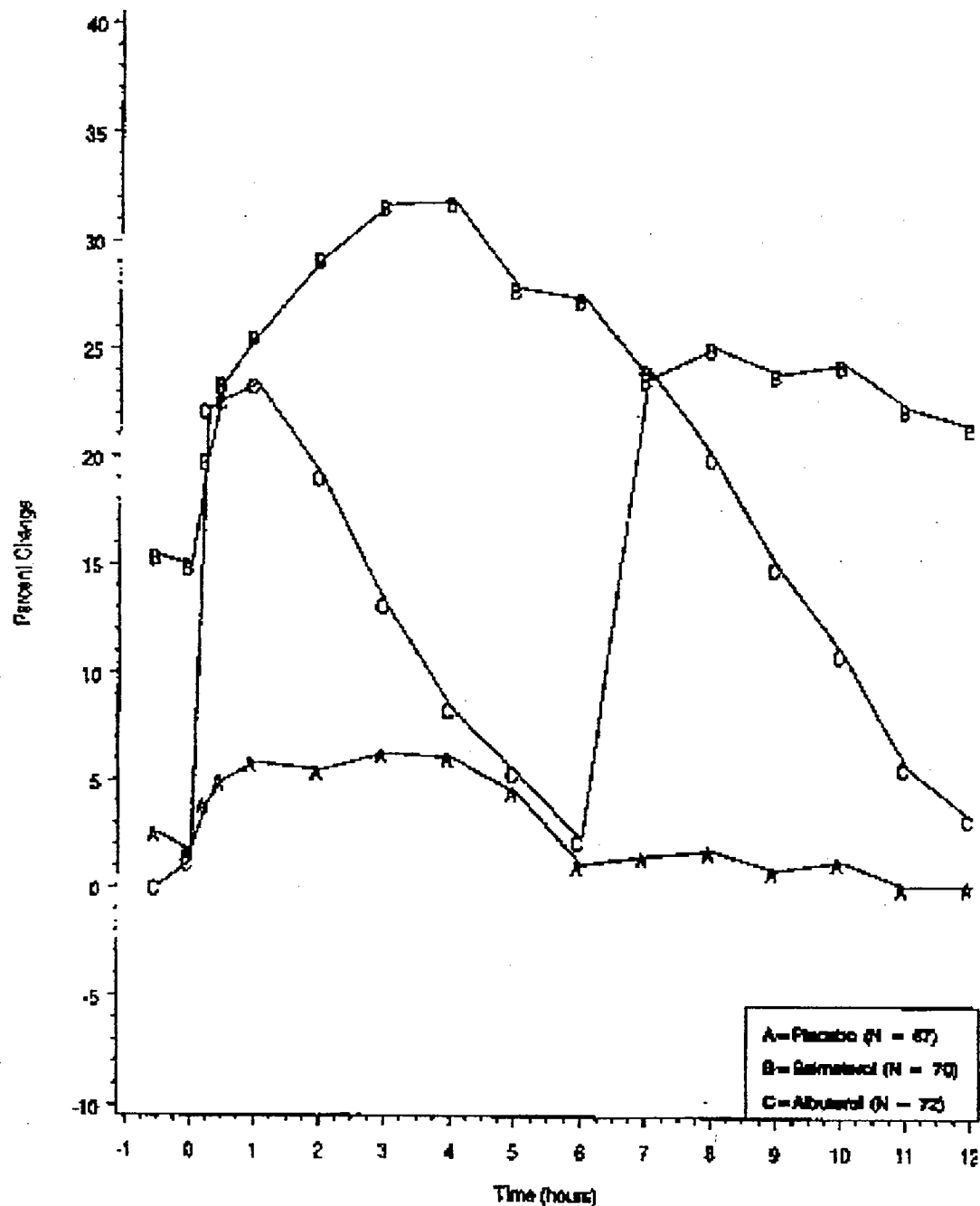


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APPENDIX 4

Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 16
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Week 12



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Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

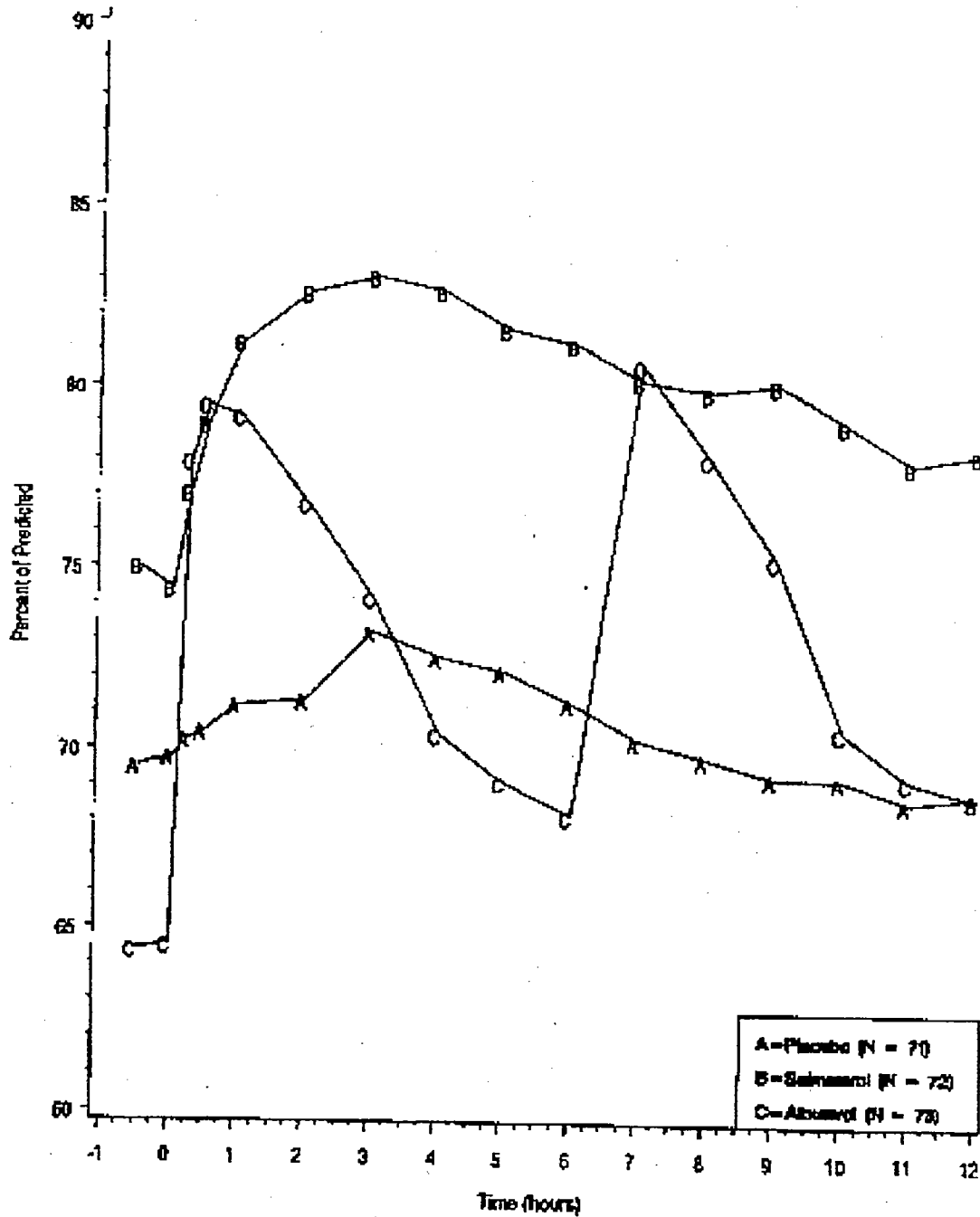
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APPENDIX 6

Salmeterol Xinaolone Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 18
FEV1: PERCENT OF PREDICTED
Treatment Week 4



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Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

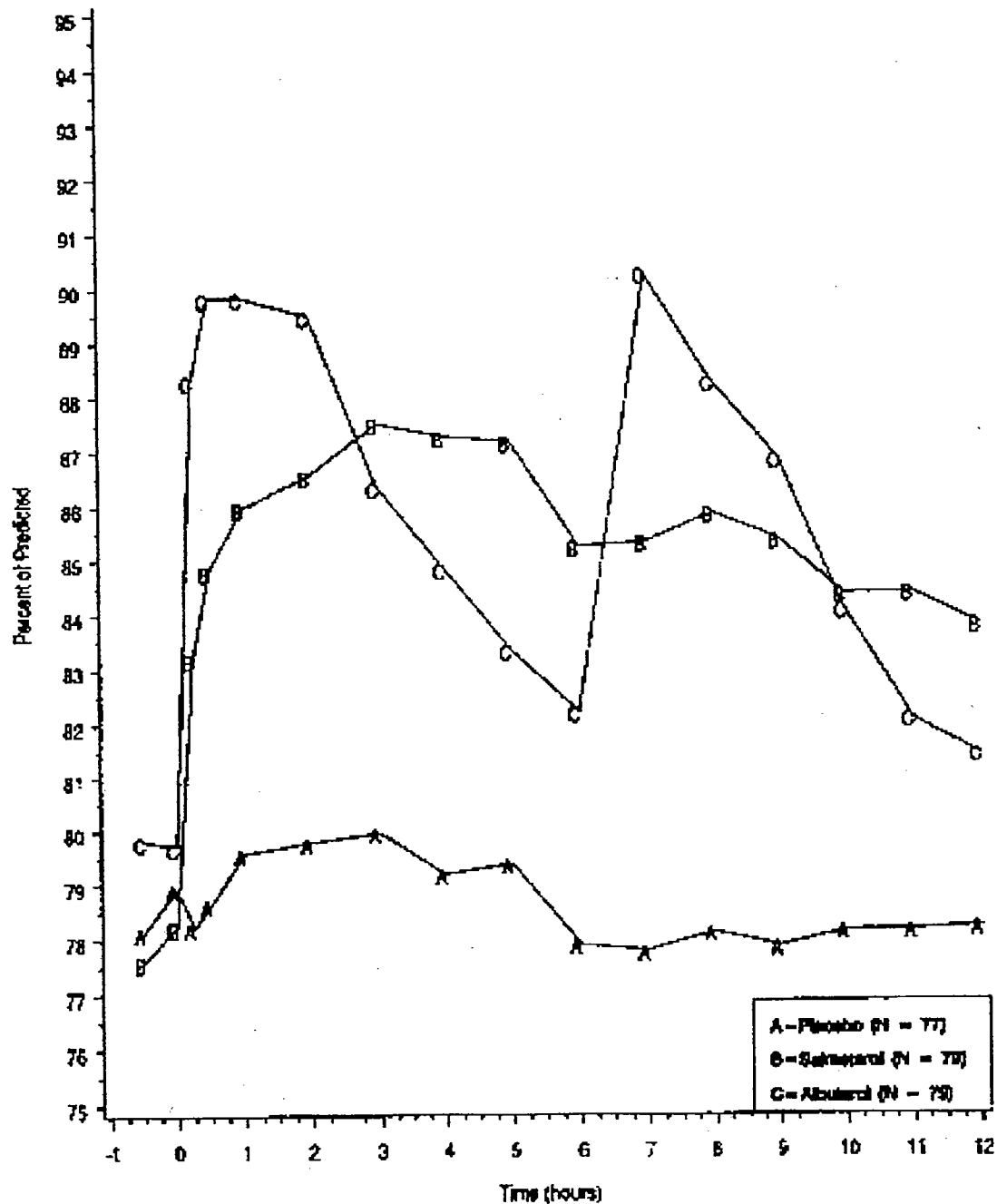
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APPENDIX 8

Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 25
FVC: PERCENT OF PREDICTED
Treatment Day 1

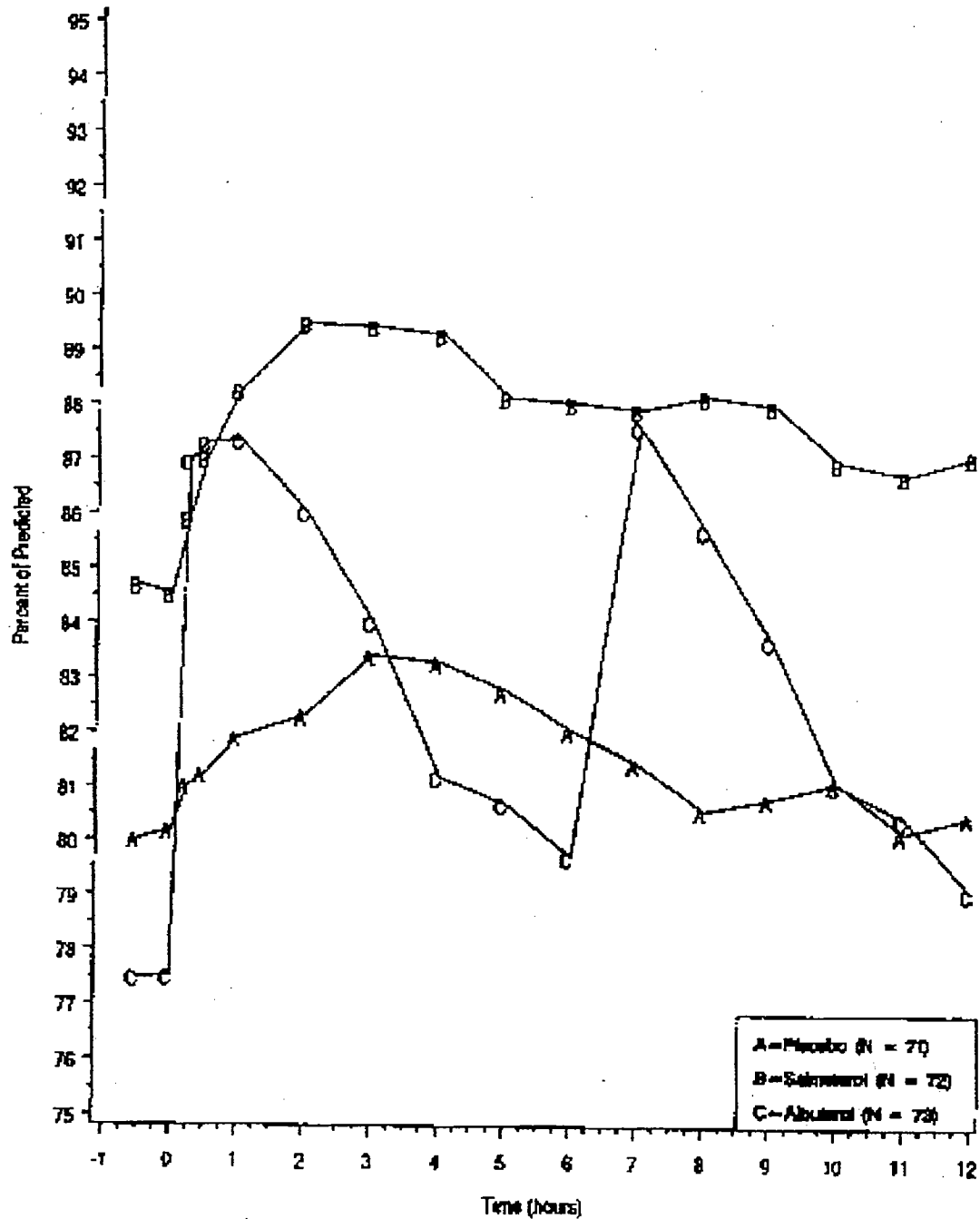


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APPENDIX 9

Salmeterol Xinafoate Powder
Protocol: SLD-SH
Population: Efficacy

FIGURE 28
FVC: PERCENT OF PREDICTED
Treatment Week 4

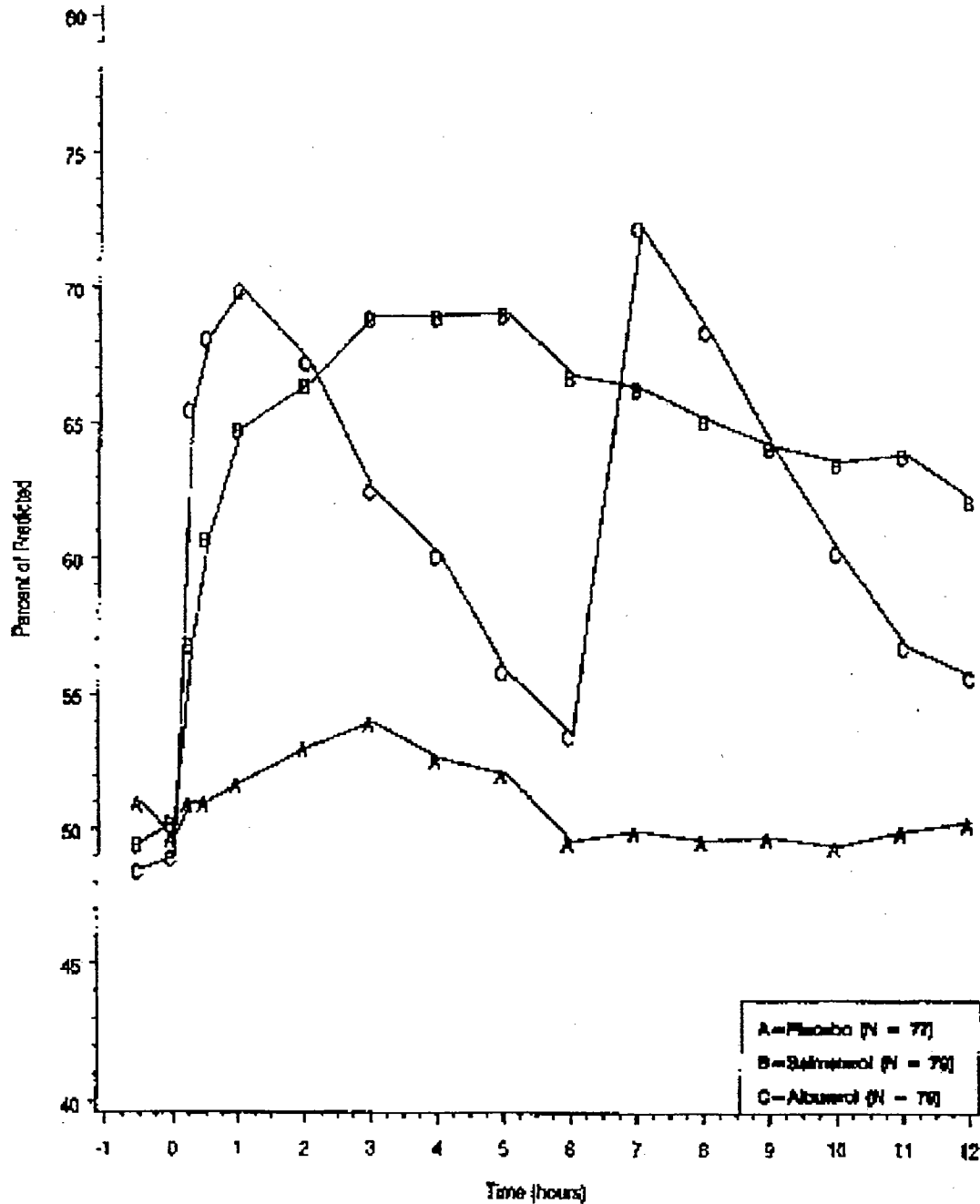


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APPENDIX 10

Salmeterol Xingstone Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 21
FEF: PERCENT OF PREDICTED
Treatment Day 1

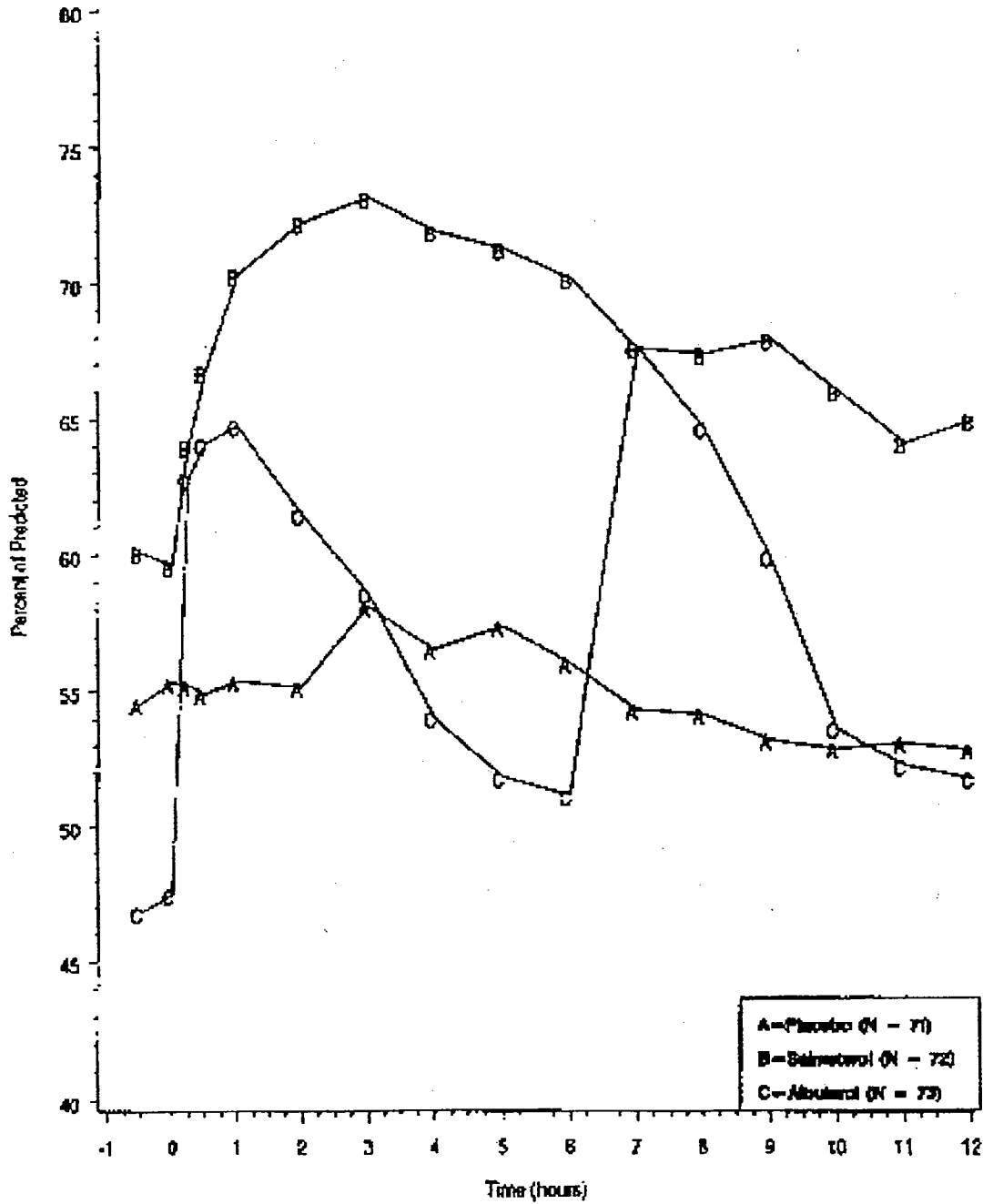


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APPENDIX 11

Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 22
FEF: PERCENT OF PREDICTED
Treatment Week 4



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Salmeterol Xinafoate Powder
Protocol: SLD-312
Population: Efficacy

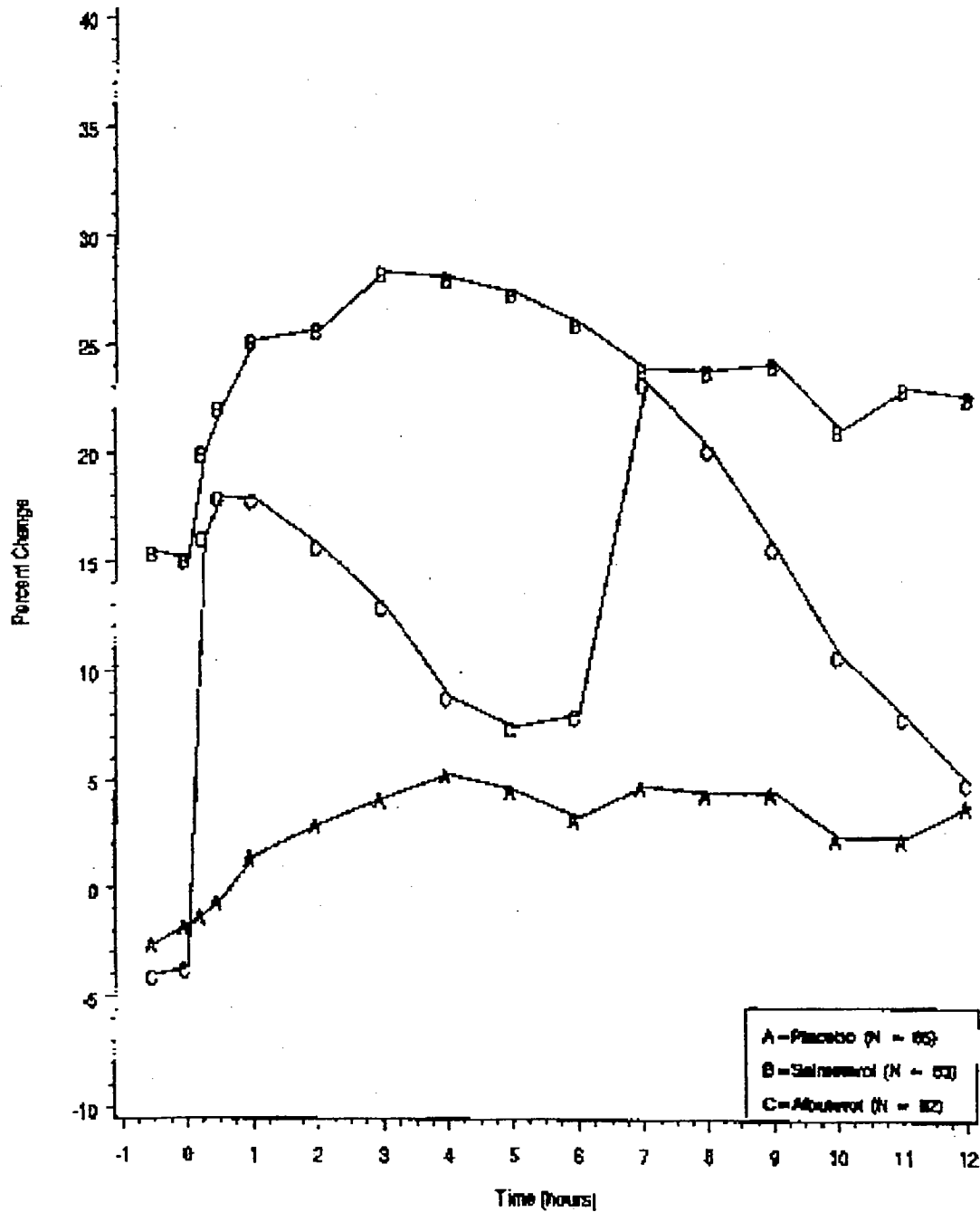
Time (hours)	A-Placebo (N=80)	B-Salmeterol (N=80)	C-Abuseol (N=80)
-1	-0.5	-0.5	-0.5
0	0.5	0.5	0.5
1	5.0	18.0	22.5
2	6.5	23.0	19.5
3	8.0	24.5	16.0
4	7.8	24.0	13.5
5	8.8	23.0	11.0
6	9.0	22.5	8.5
7	6.0	21.5	26.0
8	6.0	20.5	25.0
9	5.0	21.0	18.5
10	4.5	19.0	12.5
11	4.5	19.5	10.5
12	4.0	19.5	10.0

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APPENDIX 13

Salmeterol Xinafoate Powder
Protocol: SLD-312
Population: Efficacy

FIGURE 14
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Week 4



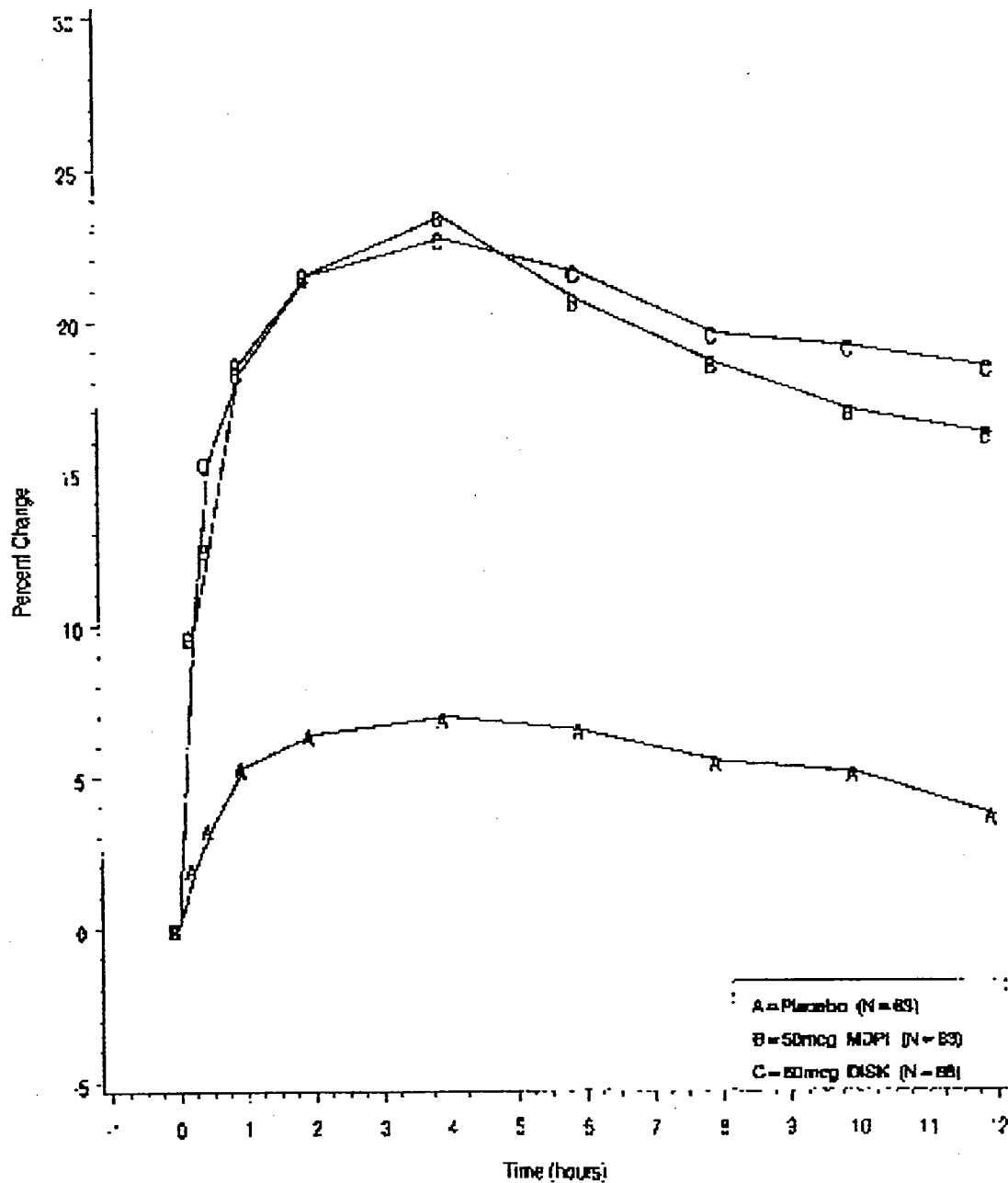
UNDA/USK/STAT SLD-312/22 BASELINE/AN/IMP/CT/04/04 PM 2:44

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APPENDIX 14

Salmeterol Xinafoate MDPI
Protocol: SLGA2004
Population: Efficacy

FIGURE 5
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Day 1

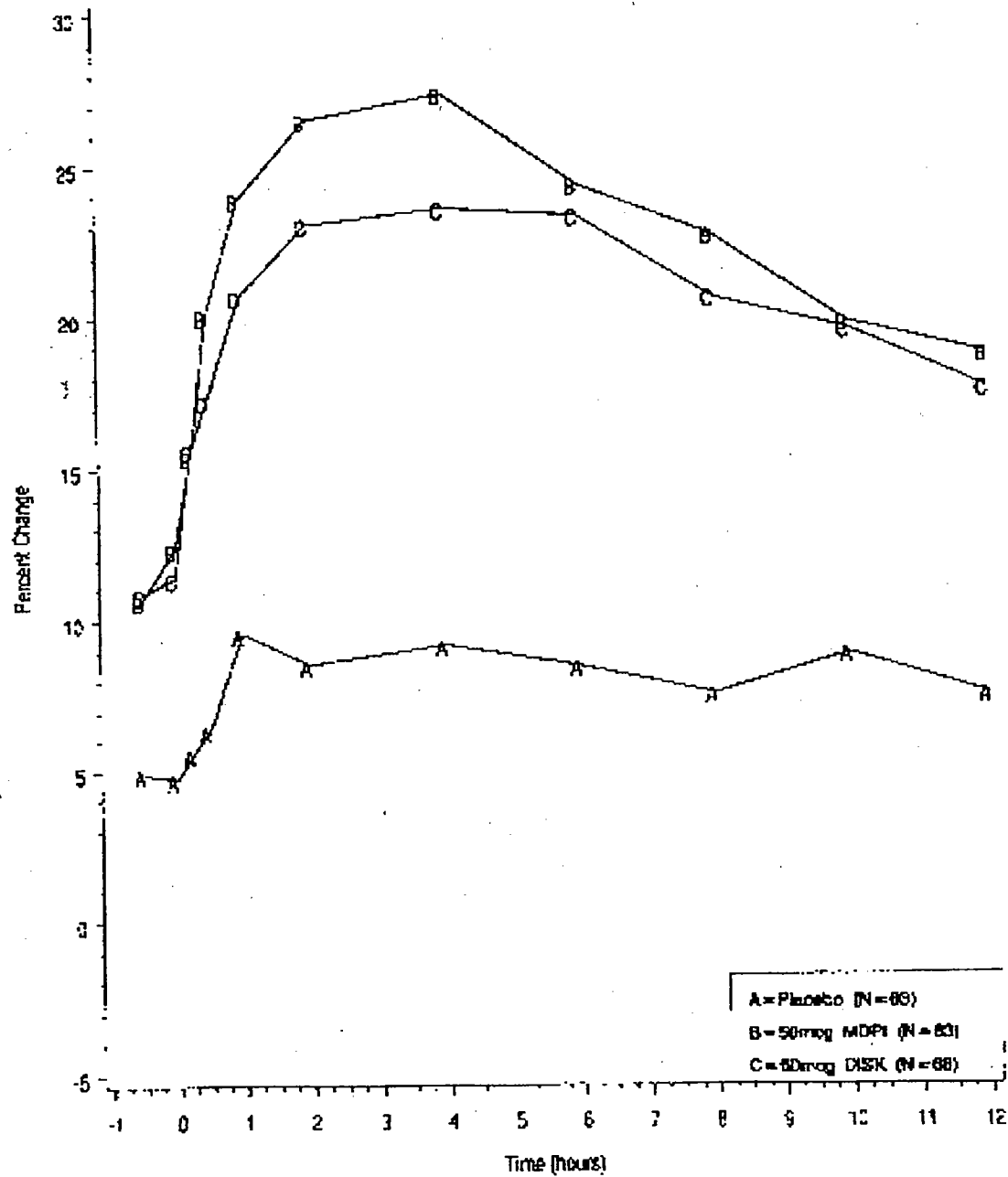


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APPENDIX 15

Salmeterol Xinafoate MDPi
Protocol: SLOA2004
Population: Efficacy

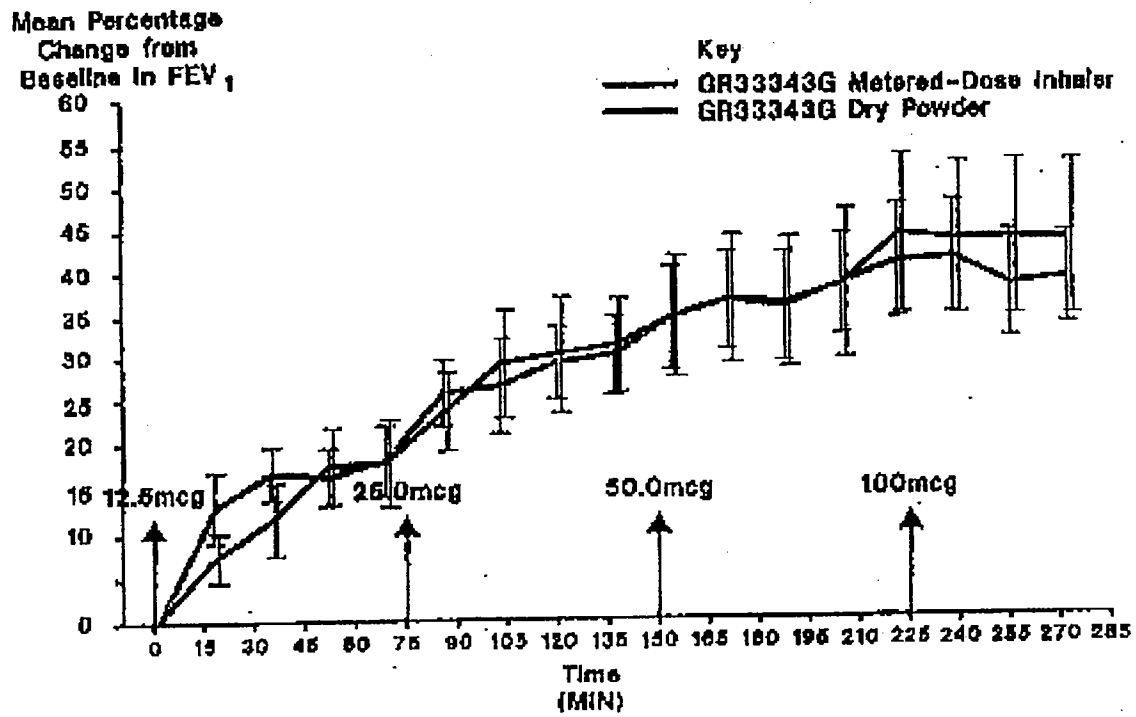
FIGURE 6
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Day 29



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APPENDIX 16

MEAN PERCENTAGE CHANGE IN BASELINE IN FEV₁ FOR EACH TREATMENT

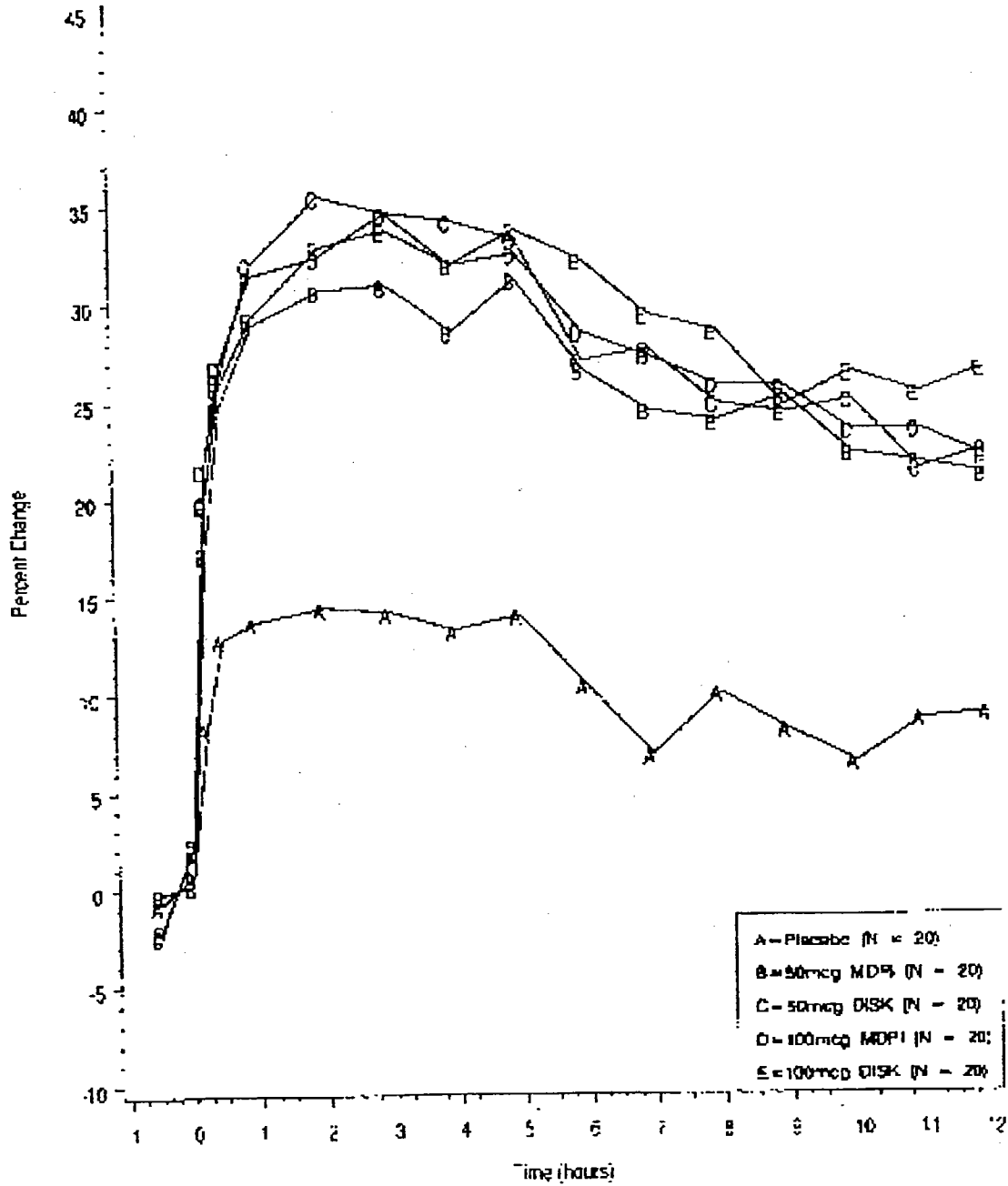


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APPENDIX 17

Salmeterol Xinafoate MDPi
Protocol: SLGA2001
Population: Intent-to-Treat

FIGURE 3
FEV1: PERCENT CHANGE FROM BASELINE



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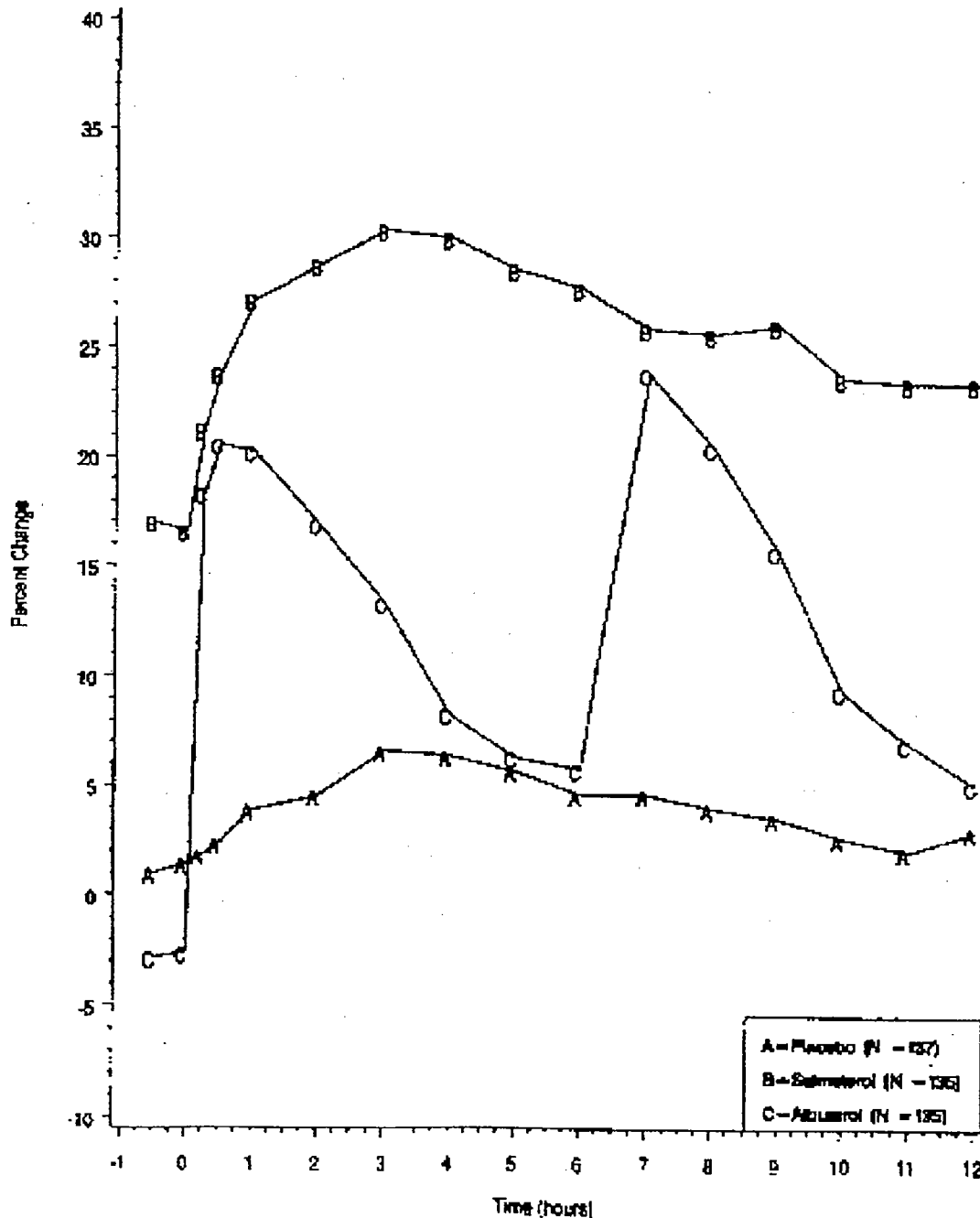
APPENDIX 18

Salmeterol Xinafoate Powder
 Protocols: SLD-311 and SLD-312
 Population: Efficacy

Figure C1 (continued)

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 4



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MEDICAL OFFICER FILING REVIEW

NDA #: 20-692
SPONSOR: Glaxo Wellcome
PRODUCT NAME: Serevent Diskus Inhalation Powder (MDPI)
DATE OF SUBMISSION: June 19, 1996
DATE OF REVIEW: July 15, 1996

A pre-NDA meeting for this submission was held on September 18, 1995. The requirements from the division and other agreements related to the clinical portion of the application are outlined. The development program was primarily conducted on the Diskhaler/Rotadisk (DPI) device, rather than the Diskus (MDPI) device. The DPI device uses foil disks with either — cells containing drug substance, while the MDPI contains a foil cell strip of 28 or 60 cells. In addition, part of the development program was completed with the standard fill formulation of the DPI (50 mcg of salmeterol with lactose fill to —) and the remainder was completed with the reduced fill formulation DPI (50 mcg salmeterol with lactose fill to 12.5 mg) or with the MDPI, which uses the reduced fill formulation only.

Clinical Trials

The pivotal safety and efficacy trials are SLD-311 and SLD-312. These 12-week trials were conducted with the DPI rather than the MDPI device. Both were conducted in the U.S. using the DPI, reduced fill formulation. Each trial included an albuterol MDI control arm without a salmeterol MDI arm.

At the request of the division, the sponsor conducted an additional 4-week safety and efficacy trial in the U.S., SLGA2004, designed to examine patient use and misuse of the MDPI, over the life of the device.

No dose ranging trials were conducted for the MDPI. Dose ranging is based on non-U.S. trials of the DPI, both standard and reduced fill. This is acceptable provided that appropriate clinical comparability between the two devices is demonstrated. The basis for clinical comparability are four primary studies which compare the reduced fill DPI and the MDPI: SLGA2001, SLGA2004, SLGA2006, and C94-041. SLGA2001 and SLGA2006 are single dose U.S. studies and C94-041 is a non-U.S. study.

Comparative pharmacokinetic data were required for the reduced fill MDPI versus the reduced fill DPI and the MDI, including time to peak and peak plasma concentration. Results of this trial will be submitted by the 120 day safety update. This study was to have used the to-be marketed MDPI formulation, but a — was made to the mouthpiece after the initiation of this trial. It has

been determined that because the modified component is not part of the drug delivery channel and does not contact the drug substance, this is unlikely to affect medication delivery. *In-vitro* testing for particle size was conducted with the new mouthpiece and sufficiently addresses formulation changes.

The new does contact the patient. Therefore, the chemistry and pharmacology reviewers will determine whether an has been submitted for the whether the for the ; differs from that of the old and whether USP testing for is needed.

Twelve month safety data for the standard fill formulation DPI from the U.K. is included in the submission (trial SLGT06). Long term safety data for the reduced fill DPI (not the MDPI) U.S. formulation will be submitted by the 120 day safety update (SLD-320).

Additional study reports for EIB, pediatric asthma and COPD have been submitted, however, there are no by-variable or by-patient (CRF tabulations) available in the NDA. These indications are not being sought at this time.

The sponsor has undertaken a study to determine whether patients with low inspiratory flow rates can use the device. This trial will be submitted by the 120 day safety update.

The MDI and MDPI have not been compared clinically. At the pre-NDA meeting, the division stated that the labeling for MDPI should discuss this issue. The proposed labeling does not and this issue should be revisited in the labeling review.

Pre-clinical studies were required to investigate the safety of the impurity. Twelve week studies of the impurity were required in 2 species, one of which should be the rat. The submission contains a study report of a 12 week inhalation study of degraded salmeterol in rats. A 12 week inhalation study of the impurity in dogs will be submitted by the 120 day safety update. In addition, a 12 week inhalation study of the MDI in rats has been requested.

The division did not comment at the pre-NDA meeting on the adequacy of the proposed *in-vitro* data in demonstrating the comparability of the devices. Detailed information for DPI and MDPI batches and formulations has been provided for each clinical trial.

NDA Format

Patient listings were provided for the following trials: SLD-311, SLD-312, SLGA2001, SLGA2004, SLGA2006, C94-041 and SLGT06. The latter two trials

are non-U.S. trials. Each study report for these trials contains by-variable line listings of patient data from all patients who received study drug. For some studies there are data for all enrolled patients and in other trials there are data for all randomized patients. However, the NDA does not contain case report form tabulations. The sponsor has indicated that they believe the agency agreed to this format, however, the division's meeting minutes do not record any discussion of this issue.

According to 21 CFR 314.50 (f) (1), "tabulations are required to include the data on each patient in each study, except that...the FDA may discuss with the applicant in a pre-NDA conference those tabulations that may be appropriate for deletion." The sponsor will propose the studies for which they now intend to submit tabulations. This issue is not considered to be an impediment to filing this NDA.

A summary report, including serious adverse events, was provided for ongoing trials.

Trials which were conducted by "Local Operating Companies", Glaxo's term for their extensions in other countries which are composed primarily of regulatory and marketing personnel, have been briefly described in the NDA. Each description is accompanied by narratives of any serious adverse events. This approach is acceptable for these small, marketing-type studies which are not used to support product efficacy.

The ISE contains integrated data from SLD-311 and SLD-312. Trials SLGA2001, SLGA2004, SLGA2006 and SLGT06 are presented in the ISE, but not integrated. Data for pediatrics (4-11 year olds) and for adult EIB and COPD trials are not contained in the ISE.

The ISS contains from 17 adult and adolescent acute dosing trials integrated into a single section and from 29 chronic dosing trials and 3 long term trials (12 months), integrated into a second section. Pediatric safety data from 16 studies are included in ISS in a third integrated section, but are not integrated into the adult data. Deaths and serious adverse events from the weekly safety reports for the MDI are included as a duplication of the safety update submitted to the agency for the MDI on February 29, 1996.

CRFs have been submitted from GlaxoWellcome trials for patients who died or withdrew due to adverse events. CRFs from studies conducted by local operating companies will not be submitted.

SAS data files have been submitted to Dr. Gebert, the biometrics reviewer. A preliminary look at the submission for trials SLD-311 and SLD-312, indicated that

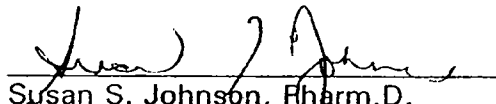
the primary review of these trials is based on an "efficacy" population, rather than an intent to treat group. It appears that the analyses of this subgroup can be reconstructed, accounting for each patient enrolled in the trial.

The sponsor has arranged for ZIP drive files to be installed in the division and has provided a ZIP disk containing study reports for trials SLD-311, SLD-312, SLGA2001, SLGA2004, SLGA2006 and SLGT06, including data tables. Mr. Potter is following up with DISD regarding the installation.

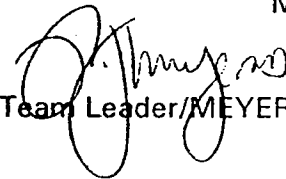
RECOMMENDED REGULATORY ACTIONS

The sponsor has provided a submission which meets the criteria stipulated by the division at the pre-NDA meeting. The sponsor has agreed to provide CRF tabulations in response to the division's request and does not constitute a filing issue.

At the filing meeting held July 15, 1996, it was suggested that the tradename may need to be modified to include the 50 mcg strength to distinguish it from the MDI product (25 mcg ex-valve per puff). In addition, it was suggested that study compliance audits be conducted on a limited number of sites and include the comparative (DPI vs. MDPI) trials, as well as the pivotal trials.


Susan S. Johnson, Pharm.D.
Medical Reviewer

Concurrence:


Team Leader/MEYER

cc: NDA 20-692
DIV FILE
HFD-570/SJOHNSON
HFD-570/JANI

MEDICAL OFFICER REVIEW
Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: 20-692

APPLICATION TYPE: NDA

SPONSOR: Glaxo Wellcome

PRODUCT/PROPRIETARY NAME: Serevent Diskus

USAN / Established Name: Salmeterol Xinafoate
Inhalation Powder

CATEGORY OF DRUG: Long Acting β
Agonist

ROUTE OF ADMINISTRATION: Oral Inhalation

MEDICAL REVIEWER: Susan Johnson,
Pharm.D.

REVIEW DATE: September 16, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
April 23, 1997	April 24, 1997	Amendment	MDI vs. DPI Clinical Comparison
July 25, 1997	July 28, 1997	Response to Comments	
August 26, 1997	August 27, 1997	Safety Update	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
June 19, 1996	Original NDA	The current submission amends NDA.

Overview of Application/Review:

This review includes the final study reports for Trial SLGA2015, a dose ranging bronchodilator challenge study and Trials SLGA 3010 and 3011, both twelve week safety and efficacy evaluations of the 50 mcg BID dose. The review also addresses responses to clinical comments generated in the previous review, an overview of the pre-approval safety update and labeling comments. The safety update provided safety information on the single U.S. 12 month study conducted with the Diskus formulation. Conclusions generally support those from the previous review, however, the 50 mcg Diskus and 50 mcg MDI doses have not been shown to be completely comparable. Labeling modifications have been made to reflect this.

Outstanding Issues:

See Recommended Regulatory Action

Recommended Regulatory Action: Approvable

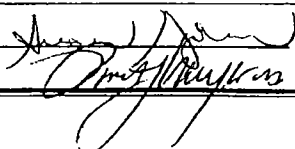
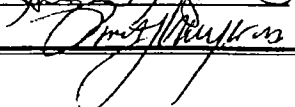
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New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: _____ Approvable _____ Not Approvable

Signed: Medical Reviewer: 
Medical Team Leader: 

Date: 9-16-97
Date: 9/17/97

I. Review of Clinical Trials Comparing MDI and Diskus Formulations

Trial SLGA2015: A Randomized, Double-Blind, Double-Dummy, Five-Way Crossover Clinical Trial of Single Doses of Salmeterol 25 mcg, 50 mcg and 100 mcg via Diskus, Salmeterol 50 mcg via Metered-Dose and Placebo in Adolescent and Adult Subjects with Moderate Asthma.

Investigators:

Objective:

The purpose of this trial was to compare the clinical efficacy and safety of a range of salmeterol Diskus doses (25, 50 and 100 mcg) with the 50 mcg MDI dose and placebo.

Protocol:

Adults and children over the age of 12 were eligible to participate in the study if they were moderate asthmatics with a demonstrated baseline of 50 to 75 percent of predicted normal and airway reversibility of 15 percent over baseline following two puffs of Ventolin MDI. Patients were required to otherwise be in good health. Concurrent use of inhaled or intranasal corticosteroids, cromolyn or nedocromil was allowed, provided that a fixed dosage regimen was maintained one month prior to, and throughout, the study.

The screening visit occurred between two and 14 days prior to Treatment Visit 1. Each additional visit, Treatment Visits 2 through 5 and a post-treatment visit, were separated by a period of between three and 14 days. At screening, patients were dispensed a Ventolin MDI for as needed relief of asthma-related symptoms throughout the study. At each treatment visit, patients received one of the following treatments and corresponding double-dummy placebo: placebo, 25, 50 or 100 mcg salmeterol via Diskus with corresponding double-dummy MDI placebo or 50 mcg salmeterol via MDI with placebo Diskus.

Comment: At each treatment visit, patients received treatment with both a dry powder and MDI device. Therefore, the effects of the inactive components of each formulation can not be distinguished.

The primary efficacy endpoint was the serial spirometric record of FEV₁. Safety parameters included vital signs (serial assessments associated with spirometry), physical examinations (screening and post-treatment), clinical laboratory tests (pre-dose and 1.5 hours post-dose at each visit), 12-lead ECGs (pre-dose and 1.5 hours post-dose at each visit), and clinical adverse events.

Patient Disposition:

A total of 64 patients were enrolled in the study and two (Pts. #12462 and 12378) were discontinued due to asthma exacerbations which required prednisone therapy. Most patients (72 percent) had a history of asthma for over 10 years and the same portion reported having experienced nocturnal asthma symptoms which interfered with sleep. The mean age of the population was 29 years, 63 percent were male and 95 percent were Caucasian.

Efficacy Outcomes:

Baseline FEV₁ and mean change from baseline is shown in Table 1 for the five treatment groups. A plot of the dose response curves, expressed as percent change from baseline, is shown in Appendix 1.

Table 1: Mean Changes from Baseline for Serial FEV₁^a(L)

Time (Hrs)	Placebo N = 63	50 mcg MDI N = 63	25 mcg Diskus N = 64	50 mcg Diskus N = 63	100mcgDiskus N = 62
Baseline ^b	2.45	2.50	2.52	2.49	2.47
0.5	0.22	0.64	0.46	0.49	0.60
1.0	0.29	0.76	0.56	0.59	0.72
2.0	0.32	0.78	0.67	0.67	0.78
3.0	0.37	0.82	0.66	0.74	0.81
4.0	0.39	0.79	0.62	0.73	0.79
5.0	0.35	0.76	0.65	0.69	0.77
6.0	0.36	0.77	0.62	0.66	0.77
7.0	0.31	0.76	0.60	0.65	0.76
8.0	0.29	0.74	0.57	0.61	0.74
9.0	0.28	0.73	0.58	0.58	0.71
10.0	0.30	0.73	0.58	0.61	0.71
11.0	0.30	0.71	0.58	0.59	0.70
12.0	0.30	0.71	0.55	0.61	0.72
Average ^c	2.77	3.25	3.11	3.13	3.21

^a Maximum mean changes from baseline in each treatment are presented in bold-faced type.

^b The baseline mean is the average of the -0.5 hour and 0.0 hour FEV₁ values.

^c Average is the weighted average of the post-dose FEV₁ over 12 hours.

Statistically significant differences were seen between placebo and each of the four active treatment groups at each timepoint. Statistically significant differences were observed between the MDI 50 treatment and the Diskus 25 treatment at each timepoint. Comparisons of the Diskus 50 and MDI 50 treatments and the Diskus 25 and Diskus 100 treatments were statistically significant at almost all timepoints. No statistically significant differences were observed between the MDI 50 and Diskus 100 treatments and the Diskus 25 and the Diskus 50 treatments (with the exception of the Hour 4 comparison for the latter comparison). The Diskus 50 and Diskus 100 treatments were statistically significantly different from one another between Hours 3 and 7 and after Hour 10. These statistical outcomes are essentially the same as those observed in analyses of percent of predicted serial FEV₁ analyses (no analyses of percent change

from baseline were provided).

Functions of serial FEV₁ are shown in Table 2.

Table 2: Metrics of Serial FEV₁

	Placebo 52	MDI 50 94	Diskus 25 81	Diskus 50 89	Diskus 100 92
Percent w/ > 15% Response					
Onset in Hr	2.9	0.3	0.4	0.5	0.3
Pk Percent Change from Baseline (SD)	23.3 (18.0)	38.3, (16.9)	33.3 (17.0)	34.9 (17.6)	38.6 (15.7)
Duration in Hr	3.8	9.7	7.9	8.3	9.3
AUC BL in L/Hr	3.7	8.8	7.1	7.5	8.7

Comment: Overall, a dose response trend was observed among the Diskus doses, with greater separation of the Diskus 50 and Diskus 100 doses than the Diskus 25 and Diskus 50 doses, as might be expected based on the proportionality of the doses. Although it appears that among the Diskus doses the Diskus 100 dose is most similar to the MDI 50 dose, the FEV₁ data do not clearly indicate that a clinically important difference exists among the Diskus doses. FEV₁ data do show that each of the active treatments consistently performs substantially better than placebo. The proportion of patients who achieved a 15 percent response to the MDI 50, Diskus 50 and Diskus 100 treatments is essentially the same for each treatment and peak percent change response to the three doses is comparable. In this single dose study, time to onset is distinguishable among these three treatments, however, the carryover effects between Serevent doses, as seen in previous Diskus trials, negates the importance of the onset parameter during chronic use. A dose response was observed in duration of action, however, the duration of all treatments exceeded the 6 to 7 hour mean durations observed in previous chronic use studies. Other clinical parameters of MDI versus Diskus will provide additional insight into the clinical interpretation of these data.

There were a total of 24 patients (38 percent) who experienced asthma exacerbations during the trial, with a total of 39 events. Most were attributed the withholding of asthma medication and all but three exacerbations occurred at a treatment visit. Of the clinic visit episodes, there were 15 events during placebo treatments, 4 during MDI treatment, and 6, 7 and 4 during Diskus 25, 50 and 100 treatments. The highest incidence was seen, as expected, was in the placebo treatment group. The two asthma exacerbations which caused patients to discontinue occurred in Patient 12378, whose asthma symptoms worsened two days after the MDI 50 mcg treatment, and Patient 12462, whose asthma symptoms worsened five days after treatment with Diskus 25 associated with bronchitis.

Comment: A dose response trend may be suggested for the incidence of asthma exacerbations, however, it is unclear that given the design of the trial, which featured intermittent long and short acting bronchodilator treatment, this parameter is a reliable reflection of clinical outcomes.

Safety Outcomes:

There were no deaths or serious events reported, however, two patients discontinued due to asthma exacerbations. There were no other withdrawals.

Headache was reported by one placebo, one Diskus 25, one Diskus 50 and four Diskus 100 patients, but no MDI 50 patients. Upper respiratory or nasal sinus infections were reported by three placebo, one MDI 50, and two Diskus 25 patients. No other adverse events were reported by more than one treatment group. Of interest from a dose response standpoint is that one Diskus 100 patients reported migraine, while another patient reported tremor associated with the same treatment.

Despite the apparent dose response in the efficacy data, vital sign data did not reflect similar trends. Mean and shift analyses of pulse and blood pressure failed to distinguish any of the active treatments from placebo. No significant differences were observed among the treatment groups on ECG data, including QT_c and heart rate.

Clinical laboratory outcomes were not informative in providing dose comparison information or information related to potential treatment-related effects. Physical examination data were unremarkable.

Conclusion:

Serial FEV₁ data show a dose response trend among the 25, 50 and 100 mcg doses of the Diskus formulation. These data suggest that the 100 mcg dose performs most comparably to the 50 mcg MDI dose. However, adverse event data suggest that the modest additional benefit that may be derived in efficacy may not outweigh the enhanced safety concerns associated with the 100 mcg dose. The 50 mcg Diskus dose was further compared to the MDI in two, twelve week trials.

**APPEARS THIS WAY
ON ORIGINAL**

Trial SLGA3010: A Randomized, Double-Blind, Double-Dummy, Comparative Clinical Trial of Salmeterol 50mcg via the Diskus and Salmeterol 50mcg via the Metered-Dose Inhaler versus Placebo for Twelve Weeks in Adolescents and Adult Subjects with Mild-to-Moderate Asthma.

Investigators:

Objective:

The purpose of this trial was to compare the safety and efficacy of 50 mcg BID via the Diskus with 50 mcg BID via the MDI and placebo over a 12 week period. This study, as well as Trial 3011, will be evaluated to assess the clinical comparability of the 50 mcg dose of Diskus proposed for marketing to the approved dose of MDI.

Protocol:

Adults and children over the age of 12 years were eligible to participate in the study if they had a diagnosis of asthma which required chronic pharmacotherapy during the six months preceding Screening and if they demonstrated an FEV₁ of 50 to 85 percent of predicted normal at Screening. Participants were required to be otherwise healthy. Patients receiving a fixed dosage regimen of inhaled and/or intranasal corticosteroid, inhaled or intranasal cromolyn, or inhaled nedocromil were allowed to participate. Other medications, including asthma therapies, were appropriately withheld throughout the study. Ventolin Inhalation Aerosol was provided as a rescue at the Screening visit and throughout the remainder of the study.

Patients were randomized at the first treatment visit to receive one of three treatments: salmeterol powder 50 mcg (50 mcg per blister) BID via Diskus with placebo aerosol BID, salmeterol aerosol 50 mcg BID (as 25 mcg per actuation) via MDI with placebo powder BID or placebo of both powder and aerosol formulations BID. After the initial treatment visit, patients returned to the clinic at Week 2 and every two weeks thereafter until Week 12. At Week 1, Week 4 and Week 12, patients underwent 12 hour serial spirometry. Between clinic visits, patients completed a daily diary in the morning, including use of assigned treatment, PEFr assessments, rescue Ventolin use, frequency of nighttime awakenings, daily asthma symptom scores and medical events. PEFr and MDI use were recorded each evening as well. Compliance was assessed based on the dosage counter on the Diskus and via diary data for the MDI.

Asthma symptoms assessed included wheeze, shortness of breath and cough that had occurred during the 24 hours prior to the morning rating using the following scale:

- 1 = no symptoms at all; unrestricted activity
- 2 = symptoms occurred with little or no discomfort; unrestricted activity
- 3 = symptoms occurred with some discomfort; at times limiting activity
- 4 = symptoms occurred; were sometimes annoying or affected routine activity
- 5 = symptoms occurring at rest; were annoying and affected routine activity.

Nighttime awakenings due to asthma were rated the following morning as follows:

- 0 = I did not awaken because of asthma
- 1 = I woke up once because of asthma, but went readily to sleep with or without an inhalation treatment.
- 2 = I woke up more than once or had difficulty going back to sleep or did not sleep because of asthma.

Quality of life was assessed using the AQLQ but was not reviewed due to the sponsor's reluctance to pursue QOL claims for the Diskus. Device satisfaction with 12 features of the devices and device use was assessed at Week 1 and Week 12.

Patient Disposition:

A total of 240 patients enrolled in the trial; 81 were assigned to placebo, 79 to active Diskus and 80 to active MDI. Eighty percent were Caucasian, 51 percent were female and the mean age was 33 years (range 12 to 68). Of these, 19 percent of placebo patients discontinued from the trial, as did 19 percent of Diskus patients and 9 percent of MDI patients. Discontinuation was attributed to lack of efficacy for 7, 6 and 3 percent of placebo, Diskus and MDI patients, respectively. Adverse events caused discontinuation of 5, 6 and 1 percent of the placebo, Diskus and MDI patients, respectively.

Comment: Overall, the patient discontinuation rates were more similar between the placebo and Diskus treatments than between the Diskus and MDI treatments.

The percentage of patients using inhaled or intranasal corticosteroids on a regular basis was approximately the same in the MDI and Diskus groups (45 percent), and slightly higher in the placebo group (54 percent). Patient compliance was greater than 96 percent for both devices in each of the treatment groups.

Efficacy Outcomes:

Note: In addition to the Intent-to-Treat analyses which are the topic of primary discussion in this review, supplemental analyses were conducted after exclusion of patients from the Amill investigator site. The study coordinator was found to have performed pulmonary function tests incorrectly, without regard to daily baseline variation, and was believed to have "manufactured" blood pressure data. There were no instances in which supplementary analyses differed significantly from the primary analyses.

Baseline FEV₁ (average of the -0.5 and 0 hour FEV₁ at Week 1 visit) was 2.37, 2.48 and 2.45 for the placebo, Diskus and MDI treatments, respectively. Inferential and covariate analyses (using baseline FEV₁ as the covariate) were conducted on absolute serial FEV₁ data. At all timepoints of Weeks 1, 4 and 12, both Diskus and MDI were shown to be statistically superior to placebo. At no time were there statistical differences between the Diskus and MDI treatments.

Table 3 summarizes the functions of serial FEV₁ at Weeks 1, 4 and 12. Both Diskus and MDI were statistically superior to placebo for each parameter at Weeks 1 and 4, but there were no statistical differences between the active treatments. At Week 12, the only statistically significant differences between treatments were that the duration of effect for the Diskus was longer than that of placebo and the AUC of both Diskus and MDI were greater than that of placebo.

Table 3: Functions of Serial FEV₁

	Placebo	Diskus	MDI
Percent w/ 15% Response			
Week 1	43	78	80
Week 4	47	75	83
Week 12	61	77	73
Onset of Effect in Hr			
Week 1	12	0.67	0.50
Week 4	12	0.38	0.43
Week 12	1.36	0.49	0.25
Pk Percent Change from Baseline (SE)			
Week 1	19.1 (1.5)	28.1 (1.9)	30.1 (1.7)
Week 4	17.9 (2.0)	28.6 (2.7)	30.7 (2.2)
Week 12	21.6 (2.6)	28.6 (2.4)	27.1 (2.2)
Duration in Hr			
Week 1	2.9	6.9	7.5
Week 4	3.2	7.0	7.0
Week 12	5.5	6.9	6.7
AUC BL in L/Hr			
Week 1	2.3	5.6	6.2
Week 4	1.9	5.4	6.2
Week 12	3.0	5.8	5.6

Appendices 2, 3 and 4 show the percent change from baseline outcomes for Week 1, Week 4 and Week 12, respectively. As in the serial FEV₁ analyses, it appears that at Week 12, the overall response to placebo appears to be enhanced from Week 1 and Week 4 and the response to MDI appears to be shifted downward. No explanation is offered for this variation from the previous weeks.

Comment: Because the response to Diskus is similar between Weeks 4 and 12, it does not appear that the difference between treatment weeks for the MDI and placebo are related to total treatment duration.

Analyses of change from baseline for Weeks 1-4, Weeks 5-8, Weeks 9-12 and Weeks 1-12 failed to show any differences among the three treatment groups for AM PEF, PM PEF or AM/PM differential. Baseline PEF (average of the seven days prior to the first treatment day) was slightly higher in the Diskus group (402 L/min) versus the placebo (373 L/min) and the MDI (392 L/min) groups, although this modest difference does not suggest a clinically significant difference in the status of the patients in the various groups. For the Diskus and placebo groups, AM and PM PEF scores appeared to become enhanced during the twelve week evaluation, with the AM/PM differential remaining constant. For the MDI, however, PM scores declined while AM scores remained stable such that the differential was enhanced.

Use of rescue Ventolin was comparable among the groups at baseline. Reduction in mean rescue use was lowest in the placebo group (decrease of 0.7 puffs per day for Weeks 1-12), followed in sequence by the Diskus (decrease of 1.5 puffs per day mean for Weeks 1-12) and the MDI (decrease of 1.8 puffs per day for Weeks 1-12) groups. Statistically significant differences were seen in comparisons of the Diskus with placebo and of the MDI with placebo. No statistically significant differences were observed between Diskus and MDI.

Percent of nights with no awakenings during treatment was consistently highest for MDI (84 percent mean for Weeks 1-12), followed by Diskus (79 percent mean for Weeks 1-12) and placebo (73 percent mean for Weeks 1-12). Statistically significant differences were noted overall for Diskus versus placebo and for MDI versus placebo, but not for Diskus versus MDI. However, in analyses of Weeks 1-4 and Weeks 5-8, there was a statistical advantage of the MDI versus the Diskus.

Percent of days with no symptoms showed trends which were similar to the nighttime awakening analyses. For Weeks 1-12 mean percent of days with no symptoms was 47 for MDI, 40 for Diskus and 35 for placebo. Statistical differences were observed between both of the active treatments and placebo, but not between the active treatments.

Mean daily symptom scores were virtually indistinguishable for the three treatment groups, differing by 0.4 or less (on a 5 point scale) at all times among the groups. However, there was a statistical superiority of Diskus versus placebo for Weeks 1-12 and for MDI versus placebo for Weeks 1-4 and Weeks 5-8. No statistically significant differences were observed between Diskus and MDI.

The percentage of patients who experienced asthma exacerbations during treatment was similar, but favored the MDI with 10 percent of patients experiencing one or more exacerbations in the MDI group, 15 percent in the Diskus group and 12 percent in the placebo group.

The incidence of patients reporting favorable scores for the MDI and Diskus were similar for most attributes. A higher proportion of patients found the MDI durable and convenient to carry than the Diskus, however a far greater proportion of Diskus patients reported favorable evaluations of the ease in telling the number of doses left in the device.

Efficacy Conclusion: FEV₁ data suggest that, while both the MDI and Diskus devices are superior to placebo, there may be a slight advantage to the MDI. This trend was observed at Weeks 1 and 4, but was reduced at Week 12. However, the Week 12 data for the MDI and placebo do not appear to be consistent with the previous data and may have obscured the potential differences between Diskus and MDI. The clinical relevance of these findings are supported by the consistency with which MDI was favored over Diskus in the evaluation of rescue Ventolin use, nocturnal symptoms, asthma symptom severity and asthma exacerbation rate. Only PEFr scores failed to favor the MDI and suggested no substantive differences between the Diskus and MDI. Statistical support of these findings was minimal, however, it appears that there may be a potential for some patients to experience different clinical outcomes from the two devices.

Safety Outcomes:

There were no deaths reported in the trial. Six serious adverse events were reported, including one in the placebo group (pneumonia) and five in the Diskus group (3 asthma exacerbations and two bronchitis events, one with abnormal pO₂). One Diskus patient completed the trial and the remainder of those who experienced an SAE were discontinued. All of the Diskus events, with the exception of a single asthma event, were thought to be related to an acute infectious condition.

Other adverse events which led to discontinuation included, for placebo: bronchitis (1) and URTI (2), for Diskus: a reproductive infection (1) and for the MDI: nausea and vomiting (1).

Comment: The serious event and dropout rates appear to again suggest a numerical advantage for the MDI. However, with the exception of a single asthma exacerbation in a Diskus patient, all of the events can be largely attributed to another causal event. While it is difficult to conclude based on these data alone that there was a clinically relevant difference between the active treatments, these data do raise a concern over differential tolerability of the two products.

Diskus patients experienced the highest incidence of adverse events. The difference between overall Diskus and MDI incidence rates appears have been significantly affected by an increase in the number of URTI among Diskus patients (25 percent of the placebo group, 24 percent of the Diskus group and 15 percent of the MDI group).

Adverse events which occurred in at least two percent of any treatment group, in a greater proportion of either active group than placebo, and which appear to have potential bearing on the active treatment or disease of interest are listed in Table 4.

Table 4: Percentage of Treatment Groups Experiencing Adverse Events

Event	Placebo	Diskus	MDI
Total	53	70	63
Throat Irritation	5	8	20
Sinusitis	4	5	4
Sinus Infection	1	4	0
Viral Respiratory Inf	6	10	9
Cough	6	4	8
Bronchitis	5	6	1
Asthma	0	3	0
Headache	11	14	13
Migraine	0	0	3
Nausea & Vomiting	2	6	3
Diarrhea	1	3	4
Muscle Pain	0	3	0
Temperature Regulation	1	3	4
Disturbance			
Lymphatic Signs and Sx	0	0	2

Mean change and shift analyses of pulse data collected during serial FEV₁ did not suggest clinically relevant differences among the three treatment groups. A number of patients in each of the treatment groups experienced a lowering of systolic blood pressure. This occurred in the highest proportion of MDI patients, followed by Diskus and placebo. Differences between the Diskus and MDI were not echoed in the diastolic blood pressure data. It is notable that these findings are consistent with the supplemental analyses which were conducted after excluding the potentially fraudulent data. EKG, QTc and heart rate data, collected at Screening and Week 12, did not reveal statistical or other differences among the treatment groups, which suggested treatment effects. Analyses of clinical laboratory data and physical evaluations did not illuminate substantive differences among the groups.

Safety Conclusion: While adverse event rates may suggest that the Diskus is associated with an enhanced incidence of adverse events relative to the MDI, this rate does not appear to be directly attributable to an identifiable event or type of events. The spontaneous occurrence of URTI was higher in the Diskus group and may account for the majority of the discrepancy. Other safety parameters do not suggest that the Diskus and MDI are clinically distinguishable.

Conclusions:

Because this trial was not designed as a crossover study, direct comparisons of the Diskus and MDI can not be made on a per patient basis. However, it appears clear that mean data reflect a trend toward marginally enhanced efficacy with the MDI device

relative to the Diskus, particularly in the initial weeks of treatment. The clinical implication of this difference for a given patient, when switched from the MDI to the Diskus, can not be described based on the available data. It is notable that the development program of the Diskus was considered at "stand-alone" program, rather than a "switch" from the MDI device, and has clearly demonstrated the efficacy of the Diskus device relative to placebo in all controlled trials. However, the labeling should reflect that the Diskus device may not be completely comparable to the MDI in the clinical setting. No substantive differences were observed in the safety profile of the two active treatments.

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Trial SLGA3011: A Randomized, Double-Blind, Double-Dummy, Comparative Clinical Trial of Salmeterol 50mcg via the Diskus and Salmeterol 50mcg via the Metered-Dose Inhaler versus Placebo for Twelve Weeks in Adolescents and Adult Subjects with Mild-to-Moderate Asthma.

Investigators:

Objective & Protocol: Trials SLGA3010 and 3011 had identical objectives and protocols. See descriptions for SLGA3010.

Patient Disposition:

Of the 258 patients enrolled in the trial, 86 were randomly assigned to each of the three treatment groups. Seventy eight percent of the patients were Caucasian and 54 percent were female. The mean age was 34 years, with a range of 12 to 79 years. Discontinuation rates were similar among the Diskus and MDI groups, 19 and 23 percent respectively, however, 35 percent of the placebo group discontinued prematurely. Lack of efficacy was cited as the reason for discontinuation in 10, 2 and 9 percent of the placebo, Diskus and MDI groups, respectively, while adverse events were responsible for discontinuation of 2, 3 and 0 percent of each of the same groups.

Comment: Although the discontinuation rates for lack of efficacy favored the MDI over the Diskus in SLGA3010, (6 versus 3 percent, respectively), Trial SLGA3011 does not confirm that finding.

The percentage of patients using inhaled and intranasal corticosteroids on a regular basis was slightly higher than seen previous study, at approximately 55 percent of each group. Patient compliance was again high, at greater than 92 percent in each treatment group.

Efficacy Outcomes:

Note: Dr. — site in PR was involved in both Trial SLGA3010 and Trial SLGA3011. Supplementary analyses were again conducted to determine whether the potentially fraudulent data from that site had any bearing on the outcomes of the trial.

Mean baseline FEV₁ was 2.41 L for placebo and 2.40 for both Diskus and MDI treatments. Analyses of absolute data reveal statistically significant differences between Diskus and placebo, and between MDI and placebo, at all timepoints. No

differences were found between Diskus and MDI treatments at any time, as in Trial SLGA3010.

Table 5 summarizes the various analyses of serial FEV₁ metrics at Weeks 1, 4 and 12.

Table 5: Metrics of Serial FEV₁

	Placebo	Diskus	MDI
Percent w/ 15% Response			
Week 1	31	64	78
Week 4	34	71	68
Week 12	37	73	74
Onset of Effect in Hr			
Week 1	12.0	1.08	0.56
Week 4	12.0	0.84	0.62
Week 12	12.0	0.44	0.35
Pk Percent Change from Baseline (SE)			
Week 1	14.4 (1.4)	27.4 (2.4)	30.7 (2.1)
Week 4	14.1 (2.0)	25.6 (2.3)	29.2 (3.0)
Week 12	14.1 (2.4)	28.6 (2.4)	29.6 (2.5)
Duration in Hr			
Week 1	2.1	5.6	7.3
Week 4	2.5	5.9	6.3
Week 12	3.0	6.9	7.6
AUC BL in L/Hr			
Week 1	1.3	5.1	6.1
Week 4	1.3	4.4	5.4
Week 12	1.3	5.4	5.8

Statistically significant differences were seen in each comparison of Diskus versus placebo and of MDI versus placebo. Statistically significant differences were also seen between Diskus and MDI for onset of effect and peak percent change from baseline at Week 1. Appendices 5, 6 and 7 show the percent change from baseline outcomes for Week 1, Week 4 and Week 12, respectively. The apparent reduction in effect of the MDI at Week 12 in SLGA3010 was not evident in this trial.

Analyses of AM PEFR as change from baseline for Weeks 1-4, Weeks 5-8, and Weeks 1-12 showed statistically significant differences in both Diskus versus placebo and MDI versus placebo. The same analyses of PM PEFR showed statistically significant differences between Diskus and placebo at Weeks 1-4, 5-8 and 9-12, as well as overall.

The MDI versus placebo comparison was statistically significant at Weeks 1-4 and overall. The AM/PM differential analyses showed statistical significance only for MDI versus placebo for Weeks 1-4. There was a general trend toward improvement on AM and PM scores in all three treatment groups over the 12 week trial. This finding also appears to offset concerns raised in Trial SLGA3010 regarding the unexplained apparent decline in MDI function during the 12 week treatment period of that trial.

Statistical differences between Diskus and placebo, and between MDI and placebo, were noted for each analysis of daily use of rescue Ventolin, although no statistical differences were noted between the two active treatments. Unlike the previous trial, reduction in rescue use occurred to the greatest degree in the Diskus group (decrease of 2.3 puffs per day for mean of Weeks 1-12), followed by MDI (decrease of 1.6 puffs per day for mean of Weeks 1-12) and placebo (decrease of 0.7 puffs per day for mean of Weeks 1-12).

There were no statistically significant differences among the treatment groups with regard to percent of nights with no awakenings. For Weeks 1-12, the mean percentage was 68 for placebo, 75 for Diskus and 81 for MDI. Percent of days with no symptoms showed no statistically significant differences between placebo and the active treatments except for Weeks 5-8 when the Diskus treatment was statistically superior to placebo. Trends in the data support the ranking of placebo, Diskus and MDI as lowest to highest. Mean daily asthma symptom scores were nearly identical for the Diskus and MDI, and slightly higher for the placebo group. As in the previous trial, weekly mean values for all treatments remained clustered in a very tight range (1.7 to 2.1). Only eight percent of the Diskus treatment group experienced one or more exacerbations during treatment, while 16 percent of the placebo group and 15 percent of the MDI group exacerbated.

Results of device assessment ratings were comparable to those described for Trial SLGA3010.

Efficacy Conclusion: The findings of Trial SLGA3010 regarding the apparent superiority of the MDI relative the Diskus formulation are not fully substantiated in Trial SLGA3011. While similar trends are observed, reiterating the need for a labeling statement regarding the potential for inconsistent clinical outcomes from the two treatments, the data from Trial SLGA3011 do not suggest that the discrepancy is as pronounced as in the previous trial.

Safety Outcomes:

There were no deaths during the study and one patient experienced a serious adverse event (cholecystitis). Two patients discontinued due to adverse events in the placebo group; one due to a combination of viral (mononucleosis and herpes lesions) and bacterial infections (strep infection). Three patients discontinued from the Diskus treatment group; one due to an anaphylactic reaction to an allergy shot, one due to "moderate syncope" after 12 weeks of therapy and one due to cholecystitis.

Comment: As in Trial SLGA3010, the numerical analysis of adverse events leading to withdrawal favors the MDI, however, in this instance, there were no events which appear to be potentially related to salmeterol's effect or lack thereof.

Unlike Trial SLGA3010, the MDI patients in SLGA3011 experienced the highest rate of

adverse events. Adverse events which occurred in at least two percent of any treatment group, in a greater proportion of either active group than placebo, and appear to have potential bearing on the active treatment or disease of interest are listed in Table 6.

Table 6: Percentage of Treatment Groups Experiencing Adverse Events

Event	Placebo	Diskus	MDI
Total	62	60	65
URTI	35	19	31
Throat Irritation	5	8	8
Upper Resp. Inflam.	1	3	1
Rhinorrhea	1	3	1
Laryngitis	0	2	0
Epistaxis	0	0	2
Headache	12	19	16
Viral Resp. Inf.	5	6	3
Cough	3	6	2
Bronchitis	0	7	3
Viral GI Inf.	3	2	5
GI Signs & Sx	0	3	2
Diarrhea	0	2	3
Gastroenteritis	0	0	5
Musculoskeletal Pain	3	5	7
Muscle Cramps & Spasms	0	0	3
Allergic Eye Disorder	0	2	0

Other safety data, including cardiovascular, clinical laboratory and physical evaluations did not establish clinically important differences among the treatments.

Safety Conclusion: The safety data do not appear to suggest that there are meaningful clinical differences between that active treatments or that they differ in an unexpected fashion from placebo.

Overall Conclusion for MDI versus Diskus Comparisons:

The efficacy data from Trial SLGA3010 and Trial SLGA3011 are similar in they appear to suggest that the findings of the dose ranging, SLGA 2015, have at least limited clinical consequence. The 50 mcg Diskus and 50 mcg MDI doses do not appear to be completely comparable. Data from the two 12 week trials are supportive of a statement in the labeling which alerts prescribers to the potential for different clinical outcomes with the two treatments.

It should be noted that none of the data from comparative trials of MDI and Diskus have been audited. Given the potential fraudulent activity of at least one of the investigators in both trials, these data are less suitable for labeling purposes than the trials which have been included in the current versions of the draft labeling.

II. Response to Clinical Comments (June 20, 1997 facsimile)

1. Analysis of PEFR and diary data from post-treatment week of Trials SLD-311 and SLD-312.

Withdrawal effects were examined in Trials SLD-311 and SLD-312 during a one week period following 12 weeks of therapy with 50 mcg BID Diskus, 180 mcg QID albuterol or placebo. In the post-treatment period, patients recorded the frequency of albuterol use, morning and evening PEFR and asthma symptom severity scores and nocturnal awakenings. Posttreatment values were compared to the baseline data collected during the seven days prior to the 12 week treatment period. Of the 451 patients who had baseline values recorded, 415 completed the posttreatment evaluations.

Both AM and PM PEFR mean values were nearly identical among the three treatment groups at baseline. During the treatment period for the salmeterol group, both AM and PM PEFR means rose (mean change from baseline of 33 L/min for AM and 15 L/min for PM scores) and then fell again toward baseline during the posttreatment period (mean change from baseline of 15 L/min for AM and 6 L/min for PM scores). AM and PM PEFR means for albuterol and placebo stayed approximately the same between baseline and treatment periods. All four means rose slightly during the posttreatment periods (maximum change of 9 L/min).

The mean asthma symptom scores stayed within a small range for all treatments throughout the entire trial (0.8 to 1.2), however a small reduction from baseline in the mean score of the salmeterol group was detected during treatment which was essentially reversed in the posttreatment phase. Mean albuterol MDI use among salmeterol patients was 4.3 puffs per day during the baseline period, 1.6 puffs during treatment and 3.3 puffs during posttreatment. A similar pattern was seen in the albuterol and placebo groups, although the reduction in use seen during treatment was not as great as with salmeterol. The percent of nights with no awakenings were increased from baseline levels during treatment for each group, with the largest increase seen in the salmeterol group (up to 85 percent from a baseline of 63 percent). Some decline was seen following treatment, but baseline levels were not reached during the one week posttreatment period. Finally, the incidence of asthma exacerbations was compared during the posttreatment period and found to be five percent (7/142) among salmeterol patients, three percent (4/148) with placebo and one percent (1/149) with albuterol. The average weekly incidence was approximately 2.4 episodes for each of the treatment groups while in the treatment phase and the salmeterol group experience a greater number of events in the posttreatment period than they had throughout the trial.

Conclusion: No evidence of "rebound", i.e. worsening of the patients' condition beyond baseline levels, was detected for any of the parameters, although patients using salmeterol during treatment did experience the highest asthma exacerbation rate during posttreatment. This may be reflective of the lack of long acting control of asthma

symptoms. It should be noted that no pulmonary function testing was conducted during the posttreatment phase which may have helped to confirm the functional status of the patients, but that PEFR scores do not appear to confirm the suggestion of any serious withdrawal effects.

2. Study report for Trial SLGA3009.

The final study report for this 12 month trial was not available as of the July 25, 1997 submission. However, safety data have been submitted in the Final Safety Update, August 26, 1997 and will be reviewed in the subsequent section. Review of the efficacy data for this trial is not imperative prior to approval of the product, as this trial was predominantly designed to examine long term safety of the Diskus formulation.

3. Evidence of failures of the Diskus or Diskhaler devices in clinical trials or general use.

Due to the marked dissimilarity between the two devices, the sponsor concluded that Diskhaler information would not be predictive of Diskus device failures and has submitted no information related to the Diskhaler. This is acceptable.

Device failures which have been observed during the ex-U.S. sales of over devices were estimated at 12 failures per million. Those which occurred at a rate of 1 part per million or more included foil assembly problems, damaged components and malformed components. The sponsor has altered their manufacturing process to better detect these failures.

In U.S. clinical trials, two failure types were reported, both of which have been addressed with design changes, notably the lever button twisting off and jamming during use.

Glaxo Wellcome identified two additional issues. The first is that the dose counter may not move from one to zero. This has been addressed with a design change. The second, and apparently the only known problem that has not been addressed, is that the dose counter may occasionally re-start after all 60 doses have been used. The chemistry reviewers will be asked to determine whether the potential for this to happen should be identified in the patient use section of the label.

4. Use of Diskus with a spacer device.

The sponsor has no data related to this topic. A statement cautioning against use of a spacer should be added to the patient use section of the label.

5. Labeling statement re: comparability between MDI and Diskus.

See Section I.

III. Final Safety Update (Submitted August 26, 1997)

The final safety update contains data from 10 trials; four considered of primary importance to the approvability of the application and labeling and six considered secondary. Trials SLGA3010, SLGA3011 and Trial SLGA2015 are primary trials and were previously reviewed in Section I. Trial SLGA 3009 is the final trial of primary interest. It was a 12 month study which employed the Diskus formulation in the U.S. Other trials included Trials SLGA2013 and 2017, which are U.S. single dose crossover studies of various doses of Diskus compared to MDI and placebo designed to examine the effect of Diskus on the prevention of exercise induced bronchospasm. The remaining four trials are non-U.S. studies including SLGT29, a 24 week comparison of salmeterol and albuterol, SLPT10, examining the safety of salmeterol in combination with beclomethasone dipropionate, SLPT16, a one year trial comparing salmeterol to inhaled corticosteroid treatment and SLPT15, a one year study comparing the addition of salmeterol to increased doses of inhaled corticosteroid. Trials SLPT10, 15 and 16 were conducted in children age 12 to 18 and the remainder of the trials were conducted in adult and adolescents.

These newly reported trials describe a substantive number of patients, a total of 1317, corresponding to 2018 treatment exposures (including crossover trials). This number is compared to the total of 5551 exposures reported in the original NDA submission and 120-day safety update, previously reviewed, and the total worldwide trial database of 9210 exposures in adults and adolescents.

The following figures relate to the cumulative database. Of the 1487 exposures in acute studies, 345 exposures were to salmeterol powder. In the 6082 exposures during chronic dosing studies, approximately half were to salmeterol powder. In studies of ≥ 12 months duration, 83 percent of the 1641 exposures were to salmeterol powder. Approximately the same number of males and females were exposed to salmeterol powder during the trials. Over 90 percent of the exposures were in Caucasian patients and in patients between the ages of 12 and 64. Approximately seven percent of the exposures were in patients age 65 and over.

Twenty five of the 26 deaths which have occurred during clinical trials were described in the NDA and have been previously reviewed. An additional death was reported in a patient receiving albuterol treatment in a non-U.S. trial. The 65 year old patient died of cancer of the kidney. One additional spontaneous report of death was associated with the marketed product (non-U.S.) has not yet been described. A nine year old male treated with salmeterol powder developed a fatal asthma attack after a sporting event. The total number of deaths reported in association with the marketed product is 21.

Serious adverse events, as well as adverse events in general, have been adequately described for the clinical trials of primary importance to this application, with the exception of Trial SLGA3009. Trial SLGA3009 was an open label investigation of the

safety of 50 mcg doses via Diskus for 12 months. There was no active comparator. In the safety update, these data have been integrated with data from seven additional one year trials and the following observations can be made. The withdrawal rates adverse events, insufficient efficacy and exacerbations were each low and totaled only 6 percent of the patient population who used the 50 mcg Diskus formulation in long term trials. For Trial SLGA3009 specifically, the rate of withdrawal appeared to be consistent throughout the trial. Adverse events were similar in type to those proposed for product labeling. Rate of nearly all events is higher than in the proposed labeling, most likely due to the duration of the trials. Comparison of the frequency of events during the first three months of therapy to that of the last nine months of therapy showed no notable trend. In addition, the frequency of asthma exacerbations per month appeared consistent throughout the trial. In Trial SLGA3009, ECG monitoring and laboratory data were collected at the initiation of treatment and after six and 12 months of therapy. These data did not appear to reflect clinically significant trends or notable outliers. No Holter monitoring was done during SLGA3009.

For the purposes of labeling, the rate of adverse events from the combined safety database of Trials 3010 and 3011 was examined. Adverse events which occurred in three percent or more of the patients treated with 50 mcg salmeterol via Diskus, and were more common than in patients receiving placebo included throat irritation (8 percent salmeterol versus 5 percent placebo), headaches (16 versus 11 percent), viral respiratory infections (8 percent versus 5 percent), bronchitis (6 percent versus 2 percent), nausea and vomiting (4 percent versus 2 percent) and muscle injuries (4 percent versus 1 percent).

Conclusion: Data in the safety update, including the results of the single U.S. one year trial conducted with the Diskus formulation, appears to support the proposed labeling.

IV. Labeling

The clinical edits for the labeling are contained in the attached draft document. In addition, the sponsor should be asked to include the following in the revised labeling. Additional modifications of the labeling are expected in negotiation with the sponsor.

Please include a statement in the Description section which relates the describes the patient generated airflow through the device. The approved labeling of Pulmicort Turbuhaler® contains an exemplary statement.

The figures which convey pulmonary function outcomes in the Pharmacodynamics and Clinical Trials section should be constructed using FEV₁ as a percent of predicted. In addition, the key for these figures should include daily dosage.

The proposed brand name, _____, is not acceptable from a clinical perspective. It is felt to be promotional in that it _____.

V. Recommended Regulatory Action

It should be noted that the results of clinical trial audits for SLGA2001 (Investigator James Grady, M.D.), SLGA2004 (Investigator Anthony Rooklin, M.D.) and SLD-312 (Investigator Kathryn Blake, M.D. for Elliot Ellis) were acceptable (VAI).

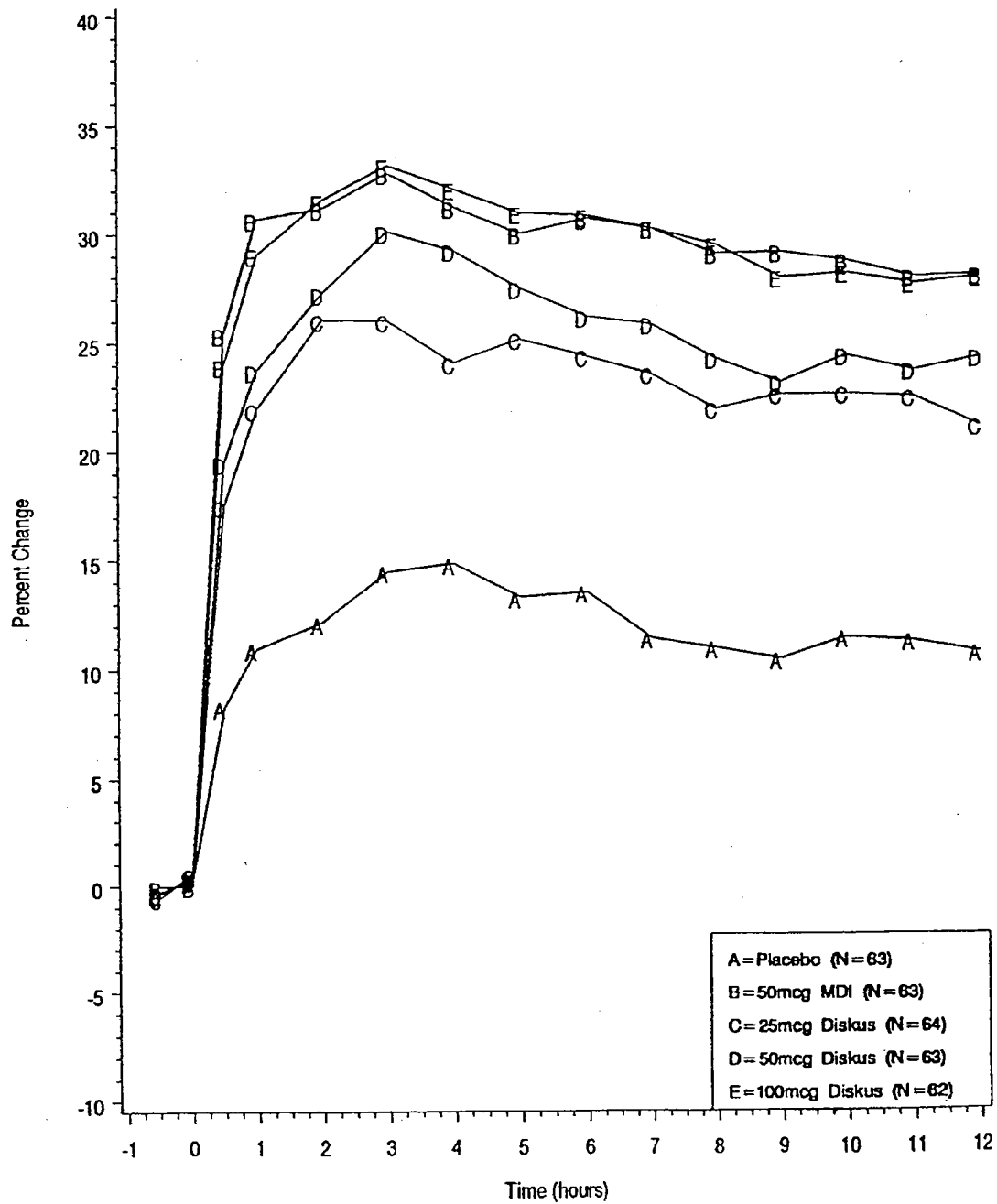
1. The labeling changes and comments from Section IV should be conveyed to the sponsor.
2. The chemistry reviewers will determine whether additional statements regarding potential device failures should appear in the label based on their perception of the likelihood of the events.
3. Upon adequate documentation of the sponsor's acceptance of these changes, the NDA may be approved from a clinical standpoint.

**APPEARS THIS WAY
ON ORIGINAL**

APPENDIX 1

Salmeterol Xinafoate Powder
Protocol: SLGA2015
Population: Intent-to-Treat

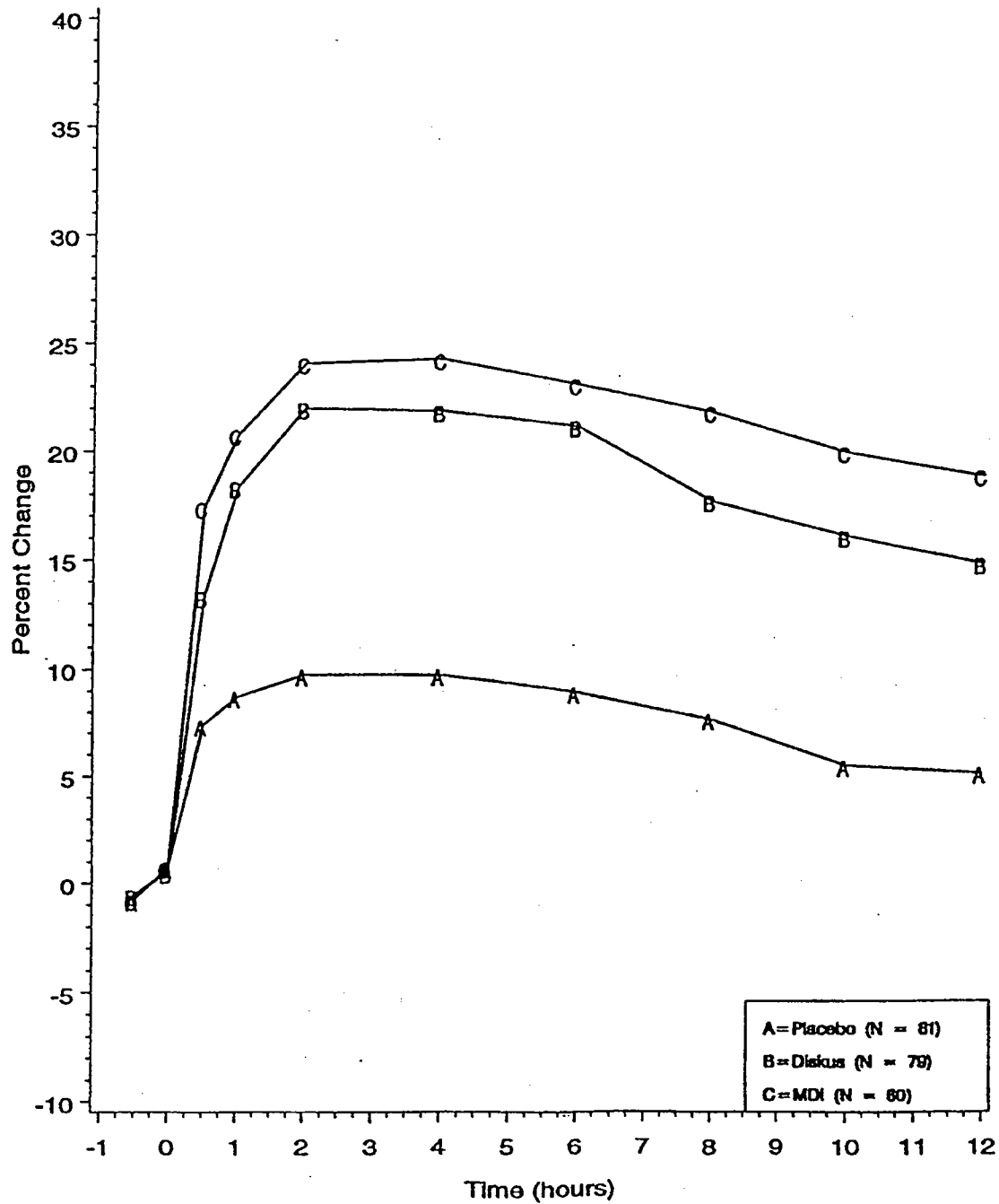
FIGURE 3
FEV1: PERCENT CHANGE FROM BASELINE



APPENDIX 2

Salmeterol Xinafoate Powder
Protocol: SLGA3010
Population: Intent-to-Treat

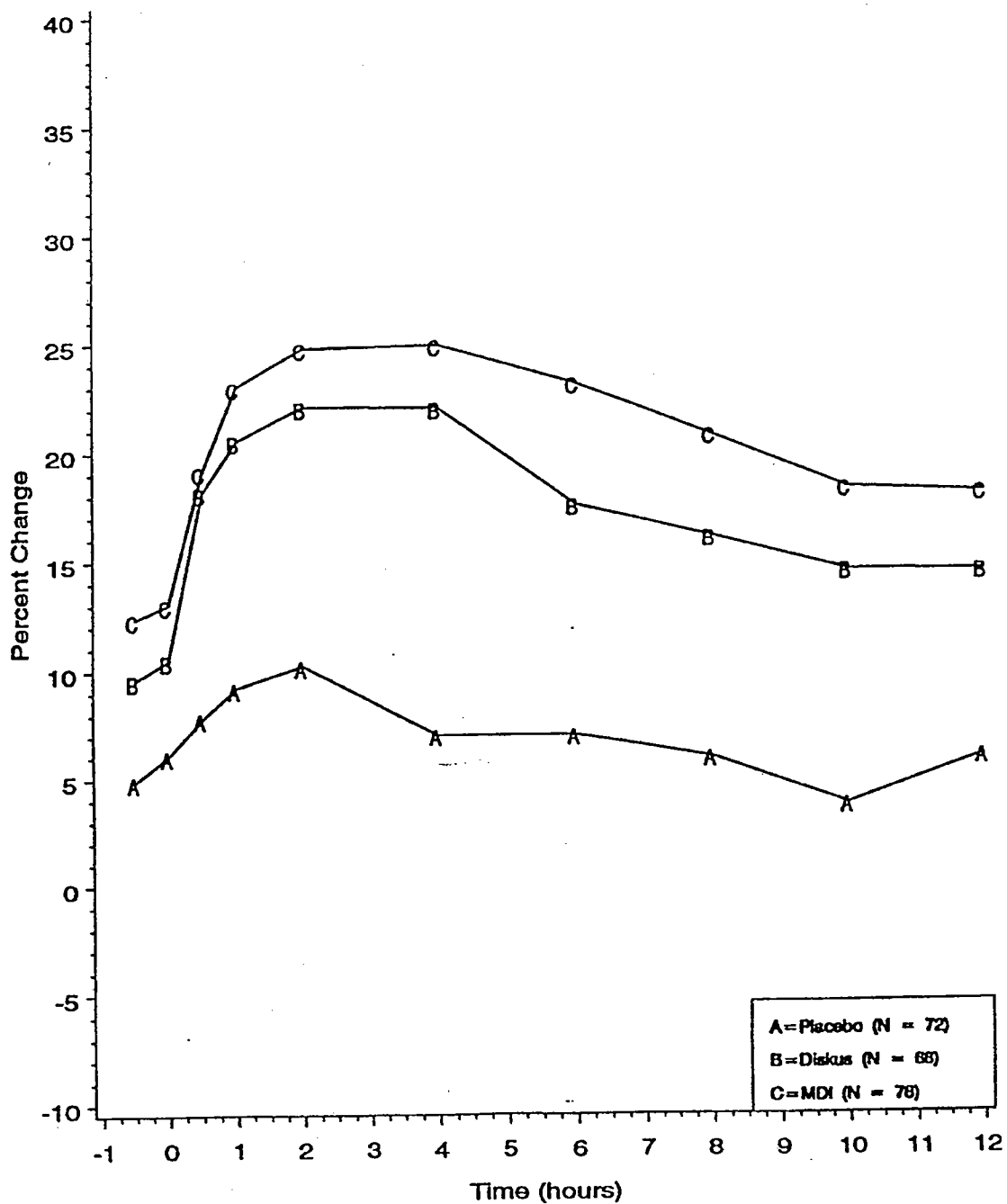
FIGURE 7
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Day 1



APPENDIX 3

Salmeterol Xinafoate Powder
Protocol: SLGA3010
Population: Intent-to-Treat

FIGURE 8
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Week 4



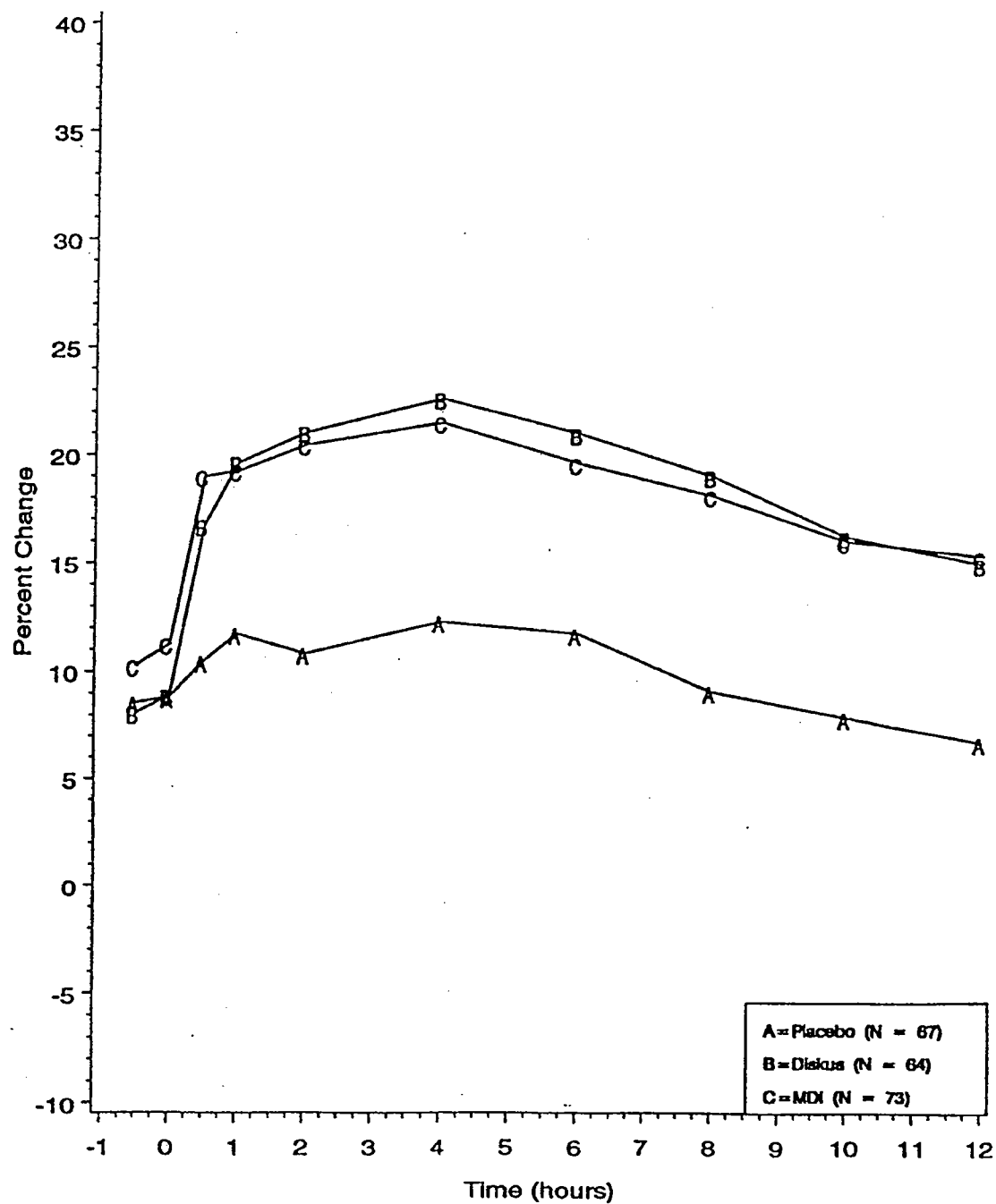
APPENDIX 4

Salmeterol Xinafoate Powder

Protocol: SLGA3010

Population: Intent-to-Treat

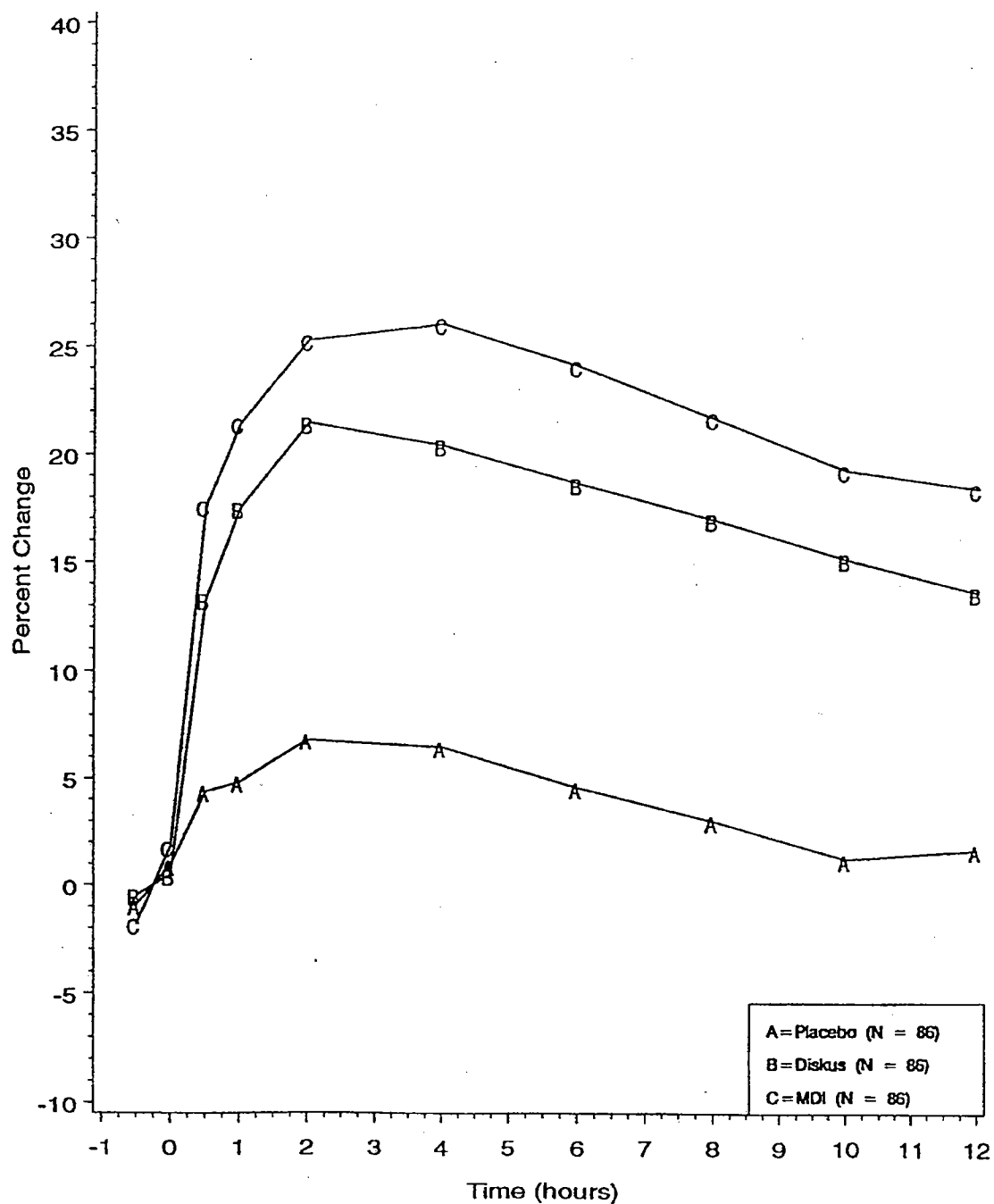
FIGURE 9
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Week 12



APPENDIX 5

Salmeterol Xinafoate Powder
Protocol: SLGA3011
Population: Intent-to-Treat

FIGURE 7
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Day 1



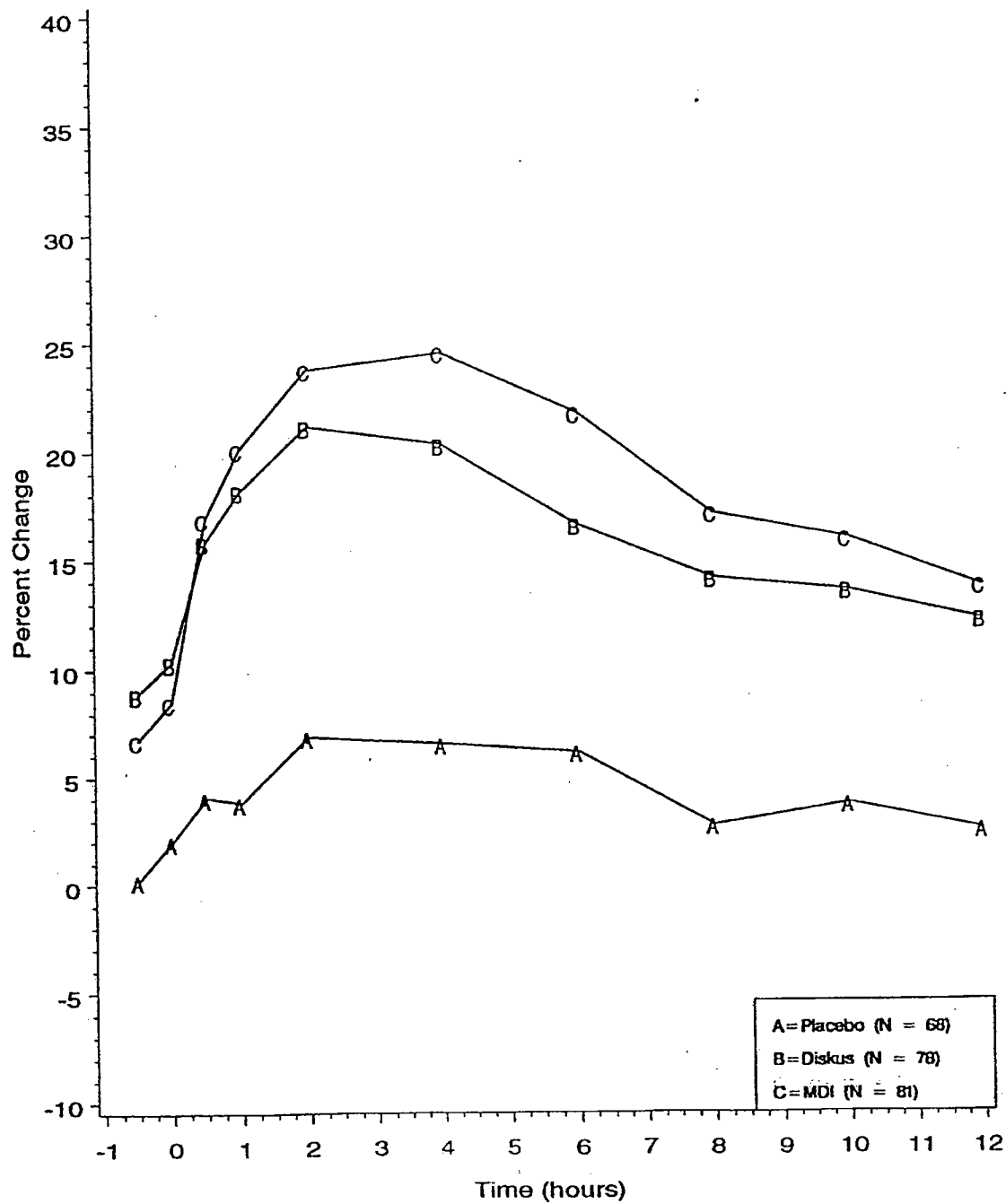
APPENDIX 6

Salmeterol Xinafoate Powder

Protocol: SLGA3011

Population: Intent-to-Treat

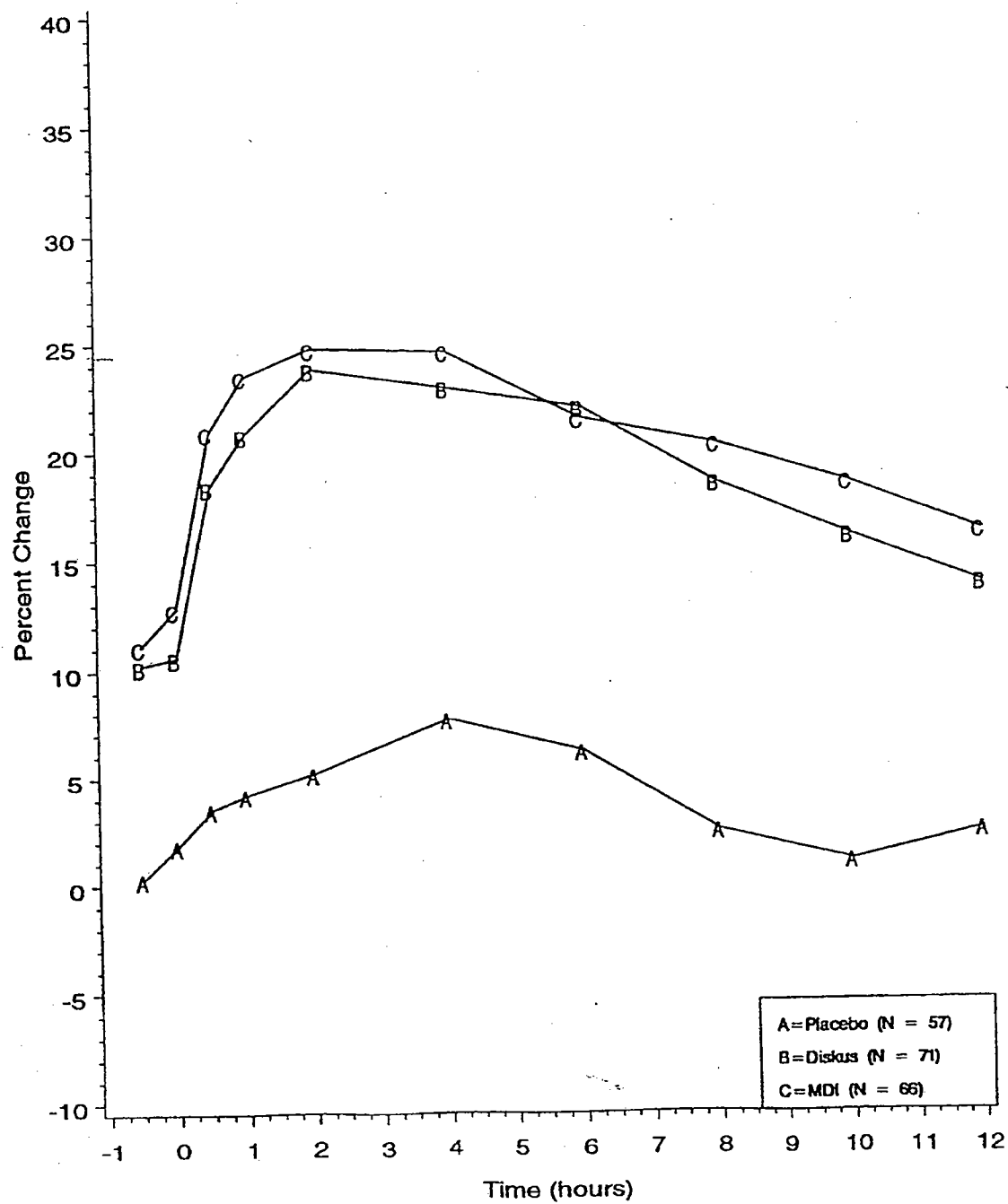
FIGURE 8
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Week 4



APPENDIX 7

Salmeterol Xinafoate Powder
Protocol: SLGA3011
Population: Intent-to-Treat

FIGURE 9
FEV1: PERCENT CHANGE FROM BASELINE
Treatment Week 12



19 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling