U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 20236 (b) (4)

Drug Name: Serevent (salmeterol xinafoate)Inhalation Aerosol

Indication(s): Asthma in patients ages 6 to 48 months

Applicant: GlaxoSmithKline

Date(s): Submission dated: December 21, 2005

Review Priority: 6 months

Biometrics Division: Division of Biometrics 2

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Concurring Reviewers: NA

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Keywords:
(b) (4)

1.0 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor has submitted the results of two efficacy and safety studies of Serevent Inhalation in response to the Agency's Written Request dated May 20, 1999 (and amended on February 9, 200, May 2, 2000, July 3, 2000, May 7, 2004, and November 18, 2004). Each of the studies were 4-week, randomized, double-blind, double-dummy, placebo-controlled, parallel-group (Serevent 25 mcg BID, Serevent 50 mcg BID, and placebo), and multicenter. Study SMS30076 enrolled subjects 24 to 47 months of age. Study SMS30077 enrolled subjects 6 to 23 months of age.

The primary efficacy endpoint for both studies was the average of the change from baseline in composite (daytime and nighttime) asthma symptom scores during the 4-week treatment period (measured on a scale of 0 to 3). Secondary endpoints included individual daytime and nighttime asthma symptom scores, the percentage of symptom-free days, percentage of symptom-free and albuterol-free days, supplemental albuterol use, percentage of nights with no awakenings, number of asthma exacerbations, subject discontinuations, and child health status as assessed by the Functional Status II(R).

Approximately 390 subjects (130 per treatment group) were planned for enrollment in Study SMS30076 to achieve the Written Request requirement of at least 100 completed subjects per treatment group. According to the sponsor's power calculations and assuming a standard deviation of 0.55 (based on previous studies) and using a two-sided t-test with a 0.05 two-sided significance level, 100 subjects per group would provide at least 90% power to detect a difference of 0.3 between any two treatment groups. Three hundred thirty eight subjects (113 placebo, 112 Serevent 25 mcg BID, and 113 Serevent 50 mcg BID) were enrolled in the study. Three hundred and fifteen subjects (107 placebo, 107 Serevent 25 mcg BID, and 101 Serevent 50 mcg BID) completed the study.

Approximately 167 subjects (55-56 per treatment group) were planned for enrollment in Study SMS30077 to achieve the amended Written Request requirement of at least 45 completed subjects per treatment group. According to the sponsor's power calculations and assuming a standard deviation of 0.47 (based on previous studies) and using a two-sided t-test with a 0.05 two-sided significance level, 45 subjects per group would provide at least 80% power to detect a difference of 0.28 between any two treatment groups. One hundred sixty seven subjects (55 placebo, 56 Serevent mcg BID, and 56 Serevent 50 mcg BID) were enrolled in the study. One hundred fifty three subjects (50 placebo, 50 Serevent 25 mcg BID, and 53 Serevent 50 mcg BID) completed the study.

For both studies, the intent-to-treat population was defined as all randomized subjects who received at least one dose of study drug and was used as the primary efficacy analysis group. To control for multiplicity (i.e., two doses of Serevent), a fixed sequence testing method was used. Analysis of covariance controlling for baseline, region, holding chamber (study SMS30076 only), age (months), gender, language, and concurrent asthma medication was the primary analysis method of the primary efficacy endpoint.

2.0 STATISTICAL ISSUES AND FINDINGS

In general, this reviewer is in agreement with the methods proposed and implemented by the sponsor in the conduct and analysis of these studies and therefore is in agreement with the sponsor's overall conclusions.

Regarding Study SMS30076, the sponsor stated, "This study was unable to demonstrate efficacy of Serevent Inhalation aerosol 25 mcg BID and 50 mcg BID administered via valved holding chamber in the primary efficacy measure, composite asthma symptom scores, in children with asthma aged 24-47 months". The sponsor continues, "Similarly, efficacy was not demonstrated in any of the secondary efficacy measures".

Regarding Study SMS300777, the sponsor stated, "This study was unable to demonstrate efficacy of Serevent Inhalation aerosol 25 mcg BID and 50 mcg BID administered via valved-holding chamber with attached facemask compared with placebo in the primary efficacy measure, composite asthma symptom scores, in children with asthma aged 6-23 months". The sponsor continues, "Similarly, efficacy was not demonstrated in any of the secondary efficacy measures".

As the sponsor has not made efficacy claims based on either of these studies, no further investigation or analysis of these data by this reviewer are warranted. The reader is referred to the clinical review for this application for further summary and discussion of the efficacy and safety results provided by these studies.

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Ruth Davi
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