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)

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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 4-place, 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 FEV_1 of 70 to 90 percent of predicted normal during screening, demonstrated an increase in FEV_1 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 PD_{20} at concentrations of ≤ 7.5 mg/ml of methacholine. PD_{20} 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 FEV_1, 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 FEV_1, patients received five breaths each of increasing concentrations of methacholine (Provocholine by Roche) until the patient had three consecutive FEV_1 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 PD_{20} evaluation from the methacholine challenges. Secondary efficacy endpoints included the 12 hour serial spirometry evaluations, daily PEFR, 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 FEV_1 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 FEV_1. The sponsor indicated that a reliable estimate for standard deviation in PD_{20} 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 PD_{20} 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.

Reason	Placebo	Salmeterol
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 FEV_1 was 2.9 L, or 79 percent of predicted normal, for both treatment groups and percent reversibility was 20 to 21 percent. The PD_{20} (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 PD_{20} 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 PD_{20} 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 PD_{20} 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 FEV_1 values were consistently statistically and clinically superior for the salmeterol group as compared to the placebo group, as were the associates FEV_1 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.

Patient No.	Adverse Event
Salmeterol	
Chervinsky 429	Bone graft to repair fractured wrist
Kemp 228	Appendectomy
Kemp 437	Hospitalization for asthma exacerbation and gastroenteritis
Rosenthal 165	Appendectomy
Scanlon 184	Asthma exacerbation
Placebo	
Chervinsky 237*	Supraventricular tachycardia
Ramsdell 266	TIA
Rosenthal 518	Bilateral hernia
Shapiro 36	Status Asthmaticus
Sim 169*	Adenocarcinoma
Wolfe 83	Fracture and laceration of arm

Two additional patients were discontinued due to adverse events. Chervinsky 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, Kemp 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.

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.

Subject No.	Adverse Event
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	Myosis 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 FEV_1 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 treatments 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.

Subject No.	Adverse Event
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.

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 4-place, 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 FEV_1 and parameters derived from FEV_1 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 FEV_1 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 FEV_1 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 FEV_1 value and percent of predicted. Thereafter, data indicate mean percentage change from Treatment Day 1 baseline.

Parameters derived from FEV_1 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 FEV_1. 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 FEV_1 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 FEV_1 response in terms of AUC and maximum effect. Peak expiratory flow data corroborated the trend in FEV_1 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 FEV_1 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 FEV_1. 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 FEV_1 data showed that within treatment effects (FEV_1 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 FEV_1 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 FEV_1 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 FEV_1 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 FEV_1.

In Trial SLGA2004, the serial FEV_1 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 FEV_1 treatment outcomes in these trials.

Inhaled Corticosteroid Use

Baseline values for FEV_1 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 FEV_1 was presented.

In Trial SLGA2004, patients using no inhaled corticosteroids had lower baseline FEV_1 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 FEV_1 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 8-place 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 8-place 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 FEV_1 and related parameters as primary endpoints. Further, the 8-place standard fill DH was compared to the 4-place standard fill DH in Trial SLGH18. This was in turn compared to the 4-place reduced fill DH in Trials SLGH28 and SLGH29. Overall, the comparisons of FEV_1 data suggested clinical comparability among the dosage forms. It was the 4-place 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 4-place 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 FEV_1 bronchodilatory response and PD_{20} 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 4-place 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 4-place, 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.

Assessment	MDPI	DPI
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 be 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 MDPI	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

	Salmeterol 50 mcg N = 149	Placebo N = 152	Albuterol 180 mcg N = 150
Ear, Nose & Throat			
Disease nasal cavity/sinus	14 (9)	9 (6)	12 (8)
Rhinitis	7 (5)	6 (4)	6 (4)
Respiratory System Disorders			
Tracheitis/Bronchitis	10 (7)	6 (4)	5 (3)
Influenza	7 (5)	3 (2)	8 (5)
Asthma	5 (3)	2 (1)	1 (<1)
Gastrointestinal			
Diarrhea	4 (3)	1 (<1)	5 (3)
Nausea	4 (3)	3 (2)	3 (2)
Body as a Whole			
Localized Aches/Pains	4 (3)	2 (1)	3 (2)
Pyrexia of Unknown Origin	4 (3)	2 (1)	2 (1)
Mouth and Teeth			
Oral Mucosal Abnormality	4 (3)	1 (<1)	3 (2)
Neurological			
Headache	20 (13)	13 (9)	18 (12)

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: ear ache, otitis externa, sinus headache, disorder of the eye, exophthalmic conditions, conjunctivitis, **gastritis**, hemorrhage of rectum/anus,

decreased WBC count, **allergy**, ill-defined conditions, contusion of shoulder/upper arm, periocular laceration, postoperative pain, **conditions of the tongue, periapical abscess**, pain in joint, myalgia/myositis, sprain/strain:knee/leg, fracture:metatarsus, torticollis, **muscle cramp/contraction**, strain: shoulder/upper arm, sprain/strain of back, **sleep disturbance, paresthesia**, memory/thought disorder, **disturbance: smell + taste, agitation**, respiratory abnormalities, pneumonia, **disease:trachea/bronchus, adverse effect:drug/biol., contact dermatitis**/eczema, contusion, disease of skin, bruise:face/scalp/neck, cystitis.

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, particulary 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 (Wolfe 233) and in Trial SLD-312 (Grady 79) who were reported to have elevated liver enzymes during treatment with salmeterol and a single SLD-312 patient (Ellis 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 FEV_1 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 PEFR 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.

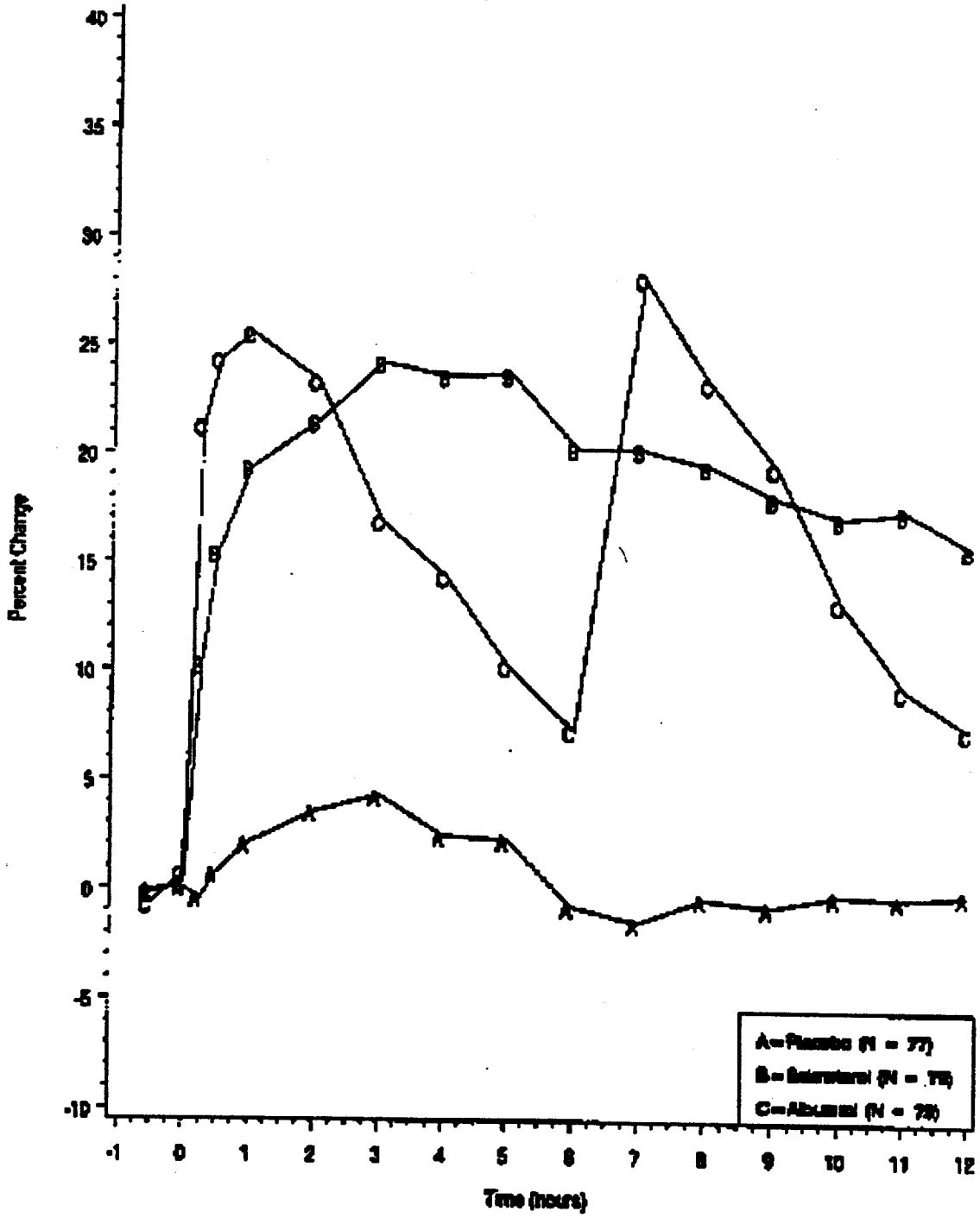
APPENDIX 1

Salmeterol Xinafoate Powder
Protocol: SLD-911
Population: Efficacy

FIGURE 19

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Day 1



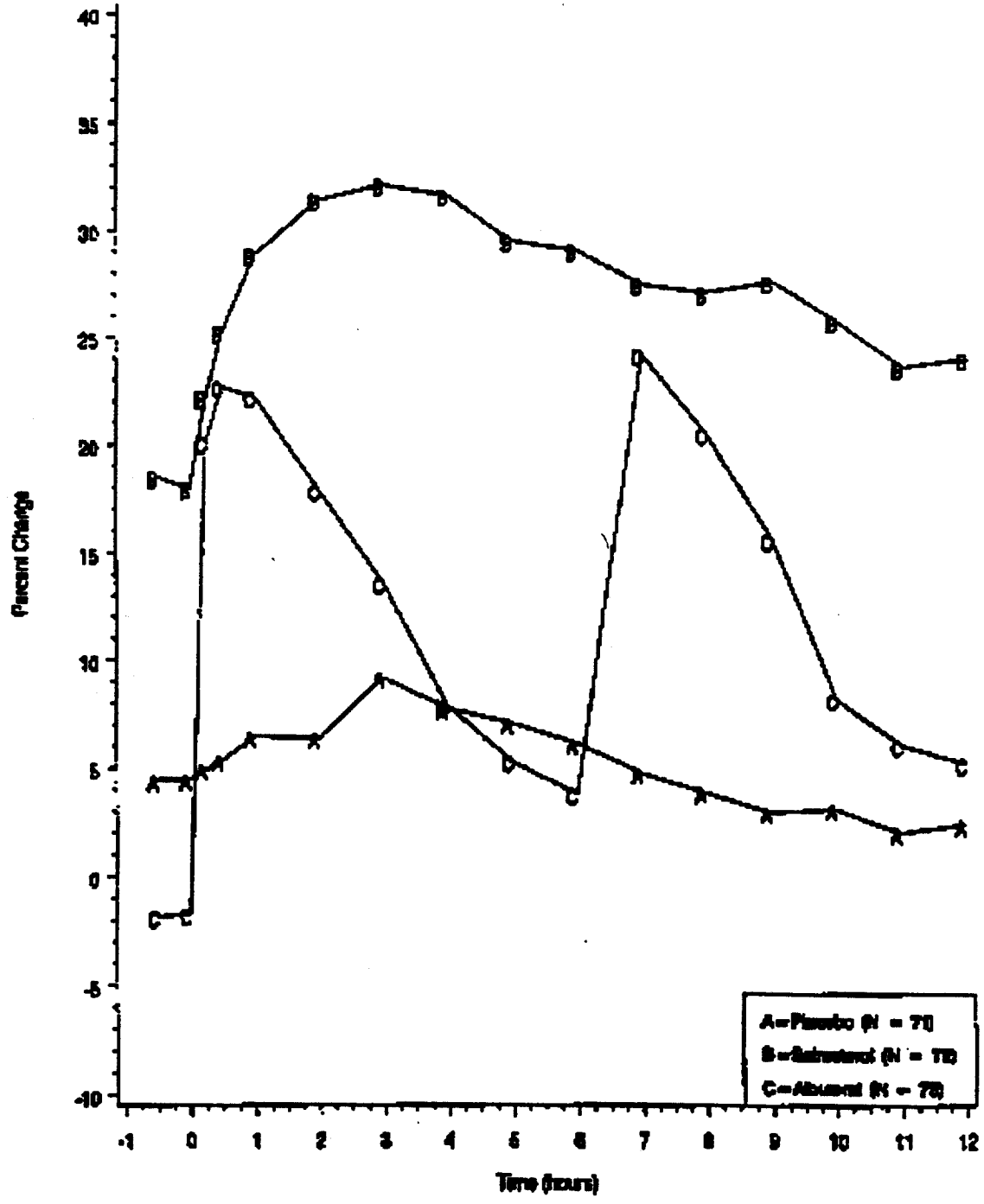
APPENDIX 2 **BEST POSSIBLE COPY**

Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 14

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 4



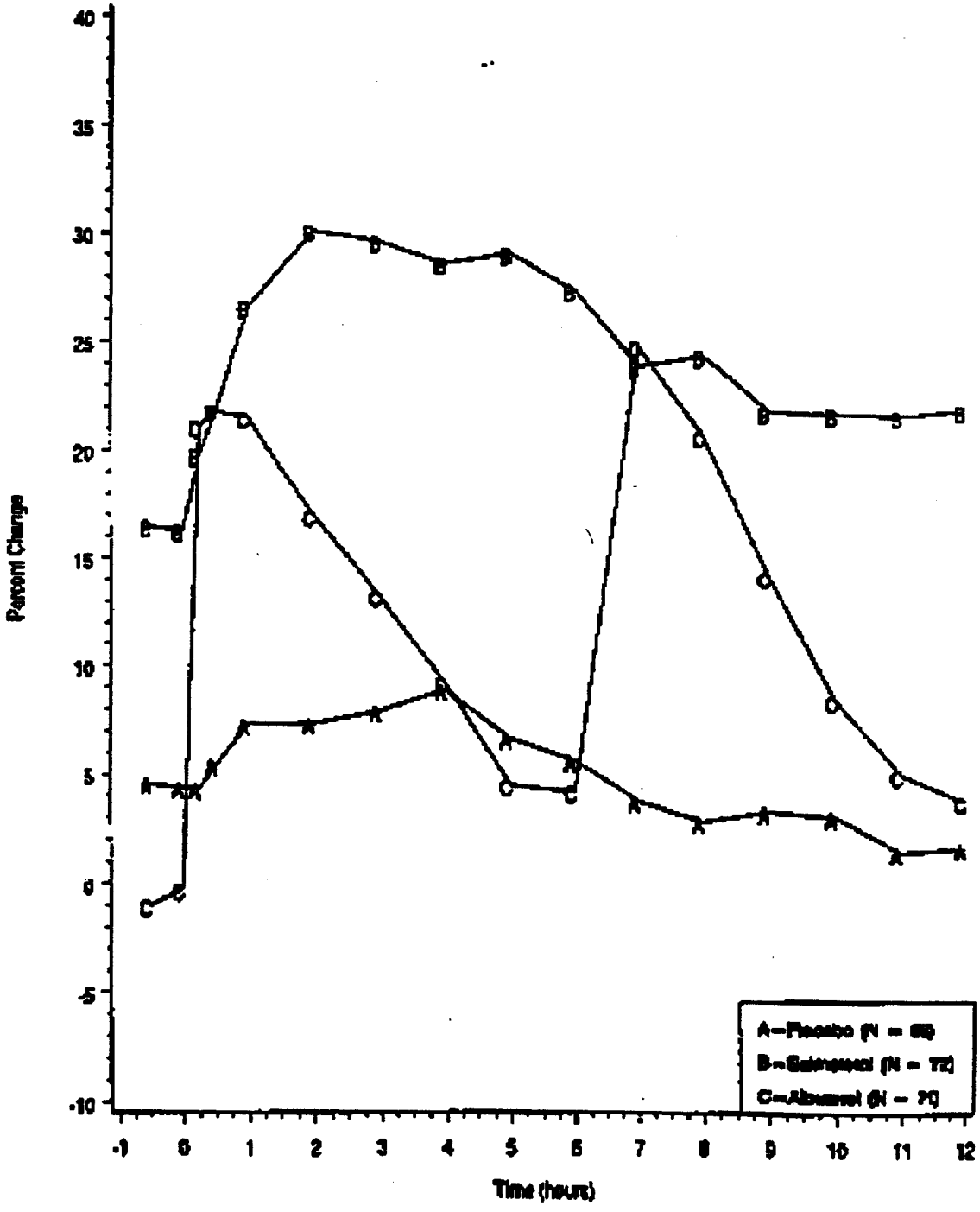
APPENDIX 3

Salmeterol Xinafoate Powder
Protocol: SLD - 311
Population: Efficacy

FIGURE 15

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 8



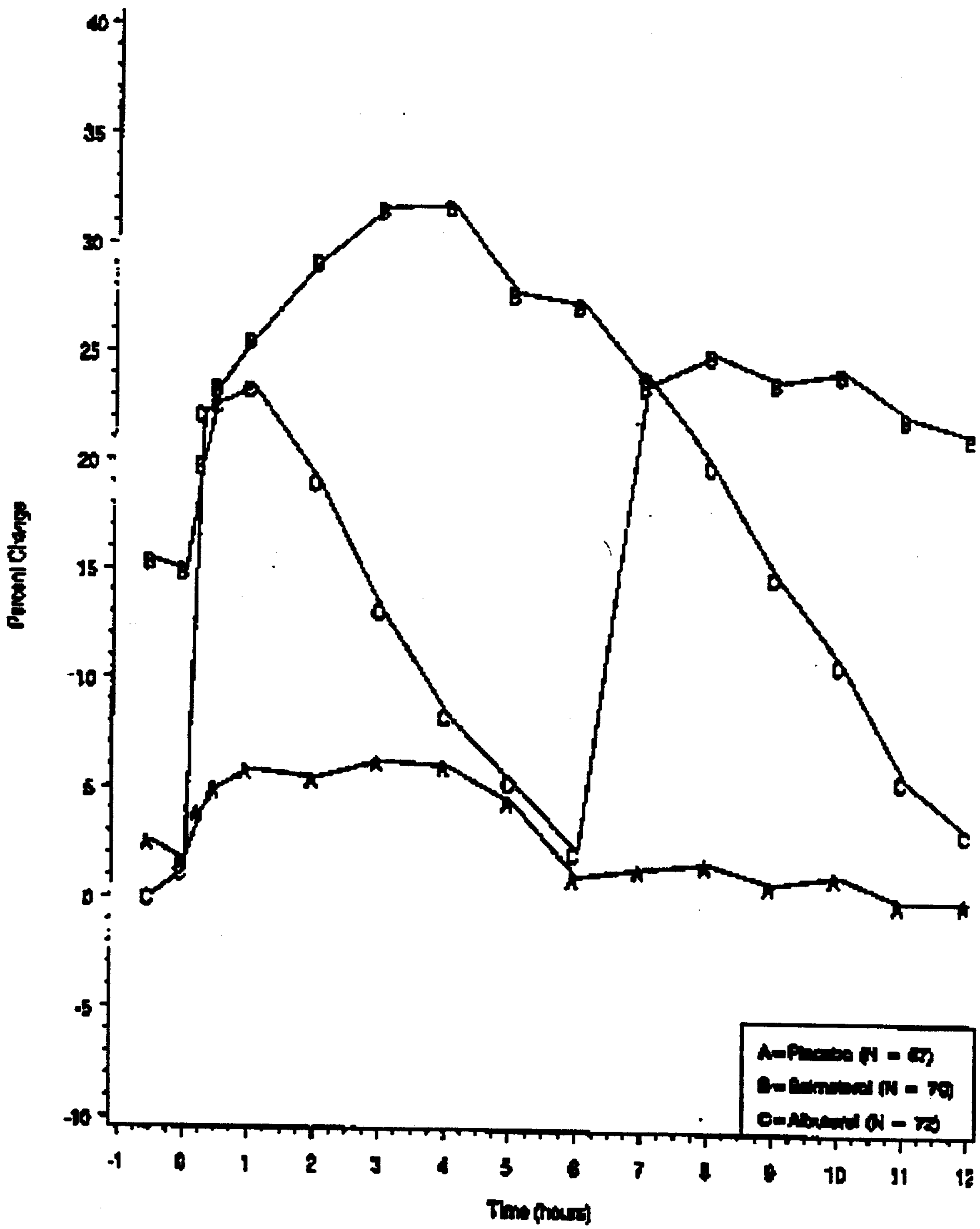
APPENDIX 4 **BEST POSSIBLE COPY**

Salmeterol Xinafoate Powder
Protocol: SLD - 3[illegible]
Population: Efficacy

FIGURE 18

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 12



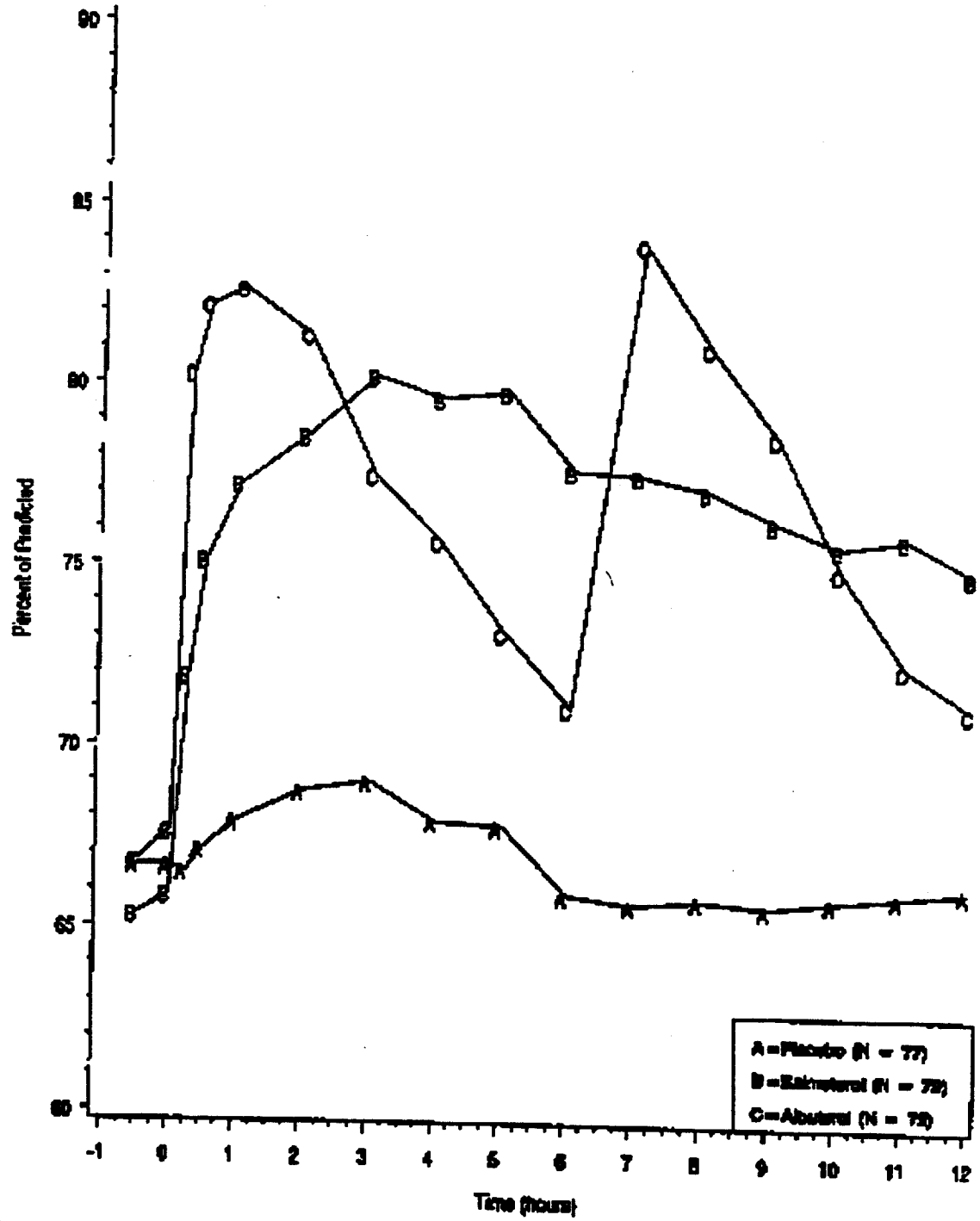
APPENDIX 5

Salmeterol Xinafoate Powder
Protocol: SLD – 311
Population: Efficacy

FIGURE 17

FEV1: PERCENT OF PREDICTED

Treatment Day 1



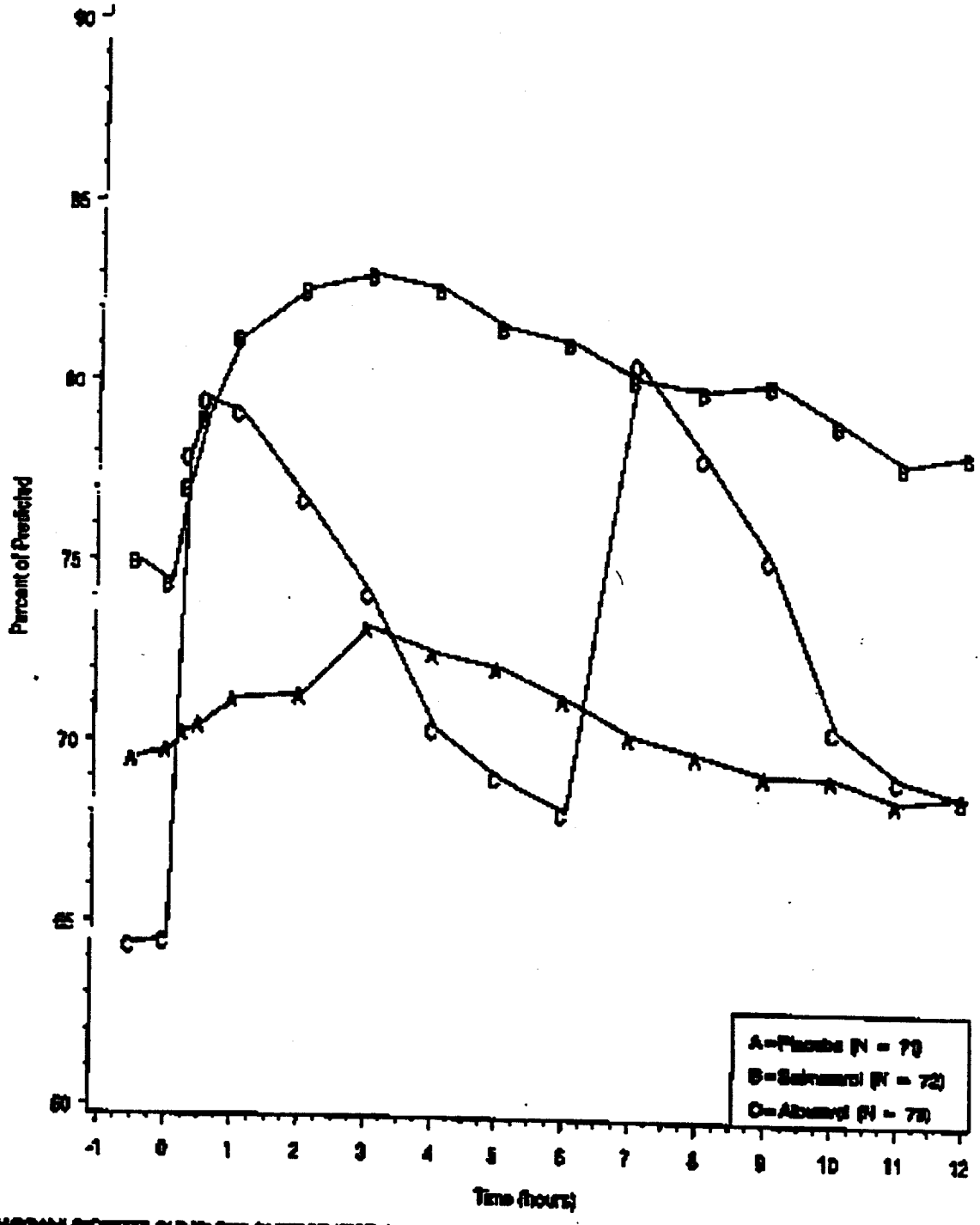
APPENDIX 6

Salmeterol Xinafoate Powder
Protocol: SLD – 911
Population: Efficacy

FIGURE 18

FEV1: PERCENT OF PREDICTED

Treatment Week 4



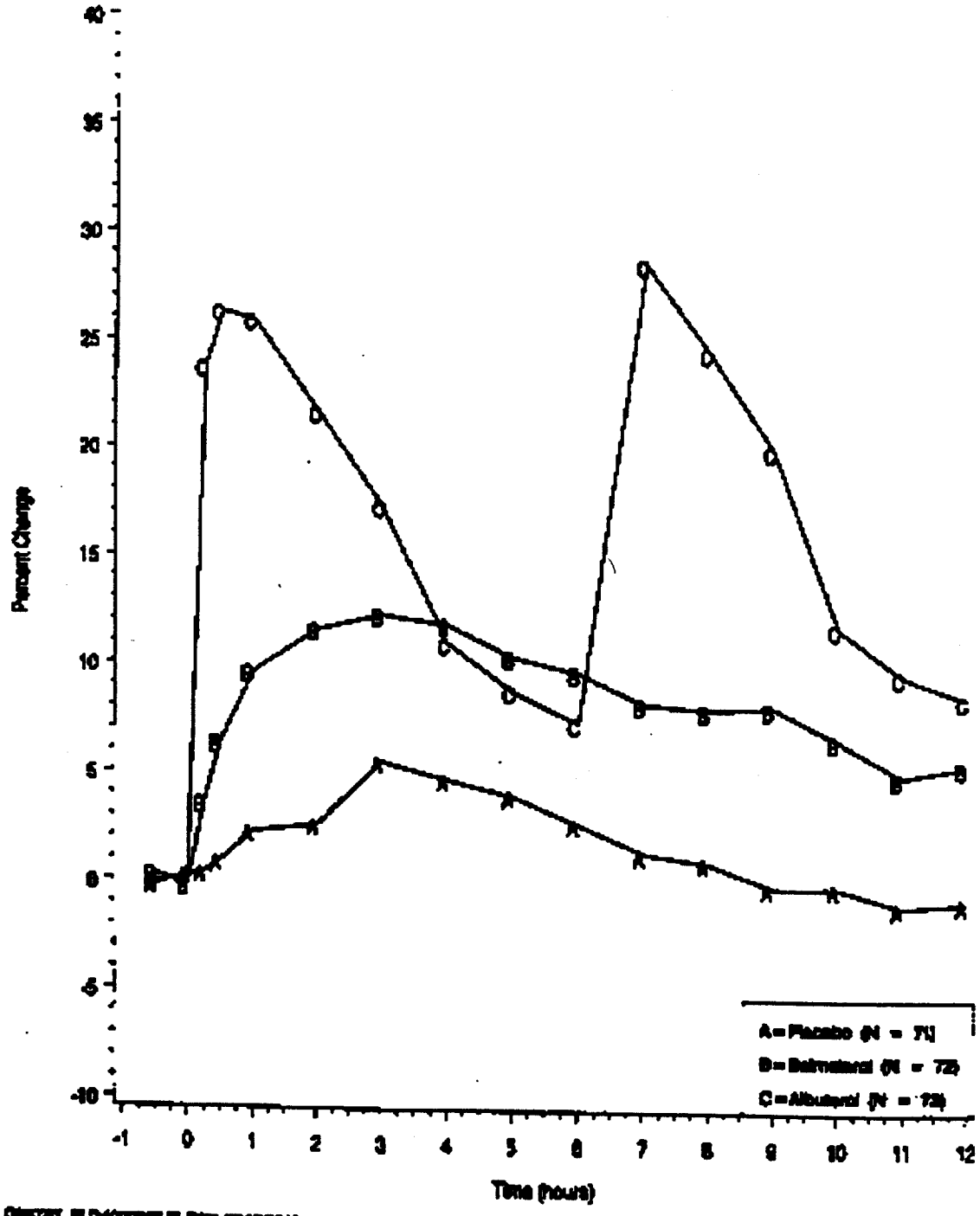
APPENDIX 7

Salmeterol Xinafoate Powder
Protocol: SLD – 311
Population: Efficacy

FIGURE 2

FEV1: PERCENT CHANGE FROM DAILY BASELINE

Treatment Week 4



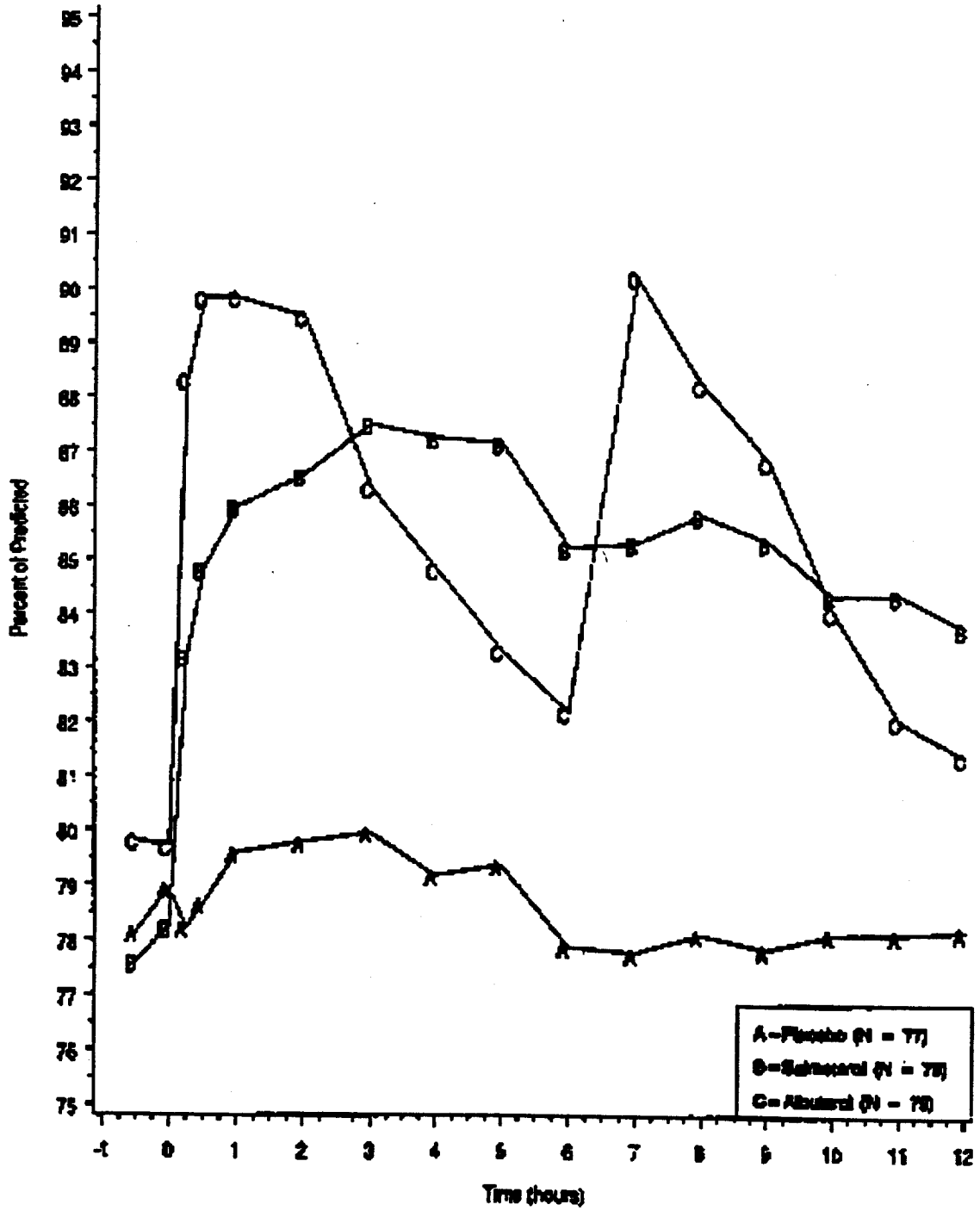
APPENDIX 8

Salmeterol Xinafoate Powder
Protocol: SLD – 311
Population: Efficacy

FIGURE 25

FVC: PERCENT OF PREDICTED

Treatment Day 1



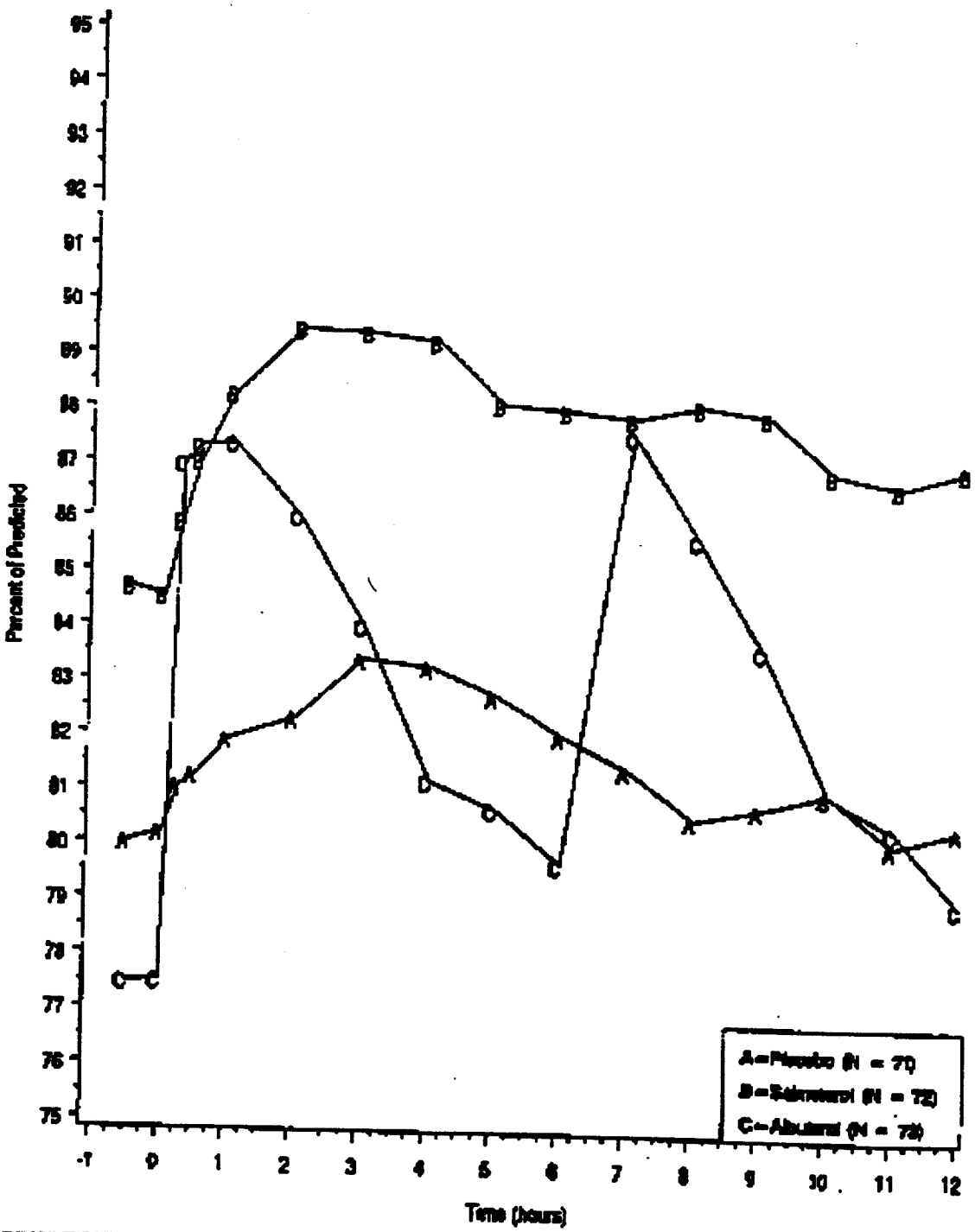
APPENDIX 9

Salmeterol Xinafoate Powder
Protocol: SLD – 311
Population: Efficacy

FIGURE 28

PVC: PERCENT OF PREDICTED

Treatment Week 4



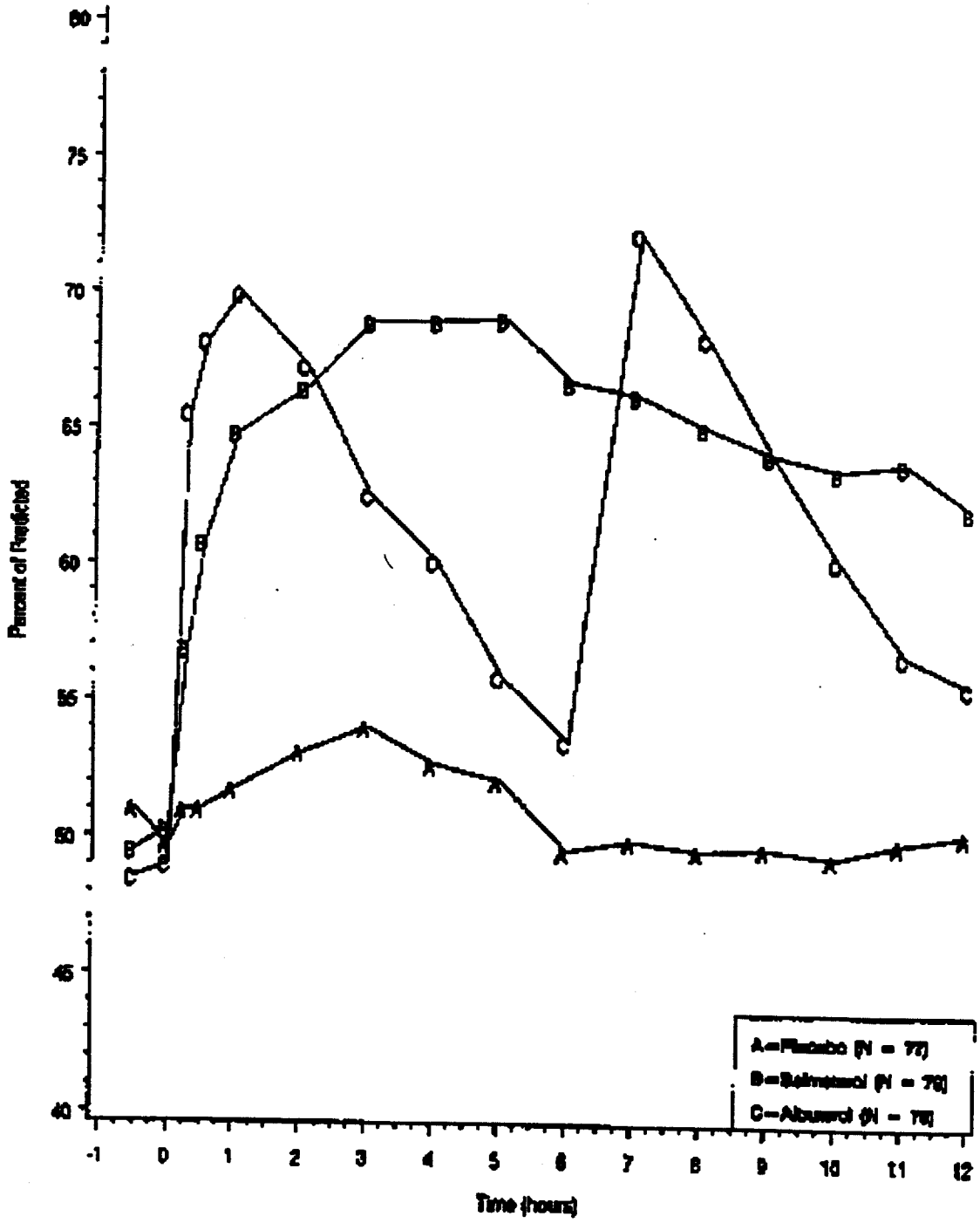
APPENDIX 10

Salmeterol Xinafoate Powder
Protocol: SLD – 311
Population: Efficacy

FIGURE 21

FEF: PERCENT OF PREDICTED

Treatment Day 1



[illegible]

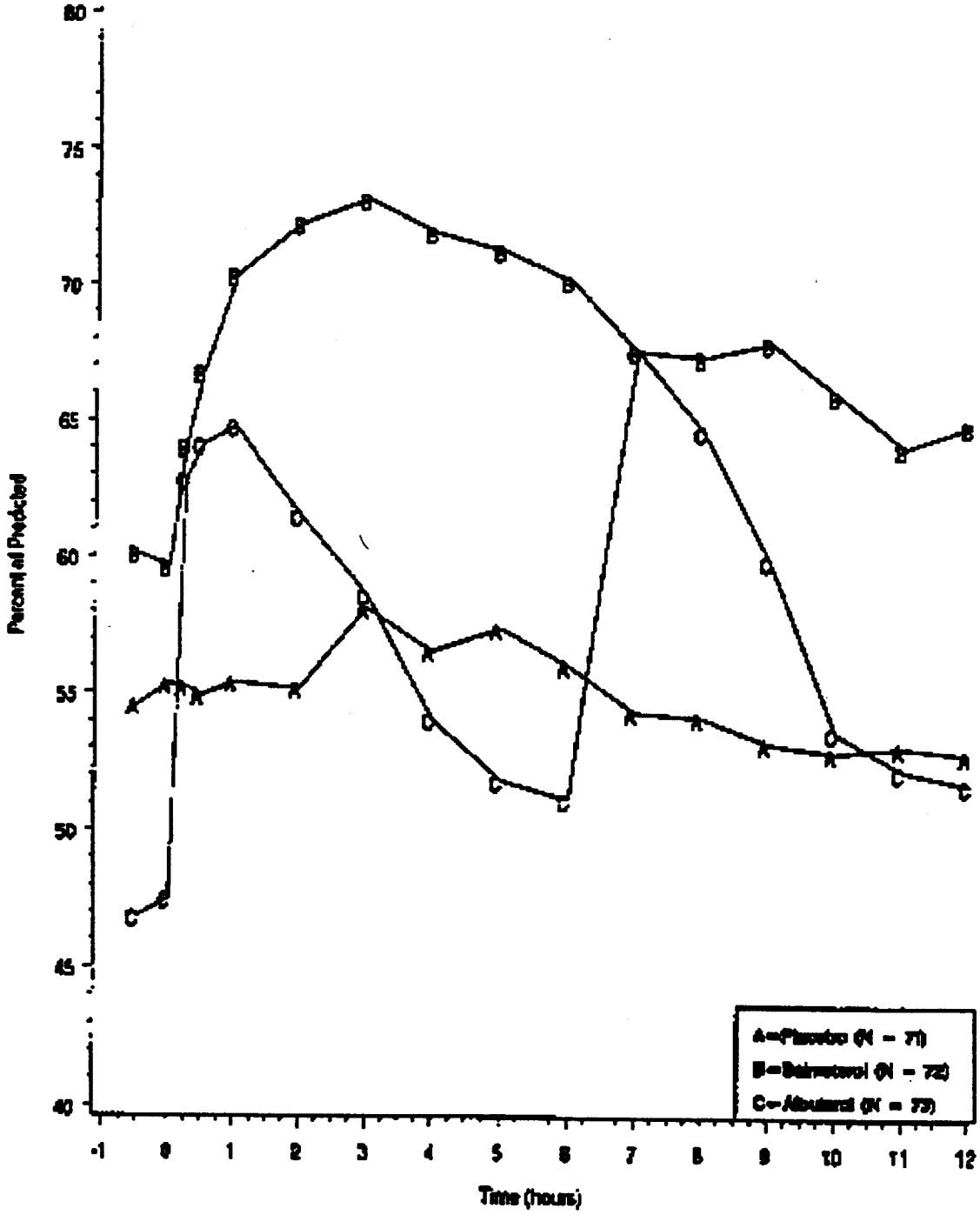
APPENDIX 11

Salmeterol Xinafoate Powder
Protocol: SLD-311
Population: Efficacy

FIGURE 22

FEF: PERCENT OF PREDICTED

Treatment Week 4



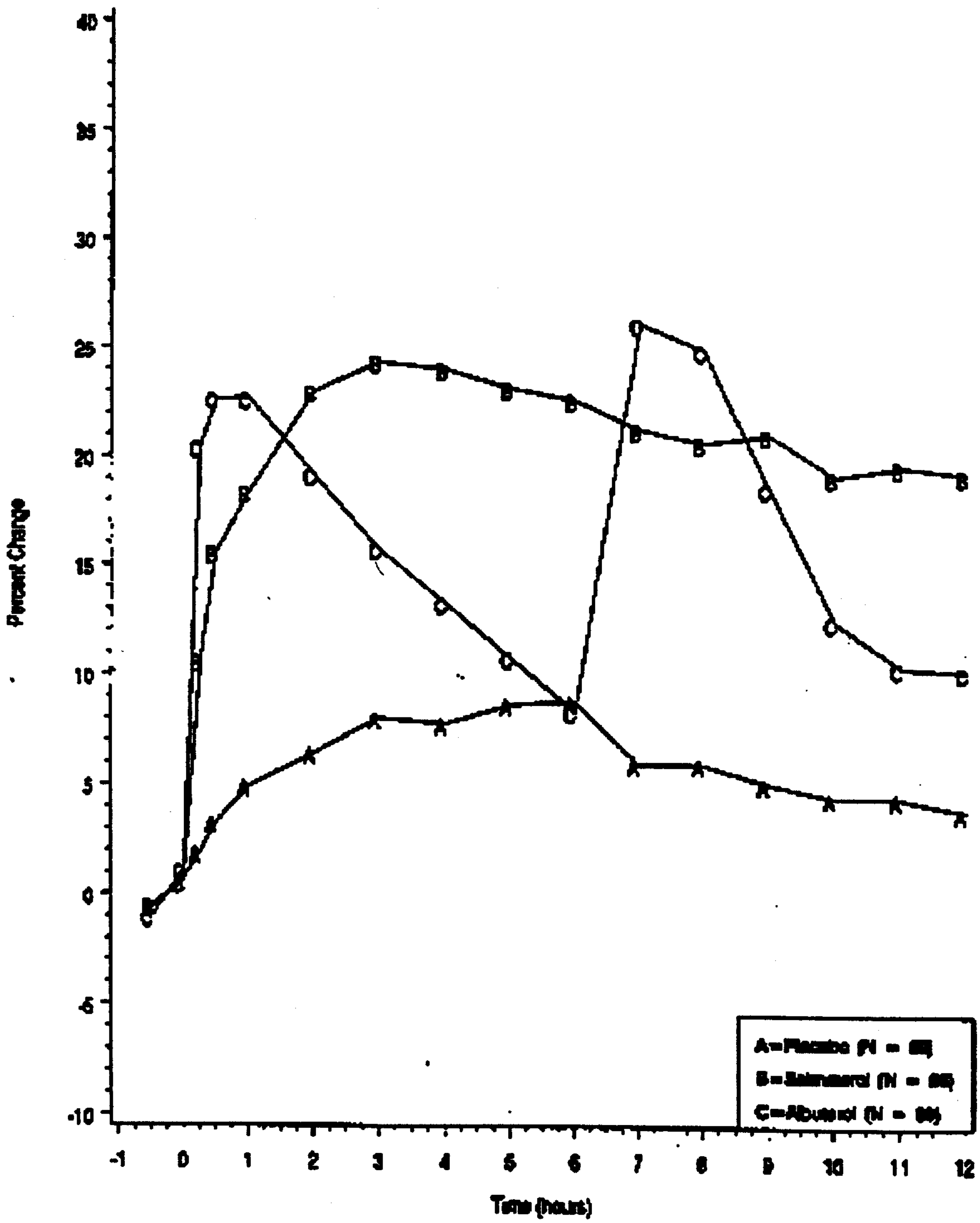
APPENDIX 12

Salmeterol Xinafoate Powder
Protocol: SLD-312
Population: Efficacy

FIGURE 13

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Day 1



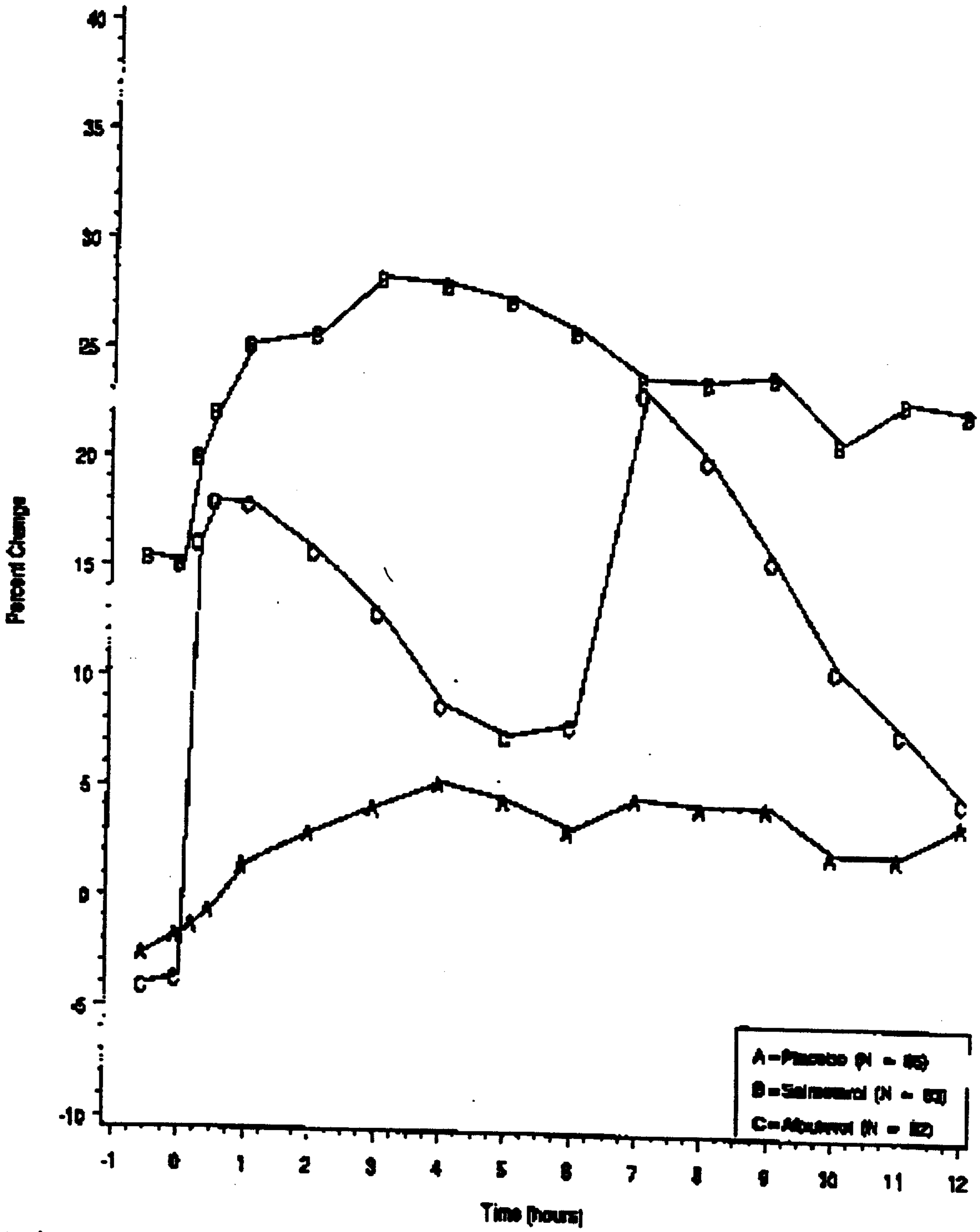
APPENDIX 13

Salmeterol Xinafoate Powder
Protocol: SLD-312
Population: Efficacy

FIGURE 14

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 4



[illegible]

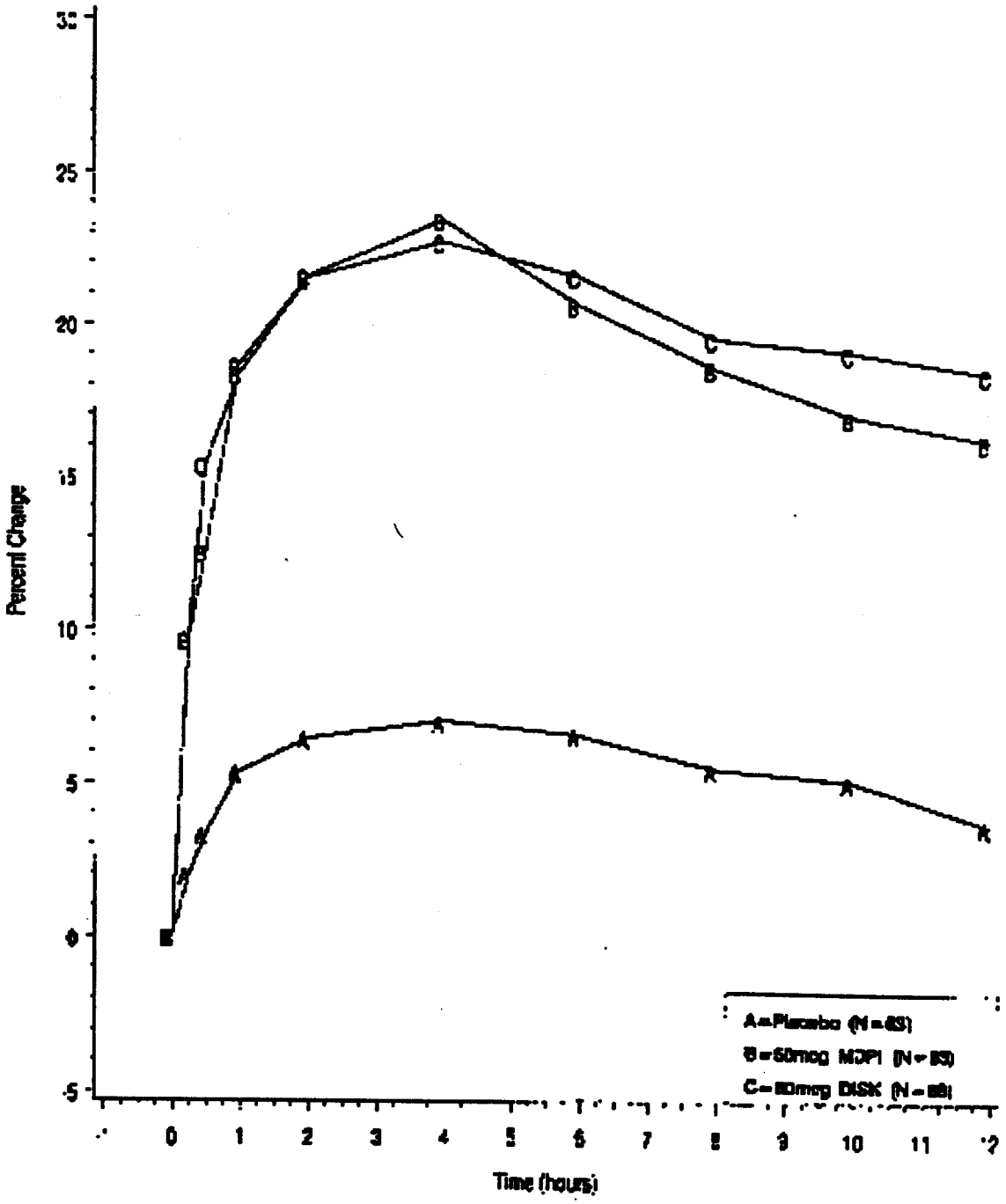
APPENDIX 14

Salmeterol Xinafoate MDPI
Protocol: SLGA2004
Population: Efficacy

FIGURE 5

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Day 1



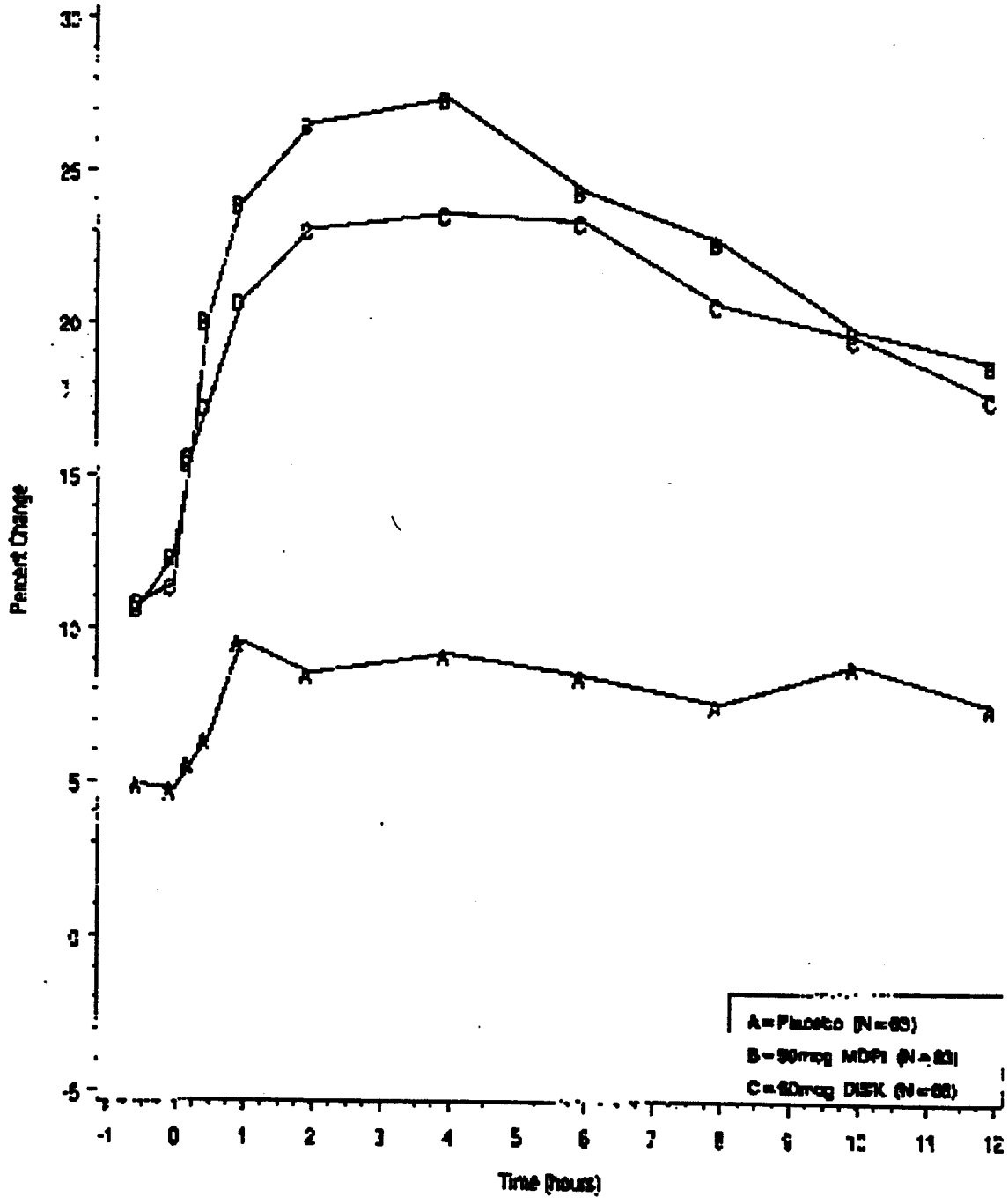
APPENDIX 15

Salmeterol Xinafoate MDPI
Protocol: SLGA2004
Population: Efficacy

FIGURE 6

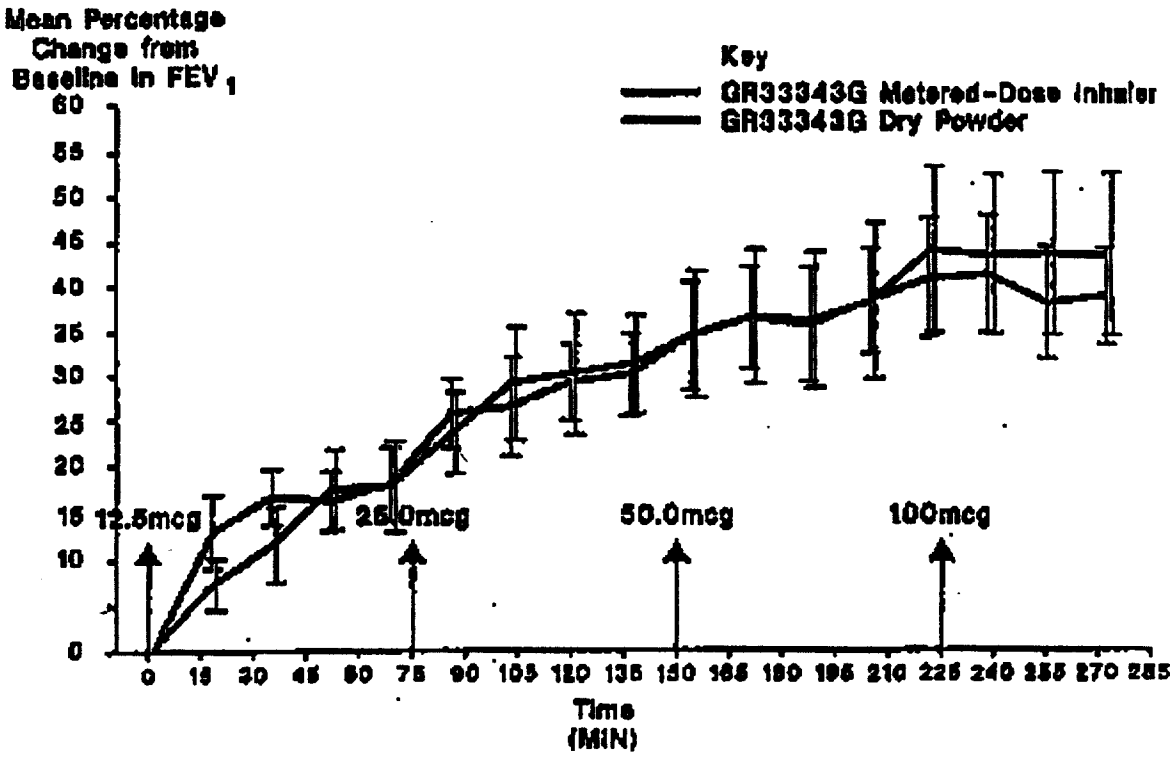
FEV1: PERCENT CHANGE FROM BASELINE

Treatment Day 29



APPENDIX 16

MEAN PERCENTAGE CHANGE IN BASELINE IN FEV_1 FOR EACH TREATMENT

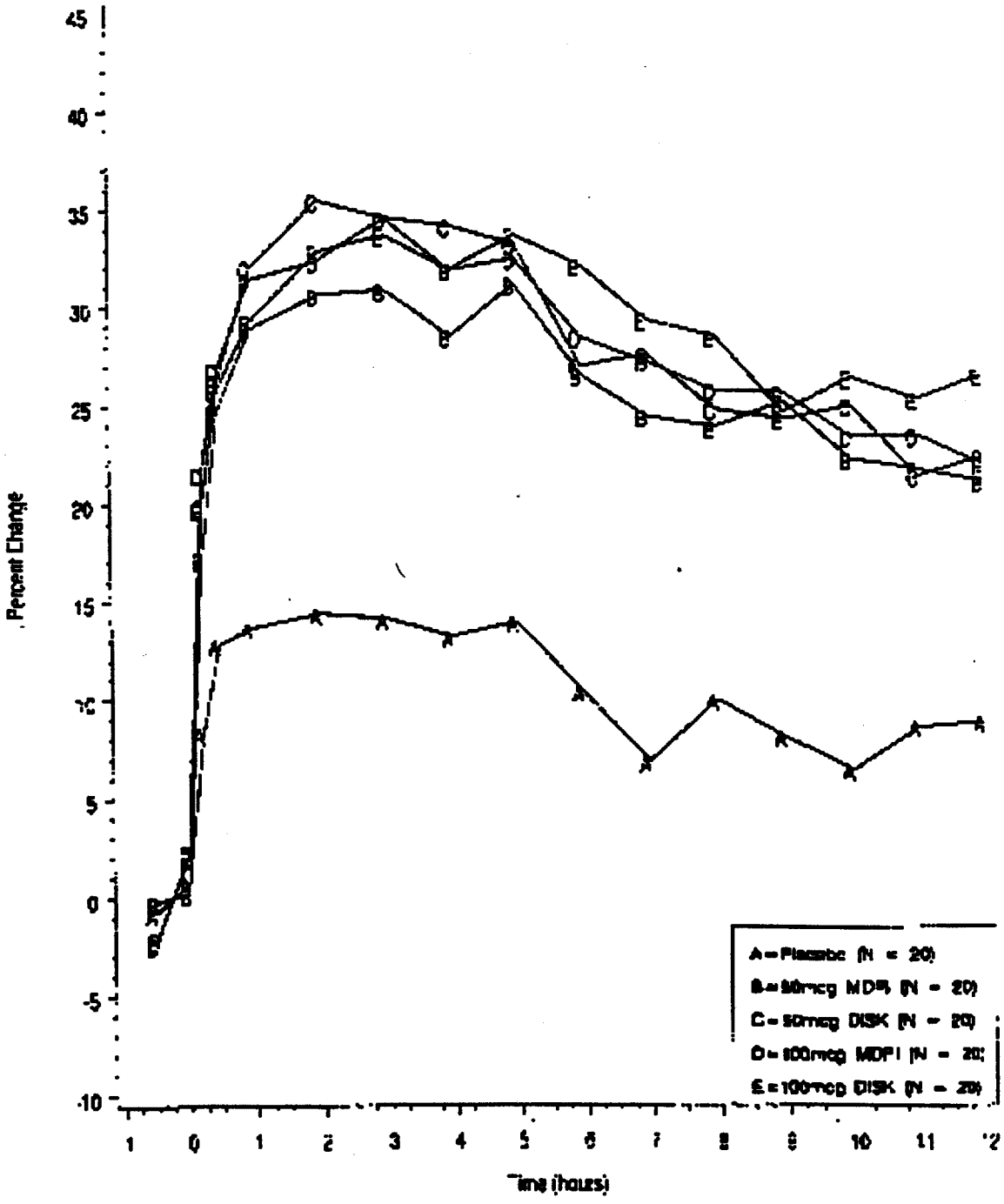


APPENDIX 17

Salmeterol Xinafoate MDPI
Protocol. SLGA2001
Population: Intent-to-Treat

FIGURE 3

FEV1: PERCENT CHANGE FROM BASELINE



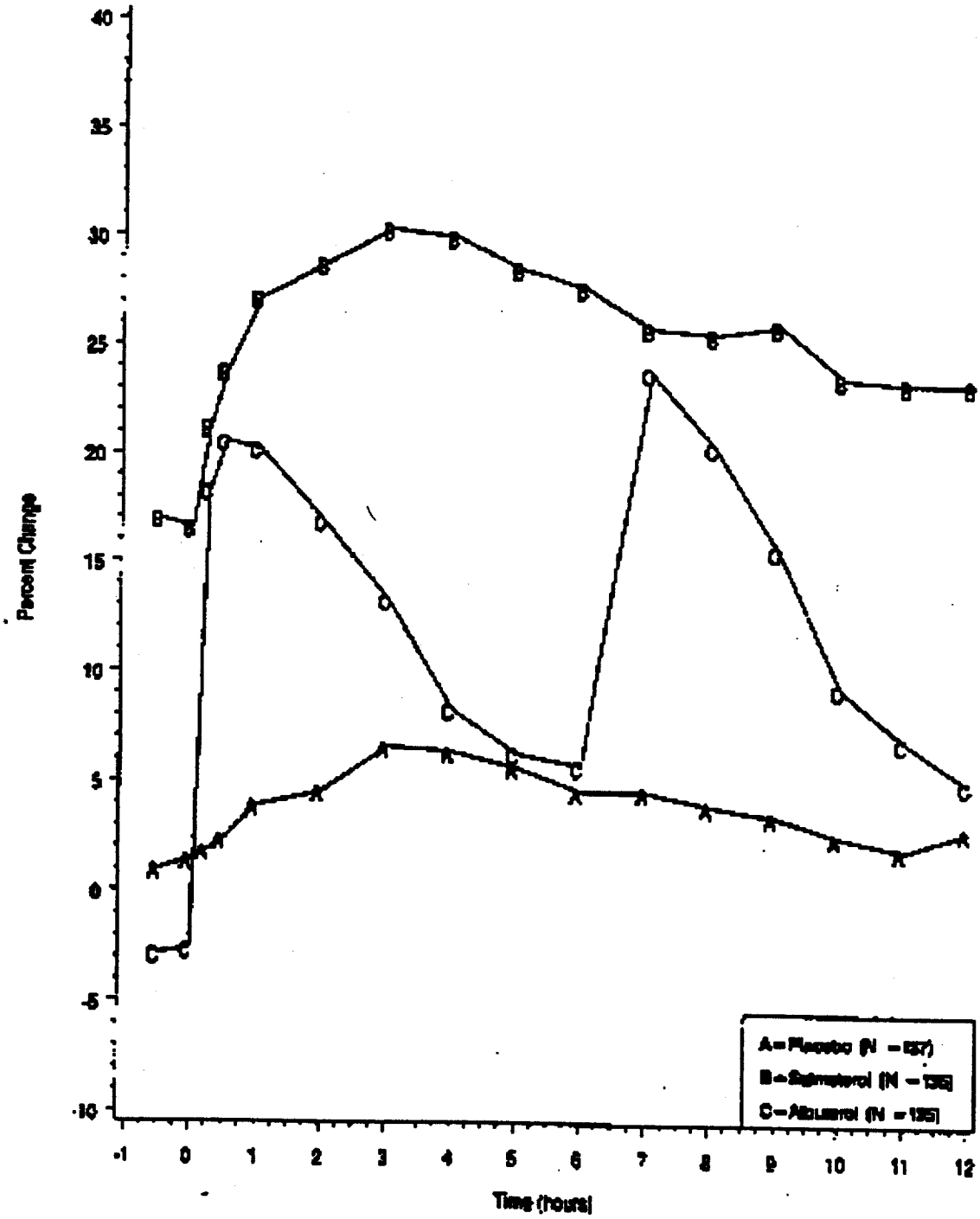
APPENDIX 18

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

Figure C1 (continued)

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 4



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

N drive location: N:\nda\20692\clin\97-09-26.rev

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: _____ Approvable _____ Not Approvable

Signed: **Medical Reviewer:** _____ **Date:** 9-16-97

Medical Team Leader: _____ **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: James Grady, M.D., Boulder CO
Robert Nathan, M.D., Colorado Springs CO
David Pearlman, M.D., Aurora CO

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 FEV_1. 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 FEV_1 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 FEV_1 [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 FEV_1 values.
[c] Average is the weighted average of the post-dose FEV_1 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 FEV_1 analyses (no analyses of percent change

from baseline were provided).

Functions of serial FEV_1 are shown in Table 2.

Table 2: Metrics of Serial FEV_1

	Placebo	MDI 50	Diskus 25	Diskus 50	Diskus 100
Percent w/ > 15% Response	52	94	81	89	92
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 FEV_1 data do not clearly indicate that a clinically important difference exists among the Diskus doses. FEV_1 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 FEV_1 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:

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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 FEV_1 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 FEV_1 (average of the –0.5 and 0 hour FEV_1 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 FEV_1 as the covariate) were conducted on absolute serial FEV_1 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 FEV_1 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 FEV_1

	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 FEV_1 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 PEFR, PM PEFR or AM/PM differential. Baseline PEFR (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 PEFR 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: FEV_1 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 pO_2). 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 Disturbance	1	3	4
Lymphatic Signs and Sx	0	0	2

Mean change and shift analyses of pulse data collected during serial FEV_1 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.

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.

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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. Amill's 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 FEV_1 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 FEV_1 metrics at Weeks 1, 4 and 12.

Table 5: Metrics of Serial FEV_1

	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 posttreament 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 failures pe Those which occurred at a rate of part per 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 FEV_1 as a percent of predicted. In addition, the key for these figures should include daily dosage.

The proposed brand name, Serevent Accuhaler, is not acceptable from a clinical perspective. It is felt to be promotional in that it suggests that the Diskus device performance is in some respect more precise than with other devices.

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.

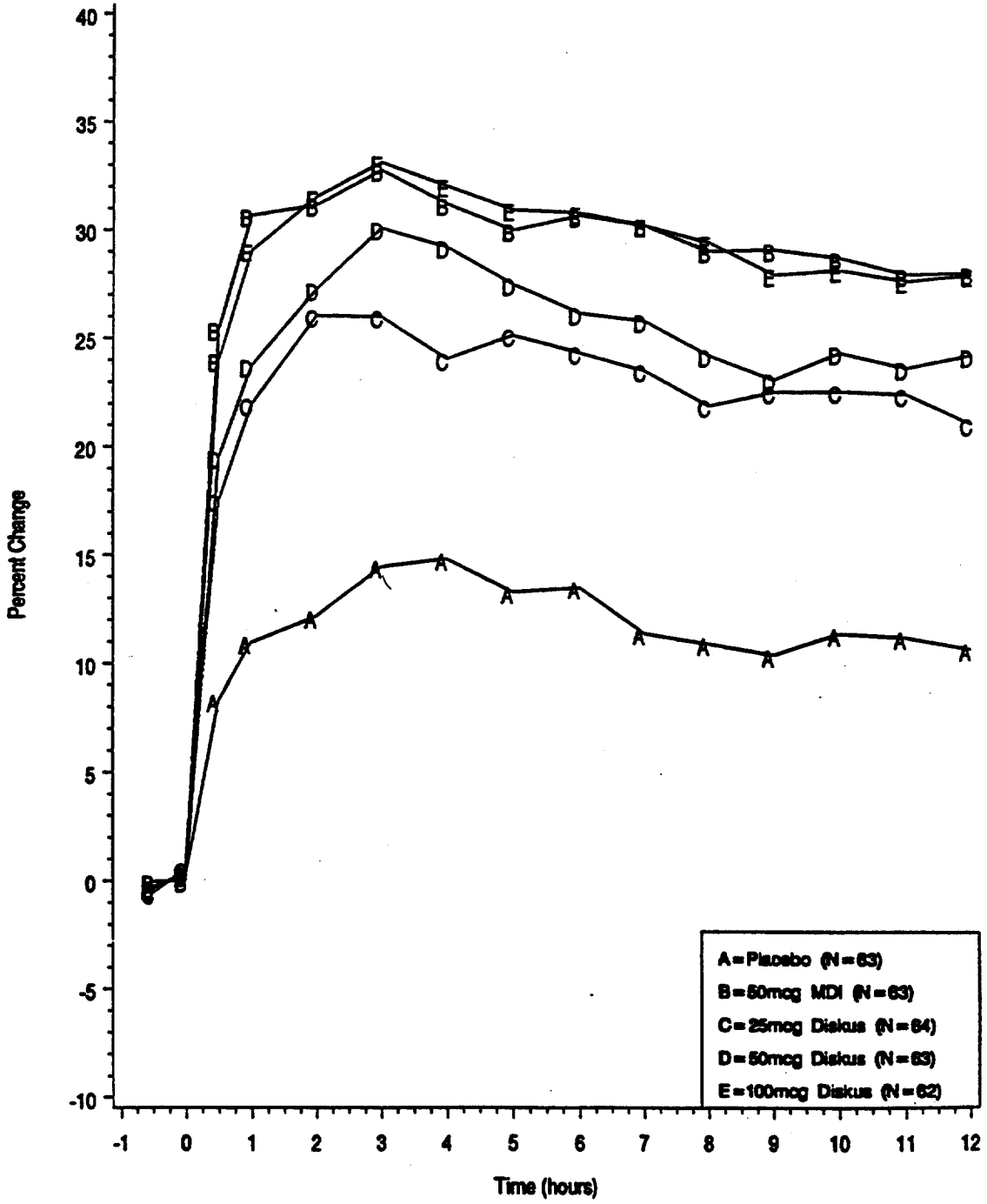
3. Upon adequate documentation of the sponsor's acceptance of these changes, the NDA may be approved from a clinical standpoint.

APPENDIX 1

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

FIGURE 3

FEV1: PERCENT CHANGE FROM BASELINE

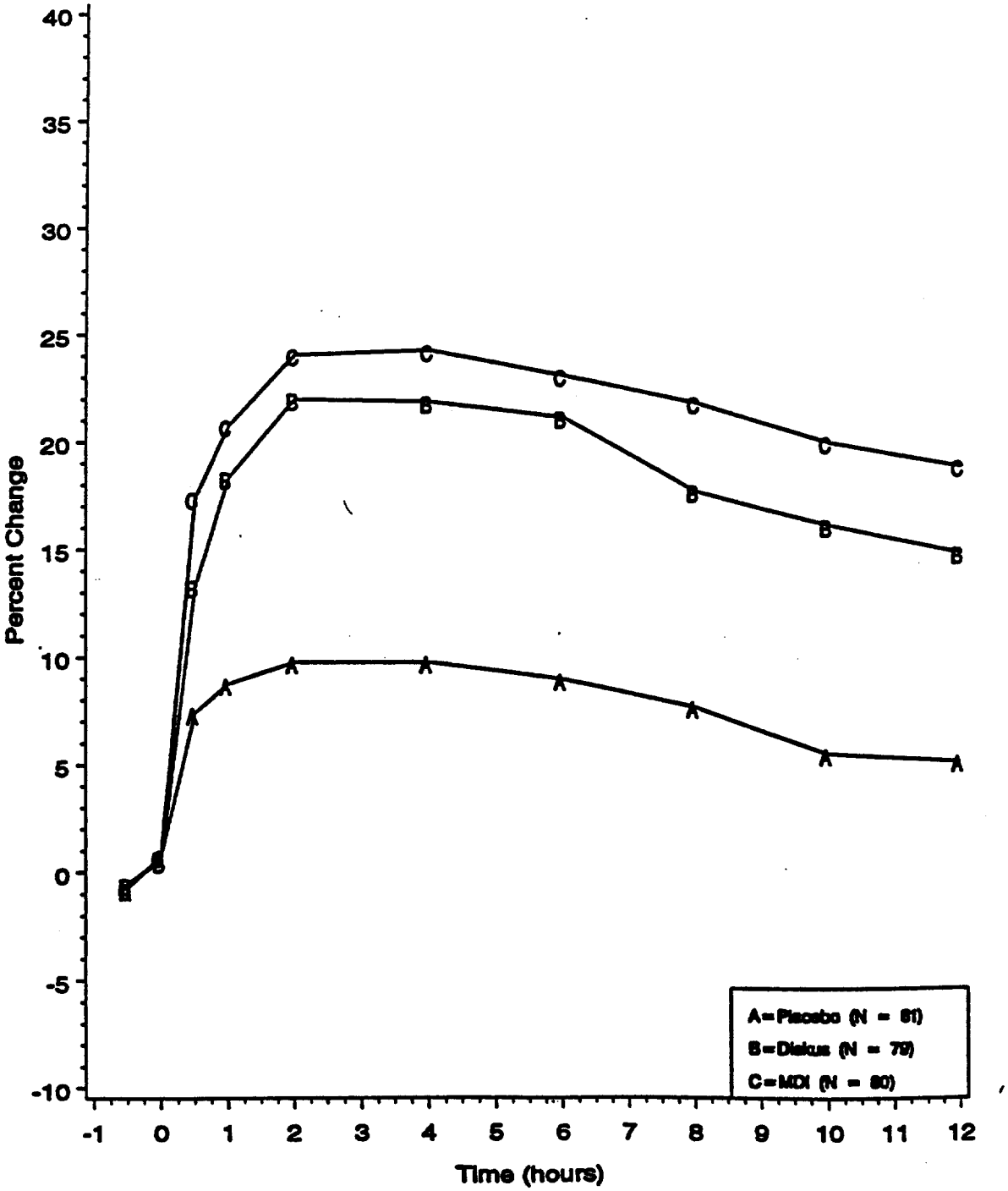


Salmeterol Xinafoate Powder
Protocol: SLGA3010
Population: Intent-to-Treat

FIGURE 7

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Day 1



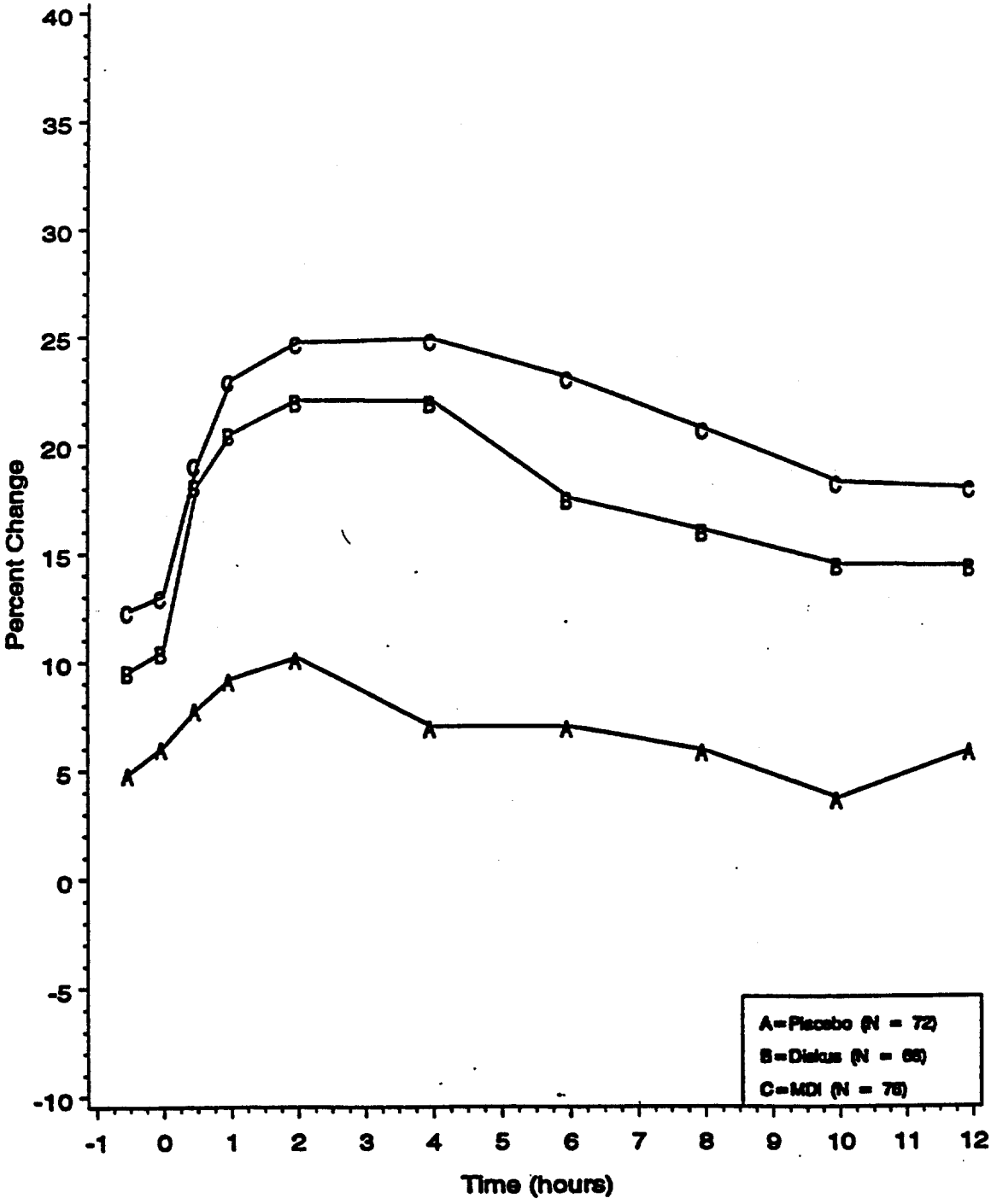
APPENDIX 3

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

FIGURE 8

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 4



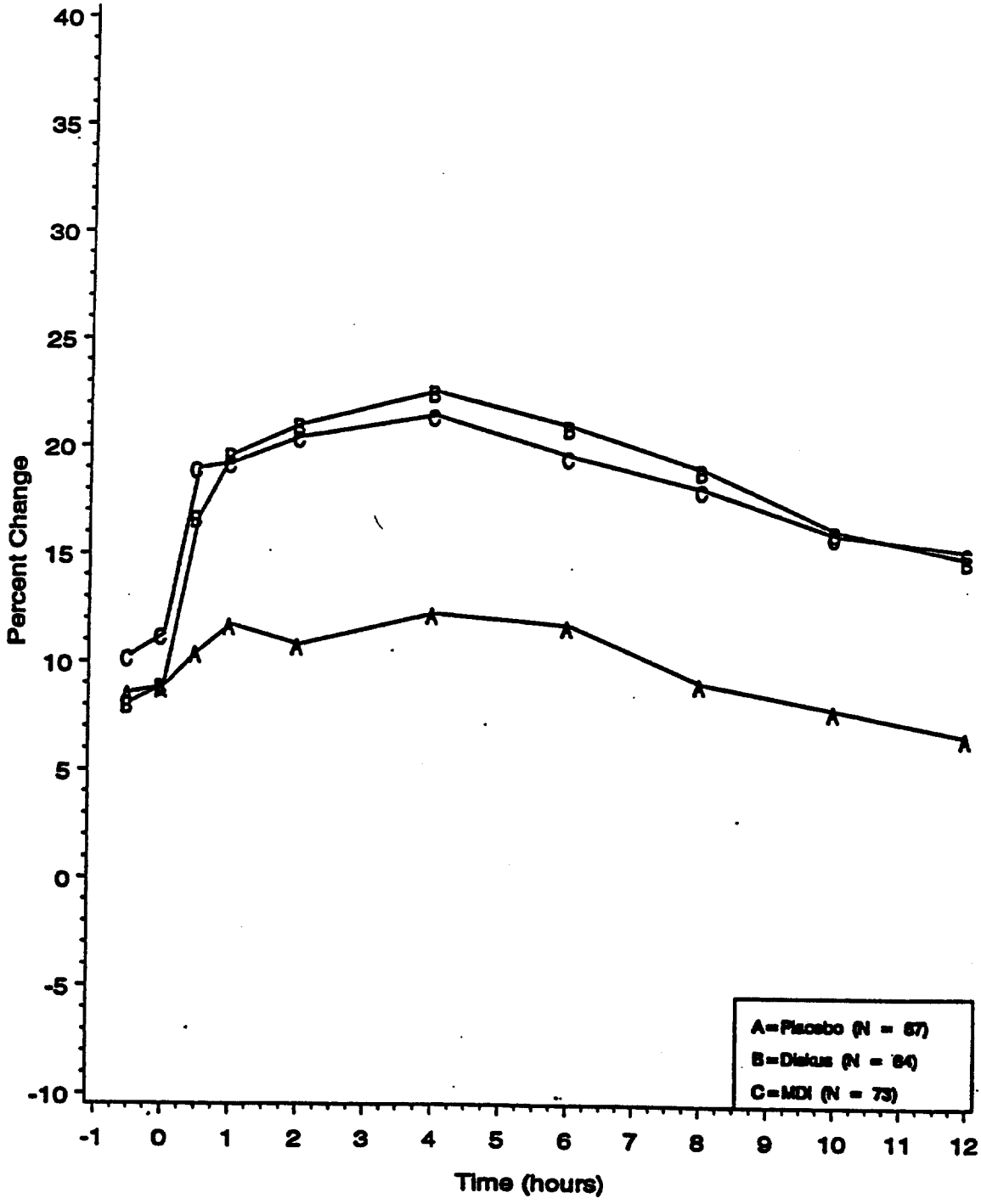
APPENDIX 4

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

FIGURE 9

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 12

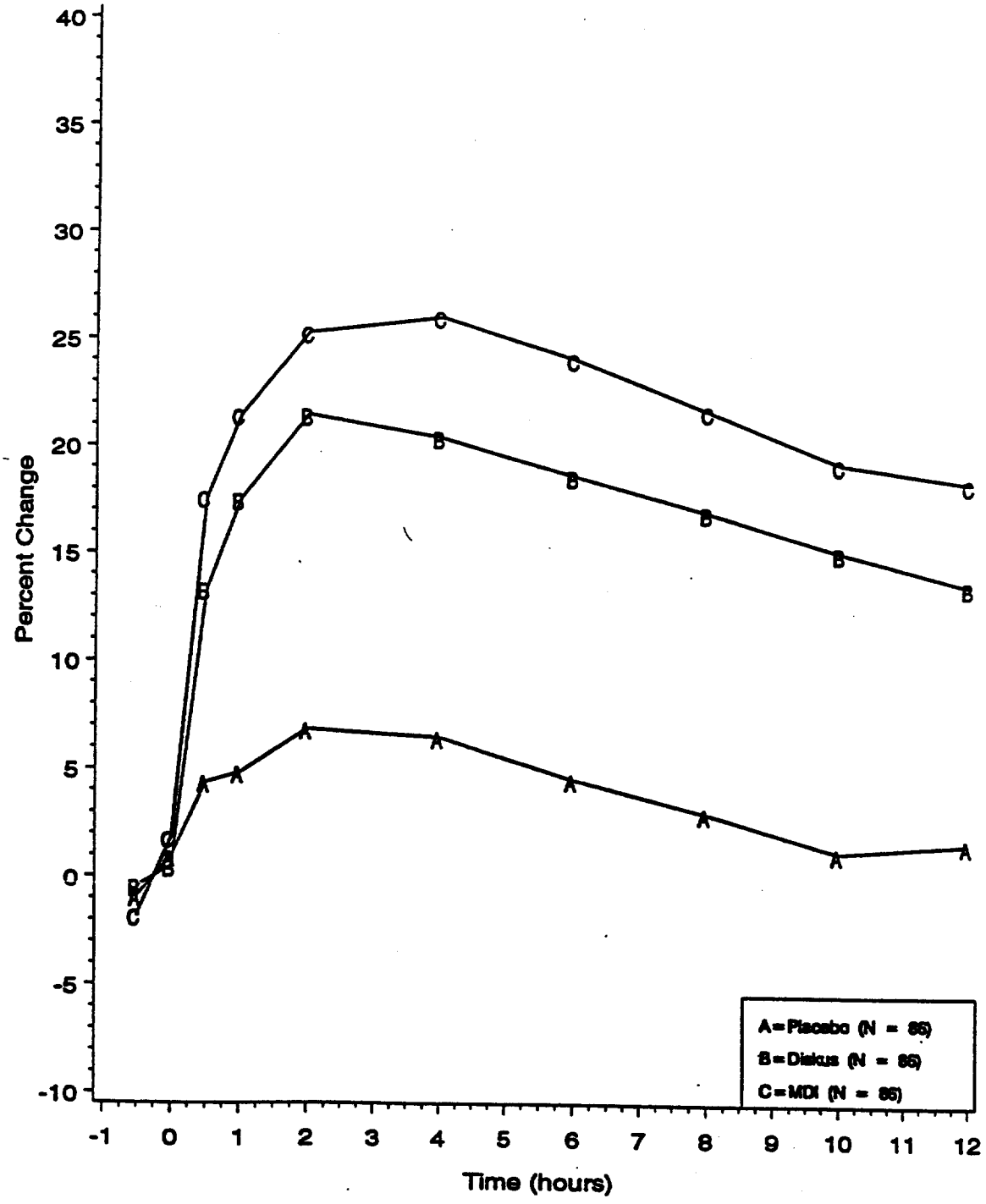


Salmeterol Xinafoate Powder
Protocol: SLGA3011
Population: Intent-to-Treat

FIGURE 7

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Day 1



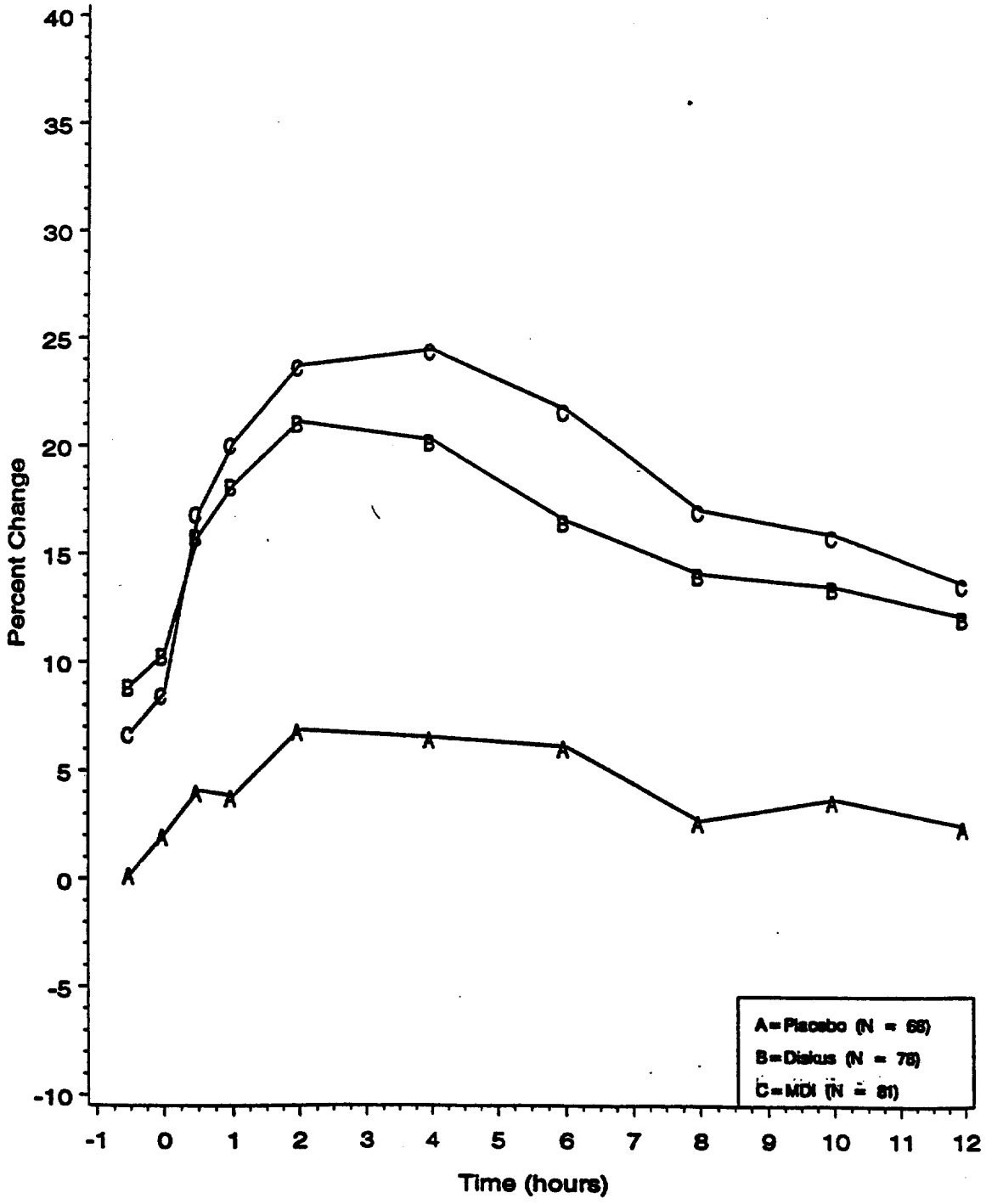
APPENDIX 6

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

FIGURE 8

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 4



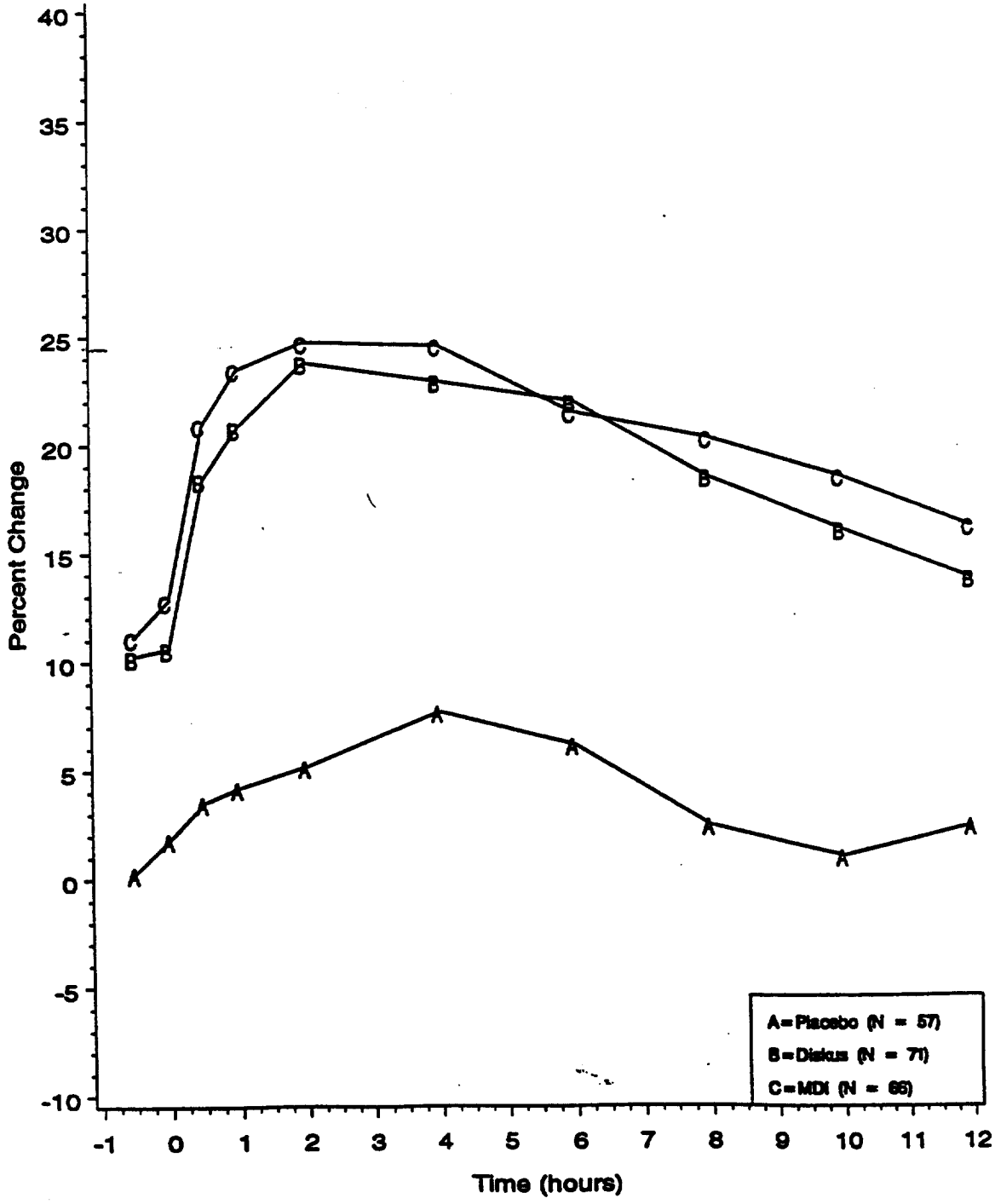
APPENDIX 7 BEST POSSIBLE COPY

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

FIGURE 9

FEV1: PERCENT CHANGE FROM BASELINE

Treatment Week 12



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