

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA# 20-236/S-030 NDA# 20-692/S-026 NDA# 21-077/S-022	TRADE NAME:	Serevent Inhalation Aerosol Serevent Diskus Advair Diskus
APPLICANT/SPONSOR:	GlaxoSmithKline	USAN NAME:	Salmeterol xinafoate; Fluticasone propionate and salmeterol xinafoate
MEDICAL OFFICER:	Sally Seymour, MD	CATEGORY:	Long acting beta agonist; Inhaled corticosteroid and long acting beta agonist
DEPUTY DIRECTOR:	Eugene Sullivan, MD, FCCP	ROUTE:	Oral inhalation
REVIEW DATE:	September 20, 2004		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
February 24, 2004		Supplement, Prior Approval, Labeling	Electronic
April 26, 2004		Response to request for information	
May 24, 2004		Response to request for information	Electronic
June 8, 2004		Response to request for information	
July 29, 2004		Response to request for information	Electronic
August 25, 2004		Response to request for information	Electronic
August 27, 2004		Response to request for information	Electronic

REVIEW SUMMARY: Salmeterol Inhalation Aerosol is a long acting β_2 -agonist, which was approved for asthma in 1994. Because of concerns regarding possible detrimental effects of chronic β_2 -agonist use, the Sponsor initiated a large, randomized, placebo-controlled study, the Salmeterol Multicenter Asthma Research Trial (SMART, Study #SLGA5011), in 1996. The SMART trial was halted prematurely in January 2003, because of concerning findings in a planned interim analysis. Because of the important new data from the SMART trial, in August 2003, a boxed warning was placed on all salmeterol containing products, which warned of a small increase in risk of asthma related deaths with salmeterol use in the SMART study. The Boxed Warning also stated that subgroup analysis suggested African Americans may be at increased risk compared to Caucasians.

In this labeling supplement (NDA #20-236, S-030; NDA #20-692, S-026; NDA #21-077, S-022), the Sponsor proposes labeling changes based upon an amended clinical study report for the SMART study. Although not specified in the protocol for the SMART study, the Sponsor performed a National Death Index (NDI) search to capture as many primary outcome events as possible. The current submission contains the amended clinical study report with the adjudicated cases from the NDI search up through January 2002.

During the review period, the dataset utilized by the Sponsor for the primary and secondary outcomes of the SMART study became an issue. The treatment period for the SMART study was 28 weeks, however, the Sponsor collected spontaneously reported, post-study adverse events for 6 months following the treatment period. Although not specified in the protocol, all the SMART study reports submitted by the Sponsor to the Agency included the 6 month post-study adverse event data in the analysis of the primary and secondary outcomes. The Division disagrees with the inclusion of the post-study adverse event data in the analysis of the SMART study outcomes. The Division believes the dataset utilized for analysis of the SMART study should be events that occurred during the 28-week treatment period. Furthermore, the Division recommends the product label reflect the outcomes of the SMART study based upon the 28-week treatment period.

With regards to the NDI search, although not specified in the protocol, the Division believes the inclusion of the NDI search data is acceptable. However, the NDI search should only include outcomes which occurred during the 28-week treatment period.

Another issue determined during the review period was the method of calculating relative risks. The method of calculation submitted by the Sponsor did not account for censoring; therefore, the Sponsor was asked to determine the relative risks of outcomes at 28 weeks based on life table analyses.

The Division recommends the Sponsor revise the label of all salmeterol containing products to reflect the SMART study outcomes based upon life table analyses for the 28-week treatment period. The Division faxed proposed labeling changes to GSK on September 10, 2004.

OUTSTANDING ISSUES: Labeling negotiations are ongoing.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	X	APPROVAL	APPROVABLE	NOT APPROVABLE
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CLINICAL REVIEW OF LABELING SUPPLEMENT

1. INTRODUCTION

Salmeterol Inhalation Aerosol was approved for asthma in 1994. Because of concerns regarding possible detrimental effects of chronic β_2 -agonist use, the Sponsor initiated a large, randomized, controlled study, the Salmeterol Multicenter Asthma Research Trial (SMART, Study #SLGA5011), in 1996. The SMART trial was halted prematurely in January 2003 because of concerning findings in a planned interim analysis. This interim analysis was performed after approximately 26,000 of a planned 60,000 patients had been enrolled. The interim analyses suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations, including death, and that the subpopulation of African Americans may be particularly at risk.

Because of the data from the SMART study, the Agency requested the Sponsor revise the product label to include the important new information from the SMART study. After multiple discussions and meetings with the Sponsor, labeling changes, including a Boxed Warning, were approved on August 11, 2003, for all salmeterol containing products.

The Sponsor submitted this Supplement: Prior Approval, Labeling on February 24, 2004, in which it proposes a change in the labeling for salmeterol based upon updated results from the SMART study, which now includes 13 adjudicated cases from an NDI search.

During the review period, several requests for information were sent to the Sponsor by the Division. This review incorporates the Sponsor's response to the requests for additional information.

2. BACKGROUND - SMART

2.1. Overview

The SMART study was a large randomized trial initiated in 1996 to evaluate the effects of chronic β_2 -agonist use. Subjects with asthma were randomized to either salmeterol 42 mcg twice-daily or placebo for 28 weeks. Initially the protocol specified enrolling 15,000 subjects per treatment arm. However, after 15,000 subjects were enrolled, the observed occurrence rate of the primary endpoint was approximately half of what had been expected; therefore, the sample size was revised to enroll 30,000 subjects per treatment arm [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 1635]. The primary endpoint for the SMART trial was combined respiratory related deaths and respiratory related life-threatening experiences (intubation and mechanical ventilation). The secondary endpoints included asthma-related deaths and life-threatening experiences and all-cause hospitalizations [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 1624].

2.2. Brief Synopsis of SMART Protocol (SLGA5011)

[N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 1617-1644]

SMART was a multi-center, double-blind, parallel-group, placebo-controlled study conducted over 28 weeks designed to compare respiratory and asthma event outcomes in subjects receiving usual asthma pharmacotherapy (plus placebo) with event outcomes in subjects receiving usual pharmacotherapy plus salmeterol.

The protocol-defined primary endpoint was the occurrence of combined respiratory-related deaths or respiratory life-threatening experiences (intubation and mechanical ventilation).

Protocol-defined secondary endpoints were the following:

- Asthma-related deaths
- Asthma-related deaths or life-threatening experiences
- All cause deaths
- Serious adverse events
- Reason(s) for withdrawal from the study
- Changes in concurrent medications and the addition of new medications
- Subject reported status (overall quality of life, activity limitations, emotions, and symptoms), as related to their asthma after 28 weeks of treatment or upon withdrawal.

The study consisted of a single clinic visit during which eligibility status was evaluated.

Pertinent inclusion criteria included the following:

- Male and non-pregnant females age 12 years and older
- Clinical diagnosis of asthma and currently taking prescription asthma medications.

Pertinent exclusion criteria included the following:

- Significant systemic disease
- A history of any adverse reaction to any sympathomimetic amine drug
- Current beta blocker use
- Previous or current use of long acting beta agonists (e.g. salmeterol and formoterol).

During Visit 1, which was the only clinic visit, baseline demographic information, medical history, asthma history, concomitant medication use, vital signs, and peak expiratory flow measurements were obtained. Eligible subjects were randomized to receive either salmeterol 42mcg (2 puffs of 21mcg/puff) twice daily or placebo (2 puffs) twice daily. A 28-week supply of study medication was issued along with instruction on proper use of an MDI.

Subjects were contacted at approximately 4, 8, 12, 16, 20, 24, and 28 weeks after receiving the study drug. The following information was collected during the phone contact:

- Respiratory related life threatening experiences (intubation and mechanical ventilation)
- SAEs
- Compliance

- Asthma status questions
- Changes in concurrent medication and addition of new medication.

During the phone call, subjects were also reminded to begin use of a new inhaler.

At the end of the 28-week treatment period, subjects were to return all study medication to the Sponsor.

Investigators were instructed to report within 48 hours of any death or serious adverse event, which occurred at any time up to 6 months after a subject had completed participation in the study. However, the investigator was not obligated to actively seek to learn of occurrence of serious adverse events in such former study participants during this time interval.

Based on the expected occurrence rate of the primary endpoint for a 28 week period, the Sponsor initially estimated that 15,000 subjects per treatment arm would provide approximately 80% power to rule out a 40% increase in the proportion of subjects experiencing mortality or intubation/mechanical ventilation at a significance level of 0.05. However after approximately 15,000 subjects had been enrolled, the occurrence rate of the primary event was about half what had been expected. Therefore, the sample size was revised to approximately 30,000 subjects per treatment arm.

An interim analysis was specified after approximately 30,000 subjects had been enrolled. According to the protocol, the study was to be stopped if there was evidence salmeterol was causing an increase in 1) the combined respiratory-related deaths and respiratory-related life-threatening experiences or 2) asthma-related deaths. The protocol specified the stopping criteria were to be based upon detecting a risk ratio of 1.4 for the primary outcome and a risk ratio of 3 for asthma-related deaths. A significance level of 0.01 was to be used to determine confidence limits at the interim analysis

An independent review board (the Mortality and Morbidity Review Committee), which was specified to consist of 3-5 medical specialists, reviewed and established the causality of all deaths and life-threatening events, which occurred during the study. The DSMB assessed ongoing subject safety throughout the study.

2.3. Interim Analysis

As stated in the previous section, an interim analysis was planned after approximately 30,000 subjects had been enrolled. According to the protocol, the study was to be stopped if there was evidence salmeterol was causing an increase in 1) the combined respiratory-related deaths and respiratory-related life-threatening experiences or 2) asthma-related deaths. The protocol specified the stopping criteria were to be based upon detecting a risk ratio of 1.4 for the primary outcome and a risk ratio of 3 for asthma-related deaths. A significance level of 0.01 was to be used to determine confidence limits at the interim analysis [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 1682].

The interim analysis was performed in 2002 after 25,858 subjects had been enrolled. In a closed meeting on September 11, 2002, the DSMB learned that the salmeterol treatment group had a point estimate for the relative risk of 1.26 (95% CI 0.74, 2.13) for the primary outcome and a point estimate for the relative risk of 3.25 (95% CI 0.86, 12.27) for asthma-related deaths [DSMB Meeting Minutes, September 11, 2002]. The point estimates for the relative risks were similar to the hypothetical risks that the study was designed to exclude. The following excerpt is taken from the minutes of the September 11, 2002, DSMB meeting.

It was agreed that it would be optimal to continue recruitment of new subjects for the study IF such recruitment realistically could be expected to lead to sufficient numbers of subjects (an additional 10,000 at least) or outcomes events (an additional 100 primary outcomes events) to provide conclusive findings within a reasonable period of time, e.g. within the next two years. If such recruitment is not feasible, as strongly suggested by the current recruitment rate of 80 subjects per month despite a reportedly maximal recruitment effort over the past year, then the study should be terminated with dissemination of findings as quickly as possible, including presentation of the findings to the clinical and research communities within 3-6 months, e.g. at a national meeting, followed by timely formal publication.

SMART was subsequently terminated early by GSK on January 23, 2003, with a total of 26,355 subjects evaluated in the study. The last subject contact was on July 23, 2003 [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 2].

Reviewer's Comment: The SMART study did not actually meet the pre-specified stopping criteria at the interim analysis. The lower bound of the 99% CI around the point estimate of the RR for the primary endpoint was not ≥ 1.4 . In addition, the lower bound of the 99% CI around the point estimate of the RR for asthma-related deaths was not ≥ 3 .

2.4. Labeling Changes Based Upon SMART

After the SMART study was terminated, the Division requested the Sponsor revise the product label to include the important new information from the SMART study. After multiple discussions and meetings with the Sponsor, the following Boxed Warning was approved on August 11, 2003, for all salmeterol containing products.

WARNING: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

Reviewer's Comment: The Advair label included a similar Warning Box with the only difference in the last sentence, which ends with "(see WARNINGS)."

In addition, the Clinical Pharmacology Section of the salmeterol inhalation aerosol product label and the salmeterol inhalation powder (diskus) product label were revised to include the SMART study results as follows:

Clinical Trials:

Salmeterol Multi-Center Asthma Research Trial: The Salmeterol Multi-center Asthma Research Trial (SMART) enrolled long-acting beta2-agonist-naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African-American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol, 42 mcg twice daily over 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Other endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,353).

Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. The analysis showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4) occurred in the patients treated with salmeterol. Post hoc subgroup analyses revealed no significant increase in respiratory- or asthma-related episodes, including deaths, in Caucasian patients. In African-Americans, the study showed a small, though statistically significantly greater, number of primary events (20 vs. 7), asthma-related deaths or life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking salmeterol compared to those taking placebo. The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African-American patients and difficulties in enrollment.

Reviewer's Comment: The Advair product label did not include the above labeling regarding the SMART study.

The Warnings Section of the salmeterol inhalation aerosol product label and salmeterol inhalation powder (diskus) product label were revised to include the following language:

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study, called the Salmeterol Multi-center Asthma Research Trial (SMART), further suggest that the risk might be greater in African-American patients, in whom the increased risk was statistically significant at the time of the interim analysis. These results led to stopping the study prematurely (see CLINICAL TRIALS: Asthma: Salmeterol Multi-center Asthma Research Trial). The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of action of beta2-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect. Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

The Warnings Section of the Advair product label was revised to include the following language:

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. The Salmeterol Multi-center Asthma Research Trial (SMART) enrolled long-acting beta2-agonist-naive patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to placebo, when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Other endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,353). The analysis showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4) occurred in the patients treated with SEREVENT Inhalation Aerosol. Post hoc subgroup analyses revealed no significant increase in respiratory- or asthma-related episodes, including deaths, in Caucasian patients. In African Americans, the study showed a small, though statistically significantly greater, number of primary events (20 vs. 7), asthma-related deaths or life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking SEREVENT Inhalation Aerosol compared to those taking placebo. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African American patients and difficulties in enrollment. The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk. Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would apply to ADVAIR DISKUS.

Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

Given the similar basic mechanisms of action of beta2-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

Reviewer's Comment: The above labeling changes were based upon limited SMART study results submitted by the Sponsor. The full data set for the SMART study was submitted August 29, 2003, as part of a labeling supplement; however, the Sponsor did not propose any new labeling changes. The Sponsor was subsequently notified by the Division via a letter dated February 11, 2004, that the August 29, 2003, submission was considered correspondence and was not accepted as a supplement.

3. REVIEW ISSUES

3.1. NDI Search

In this supplement, the Sponsor requests revising the product label for all salmeterol containing products based upon updated results from the SMART study that now include data from a National Death Index (NDI) search.

Reviewer's Comment: The NDI is a database of death record information submitted by state vital statistics offices. Death records are added to the NDI file annually, approximately 12 months after the end of a particular calendar year; therefore, there is a delay in accessing the information. According to the NDI website (www.cdc.gov/nchs/r&d/ndi/ndi.htm), data for the year 2002 will be updated in spring 2004.

Performing an NDI search was not specified in the original SMART study protocol. The protocol did, however, specify the following for subjects lost to follow-up [N20236\S_030\2004-02-24\clinstat\slga5011.pdf, page 1632].

Subjects lost to follow-up:

For the lost subject, the investigator will attempt to collect mortality and asthma-related life-threatening information (as necessary) through medical record review.

According to the Sponsor, the NDI search was recommended by the DSMB to help capture as many of the primary outcome events as possible [NDA# 20-236/S-030, Response to FDA Request, April 26, 2004].

Reviewer's Comment: Although not specified in the protocol, it is the opinion of this reviewer that performing an NDI search on subjects lost to follow-up is acceptable to capture additional safety outcome data.

Reviewer's Comment: Although Dr. Lisa Kammerman, the Biometrics reviewer, noted that mortality rates for minorities may be understated in the NDI,¹ the NDI demonstrated the highest sensitivity (87%-97%) when compared to other mortality sources, such as the Social Security Administration and the Department of Veterans Affairs databases.²

Overall, the Division believes inclusion of the NDI search data is acceptable to capture safety outcomes for subjects lost to follow-up.

¹ Patel KV, Eschbach K, et al. *Am J Epidemiol* 2004; 159:707-715.

² Cowper DC, Kubal JD, et al. *Annals of Epid* 2002; 12(7) :462-468.

3.1.1. NDI Search Results

The Sponsor conducted a National Death Index search for the period from 1996 to the end of 2001. The adjudication of 13 new cases from the NDI search resulted in the following changes to the database [N20236\ S_030\2004-02-24\cover.pdf]:

- 7 new primary outcome events (combined respiratory-related death or life threatening experiences)
 - 4 in salmeterol group & 3 in placebo group
 - All 7 events in Caucasians
 - 4 were asthma-related (2 salmeterol, 2 placebo).

Reviewer's Comment: Because of the delay in the NDI database, the Sponsor was asked to specify if further NDI searches would be performed. The Sponsor proposes to initiate a final query of the NDI database in 2005 to capture the events that may have occurred in the period between January 2002 and January 2003 [NDA# 20-236/S-030, Response to FDA Request, April 26, 2004].

Reviewer's Comment: The Sponsor did not submit details describing the NDI search process, which would include search terms, assessment of quality of NDI match, and the handling of multiple reports per subject.

In this submission, the Sponsor submitted the updated results for SMART, which included the NDI search data. One interesting detail regarding the updated study results was the increase in the overall N of SMART by two subjects. During the review period, the Division requested clarification of the increase in the overall N. The Sponsor stated that two CRF were misplaced at a site during the SMART study. The CRFs were subsequently located and returned to the CRO after the initial study results were reported to the FDA on August 6, 2003. The two subjects' data are included in this study report. The Sponsor stated that neither subject contributed any additional primary or secondary outcome events [NDA# 20-236/S-030, Response to FDA Request, April 26, 2004].

The Sponsor reanalyzed the SMART study incorporating the NDI search data. Table 7 in the Appendix displays a comparison of the primary and secondary outcomes with and without the additional NDI search data. In this labeling supplement, the Sponsor requested labeling changes to include the results of the NDI search. The labeling changes included updating a few numbers in the Boxed Warning and Clinical Trials Section as well as removing the phrase "but significant" from the Boxed Warning. The labeling for this supplement is discussed in detail in Section 7.

Reviewer's Comment: It is the opinion of this reviewer the addition of the NDI search data does not change the overall interpretation of the SMART study results.

Prior to a discussion of the results of the SMART study, the primary dataset will be addressed in the following section. During the review period, the dataset the Sponsor had been utilizing for analyses and reporting of the SMART study outcomes came under question.

3.2. Primary Analysis Dataset

3.2.1. SMART Protocol

The SMART protocol did not specify the dataset to be utilized for the analyses of the safety outcomes. The treatment period for the SMART study was 28 weeks. A clinic visit was conducted at the beginning of the treatment period. Subjects were then contacted by phone every 4 weeks for the collection of adverse event information, compliance, and changes in medications. During the final 28 week telephone contact, the subjects were instructed to return the study drug inhalers. No further contact with the subjects was scheduled unless to follow-up on adverse events occurring during the 28-week treatment period, which was at the discretion of the investigator.

Although the treatment period was 28 weeks, according to the protocol, “post-study adverse events” were collected as follows [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 1592].

7.1.6. Post-study adverse events

The investigator should notify the CRO or Glaxo Wellcome within 48 hours of any death or serious adverse event occurring at any time up to 6 months after a subject has completed participation in the study. However, the investigator is not obligated to actively seek to learn of occurrence of serious adverse events in such former study participants during this time interval.

Although the protocol specified collection of the “post-study adverse events” data, the protocol did not specify that this spontaneously reported post-study adverse event data was to be utilized in the analysis of the safety outcomes.

3.2.2. Statistical Methods Appendix

The Statistical Methods Appendix, which was finalized on August 20, 2003, and first submitted to the Division on August 29, 2003, indicated that the 6-month post-study adverse event data would be included in the primary analysis. The following is an excerpt from the Statistical Methods Appendix (Safety Analyses Section) [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 1538 & 1556].

10.2 Primary Safety Measurement and Analysis

The primary safety measure was the relative risk of experiencing respiratory-related death or respiratory-related life-threatening experience (defined as the occurrence of endotracheal intubation and mechanical ventilation) for subjects receiving Salmeterol 42 mcg (2 puffs) twice daily plus current pharmacotherapy versus subjects receiving placebo (2 puffs) twice daily plus current pharmacotherapy over a 28-week period.

The study population was actively solicited for any primary outcome events that would have occurred during the 28-week treatment period. If a primary outcome event occurred within 6-months after the 28-week treatment period and was spontaneously reported to the center, then this event was included in analyses of the primary event. Any primary events spontaneously reported more than 6-months after the 28-week treatment period were not included in analyses of the primary endpoint.

Reviewer's Comment: The Statistical Methods Appendix was finalized on August 20, 2003, and submitted to the Division on August 29, 2003. The Statistical Methods Appendix was finalized after the results of the interim analysis were known. In addition, the finalization and submission of the Statistical Methods Appendix followed the August 11, 2003, approval of the labeling changes based upon the SMART study results.

3.2.3. Submitted SMART Study Reports

The tabular data in the study reports submitted by the Sponsor do not specify the dataset utilized in the analyses. In a fax to the Sponsor, the Division asked for clarification of this issue [Fax dated April 19, 2004]. The Sponsor responded that the information in this submission and all previous submissions included primary and secondary safety outcomes for the 28-week treatment period and the 6-month post-study adverse event data combined [NDA# 20-236/S-030, Response to FDA Request, April 26, 2004].

Reviewer's Comment: The Division was not aware the SMART study reports submitted to the Division included data from the 6-month post-study adverse event data. As stated above, the protocol did not specify inclusion of the 6-month post study data and the tables in the SMART study reports submitted to the Division do not indicate the data includes the 6 month post-study adverse event data. The Division had presumed the data represented the 28-week treatment period as the 28-week treatment period is clinically the period of interest.

3.2.4. Sponsor's Rationale for Dataset

The Sponsor was asked to clarify when it specified including the 6 month post-study adverse event data in the analyses of the safety outcomes. The Sponsor acknowledged that the protocol did not state the primary analysis would be based upon events occurring during the 28-week treatment period and the 6-month post-treatment period. According to the Sponsor, the following circumstances and actions were taken into account when including events from both time periods in the primary analysis (bulleted items) [NDA# 20-236, Response to FDA Request, April 26, 2004].

- Study SLGA 5011 was originally designed with Agency input to be a large simple study with minimal patient contact. With only one patient clinic visit at baseline and monthly patient telephone contacts, patient compliance to the study protocol; particularly compliance to the taking of study medication; was not expected to be monitored at the same level as would be expected in a more traditional clinical trial with multiple patient clinic visits during the study treatment period. In addition, the 28-week end of study phone contact, was the single mechanism employed by which return of unused study drug (via mail) was requested. Therefore, it was considered likely that patients would have access to unused study medication after the planned 28-week treatment period and would continue to use study medication until the source was exhausted.

Reviewer's Comment: The possible continuation of study medication post 28-week treatment period is purely speculative and does not support including the 6 month post-study adverse event data in the primary analysis. The medications subjects were taking beyond the 28-week treatment period are unknown. Because salmeterol was an approved product, it is quite possible that patients randomized to placebo during the treatment period may have initiated salmeterol treatment following completion of the study.

- The original protocol for study SLGA5011 submitted to IND 30,905 on November 6, 1995, indicated the following in section 7.1.6 Post-Study Adverse Events. “The investigator should notify the CRO or Glaxo Wellcome within 48 hours of any death or serious adverse event occurring at any time up to 6 months after a subject has completed participation in the study. However, the investigator is not obligated to actively seek to learn of occurrence of serious adverse events in such former study participants during this time interval.” Consequently, the protocol contained instructions in Section 7.1.6 for the reporting of known deaths or serious adverse events, which occurred within a 6-month post treatment period. This post-treatment period was prospectively included and is unique to SLGA5011 for the reasons described above.

Reviewer’s Comment: The “post-study adverse events” were not uniformly collected. The investigators could spontaneously report the events. No follow-up calls or questionnaires were utilized to collect the data. Therefore, the post study adverse events data is not as robust as the data collected during the 28-week treatment period.

- The reporting of data in SMART has consistently included events occurring during weeks 1-28 and during the 6-month post treatment period. For example, from the onset of study SLGA5011, the DSMB periodically reviewed blinded results. From the first report to the final data, all the DSMB reports included events that occurred during the 28-week treatment period and the 6-month post-treatment period. This included the formal statistical interim analysis reviewed by the DSMB, from which the study was terminated.

Reviewer’s Comment: In the SMART study reports submitted to the Division, the tables do not indicate the data includes the 6 month post-study adverse event data. The Division does not have access to the data reviewed by the DSMB. Minutes from the September 11, 2002, DSMB meeting indicate the DSMB was presented data for the 28-week treatment period in addition to data for the 28-week treatment period plus the 6 month post-study period.

- Adherence to reporting events during the 28-week treatment period and the 6-month post-treatment period was also maintained when 2 events, which occurred after the 6 month post-treatment, were not included in the database. These events were reviewed and adjudicated by the Medical Monitoring Review Committee (MMRC) in a blinded fashion to determine if the events were Respiratory related, but as stated above, were not included in any analyses. This was indicated in section 10.2 of the SLGA5011 Statistical Analysis Methods Appendix.

3.2.5. Division’s Rationale for Dataset

The Division believes the analyses of the SMART study should be based upon the safety outcomes for the 28-week treatment period, for the following reasons.

- The 28-week treatment period is clinically and scientifically the period of interest. The concern prompting the SMART study was the question of whether chronic beta₂ agonist use increased asthma morbidity and mortality, not the residual effects of beta₂ agonists that might persist up to 6 months after discontinuing salmeterol.

- The Sponsor powered the study based upon the number of expected events in a 28-week period, not for a 28-week period and 6-month follow up [N20236\S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 1546].

Reviewer’s Comment: Powering the study based upon the 28-week treatment period leads this reviewer to believe that the primary period of interest when designing/powering the study was the 28-week treatment period.

- Since the post-study adverse events data relied upon discretionary spontaneous reporting, it is not as robust as the data collected during the 28-week treatment period.
- Medication use during the 6 month post-study period is unknown.
- In the protocol, the Sponsor terms the data collected in the 6 month period following the 28-week treatment period “post-study adverse events,” which indicates the subjects had completed the study.

Because the Division believes the analysis of the SMART study data should utilize the safety outcomes for the 28-week treatment period, the Division requested the Sponsor submit the primary and secondary safety outcomes for the SMART study, using the 28-week treatment period safety outcome data. The data for the 28-week treatment period had not previously been submitted to the Division and is presented in detail in the following section.

4. SMART RESULTS BASED UPON 28-WEEK TREATMENT PERIOD

The SMART study reports provided to the Division in this submission and previous submissions regarding the SMART study included data representing events occurring during the 28-week treatment period and the 6 month post-study period combined. During the review cycle, the Division asked for the data for the primary and secondary outcomes for the 28-week treatment period [Request for Information, dated May 7, 2004].

4.1. Overall Primary and Secondary Outcomes

Table 1 displays a side by side comparison of the analyses of the primary safety outcome for the SMART study for the 28-week treatment period versus the 28-week treatment period and the 6 month post-study period combined.

Reviewer’s Comment: All the data included in the following tables are believed to include the data from the NDI search. The Division determined the inclusion of the NDI search data is acceptable.

Table 1 Overall Incidence of Primary Safety Outcome Events28-Week Treatment Period vs. 28-Week Treatment Period and 6 Month Post-Study Combined, Unadjusted RR¹

	Salmeterol N=13,176		Placebo N=13,179		RR ¹ (95% CI) ²	
	Wk 1-28 & 6 mo post- study	Wk 1-28	Wk 1-28 & 6 mo post- study	Wk 1-28	Wk 1-28 & 6 mo post-study	Wk 1-28
Combined respiratory- related death or life threatening experience ³ , n (%)	52 (<1)	50 (<1)	45 (<1)	36 (<1)	1.1558 (0.7761, 1.7214)	1.3892 (0.9057, 2.1307)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

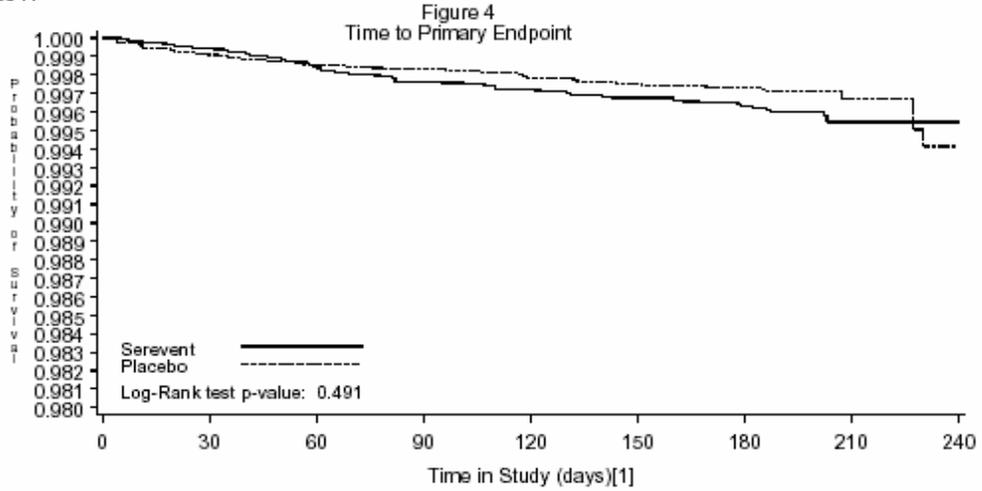
Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.2.

The relative risk for the primary outcome in the salmeterol group relative to the placebo group is higher when outcomes were analyzed for the 28-week treatment period. Although not statistically significant, the relative risk for the primary outcome in the salmeterol group relative to the placebo group approaches 1.4, which is what the study was designed to exclude.

Reviewer's Comment: The lower bound of the 95% confidence interval for the relative risk in the salmeterol group approaches one.

The following Kaplan-Meier curves, which were submitted to the Division by the Sponsor, describe the time to primary endpoint [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 132].

Protocol: SLGA5011



	Time in Study (days)[1]									
	0	30	60	90	120	150	180	210	240	
Serevent										
Survival Rate	100.00%	99.95%	99.84%	99.77%	99.72%	99.67%	99.63%	99.55%	99.55%	
Patients at Risk	13176	12867	12582	12284	11984	11636	11056	2183	862	
First Event	7	14	9	5	6	5	5	0	1	
Censored	302	271	289	295	342	575	8868	1321	861	
Placebo										
Survival Rate	100.00%	99.91%	99.85%	99.83%	99.78%	99.75%	99.73%	99.67%	99.41%	
Patients at Risk	13179	12827	12508	12214	11910	11609	11060	2206	826	
First Event	12	7	3	6	3	3	3	3	5	
Censored	340	312	291	298	298	546	8851	1377	821	

[1] Kaplan-Meier estimate of the survival curve. Survival Rate and Patients at Risk reflect a snapshot at the beginning of the interval, while First Event and Censored frequencies reflect events occurring in the following interval.
 /data/usmedstat/slga5011/programs/dec03/km_plots_survival.ps.sas KMK4236 08DEC03 15:36

Table 2 displays a side by side comparison of the analysis of the secondary safety outcomes for the SMART study for the 28-week treatment period versus the 28-week treatment period and the 6 month post-study period combined.

Table 2 Overall Incidence of Secondary Safety Outcome Events

28-Week Treatment Period vs. 28-Week Treatment Period and 6 Months Post-Study Combined, Unadjusted RR¹

	Salmeterol N=13,176		Placebo N=13,179		RR ¹ (95% CI) ²	
	Wk 1-28 & 6 mo post- study	Wk 1-28	Wk 1-28 & 6 mo post- study	Wk 1-28	Wk 1-28 & 6 mo post- study	Wk 1-28
Respiratory-related death	27 (<1)	24 (<1)	20 (<1)	11 (<1)	1.3503 (0.7578, 2.4062)	2.1823 (1.0695, 4.4532)
Combined asthma-related death or life threatening experience ³	38 (<1)	37 (<1)	25 (<1)	22 (<1)	1.5203 (0.9183, 2.5170)	1.6822 (0.9930, 2.8497)
Asthma-related death	15 (<1)	13 (<1)	6 (<1)	3 (<1)	2.5006 (0.9705, 6.4428)	4.3343 (1.2354, 15.2064)
Combined all cause death or life threatening experience ³	77 (<1)	70 (<1)	73 (<1)	59 (<1)	1.0550 (0.7667, 1.4518)	1.1867 (0.8400, 1.6765)
All cause death	49 (<1)	42 (<1)	47 (<1)	32 (<1)	1.0428 (0.6994, 1.5548)	1.3128 (0.8294, 2.0780)
All cause hospitalization	499 (4)	469 (4)	449 (3)	420 (3)	1.1116 (0.9808, 1.2599)	1.1169 (0.9813, 1.2713)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

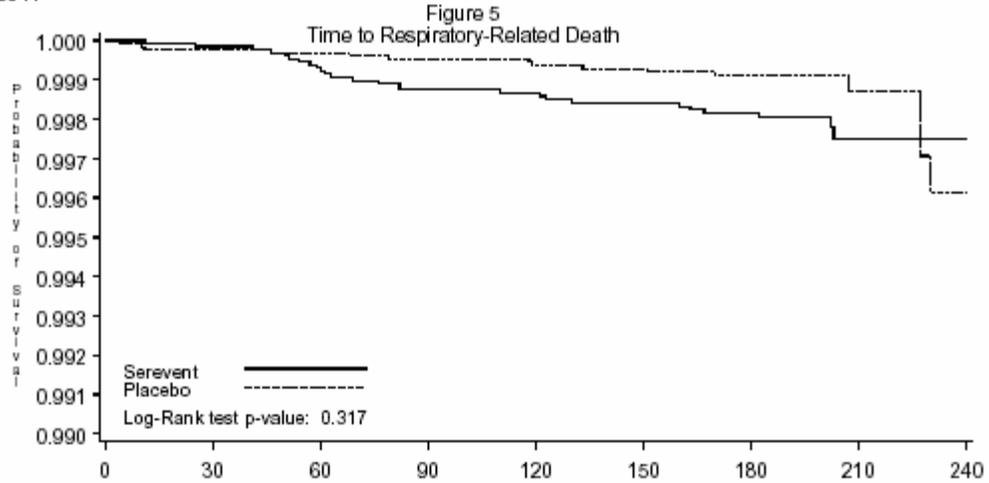
Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Tables 13.2.

Overall, the analyses based on the 28-week treatment period data indicate a higher relative risk of secondary outcomes in the salmeterol group relative to the placebo group as compared to analyses based on the 28-week treatment period and 6 month post-study period data combined. The relative risk of respiratory-related deaths, asthma-related deaths, and combined asthma-related deaths or life threatening experiences are higher in the salmeterol group relative to the placebo group for the 28-week treatment period.

Reviewer's Comment: The relative risks for secondary safety outcomes in the salmeterol group relative to the placebo group are higher for the 28-week treatment period than for the 28-week treatment period and 6 month post-study period combined.

The following Kaplan-Meier curves, which were submitted to the Division by the Sponsor, describe the time to respiratory-related death [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 133].

Protocol: SLGA5011

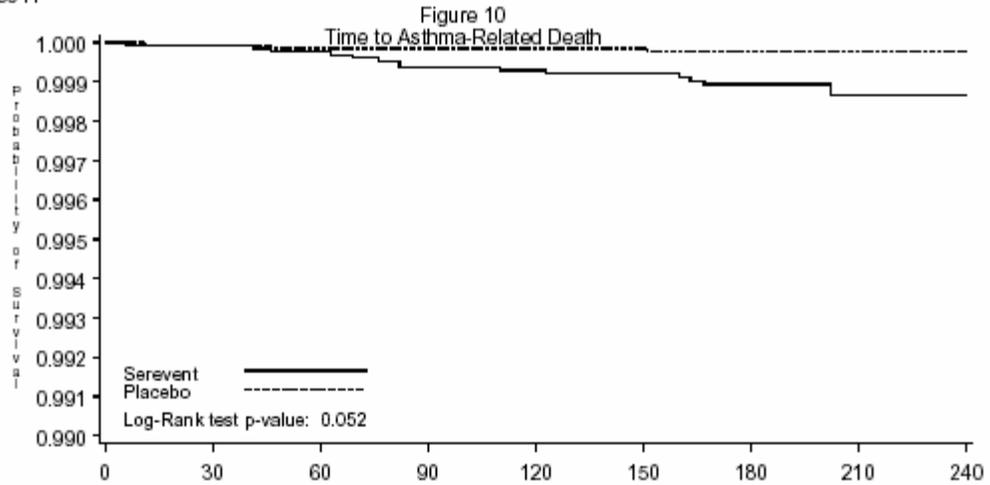


	Time in Study (days)[1]									
Serevent										
Survival Rate	100.00%	99.98%	99.92%	99.87%	99.87%	99.84%	99.82%	99.75%	99.75%	
Patients at Risk	13176	12872	12594	12298	12004	11657	11077	2186	865	
First Event	2	8	6	1	3	3	3	0	1	
Censored	302	270	290	293	344	577	8888	1321	864	
Placebo										
Survival Rate	100.00%	99.98%	99.97%	99.95%	99.94%	99.93%	99.91%	99.87%	99.62%	
Patients at Risk	13179	12836	12524	12228	11930	11631	11080	2214	830	
First Event	3	1	2	2	1	2	1	3	5	
Censored	340	311	294	296	298	549	8865	1381	825	

[1] Kaplan-Meier estimate of the survival curve. Survival Rate and Patients at Risk reflect a snapshot at the beginning of the interval, while First Event and Censored frequencies reflect events occurring in the following interval.
/data/usmedstat/slga4/a5011/programs/dec03/km_plots_survival_ps.sas KMK4236 08DEC03 15:36

The following Kaplan-Meier curves, which were submitted to the Division by the Sponsor, describe the time to asthma-related death [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 137].

Protocol: SLGA5011

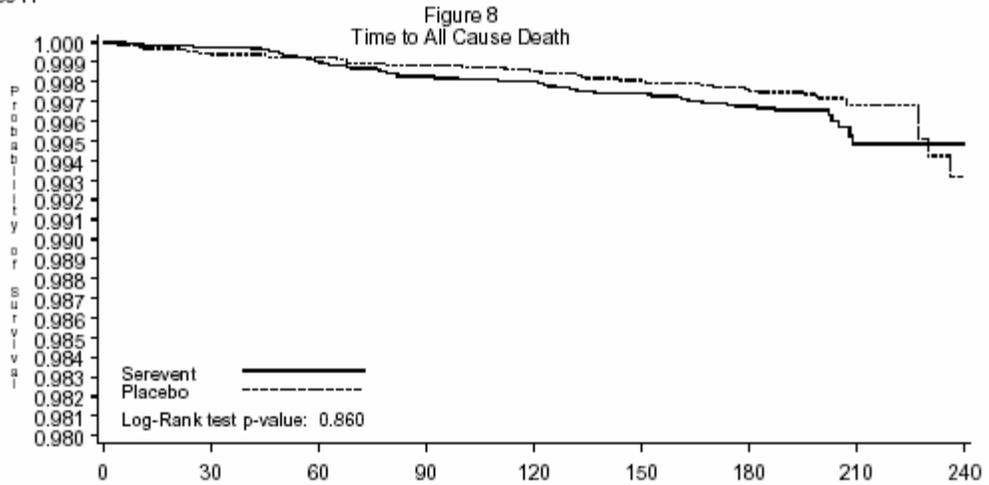


	Time in Study (days)[1]									
	0	30	60	90	120	150	180	210	240	
Serevent										
Survival Rate	100.00%	99.99%	99.98%	99.94%	99.93%	99.92%	99.89%	99.87%	99.87%	
Patients at Risk	13176	12872	12594	12298	12004	11657	11077	2186	865	
First Event	1	2	5	1	1	3	1	0	1	
Censored	303	276	291	293	346	577	8890	1321	864	
Placebo										
Survival Rate	100.00%	99.99%	99.98%	99.98%	99.98%	99.98%	99.98%	99.98%	99.98%	
Patients at Risk	13179	12836	12524	12228	11930	11631	11080	2214	830	
First Event	1	1	0	0	0	1	0	0	3	
Censored	342	311	296	298	299	550	8866	1384	827	

[1] Kaplan-Meier estimate of the survival curve. Survival Rate and Patients at Risk reflect a snapshot at the beginning of the interval, while First Event and Censored frequencies reflect events occurring in the following interval.
/data/usmedstat/slga/a5011/programs/dec03/km_plots_survival_ps.sas KMK4236 08DEC03 15:36

The following Kaplan-Meier curves, which were submitted to the Division by the Sponsor, describe the time to all cause death [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 136].

Protocol: SLGA5011



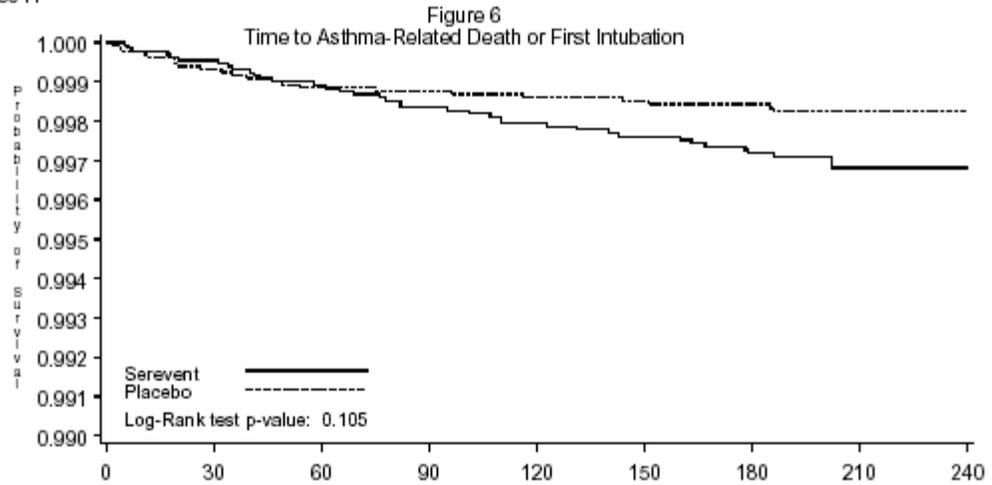
	Time in Study (days)[1]									
Serevent										
Survival Rate	100.00%	99.98%	99.90%	99.83%	99.80%	99.74%	99.67%	99.48%	99.48%	
Patients at Risk	13176	12872	12594	12298	12004	11657	11077	2186	865	
First Event	3	10	9	3	7	8	7	0	2	
Censored	301	268	287	291	340	572	8884	1321	863	
Placebo										
Survival Rate	100.00%	99.94%	99.92%	99.88%	99.85%	99.81%	99.76%	99.68%	99.31%	
Patients at Risk	13179	12836	12524	12228	11930	11631	11080	2214	830	
First Event	8	2	5	4	5	6	4	4	9	
Censored	335	310	291	294	294	545	8862	1380	821	

[1] Kaplan-Meier estimate of the survival curve. Survival Rate and Patients at Risk reflect a snapshot at the beginning of the interval, while First Event and Censored frequencies reflect events occurring in the following interval.

/data/usmedstat/slg4/a5011/programs/dec03/km_plots_survival_ps.sas KMK4236 08DEC03 15:36

The following Kaplan-Meier curves, which were submitted to the Division by the Sponsor, describe the time to asthma-related death or first intubation [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 134].

Protocol: SLGA5011

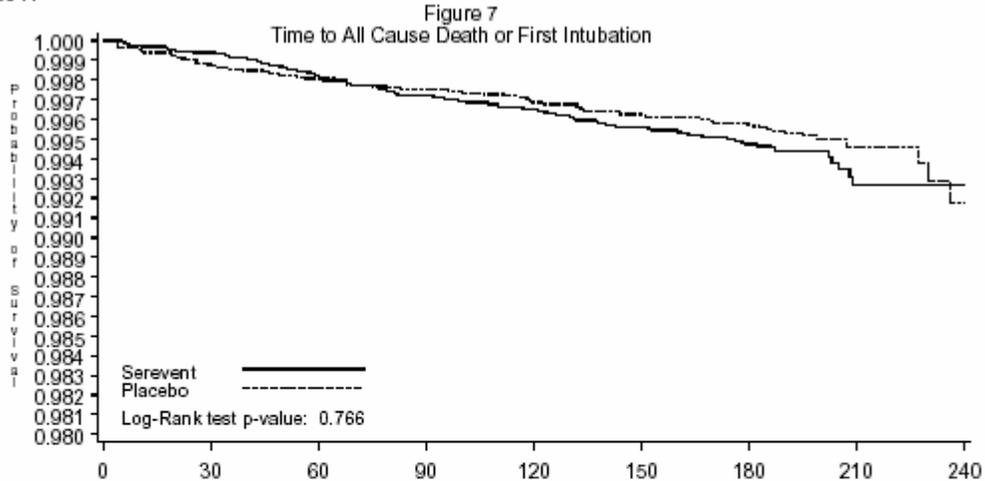


	Time in Study (days)[1]									
	0	30	60	90	120	150	180	210	240	
Serevent										
Survival Rate	100.00%	99.95%	99.89%	99.84%	99.80%	99.76%	99.72%	99.68%	99.68%	
Patients at Risk	13176	12863	12580	12282	11981	11635	11055	2183	862	
First Event	6	8	7	5	4	5	2	0	1	
Censored	307	275	291	296	342	575	8870	1321	861	
Placebo										
Survival Rate	100.00%	99.93%	99.88%	99.88%	99.86%	99.85%	99.84%	99.82%	99.82%	
Patients at Risk	13179	12826	12507	12214	11912	11612	11063	2203	825	
First Event	9	6	1	2	1	1	2	0	3	
Censored	344	313	292	300	299	548	8858	1378	822	

[1] Kaplan-Meier estimate of the survival curve. Survival Rate and Patients at Risk reflect a snapshot at the beginning of the interval, while First Event and Censored frequencies reflect events occurring in the following interval.
/data/usmedstat/slg4/a5011/programs/dec03/km_plots_survival_ps.sas KMK4236 08DEC03 15:36

The following Kaplan-Meier curves, which were submitted to the Division by the Sponsor, describe the time to all cause death or first intubation [N20236\ S_030\2004-02-24\clinstat\asthma\slga5011.pdf, page 135].

Protocol: SLGA5011



	Time in Study (days)[1]								
	0	30	60	90	120	150	180	210	240
Serevent									
Survival Rate	100.00%	99.94%	99.81%	99.72%	99.65%	99.56%	99.47%	99.27%	99.27%
Patients at Risk	13176	12869	12585	12286	11988	11638	11058	2184	863
First Event	8	16	12	8	11	10	9	0	3
Censored	299	268	287	290	339	570	8865	1321	860
Placebo									
Survival Rate	100.00%	99.87%	99.81%	99.75%	99.69%	99.63%	99.57%	99.46%	99.18%
Patients at Risk	13179	12829	12514	12218	11916	11615	11065	2208	829
First Event	17	8	7	8	7	7	7	3	9
Censored	333	307	289	294	294	543	8850	1376	820

[1] Kaplan-Meier estimate of the survival curve. Survival Rate and Patients at Risk reflect a snapshot at the beginning of the interval, while First Event and Censored frequencies reflect events occurring in the following interval.
/data/usmedstat/slga4/a5011/programs/dec03/km_plots_survival_ps.sas KMK4236 08DEC03 15:36

4.2. Primary and Secondary Outcomes by Ethnicity

Although subgroup analyses based upon race were not specified in the SMART protocol, the initial interim analysis results indicated the risk of salmeterol use in African Americans may be greater than in Caucasians; therefore, the subgroup analyses by ethnic groups will be reviewed here. Table 3 and Table 4 show a side by side comparison of the analyses of the primary and secondary safety outcomes for the SMART study for the 28-week treatment period versus the 28-week treatment period plus the 6 month post-study period in Caucasians and African Americans, respectively

Table 3 Overall Incidence of Primary & Secondary Safety Outcome Events in Caucasians
 28-Week Treatment Period vs. 28-Week Treatment Period and 6 Months Post-Study Combined, Unadjusted RR¹

	Salmeterol N=9281		Placebo N=9361		RR ¹ (95% CI) ²	
	Wk 1-28 & 6 mo post- study	Wk 1-28	Wk 1-28 & 6 mo post- study	Wk 1-28	Wk 1-28 & 6 mo post-study	Wk 1-28
Primary Outcome						
Combined respiratory-related death or life threatening experience ³ , n (%)	31 (<1)	29 (<1)	35 (<1)	28 (<1)	0.8933 (0.5514, 1.4474)	1.0446 (0.6220, 1.7545)
Secondary Outcomes						
Respiratory-related death	18 (<1)	16 (<1)	14 (<1)	7 (<1)	1.2968 (0.6454, 2.6058)	2.3054 (0.9489, 5.6012)
Combined asthma-related death or life threatening experience ³	18 (<1)	17 (<1)	19 (<1)	16 (<1)	0.9555 (0.5018, 1.8195)	1.0717 (0.5418, 2.1197)
Asthma related death	7 (<1)	6 (<1)	4 (<1)	1 (<1)	1.7651 (0.5169, 6.0275)	6.0517 (0.7287, 50.2570)
Combined all cause death or life threatening experience ³	49 (1)	44 (<1)	53 (<1)	44 (<1)	0.9325 (0.6330, 1.3737)	1.0086 (0.6648, 1.5303)
All cause death	33 (<1)	29 (<1)	31 (<1)	22 (<1)	1.0737 (0.6582, 1.7515)	1.3295 (0.7645, 2.3123)
All cause hospitalization	341 (4)	323 (3)	340 (4)	317 (3)	1.0116 (0.8729, 1.1723)	1.0277 (0.8826, 1.1967)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Tables 13.8;

Table 4 Overall Incidence of Primary & Secondary Safety Outcome Events in African Americans

28-Week Treatment Period vs. 28-Week Treatment Period and 6 Months Post-Study Combined, Unadjusted RR¹

	Salmeterol N=2366		Placebo N=2319		RR ¹ (95% CI) ²	
	Wk 1-28 & 6 mo post- study	Wk 1-28	Wk 1-28 & 6 mo post- study	Wk 1-28	Wk 1-28 & 6 mo post-study	Wk 1-28
Primary Outcome						
Combined respiratory-related death or life threatening experience ³ , n (%)	20 (<1)	20 (<1)	7 (<1)	5 (<1)	2.8004 (1.1864, 6.6100)	3.9205 (1.4739, 10.4284)
Secondary Outcomes						
Respiratory-related death	9 (<1)	8 (<1)	4 (<1)	2 (<1)	2.2053 (0.6801, 7.1511)	3.9205 (0.8334, 18.4425)
Combined asthma-related death or life threatening experience ³	19 (<1)	19 (<1)	4 (<1)	4 (<1)	4.6556 (1.5863, 13.6641)	4.6556 (1.5863, 13.6641)
Asthma related death	8 (<1)	7 (<1)	1 (<1)	1 (<1)	7.8411 (0.9815, 62.6425)	6.8609 (0.8448, 55.7207)
Combined all cause death or life threatening experience ³	26 (1)	24 (<1)	15 (<1)	11 (<1)	1.6989 (0.9022, 3.1991)	2.1385 (1.0500, 4.3555)
All cause death	15 (<1)	12 (<1)	12 (<1)	7 (<1)	1.2252 (0.5747, 2.6117)	1.6802 (0.6627, 4.2602)
All cause hospitalization	113 (5)	102 (4)	83 (4)	77 (3)	1.3344 (1.0111, 1.7612)	1.2984 (0.9712, 1.7357)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Tables 13.9.

For the 28 week treatment period, in the African American subpopulation, the relative risk for combined respiratory-related deaths or life threatening experiences, which was the primary outcome, was higher in patients treated with salmeterol, relative to patients treated with placebo. In addition, in the African American subpopulation the relative risk for combined all cause death or life threatening experience and asthma related death or life threatening experience was higher in patients treated with salmeterol relative to patients treated with placebo.

Reviewer's Comment: Overall, the data from the 28-week treatment period appears to be more compelling than the original data submitted by the Sponsor, which included the 6 month post-study adverse event data. African Americans treated with salmeterol relative to African Americans treated with placebo have a higher relative risk for the following:

- *Combined respiratory-related deaths or life threatening experiences*
- *Combined asthma-related death or life threatening experience*
- *Combined all cause death or life threatening experience.*

However, because the SMART study was terminated early and because of the nature of post hoc subgroup analyses, the data are not conclusive.

4.3. Inhaled Corticosteroid (ICS) Use

During the 2003 discussions of labeling changes based upon the SMART study outcomes, the Sponsor suggested that the use of ICS ameliorates the risk of salmeterol [June 13, 2003, Meeting Minutes]. Therefore, a review of the outcomes for the 28-week treatment period based upon inhaled corticosteroid use is warranted. For the purposes of the ICS discussion, all the data presented in the following tables are based upon the outcomes for the 28-week treatment period.

As shown in Table 5, overall 47% of the total population reported baseline ICS use. In the Caucasian subgroup, 50% reported baseline ICS use, while only 38% of African Americans reported baseline ICS use. Table 5 displays a comparison of selected outcomes based upon baseline ICS use and ethnicity.

Reviewer's Comment: The SMART study did not dictate or monitor ICS use closely, so we used baseline reports of ICS use only.

Table 5 Primary and Secondary Endpoints by Baseline ICS Use28-Week Treatment Period, Unadjusted RR¹

	Inhaled Corticosteroids		Relative Risk ¹ (95% CI) ²	No Inhaled Corticosteroids		Relative Risk ¹ (95% CI) ²
	Salmeterol	Placebo		Salmeterol	Placebo	
Number of Subjects						
Total (N=26,355)	6127	6138		7049	7041	
Caucasians (N=18,642)	4586	4637		4695	4724	
African Americans (N=4,685)	906	875		1460	1444	
Combined respiratory-related death or life-threatening experience ³ (Primary Endpoint)						
Total	23	19	1.21 (0.66, 2.22)	27	17	1.59(0.86, 2.91)
Caucasians	13	15	0.88 (0.41, 1.84)	16	13	1.24 (0.59, 2.57)
African Americans	9	3	2.90 (0.78, 10.67)	11	2	5.44 (1.20, 24.50)
Combined asthma-related death or life-threatening experience ³ (Secondary Endpoint)						
Total	16	13	1.23 (0.59, 2.56)	21	9	2.33 (1.06, 5.09)
Caucasians	6	9	0.67 (0.24, 1.89)	11	7	1.58 (0.61, 4.08)
African Americans	9	3	2.90 (0.89, 10.67)	10	1	9.89 (1.26, 77.16)
Combined all cause death or life-threatening experience ³ (Secondary Endpoint)						
Total	31	26	1.19 (0.71, 2.01)	39	33	1.18 (0.74, 1.87)
Caucasians	20	22	0.92 (0.50, 1.68)	24	22	1.10 (0.62, 1.95)
African Americans	10	3	3.22 (0.88, 11.66)	14	8	1.73 (0.72, 4.11)
Respiratory-related death (Secondary Endpoint)						
Total	10	5	2.00 (0.68, 5.86)	14	6	2.33 (0.89, 6.06)
Caucasians	7	3	2.36 (0.61, 9.12)	9	4	2.26 (0.69, 7.35)
African Americans	3	1	2.90 (0.30, 27.80)	5	1	4.95 (0.57, 42.28)
Asthma-related death (Secondary Endpoint)						
Total	4	3	1.34 (0.29, 5.97)	9	0	
Caucasians	1	1	1.01 (0.06, 16.16)	5	0	
African Americans	3	1	2.90 (0.30, 27.80)	4	0	

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Tables 13.52-13.57.

Interpretation of the outcomes from the SMART study based upon ICS use is problematic because the study was not designed or intended to address potential effects of ICS in modifying the risk of adverse effects of salmeterol. For instance, ICS use was not randomly assigned; therefore, there may be other important differences between groups (ICS vs. no ICS) which could affect the outcomes (e.g. disease severity, demographics, and quality of medical care). In addition, the best data for ICS use was collected at baseline and not rigorously collected during the treatment period. Therefore, no conclusions regarding ICS use can be interpreted from the data from the SMART study.

Reviewer's Comment: For the reasons listed above, conclusions regarding ICS use cannot be determined from the SMART study. Therefore, during labeling negotiations in 2003, the Agency recommended that the Sponsor's combination product, salmeterol and fluticasone (Advair®), also contain a Boxed Warning and information about the SMART study. This is consistent with the Agency's practice of including relevant safety information in product labels for all products containing a drug substance for which a risk has been identified.

5. STATISTICAL ISSUES

During the review period, the following statistical concerns were identified: primary analysis dataset and the method utilized for calculation of relative risks. The primary analysis dataset was discussed in detail in Section 3.2. The calculation of relative risk will be discussed briefly below. For a detailed Statistical Review and Evaluation of this submission, please refer to the review by Dr. Lisa Kammerman from the Office of Biometrics.

5.1. Relative Risk Calculation

During the review period, the statistical reviewer determined that the Sponsor's method of calculating the relative risks did not account for censoring. Due to the study design, the exact dates of censoring were not known. The subjects were contacted by phone every 4 weeks; therefore, the censoring times appeared in the database as multiples of 4 weeks. Due to the degree of censoring, the Division requested the Sponsor calculate the relative risks using life table analyses, which used intervals of four weeks and were limited to the 28-week treatment period.

The following table displays the relative risks using life table analyses, which were submitted by the Sponsor. The relative risks are quite similar to the Sponsor's original relative risk calculation.

Table 6 Relative Risks Utilizing Life Table Analyses

Relative Risks and 95% Confidence Intervals at 28 Weeks- Life Table Analyses				
	Salmeterol	Placebo	Relative Risk	95% Confidence Interval
Primary Endpoint – Combined Respiratory Related Deaths or Respiratory Related Life Threatening Experiences*				
All (N=26,355)	50	36	1.40	(0.91, 2.14)
Caucasian (N= 18,642)	29	28	1.05	(0.62, 1.76)
African American (N=4685)	20	5	4.10	(1.54, 10.90)
Asthma Related Deaths				
All (N=26,355)	13	3	4.37	(1.25, 15.34)
Caucasian (N= 18,642)	6	1	5.82	(0.70, 48.37)
African American (N=4685)	7	1	7.26	(0.89, 58.94)
Respiratory Related Deaths				
All (N=26,355)	24	11	2.16	(1.06, 4.41)
Caucasian (N= 18,642)	16	7	2.29	(0.94, 5.56)
African American (N=4685)	8	2	3.88	(0.83, 18.26)
Combined All Cause Deaths or Life Threatening Experiences*				
All (N=26,355)	70	59	1.19	(0.84, 1.68)
Caucasian (N= 18,642)	44	44	1.01	(0.67, 1.53)
African American (N=4685)	24	11	2.17	(1.06, 4.41)
Combined Asthma Related Deaths or Life Threatening Experiences*				
All (N=26,355)	37	22	1.71	(1.01, 2.89)
Caucasian (N= 18,642)	17	16	1.08	(0.55, 2.14)
African American (N=4685)	19	4	4.92	(1.68, 14.45)
All Cause Death				
All (N=26,355)	42	32	1.30	(0.82, 2.06)
Caucasian (N= 18,642)	29	22	1.32	(0.76, 2.30)
African American (N=4685)	12	7	1.69	(0.67, 4.28)

*Intubation and mechanical ventilation

Source: N20236\S_030\2004-08-27\clinstat\life_tables_28wks.pdf, Table 1.1-12.4.

Reviewer’s Comment: The Division’s statistician believes life table analysis is the appropriate method for determining the relative risk in this study.

6. SUMMARY

Salmeterol Inhalation Aerosol is a long acting β_2 -agonist, which was approved for asthma in 1994. Because of concerns regarding possible detrimental effects of chronic β_2 -agonist use, the Sponsor initiated a large, randomized, controlled study, the Salmeterol Multicenter Asthma Research Trial (SMART, Study #SLGA5011), in 1996. The SMART trial was halted prematurely in January 2003, because of concerning findings in a planned interim analysis. Because of the data from the SMART trial, in August 2003, a boxed warning was placed on all salmeterol containing products, which warned of a small increase in risk of asthma related deaths with salmeterol use in the SMART study. The Boxed Warning also stated that subgroup analysis suggested African Americans may be at increased risk compared to Caucasians.

In this labeling supplement (NDA #20-236, S-030; NDA #20-692, S-026; NDA #21-077, S-022), the Sponsor proposes labeling changes based upon an amended clinical study report for the SMART study. Although not specified in the protocol for the SMART study, the Sponsor performed an NDI search to capture as many primary outcome events as possible. The current submission contains the amended clinical study report with the adjudicated cases from the NDI search up through January 2002.

During the review period, the dataset utilized by the Sponsor for the primary and secondary outcomes of the SMART study became an issue. The treatment period for the SMART study was 28 weeks, however, the Sponsor collected spontaneously reported, post-study adverse events for 6 months following the treatment period. Although not specified in the protocol, all the SMART study reports submitted by the Sponsor to the Agency included the 6 month post-study adverse event data in the analyses of the primary and secondary outcomes. The Division was unaware of the inclusion of the post study adverse event data and disagrees with its inclusion in the analysis. The Division believes the dataset utilized for analysis of the SMART study should be events occurring during the 28 week treatment period. Furthermore, the Division recommends the product label reflect the outcomes of the SMART study be based upon the 28 week treatment period.

With regards to the NDI search, although not specified in the protocol, the Division believes the inclusion of the NDI search data is acceptable. However, the NDI search should only include outcomes which occurred during the 28-week treatment period.

Another issue determined during the review period was the method of calculating relative risks. The method of calculation submitted by the Sponsor did not account for censoring; therefore, the Sponsor was asked to determine the relative risks of outcomes at 28 weeks based on life table analyses.

The Division recommends the Sponsor revise the label of all salmeterol containing products to reflect the SMART study outcomes based upon life table analyses for the 28-week treatment period.

7. PROPOSED LABELING CHANGES

In this submission, the Sponsor proposes a change in the labeling for all salmeterol containing products based upon updated results from the SMART study, which would include additional adjudicated cases from an NDI search. The Division believes incorporation of the NDI search data in the product label is reasonable to identify primary and secondary outcomes for subjects lost to follow-up. However, as discussed in the review, the Division strongly believes the most clinically relevant period of interest in the SMART study is the 28-week treatment period. Therefore, the Division proposes the Sponsor change the label of all salmeterol containing products to correspond to the results of the SMART study for the 28-week treatment period.

In addition, to account for censoring, the Division believes the appropriate method of analysis to calculate the relative risk in this study is life table analysis. The Sponsor was asked to calculate the relative risks using life table analysis during the review period. The results are presented in Table 6. The Division proposes that the label reflect the relative risks calculated by life table analyses for the 28 week treatment period.

The following pages contain the labeling changes proposed by the Division for all salmeterol containing products, based upon the SMART study outcomes for the 28-week treatment period. Labeling revisions are recommended for the Boxed Warning, the Clinical Pharmacology, and the Warning sections of the salmeterol inhalation aerosol and salmeterol diskus product label. In addition, similar labeling revisions are recommended for the Boxed Warning and the Warnings section of the Advair product label.

The following are the proposed labeling revisions for the salmeterol inhalation aerosol and salmeterol diskus product.

WARNING: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (135 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (36 of 13,179). ~~Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians~~ (see WARNINGS and CLINICAL TRIALS: Asthma: Salmeterol Multi-center Asthma Research Trial).

Reviewer's Comment: The Division proposed deleting the last sentence of the Warning Box because as shown in Table 6, the relative risk for asthma-related deaths in Caucasians and African Americans treated with salmeterol relative to being treated with placebo were quite similar with overlapping confidence intervals.

Clinical Pharmacology

Clinical Trials: Salmeterol Multi-Center Asthma Research Trial: The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta2-agonist naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African-American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol, 42 mcg twice daily over 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). ~~Other~~Secondary-endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,353).

Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. However, analyses of secondary endpoints suggested that patients receiving salmeterol may be at increased risk for many of these events compared to patients receiving placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.90, 2.14) for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176 vs. 36 out of 13,179, respectively). In the total population, a higher number of asthma-related deaths (13 vs. 3, RR 4.37, 95% CI 1.24, 15.34) and combined asthma-related deaths or life-threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with salmeterol than those treated with placebo. The analysis of the African American subgroup showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated with salmeterol relative to those treated with placebo (20 out of 2366 vs. 5 out of 2319, respectively). In African Americans, a higher number of asthma-related deaths (7 vs. 1, RR 7.26, 95% CI 0.89, 58.94) and combined asthma-related deaths or life threatening experiences (19 vs. 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62, 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with placebo (29 out of 9281 vs. 28 out of 9361, respectively). In Caucasians, a higher number of

~~asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with salmeterol than in patients treated with placebo. The analysis showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4) occurred in the patients treated with salmeterol. Post hoc subgroup analyses revealed no significant increase in respiratory or asthma-related episodes, including deaths, in Caucasian patients. In African-Americans, the study showed a small, though statistically significantly greater, number of primary events (20 vs. 7), asthma-related deaths or life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking salmeterol compared to those taking placebo.~~ The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African-American patients and difficulties in enrollment.

WARNINGS

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study, called the Salmeterol Multi-center Asthma Research Trial (SMART), further suggest that the risk might be greater in African-American patients, ~~in whom the increased risk was statistically significant at the time of the interim analysis.~~ These results led to stopping the study prematurely (see CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of action of beta2-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect. Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

The following are the proposed labeling revisions for the Advair product label.

WARNING: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (135 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (36 of 13,179). ~~Subgroup analyses suggest the risk may be greater in African American patients compared to Caucasians~~(see WARNINGS).

WARNINGS

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta2-agonist-naive patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to placebo, when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). ~~Other Secondary~~ endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,353). Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. However, analyses of secondary endpoints suggested that patients receiving salmeterol may be at increased risk for many of these events compared to patients receiving placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.90, 2.14) for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176 vs. 36 out of 13,179, respectively). In the total population, a higher number of asthma-related deaths (13 vs. 3, RR 4.37, 95% CI 1.24, 15.34) and combined asthma-related deaths or life-threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with salmeterol than those treated with placebo. The analysis of the African American subgroup showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated with salmeterol relative to those treated with placebo (20 out of 2366 vs. 5 out of 2319, respectively). In African Americans, a higher number of asthma-related deaths (7 vs. 1, RR 7.26, 95% CI 0.89, 58.94) and combined asthma-related deaths or life-threatening experiences (19 vs. 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62, 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with placebo (29 out of 9281 vs. 28 out of 9361, respectively). In Caucasians, a higher number of asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with salmeterol than in patients treated with placebo. The analysis showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4) occurred in

~~the patients treated with SEREVENT Inhalation Aerosol. Post hoc subgroup analyses revealed no significant increase in respiratory or asthma-related episodes, including deaths, in Caucasian patients. In African Americans, the study showed a small, though statistically significantly greater, number of primary events (20 vs. 7), asthma-related deaths or life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking SEREVENT Inhalation Aerosol compared to those taking placebo.~~ Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African American patients and difficulties in enrollment. The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk. Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would apply to ADVAIR DISKUS.

Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

Given the similar basic mechanisms of action of beta2-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

8. CORRESPONDENCE WITH SPONSOR DURING THE REVIEW PERIOD

As stated in the introduction, multiple requests for information were sent to the Sponsor during the review period. The review incorporates the Sponsor's responses to the Division's requests for information. In addition, a teleconference was held with the Sponsor on July 26, 2004, to discuss the Division's recommendation to revise the product label to reflect the results of the SMART study based upon the 28 week treatment period.

A teleconference was also held with the Sponsor on September 13, 2004, to discuss the details of the Division's recommended revised product labels. Labeling negotiations are ongoing.

Reviewed by:

Sally Seymour, MD
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Deputy Director, Division of Pulmonary and Allergy Drug Products

APPENDIX

1. SMART RESULTS INCLUDING NDI SEARCH

Table 7 is based upon initial study reports submitted by the Sponsor, which included outcomes for the 28-week treatment period and the 6 month post-study period.

Table 7 Comparison of the SMART Primary and Secondary Safety Outcomes with and without the Additional NDI Data

Includes outcomes for the 28-week treatment period and 6 month post-study period, Unadjusted RR¹

	Salmeterol		Placebo		RR ¹ (95% CI) ²	
	N=13,174	+ NDI DATA N=13,176	N=13,179	+ NDI DATA N=13,179		+NDI DATA
Primary Outcome						
Combined respiratory-related death or life threatening experience ³ , n (%)	48 (<1)	52 (<1)	42 (<1)	45 (<1)	1.1433 (0.7562, 1.7286)	1.1558 (0.7761, 1.7214)
Secondary Outcomes						
Respiratory-related death	23 (<1)	27 (<1)	17 (<1)	20 (<1)	1.3535 (0.7234, 2.5322)	1.3503 (0.7578, 2.4062)
Combined asthma-related death or life threatening experience ³	36 (<1)	38 (<1)	23 (<1)	25 (<1)	1.5658 (0.9285, 2.6407)	1.5203 (0.9183, 2.5170)
Asthma related death	13 (<1)	15 (<1)	4 (<1)	6 (<1)	3.2512 (1.0604, 9.9685)	2.5006 (0.9705, 6.4428)
Combined all cause death or life threatening experience ³	69 (<1)	77 (<1)	68 (<1)	73 (<1)	1.0151 (0.7268, 1.4177)	1.0550 (0.7667, 1.4518)
All cause death	41 (<1)	49 (<1)	42 (<1)	47 (<1)	0.9766 (0.6355, 1.5007)	1.0428 (0.6994, 1.5548)
All cause hospitalization	498 (4)	499 (4)	449 (3)	449 (3)	1.1096 (0.9789, 1.2576)	1.1116 (0.9808, 1.2599)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2003-08-29\clinstat\slga5011.pdf, Table 13.2, page 1414

Source Data: N20236\S_030\2004-02-24\clinstat\slga5011.pdf, Table 13.2, page 1460

2. SMART RESULTS BASED UPON 28-WEEK TREATMENT PERIOD

The following tables display the primary and secondary safety outcomes for the SMART study as reported by the Sponsor for the 28 week treatment period. In addition, post-hoc subgroup analyses are included. All relative risk and confidence interval calculations were performed by the Sponsor.

2.1. Overall Incidence of Primary Safety Outcome Events

Table 8 Overall Incidences of Primary Safety Outcome Events during 28-Week Treatment Period, Unadjusted RR¹

	Salmeterol N=13,176	Placebo N=13,179	RR ¹ (95% CI) ²
Combined respiratory-related death or life threatening experience ³ , n (%)	50 (<1)	36 (<1)	1.3892 (0.9057, 2.1307)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.2, page 16.

2.2. Overall Incidence of Secondary Safety Outcome Events

Table 9 Overall Incidences of Secondary Safety Outcome Events during 28-Week Treatment Period, Unadjusted RR¹

	Salmeterol N=13,176	Placebo N=13,179	RR ¹ (95% CI) ²
Respiratory-related death, n (%)	24 (<1)	11 (<1)	2.1823 (1.0695, 4.4532)
Combined asthma-related death or life threatening experience ³ , n (%)	37 (<1)	22 (<1)	1.6822 (0.9930, 2.8497)
Asthma related death, n (%)	13 (<1)	3 (<1)	4.3343 (1.2354, 15.2064)
Combined all cause death or life threatening experience ³ , n (%)	70 (<1)	59 (<1)	1.1867 (0.8400, 1.6765)
All cause death, n (%)	42 (<1)	32 (<1)	1.3128 (0.8294, 2.0780)
All cause hospitalization, n (%)	469 (4)	420 (3)	1.1169 (0.9813, 1.2713)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.2, page 16.

2.3. Overall Incidence of Primary Safety Outcome Events in Caucasians

Table 10 Overall Incidences of Primary Safety Outcome Events in Caucasians during 28-Week Treatment Period, Unadjusted RR¹

	Salmeterol N=9281	Placebo N=9361	RR ¹ (95% CI) ²
Combined respiratory-related death or life threatening experience ³ , n (%)	29 (<1)	28 (<1)	1.0446 (0.6220, 1.7545)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.8, page 23.

2.4. Overall Incidence of Secondary Safety Outcome Events in Caucasians

Table 11 Overall Incidences of Secondary Safety Outcome Events in Caucasians during 28-Week Treatment Period, Unadjusted RR¹

	Salmeterol N=9281	Placebo N=9361	RR ¹ (95% CI) ²
Respiratory-related death, n (%)	16 (<1)	7 (<1)	2.3054 (0.9489, 5.6012)
Combined asthma-related death or life threatening experience ³ , n (%)	17 (<1)	16 (<1)	1.0717 (0.5418, 2.1197)
Asthma related death, n (%)	6 (<1)	1 (<1)	6.0517 (0.7287, 50.2570)
Combined all cause death or life threatening experience ³ , n (%)	44 (<1)	44 (<1)	1.0086 (0.6648, 1.5303)
All cause death, n (%)	29 (<1)	22 (<1)	1.3295 (0.7645, 2.3123)
All cause hospitalization, n (%)	323 (3)	317 (3)	1.0277 (0.8826, 1.1967)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.8, page 23.

2.5. Overall Incidence of Primary Safety Outcome Events in African Americans

Table 12 Overall Incidences of Primary Safety Outcome Events in African Americans during 28-Week Treatment Period, Unadjusted RR¹

	Salmeterol N=2366	Placebo N=2319	RR ¹ (95% CI) ²
Combined respiratory-related death or life threatening experience ³ , n (%)	20 (<1)	5 (<1)	3.9205 (1.4739, 10.4284)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.9, page 25.

2.6. Overall Incidence of Secondary Safety Outcome Events in African Americans

Table 13 Overall Incidences of Secondary Safety Outcome Events in African Americans during 28-Week Treatment Period, Unadjusted RR¹

	Salmeterol N=2366	Placebo N=2319	RR ¹ (95% CI) ²
Respiratory-related death, n (%)	8 (<1)	2 (<1)	3.9205 (0.8334, 18.4425)
Combined asthma-related death or life threatening experience ³ , n (%)	19 (<1)	4 (<1)	4.6556 (1.5863, 13.6641)
Asthma related death, n (%)	7 (<1)	1 (<1)	6.8609 (0.8448, 55.7207)
Combined all cause death or life threatening experience ³ , n (%)	24 (<1)	11 (<1)	2.1385 (1.0500, 4.3555)
All cause death, n (%)	12 (<1)	7 (<1)	1.6802 (0.6627, 4.2602)
All cause hospitalization, n (%)	102 (4)	77 (3)	1.2984 (0.9712, 1.7357)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.9, page 25.

2.7. Overall Incidence of Primary and Secondary Safety Outcome Events for Subjects with Baseline ICS Use

Table 14 Overall Incidence of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period for Subjects Reporting Baseline ICS Use, Unadjusted RR¹

	Salmeterol N=6127	Placebo N=6138	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	23 (<1)	19 (<1)	1.2127 (0.6612, 2.2243)
Secondary Outcomes			
Respiratory-related death, n (%)	10 (<1)	5 (<1)	2.0036 (0.6852, 5.8584)
Combined asthma-related death or life threatening experience ³ , n (%)	16 (<1)	13 (<1)	1.2330 (0.5936, 2.5610)
Asthma related death, n (%)	4 (<1)	3 (<1)	1.3357 (0.2991, 5.9656)
Combined all cause death or life threatening experience ³ , n (%)	31 (<1)	26 (<1)	1.1944 (0.7101, 2.0091)
All cause death, n (%)	17 (<1)	12 (<1)	1.4192 (0.6784, 2.9690)
All cause hospitalization, n (%)	255 (4)	231 (4)	1.1059 (0.9288, 1.3167)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.52, page 69.

2.8. Overall Incidence of Primary and Secondary Safety Outcome Events for Subjects with No Baseline ICS Use

Table 15 Overall Incidence of Primary and Secondary Safety Outcome Events during 28 week Treatment Period for Subjects Reporting No Baseline ICS Use, Unadjusted RR¹

	Salmeterol N=7049	Placebo N=7041	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	27 (<1)	17 (<1)	1.5864 (0.8655, 2.9079)
Secondary Outcomes			
Respiratory-related death, n (%)	14 (<1)	6 (<1)	2.3307 (0.8962, 6.0615)
Combined asthma-related death or life threatening experience ³ , n (%)	21 (<1)	9 (<1)	2.3307 (1.0682, 5.0852)
Asthma related death, n (%)	9 (<1)	0	
Combined all cause death or life threatening experience ³ , n (%)	39 (<1)	33 (<1)	1.1805 (0.7434, 1.8745)
All cause death, n (%)	25 (<1)	20 (<1)	1.2486 (0.6942, 2.2458)
All cause hospitalization, n (%)	214 (3)	189 (3)	1.1310 (0.9326, 1.3715)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.53, page 71.

2.9. Overall Incidence of Primary and Secondary Safety Outcome Events for Caucasian Subjects with Baseline ICS Use

Table 16 Overall Incidence of Primary and Secondary Safety Outcome Events during 28 week Treatment Period for Caucasian Subjects Reporting Baseline ICS Use, Unadjusted RR¹

	Salmeterol N=4586	Placebo N=4637	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	13 (<1)	15 (<1)	0.8763 (0.4174, 1.8396)
Secondary Outcomes			
Respiratory-related death, n (%)	7 (<1)	3 (<1)	2.3593 (0.6105, 9.1179)
Combined asthma-related death or life threatening experience ³ , n (%)	6 (<1)	9 (<1)	0.6741 (0.2401, 1.8923)
Asthma related death, n (%)	1 (<1)	1 (<1)	1.0111 (0.0633, 16.1604)
Combined all cause death or life threatening experience ³ , n (%)	20 (<1)	22 (<1)	0.9192 (0.5024, 1.6819)
All cause death, n (%)	13 (<1)	10 (<1)	1.3145 (0.5770, 2.9946)
All cause hospitalization, n (%)	187 (4)	184 (4)	1.0276 (0.8419, 1.2543)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.54, page 72.

2.10. Overall Incidence of Primary and Secondary Safety Outcome Events for Caucasian Subjects with No Baseline ICS Use

Table 17 Overall Incidence of Primary and Secondary Safety Outcome Events during 28 week Treatment Period for Caucasian Subjects Reporting No Baseline ICS Use, Unadjusted RR¹

	Salmeterol N=4695	Placebo N=4724	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	16 (<1)	13 (<1)	1.2384 (0.5964, 2.5716)
Secondary Outcomes			
Respiratory-related death, n (%)	9 (<1)	4 (<1)	2.2639 (0.6977, 7.3462)
Combined asthma-related death or life threatening experience ³ , n (%)	11 (<1)	7 (<1)	1.5811 (0.6135, 4.0752)
Asthma related death, n (%)	5 (<1)	0	
Combined all cause death or life threatening experience ³ , n (%)	24 (<1)	22 (<1)	1.0976 (0.6164, 1.9548)
All cause death, n (%)	16 (<1)	12 (<1)	1.3416 (0.6354, 2.8327)
All cause hospitalization, n (%)	136 (3)	133 (3)	1.0289 (0.8129, 1.3022)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.55, page 73.

2.11. Overall Incidence of Primary and Secondary Safety Outcome Events for African American Subjects with Baseline ICS Use

Table 18 Overall Incidence of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period for African American Subjects Reporting Baseline ICS Use, Unadjusted RR¹

	Salmeterol N=906	Placebo N=875	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	9 (<1)	3 (<1)	2.8974 (0.7870, 10.6668)
Secondary Outcomes			
Respiratory-related death, n (%)	3 (<1)	1 (<1)	2.8974 (0.3020, 27.8007)
Combined asthma-related death or life threatening experience ³ , n (%)	9 (<1)	3 (<1)	2.8974 (0.7870, 10.6668)
Asthma related death, n (%)	3 (<1)	1 (<1)	2.8974 (0.3020, 27.8007)
Combined all cause death or life threatening experience ³ , n (%)	10 (<1)	3 (<1)	3.2193 (0.8890, 11.6583)
All cause death, n (%)	4 (<1)	1 (<1)	3.8631 (0.4326, 34.4950)
All cause hospitalization, n (%)	47 (5)	37 (4)	1.2268 (0.8056, 1.8683)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.56, page 74.

2.12. Overall Incidence of Primary and Secondary Safety Outcome Events for African American Subjects with No Baseline ICS Use

Table 19 Overall Incidence of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period for African American Subjects Reporting No Baseline ICS Use, Unadjusted RR¹

	Salmeterol N=1460	Placebo N=1444	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	11 (<1)	2 (<1)	5.4397 (1.2079, 24.4984)
Secondary Outcomes			
Respiratory-related death, n (%)	5 (<1)	1 (<1)	4.9452 (0.5785, 42.2760)
Combined asthma-related death or life threatening experience ³ , n (%)	10 (<1)	1 (<1)	9.8904 (1.2677, 77.1619)
Asthma related death, n (%)	4 (<1)	0	
Combined all cause death or life threatening experience ³ , n (%)	14 (<1)	8 (<1)	1.7308 (0.7283, 4.1132)
All cause death, n (%)	8 (<1)	6 (<1)	1.3187 (0.4587, 3.7911)
All cause hospitalization, n (%)	55 (4)	40 (3)	1.3599 (0.9109, 2.0303)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.57, page 75.

2.13. Overall Incidence of Primary and Secondary Safety Outcome Events in Subjects with Baseline Percent Predicted PEF ≤ 60%

Table 20 Overall Incidence of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period in Subjects with Baseline Percent Predicted PEF ≤ 60%, Unadjusted RR¹

	Salmeterol N=2338	Placebo N=2350	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	29 (<1)	15 (<1)	1.9433 (1.0446, 3.6149)
Secondary Outcomes			
Respiratory-related death, n (%)	15 (<1)	4 (<1)	3.7692 (1.2529, 11.3398)
Combined asthma-related death or life threatening experience ³ , n (%)	20 (<1)	8 (<1)	2.5128 (1.1090, 5.6935)
Asthma related death, n (%)	7 (<1)	0	
Combined all cause death or life threatening experience ³ , n (%)	35 (1)	27 (1)	1.3029 (0.7913, 2.1455)
All cause death, n (%)	20 (<1)	15 (<1)	1.3402 (0.6878, 2.6112)
All cause hospitalization, n (%)	143 (6)	139 (6)	1.0341 (0.8246, 1.2967)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.43, page 59.

2.14. Overall Incidence of Primary and Secondary Safety Outcome Events in Subjects with Baseline Percent Predicted PEF > 60%

Table 21 Overall Incidence of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period in Subjects with Baseline Percent Predicted PEF > 60%, Unadjusted RR¹

	Salmeterol N=10,540	Placebo N=10,486	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	21 (<1)	20 (<1)	1.0446 (0.5666, 1.9260)
Secondary Outcomes			
Respiratory-related death, n (%)	9 (<1)	6 (<1)	1.4923 (0.5314, 4.1911)
Combined asthma-related death or life threatening experience ³ , n (%)	17 (<1)	13 (<1)	1.3010 (0.6322, 2.6771)
Asthma related death, n (%)	6 (<1)	2 (<1)	2.9846 (0.6025, 14.7841)
Combined all cause death or life threatening experience ³ , n (%)	35 (<1)	31 (<1)	1.1232 (0.6932, 1.8201)
All cause death, n (%)	22 (<1)	16 (<1)	1.3680 (0.7189, 2.6032)
All cause hospitalization, n (%)	326 (3)	280 (3)	1.1583 (0.9896, 1.3558)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.44, page 60.

2.15. Overall Incidence of Primary and Secondary Safety Outcome Events in Caucasian Subjects with Baseline Percent Predicted PEF ≤ 60%

Table 22 Overall Incidences of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period in Caucasian Subjects with Baseline Percent Predicted PEF ≤ 60%, Unadjusted RR¹

	Salmeterol N=1513	Placebo N=1523	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	18 (<1)	13 (<1)	1.3938 (0.6854, 2.8344)
Secondary Outcomes			
Respiratory-related death, n (%)	11 (<1)	3 (<1)	3.6909 (1.0317, 13.2036)
Combined asthma-related death or life threatening experience ³ , n (%)	10 (<1)	7 (<1)	1.4380 (0.5488, 3.7679)
Asthma related death, n (%)	4 (<1)	0	
Combined all cause death or life threatening experience ³ , n (%)	21 (<1)	20 (<1)	1.0569 (0.5753, 1.9418)
All cause death, n (%)	13 (<1)	9 (<1)	1.4540 (0.6234, 3.3913)
All cause hospitalization, n (%)	96 (6)	105 (7)	0.9203 (0.7043, 1.2025)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.45, page 61.

2.16. Overall Incidence of Primary and Secondary Safety Outcome Events in Caucasian Subjects with Baseline Percent Predicted PEF > 60%

Table 23 Overall Incidence of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period in Caucasian Subjects with Baseline Percent Predicted PEF > 60%, Unadjusted RR¹

	Salmeterol N=7572	Placebo N=7614	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	11 (<1)	15 (<1)	0.7374 (0.3389, 1.6044)
Secondary Outcomes			
Respiratory-related death, n (%)	5 (<1)	4 (<1)	1.2569 (0.3377, 4.6790)
Combined asthma-related death or life threatening experience ³ , n (%)	7 (<1)	9 (<1)	0.7821 (0.2914, 2.0989)
Asthma related death, n (%)	2 (<1)	1 (<1)	2.0111 (0.1824, 22.1741)
Combined all cause death or life threatening experience ³ , n (%)	23 (<1)	24 (<1)	0.9636 (0.5444, 1.7057)
All cause death, n (%)	16 (<1)	13 (<1)	1.2376 (0.5957, 2.5711)
All cause hospitalization, n (%)	227 (3)	211 (3)	1.0818 (0.8993, 1.3013)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.46, page 62.

2.17. Overall Incidence of Primary and Secondary Safety Outcome Events in African American Subjects with Baseline Percent Predicted PEF ≤ 60%

Table 24 Overall Incidence of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period in African American Subjects with Baseline Percent Predicted PEF ≤ 60%, Unadjusted RR¹

	Salmeterol N=544	Placebo N=577	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	10 (2)	1 (<1)	10.6066 (1.3623, 82.5799)
Secondary Outcomes			
Respiratory-related death, n (%)	4 (<1)	0	
Combined asthma-related death or life threatening experience ³ , n (%)	9 (2)	1 (<1)	9.5460 (1.2134, 75.0968)
Asthma related death, n (%)	3 (<1)	0	
Combined all cause death or life threatening experience ³ , n (%)	13 (2)	5 (<1)	2.7577 (0.9897, 7.6839)
All cause death, n (%)	7 (<1)	4 (<1)	1.8562 (0.5464, 6.3053)
All cause hospitalization, n (%)	33 (6)	27 (5)	1.2964 (0.7903, 2.1266)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.47, page 63.

2.18. Overall Incidence of Primary and Secondary Safety Outcome Events in African American Subjects with Baseline Percent Predicted PEF > 60%

Table 25 Overall Incidence of Primary and Secondary Safety Outcome Events during 28-Week Treatment Period in African American Subjects with Baseline Percent Predicted PEF > 60%, Unadjusted RR¹

	Salmeterol N=1770	Placebo N=1679	RR ¹ (95% CI) ²
Primary Outcome			
Combined respiratory-related death or life threatening experience ³ , n (%)	10 (<1)	4 (<1)	2.3715 (0.7452, 7.5467)
Secondary Outcomes			
Respiratory-related death, n (%)	4 (<1)	2 (<1)	1.8972 (0.3479, 10.3443)
Combined asthma-related death or life threatening experience ³ , n (%)	10 (<1)	3 (<1)	3.1620 (0.8717, 11.4692)
Asthma related death, n (%)	4 (<1)	1 (<1)	3.7944 (0.4245, 33.9131)
Combined all cause death or life threatening experience ³ , n (%)	11 (<1)	6 (<1)	1.7391 (0.6446, 4.6919)
All cause death, n (%)	5 (<1)	3 (<1)	1.5810 (0.3784, 6.6051)
All cause hospitalization, n (%)	69 (4)	50 (3)	1.3091 (0.9153, 1.8722)

1. RR=relative risk=quotient of event rate for salmeterol group divided by event rate for placebo group, does not account for censoring

2. CI = confidence interval

3. Life-threatening experiences defined as occurrence of endotracheal intubation and/or mechanical ventilation

Source Data: N20236\S_030\2004-05-24\clinstat\response.pdf, Table 13.48, page 64.

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