

CHEST[®]

Official publication of the American College of Chest Physicians



The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol

Harold S. Nelson, Scott T. Weiss, Eugene R. Bleeker, Steven W. Yancey, Paul M. Dorinsky and the SMART Study Group

Chest 2006;129;15-26
DOI 10.1378/chest.129.1.15

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournals.org/cgi/content/abstract/129/1/15>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2007 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder (<http://www.chestjournal.org/misc/reprints.shtml>). ISSN: 0012-3692.

A M E R I C A N C O L L E G E O F
 C H E S T
P H Y S I C I A N S[®]



The Salmeterol Multicenter Asthma Research Trial*

A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol

Harold S. Nelson, MD; Scott T. Weiss, MD, MS; Eugene R. Bleeker, MD; Steven W. Yancey, MS; and Paul M. Dorinsky, MD; and the SMART Study Group

Study objective: To compare the safety of salmeterol xinafoate or placebo added to usual asthma care.

Design: A 28-week, randomized, double-blind, placebo-controlled, observational study.

Setting: Study subjects were seen once in the study physician's office for screening and were provided all blinded study medication for the entire study period. Follow-up by telephone was scheduled every 4 weeks.

Participants: Subjects (> 12 years old) with asthma as judged by the study physician were eligible. Individuals with a history of long-acting β_2 -agonist use were excluded.

Interventions: Salmeterol, 42 μg bid via metered-dose inhaler (MDI), and placebo bid via MDI.

Measurements and results: Following an interim analysis in 26,355 subjects, the study was terminated due to findings in African Americans and difficulties in enrollment. The occurrence of the primary outcome, respiratory-related deaths, or life-threatening experiences was low and not significantly different for salmeterol vs placebo (50 vs 36; relative risk [RR] = 1.40; 95% confidence interval [CI], 0.91 to 2.14). There was a small, significant increase in respiratory-related deaths (24 vs 11; RR, 2.16; 95% CI, 1.06 to 4.41) and asthma-related deaths (13 vs 3; RR, 4.37; 95% CI, 1.25 to 15.34), and in combined asthma-related deaths or life-threatening experiences (37 vs 22; RR, 1.71; 95% CI, 1.01 to 2.89) in subjects receiving salmeterol vs placebo. The imbalance occurred largely in the African-American subpopulation: respiratory-related deaths or life-threatening experiences (20 vs 5; RR, 4.10; 95% CI, 1.54 to 10.90) and combined asthma-related deaths or life-threatening experiences (19 vs 4; RR, 4.92; 95% CI, 1.68 to 14.45) in subjects receiving salmeterol vs placebo.

Conclusions: For the primary end point in the total population, there were no significant differences between treatments. There were small, but statistically significant increases in respiratory-related and asthma-related deaths and combined asthma-related deaths or life-threatening experiences in the total population receiving salmeterol. Subgroup analyses suggest the risk may be greater in African Americans compared with Caucasian subjects. Whether this risk is due to factors including but not limited to a physiologic treatment effect, genetic factors, or patient behaviors leading to poor outcomes remains unknown. (CHEST 2006; 129:15–26)

Key words: asthma; long-acting β_2 -agonist; salmeterol

Abbreviations: CI = confidence interval; ED = emergency department; ICS = inhaled corticosteroid; MDI = metered-dose inhaler; MMRC = Morbidity and Mortality Review Committee; RR = relative risk; SMART = Salmeterol Multicenter Asthma Research Trial

Published studies¹ have suggested a progressive increase in the incidence of asthma-related mortality over the past several decades. Risk factors associated with asthma-related death include overuse of β -agonists or theophylline, underuse of controller medications, disease severity, pollution, gen-

der, age, substance abuse, and ethnic background.² Among these risk factors, the link between specific asthma therapies, in particular β_2 -agonists, and the rising asthma death rate has been the subject of ongoing debate.

For example, in the 1960s an increase in asthma

deaths was reported in countries where a high-dose preparation of isoprenaline aerosol was available.³ After careful review, the researchers concluded that overuse of isoprenaline was the major factor associated with these asthma deaths.⁴ In the 1970s, an increase in asthma deaths in association with the use of fenoterol, a potent, full β_2 -agonist, was reported.⁵⁻⁷ While these reports⁵⁻⁷ raised questions about a possible class effect with β_2 -agonist bronchodilators, ultimately these reports were ascribed to isolated overuse of β -agonists for poorly controlled asthma.

For editorial comment see page 3

Salmeterol and formoterol are highly selective, third-generation β_2 -agonists that have been available for use since the early 1990s and were designed to provide long-lasting bronchodilation and improved pharmacokinetic properties to minimize unwanted side effects. In this regard, large-scale clinical and observational studies⁸⁻¹¹ have supported the profile of this new generation of β_2 -agonists relative to their less selective, short-acting predecessors. Nonetheless, in a 16-week, randomized controlled trial¹² conducted in the United Kingdom in the mid 1990s, serious exacerbations and asthma deaths were compared in subjects who received salmeterol twice daily or albuterol four times daily. In this study,¹² there were significantly fewer withdrawals due to worsening asthma with salmeterol. However, the frequency of asthma-related death, although low in both treatment groups, was numerically but not significantly higher in the salmeterol group. In order to further evaluate the effects of salmeterol on respiratory- and asthma-related deaths or life-threatening episodes,

*From the National Jewish Medical and Research Center (Dr. Nelson), Denver, CO; Brigham and Women's Hospital and Harvard Medical School (Dr. Weiss), Boston, MA; Wake Forest University School of Medicine (Dr. Bleeker), Winston Salem, NC; and GlaxoSmithKline (Mr. Yancey and Dr. Dorinsky), Research Triangle Park, NC.

These data were presented in part at the American College of Chest Physicians Conference in Orlando, FL, October 25-30, 2003.

Dr. Nelson is a consultant, speaker, and recipient of research grants from GlaxoSmithKline, and was also a member of the MMRC for this study. Dr. Weiss is a consultant for GlaxoSmithKline, and was also a member of the MMRC for this study. Dr. Bleeker is a consultant, speaker, and recipient of research grants from GlaxoSmithKline, and was a member of the MMRC for this study. Mr. Yancey is an employee of GlaxoSmithKline. Dr. Dorinsky is an employee of GlaxoSmithKline.

Manuscript received November 19, 2004; revision accepted March 1, 2005.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Paul M. Dorinsky, MD, GlaxoSmithKline, 5 Moore Dr, Research Triangle Park, NC 27709; e-mail: paul.m.dorinsky@gsk.com

these events were examined in a 28-week study in which salmeterol or placebo was added to usual asthma care.

MATERIALS AND METHODS

Patient Selection

Male and female subjects aged ≥ 12 years were eligible if they had a diagnosis of asthma (per investigator clinical judgement) and were currently receiving a prescription asthma medication. However, subjects could not have previously used inhaled long-acting β_2 -agonists. Concurrent use of other prescription asthma medication(s) was permitted. Exclusion criteria included pregnancy and/or lactation, or any significant systemic disease that in the opinion of the investigator may place a subject at risk; history of any adverse reaction (including immediate or delayed hypersensitivity reaction) to any sympathomimetic amine drug; or current use of β -blockers.

Two methods of recruitment were utilized during the study. Initially, subjects were recruited via print, radio, and television advertising and were assigned to a study investigator by geographic location during 1996 to 1999 (phase 1). However, when recruitment waned, the large-scale advertising campaign was stopped and study investigators were added to facilitate enrollment during from 2000 to 2003 (phase 2). During phase 2, subjects were recruited directly by the study investigators.

Study Design and Intervention

The Salmeterol Multicenter Asthma Research Trial (SMART) was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, observational surveillance study conducted at 6,163 sites in the United States; 1,316 investigators randomized subjects into the trial. SMART was initiated on June 30, 1996. Institutional review boards approved the study protocol, and all subjects signed a written informed consent document prior to enrollment. SMART was designed to compare respiratory-related and asthma-related outcomes in subjects receiving usual asthma pharmacotherapy alone or usual asthma pharmacotherapy plus salmeterol.

The study consisted of a single clinic visit (visit 1) during which eligibility was evaluated, and informed consent and baseline information were obtained. Eligible subjects were randomized to treatment with either salmeterol 42 μg bid via metered-dose inhaler (MDI) or placebo MDI bid (Fig 1). At visit 1, subjects were given a 28-week supply of study medication and study procedures were reviewed. Subjects were instructed on the proper use of the MDI. In addition, they were instructed to continue use of current asthma medications, as the study drug was a supplement, not a replacement, for current therapy. Subjects not currently receiving short-acting β -agonists were supplied albuterol. Short-acting β -agonist use was recorded at baseline only and not throughout the study. Study medication was to be administered on arising and before bedtime (approximately 12 h apart), and a new inhaler was to be used every 4 weeks.

Following visit 1, subjects were not required to return for clinic visits but instead were to be contacted every 4 weeks by telephone for evaluations and data collection related to respiratory-related life-threatening events, serious adverse events (if applicable, these required physician completion of a US Food and Drug Administration MedWatch form), concomitant medication use, and subjective study medication compliance assess-

or continuing the study through examination of the relative risk (RR) and associated 99% confidence interval (CI) comparing event rates of the primary end point and the secondary end point of asthma-related death for salmeterol vs placebo in the overall population.

Predefined criteria for study termination were not met at the interim analysis. However, the sponsor (GlaxoSmithKline; Research Triangle Park, NC) elected to terminate the study due to preliminary findings in African Americans and difficulties in enrollment. After the interim results were analyzed, information was obtained about eight additional cases that were identified from a National Death Index search. These additional cases were identified from the small cohort of subjects who were unavailable for follow-up and for whom data were not available at the time of study termination.

Population

All analyses were based on the intent-to-treat population, which consisted of all subjects who were randomized to study medication and for whom case report form data were available. All available data are reported.

Statistical Methods for Planned Outcome Events Analysis

Inferential analyses of all outcome events were based on the CI for the RR of each outcome for salmeterol vs placebo. At the planned interim analysis, assessments were made based on a 99% CI. Since the study was stopped after the interim analysis, assessments on final data were made based on 95% CI. Due to extensive censoring in the outcome event data, it was determined that the most appropriate estimates of RR would be derived from life table methodology. Therefore, throughout this article the life table estimates of RR are considered the primary analysis. In addition, Kaplan-Meier estimates of the time to each outcome event (first occurrence if appropriate) were generated. Inferential analyses of the time to each outcome event were based on the log-rank test.

Statistical Methods for Exploratory Outcome Event Analysis

Following the review of the interim analysis, exploratory analyses of each outcome event within subpopulations were conducted. Subpopulations were based on baseline characteristics such as inhaled corticosteroid (ICS) use and study phase. Additionally, outcome events were analyzed separately for white and African-American subjects.

The incidence of serious adverse events (defined as death [from all causes]; life-threatening events, including endotracheal intubation and mechanical ventilation; events that are disabling or incapacitating; events that require or prolonged inpatient hospitalization; significant laboratory abnormalities; any congenital anomaly in the offspring of a subject exposed to study drug *in utero*; events resulting from an overdose of study drug; and any cancer) was determined for each treatment group, and a plot of Kaplan-Meier estimates of time to first serious event was produced. A log-rank test was used to test for differences between treatment groups in the time to first serious event.

RESULTS

There were 26,355 subjects randomized to study treatment. Demographic characteristics and asthma history were similar between treatment groups and

Table 1—Demographic and Baseline Characteristics for the Total Population

Characteristics	Salmeterol (n = 13,176)	Placebo (n = 13,179)
Mean age (range), yr	39.2 (9–100)	39.1 (11–93)
Sex, No. (%)		
Female	8,334 (64)	8,337 (64)
Male	4,703 (36)	4,686 (36)
Ethnic origin, No. (%)		
Caucasian	9,281 (71)	9,361 (72)
African American	2,366 (18)	2,319 (18)
Hispanic	996 (8)	999 (8)
Asian	173 (1)	149 (1)
Other	230 (2)	224 (2)
Mean PEF (SD), L/min	354.9 (124.77)	355.6 (125.70)
PEF % predicted (SD), %	84.0 (25.65)	83.8 (25.44)
Mean duration (SD) of asthma, yr	16.3 (14.51)	16.3 (14.44)

are summarized in Tables 1, 2. In the previous 12 months, asthma emergency department (ED) visits and hospitalizations were reported by 26% and 8% of all subjects, respectively, while at least weekly symptoms of nocturnal asthma were reported by approximately 61% of all subjects. Baseline ICS use was reported by 47% of the overall population, with 49% in Caucasians and 38% in African Americans. Data for asthma history and current nocturnal symptoms indicate greater disease severity at baseline in the African-American subgroup as compared with Caucasian subjects (Table 2). For demographic and baseline characteristics, there were no statistically significant differences identified between the salmeterol and placebo groups within the Caucasian and African-American subgroups.

Table 2—Demographic and Baseline Characteristics for Caucasians and African Americans*

Characteristics	Caucasians (n = 18,642)	African Americans (n = 4,685)
Mean age, yr	40.3	36.5
Sex, No. (%)		
Female	11,719 (64)	3,088 (67)
Male	6,732 (36)	1,545 (33)
Peak expiratory flow, % predicted (SD)	85.3 (25.40)	78.1 (25.13)
Baseline ICS use	49	38
≥ 1 ED visit in last 12 mo	22	41
≥ 1 ED visit in lifetime	59	72
≥ 1 hospitalization in last 12 mo	6	15
≥ 1 hospitalization in lifetime	30	44
≥ 1 intubations for asthma in lifetime	4	8
Nocturnal symptoms present	59	67

*Data are presented as % unless otherwise indicated.

Exposure to study medication, subject disposition, baseline medication use history, and compliance with double-blind medication, expressed as the mean compliance rate, are displayed in Table 3. Compliance was assessed by self-report during each 4-week telephone contact using a scale of 0 to 10 (0 = missed all doses; 10 = took all doses). Mean study drug compliance was similar between groups.

Primary and Secondary End Points

Total Population: The primary and secondary end point results are shown in Table 4. For the primary end point, there were no significant differences between treatment groups in the number of subjects with respiratory-related death or life-threatening experiences over the 28-week treatment period. There were small, but statistically significant differences between salmeterol and placebo for secondary end points associated with asthma-related and respiratory-related deaths and combined asthma-related death or life-threatening experiences. Specifically, there were 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in subjects receiving salmeterol, and there were 3 asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo. The cause of death, as listed on death certificates, is provided in Table 5 for all asthma-related deaths.

Table 3—Exposure to Study Medication, Patient Disposition, Concurrent Baseline Medications, and Compliance With Therapy*

Characteristics	Salmeterol (n = 13,176)	Placebo (n = 13,179)
Median exposure (25 to 75th percentile), d	197 (179–201)	197 (171–200)
Completed treatment	9,654 (73)	9,474 (72)
Discontinued prematurely	2,959 (22)	3,143 (24)
Concurrent medications		
Subjects reporting asthma medications at baseline	12,715 (97)	12,660 (96)
Subjects reporting no asthma medications at baseline	461 (3)	519 (4)
Inhaled or oral β_2 -agonists (excluding salmeterol)	12,059 (92)	12,043 (91)
ICS	6,127 (47)	6,138 (47)
Methylxanthine	1,766 (13)	1,767 (13)
Leukotriene modifiers	1,437 (11)	1,402 (11)
Mean compliance (SD) with study medications†	8.0 (2.58)	7.8 (2.67)

*Data are presented as No. (%) unless otherwise indicated.

†Scale = 0 to 10 (0 = no doses taken; 10 = all doses taken); mean compliance for each subject from all responses collected during monthly telephone interviews.

Table 4—Primary and Secondary End Points During the 28-Week Study Period*

Outcomes	Total Population			Caucasians			African Americans		
	Salmeterol (n = 13,176)	Placebo (n = 13,179)	RR (95% CI)	Salmeterol (n = 9,281)	Placebo (n = 9,361)	RR (95% CI)	Salmeterol (n = 2,366)	Placebo (n = 2,319)	RR (95% CI)
Primary end point									
Combined respiratory-related deaths or life-threatening experiences	50 (<1)	36 (<1)	1.3952 (0.9097 to 2.1398)	29 (<1)	28 (<1)	1.0478 (0.6239 to 1.7597)	20 (<1)	5 (<1)	4.0997 (1.5414 to 10.9042)
Secondary end points									
Combined asthma-related death or life-threatening experiences	37 (<1)	22 (<1)	1.7068 (1.0075 to 2.8912)	17 (<1)	16 (<1)	1.0835 (0.5478 to 2.1430)	19 (<1)	4 (<1)	4.9244 (1.6779 to 14.4519)
All-cause death	42 (<1)	32 (<1)	1.3037 (0.8236 to 2.0635)	29 (<1)	22 (<1)	1.3211 (0.7597 to 2.2975)	12 (<1)	7 (<1)	1.6885 (0.6660 to 4.2807)
All-cause hospitalization	469 (4)	420 (3)	1.1096 (0.9750 to 1.2627)	323 (3)	317 (3)	1.0222 (0.8780 to 1.1901)	102 (4)	77 (3)	1.2597 (0.9652 to 1.7233)
Combined all-cause death or life-threatening experience	70 (<1)	59 (<1)	1.1887 (0.8415 to 1.6793)	44 (<1)	44 (<1)	1.0116 (0.6668 to 1.5347)	24 (1)	11 (<1)	2.1668 (1.0640 to 4.4125)
Respiratory-related death	24 (<1)	11 (<1)	2.1627 (1.0599 to 4.4130)	16 (<1)	7 (<1)	2.2879 (0.9417 to 5.5585)	8 (<1)	2 (<1)	3.8819 (0.8253 to 18.2593)
Asthma-related death	13 (<1)	3 (<1)	4.3715 (1.2460 to 15.3367)	6 (<1)	1 (<1)	5.8247 (0.7014 to 48.3707)	7 (<1)	1 (<1)	7.2580 (0.8937 to 58.9439)

*Data are presented as No. (%) unless otherwise indicated. If the 95% CI of the RR does not contain a value of 1, then the difference between the salmeterol and placebo group rates is statistically significant at the $p < 0.05$ level.

Table 5—Primary Cause of Death as Recorded on the Death Certificate for All Asthma-Related Deaths

Treatment	Race	Age, yr	Sex	Comorbidities	Reported Baseline Asthma Medications	Cause of Death
Salmeterol	Caucasian	67	Female		Zafirlukast, albuterol, prednisone	Not listed
Salmeterol	Caucasian	46	Female	Allergic rhinitis, depressive disorder	Albuterol	Not available
Salmeterol	Caucasian	56	Male	Allergic rhinitis, arthritis	Ipratropium bromide, albuterol, theophylline	Bronchial asthma
Salmeterol	Caucasian	62	Male	Other	Cromolyn, ipratropium bromide/albuterol, albuterol, theophylline, prednisone	Emphysema
Salmeterol	Caucasian	60	Female	Allergic rhinitis, chronic hypertension, hypercholesterolemia, anxiety	Beclomethasone dipropionate	(1) Respiratory failure, (2) Status asthmaticus
Salmeterol	Caucasian	46	Male		Albuterol, theophylline	Chronic bronchial and bronchiolar asthma with acute asthmatic bronchitis
Salmeterol	African American	37	Female		Metaproterenol, albuterol, triamcinolone acetonide, prednisone	Not available
Salmeterol	African American	47	Male	Allergic rhinitis, chronic sinusitis	Ipratropium bromide, albuterol, theophylline	Acute exacerbation of asthma
Salmeterol	African American	41	Female	Allergic rhinitis, hypertension	Albuterol, theophylline	Asthma
Salmeterol	African American	47	Female	Allergic rhinitis, bronchitis, chronic hypertension, headache, arthritis, depressive disorder	Albuterol, terbutaline, triamcinolone acetonide	Hypertensive cardiovascular disease
Salmeterol	African American	56	Male	Diabetes	Ipratropium bromide, albuterol, fluticasone, theophylline	Atherosclerotic heart disease*
Salmeterol	African American	14	Male		Albuterol, theophylline	Bronchial asthma
Salmeterol	African American	51	Male	Bronchitis, chronic sinusitis, chronic hypertension, ulcers	Montelukast, prednisone	Congestive heart failure
Placebo	Caucasian	34	Female	Allergic rhinitis, bronchitis, chronic depressive disorder	Zafirlukast, albuterol, beclomethasone dipropionate, prednisone	Coronary atherosclerosis
Placebo	African American	67	Male		Budesonide, triamcinolone acetonide, theophylline, oxygen	(1) COPD, (2) Hypertension, (3) Microcytic anemia
Placebo	Not provided	61	Female		Fluticasone propionate, triamcinolone acetonide	(1) Respiratory failure, (2) Complication of pneumonia

*Coroner's report rather than death certificate.

In addition to the results of the 28-week analysis that were presented in Table 4, the primary and secondary outcomes were analyzed using events identified during the 28-week treatment period as well as those identified within 6 months of completion of the 28-week treatment period (Table 6). This additional planned analysis was carried out since rigid procedures for return of study medication after 28 weeks were absent; as such, it was considered possible that subjects would continue to take blinded study medication after completion of randomized phase of the study. Overall, results of analyses that

included data from the 28-week treatment period plus the 6-month posttreatment period are similar to those obtained during the 28-week treatment period alone.

Occurrence of Events by Study Phase and by Year: Events by study phase 1, when subjects were recruited by advertising, and phase 2, when subjects were recruited directly by investigators, are provided in Table 7 and show that, proportionally, more events occurred during phase 1 compared with phase 2 and that the imbalance between treatment groups in outcome events occurred primarily during

Table 6—Primary and Secondary End Points During the 28-Week Study Period and a 6-Month Follow-up Period*

Outcomes	Total Population			Caucasians			African Americans		
	Salmeterol (n = 13,176)	Placebo (n = 13,179)	RR (95% CI)	Salmeterol (n = 9,281)	Placebo (n = 9,361)	RR (95% CI)	Salmeterol (n = 2,366)	Placebo (n = 2,319)	RR (95% CI)
Primary end point									
Combined respiratory-related deaths or life-threatening experiences	52 (< 1)	45 (< 1)	1.1558 (0.7761 to 1.7214)	31 (< 1)	35 (< 1)	0.8933 (0.5514 to 1.4474)	20 (< 1)	7 (< 1)	2.8004 (1.1864 to 6.6100)
Secondary end points									
Combined asthma-related deaths or life-threatening experiences	38 (< 1)	25 (< 1)	1.5203 (0.9183 to 2.5170)	18 (< 1)	19 (< 1)	0.9555 (0.5018 to 1.8195)	19 (< 1)	4 (< 1)	4.6556 (1.5863 to 13.6641)
All-cause death	49 (< 1)	47 (< 1)	1.0428 (0.6994 to 1.5548)	33 (< 1)	31 (< 1)	1.0737 (0.6582 to 1.7515)	15 (< 1)	12 (< 1)	1.2252 (0.5747 to 2.6117)
All-cause hospitalization	499 (4)	449 (3)	1.1116 (0.9808 to 1.2599)	341 (4)	340 (4)	1.0116 (0.8729 to 1.1723)	113 (5)	83 (4)	1.3344 (1.0111 to 1.7612)
Combined all-cause death or life-threatening experience	77 (< 1)	73 (< 1)	1.0550 (0.7667 to 1.4518)	49 (< 1)	53 (< 1)	0.9325 (0.6330 to 1.3737)	26 (1)	15 (< 1)	1.6989 (0.9022 to 3.1991)
Respiratory related deaths	27 (< 1)	20 (< 1)	1.3503 (0.7578 to 2.4062)	18 (< 1)	14 (< 1)	1.2968 (0.6454 to 2.6058)	9 (< 1)	4 (< 1)	2.2053 (0.6801 to 7.1511)
Asthma-related deaths	15 (< 1)	6 (< 1)	2.5006 (0.9705 to 6.4428)	7 (< 1)	4 (< 1)	1.7651 (0.5169 to 6.0275)	8 (< 1)	1 (< 1)	7.8411 (0.9815 to 62.6425)

*Data are presented as No. (%) unless otherwise indicated. Raw RRs are used throughout this table (as opposed to the RR derived from life table methodology). If the 95% CI of the RR does not contain a value of 1, then the difference between the salmeterol and placebo group rates is statistically significant at the p < 0.05 level.

study phase 1. For example, the occurrence of asthma-related death by year was similar between treatment groups except during 1998, which occurred during phase 1 (Fig 2).

Caucasians: In the total population, Caucasian subjects represented the largest racial subgroup (71%), followed by African Americans (18%). In Caucasians, there were no statistically significant differences seen in the primary or secondary end points between treatments (Table 4). Twenty-nine subjects (< 1%) receiving salmeterol had a respiratory-related death or life-threatening experience, compared with 28 subjects (< 1%) in the placebo group. The incidence of one of the key secondary end points, combined asthma-related death or life-threatening experiences, occurred in 17 subjects (< 1%) receiving salmeterol compared with 16 subjects (< 1%) receiving placebo. There were no statistically significant differences in the number of asthma-related deaths in subjects receiving salmeterol (n = 6; < 1%) compared with subjects receiving placebo (n = 1; < 1%). The number of all-cause deaths was similar between treatments, with 29 events (< 1%) and 22 events (< 1%) reported for salmeterol and placebo, respectively.

African Americans: In the African-American population, there were statistically significant differences in the primary end point and for two of the secondary end points between treatment groups (Table 4). Significantly more subjects receiving salmeterol (n = 20; < 1%) had a respiratory-related death or life-threatening experience compared with the placebo group (n = 5; < 1%). The number of combined asthma-related deaths or life-threatening experiences was significantly greater in subjects receiving salmeterol (n = 19; < 1%) compared with placebo (n = 4; < 1%). The numbers of asthma-related deaths and all-cause deaths were not statistically significantly different in subjects receiving salmeterol compared with placebo (Table 4).

Effects of Concurrent ICS Use: While SMART was not designed to assess the effect of ICS use on the end points, *post hoc* analyses were conducted to explore the effect of ICS use on the results of SMART. In the intent-to-treat population, the number of events for the primary outcome and all secondary outcomes was similar for subjects reporting baseline use of ICS in both treatment groups, and no significant differences were found between treatment groups (Table 8). The number of primary and secondary outcome events for subjects reporting no baseline ICS use was greater in the salmeterol

Table 7—Primary and Secondary End Points by Study Phase*

Variables	Phase 1			Phase 2		
	Salmeterol (n = 7,670)	Placebo (n = 7,672)	RR (95% CI)	Salmeterol (n = 5,506)	Placebo (n = 5,507)	RR (95% CI)
Primary end point						
Combined respiratory-related deaths of life-threatening experiences	35 (< 1)	24 (< 1)	1.4560 (0.8670 to 2.4452)	15 (< 1)	12 (< 1)	1.2742 (0.5970 to 2.7193)
Secondary end points						
Combined asthma-related deaths or life-threatening experiences	31 (< 1)	17 (< 1)	1.8350 (1.0165 to 3.3124)	6 (< 1)	5 (< 1)	1.2543 (0.3830 to 4.1071)
All-cause death	24 (< 1)	15 (< 1)	1.6110 (0.8458 to 3.0683)	18 (< 1)	17 (< 1)	1.0304 (0.5316 to 1.9969)
All-cause hospitalization	256 (3)	216 (3)	1.1793 (0.9868 to 1.4092)	213 (4)	204 (4)	1.0348 (0.8574 to 1.2488)
Combined all-cause death or life-threatening experience	45 (< 1)	33 (< 1)	1.3656 (0.8725 to 2.1374)	25 (< 1)	26 (< 1)	0.9656 (0.5585 to 1.6697)
Respiratory-related death	14 (< 1)	6 (< 1)	2.3490 (0.9032 to 6.1093)	10 (< 1)	5 (< 1)	1.9209 (0.6570 to 5.6158)
Asthma-related death	10 (< 1)	3 (< 1)	3.3736 (0.9288 to 12.2532)	3 (< 1)	0	

*Data are presented as No. (%) unless otherwise indicated. RR = quotient of the event rate for the salmeterol group divided by the event rate for the placebo group. If the 95% CI of the RR does not contain a value of 1, then the difference between the salmeterol and placebo group rates is statistically significant at the $p < 0.05$ level.

group compared with placebo. However, only asthma-related death and combined asthma-related death or life-threatening experiences were found to be significantly different between the two treatments (Table 8).

Examined by subgroup, a total of seven Caucasian subjects had an asthma-related death, of whom five

subjects were not receiving an ICS at baseline. Eight asthma-related deaths occurred in African-American subjects, of which four deaths occurred in subjects reporting no baseline use of ICS. Since SMART was not designed to evaluate the effects of ICS on study outcomes, the results of these *post hoc* analyses are not adequate to draw conclusions.

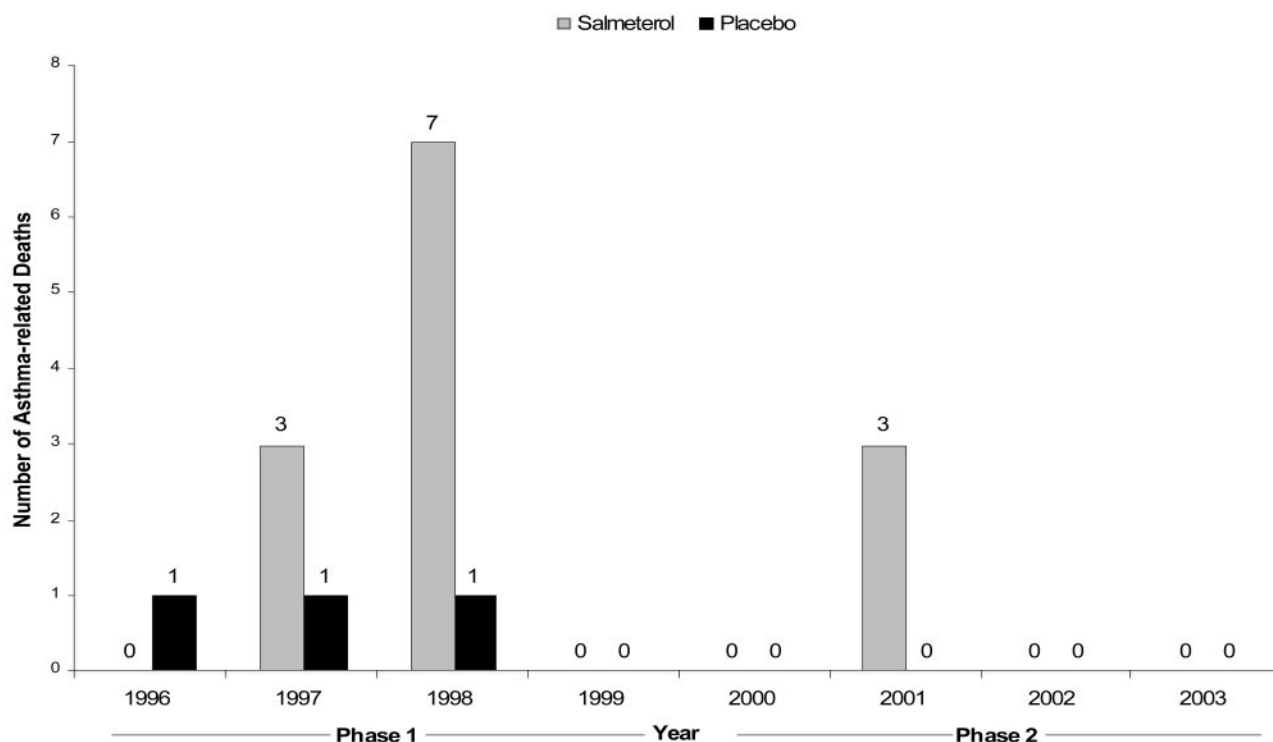


FIGURE 2. Occurrence of asthma-related deaths by phase and study year.

Table 8—Outcomes by Baseline ICS Use*

Variables	Total Population												Caucasians						African Americans																																						
	ICS at Baseline			No ICS at Baseline			ICS at Baseline			No ICS at Baseline			ICS at Baseline			No ICS at Baseline			ICS at Baseline			No ICS at Baseline																																			
	Salmeterol (n = 6,127)	Placebo (n = 6,138)	RR (95% CI)	Salmeterol (n = 7,049)	Placebo (n = 7,041)	RR (95% CI)	Salmeterol (n = 4,586)	Placebo (n = 4,637)	RR (95% CI)	Salmeterol (n = 4,695)	Placebo (n = 4,724)	RR (95% CI)	Salmeterol (n = 1,460)	Placebo (n = 1,444)	RR (95% CI)	Salmeterol (n = 6,127)	Placebo (n = 6,138)	RR (95% CI)	Salmeterol (n = 7,049)	Placebo (n = 7,041)	RR (95% CI)	Salmeterol (n = 4,586)	Placebo (n = 4,637)	RR (95% CI)	Salmeterol (n = 4,695)	Placebo (n = 4,724)	RR (95% CI)	Salmeterol (n = 1,460)	Placebo (n = 1,444)	RR (95% CI)																											
Primary end point	23 (<1)	19 (<1)	1.2146 (0.6622 to 2.2277)	27 (<1)	17 (<1)	1.5974 (0.8715 to 2.9277)	13 (<1)	15 (<1)	0.8752 (0.4169 to 1.8370)	16 (<1)	13 (<1)	1.2503 (0.6021 to 2.5962)	9 (<1)	3 (<1)	3.0193 (0.8202 to 11.1147)	11 (<1)	2 (<1)	5.6094 (1.2457 to 25.2598)	25 (<1)	20 (<1)	1.2485 (0.6942 to 2.2455)	27 (<1)	17 (<1)	1.5974 (0.8715 to 2.9277)	13 (<1)	15 (<1)	0.8752 (0.4169 to 1.8370)	16 (<1)	13 (<1)	1.2503 (0.6021 to 2.5962)	9 (<1)	3 (<1)	3.0193 (0.8202 to 11.1147)	11 (<1)	2 (<1)	5.6094 (1.2457 to 25.2598)																					
Combined respiratory-related death or life-threatening experience	16 (<1)	13 (<1)	1.2402 (0.5971 to 2.5759)	21 (<1)	9 (<1)	2.3920 (1.0964 to 5.2188)	6 (<1)	9 (<1)	0.6763 (0.2409 to 1.8984)	11 (<1)	7 (<1)	1.6191 (0.6282 to 4.1728)	9 (<1)	3 (<1)	3.0193 (0.8202 to 11.1147)	10 (<1)	1 (<1)	10.4579 (1.3406 to 81.5833)	17 (<1)	12 (<1)	1.3993 (0.6689 to 2.9273)	25 (<1)	20 (<1)	1.2485 (0.6942 to 2.2455)	27 (<1)	17 (<1)	1.5974 (0.8715 to 2.9277)	13 (<1)	15 (<1)	0.8752 (0.4169 to 1.8370)	16 (<1)	13 (<1)	1.2503 (0.6021 to 2.5962)	9 (<1)	3 (<1)	3.0193 (0.8202 to 11.1147)	11 (<1)	2 (<1)	5.6094 (1.2457 to 25.2598)																		
Secondary end points	17 (<1)	12 (<1)	1.3993 (0.6689 to 2.9273)	25 (<1)	20 (<1)	1.2485 (0.6942 to 2.2455)	27 (<1)	17 (<1)	1.5974 (0.8715 to 2.9277)	13 (<1)	15 (<1)	0.8752 (0.4169 to 1.8370)	16 (<1)	13 (<1)	1.2503 (0.6021 to 2.5962)	9 (<1)	3 (<1)	3.0193 (0.8202 to 11.1147)	11 (<1)	2 (<1)	5.6094 (1.2457 to 25.2598)	25 (<1)	20 (<1)	1.2485 (0.6942 to 2.2455)	27 (<1)	17 (<1)	1.5974 (0.8715 to 2.9277)	13 (<1)	15 (<1)	0.8752 (0.4169 to 1.8370)	16 (<1)	13 (<1)	1.2503 (0.6021 to 2.5962)	9 (<1)	3 (<1)	3.0193 (0.8202 to 11.1147)	11 (<1)	2 (<1)	5.6094 (1.2457 to 25.2598)																		
Combined asthma-related death or life-threatening experience	17 (<1)	12 (<1)	1.3993 (0.6689 to 2.9273)	25 (<1)	20 (<1)	1.2485 (0.6942 to 2.2455)	27 (<1)	17 (<1)	1.5974 (0.8715 to 2.9277)	13 (<1)	15 (<1)	0.8752 (0.4169 to 1.8370)	16 (<1)	13 (<1)	1.2503 (0.6021 to 2.5962)	9 (<1)	3 (<1)	3.0193 (0.8202 to 11.1147)	11 (<1)	2 (<1)	5.6094 (1.2457 to 25.2598)	25 (<1)	20 (<1)	1.2485 (0.6942 to 2.2455)	27 (<1)	17 (<1)	1.5974 (0.8715 to 2.9277)	13 (<1)	15 (<1)	0.8752 (0.4169 to 1.8370)	16 (<1)	13 (<1)	1.2503 (0.6021 to 2.5962)	9 (<1)	3 (<1)	3.0193 (0.8202 to 11.1147)	11 (<1)	2 (<1)	5.6094 (1.2457 to 25.2598)																		
All-cause death	255 (4)	231 (4)	1.0962 (0.9209 to 1.3049)	214 (3)	189 (3)	1.1275 (0.9300 to 1.3671)	187 (4)	184 (4)	1.0180 (0.8341 to 1.2424)	136 (3)	133 (3)	1.0316 (0.8153 to 1.3053)	47 (5)	37 (4)	1.2311 (0.8090 to 1.8735)	55 (4)	40 (3)	1.3349 (0.8947 to 1.9917)	255 (4)	231 (4)	1.0962 (0.9209 to 1.3049)	214 (3)	189 (3)	1.1275 (0.9300 to 1.3671)	187 (4)	184 (4)	1.0180 (0.8341 to 1.2424)	136 (3)	133 (3)	1.0316 (0.8153 to 1.3053)	47 (5)	37 (4)	1.2311 (0.8090 to 1.8735)	55 (4)	40 (3)	1.3349 (0.8947 to 1.9917)	255 (4)	231 (4)	1.0962 (0.9209 to 1.3049)	214 (3)	189 (3)	1.1275 (0.9300 to 1.3671)	187 (4)	184 (4)	1.0180 (0.8341 to 1.2424)	136 (3)	133 (3)	1.0316 (0.8153 to 1.3053)	47 (5)	37 (4)	1.2311 (0.8090 to 1.8735)	55 (4)	40 (3)	1.3349 (0.8947 to 1.9917)			
Combined all-cause death or life-threatening experience	31 (<1)	26 (<1)	1.1898 (0.7074 to 2.0012)	39 (<1)	33 (<1)	1.1898 (0.7494 to 1.8891)	20 (<1)	22 (<1)	0.9162 (0.5008 to 1.6763)	24 (<1)	22 (<1)	1.1106 (0.6237 to 1.9776)	10 (1)	3 (<1)	3.3421 (0.9230 to 12.1021)	14 (<1)	8 (<1)	1.7383 (0.7317 to 4.1299)	31 (<1)	26 (<1)	1.1898 (0.7074 to 2.0012)	39 (<1)	33 (<1)	1.1898 (0.7494 to 1.8891)	20 (<1)	22 (<1)	0.9162 (0.5008 to 1.6763)	24 (<1)	22 (<1)	1.1106 (0.6237 to 1.9776)	10 (1)	3 (<1)	3.3421 (0.9230 to 12.1021)	14 (<1)	8 (<1)	1.7383 (0.7317 to 4.1299)	31 (<1)	26 (<1)	1.1898 (0.7074 to 2.0012)	39 (<1)	33 (<1)	1.1898 (0.7494 to 1.8891)	20 (<1)	22 (<1)	0.9162 (0.5008 to 1.6763)	24 (<1)	22 (<1)	1.1106 (0.6237 to 1.9776)	10 (1)	3 (<1)	3.3421 (0.9230 to 12.1021)	14 (<1)	8 (<1)	1.7383 (0.7317 to 4.1299)			
Respiratory-related death	10 (<1)	5 (<1)	2.0058 (0.6860 to 5.8648)	14 (<1)	6 (<1)	2.2842 (0.8783 to 5.9404)	7 (<1)	3 (<1)	2.3119 (0.5982 to 8.9346)	9 (<1)	4 (<1)	2.2876 (0.7050 to 7.4226)	3 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)	5 (<1)	1 (<1)	4.4324 (0.5185 to 37.8881)	10 (<1)	5 (<1)	2.0058 (0.6860 to 5.8648)	14 (<1)	6 (<1)	2.2842 (0.8783 to 5.9404)	7 (<1)	3 (<1)	2.3119 (0.5982 to 8.9346)	9 (<1)	4 (<1)	2.2876 (0.7050 to 7.4226)	3 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)	5 (<1)	1 (<1)	4.4324 (0.5185 to 37.8881)	10 (<1)	5 (<1)	2.0058 (0.6860 to 5.8648)	14 (<1)	6 (<1)	2.2842 (0.8783 to 5.9404)	7 (<1)	3 (<1)	2.3119 (0.5982 to 8.9346)	9 (<1)	4 (<1)	2.2876 (0.7050 to 7.4226)	3 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)	5 (<1)	1 (<1)	4.4324 (0.5185 to 37.8881)			
Asthma-related death	4 (<1)	3 (<1)	1.3522 (0.3028 to 6.0389)	9 (<1)	0		1 (<1)	1 (<1)	0.9604 (0.0601 to 15.3502)	5 (<1)	0		3 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)	4 (<1)	0		4 (<1)	3 (<1)	1.3522 (0.3028 to 6.0389)	9 (<1)	0		1 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)	5 (<1)	0		3 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)	4 (<1)	0		4 (<1)	3 (<1)	1.3522 (0.3028 to 6.0389)	9 (<1)	0		1 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)	5 (<1)	0		3 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)	4 (<1)	0		3 (<1)	1 (<1)	3.1189 (0.3251 to 29.9241)

*Data are presented as No. (%) unless otherwise indicated. If the 95% CI of the RR does not contain a value of 1, then the difference between the salmeterol and placebo group rates is statistically significant at the $p < 0.05$ level.

Kaplan-Meier Survival Analysis

Log-rank tests found no significant differences for time to primary end point, time to withdrawal related to a medical condition other than asthma, time to all-cause death, or time to first all-cause hospitalization (data not shown). Figures 3, 4 show that there were significant increases in time to withdrawal due to worsening asthma ($p < 0.001$), and time to withdrawal not related to a medical condition ($p = 0.016$) for salmeterol compared with placebo.

Adverse Events

Overall, 1,093 subjects (4% in each treatment group) had serious adverse events during the study. The most common serious adverse events, which occurred in 2% of all subjects, were events classified as lower respiratory tract in nature. All other serious adverse events occurred at an incidence of $< 1\%$. Based on Kaplan-Meier analyses, there were statistically significant differences between the treatment groups for time to first serious adverse event causing discontinuation (salmeterol survival rate, 95.61%; placebo survival rate, 96.18%; $p = 0.022$).

DISCUSSION

This randomized, double-blind, clinical trial was planned for 60,000 subjects, or 238 primary events,

but was terminated following a planned interim analysis when approximately one half of the subjects were enrolled, subsequently providing 86 primary events. Predefined criteria for study termination were not met at the interim analysis. However, the study was terminated by GlaxoSmithKline due to preliminary findings in African Americans and difficulties in enrollment.

The results in the total population for the primary end point, the number of subjects with respiratory-related death or life-threatening experiences, showed no significant differences between treatments for the total population. There were small, but significant differences between treatments for respiratory- and asthma-related deaths and combined asthma-related death or life-threatening experiences. Although the study was active from 1996 to 2003, the imbalance in outcomes between treatment groups in respiratory- and asthma-related events was largely isolated to 1998.

To further explore the data, *post hoc* analyses were conducted. For example, although there was a higher number of respiratory- and asthma-related death or life-threatening experiences in the total population treated with salmeterol compared with placebo, *post hoc* analyses showed no significant differences between treatments for these outcomes in the Caucasian population.

By comparison, there was a small, but significant increase in several respiratory- and asthma-related

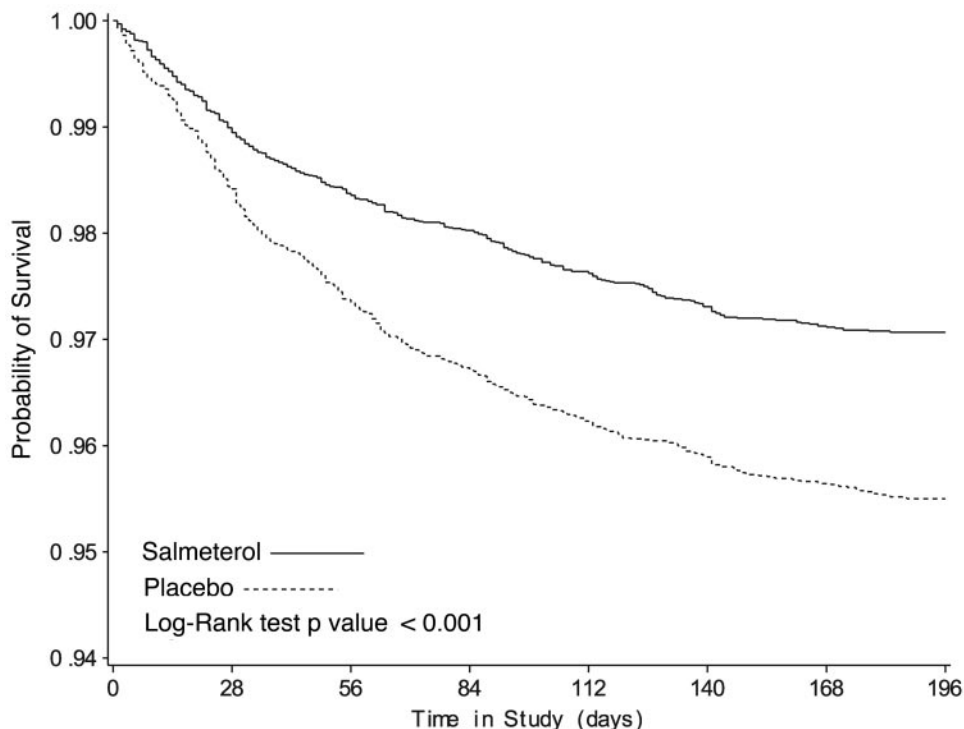


FIGURE 3. Time to withdrawal due to worsening asthma.

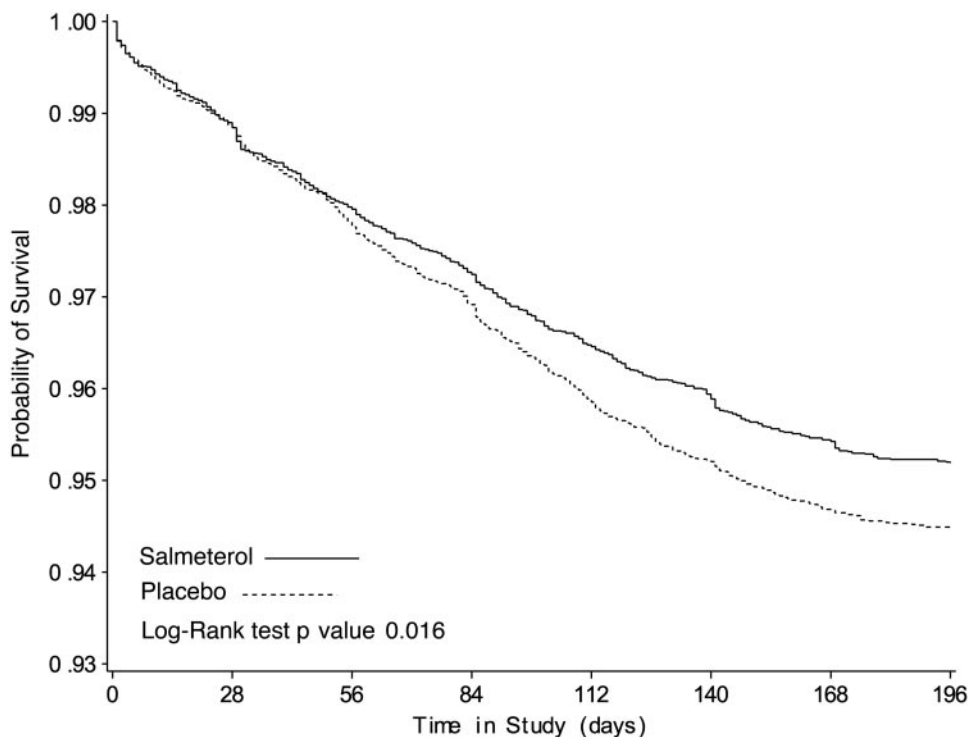


FIGURE 4. Time to withdrawal not related to medical condition.

secondary outcomes in African Americans treated with salmeterol compared with placebo. When examining subpopulations at screening, African Americans had lower peak expiratory flow, reported less ICS use, and higher percentages of hospitalizations and ED visits compared with Caucasians. Whether these factors or other factors including but not limited to a physiologic treatment effect, a genetic predisposition, or patient behaviors leading to poor outcomes (*eg*, delay in seeking care, compliance with study treatments or asthma medications) influenced the study outcomes in African Americans remains unknown. For example, it is hypothesized that a genetic variation in the β -adrenergic receptor may influence the response to β -adrenergic therapy, and the frequency of genetic variations in the β -adrenergic receptor are higher in subgroups such as African Americans compared with the overall population.¹³ However, the effect of these genetic variations in the β -adrenergic receptor on serious asthma outcomes is unclear, and there are limited data suggesting that genotype does not affect the phenotypic response to salmeterol.¹⁴ The current study was not designed to evaluate these possibilities and additional studies are needed to evaluate whether these and other factors have an impact on serious asthma outcomes in African Americans.

While the risk for all-cause death was not statistically different between treatments in African Amer-

icans, the risk for all cause hospitalization and the risk for the combined outcome of all cause death or life-threatening experiences were increased for salmeterol recipients in this population. It is not known whether this increase may be the result of a treatment effect, an imbalance between controller treatments, or in treatment for concurrent medical conditions, socioeconomic status, or a result of chance. Detailed information relative to all-cause events and socioeconomic status were not collected during the study; therefore, SMART was unable to determine the cause of this imbalance between treatments.

The effect of ICS in reducing asthma mortality and major morbidity in children and adults is well documented.^{15,16} Determining the effect of ICS use on the outcomes of SMART was not an objective of this study. As such, SMART was not adequate to determine whether or not ICS use affected the incidence of the key outcome events in this study. Nonetheless, the available data from SMART are consistent with prior observational studies^{15,17} with salmeterol indicating that outcomes such as hospitalizations due to asthma and asthma exacerbations are reduced when salmeterol is used in conjunction with an ICS.

The asthma-related death rate for subjects exposed to salmeterol in SMART (1.22 per 1,000 person-years) is lower than that reported previously by Castle *et al*¹² (2.32 per 1,000 person-years), as

well as by Martin and Shakir¹⁸ (2.76 per 1,000 person-years). These UK studies included a larger proportion of subjects > 60 years old, which may, in part, account for the differences. Asthma-related death rates by race or ethnicity were not reported in these UK studies, and thus a direct comparison with SMART cannot be made.

Other valid methods for studying rare events such as asthma death and asthma morbidity include observational study designs. In such studies, salmeterol use has not been found to be associated with an increased risk of serious asthma outcomes relative to theophylline,¹⁰ ipratropium bromide,¹⁰ or short-acting β -agonists,¹¹ even among patient with the most severe asthma. In the largest matched case-control study¹⁹ to date (532 patients), salmeterol use in the prior 3 months was not associated with an increased risk of asthma death (odds ratio, 1.05).

As noted previously, SMART was active from 1996 to 2003; for unclear reasons, the imbalance between treatment groups in respiratory- and asthma-related events was largely isolated to 1998 during phase 1. There was a change in patient recruitment strategies between phase 1 (from 1996 to 1999) and phase 2 (from 1999 to 2003). In phase 1, subjects unknown to the study investigator were directed to centralized study clinics via independent telephone screening services in response to subjects' calls following media advertising. In contrast, phase 2 used the recruitment methodology of enrolling subjects known within the practice of the physician investigator. It is known that an established doctor-patient relationship can impact the quality of overall asthma care for individual subjects.²⁰ To the extent that this was true of phase 1 vs phase 2, it may, in part explain why there were fewer incidences and no imbalances between treatment groups in the number of serious respiratory- and asthma-related events in phase 2 as compared with phase 1.

In summary, the results of SMART indicate that for the primary end point in the total population, there were no significant differences between treatments. However, there were small, but statistically significant increases in respiratory- and asthma-related deaths and combined asthma-related death or life-threatening experiences in the total population in the salmeterol group compared with placebo. The imbalance occurred largely in the African-American subpopulation. Whether this risk in African Americans is due to factors including but not limited to a physiologic treatment effect, genetic factors, or patient-level behaviors leading to poor outcomes remains unknown.

REFERENCES

- Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for Asthma-United States, 1980-1999. *MMWR Morb Mortal Wkly Rep* 2002; 51(SS-1):1-14
- Strunk RC, Ford JG, Taggart V. Reducing disparities in asthma care: priorities for research; National Heart, Lung, and Blood Institute workshop report. *J Allergy Clin Immunol* 2002; 109:229-237
- Speizer FE, Doll R, Heaf P, et al. Investigation into use of drugs preceding death from asthma. *BMJ* 1968; 1:339-343
- Stolley PD. Asthma mortality: why the United States was spared an epidemic of deaths due to asthma. *Am Rev Respir Dis* 1972; 105:883-890
- Crane J, Pearce N, Flatt A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-83: a case-control study. *Lancet* 1989; 917-922
- Pearce NE, Grainger J, Atkinson M. Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977-1981. *Thorax* 1990; 170-175
- Grainger J, Woodman K, Pearce NE, et al. Prescribed fenoterol and death from asthma in New Zealand 1981-7: a further case-control study. *Thorax* 1991; 46:105-111
- Mann RD, Kubota K, Pearce G, et al. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996; 49:247-250
- Lanes SF, Lanza L, Wentworth CE. Risk of emergency care, hospitalization, and ICU stays for acute asthma among recipients of salmeterol. *Am J Respir Crit Care Med* 1998; 158:857-861
- Meier CR, Jick H. Drug use and pulmonary death rates in increasing symptomatic asthma patients in the UK. *Thorax* 1997; 52:612-617
- Williams C, Crossland L, Finnerty J, et al. A case-control study of salmeterol and near-fatal attacks of asthma. *Thorax* 1998; 53:7-13
- Castle W, Fuller R, Hall J, et al. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993; 306:1034-1037
- Drysdale CM, McGraw DW, Stack CB, et al. Complex promoter and coding region β_2 -adrenergic receptor haplotypes alter receptor expression and predict *in vivo* responsiveness. *Proc Natl Acad Sci* 2000; 97:10483-10488
- Taylor DR, Kennedy MA. β -Adrenergic receptor polymorphisms and drug responses in asthma. *Pharmacogenomics* 2002; 3:173-184
- Suissa S, Ernst P, Benayoun S, et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; 343:332-336
- Donahue G, Weiss ST, Livingston JM, et al. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997; 277:887-891
- Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000; 320:1368-1373
- Martin RM, Shakir S. Age- and gender-specific asthma death rates in patients taking long-acting β -2 agonists. *Drug Safety* 2001; 24:475-481
- Anderson HR, Ayres JG, Sturdy PM, et al. Bronchodilator treatment and deaths from asthma: case-control study. *BMJ* 2005; 330:117-124
- Adams RJ, Weiss ST, Fuhlbrigge A. How and by whom care is delivered influences anti-inflammatory use in asthma: results of a national population survey. *J Allergy Clin Immunol* 2003; 112:445-450

The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol

Harold S. Nelson, Scott T. Weiss, Eugene R. Bleecker, Steven W. Yancey, Paul M. Dorinsky and the SMART Study Group

Chest 2006;129;15-26

DOI 10.1378/chest.129.1.15

This information is current as of June 7, 2007

Updated Information & Services	Updated information and services, including high-resolution figures, can be found at: http://chestjournals.org/cgi/content/full/129/1/15
References	This article cites 18 articles, 9 of which you can access for free at: http://chestjournals.org/cgi/content/full/129/1/15#BIBL
Citations	This article has been cited by 19 HighWire-hosted articles: http://chestjournals.org/cgi/content/full/129/1/15
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://chestjournals.org/misc/reprints.shtml
Reprints	Information about ordering reprints can be found online: http://chestjournals.org/misc/reprints.shtml
Email alerting service	Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]